

Genetic correlations between suicide attempts and psychiatric and intermediate phenotypes adjusting for mental disorders

Original Article

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Abstract

Background. Suicide attempts are a moderately heritable trait, and genetic correlations with psychiatric and related intermediate phenotypes have been reported. However, as several mental disorders as well as major depressive disorder (MDD) are strongly associated with suicide attempts, these genetic correlations could be mediated by psychiatric disorders. Here, we investigated genetic correlations of suicide attempts with psychiatric and related intermediate phenotypes, with and without adjusting for mental disorders.

Methods. To investigate the genetic correlations, we utilized large-scale genome-wide association study summary statistics for suicide attempts (with and without adjusting for mental disorders), nine psychiatric disorders, and 15 intermediate phenotypes.

Results. Without adjusting for mental disorders, suicide attempts had significant positive genetic correlations with risks of attention-deficit/hyperactivity disorder, schizophrenia, bipolar disorder, MDD, anxiety disorders and posttraumatic stress disorder; higher risk tolerance; earlier age at first sexual intercourse, at first birth and at menopause; higher parity; lower childhood IQ, educational attainment and cognitive ability; and lower smoking cessation. After adjusting for mental disorders, suicide attempts had significant positive genetic correlations with the risk of MDD; earlier age at first sexual intercourse, at first birth and at menopause; and lower educational attainment. After adjusting for mental disorders, most of the genetic correlations with psychiatric disorders were decreased, while several genetic correlations with intermediate phenotypes were increased.

Conclusions. These findings highlight the importance of considering mental disorders in the analysis of genetic correlations related to suicide attempts and suggest that susceptibility to MDD, reproductive behaviors, and lower educational levels share a genetic basis with suicide attempts after adjusting for mental disorders.

Introduction

Suicide is a major concern for global public health and a leading cause of death globally. According to the World Health Organization (WHO), over 800 000 people die by suicide each year, and many more attempt suicide during their lifetime (WHO, 2019). A suicide attempt refers to a deliberate, self-inflicted act with the intent to end one's life that fails to result in death. Suicide attempts can range from self-harm behaviors to serious, life-threatening actions. The lifetime prevalence of suicide attempts ranges from 3% to 4% in high-income countries (WHO, 2019). Family, twin and adoption studies have shown a familial aggregation of suicidal behaviors (Runeson & Asberg, 2003; Tidemalm et al., 2011) and have indicated that genetic factors account for approximately 30–50% of the observed familial aggregation (Fu et al., 2002; Statham et al., 1998).

To date, several large-scale genome-wide association studies (GWASs) have been conducted to determine the genetic factors that contribute to suicide attempts, suicide death, and suicidal behaviors (Erlangsen et al., 2020; Li et al., 2023; Mullins et al., 2022; Ruderfer et al., 2020; Strawbridge et al., 2019). These studies have identified a few genome-wide significant loci related to the risks of suicide and suicidal behaviors; however, the identified loci varied among studies. Since psychiatric disorders, particularly major depressive disorder (MDD), are strongly linked to suicide (Bachmann, 2018), several GWASs have investigated genetic associations with and without adjusting for MDD (Li et al., 2023; Mullins et al., 2022), determining that the genetic basis for suicide and suicidal behavior is affected by MDD. However, most cases and some controls in these GWASs had various mental disorders, such as attention-deficit/hyperactivity disorder (ADHD), autism spectrum disorder (ASD), schizophrenia (SCZ) and bipolar disorder (BD) as well as MDD (Erlangsen et al., 2020; Li et al., 2023; Mullins et al., 2022; Ruderfer et al., 2020; Strawbridge et al., 2019). We cannot exclude

the possibility that these GWAS findings were driven by the mixed and different genetic loadings for psychiatric disorders between suicidal and nonsuicidal participants. Among these GWASs, Erlangsen et al. (2020) in the Integrative Psychiatric Research (iPSYCH) consortium explored suicide attempts with and without adjusting for MDD as well as other mental disorders in individuals with one or more suicide attempts ($n = 6024$) and those without any suicide attempts ($n = 44\,240$). These GWASs have indicated that genome-wide significant loci are affected by adjusting for mental disorders, including MDD.

The specific genetic factors that may contribute to the risk of suicide attempts are not fully understood. Understanding the genetic basis of suicide attempts can help inform prevention and intervention efforts. Genetic correlations, i.e. shared genetic factors, refer to the extent to which the same genetic factors contribute to the risk of developing psychiatric disorders and/or the related intermediate phenotypes. It is important to note that genetic correlations do not necessarily imply that one disorder or phenotype causes the other or that the disorders and/or phenotypes are the same. Rather, they suggest that there may be shared genetic risk factors that contribute to the development of psychiatric disorders and/or the related intermediate phenotypes. Several studies have investigated genetic correlations between suicide attempts and psychiatric disorders and the related intermediate phenotypes (Li et al., 2023; Mullins et al., 2022; Ruderfer et al., 2020; Strawbridge et al., 2019). Suicide attempts were genetically correlated with risks of MDD, anxiety disorders, SCZ, BD, ADHD, ASD, posttraumatic stress disorder (PTSD), anorexia nervosa (AN), insomnia, and alcohol use disorder; earlier age at first birth; higher neuroticism; lower educational attainment; and higher smoking initiation (Li et al., 2023; Mullins et al., 2022; Ruderfer et al., 2020; Strawbridge et al., 2019). After adjusting for MDD, the genetic correlations with psychiatric disorders, particularly MDD, anxiety disorders, ASD, PTSD and AN, were reduced (Li et al., 2023; Mullins et al., 2022). However, given that a wide range of mental disorders, such as SCZ, BD, ADHD, and PTSD, is associated with increased risk of suicide attempts, genetic factors underlying suicide attempts might be mediated through their impacts on other mental disorders as well as MDD.

The clinical as well as genetic basis between suicide and various psychiatric disorders and related intermediate phenotypes (Bachmann, 2018; Lewis, Johnson, Cohen, Garcia, & Velez, 1988; Li et al., 2023; Mota, Cox, Katz, & Sareen, 2010; Mullins et al., 2022; Ruderfer et al., 2020; Strawbridge et al., 2019) motivated us to investigate whether we would find a genetic correlation with suicide even after correcting for various psychiatric disorders in this study. We hypothesized that even after adjusting for mental disorders including SCZ, BD, ASD, AN, or any other mental disorder in addition to MDD, some psychiatric disorders and related intermediate phenotypes would have genetic correlations with suicide attempts. Here, we investigated genetic correlations of suicide attempts (with and without adjusting for mental disorders) (Erlangsen et al., 2020) with nine psychiatric disorders and the 15 related intermediate phenotypes selected based on the clinical and genetic associations using linkage disequilibrium score regression (LDSC) analyses.

Methods

To investigate genetic correlations of suicide attempts (with and without adjusting for mental disorders) with psychiatric and

intermediate phenotypes, we extracted GWAS summary statistics for suicide attempts (without and with adjusting for mental disorders; Models 1 and 2, respectively) (Erlangsen et al., 2020), and nine psychiatric disorders and 15 similar but independent intermediate phenotypes selected based on the clinical and genetic associations with suicide attempts (Bachmann, 2018; Lewis et al., 1988; Li et al., 2023; Mota et al., 2010; Mullins et al., 2022; Ruderfer et al., 2020; Strawbridge et al., 2019) from individuals with European ancestry (Table 1). The detailed sample information regarding sample collection, genotyping, quality control, and imputation procedures applied in each GWAS has been described previously (Arnold et al., 2018; Barban et al., 2016; Benyamini et al., 2014; Davies et al., 2018; Demontis et al., 2023; Duncan et al., 2017; Erlangsen et al., 2020; Furberg et al., 2010; Grove et al., 2019; Karlsson Linnér et al., 2019; Lee et al., 2018; Loh, Kichaev, Gazal, Schoech, & Price, 2018; Luciano et al., 2018; Mills et al., 2021; Mullins et al., 2021; Nievergelt et al., 2019; Okbay et al., 2016; Purves et al., 2020; Trubetskoy et al., 2022; van den Berg et al., 2016; Wray et al., 2018). Informed consent was obtained from all participants and/or their families in each study cohort. Data availability was approved by each local ethical committee of the relevant institutions.

Suicide attempts with and without adjusting for mental disorders

GWAS summary statistics regarding suicide attempts with (Model 2) and without (Model 1) adjusting for mental disorders (Erlangsen et al., 2020) are available in the iPSYCH public database (<https://ipsych.dk/en/research/downloads>).

Case-control samples were registered through the Danish iPSYCH registration systems. Individuals who were diagnosed with one or more severe mental disorders (ADHD, ASD, SCZ, BD, affective disorders, or AN) according to the 10th revision of the International Classification of Diseases (ICD-10) were included. In addition, a population-based random sample of individuals was also included. Among these subjects, cases ($n = 6024$) were defined as individuals with one or more recorded incidents of nonfatal suicide attempts. Suicide attempts and a proxy for suicide attempts, such as a mental disorder together with a diagnosis of poisoning by drugs or other substances or injuries to the hand, wrist, or forearm, were identified according to the ICD-10 codes through the Danish iPSYCH registration systems. Controls ($n = 44\,240$) were defined as all persons without one or more suicide attempts. The case-control group consisted of persons with mental disorders (case, 97.8%; control, 70.0%) and those with no mental disorders (case, 2.2%; control, 30.0%) (Erlangsen et al., 2020). Two different GWAS models (Models 1 and 2) were constructed. Model 1 did not adjust for mental disorders. Model 2 contained binary covariates for the diagnosis of SCZ, BD, affective disorders, ASD, AN, or any other mental disorder.

Psychiatric disorders

GWAS summary statistics for nine psychiatric disorders, including ADHD (Demontis et al., 2023), ASD (Grove et al., 2019), SCZ (Trubetskoy et al., 2022), BD (Mullins et al., 2021), MDD (Wray et al., 2018), anxiety disorders (Purves et al., 2020), PTSD (Nievergelt et al., 2019), AN (Duncan et al., 2017), and obsessive-compulsive disorder (OCD) (Arnold et al., 2018), are available in public databases from the iPSYCH (<https://ipsych.dk/en/research/downloads>), the Psychiatric Genomics

Table 1. Demographic information for genome-wide association studies (GWASs) of suicide attempts, psychiatric disorders and intermediate phenotypes

		PMID	GWS loci	Sample size			SNP heritability h^2 (s.e.)
				Total	Cases	Controls	
SA without adjusting for MD (Model 1)	Erlangsen et al. (2020)	30 116 032	0	50 264	6024	44 240	0.099 (0.021)
SA with adjusting for MD (Model 2)	Erlangsen et al. (2020)	30 116 032	1	50 264	6024	44 240	0.038 (0.019)
Psychiatric disorders							
Attention-deficit/hyperactivity disorder	Demontis et al. (2023)	36 702 997	27	225 534	38 691	186 843	0.156 (0.007)
Autism spectrum disorder	Grove et al. (2019)	30 804 558	5	46 350	18 381	27 969	0.127 (0.011)
Schizophrenia	Trubetsky et al. (2022)	35 396 580	178 ^a	130 644	53 386	77 258	0.200 (0.007)
Bipolar disorder	Mullins et al. (2021)	34 002 096	64	413 466	41 917	371 549	0.105 (0.004)
Major depressive disorder	Wray et al. (2018)	29 700 475	44	173 005	59 851	113 154	0.109 (0.007)
Anxiety disorders	Purves et al. (2020)	31 748 690	5	83 566	25 453	58 113	0.161 (0.011)
Posttraumatic stress disorder	Nievergelt et al. (2019)	31 594 949	2	174 659	23 212	151 447	0.031 (0.006)
Anorexia nervosa	Duncan et al. (2017)	28 494 655	1	14 477	3495	10 982	0.181 (0.029)
Obsessive-compulsive disorder	Arnold et al. (2018)	28 761 083	0	9725	2688	7037	0.264 (0.041)
Intermediate phenotypes							
Extraversion	van den Berg et al. (2016)	26 362 575	0	63 030	–	–	0.052 (0.008)
General risk-tolerance	Karlsson Linnér et al. (2019)	30 643 258	107	466 571	–	–	0.051 (0.002)
Neuroticism	Luciano et al. (2018)	29 255 261	116	329 821	–	–	0.094 (0.007)
Subjective well-being	Okbay et al. (2016)	27 089 181	3	204 966	–	–	0.025 (0.002)
Age at menarche	Loh et al. (2018)	29 892 013	294 ^a	279 470	–	–	0.246 (0.010)
Age at first sexual intercourse	Mills et al. (2021)	34 211 149	275	387 338	–	–	0.145 (0.004)
Age at first birth	Mills et al. (2021)	34 211 149	88	542 901	–	–	0.054 (0.002)
Parity	Barban et al. (2016)	27 798 627	2	343 072	–	–	0.025 (0.002)
Age at menopause	Loh et al. (2018)	29 892 013	82 ^a	156 364	–	–	0.121 (0.009)
Childhood IQ	Benyamin et al. (2014)	23 358 156	0	12 441	–	–	0.276 (0.045)
Educational attainment	Lee et al. (2018)	30 038 396	1271	1 131 881	–	–	0.072 (0.002)
General cognitive ability	Davies et al. (2018)	29 844 566	148	282 014	–	–	0.143 (0.005)
Smoking initiation	Furberg et al. (2010)	20 418 890	0	74 035	–	–	0.039 (0.003)
Smoking quantity	Furberg et al. (2010)	20 418 890	1	38 181	–	–	0.058 (0.013)
Smoking cessation	Furberg et al. (2010)	20 418 890	0	41 278	–	–	0.040 (0.007)

Suicide attempts, SA; Mental disorders, MD; PMID, PubMed ID; GWS, genome-wide significant.

^aGWS loci were determined by using FUMA (<https://fuma.ctglab.nl/>). The observed scale heritability h^2 for suicide attempts and psychiatric disorders was converted to liability scale heritability using population prevalence and sample prevalence in each study.

Consortium (PGC) (<https://www.med.unc.edu/pgc/results-and-downloads>), and the UK Biobank (UKBB) (<https://www.kcl.ac.uk/people/kirstin-purves>).

Intermediate phenotypes

GWAS summary statistics for 15 intermediate phenotypes, including personality traits, reproductive behaviors, cognitive functions, smoking behaviors, extraversion (van den Berg et al., 2016), general risk tolerance (Karlsson Linnér et al., 2019), neuroticism (Luciano et al., 2018), subjective well-being (Okbay et al., 2016), age at menarche (Loh et al., 2018), age at first sexual intercourse (Mills et al., 2021), age at first birth (Mills et al., 2021), parity (Barban et al., 2016), age at menopause (Loh et al., 2018), childhood IQ (Benyamin et al., 2014), educational attainment

(Lee et al., 2018), general cognitive ability (Davies et al., 2018), smoking initiation (Furberg et al., 2010), smoking quantity (Furberg et al., 2010), and smoking cessation (Furberg et al., 2010), were utilized through public databases from the Center for Cognitive Aging and Cognitive Epidemiology at the University of Edinburgh (CCACE) (<http://www.ccace.ed.ac.uk/node/335>), the iPSYCH (<https://ipsych.dk/en/research/downloads>), the Genetics of Personality Consortium (GPC) (<http://www.tweelingenregister.org/GPC/>), the Social Science Genetic Association Consortium (SSGAC) (<http://www.thessgac.org/data>), the GWAS Catalog (<https://www.ebi.ac.uk/gwas/summary-statistics>), and the Tobacco and Genetics Consortium. These intermediate phenotypes especially among personality traits, reproductive behaviors, cognitive functions, and smoking behaviors are genetically similar but independent phenotypes (Davies et al., 2018; Furberg et al., 2010;

Luciano et al., 2018; Mills et al., 2021; Ohi et al., 2022a; Ohi, Muto, Takai, Sugiyama, & Shioiri, 2022b).

Linkage disequilibrium score regression analysis

To estimate the genetic correlations of single-nucleotide polymorphisms (SNPs) (r_g) between two GWASs, LDSC analyses were performed (Bulik-Sullivan et al., 2015; Ohi et al., 2020b, 2022a; Ohi, Otowa, Shimada, Sasaki, & Tani, 2020a). For each GWAS, we filtered the imputed and directly genotyped SNPs in each GWAS to SNPs that overlapped with a HapMap3 SNP panel to restrict the analysis to well-imputed SNPs. Furthermore, insertion-deletion polymorphisms (indels), structural variants, strand-ambiguous SNPs and SNPs with extremely large effect sizes were removed. Only SNPs with an imputation INFO score >0.90 and minor allele frequency >0.01, if this information was available, were included in the analysis. Regression weights (LD scores, 'eur_w_ld_chr' files, <https://github.com/bulik/ldsc>) were precomputed using the European-ancestry samples of the 1000 Genomes Project. For each GWAS, LD regression was carried out by regressing the GWAS test statistic (χ^2) onto each SNP's LD score. Then, genetic correlations between the two GWASs were calculated. We set a Bonferroni-corrected p value threshold of $p < 2.08 \times 10^{-3}$ ($=0.05/24$ psychiatric and intermediate phenotypes) to avoid type I error.

Results

Genetic correlations between suicide attempts and psychiatric disorders, with and without adjusting for mental disorders

We first investigated genetic correlations between suicide attempts and psychiatric disorders with and without including mental disorders as covariates (Fig. 1). Suicide attempts were significantly genetically correlated with psychiatric disorders without adjusting for mental disorders; specifically, suicide attempts were genetically correlated with risks of ADHD ($r_g \pm \text{s.e.} = 0.61 \pm 0.08$, $p = 3.33 \times 10^{-13}$), SCZ (0.23 ± 0.06 , $p = 4.00 \times 10^{-4}$), BD (0.27 ± 0.06 , $p = 2.67 \times 10^{-5}$), MDD (0.69 ± 0.08 , $p = 3.61 \times 10^{-17}$), anxiety disorders (0.48 ± 0.10 , $p = 6.58 \times 10^{-7}$) and PTSD (0.72 ± 0.18 , $p = 6.68 \times 10^{-5}$).

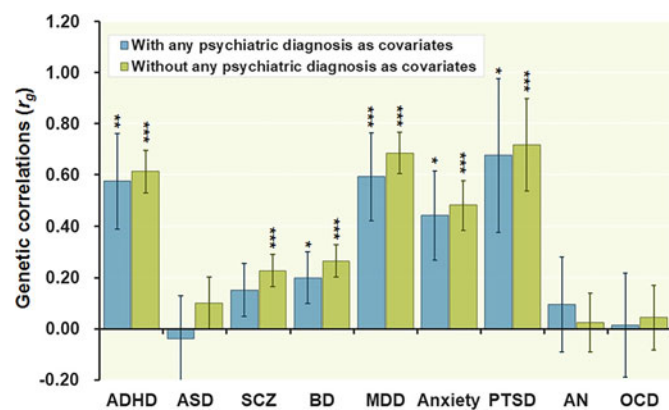


Figure 1. Genetic correlations (r_g) between suicide attempts and psychiatric disorders, with and without adjusting for any psychiatric diagnosis. A positive r_g indicates that suicide attempts were genetically correlated with the risk of each psychiatric disorder. Error bars represent the standard error. * $p < 0.05$, ** $p < 0.01$, *** $p < 2.08 \times 10^{-3}$. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; SCZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder; Anxiety, anxiety disorders; PTSD, posttraumatic stress disorder; AN, anorexia nervosa; OCD, obsessive-compulsive disorder.

In contrast, after adjusting for mental disorders, most of the genetic correlations were decreased (Fig. 3, 14.2% decrease, mean $r_g \pm \text{s.e.} = -0.05 \pm 0.06$). After adjusting for mental disorders, suicide attempts were significantly genetically correlated with only the risk of MDD (0.59 ± 0.17 , $p = 6.00 \times 10^{-4}$). Risks of ADHD, BD, anxiety disorders and PTSD were not significantly but nominally genetically correlated with suicide attempts after adjusting for mental disorders ($p > 2.08 \times 10^{-3}$ but $p < 0.05$).

Genetic correlations between suicide attempts and intermediate phenotypes, with and without adjusting for mental disorders

We next investigated genetic correlations between suicide attempts and intermediate phenotypes, including personality traits, reproductive behaviors, cognitive functions, and smoking behaviors, with and without any mental disorders as covariates (Fig. 2). Among several intermediate phenotypes, suicide attempts were significantly genetically correlated with higher risk tolerance (0.33 ± 0.07 , $p = 1.64 \times 10^{-6}$), earlier age at first sexual intercourse (-0.64 ± 0.08 , $p = 3.92 \times 10^{-15}$), earlier age at first birth (-0.69 ± 0.09 , $p = 1.74 \times 10^{-14}$) and earlier age at menopause (-0.41 ± 0.07 , $p = 1.33 \times 10^{-8}$), higher parity (0.36 ± 0.10 , $p = 5.00 \times 10^{-4}$), lower childhood IQ (-0.58 ± 0.15 , $p = 1.00 \times 10^{-4}$), lower educational attainment (-0.41 ± 0.06 , $p = 8.43 \times 10^{-12}$), lower cognitive ability (-0.33 ± 0.06 , $p = 3.10 \times 10^{-8}$), and lower smoking cessation (-0.60 ± 0.18 , $p = 7.00 \times 10^{-4}$), without adjusting for mental disorders. Higher neuroticism, lower subjective well-being, and higher smoking initiation were not significantly but nominally genetically correlated with suicide attempts without adjusting for mental disorders ($p > 2.08 \times 10^{-3}$ but $p < 0.05$).

In contrast to the psychiatric disorder results, after adjusting for mental disorders, several genetic correlations with intermediate phenotypes were increased (Fig. 3, 33.5% increase, mean $r_g \pm \text{s.e.} = 0.06 \pm 0.09$). After adjusting for mental disorders, suicide attempts had significant genetic correlations with earlier age at first sexual intercourse (-0.71 ± 0.20 , $p = 4.00 \times 10^{-4}$), earlier age at first birth (-0.77 ± 0.23 , $p = 6.00 \times 10^{-4}$), earlier age at menopause (-0.52 ± 0.16 , $p = 1.00 \times 10^{-3}$) and lower educational attainment (-0.43 ± 0.13 , $p = 5.00 \times 10^{-4}$). Higher risk tolerance, lower childhood IQ, lower cognitive ability, and lower smoking cessation had not significantly but nominally genetic correlations with suicide attempts after adjusting for mental disorders ($p > 2.08 \times 10^{-3}$ but $p < 0.05$).

Discussion

This is the first study to investigate genetic correlations of suicide attempts with psychiatric disorders and the related intermediate phenotypes, with and without including mental disorders (such as MDD) as covariates. Without adjusting for mental disorders, suicide attempts had significant genetic correlations with risks of ADHD, SCZ, BD, MDD, anxiety disorders and PTSD; higher risk tolerance; earlier age at first sexual intercourse, age at first birth and age at menopause; higher parity; and lower childhood IQ, educational attainment, cognitive ability and smoking cessation. After adjusting for mental disorders, suicide attempts had significant genetic correlations with the risk of MDD, earlier age at first sexual intercourse, earlier age at first birth, earlier age at menopause, and lower educational attainment. These findings highlight the importance of considering mental disorders as

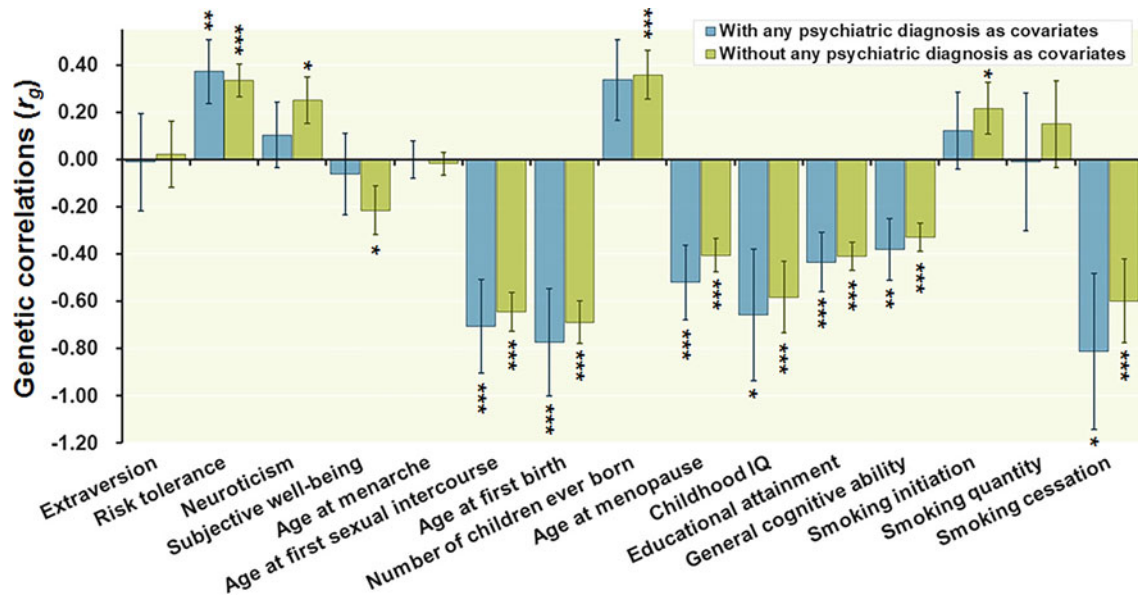


Figure 2. Genetic correlations between suicide attempts and intermediate phenotypes, with and without adjusting for any psychiatric diagnosis. Positive and negative r_g values indicate that suicide attempts were genetically correlated with high or low intermediate phenotypes, respectively. * $p < 0.05$, ** $p < 0.01$, *** $p < 2.08 \times 10^{-3}$.

covariates in the analysis of genetic correlations between suicide attempts and psychiatric and intermediate phenotypes.

Most participants in GWAS of suicide attempts had mental disorders, in terms of cases with suicide attempts (97.8%) and controls without suicide attempts (70.0%) (Erlangsen et al., 2020). The mental disorders consisted of MDD (cases, 71.4%; controls, 33.8%) as well as other disorders, such as AN, SCZ, ASD and ADHD. Therefore, differences in the prevalence of mental disorders (except for MDD) between case-control groups would affect genetic correlations between suicide attempts and psychiatric disorders and the related intermediate phenotypes. Thus, it is important to consider the effects of differences in

prevalence rates of mental disorders (except for MDD) on the genetic correlations and to investigate the shared genetic basis of suicide attempts and psychiatric disorders not mediated by various mental disorders.

We found that suicide attempts shared genetic risk factors with susceptibility to MDD ($r_g = 0.59$), even after adjusting for several mental disorders, including MDD. Previous studies have investigated whether genetic correlations between suicide attempts and psychiatric and intermediate phenotypes are mediated by MDD (Li et al., 2023; Mullins et al., 2022). Several genetic correlations with psychiatric disorders, such as ADHD, SCZ and BD, were not affected by adjusting for MDD, while other genetic correlations with psychiatric disorders, such as anxiety disorders, PTSD and ASD, were affected by adjusting for MDD (Li et al., 2023; Mullins et al., 2022). In this study, we found that most genetic correlations with psychiatric disorders were mediated by mental disorders (Figs 1 and 3). On the other hand, suicide attempts had a genetic correlation with only MDD after adjusting for mental disorders. These findings suggest that even latent MDD susceptibility, which is not currently diagnosed as a mental disorder, may be genetically associated with an increased risk of suicide attempts; thus, early detection of the potential susceptibility to MDD can help prevent suicide.

Genetic correlations between suicide attempts and intermediate phenotypes were much less affected by adjusting for MDD (Li et al., 2023; Mullins et al., 2022). Similar to previous studies adjusting for MDD (Li et al., 2023; Mullins et al., 2022), in the present study, genetic correlations between suicide attempts and intermediate phenotypes were not decreased but rather increased by adjusting for mental disorders (Figs 2 and 3). As neuroticism and smoking behaviors are genetically and epidemiologically associated with several mental disorders (Liu et al., 2019; Luciano et al., 2018), genetic correlations of neuroticism and smoking behaviors with suicide attempts were moderately influenced by adjusting for mental disorders. In contrast, genetic correlations between suicide attempts and reproductive behaviors, such as age at first sexual intercourse ($r_g = -0.71$), age at first

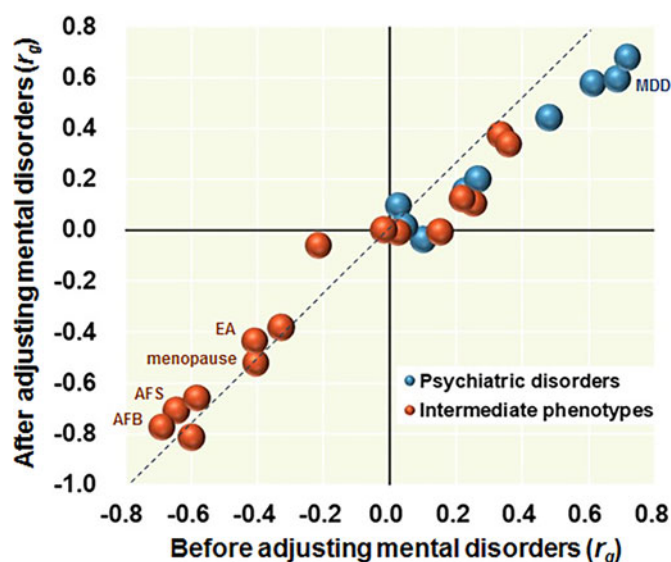


Figure 3. Genetic correlations (r_g) between suicide attempts and psychiatric disorders and intermediate phenotypes were affected by adjusting for mental disorders. MDD, major depressive disorder; EA, educational attainment; menopause, age at menopause; AFS, age at first sexual intercourse; AFB, age at first birth.

birth ($r_g = -0.77$) and age at menopause ($r_g = -0.52$), and lower educational levels ($r_g = -0.43$) were still significant even after adjusting for mental disorders. There is evidence of associations between suicide attempts and reproductive behaviors (Mota et al., 2010). Individuals who have attempted suicide are more likely to engage in risk-taking behaviors, including unprotected sexual behavior, early initiation of sexual activity and unintended pregnancy (Mota et al., 2010). Furthermore, several studies have shown that lower educational attainment is associated with a higher risk of suicide attempts (Lewis et al., 1988). Although these relationships of suicide attempts with reproductive behaviors and educational attainment might be due to a variety of factors, including increased financial stress, lower social support, and potential risks of mental disorders, our findings suggest that these associations could be partially derived from shared genetic factors.

There are some limitations to the interpretations of our findings. Sample sizes were inconsistent among GWASs for psychiatric disorders and intermediate phenotypes. As the statistical power of the LDSC analysis roughly varies with n^2 , even moderate correlations might not be significantly detectable in smaller samples, such as correlations with smoking cessation (Table 1 and Fig. 2, $r_g > 0.60$). Therefore, careful interpretation is needed when comparing genetic correlations among GWASs with different sample sizes. The S.E. of the genetic correlations (r_g) might serve as a reference for comparisons among GWASs with different sample sizes. If the power of further GWASs of suicide attempts is increased, a Mendelian randomization study could investigate potential causal relationships between these risk phenotypes, such as reproductive behaviors and suicide attempts.

In conclusion, we investigated whether genetic correlations of suicide attempts with psychiatric and intermediate phenotypes were mediated by mental disorders. After adjusting for mental disorders, the strength of genetic correlations between suicide attempts and psychiatric disorders were reduced, while those between suicide attempts and intermediate phenotypes were increased. Our findings suggest that susceptibility to MDD, reproductive behaviors, and lower educational levels share a genetic basis with suicide attempts even after adjusting for mental disorders.

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Competing interest. None.

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