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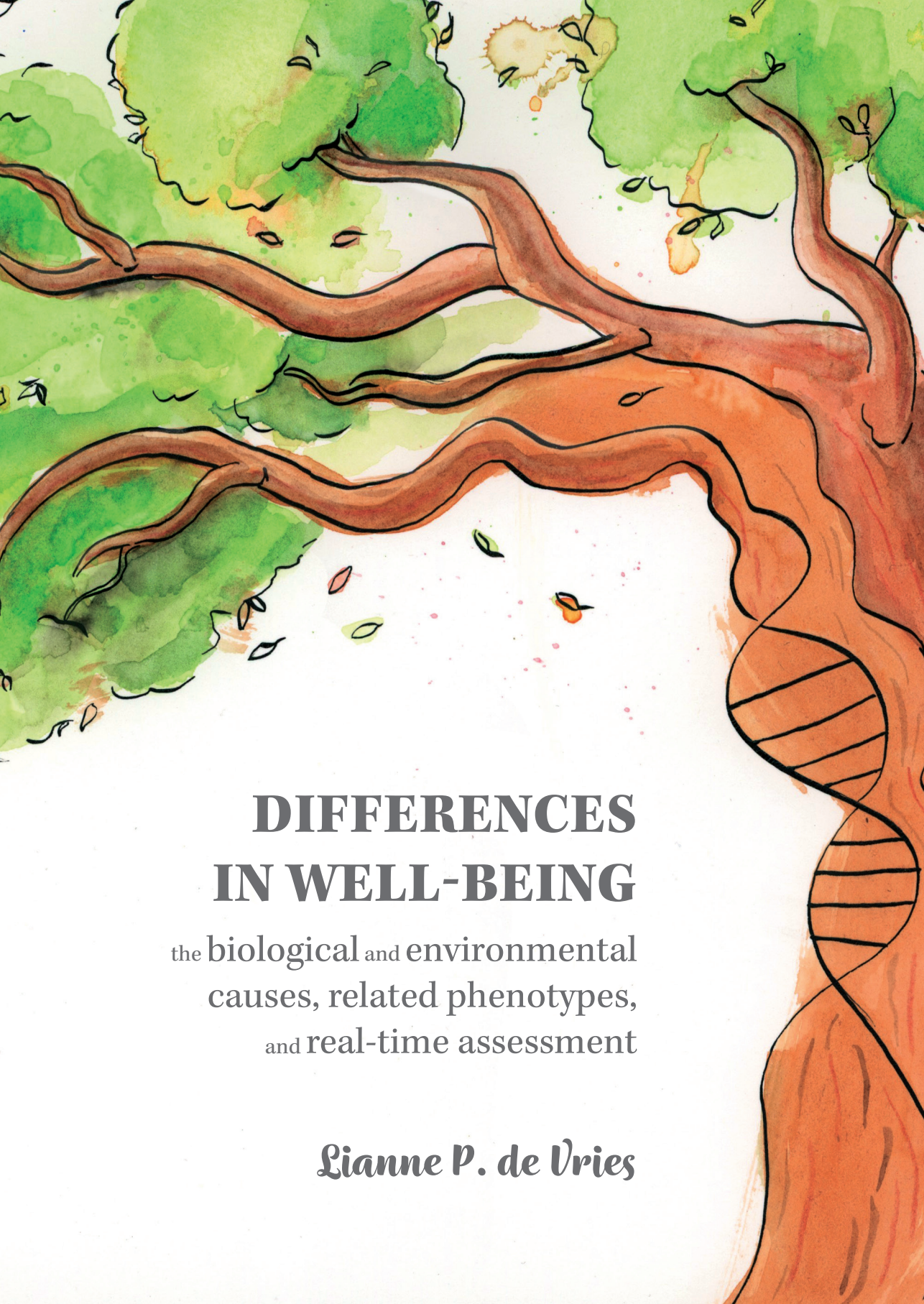
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DIFFERENCES IN WELL-BEING

the biological and environmental
causes, related phenotypes,
and real-time assessment

Lianne P. de Vries



**Differences in well-being:
the biological and environmental causes, related
phenotypes, and real-time assessment**

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VRIJE UNIVERSITEIT

**DIFFERENCES IN WELL-BEING: THE BIOLOGICAL AND ENVIRONMENTAL
CAUSES, RELATED PHENOTYPES, AND REAL-TIME ASSESSMENT**

ACADEMISCH PROEFSCHRIFT

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Chapter 1.

Introduction

Partly based on

van de Weijer, M. P., **de Vries, L. P.**, & Bartels, M. (2022). Happiness and well-being: The value and findings from genetic studies. In A. Tarnoki, D. Tarnoki, J. Harris, & N. Segal (Eds.), *Twin Research for Everyone* (pp. 295–322). Academic Press. doi: 10.1016/B978-0-12-821514-2.00016-7

and

Bartels, M., Nes, R.B., Armitage, J.M., van de Weijer, M.P., **de Vries, L.P.**, & Haworth, C.A.M. (2022). Exploring the biological basis for happiness. *World Happiness Report 2022*.

Well-being is a broad, complex, and multifaceted construct that includes feeling good and functioning well (Ryan & Deci, 2001). There is a growing global recognition of well-being as an important public policy goal. Since 2015, mental health and well-being are included in one of the Sustainable Development Goals (SDG) of the United Nations (United Nations, 2015). In this goal, mental health and well-being are defined as a priority for global development. Similarly, different governments across the world recognize the important of well-being and highlight the need of well-being measures to inform decisions (Boelhouwer, 2010; Stiglitz et al., 2009; Zencey, 2014). For example, when Finland was the chair of the Council of the European Union, their priority was the concept of the Economy of Wellbeing. This concept states that *while people's wellbeing is a value in itself, it is also vitally important for the Union's economic growth, productivity, long-term fiscal sustainability, and societal stability* (Llena-Nozal et al., 2019). Recently, the Wellbeing Economy Governments (WEGo) was established, a collaboration of national and regional governments to build economies focused on well-being (WEGo - Wellbeing Economy Alliance, 2022). Currently, Scotland, New Zealand, Iceland, Wales, Finland, and Canada are part of this collaboration. Instead of using the gross domestic product (GDP), these countries propose to use a range of different well-being measures, including human health, safety, and flourishing, to assess the success of the country and of national policies.

Similarly, the number of scientific publications on well-being, happiness and other positive psychology traits increased every year in the past 25 years across different disciplines (Barrington-Leigh, 2022; Kim et al., 2018), indicating the increasing interest in and importance of well-being in the scientific field. In contrast to earlier views of well-being as the opposite of psychopathology and ill-being, the positive effects of well-being are found to be, at least partly, independent from the negative effects of ill-being on life. This finding indicates that well-being is more than the absence of disease or mental illness and it is therefore important to investigate (Howell et al., 2007; WHO, 2022). Well-being is related to less behavioral and emotional problems, and is associated with many positive aspects of daily life, including longevity (James et al., 2019; Steptoe, 2019; Zaninotto & Steptoe, 2019), higher educational achievement, happier marriage, and more productivity at work (Chapman & Guven, 2016; Lyubomirsky et al., 2005; Maccagnan et al., 2019; Oswald et al., 2015).

Different definitions and conceptualizations of well-being have emerged across disciplines and contexts (Lambert et al., 2015). In the current psychological definitions of well-being, a distinction is often made between measures of hedonic/subjective well-being and eudaimonic/psychological

well-being (Ryan & Deci, 2001). The subjective well-being theory originated from hedonistic philosophical ideas on well-being (Lambert et al., 2015; Ryan & Deci, 2001). This philosophical definition of hedonism includes maximizing pleasure and minimizing pain as the ultimate goal of life. Modern-day hedonic or subjective well-being measures therefore focus on levels of positive affect and negative affect and satisfaction with life (Diener et al., 2018). The psychological well-being has emerged from eudaimonic philosophical theories (Lambert et al., 2015; Ryan & Deci, 2001). The eudaimonic philosophical theory extends beyond pleasure and pain only, and emphasizes positive psychological functioning and living a virtuous life. Current eudaimonic or psychological well-being measures include measures of positive functioning, thriving, and judgments about the meaning and purpose of an individual's life (Ryff, 1989). Hedonic and eudaimonic measures of well-being have been found to load on separate, but correlated factors ($>.60$) (Gallagher et al., 2009; Joshanloo, 2016; Thorsteinsen & Vittersø, 2020).

People differ in their levels of well-being, i.e., some people are in general happier or more satisfied with their lives than others. These individual differences in well-being can arise from many different factors, including biological (genetic) influences and environmental influences. To enhance the development of future mental health prevention and intervention strategies to increase well-being, more knowledge about these determinants and factors underlying well-being is needed. As outlined briefly below, we are starting to understand the different factors that influence individual differences in well-being, but several gaps in the literature remain. In this dissertation, I aim to increase the understanding of the etiology of well-being by investigating the neural, physiological, genetic, and environmental influences on well-being in more detail, and by examining the relationship and causality between well-being and related traits. In this introduction, I introduce the different chapters and describe the outline of the dissertation in more detail.

Genetic and environmental influences on well-being

Genetically informative designs, such as the classical twin design, can be applied to decompose differences between people (i.e., the observed variance of a trait) into genetic and environmental sources of variation. The twin design uses data from reared together monozygotic (MZ) and dizygotic (DZ) twins (Boomsma et al., 2002). MZ twin pairs share all genes, whereas DZ twin pairs share on average half of their segregating genes. Based on this difference in genetic relatedness, phenotypic variance of traits can be decomposed into (additive and dominant) genetic and (shared) environmental variance

components. Additive genetic variance (A) represents the additive variance explained by summing the effects of all alleles that influence the phenotype. Non-additive genetic variance (D) arises due to interactions between alleles at the same locus (dominance) or between alleles at different loci (epistasis). The environmental variance consists of a shared environmental variance component (C) (variance shared by family members) and a non-shared environmental component (E) (part of the variance that is unique for an individual).

Two comprehensive reviews of twin studies on the heritability of well-being, i.e., the relative influence of genetic effects on well-being, revealed a range of heritability estimates across the included studies (Bartels, 2015; Nes & Røysamb, 2015). Meta-analyzing the results of the included studies resulted in a similar heritability estimate of around 40% in both reviews. Nes and Røysamb reported a weighted average heritability of 40% (95%CI: 37%-42%) across 13 independent studies including more than 30,000 twins (Nes & Røysamb, 2015). The weighted average heritability in (Bartels, 2015) was similar with 36% (95%CI: 34%–38%) for well-being based on a sample size of 55,974 individuals, and 32% (29%–35%) for satisfaction with life ($n = 47,750$). This robust estimate of the relative influence of genetic effects on well-being indicates that both genetic (~40%) and environmental influences (~60%) are important in explaining individual differences in well-being.

However, twin studies only indicate the heritability and proportion of environmental influence and do not provide information about the genetic locations that potentially influence well-being nor specify which environmental factors are important. Genome-wide association studies (GWAS) can be used to identify specific genetic variants associated with complex traits such as well-being. In a GWAS, millions of genetic variants are measured and regressed on a phenotype in a large group of individuals. In this way, the association between each genetic variant and an outcome of interest is tested with a strong correction for multiple testing to reduce the chance of finding false positives (Visscher et al., 2012, 2017). Four GWASs so far investigated the genetic etiology underlying well-being (Baselmans, Jansen, et al., 2019; Baselmans & Bartels, 2018; Okbay et al., 2016; Turley et al., 2018). The first successful GWAS ($n = 298,420$) led to the identification of three genetic variants associated with well-being (defined as life satisfaction and positive affect) (Okbay et al., 2016). The SNPs had small estimated effects on well-being (each $R^2 \approx 0.01\%$). To increase power to identify associated genetic variants, the latest GWAS for well-being combined life satisfaction, positive affect, neuroticism, and depressive symptoms in ‘the well-being spectrum’ (Baselmans, Jansen, et al., 2019). These traits show strong

genetic correlations ($r_g > .75$), suggesting a common liability. This multivariate Genome-wide Association Meta-Analysis (GWAMA) resulted in 304 independent significant variant-phenotype associations for the well-being spectrum, with 148 and 191 associations specific for life satisfaction and positive affect, respectively. The results of GWASs can be used in several bioinformatics follow-up analyses to investigate the possible biological mechanisms underlying the trait of interest. The biological annotation in the latest GWAMA for well-being revealed evidence for enrichment of genes differentially expressed in the subiculum (part of the hippocampus) and enrichment of genes differentially expressed in GABAergic interneurons (Baselmans, Jansen, et al., 2019).

These molecular genetic analyses and follow-up analyses revealed a complex genetic etiology of well-being, with likely thousands of genetic variants contributing to the trait. Each genetic variant only contributes a tiny amount to the variation in well-being. Therefore, we cannot speak of a single “happiness gene” or a few “happiness genes” that assert substantial influence on well-being. Even with the progress made in identifying more genetic variants for well-being and the few indications for the biological mechanisms, we still have a long road ahead to understand the genetics and biology underlying well-being.

Besides genes, the environment explains a substantial part of the variance in individual differences in well-being (~60%). Compared to the investigation of specific genetic influences, systematic investigations of the precise environmental influences on well-being are scarce. We can only draw a few conclusions from the existing literature on the association between well-being and environmental factors. For example, social connectedness, such as the quality of social contacts (Pinquart & Sörensen, 2000) and social support (Wang et al., 2003) are reported to be important for well-being. For the contextual/physical environmental factors, there is less consensus on the importance for well-being. Studies produce contradicting results and results are hard to compare directly because of varying designs. For example, Lovell and colleagues examined the association between exposure to biodiverse environments and well-being and concluded that there might be a small positive effect, but most evidence is inconclusive (Lovell et al., 2014). Similarly, Vanaken and Danckaerts (2018) and Houlden et al. (2018) examined the literature on green space exposure and well-being in children and adults, respectively. Both reviews conclude there is limited evidence for a positive effect.

Recently, van de Weijer and colleagues (2022) performed the first systematic Environment-Wide Association Study (EnWAS) of well-being, including objective environmental indicators. Of the 139 included neighborhood-level environmental exposures, 21 environmental factors were significantly

associated with well-being. The factors were mainly in the domains: housing stock, income, core neighborhood characteristics, safety, livability, and socioeconomic status, with socioeconomic status and safety being the most important environmental factors in explaining differences in well-being.

In sum, although there is a vast body of literature on the association between different environmental variables and well-being, the importance of environmental influences remains mostly unclear and needs more investigation. One complexity in research on the environmental factors in relation to well-being is that most environmental variables are heritable as well (Kendler & Baker, 2007; Plomin & Bergeman, 1991). For example, people are actively involved in creating their own environment, based on their genetic predisposition. Similarly, the behavior of people, which is under substantial genetic control (Polderman et al., 2015), triggers environmental reactions. This interplay between genes and the environment is important to take into account when investigating individual differences in happiness and well-being

Biology of well-being

The genetic influence on well-being, as discussed above, indicates that there are biological influences on well-being. Biological psychology is the study of physiological, evolutionary, and developmental mechanisms, and includes the investigation of biological processes underlying or influencing behavior and complex traits (Kalat, 2019). Different biological processes of interest in biological psychology include the brain and nervous system, physiological processes, including hormones and neurotransmitters, and more recently the microbiome (Cryan & Dinan, 2019; Kalat, 2019).

Big claims are made about the role of these different biological factors for well-being and happiness, both in the popular media and in the scientific field. For example, dopamine, serotonin and oxytocin are often called “Feel good hormones” or “Happy chemicals”, as they are thought to play an important role in feelings of well-being. There are even claims that boosting these hormones is thought to increase your happiness substantially (see for example <https://www.healthline.com/health/happy-hormone>). In addition, the highly complex brain mechanisms are often reduced to be simply malleable in popular science articles (e.g., https://greatergood.berkeley.edu/article/item/how_to_trick_your_brain_for_happiness), based on studies with questionable quality and small samples (Dunbar et al., 2012; Manninen et al., 2017). To better understand the biological pathways that explain individual differences in well-being and its association with (mental) health, well-powered research into biological mechanisms underlying well-being is needed.

In biological psychology, neuroscience is currently the dominant approach to investigate differences in well-being among individuals. The human brain is the central organ of the human nervous system and is a key player in mood and emotion regulation. The neural correlates of psychopathology, such as depression, and other mental illnesses related to well-being have been investigated extensively (Harrewijn et al., 2021; Phillips et al., 2015; Schmaal et al., 2020), whereas the involvement of the brain in well-being has received far less attention until recently. Because of the increasing interest in well-being and rapid technological advancements in neuroscience methods, an increasing number of studies on the association between well-being and the brain with innovative analysis methods have been published recently. The results of these studies differ widely and this raises the question if brain volume or activity of specific brain areas is related to feelings of well-being. In **chapter 2**, we therefore systematically reviewed the published neural correlates of well-being, i.e., measures of brain volumes, brain functioning, and brain connectivity. The systematic review and meta-analysis allowed us to bring together the literature to develop a more complete picture on the involvement of the brain in well-being.

Besides the brain, many different physiological systems in the human body play a role in behavior, experiences, and emotions, including hormones, neurotransmitters, the activity of the immune system, and the microbiome. Each of these systems are hypothesized to explain part of the individual differences in happiness and well-being among individuals. For example, different hormones and neurotransmitters, including serotonin, dopamine, and cortisol, have an influence on mood and have been consistently found to be involved in mood related forms of psychopathology, such as depression and bipolar disorder (Kennis et al., 2020; Krishnan & Nestler, 2010). However, a recent large review found inconsistent evidence for the serotonin theory of depression, and concluded that there is no support for the hypothesis that depression is caused by lowered serotonin concentrations (Moncrieff et al., 2022). The immune system, important for the body's defence against infections and diseases, has been linked to mental health and mood disorders as well (Khandaker et al., 2014; Osimo et al., 2019). Finally, interest in the relation between the (gut) microbiome (i.e., all micro-organisms, such as bacteria, that live in our gut or total body) and mental health increased substantially recently (Cryan & Dinan, 2012; Winter et al., 2018), suggesting a role of the microbiome in well-being as well. These four different physiological systems interact in their influence on mental health and possibly well-being (Adam et al., 2017; Liu et al., 2020; Morey et al., 2015; Peirce & Alviña, 2019), but most studies into the

physiology of well-being include only factors from one category, for example, either hormones or immune parameters. Integrating the areas will lead to a complete picture of the human physiology of well-being.

As a first step, in **chapter 3**, we created an overview of all reported associations of different physiological markers and well-being in the literature so far. We reviewed the literature on the association of well-being and physiological factors across four distinct categories of human physiology: neurotransmitters, hormones, inflammatory markers, and the microbiome. Based on the findings, we highlighted the directions for future research.

Well-being and related phenotypes

Well-being is a complex phenotype that is closely related to different psychological phenotypes and outcomes. For example, well-being shows a negative correlation with depressive symptoms and other forms of psychopathology (Bartels et al., 2013; Greenspoon & Saklofske, 2001; Lamers et al., 2015; Suldo & Shaffer, 2008) and a positive association with positive traits like optimism, self-esteem, and resilience (Alarcon et al., 2013; Caprara et al., 2009; Wootton et al., 2017). Investigating the nature of the overlap between well-being and related phenotypes can result in more knowledge on the etiology of well-being. Different genetic methods, including twin models, and molecular genetic methods, e.g., GWAS and follow-up analyses, can be used to investigate the (genetic) overlap.

For example, bivariate twin designs can answer the question how much of the phenotypic correlation between two traits is accounted for by genetic and environmental factors (Eaves & Gale, 1974; Martin & Eaves, 1977). Furthermore, genetic correlations estimated in the model indicate the extent to which the genetic factors underlying one trait overlap with the genetic factors that influence the other trait. Similarly, environmental correlations indicate the extent to which the environmental factors underlying one trait overlap with the environmental factors influencing the other trait. Bivariate twin designs can help to understand why traits are related or tend to co-occur.

In **chapter 4**, we explained the value and potential of bivariate twin models and used these models to investigate the phenotypic and genetic overlap between well-being and four different traits. The included traits, optimism, depressive symptoms, aggression, and educational attainment, differ in the size and direction of the phenotypic correlations with well-being. Whereas optimism is strongly positively related to well-being, depressive symptoms and aggression are respectively strong and moderate negatively related to well-being, and there is only a small positive association with educational

attainment. We separately described the bivariate heritability, (i.e., the contribution of genetic factors to the covariance between well-being and the traits) and the genetic correlations between well-being and the traits to discuss the distinctive information and (clinical) implications of these two outcomes for well-being.

In **chapter 5** and **chapter 6**, we investigated the overlap and relation between well-being and two specific related traits in detail using a range of (molecular) genetic designs. In **chapter 5**, we focused on the relation between well-being and resilience, because of the strong relation reported in earlier research. Resilience can be defined as an individual's ability to recover after the experience of stress or trauma, returning to an optimal mental state or as the psychological outcome after adverse events (Satici, 2016). Resilience and well-being have been associated strongly in many studies with a phenotypic correlation of around .50 (Hu et al., 2015). In chapter 5, we further investigated the association and causality between resilience and well-being in a large sample of twins and their siblings of the Netherlands Twin Register, using a range of (molecular) genetic designs. We used (longitudinal) bivariate twin-sibling models and polygenic score (PGS) prediction to assess the (genetic) overlap between resilience and well-being. A PGS is a measure of an individual's genetic probability to develop a certain disorder or have a certain trait (Wray et al., 2007). Using GWAS summary statistics, the PGS for a phenotype can be calculated in an independent sample by summing all genotype scores (at individual single-nucleotide polymorphisms) for a person after weighting them by their estimated effect size. The PGS can be used to test the predictive value towards another trait, or to investigate the shared genetic etiology between traits (Purcell et al., 2009).

Next, we used the monozygotic (MZ) within-twin pair differences method (De Moor et al., 2008), and the Mendelian Randomization Direction of Causality (MR-DoC) model (Minică et al., 2018) to assess the causality between the traits. The MZ within-twin pair differences method predicts that, under a causal model, the within-twin pair differences of genetically identical (MZ) twins in one trait are associated with within-twin pair differences in the other trait (De Moor et al., 2008). To explicitly test causality, allowing for coexisting genetic confounding, we applied the MR-DoC model. The MR-DoC model uses twin data and polygenic scores, combining the strengths of Mendelian Randomization and the Direction of Causation twin model (Minică et al., 2018).

The advantage of using multiple methods, i.e., a triangulation approach (Lawlor et al., 2016) in this chapter, is that all methods have different assumptions, strengths and weaknesses. If the results of the different analyses

converge on the relation between well-being and resilience, the reliability of the findings is higher compared to using a single analysis method.

In **chapter 6**, we further investigated the relation between well-being and depressive symptoms. Depressive symptoms include, among others, feeling down, or hopeless, and having little interest or pleasure in doing things (American Psychiatric Association, 2013a). Depressive symptoms have been often studied in relation to well-being and a moderate to high negative phenotypic and genetic correlation between well-being and depressive symptoms is consistently reported (Bartels et al., 2013; Baselmans et al., 2018; Greenspoon & Saklofske, 2001; Suldo & Shaffer, 2008). However, the correlation is not equal to one, indicating that well-being is more than the absence of depressive symptoms and psychopathology. In chapter 6, we zoomed in on the (genetic) overlap between well-being and depression and investigated the part that makes well-being unique using the GWAS-by-subtraction method (Demange et al., 2021). GWAS-by-subtraction removes the genetic variants associated with depressive symptoms from the well-being GWAS, resulting in genetic signal that is only associated with well-being and unrelated to depressive symptoms. We used the resulting ‘pure well-being’ GWAS to investigate the genetic overlap with a range of other phenotypes to learn more about the unique part of well-being, independently from depressive symptoms.

Extreme environmental effects on well-being

In the beginning of 2020, half way the first year of my PhD project, huge (environmental) changes occurred suddenly across the world due to the corona virus disease (COVID-19). In March 2020, the World Health Organization declared a pandemic. During the first year of this pandemic, prolonged restrictions were needed to control the virus, and to make sure that the healthcare systems could cope, since there was no effective cure and vaccination yet. In the Netherlands, the first lockdown was enforced in March 2020, with major restrictions including social distancing, closing of schools, offices, gyms, and other public places, and individuals were strongly advised to work from home. People’s daily life and society were severely impacted. The COVID-19 pandemic can therefore be seen as an extreme environmental influence and a universal exposure affecting everyone.

This unique period not only strongly affected the course of my PhD project, but also allowed us to study the effects of such an extreme environmental change on well-being. The initial research on the effects of the pandemic and lockdown on mental health and well-being focused on the detrimental effects averaged across large population samples. Across the world, increased anxiety

and depression, and decreased well-being (i.e., life satisfaction and positive affect) have been reported in response to the first phase of the pandemic and first lockdown (Ahmed et al., 2020; Kwong et al., 2020; Lades et al., 2020; Prati & Mancini, 2021; Ueda et al., 2020; Zacher & Rudolph, 2020). However, the effects were less extreme than expected (Helliwell et al., 2021) and the average negative effect on well-being disappeared quickly. By mid-2020 average mental health had recovered to pre-pandemic levels (Robinson et al., 2022).

Because of the differences in genetic predispositions for well-being between individuals, and individual differences in sensitivity to extreme environmental changes, individuals can be expected to differ substantially in the effect of the pandemic on mental health and well-being. In **chapter 7**, we used longitudinal data of a large sample of twins and their family members from the Netherlands Twin Register to investigate the individual differences in the effect of the COVID-19 pandemic and first lockdown on well-being. Using data from before the pandemic and during the first phase of the pandemic, i.e., May and June 2020, we investigated the gene-by-crisis interaction effect on optimism and meaning in life. By applying bivariate twin modelling we could investigate the impact of the pandemic on both the genetic and environmental variance underlying the well-being traits.

Chapter 7 and other research on the effects of the pandemic on well-being (Prati & Mancini, 2021; Robinson et al., 2022) focused mainly on the immediate effects of the initial phase of the COVID-19 pandemic and lockdown. This resulted in insight into the acute response to the pandemic and the individual differences in these effects. However, across the world, multiple waves of COVID-19 infections occurred, leading to multiple lockdowns. In the Netherlands, the second strict lockdown was introduced in December 2020, with again strict distance regulations and closing of schools, shops, and other public places. Investigating the effect of later lockdowns on well-being can help to understand the more prolonged effects of the pandemic and is needed to inform policy with regard to expected psychological impact of future lockdowns. Therefore, in **chapter 8**, we investigated the effect of the second lockdown in the Netherlands on well-being. Instead of the effect on general well-being, we investigated the more subtle or dynamic effects of the lockdown on daily well-being. Using daily diary data of 50 days before and 50 days during the second lockdown in the Netherlands, we investigated the effect of the lockdown on everyday positive and negative affect intensity and variability. Affect intensity and variability are, within boundaries, adaptive and important for mental health and well-being as it helps to respond to environmental changes and demands (Carver, 2015; Frijda & Mesquita, 1994; Kashdan & Rottenberg, 2010). However, if emotions change

too strongly or not at all it may signal dysregulation (Aan het Rot et al., 2012; Houben et al., 2015; Maciejewski et al., 2019; Reitsema et al., 2022; Schoevers et al., 2021). Using piecewise growth models in both an adolescent and adult sample, we tracked the longitudinal effect of the second lockdown on affect intensity and variability.

Real-time assessment

Most of the research in the field of well-being, including part of my work as described in this dissertation, is based on retrospective self-reported measures of well-being. Well-being questionnaires ask about the general well-being or happiness and include for example the Satisfaction with Life Scale (Diener et al., 1985), or the Subjective Happiness Scale (Lyubomirsky & Lepper, 1999). These questionnaires are completed by participants at a single time point or multiple times. This kind of questionnaire research has many advantages, including the ability to reach very large samples and providing reliable general well-being assessments. However, retrospective self-reports also have disadvantages, including recall biases and a low measurement frequency. When interested in dynamic behavior or phenotypes that fluctuate across time, a single measurement is not enough and multiple measurements in real life and real-time are needed. For example, although the scores on well-being questionnaires are found to be relatively stable and reliable over time (Fujita & Diener, 2005; Pavot, 2008; Schimmack & Oishi, 2005), momentary feelings of well-being (e.g. mood) fluctuate over time and across different contexts (Eid & Diener, 2004; Li et al., 2014; Lyubomirsky, 2001). Individuals differ in these well-being fluctuations, some people show relatively stable levels of well-being over the day and/or week, while others fluctuate more (Eid & Diener, 1999; Gadermann & Zumbo, 2007; Röcke et al., 2009). These fluctuations cannot be captured in single well-being questionnaires.

Different methods have been developed to repeatedly assess behavior and experiences to avoid recall bias and to zoom in on the moment-to-moment experiences in real-time and daily life. These real-time assessment methods include Ambulatory Assessment, Ecological Momentary Assessment (EMA), and the Experience Sampling Methods (ESM). Ambulatory Assessment is nowadays used as an umbrella term to describe methods to study people in their natural environment, including self-report, observational, biological, physiological, and behavioral data, but originated from observational and physiological data in medicine (Trull & Ebner-Priemer, 2013; Wilhelm et al., 2012). EMA and ESM have been developed from different disciplines, but are very similar, and can be defined as the repeated sampling of people's current thoughts, emotions,

behavior, physiological states, and context, in the natural environment and daily life of the participants (Csikszentmihalyi & Larson, 1987; Shiffman et al., 2008; Stone & Shiffman, 1994). Before technological developments, EMA/ESM studies required participants to carry beepers and booklets of questionnaires. After each random timed beep, participants had to complete the questions using pen and paper. Nowadays, EMA/ESM studies can be conducted more easily with smartphones (Runyan & Steinke, 2015). Using smartphones, it is also easier to collect both real-time active data, i.e., self-reports, and passive data, i.e., observational data, without the active involvement of participants.

In **chapter 9**, we reviewed the literature on smartphone-based Ecological Momentary Assessment of well-being in healthy participants. This review allowed us to bring together the literature and, besides describing the available studies on design characteristics, such as sampling, measures, and objective data, created a more complete picture of the associations between momentary well-being and environmental factors in real-time and daily life. Based on the results, we provided directions for future research and guidelines for using EMA in future well-being research.

One of the recommendations resulting from chapter 9 was to include passive and objective data in addition to self-report. An important advantage of objective data is the passive nature of the data and thereby the ecological validity, i.e., data is collected without necessary active participation of the participant in their natural setting. Furthermore, objective data can provide more reliable information compared to self-report that can be biased. For example, in physical activity and sedentary behavior research, only a weak relation between self-report and objectively assessed accelerometer data has been found, indicating biases in self-report (Dyrstad et al., 2014; Prince et al., 2008).

Both in our review in chapter 9 and other literature, physical activity and sedentary behavior have been related to well-being. In self-report research, higher levels of well-being have been associated with more time spent being physically active, and less time spent in sedentary behavior (Pengpid & Peltzer, 2019; Richards et al., 2015; Zhang & Chen, 2019). The results of studies on the association between accelerometer-assessed physical activity or sedentary behavior (i.e., more objective measures) and well-being are less consistent. Accelerometer data are very rich, since data on physical activity and sedentary behavior are collected continuously. However, most studies so far using accelerometer data included only the total or average time of physical activity or sedentary behavior. Recently, focus has shifted towards using the richness

of the data and investigating more detailed aspects, such as the daily or weekly patterns of physical activity and sedentary behavior instead of total volumes.

These new developments enable more in-depth analyses into the association between physical activity, sedentary behavior, and well-being. In **chapter 10**, we used the available accelerometer data of the Netherlands Twin Register to investigate the association between a range of measures of physical activity and sedentary behavior and well-being. We created novel and diverse accelerometer-assessed physical activity and sedentary behavior measures by going beyond the total volumes and including the timing and accumulation patterns of physical activity and sedentary behavior.

Outline of this dissertation

To summarize, in this dissertation we investigated the different biological, genetic and environmental factors influencing well-being in more detail to increase our understanding of the etiology of well-being. We did so by investigating a range of biological factors in relation to well-being in part I (**chapter 2 and 3**). In part II, we aimed to gain more insight into the etiology of well-being by investigating the overlap and causality between well-being and related traits (**chapter 4, 5 and 6**). In part III, taking advantage of the occurrence of an extreme environmental stressor, i.e., the COVID-19 pandemic, we investigated the effect of this extreme environmental factor on well-being and took into account the individual differences in the effects (**chapter 7 and 8**). In part IV, we explored the real-time assessment of well-being and (environmental) factors that influence well-being in daily life (**chapter 9 and 10**). Finally, in **chapter 11**, I summarize and discuss the results and conclusions of the different chapters. Furthermore, I will discuss implications of the research and the next steps and future of well-being research, including my next step, a large scale well-being EMA study in a genetically informative design.



The background is an abstract watercolor painting. It features a mix of colors: a vibrant green at the top, a bright yellow in the middle, and a warm orange at the bottom. The colors are blended together with soft, feathered edges, creating a textured, organic feel. There are some darker spots and variations in tone, giving it a sense of depth and movement.

Part I

Biology of Well-being



Chapter 2.

A systematic review of the neural correlates of well-being reveals no consistent associations

*Accepted as de Vries, L.P., van de Weijer, M.P., Bartels M. A systematic review of the neural correlates of well-being reveals no consistent associations. *Neuroscience & Biobehavioral Reviews**

ABSTRACT

Findings from behavioral and genetic studies indicate a potential role for the involvement of brain structures and brain functioning in well-being. We performed a systematic review on the association between brain structures or brain functioning and well-being, including 56 studies.

The 11 electroencephalography (EEG) studies suggest a larger alpha asymmetry (more left than right brain activation) to be related to higher well-being. The 18 Magnetic Resonance Imaging (MRI) studies, 26 resting-state functional MRI studies and two functional near-infrared spectroscopy (fNIRS) studies identified a wide range of brain regions involved in well-being, but replication across studies was scarce, both in direction and strength of the associations. The inconsistency could result from small sample sizes of most studies and a possible wide-spread network of brain regions with small effects involved in well-being. Future directions include well-powered brain-wide association studies and innovative methods to more reliably measure brain activity in daily life.

Keywords: well-being, brain, neural correlates, brain-wide associations

INTRODUCTION

Over 30 years of twin studies show that genetic influences explain a significant part of the differences in well-being. A recent review (van de Weijer et al., 2020) replicates the robust meta-analytic heritability estimate of well-being of about 40% for well-being (Bartels, 2015; Nes & Røysamb, 2015). Three genome wide association studies (GWAS) identified specific genetic variants associated with well-being (Baselmans, Jansen, et al., 2019; Okbay et al., 2016; Turley et al., 2018). The latest ‘well-being spectrum’ GWAS (combining life satisfaction, positive affect, neuroticism, and depressive symptoms) resulted in 304 significant associations, with 148 and 191 associations specific to life satisfaction and positive affect, respectively. Follow-up molecular genetic analyses, examining the underlying biology, found evidence for an association between the well-being spectrum and enrichment of genes differentially expressed in the subiculum (part of the hippocampus), and of GABAergic interneurons (Baselmans, Jansen, et al., 2019). The genetic contribution to well-being based on the estimates from twin studies and the molecular genetic evidence indicate a role for biological markers and raises question about the neurobiological foundation of well-being.

The human brain is the central organ of the human nervous system and is a key player in mood and emotion regulation. In research on the involvement of the brain, a distinction can be made between the brain structure (e.g., the size or structure of brain areas) and brain functioning (e.g., the activation of brain areas or connectivity between brain areas). Due to rapid technological developments, it is feasible to assess brain structure and brain functioning *in vivo*. We briefly discuss the different neuroscientific methods to measure brain structure and brain functioning in Box 1. For more detailed information on the methods, see textbooks on neuroscience (Purves et al., 2008; Ward, 2019).

Box 1

To assess the structure of the brain (areas), the common approach is *Magnetic Resonance Imaging (MRI)*. Using strong magnetic fields, a MRI scan of the head results in detailed images of the brain, that can be used to map the structure and size of the brain. Often in MRI research studies, voxel-based morphometry (VBM) is used to process structural MRI scans. VBM infers per voxel if the brain tissue is gray matter (GM), white matter (WM), or cerebrospinal fluid (CSF). This information can be used to calculate the volume of brain areas and to make group comparisons of gray matter volume in different groups of subjects (Ashburner & Friston, 2000).

To assess brain functioning, different methods have been developed, including *positron emission tomography (PET)*, *electroencephalography (EEG)*, *magnetoencephalography (MEG)*, *functional Magnetic Resonance Imaging (fMRI)* and *functional near-infrared spectroscopy (fNIRS)*.

In short, *PET* uses radioactive substances to visualize activity of brain areas, by measuring blood flow, regional chemical composition, and absorption. In *EEG* research, participants wear a cap with electrodes to detect the electrical changes due to signaling of the neurons at the surface of the brain. *MEG* is a technique to record brain activity by detecting magnetic fields produced by electrical signals of neurons. *fMRI* is used to detect the Blood-Oxygenation Level Dependent response (BOLD) in resting state or in response to stimuli. The BOLD response reflects the changes in amount of oxygenated blood flow in an area, indicating activity (Belliveau et al., 1991). *fNIRS* uses the BOLD response as well, but instead of lying in a scanner, participants wear a cap to record the absorption of near infrared light. The more active a brain area, the more light is absorbed (Maki et al., 1995).

Differences between the different techniques are marked by time and spatial resolution. MEG and EEG have a high temporal resolution, as neurons immediately signal in response to a stimulus and these electrical potentials and magnetic fluxes are recorded. The temporal resolution of fMRI and fNIRS is lower, as it takes several seconds for a change in blood flow to be detected. In contrast, the spatial resolution of EEG/MEG is lower than that of fMRI, as signals are only detected at the brain surface, whereas fMRI has whole-brain coverage.

The neural correlates of psychopathology and ill-being, such as depression, anxiety, and other mental illnesses have been investigated extensively (Harrewijn et al., 2021; Phillips et al., 2015; Schmaal et al., 2020), whereas the involvement of the brain in well-being has received far less attention until recently. Two recent reviews summarized the neural correlates of measures of well-being (King, 2019; Machado & Cantilino, 2016). First, based on two studies, Machado and Cantilino (2016) reported an association between well-being and the gray matter volume in the insula and the precuneus. King (2019) reviewed 22 studies published before 2018, and reported relations between the anterior cingulate cortex (ACC), the posterior cingulate cortex (PCC) (parietal lobe), the superior temporal gyrus (temporal lobe), and some subcortical areas, e.g., the putamen and thalamus, with different measures of well-being. Due to the rapid technological advancements since 2018 and increasing interest in well-being, more studies on the association between well-being and the brain with innovative analysis methods have been published. Therefore, the goal of the paper is to systematically review the studies on the association between different measures of well-being and the brain.

In the current psychological literature, often a distinction is made between hedonic well-being (i.e., positive affect and subjective satisfaction with life; Diener et al., 2018) and eudaimonic well-being (i.e., positive functioning, thriving, and judgments about the meaning and purpose of an individual's life; Ryan & Deci, 2001). Since hedonic and eudaimonic well-being are found to be strongly related, both phenotypically and genetically (Baselmans, van de Weijer, et al., 2019; Joshanloo, 2016), we refer in this review to well-being in the broadest sense.

METHODS

To bring together the literature on the association between brain structure and functioning and well-being, we performed a systematic review and reported the results in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009).

Information Source and Search Strategy

To collect relevant articles the bibliographic databases PubMed and Web of Science were searched (last search end of March 2022). Additional articles that were potentially missed during this search were identified via reference lists of the selected articles. The search strategy included combinations of search terms related to well-being (“well-being”, “wellbeing”, “satisfaction with life”, “life satisfaction”, “happiness”, “positive affect”, “flourishing”, “meaning in life”, “purpose in life”, “eudai*”, “eudem*”) and brain measures (“brain region”, “brain area”, “brain activation”, “brain volume”, “neural correlates”, “neuronal activity”, “neural activity”, “neuronal basis”, “neural basis”, “neural substrate”, “fMRI”, “MRI”, “(functional) magnetic resonance imaging”, “neuroimaging”, “electroencephalography”, “EEG”, “PET”, “positron emission tomography”). The search applied iterative combinations of these categories by employing the Boolean search operators AND and OR.

Study Selection and Data Extraction

Titles and abstracts of collected articles were screened for eligibility and were included if (1) an association between well-being (i.e., not only the absence of depression) and brain functioning or brain structure was investigated, (2) healthy, non-clinical human samples were included, (3) the study was peer-reviewed, and (4) published in English. Articles were excluded when (1) the procedure included a mood or emotion induction procedure, (2) a clinical sample, (3) the papers were review papers or (4) protocols for future studies.

In cases of insufficient information to determine eligibility, papers were subjected to further screening. The first author screened the abstracts and if necessary, the full text reports and decided whether papers met the inclusion criteria. Uncertainties and disagreement were resolved through discussions with the other authors.

Meta-analysis and publication bias

If, after reviewing, a substantial number of studies and effect sizes were considered to be relatively homogeneous with respect to study design and

reported effect, we meta-analyzed the reported associations using the Metafor package in R (R Core Team, 2017; Viechtbauer, 2010). For results to be included in the meta-analysis, a bivariate correlation (instead of a standardized regression or beta coefficient) had to be reported. Since we focus on bivariate correlations, and standardized regression coefficients are often based on regression with different covariates, we did not include (transformed) standardized regression coefficients or other effect indices in the meta-analyses as this might lead to biased estimates (Roth et al., 2018). For normalization, correlations were transformed into Fisher Z scores, using the formula:

$ESz = 0.5 * \log\left(\frac{1+r}{1-r}\right)$. After the meta-analysis, the estimate was transferred back

to a correlation for reasons of interpretation, using $r = \frac{(e^{2ESz} - 1)}{(e^{2ESz} + 1)}$ (Lipsey & Wilson, 2001).

As some studies used overlapping samples and most studies reported multiple associations and effect sizes, we applied a three-level meta-analysis (Van den Noortgate et al., 2014). This enabled us to include all effect sizes while taking into account the dependency, by specifying three levels, (1) sampling variance of the effect sizes, (2) variance between effect sizes within studies using the same dataset, and (3) variance between studies.

To assess the possible presence of a publication bias, we plotted the distribution of the effect sizes in a funnel plot and applied the Egger's test to test the significance of the asymmetry of the funnel plot (Egger et al., 1997). If the plot is too asymmetrical and the test significant, a publication bias can be expected.

RESULTS

Study selection

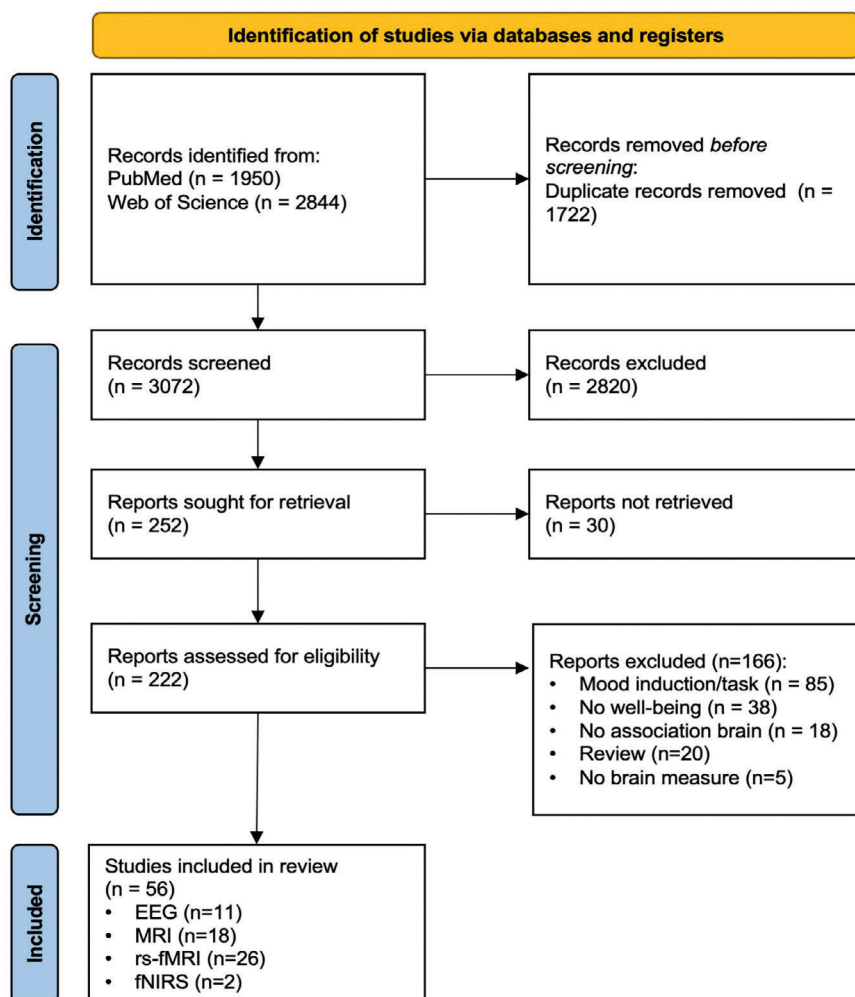
We summarized the selection progress in the PRISMA Flow diagram (see Figure 2.1). The initial electronic database searches resulted in 1950 hits in PubMed and 2844 hits in Web of Science ($n_{total} = 4794$). After removing the duplicates, 3072 articles remained. Scanning these titles and abstracts, a first selection was made based on the selection criteria ($n=252$). Of the selected articles, 30 articles could not be retrieved and were excluded. The remaining selected articles that ($n=222$) were examined and read fully. Based on the full-text reading, 56 articles met our selection criteria and were included in the review.

Study characteristics

Of the 56 studies, 18 studies used structural MRI to investigate brain structures in relation to well-being, 11 studies used electroencephalography (EEG) to assess resting-state (regional) brain activation, 26 studies used resting state fMRI to measure brain activation or connectivity at rest, and two studies used functional near-infrared spectroscopy (fNIRS) to assess functional connectivity. One study used both structural MRI and fMRI (Luo et al., 2017) and is described in both categories.

Regarding the different well-being measures, 39 studies only included hedonic well-being measures, using measures of positive affect, happiness, satisfaction with life and quality of life. Eight studies included only eudaimonic well-being measures, using the psychological well-being scale, the social well-being scale and a meaning in life questionnaire. Five studies included both a hedonic and eudaimonic well-being measure and four studies used measures consisting of both hedonic and eudaimonic aspects, such as the COMPAS-W scales and the Warwick Edinburgh Mental well-being scale. For more details on the specific measures, see the *Well-being measures* section per data collection method.

In the sections below, we describe the results of the studies in the four categories based on the data collection method. Tables 1-4 show the design characteristics and results of the 56 studies on brain structure and brain functioning in relation to well-being in the four different categories. Supplementary Table S2.1 includes the total number of times a brain region or network was associated with well-being, split by the different imaging techniques.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

Figure 2.1. PRISMA Flow Diagram of the included studies

Structural MRI

Description of study designs and samples

Eighteen studies used MRI to link well-being to the size of brain structures. Two studies used an overlapping sample of Chinese university students (Kong,

Hu, Xue, et al., 2015; Kong, Ding, Yang, et al., 2015). In addition, two other studies by Kong and colleagues used a separate overlapping sample (Kong, Yang, et al., 2019; Kong, Zhao, et al., 2019).

When only considering unique samples ($k=16$ studies), the average number of participants across the remaining studies is 196.1 participants ($SD=235$), with a range of 15 to 807 participants. The average age is 30.1 ($SD=16.8$, range=12.6-69.5). The proportion included females is on average 59% ($SD=13\%$) with a range of 43% to 100%. Most studies included only right-handed participants in their sample ($k=9$), while one sample consisted of 94% right-handed participants. Handedness was not reported for the remaining 6 studies (see Table 2.1).

Well-being measures

Of the 18 studies, 12 studies used hedonic well-being measures. This includes four studies that used the Positive and Negative Affect Schedule (PANAS, Crawford & Henry, 2004) as measure of positive affect (M7,M8,M12,M13), two studies that used the Satisfaction with Life scale (Diener et al., 1985) (M4,M13), two studies that used the subjective happiness scale (Lyubomirsky & Lepper, 1999) (M11,M15), two studies that used the WHO measure of quality of life (Power & Kuyken, 1998) (M3,M18), and single studies that used the positive affect subscale of the Center for Epidemiologic Studies Depression Scale (CES-D, Radloff, 1977) (M9), a measure of life satisfaction (M2), or a well-being factor (M10) based on multiple hedonic well-being scales. Five studies used an eudaimonic well-being measure, including three that used the psychological well-being scale (Ryff, 1989) (M8,M16,M17) and two studies that used the social well-being scale (Keyes, 1998) (M5,M14). Finally, two studies used a measure that combined hedonic and eudaimonic well-being measures, i.e., the COMPAS-W scale (Gatt et al., 2014) (M1,M6).

Results grey matter volume

Figure 2.2 shows the brain areas where grey matter volume was significantly positively (Figure 2.2 top) or negatively (Figure 2.2 bottom) related to different well-being measures.

Summarizing results across the studies, grey matter volume of the (medial) prefrontal cortex (PFC) was negatively associated with life satisfaction and social well-being in two studies (M13,M14), indicating that a smaller PFC is related to lower levels of well-being. In contrast, Kong and colleagues (2019) reported a positive correlation between the medial PFC and life satisfaction.

More of these inconsistent directions between the size of brain areas and well-being were found. First, grey matter volume of the dorsal or mid ACC

was negatively associated with hedonic well-being measures (i.e., positive affect and quality of life) in two studies (M7, M18), whereas Matsunaga et al. (2016) reported a positive correlation between the rostral part of the ACC and subjective happiness. Secondly, in the largest study included (n=724), Van 't Ent et al. (2017; M10) reports a negative association between the grey matter volume of the hippocampus and well-being, whereas in a smaller study (n=89) the relation was positive (M12). Furthermore, Sato et al. (2015) reported a positive relation between the grey matter volume of the precuneus and happiness, whereas this was negatively related to life satisfaction in a larger sample (n=299) (M13). A final inconsistent result is the positive and negative relationship between (part of) the brainstem and well-being (respectively in M16 and M6).

In single studies, the grey matter volume of the posterior parietal cortex (M7), the left and right insular cortex (M17), and right parahippocampal gyrus (M13) was positively related to well-being, whereas the grey matter volume of the left caudate (M1), left orbitofrontal cortex (M5), the left lingual gyrus (M9) was negatively related to well-being.

To summarize, the reviewed studies revealed large inconsistencies. The grey matter volumes of the (medial) PFC, ACC, precuneus, hippocampus, and brainstem were related to well-being in multiple studies, but for all these areas, there was inconsistency in the direction and strength of the associations.

Table 2.1. The design characteristics and results of the structural MRI studies to well-being.

Nr	Authors	N	Age	Females	Right-handed	WB measure	Brain area identified	Sign	Effect size
M1	(Boyes et al., 2022)	49	12.6 (0.32)	46.9%	--	COMPAS-W	GM: left caudate	-	-0.31*
M2	(Cabeen et al., 2021)	807	28.7 (3.7)	56.1%	-	Life satisfaction	frontoinsular cortical orientation dispersion	-	left $\beta = -0.13^*$, right $\beta = -0.14^*$
M3	(Ourry et al., 2021)	135	69.4 (3.8)	61.5%	-	WHOQoL-BREF	Gray matter volume WM mean kurtosis	ns	$\beta = 0.14$ $\beta = -0.25$
M4	#(Kong, Zhao, et al., 2019)	136	21.03 (2.10)	60%	100%	SWLS	GM and WM: medial PFC	+	$r = .23^*$
M5	#(Kong, Yang, et al., 2019)	136	21.03 (2.10)	60%	100%	Social WB	GM: orbitofrontal cortex	-	
M6	(Gatt et al., 2018)	263	39.69 (12.9)	100%	--	COMPAS-W	GM: pons	-	
M7	(Gupta et al., 2017)	48	26.3 (7.0)	69%	100%	PANAS	mean curvature: right intraparietal sulcus cortical thickness: ACC	+	$\beta = 0.75^*$ $\beta = -0.57^*$
M8	(Luo et al., 2017)	138	21.1 (1.7)	62%	100%	PWB and PANAS	-		
M9	(McLaren et al., 2017)	49	69.45 (6.6)	67%	100%	CES-D PA	GM: left lingual gyrus	-	
M10	(Van 't Ent et al., 2017)	724	27.0 (10.8)	58%	--	WB factor	GM: hippocampus	-	

Table 2.1. The design characteristics and results of the structural MRI studies to well-being.

Nr	Authors	N	Age	Females	Right-handed	WB measure	Brain area identified	Sign	Effect size
M11	(Matsumaga et al., 2016)	106	21.4	54%	100%	SHS	GM: rostral ACC	+	
M12	(Dennison et al., 2015)	89	12.6 / 16.4	48%	100%	PANAS	GM: hippocampus	+	Left: b = 16.4*, right: b = 12.8*
M13	#(Kong, Ding, Yang, et al., 2015)	299	21.6 (1.0)	-	94%	SWLS, PANAS	GM: right parahippocampal gyrus left precuneus, left ventromedial PFC	+ / -	r = .21* r = -.32* / -.22*
M14	#(Kong, Hu, Wang, et al., 2015)	294	21.57	53%	94%	Social WB	GM: left mid-dorsolateral PFC	-	r = -.22*
M15	(Sato et al., 2015)	51	22.5	51%	100%	SHS	GM: precuneus	+	
M16	(Singleton et al., 2014)	15	37.9	60%	100%	PWB	GM: left and right brainstem	+	r = .72* / r = .76*
M17	(Lewis et al., 2014)	70	24.6	60%	--	Ryff PWB	GM: right and left insular cortex volume	+	r = .47*
M18	(Takeuchi et al., 2014)	159	21.4	43%	100%	WHOQOL-26	GM: dorsal part of the anterior cingulate gyrus	-	

Note: WHOQoL = World Health Organization Quality of Life, SWLS= Satisfaction with Life scale, WB= well-being, PANAS= Positive and Negative Affect Scale, PWB= Psychological well-being scale, CES-D PA= Center for Epidemiologic Studies Depression Scale, Positive Affect, SHS= Subjective Happiness Scale, GM= gray matter, WM= white matter, PFC= prefrontal cortex, ACC= anterior cingulate cortex

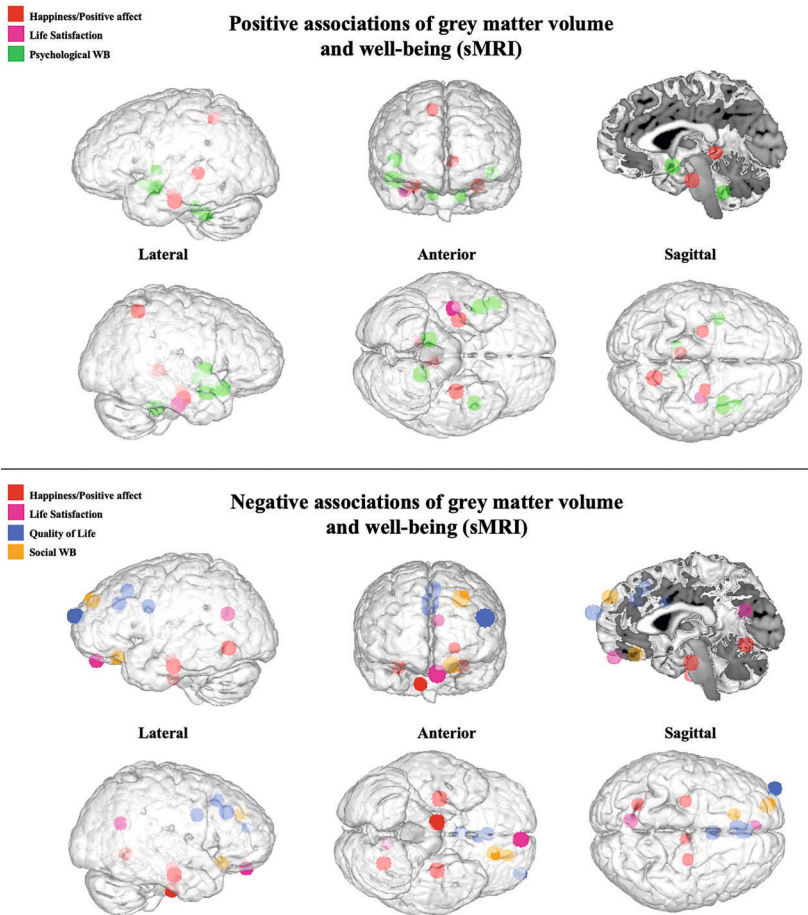


Figure 2.2. The brain areas that showed a positive (top panel) or negative (bottom panel) association to a well-being measure in one or more structural MRI studies. The different colours of the highlights indicate the different well-being measures. The coordinates are based on the MNI coordinates reported in the studies. The surface template brain and the figure are created in Mango software (v. 4.1).

Results brain structure

In a recent study, different structural characteristics of the brain (e.g., white matter mean kurtosis) were not significantly related to quality of life (Ourry et al., 2021). Cabeen et al. (2021) did report a negative relation between well-being and the fronto-insular cortical orientation dispersion, i.e., a measure of the complexity of the structure of neurites. Higher orientation dispersion is associated with brain development and dendritic complexity.

EEG

Description of study designs and samples

Eleven studies used EEG to link well-being to regional brain activation (see Table 2.2). Two studies used the same sample (Alessandri et al., 2015; De Pascalis et al., 2012). When only including one of these studies, the average number of participants across the remaining 10 studies is 94.2 participants ($SD=116$), with a range from 36 to 422 participants. The average age is 35.1 ($SD=18.8$, range=20.9-68.7). The proportion included females is on average 60.1% ($SD=30\%$), with a range of 0 to 100%. Most studies included only right-handed participants ($k=6$), while one sample consisted of 87% right-handed participants (E1). Handedness of the samples was not reported in the remaining 3 studies (E3,E4,E6).

Well-being measures

Of the 11 studies, 10 studies used different hedonic well-being measures. This includes nine studies that used the PANAS as measure of positive affect (E2,E3,E5-11 in Table 2.2) and four studies that used a measure of life satisfaction (E3,E4,E7,E8). One study used a measure of eudaimonic well-being, i.e., the psychological well-being scale (E7). Finally, one study used the COMPAS-W scale, combining hedonic and eudaimonic well-being aspects (E1).

Results frequency bands

Three studies related well-being to the profiles of resting EEG power (E1,E6,E7 in Table 2.2). Resting EEG power measures spontaneous brain activity, which can be divided into different frequencies. Slow frequency signals, like delta (<4Hz), theta (4-7 Hz) and alpha (7.5-12.5 Hz) have been related to deep sleep, rest, and relaxation, whereas faster brain oscillations, such as beta (15-30 Hz) and gamma (30-100 Hz), are related to alertness, concentration, and higher order cognitive tasks (Amzica & Lopes da Silva, 2012). Relating the power of these signals to well-being, Urry et al. (2004) reported a negative correlation between psychological well-being and left alpha power (i.e., rest signal). Similarly, Chi et al. (2005) reported a negative correlation with theta power (i.e., rest signal), but a positive correlation between positive affect and delta power (i.e., deep relaxation signal). In a recent study with a larger sample size ($n=422$), Chilver et al. (2021) reported no significant associations between the power of single frequency bands and well-being. The interaction between central alpha, beta, and delta power was related to well-being, indicating that relative amplitudes of frequency bands are important. A profile of high alpha

and delta power (i.e., slower frequencies) and low beta (i.e., faster frequencies) was associated with higher well-being.

To summarize, based on three studies, resting state brain activities as measured with EEG power shows no consistent results and the largest study suggest that the interaction between the power of different frequency bands in the brain is related to well-being.

Results alpha asymmetry

Nine EEG studies looked at resting state frontal EEG alpha asymmetry, i.e., the difference between alpha activity in the right and left frontal regions of the brain. An alpha asymmetry score is calculated as right log alpha-power minus left log alpha-power. Since alpha power is inversely related to activation, higher asymmetry scores reflect greater relative left hemisphere activation. Of the 7 studies including the PANAS, three studies reported positive correlations of positive affect and frontal alpha symmetry (E7,E8,E11), indicating greater left than right frontal activation. The other 4 studies did not report significant associations (E2,E5,E9,E10). Alessandri et al. (2015) and Urry et al. (2004) reported positive correlations between life satisfaction and alpha asymmetry in frontal areas, whereas the correlation in (Hall & Petruzzello, 1999) did not reach significance. Psychological well-being was positively related to frontal alpha asymmetry (E7). Finally, Xu et al. (2018) reported that in longitudinal data, an increase in alpha asymmetry in the frontal lobe over a 10-week timeframe was related to an increase in well-being.

Five relatively homogeneous studies with 11 associations of (frontal) alpha asymmetry and well-being reported a correlation and could be included in a meta-analysis (E2,E4,E7,E9,E11). The meta-analytic estimate for the association between (frontal) alpha asymmetry and well-being was 0.19 ($SE=.07$, $95\%CI: .04, .33$, $t= 2.9$, $p=.016$), $r= 0.19$ (see Figure 10.3), indicating a small positive relation between (frontal) alpha asymmetry and well-being. The distribution of the effect sizes of the meta-analysed studies were not symmetrical in the funnel plot (see supplementary Figure S2.1). The Egger's test was also significant with $Z = -2.71$, $p = 0.007$, suggesting a possible publication bias.

Table 2.2. The design characteristics and results of the EEG studies to well-being.

Nr	Authors	N	Age	Females	Right-handed	WB measure	Brain area identified	Sign effect	Effect size
E1	(Chilver et al., 2021)	422	40.0 (13.0)	64.9%	87%	COMPAS-W	Central alpha*beta*delta	-	$\beta = -.33^*$
E2	(Papouseket et al., 2019)	62	24 (4)	81%	100%	PANAS	frontal symmetry (F4-F3)	ns	$r = .16$
E3	(Xu et al., 2018)	48	22.0 (1.7)	56%	-	SWLS and PANAS	Change scores: frontal alpha asymmetry: F4-F3, F8-F7, FC4-FC3, FC6-FC5	+	$\sim .30$ (0.57, 0.33, 0.35, 0.29)
E4	(Alessandri et al., 2015)	51	24.1 (3.7)	100%	-	SWLS	Frontal asymmetry Parietal asymmetry	- ns	$r = -.20 - -.45^*$
E5	(De Pascalis et al., 2012)	51	24.1 (3.7)	100%	100%	PANAS	frontal (F4-F3, F8-F7, FC4-FC3), central (C4-C3), parietal (CP4-CP3, P4-P3)	ns	
E6	(Chi et al., 2005)	68	20.9 (2.0)	53%	-	PANAS	Delta power Theta power	+	$r = 0.25^*$ $r = -.29^*$
E7	(Urry et al., 2004)	84	58.49	49%	100%	PANAS	Frontocentral asymmetry (FC4-FC3)	+	$r = .21^*$
						SWLS	Frontocentral asymmetry (FC4-FC3)	+	$r = .30^*$

Table 2.2. The design characteristics and results of the EEG studies to well-being.

Nr	Authors	N	Age	Females	Right-handed	WB measure	Brain area identified	Sign effect	Effect size
						PWB	Frontocentral asymmetry (FC4-FC3)	+	$r=.33^*$
							Left alpha power	-	$r=-.21^*$
E8	(Hall & Petruzzello, 1999)	41	68.7 (5.8)	63%	100%	PANAS	Frontal (F4 - F3)	+	$\beta=.31$, $R^2=.098^*$
E9	(Hagemann et al., 1999)	36	22.3 (4.7)	33%	100%	PANAS	Frontal (F4 - F3)	ns	$r=-0.07$, -0.06 , -0.03 , 0.04
E10	(Jacobs & Snyder, 1996)	40	18-53	0%	100%	PANAS	Frontal (F4-F3), Temporal (T4-T3), Central (C4-C3), Parietal (P4-P3)	ns	
E11	(Tomarken et al., 1992)	90	17-21	100%	100%	PANAS	Midfrontal (F4 - F3), lateral frontal asymmetry (F8 - F7)	ns	$r=.20$
							Midfrontal asymmetry (F4-F3)	ns	
							Anterior frontal asymmetry (T4-T3)	+	$r=.25^*$

Note: Studies in bold indicate inclusion in the meta-analysis. PANAS= Positive and Negative Affect Scale, SWLS= Satisfaction with Life scale, PWB= Psychological well-being scale, F= frontal, FC= frontocentral. C= central, T=temporal, P=parietal.

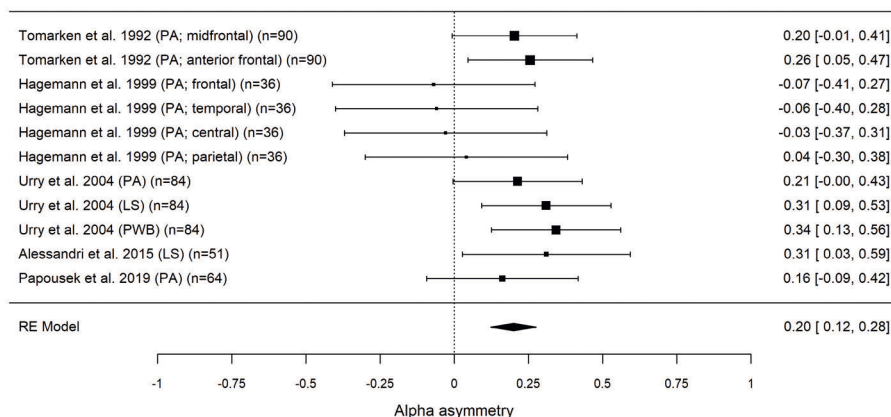


Figure 2.3. Meta-analysis on the associations of (frontal) alpha asymmetry and well-being.

Resting state functional MRI

Description of study designs and samples

Twenty-six studies used resting state fMRI data to investigate the association between well-being and brain functioning (see Table 2.3, grouped by analysis technique). Five studies used an overlapping sample of Chinese university students (Kong, Hu, Wang, et al., 2015; Kong, Liu, Wang, et al., 2015; Kong, Wang, et al., 2015, 2016; Kong, Xue, et al., 2016). Three studies by Luo and colleagues used partly overlapping samples (Luo et al., 2014, 2016, 2017), with later studies expanding the original sample. Finally, three studies by Qui included overlapping samples (He et al., 2019; Shi et al., 2018, 2019).

When only including the largest sample of the above overlapping studies and the remaining unique samples ($k=18$), the average number of participants is 205.8 participants ($SD=265$), with a range from 34 to 942 participants. The average age is 27.3 ($SD=12.7$, range=19.1-70.6). The proportion included females is on average 59% ($SD=17\%$) with a range from 31% to 100%. Most studies included only right-handed participants ($k=10$). Handedness was not reported for the remaining 9 studies.

Well-being measures

Of the 26 studies, 22 studies used different hedonic well-being measures. This includes eight studies that used the PANAS as measure of positive affect (C1,FA2,FA4,FC7,FC8, FC12,R1,R3 in Table 2.3), seven studies that used a measure of life satisfaction (FA2,FA4,FC1, FC14,R2,R3,NV1), two studies that used the subjective happiness scale (FA1/FC9,FC2) and two studies that used an Index of Well-Being (FC3,FC12). In addition, single studies used the multidimensional personality questionnaire MPQ (Patrick et al., 2002) (C2), the Chinese Affect Scale (FC4), and the WHO Quality of Life scale (FC5, see Table 2.3).

Five studies used different eudaimonic well-being scales, including four studies that used the psychological well-being scale (FA5/FC14, FC12,R1), a single study that used the social well-being scale (FA3) and a meaning in life measure (FC11). One study used a measure that combines hedonic and eudaimonic aspects of well-being, i.e., the Warwick Edinburgh Mental well-being scale (Tennant et al., 2007).

Results

The resting state fMRI studies applied different techniques to analyse the raw scanning data. We grouped the results by the following analyses techniques: (1) cerebral blood flow, (2) the fractional amplitude of low-frequency fluctuation (fALFF), (3) functional connectivity analyses, (4) regional homogeneity analyses, and (5) diversity and variability analyses. Figure 2.4 depicts the brain areas where activity or connectivity with other brain areas was significantly positively (Figure 2.3 top) or negatively (Figure 2.3 bottom) related to the different well-being measures across the different fMRI analyses.

Cerebral blood flow. Two studies looked at the cerebral blood flow (C1, C2 in Table 2.3). Hermes et al. (2011) reported a negative relation between positive affect and the blood flow in a range of areas, including the striatum, caudate nucleus and ACC. In contrast, Volkow et al. (2011) reported a positive relation between positive emotionality and blood flow, mainly in the orbitofrontal cortex, ACC, and precuneus. Furthermore, they reported a positive correlation with whole brain metabolism.

fALFF. Five studies used a measure of regional neuronal activity, i.e., the fractional amplitude of low-frequency fluctuations (fALFF) (FA1-5 in Table 2.3). fALFF measures the relative contribution of low frequency fluctuations to the whole frequency range and reflects spontaneous neural activity (Zou et al., 2008). Negative relations with happiness or life satisfaction and fALFF in the precuneus, superior frontal gyrus, inferior temporal gyrus, and/or

the orbitofrontal cortex were reported (FA1,FA2,FA4). Additionally, positive relations between the different well-being measures and fALFF in the thalamus, insula, superior temporal gyrus, anterior cingulate gyrus, and/or amygdala were reported (FA3-FA5). To summarize, the associations with the different brain areas were mostly reported in single studies and not replicated across multiple studies.

Functional connectivity. Sixteen studies investigated the functional connectivity between brain regions, i.e., the degree of synchrony of the BOLD response between different brain regions. One small study (n=34) found no association between connectivity and well-being in healthy controls (FC7). In two studies, a negative relation between well-being and the functional connectivity in the default mode network was found (FC5,FC14), meaning that a stronger functional connectivity within the default mode network is related to lower well-being. Furthermore, in other studies a negative relation between well-being and functional connectivity between the salience network and default mode network (FC12), between the insula and medial PFC (FC3), between the insula and ventral striatum (FC4), between the PFC and precuneus (FC13), between the thalamus and insula (FC16), between the PFC and PCC (FC14), and between nodes in the dorsal and ventral attention networks and the visual and somatomotor networks (FC10) were reported.

In addition, positive associations between well-being and functional connectivity in the left orbitofrontal cortex and inferior frontal gyrus (FC8), right amygdala and medial parietal regions (FC9), connectivity within the medial temporal lobe (FC15), connectivity in the default mode network and subcortical networks (FC10) and connectivity in the default mode network and limbic network were reported (FC11). This indicates that stronger connectivity between these areas is related to higher well-being.

Itahashi et al. (2021) reported that functional connectivity in the visual, ventral attention, and limbic networks was positively related to life satisfaction. Functional connectivity stemming from the visual and cerebellar networks to other networks was negatively related to life satisfaction.

Katsumi et al. (2021) reported that well-being was related to decreased connectivity of the dorsolateral PFC with brain regions important for the representation of unimodal sensorimotor information (e.g., primary sensory cortices) or multi-modal summaries of brain states (e.g., default mode network) and increased functional connectivity with regions important for the attentional modulation of these representations (e.g., frontoparietal, attention networks).

Lastly, a negative relation between positive affect and segregation within key nodes (SWKN) in the frontoparietal control network has been reported (FC6). The SWKN represents stronger within-network correlations in relation to between-network correlations.

To summarize, functional connectivity in a wide range of networks have been reported to be associated to well-being measures. However, replication of the involvement of functional connectivity of brain areas and networks in well-being across multiple studies was scarce and several opposite effects were reported with positive and negative correlations between connectivity and well-being.

Regional Homogeneity. Three studies investigated the local synchronization and functional connectivity of rs-fMRI signals among neighbouring voxels, i.e., the regional homogeneity (aka ReHo; Zang et al., 2004). Negative associations between well-being and ReHo in the inferior frontal gyrus, superior frontal gyrus, PFC, putamen, thalamus, and/or ACC were reported (R1-R3). In addition, two studies reported positive relations between ReHo in the orbitofrontal cortex, medial and lateral PFC, hippocampus and the PCC and well-being (R1, R3: Kong, Wang, et al., 2016; Luo et al., 2014).

Diversity and variability. Tian and Zalesky (2018) reported a positive relation between positive affect and the connection diversity in the anterior insula. People with higher positive affect had more diversity in the connections of the insula with other brain regions. Similarly, Fan et al. (2021) reported that the whole brain self-dependent neural variability (i.e., the variability of functional connectivity between all regions across the brain) is associated to higher satisfaction with life.

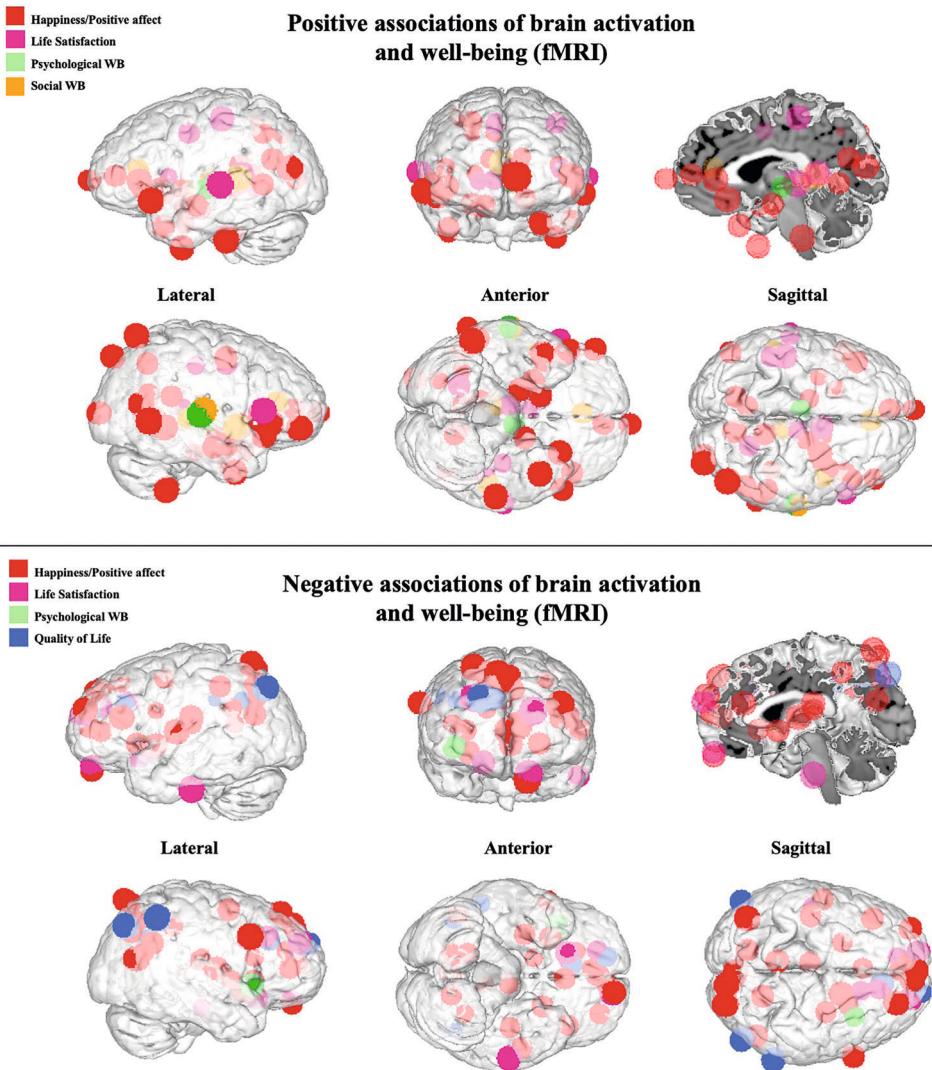


Figure 2.4. The brain areas of that showed a positive (top panel) or negative (bottom panel) association to a well-being measure in one or more functional MRI studies. The different colours of the highlights indicate the different well-being measures. The coordinates are based on the MNI coordinates reported in the studies. The surface template brain and figure are created in Mango software (v. 4.1).

Table 2.3. The design characteristics and results of the resting state fMRI studies to well-being.

Analysis technique	Nr	Authors	Sample N	Age	Females	Right-handed	WB measure	Brain area identified	Sign effect	Effect size
cerebral blood flow	C1	(Hermes et al., 2011)	38	24.5 (2.6)	50%	100%	PANAS	left + right ventral striatum (r= -.35, -.43), left OFC (r=-.21), left and right caudate nucleus (-.58) and left olfactory cortex (-.58), left Rolandic operculum (r=-.41), bilateral putamen (r=-.40), left pallidum (r=-.40), left insula (-.37), and bilateral ACC (r=-.33)	-	r~ -.58 / -.20
	C2	(Volkow et al., 2011)	84	25.34	51%	--	MPQ	left and right OFC, ACC, areas in frontal cortex, temporal gyrus, parietal (precuneus), left and right occipital cortex (fusiform gyrus and superior occipital gyrus)	+	r~ .50
fALFF	FA1	(Sato et al., 2019)	51	22.5 (4.5)	51%	100%	SHS	right precuneus	-	r= .49
	FA2	(Kong et al., 2018)	100	20.9 (2.0)	58%	100%	SWLS, PANAS	OFC	-	r= -.31
	FA3	#(Kong, Xue, et al., 2016)	292	21.6 (1.0)	54%	94%	Social WB	right + left posterior STG, right thalamus, right insula, right ACC	+	r= .27 / r=.24 / r=.29 / =.24 / r=.21

Table 2.3. The design characteristics and results of the resting state fMRI studies to well-being.

Analysis technique	Nr	Authors	Sample N	Age	Females	Right-handed	WB measure	Brain area identified	Sign effect	Effect size
FA4		#(Kong, Hu, Wang, et al., 2015)	294	21.56	54%	--	SWLS, PANAS	Cognitive: STG ($r = .23/.28$), planum temporale ($r = .25$), PCC ($r = .27$), lingual gyrus ($r = .21$), right thalamus ($r = .25$) and postcentral gyrus ($r = .26$). Affective: right amygdala ($r = .26$).	+	$r \sim .25$
FA5		#(Kong, Liu, Wang, et al., 2015)	286	21.6 (1.0)	54%	--	PWB	Cognitive: SFG ($r = -.30/-.26$), inferior temporal gyrus ($r = -.26$) and right OFC ($r = -.25$).	-	$r \sim -.25$
FC1		(Itahashi et al., 2021)	100 + 766	22-35	54%, 53%	--	SWLS	right pSTG, thalamus.	+	$r = .28 / r = .30$
functional connectivity								Visual, ventral attention, or limbic networks to dorsal attention network and DMN	+	
								Visual and cerebellar networks to dorsal attention network, DMN, and limbic networks	-	
FC2		(Katsumi et al., 2021)	68	21.7 (1.8)	100%	100%	SHS	left dlPFC - bilateral middle/inferior frontal gyri, insula, inferior parietal lobule, pre-supplementary motor area, and precuneus	+	

Table 2.3. The design characteristics and results of the resting state fMRI studies to well-being.

Analysis technique	Nr	Authors	Sample N	Age	Females	Right-handed	WB measure	Brain area identified	Sign effect	Effect size
								left dlPFC- midline cortical areas (e.g., mPFC, pregenual and subgenual cingulate, posterior cingulate, retrosplenial cortex), superior frontal gyrus, angular gyrus, lateral temporal gyri/ anterior temporal lobe, and lateral occipital cortex	-	
FC3		(Li et al., 2020)	75	70.6 (5.5)	53%	100%	Index of Well-Being	left dorsal anterior insula - anterior medial PFC	-	$r = -0.26^*$
FC4		(Qi et al., 2021)	63	23.9 (2.3)	52%	100%	Chinese Affect Scale	left dorsal anterior insula - right inferior parietal lobe SEN connectivity	-	$r = -0.46^*$ $r = -.25^*$
FC5		(Kraft et al., 2019)	42	42.9 (8.5)	100%	100%	WHOQOL-BREF	DMN connectivity left anterior insula - left inferior ventral striatum	ns	$r = -.16$ $r = -.36^*$
FC6		~(He et al., 2019)	368	19.4 (1.4)	72%	100%	PANAS, Urban Happiness Index	DMN: left - right lateral parietal cortex frontoparietal control network	-	$r = -.407$ $r = -.15$
FC7		(He et al., 2019)	34	34.8 (11)	70%	100%	PANAS	No effects		

Table 2.3. The design characteristics and results of the resting state fMRI studies to well-being.

Analysis technique	Nr	Authors	Sample N	Age	Females	Right-handed	WB measure	Brain area identified	Sign effect	Effect size
FC8		~(Shi et al., 2019)	212	22.4 (1.5)	54%	100%	PANAS	OFC-inferior frontal gyrus	+	r= .163
FC9		(Sato et al., 2019)	51	22.5 (4.5)	51%	100%	SHS	right amygdala - right precuneus	+	
FC10		(Mihalik et al., 2019)	281	19.1 (2.9)	54%	-	Warwick Edinburgh Mental WB scale	DMN and subcortical networks Dorsal and ventral attention networks	+	
FC11		(Mwilambwe-Tshilobo et al., 2019)	942	28.0 (3.5)	54%	-	Meaning and Purpose survey	DMN - limbic network: posterior parietal regions, anterior regions of the frontoparietal network	+	r=.13
FC12		~(Shi et al., 2018)	331/ 212	20.2 (1.3) 22.4 (1.5)	65%	100%	Index of Well-being	Salience network - anterior DMN	-	r= -.16
FC13		*(Luo et al., 2017)	138	21.1 (1.7)	62%	100%	PWB PANAS	Connectivity: ventral medial PFC, precuneus Connectivity: ventral and dorsal MPFC, precuneus	+	
FC14		*(Luo et al., 2016)	148	20.9 (1.7)	55%	--	Chinese Happiness Inventory	DMN: bilateral MPFC, PCC and left inferior	-	
FC15		(Waytz et al., 2015)	84	25.34	51%	--	Meaning in Life, SWLS, PWB	Medial temporal lobe	+	r= .25

Table 2.3. The design characteristics and results of the resting state fMRI studies to well-being.

Analysis technique	Nr	Authors	Sample N	Age	Females	Right-handed	WB measure	Brain area identified	Sign effect	Effect size
	FC16	(Kong, Liu, Wang, et al., 2015)	286	21.6 (1.0)	54%	--	PWB	thalamus - right insula.	-	r= -.20
ReHo	R1	*(Kong, Wang, et al., 2016)	290	21.6 (1.0)	54%	94%	PANAS, PWB	right IFG, left orbitofrontal cortex	+	r= -0.15 r= .17
	R2	*(Kong, Wang, et al., 2015)	276	21.6 (1.0)	54%	--	SWLS	Dorsal ACC	-	r= -.21
	R3	*(Luo et al., 2014)	50	20.26	72%	--	PANAS, SWLS	bilateral MPFC, right ventrolateral PFC, STG, hippocampus, parahippocampal gyrus and PCC.	-	
diversity	D1	(Tian & Zalesky, 2018)	100	22-35	50%	-	PA	Dorsolateral PFC, SFG, MCG, putamen, left thalamus	+	
neural variability	NV1	(Fan et al., 2021)	61	20.1 (2-3)	31%		SWLS	anterior insula	+	
								whole brain self-dependent neural variability	+	r = 0.41

Note: PANAS = Positive and Negative Affect Scale, MPQ= multidimensional personality questionnaire, SHS= subjective happiness scale, SWLS= Satisfaction with Life Scale, WB= well-being, PWB= Psychological well-being scale, WHOQOL= World Health Organization Quality of Life, OFC= orbitofrontal cortex, PFC= prefrontal cortex, ACC= anterior cingulate cortex, STG= superior temporal gyrus, SFG= superior frontal gyrus, PCC= posterior cingulate cortex, DMN= default mode network, SEN= salience and emotion network, SN=salience network.

fNIRS

Description of study designs and samples

Two studies used fNIRS to assess the relation between flourishing and functional connectivity between different brain areas. Both studies used the same sample of 43 participants. Based on the flourishing scale (Diener et al., 2010), the participants were divided in two groups, a high flourishing group (n=23) and a normal group (n=20). The participants in these groups were on average respectively 31.0 ($SD=11.4$) and 28.0 ($SD=9.6$) years old. In both groups, 65% of the participants was female (see Table 2.4).

Results

People in the high flourishing group had an increased functional connectivity within a network of the default mode network, bilateral somatosensory and visual cortex, and left fusiform gyrus (Goldbeck et al., 2019). Furthermore, flourishing was negatively related to the connectivity between the right third visual cortex and the right somatosensory association cortex (Eken, 2021).

Table 2.4. The design characteristics and results of the fNIRS studies to well-being.

Nr	Authors	Sample N	Age	Females	WB measure	Brain area identified	Sign effect	Effect size
FN1	(Eken, 2021)	43 (high FL 23, normal FL 20)	31.0 (11.4), 28.0 (9.6)	65.2%, 65%	Flourishing scale	Right third visual cortex – right somatosensory association cortex	-	r=-.55
FN2	(Goldbeck et al., 2019)	43 (high FL 23, normal FL 20)	31.0 (11.4), 28.0 (9.6)	65.2%, 65%	Flourishing scale	DMN (right angular gyrus, right Superior gyrus, left medial temporal gyrus), bilateral somatosensory and visual cortex, left fusiform gyrus.	+	

Note: FL= flourishing, DMN= default mode network

DISCUSSION

To understand observed differences in well-being between people in more detail, it is essential to identify the biological and neural factors related to well-being. The goal of this systematic review was to bring together the available literature on well-being and brain structures and brain functioning. We first summarize and discuss the findings and based on the results, we propose directions for future research.

Brain structure

The systematic review of the brain areas where grey matter volume was associated with well-being revealed large inconsistencies. While the grey matter volumes of the (medial) PFC, ACC, the precuneus, hippocampus, and brainstem were related to well-being in multiple studies, for all these areas, there was inconsistency in the direction of the associations. Whereas in some studies smaller grey matter volume of the PFC, ACC, precuneus, hippocampus, or brainstem was related to higher levels of well-being, in other studies a larger grey matter volume of these areas was related to higher well-being. These discrepancies might be the result of the small sample sizes (ranging from 15 to 724) in most structural MRI studies. Especially if the effect sizes are small, a large sample size is needed to have enough power to detect associations (Marek et al., 2022). Only two studies included more than 700 participants and only five studies more than 200 participants, indicating the need for larger sample sizes before we are able to reliably test for an association between the structure and volume of brain areas and well-being.

More recent studies went beyond brain volume and reported for example that well-being was associated with higher orientation dispersion, i.e., brain development and more dendritic complexity (Cabeen et al., 2021). This suggests that other, more detailed, features of brain structures might be related to well-being. The development and application of higher resolution imaging sequences allows us to, for example, investigate the cortical microstructure and complexity of brain structures in relation to phenotypes in more detail (Zhang et al., 2012).

Brain functioning

EEG

Three studies related well-being to the profiles of resting EEG power. Resting EEG power measures spontaneous brain activity, which can be divided into

different frequencies. In single studies, the slower frequency signals, theta and alpha, were negatively related to well-being, whereas delta power, a faster brain oscillation, was positively related to well-being. A recent and larger study reported only a relation between the interaction between alpha, beta, and delta power and well-being, whereas the relation between the power of the single frequency bands and well-being was not significant. This could indicate that the relative amplitude of different frequency bands is important for well-being instead of the absolute power of single frequency bands. However, replication in studies with larger sample sizes is needed to draw a conclusion on the association between well-being and the different frequency bands in the brain.

(Frontal) alpha asymmetry was examined in more studies and positively associated with a measure of well-being in seven of the nine studies, whereas the other studies did not report a significant effect. Additionally, the small meta-analysis of alpha asymmetry and well-being indicated a positive relation ($r=.19$), but also suggested a possible publication bias. If replicated, greater left than right frontal activation is associated with well-being. This is in line with theory that alpha asymmetry is related to approach motivation and therefore the experience of positive feelings (Angus & Harmon-Jones, 2016). The opposite asymmetry, greater right-frontal activity, is assumed to be involved in withdrawal motivation, and some studies have found a relation with depression (but see Olbrich and Arns (2013) for a discussion about the unsuccessful replications). Noteworthy is that all studies on alpha asymmetry included measures of positive affect and/or life satisfaction, whereas the psychological well-being scale was only included in one study. More research on the moderating effect of the well-being scale used is therefore needed.

fMRI/fNIRS

The results of the included studies on the associations of well-being and brain activity and functional connectivity across brain regions/networks are very heterogenous. As can be seen in Figure 2.4, many brain regions across the whole brain were associated with well-being in the different studies. However, replication of the associations across multiple studies was mostly absent. Furthermore, if a brain region was associated with well-being in multiple studies, the direction of the association was inconsistent. For example, in the fMRI studies that associated the activity or functional connectivity of the PFC, orbitofrontal cortex or precuneus to well-being (respectively 14, 5 and 4 studies in total, see Supplementary Table S2.1), for all brain areas half of the associations with well-being were negative, whereas the other half were positive. The most consistent finding in fMRI studies that investigated the

connectivity between brain areas in relation to well-being is that a stronger functional connectivity within the default mode network (DMN) is related to lower well-being. The DMN consists of brain regions in the ventral and dorsal medial PFC, and the PCC. This network of cooperating brain regions is active when a person is in resting state or when not focused on the outside world (Raichle, 2015). The DMN has been involved in daydreaming and mind wandering. The positive correlation between connectivity in the DMN and well-being suggests that the activity of several brain areas related to thinking spontaneously is connected stronger in happier people.

Interpretation

The results of the reviewed studies on the neural correlates of well-being are very heterogeneous. Across all studies and methods, brain areas most often associated with well-being were the PFC, ACC, insula, default mode network, orbitofrontal cortex, visual networks, precuneus, and somatosensory networks (see supplementary Table S2.1). The association between well-being and the structure and/or functioning of the PFC, ACC, insula, and precuneus was reported in studies using different techniques (e.g., fMRI, MRI and EEG). However, the direction and strength of these associations differed to a great extent and many other brain areas have been identified in single studies, but not replicated in other studies. We replicated part of the conclusions of Machado and Cantilino (2016) and King (2019) about the relations between well-being and various brain areas. However, the involvement of networks, like the DMN, visual, and somatosensory networks emerged mostly in more recent studies included in the current review.

A first explanation of the inconsistent results is the large differences in brain imaging methods and analysis techniques. Different brain functioning imaging methods might lead to different results, e.g., EEG and fMRI both assess brain functioning, but are completely different techniques with different temporal and spatial characteristics. The brain areas covered with these techniques are at the surface with EEG assessment, but include the whole brain with fMRI assessments. Furthermore, when using the same imaging technique, the analysis techniques differed a lot. For example, the resting state fMRI studies either applied fALFF, functional connectivity analyses, or regional homogeneity (ReHo) to assess the regional neural activity or connectivity between brain areas. Lastly, although it has been shown that the function of a brain area and its structure are related (Sui et al., 2014; Toosy et al., 2004), the findings of MRI and fMRI are not completely comparable. These differences

in methods and analyses add a first difficulty in comparing the results of the studies and harmonization is needed in future studies.

In addition, a limitation in the field of imaging is the small sample sizes, mainly due to the costs, leading to low power of the study and low reproducibility of results (Button et al., 2013). As discussed in more detail in the section below, the small samples in combination with potential small effects of the involvement of single brain regions in well-being can explain the failure to replicate findings.

Brain-wide association studies

Similar to the inconsistent results of our review, meta-analyses and reviews on the association of brain regions with other behaviors or complex traits reported largely inconsistent results and a wide range of potentially associated brain regions as well. For example, in a meta-analysis of resting state fMRI studies of attention deficit hyperactivity disorder (ADHD), Cortese et al. (2021) did not find any convergence of connectivity patterns across studies. The same replication problem was shown in a meta-analysis of brain regions in relation to depression (Müller et al., 2017). Across 99 neuroimaging experiments there were large inconsistencies in results.

In light of these wide-spread replication problems across behaviors and traits, and related to the small sample sizes used in neuroimaging research, an explanation for the diversity in results could be the small effects of the involvement of single brain regions in well-being and other human behaviors and traits. Similar to findings of genome-wide association studies (GWAS) that indicate that there are no “well-being genes” with a large effect on well-being, but many genes with small effects (Baselmans, Jansen, et al., 2019; Okbay et al., 2016), it is unlikely that there is a “well-being brain region” or a few brain areas that have large effects on well-being. In contrast, a wide network of brain areas that all have small effects on well-being is to be expected. Using GWAS as example, brain-wide association studies (BWAS) have been proposed to reliably and without a priori hypotheses investigate the involvement of the brain in human behavior and traits (Gong et al., 2018; Marek et al., 2022). BWAS with sufficiently large sample sizes, i.e., samples with thousands of individuals, are needed improve reproducibility and the reliability of the brain-behavioral phenotype associations. Following the example of the genetic community, neuroimaging research should start large-scale collaborations to create the needed large sample sizes that are mostly missing in brain-wide association analyses (Poldrack et al., 2017).

An example of an already worldwide collaborative network is the Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA) consortium, including 100k+ participants and 45 countries that focuses on disorders (Thompson et al., 2014). For Major Depressive Disorder (MDD), this consortium has already led to reproducible results, including a smaller hippocampal volume in MDD participants ($n=1728$) compared with healthy controls ($n=7199$) and lower cortical thickness in the cingulate cortex, bilateral medial OFC and insula (Schmaal et al., 2020). Similarly, for other disorders like ADHD, bipolar disorder, and schizophrenia, robust brain correlates have been found in the large ENIGMA samples. In a recent application of BWAS to cognitive ability and psychopathology with more than 10 thousand participants, Marek et al. (2022) showed a widely distributed circuitry of associations. These patterns indicate the involvement of many brain areas not detected in studies with the typical smaller sample sizes. This approach of well-powered brain-wide association studies is needed to investigate the brain-well-being associations as well.

Furthermore, following the polygenic scores in the field of genetics, recently, the use of polyneuro scores has been proposed (Mooney et al., 2021). Polyneuro scores are summary scores of the cumulative effect of brain-wide measures that capture effects across widely distributed brain systems and regions that are involved in different human traits (Mooney et al., 2021). Applied to ADHD, Mooney et al. (2021) showed that such summary scores of functional connectivity across the brain have increased predictive power for ADHD symptoms. The scores explained around 8 times more variation than the variation explained by the most significant connection in the brain. However, the explained variance is still small, ~4% of the variation in symptoms is explained by the polyneuro scores.

Returning to the results of our review on well-being, this idea of brain wide associations for well-being is supported by the wide range of brain areas potentially associated with well-being. Furthermore, some specific findings of the more recent studies are in line with brain wide associations. For example, the association of neural diversity or variability in functional connectivity and higher well-being suggests that a higher complexity or more connectivity, i.e., more collaboration between brain areas leads to higher well-being (Cabeen et al., 2021). However, future brain-wide association studies are needed to support this idea for well-being.

Innovative methods and analyses

The rapid development in the methods and techniques that measure brain structure and functioning at smaller temporal and spatial resolution give rise

to new opportunities. For example, recent studies on the microstructure of the brain enables investigations of the relation between well-being and more detailed aspects of brain structures and functioning. However, also with such research to microstructures, a brain-wide approach should be applied to prevent non-replicable results.

Another direction for future research is the improvement of ecological validity in neuroscience research. At the moment, most brain imaging research is conducted in MRI scanners or in a controlled setting in the lab. This raises the question of the ecological validity, i.e., the generalizability to daily life or to which extent the results predict behaviour outside the testing environment (Matusz et al., 2019). Various solutions have been thought of to enhance the ecological validity in neuroscience. As an example of using more naturalistic stimuli and tasks, Reggente et al. (2018) reviewed the use of virtual reality in fMRI research to memory and suggests the neural correlates associated with virtual reality (VR) images are more likely to generalize to real-world behaviors, although further improvement of these methods is needed. Another way to enhance ecological validity is by using portable devices, such as portable EEG and fNIRS caps (Balardin et al., 2017). Recently a portable MEG helmet has been developed as well (Boto et al., 2018). These mobile methods lead to many more possibilities to measure and understand brain activity and functioning in real-life settings and scenarios. EEG has already been recorded during walking, cycling, sports, and even skateboarding (Ladouce et al., 2019; Park et al., 2015; Robles et al., 2021; Scanlon et al., 2019). Furthermore, people from all ages, including babies and children can participate more easily, as movement is less of an issue with the portable devices.

Related to innovations in the methods for neuroimaging, there are also rapid developments in the approaches to analyse (big) data. Using the developments in the artificial intelligence and machine learning fields, patterns can be detected in imaging data that we would not predict or expect. These approaches enable us to focus more on data-driven research instead of hypothesis driven research (Scheel et al., 2020). Using a data driving approach, Liu et al. (2020) analysed fMRI data from major depressive patients and healthy controls. Their models could distinguish between the patients and healthy controls ($accuracy=0.77$) and the authors reported several brain-wide features that differed between patients and controls.

Limitations

Because of the inconsistency in study design, measures, neuroimaging analyses, and reported results, a meta-analysis on the association of brain areas

and well-being was mostly not possible. Conclusions should therefore be drawn with caution. Although more studies are being performed currently, future research should be harmonised to allow meta-analyses and to reach the desired sample size of thousands of participants. Whereas we did perform a small meta-analysis on the association between frontal asymmetry and well-being, the estimate was based on only a few studies and the analysis pointed towards a potential publication bias. Therefore, these results should be interpreted with caution as well.

Furthermore, it is difficult to compare earlier neuroimaging studies to the more recent studies, because of the rapid technological advancements and changing guidelines and methods in the neuroscience field. In earlier research, regions of interest (ROIs) were decided up front, whereas nowadays a voxel-wise whole brain analysis is preferred. However, as mentioned before, most brain-wide studies did not include sufficiently large sample sizes. The often small sample sizes in neuroscience research are a limitation for interpreting the results reliably, since this increases the variability and reduces statistical power. As proposed, future studies should perform power calculations before running imaging studies and start collaborations to reach the required sample sizes for brain-wide association studies (Marek et al., 2022; Szucs & Ioannidis, 2020).

Conclusion

The current systematic review of 56 studies on the neural correlates of well-being showed mostly heterogenous results of the involvement of different brain regions across studies. The direction and strength of the associations between well-being and different brain structures and regions differed to a great extent. An explanation for the inconsistencies could be the small sample sizes of most studies and a possible wide-spread network of brain regions with small effects involved in well-being. Future directions include well-powered brain-wide association studies and innovative methods to measure brain activity more reliably or in daily life.

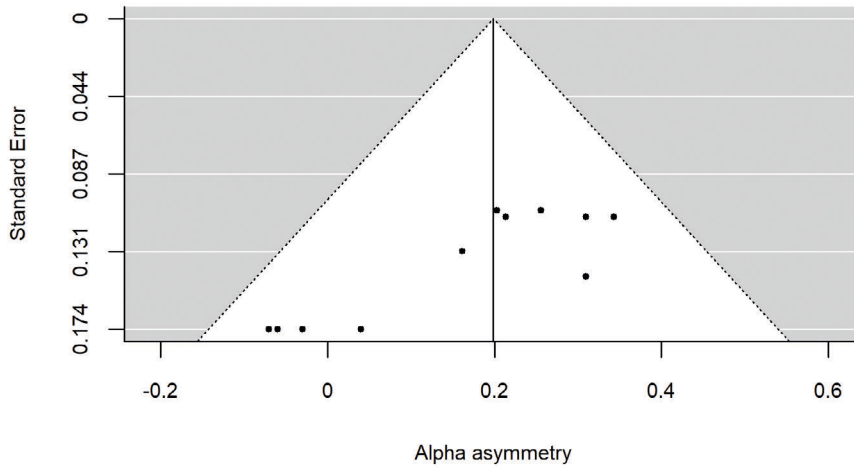
Supplementary Material Chapter 2

Supplementary Table S2.1. Number of brain regions/networks associated with well-being, separately for the different imaging techniques.

Brain region/network	TOTAL					N studies			
	Structural MRI	rsfMRI		fNIRS functional connectivity	EEG	Activity	Functional connectivity		
		3	2				4	5	
Prefrontal cortex (PFC)	14	3	2	4	5				
Anterior cingulate cortex (ACC)	6	3	3						
Insula	6	2	2	2					
Default mode network (DMN)	7			6	1				
Orbitofrontal cortex (OFC)	5	1	3	1					
Visual networks	5			3	2				
Precuneus	4	2	2						
Somatosensory networks	4			2	2				
Hippocampus	3	2	1						
Inferior frontal gyrus (IFG)	3		1	1					
Attention networks	3			3					
Posterior cingulate cortex (PCC)	2		1	1					
Brainstem (pons)	2	2							
Caudate	2	1	1						

Supplementary Table S2.1. Number of brain regions/networks associated with well-being, separately for the different imaging techniques.

Brain region/network	N studies				
	TOTAL	Structural MRI	rsfMRI		fNIRS functional connectivity
			Activity	Functional connectivity	
Striatum	2		1	1	
Superior frontal gyrus (SFG)	2		2		
Thalamus	2		2		
Amygdala	2		1	1	
subcortical networks	2			2	
Frontoparietal control network	3			3	
Posterior parietal cortex	1	1			
Parahippocampal gyrus	1	1			
Lingual gyrus	1	1			
Superior temporal gyrus (STG)	1		1		
Inferior temporal gyrus (ITG)	1		1		
Anterior cingulate gyrus	1		1		
Putamen	1		1		
Saliience network (SN)	1			1	
Temporal lobe	1			1	



Supplementary Figure S2.1. Funnel plot of the meta-analysis of the association between alpha asymmetry and well-being.

Chapter 3.

The human physiology of well-being: A systematic review on the association between neurotransmitters, hormones, inflammatory markers, the microbiome and well-being

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ABSTRACT

To understand the pathways through which well-being might contribute to health, we performed a systematic review according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines on the association between physiological markers in four categories, neurotransmitters, hormones, inflammatory markers, and the microbiome, and well-being. We identified 91 studies. The neurotransmitter studies ($k_{\text{number of studies}}=9$) reported only a positive association between serotonin and well-being. For the hormone studies ($k=48$), a lower momentary level of cortisol was related to higher well-being (meta-analytic $r=-.10$), and a steeper diurnal slope of cortisol levels. The inflammatory marker studies ($k=36$) reported negative or non-significant relations with well-being, with meta-analytic estimates of respectively $r=-.06$ and $r=-.04$ for C-reactive protein and interleukin-6. The microbiome studies ($k=4$) reported inconsistent associations between different bacteria abundance and well-being. Serotonin, cortisol, and the immune system are involved in explaining differences in well-being. The limited results for other markers and the microbiome require further research. Future directions to get a complete picture of the physiological factors underlying well-being are proposed.

Keywords: well-being, physiology, neurotransmitters, hormones, inflammatory markers, microbiome

INTRODUCTION

Mental health is defined by the World Health Organization as “*a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively, and is able to make a contribution to his or her community*” (World Health Organization, 2005). As such, mental health is more than the absence of mental disorders and includes the concept of well-being. Well-being is defined by the OECD as *good mental states, including all of the various evaluations, positive and negative, that people make of their lives, and the affective reactions of people to their experiences* (OECD, 2013). In line with these definitions of mental health and well-being, the attention and interest for well-being and happiness has increased a lot in the past 20 years with a growing number of scientific publications every year in different disciplines (see the review of Kim et al., 2018). Besides being a protective factor associated with overall physical and mental health (Diener et al., 2017; Greenspoon & Saklofske, 2001), the positive effects of well-being are found to be independent from the negative effects of ill-being, such as depression, indicating the importance of investigating well-being (Howell et al., 2007). In addition, well-being is related to various positive life outcomes and functioning, such as a long, healthy life (James et al., 2019; Kim et al., 2019; Steptoe, 2019; Zaninotto & Steptoe, 2019), educational achievement, happy marriage, and productivity at work (Chapman & Guven, 2016; Lyubomirsky et al., 2005; Maccagnan et al., 2019; Oswald et al., 2015).

The findings of behavioral and molecular genetics studies indicate a substantial role of biological and physiological factors underlying differences in well-being. Twin studies have estimated the heritability of well-being, i.e., the genetic contribution to the variation in well-being, to be around 40% (Bartels, 2015; Nes & Røysamb, 2015; van de Weijer et al., 2020). Recently, three genome wide association studies (GWAS) related specific genetic variants to well-being (Baselmans, Jansen, et al., 2019; Okbay et al., 2016; Turley et al., 2018), with the latest GWAS reporting 148 and 191 associations for life satisfaction and positive affect, respectively. Follow-up analyses found evidence for enrichment of genes differentially expressed in the subiculum (part of the hippocampus) and enrichment for GABAergic interneurons to be related to the well-being spectrum (Baselmans, Jansen, et al., 2019). These genetic results provide suggestions and starting points for the physiology of well-being, but a systematic overview of the research to physiological measures is currently missing.

In contrast to the large body of evidence on the relation between different human physiological factors, for example inflammatory markers and hormones, and ill-being (e.g., Dowlati et al., 2010; Knorr et al., 2010), the association with well-being is investigated less. However, it is hypothesized that well-being is associated with functioning of multiple physiological systems. To understand the pathways through which well-being might contribute to health and to enhance the development of future (more precise) mental health prevention and intervention strategies, it is crucial to better understand the association between physiological factors and well-being.

The goal of this paper is to systematically review the available studies on the association between physiological markers in four categories, namely neurotransmitters, hormones, inflammation, and the microbiome, and well-being. First, we briefly describe the definitions of well-being and the different categories of physiological markers studied in relation to well-being. Next, we describe the systematic review strategy and its outcomes, and finally we discuss the results and future directions.

Well-being

While there are multiple definitions and conceptualizations of well-being in the current psychological literature (Lambert et al., 2015), a distinction is often made between hedonic/subjective well-being and eudaimonic/psychological well-being (Ryan & Deci, 2001). The subjective well-being theory has been associated with hedonistic philosophical ideas on well-being (Lambert et al., 2015; Ryan & Deci, 2001). This philosophical definition of hedonism includes maximizing pleasure and minimizing pain as the ultimate goal of life. Modern-day subjective well-being measures therefore focus on levels of positive affect and negative affect and subjective satisfaction with life (Diener et al., 2018). The psychological well-being has emerged from eudaimonic philosophical theories (Lambert et al., 2015; Ryan & Deci, 2001). The eudaimonic philosophical theory extends beyond pleasure and pain only, and emphasizes living a virtuous life. Based on this idea, current psychological well-being measures include measures of positive functioning, thriving, and judgments about the meaning and purpose of an individual's life (Ryff, 1989).

The WHO definition of mental health mentioned before mostly focuses on the eudaimonic well-being concepts like realizing abilities and making contributions to the community. The hedonic well-being constructs are less clear in this definition, while there is more research on hedonic well-being compared to eudaimonic well-being. For example, the mentioned twin studies of well-being mainly include hedonic measures of well-being, i.e., life satisfaction

and positive affect, and all available GWASs only include hedonic well-being measures. Hedonic and eudaimonic well-being are found to be strongly related, both phenotypically and genetically (Baselmans, van de Weijer, et al., 2019; Joshanloo, 2016), although they also capture different aspects of well-being. In this review, we refer to well-being in the broadest sense, including all definitions and constructs. We discuss the effect of the diversity of well-being measures on the association of the physiological correlates and well-being, mainly distinguishing between hedonic and eudaimonic well-being.

Neurotransmitters

Neurotransmitters are chemicals in the nervous system that transmit messages between neurons, between neurons and muscles, or influence the electrochemical state of other cells (see Snyder & Ferris (2000) for a review). Neurotransmitters have their primary functions within the central nervous system (CNS), but are present throughout the body and in several biological fluids, such as blood, plasma, cerebral spinal fluid (CSF), saliva, and urine. Neurotransmitters can be classified in two types, small molecule (classic) transmitters and neuropeptides. Small-molecule transmitters, like dopamine and serotonin, have quick direct effects on near cells. Neuropeptides, like oxytocin, have more subtle effects and can have more distant effects in the body.

Neurotransmitters are transported from the central nervous system to the periphery, via the blood– brain barrier and after filtration by the kidneys excreted in urine. In human research, levels of neurotransmitters are usually assessed in blood or urinary samples. Yet, it is not clear what blood plasma and urine measures of neurotransmitters reflect. Neurotransmitter levels from urinary samples are not seen as a reliable indicator of CNS activity, but is suggested to reflect changes in the peripheral autonomic system (Ailts et al., 2007). However, both human and animal studies suggest at least a positive correlation between neurotransmitter levels in the brain and the rest of the body (Marc et al., 2011).

Neurotransmitters are important for human mental and physical health and abnormalities in their levels or activity can lead to mental disorders. For example, serotonin has found to be important for mood, movement, pain, and the sleep-wake cycle and is implicated in various psychiatric and brain disorders, such as depression, and obsessive-compulsive disorders (Blows, 2000). Norepinephrine and epinephrine have mostly been related to arousal and the level of activity within a person. Dopamine has been associated mainly with movement, reward (learning), and addictions. Decreased dopamine levels

have been related to increased anhedonia or emotional apathy as well (Bressan & Crippa, 2005). Furthermore, increasing dopamine levels using levodopa subsequently increased happiness in an economic decision game (Rutledge et al., 2015).

These associations suggest the involvement of neurotransmitters in well-being as well. However, the detection of levels of neurotransmitters in humans is challenging due to the short term effects, low levels in the brain, and their mixture with other molecules (Niyonambaza et al., 2019). Therefore, research on well-being and neurotransmitters is scarce and a systematic review can help to identify areas for future research.

Hormones

Hormones are chemical messengers produced in the endocrine glands and released into the blood stream to organs and tissues of the body to control or regulate different physiological processes, including growth, metabolism, and reproduction (Neave, 2007). Hormones are present throughout the body and in several biological fluids, such as blood, urine and saliva, but also in hair. Like neurotransmitters, hormones are messengers. However, the difference with neurotransmitters is the site of release, site of action, and speed of action. Hormones are produced in the endocrine glands, are secreted into the blood stream and act throughout the whole body, whereas neurotransmitters are produced and released in the central nervous system and more locally. Compared to neurotransmitters, the effects of hormones are slower and longer lasting and the hormone levels are easier to detect and measure in humans.

In a narrative review, Rector and Friedman (2018) discussed the state of the field of the association between well-being and hormones. Adrenal hormones, such as cortisol and DHEA(S) can cross the blood-brain barrier and can exert their influences on subjective experiences, such as well-being, directly via the brain. The most often studied hormone in relation to psychological experiences and well-being is cortisol (Rector & Friedman, 2018). A distinction can be made between the levels of cortisol, decline over the day (diurnal slope) and the cortisol response after waking up (the cortisol awakening response, aka CAR) (Chida & Steptoe, 2009; Fries et al., 2009). All cortisol measures have been linked to well-being in some studies, but inconsistent effects are present in the literature and a systematic review is currently missing.

In addition, the sex hormones testosterone and estrogen have been associated with mood and well-being (Johnson et al., 2013; Wharton et al., 2012). For example, the fluctuations of estrogen levels in the menstrual cycle have been suggested to play a role in mood and affect fluctuations. Similarly,

the levels and/or change in testosterone could be related to well-being, although recent studies report insignificant associations (Rector & Friedman, 2018).

In this systematic review, we review all available studies on different hormones and their association with well-being, taking into account the effect of the diversity of well-being measures. Furthermore, as hormone levels can differ across age and sex, we discuss these possible moderating effects on the association.

Inflammatory markers

The immune system is the body's defence system against infections and diseases and consists of many biological structures and processes (Delves & Roitt, 2000). Activation of the immune system and the resulting inflammatory response is related to an increased production of inflammatory markers such as interleukin (IL)-1 β , IL-6, interferon (IFN)- γ , tumor necrosis factor (TNF)- α and C-reactive protein (CRP). These cytokines are signalling molecules and act as chemical messengers to activate different parts of the cellular immune system response. The (baseline) levels of different cytokines have been related to different traits and behaviors. For example, CRP levels increase in response to acute stress, but people also differ in their baseline levels, i.e., depressed people show higher CRP levels (Khandaker et al., 2014; Osimo et al., 2019).

For well-being, in the large Whitehall study of nearly 3,000 healthy middle-aged adults, negative associations between IL-6 and CRP and positive affect have been reported, but only in women (Steptoe et al., 2008). These associations were independent from age, BMI, and depressed mood. However, more recently, large studies to the association of levels of inflammatory markers and different well-being measures reported inconsistent effects, possibly depending on the sample and/or measure of well-being. For example, Fancourt and Steptoe (2020) reported only a small relation between CRP and self-realisation, and not positive affect and life satisfaction in a large sample of older adults ($n \sim 9000$).

Recently, Jones and Graham-Engeland (2021) reviewed the association between inflammatory markers and positive affect and concludes that there is mixed support for the relation between the level of inflammatory markers and positive affect. In the current systematic review, we review the association of inflammatory markers with different measures of well-being and report on the moderating effects of age and sex.

Microbiome

The microbiome is defined as all the microorganisms, such as bacteria, fungi (e.g., yeasts and molds), protozoa (one-celled organisms) and viruses

living on and inside the human body (Turnbaugh et al., 2007). The human gut microbiome is dominated by bacteria and each healthy person has a unique and relatively stable microbiota in their gut (Turnbaugh et al., 2007). It is estimated that more than 1000 species make up the diversity of the human gut microbial ecosystem (Blaut & Clavel, 2007; Siezen & Kleerebezem, 2011). The microbiome bacteria help to digest food, produce vitamins and control our physical health and immune system (Lloyd-Price et al., 2016; Nicholson et al., 2012). The microbiome composition can be measured non-invasively in humans, by extracting information about bacteria abundance and diversity from a fecal sample of participants.

More recently, researchers started to investigate the relation between the composition of the microbiome and mental health or complex traits, such as personality. Most research focused on depression and reported an association with an altered gut microbiota composition, i.e., reduced diversity (Foster & McVey Neufeld, 2013; Neufeld et al., 2011; Winter et al., 2018). Personality traits, including neuroticism and sociability, have also been related to different abundances of different gut microbiome bacteria (Johnson, 2020). These findings suggest that the composition of the microbiome might play a role in well-being as well, and therefore we review the available literature.

METHODS

To bring together the literature on the association between the four physiological categories and well-being, four systematic reviews (for each category separately) were conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). The four categories we included were (1) neurotransmitters, (2) hormones, (3) inflammatory markers, and (4) the microbiome.

Information Source and Search Strategy

Until September 2th 2021, the search for relevant articles was conducted in the bibliographic databases PubMed and Web of Science. Additional articles that were missed during this search were identified via reference lists of the selected articles. The search strategy included combinations of search terms related to well-being and the search words of one of the other categories (see Table 3.1 for the full list of search). The search applied iterative combinations of these categories by employing the Boolean search operators AND (horizontal) and OR (vertical).

Table 3.1. Keywords for systematic reviews of well-being and the physiological categories.

Well-being	Neurotransmitters	Immune system	Hormones	Microbiome
Well-being	Neurotransmitter	Immune system	Hormone	Microbiome
Wellbeing	Dopamine	Immune response	Cortisol	Microbiota
Well being	Serotonin	Inflammatory pathway	Oxytocin	Gut bacteria
Satisfaction with life	Norepinephrine	Inflammatory marker(s)	Estrogen	Gut
Life satisfaction	Endorphin	Inflammatory response	Testosterone	
Happiness	GABA	Cytokine(s)	Progesterone	
Positive affect	Glutamate			
	Acetylcholine			
	Neuropeptide			
	Neurotrophin			

Study Selection and Data Extraction

Titles and abstracts of collected articles were screened for eligibility and were included if (1) an association between one of the physiological categories and a measure of well-being (i.e., not only the absence of depression) was investigated, (2) healthy, non-clinical human samples were included, (3) the studies were peer-reviewed, and (4) published in English. Articles were excluded when (1) the procedure included a mood or emotion induction procedure, (2) a clinical sample was included, (3) the papers were review papers or (4) descriptive planned studies.

In cases of insufficient information to determine eligibility, papers were subjected to further screening. The first author screened the full text reports and decided whether papers met the inclusion criteria. Uncertainties and disagreement were resolved through discussions with the other authors.

Meta-analysis and publication bias

If, after reviewing, a substantial number of studies were considered to be relatively homogeneous with respect to study design and reported effect, we meta-analyzed the reported associations using the Metafor package in R (R Core Team, 2017; Viechtbauer, 2010). For results to be included in the meta-analysis, a bivariate correlation (instead of a standardized regression or beta coefficient) had to be reported. Since we focus on bivariate correlations and standardized regression coefficients are often based on regression with different covariates, we did not include (transformed) standardized regression coefficients or other effect indices in the meta-analyses as this might lead to biased estimates (Roth et al., 2018). If bivariate correlations were not reported, study authors were contacted to ask for the missing data.

For normalization, correlations were transformed into Fisher Z scores, using the

formula: $ESz = 0.5 * \log\left(\frac{1+r}{1-r}\right)$. After the meta-analysis, the estimate was transferred

back to a correlation for reasons of interpretation, using $r = \frac{(e^{2ESz} - 1)}{(e^{2ESz} + 1)}$ (Lipsey & Wilson, 2001).

As some studies used overlapping samples and most studies reported multiple associations and effect sizes, we applied a three-level meta-analysis (Van den Noortgate et al., 2014). This enabled us to include all effect sizes while taking into account the dependency, by specifying three levels, (1) sampling variance of the effect sizes, (2) variance between effect sizes within studies using the same dataset, and (3) variance between studies.

As a potential moderator of the effect between the physiological measure and well-being, we included the type of well-being measure as a categorical variable (i.e., (1) positive affect (hedonic well-being), (2) life satisfaction (hedonic well-being) and (3) eudaimonic well-being measures). Furthermore, we tested the moderation by average age of the sample (continuous variable) and percentage of females in the sample (continuous variable).

To assess the possible presence of a publication bias, we plotted the distribution of the effect sizes in a funnel plot and applied the Egger's test to test the significance of the asymmetry of the funnel plot (Egger et al., 1997). If the plot is too asymmetrical and the test significant, a publication bias can be expected.

RESULTS

Study selection

Across the four categories, the initial electronic database searches resulted in almost 12000 hits in PubMed and Web of Science. We summarized the selection progress in PRISMA Flow diagrams (see Figure 3.1). By removing the duplicates and scanning the titles and abstracts of the remaining articles, a first selection was made based on the selection criteria. In addition, we included additional articles based on references. The selected articles were examined and read fully. Based on the full-text reading, 91 articles met our selection criteria and were included in our review. Note that some studies were included in multiple categories.

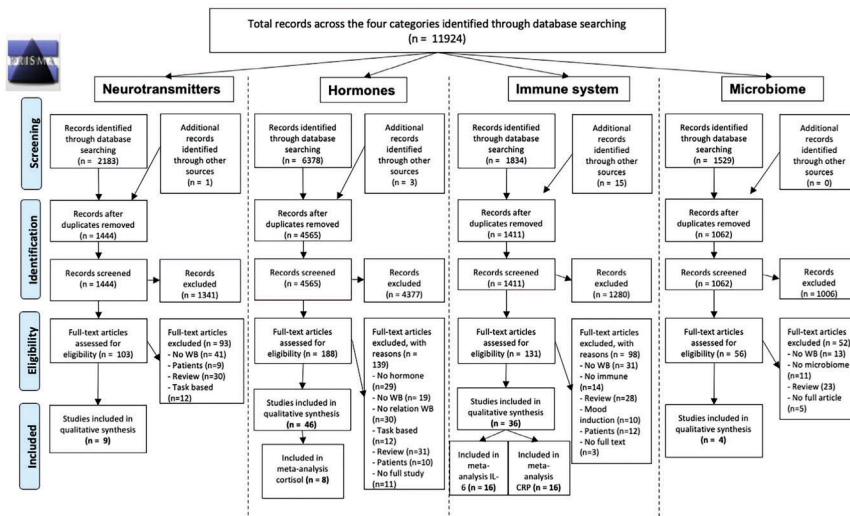


Figure 3.1. PRISMA Flow Diagram of the included studies per physiological category.

Neurotransmitters

Nine studies investigated the relation between different neurotransmitters and well-being (see Table 3.2 for the details).

Description of study designs and samples

The average number of participants across the studies is 193 ($SD=311$), with a range from 11 to 985. The average age of the included participants is 46.2 ($SD=16.5$, range = 25-74) and the percentage included females is on average 57% ($SD=39\%$) with a range from 0 to 100%. All studies were cross-sectional studies, correlating the levels of neurotransmitters to the well-being measures.

Neurotransmitter measures

Four studies (studies N1-4 in Table 3.2) included a measure of the urinary levels of epinephrine and norepinephrine. Four other studies (N5-8 in Table 3.2) investigated serotonin in relation to well-being in blood samples. Of these 4 studies, two (N5-6) assumed the serotonergic functioning from the prolactin (PRL) response to fenfluramine. A lower PRL response is a marker of diminished serotonergic function (Rowland & Carlton, 1986). The other two studies (studies N7-8 in Table 3.2) directly measured levels of serotonin in the blood. The last study (study N9 in Table 3.2) assessed the relation between well-being and blood levels of β -endorphin, a neuropeptide that blocks the sensation of pain.

Well-being measures

Seven studies (studies N2,N4-9 in Table 3.2) included a measure of positive affect or happiness and three studies included the Ryff's Psychological well-being (PWB) scales (N1-3).

The association with well-being

Since we only identified a few studies per neurotransmitter, we could not perform meta-analyses, but provide a description of study results instead. Three of the four epinephrine and norepinephrine studies reported the absence of a cross-sectional relation between the blood levels of epinephrine or norepinephrine and positive affect or purpose in life (Dos Santos et al., 2019; Lindfors & Lundberg, 2002; Zilioli, Slatcher, et al., 2015). Ryff et al. (2006) did report a positive association between the positive relations subscale of the PWB scale and epinephrine and between the autonomy scale and norepinephrine. Compared to the other studies, the sample of Ryff et al. (2004) was older (mean age=74.0) and only included women, indicating a possible moderating effect of age on the association.

Regarding serotonin, the first PRL response study unexpectedly reported a negative association between serotonergic functioning and positive affect in a small sample of men (n=31) (Zalda & Depue, 2001), indicating that lower serotonergic functioning is related to higher positive affect. With a larger sample (n=254, 47% female) and a similar design, Flory et al. (2004) reported a positive association between serotonergic functioning and positive affect with no sex differences. This indicates that in both men and women a higher average positive mood was associated with a larger PRL response, i.e., better serotonergic functioning. Furthermore, the relation between positive affect and serotonin was significant when controlling for negative affect, suggesting independent effects for positive affect and serotonin (Flory et al., 2004). In direct blood measures of serotonin, both Duffy et al. (2006) and Williams et al. (2006) (N7, N8) replicated the positive association between positive affect and serotonin levels in respectively a female and male sample. Overall, based on the limited number of available studies, higher positive affect is likely to be associated with higher levels of serotonin.

Lastly, levels of β -endorphin (β -END) in the blood were not related to a happy mood in a small sample (n=11) (Toledo et al., 2019).

Summary

To summarize, our systematic review revealed a possible association between serotonin and well-being. Serotonin levels were positively related to

positive affect, i.e., hedonic well-being in three out of four studies. Furthermore, the effect was independent of negative affect in one study. The relation between serotonin and other measures of well-being, e.g., life satisfaction, quality of life or eudaimonic well-being measures has not been investigated so far. In studies with larger sample sizes, the moderation by age and sex should be investigated as well.

Levels of epinephrine and norepinephrine were mostly unrelated to measures of hedonic and eudaimonic well-being. Only in a sample of older women (age=74), there was a moderate positive correlation between subscales of the psychological well-being scale and (nor)epinephrine. More research to the moderating effects of the well-being measure, age and sex is needed to confirm the findings.

Table 3.2. Characteristics and results of the neurotransmitter studies.

No	Study	Neurotransmitter	Neuro sample	Sample N	Age M (SD)	% female	Design	Control for NA	WB measure ^{H/E}	Relation WB
N1	(Lindfors & Lundberg, 2002)	epinephrine + norepinephrine	urine	23		52%	Cross-sectional	No	Ryffs PWB ^E	ns
N2	(Ryff et al., 2006)	epinephrine + norepinephrine	urine	135	74 (7.1)	100%	Cross-sectional	No	Ryffs PWB ^E , PANAS ^H	positive relations + epinephrine: $r=0.20^*$, $p<.05$
										autonomy + norepinephrine: $r=0.21^*$, $p<.05$
N3	(Zilioli, Slatcher, et al., 2015)	epinephrine + norepinephrine	urine	985	46.1 (11.7)	56%	Cross-sectional ⁺	No	Ryffs PWB ^E	$r = -.027$
N4	(Dos Santos et al., 2019)	epinephrine + norepinephrine	urine	233		57%	Cross-sectional	No	Positive affect ^H	ns
N5	(Zalda & Depue, 2001)	serotonin/ prolactin	blood	34	25 (3.1)	0%	Cross-sectional	No	PANAS ^H	$r=-0.49^*$, $p=0.005$
N6	(Flory et al., 2004)	serotonin/ prolactin	blood	254	45	47%	Cross-sectional	Yes	Happiness ^H	$\beta=0.14^*$, $p=.007$

Table 3.2. Characteristics and results of the neurotransmitter studies.

No	Study	Neurotransmitter	Neuro sample	Sample N	Age M (SD)	% female	Design	Control for NA	WB measure ^{H/E}	Relation WB
N7	(Duffy et al., 2006)	serotonin	blood	39	60 (5.1)	100%	Cross-sectional	No	PANAS ^H	r=-.35* , p=.03
N8	(Williams et al., 2006)	serotonin	blood	23	32 (5)	0%	Cross-sectional	No	PANAS ^H	β = 8.2* , p = 0.002
N9	(Toledo et al., 2019)	β-endorphin	blood	11	41.6 (11.2)	100%	Cross-sectional	No	Mood ratings ^H	r =.43, p = .18

Note. PANAS = Positive and Negative Affect Schedule, Ryff PWB= Ryff Scales of Psychological Well-Being. *Superscript H indicates a hedonic well-being measure, whereas E indicates a eudaimonic well-being measure.

+ Although this is a longitudinal study, we reported the correlation at baseline, i.e., cross-sectional.

Hormones

The details and results of the 48 different studies on hormones in relationship to well-being are reported in Table 3.3 (cortisol) and Table 3.4 (other hormones).

Description of study designs and samples

The average number of participants in the studies is 608 ($SD=1542$), with a range of 11 to 9127 participants. The average age is 40.1 ($SD=19.6$, range=13.9-80.3). The percentage included females is on average 59.5% ($SD=28.3\%$) with a range from 0 to 100%.

One study had an experimental design in which participants received oxytocin for 10 days and well-being levels were assessed (Barraza et al., 2013). Six studies were longitudinal studies, relating hormone levels to well-being a few years later or vice versa (Hou et al., 2015; Hoyt et al., 2015; Lacker et al., 2020; Stafford et al., 2017; Steptoe & Wardle, 2005; Wendsche et al., 2020). The remaining 41 studies were cross-sectional studies, of which 17 studies were experience sampling studies with multiple measurements of hormones and/or well-being per day or across days (see Table 3.3 and 3.4).

Hormone measures

The hormones most often studied in relation to well-being are cortisol ($k=39$) (see Table 3.3), dehydroepiandrosterone sulfate (DHEA-S; $k=7$), testosterone ($k=4$), vitamin D ($k=2$), and estradiol ($k=2$). Single studies looked at oxytocin, FSH, LH, prolactin (PRL), IGF-I and IGFBP-3 and thyroid-stimulating hormone (TSH) (see Table 3.4, ordered by hormone).

For cortisol, most studies used saliva samples to assess the cortisol level ($k=37$), two studies used hair samples (Smyth et al., 2016; Wendsche et al., 2020), two studies blood samples (Sonnenblick et al., 2018; Toledo et al., 2019), and a single study used urine (Zilioli, Slatcher, et al., 2015). A distinction is made between the association of well-being with momentary levels of cortisol ($k=33$), the cortisol awakening response (CAR) ($k=16$), the diurnal response ($k=14$), and the area under the curve (AUC) ($k=7$) (see Table 3.3).

DHEA-S was measured in saliva ($k=3$), blood ($k=3$), or in urine ($k=1$). Testosterone levels were mostly assessed in saliva ($k=3$), whereas one study looked at the blood levels. Vitamin-D levels were assessed in the blood ($k=2$). Estradiol was either assessed in blood or saliva. Finally, the levels of other hormones (FSH, LH, prolactin, IGFBP-3 and IGF-I) were assessed in blood (see Table 3.4).

Well-being measures

Positive affect items (k=26), Satisfaction with Life scale (k=8), the WHO-index in different forms (k=7), and Ryff's psychological well-being scale (k=8) were mostly included in the studies. Other scales and items, such as the Subjective Happiness Scale, POMS and the Warwick Edinburgh Mental well-being scale were only included in single or a few studies (see Table 3.3 and 3.4).

The association between well-being and cortisol

Cortisol level. The average or momentary level of cortisol was negatively related to well-being in 7 studies (CL2,3,5,9,10,17,21 in Table 3.3), whereas in 14 studies the relation did not reach significance. The studies with the largest sample sizes (respectively n=2873 and n=1657) reported significant, but small effects (Sin et al., 2017; Steptoe et al., 2008). Furthermore, 4 of the 8 studies (CL5,9,10, 17 vs CL1,6,7,8), that did control for negative affect or depression, including the two large studies mentioned before, reported a significant negative association between well-being and cortisol levels, suggesting independent effects for well-being.

Eight relatively homogeneous studies with 15 associations of salivary cortisol level and well-being could be included in a meta-analysis (CL3,4,7,8,11,12,16,17, see Figure 3.2). One of these associations was provided by the authors. We excluded eleven studies due to reporting only a beta coefficient or not reporting effect sizes and nonresponse to our request for extra information. The remaining two excluded studies used blood samples.

Based on the included studies, the distribution of the effect sizes in the funnel plot appeared to be symmetrical (see Figure S3.1) and the Egger's test was non-significant with $Z = -2.40$, $p = .017$, suggesting no publication bias. The meta-analysis resulted in an estimate of $-.06$ ($SE = .03$, $95\%CI: -.11, -.001$, $t = -2.19$, $p = .046$, $r = -.06$). This indicates a small negative association between momentary or average level of cortisol and well-being. The moderation by well-being measure (i.e., positive affect vs life satisfaction or eudaimonic well-being measures) was not significant ($\beta = -.08$, $SE = .10$, $p = .422$ and $\beta = -.16$, $SE = .10$, $p = .113$). Age ($\beta = .00$, $SE = .002$, $p = .736$) and the percentage of females in the sample ($\beta = .23$, $SE = .30$, $p = .472$) were not significant moderators of the association.

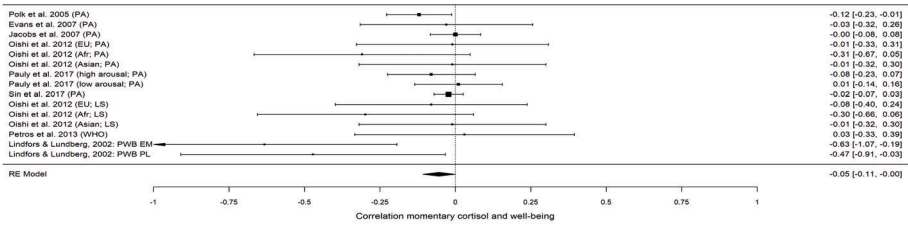


Figure 3.2. Results of the meta-analysis on the correlation between momentary cortisol and well-being, based on 8 studies and 15 effect sizes.

Of the studies that specifically investigated morning levels of cortisol, one study reported a lower level of cortisol to be related to higher well-being (Sjögren et al., 2006), one study a higher level (Lindfors & Lundberg, 2002) and in the other 7 studies (CM1,CM4-9) the association did not reach significance.

Evening cortisol was negatively related to well-being in 3 out of the 4 studies in both adult and adolescent samples (Hoyt et al., 2015; Simpson et al., 2008; Stafford et al., 2017).

The two studies with hair cortisol concentration differed in their results. (Wendsche et al., 2020) did not find a relation with well-being, whereas (Smyth et al., 2016) did report a positive relation between hair cortisol and well-being, independent from negative affect, but only in the older adults ($M_{age} = .78.6$).

Cortisol awakening response. The reported effects and designs of the studies to the cortisol awakening response (CAR) differed a lot, therefore we could not perform a meta-analysis and we only describe the results. Sixteen studies investigated the CAR, with 12 of these not finding an association with different measures of well-being, including the studies with the largest sample sizes ($n > 1500$) (Sin et al., 2017; Stafford et al., 2017; Steptoe et al., 2008). Two studies reported a negative relation, with a lower CAR related to higher scores on different well-being measures in an adult and adolescent sample respectively (Miller et al., 2016; Rickard et al., 2016), whereas Pasquali et al. (2021) reported a significant positive relation, with a higher CAR related to higher positivity in a small sample ($n = 20$). The last study found individual differences in the relation between well-being and the CAR response in healthy participants (Booij et al., 2016; CAR10 in Table 3.3).

Diurnal Slope. Fourteen studies related the diurnal slope of cortisol (over the day) to well-being, with 4 studies reporting a non-significant association (CS3,4,8,14). Seven studies reported that a steeper slope (faster decrease of cortisol levels over the day after the CAR) was significantly related to higher

well-being, i.e., positive affect or satisfaction with life (CS2,5,6,7,9,11,13) whereas two studies found a flatter slope related to higher well-being (CS1,12). Lastly, Booij et al. (2016) reported a significant relation between the diurnal slope of cortisol and well-being for the majority of their participants, but individual differences in the direction and strength. Suggesting an independent effect of well-being, of the five studies that did control for negative affect or depressive symptoms, four did find a significant association between a steeper diurnal slope of cortisol and well-being (CS2,7,9,12 in Table 3.3).

AUC. Seven studies looked at the total cortisol secretion captured in the area under the curve (AUC). Four reported no relation with well-being (AUC2,3,5,6). Small studies reported a positive (Pasquali et al., 2021) or negative relation (Rickard et al., 2016) with well-being. Finally, Smyth et al. (2015) showed total cortisol secretion is only significantly related to higher well-being when the participant is accurate in the time of sampling.

Summary. The meta-analysis showed that a lower momentary level of overall cortisol is related to higher well-being, however the effect is small. Furthermore, based on the descriptive results, a steeper diurnal slope of cortisol levels could be linked to higher well-being. For the CAR and AUC, the results of the available studies are inconsistent, and based on the larger studies an association between these cortisol measures and well-being is not likely. As pointed out by Booij et al. (2016), there are individual differences in the association. Therefore, future studies should investigate the relation between cortisol and affect within individuals to prevent the blurring of the effect by aggregating all individual effects or take into account the moderating effects of age and sex.

Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
Hair cortisol	HC1	(Smyth et al., 2016)	hair	88 young 27 old	19.5 (2.2); 78.6 (6.7) Only in elderly	100%	Cross-sectional	SHS ^H , SWLS ^H and Ryffs PWB ^E	B = -.060*
	HC2	(Wendsche et al., 2020)	hair	194	40.9 (11.3)	90%	Cross-sectional / longitudinal	WHO-5 ^{H/E}	r = -.01 / -.05
Cortisol level	CL1	(van Eck et al., 1996)	saliva	87	42.1	0%	ESM	Positive affect ^H	ns
	CL2	(Smyth et al., 1998)	saliva	120	36.7 (12)	71%	ESM	Positive affect ^H	-*, p < .05
	CL3	(Lindfors & Lundberg, 2002)	saliva	23	-	52%	Cross-sectional	Ryffs PWB ^E	Environmental mastery: r = -.56* Purpose life: r = -.44*
								No	
	CL4	(Polk et al., 2005)	saliva	334	28.8 (10.4)	75%	ESM	Positive affect ^H	r = -.0.12
	CL5	(Steptoe et al., 2005)	saliva	228	45-59	46%	ESM	Happiness ^H	-*, p = .009
	CL6	(Steptoe & Wardle, 2005)	saliva	162	45-59		Longitudinal	Happiness ^H	- , p = .07
	CL7	(Evans et al., 2007)	saliva	50	74.0 (7.0)	68%	Cross-sectional	POS-GHQ ^H	r = -0.03



Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
CL8	(Jacobs et al., 2007)	saliva	556	27 (8)	100%	ESM	Yes	Positive affect ^H	$r = -0.00005$
CL9	(Steptoe et al., 2008)	saliva	2,873	50-74	73%	ESM	Yes	Positive affect ^H	Average: -7%*
CL10	(Matias et al., 2011)	saliva	44	21 (3.4)	100%	ESM	Yes	Positive affect ^H	moment: B = -.03*
CL11	(Oishi et al., 2012)	saliva	41/33/46	-	71%	ESM	No	SWLS ^H ,	$r = -.08, -.29, -.01$
			EU/Afr/As	-	-			Positive affect ^H	$r = -.01, -.30, -.01$
CL12	(Petros et al., 2013)	saliva	32	29 (5.7)	63%	Cross-sectional	No	WHO WB index	$r = .03$
CL13	(Smyth et al., 2015)	saliva	49	20.5 (2.8)	100%	ESM	No	Factor score: SHS ^H , SWLS ^H , PA ^H , Meaning in life ^E , Ryffs PWB ^E	$B = -.289$
CL14	(Booij et al., 2016)	saliva	30 (15 MDD 15 HC)	35	72%	ESM	No	Positive affect ^H	Average: $\beta = -0.08$
CL15	(Zimmaro et al., 2016)	saliva	85	19.3 (1.4)	69%	Cross-sectional	No	Ryffs PWB ^E	Daily mean: ns

Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
CL16	(Pauly et al., 2017)	saliva	185	49	51%	ESM	No	Positive affect ^H	H arousal: $r = -.08$, L arousal: $r = .01$
CL17	(Sin et al., 2017)	saliva	1657	56.4 (12.1)	57%	ESM	Yes	Positive affect ^H	B = -.065*
CL18	(Smyth et al., 2017)	saliva	115	41.23 (11.87)	76%	ESM	No	SASS ^H	Moment: B = -.04*
CL19	(Lackner et al., 2020)	saliva	97	61.3 (10.0)	0%	Longitudinal	No	SF-36, psychological WB ^E	B = -.121
CL20	(Sonnenblick et al., 2018)	blood	60	56.7 (17.8)	32%	Cross-sectional	No	POMS ^H , VAS ^H , WHO-5 ^{H/E}	ns
CL21	(Toledo et al., 2019)	blood	11	41.6 (11.2)	100%	Cross-sectional	No	Mood items ^H	r = -.57*
CM1	(van Niekerk et al., 2001)	saliva	40	60-80	0%	Cross-sectional	No	Positive mood ^H	$r = -.0.13$
CM2	(Lindfors & Lundberg, 2002)	saliva	23	-	52%	Cross-sectional	No	Ryff's PWB ^E	Self-Acceptance: r = -.46* Environmental mastery: r = -.64*
CM3	(Sjögren et al., 2006)	saliva	257	30-64	50%	Cross-sectional	No	Ladder of life ^H	r = .17*

Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
CM4	(Steptoe et al., 2007)	saliva	72	33.6 (8.8)	0%	ESM	Yes	PANAS ^H	$\beta = -.19$
CM5	(Daly et al., 2011)	saliva	174	23 (5.7)	66%	ESM	No	Positive affect ^H	$B = .147$
CM6	(Slatcher et al., 2015)	saliva	1078		52%	Cross-sectional	No	Positive affect ^H	ns
CM7	(Zilioli, Imami, et al., 2015)	saliva	1325	55.6 (11.7)	55%	Cross-sectional	Yes	SWLS ^H	$\beta = -.02$
CM8	(Stafford et al., 2017)	saliva	7515	-	-	Longitudinal	No	Warwick Edinburgh WB ^{H/E}	$\beta = -.02$
CM9	(Zilioli, Slatcher, et al., 2015)	urine	985	46.14, 11.7	56%	Cross-sectional	No	Ryffs: Purpose in life ^E	$r = -0.018$
CE1	(van Niekerk et al., 2001)	saliva	40	60-80	0%	Cross-sectional	No	Positive mood ^H	$r = -0.08$
CE2	(Simpson et al., 2008)	saliva	41	61.8	56%	ESM	No	PANAS ^H	$r = -0.47^*$
CE3	(Hoyt et al., 2015)	saliva	315	17.1 (0.4)	73%	Longitudinal	Yes	Positive affect ^H	$\beta = -.66^*$

Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
CE4	(Stafford et al., 2017)	saliva	1756		-	Longitudinal	No	Warwick Edinburgh WB ^{H/E}	$\beta = -.47^*$
CAR1	(Lai et al., 2005)	saliva	80	28.3 (8.6)	52%	Cross-sectional	Yes	Chinese Affect Scale: Positive affect ^H	ns
CAR2	(Polk et al., 2005)	saliva	334	28.8 (10.4)	75%	ESM	No	Positive affect ^H	$r = -0.08$
CAR3	(Evans et al., 2007)	saliva	50	74.0 (7.0)	68%	Cross-sectional	Yes	POS-GHQ ^H	$F = 0.02$
CAR4	(Stepptoe et al., 2007)	saliva	72	33.6 (8.8)	0%	ESM	Yes	PANAS ^H	$\beta = -.32$
CAR5	(Stepptoe et al., 2008)	saliva	2,873	50-74	73%	ESM	Yes	Positive affect ^H	ns
CAR6	(Hou et al., 2015)	saliva	105	21.0 (1.2)	55%	Longitudinal	No	Chinese Affect Scale: Positive affect ^H	$\beta = .003$
CAR7	(Hoyt et al., 2015)	saliva	315	17.1 (0.4)	73%	Longitudinal	Yes	Positive affect ^H	$\beta = -.030$
CAR8	(Slatcher et al., 2015)	saliva	1078	-	52%	Cross-sectional	No	Positive affect ^H	$\beta = .033^*$

Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
CAR9	(Zilioli, Imami, et al., 2015)	saliva	1325	55.6 (11.7)	55%	Cross-sectional	Yes	SWLS ^H	$\beta = .019$
CAR10	(Booij et al., 2016)	saliva	30 (15 MDD 15 HC)	35	72%	ESM	No	Positive affect ^H	indiv diff
CAR11	(Miller et al., 2016)	saliva	490	43	54%	ESM	No	PANAS ^H	$\beta = -.26^*$
CAR12	(Rickard et al., 2016)	saliva	47	13.9 (.7)	70%	Cross-sectional	No	Warwick-Edinburgh WB ^{H/E}	$r = -.43^*$
								PANAS ^H	$r = -.35^*$
								SWLS ^H	$r = -.32^*$
								Happiness ^H	$r = -.32$
CAR13	(Chong et al., 2017)	saliva	32	20.5 (2.3)	53%	Cross-sectional	No	SWLS ^H	$r = -.17$
CAR14	(Sin et al., 2017)	saliva	1657	56.4 (12.1)	57%	ESM	Yes	Positive affect ^H	$B = -.010$
CAR15	(Stafford et al., 2017)	saliva	1612	-	-	Longitudinal	No	Warwick-Edinburgh WB ^{H/E}	$\beta = -.19$

Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
CAR16	(Pasquali et al., 2021)	saliva	20 (10 POS high, 10 POS low)	21 (1.3)	0%	Cross-sectional	No	Positivity ^H	Higher
CS1	(Ryff et al., 2006)	saliva	135	74	100%	Cross-sectional	No	Ryffs PWB ^F , PANAS ^H , MQS ^H	75+ subsample: r=-.29* flatter
CS2	(Lai et al., 2005)	saliva	80	28.3 (8.6)	52%	Cross-sectional	Yes	Chinese Affect Scale: Positive affect ^H	steeper
CS3	(Polk et al., 2005)	saliva	334	28.8 (10.4)	75%	ESM	No	Positive affect ^H	r= -0.04
CS4	(Stephoe et al., 2005)	saliva	228	45-59	46%	ESM	Yes	Happiness ^H	ns
CS5	(Sjogren et al., 2006)	saliva	257	30-64	50%	Cross-sectional	No	Ladder of life ^H	r=-.16* steeper
CS6	(Daly et al., 2011)	saliva	174	23 (5.7)	66%	ESM	No	Positive affect ^H	B= -.02* steeper
CS7	(Hoyt et al., 2015)	saliva	315	17.1 (0.4)	73%	Longitudinal	Yes	Positive affect ^H	β= -.038* steeper
CS8	(Slatcher et al., 2015)	saliva	1078	-	52%	Cross-sectional	No	Positive affect ^H	β= -.011* steeper



Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
CS9	(Zilioli, Imami, et al., 2015)	saliva	1325	55.6 (11.7)	55%	Cross-sectional	Yes	SWLS ^H	$\beta = -.002^*$ steeper
CS10	(Booij et al., 2016)	saliva	30 (15 MDD 15 HC)	35	72%	ESM	No	Positive affect ^H	indiv diff
CS11	(Miller et al., 2016)	saliva	490	43	54%	ESM	No	PANAS ^H	$\beta = -.19^*$ steeper
CS12	(Sin et al., 2017)	saliva	1657	56.4 (12.1)	57%	ESM	Yes	Positive affect ^H	B = .012* flatter
CS13	(Smyth et al., 2017)	saliva	115	41.23 (11.87)	76%	ESM	No	SASS ^H	B = -.01*
CS14	(Stafford et al., 2017)	saliva	6490			Longitudinal	No	Warwick Edinburgh WB ^{H/E}	$\beta = -.07$
AUC								Factor score: SHS ^H , SWLS ^H , PA ^H , Meaning in life ^E , Ryffs PWB ^E	B = -.037* only when accurate sampling
ground or increase								SWLS ^H , Positive Emotional Style and Flourishing scale ^E	ns

Table 3.3. Characteristics and results of the cortisol studies.

No	Study	Sample	Sample N	Age M (SD)	% female	Design	Correct NA	WB measure ^{H/E}	Result
AUC3	(Miller et al., 2016)	saliva	490	43	54%	ESM	No	PANAS ^H	$\beta = .14$
AUC4	(Rickard et al., 2016)	saliva	47	13.9 (7)	70%	Cross-sectional	No	Warwick-Edinburgh WB ^{H/E}	$r = -.27^*$
								PANAS ^H	$r = -.25^*$
								SWLS ^H	$r = -.21^*$
								Happiness ^H	$r = -.27$
AUC5	(Chong et al., 2017)	saliva	32	20.5 (2.3)	53%	Cross-sectional	No	SWLS ^H	$r = -.01$
AUC6	(Sin et al., 2017)	saliva	1657	56.4 (12.1)	57%	ESM	Yes	Positive affect ^H	$B = -.001$
AUC7	(Pasquali et al., 2021)	saliva	20 (10 POS high, 10 POS low)	21 (1.3)	0%	Cross-sectional	No	Positivity ^H	Higher*

Note: * are significant effects, ns is not significant + no effect reported. Studies in bold are included in the meta-analysis. WB= well-being, SHS= subjective happiness scale, SWLS= satisfaction with life scale, PWB= psychological well-being, PANAS = Positive and Negative Affect Schedule, WHO-5= World Health Organization well-being index, WHOQOL = World Health Organization Quality of Life Instruments, Ryff PWB= Ryff Scales of Psychological Well-Being, PA= positive affect, SASS= Self-Anchoring Striving Scale, SF-36= 36-Item Short Form Survey, POMS= Profile of mood states, VAS= Visual analogue mood scale. ^{H/E} Superscript H indicates a hedonic well-being measure, E indicates a eudaimonic well-being measure and H/E indicates a measure that includes both hedonic and eudaimonic concepts.

The association between other hormones and well-being

Table 3.4 shows the designs and results of studies that investigated the levels of other hormones in relation to well-being.

DHEA-S. Dehydroepiandrosterone sulfate (DHEA-S) was not related to different measures of well-being in 6 of the 7 studies (H1-5,7). One study found a positive relation between change of DHEA-S levels and change in positive affect after exercise, but only in older men (Sonnenblick et al., 2018).

Testosterone. Only one of the four studies on testosterone reported a positive correlation with quality of life in an elderly sample ($M_{age} = 65$) (Masuda et al., 2014). No relation between testosterone level and quality of life (Castanho et al., 2014), psychological well-being (Lacker et al., 2020), or positive affect was found (Martin & Ter-Petrosyan, 2019) in the other studies.

Vitamin-D. In a large sample of adolescents (n=5066), Schaefer et al. (2016) reported that higher levels of vitamin D (25(OH)D3) in blood were related to higher levels of well-being. This positive relation was replicated in a small sample of adults (n=11) (Toledo et al., 2019).

Other hormones. Insulin-like growth factor-binding protein (IGFBP-3) and Insulin-like growth factor (IGF-I) levels were respectively positively and negatively associated with the WHO-5 well-being index, but only in females (Emeny et al., 2014). Prolactin was negatively related to quality of life in males only, whereas estradiol, FSH and LH were not associated with quality of life in both males and females (Castanho et al., 2014). Finally, a 10-day oxytocin trial did not affect life satisfaction (Barraza et al., 2013).

Summary. To summarize, most studies that included blood level measures of DHEA-S and testosterone did not report a significant association with well-being, or only in a specific subsample. The finding of a positive relation between vitamin D and well-being was consistent, but as only two studies have been published on this relation, replication is needed. Furthermore, the single studies that investigated the association between other hormones and well-being reported mainly non-significant relations.

Table 3.4. Characteristics and results of the other hormone studies.

No	Hormone	Study	Sample	Sample N	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
H1	DHEA-S	(van Niekerk et al., 2001)	saliva	40	60-80	0%	Cross-sectional	No	Positive affect ^H	Morning: -0.13 Evening: -0.08
H2		(Petros et al., 2013)	saliva	32	29 (5.7)	63%	Cross-sectional	No	WHO WB index	r = .23
H3		(Pauly et al., 2017)	saliva	185	49	51%	ESM	No	Positive affect ^H	High arousal: r = -.07 Low arousal: r = -.06
H4		(Castanho et al., 2014)	blood	120	65.2 (8.8)	48%	Cross-sectional	No	WHOQOL-BREF ^H	Males: $\beta = .220$ Females: $\beta = .265$
H5		(Yoo et al., 2016)	blood	1043	55.24	55%	Cross-sectional	No	Positive affect ^H	Japan: $\beta = -.086$ US: $\beta = -.009$
H6		(Sonnenblick et al., 2018)	blood	60	56.7 (17.8)	32%	Cross-sectional	No	POMS ^H , VAS ^H , WHO-5 ^{H/E}	Change: r = .36* , Only older (r = .38*) and males (r = .35*).

Table 3.4. Characteristics and results of the other hormone studies.

No	Hormone	Study	Sample	Sample N	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
H7		(Zilioli, Slatcher, et al., 2015)	urine	985	46.1 (11.7)	56%	Cross-sectional	No	Ryffs PWB; Purpose in life ^E	r = -.018
H8	Testosterone	(Masuda et al., 2014)	saliva	79	65.4 (11.1)	37%	Cross-sectional	No	WHO-QOL26 ^H	Males > 65 years: r = .474* Females: r = .432*
H9		(Martin & Ter-Petrosyan, 2019)	saliva	87	21.2 (6.1)	100%	Cross-sectional	No	PANAS ^H	r = -.14
H10		(Lacker et al., 2020)	saliva	97	61.3 (10.0)	0%	Longitudinal	No	SF-36 ^H , PWB scale ^E	b = 1.17
H11		(Castanho et al., 2014)	blood	120	65.2 (8.8)	48%	Cross-sectional	No	WHOQOL-BREF ^H	Males: $\beta = .093$ Females: $\beta = -.149$
H12	Estradiol	(Lacker et al., 2020)	saliva	97	61.3 (10.0)	0%	Longitudinal	No	SF-36 ^H , PWB scale ^E	b = -1.01* T and F2 ratio: b = 1.076*
H13		(Castanho et al., 2014)	blood	120	65.2 (8.8)	48%	Cross-sectional	No	WHOQOL-BREF ^H	Males: $\beta = .114$ Females: $\beta = .106$

Table 3.4. Characteristics and results of the other hormone studies.

No	Hormone	Study	Sample	Sample N	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
H14	Vitamin D	(Schaefer et al., 2016)	blood	5066	14.7	49%	Cross-sectional	No	Emotional WB ^H	Self-rating: E = 1.327* Parent rating: E = 1.927*
H15		(Toledo et al., 2019)	blood	11	41.6 (11.2)	100%	Cross-sectional	No	Mood items ^H	Baseline: r = 0.54* Change: r = 0.14
H16	Oxytocin	(Barraza et al., 2013)	intranasal OT	39	80.3	38%	Experimental	No	SWLS ^H , POMS ^H	No effect of the oxytocin treatment ($p > .05$).
H17	FSH, LH, PRL	(Castanho et al., 2014)	blood	120	65.2 (8.8)	48%	Cross-sectional	No	WHOQOL-BREF ^H	Prolactin: males ($\beta = -.328^*$), females ($\beta = -.009$) FSH: males ($\beta = -.044$), females ($\beta = -.001$) LH: males ($\beta = -.042$), females ($\beta = -.055$)

Table 3.4. Characteristics and results of the other hormone studies.

No	Hormone	Study	Sample	Sample N	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
H18	IGFBP-3	(Emeny et al., 2014)	blood	985	75	50%	Cross-sectional	No	WHO-5 ^{H/E}	women ($\beta = .14^*$), men ($\beta = .10$).
H19	IGF-I	(Emeny et al., 2014)	blood	985	75	50%	Cross-sectional	No	WHO-5 ^{H/E}	women ($\beta = -.14^*$), men ($\beta = -.03$)

Note: WB= well-being, WHO= World Health Organization, PA= positive affect, WHOQOL = World Health Organization Quality of Life Instruments, POMS= Profile of mood states, VAS= Visual analogue mood scale, WHO-5= World Health Organization well-being index, Ryff PWB= Ryff Scales of Psychological Well-Being, PANAS = Positive and Negative Affect Schedule, SF-36 = 36-Item Short Form Survey. ^{H/}E Superscript H indicates a hedonic well-being measure, E indicates a eudaimonic well-being measure and H/E indicates a measure that includes both hedonic and eudaimonic concepts.

Inflammatory markers

Table 3.5 shows the details and results of the 36 studies on the association between markers of the inflammatory immune response and well-being.

Description of study designs and samples

The average number of participants in the studies is 1568 ($SD=2190$), with a range of 11 to 8780 participants. The average age is 52.6 ($SD=13.7$, range 20.5-77.4). The percentage included females is on average 59.1% ($SD=15.1$) with a range from 29% to 100%.

Thirty studies were cross-sectional studies, of which 5 studies were experience sampling studies with multiple measurements of inflammatory markers and/or well-being per day or across days. Six studies were longitudinal studies, relating well-being to hormone levels a few years later or vice versa (see Table 3.5).

Inflammatory markers

In the 36 studies, CRP (number of studies: $k=26$), IL-6 ($k=25$), fibrinogen ($k=7$), other inflammatory cytokines ($k=7$), a composite score of inflammatory markers ($k=3$), and tumor necrosis factor (TNF) ($k=5$) were included in relation to well-being. Single studies included the number of white blood cells, and matrix metalloproteinase (MMP)-9 (see Table 3.5, ordered by inflammatory marker).

Well-being measures

Positive affect items or the Positive and Negative Affect Schedule (PANAS) ($k=20$), Satisfaction with Life scale ($k=7$), Ryff's psychological well-being scale ($k=5$), and Quality of life ($k=4$) were mostly included in the different studies as well-being measures. Other well-being scales and items, such as the WHO-index, Subjective Happiness Scale and mood items were only included in one or two studies (see Table 3.5).

The association between C-reactive protein (CRP) and well-being

Fourteen studies reported a negative association of CRP with different well-being measures, whereas the other 12 studies did not report a significant relation. Nine studies with a significant association also controlled for negative affect or depressive symptoms, suggesting independent associations between CRP levels and well-being (CRP1,2,3,5,6,15,18,25,26).

Sixteen relatively homogeneous studies reporting 26 associations between CRP and well-being reported a correlation and were included in a meta-

analysis (CRP4,5,7,8,9,12-21,23). Nine of these associations from six studies were provided by the author. We excluded 10 studies, since they reported only a beta coefficient, an odds ratio or relative risk or no effect size, and did not respond to our request for extra information. Based on the included studies, the distribution of the effect sizes in the funnel plot appeared to be symmetrical (see Figure S3.1) and the Egger’s test was non-significant with $Z = -1.33$ and $p = 0.182$, suggesting no publication bias.

The meta-analysis resulted in an estimate of $-.067$ ($SE=.01$, $95\%CI: -.10, -.04$, $t=-4.68$, $p<.001$, $r = -.067$) (see Figure 3). This indicates a small negative relation between CRP and well-being. The moderation by well-being measure (i.e., positive affect vs life satisfaction or eudaimonic well-being measures) was not significant ($\beta=-.02$, $SE=.03$, $p=.545$ and $\beta=.03$, $SE=.03$, $p=.295$). Age ($\beta=.00$, $SE=.001$, $p=.846$) and the percentage of females in the sample ($\beta=.07$, $SE=.26$, $p=.777$) were not significant moderators of the association.

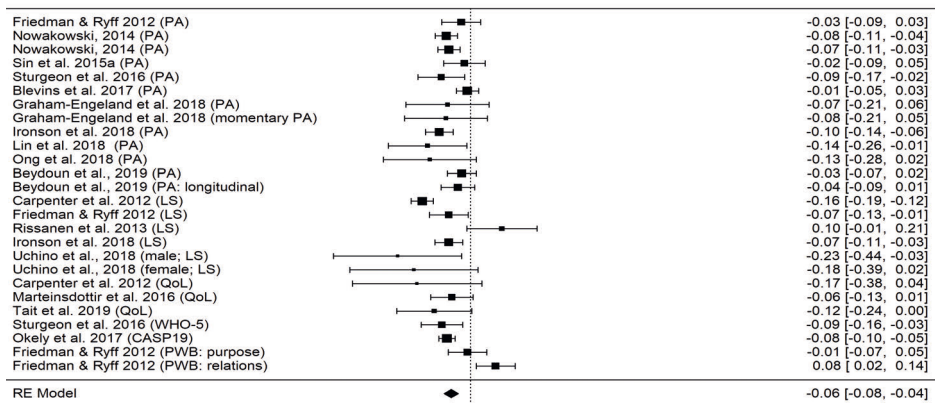


Figure 3.3. Results of the meta-analysis on the correlation between CRP levels and well-being, based on 16 studies and 26 effect size.

The association between well-being and Interleukin-6 (IL-6)

IL-6 was negatively related to different measures of well-being in 11 studies, whereas the other 14 studies reported no significant association with IL-6. The significant relations were mainly with positive affect, quality of life, and life satisfaction. Only three (IL2,3,6 in Table 3.5) of the seven studies that controlled for negative affect reported significant associations between IL-6 levels and well-being (IL2,3,6,12,18,22,25).

Sixteen studies with 35 associations between IL-6 and well-being reported a correlation and were included in a meta-analysis (IL1,4,6-11,15-20,22,23). Six of

these associations from four studies were provided by the author. We excluded 9 studies since they reported only a beta coefficient, an odds ratio or relative risk or no effect size, and did not respond to our request for extra information. The distribution of the effect sizes in the funnel plot appeared to be symmetrical (see Figure S3.1) and the Egger's test was non-significant with $Z = -1.34$ and $p = 0.179$, suggesting no publication bias.

The meta-analysis resulted in an estimate of $-.051$ ($SE=.01$, $95\%CI: -.08, -.03$, $t=-3.91$, $p=.001$, $r= -.051$) (see Figure 3.4), and indicates a small negative relation between IL-6 and well-being. The moderation by well-being measure (positive affect vs life satisfaction or eudaimonic well-being measures) was not significant ($\beta=-.01$, $SE=.04$, $p=.914$ and $\beta=.00$, $SE=.03$, $p=.923$). Age ($\beta=-.00$, $SE=.002$, $p=.152$) and the percentage of females in the sample ($\beta=.14$, $SE=.10$, $p=.174$) were not significant moderators of the association.

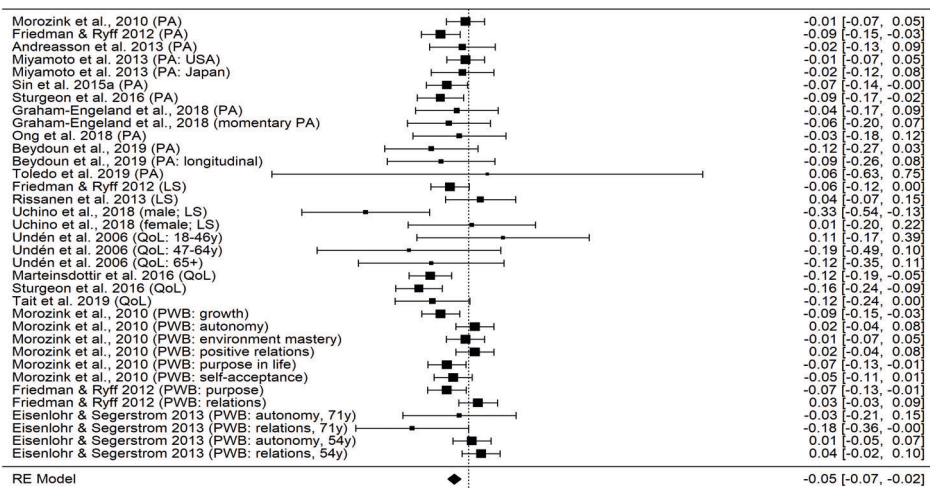


Figure 3.4. Results of the meta-analysis of the correlation between IL-6 levels and well-being, based on 16 studies and 35 effect sizes.

The association between other inflammatory markers and well-being

Fibrinogen was negatively related to different measures of well-being in three studies (F2,3,7 in Table 3.5), whereas the other four studies reported no association with well-being (F1,4,5,6). In the large study of Steptoe et al. (2012), there was a small effect between fibrinogen levels and well-being, but only in women, suggesting a moderation of sex on this effect. Furthermore, the average age of the participants was above 50 in all 7 studies, limiting the possibility to find age effects on the association.

Five studies assessed TNF- α and only in a small subsample of 65+ years (n=73 participants), Undén et al. (2007; study TNF1 in Table 3.5) reported a significant association with quality of life, whereas in the other larger studies no effects were found. In single studies, a cytokine composite score or other cytokines such as IL-10, IL-1B, and IFN- γ were negatively related to well-being in specific subsamples (IM1,4,8,9). The white blood cell count (WBC) was negatively associated with positive affect and self-realisation, but not life satisfaction in the study by Fancourt and Steptoe (2020). Finally, one study looked at matrix metalloproteinase (MMP)-9, a collagen-degrading enzyme that is up-regulated in inflammation (Marteinsdottir et al., 2016). The negative relation with quality of life did not reach significance after adjusting for medical conditions and cardiovascular risk factors.

Summary

To summarize, consistent negative associations between the inflammatory markers CRP and IL-6 and well-being were reported. A meta-analysis on a subset of 16 studies confirmed the small negative association between CRP ($r=-.067$) and IL-6 levels ($r=-.051$) and well-being. The effect was not different for hedonic and eudaimonic well-being measures. Other inflammatory markers such as fibrinogen, and TNF- α were either negatively or non-significantly related to well-being, suggesting a possible negative relation between inflammatory markers and well-being in general. The results might indicate moderating effects of age and sex, as some associations were only found in specific subsamples.

Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
CRP	CRP1	(Step toe et al., 2008)	blood	2,873	50-74	73%	ESM	Yes	Positive affect ^H	Women: OR=0.53
	CRP2	(Deverts et al., 2010)	blood	2544	40.2 (3.6)	52%	Longitudinal	Yes	CES-D: positive affect ^H	b = -.066*, only blacks
	CRP3	(Hamer & Chida, 2011)	blood	797	52.1 (16.8)	54%	Cross-sectional	Yes	SWLS	$\beta = -.24^*$
CRP4		(Carpenter et al., 2012)	blood	92	30.5 (9.2)	51%	Cross-sectional	No	QoL ^H	r = -.170
									Enjoyment Satisfaction ^H	r = -.154
CRP5		(Friedman & Ryff, 2012)	blood	998	58 (0.4)	55%	Cross-sectional	Yes	SWLS ^H	r = -.07*
									PANAS ^H	r = -.03
CRP6		(Step toe et al., 2012)	blood	7795	65.6	55%	Cross-sectional	Yes	PWB: Purpose life ^E	r = -.01
									Positive relations ^E	r = .08*
CRP7		(Rissanen et al., 2013)	blood	305	.		Longitudinal	No	QoL ^H , eudaimonic WB CASP-19 ^E	B = -.24* (women)
									Life satisfaction ^H	r = .043
CRP8		(Nowakowski, 2014)	blood	3005	69.3 (7.9)	52%	Cross-sectional	No	General happiness ^H	OR = .90*, r = -.08
									Relation happiness	OR = .92*, r = -.07

Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
CRP9		(Sin, Graham-Engelard, Ong, et al., 2015)	blood	872	57.9 (11.4)	57%	Cross-sectional	No	Positive affect ^H	$r = -.02$
CRP10		(Sin, Graham-Engelard, & Almeida, 2015)	blood	969	58 (11.5)	57%	Cross-sectional	Yes	Positive affect ^H	$B = .02$
CRP11		(Zilioli, Slatcher, et al., 2015)	blood	985	46.14, 11.7	56%	Cross-sectional	No	Life purpose: Ryff Psych WB ^E	nr
CRP12		(Martensdottir et al., 2016)	blood	944	45-69	50%	Cross-sectional	No	QoL ladder ^H	$\beta = -.09^*$
CRP13		(Sturgeon et al., 2016)	blood	688	53.9 (7.2)	52%	Cross-sectional	No	PANAS ^H WHO-5 ^{H/E}	$r = -.094^*$ $r = -.092^*$
CRP14		(Blevins et al., 2017)	blood	3093	29 (1.8)	51%	Cross-sectional	Yes	Happiness ^H	$r = -.01$
CRP15		(Okely et al., 2017)	blood	5622	62	50%	Longitudinal	Yes	QoL CASP-19 ^H	risk = -2%* , $r = -.08$
CRP16		(Graham-Engelard et al., 2018)	blood	220	46.2 (11.1)	65%	ESM	No	PANAS ^H Moment PA ^H	$\beta = -.011, r = -.07$ $\beta = -.025, r = -.08$
CRP17		(Ironson et al., 2018)	blood	1979	51.9 (19.2)	58%	Cross-sectional	Yes	SWLS ^H Positive affect ^H	$r = -.07^*, ns$ after control depression $r = -.10^*, ns$ after control depression

Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
CRP18	(Lin et al., 2018)	246	blood	41.1 (12.2)	43%	Cross-sectional	Yes	PANAS ^H	r = -.137*	
CRP19	(Ong et al., 2018)	175	blood	53.4 (7.6)	54%	ESM	Yes	PANAS ^H , PA items ^H	r = -.13	
CRP20	(Uchino et al., 2018)	94	blood	56.2 (7.3)		Cross-sectional	No	SWLS ^H	r = -.23* (male) r = -.18 (female)	
CRP21	(Beydoun et al., 2019)	1767/150	blood	48	56%	Longitudinal	No	CES-D: positive affect ^H	$\gamma = .001/-0.005$	
CRP22	(Dos Santos et al., 2019)	233	blood	.	57%	Cross-sectional	No	Positive affect ^H	ns	
CRP23	(Tait et al., 2019)	268	blood	77.4 (6.8)	72%	Cross-sectional	Yes	SF-36 HR-QoL ^H SWLS ^H	$\beta = -.71, r = -.12$	
CRP24	(Deen et al., 2020)	5919	blood	50	29%	Longitudinal	No	Emotion vitality SF-36	risk = .99	
CRP25	(Fancourt & Steptoe, 2020)	8780	blood	>50	55%	Longitudinal	Yes	Positive affect ^H SWLS ^H	B = -.002 B = -.002	
CRP26	(Slavish et al., 2019)	108	saliva	20.5 (1.5)	60%	ESM	Yes	Self-realisation ^E PANAS ^H	B = -.007* $\beta = -.02*$	
IL-6	(Undén et al., 2007)	18-49= 53, 50-64= 47, 65+= 73	blood	-	66%	Cross-sectional	No	Ladder of life ^H	r=0.11, r=-.19, r=-.12	

Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
IL2		(Friedman et al., 2007)	blood	135	74 (7.1)	100%	Cross-sectional	Yes	Ryff's PWB ^E	Positive relations: $\beta = -.18^*$
IL3		(Steptoe et al., 2008)	blood	2,873	50-74	73%	ESM	Yes	Positive affect ^H	$\beta = -.06$
IL4									PA MASQ ^H	$r = -.01$
									Ryff's PWB ^E :	
									growth	$r = -.09^*$
		(Morozink et al., 2010)	blood	1028	58.0 (11.6)	55%	Cross-sectional	No	Autonomy Environment mastery Positive relationships Purpose in life Self-acceptance	$r = .02$ $r = -.01$ $r = .02$ $r = -.07^*$ $r = -.05$
IL5		(Matsunaga et al., 2011)	blood	160	.	52%	Cross-sectional	No	SHS ^H	, ns
IL6									SWLS ^H	$r = -.06^*$
		(Friedman & Ryff, 2012)	blood	998	58 (0.4)	55%	Cross-sectional	Yes	PANAS ^H PWB: Purpose life ^E	$r = -.09^*$ $r = -.07^*$
IL7		(Andreasson et al., 2013)	blood	347	.	100%	Cross-sectional	No	Positive relations ^F CES-D: positive affect ^H	$r = .03$ $r = -.02$

Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
IL8		(Eisenlohr-Moul & Segerstrom, 2013)	blood	119/1082	71.1 54.5	55% 45%	Cross-sectional	No	(Ryff PWB): Autonomy ^E Positive relationships ^E	r = -.03 r = -.18*
IL9		(Miyamoto et al., 2013)	blood	1044 / 382	55.2 54.2	55% 56%	Cross-sectional	No	Positive affect ^H	r = -.01 (US) r = -.02 (Japan)
IL10		(Rissanen et al., 2013)	blood	305	.	.	Longitudinal	No	Life satisfaction ^H	r = .038
IL11		(Sin, Graham-Engeland, Ong, et al., 2015)	blood	872	57.9 (11.4)	57%	Cross-sectional	No	Positive affect ^H	r = -.07*
IL12		(Sin, Graham-Engeland, & Almeida, 2015)	blood	969	58 (11.5)	57%	Cross-sectional	Yes	Positive affect ^H	B = -.02
IL13		(Stellar et al., 2015)	blood	94/119	.	66%/70%	Cross-sectional	No	PANAS ^H , PA items ^H	B = -.30*
IL14		(Zilioli, Slatcher, et al., 2015)	blood	985	46.14, 11.7	56%	Cross-sectional	No	Life purpose: Ryff Psych WB ^E	nr
IL15		(Martensdottir et al., 2016)	blood	944	45-69	50%	Cross-sectional	No	QoL ladder ^H	β = -.38*
IL16		(Sturgeon et al., 2016)	blood	688	53.9 (7.2)	52%	Cross-sectional	No	PANAS ^H WHO-5 ^{H/E}	r = -.091* r = -.159*
IL17		(Graham-Engeland et al., 2018)	blood	220	46.2 (11.1)	65%	ESM	No	PANAS ^H Moment PA ^H	β = .002, r = -.04 β = -.001, r = -.06

Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
IL18		(Ong et al., 2018)	blood	175	53.4 (7.6)	54%	ESM	Yes	Moment PA ^H	$\beta = -.025, r = -.03$
IL19		(Uchino et al., 2018)	blood	94	56.2 (7.3)		Cross-sectional	No	SWLS ^H	$r = -.32^*$ (male) $r = .01$ (female)
IL20		(Beydoun et al., 2019)	blood	1767/150	48	56%	Longitudinal	No	CES-D: positive affect ^H	$\gamma = -.006/.002$
IL21		(Dos Santos et al., 2019)	blood	233	.	57%	Cross-sectional	No	Positive affect ^H	ns
IL22		(Tait et al., 2019)	blood	268	77.4 (6.8)	72%	Cross-sectional	Yes	SF-36 HR-QoL ^H SWLS ^H	$\beta = -.87, r = -.12$
IL23		(Toledo et al., 2019)	blood	11	41.6 (11.2)	100%	Cross-sectional	No	Mood items ^H	$r = .06$
IL24		(Deen et al., 2020)	blood	5919	50	29%	Longitudinal	No	Emotion vitality SF36	risk = .93*
IL25		(Slavish et al., 2019)	saliva	108	20.5 (1.5)	60%	ESM	Yes	PANAS ^H	$\beta = -.03$
F1		(Steptoe et al., 2005)	blood	228	45-59	46%	ESM	Yes	Happiness (1-5) ^H	ns
F2		(Hamer & Chida, 2011)	blood	797	52.1 (16.8)	54%	Cross-sectional	Yes	SWLS ^H	$\beta = -.24^*$
F3		(Steptoe et al., 2012)	blood	7795	65.6	55%	Cross-sectional	Yes	QoL ^H eudaimonic WB CASP-19 ^E	B = -.02* (women)
F4		(Sin, Graham-Engeland, & Almeida, 2015)	blood	969	58 (11.5)	57%	Cross-sectional	Yes	Positive affect ^H	B = .01

Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
	F5	(Okely et al., 2017)	blood	5622	62	50%	Longitudinal	Yes	QoL CASP-19 ^H	nr
	F6	(Ong et al., 2018)	blood	175	53.4 (7.6)	54%	ESM	Yes	PANAS ^H , PA items ^H	r = -.10
	F7	(Fancourt & Steptoe, 2020)	blood	8780	>50	55%	Longitudinal	Yes	Positive affect ^H SWLS ^H Self-realisation ^E	B = .001 B = .002 B = -.008*
TNF-α	TNF1	(Undén et al., 2007)	blood	18-49= 53, 50-64= 47, 65+= 73	-	66%	Cross-sectional	No	Ladder of life ^H	r = -.10, r = .08, r = .30*
	TNF2	(Matsunaga et al., 2011)	blood	160	.	52%	Cross-sectional	No	SHS ^H	, ns
	TNF3	(Rissanen et al., 2013)	blood	305	.		Longitudinal	No	Life satisfaction ^H	adiponectin: .139, 0.043
	TNF4	(Dos Santos et al., 2019)	blood	233	.	57%	Cross-sectional	No	Positive affect ^H	ns
	TNF5	(Tait et al., 2019)	blood	268	77.4 (6.8)	72%	Cross-sectional	Yes	SF-36 HR-QoL ^H SWLS ^H	β = .04
Composite interleukins	IM1	(Zilioli, Slatcher, et al., 2015)	blood	985	46.14, 11.7	56%	Cross-sectional	No	Life purpose: Ryff Psych WB ^E	r = -.07*
	IM2	(Graham-Engeland et al., 2018)	blood	220	46.2 (11.1)	65%	ESM	No	PANAS ^H Moment PA ^H	β = -.037 β = .001
	IM3	(Tait et al., 2019)	blood	268	77.4 (6.8)	72%	Cross-sectional	Yes	SF-36 HR-QoL ^H SWLS ^H	β = -.30,



Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
IFN-γ	IM4	(Matsunaga et al., 2011)	blood	160	.	52%	Cross-sectional	No	SHS ^H	r = -.23*
IL-10	IM5	(Beydoun et al., 2019)	blood	1767/150	48	56%	Longitudinal	No	CES-D: positive affect ^H	0.01
IL-12	IM6	(Dos Santos et al., 2019)	blood	233	.	57%	Cross-sectional	No	Positive affect ^H	ns
IL-1β	IM7	(Beydoun et al., 2019)	blood	1767/150	48	56%	Longitudinal	No	CES-D: positive affect ^H	0.04
IL-1β	IM8	(Undén et al., 2007)	blood	18-49= 53, 50-64= 47, 65+= 73	-	66%	Cross-sectional	No	Ladder of life ^H	r = -.02, r = -.06, r = .30*
IL-1ra	IM9	(Undén et al., 2007)	blood	18-49= 53, 50-64= 47, 65+= 73	-	66%	Cross-sectional	No	Ladder of life ^H	r = .04, r = -.38*, r = .15
IL-1β, IL-1ra, sIL-1rII, sIL-2r, IL-6	IM10	(Andreasson et al., 2013)	blood	347	.	100%	Cross-sectional	No	CES-D: positive affect ^H	r = .07, -.08, -.05, .05
White blood cells	IM11	(Fancourt & Steptoe, 2020)	blood	8780	>50	55%	Longitudinal	Yes	PA ^H SWLS ^H Self-realisation ^F	B = -.034* B = -.005 B = -.044*

Table 3.5. Characteristics and results of the inflammatory marker studies.

Immune marker	No	Study	Immune sample	Sample	Age M (SD)	% female	Design	Control NA	WB measure ^{H/E}	Result
(MMP)-9	IM12	(Martensdottir et al., 2016)	blood	944	45-69	50%	Cross-sectional	No	QoL ladder ^H	$\beta = -1.05$

Note: Bold numbered studies are included in the meta-analyses of CRP and IL-6. * are significant effects, nr is not reported, ns is not significant + no effect reported. CES-D= Center for Epidemiological Studies Depression Scale, QoL= quality of life, PANAS = Positive and Negative Affect Schedule, SWLS= satisfaction with life scale, PA= positive affect, WB= well-being, SHS= subjective happiness scale, PWB= psychological well-being, WHO-5= World Health Organization well-being index, WHOQOL = World Health Organization Quality of Life Instruments, Ryff PWB= Ryff Scales of Psychological Well-Being, CASP-19= Control, Autonomy, Self-Realization and Pleasure measure. ^{H/E}Superscript H indicates a hedonic well-being measure, E indicates a eudaimonic well-being measure and H/E indicates a measure that includes both hedonic and eudaimonic concepts.

Microbiome

Table 3.6 shows the details and results of the 4 studies on measures of the microbiome related to well-being.

Description of study designs and samples

In the four studies, the number of participants ranged widely from 3 to 1054 adults. The age of the samples differed as well, ranging from adolescents to 30 year olds and average ages of around 50 (see Table 3.6). All studies were cross-sectional studies, correlating measures of the gut microbiome to the well-being measures.

Microbiome measures

All four studies used a fecal sample to extract bacterial DNA. Bacterial DNA can be studied on different taxonomic classification levels, including the phylum level, and genus or species level. For example, the phylum *Bacteroidetes* consist of a variety of bacterial genera, such as the *Prevotella* and *Parabacteroides* bacteria. Similarly, the phylum *Firmicutes* includes the genera *Roseburia*, *Coprococcus* and *Flavonifractor* and many other genera (Ciccarelli et al., 2006; Wakita et al., 2018).

Well-being measures

The well-being measures used in the four studies were all hedonic measure, i.e., a happiness rating from 1-10, the PANAS, Profile of Mood States (POMS) and the RAND-36 health-related quality of life survey including an emotional well-being measure.

The association with well-being

Li et al. (2016) performed a closed experimental (105 days) in a lunar like environment on three healthy adults with minimal interference on gut microbiota by other factors. Every two weeks, stool samples and answers on the POMS questionnaire were collected, resulting in a total of 17 samples. The results were reported on genera level (i.e., a taxonomic rank in the biological classification of bacteria). The relative abundance (percent composition relative to all bacteria) of the genera *Roseburia*, *Phascolarctobacterium*, *Lachnospira*, and *Prevotella* bacteria showed consistent positive correlations with positive mood, whereas *Faecalibacterium*, *Parabacteroides*, *Bacteroides*, and *Anaerostipes* were negatively correlated with positive mood. The *Prevotella*, *Parabacteroides*, and *Bacteroides* genera are part of the *Bacteroides* phylum, whereas the other genera are part of the *Firmicutes* phylum.

In a larger sample of adults, Valles-Colomer et al. (2019) reported consistent positive associations between the relative abundance of the genera *Faecalibacterium* and *Coprococcus* bacteria, both from the *Firmicutes* phylum, and emotional well-being.

In children and adolescents, Michels et al. (2019) reported a positive association between the relative abundance of the phylum *Firmicutes* and happiness. With respect to genera levels, this association was mainly in the genera *Lachnospiraceae* and *Ruminococcaceae*. The abundance of the phylum Bacteroidetes (mainly the order *Bacteroidales*) and *Euryarchaeota* was negatively associated with happiness. Furthermore, a higher *Firmicutes/Bacteroidetes* ratio and a higher Simpson index (i.e., more diversity) was related to higher happiness.

Finally, Lee et al. (2020) divided participants in two groups for who respectively the *Bacteroides* or *Prevotella* were more abundant. In the *Prevotella*-dominant group, a greater diversity of the gut microbiome (*Shannon index*) was related to higher positive affect. Furthermore, in the total sample, the abundance of the genera *Agathobaculum* (*Firmicutes* phylum) and *Collinsella* (*Actinobacteria* phylum) were negatively related to positive affect, whereas a greater abundance of PAC001043_g (a novel genus in the *Lachnospiraceae* family, *Firmicutes* phylum) was associated with higher positive affect.

Summary

To summarize, although all four studies significantly related well-being to certain bacteria or diversity of the microbiome, more research in larger samples is needed to replicate the findings and have a clear picture of the association between the microbiome and well-being. With respect to genera, a consistent result based on three studies was the positive relation between the abundance of the genera *Lachnospiraceae* and well-being. Furthermore, two studies reported that measures of gut microbiome diversity were related to higher well-being.

Table 3.6. Characteristics and results of the microbiome studies.

No	Study	Microbiome sample	Sample N	Age M (SD)	% female	Design	Control NA	Well-being measure ^{H/E}	Result
M1	(Li et al., 2016)	Bacterial DNA from fecal samples	3	~ 30	.67	Cross-sectional	No	POMS ^H	+ Roseburia, Phascolarctobacterium, Lachnospira, and Prevotella, - Faecalibacterium, Parabacteroides, Bacteroides, and Anaerostipes
M2	(Michels et al., 2019)	Bacterial DNA from fecal samples	93	8-16		Cross-sectional	No	Happiness ^H	+ Cyanobacteria ($\rho = 0.21$), Firmicutes ($\rho = 0.31$), Firmicutes/Bacteroidetes ratio ($\rho = 0.22$) and Simpson diversity ($\rho = 0.21$). - Euryarchaeota ($\rho = -0.24$), Proteobacteria ($\rho = -0.22$),
M3	(Valles-Colomer et al., 2019)	Bacterial DNA from fecal samples	1054 /1070	50.9 /57.9	.55 / .58	Cross-sectional	No	RAND-36 QoL ^H	+ Faecalibacterium ($b = 0.14$) and Coprococcus ($b = 0.10$)
M4	(Lee et al., 2020)	Bacterial DNA from fecal samples	83	48.9 (13.2)	0.56	Cross-sectional	No	PANAS ^H	+ Shannon diversity ($b = 0.31$), - Agathobaculum and Collinsella ($b = -0.05$), + PAC001043_g (Lachnospiraceae) ($b = 0.01$)

Note: POMS= Profile of Mood States, QoL= quality of life, PANAS = Positive and Negative Affect Schedule. ^{H/E}Superscript H indicates a hedonic well-being measure, whereas E indicates a eudaimonic well-being measure.

DISCUSSION

To understand observed differences in well-being between people in more detail, and in order to enhance the development of future mental health prevention and intervention strategies, it is essential to identify physiological markers related to well-being. Therefore, the goal of this systematic review was to bring together the available literature on physiological markers related to well-being in four categories, namely neurotransmitters, hormones, inflammatory markers, and the microbiome. The systematic review resulted in respectively 48 and 36 studies on the association of hormones or inflammatory markers and well-being, whereas only 9 and 4 studies examined the relation between neurotransmitters or the microbiome and well-being. We first summarize and discuss the findings per category. Next, we propose directions for future research based on our current results.

Neurotransmitters

Nine studies investigated the association between levels of different neurotransmitters and well-being, mainly focusing on (nor)epinephrine and serotonin. In contrast to our expectations, we did not find studies that related dopamine levels to well-being and only a few studies related to (nor)epinephrine and serotonin. Levels of epinephrine and norepinephrine were mostly unrelated to measures of psychological well-being and positive affect. Only in a sample of older women (mean age=74), there was a moderate positive correlation between (nor)epinephrine and subscales of Ryff's psychological well-being scale. More research on the moderating effects of well-being measure, age and sex is needed to confirm these findings.

Serotonin levels were more consistently positively related to the hedonic well-being measure positive affect, but the effect sizes were small. The relation between serotonin and other measures of hedonic well-being, e.g., life satisfaction, or eudaimonic well-being has not been investigated so far. In studies with larger sample sizes the moderation by age and sex should also be investigated.

The results should be interpreted in light of the difficulties of measuring neurotransmitters levels in humans due to their short term effects, low levels in the brain, and their mixture with other molecules (Niyonambaza et al., 2019). Furthermore there is an ongoing discussion whether urine or blood plasma measures of neurotransmitters reflect brain activity (Ailts et al., 2007; Marc et al., 2011). The suggested positive correlation between neurotransmitter levels in the brain and the rest of the body, i.e., urine or blood (Marc et al., 2011) does

suggest that the detected association between serotonin in the blood plasma and well-being indicates the involvement of serotonin resulting from brain activity in well-being.

Applying positron emission tomography (PET) and labeling neurotransmitters can help to identify the regional specificity in the brain of neurotransmitters associated with well-being. For example, in the field of anxiety, it has been found that neurotransmission in social anxiety disorder is characterized by an overactive serotonin system in the amygdala, caudate nucleus, putamen, hippocampus and anterior cingulate cortex (Frick et al., 2015). Similarly, PET studies can directly give insight in the association of well-being and functioning of neurotransmitters in specific brain regions.

Furthermore, there is a lot of development in new ways to assess serotonin in different tissues and with new techniques, such as real-time continuous monitoring (Si & Song, 2018; Su et al., 2020). This might enable researchers to assess the level of different neurotransmitters more easily in the future and replicate the possible involvement of serotonin in complex traits like well-being.

Hormones

The association of different hormones with well-being has been investigated more often compared to the neurotransmitter research, as hormones are currently easier to assess via, for example, saliva samples. Of the 48 hormone studies, 39 studies included one or more measures of cortisol. The meta-analysis on the association between the level of momentary cortisol and well-being resulted in a small negative effect, $r=-.06$, indicating that lower cortisol levels are related to higher levels of well-being. In addition, although a meta-analysis could not be performed, another relatively consistent finding was the association of a faster decrease of cortisol levels over the day (i.e., steeper slope) with higher well-being. The results of the relation between the cortisol awakening response and total cortisol secretion and well-being were less consistent. However, as reported by Smyth et al. (2015), the timing of cortisol sampling is important. In their study, only when the participants strictly adhered to the sampling protocol, lower cortisol awakening response was associated with higher well-being. Furthermore, as indicated by Booij et al. (2016), large individual differences in the relation between different measures of cortisol and well-being were present in their sample. This makes it difficult, if not impossible, to find consistent associations when averaging the relation within a large sample. In an earlier review, the inconsistency of findings regarding hormones and positive affects is also suggested to be due to the variability in samples, age, measures of well-being and timing (Dockray &

Stephoe, 2010). Furthermore, as cortisol is “the stress hormone” and there is a clear negative association between stress and well-being (Schiffman et al., 2009), stress might mediate the relation between diurnal cortisol and well-being and controlling for stress is needed in future studies.

Cortisol can be sampled in saliva, urine, or hair and the levels in the different samples reflect different processes. Whereas salivary and urinary cortisol reflect the real-time levels of cortisol, hair cortisol reflects the cortisol exposure over longer periods of time and is related to chronic stress (Russell et al., 2012). Cortisol measured in cortisol and urine versus hair is therefore not directly comparable. We identified two studies using a hair sample of cortisol and only one (Smyth et al., 2016) reported a small negative association with well-being in elderly participants. Research in larger samples is needed to examine the relation of hair cortisol (i.e., long-term cortisol exposure) and well-being.

To summarize, most measures of cortisol were not consistently related to well-being and individual differences could play a large role in the association. However, the small associations between momentary levels of cortisol and the slope of the cortisol decrease over the day and well-being were consistent. This effect was not different for hedonic and eudaimonic well-being. In future research, researchers need to be stricter on the timing of the cortisol sample and avoid variability, e.g., by using tube caps with time recording and strict instructions to the participants. In addition, focusing on the individual patterns instead of the average cortisol response or level across individuals is necessary to understand the relation between cortisol and well-being in more detail.

The association of other hormones with well-being were investigated in only a few studies and most of these studies did not report a (consistent) significant association, limiting the ability to draw conclusions. DHEA-S and testosterone were not related to different measures of well-being in respectively 5 of the 6 studies and 3 of the 4 studies. This might reflect a power issue, as most sample sizes of the discussed studies are small ($n < 100$) or the absence of a detectable association between the levels of these hormones and well-being. More promising is the positive relation between vitamin-D in the blood and well-being. However, since this is based on only two studies, more research is needed to confirm this association.

Whereas oxytocin has mainly been investigated in relation to positive social behaviour, oxytocin is also suggested to play a role in different behaviors and traits related to well-being, such as emotional processing, trust and depressive behaviors (IsHak et al., 2011). However, surprisingly, the direct relation between oxytocin and well-being has only been investigated in a single study (Barraza et

al., 2013). In a small sample ($n_{\text{oxytocin}}=21$) of older adults ($M_{\text{age}}=80$) no association could be reported. Future direct and powerful studies should shed more light on the hypothesized association between well-being and oxytocin.

Finally, most studies on the different hormone levels included relatively older samples (average age: 53.1, and in 6 of the 14 studies the average age is above 65). Since hormone production and levels are affected by age (Sternbach, 1998; Van Cauter et al., 1996), more research is needed to study the effects of age on the association between hormones and well-being in age diverse samples.

Inflammatory markers

The results of the 36 studies on the inflammatory markers and well-being showed more consistent results compared to the previous categories. CRP was negatively associated with well-being in 14 of the 26 studies and IL-6 was negatively associated with well-being in 11 of the 25 studies, whereas the other studies did not find a significant effect. Additionally, both CRP ($r=-.07$) and IL-6 ($r=-.05$) showed small but significant negative relations with well-being in a meta-analysis. Based on the available studies, the well-being measure was not a significant moderator, suggesting that the inflammatory markers have an influence on overall well-being and not on specific aspects of hedonic or eudaimonic well-being.

Besides CRP and IL-6, fibrinogen was negatively related to well-being in three of the seven studies, and other inflammatory markers such as other interleukins or white blood cell count were either negatively related with well-being or non-significantly. Based on these results, a consistent pattern of negative associations between different inflammatory markers and well-being emerges. Lower levels of baseline inflammatory markers, i.e., reflecting less activation of the immune system, is linked to higher well-being. The non-significant findings can either be due to weaker designs or smaller samples, leading to lower power.

Similar to the hormone studies, the reviewed inflammatory marker studies included relatively older samples. The average age of the samples is 52.6 ($SD=13.7$) and in 17 of the 36 studies the average age is above 50, while only two studies the average age is below 30 years. As some studies suggested moderation by age (Fancourt & Steptoe, 2020), more research is needed into the effects of age on the association between inflammation and well-being in younger and age diverse samples.

A next step in the research on inflammation and well-being is the direction of effect. The direction of effect between inflammation and mental ill-being, i.e., depression, appears to be bidirectional. Patients with inflammatory

diseases have a higher likelihood to develop major depressive disorder and often individuals with major depression show increased inflammatory markers, and the levels decrease with the recovery from depression (Amodeo et al., 2018a; Dahl et al., 2014). As well-being and mental ill-being are related but have independent effects on health and other outcomes, the direction of effect between inflammation and well-being should be investigated. Some longitudinal studies in this review showed significant associations between inflammatory markers and well-being a few years later, indicating a possible causal effect from inflammation to well-being.

Microbiome

Lastly, the composition and diversity of the gut microbiome in relation to well-being is a relatively new and fast developing research field. We could only identify four studies that related the gut microbiome diversity or composition to well-being. All studies reported significant results with the abundance of different bacteria or the diversity of the microbiome associated with higher hedonic well-being, i.e., positive affect or quality of life, indicating that it is likely that the microbiome plays a role in well-being. However, more research is needed to be confident about the specific associations between the microbiome composition and well-being, because one study only included 3 participants, different effects of different bacteria have been studied, and there might be a publication bias in that only studies with significant effects are published in this upcoming field.

Microbiome research is further complicated by the possible effects of variation in dietary habits and geography on the composition of the gut microbiota. Ideally, when investigating the microbiome, participants should be in a stable environment, keep a constant diet and living habit, and maintain a certain activity level. As this can be difficult in daily life, Li et al. (2016) minimized the possible confounding by other factors by investigating three participants that stayed 105 days in a closed human life support system with minimal interference, i.e., a laboratory that simulates a lunar-like environment. This study gave the first insights in the unconfounded relation between the gut microbiome and well-being. In future studies outside such a system, the possible confounding by diet, environment and activity should be taken into account.

Another point of discussion is the current sampling methods for gut microbiome. Tang et al. (2020) reviewed the methods and concluded that more precise sampling methods for the composition and diversity of the gut microbiome are needed. Current measures from fecal samples (and other non-

invasive methods) are just a proxy for the composition of the gut microbiome. More precise sampling methods are needed to increase the reliability of the microbiome research and to replicate findings.

Future directions

In different categories consistent relationships between physiological markers and well-being (e.g., the hormone cortisol, and inflammatory markers CRP and IL-6) were reported. With respect to these effects, further research should be conducted to investigate the direction of the effect or possible moderators or confounders on the effect, as suggested above. In other categories, such as neurotransmitters and the microbiome, additional research is needed to get a complete picture of the role of these physiological markers in relation to well-being. Besides further research into the association of physiological markers related to well-being in the single categories, promising fields for future research include the integration or combination of multiple physiological categories in relation to well-being, the direction of causality, and innovative ways to measure and analyze physiological data.

Integration

A first observation based on the reviewed studies is that the findings of the different studies are diverse and not connected. Most studies investigated the relation between one physiological marker and well-being. Similar to the criticized candidate gene literature (i.e., investigating the association of a single or a few candidate genes with well-being, depression or other genetically complex phenotypes) in which results are mixed and do not seem to replicate (Border et al., 2019; Johnson et al., 2017; van de Weijer, Pelt, de Vries, Baselmans, et al., 2022), the pick-and-choose strategy for physiological markers might have led to similar inconsistent results. Where the genome-wide association approach has been introduced to systematically search for genetic variants for complex traits, a similar data-driven approach should be used for future research into the physiology of well-being. Combining multiple physiological markers across the different categories, aka an multi-omics approach, could result in a more complete picture of the physiology underlying well-being.

Combining multiple physiological markers across the different categories could result in a more complete picture of the physiology underlying well-being. An example of combining data is multi-omics approaches, that combine and integrate multiple types of omics data, such as genomics, proteomics, transcriptomics, epigenomics, metabolomics, and microbiomics (Hasin et al., 2017). All the different processes influence each other and by combining these

data, researchers can get a broader picture and a more comprehensive insight in the physiological markers and human biology underlying traits or diseases. To learn more about multi-omics, Wörheide et al. (2021) and Subramanian et al. (2020) provide helpful overviews and different applications of this approach within the domain of mental ill-being, e.g., for aggressive behavior and psychiatric disorders, can be found (Hagenbeek et al., 2021; Korologou-Linden et al., 2021).

To understand the physiology underlying well-being, multi-omics approaches can also be applied to the combination of hormones, neurotransmitters, inflammatory markers, and the microbiome. For example, the stress hormone cortisol, and inflammation, the reaction of the immune system, are strongly linked (e.g., Adam et al., 2017; Morey et al., 2015). Furthermore, recent research reported an influence of the gut microbiome on mental health via the level of neurotransmitters (Liu et al., 2020). The gut microbiome can alter the levels of different neurotransmitter and this alteration of neurotransmitters influences mental health. Similarly, an interaction between three categories, namely the gut microbiome, the stress response, including cortisol, and immune system is suggested to play a role in depression, and anxiety (Peirce & Alviña, 2019). As we have shown that cortisol, different immune factors and possibly the microbiome are associated with well-being, investigating these factors at the same time might lead to a clearer picture about the relation between the human physiology and well-being. To conclude, for a complete overview of the physiological markers underlying well-being, combining measures of multiple physiological markers into a large well-being study is needed.

Direction of effect

As we reported consistent associations of (diurnal) cortisol and different inflammatory markers with well-being, a next step is to investigate the direction of the effect between the physiological marker and well-being. Can the association be explained by a causal relationship from the physiological marker to well-being, vice versa, in both directions or is the association explained by another factor? If the direction of causation is known, this can help to design interventions to enhance well-being or prevent poorer mental health. The reported associations in this review are only correlational and it is impossible to determine causality in cross-sectional observational studies. Causality analyses, such as longitudinal (intervention) studies and Mendelian Randomization can enable future researchers to investigate the direction of causality in this field.

Longitudinal studies in which either well-being or the level of physiological factors, such as hormones or neurotransmitters are observed over time, or manipulated (e.g., by triggering their response or substitution) can allow for causal interferences to be made. For example, in the experimental design of Barraza et al. (2013) half of the participants received oxytocin for 10 days and the other half a placebo. The levels of well-being were compared before and after the treatment. There was no effect of the treatment on well-being in both groups. However, if an increase in well-being the oxytocin group, but not the placebo group had been reported, this would be evidence for a causal relation between oxytocin and well-being. Similarly, the other way around, interventions that increase well-being can be used to investigate if well-being has a causal effect on various physiological factors. For example, a meta-analysis across 20 randomized control trials (RCT) reported that mindfulness meditation is associated with immune system processes involved in inflammation, and biological aging, i.e., meditation resulted in a decrease in CRP levels (Black & Slavich, 2016). Similarly, a recent meta-analysis on the effects of meditation interventions on cortisol levels reported that such interventions resulted in reduced cortisol levels, but only when assessed in blood compared to saliva and in people at risk for somatic illnesses (Koncz et al., 2021). As mindfulness and meditation have also been linked to increased well-being, these findings could indicate a causal link between well-being and different physiological factors. Future randomized control studies specific to well-being interventions or physiological manipulations are needed to confirm these hypotheses and investigate the direction of causation.

Another approach to study the direction of causation, that does not need longitudinal data or any intervention, is Mendelian Randomization (MR), which uses genetic variants to test the causal relationships between an exposure variable and outcome. MR relies on the natural, random assortment of genetic variants resulting in a random distribution of genetic variants in a population (Smith & Ebrahim, 2003). In short, if the assumptions are met and a genetic variant is associated both with the exposure (e.g., inflammatory marker levels) and the outcome (e.g., well-being), this would provide supportive evidence for a causal effect of the immune response on well-being. To learn more about Mendelian Randomization, see Gagliano Taliun and Evans, (2021) and Smith and Ebrahim, (2003) for an overview and guidelines. Different applications of this approach within the domain of mental ill-being with physiological factors can be found as well (for example Kappelmann et al., 2021; Perry et al., 2021).

Finally, results of animal studies can indicate possible causal effects of well-being and physiological factors. Although there are limitations in generalizing

results from animal studies to human well-being, these results can be the starting point for research in humans and provide clues about the mechanisms and causality. Animal research has been helpful in health-related research areas, but is rare in the well-being field, largely because of the subjective nature of well-being. In the field of depression and stress, animal research on physiological factors has reported different causal mechanisms. For example, in rats, a microbiome transplantation from severely depressed patients to the rats induced depression-like behaviors, like anhedonia and anxiety-like behaviours (Kelly et al., 2016). Similarly, rodents that experienced more induced stress showed higher levels of inflammatory markers (Powell et al., 2013). These results could indicate a possible causal effect between well-being and different physiological factors and future animal research to well-being can be used to investigate causality and confirm these hypotheses.

Innovations and data-driven research

Related to innovations in the methods to measure physiological markers, e.g., real-time continuous monitoring (Si & Song, 2018; Su et al., 2020), there are also rapid developments in the approaches to collect and analyse (big) data. Using the developments in the artificial intelligence and machine learning fields, patterns can be detected in physiological data that we would not predict. These approaches enable us to focus more on data-driven research instead of hypothesis driven research (Scheel et al., 2020). For example, using a data driving approach, and applying machine learning, Poletti et al. (2021) could distinguish between unipolar and bipolar depression based on the plasma levels of 54 cytokines, chemokines and growth factors (i.e., the immune-inflammatory signature) of the participants. For more information about artificial intelligence and machine learning, see overview articles (Jordan & Mitchell, 2015; LeCun et al., 2015). Different applications of this approach within the domain of mental ill-being with physiological factors can be found as well (for example Poletti et al., 2021; Wardenaar et al., 2021).

Limitations

The low number of studies in some categories of this systematic review limits our ability to draw more firm conclusions about the association between the physiological factors and well-being and this highlights the need for more studies investigating the physiology of well-being. Furthermore, the low number of studies could indicate a possible publication bias, especially in the newer fields, if studies with non-significant findings are not published.

Another limitation, touched upon briefly in the results of the different categories, is that only a limited number of studies controlled for negative affect and depressive symptoms when investigating physiological factors in relation to well-being. Since well-being and ill-being are related (Baselmans et al., 2018; Okbay et al., 2016), controlling for ill-being when investigating the relation between physiological factors and well-being can help to disentangle the independent associations of physiological factors with well-being and ill-being.

A similar approach of controlling for confounding effects could be interesting for hedonic and eudaimonic well-being measures. Although hedonic and eudaimonic well-being measures are strongly correlated, they also capture slightly different parts of well-being. As proposed by Ryff et al. (2004) hedonic and eudaimonic well-being could have partly different neurobiological and physiological correlates. To learn more about the distinction between hedonic and eudaimonic well-being, future studies should include both measures and when examining the effects of hedonic well-being control for eudaimonic well-being and vice versa.

A quantitative meta-analysis on the association between cortisol levels, two inflammatory markers (CRP and IL-6), and well-being was possible due to a substantial number of homogenous study designs and reported effects. We only included studies that reported bivariate correlations, not including standardized regression coefficients and other effect sizes, since in many regression different covariates are added, leading to biased estimates when including the partial correlations between the markers and well-being. As a result, for the other categories and factors, a meta-analysis was not possible, since the studies were too heterogeneous in study methods, analysis techniques, and reported statistics. Furthermore, even though we performed a detailed literature search according to the PRISMA guidelines, it is possible we missed some papers.

Finally, in all included studies, well-being is measured with self-report measures. While self-report has its limitations, i.e., recall and reporting biases, well-being is conceptually a subjective experience and currently it is not possible to reliably measure well-being objectively.

Conclusion

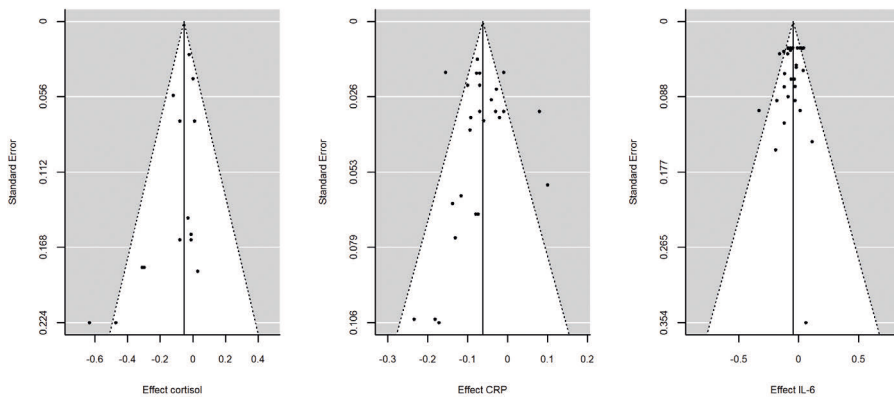
This systematic review of 91 studies on the association between physiological markers across four categories and well-being showed that more research is needed to understand the physiological markers underlying well-being in certain categories. Relatively robust negative, but small associations between

cortisol and inflammatory markers such as CRP and IL-6, and well-being were reported, indicating that lower cortisol levels and lower response of the immune system are associated with higher levels of well-being. In the meta-analyses, these associations were not moderated by the type of well-being measure, indicating an association with overall well-being.

Future directions include innovative ways to measure the physiological markers and analyze the data, to investigate multiple physiological markers across the different categories at the same time in relation to well-being, and to investigate the direction of causality between the physiological markers and well-being.

Supplementary Material Chapter 3

3



Supplementary Figure S3.1. Funnel plots of the meta-analyses on the association between respectively cortisol, CRP, and IL-6.



The background is an abstract watercolor-style illustration. It features soft, blended washes of color. The top half is dominated by various shades of green, from light lime to a slightly darker, muted green. The middle and bottom sections transition into warm tones of yellow and orange, with some areas appearing more saturated and others more faded. The overall texture is soft and painterly, with visible brushstrokes and color gradients. The text is centered in the middle of the page.

Part II:

Well-being and Related Traits



Chapter 4.

Genetic influences on the covariance and genetic correlations in a bivariate twin model: an application to well-being

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ABSTRACT

The distinction between genetic influences on the covariance (or bivariate heritability) and genetic correlations in bivariate twin models is often not well-understood or only one is reported while the results show distinctive information about the relation between traits. We applied bivariate twin models in a large sample of adolescent twins, to disentangle the association between well-being (WB) and four complex traits (optimism, anxious-depressed symptoms (AD), aggressive behaviour (AGG), and educational achievement (EA)). Optimism and AD showed respectively a strong positive and negative phenotypic correlation with WB, the negative correlation of WB and AGG is lower and the correlation with EA is nearly zero. All four traits showed a large genetic contribution to the covariance with well-being. The genetic correlations of well-being with optimism and AD are strong and smaller for AGG and EA. We used the results of the models to explain what information is retrieved based on the bivariate heritability versus the genetic correlations and the (clinical) implications.

Keywords: bivariate twin model, bivariate heritability, genetic correlation, well-being, adolescents.

INTRODUCTION

The main goal of behavior genetics research is to understand the causes of individual differences in human traits and behavior. A genetically informative design, such as the classical twin design, can be applied to decompose the observed variance of a trait into genetic and environmental sources of variation using data from reared together monozygotic (MZ) and dizygotic (DZ) twins. The difference in genetic relatedness of MZ twins (who share all genes) and DZ twins (who share on average half of their segregating genes) allows the decomposition of the observed variance in genetic and environmental sources (Boomsma et al., 2002). When investigating the sources of individual variation in a single trait, a univariate twin model is used. The heritability of the trait is estimated by dividing the genetic variance by the total variance, indicating how much of the total variance is accounted for by genetic influences. A meta-analysis of the heritability of more than 17,000 human traits showed an average heritability of 49% for all traits (Polderman et al., 2015). For most traits, the remainder of the variance is explained by non-shared environmental components and measurement error, whereas the influences from shared environmental or dominant genetic effects are usually absent or small.

By extending the univariate model, two or more traits can be included in twin models to understand the causes of covariation between traits (Eaves & Gale, 1974; Martin & Eaves, 1977). In a bivariate (two traits) or multivariate (multiple traits) model, the covariation between two or more traits is decomposed in genetic and environmental components, in addition to the trait specific variance decomposition. The covariance decomposition answers the question how much of the phenotypic correlation between the traits is accounted for by genetic and environmental factors. The proportion of covariance explained by genetic factors is called bivariate heritability.

Additionally, in a bi- or multivariate model, the genetic and environmental correlations between traits can be computed. The genetic correlation reflects the extent to which the genetic factors underlying one trait overlap with the genetic factors that influence the other trait in the model. Similarly, the environmental correlation reflects the overlap of the environmental factors underlying the traits. A genetic (or environmental) correlation of 1 indicates a perfect overlap of the genetic (or environmental) factors, indicating that the factors that influence both traits are identical. In contrast, a correlation of 0 indicates no overlap and thus independent genetic (or environmental) factors for both traits.

For example, applying a bivariate model to well-being and depressive symptoms, Baselmans et al. (2018) found that additive genetic effects explained 46% of the covariance between these traits in adults. This bivariate heritability means that 46% of the phenotypic correlation between well-being and depressive symptoms is accounted for by genetic factors, whereas the remainder is explained by unique environmental factors. In addition, the modelling resulted in strong genetic (-0.60) and environmental (-0.48) correlations. The genetic correlation of -0.60 indicates that more than half of the genetic factors influencing well-being also have an influence on depression. The negative signs indicate that the effect of the genetic factors on the traits is in the opposite direction, so those genetic factors that increase well-being, also decrease depressive symptoms and vice versa. The same applies to the negative environmental correlation. Around half of the environmental factors influencing well-being are shared with and have an opposite effect on depressive symptoms.

Goal of the present study

In behavior genetics studies, often the distinction between the results of the covariance decomposition and the genetic/environmental correlation is either not well-understood or only one of the two is reported while the results show distinctive information about the covariance and overlap between traits. For example, while the influence of genetic factors on the phenotypic correlation can be rather substantial, the genetic correlation can be low, indicating that although genes play an important role in the observed overlap between traits, most of the genetic influences are trait specific. Or the opposite can be observed, that is while there is only a small influence of genetic factors on the covariance, the genetic correlation is substantial. This indicates that the sets of genes that influence each trait are shared to a large extent, but that genes are actually not that important in understanding the association between two traits.

Therefore, in this paper we will explain the difference between the results of the covariance decomposition and genetic and environmental correlations in greater depth. Given our longstanding interest, we will apply the bivariate model to well-being and four other traits known to have a different phenotypic association with well-being in a large sample of adolescent twins. The four traits included are optimism, symptoms of anxiety or depression, aggressive behavior, and educational achievement. We chose these traits based on previous work (summarized below), since we expect different associations of the traits with well-being (i.e. different phenotypic correlations, bivariate heritability estimates and genetic and environmental correlations). These differences (e.g.

high/low bivariate heritability and high/low genetic correlation) have different (clinical) implications and will help clarify the difference between both sets of results of the bivariate twin model.

Well-being is characterized by high levels of positive affect, low levels of negative affect, and a positive subjective evaluation of life satisfaction (Diener et al., 2018). As our well-being measure we include satisfaction with life, i.e. the subjective evaluation of life. Using slight different inclusion criteria, two meta-analyses summarized all studies applying the twin model to well-being and found a meta-analytic heritability of 36% (CI: 34-38%) and 40% (CI: 38-43%) for well-being based on all measures (Bartels, 2015; Nes & Røysamb, 2015) and 32% (CI: 29-35%) for satisfaction with life (Bartels, 2015).

Optimism can be defined as the tendency to expect positive outcomes in the future in any situation and is, like well-being, related to physical and mental health (Rasmussen et al., 2009; Scheier & Carver, 1992, 1993). A large meta-analysis showed strong phenotypic correlations between optimism and the different aspects of well-being in large samples, e.g. the correlations with life satisfaction (N=19,831), quality of life (N=2,824) and happiness (N=5,470) were 0.55, 0.53, and 0.36 respectively (Alarcon et al., 2013). Furthermore, like well-being, individual differences in optimism have been found to be accounted for by genetic influences (around 30%) and non-shared environmental influences (Bates, 2015; Caprara et al., 2009; Mavioğlu et al., 2015; Mosing et al., 2010; Plomin et al., 1992; Yuh et al., 2010). Therefore, we expect a genetic contribution to the strong correlation between well-being and optimism and an overlap in the genetic and environmental factors underlying both traits, resulting in strong genetic and environmental correlations.

Anxious-depressed symptoms refers to the number of anxiety and depression related symptoms experienced. The negative moderate phenotypic association between well-being and these internalizing symptoms is well-established. In a recent study, Baselmans et al. (2018) investigated the contribution of genetic and environmental factors to the relation between well-being and depressive symptoms across the lifespan. In adolescents, a phenotypic correlation of -0.47 in adolescents, a high bivariate heritability (68%) and strong genetic (-0.59) and environmental (-0.32) correlations were found. Given the overlap in sample used for this study we expect similar results, but we included it as comparison to the other bivariate results.

Aggressive behavior can be defined as any threatening, upset, verbally or physically violent behavior (Achenbach & Rescorla, 2001). Meta-analytic heritability estimates of 48-65% have been found for aggression (Burt, 2009; Miles & Carey, 1997). Between well-being and aggression, a moderately negative

correlation (around -0.2) is reported, indicating that happier adolescents display less violent and aggressive behavior (Buelga et al., 2008; Macdonald et al., 2005; Valois et al., 2001). Furthermore, large genetic contributions (72% and 90% in adolescent males and females respectively) to the covariance and moderate genetic correlations (-.38 and -.39) between well-being and aggressive behavior have been found (Bartels et al., 2013). In our sample, we expect a similar genetic contribution to the covariance and overlap in genetic and environmental factors.

Lastly, we included educational achievement or performance, as the literature describes only a slightly positive association with well-being in adolescents (Gilman & Huebner, 2006; Verkuyten & Thijs, 2002). In children and adolescents, differences in educational achievement are highly heritable in primary and secondary education (around 60%) (Bartels et al., 2002; de Zeeuw et al., 2015; Krapohl et al., 2014). Despite the high heritability of educational achievement, we expect a small genetic contribution to the association between well-being and educational achievement, with most of the genetic influences being trait specific. Furthermore, the small phenotypic correlation suggests low genetic and environmental correlations with well-being.

METHODS

Participants

Participants are registered at the Netherlands Twin Register (NTR), established by the Department of Biological Psychology, Vrije Universiteit Amsterdam (Ligthart et al., 2019; Van Beijsterveldt et al., 2013). The NTR sample is a population-wide, non-clinical sample, including children, adolescents, and adults. Young twins are registered in the Young Netherlands Twin Register (YNTR) at birth by their parents with the help of a commercial ‘birth felicitation’ service and the support of the Dutch Society of Parents of Multiples (Nederlandse Vereniging van Ouders van Meerlingen: NVOM; <https://www.nvom.nl>) (Ligthart et al., 2019; Van Beijsterveldt et al., 2013). In childhood, the parents were asked to complete questionnaires about their children. From the age of 14, the twins and their siblings were invited, after parental consent, to complete questionnaires themselves. The current study used data of the Dutch Health and Behavior Questionnaire (DHBQ), a self-report instrument which assesses health, lifestyle, and behaviour when twins are 14 and 16 years old (Bartels et al., 2011; Van Beijsterveldt et al., 2013).

We used DHBQ data of 14-year-old same-sex twins. To increase the sample size, for twins without data in the 14-year sample, we included data collected at age 16, if available. The final sample included data of 9648 twins with an average age of 15.18 years old ($SD=1.13$), 42.3% of the participants were male. The sample included 5242 MZ twins and 4442 DZ twins, from complete or incomplete same sex twin pairs. For the bivariate models, subsets of the sample were used with data on well-being and optimism ($N=8697$; $MZ=4696$, $DZ=4001$), well-being and anxious/depressed symptoms ($N=8363$; $MZ=4541$, $DZ=3822$), well-being and aggressive behavior ($N=8351$; $MZ=4536$, $DZ=3816$) and well-being and educational achievement ($N=8076$; $MZ=4383$, $DZ=3693$).

Zygosity for same-sex twin pairs was determined by DNA analysis (27%) or by previously collected parental report on physical similarity and the frequency of confusion of the twins by parents, other family members and strangers (Willemsen et al., 2013). Agreement between the replies to the longitudinal questionnaire and DNA determined zygosity was around 93% (Rietveld et al., 2000).

Material

Well-being

Well-being was assessed using the Satisfaction with Life scale (Diener et al., 1985). The Satisfaction with Life scale has five items to report life satisfaction on a 7-point Likert scale, ranging from 1 = *strongly disagree* to 7 = *strongly agree*. An example item is '*In most ways my life is close to ideal*'. As in all following scales, the total score was only computed when all items were completed, i.e. when participants had no missing data. The Satisfaction with Life scale shows high internal consistency and high temporal reliability (2-month test-retest: 0.82, and coefficient alpha was 0.87) (Diener et al., 1985). The internal consistency of the SWLS in our sample is similar, with a Cronbach's alpha of 0.86.

Optimism

Optimism was assessed with the revised Life Orientation Test (LOT-R) (Scheier et al., 1994). The scale consists of 10 items, three for optimism, three for pessimism, and four filler items. Participants had to rate their agreement with the items on a 5-point Likert scale (1 = *strongly disagree*, 5 = *strongly agree*). As (Mavioğlu et al., 2015) concluded that the LOT-R should be considered a bi-dimensional scale with two correlated constructs of optimism and pessimism, we summed the scores on the three optimism items to create an optimism

score instead of using all six optimism and (reverse coded) pessimism items. An example item is “*In uncertain times, I usually expect the best*”. The LOT-R has a high internal consistency (Cronbach’s $\alpha=.78$) and temporal reliability (4 month test-retest: .68) (Scheier et al., 1994).

Anxious-depressed symptoms

Symptoms of anxiety and depression were assessed with the Anxious-Depressed subscale of the ASEBA Youth Self Report (Achenbach & Rescorla, 2001). This subscale consists of 13 items and adolescents have to rate the occurrence of the behavior, now or within the past 6 months, on a 3-point scale (0 if the problem item is not true, 1 if it is sometimes true, and 2 if it is very true or often true). An example item is “*I am unhappy, sad, or depressed*”. The anxious-depressed score was computed by summing the items. The internal consistency (Cronbach’s $\alpha=.87$) and temporal reliability (1 week test-retest: .88) of the anxious-depressed scale are both high (Achenbach & Rescorla, 2003).

Aggressive behavior

Aggressive behavior was assessed with the Aggressive Behavior subscale of the ASEBA Youth Self Report (Achenbach & Rescorla, 2001). This subscale consists of 17 items and adolescents have to rate the occurrence of certain behavior, now or within the past 6 months, on a 3-point scale, ranging from 0 (not true) to 2 (very true). An example item is “*I get in many fights*”. The aggressive behavior score was computed by summing the items. The internal consistency (Cronbach’s $\alpha=.87$) and temporal reliability (1 week test-retest: .83) of the aggressive behavior scale are both high (Achenbach & Rescorla, 2003).

Educational achievement

For educational achievement, we used the Dutch Cito-elementary test score. The Cito-test is a standardized test for educational achievement in the Netherlands. Children take the test in the final grade of elementary school (around 11 or 12 years old) (see Eindtoets Basisonderwijs; www.cito.nl). The Cito-test consists of four parts, including items on language, mathematics, study skills, and world orientation. Combining the scores on the four tests results in a standardized Cito-score, ranging from 500 to 550. The Cito-test results are used in the primary school’s advice on the most appropriate level of secondary education and reflects educational achievement. In the DHBQ, adolescents were asked whether they took the Cito-test and if so, to report their Cito score.

Statistical analysis

To decompose the variances and covariance in genetic and environmental components and to estimate genetic and environmental correlations between well-being and each of the four different traits, we conducted bivariate twin models using data of same sex MZ and DZ twins. Twin models use the different degree of genetic relatedness between monozygotic (share 100% of their genes) and dizygotic twins (share on average 50% of their genes) to decompose the variance and covariance in genetic and environmental components. In bivariate models, the within-twin cross-trait covariances/correlations show whether there are common etiological influences in the traits; importantly, the cross-twin cross-trait covariances/correlations give information about whether familial (genetic or environmental) common etiological influences contribute to the covariation.

The genetic variance and covariance components are additive genetic variance (A) and non-additive genetic variance (D). Whereas A represents the additive variance explained by summing the effects of all alleles that influence the phenotype, D arises due to interactions between alleles at the same locus (dominance) or between alleles at different loci (epistasis) and cannot be explained by a linear model. The environmental variance and covariance consist of a common environmental variance component (C) (variance shared by family members) and a non-shared environmental component (E) (unique for an individual). The effects of C and D cannot be estimated in the same model unless an extended family design is applied. Therefore, a choice for an ACE or ADE model was made based on the ratio of the cross-twin cross-trait correlations. If the MZ correlations are smaller than twice the DZ correlations, common environment (C) effects are expected and an ACE model is used. If the MZ correlations are larger than twice the DZ correlations, dominant genetic (D) effects are expected and an ADE model is appropriate (Neale & Maes, 2004). We used the variance component approach, which has better statistical properties (Verhulst et al., 2019).

First, phenotypic correlations, twin correlations, and cross-twin cross-trait correlations were estimated using a saturated model in OpenMx in R (Boker et al., 2011). Next, using a bivariate ACE or ADE model, we estimated genetic and environmental contributions to variance of the traits and to the bivariate phenotypic covariance, - that is, how much of the phenotypic correlation between the traits is accounted for by genetic and (shared and unique) environmental factors. Additionally, we obtained the genetic and environmental correlations between the traits. The genetic correlation is computed by dividing the genetic covariance by the square root of the

product of the genetic variances of the two variables ($r_g = \frac{VA_{12}}{\sqrt{VA_{11} * VA_{22}}}$). Similarly, the (shared or unique) environmental correlation is computed by dividing the (shared or unique) environmental covariance by the square root of the product of the (shared or unique) environmental variances of the two variables ($r_e = \frac{VE_{12}}{\sqrt{VE_{11} * VE_{22}}}$). These correlations reflect the overlap between genetic and environmental factors underlying the traits. The scripts we used for the bivariate saturated and ACE/ADE model can be found in the supplementary information.

First, we tested the contribution of the C or D component to the total variance and covariances between traits. However, if there are sex differences in the factors contributing to the variation, dropping 6 parameters might result in a significant deterioration of the fit, even though the contribution of C/D is small. Therefore, based on the twin correlations and the full model, we tested the contribution of C/D separately for males and females if necessary.

Next, we tested for quantitative sex differences in the variance components (A, possibly C/D and E) by constraining the variance estimates of both phenotypes and the covariance between the phenotypes of females and males to be equal. We did not test for qualitative sex differences, as modelling sex specific genes in multivariate models has inherent limitations (Neale et al., 2006) and no qualitative sex effects in well-being are expected based on the literature (Stubbe et al., 2005) or are found in univariate models of the traits.

The fit of the different models and nested models (both for the saturated as well as the genetic models) was compared by means of the log-likelihood ratio test (LRT). The difference in minus two times the log-likelihood (-2LL) between two nested models has a χ^2 distribution with the degrees of freedom (df) equalling the difference in df between the two models. If a p value from the χ^2 -test is significant (threshold for the genetic models $p < 0.01$ due to multiple testing), the fit of the constrained model is significantly worse than the fit of the more complex model. For the best fitting model, 95% confidence intervals were estimated for the parameters.

RESULTS

Table 4.1 contains the means and standard deviations for all the measures. Based on the saturated model results, there were significant mean differences between females and males for all measures. Males scored higher on well-being, optimism, aggressive behavior, and educational achievement, whereas females scored higher on anxious-depressed symptoms (all: $p < .001$).

Table 4.1. Descriptives of the measures, separately for females and males.

	Females				Males			
	<i>N</i>	<i>M</i>	<i>SD</i>	<i>Range</i>	<i>N</i>	<i>M</i>	<i>SD</i>	<i>Range</i>
Well-being	4687	27.21	5.34	5-35	3338	27.84	4.95	5-35
Optimism	3598	10.09	1.78	3-15	2475	10.64	1.74	3-15
Anxious-depressed symptoms	4493	5.04	3.85	0-23	2849	3.23	2.89	0-26
Aggressive behavior	4497	4.68	3.49	0-27	3203	4.97	3.87	0-34
Educational achievement	2705	537.78	8.62	501-550	1927	539.52	8.07	503-550

Note: based on the saturated model, sex differences are significant in all measures, $p < .001$.

All phenotypic correlations between well-being and the measures were significant and are reported in Table 4.2 separately for females and males. The correlations with optimism and anxious-depressed symptoms were moderately positive and negative respectively. The negative correlation of well-being with aggressive behavior was lower and the positive correlation with educational achievement was close to zero.

Table 4.2. Phenotypic correlations with Well-being (Satisfaction with Life), with 95% confidence intervals.

	Females	Males
Optimism	0.403 (.374, .432)	0.334 (.295, .372)
Anxious-Depressed symptoms	-0.460 (-.484, -.435)	-0.337 (-.371, -.301)
Aggressive behavior	-0.238 (-.268, -.209)	-0.096 (-.160, -.031)
Educational Achievement	0.060 (.018, .101)	0.057 (.007, .106)

The twin correlations (see Table 4.3) showed that for all measures part of the variance is explained by additive genetic influences, as the MZ correlation was consistently higher than the DZ correlation. The cross-twin cross-trait correlations are higher for MZ than for DZ twins as well, indicating an influence of genetic effects on the association between well-being and the other measures. As there was no evidence for dominant genetic effects, we continued with ACE models.

The model fitting results showed that there were quantitative sex differences in all bivariate models. The best fitting model for all phenotypes using an alpha of .01 was an AE model for both females and males (see Table 4.4). In supplementary Table S4.1, and S4.2 the standardized and unstandardized variance estimates of males and females in the full ACE models can be found. In Table S4.3 the genetic and environmental correlations of the full ACE models can be found.

Table 4.3. Cross-twin cross-trait correlations.

	MZf/DZf		MZm/DZm	
	WB	Opt	WB	Opt
WB	.409/.286		.374/.198	
Opt	.249/.163	.274/.247	.139/.121	.261/.111
	WB	Anx-Dep	WB	Anx-Dep
WB	.402/.280		.394/.224	
Anx-Dep	-.264/-.160	.395/.214	-.301/-.226	.527/0.378
	WB	Aggr	WB	Aggr
WB	.412/.480		.379/.187	
Aggr	-.167/-.106	.532/.252	-.114/-.109	.426/0.223
	WB	Educ	WB	Educ
WB	.411/.278		.378/.189	
Educ	.038/.020	.799/.378	.070/-.002	.812/.478

Note: WB=Well-being, Opt= Optimism, Anx-Dep= Anxious-Depressed symptoms, Aggr= Aggressive Behavior, Educ= Educational Achievement.

Table 4.5 shows the standardized bivariate genetic and environmental estimates for the variance and covariance of the four best fitting models (the unstandardized estimates can be found in supplementary Table S4.4). The phenotypic correlations between well-being and the four other measures and the proportions that were accounted for by genetic (i.e. the bivariate heritability), and non-shared environmental influences are presented in Figure 4.1. Genetic factors contributed to the covariance with well-being in all four traits to a different extent.

In Figure 4.2 (and supplementary Table S4.5) the genetic and non-shared environmental correlations between well-being and the four measures can be found. The genetic correlations ranged from .07 to .72 and environmental correlations ranged from .01 to .28 across the traits, indicating variation in the genetic and environmental overlap of the traits with well-being.

Table 4.4. Model fitting results of the bivariate models with well-being.

Optimism	base	comparison	ep	-2LL	df	AIC	Δ LL	Δ df	p
1	ACE		22	71574.8	14019	43536.8			
2	ACE	AE with sex diff	16	71591.5	14025	43541.5	16.7	6	0.0105
3	AE	No sex diff	10	71622.4	14031	43560.4	30.9	6	<.0001
Anx-Dep symptoms	base	comparison	ep	-2LL	df	AIC	Δ LL	Δ df	p
1	ACE		22	85432.1	15241	54950.1			
2	ACE	AE with sex diff	16	85440.7	15247	54946.7	8.6	6	0.1954
3	AE	No sex diff	10	85701.5	15253	55195.5	260.8	6	<.0001
Aggressive behavior	base	comparison	ep	-2LL	df	AIC	Δ LL	Δ df	p
1	ACE		22	88937.8	15594	57749.8			
2	ACE	AE with sex diff	16	88947.0	15600	57747.0	9.2	6	0.1638
3	AE	No sex diff	10	89027.7	15606	57815.7	80.7	6	<.0001
Educational Achievement	base	comparison	ep	-2LL	df	AIC	Δ LL	Δ df	p
1	ACE		22	79796.7	12554	54688.7			
2	ACE	AE with sex diff	16	79805.8	12560	54685.8	9.1	6	0.1694
3	AE	No sex diff	10	79837.6	12566	54705.6	31.8	6	<.0001

Note: Base= baseline model, ep= estimated parameters, -2LL= minus two times the log-likelihood, df= degrees of freedom, AIC= Akaike Information Criterion, p = p-value, Anx-Dep symptoms = Anxious-Depressed symptoms; best-fitting model in bold letters.

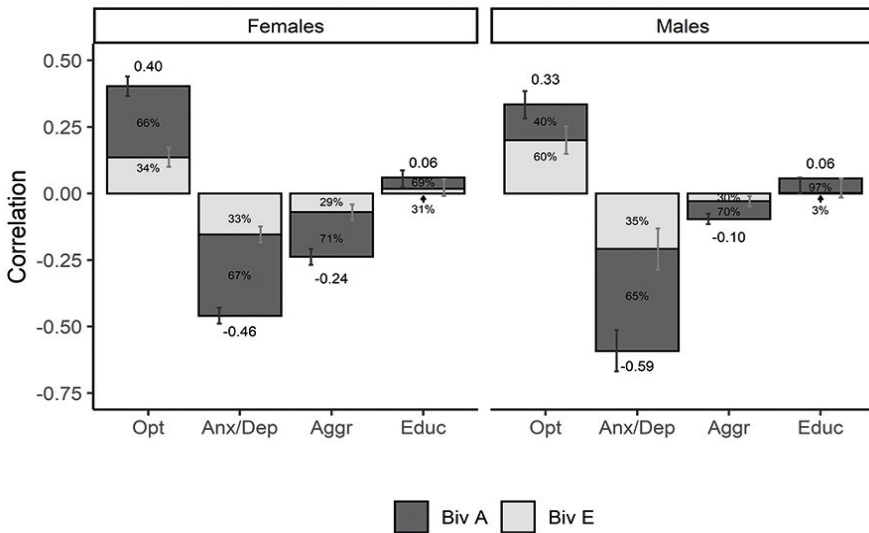


Figure 4.1. Phenotypic correlations between well-being and the traits optimism, anxious-depressed symptoms, aggressive behavior and educational achievement with the proportions that are accounted for by additive genetic (Biv A) and non-shared environmental influences (Biv E). The error bars indicate the 95% confidence intervals.

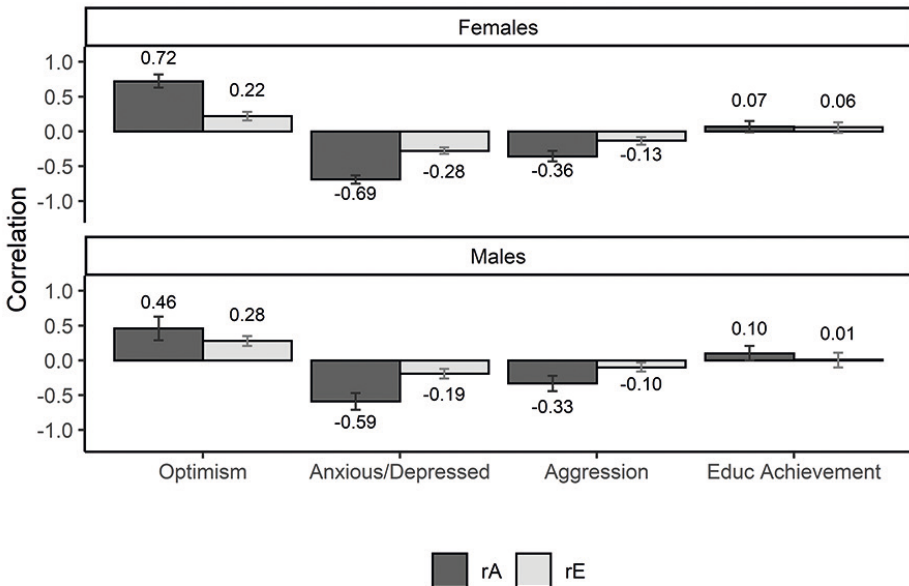


Figure 4.2. The genetic (r_A) and non-shared environmental correlations (r_E) between well-being and the other traits, optimism, anxious-depressed symptoms, aggressive behavior and educational achievement. The error bars indicate the 95% confidence intervals.

Optimism

The phenotypic correlation between optimism and well-being ($r_{\text{females}} = .40$ and $r_{\text{males}} = .33$) was explained by genetic influences for respectively 66% and 40% in females and males, whereas the rest was explained by non-shared environmental influences.

The genetic correlations between well-being and optimism were relatively strong in females ($rg_{\text{females}} = .72$) and lower in males ($rg_{\text{males}} = .47$), indicating that the genetic factors underlying both traits overlap to a significant extent and to a greater extent in females than in males. In addition, the non-shared environmental correlations were moderate, with .22 and .28 for females and males, respectively, indicating an overlap in environmental factors as well.

Anxious-depressed

The phenotypic correlation between well-being and anxious-depressed symptoms ($r_{\text{females}} = -.46$ and $r_{\text{males}} = -.34$) was primarily influenced by genetic influences (67% and 65% for females and males respectively), whereas the rest was explained by non-shared influences.

The genetic correlation between well-being and anxious-depressed symptoms was negative and strong in both sexes ($rg_{\text{females}} = -.69$, $rg_{\text{males}} = -.59$) as well, indicating that there were largely overlapping genetic influences on the phenotypes. The non-shared environmental correlations were $-.28$ and $-.19$ for females and males respectively. The negative correlations indicated that the effects of the influences are in opposite directions.

Aggressive behavior

For well-being and aggressive behavior, the phenotypic correlation ($r_{\text{females}} = -.24$ and $r_{\text{males}} = -.10$) was mainly explained by genetic influences (71% and 70% respectively), whereas the rest was explained by non-shared environmental influences.

The genetic correlation between well-being and aggressive behavior was moderately negative ($rg_{\text{females}} = -.36$ and $rg_{\text{males}} = -.33$). Overlapping genetic factors influence both well-being and aggressive behavior, but the effects of the genetic factors on the traits were opposite. The non-shared environmental correlations were $-.13$ in females and $-.10$ in males, indicating some overlap in the environmental factors underlying the traits as well, and they also went in the opposite direction.

Educational achievement

Lastly, the small phenotypic correlation between well-being and educational achievement ($r=.06$ for both sexes) was made up of genetic (69% and 97%) and non-shared environmental (31% and 3%) influences in females and males respectively. However, there are large confidence intervals, as can be seen in Figure 4.1.

The genetic and environmental correlations between well-being and educational achievement were close to zero ($<.10$) in both sexes, with zero in the confidence intervals, indicating no significant overlapping genetic and environmental influences on well-being and educational achievement.

Table 4.5. The bivariate estimates (with 95% confidence intervals) of the variance and covariance of well-being and the four other phenotypes of the four best fitting bivariate models.

	A		E	
	WB	Opt	WB	Opt
Females				
WB	.444 (.401, .484)		.556 (.516, .599)	
Opt	.663 (.570, .752)	.311 (.256, .363)	.337 (.248, .430)	.689 (.637, .744)
Males				
WB	.344 (.284, .400)		.656 (.600, .716)	
Opt	.403 (.246, .554)	.244 (.171, .314)	.597 (.446, .754)	.756 (.686, .829)
	A		E	
	WB	Anx-Dep	WB	Anx-Dep
Females				
WB	.443 (.400, .483)		.557 (.517, .600)	
Anx-Dep	.666 (.599, .730)	.444 (.400, .485)	.334 (.270, .401)	.556 (.515, .600)
Males				
WB	.364 (.287, .402)		.654 (.598, .713)	
Anx-Dep	.649 (.515, .778)	.394 (.330, .452)	.351 (.222, .485)	.606 (.548, .670)

Table 4.5. The bivariate estimates (with 95% confidence intervals) of the variance and covariance of well-being and the four other phenotypes of the four best fitting bivariate models.

		A		E	
		WB	Aggr	WB	Aggr
Females					
WB		.444 (.401, .484)		.556 (.516, .599)	
Aggr		.706 (.578, .829)	.495 (.451, .536)	.294 (.171, .422)	.505 (.464, .549)
Males					
WB		.344 (.284, .400)		.656 (.600, .716)	
Aggr		.699 (.496, .900)	.459 (.406, .509)	.301 (.100, .504)	.541 (.491, .594)
		A		E	
		WB	Educ	WB	Educ
Females					
WB		.444 (.402, .485)		.556 (.510, .598)	
Educ		.693 (.100, 1.15)	.804 (.778, .826)	.307 (-.15, .900)	.196 (.174, .222)
Males					
WB		.346 (.286, .402)		.654 (.598, .714)	
Educ		.966 (NA, NA)	.801 (.769, .828)	.034 (NA, NA)	.199 (.172, .231)

Note: WB=Well-being, Opt= Optimism, Anx-Dep= Anxious-Depressed symptoms, Aggr= Aggressive Behavior, Educ= Educational Achievement

DISCUSSION

The four bivariate twin models fitted to data of adolescent females and males using well-being (WB; satisfaction with life) and four other complex traits, namely optimism, anxious-depressed symptoms, aggressive behavior, and educational achievement resulted in variability in the phenotypic correlations, bivariate heritability, and genetic and environmental correlations. Bivariate models like the ones that we applied in this paper provide insight into the underlying source of overlap between two traits and provide an indication of how strong the genetic link is between two phenotypes. If interested in exploring the relationship is between all these traits taken together, other models (e.g. multivariate models) that were not the scope of this paper have to be fitted.

The bivariate heritability indicates the proportion of the correlation between the phenotypes that is accounted for by additive genetic influences. While the phenotypic correlation between WB and the four phenotypes varied from moderate (r about .4 for WB with optimism and anxious-depressed symptoms) to small (around .2 for WB with aggressive behavior and .05 with educational achievement), a significant part of all these varying phenotypic correlations was accounted for by genetic factors. For optimism, anxious-depressed symptoms and aggressive behavior the bivariate heritability with well-being ranged between .40-.70, indicating that around half to more than half of the overlap between well-being and these phenotypes can be explained by genetic factors. For educational achievement, the estimates for the bivariate heritability are 69% and even 97% in females and males respectively, indicating that almost all covariance between educational achievement and well-being was explained by genetic factors. However, as the phenotypic correlation between well-being and educational achievement is really small and the confidence intervals around the bivariate heritability estimate were large, this estimate may not be relevant and must be interpreted with care.

The genetic correlation reflects a measure of overlap in the genetic factors underlying the traits and is different than the bivariate heritability. For example, if the bivariate heritability is large and the genetic correlation is low, genes do play a substantial role in the observed overlap between traits, but most of the genetic influences are trait specific. In our examples, the bivariate heritability between well-being and anxious-depressed symptoms and well-being and aggressive behavior was similar, whereas the genetic correlation between well-being and anxious-depressed symptoms was higher than between well-being and aggressive behavior. This indicated that genes play a role in the

overlap between WB and the traits to a similar extent, whereas the biological mechanisms underlying well-being and anxious-depressed symptoms are more similar than those underlying well-being and aggressive behavior. The genetic correlation between well-being and optimism was relatively strong as well, indicating that the biological mechanism underlying the positive traits well-being and optimism is similar as well. The genetic factors underlying well-being and educational achievement overlapped only a little or not at all, as indicated by a genetic correlation lower than 0.1 and the biological mechanisms underlying well-being and educational achievement are almost completely separate.

A similar pattern can be observed in the unique environmental influences on the covariance between the traits and the unique environmental correlations between well-being and the four traits. Although the phenotypic correlations between well-being and the other traits vary, roughly a similar proportion is accounted for by environmental factors. Additionally, as indicated by the environmental correlations, more environmental factors underlying well-being and both optimism and anxious-depressed symptoms (~ 30) overlapped compared to aggressive behavior (~ 10). For educational achievement, none of the environmental factors overlapped, indicated by an environmental correlation of zero.

For every bivariate model, the best fitting model included quantitative sex differences, i.e. the (bivariate) heritability for males and females differed. Sex differences in the genetic architecture of traits might be quantitative (either scalar or non-scalar) or qualitative. As mentioned before, the literature and our data indicated no differences in qualitative sex effects, therefore we did not test these sex differences. An alternative model, to the model used in the paper, to test quantitative sex differences is the scalar sex limitation model. In this model, the total variance in males and females is allowed to differ with a factor k (i.e. $\text{variance}_{\text{female}} = k * \text{variance}_{\text{male}}$), whereas the heritability is constrained to be equal. To be complete, we compared the fit of those models to our non-scalar quantitative sex limitation models. The scalar sex limitation model was only a good fit for the bivariate model of well-being and educational achievement ($\Delta-2LL = 13.9$, $\Delta df = 8$, $p = .085$). This indicates scaled sex differences in the unstandardized variance components, but not in the standardized variance components (i.e. the heritability). However, the difference between the standardized variance components of this scalar AE model and the reported non-scalar AE model are small.

Added value of bivariate twin models

An advantage of the bivariate or multivariate models is the increase in power compared to the univariate twin model (Schmitz et al., 1998). As in all models, the size of the sample and the ratio of MZ and DZ twin pairs is important for sufficient power. However, often in univariate models, there is not enough power to discriminate between genetic and shared environmental variance components for a single trait. In bivariate models, the within twin pair covariance and the cross-trait and within-person covariance provide unique additional information, leading to more powerful models to estimate both the heritability of the single traits and the bivariate heritability. However, for bivariate models to increase the power, there has to be a significant phenotypic correlation between the traits (Schmitz et al., 1998). If there is only a small phenotypic correlation between the traits, like in our well-being and educational achievement example, the models will still be unpowered. This is also indicated by the large confidence interval around the bivariate heritability in the educational achievement example.

Furthermore, the value of bivariate twin models also rests in the genetic correlations, which can be compared and provide a reference for those based on molecular genetic data. Molecular genetic correlations can be estimated using summary statistics of large Genome Wide Association Studies (GWAS) and LD score regression (Bulik-Sullivan, Loh, et al., 2015). Comparing the results of our twin model and recent GWASs, the genetic correlations are very similar. For anxious-depressed symptoms and well-being, the genetic correlation in our twin study was $-.69$ in females and $-.59$ in males, whereas the molecular genetic correlation between well-being and depressive symptoms (without taking sex differences into account) is estimated around $-.70$ (Baselmans, Jansen, et al., 2019; Okbay et al., 2016). For aggressive behavior and well-being, the genetic correlation in our study was $-.36$ in females and $-.33$ in males. The molecular genetic correlation based on GWAS summary statistics is almost the same and estimated at $-.39$ (Ip et al., 2021). Finally, for educational achievement the genetic correlation in our study was non-significant and estimated at $.07$ in females and $.11$ in males. The molecular genetic correlation is low as well and slightly negative, with $-.15$ (Baselmans, Jansen, et al., 2019). Therefore, using far fewer participants and other (frequently less expensive) resources, the genetic correlations based on twin models provide reliable estimates about the overlap in genes between complex traits. Therefore, twin studies and the large longitudinal phenotypically rich twin registries all around the world provide a valuable resource for a first indication of genetic overlap between traits or stability of genetic influences over time.

Besides investigating the overlap between two or more traits, different forms of bivariate or multivariate twin models exist. Examples of other powerful bivariate models are a multiple rater twin model or a multiple measurement model of one trait (or more traits) over time (Bartels et al., 2007; Hewitt et al., 1992). In a multiple rater model, multiple informants, such as the parents and/or teacher rate a child on specific traits. Based on common (co)variance, the sources of overlap between two traits can be estimated more reliably as the measurement error decreases (e.g. see Bartels et al. (2003) for a bivariate model including two traits and two raters). Similarly, bivariate or multivariate twin models can be applied to longitudinal data including data of multiple time points to give insight into the development of traits over time. In such models, the genetic and environmental correlations reflect the overlap of genetic and environmental factors over time and thus the underlying stability of the trait (Baselmans et al., 2018; Kan et al., 2013; Nivard et al., 2015). For example, the bivariate heritability and genetic correlations between the measurements of anxiety and depression symptoms across the life span indicated that the stability in anxiety or depression symptoms is mainly due to genetic effects, with the importance of environmental effects increasing with age (Nivard et al., 2015).

Implications

The results of bivariate twin modelling in different forms can lead to information about the overlap between traits and about the development over the life span. This information can be used to inform the development of prevention and intervention programs for psychopathology. For example, returning to our well-being application, prevention of psychopathology and increasing well-being in adolescence is of great importance. The genetic correlations between well-being and anxious-depressed symptoms in our adolescent sample indicated a high overlap in the biological mechanisms underlying the traits. With a high genetic correlation, a genetic liability for lower well-being can be indicative for a genetic liability for higher psychopathology. People at risk for psychopathology can be identified based on their well-being before any symptoms start to develop. Similarly, a high environmental correlation indicates that the same environmental influences have both an effect on well-being and psychopathology. Although well-being and symptoms of anxious-depressed are different and do not lie on the same continuum (Howell et al., 2007; Ryff et al., 2006), the results do suggest that interventions to promote well-being (e.g. targeting environmental influences) can reduce the risk for anxiety or depressive symptoms. For example, in line

with the hypothesis of a similar biological mechanism underlying well-being and depression, in adults, a meta-analysis shows that enhancing well-being with positive psychology interventions did decrease depressive symptoms significantly (Sin & Lyubomirsky, 2009). In contrast, the lower genetic and environmental correlation of well-being and aggressive behavior suggest more distinct biological and environmental mechanisms underlying both traits. Therefore, a prevention or intervention to increase well-being and decrease aggressive behavior at the same time is most likely not effective.

To conclude, bivariate twin models are powerful models to investigate the causes of covariation between traits. The phenotypic correlations, estimates of bivariate heritability, and genetic and environmental correlations resulting from bivariate twin models provide distinctive information about the covariance and overlap between phenotypes and have different (clinical) implications. It is highly recommended that future behavior genetics studies report both sets of results.

Supplementary Material Chapter 4

Table S4.1.
The bivariate genetic, shared and non-shared environmental estimates of the four full ACE models.

	A		C		E	
	WB	Opt	WB	Opt	WB	Opt
Females						
WB	.258 (.113, .406)		.170 (.041, .293)		.572 (.528, .618)	
Opt	.432 (.112, .761)	.059 (-.123, .243)	.217 (-.063, .484)	.225 (.069, .374)	.351 (.252, .453)	.716 (.658, .777)
Males						
WB	.344 (.151, .539)		.001 (-.165, .160)		.655 (.595, .720)	
Opt	.088 (-.456, .624)	.302 (.062, .544)	.276 (-.181, .732)	-.049 (-.254, .150)	.635 (.475, .804)	.747 (.674, .825)
	A		C		E	
	WB	Anx-Dep	WB	Anx-Dep	WB	Anx-Dep
Females						
WB	.259 (.114, .407)		.168 (.039, .291)		.573 (.530, .619)	

Table S4.1.
The bivariate genetic, shared and non-shared environmental estimates of the four full ACE models.

Anx-Dep	.484 (.236, .740)	.373 (.218, .533)	.172 (-.056, .387)	.067 (-.077, .202)	.344 (.276, .416)	.560 (.517, .606)
Males						
WB	.356 (.164, .550)		-.007 (-.173, .152)		.651 (.591, .715)	
Anx-Dep	.435 (-.019, .892)	.270 (.065, .476)	.191 (-.196, .567)	.111 (-.065, .277)	.374 (.233, .521)	.620 (.556, .690)
		A		C	E	
	WB	Aggr	WB	Aggr	WB	Aggr
Females						
WB	.277 (.131, .428)		.152 (.020, .277)		.570 (.527, .616)	
Aggr	.514 (.058, .974)	.530 (.385, .677)	.177 (-.223, .566)	-.030 (-.159, .093)	.309 (.177, .446)	.500 (.458, .546)
Males						
WB	.366 (.172, .560)		-.017 (-.183, .143)		.651 (.592, .715)	
Aggr	.080 (-.661, .788)	.427 (.251, .605)	.550 (-.056, 1.18)	.031 (-.124, .178)	.370 (.158, .590)	.543 (.490, .600)
	A		C		E	

Table S4.1.
The bivariate genetic, shared and non-shared environmental estimates of the four full ACE models.

	WB	Educ	WB	Educ	WB	Educ
Females						
WB	.277 (.130, .428)		.153 (-.021, .278)		.570 (.526, .616)	
Educ	.494 (NA, NA)	.824 (.671, .996)	.191 (NA, NA)	-.021 (-.190, .129)	.315 (-.161, NA)	.196 (.174, .222)
Males						
WB	.364 (.169, .560)		-.017 (-.184, .144)		.653 (.593, .717)	
Educ	2.45 (NA, NA)	.680 (.531, .846)	-1.35 (NA, NA)	.118 (-.042, .260)	-.097 (NA, NA)	.201 (.173, .235)

Note: The NA's in the CI for the covariance of WB and Educ are a consequence of the small r of .06.

Table S4.2. The unstandardized genetic, shared and non-shared environmental estimates of the four full ACE models.

	A		C		E	
	WB	Opt	WB	Opt	WB	Opt
Females						
WB	7.35 (NA, NA)		4.85 (NA, NA)		16.29 (15.07, 17.64)	
Opt	1.67 (.42, 2.95)	.19 (-.40, .78)	.84 (-.25, 1.90)	.72 (.22, 1.21)	1.36 (.96, 1.78)	2.29 (2.10, 2.51)
Males						
WB	8.40 (NA, NA)		.02 (NA, NA)		16.00 (14.53, NA)	
Opt	0.25 (-1.30, NA)	0.92 (.18, 1.67)	.80 (-.53, 2.10)	-.15 (-.78, .46)	1.83 (1.33, 2.35)	2.27 (2.04, 2.53)
	A		C		E	
	WB	Anx-Dep	WB	Anx-Dep	WB	Anx-Dep
Females						
WB	7.37 (NA, NA)		4.80 (NA, NA)		16.34 (15.11, 17.70)	
Anx-Dep	-4.57 (NA, NA)	5.49 (NA, NA)	-1.63 (NA, NA)	0.98 (NA, NA)	-3.25 (-3.96, -2.58)	8.24 (7.61, 8.93)
Males						
WB	8.72 (NA, NA)		-.18 (NA, NA)		15.92 (14.46, NA)	

Anx-Dep	-2.09 (NA, NA)	2.25 (NA, NA)	-92 (NA, NA)	0.92 (-.56, 2.34)	-1.80 (-2.53, -1.09)	5.17 (4.63, 5.77)
A						
	WB	Aggr	WB	Aggr	WB	Aggr
Females				C	E	
WB	7.93 (NA, NA)		4.35 (NA, NA)		16.29 (15.06, 17.64)	
Aggr	-2.28 (NA, NA)	6.42 (NA, NA)	-0.79 (NA, NA)	-0.37 (NA, 1.15)	-1.38 (-2.00, -0.77)	6.06 (5.57, 6.61)
Males						
WB	8.91 (NA, NA)		-0.41 (NA, NA)		15.87 (14.41, NA)	
Aggr	-0.29 (NA, NA)	6.41 (NA, NA)	-2.00 (NA, NA)	0.46 (NA, NA)	-1.34 (-2.16, -0.55)	8.15 (7.38, 9.01)
A						
	WB	Educ	WB	Educ	WB	Educ
Females			C	E		
WB	7.92 (NA, NA)		4.36 (NA, NA)		16.27 (15.05, 17.63)	
Educ	1.37 (NA, NA)	60.95 (NA, NA)	.53 (NA, NA)	-1.52 (NA, NA)	.88 (-.37, 2.12)	14.50 (13.01, NA)
Males						
WB	8.86 (NA, NA)		-41 (NA, NA)		15.91 (15.05, 17.63)	
Educ	5.56 (NA, NA)	44.99 (NA, NA)	-3.07 (NA, NA)	7.83 (NA, NA)	-.22 (-.37, 2.12)	13.32 (11.61, NA)

Table S4.3.
The genetic, shared environmental, non-shared environmental and phenotypic correlations between well-being and the four other phenotypes of the full ACE models.

	Optimism		Anxious-Depressed symptoms	
	Females	Males	Females	Males
rA	1.42 (.489, NA)	.091 (-.739, .566)	-.719 (-1.03, -.429)	-.473 (-.976, .027)
rC	.448 (-.206, .960)	NA	-.749 (NA, NA)	NA
rE	.222 (.159, .283)	.303 (.226, .376)	-.280 (-.331, -.227)	-.198 (-.272, -.122)
rP	.405 (.375, .434)	.334 (.295, .372)	-.461 (-.485, -.437)	-.337 (-.371, -.301)
	Aggression			
	Females	Males	Females	Males
rA	-.320 (-.604, -.039)	-.039 (-.370, -.347)	.062 (-.209, .331)	.279 (-.018, .610)
rC	NA	NA	NA	NA
rE	-.138 (-.198, -.078)	-.118 (-.186, -.049)	.057 (-.023, .136)	-.015 (-.122, .092)
rP	-.239 (-.269, -.209)	-.190 (-.225, -.154)	.060 (.018, .102)	.057 (.007, .106)

Note: Biv A= bivariate genetic effects, Biv E= bivariate non-shared environmental effects, rA= additive genetic correlation, rC= shared environmental correlation, rE= non-shared environmental correlation, rP= phenotypic correlation.

Table S4.4.
The unstandardized bivariate genetic and non-shared environmental estimates of the four AE models

	A		E	
	WB	Opt	WB	Opt
Females				
WB	12.60 (11.18, 14.07)		15.80 (14.68, 17.02)	
Opt	2.55 (2.13, 2.97)	0.99 (0.81, 1.18)	1.30 (0.93, 1.67)	2.20 (2.03, 2.39)
Males				
WB	8.40 (6.81, NA)		16.02 (14.64, NA)	
Opt	1.16 (0.68, 1.64)	0.74 (0.51, 0.97)	1.72 (1.25, 2.21)	2.29 (2.07, 2.54)
	A		E	
	WB	Anx-Dep	WB	Anx-Dep
Females				
WB	12.59 (11.16, 14.06)		15.85 (14.73, 17.07)	
Anx-Dep	-6.26 (-7.09, -5.46)	6.51 (5.76, 7.29)	-3.14 (-3.79, -2.52)	8.17 (7.57, 8.81)
Males				
WB	8.47 (6.89, NA)		15.99 (14.61, NA)	
Anx-Dep	-3.12 (-3.87, -2.38)	3.28 (2.70, 3.87)	-1.69 (-2.36, -1.04)	5.05 (4.57, 5.60)
	A		E	

Table S4.4.
The unstandardized bivariate genetic and non-shared environmental estimates of the four AE models

	WB	Aggr	WB	Aggr
Females				
WB	12.65 (11.21, 14.14)		15.85 (14.72, 17.08)	
Aggr	-3.13 (-3.86, -2.41)	6.00 (5.35, 6.67)	-1.30 (-1.88, -0.74)	6.11 (5.64, 6.63)
Males				
WB	8.38 (6.80, NA)		15.97 (14.59, NA)	
Aggr	-2.53 (-3.42, -1.65)	6.89 (5.95, 7.85)	-1.09 (-1.84, -0.74)	8.11 (7.39, 8.92)
	A		E	
	WB	Educ	WB	Educ
Females				
WB	12.66 (11.22, 14.15)		15.83 (14.71, 17.06)	
Educ	1.91 (NA, NA)	59.52 (NA, NA)	0.84 (-0.34, 2.03)	14.53 (13.05, NA)
Males				
WB	8.42 (6.84, NA)		15.94 (14.56, NA)	
Educ	2.21 (NA, NA)	52.58 (NA, NA)	0.08 (NA, NA)	13.06 (11.44, NA)

Table S4.5.
The genetic and non-shared environmental correlations between well-being and the four other traits of the best fitting model.

Optimism		Anxious-Depressed symptoms			
	Females	Males			
rA	.720 (.626, .816)	.465 (.294, .630)	rA	-.692 (-.752, -.630)	-.592 (-.713, -.471)
rE	.220 (.161, .277)	.283 (.210, .353)	rE	-.276 (-.324, -.226)	-.188 (-.256, -.117)
Aggression		Educational Achievement			
	Females	Males			
rA	-.359 (-.434, -.282)	-.333 (-.444, -.223)	rA	.069 (-.007, .145)	.105 (-.003, .213)
rE	-.132 (-.188, -.076)	-.096 (-.160, -.031)	rE	.056 (-.021, .132)	.005 (-.096, .107)

Note: Biv A= bivariate genetic effects, Biv E= bivariate non-shared environmental effects, rA= additive genetic correlation, rE= non-shared environmental correlation.

Chapter 5.

Genetic evidence for a large overlap and potential bidirectional causal effects between resilience and well-being

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ABSTRACT

Resilience and well-being are strongly related. People with higher levels of well-being are more resilient after stressful life events or trauma and vice versa. Less is known about the underlying sources of overlap and causality between the constructs. In a sample of 11,304 twins and 2,572 siblings from the Netherlands Twin Register, we investigated the overlap and possible direction of causation between resilience (i.e. the absence of psychiatric symptoms despite negative life events) and well-being (i.e. satisfaction with life) using polygenic score (PGS) prediction, twin-sibling modelling, and the Mendelian Randomization Direction of Causality (MR-DoC) model. Longitudinal twin-sibling models showed significant phenotypic correlations between resilience and well-being (.41/.51 at time 1 and 2). Well-being PGS were predictive for both well-being and resilience, indicating that genetic factors influencing well-being also predict resilience. Twin-sibling modeling confirmed this genetic correlation (.71) and showed a strong environmental correlation (.93). In line with causality, both genetic (51%) and environmental (49%) factors contributed significantly to the covariance between resilience and well-being. Furthermore, the results of within-subject and MZ twin differences analyses were in line with bidirectional causality. Additionally, we used the MR-DoC model combining both molecular and twin data to test causality, while correcting for pleiotropy. We confirmed the causal effect from well-being to resilience, with the direct effect of well-being explaining 11% (T1) and 20% (T2) of the variance in resilience. Data limitations prevented us to test the directional effect from resilience to well-being with the MR-DoC model. To conclude, we showed a strong relation between well-being and resilience. A first attempt to quantify the direction of this relationship points towards a bidirectional causal effect. If replicated, the potential mutual effects can have implications for interventions to lower psychopathology vulnerability, as resilience and well-being are both negatively related to psychopathology.

Keywords: resilience, well-being, twin models, polygenic scores, causality, MR-DoC model

INTRODUCTION

In life, everyone is exposed to multiple personal adverse or stressful life events, such as a traffic accident or the death of a loved one. These adverse life event, but also events like terroristic attacks or worldwide crises, can lead to stress and trauma. There are individual differences in the responses of people to (major) life stressors and potential trauma (Luthar et al., 2000; Werner & Smith, 2001), and resilience is found to be the most common response according to a recent review of 54 studies (Galatzer-Levy et al., 2018). Resilience can be defined as the process of quickly recovering after the experience of stress or trauma (Charney, 2004; Choi et al., 2019; Connor & Davidson, 2003; Galatzer-Levy et al., 2018; Kalisch et al., 2017; Luthar et al., 2000). Resilient people adapt relatively quickly, after some time their well-being levels are back to baseline (Galatzer-Levy et al., 2018). Less resilient people do not cope well in response to stress and experience chronic or long-term adverse effects, leading to the development of psychopathology (e.g., depression) (Bonanno, 2004; Bonanno et al., 2011; Galatzer-Levy et al., 2018; Galatzer-Levy & Bonanno, 2012; Kendler et al., 2000; Pietrzak et al., 2014).

For example, in response to the COVID-19 pandemic, only 13.6% of a USA representative sample (N=1468) showed psychological distress (McGinty et al., 2020). While this level of distress is higher than the 3.9% found in the same sample in 2018, 86% of the sample seemed to be resilient, as their distress did not increase. As another example, Bonanno et al. (2006) reported widespread resilience in a large sample (N=2752) that was exposed to the September 11th attacks in New York. Across all participants, 65.1% could be classified as resilient. When investigating subgroups, even in the group participants that was in the World Trade Center building at the time of the attack, more than half of the sample (53.5%) was resilient.

One of the correlates of resilience that is often suggested to play a role in bouncing back to normal is well-being. Well-being can be defined in multiple ways and a distinction between subjective/hedonic and psychological/eudaimonic well-being has been made. The subjective well-being theory originates from the hedonistic philosophy of well-being, whereas psychological well-being emerged from eudaimonic philosophy (Ryan & Deci, 2001; van de Weijer et al., 2018). Hedonic well-being is characterized by high levels of positive affect and a high subjective evaluation of life satisfaction (Diener et al., 2018), whereas eudaimonic well-being refers to thriving, positive functioning, and judgments about the meaning and purpose of an individual's life (Ryff, 1989). It has repeatedly been found that well-being plays a preventive role

in psychopathology and is important to overall physical and mental health (Diener et al., 2017; Greenspoon & Saklofske, 2001; Howell et al., 2007). Well-being associates positively with longevity and health (James et al., 2019; Kim et al., 2019; Steptoe, 2019; Zaninotto & Steptoe, 2019), satisfaction with marital relationships, productivity at work, prosocial behavior and educational achievement (Chapman & Guven, 2016; Lyubomirsky et al., 2005; Maccagnan et al., 2019; Oswald et al., 2015).

A strong positive correlation (around 0.5) between resilience and well-being has been found as well (Bajaj & Pande, 2016; Hu et al., 2015; Liu et al., 2012; Satici, 2016). That is, people with a higher well-being show more resilience and, vice versa, people who are more resilient show higher well-being (Cohn et al., 2009; Ong et al., 2006). For example, women reporting higher life satisfaction are more likely to be resilient after their spouse passes away (O'Rourke, 2004; Rossi et al., 2007). Fredrickson et al. (2003) suggests that positive emotions are the active elements in resilience. In times of crisis, the presence of positive emotions buffers against depression and adverse outcomes. Conversely, Connor & Davidson (2003) suggest resilience is a protective factor in facing negative emotions after adverse events and therefore protects people's well-being. These studies, though, are correlational, and causal interpretation is hard. It is theoretically plausible to expect a bidirectional relation between resilience and well-being. When people are able to cope with life stressors and adapt well to adversity (resilience), they feel better and evaluate their life positively (well-being) compared to people that cannot cope well. In turn, positive emotions and higher levels of well-being improve the ability to respond adaptively to life events, i.e. resilience.

Alternatively, underlying genetic or environmental confounders might induce the association between well-being and resilience - without a direct causal effect in either direction. The genetic and environmental factors contributing to both phenotypes have been investigated before. Two meta-analyses summarized all studies applying the twin model to well-being and found a meta-analytic heritability (i.e. the contribution of genetic factors to the variance) of 36% (CI: 34-38%) and 40% (CI: 38-43%) for well-being based on all measures (Bartels, 2015; Nes & Røysamb, 2015) and 32% (CI: 29-35%) for satisfaction with life (Bartels, 2015). The remaining variance was explained by unique environmental influences. Causes of individual differences in resilience have also been investigated, although less frequent and with substantial variation in operationalization, sample size, and sample composition (e.g. population vs military sample). In two studies based on military samples, the heritability estimates of self-reported resilience were 25% (CI: 21-30) and

55% (CI: 48-61) respectively (Long et al., 2017; Wolf et al., 2018). In adolescents and based on three raters (father, mother, self) a common resilience factor (excluding rater specific error) showed heritability estimates of 78% in boys and 70% in girls (Waaktaar & Torgersen, 2012). When operationalizing resilience as the residual of positive affect after controlling for stressors or the residual of internalizing symptoms after controlling for stressful life events, heritability estimates ranged from 31% to 52% (Amstadter et al., 2014; Boardman et al., 2008). Using multiple measures to reduce measurement error, Amstadter et al. (2014) found a heritability of 50% (CI: 46-59) for the latent construct of resilience.

The above studies show that resilience and well-being are strongly related phenotypically and have a similar genetic architecture. The etiology of well-being and resilience has not been addressed in a bivariate design, to formally test the overlap in genetic and environmental factors. In order to get a better hold on the nature of the association between resilience and well-being, and possible roles for genetic confounding and (bidirectional) causal effects we took a three-step approach. (1) First, we estimated the cross-sectional and longitudinal phenotypic association between well-being and resilience. (2) Next, we used genome-wide summary statistics of well-being to predict resilience and well-being. (3) Finally, we tried to falsify the causal hypotheses (in both directions) using various approaches: within-subject change score regression, bivariate psychometric twin-sibling modeling, cross-trait correlations of intrapair MZ twin differences, and the MR-DoC model which combines Mendelian Randomization and the Direction of Causation twin model.

METHODS

Sample

Participants were registered at the Netherlands Twin Register (NTR), established by the Department of Biological Psychology, Vrije Universiteit Amsterdam (Ligthart et al., 2019). The NTR sample is a population-wide, non-clinical sample. Every two/three years, longitudinal survey data about lifestyle, personality, psychopathology, and well-being in twins and their families are collected. The current study used data on life events, psychopathology, and well-being in adults collected in 2002-2003 (Time point 1) and 2009-2012 (Time point 2) (Ligthart et al., 2019; Willemsen et al., 2013).

Including twins and biological siblings, the total sample consisted of 14.055 participants with data on resilience and/or well-being collected in one or both waves. We excluded 177 participants with unknown zygosity and two

participants with unknown sex, resulting in a final sample of 13.876 participants (11.304 twins and 2.572 siblings). The sample included 1.577 monozygotic male (MZM), 967 dizygotic male (DZM), 3.859 monozygotic female (MZF), 2.112 dizygotic female (DZF) and 2.789 dizygotic opposite-sex (DOS) twins from complete and incomplete twin pairs.

When split by time of data collection, 4.447 twins and 1.407 siblings (33.8% male, $M_{age} = 32.87$, $SD_{age} = 11.41$) had data at time point 1 (T1). At time point 2 (T2), data of 9.590 twins and 1.962 siblings (32.3% male, $M_{age} = 31.73$, $SD_{age} = 14.41$) were available. Longitudinal data (both at T1 and T2) were available for 3.530 participants (2.733 twins and 797 siblings, 41.1% male, T1: $M_{age} = 33.91$, T2: $M_{age} = 40.25$, $SD_{age} = 11.6$ (see Supplementary Table S5.1 for more information).

The data collection was approved and declared to be of low risk and exempt of formal medical ethical risk assessment by the METc of the Vrije Universiteit Medical Center Amsterdam (Approval: NL25220.029.08 (ref # 2008/244), 1 December 2008 and 2011/334, 12 Oct 2011; 2012/433, dd 26 Feb 2013).

Measures

Well-being

Well-being was assessed with the Satisfaction with Life scale (Diener et al., 1985). The scale consists of five items with a 7-point Likert scale, ranging from 1 = *strongly disagree* to 7 = *strongly agree*. An example question is '*In most ways my life is close to ideal*'. Items were summed to calculate an individual's final score ranging from 0 to 35, with higher scores indicating higher levels of satisfaction with life.

Life events

The number of experienced life events was assessed with an adapted version of a Dutch life-event scale (Schokverwerkings Inventarisatie Lijst = SchIL; Van der Velden et al., 1992). At T1, 16 negative life events items were included about the experience of death of a significant other, serious disease of yourself/significant other, end of relation, traffic accident, violent or sexual assault, robbery, and getting fired. Time point 2 included 28 life events, both positive and negative events. In line with previous work, we excluded the positive life events at T2, leaving 19 items (Middeldorp et al., 2008). Possible answers were *never experienced*, *experienced last year (0-12 months)*, *1-5 year ago* and *>5 years ago*. The number of life events was computed by summing the experienced life event in the past 5 years. The maximum number of life events experienced is 16 at T1 and 19 at T2 (see Supplementary Table S5.2).

Anxious-depressed

Anxious-depressed symptoms were assessed with the anxious-depressed subscale of the Adult Self Report of the Achenbach System of Empirically Based Assessment (ASEBA; (Achenbach & Rescorla, 2003). Each item is rated from 0 = *not true*, 1 = *somewhat true*, to 2 = *very true*. An example item is “*I feel worthless*”. As T1 only included 15 (instead of 18) items of the scale, at T2s we only selected those same items and created a sum score of 15 items, with higher scores indicating higher levels of anxious-depressed behavior.

Resilience score

Resilience is operationalized as an outcome-based measure in line with Amstadter et al. (2014) and is based on the regression of internalizing problems on the total number of stressful life events experienced (e.g. Kendler et al., 2000; Kessler, 1997; Phillips et al., 2015). Resilience is defined as the difference between the predicted level of anxious-depressed symptoms based on the number of life events and the actual level. Individuals who experience less anxious-depressed symptoms than expected based on the number of stressful events in their life can be seen as resilient.

To this end, the number of life events and the anxious-depressed scores were standardized. For both T1 and T2, the resilience score was operationalized as the residuals of the anxious-depressed sum score after the effect of the number of stressful life events had been regressed out, using Generalized estimating equation (GEE) to correct for familial relations (Minică et al., 2015). This standardized residual is our measure for resilience and used in further analyses.

Genotype data

Genotype and phenotype information was available for 10867 NTR participants in our sample. Genotyping was done on several genotyping arrays, including the Axiom array (N=615), Affymetrix 6.0 (N=6144), Illumina Omni Express 1 M (N=181), Illumina 660 (N=1312), Illumina GSA (N=4044) and Perlegen/Affymetrix (N=1013) (Ehli et al., 2017; Willemsen et al., 2013). Additionally, SNPs extracted from sequence data from the Netherlands reference genome project Genome of the Netherlands (GoNL) (N=267) were used (Boomsma et al., 2014; Consortium et al., 2014).

For each platform, SNPs with a Minor Allele Frequency (MAF) <0.01 or SNPs out of Hardy-Weinberg Equilibrium (HWE) with $p < 10^{-5}$ were removed. Also, samples were excluded if there was a mismatch in expected and genotyped sex, the genotype missing rate was above 10% or the inbreeding value (Plink

F statistic) was not between -0.10 and 0.10. To control for Dutch population stratification, Principal Components Analysis (PCA) was performed and individuals with a non-Dutch ancestry based on their PCs were excluded, as described by Abdellaoui et al. (2013).

To infer the SNPs missing per platform in the combined data, the genotyped data of the different arrays were cross-platform imputed using the GoNL as a reference panel (Boomsma et al., 2014; Consortium et al., 2014; Fedko et al., 2015). SNPs were removed if alleles mismatched with the reference panel, were out of HWE with $p < 10^{-5}$, the Mendelian error rate was larger than the mean + 3 SD, or the imputation quality (R2) was below 0.90. The SNPs in the final cross-platform imputed dataset were aligned similarly to the 1000 Genomes Phase 3 v5 reference panel, and uploaded to the Michigan Imputation Server. Here, the data were phased and imputed to this 1000 genomes panel using Shapeit and Minimac3 respectively. The data were again filtered for SNPs having MAF < 0.01 , HWE $p < 10^{-5}$, alleles not being A, C, G, or T, and a call rate of 99% after all Mendel errors were removed. A random selection of 2500 second degree unrelated people were taken from this dataset. Using the summary statistics, this unrelated set and LDpred, the beta's were corrected. As described in more detail below, polygenic scores were constructed on the relevant 10867 individuals.

Analyses

Part 1. Demographics and phenotypic correlations

First, we applied a saturated twin-sibling model in OpenMx (Boker et al., 2011) including the resilience and well-being scores at both time points to test the equality of means and variances in twins and siblings, and sex differences in the means of resilience and well-being. Furthermore, the cross-sectional and longitudinal phenotypic correlations and twin and twin-sibling correlations within and across traits were estimated.

Part 2. Genetic Prediction

To investigate the molecular genetic overlap between resilience and well-being, we used summary statistics of two recent genome-wide association studies (GWASs) on resilience and well-being to create polygenic scores (PGS). PGS are a measure of an individual's genetic probability to develop a certain disorder or have a certain trait (Wray et al., 2007). Using GWAS summary statistics, the PGS of a phenotype can be calculated in an independent sample by summing all genotype scores (at individual single-nucleotide polymorphisms)

for a person after weighting them by their estimated effect size. The PGS of the phenotype can be used to test the predictive value towards another trait, or to investigate the shared genetic etiology between traits (Purcell et al., 2009).

We used PGS for resilience and well-being to investigate if and to what extent the genetic risk for well-being is a predictor for resilience and vice versa. For well-being, the polygenic scores from the most recent GWAS summary statistics for the well-being spectrum, leaving out NTR, were used (Baselmans, Jansen, et al., 2019). Using the summary statistics of the only GWAS to date on self-assessed resilience based on a sample of 11,492 army soldiers (Stein et al., 2019), we created PGS scores for resilience in the NTR sample.

The polygenic scores were computed using LDpred (Vilhjálmsón et al., 2015). LDpred takes into account linkage disequilibrium (LD) among SNPs in creating the polygenic risk scores. We calculated the mean causal effect size of each marker using the SNP effect sizes from the resilience and well-being summary statistics. The LD structure from a reference set specific for the NTR based on 1000 Genomes phase 1 genotypes (1000 Genomes Project Consortium, 2015) was used to calculate polygenic scores in the target sample, in this case the NTR sample. In order to avoid an over-estimation of the association between the polygenic scores and phenotypes, summary statistics for the well-being GWAS in the discovery set were re-computed, excluding NTR subjects. Polygenic scores were calculated with the fractions of causal genetic variants (the fraction of markers with non-zero effects) set to 1, 0.5, 0.3, 0.2, 0.1, 0.05, and 0.01 to test which fraction suited the data best. We restricted analyses to common variants, using a SNP inclusion criterion of minor allele frequency (MAF) > 5%.

Using GEE to correct for familial relations, we regressed the created PGS of resilience on well-being and vice versa and included age, age², sex, the genotyping array, and the first ten genomic principal components (PCs) as covariates. A significant association indicates that the genetic risk for resilience predicts well-being or vice versa. To correct for multiple testing, we used a Bonferroni corrected threshold of 0.001 for significance.

Part 3.Causality

Next, we investigated the possible direction of causation between resilience and well-being. Under the causal hypothesis, several predictions in cross-sectional and longitudinal data can be made (Bartels et al., 2012; De Moor et al., 2008), that are specified in in section 2.3.3.1 until 2.3.3.4. Importantly, with these test we will not be able to confirm causality, but we are able to falsify the causal hypothesis.

Within-subject change scores. First, we used regression of the within-subject changes in well-being and resilience over time. If there is a causal relation from resilience to well-being, within-subject changes in resilience over time ($T2 - T1$) should predict parallel changes in well-being over time. Under the causal hypothesis, increases in resilience over time would result in increase in well-being. The absence of a correlation of change scores over time would reject the causal hypothesis, whereas the presence of a correlation is in line with causality (Bartels et al., 2012; De Moor et al., 2008). Using GEE to correct for relatedness, regression analyses were performed to predict within-subject changes in well-being by within-subject changes in resilience over time. In reverse, if there is a causal relation from well-being to resilience, within-subject changes from T1 to T2 in well-being should predict parallel changes in resilience over time. These regression analyses exclude confounding by genetic factors, since the genotype within a subject does not change.

Bivariate twin-sibling models. Another prediction under the causal hypothesis is that if resilience is causally related to well-being, all genetic and environmental factors that influence resilience will also, through the causal chain, influence well-being (De Moor et al., 2008).

To test the significance of genetic and environmental correlations between resilience and well-being, we used twin-sibling models. Bivariate twin-sibling models use the difference in genetic overlap between monozygotic (MZ) twins and dizygotic twins (DZ) to estimate the underlying sources of phenotypic variance of two traits and their phenotypic correlation. In addition, these model results can be used to calculate genetic and environmental correlations (de Vries, van Beijsterveldt, et al., 2021). MZ twin pairs are genetically identical, whereas DZ twin pairs share on average half of their segregating genes. Based on this difference, the observed phenotypic variance and covariance between traits can be decomposed into genetic and environmental variance components. Additive genetic variance (A) is the variance explained by the independent allele effects on the phenotype. Non-additive genetic variance (D) refers to interactions between alleles at the same locus (dominance) or between alleles at different loci (epistasis). Environmental variance includes a shared environmental variance component (C) (shared by family members) and a non-shared component, the unique environment, also including measurement error (E). The effects of C and D cannot be estimated simultaneously for identification reasons and a choice between an ACE or ADE model is made based on twin correlations. The power of the classical twin design increases by adding non-twin siblings of twin pairs. These non-twin siblings share on average half of

their segregating genes with other siblings (including the twins) and can be treated as DZ twins in the models (Posthuma & Boomsma, 2000).

Using the log-likelihood ratio test (LRT), the full ACE/ADE models were compared to nested submodels. The difference in minus two times the log-likelihood (-2LL) between two nested models has a χ^2 distribution with the degrees of freedom (df) equaling the difference in df between two models. If a p-value from the χ^2 -test was higher than the alpha of 0.001 (corrected for multiple testing), the constrained and more parsimonious model fit was not significantly worse than the fit of the more complex model. The distribution of resilience and well-being scores were moderately skewed, but showed a bell-shaped curve and were therefore analyzed as continuous variables. Furthermore, whereas the skewed data might bias the parameter estimates, transformations do not remove the known and small bias (underestimation of the shared environmental effect, and overestimation of the unique environmental effect (Derks et al., 2004).

As we have data on resilience and well-being at two time points, we modelled the variance of the underlying phenotypes in a bivariate psychometric model with repeated measures. The resilience and well-being scores at T1 and T2 can be seen as an index of the true measure including measurement error (Amstadter et al., 2014). For both resilience and well-being, the variance was split into a common (latent or stable) part and two uncorrelated (time-specific) parts. Next, both the common and time-specific parts of the variance were decomposed in variance explained by A, C/D, and E. The variance of the latent factors includes less measurement error, therefore this results in more reliable estimates of the genetic and environmental effects (see supplementary Figure S5.1 for the model) and is more comparable to the earlier work by Amstadter et al. (2014).

To investigate the overlap and genetic architecture of the latent factors of resilience and well-being, we estimated genetic and environmental contributions to the variance and covariance of the latent factors. Furthermore, the genetic and environmental correlations are calculated. In this model, we first tested for quantitative sex differences (i.e. if the estimates of the genetic contribution in males and females are similar) by constraining the estimates of A, C/D and E to be equal in males and females. Next, we estimated the contribution of the variance components A and C/D to the total variance and covariance of the phenotypes. We did not test for qualitative sex differences, as modelling sex specific genes in multivariate models has inherent limitations (Neale et al., 2006) and no qualitative sex effects in well-being are expected (Stubbe et al., 2005).

If resilience and well-being are causally related, genetic and environmental factors influencing individual differences in one trait will, through the causal chain, also influence individual differences in the other trait. To test this causal effect hypothesis, we tested the genetic or environmental correlation between the latent traits in the bivariate model. Both the genetic and environmental correlation should be significant if there is causality. A significant genetic correlation but a non-significant environmental correlation falsifies the causal hypothesis and a common genetic factor is then more likely to underlie the association between resilience and well-being.

Longitudinal twin-sibling model. In a similar way, we can use the longitudinal data of resilience and well-being in a bivariate model (De Moor et al., 2008). If resilience causes higher levels of well-being, there should be a significant longitudinal association between resilience at baseline and well-being at follow-up. Similarly, if well-being causes higher levels of resilience, there should be a significant longitudinal association between well-being at T1 and resilience at T2. These phenotypic associations should be paired to significant genetic and environmental correlations. This was tested in a bivariate genetic model by testing the significance of the genetic and environmental correlations between resilience at baseline (T1) and well-being at a later time point (T2) and vice versa (well-being at T1 and resilience at T2).

MZ twin difference model. Another prediction made by the causal hypothesis is that the within-twin pair differences of genetically identical (MZ) twins in resilience should be associated with within-twin pair differences in well-being. We applied the monozygotic within-twin pair differences method. If there is a causal relation, the MZ twin differences ($\text{Resilience}_{\text{twin}_1} - \text{Resilience}_{\text{twin}_2}$) in resilience should be associated with within-twin pair differences in well-being ($\text{Well-being}_{\text{twin}_1} - \text{Well-being}_{\text{twin}_2}$) and vice versa. The twin who is more resilient should have a higher well-being score than the co-twin who is less resilient. At both time points, we regressed the MZ intra pair differences in resilience on the difference in well-being and vice versa. Since monozygotic twins are genetically identical, this test excludes confounding by genetic and shared environmental factors. However, if there is an association, also other factors in the non-shared environment of the twins can underlie this association.

Additionally, we tested whether longitudinal MZ twin intrapair differences (i.e. differences in individuals' changes) in resilience over time are associated with intrapair differences in individuals' changes in well-being over time and vice versa. Again, significant associations are in line with a causal hypothesis. The twin who has a larger increase in resilience should have a larger increase

in well-being than the co-twin who showed less increase in resilience. To test this association, we created within-individual change scores of resilience and well-being and the difference between these change scores of MZ twin pairs. We regressed the MZ intra pair differences in resilience on the difference in well-being and vice versa.

MR-DoC model. To explicitly test causality, allowing for coexisting genetic confounding, we leveraged the unique database of the Netherlands Twin Register and applied the Mendelian Randomization- Direction of Causation (MR-DoC) model. The MR-DoC model uses twin data and polygenic scores, combining the strengths of Mendelian Randomization and the Direction of Causation twin model (Minică et al., 2018). In Figure 1 the MR-DoC model is presented. The black box indicates the DoC model part and the grey box indicates the Mendelian Randomization part.

In the traditional direction of causation twin (DoC) models (Duffy & Martin, 1994; Heath et al., 1993), the covariance between traits and across twins (i.e. the cross-twin cross-trait covariance) can be used to test a causal effect from one trait on the other. The DoC model tests whether the cross-twin cross trait correlations in MZ and DZ twins reflect a unidirectional or bidirectional causal effect or a common genetic factor driving the association between the traits (i.e. significance of path $g1$ in Figure 5.1). However, to be able to distinguish between a causal effect and a common genetic factor in a DoC model, the traits do need to differ in their heritability or the sources of variance (i.e. ACE for trait 1 and AE for trait 2).

In Mendelian Randomization, genetic variants are used to test causal relationships between an exposure variable and outcome (Smith & Ebrahim, 2003). The genetic variants used to probe causal hypotheses are assumed to be: (a) well associated with the exposure variable; (b) not associated with confounders of the exposure-outcome relationship, and (c) associated with the outcome only through exposure (i.e. absence of horizontal pleiotropy). PGS can be used as strong genetic variables, but horizontal pleiotropy (assumption c) is likely to occur with complex traits (Bulik-Sullivan, Finucane, et al., 2015).

Pleiotropy can be divided into direct pleiotropy (i.e. a gene has a direct causal effect on multiple phenotypes, indicated by path $b2$ in Figure 5.1) and indirect pleiotropy. Indirect pleiotropy is when a gene has a causal effect on a phenotype, which in turn causally influences another phenotype (path $b1 * g1$), indicating a causal effect.

By combining MR with twin models, the MR-DoC model can estimate both the causal effect and the amount of pleiotropy using the polygenic scores and the covariance structure between the traits, even when the traits have a similar

heritability or underlying sources of variance (i.e. both AE traits). Using the cross-twin cross-trait correlations of MZ and DZ twins (like in the standard DoC model), the causal path (g_1) between the traits can be estimated. At the same time, using the polygenic score, the MR part of the model normally estimates the causal effect from b_1 and the observed covariance between PRS and the outcome trait (using covariance = $g_1 * b_1$), assuming pleiotropy to be absent (path $b_2=0$). As g_1 is estimated from the twin DoC part, combining the covariance structure and effect of the PGS on the outcome trait, pleiotropy (path b_2) can now be directly estimated. Moreover, when estimating the causal effect in the twin DoC part, pleiotropy is accounted for (for more details and simulations, see Minică et al., 2018). Empirical analysis of height and educational attainment indicated that the test of causality conducted with MR-DoC is relatively robust to assumption violation, such as the presence of pleiotropy or assortative mating (Minică et al., 2020).

When traits have the same genetic architecture (e.g. both AE models), as is often the case, but problematic for the DoC part of the model (see Duffy & Martin, 1994), the environmental correlation between traits has to be constrained to zero for identification purposes.

We tested whether well-being causally affects resilience using the well-being PGS, the exposure being the well-being score and the outcome being the resilience score at time point T1 and T2 separately (see Figure 5.1 for the model). If the estimate for the causal effect from well-being to resilience (g_1) is larger than zero, there is a causal effect from well-being to resilience. The b_2 estimate reflects the pleiotropy between well-being and resilience. Based on the results, the effect size (% variance) of the directional effect can be estimated, taking into account the presence of residual genetic pleiotropy.

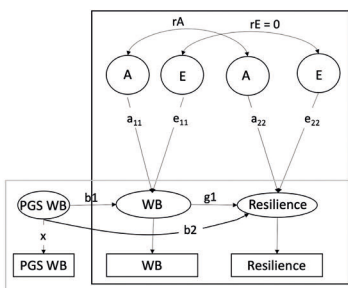


Figure 5.1. The MR-DoC model. The black box indicates the Direction of Causation model part. The grey box indicates the Mendelian Randomization part. Path g_1 indicates the causal effect, path b_1 indicates the PGS effect on well-being and path b_2 reflects the pleiotropy between well-being and resilience. WB= well-being, A= common additive genetic effect, E= common unique environmental effects, rA = additive genetic correlation, rE = environmental correlation.

RESULTS

Operationalization of resilience

The definition of the resilience assumes a positive association between stressful life events and anxious-depression and variability in the anxious-depressed score after stressful life events. Consistent with this definition, people differ in their response to stressful life events, i.e. the variance around the point estimate of anxious-depressed score increased when the number of life events experienced increased (see supplementary Figure S5.2). The number of stressful life events experienced and the anxious-depressed score were positively related at T1 ($r=.11$ [95% CI: .08-.13], $\beta_{\text{gee}}=.11$, $p<.001$) and T2 ($r=.26$ [95% CI: .24-.28], $\beta_{\text{gee}}=.27$, $p<.001$). The residuals from the GEE models were used as the measure for resilience.

Part 1. Demographic effects and phenotypic correlations

In a saturated twin-sibling model, the mean score for well-being could be constrained to be equal across males and females, ($p=.113$). For resilience, the means could not be constrained to be equal across sexes ($p<.001$). The resilience score for men was significantly higher compared to women, indicating that on average men are more resilient than women. The descriptives are given in Table 5.1.

There is a small, but significant effect of age (T1: $\beta=-.03$, $SE=.01$, $p<.001$, T2: $\beta=-.02$, $SE=.01$, $p<.001$) and age² (T1: $\beta=-0.01$, $SE<.01$, $p<.001$, T2: $\beta<-0.01$, $SE<.01$, $p<.001$) on well-being in both waves. Similarly, there is a small effect of age and age² (all: $\beta<0.01$, $SE<.01$, $p<.001$, T2: $\beta<0.01$, $SE<.01$, $p<.001$) on the resilience score. This reflects a U-shaped curve for both well-being and resilience, indicating that younger and older people score higher on resilience and well-being than people in middle adulthood.

Table 5.1. Descriptives of the measures for resilience and well-being.

		Time 1			Time 2		
		<i>N</i>	<i>M</i>	<i>SD</i>	<i>N</i>	<i>M</i>	<i>SD</i>
	Anxious-depression	5641	6.16	5.37	10804	4.99	5.05
	Number of life events	5791	1.53	1.28	9719	2.19	1.84
	Well-being	5790	26.52	0.07	11497	27.29	0.06
Male	Resilience	1894	2.97	0.21	2844	1.94	0.19
Female	Resilience	3681	-2.02	0.16	6174	-0.84	0.14

Note: the means and standard deviation for anxious-depression and number of life events are unstandardized. To compute the resilience score, these scores were standardized.

Table 5.2 shows the phenotypic correlations between resilience and well-being cross-sectionally and across the different time points. The cross-sectional phenotypic correlations between resilience and well-being are .46 (95% CI: .44-.48) and .51 (95% CI: .50-.52) at T1 and T2 respectively. The longitudinal phenotypic correlations are .35 (95% CI: .34-.36) for resilience at T1 and well-being at T2 and .43 (95% CI: .43-.44) for well-being at T1 and resilience at T2.

Table 5.2. Phenotypic correlations (with 95% CI) between resilience and well-being within and across time points.

	Well-being 1	Well-being 2	Resilience 1	Resilience 2
Well-being 1	1			
Well-being 2	0.55 (.54-.56)	1		
Resilience 1	0.46 (.44-.48)	0.35 (.34-.36)	1	
Resilience 2	0.43 (.43-.44)	0.50 (.50-.52)	0.61 (.60-.62)	1

Part 2. Genetic Prediction

The polygenic score predictions of resilience and well-being using the different fractions of included SNPs (1 to 0.01) are in Supplementary Figure S5.3. The prediction of polygenic scores using a fraction of 0.5 are optimal, therefore we proceed with a fraction of 0.5. The GEE analyses showed that the PGS of direct self-assessed resilience is not significant in predicting our

indirect resilience score at T1 ($p=.248$) and T2 ($p=.002$), predicting only around 0.04-0.20% of the variance. The prediction of well-being by the resilience PGS is not significant (T1: $p=.822$ and T2: $p=.144$) and close to zero (see Figure 5.2, left panel).

The well-being PGS is a significant predictor for both well-being and resilience at both time points ($p<.001$), explaining around 0.8-0.9% of the variance in well-being and 1.4-1.8% of the variance in resilience (see Figure 5.2, right panel), suggesting genetic overlap between resilience and well-being.

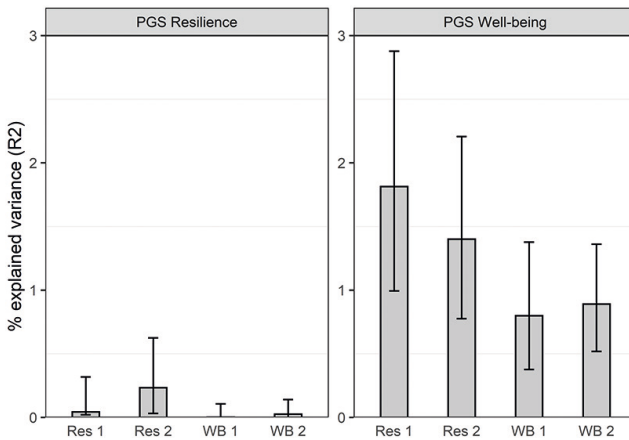


Figure 5.2. Explained variance in the phenotypic resilience and well-being scores by the polygenic scores (PGS) of resilience (left panel) and well-being (right panel). Res 1= resilience time point 1, Res 2= resilience time point 2, WB 1= well-being time point 1, WB 2= well-being time point 2..

Part 3. Causality

Within-subject change scores

A change in resilience in an individual over time predicted a parallel change in well-being over time, $\beta=.33$ (95% CI: .29 -.38), $SE=0.02$, $Z=15.67$, $p<.001$. Similarly, within individual change in well-being predict a parallel change in resilience over time, $\beta=.34$ (95% CI: .30 -.38), $SE=0.02$, $Z=15.95$, $p<.001$ (see Figure 3). These results are in line with a possible causal relation between resilience and well-being, indicating that increased well-being can lead to increased resilience and/or vice versa, after genetic confounding is taken into account.

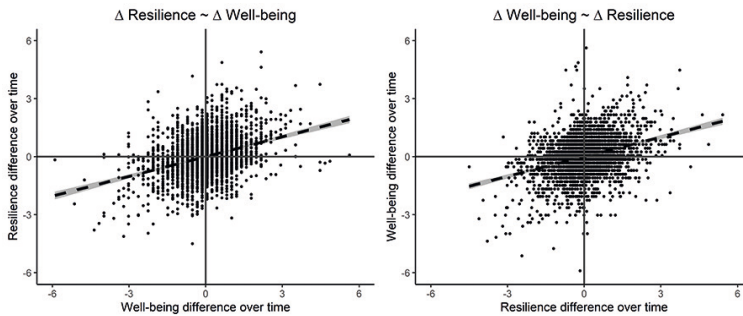


Figure 5.3. The relation between the within-subject differences over time in resilience and well-being.

Bivariate twin-sibling models

Table 5.3 shows the twin and twin-sibling correlations for resilience and well-being within and cross traits and time points. Overall, the MZ correlations are more than twice the DZ/sibling correlations, suggesting dominant genetic effects besides additive genetic effects. Therefore, we continued with ADE models. Constraining all sibling correlations to the DZ correlations did not deteriorate the fit ($p=.297$), indicating that DZ twins do not resemble each other more than siblings (i.e. no specific twin environment).

The full bivariate ADE measurement model with sex differences is shown in supplementary Figure S5.4. First, we tested the quantitative sex effect by constraining all path estimates to be equal for males and females (see Table 5.4, model 2). This model gave a significant deterioration of fit ($p<.001$). Next, we tested if only the latent factor path estimates could be constrained to be equal in males and females, whereas the path estimates of the time-specific factors were allowed to differ. This model did not lead to a deterioration of the fit, $p=.400$. Next, both specific and common dominant genetic effects (D) did not contribute significantly to the (co)variance ($p=.269$). Therefore, the final model is an AE model without sex differences in the latent factor, but with sex differences in the time-specific factors (see Figure 5.4).

Table 5.3. The twin and twin-sibling correlations for resilience and well-being within (diagonal) and cross traits and time points (off-diagonal).

	WB1	WB2	Res1	Res2	WB1	WB2	Res1	Res2
MZM								
WB1	.32 (.20,.42)				.38 (.31,.44)			
WB2	.38 (.29,.46)	.46 (.38,.52)			.34 (.29,.38)	.35 (.30,.39)		
Res1	.18 (.09,.26)	.32 (.23,.41)	.43 (.30,.53)		.28 (.24,.32)	.22 (.18,.27)	.48 (.42,.52)	
Res2	.24 (.15,.32)	.34 (.28,.34)	.37 (.28,.46)	.51 (.41,.58)	.26 (.22,.30)	.21 (.17,.24)	.39 (.35,.43)	.42 (.38,.42)
DZF								
WB1	.02 (-.12,.20)				.11 (.01,.20)			
WB2	.09 (-.06,.23)	.26 (.11,.38)			.13 (.05,.20)	.22 (.14,.29)		
Res1	.140 (.11,.27)	.12 (-.02,.25)	.22 (-.01,.41)		.08 (.03,.15)	.10 (.03,.18)	.17 (.07,.27)	
Res2	.09 (-.10,.27)	.14 (-.00,.26)	.27 (.08,.42)	.29 (.08,.30)	.06 (-.02,.13)	.11 (.05,.17)	.11 (.03,.19)	.19 (.11,.27)
DOS								
WB1	.09 (-.01,.20)				.11 (.03,.18)			
WB2	.07 (-.01,.15)	.11 (.03,.19)			.07 (.00,.13)	.13 (.05,.20)		

Table 5.3. The twin and twin-sibling correlations for resilience and well-being within (diagonal) and cross traits and time points (off-diagonal).

	WB1	WB2	Res1	Res2	WB1	WB2	Res1	Res2
Res1	.06 (-.02,.13)	.07 (-.00,.15)	.14 (.04,.24)		.09 (.03,.15)	.08 (.01,.13)	.13 (.04,.20)	
Res2	.05 (-.04,.05)	.08 (.06,.15)	.19 (.10,.25)	.16 (.07,.24)	.09 (.02,.14)	.10 (.04,.16)	.12 (.06,.19)	.14 (.05,.22)
Brothers								
WB1	.05 (-.07,.17)				.04 (-.05,.12)			
WB2	-.02 (-.13,.09)	.26 (.11,.38)			.10 (.03,.16)	.15 (.07,.22)		
Res1	.07 (-.05,.19)	.12 (-.02,.25)	.23 (.01,.38)		.07 (.010,.13)	.09 (.03,.15)	.19 (.11,.27)	
Res2	-.06 (-.19,.07)	.14 (-.00,.26)	.09 (-.09,.27)	.17 (-.10,.34)	.10 (.03,.15)	.07 (.01, .14)	.17 (.10,.23)	.16 (.07,.23)
DZ/siblings*								
WB1	.08 (.08,.09)							
WB2	.08 (.07,.10)	.15 (.13,.15)						
Res1	.08 (.07,.11)	.09 (.06,.10)	.17 (.12,.19)					

Table 5.3. The twin and twin-sibling correlations for resilience and well-being within (diagonal) and cross traits and time points (off-diagonal).

	WB1	WB2	Res1	Res2	WB1	WB2	Res1	Res2
Res2	.07 (.05,.08)	.09 (.09,.09)	.15 (.13,.17)	.16 (.16,.17)				

Note: res = resilience, WB= well-being. * Twin correlations constrained to be equal in DZ twins and siblings to test the assumption of equal environments.

Table 5.4. Results of the model fitting for the psychometric model for resilience and well-being.

Model	Variables	Constraints	vs	-2LL	df	AIC	Δ -2LL	Δ df	p
I	ADE			176426.98	27034	122358.98			
II	ADE	Equal sex	I	176614.80	27067	122480.80	187.82	33	1.43×10^{-23}
III	ADE	Equal sex only in latent part	I	176436.40	27043	122350.40	9.42	9	.400
IV	ADE	D=0	III	176449.79	27054	122341.79	13.39	11	.269

Note: df= degrees of freedom.

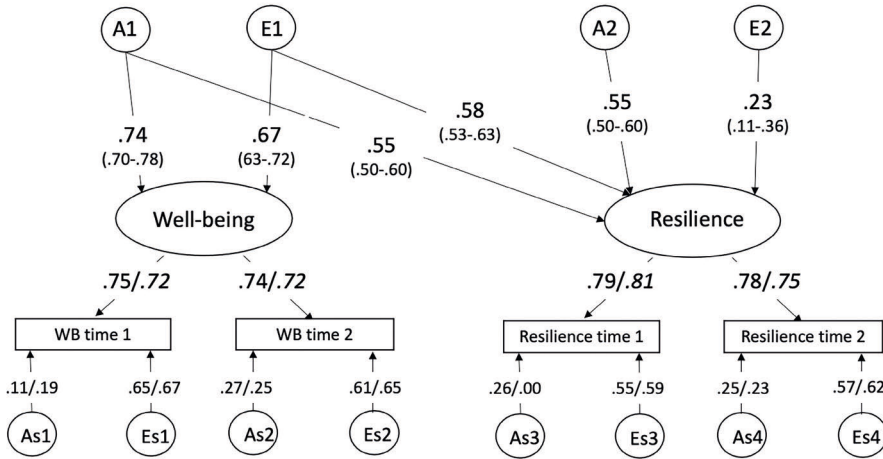


Figure 5.4. Unstandardized path estimates of the final common pathway model of resilience and well-being. The factor loadings from the common factors to the time-specific factors and the time-specific variance decomposition could not be constrained to be equal for females and males, indicated by estimates for females/males. WB= well-being, A= common additive genetic effect, E= common unique environmental effects, As= time-specific additive genetic effect, Es= time-specific environmental effect.

In the final bivariate model, the heritability of the latent well-being factor is estimated at 54.8% (95% CI: 53.1-57.1), whereas the unique environment explains 45.2% (43.1-51.4) of the variance in well-being. The heritability of the latent resilience factor is 60.9% (95% CI: 60.6- 62.3) and the unique environment explains 39.1% (38.9-41.2) of the variance. At time 1 and time 2, time specific genetic influences explained respectively 32% and 37% of the variance in well-being in females. For males, the time specific heritability of well-being was similar, with 32% and 35% at T1 and T2 respectively. For resilience, the time specific heritability was 45% and 43% for females, but lower for males, with 39% and 36% at T1 and T2 respectively.

Of the covariance between resilience and well-being, 51.2% is explained by genetic factors and 48.8% by environmental factors. The genetic and environmental correlation between the latent factors of resilience and well-being are .71 (95% CI: .70-.71) and .93 (95% CI: .86-.98) respectively. As expected under the causal model, the genetic and environmental correlations could not be constrained to zero, $p < .001$ (see supplementary Table S5.3).

Longitudinal twin-sibling models

In a bivariate longitudinal twin model with the resilience score at T1 and well-being at T2, we could not constrain the estimates to be equal across sex.

Thus we tested the significance of the genetic and environmental correlations separately for males and females, by constraining the covariance between resilience and well-being. In line with the measurement model, we dropped D dropped ($p=.005$). The genetic correlations from resilience at baseline and well-being at T2 were .62 (95% CI: .53-.74) and .63 (95% CI:.41-.85) for females and males respectively. The environmental correlations were .19 (95% CI:.11-.26) and .23 (95% CI:.10-.35). Constraining any of the correlations to zero resulted in a deterioration in fit ($p<.001$) (see supplementary Table S5.4), in line with a causal relationship from resilience at T1 to well-being at T2.

In a bivariate model with the well-being score at T1 and resilience at T2 separately for males and females, we dropped D ($p=.002$). The genetic correlation from well-being at baseline and resilience a few years later were .64 (95% CI: .52-.76) and .29 (95% CI: .24-.55) for females and males respectively. The environmental correlations were .20 (95% CI: .12-.27) and .32 (95% CI: .19-.43). Constraining the genetic correlation to zero in females or the environmental correlation to zero in males and females resulted in a deterioration of the model fit ($p<.001$). In males, constraining the genetic correlation to zero did not change the model fit ($p=.033$) (see supplementary Table S5.5) which seems to falsify the causal hypothesis in males.

MZ twin difference model

The MZ twin intrapair differences model showed that regressing the resilience MZ twin difference score on the well-being MZ twin difference score resulted in significant estimates at both time points (T1: $\beta=.38$, $SE=0.03$, $R^2 = 0.15$, $p<.001$, T2: $\beta=.47$, $SE=0.02$, $R^2 = 0.21$, $p<.001$). Similarly, regressing the well-being difference score of MZ pairs on the resilience difference score resulted in significant estimates (T1: $\beta=.40$, $SE=0.03$, $R^2 = 0.15$, $p<.001$, T2: $\beta=.44$, $SE=0.02$, $R^2 = 0.21$, $p<.001$) (see Figure 5.5 upper panels).

The MZ twin longitudinal intrapair differences model showed a significant estimate from regressing the resilience change difference score on the well-being change difference, $\beta=.32$, $SE=0.05$, $R^2 = 0.10$, $p<.001$. Similarly, regressing the well-being difference score on the resilience difference score resulted in a significant estimate, $\beta=.33$, $SE=0.05$, $R^2 = 0.10$, $p<.001$ (see Figure 5.5 lower panel).

These findings are in line with a possible causal relation between resilience and well-being, indicating that higher well-being can lead to higher resilience and/or vice versa. As MZ twins share 100% of their genes, genetic confounding is taken into account.

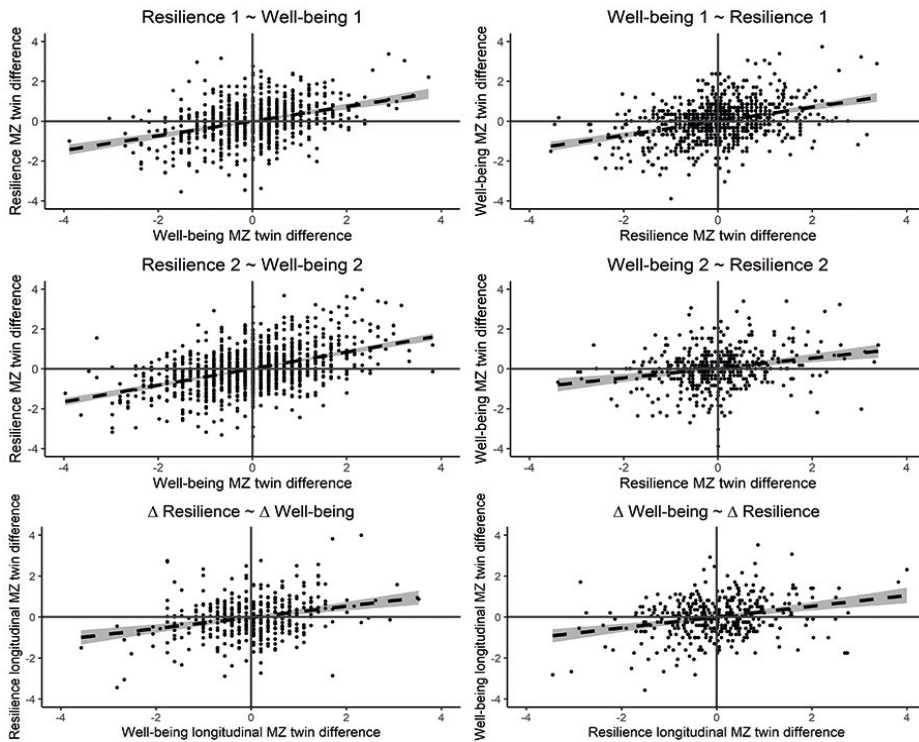


Figure 5.5. The monozygotic twin differences models. In the left upper panels, the MZ twin difference score of resilience is predicted by MZ twin differences in well-being (cross-sectional, at T1 and T2). In the right upper panels, the MZ twin difference score of well-being is predicted by MZ twin differences in resilience (cross-sectional, at T1 and T2). The lower panel shows the longitudinal association between MZ within-twin pair differences in resilience and well-being.

MR-DoC model

Lastly, we included the PGS as an instrumental variable in the twin model, applying the MR-DoC model (Minică et al., 2018) that can model causal effects while relaxing the MR no pleiotropy assumption. Due to data limitations (i.e. the resilience PGS is not powerful in predicting resilience), we could only test the effect of well-being on resilience. When including the PGS for well-being, estimating the pleiotropic effect freely and constraining the environmental correlation (r_E) to zero, the direct effect from well-being to resilience cannot be dropped from this model at both times, $p < .001$ (see Figure 5.6 and supplementary Table S5.6 and S5.7), in line with a causal relation from well-being to resilience. The explained variance in resilience by well-being is 11.6% and 19.4% at time point 1 and 2 respectively. In addition, as expected, there is

pleiotropy between well-being and resilience as indicated by the significant path b2 from the well-being PGS to resilience.

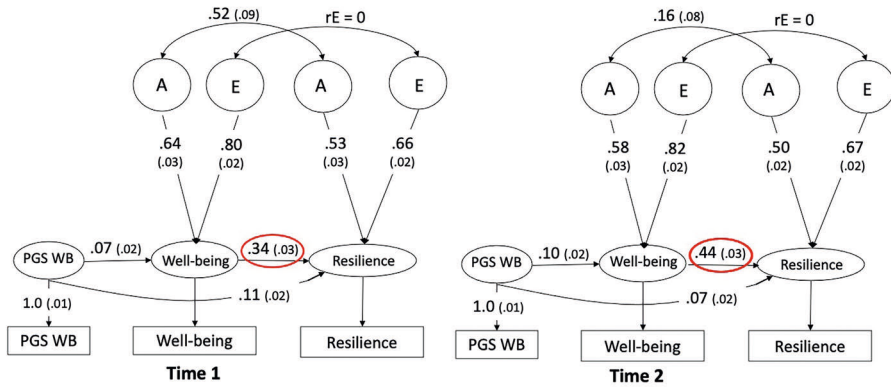


Figure 5.6. The results of the MR-DoC model. The models show the model with the well-being polygenic score and resilience as the outcome in cross-sectional data from time point 1 and 2 respectively. The causal effects can be seen in the red circle. WB= well-being, PGS= polygenic score, A= additive genetic effect, E= unique environmental effect, rE= environmental correlation.

We cannot freely estimate the environmental correlation (rE) in the model, as both well-being resilience are AE traits. However, we can fix the rE to a correlation of various sizes instead of fixing the correlation to zero. As exploratory analyses we ran different MR-DoC models fixing the rE to respectively 0.1, 0.2, 0.3, 0.4, 0.5, and 0.8 at both time points (see supplementary Table S5.8 for the model fits). As indicated by the equal model fits, we did not have the power to distinguish between the model fit of a model with rE is 0, 0.1, 0.2 and 0.3. At time point 1 (and similarly for time point 2), the estimate of the causal effect from well-being to resilience decreased from 11.6% when $rE=0$ to respectively 6.6%, 3.0% and 0.7% with a rE of 0.1, 0.2 and 0.3. With a fixed rE of 0.4 and higher, the model fit started to decrease and the causal effect estimate was not significant anymore.

DISCUSSION

Summary of results

We investigated the association between resilience and well-being in a large sample of twins and their siblings from the Netherlands Twin Register and tested whether the observed overlap between resilience and well-being was due to bidirectional causal effects, after taking into account genetic possible genetic overlap between the two traits. The twin-sibling models showed strong cross-sectional and longitudinal correlations and a large overlap in genetic and environmental factors underlying resilience and well-being. There was a sex effect in the resilience mean score (men showed more resilience than women), but no sex difference in the genetic architecture of the latent factors for resilience and well-being. Results based on studies using GWAS summary statistics provided weak support for causal effects. Polygenic score analyses showed that the genetic risk for well-being is a predictor for resilience, but the genetic risk for self-reported resilience did not predict indirect resilience or well-being. The results of different causality analyses in twin-sibling models (De Moor et al., 2008) were not successful in falsifying the bidirectional causal relation between resilience and well-being. The explicit and most informative test of causality, the MR-DoC model using both twin and PGS data, supported the unidirectional causal hypothesis from well-being to resilience, whereas we could not test the causal hypothesis from resilience to well-being, due to power issues in the resilience GWAS data.

Using a psychometric twin model with data of two time points, the heritability estimates for the latent traits well-being and resilience were similar with respectively 54.8% and 60.9%. More than half of the variance in the stable part of resilience and well-being is explained by genetic factors. Whereas the heritability estimates at the two time points were around 30-40% for both traits, the heritability estimates of the psychometric model were higher, as this is not confounded by measurement error and time-specific influences. These estimates are highly comparable to earlier studies on resilience and well-being (Amstatter et al., 2014; Bartels, 2015; Boardman et al., 2008).

About 50% of the covariance between resilience and well-being is explained by genetic factors and the strong genetic correlation (.71) indicates that the genetic factors underlying resilience and well-being overlap significantly. Environmental factors explain the other half of the covariance between resilience and well-being. The environmental correlation between the latent traits is close to unity (.93) and indicates an almost perfect overlap in the environmental factors influencing both traits.

The various analyses using genetically informative samples were not successful in falsifying the causal hypothesis, even when correcting for genetic confounding. Therefore, we suggest that our findings are in line with a bidirectional causal relation between resilience and well-being instead of an underlying set of genes and/or environmental factors. To strengthen this finding, we applied the MR-DoC model. The MR-DoC model allows us to estimate causal effects, even in the presence of pleiotropy between the phenotypes. This model yielded results consistent with a causal relation from well-being to resilience, with about 11% (T1) and 20% (T2) of the variance in resilience explained by a causal effect from well-being. Due to the limited power of the resilience PGS, the causality in the other direction, from resilience to well-being could not be tested reliably in the MR-DoC model.

The assumption that the unique environmental sources of variation for resilience and well-being equals zero is necessary in the MR-DoC model for identification and this might seem implausible as we find an environmental correlation of .93 for well-being and resilience in the latent twin-sibling model. However, the unique environmental effects on well-being can be related with resilience via the causal path only, where the unique environmental effects influence the outcome via its effect on the exposure and not directly. In bivariate twin models, this causal path is missing, what could result in a large environmental correlation.

As exploratory analyses, we fixed the environmental correlation to various sizes instead of fixing the correlation to zero. This led to equal model fits for an environmental correlation of 0, 0.1, 0.2 and 0.3, as we did not have the power to distinguish between these models. At time point 1, the estimate of the causal effect from well-being to resilience decreased from 11.6% when the environmental is zero to respectively 6.6%, 3.0% and 0.7% with a rE of 0.1, 0.2 and 0.3. With a higher environmental correlation, the model fit started to decrease and the causal effect estimate was not significant anymore. These results indicate that the model does find a causal effect between well-being and resilience. However, it is likely that there is an environmental correlation between well-being and resilience as well, reducing the size of the causal effect. More power is needed to determine the size of the causal effect.

Another explanation for the strong correlations between resilience and well-being could be a third variable underlying both traits and explaining the bidirectional relationship between them. For example, self-rated general health has a strong genetic correlation with well-being (Baselmans, van de Weijer, et al., 2019), although the direction of causation between well-being and health is not clear (Rohrer & Lucas, 2020). If general health (or another variable)

causally influences both well-being and resilience, a strong correlation between well-being and resilience does not necessarily mean the constructs have an influence on each other. Future research should include such variables in one analysis to investigate this possibility. For now, based on the converging results of the different analyses, we suggest resilience and well-being might have some causal effects on each other.

Points of discussion and limitations

Defining resilience and well-being

There is discussion about definition of resilience and well-being resulting in no universal or commonly agreed upon definition. Different questionnaires are validated to assess self-report resilience, like the Ego-Resilience scale (Block & Kremen, 1996) and Connor-Davidson Resilience Scale (Connor & Davidson, 2003). More recently, researchers are emphasizing the need for improved operationalizations of resilience (Kalisch et al., 2019; Stainton et al., 2019). Resilience is not a stable trait but a complex, interactive process leading to positive psychological outcomes in response to stress or adversity (Kalisch et al., 2017). In line with these definitions, in our sample, direct self-reported resilience seems to be different from resilience measured as the response to exposure to stress, based on the non-significant polygenic score predictions in our study. Therefore, the results also underscore the need for a clear and commonly agreed upon definition of resilience.

We defined resilience as the better than predicted psychological outcome based on the number of stressful life events experienced. A difficulty in this definition is the inclusion of the type and number of life events experienced. In our study, we included 16 and 19 (time 1 and 2) life events about illness, death of close others and events like robbery and accidents. This is not an exhaustive list of life events and the personal impact of life events might differ per individual. Furthermore, treating all these different types of stressful events as equivalent is not likely to be true. Therefore, further research should weight the personal impact of life events or group the life events in different categories to better operationalize resilience and to get a better hold on the direction of causation between resilience and wellbeing.

Furthermore, whereas we focused on the absence of psychopathological symptoms after stress as our resilience measure to compare the overlap with well-being, another approach to measure resilience is to assess the positive adaptation after stress (e.g. see Fletcher & Sarkar, 2013; Luthar, 2006). As mental health is more than the absence of psychopathology, instead of assessing

anxious-depressive symptoms, well-being can be assessed as the outcome measure after stress. If people experience higher well-being than expected based on the stress experienced, this could be a sign of resilience as well.

Multiple theories about the definition of well-being exist as well and as mentioned in the introduction, often a distinction between hedonic and eudaimonic well-being is made. Factor analytic studies showed that hedonic and eudaimonic aspects of well-being load on separate yet highly correlated factors, with correlations in the range of 0.81 to 0.92 (Bobowik et al., 2015; Gallagher et al., 2009; Keyes, 2002; Keyes et al., 2002). Application of less restrictive exploratory structural equation modelling results in a correlation of 0.60 between hedonic and eudaimonic well-being (Joshani, 2016). In previous work we replicated the phenotypic correlation ($r = 0.53$) and reported an even stronger genetic correlation ($r_g = 0.78$) between eudaimonic and hedonic well-being (Baselmans & Bartels, 2018). In the present study, we included life satisfaction as a measure of hedonic well-being. Further research should investigate the relation between resilience and other measures of hedonic and eudaimonic well-being. However, because of the strong (genetic) overlap between the different well-being measures, we expect similar results.

Resilience GWAS

The GWAS summary statistics used to compute polygenic scores for resilience were based on the only GWAS to date on (self-reported) resilience (Stein et al., 2019). The GWAS in the relatively small US army soldiers sample ($N=11,492$) resulted in one independent significant locus. The use of these GWAS summary statistics comes with the following limitations. First, the discovery sample size is small, resulting in less power to detect genetic associations and subsequently less power to predict resilience using the summary statistics of the GWAS (Dudbridge, 2013). Secondly, a sample restricted to soldiers might not reflect the general population (i.e., results based on this sample might not generalize to the population). Third, in contrast to our indirect measure of resilience, the GWAS included a direct measure of self-reported resilience (STARRS 5-item questionnaire, rating of the ability to handle stress). Therefore, the PGS based on these summary statistics reflects the genetic risk for self-report resilience.

As can be seen in our results, the power to detect association between the resilience PGS and the resilience measure was low. The resilience PGS did predict indirect resilience to some extent, but the variance explained was almost zero ($<.001\%$). Furthermore, although there is an indication for a genetic relation and overlap between resilience and well-being, the self-reported

resilience PGS did not predict well-being. Due to the low power of the resilience PGS and the small association between the resilience PGS and resilience score, applying the MR-DoC model including the resilience PGS would not lead to reliable results. Not all MR assumptions (i.e. the strong association between the genetic instrument and exposure) are fully met.

The MR-DoC model can be extended to test a bidirectional relationship, including both PGS of resilience and well-being at the same time. Such a model can strengthen the results and the constraint of the environmental correlation to zero is not necessary anymore. However, for this model two sets of powerful polygenic scores are needed. As the resilience PGS lacks power, we did not model such a bidirectional MR-DoC model. Similarly, as the resilience GWAS is not predictive of our outcome-based measure of resilience and did not have much power, we did not apply SNP based MR methods, such as two-sample MR methods, like MR-Egger. Even if these methods would show causality, the results will not be informative about the relation between well-being and outcome-based resilience, as it has been shown that there is only a moderate degree of genetic overlap between self-reported and outcome-based resilience, using twin models (Sawyers et al., 2020).

The less powerful PGS for resilience due to the small GWAS discovery sample and different operationalization of resilience limits the interpretation of the molecular genetic analyses in our study. To replicate and strengthen our findings on the overlap and direction of effect between resilience and well-being with molecular genetic data, a powerful GWAS for resilience as response to stress (instead of direct self-reported resilience) carried out in a large sample from the general population is needed. In line with our operationalization, a measure of internalizing problems (e.g. anxiety and/or depression) and the number of experienced life events can be combined to create such a measure of resilience in a large genotyped sample.

Lastly, as with most GWASs, we used the summary statistics resulting from studies restricted to individuals with European ancestry. Therefore, our results might not generalize to populations of different genetic ancestries. Recently, large projects to include individuals from other ancestries have been started as analyzing a more inclusive and diverse dataset might increase power to detect associations (Pan-UKB-team, 2020).

Implications

The results in our large genetically informative sample suggest a large overlap and a potential bidirectional relationship between resilience (psychological outcome after negative life events) and well-being (life

satisfaction). If replicated, the results implicate that increasing well-being might lead to increased resilience (i.e. a positive psychological outcome after negative life events or trauma) as well and vice versa. As resilience and well-being are both negatively related to psychopathology (Amstadter et al., 2016; Diener et al., 2017; Greenspoon & Saklofske, 2001; Howell et al., 2007), the bidirectionality between the positive constructs of resilience and well-being can have implications for interventions to prevent or lower vulnerability for psychopathology. Increasing well-being can be important to prevent trauma-related psychopathology and psychiatric symptoms. Vice versa, increasing resilience (i.e. decreasing the likelihood of psychopathological or psychiatric symptoms after trauma) can protect an individual's well-being after stress. The independent interventions related to increasing well-being and separate interventions for coping with trauma might supplement each other.

Supplementary Material Chapter 5

The age of siblings and twins is not significantly different at both time points (Time 1: Twins: $M=32.28$, $SD=11.21$, Siblings: $M=34.73$, $SD=11.85$. Time 2: Twins: $M=31.07$, $SD=14.46$, Siblings: $M=34.92$, $SD=13.70$).

Table S5.1.
Number of participants per zygosity and sex for every variable.

	Resilience 1			Well-being 1			Resilience 2			Well-being 2						
	T 1	T 2	S m	S f	T 1	T 2	S m	S f	T 1	T 2	S m	S f				
MZF	769	717	127	187	795	747	126	198	1367	1259	144	220	1674	1508	171	267
MZM	323	264	74	71	333	274	76	74	506	441	69	99	649	551	87	121
DZF	412	336	67	86	433	354	70	92	708	574	82	124	891	709	96	142
DZM	178	128	35	46	184	125	35	47	293	224	40	66	394	283	49	78
DZO	392	358	82	110	405	377	83	119	629	621	89	147	914	813	105	183
Total	2074	1803	385	500	2150	1877	390	530	3503	3119	424	656	4522	3864	508	791

Note: T1= twin 1, T2= twin 2, Sm= sibling male, Sf= sibling female.

Table S5.2.
The stressful life events included in the questionnaire at both time points.

Time 1	Time 2
1. Death of life partner,	1. Financial problems,
2. Death of father,	2. Job loss,
3. Death of mother,	3. Drop out of education,
4. Death of child,	4. Relationship problems with partner,
5. Death of sibling,	5. Relationship problems with child,
6. Death of other loved one,	6. Relationship problems with other loved one,
7. Serious disease of yourself,	7. Getting hospitalized,
8. Serious disease of life partner,	8. Serious illness yourself,
9. Serious disease of child,	9. Serious illness partner,
10. Serious disease of other loved one,	10. Serious illness child,
11. End of relation,	11. Serious illness parent,
12. Traffic accident,	12. Serious illness other loved one,
13. Violent crime,	13. Death of partner,
14. Sexual crime,	14. Death of child,
15. Theft,	15. Death of other loved one,
16. Getting fired.	16. Traffic accident,
	17. Theft,
	18. Violent crime,
	19. Sexual crime.

Table S5.3.
Results of the psychometric model constraining the genetic and environmental correlation.

Base	Comparison	-2LL	df	AIC	Δ LL	Δ df	p
AE		176449.79	27054	122341.79			
AE	rA=0	176731.08	27055	122621.08	281.29	1	3.93E-63
AE	rE=0	176966.24	27055	122856.24	516.46	1	2.50E-114

Note: rA= genetic correlation, rE= environmental correlation.

Table S5.4.

Results of the longitudinal twin model fitting for resilience at baseline and well-being a few years later.

Base	Comparison	ep	-2LL	df	AIC	Δ LL	Δ df	p
AE		16	93841.40	14431	64979.40			
AE	rAf=0	15	93946.52	14432	65082.52	105.13	1	<.0001
AE	rAm=0	15	93867.60	14432	65003.60	26.20	1	<.0001
AE	rEf=0	15	93863.40	14432	64999.37	21.97	1	<.0001
AE	rEm=0	15	93853.11	14432	64989.12	11.73	1	<.0001

Note: ep= estimated parameters, rAf= genetic correlation females, rAm= genetic correlation males, rEf= environmental correlation females, rEm= environmental correlation males.

Table S5.5.

Results of the longitudinal twin model fitting for well-being score at baseline and resilience a few years later.

base	comparison	ep	-2LL	df	AIC	Δ LL	Δ df	p
AE		16	86832.88	12633	61566.88			
AE	rAf=0	15	86909.84	12634	61641.84	76.96	1	<.0001
AE	rAm=0	15	86837.44	12634	61569.44	4.55	1	.0329
AE	rEf=0	15	86855.64	12634	61587.64	22.76	1	<.0001
AE	rEm=0	15	86854.52	12634	61586.52	21.63	1	<.0001

Note: ep= estimated parameters, rAf= genetic correlation females, rAm= genetic correlation males, rEf= environmental correlation females, rEm= environmental correlation males.

Table S5.6.
Results of the MR-DoC model fitting for the different time points.

base	comparison	ep	-2LL	df	AIC	Δ LL	Δ df	p
Time 1								
WB -> RES		35	22796.60	8442	5912.6			
WB -> RES	g1=0	34	22898.07	8443	6012.1	101.5	1	7.27E-24
Time 2								
WB -> RES		35	30263.71	11243	7777.707			
WB -> RES	g1=0	34	30560.39	11244	8072.391	296.684	1	1.74E-66

Note: WB= well-being, RES= resilience, g1= causal effect, ep= estimated parameters, df= degrees of freedom.

Table S5.7.
Estimates of the MR-DoC models for the different time points.

Standardized	Time 1: WB -> Resilience		Time 2: WB -> Resilience		
	name	Estimate	Std.Error	Estimate	Std.Error
Causal effect	g1	0.337	0.033	0.443	0.025
PGS exposure	b1	0.077	0.022	0.098	0.017
PGS outcome	b2	0.109	0.019	0.069	0.016
A effect exposure	ab	0.638	0.032	0.581	0.025
E effect exposure	eb	0.795	0.022	0.816	0.016
A effect outcome	as	0.530	0.029	0.502	0.022
E effect outcome	es	0.659	0.018	0.673	0.015
PGS to PGS	x	1.001	0.012	1.001	0.012
Genetic correlation	ra	0.521	0.090	0.159	0.082

Note: WB= well-being.

Table S5.8.
Model fit of models with various fixed *rE* values.

Time 1	rE	parameters	-2LL	df	AIC	g1	R2 (%)
	0	35	8442	22796.6	5912.6	0.337	11.36%
	0.1	35	8442	22796.6	5912.6	0.2536	6.43%
	0.2	35	8442	22796.6	5912.6	0.168	2.81%
	0.3	35	8442	22796.6	5912.6	0.076	0.58%
	0.4	35	8442	22797.1	5913.08	0	0.00%
	0.5	35	8442	22811.3	5927.3	0	0.00%
	0.8	35	8442	23106.7	6222.7	0	0.00%
Time 2	rE	parameters	df	-2LL	AIC	g1	R2 (%)
	0	35	11243	30263.7	7777.71	0.443	19.62%
	0.1	35	11243	30263.7	7777.71	0.36	12.96%
	0.2	35	11243	30263.7	7777.71	0.275	7.56%
	0.3	35	11243	30263.7	7777.71	0.184	3.39%
	0.4	35	11243	30263.7	7777.71	0.083	0.69%
	0.5	35	11243	30265.1	7779.07	1.1E-14	0.00%
	0.8	35	11243	30832.1	8346.13	3.9E-10	0.00%

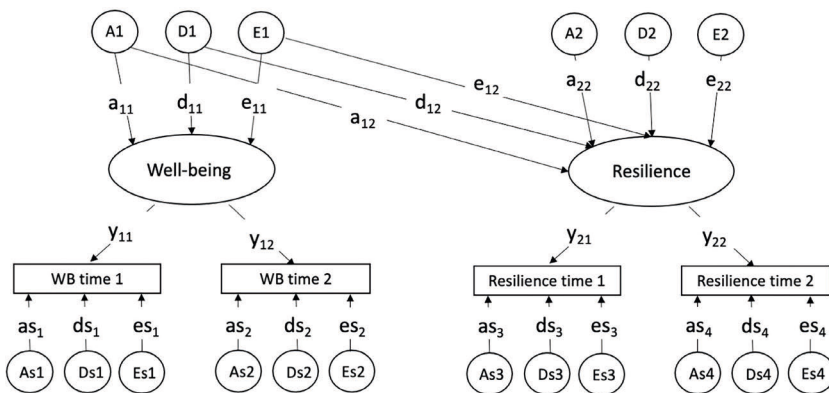


Figure S5.1. Longitudinal measurement model. WB= well-being, A= common additive genetic effect, E= common unique environmental effects, As= time-specific additive genetic effect, Es= time-specific environmental effect.

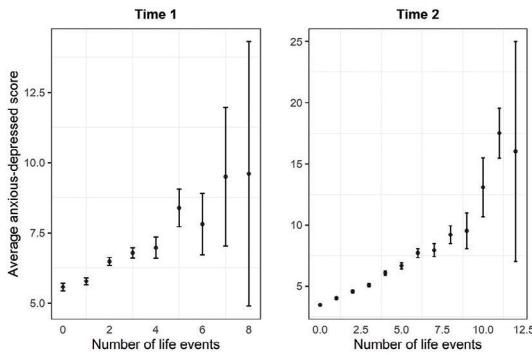


Figure S5.2. Association between the number of life events and the anxious depressed score.

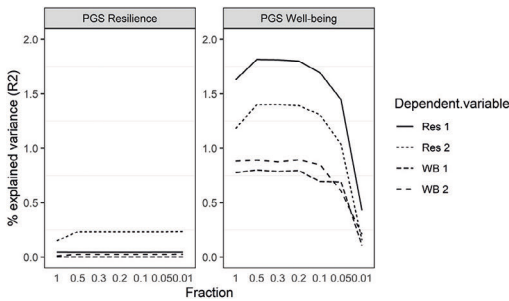


Figure S5.3. Explained variance by the resilience and well-being PGS for the different fractions of SNPs included.

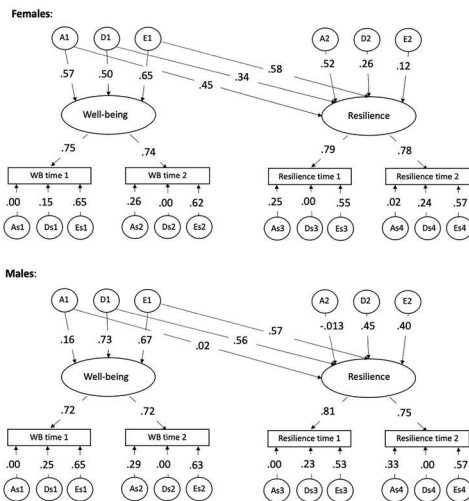


Figure S5.4. Path estimates of the full common pathway model of resilience and well-being for females and males. WB= well-being, A= common additive genetic effect, E= common unique environmental effects, As= time-specific additive genetic effect, Es= time-specific environmental effect.



Chapter 6.

Distinguishing Happiness and Meaning in Life from Depressive Symptoms: a GWAS-by-subtraction study in UK Biobank

In preparation as de Vries, L.P., Demange, P., Vinkers, C.H, Pelt, H.M., & Bartels, M. Distinguishing Happiness and Meaning in Life from Depressive Symptoms: a GWAS-by-subtraction study in UK Biobank.

ABSTRACT

Hedonic (e.g., happiness) and eudaimonic (e.g., meaning in life) well-being are moderately negatively related to depressive symptoms. Genetic variants play a role in this association, reflected in substantial genetic correlations. To investigate the (genetic) overlap and differences between these traits, we used results of Genome-Wide Association studies (GWAS) and applied GWAS-by-subtraction in the UK Biobank sample. Analyses were pre-registered.

Subtracting the GWAS summary statistics of depressive symptoms from those of happiness and meaning in life, we obtained GWASs of respectively “pure happiness” (n= 216,497) and “pure meaning” (n=102,300). For pure happiness and pure meaning, we identified one genome-wide significant SNP each (respectively rs1078141 and rs79520962). After the subtraction of the depressive symptoms GWAS, SNP heritability reduced from 6.3% to 3.3% for pure happiness and from 6.2% to 4.2% for pure meaning. The genetic correlation between the well-being measures reduced from .78 to .65, indicating that only a marginal part of the genetic overlap between happiness and meaning in life is due to overlap with depressive symptoms. As expected, pure happiness and pure meaning became genetically unrelated to traits strongly associated with depressive symptoms, including tiredness, loneliness, and psychiatric disorders. For several other traits, including ADHD, income, educational attainment, smoking, and drinking alcohol, the genetic correlations of well-being versus pure well-being changed substantially.

GWAS-by-subtraction allowed us to investigate the genetic variance of well-being unrelated to depressive symptoms. Genetic correlations with different traits led to new insights about this unique part of well-being. The findings can have implications for interventions to increase well-being and/or decrease depressive symptoms.

Keywords: well-being, happiness, meaning in life, depressive symptoms, GWAS-by-subtraction, genetic correlations

INTRODUCTION

In the past, well-being and ill-being, such as depressive symptoms, have been considered opposite ends of a continuum (i.e., fewer depressive symptoms indicate higher levels of well-being, and vice versa). Nowadays, well-being and ill-being are seen as distinct, but related domains of mental health. Current definitions of mental health include both the absence of mental illness as well as the presence of well-being. For example, the World Health Organization (WHO) constitution states: “*Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.*” An important implication of this definition is that mental health is more than just the absence of mental disorders or disabilities. The WHO therefore defines it as “*a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community*” (World Health Organization, 2005). In line with this definition, the overlap between well-being and ill-being, such as depressive symptoms, is only moderate. Phenotypic correlations range between $-.40$ and $-.60$ (Bartels et al., 2013; Baselmans et al., 2018; Greenspoon & Saklofske, 2001) and genetic correlations based on twin studies or molecular genetic studies range from $-.50$ to $-.81$ (Baselmans et al., 2018; Baselmans & Bartels, 2018; Okbay et al., 2016). This degree of overlap indicates that well-being and depressive symptoms are partly overlapping domains of mental health and partly influenced by the same genetic factors. In the current study, we investigated what is unique to well-being and not shared with depressive symptoms.

In the well-being literature, a distinction is often made between hedonic/subjective well-being and eudaimonic/psychological well-being (Ryan & Deci, 2001). The subjective well-being theory originates from hedonistic philosophical ideas on well-being (Lambert et al., 2015; Ryan & Deci, 2001) that includes maximizing pleasure and minimizing pain as the ultimate goal in life. Modern-day hedonic well-being measures focus on levels of positive affect and negative affect, and subjective satisfaction with life (Diener et al., 2018). In this project we operationalized hedonic well-being with a measure of happiness. The psychological well-being theory emerged from eudaimonic philosophical theories that extend beyond pleasure and pain only, and emphasizes living a virtuous life (Lambert et al., 2015; Ryan & Deci, 2001). Therefore, current eudaimonic well-being measures include measures of positive functioning, thriving, and judgments about the meaning and purpose of an individual’s life

(Ryff, 1989). In this project we operationalized eudaimonic well-being with a measure of meaning in life.

The overlap and distinction between the two forms of well-being have been investigated empirically. Using factor analyses and exploratory structural equation modelling, studies showed that hedonic and eudaimonic measures of well-being load on separate, but correlated factors ($>.60$) (Gallagher et al., 2009; Joshanloo, 2016; Thorsteinsen & Vittersø, 2020). In recent molecular genetic work, the moderate phenotypic correlation between happiness (hedonic well-being) and meaning in life (eudaimonic well-being) was replicated ($r_{ph} = 0.53$) and a strong genetic correlation ($r_g = 0.78$) was observed (Baselmans & Bartels, 2018), suggesting a largely shared genetic etiology.

Furthermore, genetic correlations with related traits were found to be similar for happiness and meaning in life, adding further evidence for the shared etiology between the well-being measures (Baselmans & Bartels, 2018). The only genetic correlation that differed for happiness compared to meaning in life was with depressive symptoms. The genetic correlation between depressive symptoms and happiness was found to be moderate ($r_g = -0.53$, $SE = .04$) while it was smaller between depressive symptoms and meaning in life ($r_g = -0.32$, $SE = .05$), with non-overlapping confidence intervals.

The reported phenotypic and genetic correlations between happiness, meaning in life and depressive symptoms indicate substantial overlap between well-being and depressive symptoms. However, less is known about this shared part and the part that makes well-being unique, i.e., independent from depressive symptoms. Recently, GWAS-by-subtraction was developed in order to disentangle the shared and unique genetic variance between traits (Demange et al., 2021). To further investigate the (genetic) overlap and differences between happiness and meaning in life, and the overlap with depressive symptoms, we applied GWAS-by-subtraction on UK Biobank data. Subtracting a depressive symptoms GWAS from the happiness and meaning GWASs in UK Biobank (Baselmans & Bartels, 2018), we obtained GWASs of respectively “pure happiness” and “pure meaning”. In follow-up analyses, we compared the genetic variants associated with pure happiness and pure meaning using functional annotation and genetic correlations with a range of other traits. The results led to new insights into the overlap and distinction between happiness, meaning in life and depressive symptoms.

METHODS

Participants

The UK Biobank (UKB) is a large, population-based prospective study with data from over half a million participants of middle to old age from all over the UK (Sudlow et al., 2015). During the initial assessment visit (2006-2010) a touchscreen questionnaire was used to collect extensive information, including sociodemographic characteristics, lifestyle exposures and general health. In a later follow-up (2016), participants completed online questionnaires, including questions about their mental health and well-being.

In this study, we used data from 427,580 participants with genetic data and data on depressive symptoms from the initial assessment visit to run a GWAS on depressive symptoms. Permission to access both the phenotypic and genetic data of the UK Biobank was obtained under application number 40310. Furthermore, we used the summary statistics of (Baselmans & Bartels, 2018) on happiness (N = ~222k individuals) and meaning in life (N = 108k individuals) in UK Biobank participants.

Depressive symptoms

For depressive symptoms, we combined, in line with (Okbay et al., 2016), the scores on two items; *Over the past two weeks, how often have you felt down, depressed or hopeless?* (UKB Data-Field 2050), and *Over the past two weeks, how often have you had little interest or pleasure in doing things?* (UKB Data-Field 2060). Participants answered on a 4-item Likert scale that ranged from “Not at all” (score 1) to “Nearly every day” (score 4). The depressive symptoms score was created by summing the responses to both questions and standardizing the score.

Genetic data

Genome-wide genotype data for the participants have been collected, processed, quality controlled and imputed by UK Biobank (see for a full description Bycroft et al., 2018). To briefly summarize the process, participants were assayed using two very similar genotyping arrays, the Affymetrix UK BiLEVE or UK Biobank Axiom Arrays. The phasing and imputing was performed using the Haplotype Reference Consortium and merged UK10K and 1000 Genomes phase 3 reference panels. The quality control process was designed to address issues specific to a large-scale dataset that will be used for many different research questions. Quality control steps for markers included testing for batch effects, plate effects, departures from Hardy-Weinberg equilibrium,

sex effects, array effects, and discordance across control replicates. Samples were excluded based on non-European ancestry, sex mismatch between genetic result and self-report, and metrics of missing rate and heterozygosity (Bycroft et al., 2018).

Statistical analyses

This study was a secondary data analysis of previously collected data in UK Biobank. The analyses were pre-registered before data analysis (<https://osf.io/pnc2z>).

GWAS depressive symptoms

We ran a genome-wide association studies (GWAS) on the created depressive symptoms scores in the UK Biobank sample. The association analysis were performed in GCTA using linear mixed modelling (LMM). This controls for population stratification by including a genetic relatedness matrix (GRM) (Jiang et al., 2019), as the GRM includes genetic relationships between all individuals in the sample. As additional controls, we included sex, age, sex*age and 100 genetic principal components as covariates. We used the recommended threshold of $p < 5 \times 10^{-8}$ for significant SNPs and the threshold of $p < 1 \times 10^{-5}$ for possible implicated SNPs (Dudbridge & Gusnanto, 2008).

GWAS-by-subtraction

We used Genomic Structural Equation Modelling (Genomic SEM) (Grotzinger et al., 2019) and applied GWAS-by-subtraction following the approach of Demange et al. (2021) to investigate the overlap between depressive symptoms and happiness and meaning in life (see Figure 1). We applied the GWAS-by-subtraction model twice including depressive symptoms and respectively happiness and meaning in life.

For each SNP, GWAS-by-subtraction estimates the association with a trait of interest that is independent of the association of that SNP with another trait, in our case well-being and depressive symptoms. In the model, the GWAS summary statistics of both traits are regressed on two latent variables, i.e., *Depressive Symptoms* and *Pure Happiness* or *Pure Meaning* (see lower part of Figure 1). These latent factors are regressed on each SNP (see top part of Figure 1). For each SNP, this model results in two paths of association. In one path, the SNP effects are mediated by depressive symptoms. The other path is independent from depressive symptoms and indicates the SNP effects for pure well-being. In other words, the variance of well-being is separated in a part shared between well-being and depressive symptoms, and in a part unique for well-being, i.e.,

pure well-being. The genetic variance for pure happiness and pure meaning is by design independent of the genetic variance for depressive symptoms ($r_g = 0$).

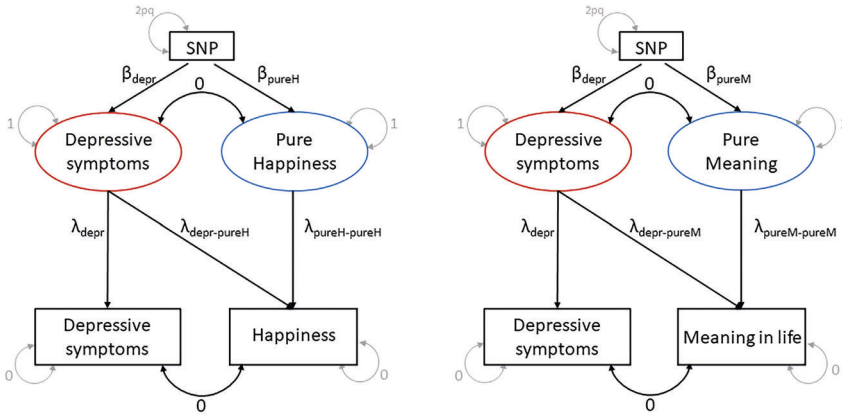


Figure 1. Schematic overview of the GWAS-by-subtraction approach to create a GWAS of “pure happiness” and “pure meaning”.

GWAS follow-up analyses

SNP heritability and genetic correlation. Univariate LD score regression (LDSC) (Bulik-Sullivan, Loh, et al., 2015) was used to estimate the SNP heritability for pure happiness and pure meaning. In addition, bivariate LDSC was used to compute the genetic correlation between happiness and pure happiness and between meaning in life and pure meaning.

Functional annotation. After the GWAS-by-subtraction, we looked up the lead significant SNPs ($p < 10 \times 5^{-8}$) or (when none or only a few SNPs were genome-wide significant) the suggestive significant SNPs ($p < 1 \times 10^{-5}$) for pure happiness and pure meaning in the NHGRI-EBI catalogue of human genome-wide association studies (www.ebi.ac.uk/gwas/). We compared these SNPs to previously reported SNPs in association analyses of related traits.

To follow-up on the SNP based association test for pure happiness and pure meaning in life, we performed gene mapping in FUMA (<http://fumactglab.nl>, Watanabe et al., 2017). Gene mapping was based on three strategies, namely positional mapping (i.e. physical distance from the gene, within 10 kb window), eQTL mapping (i.e. the gene expression is associated with allelic variation at the SNP), and chromatin interaction mapping.

Next, we applied genome-wide gene-based association tests using MAGMA (de Leeuw et al., 2015) in FUMA. The gene-based test combines results from multiple SNPs within a gene to test the association between genes and pure

happiness or pure meaning in life, while accounting for LD between SNPs. We used a Bonferroni corrected threshold based on the number of tested genes.

Genetic correlations

To further investigate the distinction between pure happiness, pure meaning, and depressive symptoms, we calculated genetic correlations between these traits and a range of other traits. Using bivariate LDSC regression, we computed the genetic correlations between pure happiness, pure meaning, happiness, meaning, depressive symptoms, and a range of selected traits across 12 categories for which well-powered GWAS data were available ($N=75$, see Table 6.1). We used a Bonferroni corrected threshold of $p = 0.05/(75*5) = 1.3 \times 10^{-5}$ to correct for the multiple testing.

Sensitivity analysis

The GWAS-by-subtraction model assumes that the genetic effects on depressive symptoms also have an effect on happiness or meaning in life. There could be a possible bidirectional effect between depressive symptoms and well-being. The possible bidirectional causal effect can be considered a violation of the assumption. To investigate the impact of a bidirectional effect between depressive symptoms and well-being, we allowed for this effect in the model (see supplementary Figure S6.5 for the adjusted model). We cannot estimate the effect freely, because of identification issues and therefore included a small effect of 0.2. Including this small effect of well-being on depressive symptoms, we reanalyzed and investigated the change in the Z-statistics of the genome-wide and suggestive SNPs for happiness and meaning in life. There was a minimal change in the Z-statistics, both for pure happiness and pure meaning (see supplementary Figure S6.6 for the comparison in Z-statistics).

Table 6.1. Included traits for genetic correlations.

Category	Trait	Category	Trait
Psychological/ Social	Loneliness	Anthropomorphic	Body fat
	Risk taking		BMI
	Friends relationship satisfaction		Waist-circumference
	Family relationship satisfaction		Hip-circumference
Psychiatric	ADHD		Height
	MDD		Birth weight
	PTSD	Brain volumes	ICV
	Anxiety	Total brain volume	Mean Accumbens
	Schizophrenia	White matter	Mean Caudate
	Bipolar disorder	Grey matter	Mean Hippocampus
	Anorexia	Brainstem	Mean Pallidum
	Autism Spectrum Disorder		Mean Putamen
Personality	Openness	Cardiovascular	Mean Thalamus
	Conscientiousness		Type-2 diabetes
	Extraversion		Coronary Artery Disease
	Agreeableness		Triglycerides
	Neuroticism		Myocardial Infarction
Cognition/SES	Townsend (Social deprivation)	Autoimmune	Total Cholesterol
	Job Satisfaction		LDL Cholesterol
	Childhood IQ		HDL Cholesterol
	Income		Crohn's disease
	Educational attainment		Inflammatory Bowel Disease
	Intelligence		Rheumatoid Arthritis
Substance use	Verbal-numerical reasoning		Ulcerative Colitis
	Cannabis use disorder		Atopic Dermatitis
	Cigarettes per day		Asthma

Table 6.1. Included traits for genetic correlations.

Category	Trait	Category	Trait
	Caffeine	Fertility	Nr of children
	Age at smoking initiation		Age at menarche
	Smoking cessation		Age at menopause
	Alcohol consumption		Age at first birth
	Alcohol Dependence	Other health risk	Tiredness
	Drinks per week		Sleep duration
			Chronotype
			morningness
			Self-rated health
			Mother's age at death
			Father's age at death
Neurological	Alzheimer's disease		
	ALS		
	Parkinson's disease		

RESULTS

GWAS depressive symptoms

For 467,389 participants, the depressive symptoms score could be computed, resulting in a mean of 2.58 ($SD = 1.12$, range = 2-8). The scores were transformed to Z-scores with a mean of 0 and SD of 1. Of this sample, 427,580 individuals had genetic data available and could be included in the GWAS. The depression GWAS resulted in 14 independent genome-wide significant SNPs ($\lambda_{GC} = 1.32$, LD intercept = 1.02) and a SNP heritability of 4.4% ($SE=0.002$). The results from the depressive symptoms GWAS are presented in the Manhattan plot in supplementary Figure S6.1 and more information can be found in supplementary Table S6.1.

GWAS-by-subtraction depressive symptoms and happiness

The GWAS-by-subtraction of depressive symptoms and happiness resulted in one independent genome-wide significant SNP for pure happiness ($N_{\text{effective}} = 216,497$) ($\lambda_{GC} = 1.13$, LD intercept = 0.99). The significant SNP was rs1078141 (CHR:BP = 8:142619393, $\beta = 0.102$, $SE=0.018$, $Z = 5.73$, $p = 1.03 \times 10^{-8}$). The results from the pure happiness GWAS are shown in the Manhattan plot in Figure 6.2 and the QQ plot in supplementary Figure S6.2. The comparison

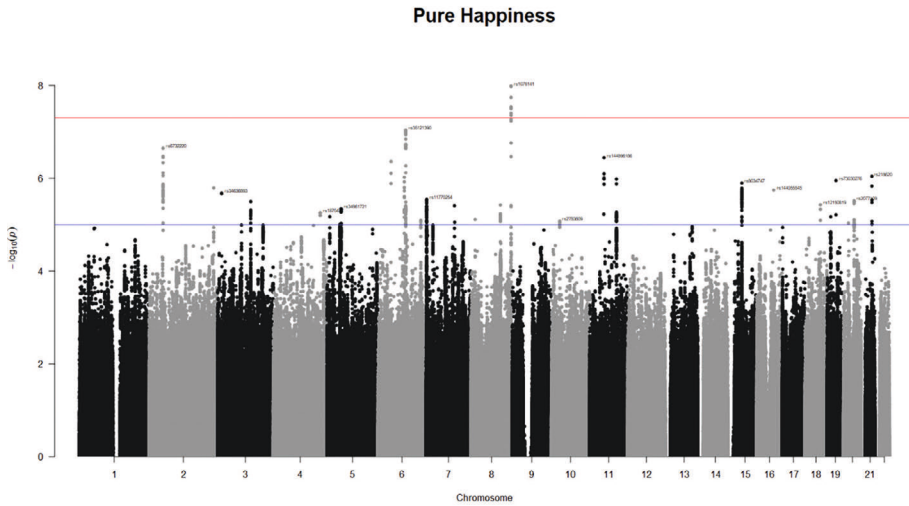


Figure 6.2. Manhattan plot for the GWAS results of pure happiness.

SNP heritability and genetic correlation. The SNP heritability of pure happiness was estimated to be 3.3% ($SE = 0.003$), a reduction of ~3% compared to the SNP h^2 of 6.3% ($SE = 0.005$) for uncorrected happiness in the sample of Baselmans and Bartels (2018). The genetic correlation between pure happiness and happiness was 0.802 ($SE = .015$, $Z = 52.51$, $p < .001$), indicating a reduction in genetic (co)variance because of the removal of genetic variance related to depressive symptoms.

Functional annotation. The effect of the significant SNP rs1078141 of pure happiness ($\beta = .102$, $p = 1.03 \times 10^{-8}$) is similar to the effect of this SNP in Baselmans and Bartels (2018) ($\beta = .017$, $p = 5.57 \times 10^{-8}$). The look-up showed that the significant SNP has been associated with general cognitive ability as well (Davies et al., 2018).

Applying FUMA, no genes were significantly associated with pure happiness based on positional mapping, eQTL mapping, or chromatine interaction-mapping. Furthermore, the results of the gene-based test as computed by MAGMA including all SNPs with a p-value below 0.05, also indicated no associations between specific genes and pure happiness. In addition, no significant enrichment of genes in certain tissues was found for pure happiness.

GWAS-by-subtraction Depressive Symptoms and Meaning

The GWAS-by-subtraction of depressive symptoms and meaning resulted in 1 genome-wide significant SNP for pure meaning ($N_{\text{effective}} = 102,300$) ($\lambda_{GC} = 1.08$, LD intercept = 0.99). The significant SNP was rs79520962 (CHR:BP = 7:127671511,

$\beta = 0.304$, $SE = 0.054$, $Z = 5.62$, $p = 1.86 \times 10^{-8}$). The results from the pure meaning GWAS are shown in the Manhattan plot in Figure 6.3 and the QQ plot in supplementary Figure S6.3. The comparison of the significant SNPs for meaning in life (Baselmans & Bartels, 2018) and pure meaning in life can be found in supplementary Table S6.2.

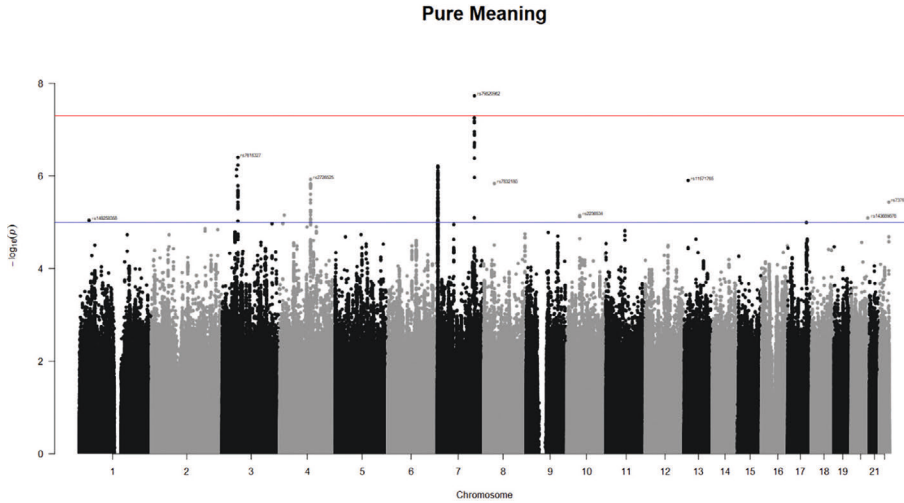


Figure 6.3. Manhattan plot for the GWAS results of pure meaning in life.

SNP heritability and genetic correlation. The SNP heritability of pure meaning was estimated to be 4.2% ($SE = 0.005$), a reduction of 2% compared to the SNP h^2 of 6.2% ($SE = 0.005$) (Baselmans & Bartels, 2018). The genetic correlation between pure meaning and meaning was 0.793 ($SE = .043$, $Z = 18.36$, $p = 3.0 \times 10^{-75}$), indicating a reduction in genetic (co)variance because of the removal of genetic variance related to depressive symptoms.

Functional annotation. The top hit rs79520962 ($\beta = 0.304$, $p = 1.86 \times 10^{-8}$) was also genome-wide significant in Baselmans and Bartels (2018) ($\beta = 0.051$, $p = 2 \times 10^{-9}$), with a similar effect size. The look-up showed no other associations for this SNP.

Applying FUMA, no gene replicated across the three different mapping method. However, two genes, i.e., SND1 and LRRC4, were found through positional mapping, and SND1 was also found in the eQTL mapping. SND1 was reported to be associated to meaning in life before the subtraction (Baselmans & Bartels, 2018). The proteins encoded by SND1 are involved in cell growth. No genes were associated with pure meaning based on the results of the gene-

based test as computed by MAGMA including all SNPs with a p -value below 0.05. In addition, no significant enrichment of genes in certain tissues was found.

Genetic correlations

The genetic correlation between the measures of pure well-being, i.e., pure happiness and pure meaning, was estimated to be .65 ($SE = .05$, $p = 1.25 \times 10^{-40}$). This is a reduction compared to the genetic correlation between happiness and meaning in life of .78 (Baselmans & Bartels, 2018), indicating that depressive symptoms explain a small part of the genetic overlap between happiness and meaning in life, but most overlap between these well-being measures is unique to well-being. The genetic correlations between pure happiness, pure meaning, happiness, meaning and depressive symptoms can be found in supplementary Table S6.3.

The genetic correlations of pure happiness, pure meaning, happiness, meaning and depressive symptoms with all traits across 12 categories ($N = 75$) can be found in supplementary Figure S6.4 and Table S6.4. All correlations between the included traits and respectively pure happiness and pure meaning indicated a similar pattern, with overlapping confidence intervals. Therefore, in the next part, we mostly refer to pure well-being instead of discussing the correlations separately for pure happiness and pure meaning.

In Figure 6.4 and 6.5, the genetic correlations with selected traits can be seen. We selected the traits from categories with a high correlation with the well-being measures or depressive symptoms (Figure 6.4), and traits from categories for which the genetic correlation with well-being and pure well-being changed substantially or reversed after subtracting depressive symptoms (Figure 6.5).

The subtraction of depressive symptoms did not influence the high genetic correlations of happiness and meaning in life with friend and family satisfaction (see Figure 4, psychological category). In contrast, for different psychological traits, psychiatric disorders and physical health traits, the subtraction of depressive symptoms GWAS did influence the genetic correlations with well-being substantially. These traits, including tiredness, loneliness, sleep duration, health satisfaction, post-traumatic stress disorder (PTSD), bipolar disorder and schizophrenia, have a strong positive genetic correlation with depressive symptoms. Before subtracting depressive symptoms GWAS, happiness and meaning in life showed (strong) negative genetic correlations with most of these traits, whereas pure happiness and pure meaning became genetically unrelated to these traits, with genetic correlations around zero (see Figure 6.4). This indicates that the original genetic correlations between well-being and

depression-related psychological, psychiatric and physical health traits are mostly or fully due to the genetic overlap with depressive symptoms.

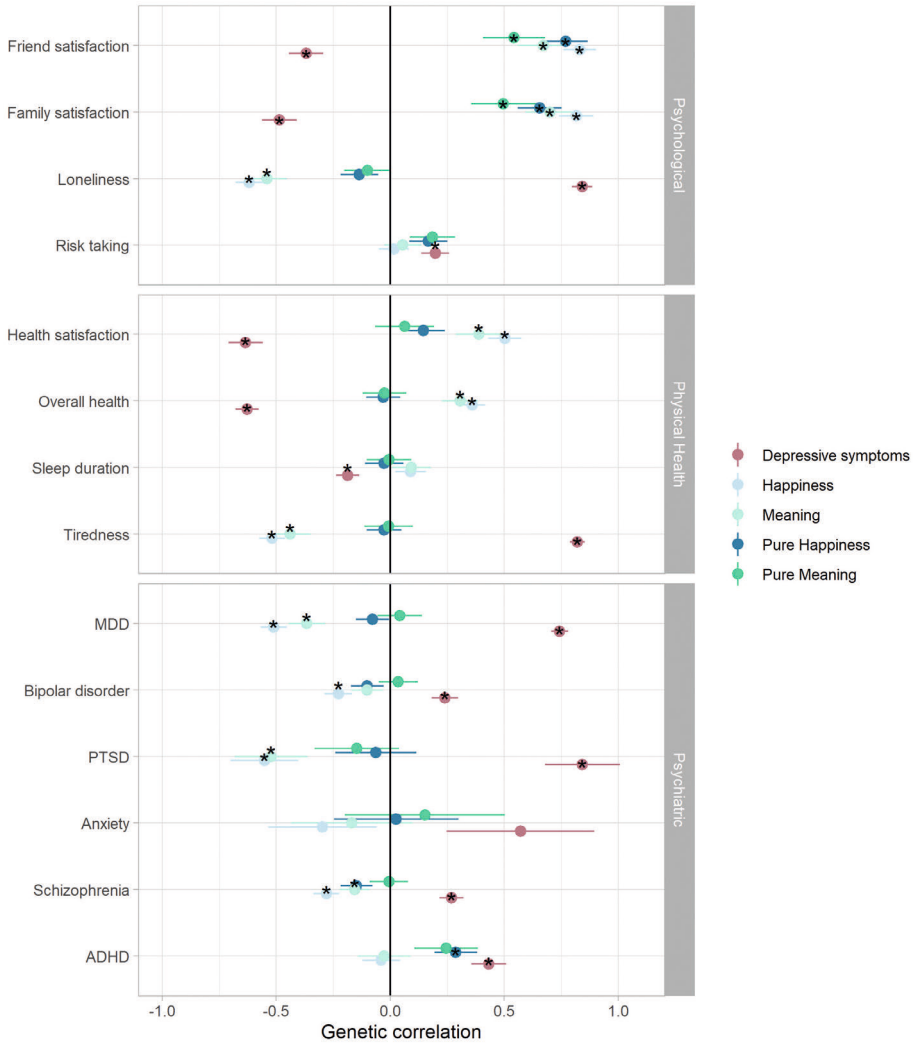


Figure 6.4. Genetic correlations of pure happiness, pure meaning, happiness, meaning and depressive symptoms and selected psychological traits, psychiatric disorders and physical health. * indicates significant genetic correlations with a Bonferroni corrected threshold of $p < 1.3 \times 10^{-5}$.

A different pattern of genetic correlations for pure well-being appeared with Attention deficit hyperactivity disorder (ADHD, see Figure 6.4), and traits in the cognition and socio-economic status (SES) category, substance use, and body fat and body mass index (see Figure 5). ADHD was genetically unrelated to happiness ($r_g = -.04$) and meaning in life ($r_g = -.03$), and positively correlated to depressive symptoms ($r_g = .43$). Subtracting depressive symptoms from well-being, the genetic correlations became positive for both pure happiness ($r_g = .29$) and pure meaning ($r_g = .25$). This indicates that a higher genetic predisposition for pure well-being is related to a higher genetic risk of ADHD, when corrected for the genetic predisposition for depressive symptoms. Similar findings were found for risk taking.

Opposite effects were found for the SES traits. Income was slightly positively associated with happiness ($r_g = .12$) and meaning in life ($r_g = .11$) before subtraction, and stronger negatively correlated to depressive symptoms ($r_g = -.51$). Subtracting depressive symptoms from well-being, the genetic correlations reversed for both pure happiness ($r_g = -.23$) and pure meaning ($r_g = -.18$). Similarly, the genetic correlations between educational attainment and pure well-being became significantly negative (respectively $r_g = -.46$ and $-.35$ for pure happiness and pure meaning), compared to the smaller correlations ($r_g = -.13$ and $-.09$) for happiness and meaning before subtraction. This indicates that higher pure well-being is genetically related to a lower income and a lower educational level, when corrected for the genetic predisposition for depressive symptoms.

The genetic correlations between pure well-being and substance use revealed a consistent pattern of reversed genetic associations as well, although not all correlations reached significance after correcting for multiple testing (see Figure 6.5). Before subtraction, current smoking and alcohol intake frequency were genetically unrelated or slightly negatively associated with well-being (r_g between $-.08$ and $-.13$), whereas the association with pure well-being became positive (r_g between $.05$ and $.20$) after subtracting depressive symptoms. This indicates that a higher genetic predisposition for pure well-being is related to a higher genetic predisposition for smoking and alcohol intake, independently from depressive symptoms.

A similar positive genetic correlation emerged for pure well-being and body fat ($r_g = .22$ and $.12$ for respectively pure happiness and pure meaning) and body mass index (BMI) ($r_g = .23$ and $.13$) (see Figure 6.5). This positive genetic correlation is of similar size to the genetic correlation between depressive symptoms and body fat ($r_g = .23$) and BMI ($r_g = .24$). The changed genetic correlations indicate that a higher genetic predisposition for pure well-being

is related to a higher genetic predisposition for more body fat and a higher BMI, when corrected for the genetic predisposition for depressive symptoms.

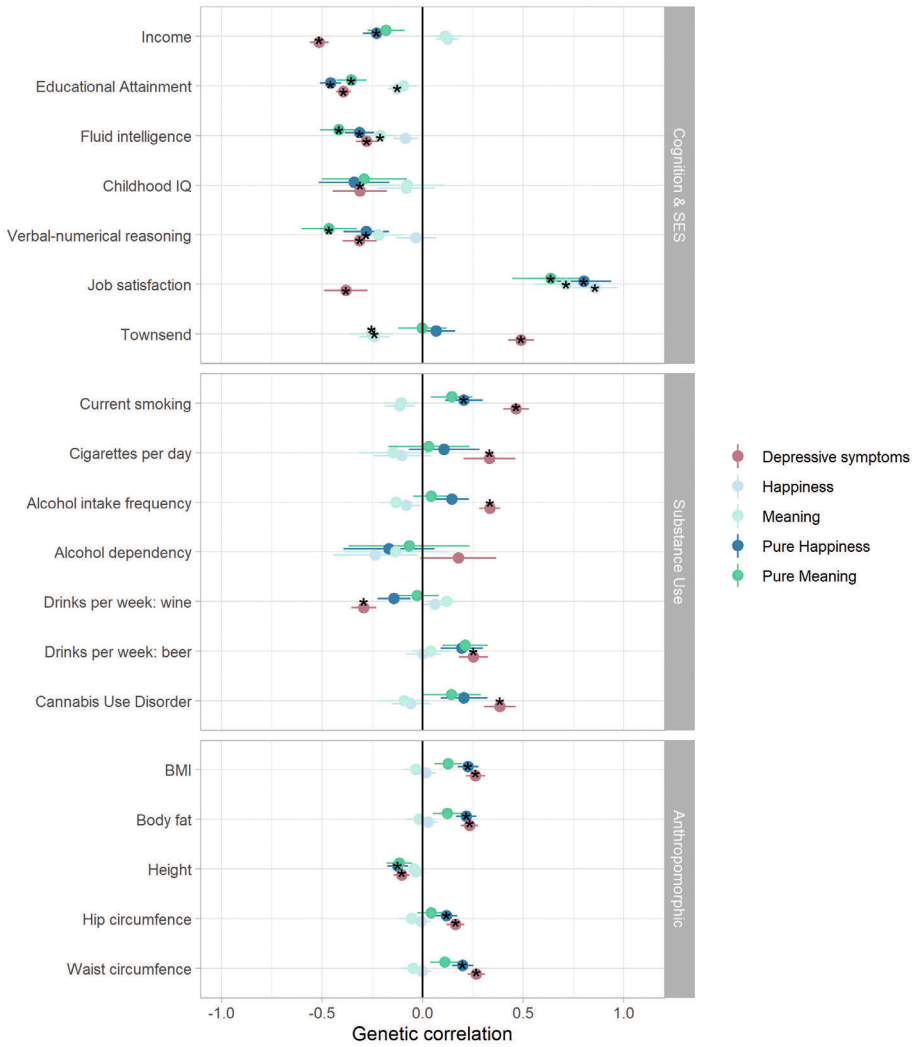


Figure 6.5. Genetic correlations of pure happiness, pure meaning, happiness, meaning and depressive symptoms and selected cognition and socio-economic status, substance use and anthropomorphic traits. * indicates significant genetic correlations with a Bonferroni corrected threshold of $p < 1.3 \times 10^{-5}$.

DISCUSSION

Using GWAS-by-subtraction, we investigated the genetic overlap and differences between depressive symptoms and two measures of well-being, i.e., happiness and meaning in life. Subtracting the depressive symptoms GWAS from the happiness and meaning in life GWASs generated new GWASs that capture the genetic variants associated with happiness and meaning in life independent of depressive symptoms, i.e. “pure happiness” and “pure meaning”. For pure happiness and pure meaning, one independent SNP reached genome-wide significance each (rs1078141 and rs79520962, respectively). In addition, the subtraction led to a reduction of the SNP heritability from 6.3% to 3.3% for pure happiness and from 6.2% to 4.2% for pure meaning. The genetic correlation between the well-being measures reduced as well, from .78 (Baselmans & Bartels, 2018) to .65 between pure happiness and pure meaning in life. Follow-up functional annotation analyses indicated no consistently significantly associated genes with pure happiness and pure meaning. The genetic correlations between pure happiness and pure meaning and a range of other traits resulted in novel insights about the unique part of well-being that is unshared with depressive symptoms.

Hedonic and eudaimonic well-being

Our findings on the genetic architecture of (pure) happiness and meaning in life are in line with the often reported separate, but highly correlated factors of hedonic and eudaimonic well-being (Gallagher et al., 2009; Joshanloo, 2016; Thorsteinsen & Vittersø, 2020). Furthermore, consistent with the larger genetic overlap of depression with happiness ($r_g = -.53$) compared to meaning in life ($r_g = -.32$) (Baselmans & Bartels, 2018), we report a greater reduction in SNP heritability of happiness (48%) compared to meaning in life (32%) after the subtraction of the depressive symptoms GWAS. The small reduction of the genetic correlation between happiness and meaning in life after the subtraction of depressive symptoms ($r_g = .78$ to $r_g = .65$) indicates that only part of the overlap between happiness and meaning in life is because of the overlap of the well-being measures with depressive symptoms. Therefore, even when taking depressive symptoms into account, the largest part of genetic factors underlying happiness and meaning in life remain shared. Furthermore, the similar patterns of genetic correlations for pure happiness and pure meaning with a range of other traits are in line with a largely shared genetic etiology.

Pure well-being correlates

The genetic correlations of well-being with a range of other traits before and after the subtraction of depressive symptoms led to insights about the part of well-being that is unique, i.e., pure well-being, and not shared with depressive symptoms. Different patterns of genetic correlations of well-being versus pure well-being emerged, including non-changing genetic correlations (1), changed correlations from significant to zero (2), and reversed genetic correlations (3). These different patterns suggest that part of the genetic variance of well-being could be seen as on a continuum of well-being and depressive symptoms, whereas the other part of genetic variance of well-being is unique genetic variance, unrelated to depressive symptoms. We discuss the meaning and implications of these different patterns of genetic correlations below.

First, the genetic correlations between pure well-being (i.e., both pure happiness and pure meaning in life) and respectively family satisfaction, friend satisfaction, and job satisfaction did not change compared to the genetic correlations with well-being before the subtraction. There is no substantial effect of taking depressive symptoms out, suggesting that the genetic predisposition to be satisfied with different aspects of life is related to the unique part of happiness and meaning and unrelated to the genetic predisposition for depressive symptoms. An exception is health satisfaction, being strongly related to depressive symptoms, the genetic correlation with pure well-being became non-significant, in line with the genetic correlations discussed next.

Second, as one could expect, pure happiness and pure meaning became genetically unrelated to traits that correlate strongly with depressive symptoms, i.e., tiredness, overall health, and psychiatric disorders like post-traumatic stress disorder, bipolar disorder, and schizophrenia. This pattern indicates that part of the genetic variance of well-being can be seen on the continuum from depressive symptoms to well-being. The (genetic) associations of well-being with these depression-related traits are therefore mostly likely to arise from the overlap with depressive symptoms and should be interpreted considering these findings.

Third, for several other traits, including attention-deficit/hyperactivity disorder (ADHD), income, educational attainment, smoking, and alcohol intake frequency, the genetic correlations with well-being changed substantially or reversed after the subtraction of depressive symptoms. This indicates unique genetic overlap between pure well-being and these traits, independently from depressive symptoms. For each of these highlighted traits, we discuss possible explanations and mechanisms underlying the changed genetic correlations.

Attention-deficit/hyperactivity disorder

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopment disorder including symptoms of impaired attention, hyperactivity and impulsivity (American Psychiatric Association, 2013). ADHD has been related to poor outcomes in academic achievement, work performance, and social relationships, especially in individuals with untreated ADHD (Arnold et al., 2020; Harpin et al., 2016; Sciberras et al., 2009). In the current study, we reported a positive genetic correlation between ADHD and depressive symptoms, as reported before (e.g., see Thapar, 2018), and no significant genetic correlation with well-being, before the subtraction of depressive symptoms. In contrast, the genetic correlation between ADHD and pure well-being became positive, such that higher genetic predisposition for pure well-being is related to a higher genetic predisposition for ADHD.

An explanation for the positive genetic correlation between pure well-being and ADHD could be the benefits and positive effects of ADHD symptoms in daily life in well-functioning individuals. Positive traits often associated with ADHD include hyperfocus, creativity, spontaneity, resilience, and high energy (Ashinoff & Abu-Akel, 2021; Boot et al., 2017, 2020; Sedgwick et al., 2019). Some of these benefits have been related to well-being as well (Conner & Silvia, 2015; de Vries et al., 2021). This suggests that the genetic correlation between pure well-being and ADHD captures the high-functioning part of ADHD, and possibly the well-being related benefits, such as creativity and resilience, when taking out the genetic predisposition for depressive symptoms. Similar to this genetic finding, phenotypically, depressive symptoms have been found to mediate the association between ADHD symptoms and well-being as well (Pan & Yeh, 2017; Yang et al., 2013). Adding depressive symptoms to the models, the negative correlation between well-being measures and ADHD symptoms disappeared or decreased substantially, indicating that the negative association between ADHD and well-being is due to the overlap with depressive symptoms.

Income

Income is genetically negatively related to depressive symptoms, and slightly positively related to well-being, before the subtraction of depressive symptoms. The negative genetic correlation between depressive symptoms and income has been reported before (Marees et al., 2021) and different mechanisms are proposed to underlie this correlation. Low income can increase the risk of depression or vice versa, depressive symptoms have detrimental effects on the ability to actively and optimally participate in the labor force, leading to lower incomes (Lorant et al., 2003). The slightly positive genetic correlation between

well-being and income (before subtraction) seems to be driven by the shared part with depressive symptoms, i.e., the opposite of the effect of depressive symptoms.

Subtracting the part of well-being that is shared with depressive symptoms, the genetic correlation between income and pure well-being became negative, such that higher pure well-being is genetically related to a lower income. This indicates that people with a higher genetic predisposition for pure well-being also have a genetic predisposition for attaining lower incomes. Possible explanations for the negative relation between pure well-being and income could be that people with a higher genetic predisposition for pure well-being also have a genetic predisposition to prefer to work less hours or jobs with less responsibility or stress, often resulting in lower income. For example, people with a higher genetic predisposition for pure well-being could consider income of less importance and instead have (lower-paid) jobs based on meaning or interests, such as jobs related to creativity, or have part-time jobs to have more free time, e.g., to spend time with their family.

Although this suggestion and the causality of the relation should be investigated in future research, there is some literature in line with these suggestions. For example, higher income has been associated with more working hours and stressful jobs, and satiation and turning points for the effect of income on well-being have been found (Jebb et al., 2018; Kahneman & Deaton, 2010; Kudrna & Kushlev, 2022). The satiation point of income suggests that above a certain level of income (estimates differ per measure, country and individual), higher income does not lead to higher levels of well-being. Once income is sufficient to fulfil basic physical needs, well-being will not increase further when income raises (Kahneman & Deaton, 2010). The turning point of income indicates that people with very high incomes report lower well-being levels compared those with lower incomes (Jebb et al., 2018), however, note that results tend to depend on analytic approaches (see Kudrna & Kushlev, 2022). Very high income is often acquired in jobs with more responsibility, more stress, and more working hours. In turn, working hours and a lack of free time as a result of too many working hours, is associated with lower levels of well-being and happiness (Sharif et al., 2021).

To further explore the negative genetic associations between pure well-being and income, we did an exploratory phenotypic analysis and compared the phenotypic correlations between income and happiness/meaning in life in a high and low income group (median 50% split). In contrast to these suggestions of the highest incomes to be related to lower well-being, we found a small positive correlation between income and respectively happiness and meaning

in life for both the high ($r_{ph} = .05$ and $.04$) and low income group ($r_{ph} = .08$ and $.06$). A limitation of this analysis is that the UK Biobank sample has a relatively higher income compared to the general population. Furthermore, the relation between lower well-being and income is suggested to only occur in the highest incomes, probably not captured by the median split. Finally, we did not take out the effects of depressive symptoms on income in the phenotypic correlations. Therefore, more research on the association between income, well-being, and depressive symptoms in a multivariate design and in appropriate samples is needed to test the associations.

Educational attainment and intelligence

Similar changing genetic correlations for (pure) well-being and educational attainment (EA) and intelligence-related traits, including verbal-numerical reasoning and fluid intelligence were found as well. EA and intelligence traits were genetically unrelated or slightly negatively genetically associated with happiness and meaning in life before subtracting depressive symptoms. After subtraction, stronger negative genetic correlations between pure well-being and EA and intelligence emerged, indicating that higher pure well-being is genetically related to lower EA and intelligence. The correlation became similar in magnitude to the negative genetic correlation of EA/intelligence and depressive symptoms. Income is strongly related to higher EA (Demange et al., 2021; Hill et al., 2016), therefore the negative association with pure well-being could be partly explained by the associations with income.

Another possible explanation for the positive genetic correlation between pure well-being and the EA and intelligence traits could be the suggested turning point for the effect of intelligence on well-being (Pollet & Schnell, 2017; Vötter & Schnell, 2019). In highly intellectually “gifted” individuals (i.e., very high intellect, $IQ \geq 130$), lower levels of well-being have been found compared to high-achieving individuals (i.e., only a high performance) and the general population (Pollet & Schnell, 2017; Vötter & Schnell, 2019). It is hypothesized that intellectually gifted individuals are at a greater risk for the development of a crisis of meaning in life, in turn related to lower well-being.

Consistent with this hypothesis, meaning in life was already significantly genetically negatively related to fluid intelligence before subtracting depressive symptoms ($r_g = -.21$) and this negative genetic association became stronger after the subtraction ($r_g = -.41$). As exploratory analysis, we compared the phenotypic correlations between intelligence and happiness/meaning in life in a high and low intelligence group (median 50% split). Although the correlations are very small, we found small phenotypic correlations in line with these ideas. For

happiness, we found a positive correlation between income and happiness in the low intelligence group ($r_{ph} = .03$) and a small negative correlation in the high intelligence group ($r_{ph} = -.01$). For meaning in life, the negative correlation with intelligence was stronger in the high intelligence group ($r_{ph} = -.04$) compared to the low intelligence group ($r_{ph} = -.01$). However, as the UK Biobank sample has a higher socioeconomic status compared to the general population, we did not take depressive symptoms into account, and the phenotypic correlations are very small, more research on the (phenotypic) associations between intelligence, well-being and depressive symptoms is needed to test these hypotheses.

Substance use and food-related traits

An interesting and consistent pattern of genetic correlations between (pure) well-being and substance use and food-related traits appeared as well, although not all correlations reached significance after correcting for multiple testing. Current smoking, alcohol intake frequency, body mass index, and body fat were genetically positively related to depressive symptoms and unrelated or slightly negatively associated to well-being before the subtraction of depressive symptoms. Pure well-being became positively genetically related to these traits after subtracting depressive symptoms. Therefore, more smoking, drinking, and eating (i.e., resulting in a higher BMI and body fat) appears to be genetically related to higher pure well-being, when taking out the effect of depressive symptoms on substance use.

A possible explanation for these reversed genetic correlations for pure well-being could be the different underlying reasons why people smoke, drink, and eat. The genetic overlap between depressive symptoms and these traits can arise from self-medication, i.e., smoking, drinking and eating to cope and reduce the negative mood and other depressive symptoms (Armeli et al., 2018; Hooshmand et al., 2012; Kuntsche et al., 2005; Lazarevich et al., 2016; Magee & Clarke, 2021). The part of well-being shared with depressive symptoms has similar opposite effects, i.e., higher well-being is related to less self-medication by smoking, drinking, or eating. In contrast, the smoking, drinking, and eating that is genetically related to pure well-being (i.e., unrelated to depressive symptoms) could arise from these behaviors in social settings. For example, higher pure well-being could be genetically related to more social drinking, smoking, and eating by going out more often or being more often in the company of other people. In line with this idea, in a study on drinking motivations of adults, a positive phenotypic relation between well-being and drinking for social reasons compared to conformity or coping reasons has been reported (Appleton et al.,

2018). Future research is needed to investigate the specific associations and conditions in which well-being is phenotypically related to substance use and eating variables, and, as the current study only looks at (genetic) correlations, the causation should be investigated.

Limitations

In this study, we investigated the overlap between well-being depressive symptoms using GWAS-by-subtraction. The results should be interpreted in light of some limitations. First, both the well-being and depressive symptoms GWASs are based on data from the UK Biobank. The sample of UK Biobank participants is known to be biased, i.e., participants are on average older, healthier, include more females, and have a higher socioeconomic status compared to the general population (Fry et al., 2017). Therefore, the GWAS for depressive symptoms might be biased, and subtracting the GWAS from the well-being GWASs might have introduced extra bias in the pure well-being GWASs. This sampling bias can have influenced the GWAS results and the associations of pure well-being with income, educational attainment, BMI, and substance use. For example, the UKB sample is higher educated and has a higher socioeconomic status compared to the general population, possibly affecting the associations of income and intelligence with pure well-being. Furthermore, age is expected to play a role in the motivations to drink alcohol or smoke. Individuals in their 20s can be expected to drink for other reasons compared to individuals of 50 or 60 years old. Therefore, replication in less biased samples is needed.

Furthermore, a limitation of the UK Biobank GWASs is the focus on samples from European ancestry. Well-being is differently conceptualized in different cultures (Lambert et al., 2020). Therefore, the results and the genetic correlations cannot be generalized across samples with other ancestries. Replication of these results using larger GWAS from population-wide samples and more ancestry-diverse samples is needed.

In addition, in this study we mostly focus on the genetic correlations. Based on these findings, we speculate and suggest potential explanations for the change in genetic correlations. However, correlations do not indicate causation, and more research is needed to test the hypotheses and possible causal relations between the variables.

Implications

The current findings can have important implications for mental health research and depressive symptoms and well-being preventions and

interventions. The genetic correlations of well-being and pure well-being with the above described traits indicate that the genetic variance of well-being can be split into two parts that can have different associations with the other traits. Part of the variance of well-being can be seen as overlapping with depressive symptoms, whereas the other part is the unique or extra part that is unrelated to depressive symptoms. Subtracting the shared effects of depressive symptoms from well-being allowed us to investigate these unique genetic associations of pure well-being with other traits. If replicated, these findings and associations can be a starting point for new insights in the associations of well-being, independently from depressive symptoms.

When interpreting the results, it is important to keep in mind that genetic correlations are reported, indicating genetic sensitivity to both traits and not the direct phenotypic associations or causal effects. High genetic correlations indicate a (partly) similar biological mechanism underlying both traits. If the relation between the traits is causal, applying an intervention to change a certain trait could therefore also affect the highly genetic correlated trait, via this similar mechanism. Based on our results, different associations could be taken into account depending on the goal of the interventions, i.e., to increase well-being and/or decrease depressive symptoms. If the goal is to decrease depressive symptoms as well as increase well-being, the overlap between depressive symptoms and well-being should be taken into account. The genetic overlap between depressive symptoms and well-being indicates that an intervention to increase well-being could reduce depressive symptoms at the same time. Therefore, such interventions should focus on variables that are (causally) related to both depressive symptoms and well-being.

Interventions to increase well-being specifically can focus on other associations as well. Positive psychology interventions have been developed with the intent to increase the well-being of participants, instead of just reducing depressive symptoms or other psychopathological problems (Seligman & Csikszentmihalyi, 2000). Well-known examples of interventions include for example practicing gratitude or forgiveness, being kind to others, writing about positive, meaningful or successful experiences and finding flow. According to two recent systematic reviews and meta-analyses, positive psychology interventions are effective in increasing well-being, however the effects are small and the evidence quality was generally low to moderate across the studies (Carr et al., 2021; van Agteren et al., 2021). The significant effects indicate that positive psychology interventions can be used to prevent low well-being or as a treatment strategy to increase well-being. The results of the current study

and the genetic correlates of pure well-being can be used as basis for future research to find variables for more effective well-being specific interventions.

Conclusion

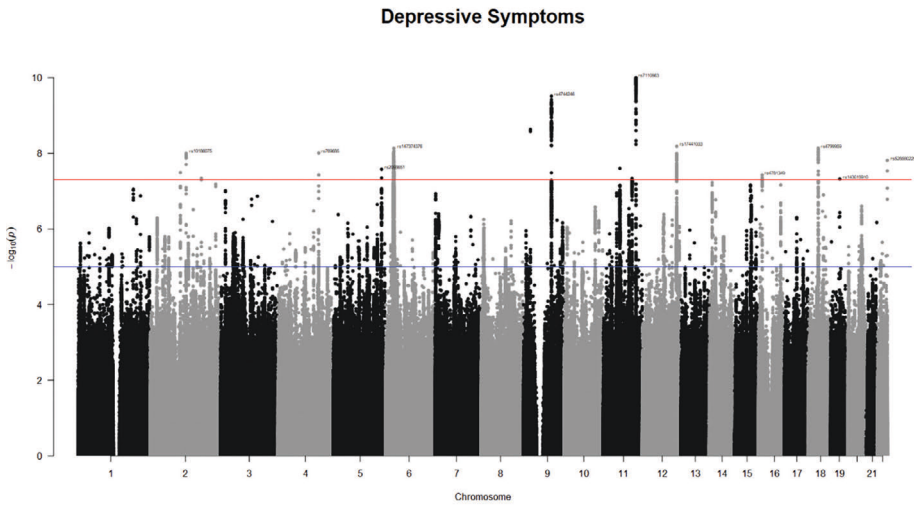
To conclude, GWAS-by-subtraction allowed us to investigate the part of well-being that is unrelated to depressive symptoms. We replicated the largely shared genetic etiology of happiness and meaning in life, taking into account the overlap with depressive symptoms. Furthermore, the genetic correlations between the pure well-being measures and a range of other traits led to new insights about the part of well-being that is unique and not shared with depressive symptoms. We reported pure well-being to be genetically associated to a lower income, educational attainment and intelligence, and a higher predisposition for smoking, drinking alcohol, and eating, and discuss potential mechanisms underlying these association. Our results can be used as a starting point to design future interventions that concentrate on maintaining or increasing well-being, instead of reducing depressive symptoms.

Supplementary Material Chapter 6

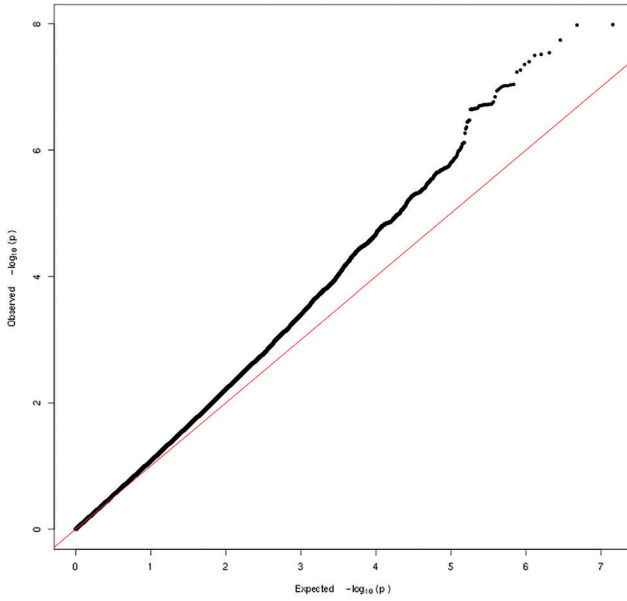
Supplementary Tables

Supplementary Tables S1-S5 can be found online, at <https://docs.google.com/spreadsheets/d/1AS1NYq-gZo6jD5c9vIPUVVqhITxJ1xw1/edit?usp=sharing&oid=105075418470716004760&rtpof=true&sd=true>

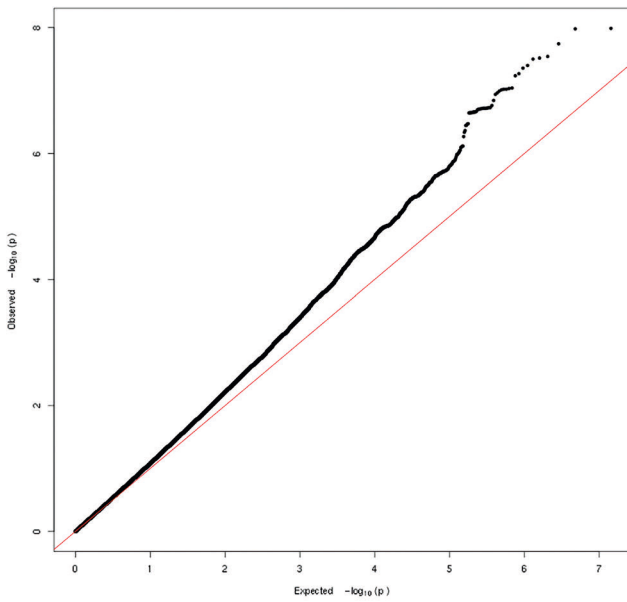
Supplementary Figures



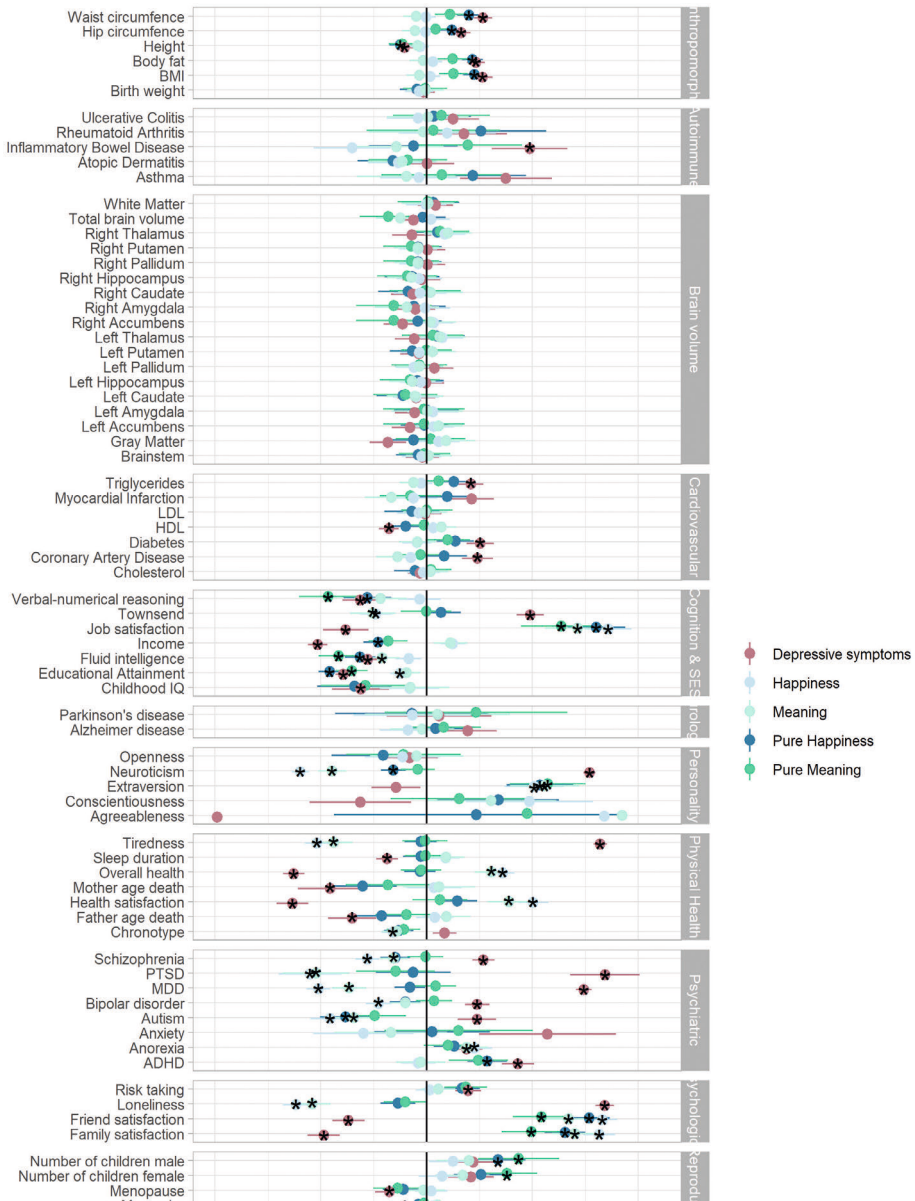
Supplementary Figure S6.1. Manhattan plot for the GWAS results of depressive symptoms



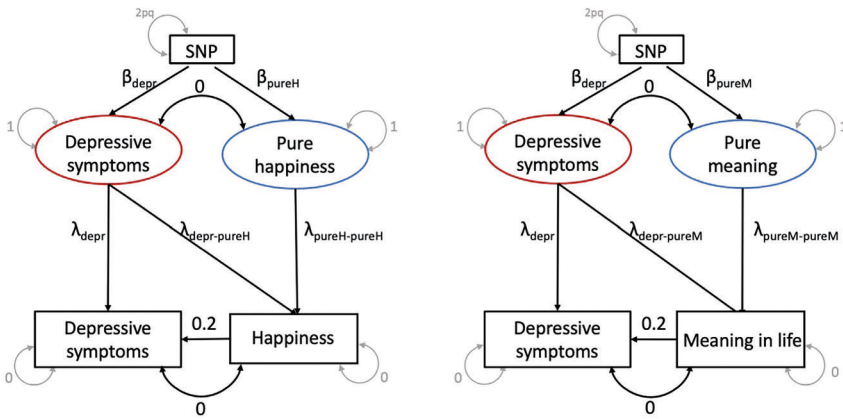
Supplementary Figure S6.2. QQ plot for pure happiness GWAS.



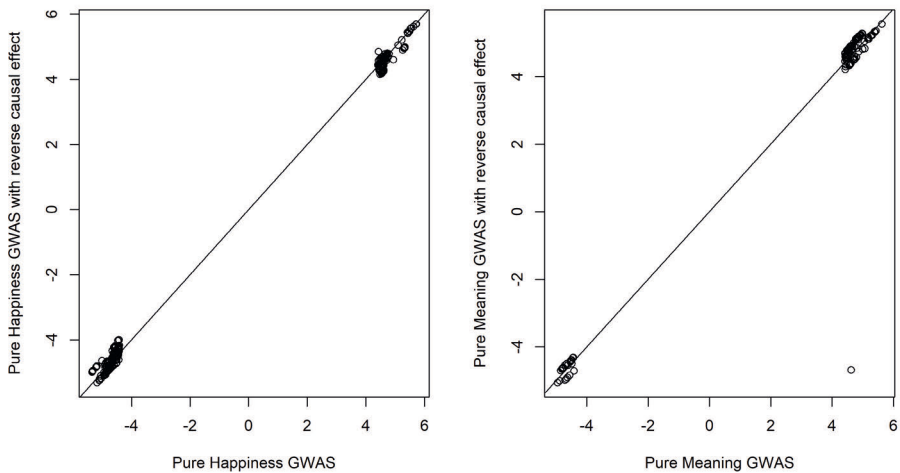
Supplementary Figure S6.3. QQ plot for pure meaning GWAS.



Supplementary Figure S6.4. Genetic correlations between happiness, meaning, depressive symptoms, pure happiness and pure meaning and a range of different traits across 12 categories (n=75). Stars indicate significant correlations, Bonferroni corrected ($p = .00013$).



Supplementary Figure S6.5. GWAS-by-subtraction model with a small reversed causal effect of 0.2 of happiness (left panel) and meaning in life (right panel) on depressive symptoms.



Supplementary Figure S6.6. Comparison of the Z-statistics of the hits and suggestive SNPs estimated in the standard GWAS-by-subtraction model and in a model with a small reversed causal effect (0.2) from happiness (left panel: 345 SNPs) and meaning in life (right panel: 138 SNPs) to depressive symptoms.





Part III:

The Effect of an Extreme Environment on Well-being

Chapter 7.

Gene-by-crisis interaction for optimism and meaning in life: the effects of the COVID-19 pandemic

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ABSTRACT

The corona virus disease 2019 (COVID-19) pandemic and the restrictions to reduce the spread of the virus has had a large impact on daily life. We investigated the individual differences in the effect of the COVID-19 pandemic and first lockdown on optimism and meaning in life in a sample from the Netherlands Twin Register. Participants completed surveys before (N=9964, Mean age: 48.2, SD=14.4) and during the first months of the pandemic (i.e. April-May 2020, N= 17464, Mean age: 44.6 SD=14.8), with a subsample completing both surveys (N=6461, Mean age T1: 48.8, SD=14.5). We applied genetic covariance structure models to twin data investigate changes in the genetic architecture of the outcome traits due to the pandemic and the interaction of genes with the environmental exposure. Although 56% and 35% of the sample was negatively affected by the pandemic in their optimism and meaning in life, many participants were stable (32% and 43%) or even showed increased optimism and meaning in life (11% and 22%). Subgroups, specifically women, higher educated people, and people with poorer health, experienced larger negative effects. During the first months of the pandemic, slightly lower heritability estimates for optimism and meaning in life (respectively 20% and 25%) were obtained compared to pre-pandemic (respectively 26% and 32%), although confidence intervals overlap. The lower than unity genetic correlations across time (.75 and .63) suggest gene-environment interactions, where the expression of genes that influence optimism and meaning in life differs before and during the pandemic. The COVID-19 pandemic is a strong exposure that leads to imbalanced effects on the well-being of individuals. Some people decrease in well-being, while others get more optimistic and consider their lives as more meaningful during the pandemic. These differences are partly explained by individual differences in genetic sensitivity to extreme environmental change. More knowledge on the person-specific response to specific environmental variables underlying these individual differences is urgently needed to prevent further inequality.

Keywords: optimism, meaning in life, pandemic, COVID-19, lockdown, heritability

INTRODUCTION

The corona virus disease 2019 (COVID-19) quickly evolved into a global pandemic that had an enormous impact on people's everyday lives. During the first year of the pandemic, there was no effective cure and vaccination for the disease and prolonged action and restrictions were needed to control the virus. In the Netherlands, the government introduced an 'intelligent' lockdown on 12 March 2020, to keep the virus under control, protect vulnerable groups, and make sure the healthcare system could cope with increasing demands. Major restrictions were social distancing, closing of schools, offices, and other public places, and individuals were strongly advised to work from home. As in many countries, people's daily life and society were severely impacted. Parents had to home-school children, entire groups of people were facing financial problems or unemployment, and social contact was limited, leading to increased loneliness (Groarke et al., 2020; Killgore et al., 2020).

Although effective to reduce the spread of COVID-19, the continued restrictions in combination with distress about the virus have an impact people's mental health and well-being. Most research on the effects of the pandemic on mental health and well-being focused on detrimental effects averaged across large population samples. Across the world, increased anxiety and depression, and decreased well-being (i.e. life satisfaction and positive affect) has been reported in response to the pandemic and first lockdown (Ahmed et al., 2020; Kwong et al., 2020; Lades et al., 2020; Prati & Mancini, 2021; Ueda et al., 2020; Zacher & Rudolph, 2020).

Average effects across large groups do not necessarily mean that everyone experienced negative effects but can hide potentially large individual differences. For example, Newby et al. (2020) reported increased depression and anxiety during the pandemic in around half of the Australian sample, i.e. implying that not everyone experienced an increase. Some individuals remained stable or even improved in mental health during the pandemic. Under certain circumstances people can experience psychological improvement after acute adversity (Mancini, 2019). An explanation for this effect during the pandemic could be the forced pause from a busy life, less fear of missing out, and time to focus on social connections (Mancini, 2020).

Optimism and meaning in life

Aspects of well-being on which the COVID-19 pandemic can be expected to differently impact individuals are optimism and meaning in life. During the pandemic, the daily life of individuals radically changed and uncertainty

about the future regarding the virus and lockdown, (e.g., When is an effective vaccine distributed worldwide? When are all restrictions lifted?), and the personal future (e.g., Will I keep my job?) increased. Optimism is defined as the tendency to expect positive outcomes in any situation, and is related to physical and mental health and well-being (Rasmussen et al., 2009; Scheier & Carver, 1985, 1992, 1993). People differ in their level of optimism and due to increased uncertainty during the pandemic individual differences may increase.

Meaning in life can be defined as people's beliefs that their lives are significant and purposeful, a feeling of achieving meaningful goals, and a sense of fulfilment (Reker & Wong, 1988; Steger, 2012). Feelings of meaningfulness are important for mental health, a lack is associated with psychopathology and poor well-being (Glaw et al., 2017). The lockdown can lead to a loss in meaning in life for some individuals, especially if they lose their job or have to work from home, whereas others adapt quickly to the situation and find new ways of meaningfulness.

Optimism and meaning in life are associated with each other and with other aspects of well-being, including life satisfaction (Ho et al., 2010; Krause, 2003; Steger et al., 2006).

Sources of individual differences

To understand individual differences in optimism and meaning in life, earlier research investigated the genetic and environmental influences. Twin studies have shown that around 30% of the individual differences in optimism is accounted for by genetic factors (i.e. the heritability), whereas 70% is explained by environmental influences (van de Weijer et al., 2020). The heritability of meaning in life is estimated between 33% and 52%, with the remaining variance explained by non-shared environmental factors (Steger et al., 2011; Wang et al., 2017).

Heritability is estimated as the proportion of total variance in a phenotype that is accounted for by genetic variance. Genetic variance may vary as a function of context and because heritability is a ratio, that depends on the total variance, it can also vary when environmental variance changes. If the environmental variance increases and the genetic variance is the same, the total variance increases and the heritability is lower. The COVID-19 pandemic can be regarded as a rare universal exposure but lockdown will impact individuals depending on how their work and home setting is affected. Some individuals could see their job degraded to 'non-crucial' or lose their job, whereas others see their status elevated but have to deal with high workloads. The response to lockdown thus can have differential effects on the environmental variance, as

well as depend on the genetic makeup of the individual. Here, genetic variance depends on environmental exposures. For example, experimental stress can lead to new genetic variance being expressed, as well as an increase in the effects of genes influencing a trait before stress exposure (De Geus et al., 2007). The pandemic, being a rather extreme environmental stressor, can influence the genetic variance underlying optimism or meaning in life through both mechanisms. To assess the genotype by exposure interaction, a genetically informative design (e.g. twin study) that assesses participants before and during the exposure is needed. The parameters of interest are the differences in environmental and genetic variance between the two assessments (reflecting quantitative gene-environment interaction) and the genetic correlation between the measures (reflecting qualitative gene-environment interaction, with different genes being important before and during the exposure).

Several other aspects can moderate the effect of the pandemic on optimism and meaning in life. According to a systematic review (N=19 studies), the mental health of women and younger participants was more affected during the pandemic compared to men and older participants (Xiong et al., 2020). The effect of education attainment was inconsistent; depending on the study, higher or lower educated people were more affected in their mental health during the pandemic (Daly et al., 2020; Xiong et al., 2020). Finally, people with underlying health conditions, such as chronic respiratory problems, heart problems, and autoimmune problems, have a higher risk of becoming severely ill from COVID-19 (Williamson et al., 2020) and might experience lower well-being than healthy people, out of fear or uncertainty related to attracting the virus.

We investigated the effect of the COVID-19 pandemic on optimism and meaning in life in the Netherlands during the beginning of the pandemic and the first lockdown and determinants of individual differences in these effects. We included variables that can moderate the pandemic effect: sex, age, level of education, self-rated health, and the presence of chronic illnesses. To further understand the individual differences in optimism and meaning in life before and during the pandemic, we applied longitudinal twin models.

METHODS

Sample

Participants were voluntarily registered at the Netherlands Twin Register, established by the Department of Biological Psychology, Vrije Universiteit Amsterdam (Ligthart et al., 2019). The NTR sample is a population-wide

sample consisting of twins and their relatives. Every two/three years since 1991, longitudinal survey data about lifestyle, personality, psychopathology, and well-being are collected.

For a pre-pandemic measure of optimism and meaning in life, we combined data from two assessments. Just before the COVID-19 pandemic, NTR participants (i.e. twins and their families) were invited to complete a survey including the Flourishing scale (Diener et al., 2010), with an optimism and meaning in life item. This data collection stopped in February 2020 due to the pandemic. To increase the size and representativeness of the sample, we combined this sample with a sample that completed the Flourishing scale three years earlier. The samples were similar in mean and standard deviations of optimism ($M_1=5.8$, $SD_1=1.1$ vs $M_2=5.7$, $SD_2=1.1$) and meaning in life ($M_1=5.7$, $SD_1=1.1$ vs $M_2=5.5$, $SD_2=1.1$). This combined pre-pandemic sample consist of 9964 participants. To test if the timing of the pre-pandemic data has an influence on the results, we repeated the analyses separately for the two samples (i.e. just before the pandemic and three years earlier). The results can be found in the supplementary material and the associations did not change much compared to the combined pre-pandemic sample as reported in the main results.

During the pandemic and lockdown, NTR participants were invited to complete an online COVID survey and 18035 participants returned this questionnaire. The lockdown in the Netherlands started on the 12th of March. All questionnaires were completed between 21 April 2020 and 2 May 2020. To focus on the effects of the pandemic and not of the disease, participants with a positive result on the most reliable COVID-19 test, the polymerase chain reaction (PCR) test, or an expected COVID-19 diagnosis based on the Menni model (see Blokland et al., 2021) (N=571) were excluded, leaving a sample of 17464 participants. Longitudinal data (i.e. pre-pandemic and pandemic questionnaire data) were present for 6461 participants.

For the genetic covariance structure modelling of longitudinal data, we analysed the data from a subset of the sample consisting of twins. For the pre-pandemic sample, we only included twin pairs that completed the pre-pandemic survey at the same time point. If the twin pairs did not have pre-pandemic data at the same time point, we only included the twin with the most recent data. The total subsample consisted of 8056 twins (either from complete or incomplete twin pairs), with 4178 MZ twins and 3878 DZ twins (see Table 7.1 for more details on the samples).

Measures

Optimism

Pre-pandemic optimism was assessed with a single item of the Flourishing scale (Diener et al., 2010). Participants had to rate the item “I am optimistic about my future” on a Likert scale from 1 (strongly disagree) to 7 (strongly agree).

During the pandemic, optimism was assessed with the question “How optimistic are you about the future at the moment?”. Participants had to answer on a Likert scale ranging from 1 (not at all) to 10 (very much).

Meaning in life

Pre-pandemic meaning in life was assessed with an item of the Flourishing scale (Diener et al., 2010). Participants rated the item “I lead a purposeful and meaningful life” on a Likert scale from 1 (strongly disagree) to 7 (strongly agree).

In the pandemic survey, meaning in life was assessed with a single question “How meaningful do you think your life is right now?”. Participants answered on a Likert scale ranging from 1 (not at all) to 10 (very much).

Level of education

The level of education (i.e. highest educational attainment) of a participant was based on the longitudinal assessment of educational level. In different NTR surveys, level of education was measured with the question “What is the highest educational level that you have completed?”. The answer categories varied per questionnaire. The level of education was recoded in four categories: primary education only (1), lower vocational school and lower secondary school (2), intermediate vocational school and intermediate or higher secondary school (3) and higher vocational school and university (4).

Presence of chronic illnesses

To assess the presence of chronic illnesses, participants were, in both surveys, presented with a list of illnesses and were asked to indicate if they had been diagnosed with one or more illnesses. We included the following diseases: cardiovascular disorders, heart infarcts, stroke, lung diseases (e.g. asthma), liver disorders, kidney disorders, type I and type II diabetes, auto-immune disorders, cancer, neurological disorders such as dementia or Parkinson’s disease, spleen problems, and joint inflammation. When participants indicated

that none of these illnesses was present they received a score of 0, if one or more of these illnesses was present, they scored a 1.

Self-rated health

In both surveys, self-rated health was measured with the item ‘In general, how would you rate your health?’. Participants had to answer on a 5-point Likert scale from 1 (bad) to 5 (excellent).

Statistical analysis

Overall pandemic effects

To investigate the overall effect of the pandemic on optimism and meaning in life, we created a within-person change score for the subsample of participants who completed both the pre-pandemic and pandemic survey. Since the response scales were not equal, we had to rescale the pre-pandemic measure with a scale from 1-7 to a scale from 1-10 to match the pandemic measures (using the “rescale” function of the R package “scales” v0.4.1). Although the results should be interpreted with caution, as rescaling is not the ideal solution, this will lead to information about the effect of the pandemic on the optimism and meaning in life scores of the participants. We defined participants with a negative change score larger than 1 point as showing a decrease in optimism or meaning in life during the pandemic, whereas a positive change of more than 1 point indicates an increase. Participants within 1 point change were classified as stable in their optimism or meaning in life.

Effects of sex, age, level of education, and health

To test for the moderating effects of sex, age, level of education, self-rated health, and the presence of chronic illnesses on the effect of the pandemic on optimism and meaning in life, for each variable we ran three analyses, using Generalized estimating equation (GEE) in R to correct for familial relations in the data (Minică et al., 2015).

First, we investigated the effect of sex, age, level of education, self-rated health, and the presence of chronic illnesses (i.e. the predictors) on pre-pandemic scores. Second, we investigated the effect of this set of predictors on the scores during the pandemic. Finally, we investigated the effect of the predictors on the scores during the pandemic and included the pre-pandemic level, to correct for the baseline scores of optimism/meaning in life and investigate the effects of the predictors on the part that is left, i.e. the change in scores over time.

Longitudinal twin models

In the subset of twins, we conducted a longitudinal bivariate twin analysis in which we included the pre-pandemic and pandemic scores to examine the impact of the pandemic on the genetic architecture of pre- and pandemic optimism and meaning in life and to investigate the presence of genotype-environment interaction. Age and sex were included as covariates. Twin models are based on the difference in genetic similarity between monozygotic (MZ) and dizygotic (DZ) twin pairs. MZ twin pairs share (almost) all genes, whereas DZ twin pairs share on average half of their segregating genes. Based on this difference, the observed phenotypic variance and covariance between pre-pandemic and pandemic scores can be decomposed into genetic and environmental (co)variance components. Additive genetic variance (A) is variance explained by independent allele effects on the phenotype. Non-additive genetic variance (D) refers to interactions between alleles at the same locus (dominance) or at different loci (epistasis). Environmental variance includes a shared environment component (C) (shared by family members) and a non-shared component, the unique (person-specific) environment, including measurement error (E). The effects of C and D cannot be estimated simultaneously. Therefore, a choice for an ACE or ADE model was made based on the ratio of the cross-twin cross-trait correlations. If the MZ correlations are smaller than twice the DZ correlations, common environment (C) effects are expected and an ACE model is specified. If the MZ correlations are larger than twice the DZ correlations, dominant genetic (D) effects are expected and an ADE model is appropriate (Neale & Maes, 2004).

First, phenotypic correlations, and cross-twin (cross-trait) correlations were estimated in a saturated model in OpenMx (Boker et al., 2011). Next, using a bivariate ACE/ADE model, we estimated genetic and environmental contributions to variance of the traits and to the covariance between the traits. Based on the bivariate analyses, we estimated the genetic and environmental correlations between the pre-pandemic and pandemic measures (de Vries, van Beijsterveldt, et al., 2021). To answer the question how genes interact with the extreme environmental exposure, we first compared the amount of genetic and environmental variance before and during the pandemic (quantitative gene-environment interaction). In addition, we tested if the genetic correlation between the repeated measures in different environments could be constrained to 1. If not, the genetic correlation is significantly lower than 1, indicating evidence for a qualitative gene-environment interaction (Falconer, 1952).

We tested the contribution of A and C/D and genetic correlation using the likelihood ratio test (LRT), comparing the full models to the nested submodels.

The difference in minus two times the log-likelihood (-2LL) between two nested models has a χ^2 distribution with the degrees of freedom (df) equalling the difference in df between the models. If a p-value from the χ^2 -test is significant, the fit of the constrained model is significantly worse than the fit of the more complex model. To verify the goodness of fit and the parsimony of the model, we use Akaike's Information Criterion (AIC;(Akaike, 1987). The lower the AIC value, the better the fit of the model relative to the number of parameters estimated. For the best fitting model, 95% confidence intervals were estimated.

To reduce the chance of false positive findings, we used a Bonferroni corrected *p*-value threshold (i.e. dividing 0.05 by the number of tests) of $p=0.002$ in all analyses.

RESULTS

Descriptive statistics

In Table 7.1, the descriptive statistics of the sample can be found. The samples before and during the pandemic differed significantly in proportion males and females, $t=-4.3$, $p<.001$. During the pandemic, the proportion of females (71.0%) was higher than pre-pandemic (68.5%). Furthermore, the pre-pandemic sample was older ($M=48.1$) than the pandemic sample ($M=44.6$), $t=18.6$, $p<.001$.

The scores on the pre-pandemic measures of optimism and meaning in life were relatively high with average scores of above 5.5 out of a maximum of 7. The pandemic means of optimism and meaning in life were respectively 7.0 and 7.5 out of 10. We cannot directly compare the mean scores of the pre-pandemic and pandemic measures, as the answer scales of the pre-pandemic and pandemic measures differed. The correlation between pre-pandemic and pandemic optimism was 0.36 (95%CI: .33-.38) and between pre-pandemic and pandemic meaning in life was 0.36 (95%CI: .34-.38). Optimism and meaning in life were also related, with a correlation of 0.59 (95%CI: .58-.61) pre-pandemic and 0.51 (95%CI: .50-.52) during the pandemic.

Overall pandemic effects

To report on the proportions of participants that decreased, were stable or increased in optimism and meaning in life, we rescaled the pre-pandemic scores to match the pandemic answer scale. Table 7.2 contains the distribution of the change scores in the sample based on the rescaled variables and the characteristics of the three groups (i.e. decreasing, stable and increasing). For optimism, 56.3% of the sample showed a decrease in optimism during the pandemic, 32.5% of the sample remained stable, and 11.1% of the sample showed an increase in optimism during the pandemic. For meaning in life, only 34.8% showed a decrease, 43.1% was stable and 22.1% showed an increase in meaning in life compared to pre-pandemic levels.

Table 7.1. Descriptive statistics for the samples

	N (females/males)	Age (SD)	Range	Optimism			Meaning in life		
				M (SD)	Range	M (SD)	Range	M (SD)	Range
Total sample									
Pre-pandemic	9964 (6832/3130)	48.2 (14.4)	16-102	5.7 (1.1)	1-7	5.6 (1.1)	1-7	5.6 (1.1)	1-7
Pandemic	17464 (12391/5068)	44.6 (14.8)	16-95	7.0 (1.4)	1-10	7.5 (1.5)	1-10	7.5 (1.5)	1-10
Longitudinal	6461 (4532/1928)	T1: 48.8 (14.5) T2: 50.1 (14.1)	16-102 16-92	5.7 (1.1) 7.0 (1.3)	1-7 1-10	5.6 (1.1) 7.6 (1.4)	1-7 1-10	5.6 (1.1) 7.6 (1.4)	1-7 1-10
Twins									
Pre-pandemic	3879 (2719/1159)	T1: 43.2 (15.8) T2: 36.0 (15.1)	16-92 16-90	5.7 (1.1) 7.0 (1.4)	1-7 1-10	5.5 (1.1) 7.3 (1.6)	1-7 1-10	5.5 (1.1) 7.3 (1.6)	1-7 1-10
Longitudinal	2560 (1845/721)	T1: 44.6 (16.1) T2: 46.3 (15.4)	16-102 16-92	5.7 (1.1) 7.0 (1.4)	1-7 1-10	5.5 (1.1) 7.4 (1.5)	1-7 1-10	5.5 (1.1) 7.4 (1.5)	1-7 1-10

Table 7.2. Characteristics of the subgroups that decreased, were stable, or increased in optimism or meaning in life during the pandemic.

	Optimism			Meaning in life		
	Decrease	Stable	Increase	Decrease	Stable	Increase
N	3625	2097	715	2231	2760	1416
% of total sample	56.3%	32.5%	11.1%	34.8%	43.1%	22.1%
% females in subsample	72.8%	66.4%	67.4%	75.0%	67.0%	68.8%
Mean age (SD)	49.1 (13.8)	50.9 (14.4)	52.9 (14.9)	49.3 (14.5)	50.8 (14.0)	50.5 (13.5)
Education level (SD)	3.5 (0.7)	3.5 (0.7)	3.3 (0.8)	3.5 (0.7)	3.5 (0.7)	3.3 (0.8)
Mean self-rated health (SD)	4.1 (0.7)	4.1 (0.7)	3.8 (0.8)	4.1 (0.7)	4.2 (0.7)	4.0 (0.7)
% chronic illness	16.2%	18.5%	23.5%	17.9%	16.8%	20.0%

Effects of sex, age, level of education, and health

Next, we investigated the effect of sex, age, level of education, self-rated health, and the presence of chronic illnesses on optimism and meaning in life before and during the pandemic and on the change. The results can be seen in Figure 7.1 and Table 7.3.

Optimism

Pre-pandemic, there were no effects of sex and level of education on optimism (see Table 7.3). Men ($M=5.74$, $SD=1.09$) reported similar optimism levels compared to women ($M=5.73$, $SD=1.05$). There was a small effect of age on optimism. The older the participants, the lower the level of optimism. Better self-rated health was associated with a higher optimism level. Finally, the slightly higher optimism of participants without a chronic illness ($M=5.77$, $SD=1.04$) compared to participants with an illness ($M=5.44$, $SD=1.21$) did not reach significance ($p=.002$).

During the pandemic, an effect of sex on optimism appeared. Women ($M=6.88$, $SD=1.35$) reported lower levels of optimism than men ($M=7.20$, $SD=1.36$). There was still an effect of age on optimism with older participants reporting lower optimism and an effect of self-rated health, with higher self-rated health being associated with higher optimism. Again, the higher optimism of participants without chronic illness ($M=7.00$, $SD=1.35$) compared to with a chronic illness ($M=6.82$, $SD=1.42$) did not reach significance.

When including pre-pandemic optimism as predictor, there was a significant effect of pre-pandemic optimism, sex, and self-rated health on pandemic optimism. The positive effect of pre-pandemic optimism indicates that higher pre-pandemic optimism is associated with a higher level of optimism during the pandemic as well. The effect of sex indicates that, when correcting for baseline optimism, being female compared to male was associated with lower optimism during the pandemic. The same applies to self-rated health, correcting for the baseline effect, a poorer self-rated health was associated with lower optimism compared to a better self-rated health during the pandemic.

Meaning in life

Pre-pandemic, there was no effect of sex and age on meaning in life (see Table 7.3). Men ($M=5.58$, $SD=1.08$) and women ($M=5.59$, $SD=1.08$) reported a similar level of meaning in life. There was a significant relation between level of education and meaning in life. Participants with a higher level of education reported a higher meaning in life. A better self-rated health was related to a

higher meaning in life, whereas there was no effect of the presence of chronic illnesses.

During the pandemic, an effect of sex on meaning in life appeared. Women ($M=7.42$, $SD=1.52$) reported a lower meaning in life during the pandemic than men ($M=7.64$, $SD=1.48$). There was a small but significant effect of age on meaning in life, with older participants reporting higher meaning in life. The effect of education level on meaning in life was not significant anymore. Better self-rated health was still associated with a higher meaning in life. There was no effect of the presence of chronic illnesses.

When including pre-pandemic meaning in life as predictor, there was a significant effect of pre-pandemic meaning in life, sex, and self-rated health on pandemic meaning in life. The positive effect of pre-pandemic meaning in life indicates that a higher pre-pandemic meaning in life is associated with a higher level of meaning in life during the pandemic as well. The other effects indicate that when correcting for baseline meaning in life, being female compared to male was associated with a lower in meaning in life during the pandemic and poorer self-rated health was associated with lower in meaning in life compared to a better self-rated health.

Table 7.3. The results of the GEE analysis on optimism and meaning in life.

	Pre-pandemic		Pandemic		Pandemic	
Optimism	β (SE)	p	β (SE)	p	β (SE)	p
Sex	0.01 (.04)	0.878	-0.24 (.02)	3.7x10⁻²⁹	-0.21 (.03)	4.5x10⁻¹³
Age	-0.14 (.03)	4.6x10⁻⁰⁷	-0.07 (.01)	8.5x10⁻⁰⁸	-0.03 (.02)	0.074
Education	0.05 (.02)	0.038	0.01 (.01)	0.453	-0.01 (.01)	0.693
Self-rated health	0.43 (.02)	1.8x10⁻⁶⁸	0.23 (.01)	8.9x10⁻⁹⁴	0.18 (.01)	1.7x10⁻²⁷
Chronic illness	0.11 (.05)	0.002	0.07 (.02)	0.015	0.06 (.04)	0.082
Pre-pandemic optimism					0.30 (.01)	6.8x10⁻⁶⁷
Meaning in life	β (SE)	p	β (SE)	p	β (SE)	p
Sex	0.06 (.05)	0.177	-0.11 (.02)	9.6x10⁻⁰⁹	-0.17 (.03)	7.9x10⁻⁰⁹
Age	0.05 (.03)	0.082	0.04 (.01)	7.2x10⁻⁰⁴	0.01 (.02)	0.408
Education	0.12 (.02)	1.9x10⁻⁰⁷	-0.02 (.01)	0.026	-0.04 (.01)	0.009

Table 7.3. The results of the GEE analysis on optimism and meaning in life.

	Pre-pandemic		Pandemic		Pandemic	
Self-rated health	0.29 (.02)	2.2×10^{-30}	0.26 (.01)	4.7×10^{-120}	0.22 (.01)	2.9×10^{-40}
Chronic illness	0.05 (.05)	0.337	0.05 (.03)	0.071	0.04 (.04)	0.367
Pre-pandemic meaning in life					0.33 (.01)	4.4×10^{-78}

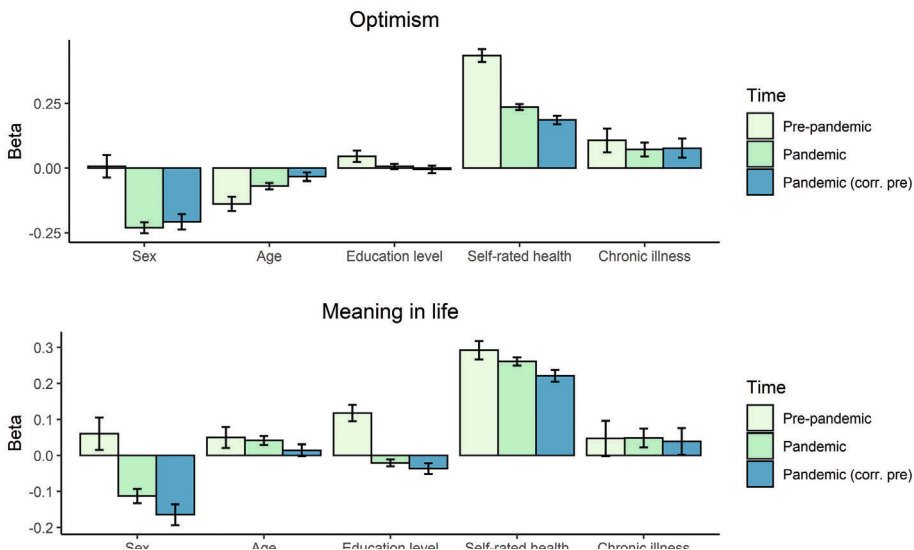


Figure 7.1. The results of the GEE analyses predicting optimism and meaning in life pre-pandemic, and during the pandemic. Note: Pandemic (corr. pre) = the effect of the predictors on optimism/meaning in life during the pandemic when correcting for the pre-pandemic score of optimism/meaning in life.

Longitudinal twin models

The twin correlations of optimism and meaning in life are reported in Table 7.4. Both pre-pandemic and during the pandemic, the monozygotic twin correlations were higher than the dizygotic twin correlations, suggesting genetic influences on optimism and meaning in life at both times. The cross-twin cross-trait correlations were also higher for MZ than for DZ twins, indicating an influence of genetic effects on the association between the pre-pandemic and pandemic measure for optimism and meaning in life. As there was no evidence for dominant genetic effects (i.e. $r_{mz} < 2 * r_{dz}$), we specified ACE models.

Table 7.4. Cross-trait cross-twin correlations for pre-pandemic and pandemic optimism and meaning in life.

	MZ		DZ	
Optimism	Pre-pandemic	Pandemic	Pre-pandemic	Pandemic
Pre-pandemic	0.25 (.18-.32)		0.15 (.01-.28)	
Pandemic	0.16 (.11-.22)	0.20 (.13-.26)	0.13 (.03-.22)	0.09 (.01-.17)
Meaning in life	Pre-pandemic	Pandemic	Pre-pandemic	Pandemic
Pre-pandemic	0.31 (.23-.38)		0.23 (.10-.34)	
Pandemic	0.17 (.12-.23)	0.26 (.20-.31)	0.12 (.04-.21)	0.09 (.01-.18)

Optimism

The model fitting showed that dropping the shared environmental component did not lead to a significant change in model fit ($p=.841$) (see supplementary Table S7.3). Dropping the additive genetic component instead of the shared environmental component did also not lead to a change in fit ($p=.119$). However, as the lower AIC suggests that the AE model is the best fitting model, the standardized estimates of the AE model are reported in Table 7.5 and Figure 7.2. In supplementary Table S7.1, the standardized estimates of the full ACE model are reported.

The standardized estimates indicate that before the pandemic 26% (95%CI: 19%-32%) of the individual differences in optimism was explained by additive genetic effects, whereas the remaining 74% (95%CI: 68%-81%) was explained by unique environmental influences. During the pandemic, the heritability estimate was 20% (95%CI: 14%-25%), with the remaining 80% (95%CI: 75%-86%) of the variance explained by unique environmental effects.

The bivariate heritability was 49% (95%CI: 34%-64%), whereas 51% (95%CI: 36%-66%) of the covariance of optimism across the two measurements was explained by environmental effects. The genetic and environmental correlations between optimism pre-pandemic and during the pandemic were respectively 0.75 (95%CI: .53-.98) and 0.23 (95%CI: .15-.30). Based on the 95% confidence interval, the genetic correlation was different from 1. Also constraining the genetic correlation between the pre-pandemic and pandemic measure of optimism to 1 resulted in a poorer model fit, although this did not reach our significance threshold, $p=.037$. The potential lower than unity correlation suggests qualitative gene-environment interaction effects with partly different genes for optimism pre-pandemic and during the pandemic.

Meaning in life

For meaning in life, the model fitting (see supplementary Table S7.3) showed that dropping the shared environmental component did not lead to a change in fit ($p=.523$). Dropping the additive genetic component also did not lead to a change in fit ($p=.010$). However, the lower AIC suggests the AE model is the best fitting model. In Table 7.5 and Figure 7.2, the standardized estimates of the AE model can be found (see supplementary Table S7.2 for the standardized estimates of the full ACE model).

Before the pandemic, 32% (95%CI: 25%-38%) of the individual differences in meaning in life was explained by additive genetic effects, whereas the remaining 68% (95%CI: 62%-75%) was explained by unique environmental influences. During the pandemic, 25% (95%CI: 20%-31%) of the individual differences in meaning in life was explained by additive genetic effects, with the remaining 75% (95%CI: 70%-81%) explained by unique environmental effects.

The bivariate heritability was 44% (95%CI: 31%-56%), whereas 57% (95%CI: 45%-69%) of the covariance of meaning of life across the two measurements is explained by environmental effects. The genetic and environmental correlation between meaning in life pre-pandemic and during the pandemic was respectively 0.63 (95%CI: .47-.80) and 0.33 (95%CI: .25-.39). Based on the 95% confidence interval, the genetic correlation was different from 1. Constraining the genetic correlation between the pre-pandemic and pandemic measure of meaning in life to 1 resulted also in a poorer model fit, $p=4.0 \times 10^{-5}$. The lower than unity correlation suggests a qualitative gene-environment interaction effect with partly different genes for meaning in life pre-pandemic and during the pandemic.

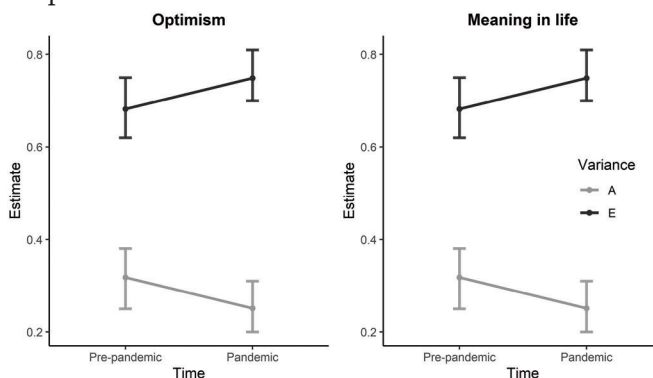


Figure 7.2. The standardized estimates for genetic and environmental variance underlying optimism and meaning in life. A: additive genetic variance, E: environmental variance.

Table 7.5. Standardized estimates for additive genetic and nonshared environmental influences on pre-pandemic and pandemic optimism and meaning in life and their covariance based on the best fitting models.

	A		E	
Optimism	Pre-pandemic	Pandemic	Pre-pandemic	Pandemic
Pre-pandemic	0.26 (.19-.32)		0.74 (.68-.81)	
Pandemic	0.49 (.34-.64)	0.20 (.14-.25)	0.51 (.36-.66)	0.80 (.75-.86)
	A		E	
Meaning in life	Pre-pandemic	Pandemic	Pre-pandemic	Pandemic
Pre-pandemic	0.32 (.25-.38)		0.68 (.62-.75)	
Pandemic	0.44 (.31-.56)	0.25 (.20-.31)	0.57 (.45-.69)	0.75 (.70-.81)

Note: A= standardized additive genetic effects, E = standardized non-shared environmental effects.

DISCUSSION

We report individual differences in the effect of the pandemic and first lockdown in the Netherlands on two aspects of well-being: optimism and meaning in life. In line with previous research a substantial part of the sample showed a decrease in optimism and meaning in life during the pandemic (respectively 48.9% and 28.4%). However, around half of the sample showed stability in optimism and meaning in life and the remaining 11% and 22% of the sample even increased compared to pre-pandemic levels. These results indicate that not everyone experienced reduced well-being in response to the pandemic and lockdown. An explanation for this stability or increase in well-being in these unprecedented times could be the forced pause from a stressful, busy life and more time to focus on social connections during the pandemic (Mancini, 2020).

To further investigate the individual differences in well-being in response to the pandemic, we tested moderation of the response by sex, age, level of education and health. A consistent finding was the lower optimism and meaning in life levels of women compared to men during the pandemic, whereas before the pandemic women and men reported similar levels. This sex effect is consistent with other research that reported the mental health of

women to be more affected during the pandemic compared to men (Pieh et al., 2020; Solomou & Constantinidou, 2020; Xiong et al., 2020). An explanation could be the different burden for women versus men during the lockdown (Alon et al., 2020). As schools and daycare closed during the lockdown, the caregiving responsibilities of families increased. Mothers have reduced their working hours more than fathers (Alon et al., 2020; Collins et al., 2020), and reported more transitions to working from home and reductions in working hours (Reichelt et al., 2020), indicating an unequal distribution of caregiving responsibilities within families. To explore the effect of caregiving responsibilities of men and women on optimism and meaning in life during the pandemic in our sample, we conducted an exploratory analysis on the interaction effect of being male or female and having children in the household (none, children > 12 and children < 12). In a subsample of around 9000 participants, using GEE, there was no main effect of children in the household ($p=.88$ and $p=.09$) or interaction effect with sex ($p=.15$ and $p=.23$) on optimism and meaning in life respectively. This indicates that the higher optimism and meaning in life for men compared to women is unlikely to be explained by caregiving responsibilities in our sample.

Additionally, the sex difference could result from the negative effect of the pandemic on the health care, retail and service industry, in which women are overrepresented. Especially health care workers report high levels of anxiety, depression, and insomnia during the COVID-19 pandemic (Pappa et al., 2020). Particularly in nurses (predominantly female), depression and anxiety scores were increased compared to doctors, as nurses may experience a greater risk of COVID-19 exposure by providing more direct care to patients.

The level of education influenced the effect of the pandemic on meaning in life. While pre-pandemic there was a clear association between meaning in life and educational attainment, this generally higher meaning in life for higher educated participants disappeared during the pandemic. Participants that decreased in meaning in life during the pandemic were higher educated, whereas participants that increased were lower educated. Explanations for this result in earlier studies included the higher news consumption and greater concerns about COVID-19 of higher educated people (Daly et al., 2020). Furthermore, during the pandemic a larger number of higher educated people are faced with stressors and demands that lower educated people are more likely to have experienced before, e.g., experiences of job instability and childcare difficulties. Finally, higher educated people might experience larger changes in daily life, as higher educated people are more likely to be forced to work from home due to pandemic measurements, whereas lower educated

people are more likely to perform practical work in the workplace that often continued under the difficult pandemic circumstances.

Lastly, self-rated health had the expected effect on optimism and meaning in life during the pandemic. As people with a poorer health are at risk for severe COVID-19 (Xiong et al., 2020) they are also more likely to be negatively affected in their well-being.

Genetic and environmental influences

The twin modelling indicated a slightly lower heritability and larger relative effect of the environmental factors during the pandemic than pre-pandemic, but confidence intervals overlap. This relatively stable heritability estimate indicates no evidence for quantitative gene-environment interaction effects and thus a stable influence of genetic effects before and during the pandemic. Alternatively, the pandemic and lockdown could have led to more variance in person-specific environmental variables such as the working situation (i.e. some people have lost their job, whereas others have to work more), home situation (i.e. living alone, with a partner or with children) and caregiving responsibilities (i.e. home schooling children), resulting in increase in total variance and the slight decrease in heritability.

The high genetic (.75 and .63 for optimism and meaning in life) correlations between the pre-pandemic and pandemic measures indicate a large overlap in the genetic factors underlying the traits at both time points. These high genetic influences are in line with the high genetic correlations between pre-pandemic and pandemic measures in a range of psychological and behavioral traits as reported by Rimfeld et al. (2021). However, although strong, the correlations are significantly different from unity, providing an indication for possible qualitative gene-environment interaction effects. Different genes express their influence under different environmental circumstances, in this case in response to the pandemic.

The environmental correlations were substantially lower (.23 and .33 for optimism and meaning in life), indicating that the environmental factors at both time points are mostly unique to that time point, as could be expected due to the strong environmental impact of the pandemic. We note that E also includes measurement error and that the two constructs were assessed by a single item. Finally, the bivariate heritability between the pre-pandemic and pandemic measure is respectively 49% and 44% for optimism and meaning in life, indicating that around half of the association between the measures can be explained by genetic factors.

Implications, limitations and future directions

Although the lockdown in the first wave of the COVID-19 pandemic was effective to suppress the spread of the virus in the Netherlands, the measures did affect people's optimism and meaning in life. In line with previous research, we report that a substantial part of the sample showed a decrease in the well-being variables optimism and meaning in life during the pandemic. However, the largest part of the sample showed stable levels or even increased levels of optimism and meaning in life during the pandemic. Special attention is needed for specific subgroups of the population (i.e. women, and people with a poorer health), as they are especially at risk for negative effects. Finally, possible qualitative gene-environment interaction underline the pandemic as a strong environmental variable.

A limitation of the current study was the different response scales for the pre-pandemic and pandemic measures and the slightly different wording of the items, limiting the possibilities to directly compare the scores. To be able to create within-subject change scores and report an average effect of the pandemic, we rescaled the pre-pandemic scores (1-7) to the answer scale of the pandemic measures (1-10). This solution has limitations and is not ideal. Therefore, we only used the within-subject scores to report on the proportion of people that are stable, increased or decreased and did not further investigate the subgroups showing a decrease or increase during the pandemic.

Furthermore, for both optimism and meaning in life we used single item measures at both time points. Whereas single item measures are time efficient, there is discussion about the decreased reliability compared to multiple item questionnaires (Bowling, 2005; Diamantopoulos et al., 2012), although in the field of well-being, the reliability of single item measures have been reported to be adequate and only slightly lower compared to the reliability of multiple item measures (Jovanović & Lazić, 2020; Krueger & Schkade, 2008).

In addition, the findings of the study might be influenced by the representativeness of our sample for the Dutch population. The subset of NTR participants in this particular study included more females (around 70%) than males and was relatively highly educated, with more than 50% indicating having attended higher vocational school or university, while in the Dutch population this percentage is around 35% (CBS, Enquête Beroepsbevolking (EBB), 2020). Also when comparing the pre-pandemic and pandemic sample, there might be a response bias. For example, the pandemic sample ($M=44.6$) was younger than the pre-pandemic sample ($M=48.1$).

The pandemic data analysed in this study was from the beginning of the pandemic (i.e. April and May 2020). During these months the pandemic and

lockdown were novel and people did not know how long the pandemic and lockdown would last. Many countries, including the Netherlands experienced multiple waves of COVID-19 infections and a prolonged lockdown. Comparing the effect of the first and the second lockdown on mental health, increased depressive symptoms and a higher psychological burden in the second lockdown were reported in Germany and Austria, although the restrictions were less strict compared to the first lockdown (Dale et al., 2021; Moradian et al., 2021). Therefore the results for optimism and meaning in life might also be different further into the pandemic or the effects might change over time. People's well-being might be more affected or genetic sensitivity might play a larger role later during the pandemic or in a later lockdown. For example, the optimism of people might decrease when the pandemic lasts longer or certain people might find another way to experience meaning in life. Therefore, in future research, the longitudinal effects of the pandemic and prolonged lockdown on the genetics of well-being should be investigated.

Another direction for future research is the specific environmental variables that lead to differences in well-being between subgroups and individuals, such as the working situation or care-giving responsibilities. We indicated a large group of people that were stable or showed an increase in optimism and meaning in life during the pandemic. This group is worth studying in more detail to get a hold of possible protective factors and resilience mechanisms. More knowledge on the person-specific response to individual specific environmental variables underlying the differences between people is urgently needed to prevent further inequality. Furthermore, to prevent the decrease of well-being in the subgroups, targeted policies and help are needed.

To conclude, the pandemic is a strong environmental variable that leads, due to genetic differences between people, to imbalanced effects on well-being of individuals. More knowledge on the person-specific response to specific environmental variables underlying these individual differences is needed to prevent further inequality. Therefore, we urge for more research to inform the development of programs to prepare individual well-being and health systems for future pandemics in different areas of the world.

Supplementary Material Chapter 7

Table S7.1. Unstandardized and standardized estimates for the full ACE twin model for optimism

	A			C			E		
	Pre-pandemic	Pandemic	SE	Pre-pandemic	Pandemic	SE	Pre-pandemic	Pandemic	SE
Pre-pandemic	0.24		0.05	0.05		0.05	0.05		0.05
	(-.10-.61)		(-.28-.37)			(.79-.96)			
Pandemic	0.12	0.39	0.12	0.12	-0.03	0.27	0.27	1.48	1.48
	(-.19-.43)	(.01-.78)	(-.16-.40)		(-.36-.30)	(.18-.36)		(1.37-1.61)	
SA									
SC									
SE									
Pre-pandemic	0.20		0.05	0.05		0.75			
	(-.09-.52)		(-.24-.31)			(.68-.82)			
Pandemic	0.23	0.21	0.24	0.24	-0.014	0.53	0.53	0.80	0.80
	(-.39-.85)	(-.01-.42)	(-.32-.80)		(-.19-.16)	(.37-.69)		(.74-.86)	
Correlation	0.37		NA	NA		0.24			
	(NA-NA)					(.16-.31)			

Note: A= unstandardized additive genetic effects, C= unstandardized shared environmental effects, E = unstandardized environmental effects, SA= standardized additive genetic effects, SC= standardized shared environmental effects, SE = standardized environmental effects.

Table S7.2. Unstandardized and standardized estimates for the full ACE twin model for meaning in life

	A		C		E	
	Pre-pandemic	Pandemic	Pre-pandemic	Pandemic	Pre-pandemic	Pandemic
Pre-pandemic	0.21 (-.14-.58)		0.18 (-.16-.48)		0.87 (.78-.97)	
Pandemic	0.18 (-.16-.53)	0.78 (.30-1.28)	0.12 (-.19-.42)	-0.17 (-.60-.25)	0.41 (.31-.51)	1.76 (1.62-1.91)
SA						
SC						
SE						
Pre-pandemic	0.17 (-.11-.46)		0.14 (-.13-.39)		0.69 (.62-.77)	
Pandemic	0.25 (-.23-.74)	0.33 (.13-.54)	0.17 (-.27-.60)	-0.07 (-.25-.10)	0.58 (.45-.71)	0.74 (.69-.80)
Correlation	0.44 (NA-NA)		NA		0.33 (.26-.40)	

Note: A= unstandardized additive genetic effects, C= unstandardized shared environmental effects, E = unstandardized environmental effects, SA= standardized additive genetic effects, SC= standardized shared environmental effects, SE = standardized environmental effects.

Table S7.3. Model fitting results for the longitudinal twin models for optimism and meaning in life before and during the pandemic

	Model	Base	Test	ep	-2LL	df	AIC	Δ LL	Δ df	P
Optimism	SAT			17	17273.9	5360	6553.9			
	1	SAT	ACE	13	17282.8	5364	6554.8	5.5	2	0.063
	2	1	AE	10	17283.6	5367	6549.6	0.8	3	0.841
	3	1	CE	10	17288.6	5367	6554.6	5.9	3	0.119
	4	1	E	7	17376.3	5370	6636.3	93.5	6	5.6x10 ⁻¹⁸
	Model	Base	Test	ep	-2LL	df	AIC	Δ LL	Δ df	P
	SAT			17	17906.6	5299	7308.6			
Meaning in life	1	SAT	ACE	13	17912.5	5303	7306.5	2.2	2	0.329
	2	1	AE	10	17914.7	5306	7302.7	2.2	3	0.523
	3	1	CE	10	17923.9	5306	7311.8	11.4	3	0.010
	4	1	E	7	18045.3	5309	7427.3	132.8	6	3.3x10 ⁻²⁶

Note: SAT= saturated model, ep=estimated parameters, -2LL= -2*loglikelihood, df= degrees of freedom, Δ LL= change in loglikelihood, Δ df= change in degrees of freedom.



Chapter 8.

Daily affect intensity and variability of adolescents and their parents before and during a COVID-19 lockdown

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ABSTRACT

The COVID-19 pandemic may have a prolonged impact on people's lives, with multiple waves of infections and lockdowns, but how a lockdown may alter emotional functioning is still hardly understood. In this 100-daily diary study, we examined how affect intensity and variability of adolescents ($N=159$, $Mage=13.3$, 61.6% female) and parents ($N=159$, $Mage=45.3$, 79.9% female) changed after the onset and during (>50 days) the second COVID-19 lockdown in the Netherlands, using preregistered piecewise growth models. We found only an unexpected increase in parents' positive affect intensity after the lockdown onset, but no immediate changes in negative affect intensity or variability. However, both adolescents and parents reported gradual increases in negative affect intensity and variability as the lockdown prolonged. Lockdown effects did not differ between adolescents and parents. However, within groups, individuals differed. Yet, we found individual differences in the effects, which were partly explained by life satisfaction, depressive symptoms, and self-reported lockdown impact. Overall, these findings suggests that a lockdown triggers changes in daily affective well-being especially as the lockdown prolongs. Individual differences in the effects indicate heterogeneity in the impact of the lockdown on daily affect that was partly explained by baseline life satisfaction and depressive symptoms. However, more knowledge on the causes of this heterogeneity is needed to be able to increase resilience to lockdown effects in the population.

Keywords: COVID-19, lockdown, well-being, affect, daily diary, piecewise growth models.

INTRODUCTION

The global corona virus (COVID-19) pandemic has a large and prolonged impact on people's everyday lives. During the first year of the pandemic, there was no effective cure, and prolonged restrictions were needed to control the virus, and make sure the healthcare systems could cope. Major restrictions during lockdowns included social distancing, and closing of schools, offices, and public places. The restrictions in combination with distress about the virus led, on average, to small increases in anxiety and depressive symptoms and decreases in well-being and life satisfaction (Masten & Motti-Stefanidi, 2020; Prati & Mancini, 2021; Robinson et al., 2022; Weeland et al., 2021). However, the negative effect of this first phase of the pandemic disappeared quickly: by mid-2020 average mental health had recovered to pre-pandemic levels (Robinson et al., 2022). These findings indicate that, in line with earlier findings in the field of resilience (Galatzer-Levy et al., 2018), most people were relatively resilient to the effects of the initial phase of the pandemic with respect to their well-being. Most people appear to be able to adapt quickly to the new situation. However, it has also been demonstrated that individuals differ in the extent to which the lockdown affects their daily life, relationships, and well-being (Bülow et al., 2021; de Vries, van de Weijer, et al., 2021; Janssen et al., 2020; Santomauro et al., 2021; van de Weijer, Pelt, de Vries, Huider, et al., 2022). Younger age groups, such as adolescents, may be more vulnerable, as they still have to build adaptive capacity to cope with such restrictions (Masten, 2021; Masten & Motti-Stefanidi, 2020; Santomauro et al., 2021).

Whereas research on the first lockdown led to knowledge about the acute response to the pandemic and feelings of uncertainty that people experienced about the virus, many countries experienced multiple waves of COVID-19 infections resulting in multiple lockdowns. Compared to the first lockdown, uncertainty about the virus might have decreased. In Germany, Austria, and Australia, for instance, individuals reported on average increased depressive symptoms and higher psychological burden during the second, less strict, lockdown compared to the first lockdown (Büssing et al., 2021; Dale et al., 2021; Johnston & Oliva, 2021; Moradian et al., 2021). Especially the 18-24 year olds showed a large increase in depressive symptoms compared to the first lockdown (Dale et al., 2021). Explanations for these findings could include a general mental exhaustion or "pandemic fatigue" as the pandemic and societal disruption continued (WHO, 2020). Furthermore, negative economic effects increased as well during the pandemic, leading to potential higher psychological burden for affected individuals. Investigating the effect of later lockdowns on

well-being helps to understand the more prolonged effects, and could inform policy with regard to expected psychological impact of future lockdowns. In the current preregistered 100-day diaries study, we therefore examined 1) the effects of a second lockdown in the Netherlands (December 2020-March 2021) on everyday positive and negative affect intensity and variability, 2) how these effects differed between adolescents and adults, i.e., their parents, 3) which individuals were most vulnerable to the impact of a lockdown by investigation of individual differences, and 4) how these differences related to baseline life satisfaction, depressive symptoms and self-reported impact of the lockdown on daily life.

Changes in daily positive and negative affect intensity and variability

Although evidence for the pandemic's impact upon general mental health and well-being is accumulating, less is known about the more subtle or dynamic effects on daily affective well-being. Affective well-being can be defined by the frequent experience of high positive affect and low negative affect (Diener et al., 2018). Using the Experience Sampling Method (ESM) in which affective well-being is assessed multiple times per day, or every day with a daily diary design, will give insights in the *daily affect intensity* and *affect variability*. Daily affect intensity can be defined as the level of daily positive or negative affect. However, feelings of positive and negative affect are not stable and fluctuate over time (i.e., across the day and week) and across different contexts (Eid & Diener, 2004; Li et al., 2014). Therefore, it is equally important to understand how everyday well-being fluctuates from one moment to the next, which we call affect variability. Individuals differ in their affect variability, some individuals show relatively stable positive and negative affect levels over the day or week, while others fluctuate considerably (Eid & Diener, 1999; Gadermann & Zumbo, 2007; Kuppens et al., 2010). Within boundaries, affect variability is adaptive and important for well-being as it helps to respond to environmental changes and demands (Carver, 2015; Frijda & Mesquita, 1994; Kashdan & Rottenberg, 2010). However, if emotions change too strongly or not at all it may signal dysregulation. Large variability of positive and negative affect have been associated with reduced well-being and increased risk for mental health problems (Aan het Rot et al., 2012; Houben et al., 2015; Maciejewski et al., 2019; Reitsema et al., 2022; Schoevers et al., 2021). Thus, in the context of this study, changes in affect dynamics during the COVID-19 pandemic could be an early marker for increased risk to develop emotional problems.

Few studies have investigated how the pandemic and lockdown has altered daily affect intensity and variability. Two studies reported a decrease in daily

positive affect intensity and an increase in negative affect intensity during the pandemic and lockdown (Deng et al., 2021; Green et al., 2021). Regarding affect variability, mixed findings were reported, i.e., a decrease in positive affect variability, but not negative affect variability (Deng et al., 2021; Green et al., 2021), or no change in affect variability at all (Asscheman et al., 2021). The first aim of the current study was to examine the effects of a lockdown on daily positive and negative affect intensity and affect variability. Based on previous studies, we expected that daily negative affect would increase, and positive affect intensity decrease (H1a). Moreover, we expected a decrease in positive affect variability at the start of the lockdown (compared to before) (H1b). We did not have a clear hypothesis about the negative affect variability because of the inconsistencies in the literature. Moreover we explored the gradual changes in daily affect intensity and variability during the first seven weeks of the lockdown. To test these hypotheses, the current study examines data of 100 consecutive days, in which adolescents and one of their parents reported on their daily positive and negative affect. The first 50 days were before the second lockdown in the Netherlands and the last 50 days were during the second lockdown.

Difference between adolescents and parents

The lockdown affects the whole family system, including adolescents and their parents (Bülow et al., 2021; Masten, 2021; Weeland et al., 2021). Yet, compared to their parents, adolescents could be more strongly affected by the lockdown (Fegert et al., 2020), because of several reasons. First, adolescence can by itself be a stressful period, which is characterized by substantial life changes, and the development of identity and emotion regulation (Maciejewski et al., 2019; Zeman et al., 2006). Second, during lockdowns, adolescents experience many restrictions which can possibly affected their development, such school closure, and restrictions in social and sport activities. Moreover, in the Netherlands, different restrictions were established for different age groups during the time in between the first (March-June 2020) and second lockdown (December 2020-March 2021). In these months *before* the second lockdown, adolescents were less restricted than adults. For adolescents (<18 years), schools and sport clubs were kept open and adolescents did not have to keep distance from each other, whereas adults had to keep 1.5m distance and could not meet to sport together. However, *during* the second lockdown, the rules for adolescents and adults were equally strict, i.e., both groups had to keep 1.5m distance and public spaces, schools and shops were closed. Therefore, for adolescents, the transition from the relatively measure-free period before

the lockdown to the strict lockdown period might be larger compared to the transition for adults. This difference could make the impact of a second lockdown potentially larger for adolescents than for their parents (see Table 1 for an overview of the restrictions before and during the second lockdown separately for adolescents and adults).

A recent study suggests that mainly adolescents are at risk for emotional problems due to COVID-19 and lockdowns (Santomauro et al., 2021). However, differences between adolescents and adults have not been examined by direct comparisons. Therefore, our second aim was to compare the lockdown effect on positive and negative affect intensity and variability between adolescents and their parents. Specifically, we expected adolescents to be more strongly affected by the lockdown than their parents, as reflected in stronger effects on affect intensity and variability, because of differences in developmental tasks and restrictions (H2).

Table 8.1. Important COVID-19 related restrictions during the study period, before (26 Oct- 14 Dec 2020) and during the second lockdown (15 Dec 2020 – 1 March 2021) in the Netherlands, separately for adolescents and adults.

	Adolescents (<18)	Adults (>=18)	General
Before 2nd lockdown (26 Oct-14 Dec 2020)	No 1.5m distance	1.5m distance	Public places open
	Schools open	Working from home	Shops open
	Sport clubs open	Sport with maximum of 4 people with 1.5m distance	
During 2nd lockdown (15 Dec 2020- 1 March 2021)	1.5m distance	1.5m distance	Public places closed
	Homeschooling	Working from home	Non-essential shops closed
	Sportclubs closed	Sportclubs closed	23 Jan: curfew

Individual differences

All psychological processes are heterogeneous (Bolger et al., 2019) and individuals also vary in their responses to stressful life events, like the COVID-19 pandemic (Galatzer-Levy et al., 2018; Mancini, 2020). Most people show resilience and adapt relatively quickly to new situations, whereas less resilient people do not cope well in response to stress and experience long-term adverse effects, i.e., lower well-being and possible development of psychopathology

(Bonanno et al., 2011; Galatzer-Levy et al., 2018). Indeed, empirical studies demonstrate such individual differences in the effects a lockdown had on daily life and well-being (de Vries, van de Weijer, et al., 2021; Janssen et al., 2020; Santomauro et al., 2021; van de Weijer, Pelt, de Vries, Huider, et al., 2022). Therefore, our third aim was to investigate how the impact of lockdown on daily affect intensity and variability would differ between individuals (i.e., effect heterogeneity; Bolger et al., 2019). Individual differences were hypothesized for all effects (H3). For example, we expected some participants to show an increase in negative affect intensity as a result of the lockdown, whereas others will show a decrease.

Furthermore, we explored why some individuals were more strongly affected, by assessing relevant moderators. Because well-being and mental health have been related to resilience and to positive and negative affect intensity and variability (Houben et al., 2015; Reitsema et al., 2022), we assessed baseline (i.e., before the second lockdown, October 2020) life satisfaction and depressive symptoms. We expected that individuals with a higher baseline life satisfaction and fewer depressive symptoms would report overall less positive and negative affect variability (H4a). Moreover, we expected that lower life satisfaction and a higher level of depressive symptoms at baseline would be related to larger changes in affect intensity and variability, i.e., indicating a larger impact of the lockdown (H4b). Finally, we explored the relation between the self-reported lockdown impact on daily life and affect intensity and variability.

METHODS

This study was preregistered using a template for experience sampling methodology (ESM) research (Kirtley et al., 2021) (<https://osf.io/8s6vn>).

Participants

We used existing data of the “100 days of my life” study, including daily data of 159 adolescents and one of their parents (Bülow et al., 2020), (<https://osf.io/5mhgk/>). Inclusion criteria were, that (1) adolescents were aged 12 – 16 years, (2) parents and adolescents owned a smartphone, and (3) parents and adolescents had contact with each other almost every day (e.g., living together). Adolescents were on average 13.3 years old ($SD = 1.2$, range = 12–16 years) and 61.6% was female (36.5% male, 1.9% other). Most adolescents were born in the

Netherlands (88.9%) and followed pre-university high school (VWO) (50.9%), whereas 28.9% of the adolescents was in higher general high school (HAVO), 15.1% followed prevocational high school (VMBO) and 5.0% was in a mixed track (VMBO/HAVO or HAVO/VWO). Parents were on average 45.3 years old ($SD = 4.5$, range = 33-55 years) and mostly female (79.9%). Most parents were born in the Netherlands (86.8%) and were highly educated with either a college or university degree (62.7%), whereas 25.3% of the parents had a vocational/technical training and 10.1% was low-educated (i.e., high school diploma).

Procedure

Participants were recruited at two Dutch high schools (via e-mails, social media, posters, and class visits) and via newsletters. During 100 consecutive days (26 Oct 2020 until 2 Feb 2021), both adolescents and their parents received daily questionnaires via the Ethica application on their Android or iOS smartphone (Ethica Data, 2020). Participants could choose when they wanted to receive the daily notification (between 7PM and 10PM). Participants were reminded three times (every 30 minutes) and one time the next morning (7AM) to answer the questionnaire. Participants could answer up to 12PM the next day. In every daily questionnaire, participants answered 20–27 items, which took approximately 3-5 minutes. The compliance rate was high, with 89% and 94% completed by respectively the adolescents and parents.

Additionally to the daily questionnaires, participants answered five longer questionnaires in Qualtrics (Qualtrics, 2021) every three months, with the first at the start of the 100 days period. In this study, we included life satisfaction and depressive symptoms from the baseline questionnaire (October 2020) and self-reported lockdown impact from the second longitudinal questionnaire (January 2021).

Participants received a monetary reward for answering each questionnaire and gained bonuses if they answered 10 questionnaires in a row or answered all 100-daily questionnaires. In total, adolescents could earn 100€ (approx. US\$ 116) and parents 50€ (approx. US\$ 58). Every day, adolescents could win 10€ (approx. US\$ 12) if they answered the questionnaire. Adolescents could choose to get a diary booklet with their own answers at the end of the study. The study and amendments of the design due to the lockdown were approved by the ethical committee of Tilburg University (RP250).

Halfway during the data collection, at day 51 (15 December 2020), the government introduced the second strict lockdown in the Netherlands, which lasted up to day 100 of the study. As shown in Figure 1, at the first day of the data collection (26 October 2020) the restrictions were less strict, schools and

sport clubs were open and adolescents until 18 years did not have to distance themselves from each other. Adults (≥ 18 years) were required to keep 1.5m distance from everyone, besides their own household and were required to work from home. During the strict lockdown, schools, public places, and non-essential shops were closed (see Figure 1 and Table 1). After the study period, the restrictions of the lockdown were released, i.e., March 1 high schools and shops opened again.

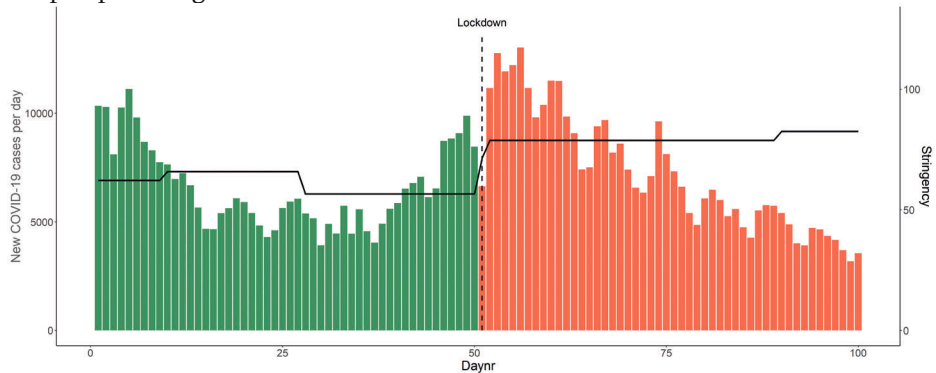


Figure 8.1. Timeline of the number of COVID-19 cases per day (left y-axis) and the stringency of the measures (right y-axis) in the Netherlands during the 100-day study period.

Note: The stringency index is a measure of the strictness of the COVID-19 regulations, based on school closure, workplace closure, travel bans (ranging from 0-100). Source: <https://ourworldindata.org/grapher/covid-stringency-index?region=Europe&country=~NLD>

Measures

Daily positive and negative affect

Daily positive and negative affect were assessed with a shortened version of the Positive and Negative Affect Scale for Children (PANAS-C) (Ebesutani et al., 2012). Items included were joyful (Dutch: *blij*) and happy (*gelukkig*) for positive affect and mad (*boos*), afraid (*angstig*) and sad (*verdrietig*) for negative affect. Participants had to rate on a visual analogue scale from 0 (*not at all*) - 100 (*very much*) to what extent they felt these emotions during the whole day. The selected items were chosen based on previous work (Bülow et al., 2022; Vogelsmeier et al., 2021). The within-person correlation for the two positive affect items was high for both adolescents ($r = .75$) and their parents ($r = .83$). The within-person and between person reliability of the three negative affect items was good for both adolescents ($\omega_{\text{within}} = .71$, $\omega_{\text{between}} = .92$) and parents ($\omega_{\text{within}} = .68$, $\omega_{\text{between}} = .80$) (Geldhof et al., 2014).

Affect intensity and variability

To investigate how positive and negative affect intensity and variability changed, we computed average intensity and variability per week for every participant ($n_{\text{total weeks}}=2192$ and 2206 for adolescents and parents respectively). Hence, 14 data points per variable were obtained i.e., seven weeks before the lockdown and seven weeks during the lockdown. Affect intensity was computed as the average score across seven days separately for positive and negative affect. Higher scores indicate higher positive or higher negative affect. We defined the variability of positive and negative affect as the square root of the Mean Square of Successive Differences (rMSSD), computed as.

$$rMSSD = \sqrt{\frac{\sum_{i=1}^{n-1} (x_{i+1} - x_i)^2}{n-1}}$$

using the R function *rmssd* (Jahng et al., 2008; Von Neumann et al., 1941). The rMSSD is often referred to as affective instability (Koval et al., 2013; Trull et al., 2015). Larger rMSSD reflects higher day-to-day variability, whereas smaller rMSSD indicates less variability (see supplementary Figure S8.1 for examples of high and low affect intensity and variability). Following Koval et al. (2013), we first computed the rMSSD of each positive and negative affect item and then averaged the rMSSD for all the positive items as the final score for positive affect variability and the negative items as the score for negative affect variability. The rMSSD is strongly related to the standard deviation (*SD*) (Dejonckheere et al., 2019; Wendt et al., 2020), which was also the case in the current study ($r > .85$). We used the rMSSD instead of *SD* to measure variability, because *SD* reflects only the size of variability, whereas the rMSSD also takes into account temporal dependence between subsequent moments (Jahng et al., 2008).

Baseline measures

Adolescents' life satisfaction. For adolescents, the Cantril's Self-Anchoring Ladder (Levin & Currie, 2014) was used to measure life satisfaction. Using a single-item measure, participants had to indicate their quality of life on a scale from 1 to 10, with a score of 10 indicating the best quality.

Adolescents' depressive symptoms. Adolescents reported on their depressive symptoms by using the Reynolds Adolescent Depression Scale Short (RADS-2) (Reynolds, 2004). Participants had to rate 10 items about occurrence of certain behavior or feeling on a scale from 1 (*almost never*) to 4 (*often*). An example item is "I've felt like nothing I was doing made sense." The Cronbach's alpha in the current study was 0.90 (95% CI: .87-.92), indicating excellent internal consistency.

Parents' depressive symptoms. Parents reported on the presence of depressive symptoms by using the Brief Depression Inventory (BDI) (Beck & Beck, 1972). The BDI included 21 items about how the parent has been feeling in the last week. For every question, parents had to choose among 4 statements (0-3) and pick the one that resembled their feelings the most. For example, an item is “*I do not feel like a failure*” (0) up to “*I feel I am a complete failure as a person*” (3). The Cronbach's alpha in the current study was 0.84 (95%CI: .80-.87), indicating a good internal consistency.

Self-reported impact of the lockdown. During the second longitudinal questionnaire (end of January), adolescents and their parents completed the COVID-19 Impact Questionnaire. This questionnaire was based on items from other surveys (Achterberg et al., 2021; Brown et al., 2020; Conway III et al., 2020; Ellis et al., 2020; Magson et al., 2021) and included seven items on the impact of the lockdown on their daily life, well-being, financial situation, school performance, and relations with family and friends. Participants answered on a scale from -3 (*very negative*) to +3 (*very positive*). We summed the scores on these 7 items to create a score for self-reported impact. Larger negative scores indicate a larger negative effect on daily life and well-being. The Cronbach's alpha of this scale was 0.78 (95%CI: .73-.84) for adolescents and 0.74 (95%CI: .68-.80) for parents, indicating good internal consistency.

Coping. During the second longitudinal questionnaire (end of January), adolescents and their parents also completed the Short version Utrecht Coping List (UCL) (Schreurs et al., 1993). The UCL consist of 19 items that measure four different coping strategies in response to problems or difficult events, namely confrontation, avoidance, social support and palliative reaction. Participants answered on a scale from 1 (seldom) to 4 (very often) how often they applied the strategy when confronted with problems. We summed the scores on the items per strategy to create a score for the four different coping strategies. Larger scores indicate more use of the particular coping strategy.

Statistical analyses

Piecewise growth models

To compare the change in positive and negative affect intensity and variability from pre-lockdown to the lockdown period, we applied latent piecewise growth models (Bülow et al., 2021; Flora, 2008) following our preregistered plan (<https://osf.io/8s6vn>). Piece-wise models allow to disentangle more sudden environmental changes from the ongoing trajectory of change

by adding additional growth factors. Conceptually, modelling the within-person change (while controlling for stable between-person differences), each individual has its own ‘control condition’: the estimated pre-lockdown level of affect and change trajectory if the lockdown had not occurred. We ran eight models, namely models with positive and negative affect intensity and variability as outcomes (2x2) separately for adolescents and parents (x2). Several sensitivity analyses replicated our main results (for more detail see supplemental materials).

In the models, we modelled ongoing levels and changes by estimating a baseline intercept (level 1: L1) and slope (S1) for the whole study period. The factor loadings of S1 were centred at the week before the lockdown, and, therefore, the intercept (L1) can be interpreted as the affect intensity or variability directly before the lockdown. The slope S1 reflects linear changes in affect intensity or variability during the whole study period (week 1-14). To assess how the lockdown period altered this trajectory, we added a second intercept (level 2: L2) and slope (S2). The loadings of S2 are centred at week 8, i.e., the first lockdown week. Therefore, the second intercept (L2) reflects the level difference between affect intensity or variability the week before the lockdown and the first lockdown week. S2 reflects the linear changes specifically during the lockdown (week 8 to 14), over and above the normative trajectory as modelled by S1. We allowed the intercepts and slopes to vary across individuals by adding their variances and added the correlations between random intercepts and slopes (see Figure 2 for the model). All available data were used. In order to deal with missing data, maximum likelihood for robust standard errors (MLR) estimation (MLR) was used. In sensitivity models, we tested the effect of stricter thresholds for data inclusion, and results did not differ (for more detail see supplemental materials). The model fit for the models was evaluated based on the root mean square error of approximation (RMSEA), ($< .08$), comparative fit index (CFI) ($> .90$) and Tucker-Lewis index (TLI) ($> .90$) (L. T. Hu & Bentler, 1999; McDonald & Ho, 2002). We interpreted the model findings if two of the three fit measures were acceptable. If not specified otherwise, in all tests, we used p -value $< .05$ as inference criteria.

Aim 1. To test the effect of the lockdown on the daily affect intensity or variability (H1), we examined the significance of the second intercept (L2). Moreover, we explored the significance of the slope during lockdown (S2).

Aim 2. To assess differences between adolescents and their parents in the lockdown effect on affect variability and intensity (H2), we constrained the intercept and slope for the lockdown (L2 and S2) of the parents to be equal to the

values of the adolescents' model and compared the model fit using chi-square difference tests.

Aim 3. To investigate individual differences within the groups in changes in the affect intensity or variability (H3), we assessed whether the variance around the second intercept (L2) and the second slope (S2) is significant (one-tailed p -value < .05).

Aim 4. To understand why the lockdown may impact individuals differentially, we further added life satisfaction (only for adolescents) and depressive symptoms (for adolescents and parents) as predictors to additional piecewise growth models. To test the overall association between affect intensity or variability and life satisfaction or depressive symptoms, we tested the significance of the association between the predictor and the intercept L1 (H4a). To investigate the association with the lockdown effect on affect intensity and variability, we tested the significance of the association between the predictor and lockdown intercept L2 and slope S2 (H4b).

Similarly, as an exploratory (i.e., not preregistered) analysis, we included self-reported impact of the lockdown and the four coping strategies as predictor in the models. We tested the significance of the association between the lockdown impact or coping strategies and the intercepts and slopes.

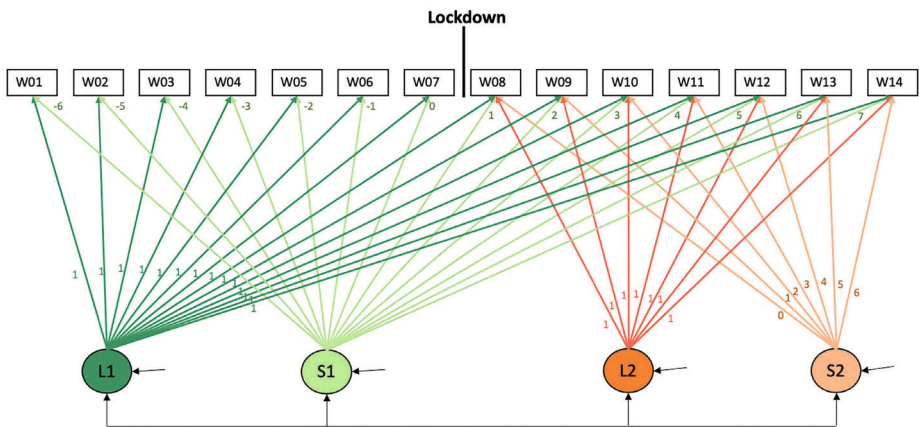


Figure 8.2. Piecewise growth model (Flora, 2008), based on (Bülöw et al., 2021) with an intercept and slope to model change during the whole study period (L1 and S1) and an intercept and slope to capture the additional impact of the lockdown period (L2 and S2), starting at week 8.

Note: W01-W14 indicates the positive or negative affect intensity or variability score of week 1 until week 14 (based on 100 days of data).

RESULTS

In Table 8.2, the descriptive statistics and average positive and negative affect intensity and variability during the weeks before and during the lockdown can be found. The variables were normally distributed (skewness <3.00 and kurtosis <10.00).

Table 8.2. Descriptives of positive and negative affect intensity and variability

Week	n	Adolescents							
		PA intensity	SD PA intensity	NA intensity	SD NA intensity	PA variability	SD PA variability	NA variability	SD NA variability
1	159	75.02	16.18	12.66	16.18	15.67	10.36	14.76	10.36
2	159	77.49	16.65	11.67	16.65	12.96	8.57	12.69	8.57
3	159	76.68	17.71	11.70	17.71	11.77	8.80	12.12	8.80
4	158	75.46	18.76	11.51	18.76	12.28	9.81	12.08	9.81
5	159	75.38	18.64	11.14	18.64	12.25	10.78	11.17	10.78
6	158	76.93	17.79	10.35	17.79	11.24	9.34	10.38	9.34
7	157	75.70	18.32	11.61	18.32	10.78	9.82	11.16	9.82
Lockdown 8	156	76.79	18.21	10.47	18.21	10.82	9.48	9.66	9.48
9	157	78.62	18.17	10.43	18.17	9.45	8.92	8.81	8.92
10	154	78.67	17.87	9.34	17.87	9.17	9.59	7.87	9.59
11	154	75.15	17.81	11.28	17.81	10.90	9.50	10.25	9.50
12	155	75.58	18.80	11.59	18.80	9.46	9.10	9.65	9.10
13	155	76.05	19.23	10.57	19.23	8.91	9.16	9.00	9.16
14	152	76.57	17.73	11.58	17.73	8.57	8.80	8.67	8.80
		Parents							

Table 8.2. Descriptives of positive and negative affect intensity and variability

Week	n	PA intensity	SD PA intensity	NA intensity	SD NA intensity	PA variability	SD PA variability	NA variability	SD NA variability
1	159	70.3	70.27	15.18	11.63	9.29	14.90	8.20	12.98
2	159	70.3	70.28	16.28	11.45	11.01	13.02	7.89	11.32
3	159	71.0	71.05	15.11	9.94	8.94	12.24	8.25	10.73
4	159	69.6	69.57	16.45	10.40	10.07	11.79	8.20	10.60
5	159	70.1	70.13	16.94	9.45	9.42	11.24	8.39	9.53
6	159	70.8	70.81	17.39	9.65	10.95	11.21	9.54	9.38
7	158	69.7	69.70	17.66	9.80	10.49	10.15	7.80	9.13
Lockdown 8	158	68.8	68.84	17.34	11.35	10.63	10.50	8.08	10.73
9	156	72.3	72.27	17.12	8.65	9.00	10.05	7.76	8.50
10	157	72.0	72.00	17.17	8.97	9.77	9.96	8.28	8.23
11	156	70.3	70.29	17.30	9.93	10.65	9.89	6.74	8.03
12	155	69.0	69.02	17.78	10.52	10.75	9.27	6.97	8.73
13	156	68.9	68.90	17.51	10.59	10.22	9.97	8.48	9.54
14	156	68.9	68.86	18.11	11.60	11.75	9.81	7.48	10.02

Note: PA= positive affect, NA = negative affect.



Aim 1. Changes in daily affect intensity and variability

All preregistered piecewise growth models had an acceptable model fit with maximum likelihood for robust standard errors (MLR) estimation (RMSEA = .04 - .10, CFI > .90 and TLI > .90, supplementary Table S8.1). Covariance matrices of all models can be found in supplementary Table S8.11- S8.18.

The first hypothesis (H1a) of direct decreases and increases in respectively daily positive affect and negative affect during the second COVID-19 lockdown was not supported. Instead, we found a small increase in positive affect intensity for parents ($M_{L2} = 1.75$, $SE = 0.63$, $p = .005$) (see Table 3, L2). We also did not find the expected decrease in positive affect variability due the lockdown (H1b) (see Table 3, L2).

More gradual changes in the affect intensity or variability during the lockdown period (S2) were significant in 5 models. For both adolescents and parents, negative affect intensity increased during the 7 weeks of the lockdown ($M_{S2} = 0.44$, $SE = 0.17$, $p = .008$ and $M_{S2} = 0.67$, $SE = 0.17$, $p < .001$, respectively). Furthermore, negative affect variability increased for both adolescents and parents ($M_{S2} = 0.58$, $SE = 0.18$, $p = .001$ and $M_{S2} = 0.66$, $SE = 0.14$, $p < .001$ respectively). Finally, for parents, positive affect variability increased during the lockdown ($M_{S2} = 0.57$, $SE = 0.16$, $p < .001$) (see Table 3, S2).

Hence, even though the expected immediate effects were not found, and parents reported slightly more positive affect in the week after the lockdown introduction, both adolescents' and parents' level of negative affect and variability in negative affect increased gradually as the lockdown prolonged.

Table 8.3. Piecewise growth models to assess the impact of a lockdown on adolescent and parents' positive and negative affective well-being.

Variable	Adolescents						Parents						
	Mean	SE	p	Variance	SE	p	Mean	SE	p	Variance	SE	p	
PA intensity	L1	76.26	1.44	<.001	312.04	37.06	<.001	70.06	1.39	<.001	290.35	34.30	<.001
	S1	0.03	0.14	.819	1.60	0.36	<.001	-0.08	0.15	.599	2.05	0.40	<.001
	L2	1.19	0.65	.066	24.47	7.35	.001	1.75	0.63	.005	17.34	7.00	.013
NA intensity	S2	-0.20	0.22	.372	5.31	0.88	<.001	-0.40	0.22	.073	4.92	0.87	<.001
	L1	10.64	0.92	<.001	119.27	14.93	<.001	9.43	0.82	<.001	98.78	12.00	<.001
	S1	-0.26	0.12	.024	1.03	0.25	<.001	-0.29	0.12	.022	1.65	0.28	<.001
PA variability	L2	-0.29	0.50	.560	5.92	4.73	.211	-0.32	0.51	.529	15.47	4.74	.001
	S2	0.44	0.17	.008	2.20	0.50	<.001	0.67	0.17	<.001	2.88	0.53	<.001
	L1	10.54	0.73	<.001	68.13	13.26	<.001	10.54	0.73	<.001	68.13	13.26	<.001
NA variability	S1	-0.60	0.12	<.001	1.11	0.42	.008	-0.60	0.12	<.001	1.11	0.42	.008
	L2	0.53	0.64	.411	17.11	10.22	.094	0.53	0.64	.411	17.11	10.22	.094
	S2	0.31	0.17	.073	1.95	0.91	.033	0.31	0.17	.073	1.95	0.91	.033
NA variability	L1	10.18	0.69	<.001	51.63	8.59	<.001	8.78	0.55	<.001	31.17	5.55	<.001
	S1	-0.59	0.13	<.001	0.99	0.33	.003	-0.58	0.11	<.001	0.50	0.23	.025
	L2	-0.53	0.65	.419	9.63	8.00	.229	0.53	0.60	.379	9.22	6.95	.184
	S2	0.58	0.18	.001	1.48	0.57	.009	0.66	0.14	<.001	0.13	0.38	.729

Note. L1 reflects the general level of affect intensity or variability before the lockdown. S1 reflects the general changes during the whole study period. L2 reflects the immediate change in intensity or variability the week before the lockdown and the first week of the lockdown. S2 reflects the gradual changes during the lockdown weeks, above and beyond the S1.



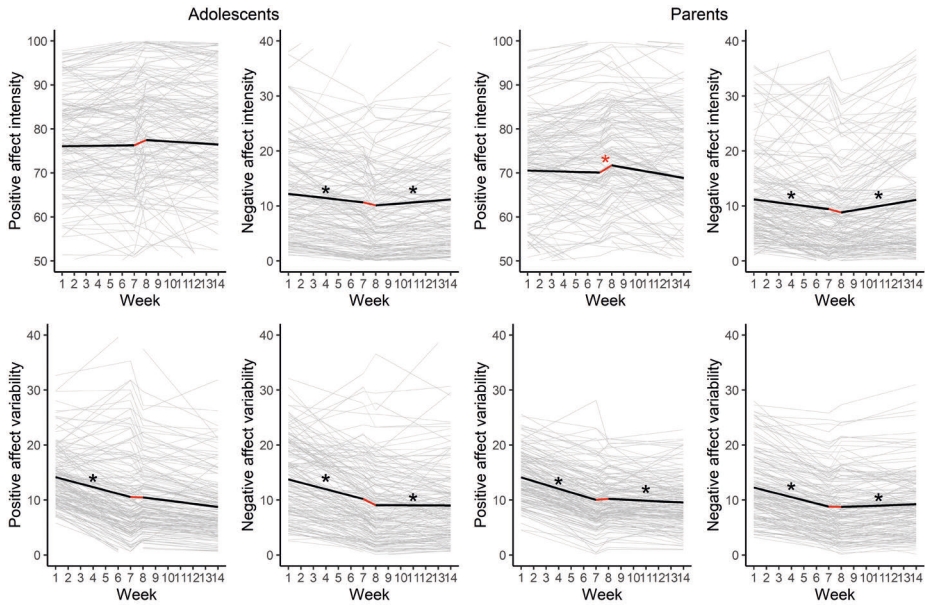


Figure 8.3. Piecewise growth models of positive and negative affect intensity and variability.

Note: The black line reflects the average estimated trajectory. The grey lines reflect the trajectories of the individual participants. The red star indicates the significant mean level change (L2), the black stars on the left of the red line indicate the significant overall slope (S1) and the black stars on the right of the red line indicate the significant slope during the lockdown weeks (S2).

Aim 2. Age difference in the effect of the lockdown on affect intensity and variability

To assess whether adolescents and parents differ in the immediate (L2) or gradual changes (S2), we constrained these growth factors to be equal across age groups (see supplementary Table S8.3). Not in line with our hypotheses, no significant differences were found between adolescents and parents in the lockdown effects on affect intensity, nor variability (H2). Adolescents and parents were, on average, affected in similar ways by the lockdown.

Aim 3. Individual differences in effects

As expected individuals differed in the immediate changes in affect intensity (H3) in three out of the eight models (Figure 8.4 – variance around L2). The effect on adolescents’ ($Var_{L2}=24.5, SE=7.35, p = .001$) and parents’ positive affect intensity ($Var_{L2}=17.3, SE=7.0, p=.013$), and parents’ negative affect intensity ($Var_{L2}=15.5, SE=4.7, p=.001$) differed significantly among participants (see Table

8.3). For instance, plotting these change rates per individual (upper panel Figure 8.4) demonstrated that some participants felt better at the lockdown start compared to the week before (i.e., decrease in negative affect intensity, increase in positive affect intensity), for others the intensity was stable, and for others well-being decreased (i.e., increase in negative affect intensity and decrease in positive affect intensity).

Exploring whether individuals differed in the gradual changes during 7 weeks of the lockdown (S2), the variance was significant in seven of the eight models (except for negative affect variability for parents). The lower panel of Figure 8.4 shows that whereas for some participants the positive or negative affect intensity or variability gradually increased, it was stable or gradually decreased for others.

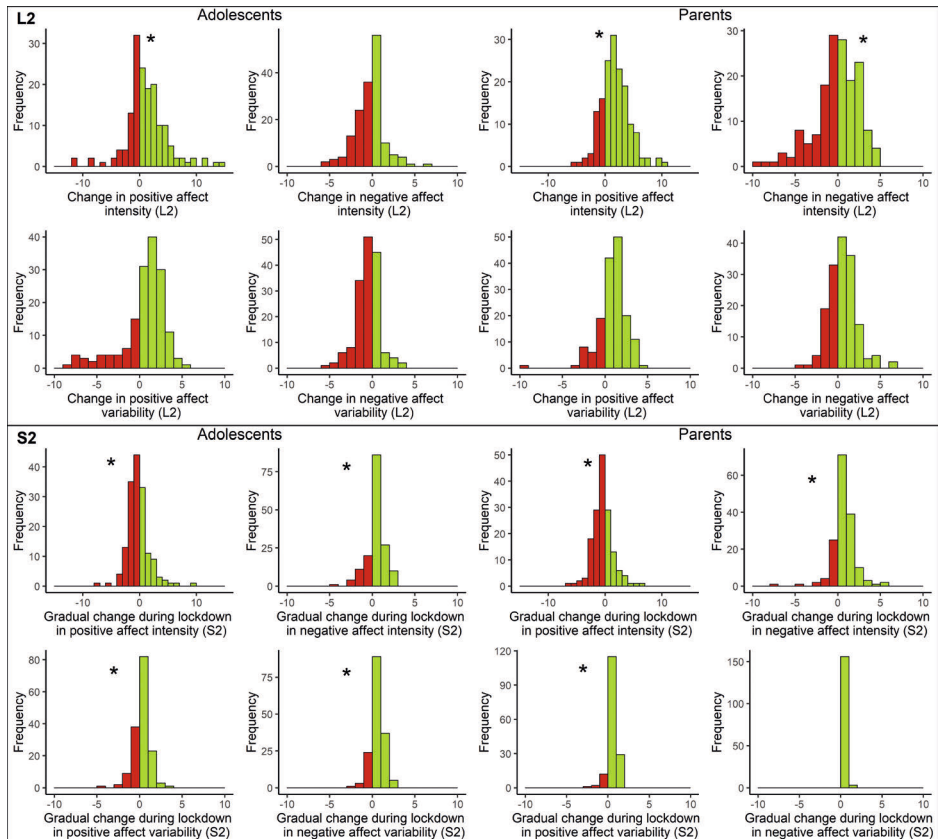


Figure 8.4. Individual differences in immediate (L2: upper panel) and gradual (S2: lower panel) change in affect intensity or variability during the weeks of the lockdown, for adolescents (left part) and their parents (right part). Stars indicate significant variance and thus individual differences in effects ($p < .05$).

Aim 4. Individual differences and baseline life satisfaction and depressive symptoms

To better understand why some participants were more resilient against lockdown effects, we examined whether changes in intensity and variability would depend on baseline life satisfaction (adolescent models) or depressive symptoms (adolescent and parent models) (see Table 4 for the results and supplementary Table S8.5 for model fit statistics). First, overall levels of affective well-being (L1) were related to depressive symptoms and life satisfaction as expected (H4a): Adolescents and parents with fewer depressive symptoms and adolescents with higher life satisfaction reported higher positive affect intensity and lower negative affect intensity, and adolescents with more depressive symptoms had higher positive and negative affect variability (see Table 4). Contrary to our expectations (H4b), depressive symptoms or life satisfaction were unrelated to immediate lockdown effects (L2). However, gradual changes in positive affect during the lockdown period (S2) were stronger for adolescents with higher baseline life satisfaction ($M_{s2} = 0.40$, $SE = .16$, $p = .011$), i.e., their positive affect decreased less strongly during the lockdown. Additionally, parents with more depressive symptoms experienced stronger increases in negative affect intensity during the lockdown ($M_{s2} = 0.09$, $SE = .03$, $p = .002$). In sum, even though depressive symptoms and life satisfactions were related to everyday experienced intensity and variability in emotional functioning over 100 days, they explained more of the gradual impact of the lockdown than the immediate impact.

Exploratory analysis: Individual differences and lockdown impact and coping

Exploring individual differences in daily affect intensity and variability in relation to the self-reported impact of the lockdown on daily life showed small effects (see Table 4). Parents with a higher level of positive affect (L1) reported a more positive influence of the lockdown on daily life ($M_{\text{change}} = 1.27$, $SE = 0.29$, $p < .001$). The other smaller effects between the self-reported impact of the lockdown and changes in positive affect intensity and variability should be interpreted cautiously, since they do not reach significance when correcting for multiple testing. In sum, self-reported impact of the lockdown on daily life explained small parts of the variance in experienced affect intensity and variability due to the lockdown.

We found a few effects of coping strategies on general positive and negative affect, i.e., confrontation and social support were related to higher general positive affect intensity. However, the coping strategies were mostly

unrelated to the lockdown effects on affect intensity and affect variability (see Supplementary Table S8.7). The only moderation effect was for confrontation on positive affect variability in the adolescent group ($M = -0.64$, $SE = 0.18$, $p < .001$). Adolescents who apply confrontation more often in response to difficulty or problems showed a stronger decrease in positive affect variability directly after the introduction of the lockdown.

Table 8.4. Effect of baseline well-being, depressive symptoms, and self-reported impact on the intercepts and slopes.

	I1			S1			I2			S2			
	M	SE	p	M	SE	p	M	SE	p	M	SE	p	
Adolescents													
PA intensity	LS	5.67	0.94	<.001	-0.17	0.1	.073	-0.32	0.46	.487	0.4	0.16	.011
NA intensity	LS	-3.15	0.62	<.001	0.1	0.08	.239	-0.35	0.36	.329	-0.06	0.12	.644
PA variability	LS	-1.13	0.61	.061	0.17	0.12	.148	-0.25	0.43	.558	-0.13	0.18	.455
NA variability	LS	-0.94	0.49	.055	0.3	0.09	.001	-0.9	0.46	.051	-0.17	0.13	.175
PA intensity	Depr	-1.32	0.2	<.001	0.03	0.02	.186	0.07	0.10	.467	-0.07	0.03	.041
NA intensity	Depr	0.74	0.13	<.001	-0.03	0.02	.147	0.06	0.08	.432	0.04	0.03	.122
PA variability	Depr	0.43	0.13	.001	0.00	0.02	.877	0.00	0.10	.985	-0.03	0.03	.377
NA variability	Depr	0.39	0.10	<.001	-0.06	0.02	.006	0.05	0.10	.637	0.06	0.03	.047
PA intensity	Impact	0.28	0.27	.308	-0.05	0.03	.038	0.25	0.12	.033	0.07	0.04	.094
NA intensity	Impact	-0.05	0.17	.767	0.03	0.02	.124	-0.16	0.09	.074	-0.04	0.03	.248
PA variability	Impact	0.05	0.20	.785	0.03	0.03	.200	-0.14	0.16	.370	-0.03	0.04	.401
NA variability	Impact	0.07	0.13	.592	0.04	0.02	.115	-0.16	0.12	.173	-0.04	0.03	.249
Parents													
PA intensity	Depr	-1.56	0.22	<.001	-0.03	0.03	.271	0.1	0.11	.374	0.00	0.04	.999
NA intensity	Depr	0.65	0.14	<.001	-0.05	0.02	.041	-0.01	0.09	.902	0.09	0.03	.002
PA variability	Depr	0.31	0.10	.002	-0.03	0.02	.147	0.08	0.11	.479	0.04	0.03	.202
NA variability	Depr	0.48	0.09	<.001	-0.05	0.02	.009	0.15	0.11	.157	0.03	0.03	.202
PA intensity	Impact	1.27	0.29	<.001	0.05	0.03	.147	0.19	0.13	.137	0.00	0.05	.974
NA intensity	Impact	-0.23	0.18	.208	0.06	0.03	.022	-0.16	0.11	.142	-0.08	0.04	.022
PA variability	Impact	0.10	0.12	.405	0.06	0.03	.013	-0.28	0.13	.036	-0.03	0.03	.447
NA variability	Impact	-0.11	0.12	.377	0.03	0.02	.184	-0.15	0.13	.262	0.01	0.03	.807

Note. LS = life satisfaction, Depr = level of depressive symptoms, Impact = self-reported impact of the lockdown on daily life and well-being.

DISCUSSION

The COVID-19 pandemic and resulting lockdowns has a large impact on people's daily life, and emotional well-being (Masten & Motti-Stefanidi, 2020; Prati & Mancini, 2021; Robinson et al., 2022), and it is unsure whether future lockdowns are needed. By investigating the effect of the second lockdown in the Netherlands on daily affect of adolescents and their parents in more detail, this study aimed to understand the specific effects of a second lockdown, instead of the effects of first lockdowns, in which the acute response to the pandemic and experienced uncertainty about the virus were combined.

Using 100 days of diary data, the average adolescent and parent experienced hardly any immediate lockdown effects on affect intensity and variability. Unexpectedly, parents reported more positive affect in the week after the lockdown introduction. However, as the lockdown prolonged and both parents and adolescents were not allowed to sport, go to school or work, and had limited contact with friends and family, the intensity of negative affect and variability in positive and negative affect increased gradually. Moreover, although adolescents and parents were affected in similar ways, there was large heterogeneity between individuals. That is, some participants experienced a gradual increase in negative affect intensity and variability and decrease in positive affect intensity, whereas others remained stable or showed opposite patterns. Baseline depressive symptoms and life satisfaction partly explained individual differences in these effects, with baseline life satisfaction promoting positive affect, and depressive symptoms related to larger increases in negative affect during the lockdown. Furthermore, individuals who reported a larger lockdown impact on daily life showed slightly stronger lockdown effects on affect intensity and variability.

Changes in daily affect intensity and variability during the lockdown

Based on extensive earlier work, we expected that the lockdown would decrease well-being immediately, as operationalized by change in daily affect intensity and variability. However, the only immediate effect we found was an *increase* in positive affect intensity of parents in first lockdown week compared to the week before the lockdown. An explanation might be relief of parents over clarity about the restrictions. In the weeks leading up to the lockdown, the number of COVID-19 cases increased steadily, and people started to expect a lockdown any time soon, leading to uncertainty about the situation and perhaps distress and anxiousness (Reizer et al., 2021). The absence of other immediate effects might be explained by the expectation and anticipation of

an upcoming lockdown (Brodeur et al., 2021). Anticipation could have prepared people mentally, reducing direct effects of the lockdown when introduced.

Even though at the start of the second lockdown, adolescents and parents were not much affected, as the lockdown endured, negative effects on daily affect emerged. The gradual decreases in positive affect intensity and increases in negative affect intensity are in line with other longitudinal studies (Brodeur et al., 2021; Pellerin & Raufaste, 2020). However, in contrast to our expected decrease in positive affect variability (Deng et al., 2021; Green et al., 2021), we report a gradual increase in positive and negative affect variability during the lockdown. Whereas earlier studies compared affect variability at two time points (i.e., pre-lockdown vs lockdown), our findings add insights about gradual and subtle increases in affect variability during the lockdown. Affect variability is useful within boundaries, but the gradual increase in positive and negative variability can be a risk factor for future emotional problems.

The gradual changes implicate the need to monitor people's well-being longitudinally during a lockdown to not miss gradually emerging adverse effects when the lockdown prolongs. As indicated by Robinson et al. (2022), on average people returned to their baseline well-being relatively quickly after the first lockdown ended. However, as individual differences in this effect are found, part of the population does not restore their well-being and are at risk for psychopathology, such as depressive symptoms or anxiety (Galatzer-Levy et al., 2018). Psychopathology symptoms do not arise overnight, but through the accumulation of negative events and feelings. Therefore, to reliably figure out the effects of later lockdowns on well-being, both short-term and longer-term effects during the lockdown and after the lockdown ends should be monitored, especially in groups at risk.

Differences between adolescents and parents

There were several reasons (i.e., different restrictions, emotional development, and stressful developmental period) why we expected adolescents to be more influenced by the lockdown compared to their parents. Yet, no such differences were found. On average, parents and adolescents in this study responded in quite similar ways. An explanation of this absence of differences might be, contrary to the expectation, that, on average, parents indicated a larger negative self-reported lockdown effect on daily life ($M = -3.80$, $SD = 4.63$) compared to adolescents ($M = -1.16$, $SD = 5.51$, $t = 5.29$, $p < .001$). Although the actual transition from pre-lockdown to lockdown in terms of regulations was objectively larger for adolescents than adults, parents felt more restricted. In line with this idea, in the first lockdown, Janssen et al. (2020) reported that

parents, but not adolescents increased in their negative affect in two-week period during the COVID-19 pandemic compared to pre-pandemic.

The direct comparison of the lockdown effects for adolescents and their own parents is a strong test, since it reduces random factors that would be there if adolescents and parents were from different households. The adolescent and parent belong to the same family, live in the same household, and experience similar stressors. They also share part of their genetic predispositions for well-being and risk for psychopathology (Bartels et al., 2013; Silberg et al., 2010). This within-household design and shared environmental factors might explain the absence of differences between adolescents and their parents. Furthermore, the affect of adolescents and their parents is related and adolescents can influence parents' affect and vice versa (Griffith et al., 2021; Kim et al., 2001). We report a positive (within-family) correlation between positive affect intensity of adolescents and their parents (see supplementary Table S8.10), suggesting this mutual influence and synchrony between affect of parents and adolescents (see the temporal interpersonal emotion systems ("TIES" model), Butler, 2011; Loughheed & Keskin, 2021).

In conclusion, the similar lockdown effects on adolescents and their parents could be because parents and children share the same environment and influence each other. However, this does not necessarily indicate that the underlying mechanism contributing to the negative effects of the pandemic on well-being is the same for adolescents and adults. We hypothesized that the prolonged stress and restriction led to decrease in affective well-being, with a larger effect for adolescents, because of missing out on opportunities for social development and growth. However, future research is needed to investigate the specific underlying mechanisms.

Individual differences

This study demonstrated heterogeneity in individuals' responses to a lockdown. Whereas some participants showed the expected effects, i.e., gradual increases in negative affect intensity and variability and decreases in positive affect, others were stable or showed opposite patterns. People differ in the effects, which can be explained by different environmental factors and stressors experienced in the lockdown, and genetic predispositions for well-being, and sensitivity to extreme environmental changes due to the pandemic (de Vries, van de Weijer, et al., 2021; Rimfeld et al., 2021; van de Weijer, Pelt, de Vries, Huider, et al., 2022).

To further understand individual differences in the effects, we investigated the association with baseline life satisfaction and depressive symptoms.

The results led to insights about the protective effects of general well-being measures in extreme environmental situations, i.e., the lockdown, on daily affective well-being. As expected (Aan het Rot et al., 2012; Houben et al., 2015; Reitsema et al., 2022), higher affect variability was associated with more depressive symptoms and lower life satisfaction. However, they only explained small parts of the differential responses to the lockdown. Among adolescents, those with higher baseline life satisfaction reported a stronger increase in positive affect during the lockdown. Similarly, for parents, those who reported more depressive symptoms experienced a stronger gradual increase in negative affect during the lockdown. If replicated, these effects could indicate more resilience to negative lockdown effects for people with a higher life satisfaction or fewer depressive symptoms. Based on the resilience theory that individuals who can cope better with stressful events are less affected by the lockdown, we investigated the association of the lockdown effects with four different coping strategies, confrontation, avoidance, social support and palliative reaction. However, these coping strategies were mostly unrelated to the lockdown effects on affect intensity and affect variability

The specific lockdown effects on people's daily life and environment differed considerably across people and this can be an explanation for individual differences in the lockdown effects on affect. For example, some parents had to work from home, whereas others continued working on site. Similarly, some adolescents might not have their own room and argue more with siblings. Moreover, some people could be more sensitive to their environment than others, and therefore, more strongly affected by lockdown restrictions and accompanied family stress (Greven et al., 2019; Pluess, 2015). To capture these individual differences in the impact of the lockdown on daily life, we explored the associations between the self-reported impact of the lockdown of the lockdown on daily life and well-being and the lockdown effects on affect intensity and variability. We found small associations. Individuals who reported a negative effect of the lockdown on daily life and well-being also showed stronger lockdown effects on daily affect intensity and variability. However, these results should be interpreted with caution, since both the daily affect and lockdown impact on daily life was based on self-reports and the effects can emerge due to the common method bias (Podsakoff et al., 2003). Furthermore, Janssen et al. (2020) reported that pandemic related characteristics (i.e., the working from home, children present at home etc.) could not explain the individual differences in positive and negative affect during the first lockdown in their sample. Therefore, more research to the causes of individual differences in response to the lockdown or any other world-wide change are

needed. For example, differences in response to (environmental) change are driven by differences in genetic background between people. Therefore gene-environment interaction and gene-environmental correlations should be taken into account in future studies either by using genetically informative designs, such as twin studies, or by adding polygenic scores to the models.

Future directions and limitations

Although the unique dataset with 100 days of data per family was sufficiently powered to answer our pre-registered hypotheses, there are some limitations to the current study. A first limitation is the sample representativeness. In both the adolescent and parent group, there was an overrepresentation of females (62% and 80% respectively). Additionally, compared to the general Dutch population, in which ~35% of the adults attended higher vocational school or university and 45% of the adolescents currently follow higher secondary education (Statistics Netherlands, 2020), the current sample is highly educated (adults: 63%, adolescents: 80%). More research to lockdown effects on daily affect in diverse samples and participants from lower socio-economic backgrounds is needed to generalize results to the whole population.

Furthermore, a possible confounding factor is the timing of the second lockdown in the Netherlands. The lockdown started in the middle of December (15 December) and lasted until the end of February, meaning a lockdown during the winter holidays. The ritual of celebrating Christmas can lead to increased well-being or, when experienced as a stressor, to conflict and lower well-being and higher negative affect (Mutz, 2016; Páez et al., 2011). Furthermore, the start of vaccination program was announced in December in the Netherlands, leading to hope. Therefore, the overlap of different events could have influenced the results.

Additionally, the results of this Dutch study might be difficult to generalize to other countries. Although the COVID-19 virus is a global pandemic, countries are differently affected by the pandemic and governments implemented necessary restrictions at different times. Especially relevant for later waves of the virus, the pace of vaccination and willingness of people to be vaccinated created diverse situations in countries.

Finally, we assessed a few potential factors that could explain individual differences. Future studies should investigate possible moderating effects of the situation and individual differences in genetic sensitivity to extreme environmental change on the lockdowns effects on daily affect. Also, individual differences in personality might play a role in the experience of the lockdown situation (Kroencke et al., 2020; Modersitzki et al., 2021), e.g., some adolescents

may enjoy spending more time at home. More knowledge on the causes of heterogeneity in the effects is needed to increase resilience to lockdown effects in the population.

Conclusion

This 100-day daily diaries study aimed to understand how everyday well-being of adolescents and parents was affected by the second COVID-19 lockdown, in which physical activity, social contact, and regular school and work patterns were disrupted. The daily affect of Dutch adolescents and their parents was, on average, not much affected immediately after the start of the lockdown. The only significant change was an increase in positive affect for parents. However, as the lockdown prolonged, more negative effects of lockdowns emerged both for parents and for adolescents, which have also been described in other studies. Specifically, negative affect intensity and variability increased and positive affect intensity decreased. However, the extent to which well-being was impacted varied significantly between individuals, with parents who already felt depressed appeared at increased risk, and adolescents with higher baseline satisfaction at lower risk for negative impacts. Hence, when policy-makers consider to use lockdowns as a means to combat the virus, these gradually emerging emotional costs for specific target groups should also be considered.

Supplementary Material Chapter 8

Sensitivity analyses

As a sensitivity analysis, we computed the positive and negative affect intensity and variability separately for the 50 days before the lockdown and the 50 days in the lockdown. Using a repeated measures test and including the two groups, we directly compared the affect intensity and variability of adolescents and their parents, the effect of the lockdown (pre-lockdown vs lockdown) and the interaction between the group and lockdown on positive and negative affect intensity and variability. This provides another test on whether adolescents and their parents reacted differently to the lockdown in terms of affect dynamics. Adolescents reported higher positive affect intensity compared to their parents, during the whole study period ($p < .001$), i.e., a difference between L1 in the main study. There are no differences between adolescents and their parents in negative affect intensity and positive and negative affect variability. Furthermore, the interaction effects between group and the lockdown period were not significant (see supplementary Table S8.4).

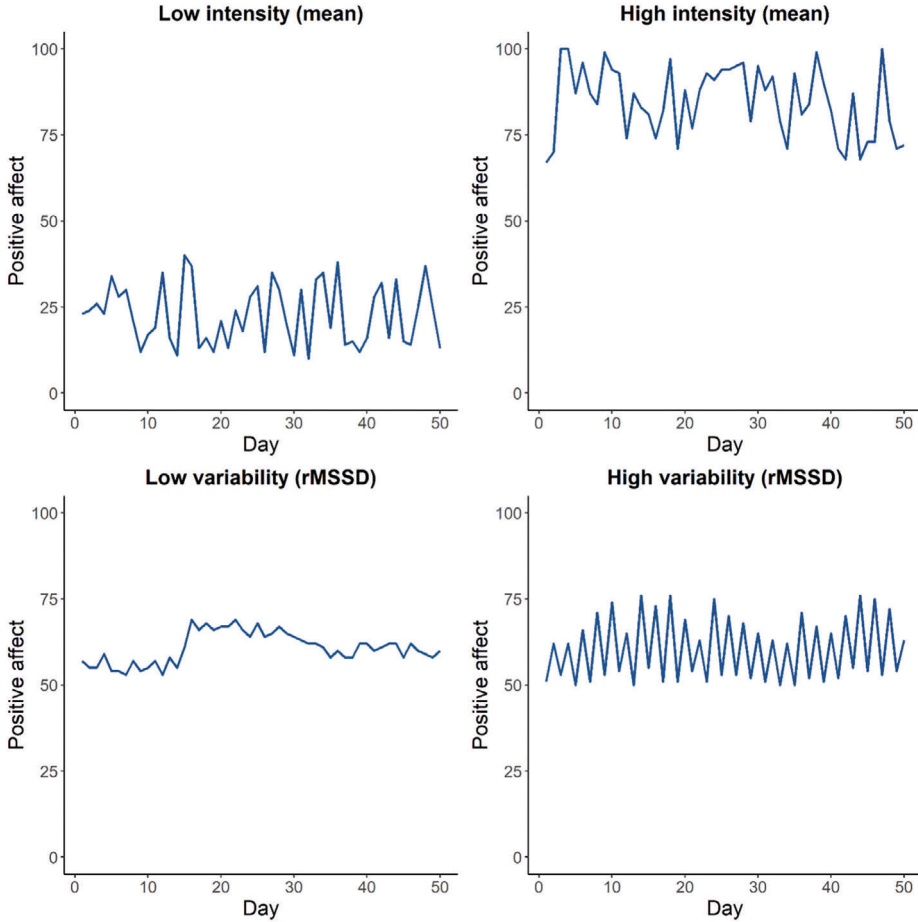
As another sensitivity analysis, we ran the main models with stricter thresholds for data inclusion. If a participant had more than 2 missing values in a week (i.e. less than 5 assessments in a week), the daily affect and variability scores were not computed for that specific week and not included in the models (resulting in the removal of 227 (10.2% of all available weeks) and 118 (5.3% of all available weeks) weeks for adolescents and parents respectively. Stricter inclusion thresholds did not affect the results (see supplementary Table S8.8 and S8.9). Therefore, the results with the larger groups are reported.

Within-family effects

As exploratory analysis, we correlated the estimated intercepts and slopes of the adolescents to the estimates of their parents. There were two significant correlations (see supplementary Table S8.10). We found a positive significant correlation between the general positive affect intensity (L1) of adolescent and parent before the lockdown ($r = .27, p < .001$), indicating that daily positive affect intensity between the adolescent and their parent is related. Furthermore, we found a significant positive correlation between the effect of the lockdown on the negative affect variability (L2) of adolescent and parent ($r = .20, p = .011$). If an adolescent showed an increased negative affect variability during the first lockdown week compared to the week before the lockdown, the same pattern was likely to occur for their parent.

Supplementary figure

Figure S8.1. Example of low and high positive affect intensity (top row) and low and high affect variability (bottom row).



Supplementary tables

Table S8.1. Model fit of main models.

	Adolescents				Parents			
	RMSEA	CFI	TLI	TLI	RMSEA	CFI	TLI	TLI
PA intensity	0.095 (.08-.11)	0.938	0.938	Acceptable	0.101 (.09-.12)	0.960	0.960	Acceptable
NA intensity	0.088 (.07-.10)	0.924	0.924	Acceptable	0.096 (.08-.11)	0.946	0.946	Acceptable
PA variability	0.058 (.04-.08)	0.909	0.909	Acceptable	0.041 (.01-.06)	0.958	0.958	Acceptable
NA variability	0.035 (.00-.06)	0.972	0.972	Acceptable	0.070 (.05-.09)	0.922	0.922	Acceptable

Note: PA= positive affect, NA = negative affect. RMSEA= root mean square error of approximation, CFI= comparative fit index, TLI= Tucker-Lewis index. PA variability model for adolescents is estimated with maximum likelihood with robust standard errors (MLR).

Table S8.2. Correlations between the intercepts and slopes.

	Adolescents							
	L1	S1	L2	S2	NA intensity	L1	S1	S2
PA intensity	1							
L1	1				L1	1		
S1	0.52	1			S1	0.48	1	
L2	-0.27	0.28	1		L2	-0.29	0.19	1
S2	-0.42	-0.84	-0.07	1	S2	-0.48	-0.84	0.33
PA variability	L1	S1	L2	S2	NA variability	L1	S1	S2
L1	1				L1	1		



Table S8.2. Correlations between the intercepts and slopes.

S1	0.78	1	S1	0.33	1
L2	-0.85	-0.75	L2	-0.26	-0.41
S2	-0.79	-0.89	S2	-0.46	-0.68
		0.66	1		1
Parents					
PA intensity	L1	S1	L2	S2	NA intensity
L1	1		L1	1	
S1	0.66	1	S1	0.59	1
L2	-0.59	-0.59	L2	-0.70	-0.96
S2	-0.50	-0.80	S2	-0.40	-0.77
PA variability	L1	S1	L2	S2	NA variability
L1	1		L1	1	
S1	0.47	1	S1	-0.03	1
L2	-0.55	-0.80	L2	0.22	-0.94
S2	-0.50	-0.74	S2	-0.03	-0.64
		0.73	1		0.81

Note. bold correlations are significant at $p < .001$, italic correlations are significant at $p < .05$. PA= positive affect, NA = negative affect. L1= level 1, L2 = level 2, S1= slope 1, S2= slope 2.

Table S8.3. Results of the model comparisons when constrain the estimates of the parent models to be equal to the adolescent models.

		Chi square	df	Δ chi square	Δ df	p-value
PA intensity	Parent model	237.18	91			
	L2 constrained	237.98	92	0.81	1	0.370
	S2 constrained	237.98	92	0.80	1	0.371
NA intensity	Parent model	224.73	91			
	L2 constrained	224.73	92	0.01	1	0.994
	S2 constrained	226.52	92	1.79	1	0.181
PA variability	Parent model	115.38	91			
	L2 constrained	115.69	92	0.31	1	0.565
	S2 constrained	118.08	92	2.70	1	0.100
NA variability	Parent model	162.38	91			
	L2 constrained	165.45	92	3.06	1	0.080
	S2 constrained	162.70	92	0.31	1	0.576

Note. The submodels with L2 or S2 constrained are compared to the parent model. PA= positive affect, NA = negative affect. L2 = level 2, S2= slope 2.



Table S8.4. Results of the repeated measures ANOVA (pre- vs lockdown) with group (adolescent vs adult) included.

PA intensity		β	SE	<i>p</i>	NA intensity	β	SE	<i>p</i>
Intercept		77.22	1.29	<2x10⁻¹⁶	Intercept	10.64	0.78	<2x10⁻¹⁶
Lockdown		-1.09	0.58	0.062	Lockdown	0.91	0.42	0.031
Group		-7.13	1.83	1.17x10⁻⁰⁴	Group	-0.39	1.10	0.720
LD*group		1.27	0.82	0.122	LD*group	-0.80	0.59	0.180
PA variability		β	SE	<i>p</i>	NA variability	β	SE	<i>p</i>
Intercept		11.23	0.53	<2x10⁻¹⁶	Intercept	11.88	0.62	<2x10⁻¹⁶
Lockdown		3.30	0.46	4.15x10⁻¹²	Lockdown	3.09	0.53	1.16x10⁻⁰⁸
Group		0.27	0.75	0.72	Group	-0.14	0.87	0.876
LD*group		-1.01	0.65	0.122	LD*group	-1.52	0.74	0.043

Note. LD= lockdown. PA= positive affect, NA = negative affect.

Table S8.5. Model fit covariate models.

Adolescents				
Depressive symptoms	RMSEA	CFI	TLI	
PA intensity	0.126 (.11-.14)	0.934	0.931	Acceptable
NA intensity	0.107 (.09-.12)	0.934	0.932	Acceptable
PA variability	0.055 (.04-.07)	0.916	0.912	Acceptable
NA variability	0.060 (.04-.08)	0.947	0.945	Acceptable
Well-being				
Depressive symptoms	RMSEA	CFI	TLI	
PA intensity	0.127 (.11-.14)	0.933	0.930	Acceptable
NA intensity	0.105 (.09-.12)	0.936	0.934	Acceptable
PA variability	0.056 (.04-.07)	0.912	0.908	Acceptable
NA variability	0.062 (.04-.08)	0.942	0.939	Acceptable
Impact				
Depressive symptoms	RMSEA	CFI	TLI	
PA intensity	0.132 (.12-.15)	0.928	0.926	Acceptable
NA intensity	0.105 (.09-.12)	0.938	0.936	Acceptable
PA variability	0.055 (.03-.07)	0.912	0.909	Acceptable
NA variability	0.066 (.05-.08)	0.930	0.927	Acceptable
Parents				
Depressive symptoms	RMSEA	CFI	TLI	
PA intensity	0.096 (.08-.11)	0.960	0.959	Acceptable



Table S8.5. Model fit covariate models.

NA intensity	0.097 (.08-.11)	0.940	0.938	Acceptable
PA variability	0.048 (.02-.07)	0.945	0.943	Acceptable
NA variability	0.069 (.05-.09)	0.923	0.920	Acceptable
Impact	RMSEA	CFI	TLI	
PA intensity	0.097 (.08-.11)	0.960	0.958	Acceptable
NA intensity	0.093 (.08-.11)	0.944	0.942	Acceptable
PA variability	0.046 (.02-.07)	0.947	0.945	Acceptable
NA variability	0.066 (.05-.08)	0.924	0.921	Acceptable

Note: PA= positive affect, NA = negative affect. RMSEA= root mean square error of approximation, CFI= comparative fit index, TLI= Tucker-Lewis index.

Table S8.6. Model fit covariate models coping strategies.

Adolescents				
Confrontation	RMSEA	CFI	TLI	
PA intensity	0.130 (.12-.15)	.931	.928	Acceptable
NA intensity	0.103 (.09-.12)	.940	.938	Acceptable
PA variability	0.050 (.03-.07)	.929	.926	Acceptable
NA variability	0.062 (.04-.08)	.937	.934	Acceptable
Avoidance	RMSEA	CFI	TLI	
PA intensity	0.132 (.12-.15)	.929	.926	Acceptable
NA intensity	0.103 (.09-.12)	.940	.938	Acceptable
PA variability	0.053 (.03-.07)	.921	.918	Acceptable
NA variability	0.061 (.04-.08)	.940	.938	Acceptable
Social support	RMSEA	CFI	TLI	
PA intensity	0.133 (.12-.15)	.928	.925	Acceptable
NA intensity	0.106 (.09-.12)	.938	.935	Acceptable
PA variability	0.057 (.04-.07)	.909	.905	Acceptable
NA variability	0.066 (.05-.08)	.929	.926	Acceptable
Palliative reaction	RMSEA	CFI	TLI	
PA intensity	0.133 (.12-.15)	.927	.925	Acceptable
NA intensity	0.107 (.09-.12)	.937	.934	Acceptable
PA variability	0.050 (.03-.07)	.928	.926	Acceptable
NA variability	0.060 (.04-.08)	.941	.938	Acceptable
Parents				
Confrontation	RMSEA	CFI	TLI	



Table S8.6. Model fit covariate models coping strategies.

PA intensity	0.097 (.08-.11)	.959	.958	Acceptable
NA intensity	0.090 (.08-.11)	.948	.946	Acceptable
PA variability	0.000 (.00-.04)	1.00	1.00	Acceptable
NA variability	0.068 (.05-.09)	.921	.918	Acceptable
Avoidance	RMSEA	CFI	TLI	
PA intensity	0.097 (.08-.11)	.959	.958	Acceptable
NA intensity	0.093 (.08-.11)	.944	.942	Acceptable
PA variability	0.013 (.00-.04)	.993	.993	Acceptable
NA variability	0.068 (.05-.09)	.919	.915	Acceptable
Social support	RMSEA	CFI	TLI	
PA intensity	0.096 (.08-.11)	.960	.959	Acceptable
NA intensity	0.098 (.08-.11)	.938	.936	Acceptable
PA variability	0.000 (.00-.04)	1.00	1.00	Acceptable
NA variability	0.075 (.06-.09)	.903	.899	Acceptable
Palliative reaction	RMSEA	CFI	TLI	
PA intensity	0.097 (.08-.11)	.959	.958	Acceptable
NA intensity	0.095 (.08-.11)	.942	.940	Acceptable
PA variability	0.000 (.00-.03)	1.00	1.00	Acceptable
NA variability	0.069 (.05-.09)	.917	.914	Acceptable

Note: PA= positive affect, NA = negative affect. RMSEA= root mean square error of approximation, CFI= comparative fit index, TLI= Tucker-Lewis index.

Table S8.7. Effect of coping strategies on the intercepts and slopes.

	L1			S1			L2			S2		
	M	SE	p	M	SE	p	M	SE	p	M	SE	p
Adolescents												
Confrontation	1.26	0.45	0.005	0.01	0.04	0.797	0.02	0.20	0.932	0.00	0.07	0.973
NA intensity	-0.33	0.29	0.264	0.03	0.04	0.444	-0.02	0.16	0.887	-0.06	0.05	0.232
PA variability	0.35	0.21	0.105	0.09	0.04	0.010	-0.64	0.18	0.000	-0.10	0.06	0.065
NA variability	0.18	0.21	0.409	0.04	0.04	0.283	-0.18	0.20	0.368	-0.07	0.05	0.195
	M	SE	p	M	SE	p	M	SE	p	M	SE	p
Avoidance	-1.61	0.91	0.078	-0.02	0.09	0.802	-0.63	0.40	0.110	0.15	0.14	0.280
NA intensity	0.01	0.58	0.987	-0.01	0.08	0.849	0.10	0.31	0.753	0.09	0.11	0.385
PA variability	0.16	0.47	0.727	-0.03	0.08	0.670	0.41	0.38	0.282	0.04	0.11	0.701
NA variability	0.32	0.42	0.449	0.04	0.08	0.654	-0.50	0.40	0.212	0.05	0.11	0.669
	M	SE	p	M	SE	p	M	SE	p	M	SE	p
Social support	1.00	0.34	0.003	-0.03	0.03	0.429	0.09	0.15	0.550	0.07	0.05	0.190
NA intensity	-0.26	0.22	0.235	0.01	0.03	0.867	-0.11	0.12	0.340	-0.04	0.04	0.331
PA variability	-0.21	0.17	0.239	0.01	0.03	0.734	-0.09	0.16	0.589	0.01	0.04	0.818
NA variability	-0.05	0.16	0.773	0.01	0.03	0.796	-0.03	0.15	0.871	-0.02	0.04	0.584
	M	SE	p	M	SE	p	M	SE	p	M	SE	p
Palliative reaction	0.56	0.59	0.343	0.06	0.05	0.290	-0.20	0.25	0.444	-0.09	0.09	0.297



Table S8.7. Effect of coping strategies on the intercepts and slopes.

	S1			I2			S2					
Parents	<i>M</i>	<i>SE</i>	<i>p</i>	<i>M</i>	<i>SE</i>	<i>p</i>	<i>M</i>	<i>SE</i>	<i>p</i>			
NA intensity	0.18	0.37	0.628	0.02	0.05	0.714	-0.18	0.20	0.373	0.00	0.07	0.994
PA variability	0.14	0.29	0.634	-0.03	0.05	0.513	0.11	0.24	0.641	0.05	0.07	0.452
NA variability	0.30	0.27	0.276	-0.04	0.05	0.492	-0.18	0.26	0.495	0.10	0.07	0.157
Confrontation												
PA intensity	1.87	0.42	0.000	0.03	0.05	0.492	-0.06	0.19	0.762	0.07	0.07	0.334
NA intensity	-0.85	0.25	0.001	0.03	0.04	0.499	0.11	0.16	0.483	-0.08	0.05	0.136
PA variability	-0.31	0.22	0.160	0.02	0.04	0.696	0.21	0.22	0.337	-0.08	0.06	0.178
NA variability	-0.51	0.17	0.003	0.06	0.03	0.059	0.00	0.19	0.988	-0.10	0.04	0.021
Avoidance												
PA intensity	-2.15	0.93	0.021	-0.04	0.10	0.672	0.42	0.40	0.292	0.07	0.15	0.655
NA intensity	0.35	0.56	0.528	-0.14	0.08	0.088	-0.13	0.34	0.702	0.27	0.11	0.020
PA variability	-0.08	0.41	0.850	-0.10	0.07	0.144	0.21	0.41	0.605	0.09	0.11	0.415
NA variability	0.17	0.37	0.652	-0.10	0.07	0.158	0.14	0.40	0.724	0.10	0.10	0.301
Social support												
PA intensity	0.81	0.36	0.023	0.02	0.04	0.697	-0.14	0.15	0.350	0.01	0.06	0.903
NA intensity	-0.29	0.21	0.173	-0.01	0.03	0.740	0.11	0.13	0.418	0.01	0.05	0.872
PA variability	-0.25	0.15	0.100	0.02	0.03	0.548	-0.06	0.16	0.710	0.02	0.04	0.689

Table S8.7. Effect of coping strategies on the intercepts and slopes.

	<i>M</i>	<i>SE</i>	<i>p</i>	<i>M</i>	<i>SE</i>	<i>p</i>	<i>M</i>	<i>SE</i>	<i>p</i>	<i>M</i>	<i>SE</i>	<i>p</i>
NA variability	-0.11	0.14	0.443	0.00	0.03	0.996	-0.05	0.16	0.744	0.02	0.04	0.608
Palliative reaction												
PA intensity	-0.49	0.61	0.422	-0.01	0.07	0.880	0.13	0.26	0.611	0.05	0.10	0.620
NA intensity	0.39	0.36	0.276	0.01	0.06	0.817	-0.01	0.22	0.971	0.02	0.08	0.749
PA variability	0.01	0.23	0.951	0.01	0.04	0.912	0.11	0.25	0.659	0.02	0.06	0.776
NA variability	0.19	0.24	0.421	0.01	0.05	0.829	0.17	0.26	0.507	-0.06	0.06	0.344

Note. PA= positive affect, NA = negative affect. L1= level 1, L2 = level 2, S1= slope 1, S2= slope 2. L1 reflects the general level of affect intensity or variability before the lockdown. S1 reflects the general changes during the whole study period. L2 reflects the immediate change in intensity or variability the week before the lockdown and the first week of the lockdown. S2 reflects the gradual changes during the lockdown weeks, above and beyond the S1. Significant effects ($p<.01$) are highlighted in bold.

Table S8.8. Model fit of the sensitivity models.

	Adolescents				Parents				
	RMSEA	CFI	TLI	RMSEA	CFI	TLI	RMSEA	CFI	TLI
PA intensity	0.134 (.12-.15)	0.926	0.926	Acceptable	0.094 (.08-.11)	0.964	0.964	0.964	Acceptable
NA intensity	0.106 (.09-.12)	0.940	0.940	Acceptable	0.097 (.08-.11)	0.944	0.944	0.944	Acceptable
PA variability	0.056 (.04-.08)	0.906	0.906	Acceptable	0.046 (.02-.07)	0.950	0.950	0.950	Acceptable
NA variability	0.071 (.05-.09)	0.925	0.925	Acceptable	0.076 (.06-.09)	0.909	0.909	0.909	Acceptable

Note: PA= positive affect, NA = negative affect. RMSEA= root mean square error of approximation, CFI= comparative fit index, TLI= Tucker-Lewis index.



Table S8.9. Estimates from the sensitivity model.

Variable	Adolescents						Parents						
	M	SE	p	Variance	SE	p	Mean	SE	p	Variance	SE	p	
PA intensity	L1	76.22	1.46	<.001	318.36	38.03	<.001	70.22	1.39	<.001	292.68	34.34	<.001
	S1	0.03	0.14	0.834	1.61	0.38	<.001	-0.02	0.15	0.902	2.15	0.39	<.001
	L2	1.36	0.71	0.055	30.62	8.44	<.001	1.49	0.65	0.023	26.35	7.62	0.001
	S2	-0.26	0.23	0.266	5.47	0.98	<.001	-0.38	0.21	0.072	4.35	0.80	<.001
NA intensity	L1	10.47	0.93	<.001	120.30	15.08	<.001	9.38	0.83	<.001	100.90	12.21	<.001
	S1	-0.30	0.12	0.012	1.15	0.26	<.001	-0.31	0.12	0.011	1.67	0.27	<.001
	L2	-0.49	0.53	0.355	11.18	4.79	0.020	-0.21	0.53	0.698	19.47	5.18	<.001
	S2	0.53	0.17	0.002	2.73	0.53	<.001	0.66	0.17	<.001	2.57	0.50	<.001
PA variability	L1	11.15	0.74	<.001	67.64	10.07	<.001	10.10	0.56	<.001	34.02	5.77	<.001
	S1	-0.51	0.13	<.001	1.05	0.36	0.003	-0.68	0.12	<.001	0.73	0.27	0.006
	L2	0.75	0.65	0.245	11.19	8.57	0.191	1.14	0.63	0.070	16.82	7.56	0.026
	S2	0.16	0.19	0.398	2.15	0.70	0.002	0.54	0.16	0.001	1.36	0.52	0.009
NA variability	L1	10.68	0.69	<.001	49.30	8.61	<.001	8.85	0.56	<.001	32.12	5.75	<.001
	S1	-0.53	0.13	<.001	0.86	0.33	0.010	-0.58	0.11	<.001	0.47	0.23	0.039
	L2	-0.62	0.67	0.360	6.15	8.33	0.460	0.76	0.63	0.232	12.59	7.59	0.097
	S2	0.61	0.20	0.002	2.05	0.70	0.004	0.65	0.15	<.001	0.12	0.40	0.763

Note: PA= positive affect, NA = negative affect. L1= level 1, L2 = level 2, S1= slope 1, S2= slope 2.

Table S10. Correlations (95% CI) between the estimated intercepts and slopes of the adolescent and their parent.

	L1			S1			L2			S2		
	<i>r</i> (95%CI)	<i>p</i>	<i>r</i> (95%CI)	<i>r</i> (95%CI)	<i>p</i>	<i>r</i> (95%CI)	<i>r</i> (95%CI)	<i>p</i>	<i>r</i> (95%CI)	<i>r</i> (95%CI)	<i>p</i>	
PA intensity	.27 (.11-.40)	.001	0.18 (.02 - .32)	0.05 (-.11 - .20)	.027	0.14 (-.02 - .29)	0.05 (-.11 - .20)	.533	0.14 (-.02 - .29)	0.14 (-.02 - .29)	.078	
NA intensity	-.002 (-.15 - .15)	.981	-0.06 (-.21 - .09)	0.01 (-.14 - .17)	.443	-0.05 (-.20 - .11)	0.01 (-.14 - .17)	.888	-0.05 (-.20 - .11)	-0.05 (-.20 - .11)	.565	
PA variability	.05 (-.10 - .20)	.526	0.05 (-.11 - .20)	0.10 (-.06 - .25)	.569	0.03 (-.13 - .18)	0.10 (-.06 - .25)	.220	0.03 (-.13 - .18)	0.03 (-.13 - .18)	.722	
NA variability	-.03 (-.18 - .13)	.728	0.15 (-.01 - .29)	0.20 (.05 - .35)	.068	0.03 (-.12 - .19)	0.20 (.05 - .35)	.011	0.03 (-.12 - .19)	0.03 (-.12 - .19)	.670	

Note: PA= positive affect, NA = negative affect. L1= level 1, L2 = level 2, S1= slope 1, S2= slope 2.

Supplementary Tables S8.11-S8.18 include the covariance matrices and can be found online, <https://osf.io/trvxfef/>. The pre-registered plan and the MPlus scripts can be found here as well.







Part IV

Real-time Assessment of Well-being

Chapter 9.

Smartphone-based Ecological Momentary Assessment of Well-Being: a Systematic Review and Recommendations for Future Studies

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ABSTRACT

Feelings of well-being and happiness fluctuate over time and contexts. Ecological Momentary Assessment (EMA) studies can capture fluctuations in momentary behavior, and experiences by assessing these multiple times per day. Traditionally, EMA was performed using pen and paper. Recently, due to technological advances EMA studies can be conducted more easily with smartphones, a device ubiquitous in our society. The goal of this review was to evaluate the literature on smartphone-based EMA in well-being research in healthy subjects. The systematic review was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Searching PubMed and Web of Science, we identified 53 studies using smartphone-based EMA of well-being. Studies were heterogeneous in designs, context, and measures. The average study duration was 12.8 days, with well-being assessed 2-12 times per day. Half of the studies included objective data (e.g. location). Only 47.2% reported compliance, indicating a mean of 71.6%. Well-being fluctuated daily and weekly, with higher well-being in evenings and weekends. These fluctuations disappeared when location and activity were accounted for. On average, being in nature and physical activity relates to higher well-being. Working relates to lower well-being, but workplace and company do influence well-being. The important advantages of using smartphones instead of other devices to collect EMAs are the easier data collection and flexible designs. Smartphone-based EMA reach far larger maximum sample sizes and more easily add objective data to their designs than palm-top/PDA studies. Smartphone-based EMA research is feasible to gain insight in well-being fluctuations and its determinants and offers the opportunity for parallel objective data collection. Most studies currently focus on group comparisons, while studies on individual differences in well-being patterns and fluctuations are lacking. We provide recommendations for future smartphone-based EMA research regarding measures, objective data and analyses.

Keywords: well-being, happiness, ecological momentary assessment, EMA, smartphone, passive sensing.

INTRODUCTION

Feelings of well-being and happiness play a preventive role in psychopathology (e.g. depression) and are important to overall physical and mental health (Diener et al., 2017; Greenspoon & Saklofske, 2001; Howell et al., 2007). Happier and more optimistic people are found to live longer and healthier lives (Steptoe, 2019; Zaninotto & Steptoe, 2019). For instance, feeling happy reduces the likelihood of a heart disease and leads to better cardiovascular health (Boehm et al., 2012; Davidson et al., 2010). Furthermore, well-being is associated with successful outcomes in life, e.g. happier people are more often married, have better relationships with their partners and are more socially engaged (Lyubomirsky et al., 2005). The effects of well-being on health are found to be independently of the negative effects of ill-being on health, indicating the importance of investigating well-being (Howell et al., 2007).

Well-being is defined in multiple ways in the literature and often a distinction between subjective and psychological well-being is made (Keyes et al., 2002). Briefly, subjective well-being is characterized by high levels of positive affect, low levels of negative affect and a higher subjective evaluation of life satisfaction (Diener et al., 2018), whereas psychological well-being refers to thriving, positive functioning, and judgments about the meaning and purpose of an individual's life (Ryff, 1989). As subjective and psychological well-being are strongly related (Baselmans, van de Weijer, et al., 2019; Joshanloo, 2016), in this paper, we refer to well-being in the broad sense, including all definitions and constructs.

The majority of studies assessing well-being (WB) make use of questionnaires that are completed by participants at a single time point or multiple times (see for a review of well-being questionnaires and well-being research (Cooke et al., 2016; Diener et al., 2012; Linton et al., 2016). Well-being questionnaires ask about the general well-being or happiness and include for example the Life Satisfaction Scale (Diener et al., 1985), the Cantril ladder (Cantril, 1965), or the Subjective Happiness Scale (Lyubomirsky & Lepper, 1999). The scores on these well-being measures are found to be relatively stable and reliable over time (e.g. Fujita & Diener, 2005; Pavot, 2008; Schimmack & Oishi, 2005).

However, like many complex human traits, momentary feelings of well-being (e.g. mood) fluctuate over time and in different contexts (Eid & Diener, 2004; Li et al., 2014; Lyubomirsky, 2001). Individuals can have similar well-being scores at different questionnaire waves, while the underlying pattern (WB over the day or week) differs substantially. Some people show relatively stable levels of WB over the day or week, while others fluctuate a lot (Eid & Diener, 1999;

Gadermann & Zumbo, 2007). To better understand the relationship between well-being and for instance psychopathology or environmental influences, it is important to understand within person fluctuations of well-being over time. One way to capture the dynamic nature of well-being is by measuring well-being multiple times a day in the natural context and daily life of participants, i.e. using an ecological momentary assessment design.

Investigating daily experiences and behavior of people in their natural context is not a novel idea. Already in the 1920's, the diary method was used to collect reports of participants about their symptoms, behavior or mood over several days (Favill & Rennick, 1924; Flügel, 1925). In different disciplines (e.g. behavioral medicine and psychology), these methods developed further and are nowadays known under different labels, such as ambulatory assessment (Fahrenberg, 1996; Fahrenberg et al., 2007), the experience sampling method (ESM: Csikszentmihalyi & Larson, 1987) and ecological momentary assessment (EMA: Stone & Shiffman, 1994). The goal of all these assessment methods is to study people in their natural environment, including measures of self-report, observational, biological, physiological and behavioral measures. Later, Kahneman et al. (2004) developed the day reconstruction method (DRM), where participants are asked to reconstruct and describe all experiences and events of the day. See Wilhelm et al. (2012) for a detailed review and historical overview of the development of the different methods. In this review we will use the term ecological momentary assessment (EMA) to describe all ambulatory assessment, ESM and EMA methods, as this term is widely used in well-being research.

Before technological developments, EMA studies required participants to carry beepers and booklets of questionnaires. After each random timed beep, participants had to complete the questions using pen and paper. In an early study and small sample, Dysinger (1938) reported individual differences in the average level of mood and the scale of fluctuations. However, averaged across participants, there was no evidence for daily or weekly periodicity in these fluctuations. Later, after technological developments, devices such as personal data assistants (PDA) and palmtop computers were introduced to collect EMA data. Data collection became easier and according to the results of larger EMA studies, on average, happiness varied both throughout the day (e.g. happier in the afternoon compared to the morning) and the week (e.g. happier on a Saturday compared to Monday) (e.g. Brandstätter, 1991; Csikszentmihalyi & Hunter, 2003; Zelenski & Larsen, 2000). Furthermore, physical, social and leisure activities were associated with higher degrees of happiness, whereas being alone or at work was associated with lower happiness (Csikszentmihalyi

& Hunter, 2003; Schwerdtfeger et al., 2008) and smoking was unrelated to momentary positive affect (Shiffman et al., 2002).

Levering the rapid technological progression in the last few years, EMA researchers have started to replace the older methods by smartphone applications (Runyan & Steinke, 2015). Using smartphones can lead to a leap forward in EMA research, since smartphones are ubiquitous in our society and data can be collected more easily. However, smartphone-based EMA research does also lead to problems and difficulties. In this paper, we first describe smartphone-based EMA studies and their advantages and difficulties. Furthermore, we systematically review the literature on smartphone-based ecological momentary assessment of well-being in healthy participants.

Since the different well-being measures show a strong phenotypic and genetic overlap and the field of smartphone-based EMA research is relatively new, we will include all measures of well-being (e.g. happiness, positive affect, life satisfaction, quality of life). Specific research questions addressed in our review are: What are the used designs (context, schedule, sampling, WB measure, applications, smartphones and statistical analyses) in smartphone-based EMA studies to well-being? To what extent is objective data, such as GPS or accelerometer data included in smartphone-based EMA well-being research? Is the response rate and compliance in smartphone-based EMA studies related to the design? What are the results of smartphone-based EMA studies with respect to well-being? Finally, what are the limitations in current smartphone-based EMA? Based on guidelines proposed by Liao et al. (2016), we will describe the studies in the areas of (1) sampling and measures, (2) schedule, (3) objective data, (4) technology and administration, (5) prompting strategy, and (6) response and compliance. Additionally, we will (7) describe the analyses, (8) summarize the findings and (9) report limitations and risk of bias in the reviewed studies. In addition, as smartphone-based EMA designs are comparable to studies using other devices to collect EMA data, such as palmtop computers or PDAs, we compare the designs and findings of smartphone-based and other device-based EMA studies. Lastly, we provide guidelines for using (smartphone-based) EMA in future well-being research based on the findings.

Smartphone-based EMA studies

Recently, more researchers are applying EMA designs in their studies, since the development of smartphones and applications facilitate the use of such designs. Nowadays, smartphone research is feasible for widespread use, especially in the more economically developed countries. The number of mobile phone users worldwide is reaching 5.2 billion, with 3.5 billion people

owning a smartphone, i.e. more than one third of the population (GSMA intelligence, 2019). In the Western world and USA, already more than 70% of the population owns a smartphone. Furthermore, the development of tailored EMA applications becomes easier nowadays, as more knowledge and app building software becomes available.

The characterizing feature of EMA studies is the design in which daily behavior and experiences are assessed multiple times per day. EMA data have a high ecological validity, since information is collected in the moment of the experience and memory or recall biases are reduced (Schwarz, 2007; Scollon et al., 2003). Different forms of sampling can be used (Shiffman et al., 2008). In time-contingent sampling designs, participants are signaled to answer questions at fixed times or random times within a predefined time frame. In interval-contingent sampling designs participants are prompted to fill in questions after a time interval has passed. In event-contingent sampling designs, participants are requested to complete questions when a predefined event happens. The latter can be subjective and initiated from the participant him- or herself (e.g. when drinking alcohol) or objective (e.g. at a specific GPS location or a specific level of physical activity). Mixed designs combine event and time or interval sampling (e.g. to prevent too little data points).

Advantages and difficulties

Integrating smartphone applications into (EMA) research has multiple advantages compared to pen-and-paper methods and older EMA devices, such as PDAs ((García et al., 2016). Whereas pen-and-paper methods could not measure the compliance with the scheduled assessment times, response logging is automated in applications, resulting in specific response time information. Second, large nation- or worldwide samples, even in more remote areas, can be reached with EMA applications, as researchers do not need to provide participants with PDAs or palm-top computers anymore. The application can also be used longitudinally. Third, EMA applications can be more easily designed and optimized according to the research question. Related, several sensors of smartphones can be used to measure passive data continuously, for example location, light and noise levels, accelerometer and gyroscope data and phone use. Adding the data of these mobile sensors to a smartphone-based EMA study is relatively easy and valuable. For example, instead of asking participants to report their physical activity or phone use, we can infer this from the continuous stream of accelerometer and screen use data, resulting in objective and rich data.

The nature of EMA data (i.e. real-time and real-life data) allows to accurately capture the variability of subjective experiences and to detect and discover patterns, which are missed when using a sum or average score. For example, in the field of physical activity, an accelerometer study of (Chinapaw et al., 2019) suggest that not the volume, but the individual pattern of accumulated physical activity is important in relation to health. Similar for EMA data, using advanced analyses (e.g. time-series analyses) can lead to new insights in patterns and fluctuations. EMA data are powerful to make inferences for an individual instead of for the (often non-existent) average person. Since subjective experiences are measured multiple times a day, the intra-individual variability can be assessed and related to other variables. For example, in a small sample of depressed and non-depressed participants, Stavrakakis et al. (2015) measured physical activity and affect multiple times per day and investigated the fluctuations for each participant. Individual differences in both the daily pattern and the strength and direction of the relationship between physical activity and affect were found, indicating important inter-individual variability. Furthermore, Wichers et al. (2016) provided evidence for an complex dynamic pattern and network of mental states underlying depression using extensive EMA data in one participant.

Designing smartphone-based EMA studies can also lead to difficulties. The main problems are issues with (personal) privacy, the intrusive design and data storage (Trull & Ebner-Priemer, 2013). Especially when combining EMA with passive sensor data, privacy and data storage are important as large amounts of personal data are collected. Passive data contains highly sensitive information and possibly identifying personal data, such as GPS location. The question is whether such data can be fully anonymized, as combining data of multiple passive measures might lead to identifying information about participants. For example, Brownstein et al. (2006) could identify the home locations for 79% of the participants in a study, based on a published image map. This clearly violates the privacy of participants. Researchers should put effort in anonymizing data and use for example the relative location data to protect privacy. Next, multiple assessments can result in a high daily burden for participants in smartphone-based EMA studies, leading to increased drop outs and decreased response rates (Shiffman et al., 2008). Related, most studies do not pay participants for their participation. The trade-off between participating and the individual benefit might be unclear for participants, leading to less willingness to participate. Lastly, the multiple assessments and passive data collection can have an effect on the battery life of (older) smartphones, affecting daily life or excluding part of the population.

METHODS

Systematic Review of smartphone-based EMA studies

Eligibility criteria

To review the literature on smartphone-based ecological momentary assessment of well-being, a systematic review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (Moher et al., 2009). Titles and abstracts of collected articles were screened for eligibility and were included if (1) (subjective) well-being, happiness, or positive affect/mood was assessed using ecological momentary assessment (EMA was defined as at least two assessments per day for a number of days in natural settings), (2) a smartphone (application) was used, and (3) healthy participants were included (adults or adolescents).

Information Source and Search Strategy

In September 2019 and an update in August 2020, the search for relevant articles was conducted in the bibliographic databases PubMed and Web of Science. Additional articles that were missed during this search were identified via reference lists of the selected articles. The search strategy included combinations of search terms related to (1) ecological momentary assessment, (2) well-being/wellbeing and (3) smartphone research (see Table 9.1). The search applied iterative combinations of these categories by employing the Boolean search operators AND (horizontal) and OR (vertical).

Table 9.1. Search terms, the search applied iterative combinations of these terms by employing the Boolean search operators AND (horizontal) and OR (vertical).

Search Term 1	Search Term 2	Search Term 3
Momentary assessment/measures	(Subjective) well-being	Smartphone
Experience sampling	(Subjective) wellbeing	Smartphone application
Ecologic(al) momentary assessment	Quality of Life	Mobile device
Ambulatory assessment	Satisfaction with Life	iPhone
Ambulatory monitoring	Happiness	Android
Ambulatory measures	Positive affect	
Moment-to-moment measures		

Study Selection and Data Extraction

A PRISMA flow diagram of the study selection process is presented in Figure 9.1. All identified titles and abstracts were screened for eligibility. In cases of insufficient information to determine eligibility, papers were subjected to further screening. The first author screened the full text reports and decided whether papers met the inclusion criteria. Uncertainties and disagreement were resolved through discussions. Articles were excluded if they met one of the following criteria: (1) no smartphone-based EMA of well-being, (2) non-healthy participants, (3) review papers; (4) descriptive planned studies or methodological papers; or (5) studies that used smartphone applications only for an intervention instead of data collection.

Other EMA data collection devices

To put the findings of smartphone-based EMA studies in perspective, we conducted an extra systematic review to EMA studies using other data collection devices, such as palm tops or PDAs with a similar search strategy as described above (see supplementary data Sheet 2 for the keywords, search details and PRISMA Flow Diagram). We compared the designs and results of the two groups of studies.

RESULTS

Study selection and characteristics

The initial electronic database search resulted in 368 hits in PubMed and 63 hits in Web of Science. When removing duplicates, 396 original articles remained. After scanning the titles and abstracts of those articles based on the selection criteria, 56 articles remained. These articles were examined and read fully. In addition, based on references we included 19 additional articles. After excluding 29 articles based on the full-text reading, 46 articles met our selection criteria and were included in the study. In the update of August 2020, we added 7 new studies, resulting in a total of 53 studies (see Figure 9.1).

Table 9.2 and 9.3 provide an overview of the included studies, the samples and the design characteristics (see supplementary file S1 for more detailed characteristics of the reviewed studies). The first smartphone-based EMA study was published in 2010 and the number of studies published increased exponentially over the years, with 38 of the 53 studies published in 2017-2020. Most studies were conducted in Germany (k=10), the UK (k=8), the Netherlands (k=9), USA (k=8), Australia (k=5) and South Korea (k=2). Single studies were

conducted in Canada, Israel, China, Japan, and Switzerland. The remaining studies ($k=6$) used participant samples from multiple countries.

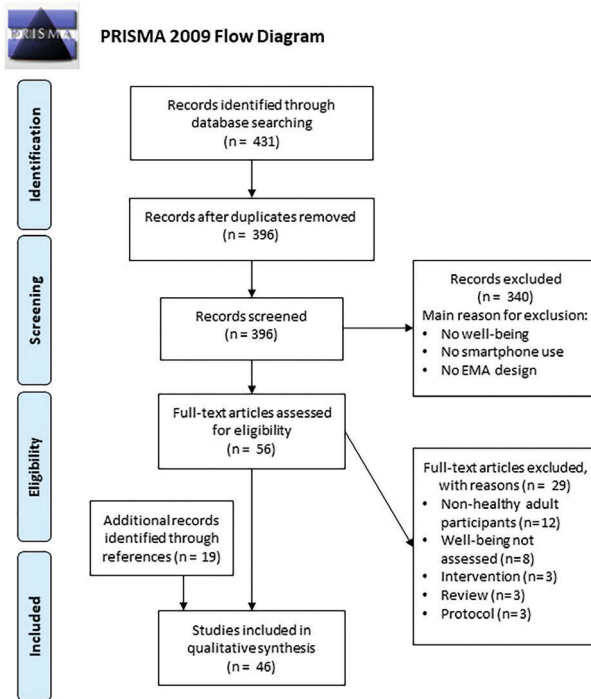


Figure 9.1. PRISMA Flow Diagram of the included studies.

(1) Sampling and measures

The median sample size of the 53 studies was 97 participants. There was a lot of variability in the sample sizes with a range of 15 participants to 31,302 participants, resulting in an average number of 2212.15 participants ($SD=6687.55$). A few studies included samples over 1000 participants, e.g. the UK-wide and freely available *Mappiness* app (studies 3, 12, 13, 18, 44 in Table 9.2) and the worldwide *Track Your Happiness* app (study 1).

The mean age of the participants was available for 41 studies and ranged from 16.0 to 60.1. Across all studies, the mean age was 30.8 ($SD=10.5$). The proportion of females included ranged from 5.2% to 100% with a mean of 57.4%. One study included adolescents (36), whereas the rest included adult participants. In 18 studies (34%), participants were only or mostly students. In three studies, participants were employees (17, 34, 38, 48) and two studies included only women (25, 53) (see Table 9.2 for a full overview of the sample characteristics).

Table 9.2. Characteristics of the samples included in the 53 reviewed studies.

Nr	Study	Study location	Sample N	Sample	Mean age	SD age	% female
[1]	(Killingsworth & Gilbert, 2010)	USA	2.250	population	34		41.2
[2]	(Bossmann et al., 2013)	Germany	62	students	21.4	1.8	14.5
[3]	(MacKerron & Mourato, 2013)	UK	21.947	population	N/S		45
[4]	(Poerio et al., 2013)	UK	24	convenience	24.17	2.9	45.8
[5]	(von Haaren et al., 2013)	Germany	29	students	21.3	1.7	N/S
[6]	(Doherty et al., 2014)	Canada	15	park visitors	20-45		33.3
[7]	(Ram et al., 2014)	USA	136	stratified	47.64	18.85	51
[8]	(Randall et al., 2014)	Australia	327	community / students	21.02	6.18	76.1
[9]	(Kanning et al., 2015)	Germany	69	random	60.1	7.1	49
[10]	(Stieger et al., 2015)	Germany	213	convenience	24.5	8.4	58
[11]	(Asselbergs et al., 2016)	Netherlands	27	students	18-25		78
[12]	(Bryson & MacKerron, 2017)	UK	26.700	population	N/S		44.4
[13]	(Geiger & MacKerron, 2016)	UK	31.302	population	35.1		N/S
[14]	(Hendriks et al., 2016)	Germany	150	students/ convenience	21.7	3.1	82
[15]	(Törnros et al., 2016)	Germany	143	-	18		57.3
[16]	(DeMasi et al., 2017)	USA	53	students	19.83	1.99	55.3
[17]	(Engelen et al., 2017)	Australia	22	population	26-45		50
[18]	(Fujiwara et al., 2017)	UK	N/S	population	N/S		47
[19]	(Lathia et al., 2017)	UK	12.838	population	N/S		43

Table 9.2. Characteristics of the samples included in the 53 reviewed studies.

Nr	Study	Study location	Sample N	Sample	Mean age	SD age	% female
[20]	(Liddle et al., 2017)	Australia	40	convenience	23	3.15	80
[21]	(Triguero-Mas et al., 2017)	Spain/UK /Netherlands/ Lithuania	406	cluster	51	26	53.2
[22]	(Van Der Krieke et al., 2017)	Netherlands	629	population	49.9	13	82
[23]	(van Wel et al., 2017)	Netherlands	34	online	32		56
[24]	(Wahl et al., 2017)	Germany	38	students	24.47	5.88	73.7
[25]	(Zenk et al., 2017)	USA	97	specific	25-65		100
[26]	(Bakolis et al., 2018)	UK	108	population	31.1	11.1	75
[27]	(Beute & de Kort, 2018)	Netherlands	57	local database	33	13.7	66.1
[28]	(Birenboim, 2018)	Israel	91	students	26.01	3.13	59.8
[29]	(Gloor et al., 2018)	Germany/USA	17	voluntary	23-56		70
[30]	(Ludwigs et al., 2018)	Germany	90	students	21.9/21.4	4.6/4.3	83.7/84.2
[31]	(Maekawa et al., 2018)	Japan	33	N/S	20-35		24.2
[32]	(von Stumm, 2018)	Multiple	770	population	35.38	1.29	31
[33]	(Wouters et al., 2018)	Netherlands	269	convenience	35	8.91	73
[34]	(Yang et al., 2018)	South Korea	97	convenience	37.7	10.8	5.2
[35]	(Zhang et al., 2018)	China	30	students	18-30		57
[36]	(Bejarano et al., 2019)	USA	26	community	15.96	1.56	42.3
[37]	(Duif et al., 2019)	Netherlands	162	community	36.07	9.23	67.2

Table 9.2. Characteristics of the samples included in the 53 reviewed studies.

Nr	Study	Study location	Sample N	Sample	Mean age	SD age	% female
[38]	(Giurgiu et al., 2019)	Australia/ Germany	86	employees	33.7	9.3	62.8
[39]	(Griffiths & Stefanovski, 2019)	Australia	108	students	19.47	2.89	78.7
[40]	(Itzhacki et al., 2019)	Netherlands	25	convenience	23.7	3.8	51.9
[41]	(Nauta et al., 2019)	Netherlands	82	students	20	1.8/1.2	67
[42]	(O'Donnell et al., 2019)	Australia	83	community	21.42	3.09	75.9
[43]	(Schultchen et al., 2019)	Germany	51	community	23.50	2.6	21.6
[44]	(Seresinhe et al., 2019)	UK	15,444	population	N/S		48
[45]	(Stieger & Reips, 2019)	Germany	213	community	24.5	8.4	58
[46]	(Triantafyllou et al., 2019)	USA	206	online	39.30	10.3	80.8
[47]	(Glasgow et al., 2019)	USA	229	online	32.67	10.5	55.1
[48]	(Giurgiu et al., 2020)	Australia/ Germany	80	employees	33.9	9.5	65
[49]	(Johannes et al., 2020)	Netherlands	75	phone users	21.9	2.5	70.7
[50]	(Kondo et al., 2020)	Spain/UK /Netherlands / Lithuania	368	cluster	51	33.6	52
[51]	(Ryu et al., 2020)	South Korea	89	convenience	37.2	10.5	5.6
[52]	(Schilling et al., 2020)	Switzerland	201	convenience	38.6	10.1	35.8
[53]	(Yang et al., 2020)	USA	185	cohort study	41.03	5.86	100

Most studies ($k_{\text{number of studies}}=30, 56.6\%$) assessed momentary happiness with a single question (variations on “To what extent are you feeling happy?”) using different scales from 0/1 (*not at all*) to 5/7/9/10/100 (*very/strongly*). Five studies used the 6-item Short Mood Scale or Multidimensional Mood Questionnaire (valence, calmness and energetic arousal) (2, 5, 9, 32, 38), five studies used positive affect items from the PANAS to rate (e.g. relaxed, excited, energetic) (33, 36, 37, 42, 52), and three a grid of valence (positive/negative) and arousal (8, 11, 19). One study used the Warwick-Edinburgh Mental Well-Being Scale with 14 items (26). Eight studies used other measures, either a qualitative measure (“Select the emotions you have experienced in the last few hours.”) (6, 25, 35) or a combination of other positive mood adjectives (e.g. relaxed, calm) (29, 34, 40, 41, 43).

The 53 studies measured well-being in different contexts. Momentary well-being in relation to natural environmental variables and contexts (e.g. nature, daylight, urban areas) was assessed in 11 studies (3, 6, 18, 21, 26, 27, 28, 36, 40, 44, 50). Well-being was assessed in relation to physical activity and/or sedentary behavior ($k=9$) (2, 5, 9, 19, 25, 38, 43, 48, 53), cognitive processes (e.g. visual search, emotion detection) (30, 31, 32), health (20, 22, 23) alcohol (13, 37, 42), mind wandering (1, 4), food (24, 33), work (12, 17, 51, 52), and sleep (16, 46). Two studies focused on fluctuations of well-being in daily life (34, 45). Single studies measured momentary well-being in the context of homesickness (41), phone use (49), immigrants (14), soccer (10), music (8), fitness exposure (39), transport (47) and social interactions (7). The goal of three studies was to predict momentary mood based on objective data and compared this to EMA data (11, 29, 35). Finally, one study compared different sampling strategies to assess the effect of context on mood (15) (see Table 9.3).

(2) Use of objective data

Of the 53 studies, 22 studies used only self-reported data, whereas 31 studies (58.5%) included objective, passively measured data. Ten studies used an accelerometer to measure movements (2, 5, 9, 16, 19, 25, 36, 38, 48, 53). Eight studies used GPS location data of the smartphone to investigate well-being in the (natural) environment (3, 12, 13, 15, 18, 26, 44, 45). Four studies used a combination of GPS and accelerometer data (6, 21, 47, 50). One study assessed phone use (49) or the heart rate variability (52). Single studies used an exposimeter of radiofrequency-electromagnetic fields (23) or a light sensor on the clothes of participants to sample the amount of daylight every minute (40). Furthermore, five studies used multiple objective measures, such as a combination of GPS data, time of day, temperature, and neighborhood

information (28) or GPS, accelerometer, light, microphone, calls, texts, and Wi-Fi (46). The studies predicting mood used objective measures of mobile phone use (call events, screen use, application use and mobile camera use) (11) or a wide range of (body) sensing data, such as acceleration meter data, heart rate, light level, Wi-Fi signals and GPS location (29, 35).

(3) Schedule

The majority of studies, ($k=43$, 81.1%) monitored participants during one specified wave of data collection. The study duration ranged from 1 to 56 uninterrupted days with a mean of 12.8 days ($SD=12.8$) and median of 7 days. In eight studies the duration was up to the participant (1, 3, 12, 13, 18, 19, 32, 44). Two studies used multiple waves of data collection (7, 28), with 3 times 21 days and 4 times 7 days (each time a different week of the month), respectively.

The average number of questions per EMA ranged from 1-57, with a mean of 13.1 ($SD=11.8$). The average completion time, based on the report of 13 studies, was somewhat more than 1.5 minute (104.9 seconds, $SD=50.5$ sec).

(4) Technology and administration

In most studies ($k=33$) participants could use their own smartphone in the study, either an Android smartphone ($k=16$), iPhone ($k=9$) or both ($k=8$). In 13 studies, research smartphones with the application installed were provided to the participants. The remaining studies ($k=7$) did not specify what type of smartphones or operating systems were used.

Applications were especially developed to answer the research question and included research specific functions. For example, to measure happiness in relation to food, the SnackImpuls application has the additional feature to quickly categorize and select food choices (33) and the MuPsych app plays music (8). The movisensXS software was used by seven different research teams to create an adapted EMA application (2, 5, 15, 24, 38/48, 40, 52). The (data of the) Mappiness app ($k=5$) (3, 12, 13, 18, 44), the Well-being Science app ($k=2$) (10, 45), SnackImpuls app ($k=2$) (33, 37), the CalFit app (21,50) and a specific movisensXS app (38,48) were used in multiple publications to answer different research questions.

Excluding the double applications, 45 publications used unique applications and 25 of those 45 studies included objective data in addition to self-report to answer the research question. In 13 of the 25 applications (52.0%), the objective data collection (e.g. GPS and accelerometer data) was integrated in the application, using smartphone sensors. In the other studies, either a different application was developed to collect the objective data ($k=2$) (6, 11),

an additional accelerometer to wear on the arm, chest or hip was provided ($k=8$) (2, 5, 9, 25, 36, 38, 40, 53) or an additional exposure meter (23) or heart rate meter (52) was used.

(5) Prompting strategy

The time or interval-contingent design was the most common sampling form ($k=42$, 79.2%). Participants received on average 5.0 prompts per day ($SD=2.9$) on random times on their smartphones, with a range of 2-12 times. Seven studies used an event-contingent design. In three of those studies the participant had to initiate the EMA after eating (24), a trip (47) or a social interaction (7, 41). In other studies participants were prompted with a questionnaire when an accelerometer measured physical activity that surpassed or fell below a predefined activity threshold (9), when they started to listen to music (8) or based on the exposimeter data (23).

Three studies used a mixed design (28, 38, 8), using a combination of time and event-contingent sampling based on physical activity or location. A mixed design was used to prevent the collection of too little data when not enough events occurred. Lastly, one study (15) compared four different sampling designs: based on time, based on combined time and distance (prompt when moving), based on location (prompt when moving to a new location) and, lastly based on land use and population density (prompt when moving to a location with a different type of land use or with a different population density). Location-based sampling resulted in less prompts compared to time-based sampling, but in more triggers for unique locations and a greater spatial spread.

In 41 of the 53 studies (77.4%), participants were prompted with a buzz or auditory signal of the smartphone application. Three studies used text messages to remind the participants to open the app and answer questions (10, 22, 45) and one study used a smartwatch to signal participants (29). In the remaining six studies, the participants had to initiate the questionnaire themselves. Participants had to start a questionnaire after a predefined event in five event-based sampling studies (7, 8, 24, 41,47). In the other two studies, participants had to initiate an EMA in the morning and the evening (21,50) or somewhere in three predefined timeslots (31).

(6) Response and Compliance

Only 25 (47.2%) studies reported information on the compliance with the EMA design. Additionally, seven studies provided enough information to calculate the compliance rate. Based on the 32 studies, participants completed on average 71.6% ($SD=14.1\%$) of all EMAs with a range of 43% - 95%.

Five studies reported a relation between compliance and another participant or study variable. Higher compliance was found in the first three days compared to the fourth until seventh day (37) and during weekends compared to weekdays (42). In study 25, no differences in compliance levels for assessments over the day has been found, whereas in study 20 surveys were most often responded to between 12-2 pm. Also, participants were found to be most often at home, alone, or involved in work/study when responding (20). In study 42, EMA compliance was unrelated to age, gender and other personal characteristics.

Based on 9 of the 13 studies with a research phone that did report the compliance, the average completion rate is 76.4% (SD=0.08). This is not significantly different from studies where participants could use their own smartphone (70.6%, SD=0.16, based on 23 studies), $p=.294$.

The compliance levels are not different in studies when participants received incentives ($k=14$, compliance based on reports of 9 studies: 72.1%) compared to when participants did not receive incentives ($k=30$, compliance based on 19 studies: 69%), $p=.614$. Participants in the remaining 9 studies received course credit, participated in a lottery or received a gift (compliance based on 4 reports: 82%). This compliance is also not different from the compliance in the paid or non-paid studies ($p=.168$ and $p=.127$).

Studies with the highest compliance rates (>84%) seem to last either 7 or 14 days with 3-6 prompts per day. Furthermore, studies with a relatively long duration tend to have lower compliance, as 30 days sampling (22) resulted in a compliance of 50% and 21 uninterrupted days of sampling in a rate of 43% (42). However, based on reports of 27 studies, there is no significant correlation between the reported compliance rates and the duration of the study ($r=-0.144$, $p=.458$) or the prompts per day ($r=0.243$, $p=.204$).

Besides overall compliance, the timing of responses to prompts is important in EMA studies. This is essential information, since the validity of EMA studies is based on momentary experiences, i.e. the answering of the questions should be in the moment. Whereas a number of studies reported a limited time (90 seconds - 1 hour) to respond to a prompt, only three studies actually reported the average latency time between the prompt and answer. The assessments were completed within 38 minutes (51), 11.6 minutes (22) or within 28 seconds (23). In addition, study 20 reported that 66.5% ($n=260$) of the EMA's was responded to within a minute, only 2 took more than 5 minutes.

Most studies ($k=43$) recruited a target sample, whereas in 10 studies anonymous participants downloaded a freely available and widely advertised application (1, 3, 12, 13, 18, 19, 22, 26, 32, 44). Both methods of recruiting lead to participant drop out during the study, resulting in a difference between the

number of participants in the initial enrollment sample and analytical sample. Thirty studies reported this attrition rate and the average dropout rate was 17.1% ($SD=20.8\%$) with a range of 0-96.8%. Based on reports of 25 and 32 studies respectively, the attrition rate was not related to study duration ($r=0.106$, $p=.550$) or the number of prompts per day ($r=0.233$, $p=.241$).

(7) Analyses

Most studies ($k=40$, 75.5%) analyzed the data using multilevel models or mixed models (fixed and random effects), taking into account the nested nature of EMA data. EMA data consists of repeated measurements of participants over multiple days. Therefore, in the analysis, adjusting for individual effects is necessary. However, five studies only looked at group differences and did not analyze differences on the individual level (10,14, 24,30,31). In addition, two studies computed the correlation between well-being and the other measure separately for every participant and averaged these correlations (5,8). One study analyzed the data at response level instead of participant level (20). Finally, two studies did not perform any data analysis (6,15) and three studies only provided a summary and descriptive data to show the feasibility of smartphone-base EMA (17,23,34).

Table 9.3. Design characteristics of the 53 included Ecological Momentary Assessment studies of well-being.

Nr	Study	Sample size	Context of assessment	WB measure	Study days	Times/day	Nr of items	EMA design	Phone	Application name	Objective data	Obj in app	Compliance % *
[1]	(Killingsworth & Gilbert, 2010)	2,250	Mind wandering	Feeling good (0-100)	N/S	3	3	Time	iPhone	Track Your Happiness	-	-	83%
[2]	(Bossman et al., 2013)	62	Physical activity	valence, calmness and arousal	7	every hour	6	Time	Research phone	MovisensXS	Accelerometer	-	
[3]	(MacKerron & Mourato, 2013)	21,947	Natural environment	Happy (0-100)	N/S	2	7	Time	iPhone	Mappiness	GPS	yes	48%
[4]	(Poerio et al., 2013)	24	Mind wandering	Happy (1-5)	7	12	7	Time	Research phone	ESAMO	-	-	88.4%/79.3%
[5]	(von Haaren et al., 2013)	29	Physical activity	Valence, calmness and arousal	2	every 2 hour	6	Time	Research phone	MovisensXS	Accelerometer	-	
[6]	(Doherty et al., 2014)	15	Nature	Select emotion	1	every 35 min	14	Time	Research phone	2 Java programs	GPS + accelerometer	no	68%
[7]	(Ram et al., 2014)	136	Social interactions	Happy (1-100)	3x21	N/A	27	Event	Research phone	N/A	-	-	
[8]	(Randall et al., 2014)	327	Music	Grid: Valence and arousal	14	2	4	Event	iPhone	MuPsych	-	-	
[9]	(Kanning et al., 2015)	69	Physical activity	Valence, calmness and arousal	3	N/A	6	Event	Research phone	MyExperience	Accelerometer	no	
[10]	(Stieger et al., 2015)	213	Soccer	Well-being (0-100)	14	3	1	Time	Android	Well-being Science App	-	-	94%*
[11]	(Asselbergs et al., 2016)	27	Predicting mood	Grid: Valence, arousal (1-10)	42	5	2	Time	Android + iPhone	eMate/iYouVU	Multiple	no	77%*
[12]	(Bryson & MacKerron, 2017)	26,700	Work	Happy (0-100)	N/S	2	7	Time	iPhone	Mappiness	GPS	yes	

Table 9.3. Design characteristics of the 53 included Ecological Momentary Assessment studies of well-being.

Nr	Study	Sample size	Context of assessment	WB measure	Study days	Times/day	Nr of items	EMA design	Phone	Application name	Objective data	Obj in app	Compliance % *
[13]	(Geiger & MacKerron, 2016)	31.302	Alcohol	Happy (0-100)	N/S	2	7	Time	iPhone	Mappiness	GPS	yes	48%
[14]	(Hendriks et al., 2016)	150	Immigrants	Happy (1-11)	14	6	4	Time	Android + iPhone	Happiness Analyzer	-	-	91%
[15]	(Törnros et al., 2016)	143	Sampling strategies	N/S	7		N/S	Multiple	N/S	MovisensXS	GPS	yes	
[16]	(DeMasi et al., 2017)	53	Sleep	Happy (1-9)	56	4	2	Time	Android	Funf Open Sensing	Accelerometer	yes	
[17]	(Engelen et al., 2017)	22	Work	Happy (1-10)	5	4	13	Time	N/S	LifeData RealLifeExp	-	-	58%
[18]	(Fujiwara et al., 2017)	N/S	Airport noise	Happy (0-100)	N/S	3	7	Time	iPhone	Mappiness	GPS	yes	
[19]	(Lathia et al., 2017)	12.838	Physical activity	Grid: Valence and arousal	N/S	2	5	Time	N/S	Mood-Tracking	Accelerometer	yes	
[20]	(Liddle et al., 2017)	40	Quality of life	Feeling good (1-7)	7	6-8	5	Time	Android	My Life Tracker	-	-	
[21]	(Triguero-Mas et al., 2017)	406	Natural environment	Happy person	7	2	29	Time	Android	CalFit	GPS + accelerometer	yes	
[22]	(Van Der Krieke et al., 2017)	629	Mental health	Feeling good (0-100)	30	3	43	Time	Android + iPhone	HND	-	-	50%*
[23]	(van Wel et al., 2017)	34	Health	Well-being (1-6)	2	N/A	11	Event	Android	ExpoMDiary	Exposimeter	no	74%
[24]	(Wahl et al., 2017)	38	Food	Eating happiness	8	N/A	6	Event	N/S	MovisensXS	-	-	75%
[25]	(Zenk et al., 2017)	97	Physical activity	Select emotion	7	5	19	Time	Research phone	N/S	Accelerometer	no	70%

Table 9.3. Design characteristics of the 53 included Ecological Momentary Assessment studies of well-being.

Nr	Study	Sample size	Context of assessment	WB measure	Study days	Times/day	Nr of items	EMA design	Phone	Application name	Objective data	Obj in app	Compliance % *
[26]	(Bakolis et al., 2018)	108	Environment	Mental Well-Being Scale	7	7	20	Time	Android + iPhone	Urban Mind	GPS	yes	61%*
[27]	(Beute & de Kort, 2018)	57	Nature and daylight	Happy (1-7)	6	8	45	Time	Research phone	N/S	-	-	80%
[28]	(Birenboim, 2018)	91	Environment	Happy (1-7)	4x7	4	21	Mixed	N/S	N/S	Multiple	yes	52%*
[29]	(Gloor et al., 2018)	17	Predicting Emotions	Pleasure and Activation	49	4-7	3	Time	N/S	Happimeter	Multiple	yes	
[30]	(Ludwigs et al., 2018)	90	Attention to WB	SWB (0-10)	14	6	6	Time	Android	N/S	-	-	
[31]	(Maekawa et al., 2018)	33	Visual processes	Happiness (0-10)	14	3	8	Time	Android + iPhone	Visual Search	-	-	95%*
[32]	(von Stumm, 2018)	770	Cognitive capacities	Valence, calmness and arousal	N/S	1-4	57	Time	iPhone	moo-Q	-	-	
[33]	(Wouters et al., 2018)	269	Food	PANAS	7	10	12	Time	Android	SnackImpuls	-	-	69%
[34]	(Yang et al., 2018)	97	Fluctuations	Positive affect	7	4	25	Time	Android	N/S	-	-	60%
[35]	(Zhang et al., 2018)	30	Predicting Emotions	Select emotion	30	3	6	Time	Android	MoodExplorer	Multiple	yes	
[36]	(Bejarano et al., 2019)	26	Environment and activity	5 items PANAS (1-5)	20	4	16	Time	Research phone	PETE App	Accelerometer	no	88%
[37]	(Duif et al., 2019)	162	Alcohol	PANAS	7	10	12	Time	Android + iPhone	SnackImpuls	-	-	72%
[38]	(Giurgiu et al., 2019)	86	Physical activity and sedentary	Valence, calmness and arousal	5	10	6	Mixed	Research phone	MovisensXS	Accelerometer	no	76%

Table 9.3. Design characteristics of the 53 included Ecological Momentary Assessment studies of well-being.

Nr	Study	Sample size	Context of assessment	WB measure	Study days	Times/day	Nr of items	EMA design	Phone	Application name	Objective data	Obj in app	Compliance % *
[39]	(Griffiths & Stefanovski, 2019)	108	Exposure to fitness inspiration	Happy (0-100)	7	6	10	Time	Android + iPhone	Life Data	-	-	78%
[40]	(Itzhacki et al., 2019)	25	Light and time of day	Relaxed, calm, energetic, happy,	7	9	22	Time	Research phone	MovisensXS	Light	no	65%*
[41]	(Nauta et al., 2019)	82	Homesickness	Happy, pleased, joyful, enjoyment	14	N/A	10	Event	N/S	TEMPEST app	-	-	
[42]	(O'Donnell et al., 2019)	83	Alcohol use	PANAS: e.g. happy (0-5)	21	3	13	Time	iPhone	-	-	-	43%
[43]	(Schultchen et al., 2019)	51	Physical activity and eating	Positive adjectives (0-100)	7	6	17	Time	Android + iPhone	PsyDiary app	-	-	84%
[44]	(Seresinhe et al., 2019)	15,444	Environment	Happy (0-100)	N/S	2	7	Time	iPhone	Mappiness	GPS	yes	
[45]	(Stieger & Reips, 2019)	213	Fluctuations	Well-being (0-100)	14	3	1	Time	Android	Well-being Science App	GPS	yes	87%
[46]	(Triantafillou et al., 2019)	206	Sleep	Mood (0-8)	42	2	6	Time	Android	Purple Robot	Multiple	yes	
[47]	(Glasgow et al., 2019)	229	Transport	Mood: happy, cheerful, optimistic, pleased, interested	7	N/A		Event	Android	Daynamica	GPS + accelerometer	yes	

Table 9.3. Design characteristics of the 53 included Ecological Momentary Assessment studies of well-being.

Nr	Study	Sample size	Context of assessment	WB measure	Study days	Times/day	Nr of items	EMA design	Phone	Application name	Objective data	Obj in app	Compliance %*
[48]	(Giorgiu et al., 2020)	80	Physical activity and sedentary	Valence, calmness and arousal	5	10	6	Mixed	Research phone	MovisensXS	Accelerometer	no	77%
[49]	(Johannes et al., 2020)	75	Online vigilance	Happy	5	8	18	Time	Android	PACO	Phone use	yes	60%
[50]	(Kondo et al., 2020)	368	Natural environment	Happy	7	2	29	Time	Android	CalFit	GPS + accelerometer	yes	
[51]	(Ryu et al., 2020)	89	Work stress	Positive affect	7	4	25	Time	Android	N/S	-	-	64.7%
[52]	(Schilling et al., 2020)	201	Work stress	Positive affect	2	8	14	Time	Research phone	MovisensXS	heart rate variability	no	80.9%
[53]	(Yang et al., 2020)	185	physical activity	Happy	7	8	N/S	Time	Android	N/S	Accelerometer	no	80.3%

- N/A: not applicable, N/S: not specified.
- The compliance rate was not reported in 7 studies, but could be computed using other data in the publication (indicated by *).
- See the supplementary table for more characteristics.

(8) Results of the studies

Table 9.4 describes the results of the reviewed studies, grouped by context, with examples of statistical results of interest. To briefly summarize, momentary well-being fluctuated daily and weekly, with on average higher well-being in the evening and weekend. Yet, often both daily and weekly fluctuations disappear when type of place, physical activity or other environmental variables are controlled for. On average, being in a natural environment in daily life (e.g. walking in the park) and physical activity over the day is associated with positive affect and higher well-being. Working was ranked lowest in happiness levels, but employees do show fluctuations based on the task, where you work (office, home or somewhere else), whether you are alone or with others; the time of day or night working and personal characteristics (e.g., lower WB associated with working when married, but higher when having children). Work stress is negatively related to positive affect.

The effects of mind wandering on positive affect are inconclusive with a negative and no relation. Eating is related to positive affect, with stronger effects for vegetable consumption and snacks. Drinking alcohol is related to higher momentary positive affect on average, but this increased well-being does not last or spill to other moments. Sleep and well-being were related, with a stronger effect of sleep on mood than of mood on sleep quality. Furthermore, on average, positive affect was associated with faster visual search reaction times, but not with other cognitive measures. Focusing attention on well-being by completing multiple questionnaires about well-being for a few weeks does increase well-being. One study investigated why internal migrants report lower levels of happiness than locals, even after accounting for socio-economic factors. EMA showed that migrants spend less time to happiness-producing activities such as active leisure, and social parties than locals. Furthermore, single studies show that exposure to fitness inspiration online and social media use is related to lower happiness, whereas listening to music and watching soccer is related to higher momentary happiness on average. Walking and cycling is better for your mood than sitting in a bus or auto. Lastly, the studies predicting mood and well-being based on objective data, such as phone use, were successful in 55% to 76% of their mood predictions. However, other models, for example based on the mean mood state, performed better than the personalized models using objective data. See Table 9.4 and the supplementary data for more detailed results and the corresponding studies.

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
Fluctuations	[34] Yang et al. (2018)	Methodological: A smartphone application is feasible to measure the fluctuations of well-being.	-
	[45] Stieger & Reips (2019)	On average, WB fluctuates daily (low in the morning, high in the evening) and over the week (low just before the beginning of the week, highest near the end of the week). Being on deviating altitudes from normal relates to higher WB (might be explained by leisure time). Weather conditions have no significant effect on WB.	Hour of the day: $b=0.64^*$ (.08) Day of the week: $b=0.40^*$ (0.18) Altitude: 0.01^* (0.01) Rainfall: -0.33 (.36), wind speed: -0.34 (0.27), temperature: 1.10 (0.80)
Natural environment	[3] MacKerron & Mourato (2013)	Participants are happier outdoors in all green or natural habitat types (e.g. in mountains or heathland) than they are in urban environments. Weather did influence WB, higher when sunny, lower when raining.	Outdoors: $FE=2.32^*$ (.45) Mountains/heathland: $FE=2.71^*$ (.87) Walking, hiking: $FE=2.55^*$ (.18) Rain: $FE=-1.37^*$ (.22), Sun: $FE=0.46^*$ (.18)
	[6] Doherty et al. (2014)	Methodological: The combination of passive and interactive techniques can enhance the ability to understand how contact with nature enhances health and well-being.	-

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
[18]	Fujiwara et al. (2017)	Being near an airport is not associated with happiness, whereas being in areas with aircraft noise (depending on the dB) is associated with lower levels of happiness and relaxation.	Being near an airport: FE=0.069 (0.45) Aircraft noise: FE=-6.344* (3.039)
[21]	Triguero-Mas et al. (2017)	More contact with natural outdoor environments is related to better well-being.	Contact with surrounding green: females: b=4.01* (0.77, 7.24), males: b=3.38 (-0.15-6.90)
[26]	Bakolis et al. (2018)	Being outdoors, exposure to natural features including trees, the sky, and birdsong has a beneficial impact on momentary mental well-being.	Being outdoors (MD: 2.90, p < .001*), seeing trees (MD: 1.31, p < .001*), hearing birds singing (3.71, p < .001*), seeing the sky (1.49, p < .05*), and feeling in contact with nature (3.51, p < .001*).
[27]	Beute & de Kort (2018)	Higher levels of nature and daylight are related to more positive affective states, whereas time of the day is not significantly associated with positive affect.	Nature: B=.025* (.009) Daylight: B=.027* (.009) Time of the day: B=.033 (.017)
[28]	Birenboim (2018)	Happiness is influenced by time of the day and day of the week and situational variables and environmental characteristics including type of activity and environment, place characteristics, and company.	Activity type: adj R ² : 0.255* Company: adj R ² : 0.214* Place type: adj R ² : 0.234* Neighborhood: adj R ² : 0.218* Temperature: adj R ² : 0.196* Clouds: adj R ² : 0.234 Time of day: adj R ² : 0.203* Weekend: adj R ² : 0.209*

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
[36]	Bejarano et al. (2019)	Being at home was negatively related to positive affect, while being at school, in the car, or outdoors was positively associated with positive affect. Too hot or cold weather was negatively related to positive affect.	At home ($\beta=-1.47^*$), At school ($\beta=1.19^*$), In the car ($\beta=0.77^*$), Outdoors ($\beta=1.66^*$) Proximity to vegetation ($\beta=0.21^*$) Weather just right ($\beta=0.66^*$). Too hot ($\beta=-0.80^*$) or too cold ($\beta=-0.53^*$) weather.
[40]	Itzhacki et al. (2019)	Time of day significantly modulated positive mood, peaking around 2 pm. Variability in light intensity did not significantly affect positive mood.	Time of day: $p=.0012^*$ Variability in light intensity: $p=.11$ Average light intensity: $p=.31$
[44]	Seresinhe et al. (2019)	People do report themselves to be happier in a more scenic location and in a more natural habitat and rural environment.	Scenicness: $b=2.77^*$, $p<.001$ Natural habitat: $b=0.57^*$, $p<.001$ Rural: $b=0.61^*$, $p<.001$
[50]	Kondo et al. (2020)	There was a positive relationship of exposure to natural outdoor environments and positive affect	OR: 1.39^* , 95% CI: 1.06, 1.81
[2]	Bossmann et al. (2013)	Energetic arousal and valence were positively influenced by the intensity of the physical activity 10-min prior to the assessment. On average, as activity increased, positive feelings and arousal increased.	Physical activity: $b=0.003$, std effect: 0.07, $p=.005^*$

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
[5]	Von Haaren et al. (2013).	No relation between activity and affect in inactive people. Inactive people hardly show any active episodes during the day. Therefore, it is difficult to analyze the relation between affect and PA of inactive people.	86% of the time in sedentary state Mean MET: $r = -0.03$, $p = .45$ Minutes light activity: $r = 0.08$, $p = .65$
[9]	Kanning et al. (2015)	When older individuals were more physically active, they felt more energized and agitated, but did not show better mood (valence).	Activity on valence: $FE = <.001$, $p = .86$ Activity on energy: $FE = .0017^*$, $p = .02$ Activity on calmness: $FE = -.0017^*$, $p < .001$
[19]	Lathia et al. (2017)	The frequency with which people physically move daily (both self-report and accelerometer data) is related to physical health and happiness. Individuals who are physically more active are happier, both in general and in the moment.	Self-report activity: $r = .08^*$, $p < .001$, $d = .16$, Sensed activity (accelerometer): $r = .03^*$, $p = .002$, $d = .06$
[25]	Zenk et al. (2017)	Daily positive affects was not related to physical activity (PA) or sedentary behavior. More PA during the day was associated with increased subsequent positive affect, while more sedentary behavior during the day was associated with reduced positive affect.	WB - daily activity (minute): $b = 0.14$ (0.1) WB - daily sedentary: $b = -14.68$ (8.9) Daily activity on WB: OR: 1.02* Daily sedentary on WB: OR: 0.99*
[38]	Giurgiu et al. (2019)	Momentary sedentary time, but not physical activity had a negative effect on valence. Time of the day is significantly associated with mood, but day of the week not.	Sedentary time: $\beta = -0.082$, $p < .001^*$ Physical activity: $\beta = -0.037$, $p = .074$ Time: $\beta = -0.212$, $p < .001^*$ Day (weekend): $\beta = .054$, $p = .059$

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
[43]	Schultchen et al. (2019)	Positive affect was related to higher subsequent physical activity and vice versa, physical activity was related to higher subsequent positive affect.	Affect to physical activity: $b=.067$, $SE = .029$, $p = .027^*$ Physical activity to affect: $b=.193$, $SE = .029$, $p<.001^*$
[48]	Giurgiu et al. (2020)	Mood did not significantly predict sedentary time between subjects, but sedentary time was negatively predicted by valence and energetic arousal and positively by calmness within subjects.	Valence: -0.03^* (0.02) Arousal: -0.06^* (0.01) Calmness: 0.07^* (0.02)
[53]	Yang et al. (2020)	When mothers experienced higher-than-usual positive affect, they engaged in more sedentary time in the same 45-min window.	
Work	[12] Bryson & MacKerron (2016)	Doing paid work is ranked low in terms of happiness. However, well-being at work varies significantly with where you work (higher when at home); what you are doing at the same time (e.g. listening to music); whether you are alone or with others (higher WB when with colleagues or family/friends); the time of day or night you are working (lower WB when working in weekend and after 6pm); and your personal characteristics (lower WB when working when married, somewhat higher WB when working and having children).	Working: $FE = -5.43^*$ Extra negative effects → + working in weekend: -2.37 + working after 6 pm: -2.59 Where: home vs at work: -4.09 With whom: colleagues (+0.64, spouse, partner (+5.91), clients (+0.72) Combined with music (+3.38), admin (-3.64), eating (+2.25).

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
[17]	Engelen et al. (2017)	The app was able to measure temporal variance and patterns of mood during work. People vary in their mood during a working day.	-
[51]	Ryu et al. (2020)	Momentary PA was negatively correlated with occupational stress in police officers. Work overload and social isolation were positively associated with PA. Work discontent, social tension, and pressure to perform were negatively associated with momentary PA.	Occ stress: $-.276^*$ (.009) .25 (.14), .48 (.10), 0.45 (.14), $-.79$ (.16) and $-.29$ (.14)
[52]	Schilling et al. (2020)	Positive affect was negatively related to feelings of stress, but not related to cardiorespiratory fitness.	Stress: $-.34^*$
Mind wandering	[1] Killingsworth & Gilbert (2010)	People were less happy when their minds were wandering than when they were not. What people were thinking (10.8% variance explained) was a better predictor of their happiness than what they were doing (4.6% explained).	Mind wandering: slope (b) = -8.79 , $p < 0.001^*$
[4]	Poerio et al. (2013)	While sadness tended to precede mind-wandering, mind-wandering itself was not associated with later mood and only predicted feeling worse if its content was negative.	Mind wandering on sadness: $t = -.29$, $B = -0.02$ (0.06), $p = .771$ Sad mind-wandering on WB: $t = 5.08$, $B = .27$, (0.05), $p < .001^*$

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
Food	[24] Wahl et al. (2017)	Vegetables consumption influenced eating happiness, sweets on average provided comparable induced happiness to "healthy" food and dinner elicited comparable happiness to snacking.	Fruits and vegetables accounted for 24% of total eating happiness score. Happiness: dinner (M = 81.47, SD = 14.73), and snacks (M = 79.45, SD = 14.94). Snacks vs lunch ($t=-4.44$, $p=.001$, $d = -0.38^*$) and breakfast, ($t=-3.78$, $p=.001$, $d = -0.33^*$)
Alcohol	[33] Wouters et al. (2018)	Men and young adults (20–30) significantly increased their food intake after experiencing positive affect, whereas no associations were found in women nor in the other age groups.	Energy intake from snacks: β (S.E.)=.01 (.01), $p = .29$. + age: $-.24$ (.08), $p < .01^*$ Interaction gender: $-.17$ (.07), $p = .02^*$ Males: β (S.E.)= $.07$ (.03), $p = .01^*$
Alcohol	[13] Geiger & MacKerron (2016)	People are happier at the moment of drinking alcohol, but the over spills to other moments are small. Younger people are happier when drinking compared to older people. Changing drinking levels over time is not related to changing life satisfaction.	Alcohol: FE= 3.65, $p < .001^*$ Happiness of younger people (+ 7.3 points) vs oldest group (+ 3.0 points).
Alcohol	[37] Duif et al. (2019)	Within-person momentary positive affect was positively associated with likelihood of next-moment alcohol consumption but not with the quantity of alcohol use. Between persons, levels of momentary affect were not related to alcohol drinking.	Within: Positive affect and likelihood alcohol use: OR= 1.21, $p=0.01^*$ Within: Positive affect and alcohol use quantity: B= .02, $p=0.82$ Between persons: likelihood: OR= 0.96, $p=.62$ and quantity: B=0.07, $p=.52$.

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
[42]	O'Donnell et al. (2019)	Being happy is correlated to the number of drinks and whether someone drinks. However, alcohol consumption does not predict happiness.	Happy and number of drinks: $r=0.09^*$ Happy and drink yes/no: $r=0.09^*$ Alcohol consumption on happiness: $B=0.31$, $p=0.11$
[16]	DeMasi et al. (2017)	. Daily physical activity and sleep duration measured with smartphones were positively correlated with and predictive of mood. Nighttime stillness, day of the week and study was not associated with mood.	Day of study: $FE=-0.059$, $p=.82$ Day of week: $FE=0.04$, $p=.60$ Sleep duration: $FE=0.072$, $p=.02^*$ Daytime activity: $FE=0.097$, $p=.004^*$ Nighttime stillness: $FE=0.04$, $p=.13$
[46]	Triantafillou et al. (2019)	The effect of sleep quality and mood is bidirectional, but the effect of sleep quality on mood was larger than the effect of mood on sleep quality	Sleep on mood: $FE=0.344$ (0.009), $p<.001^*$ Mood on sleep quality: $FE=0.132$ (0.019), $p<.001^*$
Cognitive processes	[30] Ludwigs et al. (2018)	Paying more attention to one's subjective well-being (SWB) does increase SWB in general on several questionnaires.	Increase in happiness: Happiness Core: ($p=.08$), Life Satisfaction ($p=.41$), Domain Evaluation Questionnaire ($p=.008^*$), Flourishing scale ($p=.036^*$), satisfaction with life scale ($p=.004^*$)
[31]	Maekawa et al. (2018)	Pop-out search times were unaffected by mood, serial search times were significantly faster for high happiness levels than low happiness levels. Happiness did not influence motor response speed	Happiness on serial visual search times: $\beta = -96.56$, $t = -2.18$, $p = 0.03^*$ Motor response $F(1, 32) = 0.37$, $p = 0.55$

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
[32]	von Stumm (2018)	Short-term and working memory tasks were not associated with positive affect. Having slept enough, being alone and at work was associated with improved cognitive function.	Mood and short-term memory ($\beta = .10$, $SE = .05$, $t = 2.09$, $p = .037$) Mood and working memory ($\beta = .04$, $t = 1.87$, $p = .061$).
[22]	Van der Krieke et al. (2017)	Somatic symptoms are negatively associated with quality of life, but there is significant heterogeneity in this association between persons.	Somatic symptoms on QoL: $B = -0.25$; $p < .001^*$ Heterogeneity in the within-person association (variance, 0.02 ; $p < .001^*$)
[23]	van Wel et al. (2017)	Radiofrequency-electromagnetic fields exposure had minimal influence on well-being.	No statistical report.
[20]	Liddle et al. (2017)	High momentary quality of life was significantly related to high occupational enjoyment, being in the presence of someone, being home and having an excellent health status.	Occupational enjoyment: $\beta = 4.480$ (0.634), $p < .001^*$ Home: $\beta = 0.815$ (0.379), $p = .03^*$ Social context: $\beta = 0.662$ (0.266), $p = .013^*$ Excellent health: $\beta = 0.768$ (0.327), $p = .019^*$
[39]	Griffiths & Stefanovski (2019)	Thinspiration and fitspiration were uniquely and interactively associated with lower body satisfaction, higher negative affect, and lower positive affect.	Positive affect: Thinspiration: $b = -6.36$, $p < .001$, $d = -0.09^*$ Fitspiration: $b = -2.08$, $p = .022$, $d = -0.04^*$ Dual exposure: $b = -5.82$, $p = .001$, $d = -0.08^*$
[41]	Nauta et al. (2019)	Participants felt most homesick when interacting with their parents or using video chat and feeling homesick is associated with more unpleasant and less pleasant affect.	Momentary homesickness: $\beta = -.09$, $F = 8.51$, $p = .004^*$

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
Social interaction	[7] Ram et al. (2014)	Interactions with family members and weekend days boosted happiness.	Interactions with family members and happiness: + 1.16 units ($p < .01^*$). Weekend days: +1.88 units ($p < .01^*$)
Phone use	[49] Johannes et al. (2020)	Small relations between online vigilance and well-being. More social apps time is related to worse mood.	
Music	[8] Randall et al. (2014).	Music listening elicited a significant increase in valence and mood over a 3-minute listening period. This positive shift in valence was amplified when the initial mood was negative.	Music on mood: $t(326) = 3.94, p < .001, d = 0.22^*$ When mood was negative: $t(304) = 13.39, p < .001, d = 0.65^*$
Soccer	[10] Stieger et al. (2015)	Well-being was higher among soccer spectators than non-spectators during the world cup, with effects increasing as a function of goal difference.	Soccer win: $t = 2.88, p < .01, d = 0.64^*$
Immigrants	[14] Hendriks et al. (2016)	Internal migrants distribute less time to happiness-producing activities such as active leisure, social drinking/parties, and activities outside home/work than locals. Internal migrants feel less happy than locals when spending time with friends and while eating.	Mean difference happiness locals and migrants: 0.64, $F = 4.19, p < .05, \eta^2 = 0.03^*$ Diff time spent per day locals and migrant to: Social drinks ($F = 7.66, p < .01^*$), Active leisure ($F = 4.70, p < .05^*$). Diff happiness when: With friends ($F = 4.43, p < .05^*$), eating ($F = 3.15, p < .10$).

Table 9.4. Summary of the results of the 53 reviewed studies and examples of estimated effects of interest on mood or well-being, sorted by study context.

Nr	Study	Results related to mood or well-being	Estimated effect on WB (SE)
Transport	[47] Glasgow et al. (2019)	Mood was more positive when individuals walked and bicycled versus when they used a bus or automobile. Paths near green space and water were related to positive mood.	Walking: 0.20(0.08)*, Cycling: 0.30(0.14)*, Talking with others: 0.26(0.08)**; Green: 0.002(0.01)*
Predicting mood	[11] Asselbergs et al. (2016)	Mobile phone-based unobtrusive EMA is a technically feasible and potentially powerful method to predict mood based on the data. However, the predictive performance of the personalized predictive regression models was inferior to that of naive benchmark prediction models (mean model, predicted the mood to be equal to the average observed mood) that are agnostic of mobile phone use.	The percentage of correct cross-validated predictions was 55% to 76%. But, $p < .02$ in favor of the benchmark models
	[29] Gloor et al. (2018)	Happiness and activation are negatively correlated with heart beats and with the levels of light. People tend to be happier when they are moving intensely.	Average BPM heart: $r = -.174$, $p < .01^*$ Light level: $r = -.111$, $p < .01^*$ Activation: $r = .460$, $p < .01^*$
	[35] Zhang et al. (2018)	MoodExplorer can infer user's compound emotion with exact match of 76.0% on average.	-

-: No statistical test. r : correlation coefficient, FE: fixed effect estimate, β , B or b: (standardized) regression coefficient, $\text{adjd } R^2$: adjusted explained variance, MD: mean difference, OR: odds ratio.

(9) Limitations and risk of bias

Using the checklists for EMA studies (Liao et al., 2016; van Roekel et al., 2019), we checked the risk of bias across the studies. Regarding the procedure and methods, 49 of the 53 studies reported on the type smartphone used, all studies reported on the prompt design, study duration, number of assessments per day and incentives provided and all but one study reported on the total number of items per assessment. Of the 53 studies, 37 reported the attrition rate, i.e. how many participants dropped out of the study. Fourteen of the 53 studies reported the average response time (time lag between the prompt and response) of the participants and as already noted, the overall compliance is only reported in 25 of the 53 studies and reasons for noncompliance are often lacking. In a few studies, participants were excluded based on compliance rates. Only three reviewed studies (25,27,31) reported a power analysis prior to the data collection to determine their needed sample size and reach a power of 0.8. One study performed a post-hoc power analysis (36) and concluded that their power was really low (0.18 instead of 0.8). A lot of studies miss data on compliance and all details of the design. Therefore, the reporting of the included EMA studies is often not complete and this indicates some risk of bias and selective reporting.

An often-reported limitation in the reviewed studies is the limited sample size in number or generalizability to the whole population. Samples in studies that use free available applications seem to be biased by self-selection. For example, 35 studies reported a bias in their sample, having attracted a younger ($k=10$), more highly educated ($k=10$), a mostly female ($k=21$) or male ($k=6$) sample compared to the whole population, with 12 studies having multiple biases, affecting the generalizability of the results. In addition, part of the applications ($k=25$) were only available for iPhone or Android smartphones. This biased sample might affect the results and outcomes of the studies.

Another frequently reported limitation is controlling for only a small number of environmental variables (e.g. green/urban, noise or light levels or social environment) and other confounders (e.g. personal characteristics or weather). Since EMA measures behavior and experiences in real life, there is less control over the measurement and context. Confounders such as the weather, social environment, nutritional status, alcohol consumption, but also personality traits, might have affected well-being instead of the variable of interest.

Some studies (2, 5, 6, 36) reported their sampling strategy as limitation, since the number of data points and compliance levels were lower than expected. A way to solve this is to trigger questionnaires not only based on

time, but based on variables of interest, such as location or activity. Lastly, another often reported limitation is the impossibility to determine the causality between the variable of interest and happiness with the current design and available data.

Findings of studies using other EMA data collection devices

The search to EMA studies that used palm tops, PDAs or other EMA devices to assess well-being multiple times a day resulted in 8 studies that included healthy participants (Dvorak et al., 2018; Elavsky et al., 2016; Ilies et al., 2010; Johnston et al., 2013; Juth et al., 2015; Shiffman et al., 2002; South & Miller, 2014; Yip, 2005) (see supplementary data Sheet 3 for details of the studies and the results).

To summarize, seven of the eight studies were conducted in the USA, with the remaining study in the United Kingdom. The average number of participants included was 142.9 (SD= 85.8) with a range from 62 to 304 participants. The participants were on average 31.7 years old (SD=13.9) and more females than males were included (68.1%, SD= 20.1). All studies used a measure of positive affect (e.g. PANAS) in their assessments. Positive affect was assessed in different contexts, namely in relation to smoking, stress, ethnicity, emotional coping, sedentary behavior and blood pressure. Three studies used a personal digital assistant (PDA), four used a palm-top computer and the last study used a hand held computer to deliver the prompts and assessments. The average study duration was 8.5 days (SD=4.3) with an average of 5.4 prompts per day (SD=1.4). All studies used time-contingent designs, but in the two smoking studies participant were also asked to answer questions after smoking a cigarette, i.e. event-contingent. Only two of the eight studies added objective data, either using an accelerometer to measure sedentary behavior or a cardiovascular monitor to assess blood pressure. Across the 8 studies, the average compliance rate was 78.4% (SD=8.3) with a range from 70% to 91%.

Shiffman et al. (2002) found no relation between momentary positive affect and smoking, whereas Dvorak et al. (2018) reported an association between momentary positive affect and momentary smoking. Single studies found a negative association between momentary positive affect and stress and internalizing problems (South & Miller, 2014) and sedentary behavior (Elavsky et al., 2016). Other studies found a positive association of positive affect with ethnic salience (Yip, 2005), emotional approach coping (Juth et al., 2015), and work effort and demands in nurses (Johnston et al., 2013). Finally, there was no correlation between momentary positive affect and blood pressure (Ilies et al., 2010).

DISCUSSION

We performed a systematic review on smartphone-based ecological momentary assessments in well-being research in healthy participants. Using the PRISMA guidelines we retained 53 studies (out of 398 studies), which we included in the present review. Overall, the study designs were very heterogeneous of nature, with varying sample size, used questionnaires, phones, study duration ($M=12.8$ days with most studies lasting seven days) and how often well-being was assessed during the day (range of 2-12 times a day). Additionally, well-being was assessed in relation to different (environmental) variables, from the (natural) environment, to physical activity, work and other variables. In addition to self-report data, half of the studies included some objective data measured using the smartphone sensors or additional meters (e.g. GPS, accelerometer data or telephone use). Less than half of the studies (47.2%) reported the response rate and compliance. Based on this limited information, on average 71.6% of the EMAs is responded to by the participants.

Based on the reviewed studies we can conclude that momentary well-being fluctuated daily and weekly, with higher well-being in the evening and weekend. These fluctuations disappeared when location and activity were included. On average, being in a natural environment and physical activity relates to higher well-being. Working relates to lower well-being, but workplace and company influence well-being. Besides the mentioned limitations before (e.g. relatively homogenous samples and less environmental control), a main limitation of the reviewed studies is the focus on average scores across people, and ignoring individual differences and patterns over time.

There are some notable differences between the designs of EMA studies with other data collection devices and smartphone-based EMA studies to well-being. First, the maximum sample size in smartphone-based EMA is much larger than in palm top or PDA studies. Next, the average study duration is longer when using smartphones (12.8 days) compared to other devices (8.5 days). These differences show that data collection is easier when participants can use their own devices. There are no (financial) restrictions on the both the sample size and study duration as researchers do not need to buy devices. Furthermore, smartphone studies more often add objective data to their designs, reflecting the flexibility of smartphone applications compared to other devices. Based on the limited number of studies, the compliance rates of both sets of studies are similar ($p = .204$), namely 71.6% for smartphone research and 78.4% for other devices. Only sedentary behavior is assessed in relation to well-being in both smartphone studies and a PDA study. In most studies, momentary positive

affect is associated with less sedentary behavior. The other results cannot be compared.

Our review shows that smartphone-based EMA designs are feasible, have multiple advantages over other EMA collection devices and can be used to inform our understanding of well-being in addition to traditional questionnaire research. The real-time responses in a natural environment for the participants give an insight in the fluctuations and patterns of well-being in individuals that cannot be captured with retrospective self-report measures. Furthermore, assessing well-being in different contexts and/or in response to activities or events, can contribute to understand the dynamic nature of well-being and to identify the causal influences on well-being. This might be useful in creating interventions to increase well-being if we know what makes people happy.

Guidelines for the use of smartphone-based EMA designs in well-being research

Based on findings of the reviewed studies and the current limitations we propose recommendations and future directions for EMA studies to get a better hold of the complexity of well-being (see Table 9.5 for an overview).

As a first guideline, we recommend to use smartphones instead of other data collection devices in future EMA studies. Whereas you need to provide participants with the other devices, nearly everyone nowadays owns a smartphone (already more than 70% of the Western and USA population and 45% worldwide (GSMA intelligence, 2019)). This leads to the possibility of reaching larger samples and longer study durations are possible. In addition, the flexibility and continuing developments of smartphones and applications is preferable when designing strong studies, i.e. the addition of objective data collection is easier. Only in studies where the target sample is expected not to have a smartphone, e.g. younger children, providing a device (either a smartphone or any other device), could be a good solution.

Sampling

An important advantage of smartphone-based EMA designs is the possibility of reaching many people and including unique or large samples. Advertising the nation- and worldwide applications *Track Your Happiness* and *Mappiness* resulted in the largest sample sizes ever used in EMA research (N >10.000). This review shows that a smartphone-based EMA design is feasible to use in all types of samples, ranging from adolescents to older participants. (Vilaysack et al., 2016) showed that it is even feasible to perform smartphone-based EMA research in 5-7 year old children. With the increasing rate of smartphone users

around the world and simple design of an application, more people can be reached in a smartphone study that are otherwise not included in research. Using such large and heterogeneous samples, the influence of and interplay with many factors (e.g. in culture, education, environment) can be investigated on a large scale.

Whereas some reviewed studies advertised such a freely available application, most studies recruited a convenience or specific target sample (e.g. employees or university students). Both recruitment ways have advantages and the best recruitment depends on the study goal. An anonymous sample can become really large and leads to more power, but there is more control over a targeted sample (e.g. specific characteristics or to contact them for follow-up). Large scale open recruitment can have the same drawback as large online survey studies, such as oversampling of females (Saleh & Bista, 2017). A quantity-quality tradeoff can be seen in recruiting an anonymous larger sample versus a smaller sample with more control over the representativeness (similar to the quantity-quality trade off in a genome-wide association study (Okbay et al., 2016)). We recommend to choose the recruitment method based on the specific research question and goal.

Only three reviewed studies reported a power analysis to estimate the required sample size for their study prior to data collection. A power analysis to calculate the required sample size in EMA studies is often complicated, since power in EMA studies does not only depend on the number of participants, but also on the number of prompts per day. The choice to increase power based on the number of participants or prompts depends on which level the effects are of most interest. (Mathieu et al., 2012) suggest that when interested in detecting lower level effects (e.g. relationship between environment and well-being) maximizing the number of lower-level units (number of prompts) is most beneficial, whereas when interested in higher level effects, (e.g. etiology of the within person fluctuations of well-being) increasing the sample size might be more beneficial.

Measures of well-being

Most reviewed studies used one happiness question or a combination of positive affect adjectives to assess subjective well-being (e.g. relaxed, feeling good). Only one study used a full well-being scale, the Warwick-Edinburgh Mental Well-being Scale with 14 items (Bakolis et al., 2018). Answering many questions multiple times a day might become too much of a burden for participants and could decrease the compliance and data quality. For example, in the study of Bakolis, only 25 of the 108 participants had a compliance rate

of 66% or higher. Using a full questionnaire to investigate momentary well-being is thus not recommended. Krueger and Schkade (2008) investigated the reliability of a single *momentary* affect measure (e.g. happy, depressed, angry) in the Day Reconstruction Method (DRM) and found reliabilities of 0.50-0.70 (similar to the reliability of a *general* well-being measure, Diener et al., 1985; Lyubomirsky & Lepper, 1999). As DRM and EMA designs result in nearly identical happiness ratings over the day, single item measures are also thought to be reliable in EMA research (Dockray et al., 2010; Kahneman et al., 2004). Therefore, including only one or a only a few well-being questions is preferable to keep the participant burden low.

Whereas the reviewed studies only investigated the hedonic/affective part of well-being (e.g. happiness or mood), well-being also consist of a cognitive part (e.g. satisfaction with life) and eudemonic well-being (the fulfilment of human potential; Ryan & Deci, 2001; Ryff, 1989). These components of well-being have not been assessed in smartphone-based EMA studies yet. Rating your current mood or happiness (i.e., affective WB) is relatively easy, whereas a bit more thinking and cognitive processing is needed to report on momentary life satisfaction, i.e. cognitive well-being. Nevertheless, reporting life satisfaction in the moment is possible and some variation over time is expected. In contrast, Steptoe (2019) suggest that answering questions on eudemonic well-being (the meaning of life), needs more thinking and cognitive processing, including aggregation over time and comparisons with self-selected standards. Less variance in daily or hourly eudemonic well-being is expected and therefore, this aspect of the well-being spectrum seems less suitable for EMA. We recommend to include questions in an EMA study to investigate fluctuations in both cognitive and affective well-being (e.g. “*How do you feel right now?*” (unhappy/happy) and “*How satisfied are you with your life at this moment?*” (unsatisfied/satisfied)).

Objective data

More than half of the reviewed studies combined self-report with objectively measured data, either collected from smartphone sensors or an additional (accelero-)meter. Including the measures on the same device (e.g. two different apps) or in the same application is most convenient for both the researchers and participants, as data is integrated immediately and participants do not have carry additional meters.

An important advantage of objective data in general is the passive nature of the data and thereby the ecological validity (i.e. data is collected without active participation of the participant in their natural setting). This reduces

the participant burden, and complements self-report data, with no issues of compliance. Furthermore, objective data can provide more reliable information. For example, in physical activity research, only a weak correlation between self-report and objectively assessed accelerometer data has been found, indicating biases in self-report (Dyrstad et al., 2014; Prince et al., 2008). Also in sleep and phone/Internet use research, objectively assessed data might be more reliable than self-report (Boase & Ling, 2013; Girschik et al., 2012; Junco, 2013).

Combining self-report data and sensor data is a powerful design and can lead to new insights into the interaction of mental, physical, and environmental processes in daily life. Over the next years, objective data is likely to be included more often with the continuing developments in smartphone technology, e.g. more sensors are being embedded in mobile phones (step count or heart rate) (Mohr et al., 2017). Recently, open source platforms have been developed to make the collection of passive data from smartphone sensors easier for researchers, facilitating the use of passive data in research even further. A few examples are the AWARE framework (Ferreira et al., 2015), RADAR-base (Ranjan et al., 2019) and the Insight app (Montag et al., 2019).

However, some difficulties with passive data collection remain, as also noted by Mohr et al. (2017). First, smartphone sensors vary in different phones and personal characteristics, such as age and gender, might affect the data. Older people use their phones differently than younger people and males more often carry along their phones in their pockets compared to females (Ichikawa et al., 2005). To correctly process and interpret objective data from different phones and populations more research is needed. Furthermore, with the new European General Data Protection Regulation (<https://eugdpr.org>) in action, researchers have to adhere to strict rules regarding privacy and personal data. Passive data results in large amounts of possibly identifying information, data processing is needed before storage. For example, GPS data cannot be stored with all details to prevent identifying information on the home location, but should be measured using an unknown relative location or transformed to an appropriate level (e.g. street level).

Schedule and prompting strategy

The average number of prompts per day in the reviewed studies on well-being is 5.0 (range: 2-12) and the duration 12.8 days. According to an earlier review of EMA, it is reasonable to administer up to 10 EMAs a day to participants for periods ranging from 1 week to 1 month (Aan het Rot et al., 2012). Our review shows that the frequency of prompting and the study duration is influenced

by the specific study goal and context. To capture fluctuations, the number of prompts needed depends on the time-scale of variation in the context of interest. When interested in more varying events or contexts, participants need to be prompted more often to capture all types of the context. For example, Poerio et al. (2013) prompted participants 12 times per day to investigate the effect of different types of mind wandering on well-being, whereas three or four prompts per day seem to be enough to assess well-being in different environmental contexts (e.g. Bejarano et al., 2019; MacKerron & Mourato, 2013). With rare events, event-based sampling or a combination of different sampling strategies might be preferred to capture these events and reduce the number of prompts.

Based on these findings and the literature on well-being, we recommend to prompt participants based on the context of interest, but at least three times a day (every morning, afternoon and evening) for a minimum of seven days to assess the fluctuations of momentary well-being over the day and on different weekdays. In addition, based on findings of seasonal depression (American Psychiatric Association, 2013a) and individual differences in mood changes in summer and winter (Golder & Macy, 2011; Klimstra et al., 2011), we might expect seasonal fluctuations in well-being or a different pattern of daily WB fluctuations. Therefore, we recommend to assess well-being in the different seasons using EMA as well.

A few studies let the participant decide how many prompts he/she wanted to receive, with a minimum or default level. This individual control over the number of prompts might increase the compliance levels. Unfortunately, with the limited reported data, we could not test this relation. In addition, individual differences might exist in the preference for and reaction to the number of prompts. More research is needed to assess this preference in combination with participant burden and compliance levels. Until these limitations are solved, we recommend to base the number of prompts on the time-scale of variation in well-being in the context of interest.

Applications

Most studies used applications specifically developed for the research question and context of interest. As the development of a properly working application cost a lot of time and money, collaborations with app developers or other researchers should be encouraged to create an app combining research, good usability and technical factors (McEwan et al., 2020). The application should be tested multiple times to reduce the burden for participants, since

participants drop out as soon as a problem occurs or an update is needed (McEwan et al., 2020).

Furthermore, especially when not offering incentives, providing feedback to participants after the study (e.g. in the form of a well-being graph over time) is recommended to make participation fun and keep compliance levels high. For example, in the Mappiness studies (MacKerron & Mourato, 2013), participants received personalized graphs with happiness over time, related to where they were, with whom and what they were doing. However, undesirable for research and EMA studies, this feedback may make participants aware of their well-being, leading to a reactive effect and influencing the data. Therefore, feedback should be provided after data collection is completed. Awareness of well-being might lead to people initiating more activities that make them happy. Ludwigs et al. (2018) did show that two weeks of paying more attention to your well-being has a small positive effect well-being. However, recently De Vuyst et al. (2019) showed that 10 EMAs of emotions per day does not impact participants' emotional experience over time. Both samples consisted only of (psychology) university students. More research in a more heterogeneous sample to this reactive effect of attention to well-being is necessary for a conclusive answer.

Response and compliance

Not even half of the studies reported the response rate and compliance of the participants. Based on the limited data, the EMA compliance was relatively high, with a mean of 71.6%, but most studies did not reach the preferred 80% compliance to have generalizable data of daily life (Stone & Shiffman, 2002). Furthermore, the kind of missing data (random vs. not random) is not reported in the reviewed studies, but should be taken into consideration. Based on the limited reported data, results did suggest there is no difference in compliance using a research smartphone or using the participant's own smartphone. In addition, we did not find a clear relation between compliance and other study characteristics, such as the study duration, number/timing of prompts, providing incentives or participant characteristics, similar to Jones et al. (2019). Further research is needed to confirm these findings, since this information is critical to optimize future EMA studies.

Only three studies reported the latency (time difference) between the prompt and answer. This latency is important, since the validity of EMA studies is based on momentary experiences, i.e. answering of questions should be in the moment. Though most studies did limit the answering time, this could be up to an hour, reducing the ecological validity. However, returning to the added value of passive data, if you know the timing of the answer and passive data

collection is continuously, the time difference between prompt and answer might be less of a problem.

To keep compliance levels high, subject-management procedures such as incentives, but also training and feedback might help. For example, incentives for completing assessments are found to increase compliance levels to some extent in earlier EMA studies (e.g. in substance abusers (Shiffman, 2009; Sokolovsky et al., 2014). However, this evidence is limited to non-smartphone EMA research. In our reviewed smartphone studies, compliance levels seemed to be independent of incentives. Further research to compliance and incentives in smartphone-based EMA is needed.

Analyses

Whereas most studies did apply a multilevel model to the EMA data, a main limitation of the reviewed studies is ignoring the variance (individual differences) and within person patterns over time. Focusing on group averages is common in the field of wellbeing (and beyond), but this leads to missing important information about individual differences. In EMA research, ignoring individual differences also reduces the ecological validity ((Ram et al., 2017). As individuals differ in their patterns of mood, behavior, and other experiences in life, the average person or pattern of those variables across participants does not exist in the real world. For example, in contrast to the general belief that people feel better after physical activity, strong individual differences in the affective responses during and after exercise are found (Ekkekakis et al., 2005; Rose & Parfitt, 2007; Welch et al., 2007). In the study of (Van Landuyt et al., 2000) half of the participants felt less happy during and after physical exercise compared to before. Schutte et al. (2017) showed that genetic factors explain 15% of the individual differences in affective responses.

The same individual differences might exist for well-being and other environmental variables, such as location preferences or outdoor activities. For example, MacKerron and Mourato (2013) show that people, *on average*, are happier in natural environments. However, individuals do differ in their reaction to urban or natural environments. Newman and Brucks (2016) showed that people differ in the environment needed to restore their self-control. People high on neuroticism prefer an urban environment to restore self-control, whereas people low on neuroticism prefer a more natural environment. This suggests that individual differences in the effect of natural environments on well-being might exist as well.

Another limitation of averaging data is ignoring a large part of the data. Patterns of moods or behavior over the day or week contain a lot of information

and might be more informative than a total or average score. As mentioned in the introduction, when investigating the relation between health and physical activity, the pattern of accumulation and not the total volume is more informative (Chinapaw et al., 2019). As another example, Smit et al. (2019) tried to predict an increase in depressive symptoms in six patients. Results show a rise in restlessness more than 2 months before the increase in depressive symptoms, whereas the total negative affect and positive affect scores did not have the same capacity to signal future increase in depressive symptoms.

In summary, we recommend to focus on fluctuations, patterns of well-being, and individual differences instead of the average or sum. In addition, EMA data is perfect to investigate individual differences in well-being and the relation with environmental variables or other (causal) correlates.

Table 9.5. Guidelines for future smartphone-based EMA research of well-being.

<i>Guidelines</i>	
<i>Design issue</i>	<i>Guidelines</i>
Sample	<ul style="list-style-type: none"> • Depends on the goal: • A large anonymous sample: widely advertise a free downloadable app <p>Target sample: invite participants with certain characteristic and send a link to download the app</p>
WB measure	<ul style="list-style-type: none"> • Include questions on both the affective and cognitive part of subjective well-being • Use a few WB questions, instead of a full scale to prevent answering becoming too repetitive
Objective data	<ul style="list-style-type: none"> • Include passive and objective sensor data in addition to self-report when possible • Use the new developments in technology to link self-report data to objective environmental data
Application	<ul style="list-style-type: none"> • If possible, develop the app for both the Android and iOS platform • Test the app multiple times • Offer feedback on the participants well-being levels to make participation fun, after data collection is complete, to avoid reactivity problems.
Study duration	<ul style="list-style-type: none"> • Depends on the goal and context of interest, but may range from a few days – up to a month • Include all days of the week to assess weekly fluctuations of WB • Include EMA in different seasons to assess seasonal WB fluctuations
Number of prompts per day	<ul style="list-style-type: none"> • Depends on the time-scale of variation of WB in the context of interest. • On average, prompting 2 times per day up to every hour can be reasonable. • If possible, base the number of prompts on individual differences or let participants decide their number of prompts
Compliance	<ul style="list-style-type: none"> • Be active to keep compliance levels high • Use subject-management procedures as incentives or training • Limit the latency between prompt and answer
Analyses	<ul style="list-style-type: none"> • Focus on fluctuations and patterns of well-being and other experiences/behaviour instead of the average or sum • Investigate the individual differences of well-being and the relation with environmental variables.
Report	<ul style="list-style-type: none"> • Report compliance levels and relate this to study characteristics • Follow the report guidelines of (Liao et al., 2016) for EMA studies • Use the checklist of van Roekel, Keijsers, and Chung (2019).

The future of EMA in well-being

Well-being has become a popular research topic with increasing number of publications in the last years. Well-being findings have the potential to inform policy and are applied more often in the society. Nowadays, using new technologies, detailed information about the fluctuations in well-being can lead to more insight in what people experience in their daily life and what makes them happy, from day to day or even hour to hour.

Our review shows that using a smartphone application to measure well-being multiple times a day is feasible and preferable over other EMA data collection devices. More systematic research on the fluctuations of the different components of well-being (e.g. affective and cognitive WB) in diverse contexts is needed to understand what influences momentary well-being and makes people happy. The continuing developments in smartphone technology (e.g. processing power, battery life, and new sensors and functions) and open source platforms will result in easier collection of self-report and objective data (Harari et al., 2016). The addition of objective data to self-report data is especially valuable to understand the relation between context, environmental variables, and momentary well-being. We recommend to use all aspects of EMA data and to focus on data patterns and individual differences using sophisticated analyses such as time-series analyses.

In the future, when the fluctuations and patterns of well-being and the interaction with environmental variables that make individuals happy are known, a next step in smartphone-based well-being research is a shift from EMA (assessing behavior in the moment) to EMI (ecological momentary intervention), intervening on behavior in the moment to increase well-being (Heron & Smyth, 2010). For example, the Shmapped application (McEwan et al., 2020) is developed as both a data collection and intervention tool. When prompted, participants are instructed to notice the nature around them and to recall good things. Preliminary results show improvements in wellbeing at one-month follow-up (McEwan et al., *under review*). Furthermore, a recent meta-analysis showed that smartphone-based interventions (e.g., awareness or relaxation exercises) to increase well-being in clinical samples have a small positive effect on the quality of life (Versluis et al., 2016). However, most interventions use a one size fits all approach. All participants receive the same intervention to increase well-being and individual differences and reactions to the intervention are not responded to. Taking into account individual differences might increase the effectiveness of future well-being interventions.

Limitations

A quantitative meta-analysis on the fluctuations of well-being or the effect of environmental variables was not possible, since the studies were too heterogeneous in study methods, contexts and analyses (e.g. the well-being measure, duration, number of prompts, reported statistics). Another limitation of this review might be the incomplete retrieval of articles. The field of smartphone and application based EMA research is relatively new and gaining popularity. The terminology to describe EMA studies varies and the results of EMA studies are being published in various forms and places. To be as conclusive as possible, we followed PRISMA criteria for systematic reviews.

Conclusions

The 53 reviewed studies showed that a smartphone-based form of EMA research is feasible to assess the fluctuations of momentary well-being in different contexts. Based on the used designs and findings, we provided recommendations for future smartphone-based EMA research in well-being. In the near future, with the continuing developments in smartphone technology, the use of smartphone applications combining EMA self-report and objective data can result in more specific knowledge about the fluctuations of well-being and what makes people happy.

Supplementary Material Chapter 9

The supplementary material of chapter 9 includes an excel spreadsheet with information about the studies included in the review. The supplementary material can therefore be found online, <https://doi.org/10.1007/s10902-020-00324-7>.



Chapter 10.

The association between well-being and a large variation of accelerometer-assessed physical activity and sedentary behavior measures

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ABSTRACT

Higher well-being has been associated with more physical activity (PA) and less sedentary behavior (SB), both when assessed by self-report or accelerometers. Most studies using accelerometer data only examined estimates of total volume or daily average of PA/SB in relation to well-being. Taking into account the richness of accelerometer data, we investigated the association of different measures of SB, light PA (LPA) and moderate-to-vigorous PA (MVPA) and well-being including the combined effect and the PA/SB timing and patterns. We explored whether results differed between occupational and non-occupational time. In an adult sample ($n=660$, $M_{\text{age}}: 30.4$, $SD = 8.1$, 74.5% female), we applied pre-registered analyses. First, we created different global scores of SB, LPA and MVPA based on 4 to 7-days of Actigraph data and investigated associations with well-being, i.e., defined as life satisfaction. These analyses were done using raw scores and transformed scores using compositional data analysis. Next, we applied multilevel models including time of the day and well-being as predictors of PA/SB. Finally, we clustered participants based on PA/SB intensity, timing and accumulation and explored differences in well-being across clusters. In total wear time, there were no associations between different measures of SB/LPA/MVPA and well-being. Restricting to non-occupational wear time, less total SB and more total LPA were associated with higher well-being, both in absolute and relative sense. Well-being was not associated with the PA/SB timing or patterns. In conclusion, beyond the association between total non-occupational SB and LPA and well-being, the PA/SB timing or patterns had no added value in explaining the association between PA/SB and well-being.

Keywords: well-being, physical activity, sedentary behavior, accelerometer data, compositional data, patterns

INTRODUCTION

On average, higher levels of well-being have been associated with more time spent being physically active, and less time spent in sedentary behavior (Pengpid & Peltzer, 2019; Richards et al., 2015; Zhang & Chen, 2019). Well-being can be defined as high levels of positive affect, low levels of negative affect, and a positive subjective evaluation of life satisfaction (Diener et al., 2018) or as thriving, positive functioning, and judgments about the meaning and purpose of an individual's life (Ryff, 1989). Physical activity (PA) can be defined as "any bodily movement produced by the skeletal muscle that results in energy expenditure" (Caspersen et al., 1985). Based on the intensity of PA, a distinction between light PA (LPA) and moderate to vigorous PA (MVPA) is often made. LPA includes activities such as light walking, gardening or household activities, whereas MVPA includes for example brisk walking, running, or heavy lifting. Sedentary behavior (SB) can be defined as "any waking behavior characterized by an energy expenditure of less than 1.5 metabolic equivalents (METs), either in a sitting, reclining or lying posture" (Tremblay et al., 2017). Sedentary activities include watching television or sitting in a chair. SB is not simply the lack of PA and is often reported to be independent of (moderate-to-vigorous) PA (Hamilton et al., 2008; Owen et al., 2010). Therefore, the associations between SB, LPA or MVPA and well-being may differ.

A recent meta-analysis reported a positive association between self-reported PA and well-being overall (Cohen's $d=.36$). The intensity of PA (i.e., light, moderate, vigorous) or exercise type (i.e., aerobic vs non-aerobic) did not moderate this relation. Furthermore, when only including experimental studies that directly manipulated MVPA, the meta-analysis showed a small positive effect of MVPA on well-being (Buecker et al., 2020). Regarding SB, a recent review on the relation between different indices of SB (i.e., device-measured, self-report or screen time) and well-being reported inconsistent associations (Sui et al., 2021). Based on self-report, the associations were mixed and dependent of the SB measure. Based on a limited number of device-based SB measures, SB was either negatively or not significantly associated with well-being. Larger systematic reviews and meta-analyses reported positive associations between self-reported SB and the risk of depression (Rodriguez-Ayllon et al., 2019; Teychenne et al., 2010). As depression is strongly associated with well-being (Baselmans et al., 2018; Greenspoon & Saklofske, 2001; Koivumaa-Honkanen et al., 2004), these findings suggest that SB could be negatively associated with well-being as well.

In the above-mentioned meta-analyses and reviews, the included studies mostly used self-reports to assess PA. Using self-reports, participants typically report their daily or weekly PA or SB, e.g., sitting or watching television. However, PA and SB can also be assessed more directly, for example using accelerometers. Participants wear an accelerometer on their hip or wrist that continuously records movement for a number of days and measures of PA and SB are extracted from the raw data. Correlations between self-report and direct measures of PA are mostly low-to-moderate (Prince et al., 2008). Direct measures of PA and SB are believed to result in more precise estimates as recall or social desirability biases are avoided. However, accelerometer data only give an estimation of movement and is less accurate in for example identifying posture, i.e., sitting or standing (but see Grant et al., 2006).

An advantage of accelerometer data is the richness of the available data, since data are collected continuously. Until recently, many studies using accelerometer data included only the total activity count or average daily time engaged in SB or a specific PA intensity. Recently, focus has shifted towards investigating more detailed aspects and the daily or weekly patterns of PA and SB instead of total volumes. For example, investigating the association between well-being and SB/PA in different day segments (morning, afternoon, evening) can lead to information on when people are engaging in more or less PA and SB during the day and how this timing affects well-being. Furthermore, the same total time in PA or SB may be accumulated in different patterns (Chinapaw et al., 2019). For example, if someone walks for an hour and another person walks 6 times per day for 10 minutes, they have the same total time of walking, but the accumulation over the day differs considerably. Moreover, the combination of different intensities of PA and SB could lead to different results. Thus, accumulation patterns of PA and SB jointly could be more predictive of (mental) health and well-being outcomes than total PA/SB time separately.

In addition, combining accelerometer data with daily diaries, it is possible to make a distinction between PA and SB during work hours, i.e., occupational time and during non-occupational time. Non-occupational PA/SB includes PA/SB during leisure time, transport, household activities and education. A recent meta-analysis summarized the associations between PA in the different domains and mental (ill-)health and suggests slightly different associations between well-being and occupational versus non-occupational PA (White et al., 2017). PA during leisure time or transport was significantly associated with better mental health ($r=0.13$, 95%CI: $-0.08-0.18$ and $r=0.13$, 95%CI: $0.02-0.23$), while occupational PA was associated with ill-health (i.e., symptoms of

depression or anxiety) ($r=0.09$, 95%CI: 0.03-0.15) (White et al., 2017). However, all associations were small and based on self-reported PA.

In the current study, we investigated the association between different measures of SB, LPA and MVPA and well-being (i.e., defined as life satisfaction) going beyond simple averages. More specifically, in a 4-step approach, we first investigated the association of well-being with the different well-known summary measures. Next, we investigated if the timing of SB or PA is related to well-being. Third, we clustered participants based on the timing and amount of SB or PA and compared the well-being of the different clusters. Finally, we clustered participants based on both SB and PA behaviors and compared the clusters on well-being (see Table 10.1). For all research questions, we explored whether results differed between occupational and non-occupational PA and SB.

METHODS

Sample

Participants were voluntary members of the Netherlands Twin Register (NTR). The NTR was established by the Department of Biological Psychology, Vrije Universiteit Amsterdam more than 30 years ago (Ligthart et al., 2019). Every two/three years, longitudinal survey data about lifestyle, personality, psychopathology, and well-being in twins and their families are collected. The NTR sample is a population-wide, non-clinical sample.

Accelerometer data were collected in three separate studies (n total=800), (1) a study in 2013 on the determinants of voluntary PA in 98 participants, i.e., young adult monozygotic twins discordant for PA, (2) a study in 2014-2015 in 30 participants, i.e., female monozygotic twins discordant for body mass index (BMI), and (3) a study on the heritability of SB that ran in 2016-2017 in 672 participants, both twins and non-twin siblings. Accelerometer data were collected using the same protocol in the three studies with the same instructions for every participant (for more details see Schutte et al., 2020).

Well-being data were collected in various survey waves of the NTR preceding or during the accelerometer studies. For every participant, if multiple well-being scores were available, we included the well-being score closest in time to the accelerometer data collection.

We only included participants for who the well-being and accelerometer data was collected within maximally 5 years of each other. In the final sample (n=660), the average length between the measurements was 2.2 years (range: -0.4 to +4.9 years), with well-being assessed mostly before the accelerometer data. In a sensitivity analysis, including time between the measurements as covariate, we found that the time between the well-being and accelerometer measurements did not affect the results (see Supplementary Table S10.1).

Table 10.1. Overview of the different analyses.

Part	Research question	Analysis	Accelerometer measure	Result	
1	Is WB associated with the (relative) time spent in..	SB?	SB	Non-working days: ↑ WB → ↓ SB	
		LPA?	Percentage of total time in LPA	Non-working days: ↑ WB → ↑ LPA	
		MVPA?	MVPA	-	
	Is WB associated with the average bout length of..	SB?		SB	-
		LPA?	Mean length of bouts of	LPA	-
		MVPA?	Regression well-being on average SB/PA measures	MVPA	-
	Is WB associated with the time spent in bouts of..	SB?		SB	Non-working days: ↑ WB → ↓ SB
		LPA?	Percentage of total time in bouts of	LPA	Non-working days: ↑ WB → ↑ LPA
		MVPA?		MVPA	-
	Is WB associated with the fragmentation of..	SB?		SB	-
		LPA?	Fragmentation of	LPA	-
		MVPA?		MVPA	-

Table 10.1. Overview of the different analyses.

Part	Research question	Analysis	Accelerometer measure	Result
2	Is WB associated with the timing of.. SB?		SB	↑ WB → ↓ SB in evening
	LPA?	Multilevel model including well-being and day segments (<i>morning, afternoon and evening</i>) predicting SB/PA measures	Per day segment, percentage of total time in LPA	↑ WB → ↑ LPA in evening
	MVPA?		MVPA	-
	Is WB associated with the timing of.. SB bouts?		SB	↑ WB → ↓ SB in evening
LPA bouts?	Per day segment, percentage of time in bouts of LPA	↑ WB → ↑ LPA in evening		
	M V P A bouts?		MVPA	-
3	Do participants in the different SB clusters differ on WB?		SB	
	Do participants in the different LPA clusters differ on WB?	Comparing different SB or PA clusters on well-being	Cluster amount and timing of	Non-working days: ↑ WB → ↑ LPA
	Do participants in the different MVPA clusters differ on WB?		MVPA	-
4	Do participants in the different clusters differ on WB?	Comparing different clusters on well-being	Cluster on intensity and timing of SB and PA	-

Note: SB= Sedentary behavior, LPA= light physical activity, MVPA= moderate-vigorous physical activity, WB = well-being.

Participants ($n=660$) were on average 30.4 years old ($SD=8.2$, range=18-65). The number of participants in the different analyses differed due to availability of the required data. For example, not all participants completed a daily diary indicating their working hours. Therefore, we had to exclude these participants from the occupational and non-occupational time analyses, leaving 553 participants.

The data collection was approved and declared to be of low risk and exempt of formal medical ethical risk assessment by the METc of the Vrije Universiteit Medical Center Amsterdam and performed in accordance with the Declaration of Helsinki. All participants provided written informed consent.

Measures

Accelerometer data

Participants were instructed to wear an Actigraph accelerometer (Actigraph GT3X+, Actigraph LLC) attached to an elastic belt on the right hip during waking hours for 7 consecutive days, except during water-based activities. Count data were processed and statistics were computed using the Actilife software (version 6.10.4). We used the Actigraph activity count data of the vertical axis. The raw data was converted into 60-seconds epoch data. Non-wear time was excluded and defined as zero counts during an uninterrupted time of at least 60 minutes with allowance of 2 minutes with counts between 0 and 100 within that time range. Wear time was considered acceptable when there was a minimum of 4 days of 10 hours of wear time per day.

Standard cut-points were used to define SB (<100 counts/min), light (100-<2020 counts/min), moderate (2020-5998 counts/min), and vigorous (>5999 counts/min) intensity PA (Troiano et al., 2008). Moderate and vigorous intensity PA were combined in a MVPA category. Below we describe the various metrics of SB, LPA and MVPA extracted from the accelerometer data.

During the accelerometer data collection, participants were asked to indicate (using a paper-pencil diary) each day whether it was a workday or not and if so, the start and end time. These time-points were used to classify SB/LPA/MVPA in occupational time and non-occupational time. Furthermore, we classified days on which participants worked part of the day as working days, and days on which participants did not work as non-working days. On average, the participants indicated 4.2 working days ($SD=1.7$, range =0-8) and 3.0 ($SD=1.2$, range=1-7) non-working days.

Well-being

Well-being was assessed with the Satisfaction with Life scale (Diener et al., 1985). This scale consists of five items with a 7-point Likert scale, ranging from 1 = *strongly disagree* to 7 = *strongly agree*. An example question is '*In most ways my life is close to ideal*'. Items were summed to calculate a score ranging from 0 to 35, with higher scores indicating higher levels of satisfaction with life.

Covariates

Body Mass Index (BMI) and educational attainment (EA) were included as covariates as both are associated with PA, SB, and well-being (Beenackers et al., 2012; Cooper et al., 2000; Gidlow et al., 2006; Hemmingsson & Ekelund, 2007). BMI was calculated for every participant by dividing the self-reported weight by the squared self-reported height, i.e., $BMI = \text{kg/m}^2$.

Educational attainments was enquired with the question "What is the highest educational level you have completed?". The educational attainment variable was recoded in four categories: primary education only (1), lower vocational school and lower secondary school (2), intermediate vocational school and intermediate or higher secondary school (3) and higher vocational school and university (4).

Statistical analyses

This study was a secondary data analysis of previously collected data in the Netherlands Twin Register. The analyses were pre-registered before data analysis at <https://osf.io/rxafd>. We created different indicators of SB, LPA and MVPA and divided the analyses in four different parts (see Table 1 for an overview).

We used a significance threshold that is corrected for multiple testing using a Bonferroni correction. The number of main tests is 66 ((12 (summary)+6 (multilevel)+3 (cluster 1)+1 (cluster 2)) x3 (total wear time, occupational and non-occupational)). Therefore, the threshold of significance is $p=0.05/66= 0.00076$.

Part 1: Summary scores

Summarizing all accelerometer data per participant, we computed four different summary scores of SB, LPA and MVPA.

First, we computed the total time of SB/LPA/MVPA as the percentage of total wear time for each participant.

Second, we calculated the average length of bouts in which SB/LPA/MVPA were accumulated. A bout of SB and LPA was defined as at least 10 consecutive minutes and a bout of MVPA was defined as at least 5 consecutive minutes followed by a different intensity (Chinapaw et al., 2019).

Third, we calculated the percentage of the total time spent in SB/LPA/MVPA bouts, using the above definition of a bout.

Fourth, we computed the fragmentation index of SB/LPA/MVPA, by dividing the number of bouts by the total SB/LPA/MVPA time. A higher number reflects more fragmentation of that particular intensity (Chastin & Granat, 2010).

Using Generalized Estimating Equation (GEE) (Minică et al., 2015) to correct for familial relatedness, well-being was associated with the four summary scores, adjusting for covariates, i.e., sex, age, BMI and educational attainment.

Occupational vs non-occupational time. Next, we computed the four different summary measures for participants that categorized their accelerometer wear time in occupational and non-occupational time (n=553) and repeated the GEE analyses separately for occupational and non-occupational time.

Compositional data analysis. As exploratory (not-preregistered) analysis, we redid the GEE analyses according to compositional data analysis procedures to explore the combined effects of SB and PA. Accelerometer data is compositional by nature, since the different behaviours add up to the total accelerometer wear time. We created three sets of two isometric log-ratio (ilr) partitions of SB, LPA, and MVPA (Dumuid et al., 2020). The first ilr predictor of each set reflects one activity relative to the other two activities, i.e., SB relative to LPA and MVPA, LPA relative to SB and MVPA, and MVPA relative to SB and LPA. The second ilr predictor of each set reflects then the ratio of the other activities in the denominator of ilr_1 , i.e., respectively LPA relative to MVPA, SB relative to MVPA, and SB relative to LPA. See the equations for ilr_1 and ilr_2 below for the computation for one set of predictors.

$$ilr_1 = \sqrt{\frac{2}{3}} \ln \left(\frac{SB}{\sqrt[2]{LPA * MVPA}} \right)$$

$$ilr_2 = \sqrt{\frac{1}{2}} \ln \left(\frac{LPA}{MVPA} \right)$$

Next, in three separate models, we included the set of composition predictors, i.e., ilr_1 and ilr_2 in the models to predict well-being, adjusting for covariates, i.e., sex, age, BMI and educational attainment.

Part 2: Time of the day

In part 2, we investigated the patterns of SB, LPA and MVPA over the day in relation to well-being. We divided the day in three segments (morning: 7:00-12:59 /midday: 13:00-17:59 /evening: 18:00-23:00) to investigate if well-being is differently associated with SB/LPA/MVPA in different day segments. We applied a multilevel model where the day segments (level 1: morning/afternoon/evening) were clustered in participants (level 2) and participants in families (level 3). Participants were clustered in families, since the sample consists of twins and siblings.

The model included a level 1 fixed effect of day segment and we adjusted for the covariates at level 2. Relevant to the research question, fixed effects of well-being at level 2 and the cross-level interaction of day segment and well-being were included. We tested these effects separately for the average time in SB/LPA/MVPA and percentage time in bouts of SB/LPA/MVPA, resulting in 6 models.

Workdays vs non-work days. We repeated the above analyses for non-work days and workdays. In contrast to the summary scores for which we could split the total wear time directly into occupational and non-occupational time, note that non-work days are completely non-occupational time, whereas work days include both occupational time and non-occupational time.

Part 3: Clustering based on SB, LPA or MVPA

To investigate in more detail if the patterns of SB, LPA or MVPA over the day is associated with well-being, we clustered participants based on these patterns and compared the well-being scores of the participants in the different clusters. We applied the two-phase clustering procedure of (Reuter et al., 2020) separately per activity intensity, i.e., SB, LPA and MVPA. Participants are clustered on both the timing and duration of either SB, LPA or MVPA in

two phases. In short, in phase 1, all days across all participants ($n_{\text{days}}=4189$) are clustered based on similarities in within-day timing, i.e., the trajectories. In phase 2, participants ($n_{\text{individuals}}=660$) are clustered on similarities in their between-day patterns, based on the proportion of their day trajectories of phase 1 (see Figure 10.1).

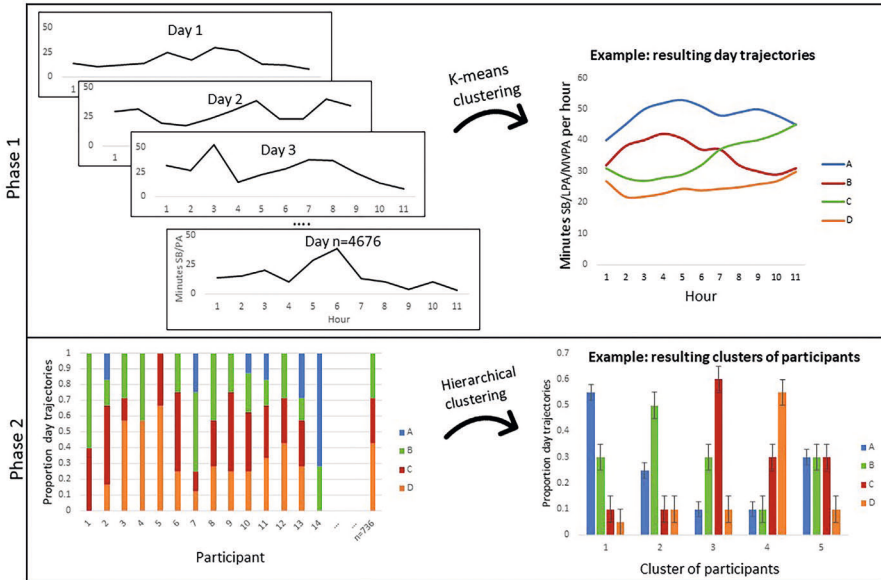


Figure 10.1. Steps and example of the two-phase clustering of participants based on SB, LPA or MVPA across the day. The upper panel shows phase 1, in which days are clustered based on similarities in within-day timing, i.e., the trajectories. The lower panel shows phase 2, in which participants are clustered based on the proportion of the phase 1 day trajectories in their data. In this example, the clustering results in four different day trajectories in phase 1 with a different amount and timing of SB/LPA/MVPA. Note that the best fitting number of clusters can also be only 2 day trajectories or any other number of trajectories. In this example, phase 2 clustering results in five clusters of participants with different proportions and mixture of A, B, C or D days. Note that the best fitting number of clusters can be any number of clusters of participants.

Phase 1

To be able to cluster day trajectories, the SB/LPA/MVPA minutes of each one-hour interval were summed per day. Then, we clustered all available days of the entire sample ($n_{\text{days}}=4189$) based on similarities in the timing of SB/LPA/MVPA during the day using a cluster technique for longitudinal data, longitudinal k-means (*kml* function in R) (Genolini & Falissard, 2011) (see upper panel Figure 10.1). Based on the convergence of the Calinski-Harabasz criteria and other criteria computed by the *kml* function (i.e. Ray & Turi and Davies & Bouldin criteria), the optimal number of clusters with different SB/LPA/MVPA

trajectories was selected. The upper right panel of Figure 10.1 shows examples of possible day trajectories.

Phase 2

In phase 2, the participants were clustered based on similarities in their between-day patterns, i.e., the proportion of the different phase 1 day trajectories (see lower panel of Figure 10.1). For every participant, the number of days in each identified trajectory were summed. Since participants did not have an equal number of days, the proportion of days assigned to each trajectory was computed by dividing the number of the days per trajectory by the total number of days. For example, if the phase 1 results in four different day trajectories (i.e., A, B, C and D), the 7-day data for a participant might be ABACBAA, and this participant has 4 A days, 2 B days, 1 C day and no D days. This would result in: proportion A= 4/7, B= 2/7, C= 1/7 and D =0/7. Next, using hierarchical clustering (*hclust* function in R), participants were clustered on the similarities of these proportions. The silhouette criterium was used to select the optimal number of clusters based on the maximum average silhouette width across observations (Maechler et al., 2019). The clusters will differ on the proportions and mixture of day trajectories (see Figure 10.1 for an example). We compared the well-being scores of the participants in the different clusters.

Workdays vs non-workdays. We repeated the clustering analyses separately for non-work days and workdays. Since there were only a few workdays or non-workdays per participant, we did not apply the two-phase clustering, but we directly clustered participants based on their minutes of SB/LPA/MVPA per hour across the days.

For this analysis, participants needed to have a similar amount of accelerometer data. Participants varied in their number of working and non-working days, i.e., some participants worked 5 from the 7 days, whereas others worked less days or not at all. To create an as large as possible sample and similar amounts of data per participant, we included the first 4 or 5 working days or 2 non-working days per participant out of the maximum of 7 days. We then used dynamic time warping (DTW: R package *dtw*; Giorgino, 2009) and hierarchical cluster analysis (function *hclust*) to cluster participants based on the similarities in the trajectories of SB/LPA/MVPA over the days. DTW tries to find trajectories, i.e., the underlying similarities, in temporal data. These sequences are allowed to vary in speed or length. Note that work days both include occupational time and non-occupational time, whereas non-work days only includes non-occupational time.

Part 4: Clustering based on sequence maps

Lastly, we clustered the participants based on sequence maps of intensity and duration of SB and PA combined, using the methods and R functions of Chinapaw et al. (2019). Based on epochs of 60 seconds, we converted the accelerometer counts over all valid days into one sequence map per participant. This sequence map is based on a combination of intensity (from SB to VPA) and the duration of the intensity (shorter or longer bouts), resulting in 12 different states and a sequence of numbers between 1-12. A bout of at least 30 minutes in SB, i.e., the lowest intensity, is classified as 1, 10-29.9 minutes SB is classified as 2, less than 10 minutes SB as 3. The states of PA behaviours start with 4, indicating less than 10 minutes of LPA, up to 12, i.e., the state with the highest intensity (VPA) and longest duration (bout of at least 10 minutes) (see supplementary Table S10.2 for the rest of the states).

Next, dynamic time warping (DTW: Rpackage *dtw*; Giorgino, 2009) and hierarchical cluster analysis (function *hclust*) were applied to identify clusters of participants with similar behavioral sequence maps. DTW tries to find the underlying similarities in temporal sequences, and these sequences can vary in length. The silhouette index was used to determine the optimal number of clusters. We compared the well-being scores of the participants in the different clusters to investigate the relation between well-being and the joint accumulation of SB and PA (see Figure 10.2 for a visualization of the analysis).

Workdays vs non-workdays. We created the sequence maps separately for non-work days and work days and repeated the clustering analyses.

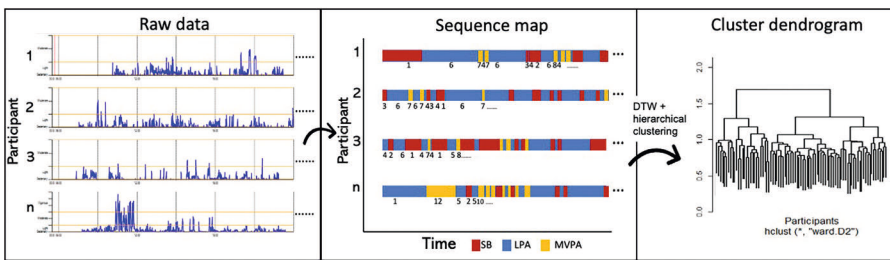


Figure 10.2. Visualisation of the sequence mapping and clustering”. First, the raw data is converted in a sequence of states, i.e., numbers between 1 and 12 reflecting the intensity and duration of activity (middle panel, see supplementary Table S10.2 for the states linked to the numbers). Using dynamic time warping (DTW) and hierarchical clustering, participants with similar sequence maps are then clustered in groups. In this example, two clusters of participants are found based on the sequence maps (right panel).

RESULTS

Descriptives

The sample included 660 participants, with a mean age of 30.4 ($SD= 8.1$), range 18-65 years, 74.5% female. See Table 10.2 for more descriptive statistics.

Table 10.2. Descriptives of the sample.

Demographics (n=660)	Mean (SD) or %	Range
Age	30.4 (8.2)	18-65
Sex (% female)	74.5%	
BMI	23.2 (3.4) kg/m ²	16.8-45.4
Well-being	27.3 (5.0)	7-35
Educational attainment (%)		
<i>Lower</i>	3%	
<i>Intermediate</i>	21%	
<i>Higher</i>	59%	
<i>Unknown</i>	17%	
Accelerometer metrics (n=660)	Mean (SD)	Range
Valid days	7.3 (0.9)	4-8
Total wear time (minutes/day)	870 (58)	686-1135
% SB	66% (8%)	34%-86%
% LPA	31% (8%)	14%-62%
% MVPA	3.3% (2.0%)	0%-16%
Average length SB bout	24.8 min (3.5)	17-41.6
Average length LPA bout	15.3 min (2.5)	10.3-51.5
Average length MVPA bout	9.7 min (4.9)	0.0-42.6
Fragmentation SB	0.03 (0.00)	0.02-0.04
Fragmentation LPA	0.02 (0.01)	0.00-0.04
Fragmentation MVPA	0.05 (0.02)	0.00-0.12
% in SB bouts	53% (11%)	13%-81%
% in LPA bouts	12% (7%)	1%-54%
% in MVPA bouts	1.8% (1.6%)	0%-13%

Part 1. Summary measures

The left panel of Figure 10.3 presents the results of the GEE analyses relating the different metrics of SB, LPA and MVPA to well-being. Controlling for the covariates, i.e., sex, age, BMI and educational attainment, none of the summary measures of SB, LPA and MVPA were associated with well-being.

Occupational time vs non-occupational time. During occupational time, the associations between SB/LPA/MVPA and well-being did not reach significance (see supplementary Table S10.3 for all estimates).

During non-occupational time, time spent in SB (bouts) ($\beta = -0.12$, 95%CI = -0.21 - -0.04 and $\beta = -0.12$, 95%CI = -0.20 - -0.04, $p < .001$) and time spent in LPA (bouts) ($\beta = 0.13$, 95%CI = 0.07 - 0.21 and $\beta = 0.16$, 95%CI = 0.09 - 0.23, $p < .001$) was significantly associated with respectively lower and higher levels of well-being (see Figure 10.3, right panel). This standardized effect indicates that a standard deviation increase in SB or LPA is associated with 0.12 SD decrease and 0.13 SD increase in well-being respectively. The associations between MVPA and well-being were not significant (see supplementary Table S10.4 for all estimates).

Compositional data analysis. The exploratory compositional data analysis showed that when total wear time and occupational time were analysed, none of the compositional predictors were associated with well-being (see supplementary Table S10.5 for the results). In non-occupational time, replacing LPA or MVPA with SB will lead to a decrease in well-being (ilr₁: $\beta = -0.56$, $SE = 0.16$, $p = .001$). Indicating that the association with well-being is strongest for the ratio of SB over LPA instead of the ratio of SB over MVPA, the separate substitutions indicated that replacing SB with LPA in non-occupational accelerometer time is associated with an increase in well-being (ilr₂: $\beta = 0.67$, $SE = 0.19$, $p = 4.4 \times 10^{-4}$), whereas replacing SB with MVPA has no significant effect (ilr₂: $\beta = 0.30$, $SE = 0.10$, $p = .004$).

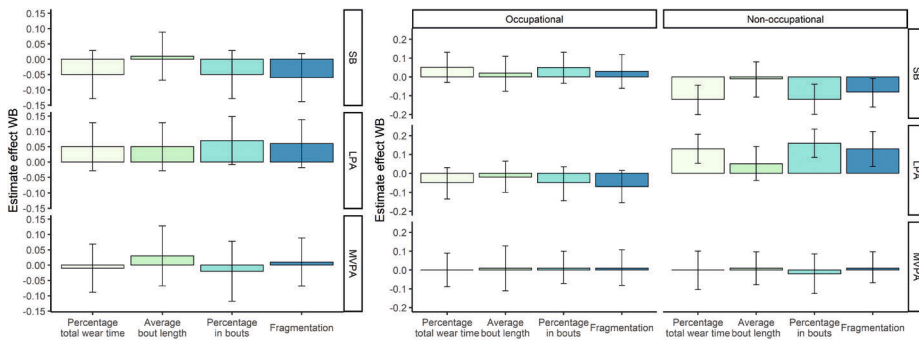


Figure 10.3. The association between the summary measures of SB, LPA and MVPA and well-being. Left panel: analyses based on total wear time. Right panel: wear time split by occupational vs non-occupational time. The error bars reflect the 99% confidence intervals.

Part 2. Time of the day

Allowing the association of PA/SB with well-being to vary over the day, the multilevel models of total wear time resulted in no main effects of well-being for the time spent in SB, LPA and MVPA and no interaction between well-being and time of the day (see Figure 10.4, left panel). The analyses of time spent in SB/LPA/MVPA bouts resulted in similar results (see Supplementary Table S10.6).

Workdays and non-workdays

When only including workdays, there was no main effect of well-being and no significant interaction effects between well-being and time of the day. However, the direction of the interaction effect between well-being and SB during the evening ($\beta=-0.12$, 95%CI= $-.20$ $-.03$, $p=.009$) and LPA ($\beta=0.12$, 99%CI= $.03$ $.20$, $p=.011$) suggests that higher well-being could be associated with less SB and more LPA during the evening (see Figure 10.4, middle panel and supplementary Table S10.7).

When only including non-working days, there was no interaction effect between well-being and the time of the day and no significant main effects of well-being. However, the direction of the main effect of well-being suggest that less time in SB ($\beta=-0.08$, 95%CI= $-.14$ $-.02$, $p=.062$) and more time in LPA ($\beta=0.10$, 95%CI= $.02$ $.17$, $p=.009$) could be associated with higher well-being (see Figure 10.4 right panel and supplementary Table S10.7).

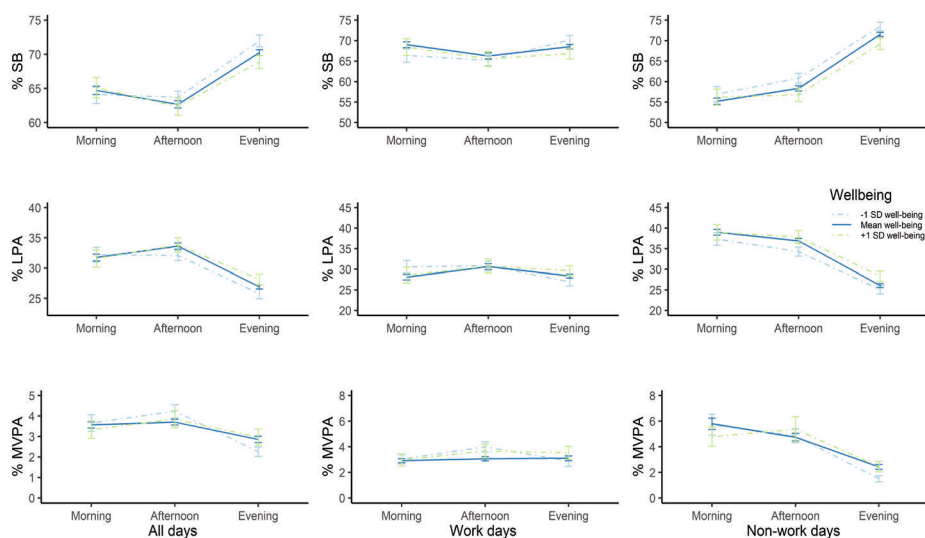


Figure 10.4. The association between well-being and the time spent in SB, LPA and MVPA across the day for all days (left panel), workdays (middle panel) and non-work days (right panel). The error bars reflect the 99% confidence intervals. The solid lines indicate the trajectory of SB/LPA/MVPA for average well-being and the dotted lines indicate the trajectory for well-being 1 SD below (blue) and 1 SD above the mean (green).

Part 3: Clustering based on SB, LPA or MVPA

SB. In phase 1, the clustering of days based on the timing and level of SB resulted in two trajectories. Days with trajectory A were characterized by higher SB levels across the day, whereas days with trajectory B were characterized by lower SB levels across the day (see Figure 10.5, top left panel). In phase 2, based on the proportion of A and B trajectories in the data of the participants, participants were clustered in 2 clusters. Participants in cluster 1 ($n=411$) had on average more high sedentary days (77%) compared to participants in cluster 2 ($n=249$; 21%) (see Figure 10.5, top panels). The well-being of participants in the different clusters did not differ (see Table 10.3).

LPA. In phase 1, the clustering based on LPA resulted in two trajectories. Days with trajectory A were characterized by a lower level of LPA across the day, whereas days with trajectory B were characterized by more LPA throughout the day (see Figure 10.5, middle left panel). In phase 2, participants were grouped in 2 clusters. Participants in cluster 1 ($n=411$) had on average more LPA days (79%) compared to participants in cluster 2 ($n=249$; 21%). The well-being of participants in the different clusters did not differ (see Table 10.3).

MVPA. In phase 1, the clustering based on MVPA resulted in three trajectories of MVPA across the day. Days with trajectory A were characterized

by a low level of MVPA across the day, whereas days with trajectory B were characterized by a higher level of MVPA in the afternoon, i.e., “MVPA afternoon days” and days with trajectory C by a higher level of MVPA in the morning, i.e., “MVPA morning days” (see Figure 10.5, bottom left panel). In phase 2, participants were grouped in 3 clusters. Most participants (cluster 1: n=614) had generally low MVPA across all days. Participants in cluster 2 (n=18) had mostly “MVPA afternoon days” and some low MVPA days. Finally, a small group of participants in cluster 3 (n=28) had a mixture of low MVPA days and “MVPA morning days” (see Figure 10.5, bottom right panel). The well-being of participants in the clusters did not differ (see Table 10.3).

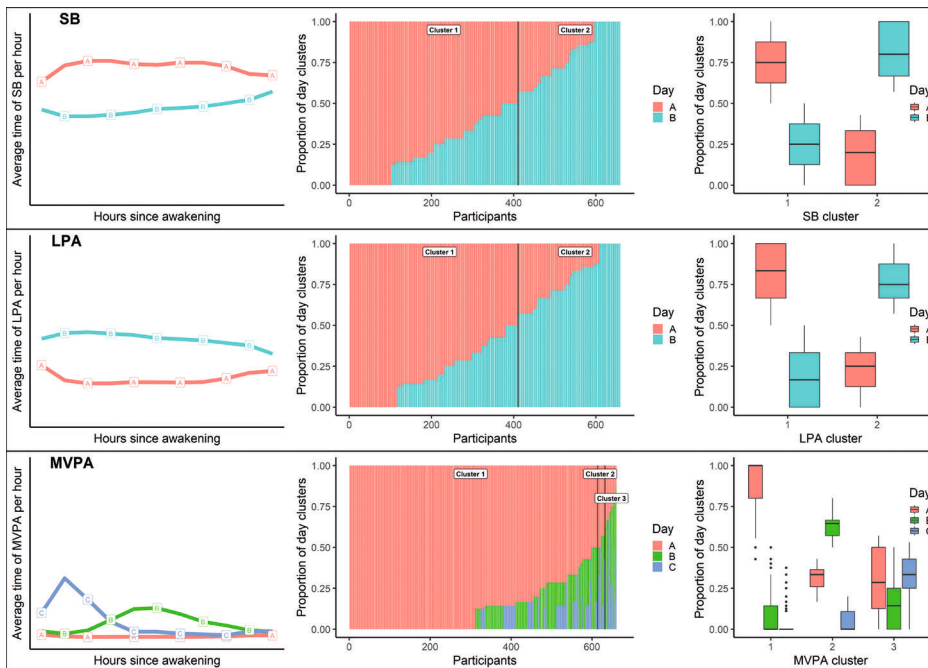


Figure 10.5. The clustering of days and participants based on minutes per hour spent in SB, LPA and MVPA. The left panel shows the clustering of days based on timing and duration of SB, LPA or MVPA across the day (phase 1). The middle panel shows the clustering of people based on the proportion of day trajectories (phase 2). The right panel shows the distribution of proportion of day trajectories per participant cluster.

Workdays

The subsample to cluster participants on workdays included 436 participants and 2044 days. For both SB, LPA and MVPA, the clustering resulted in two clusters, a high sedentary or low activity cluster and a low sedentary or high active cluster. There was no difference in well-being between the two SB/LPA/MVPA clusters of participants (see Table 10.3).

Non-work days

The subsample for clustering participants based on non-work days included 504 participants and 1008 days. The cluster analyses for SB resulted in two clusters of participants. Participants in cluster 1 (n=298) were characterized by less SB minutes per hour (i.e., low sedentary) than participants in cluster 2 (n=206), but did not differ on well-being (see Table 10.3).

Similarly, the cluster analyses for LPA resulted in two clusters. Participants in cluster 1 (n=207) were characterized by more LPA minutes per hour than participants in cluster 2 (n=297). Although participants in the high LPA (M=28.2, SD=4.6) cluster had a higher well-being compared to the lower LPA cluster (M=26.9, SD=5.0), this effect did not reach significance ($p=.003$) (see Table 10.3).

Finally, the cluster analyses for MVPA resulted in four clusters. Participants in cluster 1 (n=100) were on average active as participants in cluster 2 (n=132), but participants in cluster 1 have longer bouts of MVPA when they are active. Participants in the largest cluster 3 (n=258) were on average the least active with the most SB and least MVPA. A small group of participants in cluster 4 (n=14) were most active and had more MVPA than the other clusters. The participants in the different MVPA clusters did not differ on well-being (see Table 10.3).

Table 10.3. The average well-being score (SD) for each cluster of participants and the p-value of the comparison between the clusters of participants, based on all days, work days and non-work days.

	Total			Workdays			Non-work days		
	SB	LPA	MVPA	SB	LPA	MVPA	SB	LPA	MVPA
Cluster 1	27.3 (4.9)	27.4 (4.8)	27.3 (4.9)	27.7 (4.8)	27.2 (4.6)	27.3 (4.9)	27.1 (5.0)	28.2 (4.6)	27.0 (5.3)
	n=411	n=411	n=614	n=237	n=171	n=276	n=298	n=207	n=100
Cluster 2	27.2 (4.9)	27.1 (5.0)	28.5 (3.4)	27.2 (4.7)	27.7 (4.9)	27.9 (4.5)	27.9 (4.8)	26.9 (5.0)	27.3 (4.8)
	n=249	n=249	n=18	n=199	n=265	n=160	n=206	n=297	n=132
Cluster 3			27.1 (5.6)						27.7 (4.8)
			n=28						n=258
Cluster 4									27.4 (5.6)
									n=14
p-value	0.823	0.483	0.872	0.328	0.332	0.200	0.061	.003	0.226

Part 4: Clustering based on sequence maps of SB and PA

Based on the sequence maps of SB and PA, the analysis resulted in two participant clusters. Participants in cluster 1 ($n=338$) engaged in more SB (bouts) and less LPA (bouts) and MVPA (bouts) than participants in cluster 2 ($n=120$) (see Figure 10.6 and supplementary Table S10.8 for the estimates). The clusters did not differ on well-being ($M_1=27.3$, $SD_1=4.9$, vs $M_2=27.3$, $SD_2=4.5$).

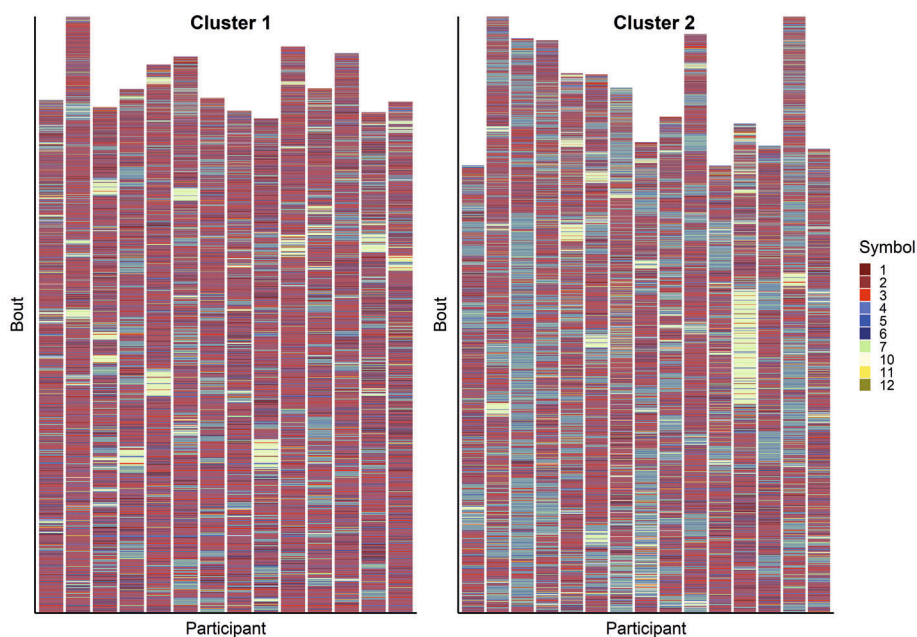


Figure 10.6. Sequence maps of a random subsample of participants in the two clusters ($n=15$). Red= sedentary behavior, blue= LPA, green=MPA, yellow= VPA.

Workdays versus non-workdays

When only including workdays, participants were clustered in two clusters. Participants in cluster 1 ($n=277$) were characterized by less PA and more SB compared to participants in cluster 2 ($n=146$) (see supplementary Table S10.8). The participants in the clusters did not differ on well-being (cluster 1: $M=27.4$, $SD=4.8$, cluster 2: $M=27.5$, $SD=5.0$), $p=.929$.

When only including non-work days, participants were clustered in three clusters. Participants in cluster 1 ($n=283$) were characterized by more LPA and MVPA and less SB compared to participants in cluster 2 ($n=290$) (see supplementary Table S10.8). The participants in the clusters did not differ on well-being (cluster 1: $M=27.6$, $SD=4.9$, cluster 2: $M=27.2$, $SD=4.9$, cluster 3: $M=27.5$, $SD=4.9$), $p=.337$.

DISCUSSION

Using a large variation of accelerometer assessed SB, LPA and MVPA measures, we found no association between well-being and SB/LPA and MVPA in total accelerometer wear time. Clustering the participants based on their timing and level of SB and/or LPA/MVPA during the day resulted mostly in two clusters, i.e., one more sedentary/less active cluster and one less sedentary/more active cluster. Participants in the different clusters did not differ on their well-being levels.

When dividing the data in occupational and non-occupational time, significant associations between the total time spent in SB and LPA (bouts) and well-being emerged during non-occupational time, but not during occupational time. Compositional data analysis indicated that the combined effect of relatively less SB and relatively more LPA is associated with higher well-being. Similarly, clustering participants based on non-working days, the less sedentary or more LPA cluster of participants reported slightly higher well-being levels compared to the more sedentary or less LPA cluster of participants. The timing or patterns of PA/SB accumulation had no added value in explaining the association between PA or SB and well-being (see Table 1 for an overview).

Occupational versus non-occupational SB, LPA and MVPA

The association between total PA and well-being during non-occupational time was only found for LPA and not for MVPA. Compared to LPA, MVPA occurs less often (mean of 31% versus 3.3% in this sample). The lower power may explain the lack of an association for MVPA. However, conflicting results on the differential associations between LPA and MVPA and well-being have been reported before. For example, self-reported leisure LPA has been associated with high well-being, whereas MPA was associated with the lowest well-being (Downward & Dawson, 2016). Other studies reported a positive association between accelerometer assessed LPA and MPA and well-being, and a non-significant or negative association between VPA and well-being (Panza et al., 2019; Wicker & Frick, 2015). Therefore, the combination in one MVPA category could explain the non-significant associations with well-being. We were unable to investigate MPA and VPA separately because of the low base rates.

A potential explanation for the positive association between LPA and well-being is that LPA is often accumulated in activities that have a social, recreational or fun purpose (Downward & Dawson, 2016). When having the freedom to choose one's activities, i.e., during leisure time, more PA can be associated with higher well-being. As leisure time is part of non-occupational

time, our findings of associations between LPA and well-being during non-occupational time but not occupational time supports this notion, but further research is needed to confirm this.

Besides leisure time PA, a large part of non-occupational LPA includes household activities, such as cleaning, gardening, and doing laundry (Van Der Ploeg et al., 2013). People who do not work or work part-time often perform a larger part of these household activities. The positive association between non-occupational LPA and well-being could therefore be confounded by work status, i.e., if people with a part-time job have a higher well-being than people with a full-time job.

In general, more research on the specific PA types and contexts that are associated with well-being in both occupational and non-occupational time is needed. Furthermore, it is important to know what the main activity is of people, both during work (i.e., physical demanding work vs white collar workers) and outside work. The amount of non-occupational time varies greatly depending on whether you work fulltime, part-time or not at all, since non-occupational LPA is strongly associated with what part of the household chores you do. We need more context about the participants and their exercise behavior when studying the associations with well-being, information which the accelerometer and the current diary method did not provide.

For SB, we found an association between lower SB and higher well-being during non-occupational time but no association during occupational time. In contrast, when investigating mental health symptoms, in a recent study, objectively assessed SB during the week, i.e., mostly working time, was associated with increased symptoms of anxiety and depression, but there was no association between weekend SB and these measures of mental health (Gibson et al., 2017). Similar to the recommendations for PA, more research on the contexts and types of SB during occupational and non-occupational time and their association with well-being is needed.

To account for the compositional nature of the accelerometer-assessed SB and PA data, we applied an exploratory compositional data analysis. Although compositional data analyses can lead to different results compared to “standard” analysis (N. Gupta et al., 2018), the results of this analysis replicated the opposite associations of SB and LPA with well-being in non-occupational time when both were included in an integrated analysis. In line with (Giurgiu et al., 2022) findings on mood, the combined effect of SB and PA indicates that more SB relative to less PA was related to lower well-being. In the current study, the strongest association was with LPA, indicating that replacing SB by LPA in non-occupational time might lead to higher well-being.

Timing and accumulation patterns of SB and PA

The timing of SB, LPA and/or MVPA over the day was not associated with well-being. In the cluster analyses, we based the number of best-fitting clusters on the silhouette index and most analyses resulted in two clusters, i.e., an less sedentary/LPA/MVPA and a more sedentary/LPA/MVPA cluster. Based on the results of previous studies, we expected to be able to distinguish between multiple clusters of participants with a different timing of SB and PA. For example, Reuter et al. (2020) reported four different clusters of older women (mean age = 79) with a different timing of SB, and this SB timing was associated with health measures. Chinapaw et al. (2019) clustered children on their sequence maps of SB/PA and reported seven different clusters of participants with different sequences.

An explanation for the higher number of clusters and more variability in PA/SB in these previous studies could be the difference in sample characteristics, i.e. children (Chinapaw et al., 2019) and elderly (Reuter et al., 2020) versus adults (current sample). Children and elderly might have less structured life's and more free time and choices in their SB/PA compared to (employed) adults. Although dependent on the job, during working hours adults might not have much of a choice in their SB or PA, resulting in more uniform patterns among adults. Furthermore, our sample is relatively homogenous in other characteristics, with an overrepresentation of women and younger, higher educated people. Therefore, the sample could be too small or homogenous to detect (smaller) differences in SB/PA patterns.

Since these more detailed measures of SB and PA require more complex and multiple processing steps, each of which may add some measurement error, we recommend future studies applying cluster analyses to patterns of SB/PA accumulation to use larger and more diverse samples.

Direction of association

In the current study, we can only report on the association between PA or SB and well-being and not on its underlying source or direction of the association. Often, studies on PA/SB and well-being focus on a presumed causal effect of PA/SB on well-being. For example, using an ecological momentary assessment (EMA) approach, a direct influence of daily PA and SB on life satisfaction was reported (Maher et al., 2014). In a longitudinal study, changes in self-reported leisure time PA were associated with changes in well-being, suggesting a possible causal effect of PA on well-being (Blomstrand et al., 2009). However, experimental or intervention studies are needed to confirm this causality.

Alternatively, the association between PA/SB and well-being could arise from reverse causality. Higher levels of well-being can cause more PA or less SB. For example, happier people might have the adequate levels of self-control to be active and do exercise whereas the characteristic of low well-being, lack of energy, anhedonia, and social withdrawal, all exert a negative influence on PA (Dishman, 1990; Goodwin, 2003). A recent longitudinal study indeed reported a *bidirectional* association between self-reported leisure time PA and well-being (Kim et al., 2021), indicating that well-being might lead to more PA and vice versa.

However, based on the results of twin studies, the association between PA and well-being seems, at least in part, to be due to non-causal mechanisms, including overlapping genetic factors underlying both PA and well-being (Bartels et al., 2012; Stubbe et al., 2007). The association reported in the current study between non-occupational time SB/LPA and well-being could therefore also be (partly) caused by genetic factors having an effect both on well-being and non-occupational time SB/LPA. This would be in keeping with the triangulation across the results from different designs for causal inference (randomized control trials, prospective studies) that supported the existence of causal effects of regular exercise on mental health and residual confounding by genetic factors (de Geus, 2021).

Limitations

A limitation of this study is the different timing of collection of the accelerometer and well-being data. Although measures of well-being are quite stable over time (Fujita & Diener, 2005; Lucas & Donnellan, 2007) and the sensitivity analysis found no influence of the time between the measures, the results should be interpreted in light of this limitation. More research should combine accelerometer data with ecological momentary assessment (EMA) to assess well-being multiple times throughout the participant's day (e.g., Giurgiu et al., 2022).

A further limitation is the representativeness of our sample for the Dutch population. Fifty-eight percent of the sample indicated to have attended higher vocational school or university, significantly higher than the 38% of adults (25-64 year-olds) in the Dutch population (OECD, 2019). As we distinguish between non-occupational and occupational PA/SB this could be important, since higher educated people more often have sedentary jobs than lower educated people. A strength of the study was the use of accelerometer data in a relatively large study sample, which allowed us to study timing and patterns. On the other hand, the accelerometer data provided no data on the type and

context of the behaviours, which would have been useful to better understand the association with well-being beyond the (non-)occupational diary data.

Conclusion

We found no associations between various measures of sedentary behaviour or physical activity and well-being in total accelerometer wear time. We did find a positive and negative association of non-occupational LPA and SB respectively with well-being, both in an absolute and relative sense. The more detailed measures including the timing or accumulation of PA/SB had no added value in explaining the association with well-being.

Supplementary Material Chapter 10

Table S10.1. Results summary measures including time between accelerometer and WB data.

	Percentage total wear time					
	SB		LPA		MVPA	
	β (SE)	p	β (SE)	p	β (SE)	p
WB	-0.04	0.04	0.251	0.04	0.187	0.842
Sex	-0.17	0.04	7.58E-05	0.04	7.32E-08	0.000
Age	-0.22	0.05	6.24E-05	0.05	2.04E-06	0.303
BMI	0.01	0.04	0.882	0.04	0.256	4.52E-06
EA	0.20	0.05	5.29E-05	0.05	4.27E-05	0.402
Time diff	-0.05	0.06	0.356	0.06	0.253	0.502
Average bout length						
	SB		LPA		MVPA	
	β (SE)	p	β (SE)	p	β (SE)	p
WB	0.01	0.04	0.793	0.04	0.198	0.615
Sex	-0.13	0.05	0.006	0.04	0.470	0.680
Age	-0.12	0.05	0.024	0.04	1.28E-05	0.024
BMI	-0.05	0.04	0.261	0.04	0.217	0.010
EA	0.14	0.05	0.003	0.04	0.779	0.267

Table S10.1. Results summary measures including time between accelerometer and WB data.

Time diff	-0.03	0.05	0.545	-0.01	0.04	0.793	-0.03	0.06	0.580
Fragmentation									
	SB			LPA			MVPA		
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	p
WB	-0.07	0.04	0.115	0.05	0.04	0.179	0.00	0.04	0.908
Sex	-0.01	0.05	0.824	0.27	0.04	2.95E-09	0.03	0.04	0.528
Age	0.04	0.05	0.467	0.26	0.05	9.44E-08	-0.14	0.05	0.007
BMI	0.07	0.04	0.113	0.09	0.04	0.036	0.02	0.06	0.765
EA	-0.02	0.05	0.733	-0.10	0.04	0.020	0.03	0.04	0.499
Time diff	0.03	0.06	0.606	0.11	0.06	0.070	0.01	0.06	0.888
Percentage in bouts of total time									
	SB			LPA			MVPA		
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	p
WB	-0.05	0.04	0.226	0.06	0.04	0.085	-0.02	0.05	0.737
Sex	-0.19	0.04	6.91E-06	0.21	0.04	1.62E-07	-0.08	0.04	0.067
Age	-0.19	0.05	4.35E-04	0.27	0.05	1.13E-08	-0.03	0.05	0.571
BMI	0.00	0.04	0.935	0.05	0.04	0.211	-0.18	0.04	3.11E-05
EA	0.20	0.05	4.71E-05	-0.15	0.05	0.001	-0.03	0.05	0.576

Table S10.1. Results summary measures including time between accelerometer and WB data.

Time diff	-0.05	0.06	0.406	0.07	0.06	0.226	-0.03	0.06	0.586
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Note: WB= well-being, BMI=body mass index, EA= educational attainment.

Table S10.2. Symbol definitions based on the intensity and duration of PA/SB for creating the sequence maps, based on Chinapaw et al. (Chinapaw et al., 2019).

Symbol	Bout length (min)	Cut point	Tolerance (%)
1	≥30	SB (≤100 counts per minute)	0
2	10-29.9	SB	0
3	0-9.9	SB	0
4	0-9.9	LPA (101- 2019 counts per minute)	0
5	10-29.9	LPA	10
6	≥30	LPA	10
7	0-4.9	MPA (2020-5998 counts per minute)	0
8	5-9.9	MPA	10
9	≥10	MPA	10
10	0-4.9	VPA (≥5999 counts per minute)	0
11	5-9.9	VPA	10

12	≥10	VPA	10
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Table S10.3. Results summary measures of occupational time.

Percentage total wear time									
	SB	LPA	MVPA						
	β (SE)	p	β (SE)	p	β (SE)	p			
WB	0.05	0.04	0.216	-0.05	0.04	0.214	0.00	0.05	0.985
Sex	-0.11	0.04	0.014	0.15	0.04	3.67E-04	-0.29	0.06	4.34E-06
Age	-0.02	0.04	0.592	0.00	0.05	0.974	0.03	0.05	0.606
BMI	-0.04	0.04	0.381	0.07	0.04	0.101	-0.14	0.05	0.004
EA	0.30	0.04	7.72E-10	-0.29	0.05	2.48E-08	-0.03	0.05	0.525
Average bout length									
	SB	LPA	MVPA						
	β (SE)	p	β (SE)	p	β (SE)	p			
WB	0.02	0.05	0.728	-0.02	0.04	0.678	0.01	0.06	0.885
Sex	-0.11	0.04	0.012	0.01	0.05	0.780	-0.06	0.07	0.411
Age	0.00	0.05	0.972	0.09	0.05	0.052	-0.03	0.07	0.728
BMI	-0.09	0.05	0.036	-0.02	0.05	0.765	-0.07	0.08	0.365
EA	0.22	0.04	1.16E-07	-0.12	0.04	0.003	0.04	0.07	0.601

Fragmentation						
SB		LPA			MVPA	
	β (SE)	p	β (SE)	p	β (SE)	p
WB	0.03	0.05	0.529	0.04	0.01	0.785
Sex	0.00	0.04	0.977	0.05	-0.10	0.034
Age	0.03	0.05	0.486	0.05	0.00	0.953
BMI	0.08	0.05	0.068	0.06	-0.05	0.362
EA	0.00	0.05	0.979	0.05	6.01E-06	0.758
Percentage in bouts of total time						
SB		LPA			MVPA	
	β (SE)	p	β (SE)	p	β (SE)	p
WB	0.05	0.04	0.248	0.05	0.01	0.741
Sex	-0.12	0.04	0.008	0.04	-0.21	0.000
Age	0.01	0.05	0.863	0.05	0.03	0.568
BMI	-0.06	0.05	0.198	0.04	-0.13	0.009
EA	0.277	0.050	2.48E-08	0.058	7.58E-06	0.596

Note: WB= well-being, BMI=body mass index, EA= educational attainment.

Table S10.4. Results summary measures of non-occupational time.

Percentage total wear time						
	SB		LPA		MVPA	
	β (SE)	p	β (SE)	p	β (SE)	p
WB	-0.12	0.04	0.13	0.04	0.00	0.978
Sex	-0.17	0.05	0.20	0.04	9.71E-04	0.333
Age	-0.34	0.05	0.37	0.05	9.50E-16	0.475
BMI	0.03	0.04	0.04	0.04	-0.19	2.12E-05
EA	0.08	0.05	-0.08	0.05	-0.01	0.859
Average bout length						
	SB		LPA		MVPA	
	β (SE)	p	β (SE)	p	β (SE)	p
WB	-0.01	0.05	0.05	0.05	0.01	0.840
Sex	0.05	0.04	-0.04	0.06	0.02	0.744
Age	-0.07	0.05	-0.04	0.05	0.09	0.100
BMI	0.08	0.05	-0.01	0.06	-0.10	0.061
EA	-0.20	0.04	0.12	0.04	0.05	0.257
Fragmentation						
	SB		LPA		MVPA	
	β (SE)	p	β (SE)	p	β (SE)	p

Table S10.4. Results summary measures of non-occupational time.

WB	-0.08	0.04	0.030	0.13	0.05	0.007	0.01	0.04	0.728
Sex	0.03	0.05	0.516	0.11	0.03	0.001	0.05	0.04	0.278
Age	0.03	0.05	0.599	0.26	0.04	2.76E-09	-0.05	0.05	0.258
BMI	0.07	0.05	0.137	0.08	0.04	0.061	0.01	0.06	0.887
EA	0.00	0.05	0.949	-0.04	0.04	0.310	0.06	0.05	0.195
Percentage in bouts of total time									
	SB			LPA			MVPA		
	β (SE)	p	β (SE)	p	β (SE)	p	β (SE)	p	
WB	-0.12	0.04	0.004	0.16	0.04	3.16E-05	-0.02	0.05	0.713
Sex	-0.19	0.04	1.67E-05	0.17	0.04	4.99E-05	-0.01	0.05	0.872
Age	-0.31	0.05	2.00E-10	0.39	0.04	3.38E-20	-0.02	0.05	0.690
BMI	0.00	0.04	0.944	0.03	0.04	0.505	-0.19	0.04	1.88E-05
EA	0.08	0.05	0.087	-0.05	0.05	0.277	-0.01	0.05	0.849

Note: WB= well-being, BMI=body mass index, EA= educational attainment.

Table S10.5. Results of the Compositional Data analysis predicting well-being in total wear time, non-occupational time and occupational time.

Total wear time							
	β	SE	p	β	SE	p	
Intercept	0.03	0.20	.889	0.03	0.20	.889	Intercept
SB/ (LPA+MVPA)	-0.19	0.16	.219	MVPA/ (LPA+SB)	-0.04	.607	LPA/ (SB + MVPA)
LPA/MVPA	0.16	0.12	.182	LPA/SB	0.24	.173	SB/MVPA
Sex	-0.09	0.04	.048	Sex	-0.09	.048	Sex
Age	-0.01	0.05	.794	Age	-0.01	.794	Age
BMI	-0.02	0.05	.619	BMI	-0.02	.619	BMI
EA	0.09	0.05	.067	EA	0.09	.067	EA
Non-occupational time							
	β	SE	p	β	SE	p	
Intercept	0.26	0.19	.171	Intercept	0.26	.171	Intercept
SB/ (LPA+MVPA)	-0.56	0.16	.001	MVPA/ (LPA+SB)	-0.04	.632	LPA/(SB + MVPA)
LPA/MVPA	0.37	0.13	.004	LPA/SB	0.67	.0004	SB/MVPA
Sex	-0.09	0.05	.077	Sex	-0.09	.077	Sex
Age	-0.03	0.06	.611	Age	-0.03	.611	Age
BMI	-0.01	0.05	.885	BMI	-0.01	.885	BMI

Table S10.5. Results of the Compositional Data analysis predicting well-being in total wear time, non-occupational time and occupational time.

EA	0.08	0.05	.111	EA	0.08	0.05	.111	EA	0.08	0.05	.111
Occupational time											
	β	SE	p		β	SE	p		β	SE	p
Intercept	-0.15	0.16	.366	Intercept	-0.15	0.16	.366	Intercept	-0.15	0.16	.366
SB/ (LPA+MVPA)	0.12	0.08	.155	MVPA/ (LPA+SB)	-0.03	0.05	.615	LPA/SB + MVPA)	-0.09	0.08	.280
LPA/MVPA	-0.04	0.06	.576	LPA/SB	-0.12	0.09	.187	SB/MVPA	0.08	0.06	.194
Sex	-0.05	0.05	.328	Sex	-0.05	0.05	.328	Sex	-0.05	0.05	.328
Age	0.04	0.05	.487	Age	0.04	0.05	.487	Age	0.04	0.05	.487
BMI	-0.01	0.06	.848	BMI	-0.01	0.06	.848	BMI	-0.01	0.06	.848
EA	0.07	0.05	.226	EA	0.07	0.05	.226	EA	0.07	0.05	.226

Note: BMI=body mass index, EA= educational attainment.

Table S10.6. Results of the multilevel models predicting time in sedentary behavior (SB), light physical activity (LPA) or moderate-vigorous physical activity (MVPA) in total wear time and time in SB, LPA or MVPA bouts in total wear time.

	Time											
	SB			LPA			MVPA					
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Intercept	-0.12	0.04	0.003	0.11	0.04	0.008	0.07	0.04	0.125			
Afternoon	-0.17	0.04	3.51E-05	0.16	0.04	7.25E-05	0.08	0.05	0.110			
Evening	0.53	0.04	2.00E-16	-0.49	0.04	2.00E-16	-0.26	0.05	2.53E-07			
WB	0.02	0.04	0.640	-0.02	0.04	0.533	0.00	0.04	0.940			
Sex	-0.11	0.03	0.001	0.16	0.03	2.30E-06	-0.12	0.03	1.02E-04			
Age	-0.17	0.04	2.31E-06	0.20	0.04	7.18E-08	-0.05	0.03	0.146			
BMI	0.01	0.03	0.789	0.03	0.03	0.413	-0.12	0.03	1.20E-04			
EA	0.12	0.03	4.10E-04	-0.12	0.03	4.79E-04	-0.02	0.03	0.477			
Afternoon*WB	-0.05	0.04	0.244	0.07	0.04	0.064	-0.07	0.05	0.136			
Evening*WB	-0.09	0.04	0.024	0.08	0.04	0.052	0.07	0.05	0.142			
Bouts												
	SB bouts			LPA bouts			MVPA bouts (0-1)					
	β	SE	p	β	SE	p	β	SE	p	β	SE	p
Intercept	-0.04	0.04	0.296	0.11	0.04	0.010	-2.39	0.22	2.00E-16			
Afternoon	-0.23	0.04	3.30E-07	0.08	0.04	0.053	-0.65	0.21	0.002			
Evening	0.43	0.04	2.00E-16	-0.50	0.04	2.00E-16	-0.11	0.20	0.559			
WB	0.02	0.04	0.685	-0.01	0.04	0.771	0.22	0.17	0.178			
Sex	-0.13	0.03	1.02E-04	0.15	0.03	1.24E-05	-0.08	0.12	0.497			

Table S10.6. Results of the multilevel models predicting time in sedentary behavior (SB), light physical activity (LPA) or moderate-vigorous physical activity (MVPA) in total wear time and time in SB, LPA or MVPA bouts in total wear time.

Age	-0.16	0.04	1.69E-05	0.22	0.04	4.72E-09	-0.05	0.13	0.729
BMI	0.00	0.03	0.915	0.03	0.03	0.337	-0.52	0.15	3.64E-04
EA	0.11	0.03	0.001	-0.09	0.03	0.006	0.14	0.13	0.291
Afternoon*WB	-0.05	0.04	0.214	0.07	0.04	0.077	-0.36	0.21	0.087
Evening*WB	-0.11	0.04	0.013	0.06	0.04	0.165	0.17	0.21	0.419

Note: WB= well-being, BMI=body mass index, EA= educational attainment.

Table S10.7. Results of the multilevel models predicting time in sedentary behavior (SB), light physical activity (LPA) or moderate-vigorous physical activity (MVPA) during workdays and non-working days.

	Work days									
	SB					MVPA				
	β	SE	p	β	SE	p	β	SE	p	p
Intercept	0.09	0.05	0.049	-0.08	0.04	0.086	-0.06	0.05	0.171	
Afternoon	-0.20	0.05	1.96E-05	0.18	0.05	5.83E-05	0.11	0.06	0.065	
Evening	0.01	0.05	0.905	-0.02	0.05	0.654	0.05	0.06	0.342	
WB	0.05	0.04	0.206	-0.06	0.04	0.150	0.00	0.05	0.924	
Sex	-0.10	0.04	0.006	0.14	0.04	9.94E-05	-0.13	0.03	0.000	
Age	-0.11	0.04	0.003	0.12	0.04	0.002	0.02	0.03	0.626	
BMI	0.00	0.04	0.897	0.03	0.04	0.380	-0.10	0.03	0.002	

Table S10.7. Results of the multilevel models predicting time in sedentary behavior (SB), light physical activity (LPA) or moderate-vigorous physical activity (MVPA) during workdays and non-working days.

	SB			LPA			MVPA		
	β	SE	p	β	SE	p	β	SE	p
EA	0.15	0.04	2.72E-05	-0.15	0.04	2.38E-05	-0.02	0.03	0.475
Afternoon*WB	-0.02	0.05	0.708	0.04	0.05	0.405	-0.07	0.06	0.203
Evening*WB	-0.12	0.05	0.009	0.12	0.05	0.011	0.05	0.06	0.389
Non-work days									
	β	SE	p	β	SE	p	β	SE	p
Intercept	-0.48	0.04	2.00E-16	0.42	0.04	2.00E-16	0.26	0.05	4.57E-08
Afternoon	0.21	0.05	3.77E-06	-0.17	0.04	1.02E-04	-0.15	0.06	0.016
Evening	1.16	0.05	2.00E-16	-1.04	0.04	2.00E-16	-0.58	0.06	2.00E-16
WB	-0.06	0.04	0.113	0.08	0.04	0.044	-0.02	0.05	0.602
Sex	-0.07	0.03	0.023	0.09	0.03	0.005	-0.02	0.03	0.458
Age	-0.18	0.03	5.51E-08	0.23	0.03	4.51E-11	-0.05	0.03	0.103
BMI	-0.01	0.03	0.671	0.06	0.03	0.079	-0.09	0.03	0.006
EA	0.03	0.03	0.356	-0.05	0.03	0.087	0.05	0.03	0.113
Afternoon*WB	-0.03	0.05	0.547	0.02	0.04	0.601	0.02	0.06	0.763
Evening*WB	0.00	0.05	0.938	-0.03	0.04	0.461	0.08	0.06	0.201

Note: WB= well-being, BMI=body mass index, EA= educational attainment.

Table S10.8. Characteristics of the two clusters based on the sequence maps in respectively total wear time, work days and non-working days with respect to their demographics, well-being, sedentary behavior and physical activity metrics and the difference between the clusters of participants.

	Total wear time		
	Cluster	2 (n=120)	<i>p</i> -value difference
Age	1 (n=338) 30.1 (8.7)	2 (n=120) 32.1 (8.5)	0.034
Sex (% females)	74%	58%	6.9x10⁻⁰⁴
BMI	22.8 (3.0) kg/m ²	23.5 (3.2) kg/m ²	0.037
Educational attainment	3.7 (0.5)	3.6 (0.6)	0.069
Well-being	27.3 (4.5)	27.3 (4.9)	0.969
% SB	67.70%	61.50%	1.6x10⁻¹³
% LPA	29.50%	33.30%	2.4x10⁻⁰⁶
% MVPA	2.60%	4.90%	2.0x10⁻¹⁶
Average length SB bout	25 min	24.3 min	0.048
Average length LPA bout	15.1 min	16.0 min	0.001
Average length MVPA bout	10.1 min	9.9 min	0.682
Fragmentation SB	0.03	0.03	0.834
Fragmentation LPA	0.02	0.03	0.006
Fragmentation MVPA	0.05	0.06	2.4x10⁻⁰⁴
% in SB bout	55.20%	48.80%	1.8x10⁻⁰⁸
% in LPA bout	11.90%	14.50%	1.2x10⁻⁰⁶
% in MVPA bout	1.60%	2.90%	3.5x10⁻¹⁴
	Work days		
	Cluster	2 (n=146)	<i>p</i> -value difference
Age	1 (n=277) 30.6 (7.1)	2 (n=146) 29.3 (6.6)	0.064
Sex (%females)	74%	64%	0.019
BMI	22.9 (2.7)	23.5 (3.9)	0.069
EA	3.7 (0.5)	3.8 (0.4)	0.013
WB	27.4 (4.9)	27.5 (5.0)	0.929
% SB	64%	71%	2.0x10⁻¹⁶
% LPA	32%	27%	2.4x10⁻¹⁰

Table S10.8. Characteristics of the two clusters based on the sequence maps in respectively total wear time, work days and non-working days with respect to their demographics, well-being, sedentary behavior and physical activity metrics and the difference between the clusters of participants.

% MVPA	4%	2%	2.0x10⁻¹⁶
Average length SB bout	24.5	25.9	7.9x10⁻⁰⁵
Average length LPA bout	15.6	14.9	0.016
Average length MVPA bout	10.2	9.6	0.236
Fragmentation SB	0.03	0.03	0.798
Fragmentation LPA	0.02	0.02	1.8x10⁻⁰⁴
Fragmentation MVPA	0.05	0.05	0.001
% in SB bout	51%	59%	2.7x10⁻¹⁵
% in LPA bout	13%	9%	1.5x10⁻⁰⁷
% in MVPA bout	2%	1%	7.7x10⁻¹³
Non-work days			
Cluster			
	1 (n=283)	2 (n=290)	p-value difference
Sex (%females)	72%	78%	0.155
BMI	23.2 (3.2)	23.1 (3.7)	0.775
EA	3.7 (0.5)	3.7 (0.5)	0.612
WB	27.6 (4.9)	27.2 (4.9)	0.337
% SB	64%	68%	6.5x10⁻⁰⁸
% LPA	32%	30%	8.1x10⁻⁰⁴
% MVPA	4%	2%	2.0x10⁻¹⁶
Average length SB bout	24.4	25.2	0.005
Average length LPA bout	15.4	15.2	0.364
Average length MVPA bout	10	9.8	0.546
Fragmentation SB	0.03	0.03	0.084
Fragmentation LPA	0.03	0.02	0.022
Fragmentation MVPA	0.05	0.05	1.0x10⁻⁰⁴
% in SB bout	51.00%	55.00%	4.9x10⁻⁶
% in LPA bout	13.00%	11.00%	0.006
% in MVPA bout	2.30%	1.40%	6.4x10⁻¹²

Chapter 11.

Summary and Discussion

Well-being can be described as feeling good and functioning well and is associated with a better mental and physical health and positive effects in daily life (Chapman & Guven, 2016; Lyubomirsky et al., 2005; Maccagnan et al., 2019; Oswald et al., 2015; Steptoe, 2019; Zaninotto & Steptoe, 2019). Due to these protective and positive effects of well-being, the interest in well-being increased exponentially over the past years, in different academic disciplines as well as in the general society. Also, during the period of my PhD, substantial progress into understanding the causes of individual differences in well-being has been made. For example, recent research focused on specific genetic regions in different samples (Baselmans, Jansen, et al., 2019; Kim et al., 2022; Røysamb & Nes, 2019; van de Weijer, Pelt, de Vries, Baselmans, et al., 2022) and specific environmental factors related to well-being (Houlden et al., 2018; Krefis et al., 2018; Krekel & MacKerron, 2021; van de Weijer, Baselmans, et al., 2022). In this dissertation, I aimed to increase the understanding of the etiology of well-being by investigating the neural, physiological, genetic, and environmental causes of individual differences in well-being in detail, by examining the relationship and causality between well-being and related traits, and by investigating the possibility and results of real-time assessment of well-being. In this chapter, I summarize and discuss the main findings of this dissertation, followed by a general discussion and my views on the next steps and future of well-being research.

Summary and discussion

Biology of well-being

Both in the popular media and in the scientific field, questionable claims have been made about the biological basis of well-being and happiness, based on studies with questionable quality and small samples. At the same time, more research on the neural and physiological correlates of well-being has been published in the last years, partly because of rapid technological advancements related to data collection and analysis methods. To investigate the claims and to better understand biological pathways through which well-being arises and can contribute to health, in part I of this dissertation we systematically investigated the involvement of the brain (**chapter 2**) and physiological processes (**chapter 3**) in well-being.

The brain

In **chapter 2** we investigated the association between brain structures or brain functioning and well-being by reviewing all available literature on the neural correlates of well-being. In total, we identified and included 56 studies in the systematic review spanning different brain assessment techniques, including electroencephalography (EEG), structural Magnetic Resonance Imaging (MRI), resting-state functional MRI, and functional near-infrared spectroscopy (fNIRS) studies.

Among the 11 included EEG studies, we observed a relatively consistent finding of a larger alpha activation asymmetry, i.e., more left than right brain activation, in relation to higher well-being. The meta-analysis on five homogenous studies with 11 associations confirmed this small positive relation between alpha activation asymmetry and well-being, resulting in a correlation of 0.19. This association between alpha activation asymmetry and well-being are in line with the often-investigated theory of hemispheric specialization (Davidson, 1995, 1998). This theory proposes that the left brain region is more active in response to positive stimuli and approach-related behaviors, whereas the right frontal region is more active in response to negative stimuli and withdrawal-related behaviors. Therefore, individuals with a relative stronger activation in the left hemisphere are suggested to be oriented toward positive stimuli and emotions, and approach-related behavior, whereas individuals with a relative stronger activation in the right hemisphere are oriented to negative stimuli and emotion, and withdrawal-related behavior (Davidson, 1995, 1998).

The association between alpha activation asymmetry and emotion, mood, or mood-related psychopathology, like depression, has been reported in many studies over the years (e.g., see the reviews of Palmiero & Piccardi, 2017; Thibodeau et al., 2006), but inconsistencies and several methodological confounds have been reported as well (e.g., Jesulola et al., 2015). For example, the location of alpha symmetry in the brain seems to be important and it has been suggested that third variables, like bodily states and hormonal responses, could mediate the relationship between alpha asymmetry and mood or emotion. Hall and Petruzzello (1999) reported, for example, an influence of physical activity on the relation between brain activity asymmetry and affect. An important limitation is the mostly right-handed samples of EEG studies. Whereas this leads to a homogenous group, this selection of right-handed participants also removes variation related to hemispheric brain activation (Willems et al., 2014). Recently, handedness was associated with alpha activation asymmetry, such that stronger right-handedness was associated with stronger right relative to left alpha power (Ocklenburg et al., 2019). Therefore, although the hemispheric

activation theory is relatively often investigated, future research in larger and diverse samples with respect to handedness is needed to confirm alpha activity asymmetry as biomarker related to well-being.

The results of the 18 included structural MRI studies, 26 resting-state fMRI studies, and two fNIRS studies were less consistent. In the different included studies, the size or activity of a wide range of brain regions was associated with well-being, but replication across studies was scarce, both in direction and strength of the associations. In addition, a meta-analysis was not possible because of the large heterogeneity in study designs and reported results.

A possible explanation for the inconsistency in the reported brain-well-being associations is the involvement a wide-spread network of brain regions with small effects in well-being. Most included studies in the review had a small sample size (most *N*s between 15 and 300, with a few studies with larger *N*s, including a maximum of 942 participants), leading to insufficient power to detect such small effects. In line with the recent recognition of the need of very large sample sizes in brain research (Liu et al., 2022; Marek et al., 2022), and similar to the progress made in the past years in genome-wide association studies, we strongly recommend future brain-wide association studies (BWAS) on well-being to include large samples to reliably investigate the associations with the brain.

In a recent successful application of BWAS to measures of cognitive ability and mental health, Marek et al. (2022) showed a widely distributed circuitry of associations between brain areas and these measures in a sample of more than 10 thousand participants. These patterns indicate the involvement of many brain areas not detected in studies with the typical smaller sample sizes. Another example of a worldwide collaborative network on brain studies is the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) consortium. The ENIGMA consortium includes more than 100 thousand participants from 45 countries and focuses on the associations between the brain and psychopathology (Thompson et al., 2014). For Major Depressive Disorder (MDD), this consortium has led to reproducible results, including a smaller hippocampal volume, lower cortical thickness in the cingulate cortex, bilateral medial OFC and insula in MDD participants ($n=1,728$) compared with healthy controls ($n=7,199$) (Schmaal et al., 2020). Similarly, for other psychopathology, including ADHD, bipolar disorder, and schizophrenia, more robust brain correlates have been found in large ENIGMA samples (Ching et al., 2022; Hoogman et al., 2022; Walton et al., 2018). Our systematic review of the neural correlates of well-being revealed, at the moment, no consistent associations. The relation between well-being and the brain needs future

powerful brain-wide research to understand the neural pathways of well-being and to be able to develop more targeted approaches to maximize well-being in the future.

Physiology

Besides the brain, many other physiological processes are thought to be involved in well-being. Therefore, in **chapter 3**, we reviewed the literature on the human physiology of well-being. Across four physiological systems, i.e., neurotransmitters, hormones, inflammatory markers, and the microbiome, we performed a systematic review and, if possible, a meta-analysis on the association between the different factors and well-being. We identified and included a total of 91 studies across the physiological categories in the review. Only a few studies were found on the association between well-being and respectively neurotransmitters and the gut microbiome. The nine neurotransmitter studies reported a relatively consistent positive association between serotonin and well-being, but no consistent associations with other neurotransmitters. The four microbiome studies reported inconsistent associations between different bacteria abundance and well-being. In these fields, more studies are needed before we can draw any reliable conclusions.

More research is available that investigates well-being in relation to immune system activity and hormone levels. The results of the systematic review led to more consistent results in these categories. The 36 inflammatory marker studies reported either negative or non-significant relations of different markers with well-being. Meta-analytic estimates indicated a small negative association between C-reactive protein ($r = -.06$) and interleukin-6 ($r = -.04$), and well-being. In the larger field of immune system activity and mental health, consistent positive associations between depression and immune system activity have been found as well (Amodeo et al., 2018b; Dantzer, 2012). The proposed mechanisms underlying these association have been investigated and include the following options. First, depression could precede inflammation, where depression is related to immune system activity via the influence that the brain has on the immune system (Gimeno et al., 2009; Liu et al., 2019). Vice versa, inflammation could precede depression, such that the depressive symptoms causes a change or impairment in the immune system and immune response (Copeland et al., 2012). Alternatively, the mechanism could be indirect, via, for example, stress. Stress plays a role in both the risk for depression and the immune response. Therefore, exposure to stressful conditions could be the common factor increasing both inflammatory markers and the likelihood of depression (García-Bueno et al., 2008; Müller et al., 2019).

Similar mechanisms might play a role in the association between the immune system and well-being. As research to the relation between immune activity and well-being is a relatively new, these hypotheses require further research because. To conclude, the results of our systematic review provide evidence for the association between immune system activity and well-being, but the mechanism underlying the association remains unknown and is an area for future research.

According to the results of the 48 hormone studies, only cortisol was related consistently to well-being. Lower momentary levels of cortisol (meta-analytic $r = -.10$) and steeper diurnal slope of cortisol, were related to higher levels of well-being. Similar to the proposed mechanisms underlying the association between the immune system activity and well-being, the association between cortisol and well-being can either be due to cortisol leading to lower well-being or vice versa. Alternatively, the indirect mechanism via stress is plausible as well, as stress is strongly related to both cortisol levels and well-being (Chida & Steptoe, 2009; Kirschbaum & Helhammer, 2000). Also in this field, the mechanism underlying the association between cortisol and well-being needs future research.

The results of the systematic review and meta-analyses indicate potential physiological correlates of well-being in some physiological systems, i.e., serotonin, inflammatory markers, and cortisol. However, as some associations are based on a few studies only, more and innovative research is needed to replicate these associations and get a complete picture of the physiological factors underlying well-being and validation of useful and reliable biomarkers. Interestingly, dopamine and oxytocin, i.e., the most often mentioned markers in the popular media in relation to well-being, were rarely or not at all investigated in the included studies. Future directions for research include combining multiple physiological markers across the different categories in a single large study, like a multi-omics approach (Hasin et al., 2017), and investigating the mechanisms underlying the associations, including causality analyses, such as longitudinal (intervention) studies and Mendelian Randomization studies (Smith & Ebrahim, 2003).

We investigated the brain and physiology of well-being in two separate systematic reviews and meta-analyses. However, besides the interplay of the different physiological processes, the brain is involved in the transmission of neurotransmitters and hormones and there is a strong interplay between the brain and both the immune system and the gut microbiome as well (Collins et al., 2012; Dantzer, 2017). Therefore, investigation of the brain and different

physiological processes in relation to well-being should ideally be combined to get the complete picture of the biology underlying well-being.

To summarize, in part I of this dissertation, we brought together all published studies on the neural and physiological factors underlying well-being. This overview allowed us to critically investigate the claims made about the biology involved in well-being. The reviews showed that the number of studies on the neural and physiological factors underlying well-being is increasing and the studies point towards potential correlates of well-being. However, samples are often still small, and studies focus mostly on a single biomarker. Therefore, following the example of genetic consortia, more well-powered, data-driven, and integrative studies across biological categories are needed to better understand the neural and physiological pathways that play a role in well-being.

Genetic overlap of well-being and related phenotypes

Well-being is a complex and multifaceted construct that is related to different phenotypes. This overlap with other phenotypes can help us gain insights in the etiology of well-being. In part II of this dissertation we therefore investigated the (genetic) association between well-being and different phenotypes in detail.

In **chapter 4**, we applied bivariate twin models in a large sample of adolescent twins to disentangle the association between well-being and four complex traits, i.e., optimism, anxious-depressed symptoms, aggressive behaviour, and educational achievement. Phenotypically, optimism and anxious-depressed symptoms showed respectively a strong positive and negative correlation with well-being, whereas the negative correlation of well-being and aggressive behaviour was lower and the correlation with educational achievement was nearly zero. While the phenotypic correlations differed, all four traits showed a large bivariate heritability with well-being, indicating that genetic factors explain a substantial part of the phenotypic correlation. The genetic correlation (i.e., the overlap in genetic factors influencing the phenotypes) of well-being with optimism and anxious-depressed symptoms was strong and smaller for aggressive behaviour and educational achievement.

The results of bivariate twin models can have important clinical implications. The genetic correlates indicate that the genetic influences, and therefore the biological mechanisms underlying well-being and optimism, or anxious-depressed symptoms are more similar than those underlying well-being and aggressive behaviour, or educational attainment. The similar biological mechanisms for well-being and anxious-depressed symptoms suggest that people at risk for psychopathology may be identified based on their well-

being before any symptoms develop. Furthermore, interventions to increase well-being and decrease anxious-depressed symptoms at the same time could be effective. In contrast, the more distinct biological mechanism for well-being and aggressive behavior suggests that an intervention to increase well-being and decrease aggressive behavior at the same time is most likely not effective.

Well-being is also strongly related to resilience, i.e., the ability to recover after the experience of stress or trauma, returning to an optimal mental state (Bajaj & Pande, 2016; Hu et al., 2015; Satici, 2016). In **chapter 5**, we investigated the relation between well-being and resilience in a large sample of more than 14 thousand twins and siblings from the Netherlands Twin Register. We used data from two time points and a range of different methods. We replicated the strong phenotypic correlations between well-being and resilience ($r = .41$ and $.51$ at time 1 and 2 respectively). Polygenic score predictions indicated that genetic factors influencing well-being also predicted resilience. Twin-sibling modeling confirmed this genetic correlation ($r_g = .71$) and showed a strong environmental correlation ($r_e = .93$). The results of within-subject and MZ twin differences analyses, which control for genetic confounding, were in line with bidirectional causality. The MR-DoC model, which explicitly tests causality, confirmed the causal effect from well-being to resilience, with the direct effect of well-being explaining 11%-20% of the variance in resilience. We could not test the directional effect from resilience to well-being because there was no strong GWAS for resilience available.

We used a triangulation approach with multiple designs that each have different strengths and weaknesses in testing the overlap or causality between well-being and resilience. This triangulation resulted in more robust evidence for the relation between well-being and resilience and potential bidirectional effects. Since resilience and well-being are both negatively related to psychopathology, the results can be used for interventions to lower psychopathology vulnerability after the experience of stressful life events.

In the field of resilience, there is ongoing discussion about the measurement and operationalization of resilience. In line with other resilience research, we used an outcome-based measure of resilience, based on the residuals approach (see for example Amstadter et al., 2014; Kalisch et al., 2021; van Harmelen et al., 2020; Veer et al., 2021). We computed resilience as the residual score of the regression of depressive symptoms on the total number of stressful life events experienced. Resilience is thus defined as the difference between the predicted level of depressive symptoms based on the number of life events experienced and the actual depression level. Prerequisite for the residuals approach is a linear relation between the number of stressful life events

experienced and the depressive symptoms score. Recently, Cahill et al. (2022) showed that this method of operationalizing resilience has good construct and predictive validity. However, when checking the literature, we found that in most cases of applying the residuals approach, including in chapter 5, the explained variance of depressive symptoms by the stressful life events is very small (<10%). In these cases of small explained variance, the residuals approach leads to a high correlation between the residual measure (i.e., resilience) and the outcome measure (i.e., depressive symptoms), because only a very small part is removed from the outcome measure. Therefore, our results of chapter 5 should be interpreted cautiously and replicated with stronger and multiple measures of resilience that differ more from depressive symptoms.

Depressive symptoms and well-being are strongly related as well, both phenotypically and genetically (Bartels et al., 2013; Baselmans et al., 2018; Baselmans & Bartels, 2018; Greenspoon & Saklofske, 2001; Okbay et al., 2016). Because of the overlap, in the past, well-being and depressive symptoms, have been considered as opposite ends of a continuum, i.e., fewer depressive symptoms indicate higher levels of well-being, and vice versa. Nowadays, well-being and ill-being are seen as distinct, but related domains of mental health. In **chapter 6**, we investigated the overlap between depressive symptoms and two forms of well-being, i.e., happiness and meaning in life, in more detail compared to earlier studies to explore what is unique to well-being and not shared with depressive symptoms. Using a GWAS-by-subtraction approach (Demange et al., 2021), we focused on the genetic part that makes well-being unique by subtracting a depressive symptoms GWAS ($n=427,580$) from happiness and meaning in life GWASs. The subtraction led to GWASs of respectively “pure happiness” ($n=216,497$) and “pure meaning” ($n=102,300$). Both for pure happiness and pure meaning, we identified one genome-wide significant SNP (rs1078141 and rs79520962, respectively). The SNP heritability reduced from 6.3% to 3.3% (48%) for pure happiness and from 6.2% to 4.2% (32%) for pure meaning after the subtraction of the depressive symptoms GWAS. Furthermore, the genetic correlation between happiness and meaning reduced from .78 to .65, indicating that the largest part of genetic etiology of happiness and meaning in life is still shared, independently from depressive symptoms.

Testing the genetic correlations with a range of other traits, pure happiness and pure meaning became genetically unrelated to traits related to depressive symptoms, such as tiredness, loneliness, and health satisfaction. The (genetic) associations of well-being with these depression-related traits are therefore mostly likely to arise from the overlap between depressive symptoms and well-being and should be interpreted in light of these findings.

For several other traits, including income, educational attainment, smoking, and alcohol intake frequency, the genetic correlations changed substantially or became reversed after subtracting depressive symptoms, indicating unique genetic associations of pure well-being, independently from depressive symptoms. Pure well-being became genetically associated to a lower income, educational attainment and intelligence, and a higher predisposition for smoking, drinking alcohol, and eating. These changed or reversed genetic correlations of well-being versus pure well-being indicate that the genetic variance of well-being can be split into two parts having different associations with the other traits. One part can be seen as the opposite of depressive symptoms, in line with aforementioned continuum, whereas the other part is unique and unrelated to depressive symptoms.

These results can lead to new insights about well-being. For example, we propose that the reversed genetic correlations for well-being versus pure well-being and smoking and drinking alcohol are a result of the different underlying reasons why people smoke and drink. The genetic overlap between the part of well-being that is shared with depressive symptoms and these traits can arise from self-medication, i.e., smoking, and drinking to cope and increase well-being and reduce negative mood and other depressive symptoms (Armeli et al., 2018; Hooshmand et al., 2012; Kuntsche et al., 2005; Lazarevich et al., 2016; Magee & Clarke, 2021). In contrast, the smoking and drinking that is genetically related to pure well-being (i.e., unrelated to depressive symptoms) could arise from these behaviors in social settings. Higher pure well-being could be genetically related to more social smoking and drinking by going out more often or being more often in the company of other people. Future research is needed to investigate the specific associations and conditions in which well-being is related to substance use.

As another example, a possible explanation for the negative genetic correlation between pure well-being and income could be that people with a higher genetic predisposition for pure well-being have also a genetic predisposition for working less hours or less stressful jobs, i.e., often resulting in lower income. This genetic overlap suggests that people with a higher pure well-being also find income less important and instead choose jobs based on meaning, or interests, such as jobs related to creativity. Similarly, individuals with a genetic predisposition for pure well-being could also be more likely to choose part-time jobs over full-time jobs to have more free time, for example to spend more time with their family, resulting in lower income. Future research is needed to investigate these hypotheses.

These results led to new insights about well-being and can have important implications for preventions to maintain high well-being and interventions to increase well-being and/or decrease depressive symptoms. Based on our results, different associations of well-being should be taken into account depending on the goal of the interventions. If the goal is to decrease depressive symptoms as well as increase well-being, the overlap between depressive symptoms and well-being should be taken into account. Therefore, such interventions should focus on variables that are related to both depressive symptoms and well-being in the opposite direction. However, interventions to increase well-being specifically can focus on other associations as well, as indicated by the genetic correlates of pure well-being. More research to the specific circumstances when and where well-being is related to other traits is needed to replicate our findings.

In part II of this dissertation, we investigated the overlap between well-being and a range of other phenotypes to learn more about the etiology of well-being. We report a large overlap with phenotypes including optimism, resilience, and depressive symptoms. Furthermore, when removing the genetic overlap between well-being and depressive symptoms, we showed that well-being has unique genetic associations with a range of phenotypes, independently from depressive symptoms. These results can be helpful in designing more effective interventions to increase well-being, taking into account the overlap and possible causality with other phenotypes.

The effect of an extreme environment on well-being

The COVID-19 pandemic resulted in a unique period that largely impacted the course of my PhD project. However, the pandemic and resulting lockdowns also allowed us to study the effects of the extreme environmental change on well-being. The pandemic can be seen as a natural experiment, as it is a universal exposure that affects everyone, but to different degrees. In part III of this dissertation, we investigated the individual differences in the effect of the pandemic and lockdown in different phases of the pandemic on several aspects of well-being.

In **chapter 7**, we leveraged the longitudinal data base of the Netherlands Twin Register to investigate the gene-by-crisis interaction for optimism and meaning in life during the first phase of the pandemic. Adults completed surveys before (N=9964) and during the first months of the pandemic (i.e. April-May 2020, N= 17464), with a subsample completing both surveys (N=6461). We observed the expected individual differences in the effect of the pandemic on optimism and meaning in life. Part of the sample (56% and 35% for optimism and meaning in life respectively) was negatively affected by the pandemic.

Especially women, higher educated people, and people with poorer health showed lower optimism and meaning in life during the pandemic. However, a large part of the sample was stable (32% and 43%) or even showed increased optimism and meaning in life (11% and 22%).

Additionally, we observed a change in the genetic architecture of optimism and meaning in life. During the pandemic, optimism and meaning in life were slightly less heritability (respectively 20% and 25%) compared to pre-pandemic (respectively 26% and 32%), indicating that the environment plays a larger role in explaining the individual differences in optimism and meaning in life during the pandemic. The lower than unity genetic correlations across time (.75 and .63) suggest gene-environment interactions as well, indicating that the genes that influence optimism and meaning in life partly differ before and during the pandemic. We conclude that the COVID-19 pandemic is a strong exposure that leads to imbalanced effects on the well-being of individuals. These differences are partly explained by individual differences in the sensitivity to extreme environmental change.

The pandemic did, unfortunately, not end after the first lockdown. Across the world, multiple waves of COVID-19 infections occurred, leading to prolonged restrictions and multiple lockdowns. Investigating the effect of later lockdowns on well-being can help to understand more prolonged effects of extreme situations, and inform policy with regard to expected psychological impact of future lockdowns. In **chapter 8**, we investigated the effect of the second lockdown in the Netherlands on daily aspects of well-being, i.e., daily affect intensity and variability. We used data of a 100 day daily diaries study (Bülow et al., 2020), including data of adolescents ($N=159$, $M_{age}=13.3$) and one of their parents ($N=159$, $M_{age}=45.3$). Using preregistered piecewise growth models, we investigated how daily well-being changed after the onset and during the lockdown.

We found, on average, an unexpected increase in parents' positive affect intensity directly after the lockdown onset. We hypothesise that this is the result of clarity about the lockdown and restrictions after a period of uncertainties due to the spread of the disease and the possible consequences such as closing of schools and working from home. There were no immediate changes in negative affect intensity or variability. However, both adolescents and parents did show gradual increases in negative affect intensity and variability as the lockdown prolonged. Yet, similar to chapter 7, we observed large individual differences in almost all effects. These individual differences in the effects were partly explained by life satisfaction, depressive symptoms, and self-reported impact of the lockdown on daily life. For example, adolescents with higher baseline

life satisfaction showed less decrease in positive affect during the lockdown and parents with more baseline depressive symptoms experienced stronger increases in negative affect intensity during the lockdown. Our findings suggest that the second lockdown in the Netherlands triggered gradual changes in affective well-being during the lockdown period, but there are individual differences in the size and direction of the impact of the lockdown on daily affect. In policies to limit the effect of future lockdowns on well-being, these individual differences and gradually emerging average negative effects should be taken into account. For example, as lockdowns need to be put in place longer than anticipated, increased monitoring for mental health issues is advisable, especially for individuals and groups at risk.

In part III of this dissertation, we showed the consequences of an extreme environmental change on well-being during different phases of the pandemic. On average, we found a negative effect of the pandemic on different aspects of well-being, especially further into the pandemic. Whereas most previous studies only looked at this average negative effect of the pandemic on well-being, we focused on the individual differences as well. We reported large individual differences in the effects of the pandemic on well-being in both chapters. This indicates that one-size-fits-all preventions or interventions to maintain or increase well-being during the pandemic or lockdowns will not be successful for the whole population. Further research on individuals and groups that are stable or increased in well-being during the pandemic and lockdown is needed for the identification of protective factors and resilience mechanisms to prevent further inequality during extreme environmental situations.

Real-time assessment

In well-being research, the majority of studies make use of general well-being questionnaires that are completed by participants at a single time point. However, like many complex human traits, momentary feelings of well-being fluctuate over time and across different contexts (Eid & Diener, 2004; Li et al., 2014; Lyubomirsky, 2001). To capture the fluctuations and dynamic nature of well-being, real-time assessment is needed, for example by applying an Ecological Momentary Assessment (EMA) design or daily diary design. This method is not new, already in the 1920's and 1930's, a diary method was used to assess mood in daily life (Dysinger, 1938; Favill & Rennick, 1924; Flügel, 1925). However, recently, the interest and application of EMA and daily diary studies increased due to rapid technological progression in the last few years.

Nowadays, smartphone applications can be used to collect data in real-time and daily life more easily (Runyan & Steinke, 2015).

To investigate the feasibility of collecting well-being data in real-time and the real-time associations of well-being with different variables, we reviewed all smartphone-based EMA studies of well-being in **chapter 9**. We identified and included 53 studies that were heterogeneous in designs, context, and measures. The average study duration was 12.8 days, with well-being assessed 2-12 times per day. Half of the studies included objective data (e.g., location or physical activity). The studies had widely different research questions and results. Studies reported well-being to fluctuate both daily and weekly, with higher well-being in evenings and weekends. These fluctuations disappeared when location and activity were accounted for. Furthermore, on average, being in nature and being physically active relates to higher well-being, whereas sedentary behavior and working relates to lower well-being, but the workplace and the company you are with play a role as well. We concluded that smartphone-based EMA research is feasible to gain insight in well-being fluctuations and its determinants. Most reviewed studies investigated only the average effects of environmental factors on momentary or daily well-being or looked at group comparisons. However, to get more specific knowledge about the fluctuations of well-being and what makes people happy, future studies should focus on the individual differences in well-being patterns and fluctuations.

Physical activity and sedentary behaviour are two of the passively assessed variables associated with well-being in real-time and daily life when assessed with accelerometers (Panza et al., 2019). In **chapter 10**, we used accelerometer data and well-being data of an NTR sample ($n=660$, M_{age} : 30.4, $SD=8.1$, 74.5% female) to investigate the relation between well-being and real-time physical activity (PA) and sedentary behaviour (SB) in more detail compared to previous studies, including the timing and accumulation patterns of PA and SB. In total wear time, we found no associations between different measures of accelerometer-assessed PA or SB and well-being. Restricting to non-occupational wear time, less total SB and more total light PA were associated with higher well-being, both in absolute and relative sense. Well-being was not associated with the PA/SB timing or patterns. In conclusion, beyond the association between total non-occupational SB and LPA and well-being, the PA/SB timing or patterns had no added value in explaining the association between PA/SB and well-being.

Based on part IV of this dissertation, we can conclude that the real-time assessment of well-being, related variables, and the environment can lead to new insights about well-being, i.e., results that we cannot capture with

traditional survey research. As discussed in more detail below, the real-time assessment of well-being is a promising area for future research to further unravel the dynamic nature of well-being fluctuations and the interaction with the environment in daily life.

General discussion

In this dissertation, we provided new insights in the neural, physiological, genetic and environmental influences on well-being. The results pointed towards directions for future research. Below I discuss the promising directions of future research on well-being, including the need for more data-driven research, investigating the interplay between factors influencing well-being, and the real-time assessment of well-being. Finally, I discuss the importance and implications of well-being research and end with a general conclusion.

Data-driven research

Many studies in the well-being field focus on one variable, i.e., one physiological marker or one environmental variable, in relation to well-being. While this can lead to detection of significant associations between well-being and that variable, this pick-and-choose strategy of one variable can also lead to inconsistent or non-reproducible results, as was shown in **chapter 2** and **chapter 3**. To prevent unreliable results from this kind of hypothesis testing, first strong and testable theories have to be developed, using data-driven approaches and large enough samples (Scheel et al., 2020). Therefore, I believe the future for well-being research is a more data-driven approach, both within and across disciplines.

An example of such a successful transition to data-driven approaches in the field of well-being is transition from candidate-gene studies to Genome-Wide Association studies (GWAS). In 1996, Hamer predicted that well-being would be influenced by around ten to twenty genetic variants. To increase the likelihood to find these specific variants, he proposed to investigate the association between well-being and genetic loci that are chosen based on their function, i.e., candidate genes (Hamer, 1996). In candidate gene studies, a single or few genes hypothesized to play a role in well-being are selected and investigated in relation to well-being. However, as we know nowadays, single genetic variants have tiny effects on phenotypes, indicating a need for very large samples. The small sample size of the candidate gene studies has led to many false positive findings for well-being, depression, and other complex traits (Border et al., 2019; van de Weijer, Pelt, de Vries, Baselmans, et al., 2022). To systematically identify genetic variants associated with complex

traits, Genome-Wide Association Studies (GWAS) emerged and quickly became successful in detecting genetic variants across the genome associated with the traits of interest (Visscher et al., 2012). As discussed in **chapter 1**, applying such a data-driven approach including the entire genome has been successful in identifying genetic variants associated with well-being (Baselmans, Jansen, et al., 2019; Kim et al., 2022; Okbay et al., 2016). As the sample sizes of GWASs increase, more genetic variants associated with well-being can be expected as well. Comparing the results of the earlier candidate-gene studies to the GWAS results of well-being, we reported no support for any of the candidate genes (van de Weijer, Pelt, de Vries, Baselmans, et al., 2022). This result indicates the importance of data-driven research before selecting a single or a few variables on the basis of theory and hypotheses.

A similar data-driven trend emerged recently for environmental factors related to complex traits. The first systematic investigation of environmental factors influencing well-being, i.e., an Environment-Wide Association Study (EnWAS), was performed recently (van de Weijer, Baselmans, et al., 2022). In contrast to investigating a single or few environmental variables with a hypothesized effect on well-being, van de Weijer and colleagues (2022) used a data-driven approach with the inclusion of 139 neighborhood-level environmental exposures. The systematic study indicated 21 environmental factors significantly associated with well-being. Of these factors, socioeconomic status and neighborhood safety were the most important environmental factors in explaining individual differences in well-being.

These data-driven approaches have been proven successful to detect genetic and environmental associations with well-being, without a-priori hypotheses. In other disciplines, including neuroscience and physiological research, the need for large samples and designs to get to reliable and reproducible results became increasingly important as well in the last few years. As discussed by Marek et al. (2022), brain-phenotype associations are smaller than previously expected, indicating the need for large sample sizes and systematic detection of associations. Following the GWAS approach, Brain-Wide Associations Studies (BWAS) with very large sample sizes are needed to reliably detect brain-phenotype associations. In **chapter 2** of this dissertation, we showed that well-being is a complex trait that is likely influenced by a wide-spread network of brain regions that each have a small effect on well-being. Consistent associations between the brain and well-being have not been detected yet, and large BWAS studies are needed.

Similarly, most research on physiological markers in relation to phenotypes is based on a a-priori hypothesis or theory. Associations between physiological

markers and behaviors or complex traits have recently been investigated more systematically and, similar to the candidate-gene literature, evidence for the hypothesized markers is found to be inconsistent and irreproducible. Taking depression as example, the serotonin theory of depression was recently investigated in a large systematic umbrella review (Moncrieff et al., 2022). Across all studies and reviews, no consistent evidence of an association or causal effect between serotonin and depression was found. Similarly, a large review across multiple biological markers for depression, including neuroimaging factors, gastrointestinal factors, immunology, neurotransmitters, and hormones, reported no consistent evidence for the physiological theories and hypotheses for depression (Kennis et al., 2020). Resembling the mostly inconsistent results of our review of well-being in **chapter 3**, most associations of depression with physiological markers were inconsistent. These findings highlight the need to first identify potential factors influencing the phenotype in large data-driven studies, before hypothesis-based testing of the association between specific biomarkers and well-being. The field of biological markers in relation to well-being should therefore shift towards data-driven approaches as well.

Interplay of factors influencing well-being

As discussed throughout this dissertation, well-being is a complex trait influenced by many different factors, including a range of neural, physiological, genetic, and environmental factors. However, while these factors are often only investigated within the single categories, i.e., only investigating genetic factors or environmental factors in relation to well-being, these factors can be expected to interact across categories as well. Investigating this interplay of different factors influencing well-being is needed in future studies to get to a more complete picture of the factors underlying well-being.

For example, a few studies have investigated and reported gene-environment interactions for well-being, in which the genetic influence on well-being depends on the environment. Nes et al. (2010) reported a moderating effect of marriage on the genetic influence on well-being, where the heritability of well-being is lower for those who are married compared to non-married individuals. Genetic predisposition for well-being is thus of lower importance when married and the environment has a larger effect. Related, Domingue et al. (2017) investigated the interplay of genes and environment following a spouse's death using polygenic scores. A higher well-being polygenic score (i.e., sum of genetic effects) protected against increased depressive symptoms and decreased well-being after the spouse's death. Another interaction has been found for financial resources, such that the heritability of life satisfaction

increases with increasing income (Johnson & Krueger, 2006). The well-being of individuals with more money is influenced more by genetic effects and less by environmental influences compared to less wealthy individuals. Furthermore, in **chapter 7**, we observed a gene-by-crisis interaction on well-being, with COVID-19 as the extreme environmental influence. We observed lower than unity genetic correlations before and during the pandemic, indicating partly different genes influencing well-being before and during the pandemic. Similar effects of changing heritability of well-being during the COVID-19 pandemic have been reported in other studies as well (van de Weijer, Pelt, de Vries, Huider, et al., 2022; Warmerdam et al., 2022). However, no change in the heritability of well-being due to the pandemic has been reported as well (Rimfeld et al., 2021). These effects of changing heritability estimates across different environments and situations indicate that the influence of genetic factors on well-being interact with or depend on the environment.

Furthermore, genes and the environment are expected to interact with neural and physiological processes as well. For example, in depression, genetic factors are thought to be associated with the function and structure of neural areas, which are related to different physiological processes as well (Cernackova et al., 2020; Tafet & Nemeroff, 2016; Tozzi et al., 2018). Furthermore, the environment can influence neural processes. For example, the effect of being in nature on positive and negative affect has been related to the amount of prefrontal activity (Tost et al., 2019). Research into these interactions of genes, environments, neural factors, and physiology is just starting, but is expected to lead to new insights about complex phenotypes. To summarize, individual differences in well-being are most likely to arise through the complex interplay of neural, physiological, genetic, and environmental factors. To further understand well-being, interdisciplinary research is needed to this interplay of factors by investigating the different factors simultaneously, instead of one by one.

Real-time assessment of well-being

A different promising area for future research is the measurement of well-being. As discussed throughout this dissertation, most research on well-being includes questionnaires at a single time point. Whereas this has the advantage of being able to reach large sample sizes, the interest in the dynamic nature of well-being in real-time and daily life is increasing as well. An example of real-time assessment methods that can capture the fluctuations and can be applied to well-being is Ecologically Momentary Assessment.

In **chapter 9**, we reported that smartphone-based Ecological Momentary Assessment (EMA) research is feasible to gain insight in well-being fluctuations and its determinants in real-time and daily life. However, studies on individual differences in well-being patterns and daily life fluctuations are still scarce and results are inconclusive. For example, the heritability of momentary well-being (e.g., positive affect or happiness in the moment) has been assessed a few times in small twin samples. Riemann and colleagues measured positive and negative affect across five different mood-inducing situations in 300 twin pairs. The estimated heritability of momentary positive affect was small across the different situations, around 5-20% (Riemann et al., 1998). Menne-Lothman et al. investigated momentary positive affect in female twins (N=260 twin pairs) in a real-life setting using the experience sampling method (Menne-Lothmann et al., 2012). Positive affect ratings were averaged for each person across the 50 measurements to a single score of momentary positive affect. Genetic influences on this rough average momentary positive affect did not reach significance, with a heritability of 19% (95% CI = .00, .50). Zheng et al. (2016) assessed daily positive affect in 275 twin pairs for a month and reported a non-significant heritability estimate for the average daily positive affect as well (18%, 95% CI = .00, .56). Finally, in a daily diary study of 237 twin pairs, genetic influences on daily positive affect were found to be significant, around 25% (Burt et al., 2015).

Furthermore, individual differences in well-being and mood fluctuations have been reported as well. Some people show relatively stable levels of well-being over the day and/or week, while others fluctuate more (Eid & Diener, 1999; Gadermann & Zumbo, 2007; Röcke et al., 2009). The recent application of intensive longitudinal designs to samples of twins allows to examine genetic influences on the variability or fluctuations in positive affect as well. Using the experience sampling design for five days in 279 twin pairs, Jacobs et al. (2013) reported a heritability estimate of 18% for positive affect variability. In the daily-diary design, Zheng et al. (2016) reported a heritability estimate of 34% (95% CI = .17, .48) for positive affect variability, indicating that genetic factors influence individual differences in well-being and mood fluctuations. However, recently, in a daily-diary study, a non-significant heritability of 9% (0–0.25) was reported for positive affect inertia, i.e., the extent to which individuals' emotions carry over from one time point to the next (Zheng & Asbury, 2019).

The inconclusive findings and large confidence intervals for the heritability of momentary positive affect, affect fluctuations and variability, and other momentary measures of well-being indicate the need for future real-time well-being research in larger twin or other genetically informative samples.

Intensive longitudinal studies, like EMA studies, can be helpful to investigate the dynamic nature of well-being in relation to the environment and other time-varying variables. In previous studies, mostly the average effects of these variables, e.g., physical activity, being in nature or working on well-being, are reported, not taking into account individual differences.

In an ongoing EMA study, we plan to investigate these individual differences in well-being fluctuations, real-time wellbeing, and the effect of the dynamic (social) environmental exposures on well-being. We invite a large sample of genotyped twins of the Netherlands Twin Register to participate in a smartphone EMA study. The study tracks adult twin pairs ($n=1500$ participants, 300 monozygotic (MZ) twin pairs and 450 dizygotic (DZ) twin pairs) in their daily life, using questionnaires and passive sensing via a smartphone application. The twins are invited to participate for 7 consecutive days, 4 times a year (each season), to capture both daily, weekly and seasonal effects. The EMA approach includes eight assessments of well-being, positive and negative affect, whereabouts, and social interactions per day. The continuous passive sensing includes data of the (social) environment, phone use, and physical activity. A subset of 600 participants receives Bluetooth beacons to supply to individuals in their social network (e.g., friends, co-twin) to objectively assess proximity of these individuals on a daily basis.

This genetically informative longitudinal design and combination of active and passive data of well-being and the environment will result in a large dataset with many variables. Applying different statistical methods and analyses, including time series analyses and (personalized) machine learning approaches, this can lead to new insights about the dynamic nature of well-being and causes of individual differences in fluctuations of well-being. For example, we plan to estimate the heritability of momentary well-being and well-being fluctuations using the difference in genetic overlap of MZ twins and DZ twins. To investigate the genetic and environmental influences on the within-person processes, we plan to apply the recently developed Multilevel Dynamic Twin Models (Schuurman et al., 2022). Furthermore, to investigate the interaction between momentary well-being and environmental variables, phone use, and physical activity, we plan to use (personalized) machine learning approaches. Finally, the genotyping of the twins enables us to investigate the interaction of genetic factors and the momentary environmental variables on well-being as well. To conclude, I believe this real-time assessment of well-being in a large twin sample is the next step to acquire more knowledge and insight in the individual differences in real-time well-being.

Importance of well-being research and implications

Well-being is related to lower levels of psychological problems, such as depressive symptoms and anxiety disorder. Furthermore, the positive effects on daily life, longevity, marriage, work productivity, and many other areas indicate that increasing and maintaining well-being reduces the economic and health care burden of societies. Research into the determinants and correlates of well-being is therefore important for society as well. For example, the recent extreme events and crises around the world, including the COVID-19 pandemic, increased conflicts, such as the war in Ukraine, and the consequences of climate change, including extreme drought and food shortage in many countries, highlight the importance of mental health and well-being in society. The stressful life events resulting from increased conflicts and the pandemic exaggerated the already existing challenges of inequality and mental health in the world.

On average, mental health problems increased and well-being decreased in response to the pandemic, as shown in recent reviews and meta-analyses (e.g., Aknin et al., 2022; Robinson et al., 2022), as well as in this dissertation (**chapter 7** and **8**). Fortunately, at least in the investigated western countries, most people are found to be resilient after the experience of stress and trauma (Galatzer-Levy et al., 2018) and returned relatively quickly to their baseline levels of well-being after the first phase and lockdown ended (Robinson et al., 2022). There is even a part of the population that increased in well-being during the pandemic. An explanation for this stability or increase in well-being could be the forced pause from a stressful, busy life and more time to focus on social connections during the pandemic (Mancini, 2020).

However, different groups, especially women, individuals who are younger, have a lower socio-economic status, or already coping with low well-being and/or mental health problems, are at risk, reporting larger adverse effects of the pandemic. These risk groups and less resilient people need extra help or interventions to maintain or increase their well-being levels. We showed large individual differences in the effects of pandemic on well-being, therefore in these interventions, a one-size-fits-all approach is likely not effective. As discussed in more detail below, interventions should be personalized and be tailored to individuals or to groups with certain characteristics to effectively maintain or increase well-being levels in individuals at risk.

Similarly to the pandemic, the climate crisis is an existential threat to our world and especially youth have been found to be affected in their mental health and well-being because of climate change (Clemens et al., 2022; Sanson & Bellemo, 2021; Sciberras & Fernando, 2022). Besides the direct effect of

climate change, i.e., natural disasters, on mental health and well-being, mental health is affected by indirect effects as well, including anxiety about the future, distress, and feelings of hopelessness and anger (Cianconi et al., 2020; Fritze et al., 2008; Léger-Goodes et al., 2022). It has been suggested that the rise in mental health problems and decreased well-being in children and adolescents (Collishaw, 2015; Pitchforth et al., 2019) is partly explained by the worry, fear, and anxiety youth experience about the impact of climate change on their future lives (Amnesty International, 2019; Bolton & Bhugra, 2020). Again, especially individuals with a lower well-being and resilience might be affected by the anxiety and extreme environmental events on their well-being and mental health, because of difficulties to prepare or adapt to the new circumstances. Therefore, research into the determinants of well-being and the individual differences in the effects of such crises on well-being is needed as well to develop effective (personalized) well-being interventions to prepare individuals for future adverse events and stressful circumstances.

Types of interventions that are designed to specifically increase well-being, instead of just reducing psychopathological symptoms, are positive psychology interventions (Seligman & Csikszentmihalyi, 2000). Well-known examples of positive psychology interventions include practicing gratitude or forgiveness, being kind to others, writing about positive, meaningful or successful experiences, and finding flow. Two recent systematic reviews and meta-analyses investigated the effectiveness of positive psychology interventions (Carr et al., 2021; van Agteren et al., 2021). Across 47 studies involving over 72 thousand participants, Carr et al. (2021) reported significant small to moderate effects of the interventions by increasing well-being, and, at the same time, decreasing depression and anxiety symptoms. Furthermore, van Agteren et al. (2021) reported moderate effects of positive psychology interventions as well, but the evidence quality was generally low to moderate across the studies. The significant effects indicate that positive psychology interventions can be used to prevent low well-being or as a treatment strategy to increase well-being and decrease depression and anxiety symptoms.

However, despite the significant effects, the conclusions of these reviews on the effectiveness of positive psychological interventions are based on the average effects across large samples, and do not take into account individual differences in the effects. For example, a gratitude type of intervention can be effective for one individual, whereas this does not work for another individual that benefits more from another intervention. Future research to well-being interventions should therefore take a personal approach into account, similar to the rapidly advancing health care field of personalized medicine.

In personalized medicine, different sorts of information of the individual, including clinical, genetic, and environmental information, are taken into account to create an integrated and personalized approach to health care (Chan & Ginsburg, 2011; Vicente et al., 2020). The goal of personalized medicine is to use this person-specific information to optimize preventive strategies and the treatment of diseases. For example, N=1 trials are being performed, where the focus is on one person and the effect of different treatments or drug are tested. Combining results of many N-of-1 trials, instead of investigating the average effect, is expected to lead to more useful information about the treatment of different groups in the population (Schork, 2015). An example of an effective N-of-1 trials study assessed 132 people for three years, comparing different drugs and treatments. The results indicate that N-of-1 trials resulted in more-effective prescriptions than the standard care, although initially more costly (Scuffham et al., 2010). Similar to these innovations in health care, more research to the effectiveness of well-being interventions is needed using a personalized approach. For example, the effectiveness of interventions should be investigated taking an individual's genetic predispositions, environmental exposures, behavior, and personality into account.

Besides individual well-being that can be targeted with positive psychology interventions, more governments start to incorporate the well-being of individuals and society in their policies, as discussed in **chapter 1**. For example, the Wellbeing Economy Governments (WEGo) is a collaboration of different countries that want to build and expand their well-being economies. Instead of focusing on economic growth and development, these countries emphasize and focus on health and well-being, safety and flourishing, as well as ecological well-being in their countries. Research on well-being can help governments to develop policies and to assess the effects of the policies on the well-being of individuals and society. Also in this case, the population should not be seen as a homogenous group, but the individual differences and group differences should be taken into account.

Conclusion

In this dissertation I investigated the causes of individual differences in well-being in a series of studies, contributing to the further understanding of well-being. Using different methods, including systematic reviews, meta-analyses, twin designs, and molecular genetic designs, we identified neural, physiological, genetic, and environmental factors that play a role in well-being. Furthermore, we examined the relationship and causality between well-being and related traits, including resilience and depressive symptoms. Finally, we looked at the real-time assessment of well-being. Integrating all results in this dissertation confirmed that well-being is a complex human trait that is influenced by many interrelated and interacting factors. I believe future directions and the key to understanding individual differences in well-being will be a data-driven approach to investigate the complex interplay of neural, physiological, genetic, and environmental factors that all play a role in well-being. As the well-being of individuals and the idea of well-being economies will become more important in (inter)national and societal policies in the coming years, I expect a lot of progress in the research to understand the causes of individual differences in well-being.





Appendices

Nederlandse samenvatting

Welbevinden is een complex en veelzijdige begrip, en kan in het algemeen gedefinieerd worden als je goed voelen en goed functioneren (Ryan & Deci, 2001). Welbevinden is een belangrijk aspect van de mentale gezondheid. Het behouden of verhogen van het welbevinden van de populatie wordt tegenwoordig vaker meegenomen als doel van overheden over de hele wereld. Sinds 2015 zijn mentale gezondheid en welbevinden opgenomen als een belangrijke *Sustainable Development Goal* (SDG) van de Verenigde Naties (United Nations, 2015). Daarnaast erkennen regeringen van verschillende landen het belang van welbevinden en gebruiken ze metingen van welbevinden in hun beslissingen (Boelhouwer, 2010; Stiglitz et al., 2009; Zencey, 2014). Een voorbeeld is de pas opgerichte *Wellbeing Economy Governments* (WEGo), een samenwerking van nationale en regionale overheden om economieën op te bouwen die gericht zijn op welbevinden (*WEGo - Wellbeing Economy Alliance*, 2022). Schotland, Nieuw-Zeeland, IJsland, Wales, Finland en Canada maken nu deel uit van deze samenwerking. In plaats van het bruto binnenlands product (BBP) worden maten van welbevinden gebruikt om het succes van het land en nationaal beleid te beoordelen.

Ook in de wetenschap is de interesse in welbevinden en de erkenning van welbevinden als belangrijk aspect van mentale gezondheid toegenomen. Het aantal wetenschappelijke publicaties over welbevinden, geluk en andere positieve psychologische kenmerken is in de afgelopen 25 jaar sterk toegenomen (Barrington-Leigh, 2022; Kim et al., 2018). In tegenstelling tot vroegere ideeën over welbevinden als het tegenovergestelde van psychopathologie, blijken de positieve effecten van welbevinden deels los te staan van de negatieve effecten van depressie en mentale problemen. Welbevinden is meer dan de afwezigheid van ziekte of mentale problemen en daarom is onderzoek naar welbevinden belangrijk (Howell et al., 2007; WHO, 2022). Welbevinden is gerelateerd aan minder gedrags- en emotionele problemen en wordt geassocieerd met positieve effecten in het dagelijks leven, waaronder een lang leven (James et al., 2019; Zaninotto & Steptoe, 2019), betere onderwijsprestaties, gelukkiger huwelijk en hogere productiviteit (Chapman & Guven, 2016; Lyubomirsky et al., 2005; Maccagnan et al., 2019; Oswald et al., 2015).

Meerdere definities en conceptualisaties van welbevinden zijn ontstaan in verschillende academische disciplines en contexten (Lambert et al., 2015). In de huidige psychologie wordt vaak een onderscheid gemaakt tussen metingen van hedonisch of subjectief welbevinden en eudaimonic of psychologisch welbevinden (Ryan & Deci, 2001). De theorie van subjectieve welbevinden is

ontstaan vanuit de hedonistische filosofische ideeën over het maximaliseren van plezier en het minimaliseren van pijn (Lambert et al., 2015; Ryan & Deci, 2001). Huidige hedonische of subjectieve maten van welbevinden zijn gericht op positieve en negatieve emoties en tevredenheid met het leven (Diener et al., 2018). Psychologisch welbevinden is voortgekomen uit eudaimonische filosofische theorieën die verder gaan dan alleen plezier en pijn, en de nadruk leggen op positief psychologisch functioneren en een deugdzaam leven leiden (Lambert et al., 2015; Ryan & Deci, 2001). Huidige eudaimonische of psychologische maten van welbevinden zijn positief functioneren, en oordelen over de zin en het doel van het leven (Ryff, 1989). Hedonistische en eudaimonische maten van welbevinden meten verschillende aspecten van welbevinden, maar zijn sterk aan elkaar gerelateerd (correlaties $>.60$) (e.g., Gallagher et al., 2009; Joshanloo, 2016; Thorsteinsen & Vittersø, 2020).

Mensen verschillen in hun mate van welbevinden, sommige mensen zijn over het algemeen gelukkiger of tevredener met hun leven dan anderen. Deze individuele verschillen in welbevinden kunnen voortkomen uit veel verschillende factoren, waaronder biologische (genetische) invloeden en omgevingsinvloeden. Meer kennis over de factoren die welbevinden beïnvloeden is nodig om preventie- en interventiestrategieën te ontwikkelen om welbevinden en de mentale gezondheid te verbeteren. Door eerder onderzoek beginnen we de verschillende factoren te begrijpen, maar veel is ook nog onduidelijk. Het doel van dit proefschrift was om welbevinden beter te begrijpen door de neurale, fysiologische, genetische, en omgevingsinvloeden op welbevinden te onderzoeken, en door de relatie en causaliteit tussen welbevinden en gerelateerde constructen te onderzoeken.

Dit proefschrift bestaat uit vier delen met verschillende onderzoeken. In deel I (hoofdstuk 2 en 3) onderzochten we systematisch de biologische factoren in relatie tot welbevinden. In deel II onderzochten we welbevinden door de overlap en causaliteit tussen welbevinden en gerelateerde constructen, zoals veerkracht, optimisme, en depressie te onderzoeken (hoofdstuk 4, 5 en 6). In deel III hebben we het effect van een extreme omgevingsstressor, de COVID-19-pandemie, op het welbevinden onderzocht en vooral gekeken naar de individuele verschillen in de effecten van de pandemie op welbevinden (hoofdstuk 7 en 8). In deel IV onderzochten we de toepasbaarheid en de resultaten van het meten van welbevinden en (omgevings-) factoren in het dagelijks leven (hoofdstuk 9 en 10). In dit hoofdstuk vat ik de hoofdstukken en resultaten samen.

Biologie van welbevinden

Over de biologische basis van welbevinden en geluk zijn zowel in de populaire media als op wetenschappelijk gebied twijfelachtige beweringen gedaan, gebaseerd op studies met lage kwaliteit en kleine steekproeven. Tegelijkertijd is er de laatste jaren meer onderzoek gepubliceerd naar de neurale en fysiologische correlaten van welbevinden, vanwege de snelle technologische vooruitgang in methodes en analysetechnieken. Om de biologische mechanismes waardoor welbevinden ontstaat beter te begrijpen, hebben we in deel I van dit proefschrift systematisch de betrokkenheid van de hersenen (**hoofdstuk 2**) en fysiologische processen (**hoofdstuk 3**) bij welbevinden onderzocht.

In **hoofdstuk 2** hebben we de associatie tussen de structuur en het functioneren van verschillende hersengebieden en welbevinden onderzocht door de beschikbare literatuur samen te vatten. We gebruikten de resultaten van 56 wetenschappelijke studies in een systematische review. Op basis van de 11 elektro-encefalografie (EEG) onderzoeken vonden we een relatief consistente bevinding van een relatie tussen hoger welbevinden en grotere alfa-activatie-asymmetrie, wat meer linker- dan rechterhersenactivatie betekent. De meta-analyse van vijf heterogene studies met 11 associaties bevestigde deze kleine positieve relatie tussen (frontale) alfa-asymmetrie en welbevinden. De resultaten van de 18 Magnetic Resonance Imaging (MRI)-onderzoeken, 26 functionele MRI-onderzoeken in rusttoestand en twee functionele near-infrared spectroscopy (fNIRS) studies waren minder consistent. In de verschillende onderzoeken was de grootte of activiteit van veel verschillende hersengebieden geassocieerd met welbevinden, maar bevestiging van de associaties in meerdere onderzoeken was zeldzaam, zowel wat betreft de richting als de sterkte van de associaties.

Een mogelijke verklaring voor deze inconsistentie in de associaties is een groot netwerk van hersengebieden dat betrokken is bij welbevinden. De meeste onderzoeken in de review hadden een kleine steekproef, wat leidde tot weinig vermogen om de kleine effecten van losse hersengebieden te vinden. In vervolgstudies zijn daarom grotere steekproeven nodig om de associaties tussen welbevinden en verschillende hersengebieden op een betrouwbare manier te kunnen onderzoeken.

Naast de hersenen zijn veel andere fysiologische processen betrokken bij individuele verschillen in welbevinden. In **hoofdstuk 3** hebben we de literatuur van de fysiologie van welbevinden samengevat. We onderzochten fysiologische factoren in vier categorieën, namelijk neurotransmitters, hormonen, ontstekingsmarkers van het immuunsysteem en kenmerken van

het microbioom in de darmen en maag. We vonden in totaal 91 onderzoeken in de verschillende categorieën en onderzochten de resultaten in de review. De negen neurotransmitterstudies rapporteerden een relatief consistente positieve relatie tussen serotonine en welbevinden, en geen consistente associaties met andere neurotransmitters. In de 48 hormoonstudies was alleen cortisol consistent gerelateerd aan welbevinden. Hogere niveaus van welbevinden waren gerelateerd aan lagere niveaus van cortisol, en een snellere afname van cortisol gedurende de dag. De 36 onderzoeken naar ontstekingsmarkers rapporteerden voornamelijk negatieve relaties van verschillende markers met welbevinden. De meta-analyses toonde een negatieve associatie tussen welbevinden en C-reefief proteïne en interleukine-6 te zijn. De vier studies naar het microbioom in de darmen rapporteerden inconsistente associaties tussen de mate van aanwezigheid van verschillende bacteriën en welbevinden.

De resultaten van deze systematische review wijzen op een paar mogelijke fysiologische factoren gerelateerd aan welbevinden, namelijk serotonine, cortisol, en ontstekingsmarkers van het immuunsysteem. Echter, sommige associaties zijn slechts op enkele onderzoeken gebaseerd. Daarom is er meer en innovatief onderzoek nodig om deze associaties te bevestigen en een volledig beeld te krijgen van de fysiologische factoren die een invloed hebben op welbevinden. Richtingen voor toekomstig onderzoek zijn het combineren van meerdere fysiologische markers over de verschillende categorieën in een enkele grote studie, of de causaliteit tussen de fysiologie en welbevinden onderzoeken.

Het overzicht van de verschillende hersengebieden en fysiologische factoren in relatie tot welbevinden in deel I van dit proefschrift stelde ons in staat om de beweringen over de biologie van welbevinden kritisch te onderzoeken. Bovendien toonden de hoofdstukken aan dat het aantal onderzoeken naar de neurale en fysiologische factoren van welbevinden toeneemt. Er zijn echter grotere en meer op data gebaseerde studies nodig om de neurale en fysiologische invloeden op welbevinden betrouwbaarder te kunnen onderzoeken.

Genetische overlap van welbevinden en gerelateerde constructen

Welbevinden is een complex en veelzijdig construct en is gerelateerd aan verschillende andere constructen. Het onderzoek naar deze overlap met andere constructen kan ons helpen meer te weten te komen over welbevinden. In deel II van dit proefschrift hebben we de (genetische) associatie van welbevinden met verschillende constructen, zoals optimisme, veerkracht, en depressie onderzocht.

In **hoofdstuk 4** hebben we tweelingmodellen toegepast in een grote steekproef van adolescente tweelingen om de associatie tussen welbevinden en optimisme, depressieve symptomen, agressief gedrag, en opleidingsniveau te onderzoeken. Welbevinden is sterk positief gerelateerd aan optimisme en sterk negatief gerelateerd aan depressieve symptomen, terwijl de negatieve correlatie tussen welbevinden en agressief gedrag lager is en de correlatie met opleidingsniveau bijna nul is. De relaties verschillen dus, maar bij alle vier constructen verklaarden genetische factoren een groot deel van de relatie met welbevinden. Er was een grote overlap in genetische factoren die welbevinden en optimisme en depressieve symptomen beïnvloeden. De overlap was kleiner voor welbevinden en agressief gedrag en opleidingsniveau.

Deze resultaten kunnen belangrijke klinische implicaties hebben. De genetische correlaties geven aan dat de genetische invloeden en biologische mechanismen van welbevinden en optimisme of depressieve symptomen vergelijkbaarder zijn dan die van welbevinden en agressief gedrag of opleidingsniveau. Deze vergelijkbaardere biologische mechanismen voor welbevinden en depressieve symptomen suggereren bijvoorbeeld dat interventies om het welbevinden te vergroten en tegelijkertijd depressieve symptomen te verminderen effectief kunnen zijn. Daarnaast zouden mensen met een risico op psychopathologie kunnen worden geïdentificeerd op basis van hun welbevinden voordat symptomen ontwikkelen. Echter, de verschillende biologische mechanismen voor welbevinden en agressief gedrag suggereren dat een interventie om het welbevinden te vergroten en tegelijkertijd agressief gedrag te verminderen hoogstwaarschijnlijk niet effectief is.

Veerkracht is een ander construct dat sterk is gerelateerd aan welbevinden. In **hoofdstuk 5** hebben we de relatie en overlap tussen welbevinden en veerkracht met behulp van verschillende analysetechnieken onderzocht. We hebben data gebruikt van twee tijdstippen van meer dan 14 duizend tweelingen en hun broers en zussen uit het Nederlandse Tweelingenregister en verschillende analyses uitgevoerd. We vonden sterke correlaties tussen veerkracht en welbevinden ($r=.41$ en $.51$ op respectievelijk tijdstip 1 en 2) zoals eerder gerapporteerd (Bajaj & Pande, 2016; Hu et al., 2015; Satici, 2016). Daarnaast vonden we met polygenetische score analyses dat genetische factoren die welbevinden beïnvloeden ook veerkracht beïnvloeden. Tweelingmodellen bevestigden deze overlap in genetische factoren ($r_g=.71$) en toonde ook een sterke omgevingscorrelatie ($r_e=.93$) tussen welbevinden en veerkracht. De resultaten van meerdere analyses kwamen overeen met een mogelijke bidirectionele causaliteit. Het *Mendelian-Randomization - Direction of Causality* (MR-DoC) model, dat expliciet de causale samenhang test, bevestigde

het causale effect van welbevinden op veerkracht, waarbij het directe effect van welbevinden 11%-20% van de variantie in veerkracht verklaart. We konden het effect van veerkracht op welbevinden niet testen omdat er geen sterke GWAS voor veerkracht beschikbaar is.

Onze triangulatiebenadering met meerdere analyses die elk verschillende sterke en zwakke punten hebben, zorgde voor sterk bewijs voor de relatie tussen welbevinden en veerkracht en mogelijke bidirectionele causale effecten. Veerkracht en welbevinden zijn beide negatief gerelateerd aan psychopathologie, daarom zouden de resultaten kunnen worden gebruikt voor interventies om negatieve psychopathologische effecten te verminderen na het ervaren van stressvolle levensgebeurtenissen.

Depressieve symptomen en welbevinden zijn ook sterk aan elkaar gerelateerd, mensen met hoog welbevinden hebben vaak weinig depressieve symptomen en andersom (Bartels et al., 2013; Baselmans et al., 2018; Baselmans & Bartels, 2018; Greenspoon & Saklofske, 2001; Okbay et al., 2016). In **hoofdstuk 6** hebben we de overlap tussen depressieve symptomen en twee vormen van welbevinden, namelijk geluk en zingeving in het leven, nader onderzocht. Met behulp van de *GWAS-by-subtraction* methode (Demange et al., 2021) hebben we ons gericht op het genetische deel dat welbevinden uniek maakt, door resultaten van een *genome-wide association study* (GWAS) voor depressieve symptomen ($n=427.580$) af te trekken van GWAS's voor geluk en betekenis in het leven. Dit leidde tot GWAS's van respectievelijk "puur geluk" ($n = 216.497$) en "puur zingeving" ($n = 102.300$). Zowel voor puur geluk als puur zingeving identificeerden we één significante genetische marker, i.e., een SNP (respectievelijk rs1078141 en rs79520962). De erfelijkheid van puur geluk op basis van de GWAS daalde van 6.3% naar 3.3% en van 6.2% naar 4.2% voor puur zingeving na het aftrekken van de depressieve symptomen GWAS. Verder daalde de genetische correlatie tussen de maten van welbevinden van 0.78 naar 0.65. De genetische correlaties tussen welbevinden versus puur welbevinden en andere constructen resulteerden in verschillende patronen. In tegenstelling tot welbevinden is puur welbevinden genetisch niet gerelateerd aan eigenschappen die verband houden met depressieve symptomen, zoals vermoeidheid, eenzaamheid en gezondheidstevredenheid. Voor verschillende andere eigenschappen, waaronder inkomen, opleidingsniveau en frequentie van roken en alcoholgebruik, zijn de genetische correlaties van puur welbevinden omgekeerd ten opzichte van welbevinden, wat wijst op unieke genetische associaties van puur welbevinden, onafhankelijk van depressieve symptomen. Deze resultaten kunnen tot nieuwe inzichten over welbevinden

leiden en kunnen belangrijke implicaties hebben voor interventies om het welbevinden te verhogen, onafhankelijk van depressieve symptomen.

In deel II van dit proefschrift hebben we de overlap tussen welbevinden en een reeks andere constructen onderzocht om meer te weten te komen over welbevinden. We rapporteren een grote overlap met constructen zoals optimisme, veerkracht en depressieve symptomen. Daarnaast toonden we aan dat welbevinden unieke associaties heeft met verschillende constructen, onafhankelijk van depressieve symptomen. Deze resultaten kunnen nuttig zijn bij het ontwerpen van effectievere interventies om het welbevinden te vergroten, rekening houdend met de overlap en mogelijke causaliteit met andere constructen.

Het effect van een extreme omgevingsfactor op welbevinden

Begin 2020, halverwege het eerste jaar van mijn PhD project, zorgde de COVID-19 pandemie plotseling voor grote veranderingen in het dagelijks leven over de hele wereld. In maart 2020 werd een pandemie uitgeroepen door de Wereldgezondheidsorganisatie. Tijdens het eerste jaar van deze pandemie waren langdurige maatregelen en restricties nodig om het virus onder controle te krijgen en om ervoor te zorgen dat de gezondheidszorg het aankon, aangezien er nog geen genezing en vaccinatie beschikbaar was. In Nederland werd de eerste lockdown in maart 2020 aangekondigd, met grote beperkingen, waaronder het houden van afstand, sluiting van scholen, kantoren, sportscholen en andere openbare plaatsen, en individuen werd sterk aangeraden om vanuit huis te werken. De COVID-19-pandemie zorgde voor een unieke periode die ook mijn PhD project sterk heeft beïnvloed. Echter, de unieke situatie zorgde er ook voor dat we de effecten van een extreme verandering van de omgeving op het welbevinden konden onderzoeken. De pandemie en de lockdowns kunnen worden gezien als een natuurlijk experiment, omdat iedereen door de extreme omgevingsfactor wordt beïnvloed, maar op verschillende manieren en in verschillende mate. In deel III van dit proefschrift hebben we de individuele verschillen onderzocht in de effecten van de pandemie en lockdowns op meerdere aspecten van welbevinden.

In **hoofdstuk 7** hebben we gebruik gemaakt van de longitudinale database van het Nederlandse Tweelingen Register om optimisme en zingeving in het leven te onderzoeken voor en tijdens de eerste fase van de pandemie. Deelnemers vulden enquêtes in voor ($N=9964$, gemiddelde leeftijd: 48.2; $SD=14.4$) en tijdens de eerste maanden van de pandemie (april-mei 2020, $N=17464$, gemiddelde leeftijd: 44.6, $SD=14.8$), en een deel van de groep vulde beide enquêtes in ($N=6461$, gemiddelde leeftijd $T1$: 48.8, $SD=14.5$). We vonden de

verwachte individuele verschillen in het effect van de pandemie op optimisme en zingeving in het leven. Een deel van de groep (respectievelijk 56% en 35% voor optimisme en zingeving in het leven) daalde in hun welbevinden tijdens de pandemie. Vooral vrouwen, hoger opgeleiden en mensen met een slechtere gezondheid rapporteerden minder optimisme en zingeving tijdens de pandemie. Het andere deel van de steekproef was stabiel (32% en 43%) of toonde meer optimisme en zingeving tijdens de pandemie (11% en 22%).

Tijdens de pandemie waren optimisme en zingeving iets minder erfelijk (respectievelijk 20% en 25%) in vergelijking met pre-pandemie (respectievelijk 26% en 32%), wat aangeeft dat genen een kleinere rol spelen bij het verklaren de individuele verschillen in optimisme en zingeving in het leven tijdens de pandemie en de omgeving speelde een grotere rol. De genetische correlaties tussen optimisme en zingeving in het leven voor en tijdens de pandemie (.75 en .63) suggereren ook gen-omgevingsinteracties, wat aangeeft dat de genen die optimisme en betekenis in het leven beïnvloeden, deels verschillen voor en tijdens de pandemie. De COVID-19-pandemie is dus een sterke omgevingsfactor die leidt tot verschillende effecten op het welbevinden van individuen. Deze verschillen worden deels verklaard door individuele verschillen in de gevoeligheid voor extreme omgevingsveranderingen.

De pandemie was helaas niet over na de eerste lockdown. Over de hele wereld vonden er meerdere golven van COVID-19-infecties plaats, wat leidde tot langdurige beperkingen en meerdere lockdowns. Onderzoek naar het effect van latere lockdowns op het welbevinden kan helpen om de langdurige effecten van extreme situaties te begrijpen en de verwachte psychologische impact van toekomstige lockdowns. In **hoofdstuk 8** onderzochten we daarom het effect van de tweede lockdown in Nederland op de dagelijkse aspecten van welbevinden. We gebruikten data van een 100 dagen durende dagboekstudie onder adolescenten ($N=159$, leeftijd=13.3, 61.6% vrouw) en één van hun ouders ($N=159$, leeftijd=45.3, 79.9% vrouw). We onderzochten hoe het dagelijks welbevinden veranderde van voor naar tijdens de tweede lockdown. We vonden een onverwachte toename van de intensiteit van het positieve gevoelens van de ouders direct na het begin van de lockdown, mogelijk vanwege duidelijkheid over de lockdown en beperkingen. Er waren geen onmiddellijke veranderingen in de intensiteit of variabiliteit van negatieve gevoelens. Zowel adolescenten als ouders vertoonden echter een geleidelijke toename van de intensiteit en variabiliteit van het negatieve gevoelens naarmate de lockdown langer werd. Toch zagen we, net als in hoofdstuk 7, grote individuele verschillen in alle effecten. Deze individuele verschillen in de effecten werden deels verklaard door tevredenheid met het leven, depressieve symptomen en zelf-

gerapporteerde impact van de lockdown. Samengevat leidde de lockdown tot veranderingen in dagelijks welbevinden, vooral naarmate de lockdown langer duurde, maar er zijn individuele verschillen in de omvang en richting van de effecten van de lockdown op het dagelijkse welbevinden.

In deel III van dit proefschrift hebben we de gevolgen van een extreme verandering van de omgeving op het welbevinden tijdens verschillende fasen van de pandemie onderzocht. Gemiddeld gezien vonden we een negatief effect van de pandemie op verschillende aspecten van welbevinden, vooral naarmate de pandemie langer duurde. Waar in de meeste eerdere studies alleen gekeken werd naar dit gemiddelde negatieve effect van de pandemie op het welbevinden, hebben wij ons in beide hoofdstukken ook gericht op de individuele verschillen. De grote individuele verschillen in de effecten van de pandemie op het welbevinden wijzen erop dat *one-size-fits-all* interventies om het welbevinden tijdens de pandemie of lockdowns te behouden of vergroten niet werken. Verder onderzoek naar groepen die stabiel of een hoger welbevinden rapporteren tijdens lockdowns is nodig voor het begrijpen van beschermende factoren om verdere ongelijkheid in de populatie te voorkomen en de negatieve effecten van toekomstige lockdowns op het welbevinden te beperken.

Real-time metingen

In onderzoek naar welbevinden wordt meestal gebruik gemaakt van vragenlijsten met algemene maten van welbevinden die door deelnemers op één tijdstip worden ingevuld. Echter, gevoelens van welbevinden fluctueren ook door de tijd en in verschillende contexten (Eid & Diener, 2004; Li et al., 2014; Lyubomirsky, 2001). Om de fluctuaties en dynamische aard van welbevinden vast te leggen is het meten van welbevinden in real-time en het dagelijks leven nodig. Dit idee en de methode van *Ecological Momentary Assessment* (EMA) is niet nieuw, al in de jaren 1920 en 1930, werd deze methode gebruikt om gevoelens in het dagelijks leven te meten (Dysinger, 1938; Favill & Rennick, 1924; Flügel, 1925). Echter, de interesse en toepassing van EMA en dagboekstudies neemt sterk toe als gevolg van de snelle technologische vooruitgang. Tegenwoordig kunnen smartphone-applicaties worden gebruikt om makkelijk data in real-time en het dagelijks leven te verzamelen (Runyan & Steinke, 2015).

In **hoofdstuk 9** hebben we de toepasbaarheid en resultaten van *Ecological Momentary Assessment* onderzoeken naar welbevinden onderzocht. We vonden 53 studies die erg verschillend waren in de designs, context en metingen. De gemiddelde duur van de studies was 12.8 dagen, waarbij het welbevinden 2-12 keer per dag werd gemeten. De helft van de onderzoeken bevatte objectieve data van de omgeving (bijvoorbeeld locatie of fysieke activiteit). De onderzoeken

hadden verschillende onderzoeksvragen en resultaten. Studies vonden bijvoorbeeld dat het welbevinden zowel dagelijks als wekelijks fluctueerde, met een hoger welbevinden in de avonden en weekenden. Deze fluctuaties verdwenen echter wanneer er rekening werd gehouden met de locatie en activiteit. Verder is het in de natuur zijn en fysiek actief zijn gerelateerd aan een hoger welbevinden, terwijl zittend gedrag en werken samenhangt met een lager welbevinden. We concludeerden dat EMA-onderzoek nuttig is om inzicht te krijgen in het real-time welbevinden en fluctuaties van welbevinden. De meeste studies waren gericht op gemiddelde effecten en groepsvergelijkingen, terwijl toekomstige studies zich ook zouden moeten richten op individuele verschillen in real-time welbevinden en fluctuaties.

Lichamelijke activiteit en sedentair (zittend) gedrag zijn twee van de variabelen die gerelateerd zijn aan welbevinden in real-time en in het dagelijks leven (zie hoofdstuk 9 en bijvoorbeeld Panza et al., 2019). In **hoofdstuk 10** hebben we het verband tussen welbevinden en real-time fysieke activiteit en zittend gedrag onderzocht met data van accelerometers van een groep NTR deelnemers ($n = 660$, leeftijd: 30.4, $SD = 8.1$, 74.5% vrouw). We creëerden verschillende maten van fysiek en zittend gedrag, inclusief de timing en patronen van dit gedrag. In de totale data vonden we geen verband tussen welbevinden en verschillende maten van fysieke activiteit en zittend gedrag. Wanneer we alleen vrije tijdsdata (tijd niet aan het werk) meenemen, is een hoger welbevinden gerelateerd aan minder zittend gedrag en meer lichte fysieke activiteit in het dagelijks leven. De timing en patronen van fysieke activiteit waren niet gerelateerd aan welbevinden.

Op basis van deel IV van dit proefschrift kunnen we concluderen dat de real-time metingen van welbevinden, gerelateerde variabelen en de omgeving kan leiden tot nieuwe inzichten over welbevinden, die we niet kunnen worden gevonden met traditioneel vragenlijstonderzoek. De real-time metingen van welbevinden is een veelbelovend gebied voor toekomstig onderzoek om de dynamische aard van welbevindensfluctuaties en de interactie met de omgeving in het dagelijks leven verder te onderzoeken.

Het belang van onderzoek naar welbevinden en de implicaties

Welbevinden is gerelateerd aan minder psychische problemen, zoals depressieve symptomen en angststoornissen. Daarnaast heeft welbevinden positieve effecten op het dagelijks leven, de levensduur, het huwelijk, de arbeidsproductiviteit en vele andere gebieden. Deze beschermende en positieve effecten van welbevinden suggereren dat het verhogen en behouden van welbevinden de economische en gezondheidslast van samenlevingen

vermindert. Onderzoek naar welbevinden is daarom ook belangrijk voor de samenleving. Kennis over welbevinden kan worden gebruikt om effectieve interventies te ontwikkelen om het welbevinden van individuen te verhogen of om te voorkomen dat welbevinden daalt in stressvolle omstandigheden. Daarnaast kan onderzoek naar welbevinden overheden helpen om beleid te ontwikkelen en de effecten van het beleid op het welbevinden van individuen en de samenleving te beoordelen.

Types interventies die specifiek bedoeld zijn om het welbevinden te vergroten, in plaats van alleen psychopathologische symptomen te verminderen, zijn *positieve psychologische interventies* (Seligman & Csikszentmihalyi, 2000). Bekende voorbeelden van zulke interventies zijn het beoefenen van dankbaarheid of vergeving, aardig zijn voor anderen, schrijven over positieve, zinvolle of succesvolle ervaringen en het vinden van flow. Twee recente systematische reviews en meta-analyses onderzochten de effectiviteit van positieve psychologische interventies (Carr et al., 2021; van Agteren et al., 2021). In 47 onderzoeken met meer dan 72 duizend deelnemers werden significante effecten van de interventies op welbevinden en depressie- en angstsymptomen gevonden (Carr et al., 2021). van Agteren et al. (2021) rapporteerden ook kleine effecten van positieve psychologische interventies, maar de kwaliteit van het bewijs was vaak laag tot matig. De significante effecten geven aan dat positieve psychologische interventies kunnen worden gebruikt om een laag welbevinden te voorkomen of als een behandelstrategie om het welbevinden te vergroten.

Echter zijn de conclusies van deze reviews over de effectiviteit van positieve psychologische interventies gebaseerd op de gemiddelde effecten over grote steekproeven en houden ze geen rekening met individuele verschillen in de effecten. Een dankbaarheidsinterventie kan bijvoorbeeld effectief zijn voor de ene persoon, terwijl dit niet werkt voor een andere persoon die meer baat heeft bij een andere interventie. Toekomstig onderzoek naar welbevindeninterventies moet daarom rekening houden met individuele verschillen die we in dit proefschrift hebben aangetoond. Er is meer onderzoek nodig naar de effectiviteit van welbevindeninterventies met een gepersonaliseerde aanpak. In zulk onderzoek zou bijvoorbeeld rekening moeten worden gehouden met de genetische aanleg, omgevingsomstandigheden, het gedrag en de persoonlijkheid van een persoon.

Conclusie

In dit proefschrift hebben we de factoren die een rol spelen bij de individuele verschillen in welbevinden onderzocht in een reeks studies. Met behulp van verschillende methoden, waaronder systematische reviews, meta-analyses, tweelinganalyses en moleculair genetische methodes, hebben we de neurale, fysiologische, genetische en omgevingsfactoren onderzocht die een rol spelen bij het welbevinden. Verder onderzochten we de relatie en causaliteit tussen welbevinden en gerelateerde eigenschappen, waaronder veerkracht en depressieve symptomen. Ten slotte hebben we gekeken naar de real-time metingen van welbevinden. Alle resultaten in dit proefschrift bevestigden dat welbevinden een complexe menselijke eigenschap is die wordt beïnvloed door vele factoren die ook onderling gerelateerd zijn en op elkaar inwerken. Meer data-driven onderzoek is nodig om een meer gedetailleerd begrip van individuele verschillen in welbevinden te verkrijgen en het complexe samenspel van neurale, fysiologische, genetische en omgevingsfactoren die een rol spelen in welbevinden te onderzoeken. Aangezien het welbevinden van individuen en het idee van welbevindenseconomieën de komende jaren belangrijker zullen worden in (inter)nationaal en maatschappelijk beleid, verwacht ik de komende jaren veel vooruitgang in het onderzoek naar de individuele verschillen in welbevinden.

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Summary of author contributions

Chapter 1

Partly based on van de Weijer, M. P., **de Vries, L. P.**, & Bartels, M. (2020). Happiness and well-being: The value and findings from genetic studies. In A. Tarnoki, D. Tarnoki, J. Harris, & N. Segal (Eds.), *Twin Research for Everyone* (pp. 295–322). Academic Press. doi: 10.1016/B978-0-12-821514-2.00016-7 and Bartels, M., Nes, R.B., Armitage, J.M., van de Weijer, M.P., **de Vries, L.P.** & Haworth, C.A.M. (2022). Exploring the biological basis for happiness. *World Happiness Report 2022*.

I contributed to both *van de Weijer et al. (2022)* and *Bartels et al. (2022)* by writing part of the chapters and editing and reviewing the drafts. I used these chapters as basis for the Introduction, but changed the text and order substantially. Furthermore, I added extra information to the Introduction not included in the chapters.

Chapter 2

Accepted as **de Vries, L.P.**, van de Weijer, M.P., Bartels M. (2022). A systematic review of the neural correlates of well-being reveals no consistent associations. *Neuroscience & Biobehavioral Reviews*

The systematic review was conceptualised by me, and both co-authors, Margot van de Weijer, and Meike Bartels. I performed the systematic literature review, extracted the information from the articles, created the tables and figures and wrote the first draft. I discussed uncertainties with both co-authors. Both co-authors actively participated in editing and reviewing the first and subsequent drafts, and I processed and integrated their comments before submission.

Chapter 3

Published as **de Vries, L.P.**, van de Weijer, M.P., & Bartels M. (2022). The human physiology of well-being: A systematic review on the association between neurotransmitters, hormones, inflammatory markers, the microbiome and well-being. *Neuroscience & Biobehavioral Reviews*, 104733. <https://doi.org/10.1016/j.neubiorev.2022.104733>

The systematic review was conceptualised by me, and both co-authors, Margot van de Weijer, Meike Bartels. I performed the systematic literature review, extracted the information from the articles, performed the meta-analyses created the tables and figures and wrote the first draft. I discussed uncertainties with both co-authors. Both co-authors actively participated in editing and

reviewing the first and subsequent drafts, and I processed and integrated their comments before submission.

Chapter 4

Published as de Vries, L.P., de Zeeuw, E.L., van Beijsterveldt, C.E.M., Maes H., Colodro-Conde, L. & Bartels, M. (2021). Genetic influences on the covariance versus genetic correlations in a bivariate twin model: an application to well-being. Behavior Genetics, 51, 191–203. <https://doi.org/10.1007/s10519-021-10046-y> The study was conceptualised by Meike Bartels, Hermine Maes, and Lucia Colodro-Conde in response to a special issue for Behavior Genetics. Toos van Beijsterveldt and Eveline de Zeeuw collected, cleaned, and preprocessed the data of the NTR. I wrote the data request, performed the analyses, created the figures and tables and wrote the first draft of the paper. Hermine Maes, Lucia Colodro-Conde, and Meike Bartels helped with the scripts and interpreting the results of the analyses. All co-authors actively participated in editing and reviewing the manuscript, and I processed all comments and feedback before submission and during the revision.

Chapter 5

Published as de Vries, L.P., Baselmans, B.M.L., Luykx, J.J., de Zeeuw, E., Minică, C., de Geus, E.J.C., Vinkers, C.H., & Bartels, M. (2021). Genetic evidence for a large overlap and possible bidirectional causal effects between resilience and well-being. Neurobiology of Stress, 14, 100315. <https://doi.org/10.1016/j.ynstr.2021.100315>

The study was conceptualised by Meike Bartels and Christiaan Vinkers. Eveline de Zeeuw collected, cleaned, and preprocessed part of the data of the NTR. I wrote the data request, performed the analyses, created the figures and tables and wrote the first draft of the paper. Bart Baselmans helped performing the analyses. Camelia Minica has developed one of the methods used in this paper and contributed with helpful feedback on interpreting the results. Jurjen Luykx, Eco de Geus, Christiaan Vinkers and Meike Bartels contributed with extensive feedback and suggestions on the first draft. All co-authors actively participated in editing and reviewing the manuscript, and I processed all comments and feedback before submission and revisions.

Chapter 6

In preparation as de Vries, L.P., Demange, P., Baselmans, B.M.L., Vinkers, C.H, Pelt, H.M., & Bartels, M. Distinguishing Happiness and Meaning in Life from Depressive Symptoms: a GWAS-by-subtraction study in UK Biobank

The study was conceptualised by me, Dirk Pelt and Meike Bartels. I performed the analyses based on the scripts from Perline Demange. Perline Demange helped in performing the analyses. I created the figures and tables and wrote the first draft of the paper. All co-authors actively participated in editing and reviewing the manuscript, and I processed all comments and feedback before submission.

Chapter 7

Published as de Vries, L.P., van de Weijer, M.P., Pelt, H.M., Ligthart, L., Willemsen, G., Boomsma, D.I., de Geus, E.J.C., & Bartels, M. (2021). Gene-by-crisis interaction for optimism and meaning in life: the effects of the COVID-19 pandemic. Behavior Genetics. <https://doi.org/10.1007/s10519-021-10081-9>

The study was conceptualised by me, Margot van de Weijer and Meike Bartels. Margot van de Weijer and Lannie Ligthart collected, cleaned and processed the data. Gonneke Willemsen, Dorret Boomsma, Eco de Geus, and Meike Bartels were involved in acquiring the funding for COVID-19 research for the Netherlands Twin Register. I performed the data analysis, created the figures and tables and wrote the first draft of the paper. Margot van de Weijer and Dirk Pelt helped with the data analysis. All co-authors actively participated in editing and reviewing the manuscript, and I processed all comments and feedback before submission and during the revision.

Chapter 8

*Published as de Vries, L.P., Bülow, A., Pelt, H.M., Boele, S., Bartels, M. & Keijsers, L. (2022). Daily affect variability of adolescents and their parents before and during the second COVID-19 lockdown. *Journal of Adolescence*, 1-18. [doi:10.1002/jad.12117](https://doi.org/10.1002/jad.12117).*

The study was conceptualised by me, with input from Anne Bülow and feedback from the other co-authors. Anne Bülow, Savannah Boele and Loes Keijsers collected, cleaned, and preprocessed the data. I wrote the data request, performed the analyses, created the figures and tables and wrote the first draft of the paper. Anne Bülow helped interpreting the results of the analyses. All co-authors actively participated in editing and reviewing the manuscript, and I processed all comments and feedback before submission and during the revision.

Chapter 9

Published as de Vries, L.P., Baselmans, B.M.L. & Bartels, M. (2020). Smartphone-based Ecological Momentary Assessment of Well-Being: a

Systematic Review and Recommendations for Future Studies. *Journal of Happiness Studies*, 22(5), 2361-2408. <https://doi.org/10.1007/s10902-020-00324-7>
The study was conceptualised by me, Bart Baselmans and Meike Bartels. I performed the systematic literature review, extracted the information from the articles, created the tables and figures and wrote the first draft. All co-authors actively participated in editing and reviewing the first and subsequent drafts, and I processed and integrated their comments before submission and revision.

Chapter 10

Published as de Vries, L.P., Pelt, H.M., van der Ploeg, H.P., Chinapaw, M.J.M, de Geus, E.J.C., & Bartels, M. (2022). The relation between well-being and a large variation of accelerometer-assessed physical activity and sedentary behavior. Mental Health and Physical Activity. <https://doi.org/10.1016/j.mhpa.2022.100446>
The study was conceptualised by me, Dirk Pelt and Meike Bartels. Hidde van der Ploeg collected the data. I performed the analyses, created the figures and tables and wrote the first draft of the paper. All co-authors actively participated in editing and reviewing the manuscript, and I processed all comments and feedback before submission and during the revision.

List of publications

First author publications

de Vries, L.P., Demange, P.A., Baselmans, B.M.L., Vinkers, C.H., Pelt, H.M., & Bartels, M. (*in preparation*). Distinguishing Happiness and Meaning in Life from Depressive Symptoms: a GWAS-by-subtraction study in UK Biobank. Pre-registration: <https://osf.io/wr3g6>

de Vries, L.P., van de Weijer, M.P., & Bartels, M. (*Accepted*). A systematic review of the neural correlates of well-being reveals no consistent associations. *Neuroscience & Biobehavioral Reviews*.

de Vries, L.P., Bülow, A., Pelt, H.M., Boele, S., Bartels, M. & Keijsers, L. (2022). Daily affect intensity and variability of adolescents and their parents before and during the second COVID-19 lockdown in the Netherlands. *Journal of Adolescence*, 1-18. <https://doi.org/10.1002/jad.12117>

de Vries, L.P., van de Weijer, M.P., & Bartels, M. (2022). The human physiology of well-being: A systematic review on the association between neurotransmitters, hormones, the immune system, the microbiome, and well-being. *Neuroscience & Biobehavioral Reviews*, 104733. <https://doi.org/10.1016/j.neubiorev.2022.104733>

de Vries, L.P., Pelt, H.M., van der Ploeg, H.P., Chinapaw, M.J.M, de Geus, E.J.C., & Bartels, M. (2022). The association between well-being and a large variation of accelerometer-assessed physical activity and sedentary behavior measures. *Mental Health and Physical Activity*, 22, 100446. <https://doi.org/10.1016/j.mhpa.2022.100446>

de Vries, L.P., van de Weijer, M.P., Pelt, H.M., Ligthart, L., Willemsen, G., Boomsma, D.I., de Geus, E.J.C., & Bartels, M. (2021). Gene-by-crisis interaction for optimism and meaning in life: the effects of the COVID-19 pandemic. *Behavior Genetics*. <https://doi.org/10.1007/s10519-021-10081-9>

de Vries, L.P., Baselmans, B.M.L., Luykx, J.J., de Zeeuw, E., Minică, C., de Geus, E.J.C., Vinkers, C.H., & Bartels, M. (2021). Genetic evidence for a large overlap and possible bidirectional causal effects between resilience and well-being. *Neurobiology of Stress*, 14, 100315. <https://doi.org/10.1016/j.yynstr.2021.100315>

de Vries, L.P., de Zeeuw, E.L., van Beijsterveldt, C.E.M., Maes H., Colodro-Conde, L. & Bartels, M. (2021). Genetic influences on the covariance versus genetic correlations in a bivariate twin model: an application to well-being. *Behavior Genetics*, 51, 191–203. <https://doi.org/10.1007/s10519-021-10046-y>

de Vries, L.P., Baselmans, B.M.L. & Bartels, M. (2020). Smartphone-based Ecological Momentary Assessment of Well-Being: a Systematic Review and Recommendations for Future Studies. *Journal of Happiness Studies*, 22(5), 2361–2408. <https://doi.org/10.1007/s10902-020-00324-7>

de Vries, L.P., van de Weijer, M.P., Ligthart, L., Willemsen, G., Dolan, C.V., Boomsma, D.I., Baselmans, B.M.L. & Bartels, M. (2020). A Comparison of the ASEBA Adult Self Report (ASR) and the Brief Problem Monitor (BPM/18-59). *Behavior Genetics*, 50, 363–373. <https://doi.org/10.1007/s10519-020-10001-3>

Other publications

Pelt, D. H., **de Vries, L. P.**, & Bartels, M. (2022). Unraveling the Relation Between Personality and Well-Being in a Genetically Informative Design. *European Journal of Personality*, 08902070221134878.

van de Weijer, M. P., **de Vries, L. P.**, & Bartels, M. (2022). Happiness and well-being: The value and findings from genetic studies. In A. Tarnoki, D. Tarnoki, J. Harris, & N. Segal (Eds.), *Twin Research for Everyone* (pp. 295–322). Academic Press. <https://doi.org/10.1016/B978-0-12-821514-2.00016-7>

van de Weijer, M.P., **de Vries, L.P.**, Pelt, D.H., Ligthart, L., Willemsen, G., Boomsma, D.I., de Geus, E.J.C., & Bartels, M. (2022). Self-rated health when population health is challenged by the COVID-19 pandemic; a longitudinal study. *Social Science & Medicine*, 115156. <https://doi.org/10.1016/j.socscimed.2022.115156>

van de Weijer, M.P., Pelt, D.H., **de Vries, L.P.**, Baselmans, B.M.L., & Bartels, M. (2022). A Re-evaluation of Candidate Gene Studies for Well-Being in Light of Genome-Wide Evidence. *Journal of Happiness Studies*, 1–23. <https://doi.org/10.1007/s10902-022-00538-x>

Bartels, M., Nes, R.B., Armitage, J.M., van de Weijer, M.P., **de Vries, L.P.** & Haworth, C.A.M. (2022). Chapter 5: Exploring the biological basis for happiness.

World Happiness Report 2022. <https://worldhappiness.report/ed/2022/exploring-the-biological-basis-for-happiness/>

van de Weijer, M.P., Pelt, D.H., **de Vries, L.P.**, Huider, F., van der Zee, M.D., Helmer, Q., Ligthart, L., Willemsen, G., Boomsma, D.I., de Geus, E.J.C., & Bartels, M. (2022). Genetic and environmental influences on quality of life: The COVID-19 pandemic as a natural experiment. *Genes, Brain and Behavior*, e12796. <https://doi.org/10.1111/gbb.12796>

van de Weijer, M.P., **de Vries, L.P.**, & Bartels, M. (2021). Les influences génétiques et environnementales sur le bonheur et le bien-être . In Martin-Krumm, C., & Tarquinio, C. (Eds): *Grand manuel de la psychologie positive* (pp.65-96). Dunod.

Vellani, V., **de Vries, L.P.**, Gaule, A., & Sharot, T. (2020). A selective effect of dopamine on information-seeking. *Elife*, 9, e59152. <https://doi.org/10.7554/eLife.59152>

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van Kesteren, M. T. R., **de Vries, L.P.**, & Meeter, M. (2019). Seeing the past: afterglow effects on familiarity judgments are category-specific. *Learning & Memory*, 26(7), 229-234. <https://doi.org/10.1101/lm.048488.118>

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