


ORIGINAL ARTICLE

Predicting loneliness with polygenic scores of social, psychological and psychiatric traits

A. Abdellaoui^{1,2}  | M. G. Nivard¹ | J.-J. Hottenga¹ | I. Fedko¹ | K. J. H. Verweij² | B. M. L. Baselmans^{1,3} | E. A. Ehli⁴ | G. E. Davies⁴ | M. Bartels^{1,3,5} | D. I. Boomsma^{1,3,5} | J. T. Cacioppo⁶

¹Department of Biological Psychology, Vrije Universiteit, Amsterdam, The Netherlands

²Department of Psychiatry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

³Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

⁴Avera Institute for Human Genetics, Sioux Falls, South Dakota

⁵Amsterdam Neuroscience, Amsterdam, The Netherlands

⁶Department of Psychology, University of Chicago, Chicago, Illinois

Correspondence

A. Abdellaoui, Department of Psychiatry, Academic Medical Center, University of Amsterdam, Meibergdreef 5, 1105 AZ, Amsterdam, The Netherlands.
Email: a.abdellaoui@amc.uva.nl

Funding information

National Institute of Mental Health, Grant/Award Number: R37 AG033590-08 ; Department of Psychology and Education of the VU University Amsterdam; Dutch Brain Foundation; Netherlands Scientific Organization (NWO), Grant/Award Number: 480-05-003; NIMH; Grand Opportunity, Grant/Award Numbers: 1RC2 MH089995-01, 1RC2MH089951-01; Foundation for the US National Institutes of Health (NIMH), Grant/Award Number: MH081802; National Institutes of Health (NIH), Grant/Award Number: R01D0042157-01A; Avera Institute for Human Genetics, Sioux Falls, South Dakota (USA); Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL), Grant/Award Number: 184.021.007; Spinozapremie, Grant/Award Number: 56-464-14192; Middelgroot, Grant/Award Number: 911-09-032; ZonMW Addiction, Grant/Award Number: 31160008; NWO-VENI, Grant/Award Number: 451-04-034; NWO-bilateral agreement, Grant/Award Number: 463-06-001; NWO: MagW/ZonMW, Grant/Award Numbers: 400-05-717, 480-04-004, 904-61-193, 985-10-002, 904-61-090; Foundation Volksbond Rotterdam Netherlands Organization for Scientific Research; Royal Netherlands Academy of Science Professor Award, Grant/Award Number: PAH/6635

Loneliness is a heritable trait that accompanies multiple disorders. The association between loneliness and mental health indices may partly be due to inherited biological factors. We constructed polygenic scores for 27 traits related to behavior, cognition and mental health and tested their prediction for self-reported loneliness in a population-based sample of 8798 Dutch individuals. Polygenic scores for major depressive disorder (MDD), schizophrenia and bipolar disorder were significantly associated with loneliness. Of the Big Five personality dimensions, polygenic scores for neuroticism and conscientiousness also significantly predicted loneliness, as did the polygenic scores for subjective well-being, tiredness and self-rated health. When including all polygenic scores simultaneously into one model, only 2 major depression polygenic scores remained as significant predictors of loneliness. When controlling only for these 2 MDD polygenic scores, only neuroticism and schizophrenia remain significant. The total variation explained by all polygenic scores collectively was 1.7%. The association between the propensity to feel lonely and the susceptibility to psychiatric disorders thus pointed to a shared genetic etiology. The predictive power of polygenic scores will increase as the power of the genome-wide association studies on which they are based increases and may lead to clinically useful polygenic scores that can inform on the genetic predisposition to loneliness and mental health.

KEYWORDS

genetic correlation, genetic prediction, loneliness, major depressive disorder, polygenic scores

Dorret I. Boomsma and John T. Cacioppo contributed equally to this study.

1 | INTRODUCTION

Loneliness is an aversive state that people experience when there is a discrepancy between desired and actual social relationships. The physiological and psychological reactions to loneliness are mechanisms which are likely to have evolved to put the body in a heightened state of alertness in order to prompt us to improve our social circumstances.^{1,2} Loneliness is an unwanted state whereas solitude indicates a preference for being alone. The capacity to tolerate solitude may have potential evolutionary benefits (eg, less stress due to dominance hierarchy, less depletion of resources, increased freedom to choose one's own mental and physical activities³), which may have contributed to the evolution of differential preference for solitude, and thereby individual differences in the susceptibility to loneliness. Like many other quantitative dimensions that show individual differences, falling in the extreme of the distribution is likely to coincide with mental or physical health problems.⁴ Chronic loneliness is characterized by high negative affectivity and social withdrawal and often encompasses psychiatric conditions such as major depression or schizophrenia.⁵ When these strong aversive signals of perceived isolation remain present for prolonged periods, they can have detrimental consequences to overall health.^{6–12} A meta-analysis of approximately 3.4 million subjects from 70 independent studies found loneliness to increase the likelihood of death with 26% to 32% within the 7 years that subjects were monitored, which is comparable to the impact of obesity and cigarette smoking.¹¹

Like all human behavioral traits,¹³ individual differences in the propensity to feel lonely are partly inherited. Heritability estimates from twin and family studies range from 26% to 58% in children, while in adults the largest study ($N = 8683$) estimated genetic influences at 37%.^{14–19} The rapid developments in human molecular genetics will likely result in an improvement of the predictive value of measured genetic variants for complex psychological and psychiatric traits. The prediction of genetic mental health risks can be particularly useful during earlier development. The ability to estimate one's genetic predisposition for loneliness and related health risks in an early stage could lead to more effective deployment of environmental interventions, which can eventually translate to improved public health and well-being. Genome-wide association studies (GWASs) have only recently reached sufficiently large sample sizes to detect robust and replicable associations between genetic variants and the highly polygenic psychiatric and psychological traits. Significantly associated single nucleotide polymorphisms (SNPs), however, generally explain very little variance individually (<1%), and all genome-wide significant SNPs together usually explain no more than a few percent, although with increases in sample size of GWASs this is rapidly changing. Several methods that look at SNP-based heritabilities, estimated by software packages such as GCTA-GREML,²⁰ and linkage disequilibrium (LD) score regression,²¹ and the association of polygenic scores with phenotypes²² explain phenotypic variation based on larger sets of SNPs than only those SNP that reach genome-wide significance. These approaches indicate that the ensemble of nonsignificant SNPs contain a substantial amount of signal due to true polygenic effects on a trait, which means that effect size estimates of many nonsignificant SNPs

may still have a predictive value. GCTA-GREML and LD score regression have shown that the aggregate of all measured SNPs explain about 14% of the individual differences in loneliness.^{23,24} The predictive value of polygenic scores based on individual level DNA data have potential clinical utility beyond that of methods that only estimate SNP-based heritability (eg, GCTA-GREML²⁵ and LD score regression²¹), that is why it is important to test their predictive value as we do in our study. Powerful polygenic scores can potentially be used in the clinic as estimates of genetic risk, and have additional applications in a research context, such as the study of interactions between genetic risk and environmental exposures.^{26,27}

In this study, we use genome-wide SNP genotypes to compute polygenic scores for a range of traits related to loneliness and assess their predictive value for loneliness. Polygenic scores are indicators of the genetic predisposition of a certain trait and are computed by summing all individual alleles weighted by the estimated effect sizes for a specific trait. The predictive power of the polygenic scores is strongly related to the statistical power of the GWASs that produce the effect size estimates.

As loneliness is associated with a wide range of psychological, social and psychiatric traits on which large GWASs have been conducted, we will construct polygenic scores with effect size estimates from a large collection of those GWASs. Loneliness has been associated with a higher prevalence of several psychiatric and neurological disorders,^{28,29} of which we included the following: major depressive disorder (MDD), bipolar disorder, schizophrenia, autism, anorexia, anxiety disorder, attention deficit hyperactivity disorder (ADHD), Alzheimer's disease and migraine. Polygenic scores were also computed for the Big Five personality dimensions, which have been associated with loneliness in several studies, with neuroticism and extraversion generally showing the strongest associations with loneliness (positive and negative associations, respectively).^{23,30–32} From epidemiological studies we also know that lonely individuals have lower levels of well-being,³³ more depressive symptoms,^{34,35} more substance use,^{36,37} more fatigue,^{38,39} lower self-rated health,⁴⁰ tend to live in poorer neighborhoods⁴¹ and reach lower educational attainment.^{18,42–44} Some of these associations may be explained by related socioeconomic factors;⁴⁵ in this paper we test whether there is a shared genetic etiology.

The primary aim of this study was to identify which social, psychological and psychiatric traits share their genetic etiology with loneliness to such an extent that they can be used to produce polygenic scores that have predictive value for loneliness in a population-based sample. Before we tested the associations of polygenic scores with loneliness, we established which polygenic scores would attain sufficient statistical power. The statistical power depends on the genetic correlation between the traits and loneliness, and the accuracy of the estimated allelic effect sizes, which depends on the power of the GWASs.

2 | METHODS AND MATERIALS

2.1 | Subjects and phenotype data

Data on loneliness were collected by the Netherlands Twin Register (NTR) in >30 000 twins and their family members across the

Netherlands between 2004 and 2016, of which 8798 adult subjects (3206 males and 5592 females; ages 18–91, mean age = 45.3, median age = 43) were genotyped.^{17,46,47} Loneliness was measured by the short scale for assessing loneliness in large epidemiological studies, developed by Hughes et al,⁴⁸ and contains 3 items from the Revised University of California, Los Angeles, (R-UCLA) loneliness scale⁴⁹: (1) *How often do you feel left out?*, (2) *How often do you feel isolated from others?* and (3) *How often do you feel that you lack companionship?*. Response categories are: (1) hardly ever, (2) some of the time and (3) often. The 3 responses were summed to obtain the loneliness score, with higher scores indicating more loneliness. Because of a skewed distribution, the loneliness score was log-transformed for all analyses. This study was approved by the Central Ethics Committee on Research Involving Human Subjects of the Vrije Universiteit (VU) University Medical Centre, Amsterdam, an Institutional Review Board certified by the US Office of Human Research Protections (IRB number IRB-2991 under Federal-wide Assurance-3703; IRB/institute codes, NTR 03-180). All subjects provided written informed consent.

2.2 | Genotyping, quality control, imputation and PCA

Genotyping was carried out on several genome-wide SNP microarrays.⁵⁰ Genotyped data were cross-platform imputed using the Genome of the Netherlands (GoNL)^{51,52} as a reference set to infer the SNPs missing per platform in the combined data.⁵³ For preimputation quality control (QC) we excluded alleles with reference set allele frequency differences of >10%, SNPs with minor allele frequency (MAF) <.005, deviation from Hardy-Weinberg Equilibrium (HWE) with $P < 10^{-12}$, and a genotyping call rate <.95. We excluded samples that met the following criteria: a genotyping call rate <.90, inbreeding coefficient from PLINK 1.90⁵⁴ (F) <-.075 or >.075, Affymetrix Contrast QC metric <.40, the Mendelian error rate >5 SD from the mean, or a gender or identity-by-state (IBS) status that did not agree with known relationship status and genotypic assessment. Phasing and imputation was performed with MaCH-Admix 2.0.203⁵⁵ software. After imputation, SNPs that were significantly associated with genotyping platform ($P < 10^{-5}$), that had an allele frequency difference of >10% with GoNL reference set, HWE $P < 10^{-5}$, Mendelian error rate >5 SD from mean over all markers, or an imputation quality $R^2 < .90$ were excluded. We then performed a principal components analysis (PCA) to exclude individuals with a non-Dutch ancestry and control for Dutch population stratification following procedures described in Abdellaoui et al.⁵⁶ All SNPs that survived QC ($N = 1\,224\,793$) were used to construct polygenic scores.

2.3 | Power analysis

GWAS summary statistics were available for 31 complex traits related to loneliness. We first investigated which of them would have sufficient power to predict loneliness assuming a genetic correlation of .8, using the power calculation method devised by Dudbridge.²² The power was computed as a function of 7 parameters in the case of continuous traits, and 9 in the case of binary traits: (1) the significance threshold (set at a Bonferroni corrected alpha of

.05/24 = .0022; where 24 is the number of *independent* polygenic scores, derived by a PCA on the polygenic scores: the number of independent polygenic scores was set at the number of principal components [PCs] that explain >95% of the variance), (2) the genetic correlation between the trait and loneliness, (3) the sample size of the GWAS, (4) the sample size of the target sample ($N = 8798$), (5) the SNP-based heritability, which were based on LD score regression²¹ estimates (with 14% for loneliness based on the Gao et al GWAS,²⁴ because our own sample was underpowered for LD score regression and gave heritability estimates of 0%; the heritability of the other traits are depicted in Table 1), (6) the number of independent SNPs in the target sample (148 681 SNPs, computed by pruning for LD in PLINK⁵⁴), (7) the assumed fraction of causal markers (which we set to .3 based on estimates of previous studies on cognitive and psychiatric traits^{74,75}), and in the case of binary traits, also (8) the trait prevalence in the general population and (9) case/control sampling fraction in the GWAS study. We only included traits in subsequent analyses that reached statistical power of >50% assuming a genetic correlation of .8. For the traits that reached sufficient power, we recomputed the power 4 times with an adjusted Bonferroni significance threshold (.05/number of independent polygenic scores computed with a PCA as the number of PCs that explain >95% of the variance) assuming genetic correlations of .2, .4, .6 and .8 (Table 1). Using the power calculation method and R-code developed by Dudbridge,²² we built a web-version of the power-calculator for general use that can be found at https://eagenetics.shinyapps.io/power_website/.

2.4 | Polygenic scores

Polygenic scores were created with the estimated effect sizes from recent large GWASs (see references in the first column of Table 1). If NTR studies were part of the meta-analysis, the summary statistics were recomputed excluding NTR subjects in order to avoid an overestimation of the association between the polygenic scores and loneliness.⁷⁶ The polygenic scores were computed using LDpred,⁷⁵ which models LD using the LD structure of a reference sample (all 5 European populations from the 1000 Genomes dataset in our case: Utah Residents with Northern and Western European Ancestry, Finnish, British, Iberian and Toscani individuals, $N = 381$). Vilhjalmsson et al⁷⁵ showed with simulations and empirically that this method outperforms traditional approaches.⁷⁵ This method needs the assumed fraction of causal markers as an input parameter, which we set at .3, based on estimates of previous studies on cognitive and psychiatric traits.^{74,75} Association analyses were carried out using generalized estimation equations (GEE) in (SPSS 22.0, IBM Corp, Armonk, NY). An exchangeable conditional covariance matrix was used to account for the relatedness among subjects (ie, we allowed for correlated residuals between members of the same family) and tests were based on the robust (sandwich-corrected) SEs.⁷⁷ The first 10 genomic PCs, age and sex were included in the model as fixed effects. The association analyses were first conducted for each polygenic score separately, then with all polygenic scores simultaneously in one model.

TABLE 1 Sample sizes (N-GWAS), heritability estimates (h^2 LDSC) of the GWAS summary statistics from LD score regression and the power to detect an association between loneliness and the polygenic scores given a genetic correlation (r_g) of .2, .4, .6 and .8

Polygenic score	N-GWAS	h^2 LDSC	Power if $r_g = .2$	Power if $r_g = .4$	Power if $r_g = .6$	Power if $r_g = .8$
MDD (23andMe) ⁵⁷	224 472	.07	.08	.61	.97	1
MDD (MDD2-PGC) ⁵⁸	160 125	.11	.11	.75	.99	1
Neuroticism (23andMe) ⁵⁹	59 206	.11	.05	.42	.89	1
Schizophrenia ⁶⁰	79 845	.45	.77	1	1	1
Neuroticism (GPC) ⁶¹	164 489	.09	.16	.87	1	1
Subjective well-being ⁶¹	298 420	.03	.08	.60	.97	1
Bipolar and Schizophrenia ⁶²	39 202	.37	.25	.95	1	1
Depressive symptoms ⁶¹	146 251	.05	.06	.48	.93	1
Tiredness ⁶³	108 976	.07	.06	.49	.94	1
Bipolar disorder ⁶²	63 766	.43	.14	.83	1	1
Conscientiousness (23andMe) ⁵⁹	59 176	.09	.04	.32	.80	.98
Self-rated health ⁶⁴	111 749	.10	.11	.73	.99	1
Extraversion (23andMe) ⁵⁹	59 225	.18	.10	.71	.99	1
Anorexia ⁶⁵	17 767	.56	.20	.92	1	1
Openness (23andMe) ⁵⁹	59 176	.10	.04	.37	.85	.99
Autism ⁶⁶	10 263	.46	.06	.51	.95	1
Social deprivation index ⁶⁷	112 151	.04	.03	.24	.68	.95
Migraine ⁶⁸	196 685	.04	.02	.16	.52	.87
Agreeableness (23andMe) ⁵⁹	59 173	.08	.03	.27	.73	.97
Alzheimer's disease ⁶⁹	54 162	.07	.01	.10	.35	.69
Educational attainment ⁷⁰	321 852	.12	.54	1	1	1
Extraversion (GPC) ⁷¹	56 614	.06	.02	.16	.52	.86
Bipolar vs schizophrenia ⁶²	16 381	.33	.06	.48	.93	1
Alcohol use ⁷²	66 700	.05	.02	.16	.51	.86
Smoking: Ever vs never ⁷³	69 207	.08	.03	.21	.63	.93
Smoking: Cigs per day ⁷³	35 173	.06	.01	.08	.27	.59
Income ⁶⁷	112 151	.06	.05	.42	.89	1

3 | RESULTS

We first investigated the statistical power of the polygenic score prediction given a genetic correlation of .8 with loneliness. There were 4 polygenic scores with less than 50% power to detect an association, namely: loneliness based on the GWAS in the Health and Retirement Study (HRS)²⁴ (continuous and categorical; power: 14% and 20%, respectively), ADHD⁷⁸ (power = 26%) and melancholic MDD⁷⁹ (power = 46%). These traits were excluded from subsequent analyses, and the power was recomputed for the 27 remaining traits assuming genetic correlations of .2, .4, .6 and .8 (Table 1).

The GEE association analyses were corrected for sex, age and the first 10 genetic PCs. When including only the covariates, only sex and age were significantly associated with loneliness, with women and younger individuals reporting higher levels of loneliness (sex: standardized $B = -.124$, $P = 8.3 \times 10^{-9}$; age: standardized $B = -.071$, $P = 2.5 \times 10^{-10}$). Out of the 27 polygenic scores that survived the power analyses, 12 were significantly associated with loneliness when tested separately, with standardized B 's varying between .04 and .08: MDD (2 distinct studies, one based on self-report in a web-based survey,⁵⁷ and one on structured clinical interviews, clinician-administered checklists, hospital/medical records or self-report⁵⁸), neuroticism (2 distinct studies, one based on a web-based

implementation of the Big Five Inventory (BFI),⁵⁹ and one on a combination of the NEO Personality Inventory, Eysenck Personality Questionnaire and the International Personality and Item Pool Inventory⁶¹), schizophrenia, subjective well-being, the genes shared between schizophrenia and bipolar disorder, depressive symptoms, tiredness, bipolar disorder, conscientiousness and self-rated health ($P < .002$; see Figure 1). Polygenic scores for extraversion, anorexia, openness and autism reached nominal significance ($P < .05$). Twelve polygenic scores did not reach significance, despite sufficient power to detect associations with traits with medium to high genetic correlations. All psychiatric disorders were positively associated with loneliness, that is, a higher genetic risk for psychiatric disease was associated with increased loneliness. A higher genetic predisposition for neuroticism, openness, tiredness or self-rated health was associated with higher levels of loneliness. Negative associations were observed for well-being, conscientiousness and extraversion.

As expected from the genetic correlations among psychological and psychiatric traits, the polygenic scores show considerable correlations with each other (see correlation matrix in Figure 2). We analyzed all 27 polygenic scores simultaneously in one model in order to assess their independent contributions: only the 2 MDD scores reached significance after multiple testing correction (Figure 1). In order to test whether these 2 MDD scores were responsible for associations with

the other traits, we repeated the analyses for all other scores while correcting for the 2 MDD scores by including them as covariates in the GEE model. Only neuroticism and schizophrenia remained significant after controlling for the 2 MDD scores (Figure 1).

The polygenic scores collectively explain 1.7% of the variance, while the 2 MDD scores together explain 1.1%.

4 | DISCUSSION

As genomic studies are advancing, it is becoming evident that much, if not most, of human phenotypic variation is influenced by genetic

variants of pleiotropic nature.⁸⁰ Psychiatric disorders show a substantial genetic overlap with each other and with nonpsychiatric cognitive and behavioral traits.⁸¹ In this study, we investigated the predictive power of polygenic scores of a large collection of personality, cognition and physical and mental health-related traits on feeling lonely. We constructed the polygenic scores from genome-wide SNP data in a Dutch population-based cohort using summary statistics from a wide range of GWASs. Significant predictive power was observed for polygenic scores of about half of the traits tested. When including all polygenic scores simultaneously in one model, only 2 polygenic scores remained significantly associated with loneliness after multiple testing correction, both for indices of MDD. The independent

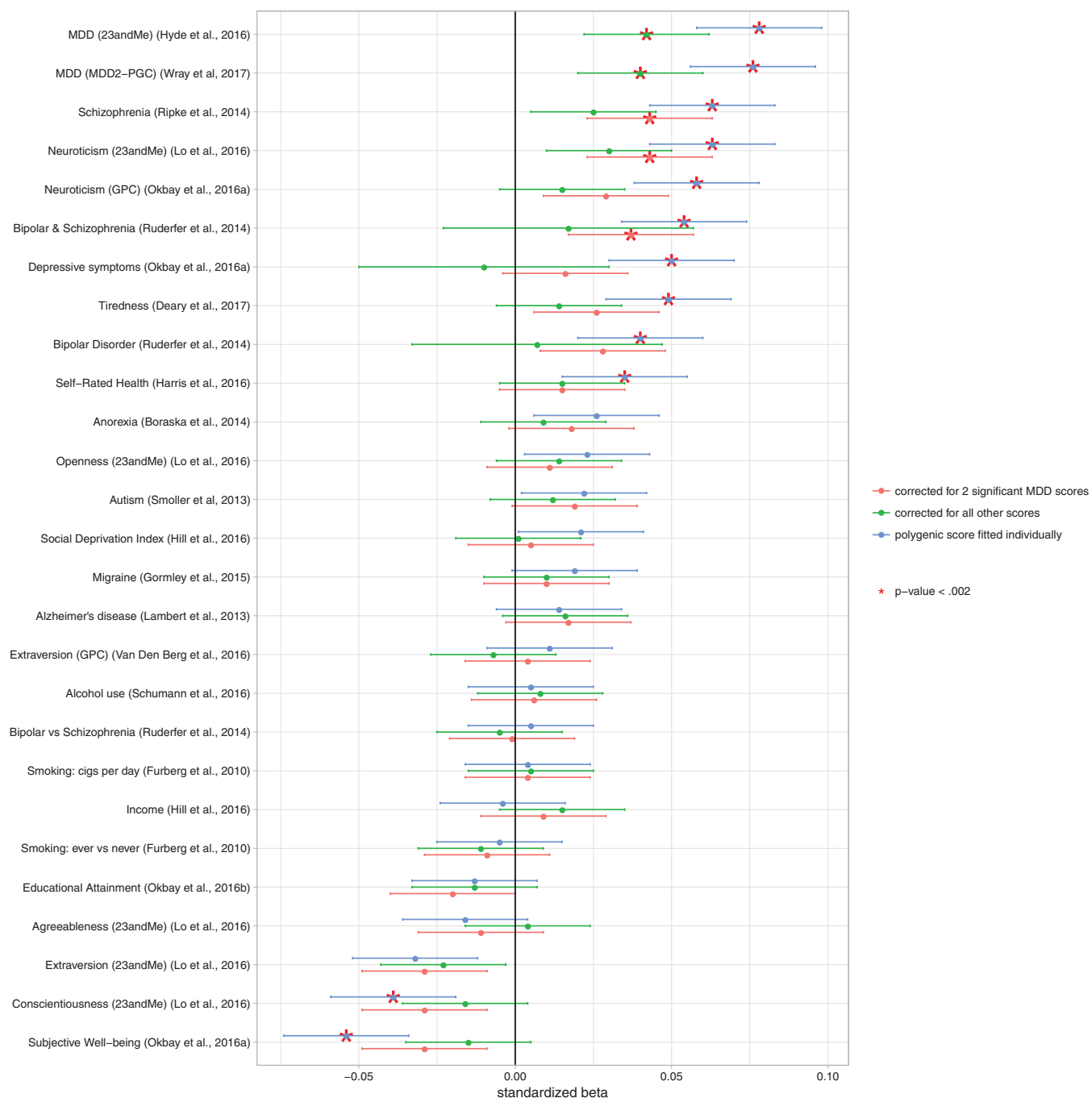


FIGURE 1 Results of the GEE association analyses between loneliness and polygenic scores (ordered on effect size of the analyses of individual scores); $N = 8798$. Bonferroni corrected $\alpha: .05/24$ independent tests = .002, where the independence was determined by PCA

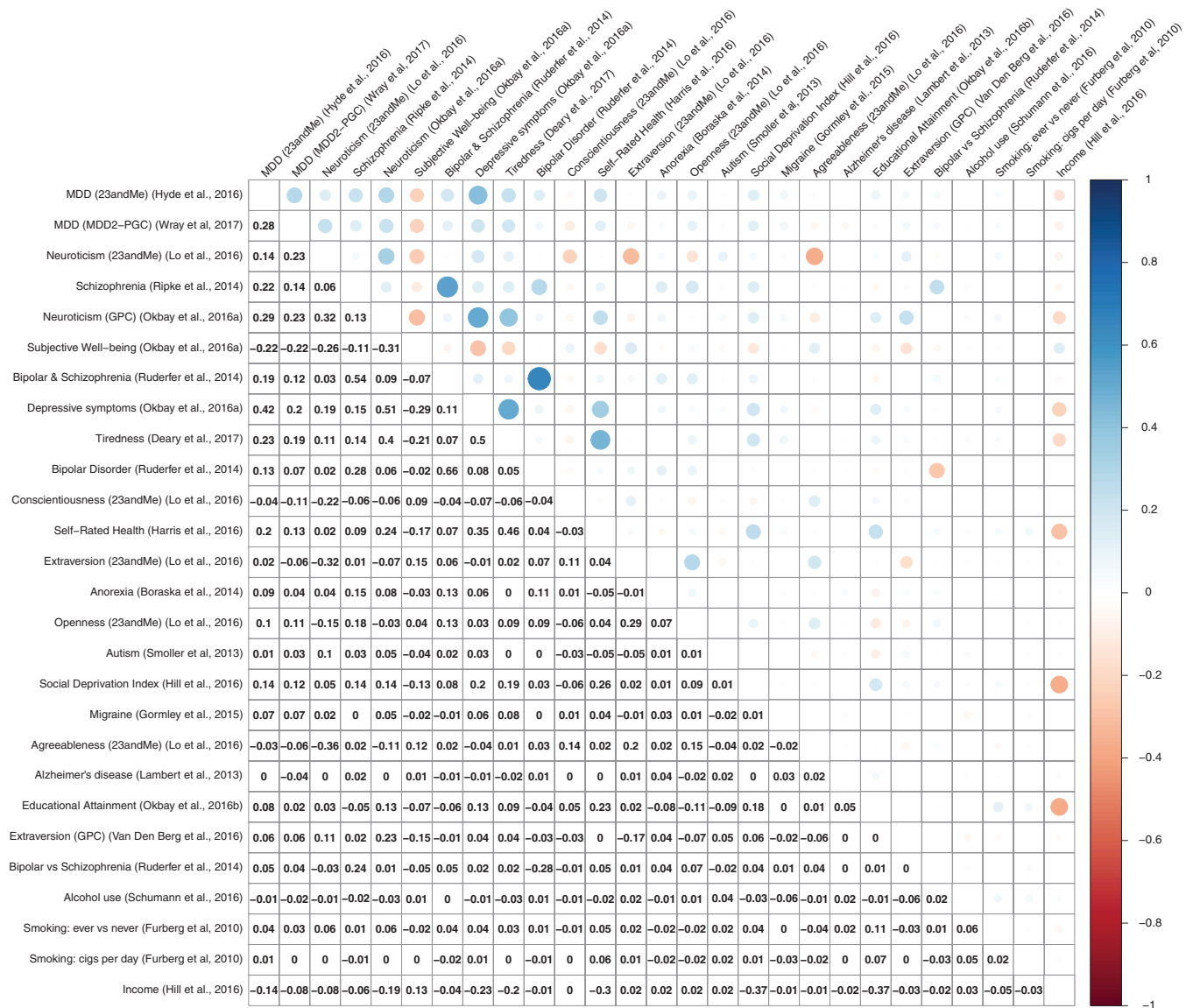


FIGURE 2 Partial correlations between 27 polygenic scores, adjusted for sex, age and the first 10 genetic principal components. The size of circles corresponds to the strength of the correlation

contributions of the 2 MDD scores, which only capture a relatively small part of MDD heritability, imply that they contain unique information about genetic risk for MDD and its overlap with loneliness (which is also reflected in the relatively low correlation between the 2 MDD scores of .28 in Figure 2). One MDD index was based on a recent large GWAS conducted by 23andMe,⁵⁷ where clinical diagnoses of depression were identified through self-report in web-based surveys. The second score was based on a GWAS from the Psychiatric Genomics Consortium,⁵⁸ where cases were identified through structured diagnostic instruments from direct interviews by trained interviewers, clinician-administered Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) checklists, hospital/medical records or self-reported clinical diagnoses. It is not clear whether the difference between the unique genetic risks captured by the 2 scores are due to a difference in the phenotype or sample ascertainment or due to chance fluctuations in effect-size estimates of individual SNPs between studies. MDD has a substantial genetic overlap with all traits that show an association with loneliness in our

study,^{57,59,61,63,64,66,81,82} and the genetic factors responsible for that overlap partly explain their association with loneliness. In other words, genes that cause a relationship between loneliness and personality, well-being, schizophrenia, bipolar disorder, tiredness or self-rated health include genes that are involved in depression as well. The MDD scores did not fully explain the associations with all other associated traits: neuroticism, schizophrenia and schizophrenia and bipolar disorder remained significant after correcting for only the 2 MDD scores.

Loneliness and depression are both aversive and unpleasant states, but there is much evidence showing that they are statistically and conceptually different constructs.^{34,35,83} Loneliness has been characterized as negative feelings about one's perceived inadequacy of social connections, while depression entails negative feelings in general.⁸⁴ Highly prevalent behavioral and mental states such as loneliness and depression may have been beneficial adaptations of our ancestors, because they may have increased their chances of survival and reproduction under certain conditions. It remains challenging to

identify such adaptive roots with much certainty.⁸⁵ The prevailing hypothesis on the evolutionary benefits of loneliness is based on humans having adapted to live in groups; for social creatures, loneliness may have increased the chances for survival and reproduction through the motivation to improve one's social circumstances.¹ A related evolutionary mechanism that has been widely proposed for depression is the social risk hypothesis, in which depression causes one to minimize the risk of social exclusion due to an imbalance of one's social value and social burden.^{86,87} The analytical rumination hypothesis⁸⁸ for depression is also in line with existing evolutionary explanations of loneliness, in which depression-related problems (in the case of loneliness: perceived social isolation) are given priority access to the limited processing resources of the brain by decreasing positive affect and desire for other activities. The analytical rumination hypothesis would explain why loneliness increases depressive symptoms, while depression influences loneliness in much lesser extent,^{34,35} and why sensitivity for negative social cues is increased in lonely people.^{7,89-92} This increase of sensitivity of negative social cues is in line with the evidence for the existence of different subtypes of low mood to cope with different kinds of fitness-relevant situations.⁹³ In this context, loneliness could be interpreted as the employment of specific biological "depression" faculties to cope with or warn against a specific fitness-threatening situation (social isolation), just as there are specific types of pain to warn against different types of physical injury. Such a relationship would likely result in the significant genetic overlap between loneliness and depression that we observe in this study.

After depression, neuroticism showed the strongest association with loneliness. Cacioppo et al³⁴ showed that the relationship between loneliness and depression is independent from the relationship with sensitivity for negative emotions, that is, neuroticism; our data showed that this independent relationship is measurable at the DNA level. An essential difference between neuroticism and depression as well as loneliness is that neuroticism is a relatively permanent individual characteristic, while depression and loneliness usually reflect a temporary change in one's state. Neuroticism nevertheless shows a strong genetic correlation with depression (.75).⁶¹ We showed in another molecular genetic study that loneliness and neuroticism also have a considerable shared genetic etiology with an estimated genetic correlation between .7 and .8.²³ When analyzing the polygenic scores separately, we see a strong negative association with the polygenic score for subjective well-being which, despite relatively low power, suggests a genetic correlation with subjective well-being in the same range (or higher) as the genetic correlation with neuroticism and depression. This genetic correlation is likely due to genes that subjective well-being shares with neuroticism and/or depression, which have genetic correlations with well-being of approximately $-.8$.⁶¹ The genetic influences these traits share are most likely those that underlie processes related to mood and/or the sensitivity to negative emotions.

After depression and neuroticism, schizophrenia showed the strongest association with loneliness. The association with schizophrenia was due to the genetic component that schizophrenia shares with bipolar disorder, which also remains significant after accounting for the 2 MDD scores. The genetic component that differentiates

between schizophrenia and bipolar disorder was not associated with loneliness, despite a relatively powerful polygenic score (standardized $B = .005$, $P = .681$). A meta-analysis on the effectiveness of interventions for loneliness proved addressing maladaptive social cognition to be the most effective intervention, as compared with interventions directed at improving social skills, enhancing social support or increasing opportunities for social contact.⁹⁴ Impaired cognition is a core feature of both schizophrenia and bipolar disorder, with schizophrenia showing more impaired social than nonsocial cognition compared with bipolar disorder,⁹⁵ which may explain the stronger association between loneliness and schizophrenia. As the predictive power of molecular genetic data increases, polygenic scores based on GWASs that capture these features may aid in further narrowing down which individuals would benefit most from interventions that target social cognition.

Gao et al²⁴ investigated the association between loneliness in approximately 7000 unrelated individuals from the HRS and polygenic scores for 6 traits: neuroticism, extraversion, schizophrenia, bipolar disorder, MDD and depressive symptoms. They found a significant association only with neuroticism and depressive symptoms. The reason that our strongest predictors, MDD, did not reach significance in their study was likely due to the differences in the sample sizes of the MDD GWASs: 18 759 in Gao et al²⁴ and over 160 000 in our study. The power to detect associations with additional traits that did not reach significance in their analyses (schizophrenia and bipolar disorder) may be due to our larger sample size and the use of LDpred to construct polygenic scores, which increases power by optimizing the effect size estimates of individual SNPs by incorporating the genome-wide LD structure.⁷⁵

Polygenic scores tend to explain a few percent of the variance for most human behavioral traits, making the 1.7% explained variance for loneliness relatively promising, especially considering the plateau has not yet been reached, and considering that age and gender combined explained only 0.9% of the individual differences. When effect sizes of genome-wide SNPs are mapped accurately enough, polygenic scores can potentially reach a stronger predictive power than that of family history. While perfect prediction will never be reached, more powerful genetic studies may lead to clinically useful polygenic scores and could be employed to help combat preclinical mental health outcomes such as loneliness. Our results show the presence of a shared genetic etiology between the propensity to feel lonely and traits related to personality, mood, negative affect, well-being, somatic health and susceptibility to psychiatric disorders.

ACKNOWLEDGMENTS

When this article was accepted for publication we lost our senior author John T. Cacioppo, who passed away on March 5 2018. It was a great honor to work with John, whose groundbreaking research on loneliness will continue to inspire us to tackle the important questions about our social needs.

The authors thank all the twins and family members. This project was made possible by the National Institutes of Health (NIH, R37 AG033590-08 to J.T.C.). KJHV is supported by the Foundation Volksbond Rotterdam. M.G.N. is supported by Royal Netherlands Academy

of Science Professor Award (PAH/6635 to D.I.B.). Data collection was supported by the Netherlands Organization for Scientific Research (NWO: MagW/ZonMW grants 904-61-090, 985-10-002, 904-61-193, 480-04-004, 400-05-717, NWO-bilateral agreement 463-06-001, NWO-VENI 451-04-034, Addiction-31160008, Middelgroot-911-09-032, Spinozapremie 56-464-14192), Biobanking and Biomolecular Resources Research Infrastructure (BBMRI-NL, 184.021.007). Genotyping was also supported by the Avera Institute for Human Genetics, Sioux Falls, South Dakota (USA) and the National Institutes of Health (NIH, R01D0042157-01A), the Genetic Association Information Network (GAIN) of the Foundation for the US National Institutes of Health (NIMH, MH081802) and by the Grand Opportunity grants 1RC2MH089951-01 and 1RC2MH089995-01 from the NIMH. Part of the analyses was carried out on the Genetic Cluster Computer (<http://www.geneticcluster.org>), which is financially supported by the Netherlands Scientific Organization (NWO 480-05-003), the Dutch Brain Foundation and the Department of Psychology and Education of the VU University Amsterdam.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

A. Abdellaoui  <http://orcid.org/0000-0003-1088-6784>

REFERENCES

- Cacioppo JT, Cacioppo S, Boomsma DI. Evolutionary mechanisms for loneliness. *Cognit Emot*. 2014;28:3-21.
- Goossens L, Van Roekel E, Verhagen M, et al. The genetics of loneliness linking evolutionary theory to genome-wide genetics, epigenetics, and social science. *Perspect Psychol Sci*. 2015;10:213-226.
- Long CR, Averill JR. Solitude: an exploration of benefits of being alone. *J Theory Soc Behav*. 2003;33:21-44.
- Plomin R, Haworth CM, Davis OS. Common disorders are quantitative traits. *Nat Rev Genet*. 2009;10:872-878.
- Cacioppo JT, Cacioppo S. Social relationships and health: the toxic effects of perceived social isolation. *Soc Personal Psychol Compass*. 2014;8:58-72.
- Cacioppo JT, Cacioppo S, Capitanio JP, Cole SW. The neuroendocrinology of social isolation. *Annu Rev Psychol*. 2015;66:733-767.
- Cacioppo S, Balogh S, Cacioppo JT. Implicit attention to negative social, in contrast to nonsocial, words in the Stroop task differs between individuals high and low in loneliness: evidence from event-related brain microstates. *Cortex*. 2015;70:213-233.
- Cole SW, Hawkley LC, Arevalo JM, Sung CY, Rose RM, Cacioppo JT. Social regulation of gene expression in human leukocytes. *Genome Biol*. 2007;8:R189.
- Hawkley LC, Cacioppo JT. Loneliness matters: a theoretical and empirical review of consequences and mechanisms. *Ann Behav Med*. 2010;40:218-227.
- Heinrich LM, Gullone E. The clinical significance of loneliness: a literature review. *Clin Psychol Rev*. 2006;26:695-718.
- Holt-Lunstad J, Smith TB, Baker M, Harris T, Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect Psychol Sci*. 2015;10:227-237.
- Miller G. Why loneliness is hazardous to your health. *Science*. 2011;331:138-140.
- Turkheimer E. Three laws of behavior genetics and what they mean. *Curr Dir Psychol Sci*. 2000;9:160-164.
- Bartels M, Cacioppo JT, Hudziak JJ, Boomsma DI. Genetic and environmental contributions to stability in loneliness throughout childhood. *Am J Med Genet B Neuropsychiatr Genet*. 2008;147:385-391.
- Boomsma DI, Cacioppo JT, Muthén B, Asparouhov T, Clark S. Longitudinal genetic analysis for loneliness in Dutch twins. *Twin Res Hum Genet*. 2007;10:267-273.
- Boomsma DI, Cacioppo JT, Slagboom PE, Posthuma D. Genetic linkage and association analysis for loneliness in Dutch twin and sibling pairs points to a region on chromosome 12q23-24. *Behav Genet*. 2006;36:137-146.
- Boomsma DI, Willemsen G, Dolan CV, Hawkley LC, Cacioppo JT. Genetic and environmental contributions to loneliness in adults: the Netherlands twin register study. *Behav Genet*. 2005;35:745-752.
- Distel MA, Rebollo-Mesa I, Abdellaoui A, et al. Familial resemblance for loneliness. *Behav Genet*. 2010;40:480-494.
- McGuire S, Clifford J. Genetic and environmental contributions to loneliness in children. *Psychol Sci*. 2000;11:487-491.
- Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: a tool for genome-wide complex trait analysis. *Am J Hum Genet*. 2011;88:76-82.
- Bulik-Sullivan BK, Loh P-R, Finucane HK, et al. LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet*. 2015;47:291-295.
- Dudbridge F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet*. 2013;9:e1003348.
- Abdellaoui A, Chen H-Y, Willemsen G, et al. Associations between loneliness and personality are mostly driven by a genetic association with neuroticism. *J Pers*. 2018; Under Review.
- Gao J, Davis LK, Hart AB, et al. Genome-wide association study of loneliness demonstrates a role for common variation. *Neuropsychopharmacology*. 2016;42(4):811-821.
- Yang J, Lee SH, Goddard ME, Visscher PM. Genome-wide complex trait analysis (GCTA): methods, data analyses, and interpretations. *Methods Mol Biol*. 2013;1019:215-236.
- Peyrot WJ, Milaneschi Y, Abdellaoui A, et al. Effect of polygenic risk scores on depression in childhood trauma. *Br J Psychiatry*. 2014;205:113-119.
- Peyrot WJ, Van der Auwera S, Milaneschi Y, et al. Does childhood trauma moderate polygenic risk for depression? A meta-analysis of 5765 subjects from the psychiatric genomics consortium. *Biol Psychiatry*. 2017. <https://doi.org/10.1016/j.biopsych.2017.09.009>.
- Booth R. Loneliness as a component of psychiatric disorders. *Med-GenMed*. 2000;2:1-7.
- Mushtaq R, Shoib S, Shah T, Mushtaq S. Relationship between loneliness, psychiatric disorders and physical health? A review on the psychological aspects of loneliness. *J Clin Diagn Res*. 2014;8:WE01-WE04.
- Atak H. Big five traits and loneliness among Turkish emerging adults. *Int J Human Soc Sci*. 2009;4:749-753.
- Cacioppo JT, Hawkley LC, Ernst JM, et al. Loneliness within a nomological net: an evolutionary perspective. *J Res Pers*. 2006;40:1054-1085.
- Teppers E, Klimstra TA, Van Damme C, Luyckx K, Vanhalst J, Goossens L. Personality traits, loneliness, and attitudes toward aloneness in adolescence. *J Soc Pers Relat*. 2013;30:1045-1063.
- Ben-Zur H. Loneliness, optimism, and well-being among married, divorced, and widowed individuals. *J Psychol*. 2012;146:23-36.
- Cacioppo JT, Hawkley LC, Thisted RA. Perceived social isolation makes me sad: 5-year cross-lagged analyses of loneliness and depressive symptomatology in the Chicago Health, Aging, and Social Relations Study. *Psychol Aging*. 2010;25:453-463.
- Cacioppo JT, Hughes ME, Waite LJ, Hawkley LC, Thisted RA. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. *Psychol Aging*. 2006;21:140-151.
- Åkerlind I, Hörnquist JO. Loneliness and alcohol abuse: a review of evidences of an interplay. *Soc Sci Med*. 1992;34:405-414.
- Kim OS. The effects of loneliness on alcohol drinking, smoking, and health perception in college students. *J Korean Acad Nurs*. 1999;29:107-116.

38. Jaremka LM, Andridge RR, Fagundes CP, et al. Pain, depression, and fatigue: loneliness as a longitudinal risk factor. *Health Psychol.* 2014; 33:948-957.
39. Jaremka LM, Fagundes CP, Glaser R, Bennett JM, Malarkey WB, Kiecolt-Glaser JK. Loneliness predicts pain, depression, and fatigue: understanding the role of immune dysregulation. *Psychoneuroendocrinology.* 2013;38:1310-1317.
40. Nummela O, Seppänen M, Uutela A. The effect of loneliness and change in loneliness on self-rated health (SRH): a longitudinal study among aging people. *Arch Gerontol Geriatr.* 2011;53:163-167.
41. Scharf T, de Jong Gierveld J. Loneliness in urban neighbourhoods: an Anglo-Dutch comparison. *Eur J Ageing.* 2008;5:103-115.
42. Bishop AJ, Martin P. The indirect influence of educational attainment on loneliness among unmarried older adults. *Educ Gerontol.* 2007;33: 897-917.
43. Page RM, Cole GE. Demographic predictors of self-reported loneliness in adults. *Psychol Rep.* 1991;68:939-945.
44. Steptoe A, Shankar A, Demakakos P, Wardle J. Social isolation, loneliness, and all-cause mortality in older men and women. *Proc Natl Acad Sci U S A.* 2013;110:5797-5801.
45. Hawkey LC, Hughes ME, Waite LJ, Masi CM, Thisted RA, Cacioppo JT. From social structural factors to perceptions of relationship quality and loneliness: the Chicago health, aging, and social relations study. *J Gerontol B Psychol Sci Soc Sci.* 2008;63:S375-S384.
46. Willemsen G, De Geus EJ, Bartels M, et al. The Netherlands Twin Register biobank: a resource for genetic epidemiological studies. *Twin Res Hum Genet.* 2010;13:231-245.
47. Willemsen G, Vink JM, Abdellaoui A, et al. The Adult Netherlands Twin Register: twenty-five years of survey and biological data collection. *Twin Res Hum Genet.* 2013;16:271-281.
48. Hughes ME, Waite LJ, Hawkey LC, Cacioppo JT. A short scale for measuring loneliness in large surveys results from two population-based studies. *Res Aging.* 2004;26:655-672.
49. Russel D, Peplau LA, Cutrona CE. The revised UCLA loneliness scale: concurrent and discriminant validity evidence. *J Pers Soc Psychol.* 1980;39:472-480.
50. Lin BD, Willemsen G, Abdellaoui A, et al. The genetic overlap between hair and eye color. *Twin Res Hum Genet.* 2016;19:595-599.
51. Boomsma DI, Wijmenga C, Slagboom EP, et al. The genome of the Netherlands: design, and project goals. *Eur J Hum Genet.* 2014;22: 221-227.
52. Francioli LC, Menelaou A, Pulit SL, et al. Whole-genome sequence variation, population structure and demographic history of the Dutch population. *Nat Genet.* 2014;46:818-825.
53. Fedko IO, Hottenga J-J, Medina-Gomez C, et al. Estimation of genetic relationships between individuals across cohorts and platforms: application to childhood height. *Behav Genet.* 2015;45:514-528.
54. Purcell S, Neale B, Todd-Brown K, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. *Am J Hum Genet.* 2007;81:559-575.
55. Liu EY, Li M, Wang W, Li Y. MaCH-admix: genotype imputation for admixed populations. *Genet Epidemiol.* 2013;37:25-37.
56. Abdellaoui A, Hottenga J-J, De Knijff P, et al. Population structure, migration, and diversifying selection in the Netherlands. *Eur J Hum Genet.* 2013;21:1277-1285.
57. Hyde CL, Nagle MW, Tian C, et al. Identification of 15 genetic loci associated with risk of major depression in individuals of European descent. *Nat Genet.* 2016;48:1031-1036.
58. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *bioRxiv.* 2017;167577.
59. Lo M-T, Hinds DA, Tung JY, et al. Genome-wide analyses for personality traits identify six genomic loci and show correlations with psychiatric disorders. *Nat Genet.* 2017;49(1):152-156.
60. Ripke S, Neale BM, Corvin A, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature.* 2014;511:421.
61. Okbay A, Baselmans BM, De Neve J-E, et al. Genetic variants associated with subjective well-being, depressive symptoms, and neuroticism identified through genome-wide analyses. *Nat Genet.* 2016; 48(6):624-633.
62. Ruderfer DM, Fanous AH, Ripke S, et al. Polygenic dissection of diagnosis and clinical dimensions of bipolar disorder and schizophrenia. *Mol Psychiatry.* 2014;19:1017-1024.
63. Deary V, Hagenaars SP, Harris SE, et al. Genetic contributions to self-reported tiredness. *Mol Psychiatry.* 2017;23(3):789-790.
64. Harris SE, Hagenaars SP, Davies G, et al. Molecular genetic contributions to self-rated health. *Int J Epidemiol.* 2017;46(3):994-1009.
65. Boraska V, Franklin CS, Floyd JA, et al. A genome-wide association study of anorexia nervosa. *Mol Psychiatry.* 2014;19:1085-1094.
66. Smoller JW, Craddock N, Kendler K, et al. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet.* 2013;381:1371-1379.
67. Hill WD, Hagenaars SP, Marioni RE, et al. Molecular genetic contributions to social deprivation and household income in UK Biobank. *Curr Biol.* 2016;26:3083-3089.
68. Gormley P, Anttila V, Winsvold BS, et al. Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat Genet.* 2016;48(8):856-866.
69. Lambert J-C, Ibrahim-Verbaas CA, Harold D, et al. Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nat Genet.* 2013;45:1452-1458.
70. Okbay A, Beauchamp JP, Fontana MA, et al. Genome-wide association study identifies 74 loci associated with educational attainment. *Nature.* 2016;533:539-542.
71. van Den Berg SM, de Moor MH, Verweij KJ, et al. Meta-analysis of genome-wide association studies for extraversion: findings from the genetics of personality consortium. *Behav Genet.* 2016;46:170-182.
72. Schumann G, Liu C, O'Reilly P, et al. KLB is associated with alcohol drinking, and its gene product β -klotho is necessary for FGF21 regulation of alcohol preference. *Proc Natl Acad Sci U S A.* 2016;113(50): 14372-14377.
73. Furberg H, Kim Y, Dackor J, et al. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nat Genet.* 2010; 42:441-447.
74. Hugh-Jones D, Verweij KJ, Pourcain BS, Abdellaoui A. Assortative mating on educational attainment leads to genetic spousal resemblance for polygenic scores. *Intelligence.* 2016;59:103-108.
75. Vilhjálmsson BJ, Yang J, Finucane HK, et al. Modeling linkage disequilibrium increases accuracy of polygenic risk scores. *Am J Hum Genet.* 2015;97:576-592.
76. Wray NR, Yang J, Hayes BJ, Price AL, Goddard ME, Visscher PM. Pitfalls of predicting complex traits from SNPs. *Nat Rev Genet.* 2013;14: 507-515.
77. Minică CC, Dolan CV, Kampert MM, Boomsma DI, Vink JM. Sandwich corrected standard errors in family-based genome-wide association studies. *Eur J Hum Genet.* 2015;23:388-394.
78. Middeldorp CM, Hammerschlag AR, Ouwens KG, et al. A genome-wide association meta-analysis of attention-deficit/hyperactivity disorder symptoms in population-based pediatric cohorts. *J Am Acad Child Adolesc Psychiatry.* 2016;55:896-905.e6.
79. Cai N, Bigdeli TB, Kretschmar W, et al. Sparse whole-genome sequencing identifies two loci for major depressive disorder. *Nature.* 2015;523:588-591.
80. Gratten J, Visscher PM. Genetic pleiotropy in complex traits and diseases: implications for genomic medicine. *Genome Med.* 2016;8(1):78.
81. Bulik-Sullivan B, Finucane HK, Anttila V, et al. An atlas of genetic correlations across human diseases and traits. *Nat Genet.* 2015;47(11): 1236-1241.
82. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet.* 2013;45:984-994.
83. Weeks DG, Michela JL, Peplau LA, Bragg ME. Relation between loneliness and depression: a structural equation analysis. *J Pers Soc Psychol.* 1980;39:1238-1244.
84. Weiss RS. *Loneliness: The Experience of Emotional and Social Isolation.* Cambridge, Massachusetts: MIT Press; 1973.
85. Smith RJ. Explanations for adaptations, just-so stories, and limitations on evidence in evolutionary biology. *Evol Anthropol.* 2016;25:276-287.
86. Allen NB, Badcock PB. The social risk hypothesis of depressed mood: evolutionary, psychosocial, and neurobiological perspectives. *Psychol Bull.* 2003;129:887-913.

87. Badcock PB, Davey CG, Whittle S, Allen NB, Friston KJ. The Depressed Brain: An Evolutionary Systems Theory. *Trends Cogn Sci.* 2017;21(3):182-194.
88. Andrews PW, Thomson JA Jr. The bright side of being blue: depression as an adaptation for analyzing complex problems. *Psychol Rev.* 2009;116:620-654.
89. Cacioppo JT, Hawkley LC. Perceived social isolation and cognition. *Trends Cogn Sci.* 2009;13:447-454.
90. Cacioppo JT, Norris CJ, Decety J, Monteleone G, Nusbaum H. In the eye of the beholder: individual differences in perceived social isolation predict regional brain activation to social stimuli. *J Cogn Neurosci.* 2009;21:83-92.
91. Cacioppo S, Bangee M, Balogh S, Cardenas-Iniguez C, Qualter P, Cacioppo JT. Loneliness and implicit attention to social threat: a high-performance electrical neuroimaging study. *Cogn Neurosci.* 2015; 7(1-4):138-159.
92. Duck S, Pond K, Leatham G. Loneliness and the evaluation of relational events. *J Soc Pers Relat.* 1994;11:253-276.
93. Keller MC, Nesse RM. Is low mood an adaptation? Evidence for subtypes with symptoms that match precipitants. *J Affect Disord.* 2005; 86:27-35.
94. Masi CM, Chen H-Y, Hawkley LC, Cacioppo JT. A meta-analysis of interventions to reduce loneliness. *Personal Soc Psychol Rev.* 2011; 15(3):219-266.
95. Lee J, Altshuler L, Glahn DC, Miklowitz DJ, Ochsner K, Green MF. Social and nonsocial cognition in bipolar disorder and schizophrenia: relative levels of impairment. *Am J Psychiatry.* 2013;170:334-341.

How to cite this article: Abdellaoui A, Nivard MG, Hottenga J-J, et al. Predicting loneliness with polygenic scores of social, psychological and psychiatric traits. *Genes, Brain and Behavior.* 2018;17:e12472. <https://doi.org/10.1111/gbb.12472>