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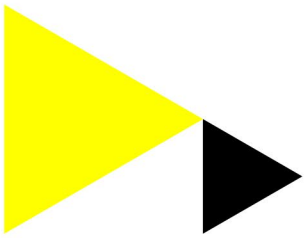

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RESEARCH ARTICLE

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Distinguishing happiness and meaning in life from depressive symptoms: A GWAS-by-subtraction study in the UK Biobank

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Abstract

Hedonic (happiness) and eudaimonic (meaning in life) well-being are negatively related to depressive symptoms. Genetic variants play a role in this association, reflected in substantial genetic correlations. We investigated the overlap and differences between well-being and depressive symptoms, using results of Genome-Wide Association studies (GWAS) in UK Biobank. Subtracting GWAS summary statistics of depressive symptoms from those of happiness and meaning in life, we obtained GWASs of respectively "pure" happiness ($n_{effective}$ = 216,497) and "pure" meaning ($n_{effective}$ = 102,300). For both, we identified one genome-wide significant SNP (rs1078141 and rs79520962, respectively). After subtraction, 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 0.78 to 0.65. Pure happiness and pure meaning became genetically unrelated to traits strongly associated with depressive symptoms, including loneliness, and psychiatric disorders. For other traits, including ADHD, educational attainment, and smoking, 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. Our results can be used as a starting point to test causal relationships with other variables, and design future well-being interventions.

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

1 | INTRODUCTION

In the past, well-being and ill-being, such as depressive symptoms, have been considered opposite ends of a continuum. However, the overlap between well-being and depressive symptoms is only moderate. Phenotypic correlations range between −0.40 and −0.60 (Bartels et al., 2013; Baselmans et al., 2018; Greenspoon & Saklofske, 2001) and genetic correlations from −0.50 to −0.81 (Baselmans et al., 2018; Baselmans & Bartels, 2018; Okbay et al., 2016). Well-being and ill-being are thus seen as distinct, but related domains of mental health.

A distinction is often made between hedonic well-being and eudaimonic well-being (Ryan & Deci, 2001). Hedonistic philosophical

ideas on well-being include maximizing pleasure and minimizing pain (Lambert et al., 2015; Ryan & Deci, 2001). Modern-day hedonic well-being measures focus on levels of positive and negative affect, and satisfaction with life (Diener et al., 2018). Eudaimonic philosophical theories extend beyond pleasure and pain, and emphasizes living a virtuous life (Lambert et al., 2015; Ryan & Deci, 2001). Current eudaimonic well-being measures include measures of positive functioning, thriving, and judgments about the meaning and purpose of life (Ryff, 1989). In this project, we operationalized hedonic well-being with a measure of happiness and eudaimonic well-being with a measure of meaning in life.

Hedonic and eudaimonic measures of well-being have been found to load on separate, but correlated factors (>0.60) (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, suggesting a largely shared genetic etiology (Baselmans & Bartels, 2018). Furthermore, genetic correlations with related traits were similar for happiness and meaning in life (Baselmans & Bartels, 2018). The only genetic correlation that differed for happiness compared to meaning in life was with depressive symptoms, with a moderate genetic correlation for happiness ($r_g = -0.53$, $SE = 0.04$), and a smaller correlation for meaning in life ($r_g = -0.32$, $SE = 0.05$).

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 the part that makes well-being unique, that is, independent from depressive symptoms. Recently, GWAS-by-subtraction was developed in order to disentangle the shared and unique genetic variance for traits (Demange et al., 2021). GWAS-by-subtraction uses two sets of results of GWASs. Leveraging structural equation modeling, it subtracts the results of one GWAS from the other GWAS, to obtain a new GWAS of a latent trait, that is, the residual variance. This method can give new insights into unmeasured genetic factors. 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 happiness and meaning GWASs in UK Biobank (Baselmans & Bartels, 2018), we obtained GWASs of respectively "pure" happiness and "pure" meaning, that is, the part of happiness and meaning that is independent of depressive symptoms. In follow-up analyses, we investigated the genetic variants associated with pure happiness and pure meaning using functional annotation and genetic correlations with other traits.

2 | METHODS AND MATERIALS

2.1 | Participants

UK Biobank is a large, population-based prospective study with data from over half a million participants of middle to old age from the United Kingdom (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 from the participants. In a later follow-up (2016), participants completed online questionnaires, including mental health and well-being questions.

We used data from 427,580 participants with genetic data and data on depressive symptoms from the initial assessment. Permission to access both phenotypic and genetic UK Biobank data was obtained under application number 40310. Furthermore, we used the summary statistics of Baselmans and Bartels (2018) on happiness ($n = \sim$222 k individuals) and meaning in life ($n = 108$ k individuals) in UK Biobank participants. In this GWAS, happiness was measured as "*In general how happy are you?*" on a scale from 1 (Extremely happy) to 6 (Extremely unhappy). Scores were reversed such that a higher score indicated higher happiness. Meaning in life was measured with the item "*To what extent do you feel your life to be meaningful?*" on a scale from 1 (Not at all) to 5 (An extreme amount).

2.2 | Depressive symptoms

In line with Okbay et al. (2016), to create a depressive symptoms score, we summed standardized 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" (1) to "Nearly every day" (4).

2.3 | 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, participants were assayed using two similar genotyping arrays, the Affymetrix UK BiLEVE and UK Biobank Axiom Arrays. The phasing and imputing were performed using the Haplotype Reference Consortium and merged UK10K and 1000 Genomes phase 3 reference panels. The quality control was designed to address issues specific to a large-scale dataset. 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).

2.4 | Statistical analyses

The analyses were pre-registered before data analysis (https://osf.io/pnc2z).

2.5 | Genome-wide association studies depressive symptoms

The genome-wide association analysis on the created depressive symptoms score was performed in GCTA using linear mixed modeling (LMM). This controls for relatedness by including a genetic relatedness matrix (GRM) (Jiang et al., 2019). Furthermore, we included sex, age, sex*age as covariates to control for these effects on depressive symptoms, as well as 100 genetic principal components as an additional control for population stratification. We used the recommended threshold of $p < 5 \times 10^{-8}$ for significant SNPs and $p < 1 \times 10^{-5}$ for possible implicated SNPs (Dudbridge & Gusnanto, 2008).

2.6 | GWAS-by-subtraction

We used Genomic Structural Equation Modeling (Genomic SEM) (Grotzinger et al., 2019) and GWAS-by-subtraction (Demange et al., 2021) to investigate the overlap between 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, that is, *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. Because of the independence between the paths, the genetic variance for pure happiness and pure meaning is by design independent of the genetic variance for depressive symptoms ($r_g = 0$). An assumption of the model is that the primary causal relationship is from depressive symptoms to well-being. This assumption likely does not hold for well-being and depressive symptoms, a bidirectional causal effect can be expected (e.g., Fergusson et al., 2015). Therefore, we performed sensitivity analyses, allowing for an effect from well-being to depressive symptoms in the model, in order to investigate the impact of a bidirectional effect (see Appendix S1). There was a minimal change in the results, suggesting that our results are not influenced by relaxing the assumption, and assuming the causal relationship is bidirectional.

2.7 | GWAS follow-up analyses

2.7.1 | SNP heritability

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

2.7.2 | Functional annotation

For pure happiness and pure meaning, we looked up the lead significant SNPs ($p < 5 \times 10^{-8}$) in the NHGRI-EBI catalogue of human genome-wide association studies (www.ebi.ac.uk/gwas/).

To follow-up on the SNP based association test for pure happiness and pure meaning in life, we performed gene mapping in FUMA

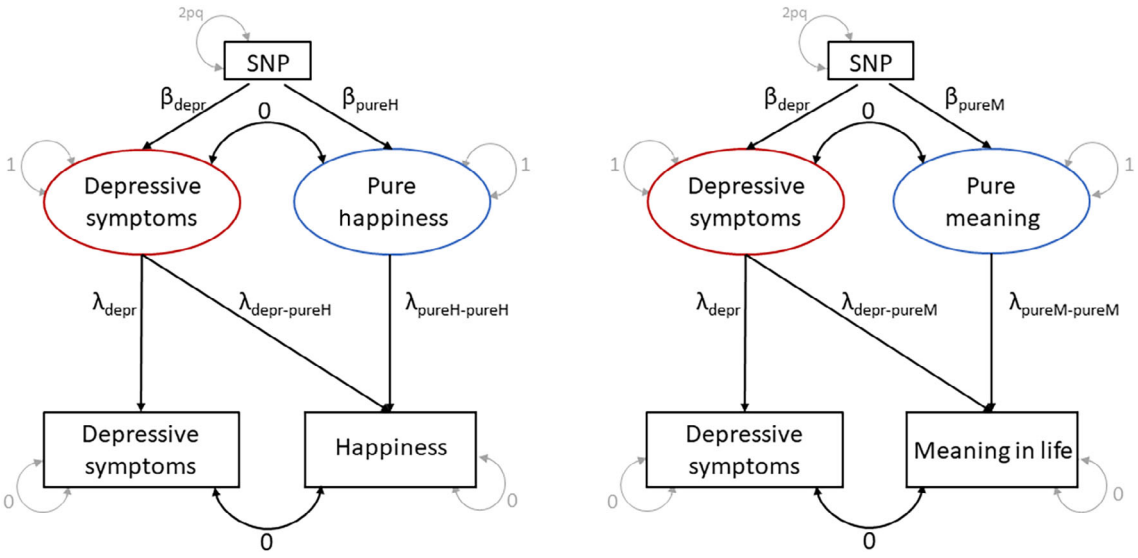

FIGURE 1 Schematic overview of the GWAS-by-subtraction approach to create a GWAS of "pure happiness" and "pure meaning."

(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. Furthermore, we applied genome-wide gene-based association tests using MAGMA (de Leeuw et al., 2015). The gene-based test combines results from multiple SNPs within a gene to test the association between genes and pure happiness or pure meaning, while accounting for LD between SNPs.

2.8 | 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 included selected traits across 12 categories with well-powered GWAS data ($N = 75$ GWAS, see Table S4) and used a Bonferroni corrected threshold ($p = 0.05/(75*5) = 1.3 \times 10^{-5}$).

3 | RESULTS

3.1 | GWAS depressive symptoms

A depressive symptoms score was computed for 467,389 participants ($M = 2.58$, $SD = 1.12$, range = 2–8). 427,580 individuals had genetic data available and were 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 and Manhattan plot can be found in Table S1 and Figure S1.

3.2 | GWAS-by-subtraction depressive symptoms and happiness

GWAS-by-subtraction of depressive symptoms and happiness resulted in one independent genome-wide significant SNP for pure happiness ($N_{effective} = 216{,}497$) ($\lambda_{GC} = 1.13$, 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 2 and the QQ plot in Figure S2. SNPs for happiness (Baselmans & Bartels, 2018) and pure happiness are compared in Table S2.

3.2.1 | 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 happiness in Baselmans and Bartels (2018). The genetic correlation between pure happiness and happiness was 0.80 ($SE = 0.02$, $Z = 52.51$, $p < 0.001$), indicating a reduction in genetic (co)variance.

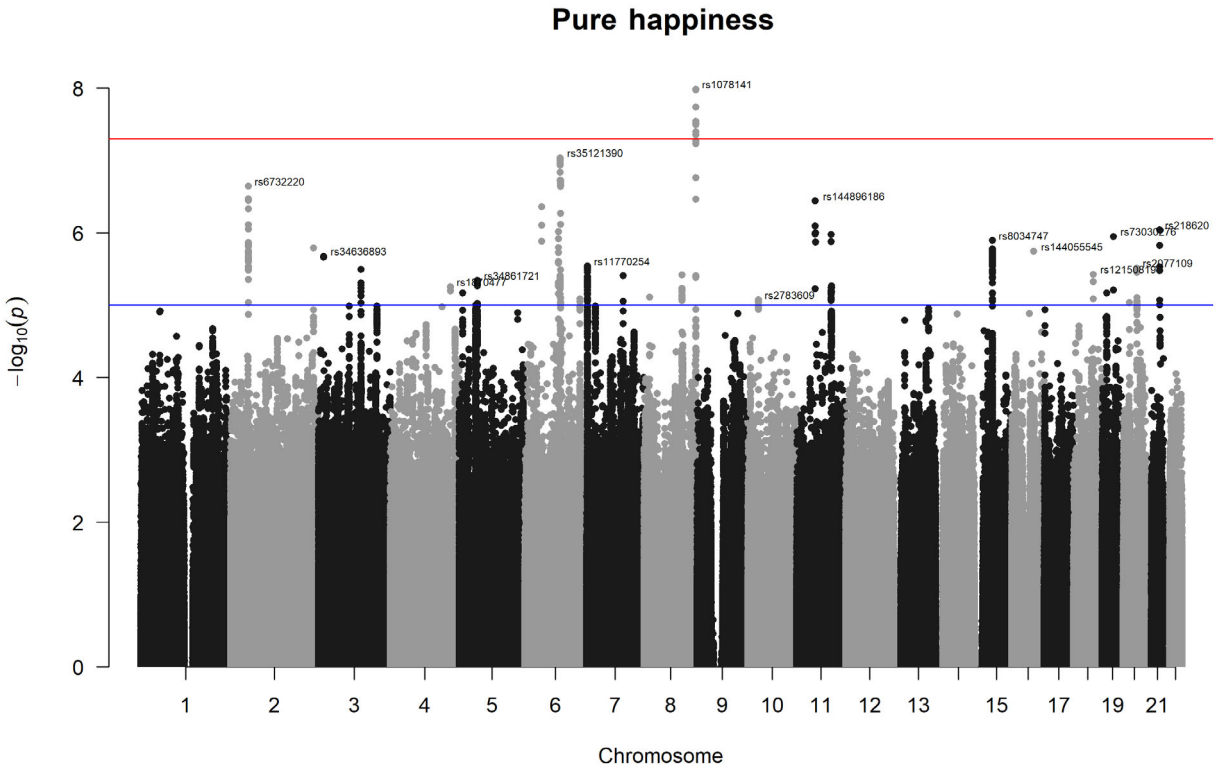

FIGURE 2 Manhattan plot for the GWAS results of pure happiness.

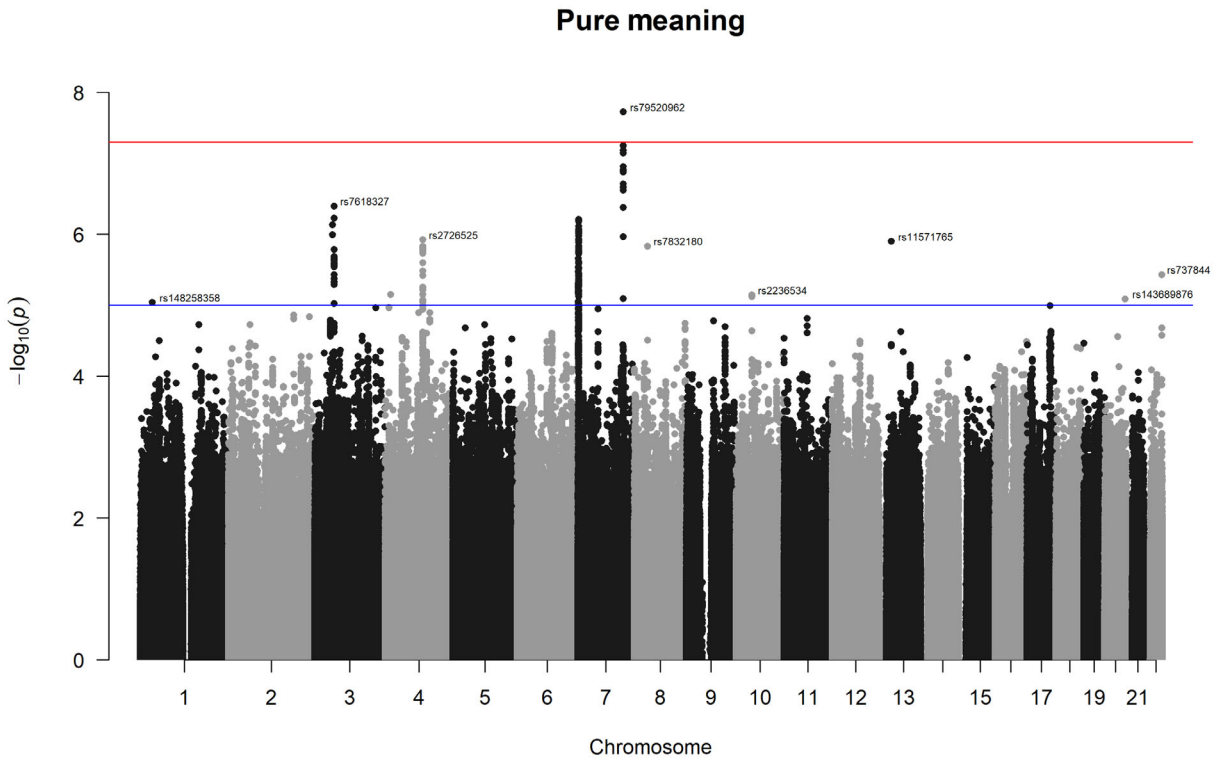

FIGURE 3 Manhattan plot for the GWAS results of pure meaning in life.

3.2.2 | Functional annotation

The effect of the significant SNP rs1078141 of pure happiness ($\beta = 0.102$, $p = 1.03 \times 10^{-8}$) is similar to the effect of this SNP in Baselmans and Bartels (2018) ($\beta = 0.017$, $p = 5.57 \times 10^{-8}$). The look-up showed that the significant SNP has also been associated with general cognitive ability (Davies et al., 2018).

Applying FUMA, no genes were associated with pure happiness based on positional mapping, eQTL mapping, or chromatine interaction-mapping. The gene-based test indicated no significant genes, and no significant enrichment of genes in certain tissues was found for pure happiness.

3.3 | 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 ($N_{effective} = 102{,}300$) ($\lambda_{GC} = 1.08$, 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 3 and the QQ plot in Figure S3. SNPs for meaning in life (Baselmans & Bartels, 2018) and pure meaning are compared in Table S2.

3.3.1 | 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 0.80 ($SE = 0.04$, $Z = 18.36$, $p < 0.001$), indicating a reduction in genetic (co) variance.

3.3.2 | Functional annotation

The significant SNP 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 methods. However, two genes, SND1 and LRRC4, were found through positional mapping, and SND1 was also found in the eQTL mapping. SND1 was also 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 gene-based tests and no significant enrichment of genes in certain tissues was found.

3.4 | Genetic correlations

The genetic correlation between pure happiness and pure meaning was estimated to be 0.65 ($SE = 0.05$, $p = 1.25 \times 10^{-40}$). Genetic correlations between happiness, meaning, pure happiness, pure meaning, and depressive symptoms can be found in Table S3.

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 Figure S4 and Table S4. All correlations between the traits and respectively pure happiness and pure meaning had overlapping confidence intervals. Therefore, we refer to pure well-being instead of discussing the correlations separately for pure happiness and pure meaning.

In Figures 4 and 5, the genetic correlations with selected traits can be seen. We selected traits with a high correlation with well-being or depressive symptoms (Figure 4), and traits for which the genetic correlation with well-being versus pure well-being changed substantially or reversed (Figure 5).

Three different patterns of genetic correlations were found. Different patterns of genetic correlations emerged, including (1) non-changing genetic correlations, (2) changed correlations from significant to zero, and (3) increased or reversed genetic correlations.

First, the subtraction of depressive symptoms did not influence the high genetic correlations of well-being with friend, family (Figure 4, psychological category), and job satisfaction (Figure 5).

Second, for psychological traits, psychiatric disorders and physical health traits related to depressive symptoms, pure well-being was not associated genetically. The subtraction of depressive symptoms GWAS removed the negative genetic correlations with well-being. This indicates that the original genetic correlations between well-being and depression-related traits are mostly due to the genetic overlap with depressive symptoms.

Third, genetic correlations for pure well-being versus well-being and several other traits increased or reversed (Figure 5). For example, the genetic correlations between Attention deficit hyperactivity disorder (ADHD) and pure happiness and meaning ($r_g = 0.29$ and 0.25) became positive, compared to the non-significant correlations of well-being ($r_g = -0.04$ and -0.03). Similar results were found for risk taking. This indicates that a higher genetic predisposition for pure well-being is related to a higher genetic risk of ADHD and risk-taking, when corrected for the genetic predisposition for depressive symptoms.

Reversed effects were also found for SES traits (Figure 5). Income was slightly positively associated with happiness and meaning in life ($r_g = 0.12$ and 0.11) before subtraction. Subtracting depressive symptoms from well-being, the genetic correlations became negative for pure happiness and meaning ($r_g = -0.23$ and -0.18). The genetic correlations between educational attainment and pure well-being became significantly negative (respectively $r_g = -0.46$ and -0.35 for pure happiness and pure meaning), compared to the smaller correlations ($r_g = -0.13$ and -0.09) before subtraction.

A consistent pattern of reversed genetic correlations between pure well-being and substance use traits, body fat, and BMI was also found, although not all correlations reached significance after correcting for multiple testing (Figure 5). Before subtraction, these traits were genetically unrelated or slightly negatively associated with well-being (r_g between -0.08 and -0.13), whereas the association with pure well-being became positive (r_g between 0.05 and 0.23) after subtracting depressive symptoms.

4 | DISCUSSION

Subtracting a depressive symptoms GWAS from happiness and meaning in life GWASs generated GWASs capturing genetic variants associated with happiness and meaning in life independent of depressive symptoms, that is, "pure" happiness and "pure" meaning. For both latent traits, one independent SNP reached genome-wide significance (rs1078141 and rs79520962, respectively). Consistent with the larger genetic overlap of depression with happiness ($r_g = -0.53$) compared to meaning in life ($r_g = -0.32$) (Baselmans & Bartels, 2018), we report a stronger 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 ($r_g = 0.78$ to $r_g = 0.65$) indicates that only part of the overlap between happiness and meaning in life is due to the overlap of the well-being measures with depressive symptoms. The largest part of genetic factors underlying happiness and meaning in life remains 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.

4.1 | Pure well-being correlates

The genetic correlations of well-being with other traits before and after the subtraction of depressive symptoms led to insights about the unique part of well-being. Different patterns of genetic correlations emerged, including (1) non-changing genetic correlations, (2) changed correlations from significant to zero, and (3) reversed genetic correlations. We discuss the meaning and possible implications of these different patterns of genetic correlations below.

First, genetic correlations between pure well-being and respectively family, friend, and job satisfaction did not change compared to the genetic correlations with well-being. The genetic predisposition to be satisfied with different life aspects is therefore related to the unique part of well-being 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 traits discussed next.

Second, as one could expect, pure well-being became genetically unrelated to traits correlating strongly with depressive symptoms, that is, tiredness, overall health, and psychiatric disorders like post-traumatic stress disorder, bipolar disorder, and schizophrenia. This

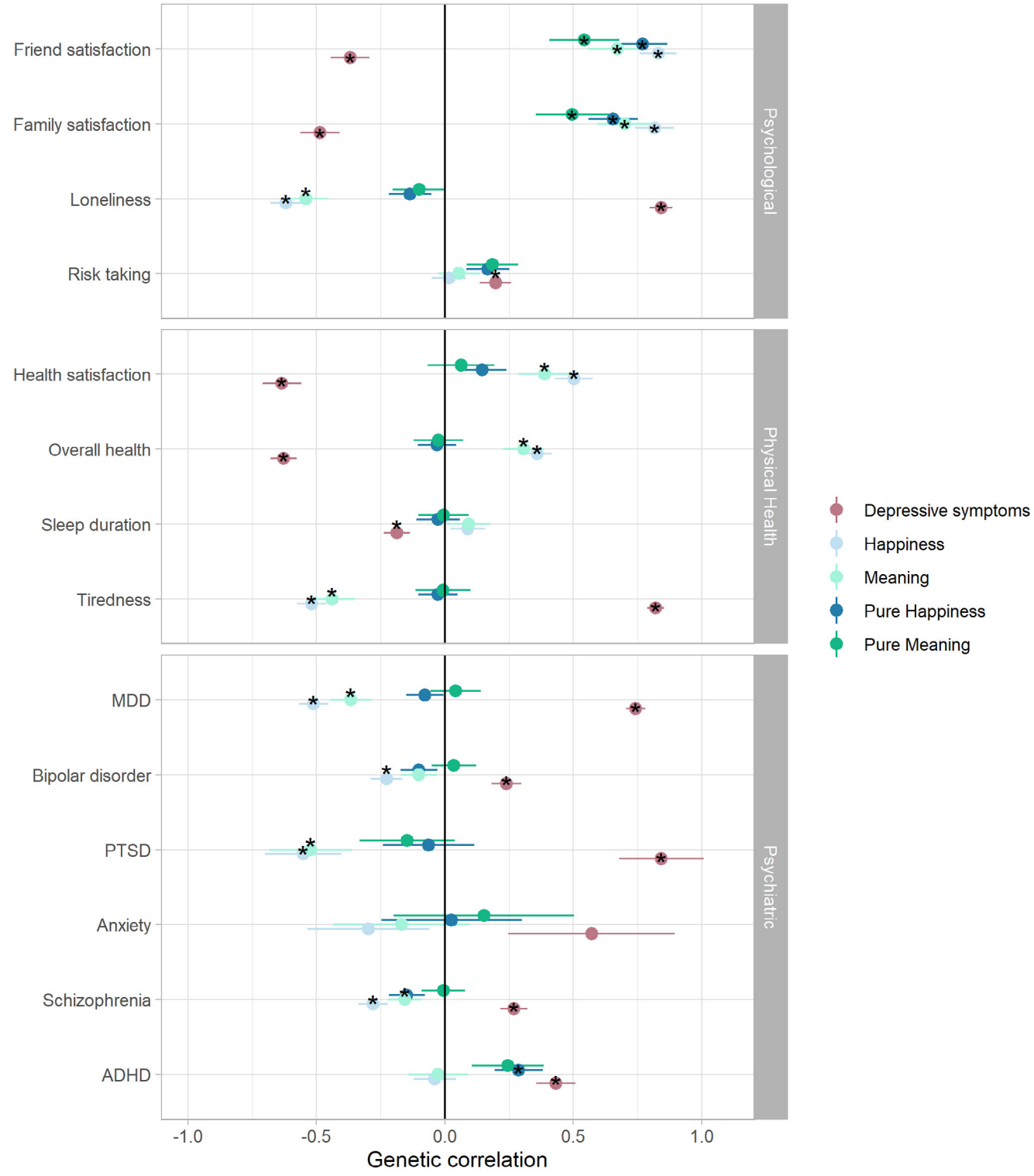

FIGURE 4 Genetic correlations of pure happiness, pure meaning, happiness, meaning, and depressive symptoms and selected psychological traits, physical health traits, and psychiatric disorders. * indicates significant genetic correlations with a Bonferroni corrected threshold of $p < 1.3 \times 10^{-5}$.

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 arise from the genetic overlap with depressive symptoms and should be interpreted considering the current findings. These results are in line with a recent study that investigated genetic associations with well-being in individuals stratified by their history of Major Depressive Disorder (MDD), that is, no MDD, single episode MDD, or

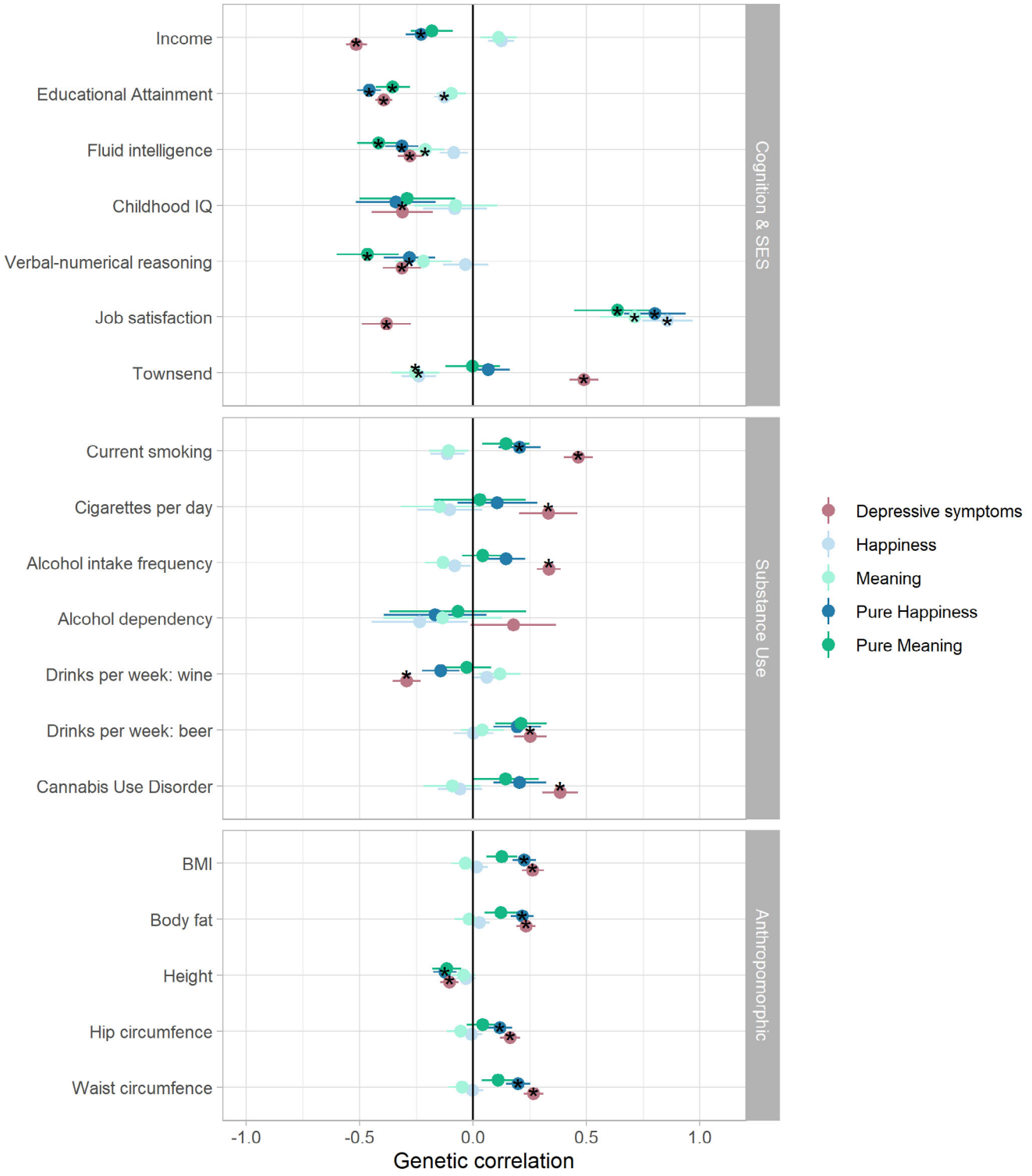

FIGURE 5 Genetic correlations of pure happiness, pure meaning, happiness, meaning, and depressive symptoms and selected cognition and socio-economic status, substance use and anthropomorphic traits. * indicates significant genetic correlations with a Bonferroni corrected threshold of $p < 1.3 \times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

recurrent MDD (Fabbri et al., 2021). Polygenic scores for most mental disorders, except ADHD, showed a similar effect size on well-being across groups, suggesting that their effect on well-being does not depend on having MDD or not.

Third, for several other traits, including ADHD, SES, and substance use, the genetic correlations with well-being changed substantially after the subtraction of depressive symptoms. This indicates unique genetic overlap between pure well-being and these traits,

independently from depressive symptoms. We shortly discuss possible explanations and mechanisms underlying the changed genetic correlations for these traits.

4.1.1 | 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 is related to poor outcomes in academic achievement, and work performance (Arnold et al., 2020; Harpin et al., 2016; Sciberras et al., 2009). Higher ADHD genetic liability has been associated with lower scores on different well-being measures (Shi et al., 2023), and positive genetic correlations between ADHD and depressive symptoms have been reported (e.g., Thapar, 2018). Our results indicate that a higher genetic predisposition for ADHD is also related to a higher genetic predisposition for pure well-being. An explanation for this finding could be the benefits and positive traits associated with ADHD symptoms in well-functioning individuals. Positive traits associated with ADHD include hyper focus, creativity, spontaneity, resilience, and high energy (Ashinoff & Abu-Akel, 2021; Boot et al., 2017, 2020; Sedgwick et al., 2019). These traits have also been related to well-being (Conner & Silvia, 2015; de Vries et al., 2021), suggesting the genetic correlation between pure well-being and ADHD could capture the benefits of ADHD, when taking out the genetic predisposition for depressive symptoms. In line with this finding, Fabbri et al. (2021) reported a stronger negative association between well-being and ADHD in people with MDD compared to no MDD. The association in this no MDD group was close to zero. However, more research on the (phenotypic) association between ADHD, well-being, and depressive symptoms in multivariate designs is needed to test these relations.

4.1.2 | Income, educational attainment and intelligence

Income, educational attainment (EA), and intelligence are strongly interrelated (Demange et al., 2021; Hill et al., 2016). We found similar effects of subtracting a depressive symptoms GWAS from well-being on the genetic correlations with these traits. The pure well-being-genetic correlations indicated that people with a higher genetic predisposition for pure well-being also have a genetic predisposition for lower income, EA, and intelligence. Furthermore, the genetic correlations became similar in magnitude to the negative correlations of these traits with depression (Marees et al., 2021).

Different mechanisms underlying the negative genetic correlation between depressive symptoms and income/EA/intelligence have been proposed. The genetic correlations can indicate that low income/EA/intelligence can increase the risk of depression or vice versa, depressive symptoms have detrimental effects on the ability to actively and optimally participate in school and the labor force, leading to lower EA and incomes (Lorant et al., 2003). The slightly positive genetic correlation between well-being and the traits before subtraction seems to be driven by the shared part with depressive symptoms, i.e., the opposite effects of depressive symptoms.

Possible explanations underlying the reversed genetic correlations for pure well-being can be non-linear relations between well-being and income, EA, or intelligence. For example, for both income and intelligence, satiation and turning points on well-being have been found. The satiation point of income suggests that above a certain level of income that is sufficient to fulfill basic physical needs, higher income does not lead to higher levels of well-being (Kahneman & Deaton, 2010). The turning point of income indicates that people with very high incomes report lower well-being levels compared to those with lower incomes (Jebb et al., 2018). However, results tend to depend on analytic approaches (Kudrna & Kushlev, 2022). Similar, in highly intellectually "gifted" individuals (i.e., very high intellect, IQ ≥ 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). Intellectually gifted individuals can be at a greater risk for the development of a meaning in life crisis. However, these speculations are based on genetic correlations, and because the UK Biobank sample has a higher socioeconomic status compared to the general population, more research on the (phenotypic) association between income/EA/intelligence, well-being, and depressive symptoms in a multivariate design is needed to test these relations.

4.1.3 | Substance use and food-related traits

A 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. Smoking, alcohol intake frequency, BMI, and body fat were genetically positively related to depressive symptoms and unrelated or slightly negatively associated to well-being. Pure well-being became positively genetically related to these traits after subtracting depressive symptoms. A possible explanation underlying 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, that is, smoking, drinking and eating to cope and reduce the negative mood or other depressive symptoms (Armeli et al., 2018; Hooshmand et al., 2012; Kuntsche et al., 2005; Lazarevich et al., 2016; Magee & Clarke, 2021). In contrast, smoking, drinking, and eating that is genetically related to pure well-being could arise from these behaviors in social settings. In line with these results, moderate alcohol drinking habits were positively associated with well-being (Fabbri et al., 2021; Stranges et al., 2014). Similarly, the associations of BMI and well-being depend on the level of well-being and level of BMI, that is, people with low well-being were more likely to be extremely overweight or obese, but people in the highest well-being category were more likely to be overweight (Stranges et al., 2014). More research is needed to investigate the specific

(phenotypic) associations of well-being and substance use and eating variables, and the direction of causation.

4.2 | Limitations and implications

The results should be interpreted in light of some limitations. First, the GWAS of happiness and meaning in life is based on a question about general well-being, whereas the depressive symptoms questions refers to the presence of depressive symptoms in the last 2 weeks. During the time of the questions, the majority of participants did not experience depression or a depressive episode. Consequently, the responses to the items about depressive symptoms mostly reflects traits associated with depression, that is, trait depression rather than state depression. Although most people are relatively stable in their level of depressive symptoms over time (Musliner et al., 2016; Nivard et al., 2015), especially in adulthood, this discrepancy (general vs. recent) could have influenced the results. Furthermore, the UK Biobank sample is known to be biased, 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, subtraction in UK Biobank GWASs might have introduced extra bias in the pure well-being GWASs, possibly influencing the results and genetic correlations of pure well-being with other traits. Another participation bias is that UK Biobank focuses on samples from European ancestry. Well-being is differently conceptualized in different cultures (Lambert et al., 2020), limiting generalization across samples with other ancestries. Replication of these results using GWASs from population-wide samples and more ancestry-diverse samples is needed.

In this study, we reported genetic correlations between traits, indicating genetic sensitivity to both traits. We did not investigate direct phenotypic associations or causal effects. The patterns of 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 other traits. Part of the variance of well-being overlaps with depressive symptoms, whereas the other part is unique to well-being. These genetic correlations between the unique part of well-being and the other traits, that is, ADHD, income, substance use, could arise from a causal relationship. To investigate the causal effects between the unique part of well-being and the other traits, Mendelian Randomization designs can be applied. However, a strong instrumental variable is needed to investigate the direction of effect between well-being and other traits. The current GWAS for "pure happiness" and "pure well-being" have a relatively small sample size and only one genetic variant reached genome-wide significance. Therefore, we cannot create a strong instrumental variable for "pure happiness" and "pure well-being."

If replicated and phenotypic and causal effects have been investigated, the findings can have important implications for mental health research and preventions or interventions. For example, different associations could be taken into account depending on the goal of the intervention. If the goal is to both decrease depressive symptoms and increase well-being, interventions should consider variables that are (causally) related to both depressive symptoms and well-being. If the goal is to increase well-being, instead of just reducing depressive symptoms, interventions should focus on variables that are (causally) related to pure well-being. Our results can be used as a starting point to find these variables, test causality, and design future interventions.

AUTHOR CONTRIBUTIONS

Lianne P. de Vries, Dirk H.M. Pelt, and Meike Bartels conceptualized the study. Lianne P. de Vries performed data analyses, with help and based on scripts of Perline A. Demange; Lianne P. de Vries drafted the manuscript text; Dirk H.M. Pelt, Bart M.L. Baselmans, Perline A. Demange, Christiaan H. Vinkers, and Meike Bartels revised manuscript drafts; Meike Bartels obtained funding, and supervised this work.

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CONFLICT OF INTEREST STATEMENT

The author(s) declared that there were no competing interest with respect to the authorship or the publication of this article.

DATA AVAILABILITY STATEMENT

This research was conducted using the UK Biobank Resource, under application number 40310. UK Biobank data is available to researchers who register with UK Biobank.

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