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Summary, General Discussion & Future Perspectives

Genetics of Well-Being; an update

Where are we now and where are we heading

Introduction

Considering the beginning of my PhD trajectory in 2014, and as described in **chapter 1**, there has been major progress in the field of (molecular) genetics and complex traits like well-being. Up until 2014, most studies investigating the molecular genetics of well-being used either linkage or candidate gene analyses. As pointed out in **chapter 1**, linkage analysis is a powerful approach to detect genetic variants with large effect but has more difficulties detecting genetic variants with small effects. The candidate gene approach, on the other hand, theoretically has enough power to detect genetic variants with small effect. It requires, however, a sound theoretical mechanism with functional candidate genes a priori, knowledge that is still limited despite our increasing understanding of biological processes of complex traits. For these reasons, results based on these methods have shown to be extremely difficult to replicate[1] and the valid question arose whether it would be possible at all to identify genetic variants explaining phenotypic variance in well-being.

Since then, though, game-changing progress in the field of molecular/statistical genetics and bioinformatics has been made, resulting in the GWAS Era. One of the first promising signs indicating that it might become possible to detect genetic variants associated with well-being arose from results of a Genome-wide Complex Trait Analysis (GCTA)[2]. Rather than testing the association of a particular SNP with well-being, GCTA estimates how much of the variance in a trait can be accounted for by the genetic variance based on common SNPs, resulting in a heritability estimate based on molecular genetic data. Using GCTA in a sample of ~11,500 unrelated individuals, it was estimated that about 5-10% the variance in well-being could be explained by common SNPs[3]. Therefore, in **chapter 1**, we hypothesized that future genome-wide large-scale efforts to search for SNPs associated with well-being might have the potential to become successful.

However, in order to make it an success, it became obvious that sample size was the key issue. For instance, the first genetic variant robustly associated with schizophrenia was identified in 2009 using a sample of ~3,300 cases and ~3,500 controls[4]. In 2014, using a sample of ~35,000 cases and 110,000 controls, 108 genetic variants were associated with schizophrenia[5]. Like Schizophrenia, well-being is a polygenic trait, i.e. each individual will carry multiple alleles that increase his or her level of well-being, and multiple alleles that will decrease his or her level of well-being. Therefore, each individual variant will typically explain only a very small proportion of the variance in well-being. In addition, because of

many potentially different combinations of these risk alleles, it is likely that each individual carries a unique set of alleles. To detect these genetic variants with small effects, large sample sizes are required. Furthermore, it has been shown that the distribution of a phenotype in the population has an effect on the power to identify SNPs associated with it[6]. Higher levels of well-being are more prevalent in the population than psychiatric disorders. As a consequence, the sample size to detect SNPs robustly associated with well-being should be even larger than the sample size to detect genetic variants for psychiatric disorders.

Genome-Wide Association Studies

Using this information as *a priori* knowledge, we, together with the Social Science Genetic Association consortium (SSGAC; https://www.thessgac.org/) collected genetic and phenotypic data from 59 cohorts with a combined sample size of 298,420 individuals. **Chapter 3** describes this large-scale GWAS meta-analysis of well-being that led to the identification of the first three independent genetic variants associated with trait variation in well-being. Supplementing this analysis, we performed a GWAS meta-analysis of depressive symptoms (N = 180,866) and neuroticism (N = 170,910) and identified the first two genome-wide significant variants for depressive symptoms and eleven genome-wide significant variants for neuroticism. Additionally, the concordance of the allelic effect between the three traits was assessed, using a recently developed software tool called *Linkage Disequilibrium Score Regression* (LDSC)[7,8]. Within this approach, an "LD score" is computed for each SNP, taking the sum of correlation between that SNP and all neighboring SNPs. Under a polygenic model, these LD scores are expected to show a linear relationship with the GWAS test statistics of the corresponding SNPs, where the slope is proportional to the SNP heritability. Using LDSC, in **chapter 3,** we report a high genetic correlation between well-being, depressive symptoms, and neuroticism ($| r_g | > .75$), which corresponded to the genetic correlations derived in **chapter 2** using a large twin design. These high genetic correlations indicate common underlying biology between the three traits.

Multivariate Genome-wide association meta-analysis

Recognizing this large overlap, together with the knowledge that increasing samples sizes are required to detect genetic variants with small effects, we introduced two multivariate genome-wide association meta-analysis methods in **chapter 4**. Both methods enable analyzing clusters of correlated traits while handling bias resulting from inevitable sample overlap. Method 1, N-

weighted multivariate genome-wide association meta-analysis (N-GWAMA), assumes a single underlying construct with a *unitary* effect of the SNP on all included traits. Method 2, model averaging GWAMA (MA-GWAMA), relaxes this assumption and allows different effects on the various traits. We applied both methods on measures of life satisfaction, positive affect, neuroticism, and depressive symptoms, which we referred to as the *well-being spectrum* (N_{obs} = 2,370,390). Collectively, we found 319 genome-wide significant genetic variants associated with this spectrum.

Thus, in just over 2 years, the field of genetics and well-being progressed from the first three genetic associated with well-being to 319 genome-wide significant genetic variants. This spectacular increase in significant associations is representative of the enormous progress in the field of complex traits genetics in the last couple of years, reflected in findings for phenotypes such as educational attainment[9,10] and neuroticsm[11,12]. A significant player in the field of this progress is the UK Biobank (http://www.ukbiobank.ac.uk/), with the release of genome-wide genetic data on ~500,000 individuals in the summer of 2017[13]. The UK Biobank is a prospective study designed to be a resource for research into the causes of disease in middle and old age. Participants were recruited between 2006 and 2010 and completed a broad range of questionnaires. By meta-analyzing (smaller) cohort-data together with data derived from the UK Biobank, many studies, including ours described in **chapter 3, 4, 6, 8, and 9,** were able to increase the statistical power to find genetic variants associated with a specific trait of interest.

Phenotypic Heterogeneity

Although combining smaller cohort-data together with UK biobank has been proven successful, there is a downside to combining multiple measures of a trait (e.g. well-being). When combining multiple measures, there is always a dilemma; on the one hand including a cohort in the meta-analysis will increase the sample-size and consequently the power to find genetic variants of interest; on the other hand, including that specific cohort may bias the GWAS results, since combining different measures introduces phenotypic heterogeneity. In the studies described in **chapter 3** and **4**, we included multiple measures of positive affect as well as life satisfaction, neuroticism, and depressive symptoms leading to more noise in the GWAs analysis. To quantify the effects of this kind of phenotypic heterogeneity, **chapter 3** describes a "quantity-quality tradeoff" analysis that shows that in a *realistic* GWAS meta-analysis scenario with high genetic correlations (r_g > 0.6) between two measures of well-

being, the inclusion of a second cohort will reduce the measurement error in most cases. Therefore, based on the analysis of the costs and benefits of pooling heterogeneous measures, it can be concluded that pooling genetically associated traits increases the statistical power to detect genetic variants.

Mixing different measures, though, will result in a drop of the SNP heritability (h^2_{SNP}), as the included measures are partly influenced by different genetic factors. This is indeed what we observed in chapter **3**, **4**, and **8.** In **chapter 8**, we performed a GWAS of a homogenous measure of hedonic well-being resulting in a h^2_{SNP} of ~6.2%. This percentage dropped to four percent in the GWAS comprised of multiple well-being measures as described in **chapter 3**. Moreover, in **chapter 4,** where we performed a multivariate GWAMA including measures of well-being, neuroticism, and depressive symptoms, SNP heritability dropped to 2.1%. On the other hand, if we consider the GCTA h^2_{SNP} estimates of 5-10% for single-item well-being measures as an upper bound[3], then we approached it pretty closely with our GWAS using a homogenous measure of well-being (h^2_{SNP} of ~6.2%). Additionally, Rietveld et al.[3] state that 12-18% of the h^2_{SNP} could be captured after correcting for measurement error. Therefore, a promising but challenging way to go forward is to re-measure well-being using similar questionnaires and perform a GWAS on the unified measures.

Biological Analyses

To shed some light on the possible biological mechanisms underlying our findings we performed several bioinformatics analyses. Previous work has demonstrated that some functional categories of the genome contribute disproportionally to the heritability of complex behavior[2,14,15]. Build on this observation Finucane et al.[16] developed stratified LD Score Regression (SLDSC), which requires only GWAS summary data together with LD information from an external reference panel matching the population structure of the GWAS. Doing so, SLDSC can distinguish between h^2_{SNP} explained by different functional categories of the genome, for instance in the central nervous system (CNS), while accounting for influence of the remaining functional categories (e.g. blood, bone, and muscle tissues). Using SLDSC, in **chapter 3** we report significant enrichment in the CNS for well-being, depression, and neuroticism, which we confirm in **chapter 4** for the well-being spectrum. **In chapter 4,** we expanded these analyses by leveraging the genome-wide results, LDSC, and an atlas of brain gene expression. Doing so, we were able to pinpoint brain regions where genes that are significantly associated with well-being are significantly enriched in their effects. We report

evidence for enrichment of genes differentially expressed in the Ventral Tegmental Area (VTA), as well as in the subiculum (part of the hippocampal formation). Furthermore, we report significant enrichment of glutamatergic neurons in the CA1 and CA3 of the hippocampus and in the prefrontal cortex as well as enrichment of GABAergic interneurons. However, as we only had specific cell types for specific regions (hippocampus and prefrontal cortex), there are some interpretational limitations. Gene expression is known to vary systematically between cell-types within the brain[17] (e.g neurons, microglia, astrocytes) and developmental phases[18] (prenatally, childhood, adulthood and old age). Although we find specific cell type enrichment for well-being, it stands to reason that the same cell type specific enrichment in other regions might exist, which we now missed. This limitation needs to be addressed in future well-being research. However, capitalizing on ongoing efforts to categorize gene expression across the human brain at increased (single cell) resolution, this will be a promising future approach to understand biological processes underlying phenotypic variation of well-being.

Epigenome-Wide Association Studies

Besides genetic influences, environmental factors play an important role in explaining variance in well-being, as evidenced by multiple twin-family studies and described in **chapter 2**. Additionally, epigenetic regulation of gene expression by mechanisms such as DNA methylation may mediate the interplay between the genetic make-up of individuals and their exposure to the environment[19,20]. In humans and animals, various early life exposures can induce stable long-term changes in DNA methylation[21–23]. Examples include early postnatal maternal behavior[23], childhood abuse [22], and prenatal maternal nutrition[21]. Later life exposures also induce changes to the methylome, for example exposure to cigarette smoke[24,25].

Recently, using epigenome-wide association studies (EWAS), changes in DNA methylation have been implicated in various complex traits such as obesity[26], type 2 diabetes[27,28,29], and educational attainment[30,31]. In **chapter 5,** we performed the first EWAS on well-being in a population-based sample (N = 2519) of adults from the Netherlands Twin Register (NTR)[32]. We identified two genome-wide significant methylation probes after correction for multiple testing (Bonferroni correction). Moreover, gene ontology (GO) analyses highlighted enrichment of several CNS categories among higher-ranking methylation probes. However, replication of these results is warranted in larger samples as (1) we are aware that potential

unmeasured confounders could have an effect on our results, and (2) we are uncertain of the direction of causation of the association between well-being and CpG methylation.

The foremost interpretational difficulty in EWAS is the uncertainty about cause and effect, e.g. does methylation causally influence complex trait outcomes, is the causal effect reverse, or does a third trait influence both methylation levels and traits? For instance, a recent study found that differential methylation is the consequence of inter-individual variation in blood lipid levels and not vice versa[33]. A second important consideration for EWAS is the assessment of methylation in trait relevant tissue. Empirical results suggest that easily accessible tissues, such as whole blood, cannot be used to address questions about inter-individual epigenomic variation in inaccessible tissues, such as the brain[34,35].

To examine these interpretational issues, we performed an EWAS meta-analysis of well-being controlled for two well-known confounders of epigenetic associations, smoking and BMI, in **chapter 6** (*N* = ~8,600). To guard against unmeasured confounding and to infer a direction of effect we performed summary-based Mendelian Randomization (SMR). In SMR, SNP effects on *cis*-methylation (*cis*-mQTLs), and a large GWAS of well-being were combined to infer the (causal) effect of CpG methylation on well-being. To assess concordance between blood and brain tissue, we performed SMR leveraging *cis*-mQTLs present in both blood and brain tissues and compared results between tissues, and between SMR and EWAS. Doing so, we found a high consistency of direction of effect ($r > .9$) between SMR results, where the mQTL was discovered in two whole blood datasets, as well as high consistency between whole blood and fetal brain datasets ($r = .72$). However, when comparing the direction of effect between our EWAS and SMR results, no notable correlations were observed. These results indicate that, if the aim is to increase our understanding of the functional consequences of epigenetic changes on wellbeing, SMR may be preferred over EWAS in whole blood. If, however, the aim is to identify ways in which well-being is itself a driver of environmental influences on differences in DNA methylation, possibly effecting gene-expression, a sufficiently powered EWAS study will provide valuable information. The concurrent use of Mendelian Randomization and epigenome-wide association analysis proved to be a potent combination to further our understanding of the relation between well-being and CpG methylation.

Well-being framework

It is well known that several mental health issues, such as anxiety, depression, neuroticism, and loneliness share a common genetic liability[36–38]. This common genetic liability offers an

explanation as to why many disorders are comorbid or present highly similar behaviors. While there have been detailed investigations of the genetic similarity and comorbidity of mental disorders, there is much less information about the genetic similarity of mental health traits such as happiness, satisfaction with life, personality, self-rated health, and flourishing. The multivariate approach in **chapter 4**, focused on the overlap within a mental health spectrum, and leveraged the genetic overlap between well-being, neuroticism, and depressive symptoms to identify genetic variant for this 3-phenotype well-being spectrum (3-WBS). Studies on traits that could additionally be considered as part of a well-being spectrum are important given the large collection of studies pointing towards the emotional, cognitive, and interpretational benefits of high levels of well-being beyond the absence of mental disorders[39–41]. In the literature, several other traits, such as loneliness, self-rated health, and personality have been found to be strongly associated with well-being. Therefore, the aim of **chapter 9** was to investigate the genetic overlap between well-being and these proposed traits. Using polygenic scoring and genetic correlations, we report that the 3-WBS is strongly genetically associated with loneliness and self-rated health. These findings suggest that these traits are interesting candidates to be included in the well-being spectrum and may increase our understanding of the causes and links between well-being and several mental and behavioral traits.

Conceptualization the well-being framework

So far, we have identified multiple genetic variants associated with well-being (**chapter 3** and **4**) and showed that well-being is related to a broad range of mental –and behavioral traits (**chapter 2**, **3**, **4**, and **9**). These studies have in common that they all use measures of life satisfaction and positive affect, which are often referred to as subjective well-being (SWB) measures. However, from a theoretical perspective, two types of well-being can predominantly be distinguished: subjective well-being (SWB) and psychological well-being (PWB), shaped by the philosophical constructs hedonism and eudaimonism, respectively. Ancient hedonism is centered around pleasure, or how good a person feels about his or her life[42]. From this perspective, well-being consists in the balance of pleasure over pain, that is: how to maximize pleasure and minimize pain (Aristippus (c. 435 – c. 356 BCE)). In contrast, eudaimonism, is more about virtue (defined as knowledge about how to live well) and human capacities. Although in contemporary sciences the terms hedonism and eudaimonism have gradually shifted to SWB and PWB, there is still an ongoing debate how these concepts relate to each other[42,44–48]. Therefore, to examine the complex framework of well-being, we

performed a literature study aiming at analyzing the current view on the relation between SWB and PWB (**chapter 7**). We found that the main consensus is that SWB and PWB are related constructs that are likely domains of a general factor well-being. However, while the constructs are related, they are not interchangeable and can be distinguished both conceptually and biologically. Based on these findings we provide some general recommendations for follow-up research.

(1) *Re-define the well-being framework.* We propose that an empirical well-being framework should be developed considering the actual empirical data rather than the ideas that inspired the research[50]. In the context of the social and behavioral sciences, the well-being framework might be best described as one hierarchical construct including both SWB and PWB constructs. This means that hedonism and eudaimonism are not to be defined as two clearly separated streams, but as related underlying domains of the same construct

(2) *Be detailed.* It is often taken for granted that when we are using the same words, we mean the same things. As it turns out, at least in the field of well-being, we should be more cautious about this assumption. For example, SWB can be referred to as "happiness", "hedonism", "subjective happiness", "emotional well-being" and "affective well-being". This inconsistency might lead to interpretational issues of study results. To overcome this, the most feasible solution would be for researchers to be detailed about the constructs they aim to be measuring and about the scope of their study. This means that researchers should: 1) be consistent in their use of terminology; 2) give detailed descriptions of their most basic terms and constructs, and; 3) keep in mind that the results of their study might not cover well-being in its entirety.

To add weight into the discussion to what extent hedonic –and eudaimonic well-being relate to each other, we had to wait for the availability of a sufficient powered molecular-genetic dataset with measures of eudaimonic well-being (**Chapter 8**). With the release of the UK Biobank data, we were able to conduct a GWAS, where the question: "*To what extent do you feel your life to be meaningful*" served a proxy-phenotype for eudaimonic well-being in ~110,000 participants. Paired to this analysis, we conducted a GWAS where the question: "*In general how happy are you*" served as a proxy phenotype for hedonic well-being. We identified the first two genetic variants associated with eudaimonic well-being as well as six genetic variants for hedonic well-being. Moreover, the genetic correlation between both measures was, as expected, large (r_g = 0.78), suggesting a large shared genetic etiology.

Further evidence for a shared genetic architecture between both measures is provided by the similar patterns of genetic correlations with other traits (e.g. depressive symptoms, personality, and loneliness). These results complement our results found in the literature review (**chapter 7**) and indicate that both constructs can be seen as two related underlying domains of the same construct.

Future perspectives

Enormous progress has been made in the field of human genetics the last four years, with a tsunami of genetic associations with numerous traits identified as a consequence. In line with this progress, we reported the first 3 genetic variants associated with well-being in 2016, while two years later, this number increased to 319 genetic variants (**chapter 3** and **4).** Similar progress has been made for other phenotypes, like depression[51], education attainment[10], neuroticism[12] and human intelligence[52]. These studies are staggering proof that the field of complex traits genetics has become increasingly successful in the last couple of years. With this progress, new questions arise. Valid questions, like how we should interpret these results and what the next steps are to take. Of course, there are no conclusive answers to these questions yet, but for (genetic)-research involving well-being, the following opportunities are worth exploring.

From association to causation

The high genetic correlation between different measures of well-being, as well as between well-being and other complex traits, such as neuroticism, depressive symptoms, and self-rated health, can be a product of a causal relationship between the traits, a third factor that influences the traits or a combination of both mechanisms. Although progress is being made in detecting causal relationships between correlated traits using Mendelian Randomization (MR), presence of horizontal pleiotropy can bias results. Horizontal pleiotropy occurs when the variant has an effect on the outcome outside of its effect on the exposure in MR. The presence of horizontal pleiotropy has been demonstrated by a recent study that developed a software tool called MR-PRESSO, showing that horizontal pleiotropy was detectable in over 48% of significant causal relationships reported in MR-analyses[53]. A solution to overcome biased results in MR analyses is to include very strong instrumental variables. Given that the genome-wide significant SNPs associated with well-being explain typically little of the phenotypic variance (~ 0.01%), it will be difficult, to construct strong instrumental variables for well-being. There is, however, reason for optimism. Many methods that are better able to

cope with pleiotropy have been proposed recently, such as the genetic instrumental variable (GIV) regression[54] and two-sample MR (2S-MR)[55–57]. In addition to these MR methods for inferring causal relationships between two traits, one could ask how much of the relationship is mediated by a third factor. Given the high correlations between well-being and numerous traits (see **chapter 8** and **9**), this would be a reasonable scenario. To test this, the recently developed Genomic structural equation modelling SEM approach[58] might be an informative way to go forward and lay the groundwork for a novel multi-faceted approach in investigating the well-being spectrum, and progress from showing association, to understanding direction of causation.

From genetic variants to biological functioning

The number of identified genetic loci for well-being has increased spectacularly in recent years as described in multiple chapters in this thesis. These findings are largely driven by the release of large-scale genetic-data sets such as the UK biobank. The next challenge is to improve our understanding of the biological effects of these genetic risk loci, especially since the actual genes mediating phenotypic variation are not necessary proximal to the lead SNPs identified in genome-wide association studies (GWASs). Supported by the observation that GWAS variants are preferentially located in enhancers and open chromatin regions[59,60], the majority of common genetic risk factors are predicted to influence gene regulation, either directly or through modifiable epi-genetic processes, rather than directly affect the coding sequence of transcribed proteins[61]. Therefore, a promising way to go forward is to first identify the causal variants (eQTL) influencing gene-expression, using for instance SMR. Next, software tools like FUMA (Functional Mapping and Annotation of Genome-Wide Association Studies[62]), which utilize information from different databases and methods can be used. Using FUMA, functional consequences on gene functions, deleteriousness, regulatory functions, and biological pathways can be revealed from the causal SNPs identified in the first step. In chapter **4** and **5** we made a first step in identifying causal variants influencing gene-expression or methylation –expression, and it is expected that this strategy will result in new insights in the biological underpinnings of the well-being spectrum.

The effect of parental genotypes

Another promising way to go forward is to include, the often ignored, genetic variants in the parental genomes that are *not* transmitted to a child in the studies of well-being. A recent paper Kong et al.[63] showed that non-transmitted alleles canstill affect a child through the

impact of the alless on the parents themselves or on other relatives (such as siblings), a phenomenon they called "genetic nurturing". Kong et al. showed, using education attainment as an example, that polygenic scores computed from the non-transmitted alleles have an estimated effect on the educational attainment of that child that is roughly 30% of the magnitude of the polygenic scores based on the transmitted alleles. It would add a novel layer to "*the genetics of well-being"* if it could be demonstrated that genetic nurturing exists and has an impact on the variance of well-being in the off-spring.

Phenotypic innovations

Beside the progress in the field of human genetics, there have been major methodological advances in measuring complex behaviors .

Social Media

For example, recent work in language use has shown its innovative power to assess complex behavior. Self-report surveys provide a snapshot in time. Online social media data, on the other hand, may 'fill in the gaps' with ongoing 'in the moment measures' of a broad range of people's thoughts and feelings and provide real-time assessment of well-being. For instance, it has been shown that patterns in a community's Twitter language predict several health outcomes, including community-level disease mortality[64], depression and mental illness[65], and ADHD[66]. Moreover, it has been shown that social media language derived personality assessments match the psychometric quality of observer-report through surveys[67]. It would be very interesting to examine whether language use expressed through social media predict levels of well-being and to assess the genetic component of it. As pointed out in in **chapter 3, 4, 8,** and **9,** well-being is related to a broad range of positive *and* negative traits. The widespread use of social media may therefore provide additional opportunities to the detection of otherwise undiagnosed cases.

Sensor data

Besides social media use, sensors in everyday devices, such as our phones, wearables, and computers, leave a stream of digital traces. These traces can be captured, analyzed ,and related to human behavior (for review see Mohr et al.)[68]. For example, by leveraging built-in sensors, a number of smartphone-based sensing systems have been developed to passively monitor sleep periods. Several groups have shown that sleep duration can be estimated with approximately 90% accuracy, without asking the user to do anything special with the

phone[69,70]. In turn, these sleep period markers have been correlated to the severity of depressive symptoms[71] and a strong genetic correlation has been onserved between well-being and insomnia (Hammerslag et al., 2017). Although numerous challenges must be overcome before these types of measures become viable for large scale epidemiological deployment, recent technological progresses in machine learning methods give rise to a certain level of optimism. It would be very interesting for future studies to focus on sensor dating in relation to well-being and related traits.

Societal Impact

Well-being and the prevention of Mental Illness

Happy people are healthy people: they live longer, function better, and are less susceptible to mental illness[41]. Given the power and potential of happiness, the previous lack of insight into the causes of individual differences in happiness and the persistence of isolated approaches from different disciplines was surprising. With the work in my thesis I have added some pieces to the complex puzzle of well-being. As a future perspective, I anticipate that a focus on well-being could be very beneficial for the society at large. In the field of epidemiology, for example, it has been proposed that larger benefits to overall public health are to be expected when the bell curve of mental health in the human population is shifted a little to the healthy side, the so-called population strategy[75,76]. So, a relatively slight increase in the level of well-being of the majority of the population may have a larger preventive effect than targeting the much smaller group of people at high risk or in the early stages of mental illness. To this end, knowledge on the causes of individual differences in well-being and modifiable risk and protective factors is crucial.

Support for the potential preventive role of well-being to prevent mental illness is provided in **chapter 2**, where I showed that the phenotypic relationship between well-being and depressive symptoms is largest in adolescence and young adults, with genetic effects explaining most of this correlation. In other words, a genetic predisposition for increased levels of well-being will probably have a protective effect in developing these depressive symptoms. In combination with the strong genetic correlations of well-being with depressive symptoms, neuroticism, loneliness, and self-rated health as reported in **chapter 3**,**4,** and **9**, it might be worth to investigate the effects of positive psychology interventions for prevention of (mental) illness.

To date, two meta-analyses that examined the overall effects of positive psychology interventions (PPI) have been published. The first meta-analysis[77] included 51 controlled studies and found that PPI significantly enhance well-being (mean r = 0.29) *and* decrease depressive symptoms (r = 0.31). The second meta-analysis included 39 randomized controlled trial studies (N ~ 6,100)[78], including PPIs such as self-help interventions, group training and individual therapy. They reported a standardized mean difference of 0.34 for subjective well-being, 0.20 for psychological well-being and 0.23 for depressive symptoms. These effect sizes attenuated at follow up (3 to 6 months) but were still significant, indicating that effects are fairly sustainable. Together, these studies indicate that engaging in simple positive activities can reliably increase an individual's level of well-being as well as decrease someone's depressive symptoms. Given that there is some evidence that Positive Psychology interventions might be effective, it is essential to understand the causes of difference in intervention response. As a first step, Haworth and colleagues[79] revealed minimal changes in the overall magnitude of genetic and environmental influence on individual differences during the intervention, despite significant improvements in overall well-being. They furthermore showed that the genetic factors important for intervention response were the same as those influencing baseline well-being scores. This indicates that the genetic findings in my thesis could be informative in the development of personalized positive prevention interventions.

To conclude, during my PhD trajectory, I have witnessed the enormous progress the field of human genetics has made from the frontline. On this wave of progress, my work has contributed to a better understanding of the factors influencing phenotypic variation in well-being, a phenotype that is affecting us all.

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