Genetic evidence for bidirectional causal effects between resilience and well-being.

de Vries, L.P.[a,b,1], Baselmans, B.M.L.[c], Luykx, J.J.[d,e,f], de Zeeuw, E.L.[a,b], Minică, C.[a,g,h], de Geus, E.J.C.[a], Vinkers, C.H.[i,j], & Bartels, M.[a,b]

a. Department of Biological Psychology, Vrije Universiteit Amsterdam, The Netherlands
b. Amsterdam Public Health Research Institute, Amsterdam University Medical Centres, Amsterdam, Netherlands,
c. Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia
d. Department of Psychiatry, UMC Utrecht, Brain Center, University Medical Center Utrecht, Utrecht, The Netherlands
e. Department of Translational Neuroscience, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands.
f. Outpatient second opinion clinic, GGNet Mental Health, Warnsveld, The Netherlands.
g. Stanley Center for Psychiatric Disease, Broad Institute of MIT and Harvard, Cambridge, MA, 02142
h. Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, 02114
i. Department of Psychiatry, Amsterdam UMC, Location VUmc
j. Department of Anatomy and Neurosciences, Amsterdam UMC, Location VUmc

[1.] **Corresponding author**: L.P. de Vries, Vrije Universiteit Amsterdam, Department of Biological Psychology, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. T: +31205986218. Email: l.p.de.vries@vu.nl

Declarations of interest: none**.**

Funding: This work is supported by an ERC consolidation grant (WELL-BEING 771057, M. Bartels), NWO large investment grant (NTR: 480-15-001/674)) and ZonMW Addiction program (31160008).

Author contributions: Lianne de Vries: Conceptualization, Methodology, Formal analysis, Writing- Original Draft, Visualization, Bart Baselmans: Methodology, Writing- Review & Editing, Jurjen Luykx: Writing- Review & Editing, Eveline de Zeeuw: Writing- Review & Editing, Camelia Minica: Methodology, Writing- Review & Editing, Eco de Geus: Methodology, Writing- Review & Editing, Christiaan Vinkers: Conceptualization, Writing- Review & Editing, Supervision, Meike Bartels: Conceptualization, Methodology, Writing- Review & Editing, Supervision, Funding acquisition.

Abstract

Resilience and well-being are strongly related. People with higher levels of well-being are more resilient after stressful life events or trauma and vice versa. Less is known about the underlying sources of overlap and causality between the constructs. In a sample of 11.304 twins and 2.572 siblings from the Netherlands Twin Register, we investigated the overlap and possible direction of causation between resilience (i.e. the absence of psychiatric symptoms despite negative life events) and well-being (i.e. satisfaction with life) using polygenic scores (PGS), twin-sibling models, and the Mendelian Randomization Direction of Causality (MR-DoC) model. The longitudinal twin-sibling models showed significant phenotypic correlations between resilience and well-being (.41/.51 at time 1 and 2). PGS analyses suggested that genetic factors influencing one trait, also predict the other. Twin-sibling modeling confirmed this genetic correlation (.71) and showed a strong environmental correlation (.93). In line with causality, both genetic (51%) and environmental (49%) factors contributed significantly to the covariance between resilience and well-being. Further causality analyses consistently showed bidirectional causality and the MR-DoC model confirmed these causal effects. Well-being explained 34% (T1) and 46% (T2) of the variance in resilience and resilience explained 44% (T1) and 51% (T2) of the variance in resilience. To conclude, we find evidence for bidirectional causality between well-being and resilience that survives correction for genetic confounding. As resilience and well-being are both negatively related to psychopathology, the mutual effects can have implications for interventions to lower psychopathology vulnerability.

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

1. Introduction

In life, everyone is exposed to multiple personal adverse or stressful life events, such as a traffic accident or the death of a loved one. These adverse life event, but also events like terroristic attacks or worldwide crises, can lead to stress and trauma. There are individual differences in the responses of people to (major) life stressors and potential trauma (Luthar et al., 2000; Werner & Smith, 2001), and resilience is found to be the most common response according to a recent review of 54 studies (Galatzer-Levy et al., 2018). Resilience can be defined as an individual's ability to quickly recover after the experience of stress or trauma, returning to an optimal mental state, or as the positive psychological outcome after stressful life events (Charney, 2004; Choi et al., 2019; Connor & Davidson, 2003; Galatzer-Levy et al., 2018; Kalisch et al., 2017; Luthar et al., 2000). For example, in response to the COVID-19 pandemic, only 13.6% of a USA representative sample (N=1468) showed psychological distress (McGinty et al., 2020). While this level of distress is higher than the 3.9% found in the same sample in 2018, 86% of the sample seemed to be resilient, as their distress does not increase. Resilient people adapt relatively quickly, after some time, their well-being levels are back to baseline (see the review of Galatzer-Levy et al., 2018). Less resilient people do not cope well in response to stress and experience chronic or long-term adverse effects, leading to the development of psychopathology (e.g. depression) (Bonanno, 2004; Bonanno et al., 2011; Galatzer-Levy et al., 2018; Galatzer-Levy & Bonanno, 2012; Kendler et al., 2000; Pietrzak et al., 2014).

It has repeatedly been found that well-being (i.e. defined as positive affect, happiness or life satisfaction) plays a preventive role in psychopathology and is important to overall physical and mental health (Diener et al., 2017; Greenspoon & Saklofske, 2001; Howell et al., 2007). Well-being associates positively with longevity and health (James et al., 2019; Kim et al., 2019; Steptoe, 2019; Zaninotto & Steptoe, 2019), satisfaction with marital relationships, productivity at work, prosocial behavior and educational achievement (Chapman & Guven, 2016; Lyubomirsky et al., 2005; Maccagnan et al., 2019; Oswald et al., 2015).

A strong positive correlation (around 0.5) between resilience and well-being has been found as well (e.g. Bajaj & Pande, 2016; Hu, Zhang, & Wang, 2015; Liu, Wang, & Li, 2012; Satici, 2016). That is, people with a higher well-being show more resilience and, vice versa, people who are more resilient show higher well-being (Cohn et al., 2009; Ong et al., 2006). For example, women reporting higher life satisfaction are more likely to be resilient after their spouse passes away (O'Rourke, 2004; Rossi et al., 2007). Fredrickson et al. (2003) suggests that positive emotions are the active elements in resilience. In times of crisis, the presence of

positive emotions buffers against depression and adverse outcomes. Conversely, Connor and Davidson (2003) suggest resilience is a protective factor in facing negative emotions after adverse events and therefore protects people's well-being. However, these studies are correlational, and causal interpretation is hard. It is theoretically plausible to expect a bidirectional relation between resilience and well-being. When people are able to cope with life stressors and adapt well to adversity (resilience), they feel better and evaluate their life positively (well-being) compared to people that cannot cope well. In turn, positive emotions and higher levels of well-being improve the ability to respond adaptively to life events, i.e. resilience.

Alternatively, underlying genetic or environmental confounders might induce the association between well-being and resilience - without a direct causal effect in either direction. The genetic and environmental factors contributing to both phenotypes have been investigated before. Using slightly different inclusion criteria, two meta-analyses summarized all studies applying the twin model to well-being and found a meta-analytic heritability (i.e. the contribution of genetic factors to the variance) of 36% (CI: 34-38%) and 40% (CI: 38-43%) for well-being based on all measures (Bartels, 2015; Nes & Røysamb, 2015) and 32% (CI: 29-35%) for satisfaction with life (Bartels, 2015). The remaining variance was explained by unique environmental influences. Causes of individual differences in resilience have also been investigated, although less frequent and with substantial variation in operationalization, sample size, and sample composition (e.g. population vs military sample). In two studies based on military samples, the heritability estimates of self-reported resilience were 25% (CI: 21-30) and 55% (CI: 48-61) respectively (Long et al., 2017; Wolf et al., 2018). In adolescents and based on three raters (father, mother, self) a common resilience factor (excluding rater specific error) showed heritability estimates of 78% in boys and 70% in girls (Waaktaar & Torgersen, 2012). When operationalizing resilience as the residual of positive affect after controlling for stressors or the residual of internalizing symptoms after controlling for stressful life events, heritability estimates ranged from 31% to 52% (Amstadter et al., 2014; Boardman et al., 2008). Using multiple measures to reduce measurement error, Amstadter et al. (2014) found a heritability of 50% (CI: 46-59) for the latent construct of resilience.

The above studies show that resilience and well-being are strongly related phenotypically and have a similar genetic architecture. The etiology of well-being and resilience has not been addressed in a bivariate design, to formally test the overlap in genetic and environmental factors. In order to get a better hold on the nature of the association between resilience and well-being, and possible roles for genetic confounding and (bidirectional) causal

effects we took a three-step approach. (1) First, we tested the existence of cross-sectional and longitudinal phenotypic associations between well-being and resilience. (2) Next, we used genome-wide summary statistics to compute the molecular genetic correlation and estimate genetic predictions for resilience and well-being to show the potential for genetic confounding. (3) Finally, we tried to falsify the causal hypotheses (in both directions) using different approaches: within-subject change score regression, bivariate psychometric twin-sibling modeling, cross-trait correlations of intrapair MZ twin differences, and the MR-DoC model which combines Mendelian Randomization and the Direction of Causation twin model.

2. Method

2.1. Sample

Participants were registered at the Netherlands Twin Register (NTR), established by the Department of Biological Psychology, Vrije Universiteit Amsterdam (Ligthart et al., 2019). The NTR sample is a population-wide, non-clinical sample. Every two/three years, longitudinal survey data about lifestyle, personality, psychopathology, and wellbeing in twins and their families is collected. The current study used data on psychopathology and well-being in adults collected in survey 6 (Time point 1: 2002-2003) and survey 8 (Time point 2: 2009-2012) (Ligthart et al., 2019; Willemsen et al., 2013).

Including twins and biological siblings, the total sample consisted of 14.055 participants with data on resilience and/or well-being collected in one or both waves. We excluded 177 participants with unknown zygosity and two participants with unknown sex, resulting in a final sample of 13.876 participants (11.304 twins and 2.572 siblings). The sample included 1.577 monozygotic male (MZM), 967 dizygotic male (DZM), 3.859 monozygotic female (MZF), 2.112 dizygotic female (DZF) and 2.789 dizygotic opposite-sex (DOS) twins from complete and incomplete twin pairs.

When split by time of data collection, 4.447 twins and 1.407 siblings (33.8% male, M_{age}= 32.87, SD_{age} = 11.41) had data at time point 1 (T1). At time point 2 (T2), data of 9.590 twins and 1.962 siblings (32.3% male, M_{age}=31.73, SD_{age}= 14.41) was available. Longitudinal data (both at T1 and T2) was available for 3.530 participants (2.733 twins and 797 siblings, 41.1% male, T1: M_{age}= 33.91, T2: M_{age}= 40.25, SD_{age}= 11.6 (see Supplementary Table S1 for more information).

The data collection was approved and declared to be of low risk and exempt of formal medical ethical risk assessment by the METc of the Vrije Universiteit Medical Center

Amsterdam (Approval: NL25220.029.08 (ref # 2008/244), 1 December 2008 and 2011/334, 12 Oct 2011; 2012/433, dd 26 Feb 2013).

2.2. Measures

2.2.1. Well-being

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

2.2.2. Life events

The number of experienced life events was assessed with an adapted version of a Dutch life-event scale (Schokverwerkings Inventarisatie Lijst = SchIL; Van der Velden et al., 1992). At T1, 16 negative life events items were included about the experience of death of a significant other, serious disease of yourself/significant other, end of relation, traffic accident, violent or sexual assault, robbery, and getting fired. Time point 2 included 28 life events, both positive and negative events. In line with previous work, we excluded the positive life events at T2, leaving 19 items (Middeldorp et al., 2008). Possible answers were *never experienced, experienced last year (0-12 months), 1-5 year ago and >5 years ago*. The number of life events was computed by summing the experienced life event in the past 5 years. The maximum number of life events experienced is 16 at T1 and 19 at T2 (see Supplementary Table S2).

2.2.3. Anxious-depressed

Anxious-depressed symptoms were assessed with the anxious-depressed subscale of the Adult Self Report (Achenbach & Rescorla, 2003). Each item is rated from 0 = *not true*, 1 = *somewhat true*, to 2 = *very true*. An example item is "*I feel worthless*". As T1 only included 15 (instead of 18) items of the scale, at T2 we only selected those items and created a sum score of 15 items, with higher scores indicating higher levels of anxious-depressed behavior.

2.2.4. Resilience score

Resilience is operationalized in line with Amstadter et al. (2014) and is based on the regression of internalizing problems on the total number of stressful life events experienced (e.g. Kendler, Thornton, & Gardner, 2000; Kessler, 1997; Phillips, Carroll, & Der, 2015). Resilience is defined as the difference between the predicted level of anxious-depressed symptoms based on the number of life events and the actual level. Individuals who

experience less anxious-depressed symptoms than expected based on the number of stressful events in their life are categorized as resilient.

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

2.2.5. Genotype data

Genotype and phenotype information was available for 9.593 NTR participants in our sample. Genotyping was done on several genotyping arrays, including the Axiom array (N=479), Affymetrix 6.0 (N=5174), Illumina Omni Express 1 M (N=110), Illumina 660 (N=1386), Illumina GSA (N=1124) and Perlegen/Affymetrix (N=1053) (see Ehli et al., 2017; Willemsen et al., 2013). Additionally, SNPs extracted from sequence data from the Netherlands reference genome project Genome of the Netherlands (GoNL) (N=267) were used (Boomsma et al., 2014; The Genome of the Netherlands Consortium, 2014).

For each platform, SNPs with a Minor Allele Frequency (MAF) <0.01 or SNPs out of Hardy–Weinberg Equilibrium (HWE) with $p< 10^{-5}$ were removed. Also, samples were excluded if there was a mismatch in expected and genotyped sex, the genotype missing rate was above 10% or the inbreeding value (Plink F statistic) was not between -0.10 and 0.10. Individuals with a non-Dutch ancestry were excluded, and to control for Dutch population stratification, Principal Components Analysis (PCA) was performed as described by Abdellaoui et al. (2013).

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

Using the summary statistics, this unrelated set and LDpred, the beta's were corrected. Polygenic scores were constructed using Plink on the relevant 9.593 individuals.

2.3. Analyses

2.3.1. Part 1: Demographics and phenotypic correlations

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

2.3.2. Part 2. GWAS Summary statistics: Polygenic scores and Genetic Correlation

To compare the genetic architectures of resilience and well-being and possible genetic confounding, we used summary statistics of two recent genome-wide association studies (GWASs) on resilience and well-being to create polygenic scores (PGS) and to compute the genetic correlation. PGS are a measure of an individual's genetic probability to develop a certain disorder or have a certain trait (Wray et al., 2007). Using GWAS summary statistics, the PGS of a phenotype can be calculated in an independent sample by summing all genotype scores (at individual single-nucleotide polymorphisms) for a person after weighting them by their estimated effect size. The PGS of the phenotype can be used to test the predictive value towards another trait, or to investigate the shared genetic etiology between traits (Euesden et al., 2015).

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

The polygenic scores were computed using LDpred (Vilhjálmsson et al., 2015). LDpred requires a prior (i.e. fraction of causal SNPs) for the genetic architecture of the trait. We tested a range of priors (varying proportions of causal SNPs) (1, 0.75, 0.5, 0.3, 0.1 and 0.03) to assess the prior at which prediction is optimal. We restricted analyses to common variants, using a SNP inclusion criterion of minor allele frequency (MAF) > 5%, and high imputation quality of $R^2 > 0.9$.

Using GEE to correct for familial relations, we regressed the created PGS of resilience on well-being and vice versa and included age, age^2, sex, and the first ten genomic principal components (PCs) as covariates. A significant association indicates that the genetic risk for resilience predicts well-being or vice versa. In addition, we applied linkage disequilibrium (LD) score regression (Bulik-Sullivan, Loh, et al., 2015) on the molecular genetic data to compute the genetic correlation between resilience and well-being.

2.3.3. Part 3. Causality

2.3.3.1. Within-subject change scores. Next, we investigated the possible (additional) causality between resilience and well-being using different tests trying to falsify the causal hypothesis. First, we used regression of the within-subject changes in well-being and resilience over time. If there is a causal relation from resilience to well-being, within-subject changes in resilience over time (T2 – T1) should predict parallel changes in well-being. The absence of a correlation of change scores over time would reject the causal hypothesis. Using GEE to correct for relatedness, regression analyses were performed to predict within-subject changes in well-being by changes in resilience over time. In reverse, if there is a causal relation from well-being to resilience, within-subject changes from T1 to T2 in well-being should predict parallel changes in resilience over time. These regression analyses exclude confounding by genetic factors, since the genotype within a subject does not change.

2.3.3.2. Bivariate twin-sibling models. Next, we used twin-sibling models to investigate the underlying sources of overlap and genetic and environmental correlations between resilience and well-being. Bivariate twin-sibling models use the difference in genetic overlap between monozygotic (MZ) twins and dizygotic twins (DZ) to estimate the underlying sources of phenotypic variance of two traits and their phenotypic correlation. MZ twin pairs share (almost) all genes, whereas DZ twin pairs share on average half of their segregating genes. Based on this difference, the observed phenotypic variance and covariance between traits can be decomposed into genetic and environmental variance components (Boomsma et al., 2002). Additive genetic variance (A) is the variance explained by the independent allele effects on the phenotype. Non-additive genetic variance (D) refers to interactions between alleles at the same locus (dominance) or between alleles at different loci (epistasis). Environmental variance includes a shared environmental variance component (C) (shared by family members) and a non-shared component, the unique environment, also including measurement error (E). The effects of C and D cannot be estimated simultaneously for identification reasons and a choice between an ACE or ADE model is made based on twin

correlations. The power of the classical twin design increases by adding non-twin siblings of twin pairs that share on average half of their segregating genes with other siblings and can be treated as DZ twins in the models (Posthuma & Boomsma, 2000).

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

As we have data on resilience and well-being at two time points, we modelled the variance of the underlying phenotypes in a bivariate psychometric model with repeated measures. The resilience and well-being scores at T1 and T2 can be seen as an index of the true measure including measurement error (Amstadter et al., 2014). For both resilience and well-being, the variance was split into a common (latent or stable) part and two uncorrelated (time-specific) parts. Next, both the common and time-specific parts of the variance were decomposed in variance explained by A, C/D, and E. The variance of the latent factors includes less measurement error, therefore this results in more reliable estimates of the genetic and environmental effects on the latent factors (see supplementary Figure S1 for the model) and is more comparable to the earlier work by Amstadter et al. (2014).

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

correlations were similar for both resilience and well-being, showing no indication for qualitative sex effects.

If resilience and well-being are causally related, genetic and environmental factors influencing individual differences in one trait will, through the causal chain, also influence individual differences in the other trait. To test this causal effect hypothesis, we constrained the genetic or environmental correlation between the latent traits in the bivariate model to zero. Both correlations have to be different from zero for causality. If only the genetic correlation is significant, a common genetic factor is more likely to underlie the association between resilience and well-being.

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

2.3.3.4. MZ twin difference model. A next test of the causal hypothesis used the monozygotic within-twin pair differences (twin 1 – twin 2), i.e. the differences in well-being and resilience in genetically identical individuals. If there is a causal relation, the MZ twin differences in resilience should be associated with within-twin pair differences in well-being and vice versa. The twin who is more resilient should have a higher well-being score than the co-twin who is less resilient. At both time points, we regressed the MZ intra pair differences in resilience on the difference in well-being and vice versa. Since monozygotic twins are genetically identical, this test excludes confounding by genetic and shared environmental factors. However, if there is an association, also other factors in the non-shared environment of the twins can underlie this association.

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

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

2.3.3.5. MR-DoC model. To explicitly test causality in both directions, allowing for coexisting genetic confounding, we leveraged the unique database of the Netherlands Twin Register and applied the MR-DoC model. The MR-DoC model uses twin data and polygenic scores, combining Mendelian Randomization with the Direction of Causation twin model (Minică et al., 2018). In Mendelian Randomization, genetic variants are used to test causal relationships between an exposure variable and outcome (Smith & Ebrahim, 2003). The genetic variants used to probe causal hypotheses are assumed to be: (a) well associated with the exposure variable; (b) not associated with confounders of the exposure-outcome relationship, and (c) associated with the outcome only through exposure (i.e. absence of horizontal pleiotropy). PGS can be used as strong genetic variables, but horizontal pleiotropy (same genes having an effect on both the exposure and outcome variable) is likely to occur with complex traits (Bulik-Sullivan, Finucane, et al., 2015). By combining MR with twin models, pleiotropy can be accounted for (Minică et al., 2018). For identification purposes the environmental correlation between traits is constrained to zero. Empirical analysis of height and educational attainment indicated that the test of causality conducted with MR-DoC is relatively robust to assumption violation (Minică et al., 2020)

We tested whether well-being causally affects resilience using the well-being PGS, the exposure being the well-being score and the outcome being the resilience score at time point T1 and T2 separately (see supplementary Figure S2 for the model). If the estimate for the causal effect from well-being to resilience (g_1) is larger than zero, there is a causal effect from well-being to resilience. We applied the same analysis for the causal effect of resilience on well-being, using the resilience PGS. Based on the results, the effect size (% variance) of the directional effect can be estimated, taking into account the presence of residual genetic pleiotropy.

3. Results

3.1. Operationalization of resilience

The definition of the resilience score assumes a positive association between stressful life events and anxious-depression and variability in the anxious-depressed score after stressful life events. Consistent with this definition, people differ in their response to stressful

life events, i.e. the variance around the point estimate of anxious-depressed score increased when the number of life events experienced increased (see supplementary Figure S3). The number of stressful life events experienced and the anxious-depressed score were positively related at T1 (r=.11 [95% CI: .08-.13], β_{gee}=.11, p<.001) and T2 (r=.26 [95% CI: .24-.28], β_{gee}=.27, p<.001). The residuals from the GEE models were used as the measure for resilience.

3.2. Part 1. Demographic effects and phenotypic correlations

In a saturated twin-sibling model, the mean score for well-being could be constrained to be equal across males and females, (p=.113). For resilience, the means could not be constrained to be equal across sexes (p<.001). The resilience score for men was significantly higher compared to women, indicating that on average men are more resilient than women. The descriptives are given in Table 1.

There is a small effect of age (T1: β=-.03, SE=.01, p<.001, T2: β=-.02, SE=.01, p<.001) and age^2 (T1: β=-0.01, SE<.01, p<.001, T2: β<-0.01, SE<.01, p<.001) on well-being in both waves. Similarly, there is a small effect of age (T1: β=.01, SE=.01, p<.001 and T2: β=.01, SE=.01, p<.001) and age^2 (T1: β<0.01, SE<.01, p<.001, T2: β<0.01, SE<.01, p<.001) on the resilience score. This reflects a U-shaped curve for both well-being and resilience, indicating that younger and older people score higher on resilience and well-being than people in middle adulthood.

---------- Insert Table 1 around here ------

Table 2 shows the phenotypic correlations between resilience and well-being cross-sectionally and across the different time points. The cross-sectional phenotypic correlations between resilience and well-being are .46 (95% CI: .44-.48) and .51 (95% CI: .50-.52) at T1 and T2 respectively. The longitudinal phenotypic correlations are slightly lower, with r=.35 (95% CI: .34-.36) for resilience at T1 and well-being at T2 and r=.43 (95% CI: .43-.44) for well-being at T1 and resilience at T2.

---------- Insert Table 2 around here ------

3.3. Part 2. GWAS Summary statistics: Polygenic scores and Genetic Correlations

The prediction of the polygenic scores for resilience and well-being using the different fractions of included SNPs (1 to 0.03) are in Supplementary Figure S4. The prediction of polygenic scores using a fraction of 1 and 0.75 are optimal and similar, therefore we proceed with a fraction of 1. The GEE analyses show that the PGS of direct self-assessed resilience is

borderline significant in predicting our indirect resilience score at T1 (p=.035) and T2 (p=.001), predicting only around 0.001% of the variance. The prediction of well-being is not significant (T1: p=.999 and T2: p=.171) and close to zero (see Figure 1, left panel).

The well-being PGS is a significant predictor for well-being and for resilience at both time points (p<.001), explaining around 0.03-0.05% of the variance (see Figure 1, right panel), suggesting some genetic overlap between resilience and well-being.

-------insert Figure 1 around here----

Using the summary statistics of the GWASs, we applied LD Score Regression (Bulik-Sullivan, Loh, et al., 2015). The estimated SNP heritability is 0.08 (*SE*=.04, p<.001) for resilience and 0.04 (*SE*=.003, p<.001) for well-being. The SNP-based genetic correlation between self-assessed resilience and well-being did not reach significance, r_g=0.27 (*SE*=0.15, *Z*=1.73, *p*=.084).

3.4. Part 3. Causality

3.4.1. Within-subject change scores

A change in resilience in an individual over time predicted a parallel change in well-being over time, β=.33 (95% CI: .29 -.38), SE=0.02, Z=15.67, p<.001. Similarly, within individual change in well-being predict a parallel change in resilience over time, β=.34 (95% CI: .30 -.38), SE=0.02, Z=15.95, p<.001 (see Figure 2). These results are in line with a causal relation between resilience and well-being, indicating that increased well-being leads to increased resilience and/or vice versa, after genetic confounding is taken into account.

-----insert Figure 2 around here-----

3.4.2. Bivariate twin-sibling models

Table 3 shows the twin and twin-sibling correlations for resilience and well-being within and cross traits and time points. Overall, the MZ correlations are more than twice the DZ/sibling correlations, suggesting dominant genetic effects besides additive genetic effects. Therefore, we continued with ADE models. Constraining all sibling correlations to the DZ correlations did not deteriorate the fit (p=.297), indicating that DZ twins do not resemble each other more than siblings (i.e. no specific twin environment).

---------- Insert Table 3 around here ------

The full bivariate longitudinal ADE measurement model with sex differences is shown in supplementary Figure S5. First, we tested the quantitative sex effect by constraining all path estimates to be equal for males and females (see Table 4, model 2). This model gave a significant deterioration of fit (p<.001). Next, we tested if only the latent factor path estimates could be constrained to be equal in males and females, whereas the path estimates of the time-specific factors were allowed to differ. This model did not lead to a deterioration of the fit, p=.400. Next, both specific and common dominant genetic effects (D) did not contribute significantly to the (co)variance (p=.269). Therefore, the final model is an AE model without sex differences in the latent factor, but with sex differences in the time-specific factors (see Figure 3).

----insert Table 4 and Figure 3 around here ----------

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

Of the covariance between resilience and well-being, 51.2% is explained by genetic factors and 48.8% by environmental factors. The genetic and environmental correlation between the latent factors of resilience and well-being are .71 (95% CI: .70-.71) and .93 (95% CI: .86-.98) respectively. As expected under the causal model, the genetic and environmental correlations could not be constrained to zero, p<.001 (see supplementary Table S3).

3.4.3. Longitudinal twin-sibling models

In a bivariate longitudinal twin model with the resilience score at T1 and well-being at T2, we could not constrain the estimates to be equal across sex. Thus we tested the significance of the genetic and environmental correlations separately for males and females. In line with the measurement model, D could be dropped (p=.005). The genetic correlations from resilience at baseline and well-being at T2 were .62 (95% CI: .53-.74) and .63 (95% CI:.41-.85) for females and males respectively. The environmental correlations were .19 (95% CI:.11-.26) and .23 (95% CI:.10-.35). Constraining any of the correlations to zero

resulted in a deterioration in fit (p<.001) (see supplementary Table S4), in line with a causal relationship from resilience at T1 to well-being at T2.

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

3.4.4. MZ twin difference model

The MZ twin intrapair differences model showed that regressing the resilience MZ twin difference score on the well-being MZ twin difference score resulted in significant estimates at both time points (T1: β=.38, SE=0.03, R^2 = 0.15, p<.001, T2: β=.47, SE=0.02, R^2 = 0.21, p<.001). Similarly, regressing the well-being difference score of MZ pairs on the resilience difference score resulted in significant estimates (T1: β=.40, SE=0.03, R^2 = 0.15, p<.001, T2: β=.44, SE=0.02, R^2 = 0.21, p<.001) (see Figure 4 upper panels).

The MZ twin longitudinal intrapair differences model showed a significant estimate from regressing the resilience change difference score on the well-being change difference, β=.32, SE=0.05, R^2 = 0.10, p<.001. Similarly, regressing the well-being difference score on the resilience difference score resulted in a significant estimate, β=.33, SE=0.05, R^2 = 0.10, p<.001 (see Figure 4 lower panel).

These findings are in line with a causal relation between resilience and well-being, indicating that higher well-being leads to higher resilience and/or vice versa, even if genetic confounding is taken into account.

---- insert Figure 4 around here --------

3.4.5. MR-DoC model

Lastly, we included the PGS as an instrumental variable in the twin model, applying the MR-DoC model (Minică et al., 2018) that can model causal effects while relaxing the MR no pleiotropy assumption. When including the PGS for well-being and estimating the pleiotropic effect freely, the direct effect from well-being to resilience cannot be dropped from this model at both times, p<.001 (see model A1 and A2 in Figure 5 and supplementary

Table S6 and S7), in line with a causal relation from well-being to resilience. The explained variance in resilience by well-being is 34% and 46% at time point 1 and 2 respectively.

Although the resilience PGS is not powerful in predicting resilience (i.e. the first MR assumption), we did explore the result from an MR-DoC model that included the resilience PGS. In line with a causal relation, the direct effect from resilience to well-being could not be dropped from this model, p<.001 (model B1 and B2 in Figure 5). The explained variance in well-being by resilience is 44% and 51% at time point 1 and 2 respectively.

----- insert Figure 5 around here--------

4. Discussion

4.1. Summary of results

We investigated the association between resilience and well-being in a large sample of twins and their siblings from the Netherlands Twin Register and tested whether it was due to bidirectional causal effects, after taking into account genetic confounding. The twin-sibling models showed strong cross-sectional and longitudinal correlations and a large overlap in genetic and environmental factors underlying resilience and well-being. There was a sex effect in the resilience mean score (men showed more resilience than women), but no sex difference in the genetic architecture of the latent factors for resilience and well-being. Results based on studies using GWAS summary statistics provided weak support for causal effects. Polygenic score analyses showed that the genetic risk for well-being is a predictor for resilience, but the genetic risk for self-reported resilience did not predict well-being. The genetic correlation based on these summary statistics did not reach significance. Results of different causality analyses in twin-sibling models consistently point towards a bidirectional causal relation between resilience and well-being. The most explicit and informative test, the MR-DoC model using both twin and PGS data, supported the unidirectional causal hypotheses between resilience and well-being.

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

About 50% of the covariance between resilience and well-being is explained by genetic factors and the strong genetic correlation (.71) indicates that the genetic factors underlying resilience and well-being overlap significantly. The environmental correlation between the traits is close to unity (.93) and indicates an almost perfect overlap in the environmental factors influencing both traits. There can be multiple explanations for the strong phenotypic, genetic, and environmental correlation between resilience and well-being. The causality analyses based on various methods with genetically informative samples consistently point towards a bidirectional causal relation between resilience and well-being instead of an underlying set of genes and/or environmental factors. To strengthen this finding, we applied the MR-DoC model. This model yielded results consistent with a causal relation from well-being to resilience and, with less power, from resilience to well-being as well. The assumption that the unique environmental sources of variation for resilience and well-being equals zero was necessary and might seem implausible as we find an environmental correlation of .93 in the twin-sibling models. However, the unique environmental effects on well-being can be related with resilience via the causal path only, where the unique environmental effects influence the outcome via its effect on the exposure and not directly. In bivariate twin models, this causal path is missing, what could result in a large environmental correlation.

Another explanation for the strong correlations between resilience and well-being could be a third variable underlying both traits and explaining the bidirectional relationship between them. For example, self-rated general health has a strong genetic correlation with well-being (Baselmans, van de Weijer, et al., 2019). If general health influences both well-being and resilience, a strong correlation between well-being and resilience does not necessarily mean the constructs have an influence on each other. Future research should include this and other variables to investigate this possibility. For now, based on the converging results of the different analyses, we suggest resilience and well-being have some causal effects on each other.

4.2. Points of discussion and limitations

4.2.1 Defining resilience and well-being

There is discussion about definition of resilience and well-being resulting in no universal or commonly agreed upon definition. Different questionnaires are validated to assess self-report resilience, like the Ego-Resilience scale (Block & Kremen, 1996) and Connor-Davidson Resilience Scale (Connor & Davidson, 2003). More recently, researchers are emphasizing the need for improved operationalizations of resilience (Kalisch et al., 2019;

Stainton et al., 2019). Resilience is not a stable trait but a complex, interactive process leading to positive psychological outcomes in response to stress or adversity (Kalisch et al., 2017). In line with these definitions, direct self-reported resilience seems to be different from resilience measured as the response to exposure to trauma in our study, based on the polygenic score predictions. Therefore, the results also underscore the need for a clear and commonly agreed upon definition of resilience.

We defined resilience as the better than predicted psychological outcome based on the number of stressful life events experienced. A difficulty in this definition is the inclusion of the type and number of life events experienced. In our study, we included 16 and 19 (time 1 and 2) life events about illness, dead of close others and events like robbery and accidents. This is not an exhaustive list of life events and the personal impact of life events might differ per individual. Therefore, further research should weight the personal impact of life events to better operationalize resilience.

Multiple theories about the definition of well-being exist as well and often a distinction between subjective and psychological well-being is made (Keyes et al., 2002). In short, subjective well-being is characterized by high levels of positive affect, low levels of negative affect, and a subjective evaluation of satisfaction with life (Diener et al., 2018), whereas psychological well-being refers to thriving, positive functioning, and judgments about the meaning and purpose of an individual's life (Ryff, 1989). Subjective and psychological well-being are strongly related, both genetically and phenotypically (e.g. Baselmans et al., 2019; Joshanloo, 2016). We included life satisfaction as a measure of well-being, but we expect a similar overlap between other aspects of well-being and resilience, because of the strong overlap between the different well-being measures.

4.2.2.Resilience GWAS

The GWAS summary statistics used to compute polygenic scores for resilience were based on the only GWAS to date on (self-reported) resilience (Stein et al., 2019). The GWAS in the relatively small US army soldiers sample (N=11.492) resulted in one independent significant locus. We identified three limitations in using these GWAS summary statistics in our study. First, the discovery sample size is small, resulting in less power to detect genetic associations. Secondly, a sample restricted to soldiers might not reflect the general population (i.e., results based on this sample might not generalize to the population). Third, in contrast to our indirect measure of resilience, the GWAS included a direct measure of self-reported resilience (STARRS 5-item questionnaire, rating of the ability to handle stress). Therefore, the PGS based on these summary statistics reflects the genetic risk for self-report resilience.

As can be seen in our results, the power to detect association between the resilience PGS and the resilience measure was low. The PGS did predict indirect resilience to some extent, but the variance explained was almost zero (<.001%). Furthermore, although there is an indication for a genetic relation and overlap between resilience and well-being, the self-reported resilience PGS did not predict well-being and the genetic correlation based on the summary statistics is lower than expected and did not reach significance.

Due to the low power of the resilience PGS and the small association between the resilience PGS and resilience score, we must interpret the results of the MR-DoC model including the resilience PGS with caution. As not all MR assumptions (i.e. the strong association between the genetic instrument and exposure) are fully met, this model should be seen as an exploratory model. We did include the results of this model for illustration purposes, but a replication with a strong resilience PGS is needed.

Furthermore, the MR-DoC model can be extended to test a bidirectional relationship, including both PGS of resilience and well-being at the same time. Such a model can strengthen the results and the constraint of the environmental correlation to zero is not necessary anymore. However, for this model two sets of powerful polygenic scores are needed. As the resilience PGS lacks power, we did not model a bidirectional MR-DoC model. Similarly, as the resilience GWAS was not powerful and only 1 SNP reached significance, we did not apply SNP based MR methods, such as MR-Egger.

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

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

4.3 Implications

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

Acknowledgements

The authors thank all NTR participants, who participated in this study. In addition, we would like to thank Wouter Peyrot for valuable feedback on an earlier version of this manuscript.

References

Abdellaoui, A., Hottenga, J. J., Knijff, P. De, Nivard, M. G., Xiao, X., Scheet, P., Brooks, A., Ehli, E. A., Hu, Y., Davies, G. E., Hudziak, J. J., Sullivan, P. F., Van Beijsterveldt, T., Willemsen, G., De Geus, E. J., Penninx, B. W. J. H., & Boomsma, D. I. (2013). Population structure, migration, and diversifying selection in the Netherlands. *European Journal of Human Genetics*, *21*(11), 1277–1285. https://doi.org/10.1038/ejhg.2013.48

Achenbach, T. M., & Rescorla, L. A. (2003). *Manual for the ASEBA Adult Forms & Profiles*. University of Vermont, Research Center for Children, Youth, & Families.

Amstadter, A. B., Maes, H. H., Sheerin, C. M., Myers, J. M., & Kendler, K. S. (2016). The relationship between genetic and environmental influences on resilience and on common internalizing and externalizing psychiatric disorders. *Social Psychiatry and Psychiatric Epidemiology*, *51*(5), 669–678. https://doi.org/10.1007/s00127-015-1163-6

Amstadter, A. B., Myers, J. M., & Kendler, K. S. (2014). Psychiatric resilience: Longitudinal twin study. *British Journal of Psychiatry*, *205*(4), 275–280. https://doi.org/10.1192/bjp.bp.113.130906

Bajaj, B., & Pande, N. (2016). Mediating role of resilience in the impact of mindfulness on life satisfaction and affect as indices of subjective well-being. *Personality and Individual Differences*, *93*, 63–67. https://doi.org/10.1016/j.paid.2015.09.005

Bartels, M. (2015). Genetics of Wellbeing and Its Components Satisfaction with Life, Happiness, and Quality of Life: A Review and Meta-analysis of Heritability Studies. *Behavior Genetics*, *45*(2), 137–156. https://doi.org/10.1007/s10519-015-9713-y

Baselmans, B. M. L., Jansen, R., Ip, H. F., van Dongen, J., Abdellaoui, A., van de Weijer, M. P., Bao, Y., Smart, M., Kumari, M., Willemsen, G., Hottenga, J. J., Boomsma, D. I., de Geus, E. J. C., Nivard, M. G., & Bartels, M. (2019). Multivariate genome-wide analyses of the well-being spectrum. *Nature Genetics*, *51*(3), 445–451. https://doi.org/10.1038/s41588-018-0320-8

Baselmans, B. M. L., van de Weijer, M. P., Abdellaoui, A., Vink, J. M., Hottenga, J. J., Willemsen, G., Nivard, M. G., de Geus, E. J. C., Boomsma, D. I., & Bartels, M. (2019). A Genetic Investigation of the Well-Being Spectrum. *Behavior Genetics*, *49*(3), 286–297. https://doi.org/10.1007/s10519-019-09951-0

Block, J., & Kremen, A. M. (1996). IQ and Ego-Resiliency: Conceptual and Empirical Connections and Separateness. *Journal of Personality and Social Psychology*, *70*(2), 349. https://doi.org/10.1037/0022-3514.70.2.349

Boardman, J. D., Blalock, C. L., & Button, T. M. M. (2008). Sex differences in the heritability of resilience. *Twin Research and Human Genetics*, *11*(1), 12–27. https://doi.org/10.1375/twin.11.1.12

Boker, S., Neale, M., Maes, H., Wilde, M., Spiegel, M., Brick, T., Spies, J., Estabrook, R., Kenny, S., Bates, T., Mehta, P., & Fox, J. (2011). OpenMx: An Open Source Extended Structural Equation Modeling Framework. *Psychometrika*, *76*, 306–317. https://doi.org/10.1007/s11336-010-9200-6

Bonanno, G. A. (2004). Loss, Trauma, and Human Resilience: Have We Underestimated the Human Capacity to Thrive after Extremely Aversive Events? *American Psychologist*, *59*(1), 20. https://doi.org/10.1037/0003-066X.59.1.20

Bonanno, G. A., Westphal, M., & Mancini, A. D. (2011). Resilience to Loss and Potential Trauma. *Annual Review of Clinical Psychology*, *7*, 511–535. https://doi.org/10.1146/annurev-clinpsy-032210-104526

Boomsma, D. I., Busjahn, A., & Peltonen, L. (2002). Classical twin studies and beyond. *Nature Reviews Genetics*, *3*(11), 872. https://doi.org/10.1038/nrg932

Boomsma, D. I., Wijmenga, C., Slagboom, E. P., Swertz, M. A., Karssen, L. C., Abdellaoui, A., Ye, K., Guryev, V., Vermaat, M., Van Dijk, F., Francioli, L. C., Hottenga, J. J., Laros, J. F. J., Li, Q., Li, Y., Cao, H., Chen, R., Du, Y., Li, N., … Van Duijn, C. M. (2014). The Genome of the Netherlands: Design, and project goals. *European Journal of Human Genetics*, *22*(2), 221–227. https://doi.org/10.1038/ejhg.2013.118

Bulik-Sullivan, B., Finucane, H. K., Anttila, V., Gusev, A., Day, F. R., Loh, P. R., Duncan, L., Perry, J. R. B., Patterson, N., Robinson, E. B., Daly, M. J., Price, A. L., & Neale, B. M. (2015). An atlas of genetic correlations across human diseases and traits. *Nature Genetics*, *47*(11), 1236. https://doi.org/10.1038/ng.3406

Bulik-Sullivan, B., Loh, P. R., Finucane, H. K., Ripke, S., Yang, J., Patterson, N., Daly, M. J., Price, A. L., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., Lee, P., Collier, D. A., Huang, H., Pers, T. H., Agartz, I., Agerbo, E., … O'Donovan, M.

C. (2015). LD score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nature Genetics*, *47*(3), 291. https://doi.org/10.1038/ng.3211

Chapman, B., & Guven, C. (2016). Revisiting the Relationship Between Marriage and Wellbeing: Does Marriage Quality Matter? *Journal of Happiness Studies*, *17*(2), 533–551. https://doi.org/10.1007/s10902-014-9607-3

Charney, D. S. (2004). Psychobiological Mechanism of Resilience and Vulnerability: Implications for Successful Adaptation to Extreme Stress. *American Journal of Psychiatry*, *161*(2), 195–216. https://doi.org/10.1176/appi.ajp.161.2.195

Choi, K. W., Stein, M. B., Dunn, E. C., Koenen, K. C., & Smoller, J. W. (2019). Genomics and psychological resilience: a research agenda. *Molecular Psychiatry*, 1–9. https://doi.org/10.1038/s41380-019-0457-6

Cohn, M. A., Fredrickson, B. L., Brown, S. L., Mikels, J. A., & Conway, A. M. (2009). Happiness Unpacked: Positive Emotions Increase Life Satisfaction by Building Resilience. *Emotion*, *9*(3), 361. https://doi.org/10.1037/a0015952

Connor, K. M., & Davidson, J. R. T. (2003). Development of a new Resilience scale: The Connor-Davidson Resilience scale (CD-RISC). *Depression and Anxiety*, *18*(2), 76–82. https://doi.org/10.1002/da.10113

Consortium, T. G. of the N., Francioli, L. C., Menelaou, A., Pulit, S. L., van Dijk, F., Palamara, P. F., Elbers, C. C., Neerincx, P. B. T., Ye, K., Guryev, V., Kloosterman, W. P., Deelen, P., Abdellaoui, A., van Leeuwen, E. M., van Oven, M., Vermaat, M., Li, M., Laros, J. F. J., Karssen, L. C., … Wijmenga, C. (2014). Whole-genome sequence variation, population structure and demographic history of the Dutch population. *Nature Genetics*, *46*(8), 818.

De Moor, M. H. M., Boomsma, D. I., Stubbe, J. H., Willemsen, G., & De Geus, E. J. C. (2008). Testing causality in the association between regular exercise and symptoms of anxiety and depression. *Archives of General Psychiatry*, *65*(8), 897–905. https://doi.org/10.1001/archpsyc.65.8.897

Derks, E. M., Dolan, C. V., & Boomsma, D. I. (2004). Effects of censoring on parameter estimates and power in genetic modeling. *Twin Research*, *7*, 659–669. https://doi.org/10.1375/1369052042663832

Diener, E., Emmons, R. A., Larsen, R. J., & Griffin, S. (1985). The Satisfaction With Life Scale. *Journal of Personality Assessment*, *49*(1), 71–75. https://doi.org/10.1207/s15327752jpa4901_13

Diener, E., Lucas, R. E., & Oishi, S. (2018). Advances and Open Questions in the Science of Subjective Well-Being. *Collabra: Psychology*, *4*(1). https://doi.org/10.1525/collabra.115

Diener, E., Pressman, S. D., Hunter, J., & Delgadillo-Chase, D. (2017). If, Why, and When Subjective Well-Being Influences Health, and Future Needed Research. *Applied Psychology: Health and Well-Being*, *9*(2), 133–167. https://doi.org/10.1111/aphw.12090

Ehli, E. A., Abdellaoui, A., Fedko, I. O., Grieser, C., Nohzadeh-Malakshah, S., Willemsen, G., De Geus, E. J. C., Boomsma, D. I., Davies, G. E., & Hottenga, J. J. (2017). A method to customize population-specific arrays for genome-wide association testing. *European Journal of Human Genetics*, *25*(2), 267–270. https://doi.org/10.1038/ejhg.2016.152

Euesden, J., Lewis, C. M., & O'Reilly, P. F. (2015). PRSice: Polygenic Risk Score software. *Bioinformatics*, *31*(9), 1466–1468. https://doi.org/10.1093/bioinformatics/btu848

Fedko, I. ., Hottenga, J. J., Van Beijsterveldt, C. E. M., Middeldorp, C. M., Bartels, M., Boomsma, D. I., Medina-Gomez, C., Pappa, I., Rivadeneira, F., Tiemeier, H., Ehli, E. A., Davies, G. E., & Swertz, M. A. (2015). Estimation of Genetic Relationships Between Individuals Across Cohorts and Platforms: Application to Childhood Height. *Behavior Genetics*, *45*(5), 514–528.

Fredrickson, B. L., Tugade, M. M., Waugh, C. E., & Larkin, G. R. (2003). What Good Are Positive Emotions in Crises? A Prospective Study of Resilience and Emotions Following the Terrorist attacks on the United States on September 11th, 2001. *Journal of Personality and Social Psychology*, *84*(2), 365. https://doi.org/10.1037/0022-3514.84.2.365

Galatzer-Levy, I. R., & Bonanno, G. A. (2012). Beyond normality in the study of bereavement: Heterogeneity in depression outcomes following loss in older adults. *Social Science and Medicine*, *74*(12), 1987–1994. https://doi.org/10.1016/j.socscimed.2012.02.022

Galatzer-Levy, I. R., Huang, S. H., & Bonanno, G. A. (2018). Trajectories of resilience and

dysfunction following potential trauma: A review and statistical evaluation. *Clinical Psychology Review*, *63*, 41–55. https://doi.org/10.1016/j.cpr.2018.05.008

Greenspoon, P. J., & Saklofske, D. H. (2001). Toward an integration of subjective well-being and psychopathology. *Social Indicators Research*, *54*(1), 81–108. https://doi.org/10.1023/A:1007219227883

Howell, R. T., Kern, M. L., & Lyubomirsky, S. (2007). Health benefits: Meta-analytically determining the impact of well-being on objective health outcomes. *Health Psychology Review*, *1*(1), 83–136. https://doi.org/10.1080/17437190701492486

Hu, T., Zhang, D., & Wang, J. (2015). A meta-analysis of the trait resilience and mental health. *Personality and Individual Differences*, *76*, 18–27. https://doi.org/10.1016/j.paid.2014.11.039

James, P., Kim, E. S., Kubzansky, L. D., Zevon, E. S., Trudel-Fitzgerald, C., & Grodstein, F. (2019). Optimism and Healthy Aging in Women. *American Journal of Preventive Medicine*, *56*(1), 116–124. https://doi.org/10.1016/j.amepre.2018.07.037

Joshanloo, M. (2016). Revisiting the Empirical Distinction Between Hedonic and Eudaimonic Aspects of Well-Being Using Exploratory Structural Equation Modeling. *Journal of Happiness Studies*, *17*(5), 2023–2036. https://doi.org/10.1007/s10902-015-9683-z

Kalisch, R., Baker, D. G., Basten, U., Boks, M. P., Bonanno, G. A., Brummelman, E., Chmitorz, A., Fernàndez, G., Fiebach, C. J., Galatzer-Levy, I., Geuze, E., Groppa, S., Helmreich, I., Hendler, T., Hermans, E. J., Jovanovic, T., Kubiak, T., Lieb, K., Lutz, B., … Kleim, B. (2017). The resilience framework as a strategy to combat stress-related disorders. *Nature Human Behaviour*, *1*(11), 784–790. https://doi.org/10.1038/s41562-017-0200-8

Kalisch, R., Cramer, A. O. J., Binder, H., Fritz, J., Leertouwer, I., Lunansky, G., Meyer, B., Timmer, J., Veer, I. M., & Van Harmelen, A.-L. (2019). Deconstructing and reconstructing resilience: a dynamic network approach. *Perspectives on Psychological Science*, *14*(5), 765–777. https://doi.org/10.5281/zenodo.3228687

Kendler, K. S., Thornton, L. M., & Gardner, C. O. (2000). Stressful life events and previous episodes in the etiology of major depression in women: An evaluation of the “kindling”

hypothesis. *American Journal of Psychiatry*, *157*(8), 1243–1251. https://doi.org/10.1176/appi.ajp.157.8.1243

Kessler, R. C. (1997). The effects of stressful life events on depression. *Annual Review of Psychology*, *48*(1), 191–214. https://doi.org/10.1146/annurev.psych.48.1.191

Keyes, C. L. M., Shmotkin, D., & Ryff, C. D. (2002). Optimizing well-being: The empirical encounter of two traditions. *Journal of Personality and Social Psychology*, *82*(6), 1007. https://doi.org/10.1037/0022-3514.82.6.1007

Kim, E. S., James, P., Zevon, E. S., Trudel-Fitzgerald, C., Kubzansky, L. D., & Grodstein, F. (2019). Optimism and Healthy Aging in Women and Men. *American Journal of Epidemiology*, *56*(1), 116–124. https://doi.org/10.1093/aje/kwz056

Ligthart, L., van Beijsterveldt, C. E. M., Kevenaar, S. T., de Zeeuw, E., van Bergen, E., Bruins, S., Pool, R., Helmer, Q., van Dongen, J., Hottenga, J.-J., van't Ent, D., Dolan, C. V., Davies, G. E., Ehli, E. A., Bartels, M., Willemsen, G., De Geus, E. J. C., & Boomsma, D. I. (2019). The Netherlands Twin Register: Longitudinal Research Based on Twin and Twin-Family Designs. *Twin Research and Human Genetics*, 1–14. https://doi.org/10.1017/thg.2019.93

Liu, Y., Wang, Z. H., & Li, Z. G. (2012). Affective mediators of the influence of neuroticism and resilience on life satisfaction. *Personality and Individual Differences*, *52*(7), 833–838. https://doi.org/10.1016/j.paid.2012.01.017

Long, E. C., Lönn, S. L., Ji, J., Lichtenstein, P., Sundquist, J., Sundquist, K., & Kendler, K. S. (2017). Resilience and Risk for Alcohol Use Disorders: A Swedish Twin Study. *Alcoholism: Clinical and Experimental Research*, *41*(1), 149–155. https://doi.org/10.1111/acer.13274

Luthar, S. S., Cicchetti, D., & Becker, B. (2000). The construct of resilience: A critical evaluation and guidelines for future work. *Child Development*, *71*(3), 543–562. https://doi.org/10.1111/1467-8624.00164

Lyubomirsky, S., King, L., & Diener, E. (2005). The benefits of frequent positive affect: Does happiness lead to success? *Psychological Bulletin*, *131*(6), 803. https://doi.org/10.1037/0033-2909.131.6.803

Maccagnan, A., Wren-Lewis, S., Brown, H., & Taylor, T. (2019). Wellbeing and Society:

Towards Quantification of the Co-benefits of Wellbeing. *Social Indicators Research*, *141*(1), 217–243. https://doi.org/10.1007/s11205-017-1826-7

McGinty, E. E., Presskreischer, R., Han, H., & Barry, C. L. (2020). Psychological Distress and Loneliness Reported by US Adults in 2018 and April 2020. *JAMA*. https://doi.org/10.1001/jama.2020.9740

Middeldorp, C. M., Cath, D. C., Beem, A. L., Willemsen, G., & Boomsma, D. I. (2008). Life events, anxious depression and personality: A prospective and genetic study. *Psychological Medicine*, *38*(11), 1557–1565. https://doi.org/10.1017/S0033291708002985

Minică, C. C., Boomsma, D. I., Dolan, C. V, de Geus, E., & Neale, M. C. (2020). Empirical comparisons of multiple Mendelian randomization approaches in the presence of assortative mating. *International Journal of Epidemiology*. https://doi.org/10.1093/ije/dyaa013

Minică, C. C., Dolan, C. V., Boomsma, D. I., de Geus, E., & Neale, M. C. (2018). Extending Causality Tests with Genetic Instruments: An Integration of Mendelian Randomization with the Classical Twin Design. *Behavior Genetics*, *48*(4), 337–349. https://doi.org/10.1007/s10519-018-9904-4

Minică, C. C., Dolan, C. V., Kampert, M. M. D., Boomsma, D. I., & Vink, J. M. (2015). Sandwich corrected standard errors in family-based genome-wide association studies. *European Journal of Human Genetics*, *23*, 388. https://doi.org/10.1038/ejhg.2014.94

Neale, M. C., Røysamb, E., & Jacobson, K. (2006). Multivariate Genetic Analysis of Sex Limitation and G × E Interaction. *Twin Research and Human Genetics*, *9*(4), 481–489. https://doi.org/10.1375/twin.9.4.481

Nes, R. B., & Røysamb, E. (2015). The heritability of subjective well-being: review and meta-analysis. In *The genetics of psychological well-being: The role of heritability and genetics in positive psychology* (pp. 75–96). https://doi.org/10.1093/acprof:oso/9780199686674.003.0005

O'Rourke, N. (2004). Psychological resilience and the well-being of widowed women. *Ageing International*, *29*(3), 267–280. https://doi.org/10.1007/s12126-996-1002-x

Ong, A. D., Bergeman, C. S., Bisconti, T. L., & Wallace, K. A. (2006). Psychological

resilience, positive emotions, and successful adaptation to stress in later life. *Journal of Personality and Social Psychology*, *91*(4), 730. https://doi.org/10.1037/0022-3514.91.4.730

Oswald, A. J., Proto, E., & Sgroi, D. (2015). Happiness and productivity. *Journal of Labor Economics*, *33*(4), 789–822. https://doi.org/10.1086/681096

Phillips, A. C., Carroll, D., & Der, G. (2015). Negative life events and symptoms of depression and anxiety: stress causation and/or stress generation. *Anxiety, Stress and Coping*, *28*(4), 357–371. https://doi.org/10.1080/10615806.2015.1005078

Pietrzak, R. H., Feder, A., Singh, R., Schechter, C. B., Bromet, E. J., Katz, C. L., Reissman, D. B., Ozbay, F., Sharma, V., Crane, M., Harrison, D., Herbert, R., Levin, S. M., Luft, B. J., Moline, J. M., Stellman, J. M., Udasin, I. G., Landrigan, P. J., & Southwick, S. M. (2014). Trajectories of PTSD risk and resilience in World Trade Center responders: An 8-year prospective cohort study. *Psychological Medicine*, *44*(1), 205–219. https://doi.org/10.1017/S0033291713000597

Posthuma, D., & Boomsma, D. I. (2000). A note on the statistical power in extended twin designs. *Behavior Genetics*, *30*(2), 147–158. https://doi.org/10.1023/A:1001959306025

Rossi, N. E., Bisconti, T. L., & Bergeman, C. S. (2007). The role of dispositional resilience in regaining life satisfaction after the loss of a spouse. *Death Studies*, *31*(10), 863–883. https://doi.org/10.1080/07481180701603246

Ryff, C. D. (1989). Happiness is everything, or is it? Explorations on the meaning of psychological well-being. *Journal of Personality and Social Psychology*, *57*(6), 1069–1081. https://doi.org/10.1037/0022-3514.57.6.1069

Satici, S. A. (2016). Psychological vulnerability, resilience, and subjective well-being: The mediating role of hope. *Personality and Individual Differences*, *102*, 68–73. https://doi.org/10.1016/j.paid.2016.06.057

Smith, G. D., & Ebrahim, S. (2003). “Mendelian randomization”: Can genetic epidemiology contribute to understanding environmental determinants of disease? *International Journal of Epidemiology*, *32*(1), 1–22. https://doi.org/10.1093/ije/dyg070

Stainton, A., Chisholm, K., Kaiser, N., Rosen, M., Upthegrove, R., Ruhrmann, S., & Wood, S. J. (2019). Resilience as a multimodal dynamic process. *Early Intervention in*

Psychiatry, *13*(4), 725–732. https://doi.org/10.1111/eip.12726 LK - http://sfx.metabib.ch/sfx_locater?sid=EMBASE&issn=17517893&id=doi:10.1111%2Feip.12726&atitle=Resilience+as+a+multimodal+dynamic+process&stitle=Early+Interven t.+Psychiatry&title=Early+Intervention+in+Psychiatry&volume=&issue=&spage=&epage=&aulast=Stainton&aufirst=Alexandra&auinit=A.&aufull=Stainton+A.&coden=&isbn=&pages=-&date=2018&auinit1=A&auinitm=

Stein, M. B., Choi, K. W., Jain, S., Campbell-Sills, L., Chen, C. Y., Gelernter, J., He, F., Heeringa, S. G., Maihofer, A. X., Nievergelt, C., Nock, M. K., Ripke, S., Sun, X., Kessler, R. C., Smoller, J. W., & Ursano, R. J. (2019). Genome-wide analyses of psychological resilience in U.S. Army soldiers. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, *180*(5), 310–319. https://doi.org/10.1002/ajmg.b.32730

Steptoe, A. (2019). Happiness and Health. *Annual Review of Public Health*, *40*, 339–359. https://doi.org/10.1146/annurev-publhealth-040218-044150

Stubbe, J. H., Posthuma, D., Boomsma, D. I., & De Geus, E. J. C. (2005). Heritability of life satisfaction in adults: A twin-family study. *Psychological Medicine*, *35*(11), 1581–1588. https://doi.org/10.1017/S0033291705005374

Vilhjálmsson, B. J., Yang, J., Finucane, H. K., Gusev, A., Lindström, S., Ripke, S., Genovese, G., Loh, P. R., Bhatia, G., Do, R., Hayeck, T., Won, H. H., Neale, B. M., Corvin, A., Walters, J. T. R., Farh, K. H., Holmans, P. A., Lee, P., Bulik-Sullivan, B., … Price, A. L. (2015). Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *American Journal of Human Genetics*, *97*(4), 576–592. https://doi.org/10.1016/j.ajhg.2015.09.001

Waaktaar, T., & Torgersen, S. (2012). Genetic and environmental causes of variation in trait resilience in young people. *Behavior Genetics*, *42*(3), 366–377. https://doi.org/10.1007/s10519-011-9519-5

Werner, E. E., & Smith, R. S. (2001). *Journeys from childhood to midlife: risk, resilience, and recovery*. Cornell University Press.

Willemsen, G., Vink, J. M., Abdellaoui, A., Den Braber, A., Van Beek, J. H. D. A., Draisma, H. H. M., Van Dongen, J., Van ’T Ent, D., Geels, L. M., Van Lien, R., Ligthart, L., Kattenberg, M., Mbarek, H., De Moor, M. H. M., Neijts, M., Pool, R., Stroo, N., Kluft,

C., Suchiman, H. E. D., … Boomsma, D. I. (2013). The Adult Netherlands Twin Register: Twenty-five years of survey and biological data collection. *Twin Research and Human Genetics*, *16*(1), 271–281. https://doi.org/10.1017/thg.2012.140

Wolf, E. J., Miller, M. W., Sullivan, D. R., Amstadter, A. B., Mitchell, K. S., Goldberg, J., & Magruder, K. M. (2018). A classical twin study of PTSD symptoms and resilience: Evidence for a single spectrum of vulnerability to traumatic stress. *Depression and Anxiety*, *35*(2), 132–139. https://doi.org/10.1002/da.22712

Wray, N. R., Goddard, M. E., & Visscher, P. M. (2007). Prediction of individual genetic risk to disease from genome-wide association studies. *Genome Research*, *17*(10), 1520–1528. https://doi.org/10.1101/gr.6665407

Zaninotto, P., & Steptoe, A. (2019). English Longitudinal Study of Ageing. *Encyclopedia of Gerontology and Population Aging. Cham: Springer International Publishing*, 1–7. https://doi.org/10.1007/978-3-319-69892-2_335-1

Figures

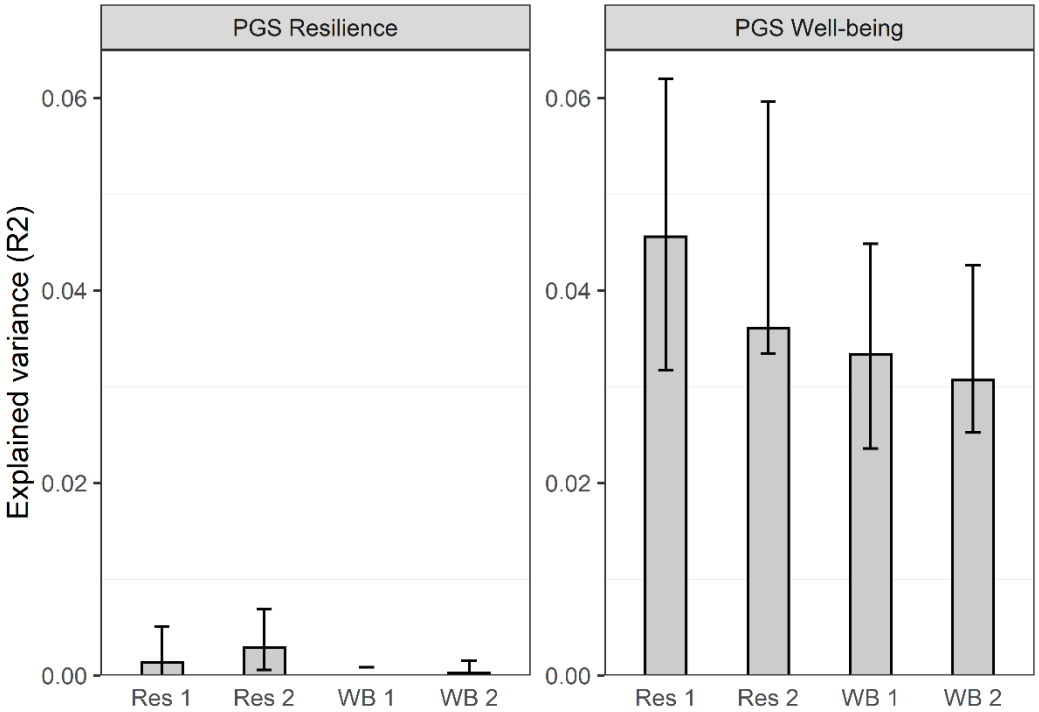

Figure 1. Explained variance in the phenotypic resilience and well-being scores by the polygenic scores of resilience (left panel) and well-being (right panel). Res= resilience, WB= well-being.

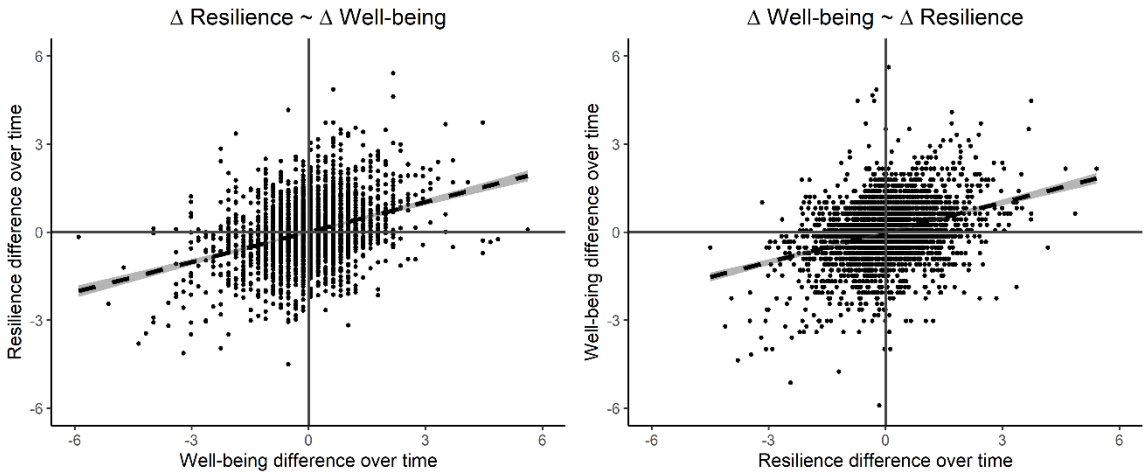

Figure 2. The relation between the within-subject differences over time in resilience and well-being.

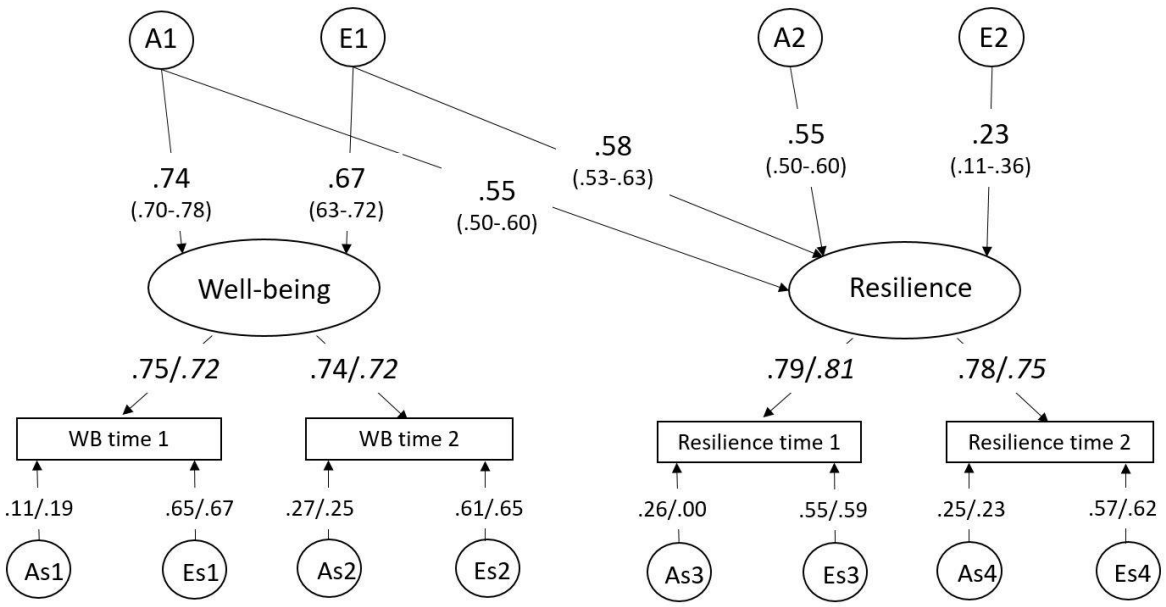

Figure 3. Unstandardized path estimates of the final common pathway model of resilience and well-being for females/males.

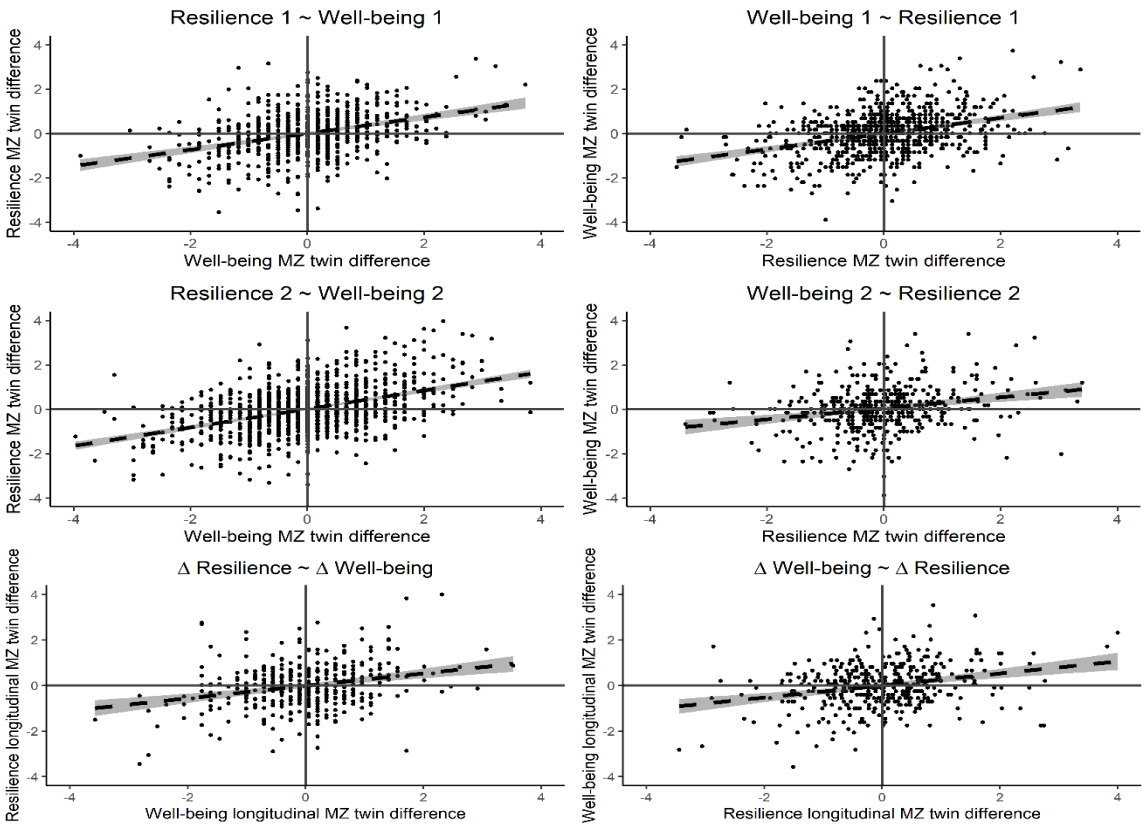

Figure 4. The MZ differences models. In the left upper panels, the MZ twin difference score of resilience is predicted by MZ twin differences in well-being (cross-sectionally, at T1 and T2). In the right upper panels, the MZ twin difference score of well-being is predicted by MZ twin differences in resilience (cross-sectionally, at T1 and T2). The lower panel shows the longitudinal association between MZ within-twin pair differences in resilience and well-being.

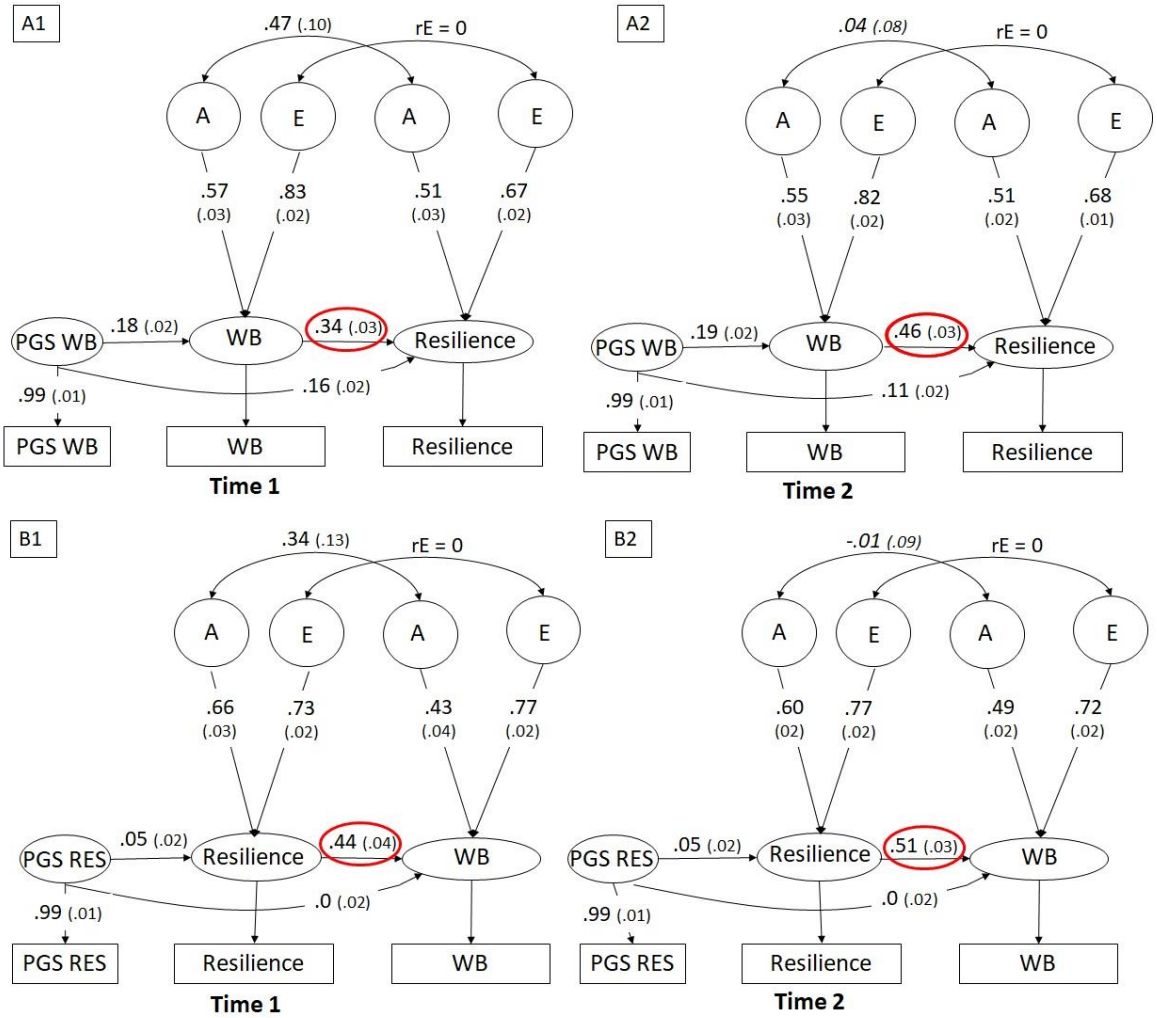

Figure 5. The results of the MR-DoC model. Model A1 and A2 show the model with the well-being PGS and resilience as the outcome in cross-sectional data from time point 1 and 2 respectively. Model B1 and B2 show the models with the resilience PGS and well-being as the outcome in cross-sectional data from time point 1 and 2 respectively. The causal effects can be seen in the red circle. WB= well-being, RES= resilience, PGS= polygenic score.

Tables

Table 1.

Descriptives of the measures for resilience and well-being.

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

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

Table 2.

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

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

Table 3.

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

	WB1	**WB2**	**Res1**	**Res2**	**WB1**	**WB2**	**Res1**	**Res2**
		MZM				**MZF**		
WB1	.32				.38			
	(.20,.42)				*(.31,.44)*			
WB2	.38	.46			.34	.35		
	(.29,.46)	*(.38,.52)*			*(.29,.38)*	*(.30,.39)*		
Res1	.18	.32	.43		.28	.22	.48	
	(.09,.26)	*(.23,.41)*	*(.30,.53)*		*(.24,.32)*	*(.18,.27)*	*(.42,.52)*	
Res2	.24	.34	.37	.51	.26	.21	.39	.42
	(.15,.32)	*(.28,.34)*	*(.28,.46)*	*(.41,.58)*	*(.22,.30)*	*(.17,.24)*	*(.35,.43)*	*(.38,.42)*
		DZM				**DZF**		
WB1	.02				.11			
	(-.12,.20)				*(.01,.20)*			
WB2	.09	.26			.13	.22		
	(-.06,.23)	*(.11,.38)*			*(.05,.20)*	*(.14,.29)*		
Res1	.140	.12	.22		.08	.10	.17	
	(.11,.27)	*(-.02,.25)*	*(-.01,.41)*		*(.03,.15)*	*(.03,.18)*	*(.07,.27)*	
Res2	.09	.14	.27	.29	.06	.11	.11	.19
	(-.10,.27)	*(-.00,.26)*	*(.08,.42)*	*(.08,.30)*	*(-.02,.13)*	*(.05,.17)*	*(.03,.19)*	*(.11,.27)*
		DOS				**Brother-sister**		
WB1	.09				.11			
	(-.01,.20)				*(.03,.18)*			
WB2	.07	.11			.07	.13		
	(-.01,.15)	*(.03,.19)*			*(.00,.13)*	*(.05,.20)*		
Res1	.06	.07	.14		.09	.08	.13	
	(-.02,.13)	*(-.00,.15)*	*(.04,.24)*		*(.03,.15)*	*(.01,.13)*	*(.04,.20)*	
Res2	.05	.08	.19	.16	.09	.10	.12	.14
	(-.04,.05)	*(.06,.15)*	*(.10,.25)*	*(.07,.24)*	*(.02,.14)*	*(.04,.16)*	*(.06,.19)*	*(.05,.22)*
		Brothers				**Sister**		
WB1	.05				.04			
	(-.07,.17)				*(-.05,.12)*			
WB2	-.02	.26			.10	.15		
	(-.13,.09)	*(.11,.38)*			*(.03,.16)*	*(.07,.22)*		
Res1	.07	.12	.23		.07	.09	.19	
	(-05,.19)	*(-.02,.25)*	*(.01,.38)*		*(.010,.13)*	*(.03,.15)*	*(.11,.27)*	
Res2	-.06	.14	.09	.17	.10	.07	.17	.16
	(-.19,.07)	*(-.00,.26)*	*(-.09,.27)*	*(-.10,.34)*	*(.03,.15)*	*(.01, .14)*	*(.10,.23)*	*(.07,.23)*
		DZ/siblings*						

WB1	.08 *(.08,.09)*			
WB2	.08 *(.07,.10)*	.15 *(.13,.15)*		
Res1	.08 *(.07,.11)*	.09 *(.06,.10)*	.17 *(.12,.19)*	
Res2	.07 *(.05,.08)*	.09 *(.09,.09)*	.15 *(.13,.17)*	.16 *(.16,.17)*

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

Table 4.

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

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

Supplementary tables and figures

Table S1.

Number of participants per zygosity and sex for every variable.

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

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

Table S2.

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

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

Table S3.

Results of the psychometric model constraining the genetic and environmental correlation.

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

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

Table S4.

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

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

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

Table S5.

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

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

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

Table S6.

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

base	comparison	ep	-2LL	df	AIC	ΔLL	Δdf	p
Time 1								
WB -> RES		35	24068.10	8924	6220.10			
WB -> RES	g1=0	34	24183.82	8925	6333.82	115.72	1	5.47E-27
Time 2								
WB -> RES		35	30920.35	11541	7838.35			
WB -> RES	g1=0	34	31235.96	11542	8151.96	315.61	1	1.31E-70
Time 1								
RES -> WB		35	24251.18	8924	6403.18			
RES -> WB	g1=0	34	24363.72	8925	6513.72	112.54	1	2.72E-26
Time 2								
RES -> WB		35	31142.78	11541	8060.78			
RES -> WB	g1=0	34	31458.05	11542	8374.05	315.27	1	1.56E-70

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

Table S7.

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

Standardized		**Time 1: WB -> Resilience**		**Time 2: WB -> Resilience**		**Time 1: Resilience -> WB**		**Time 2: Resilience -> WB**	
	name	Estimate	Std.Error	Estimate	Std.Error	Estimate	Std.Error	Estimate	Std.Error
Causal effect	g1	**0.342**	0.031	**0.455**	0.025	**0.439**	0.041	**0.510**	0.027
PGS exposure	b1	0.183	0.021	0.188	0.017	0.053	0.021	0.050	0.018
PGS outcome	b2	0.160	0.019	0.107	0.016	*0.000*	*0.019*	*0.000*	*0.015*
A effect exposure	ab	0.565	0.035	0.546	0.025	0.664	0.027	0.602	0.024
E effect exposure	eb	0.833	0.022	0.816	0.016	0.730	0.020	0.773	0.016
A effect outcome	as	0.507	0.028	0.509	0.021	0.431	0.037	0.492	0.022
E effect outcome	es	0.673	0.018	0.675	0.014	0.768	0.020	0.715	0.015
PGS to PGS	x	0.992	0.011	0.992	0.011	0.999	0.011	0.999	0.011
Genetic correlation	ra	0.471	0.101	0.039	0.083	0.344	0.126	*-0.013*	*0.086*

Note: WB= well-being.

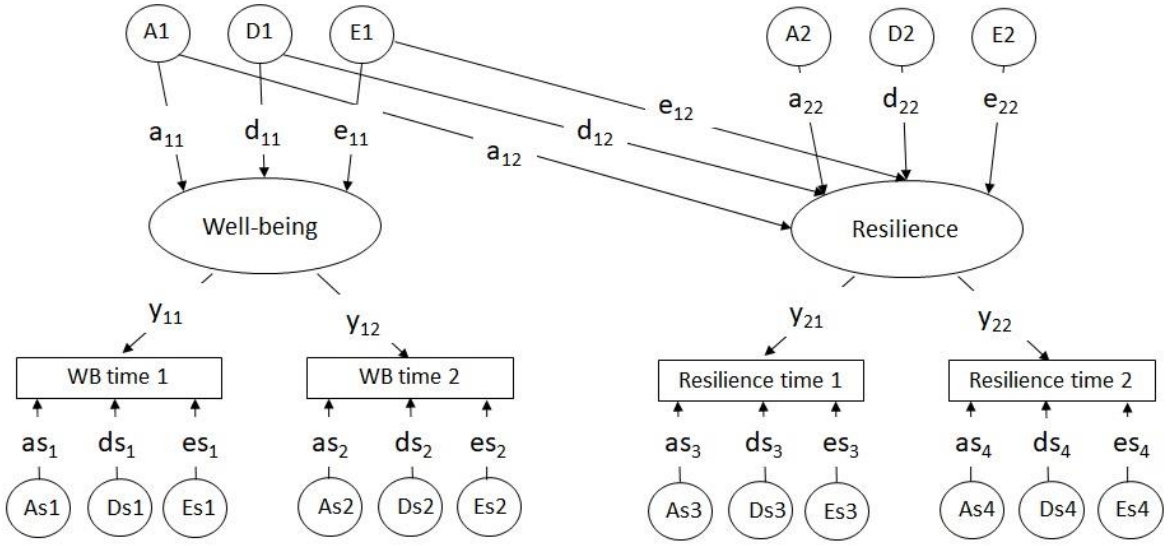

Figure S1. Longitudinal measurement model.

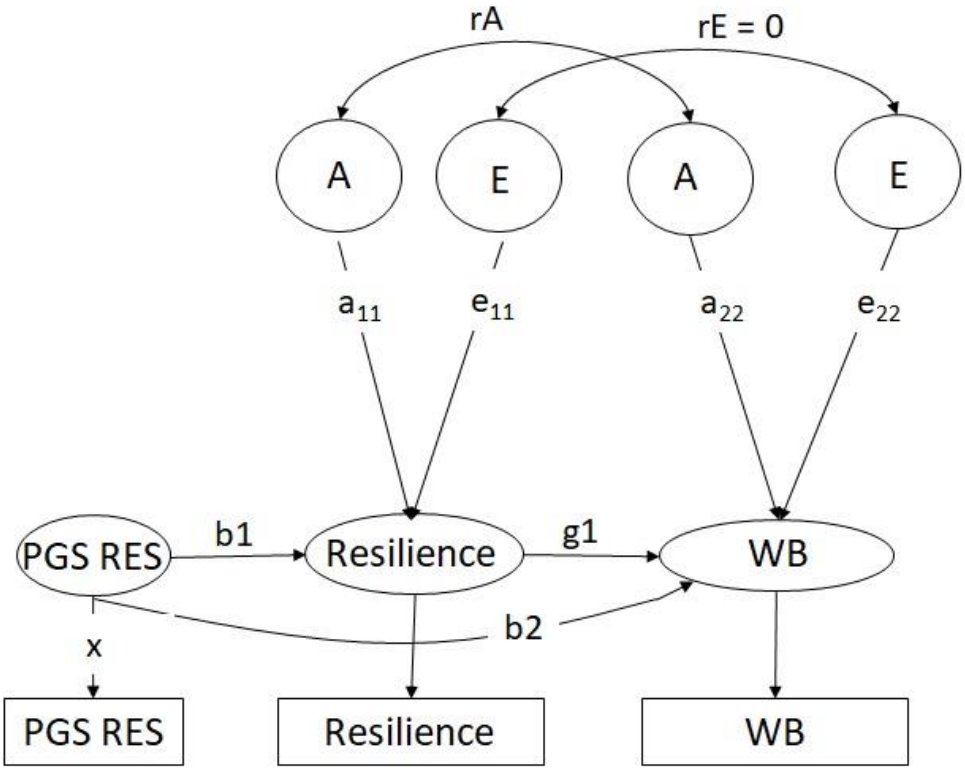

Figure S2. The MR-DoC model. In addition, we will run this model with the well-being PGS, well-being as predictor and resilience as outcome.

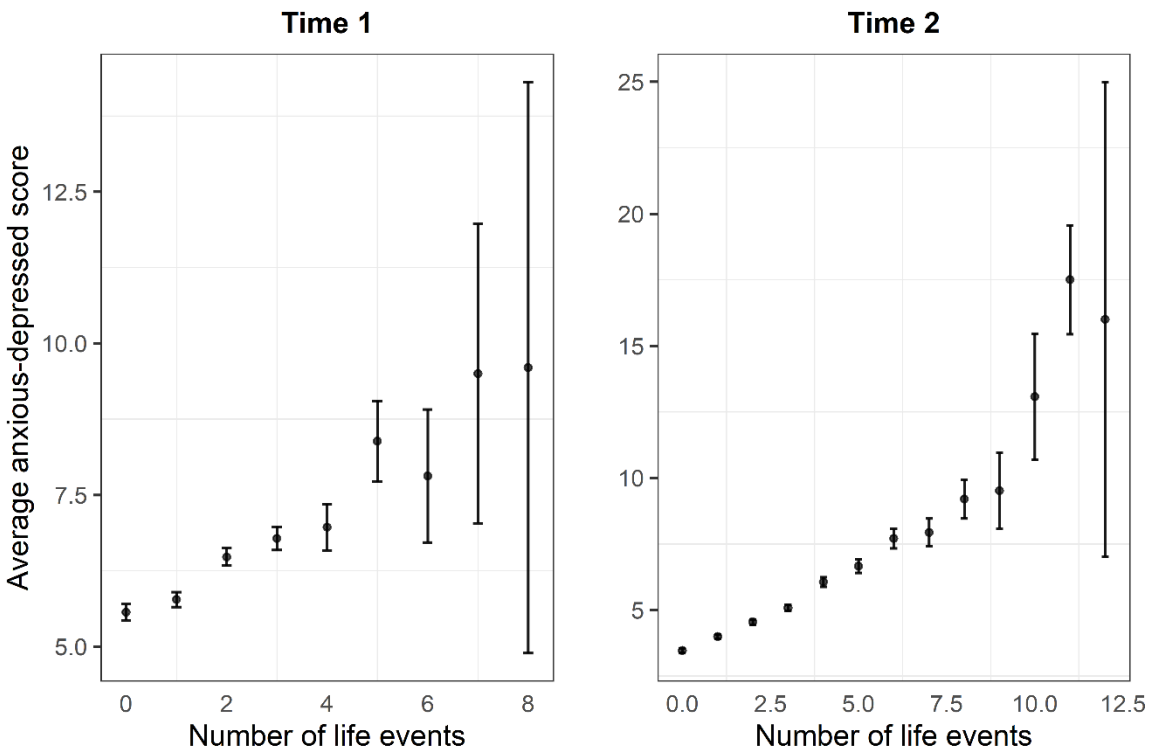

Figure S3. Association between the number of life events and the anxious depressed score.

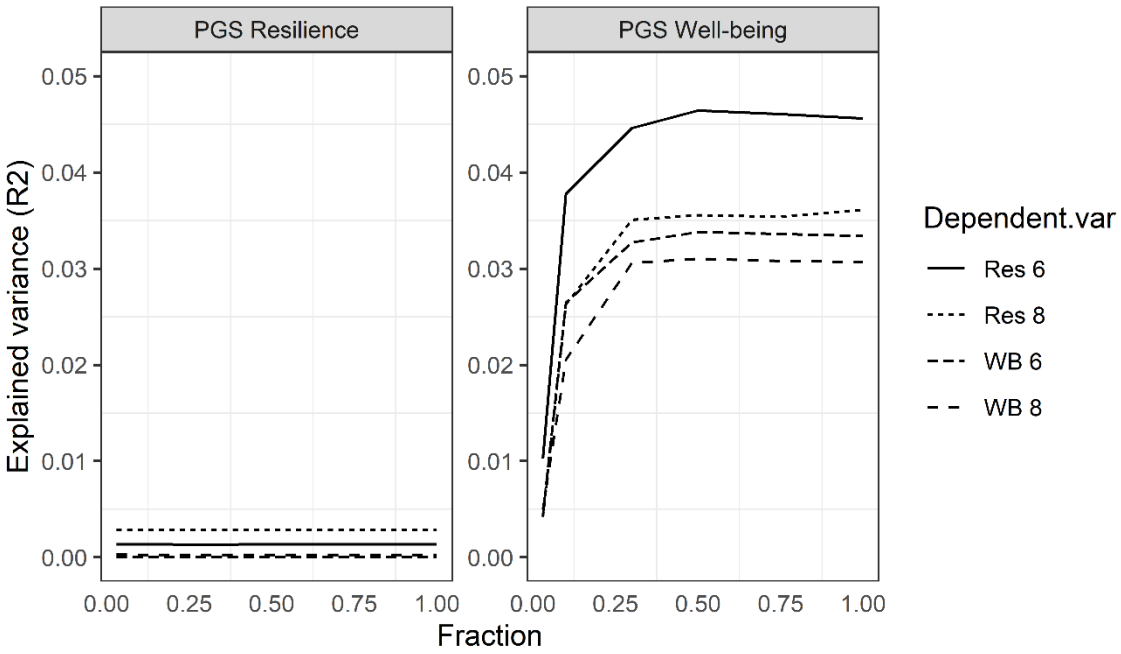

Figure S4. Explained variance by the resilience and well-being PGS for the different fractions of SNPs included.

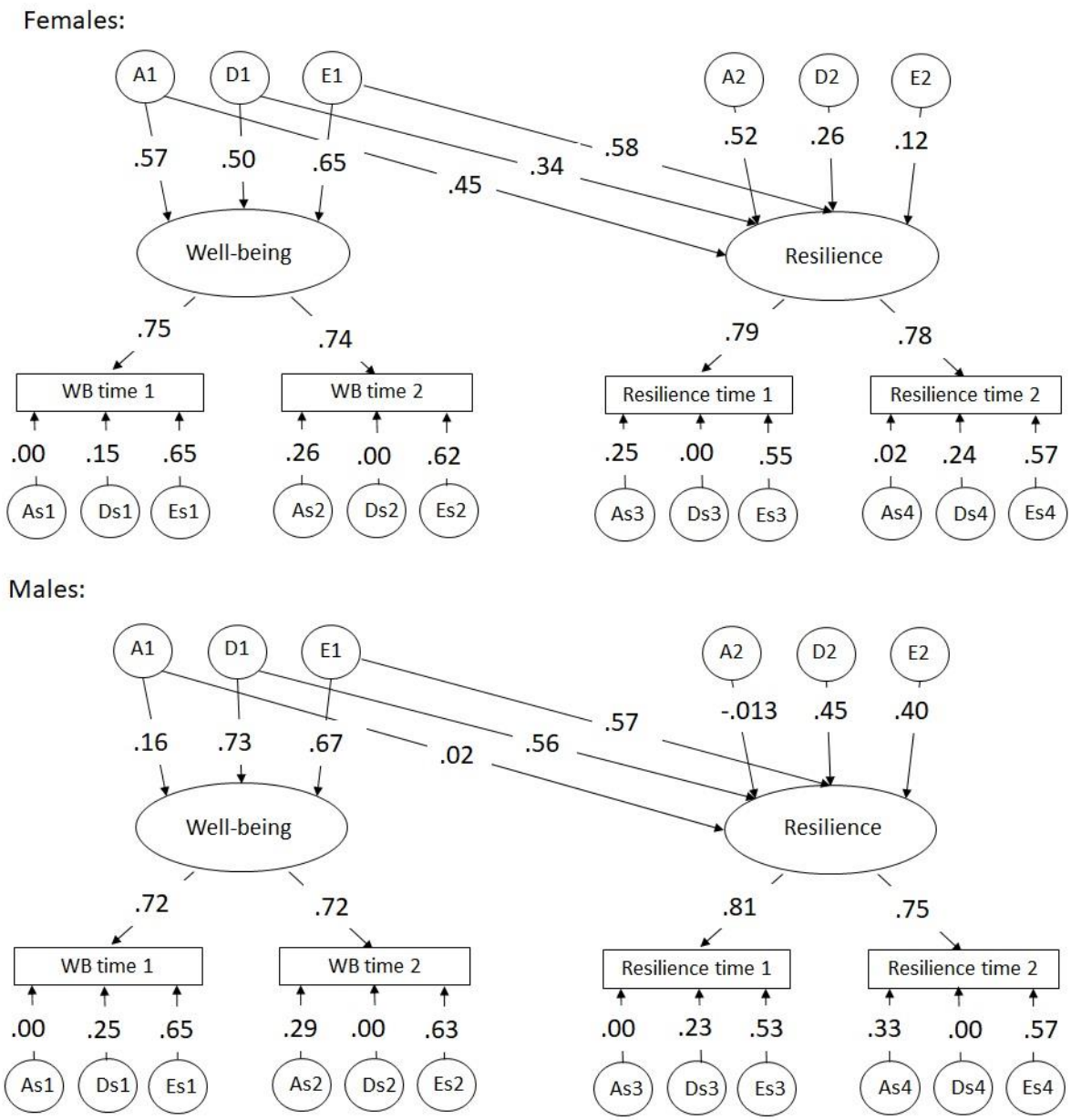

Figure S5. Path estimates of the full common pathway model of resilience and well-being for females and males.