Archival Report

Biological Psychiatry

Dissecting the Shared Genetic Architecture of Suicide Attempt, Psychiatric Disorders, and Known Risk Factors

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ISSN: 0006-3223

Biological Psychiatry February 1, 2022; 91:313–327 www.sobp.org/journal

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ABSTRACT

BACKGROUND: Suicide is a leading cause of death worldwide, and nonfatal suicide attempts, which occur far more frequently, are a major source of disability and social and economic burden. Both have substantial genetic etiology, which is partially shared and partially distinct from that of related psychiatric disorders.

METHODS: We conducted a genome-wide association study (GWAS) of 29,782 suicide attempt (SA) cases and 519,961 controls in the International Suicide Genetics Consortium (ISGC). The GWAS of SA was conditioned on psychiatric disorders using GWAS summary statistics via multitrait-based conditional and joint analysis, to remove genetic effects on SA mediated by psychiatric disorders. We investigated the shared and divergent genetic architectures of SA, psychiatric disorders, and other known risk factors.

RESULTS: Two loci reached genome-wide significance for SA: the major histocompatibility complex and an intergenic locus on chromosome 7, the latter of which remained associated with SA after conditioning on psychiatric disorders and replicated in an independent cohort from the Million Veteran Program. This locus has been implicated in risk-taking behavior, smoking, and insomnia. SA showed strong genetic correlation with psychiatric disorders, particularly major depression, and also with smoking, pain, risk-taking behavior, sleep disturbances, lower educational attainment, reproductive traits, lower socioeconomic status, and poorer general health. After conditioning on psychiatric disorders, the genetic correlations between SA and psychiatric disorders decreased, whereas those with nonpsychiatric traits remained largely unchanged.

CONCLUSIONS: Our results identify a risk locus that contributes more strongly to SA than other phenotypes and suggest a shared underlying biology between SA and known risk factors that is not mediated by psychiatric disorders.

https://doi.org/10.1016/j.biopsych.2021.05.029

Suicide is a worldwide public health problem, accounting for almost 800,000 deaths per year (1). Nonfatal suicide attempt (SA), defined as self-injurious behavior with the intent to die, has been estimated to occur over 20 times more frequently and is a major source of disability, reduced quality of life, and social and economic burden (1,2). The lifetime prevalence of SA in adults ranges from 0.5% to 5% worldwide (3). There are several well-established comorbidities and risk factors for SA, with psychiatric illness having the strongest effect on lifetime suicide rates (4,5). However, the vast majority of patients with psychiatric disorders never attempt suicide (6–8). Other major risk factors for SA include prior self-injurious thoughts and behaviors (9), physical illness or disability (10,11), sleep disorders (12–15), family history of psychiatric disorders (16), substance abuse (17), smoking (18–20), impulsivity (21) and social factors including childhood maltreatment (21), isolation (22), and stressful life events (23).

Both suicide and SA are heritable, with estimates from genetic epidemiology studies ranging from 17% to 55% (24–26). Several genome-wide association studies (GWASs) of SA have reported significant single nucleotide polymorphism (SNP)–heritability estimates of ~4%, indicating an underlying polygenic architecture (27–31). Using polygenic risk scoring or genetic correlation analyses, these studies have also demonstrated shared genetic etiology between SA and psychiatric disorders, with major depressive disorder (MDD) showing the largest genetic overlap (28,29,31). This genetic overlap, along with the high prevalence of MDD in the population (32), make it

a particularly salient risk factor. Importantly, genetic epidemiology studies have consistently indicated a genetic component of SA that is partially distinct from that of psychiatric disorders (25). Consistent with this, one GWAS of SA that covaried for cases' psychiatric diagnoses estimated a SNP-heritability of 1.9% (27).

With few genetic samples collected specifically for SA, studies often rely on individuals ascertained for psychiatric disorders. For example, a large GWAS of SA included over 6500 cases from clinical cohorts of MDD, bipolar disorder (BIP), and schizophrenia (SCZ) cases, within the Psychiatric Genomics Consortium (PGC) (31). In an "SA within psychiatric diagnosis" study design, SA cases were compared with cases of the same psychiatric disorder without SA, in order to disentangle the genetic etiology of SA and psychiatric disorders. While GWAS of SA have found genome-wide significant associations (27–31), thus far none of these loci have replicated, possibly owing to limited statistical power or different study designs that may probe varying components of the genetic etiology of SA. Depending on the method of ascertainment, the prevalence of psychiatric disorders may be much higher in SA cases than in controls in these studies, which may confound the genetics of SA. Well-powered and carefully designed studies are necessary to dissect the contribution of genetic variation to SA versus psychiatric disorders and advance our understanding of the genetics of SA.

Here, we present the first GWAS meta-analysis of SA from the International Suicide Genetics Consortium (ISGC), including over 29,000 SA or suicide cases from 18 cohorts worldwide. We identify novel loci implicated in SA, disentangle the genetic etiology of SA from that of MDD and psychiatric disorders, and characterize the genetic relationship among SA, psychiatric disorders, and a range of other risk factors.

METHODS AND MATERIALS

Cohorts and Case Definition

The primary SA meta-analysis comprised 18 cohorts (Table S1 in Supplement 2; Supplement 1) ascertained for psychiatric disorders, including substance use (12 cohorts), studies of suicide or SA (4 cohorts), and population-based biobanks (2 cohorts). Cases were individuals who made a nonfatal SA (16 cohorts) or died by suicide (2 cohorts). A nonfatal SA was defined as a lifetime act of deliberate self-harm with intent to die. Information on SA was ascertained using structured clinical interviews for 10 cohorts, self-report questionnaires for 4 cohorts, and hospital records or International Classification of Diseases codes for 2 cohorts. Cases of death by suicide were ascertained from the Utah State Office of the Medical Examiner or the Medical Examiner's Office of the Hyogo Prefecture and the Division of Legal Medicine, at the Kobe University Graduate School of Medicine in Japan. A proportion of cases in the iPSYCH and Columbia University cohorts had died by suicide, determined using the Cause of Death Register in Denmark and the Columbia Classification Algorithm for Suicide Assessment, respectively (33). Individuals only endorsing suicidal ideation or nonsuicidal self-injurious behavior were not included as cases. There were 14 cohorts of European (EUR) ancestries, 2 of admixed African American (AA) ancestries, and 2 of East Asian (EAS) ancestries. All individual studies received institutional and ethical approval from their local institutional review board. Detailed cohort information is in Supplement 1 and Table S1 in Supplement 2.

Control Definition

All controls ascertained on psychiatric disorders were screened for the absence of lifetime SA. Controls from general population cohorts were screened for the absence of SA, if possible; however, because the prevalence of SA in the general population is low (3), some cohorts included unscreened controls. No controls in this study were screened for suicidal ideation or nonsuicidal self-injurious behavior. The primary SA GWAS included 29,782 cases and 519,961 controls from 18 cohorts (Table 1). Genome-wide significant associations with SA were tested in an independent replication cohort of 14,089 SA cases and 395,359 controls from Million Veteran Program (details in Supplement 1).

Genotyping, Quality Control, and Imputation

Cohorts were required to have at least 200 cases prior to quality control for inclusion. Samples underwent standard genotyping, quality control, and imputation, performed by the collaborating research teams using comparable procedures (details per cohort available in Supplement 1). Briefly, samples were genotyped on microarrays, with the exception of the China, Oxford and Virginia Commonwealth University Experimental Research on Genetic Epidemiology (CONVERGE) study, which used low-coverage sequencing. Standard parameters were used to retain individuals and SNPs after quality control for missingness, relatedness, and Hardy-Weinberg equilibrium. Imputation was performed using the appropriate ancestry reference panels, resulting in >7.7 million SNPs that were well-represented across cohorts. Identical individuals between the PGC and UK Biobank cohorts were detected using genotype-based checksums (https://personal.broadinstitute.org/sripke/share_links/zpXkV8INxUg9bayDpLToG4g58TMtjN_PGC_SCZ_w3.0718d.76) and removed from PGC cohorts. There was no other known overlap of controls between any of the 18 cohorts.

GWASs and Meta-analysis

GWASs were performed in each cohort separately, and procedures are outlined in Supplement 1. GWASs were conducted within ancestry group, covarying for ancestry-informative principal components, genomic relatedness matrices, or factors capturing site of recruitment or genotyping batch, as required. The linkage disequilibrium score regression (LDSC) intercept was calculated for all GWAS results to estimate potential confounding from cryptic relatedness or population stratification (34). Studies with significant LDSC intercepts ($p < .05$) were corrected for confounding by multiplying the standard error per SNP by the square root of the intercept (34). A transancestry meta-analysis was conducted using an inverse variance-weighted fixed-effects model in METAL (35), implemented using the Rapid Imputation for COnsortias PIpeLIne (36). A EUR-only meta-analysis was also conducted (SA-EUR) (26,590 cases and 492,022 controls). The weighted mean allele frequency and imputation INFO score per SNP was calculated, weighted by the effective sample size per

Table 1. Numbers of Cases and Controls for 18 Cohorts in the International Suicide Genetics Consortium

Cohort (Ancestry)	SA Cases	Controls
Psychiatric Genomics Consortium MDD (EUR)	1528	16,626
Psychiatric Genomics Consortium BIP (EUR)	3214	17,642
Psychiatric Genomics Consortium SCZ (EUR)	1640	7112
Psychiatric Genomics Consortium ED (EUR)	170	5070
Army STARRS (EUR)	670	10,637
German Borderline Genomics Consortium (EUR)	481	1653
UK Biobank (EUR)	2433	334,766
iPSYCH (EUR)	7003	52,227
Janssen (EUR)	255	1684
Yale-Penn (EUR)	475	1817
GISS Ukraine (EUR)	660	660
Columbia University (EUR)	577	1233
Australian Genetics of Depression Study and QSkin Study (EUR)	2792	20,193
University of Utah (EUR)	4692	20,702
Japan (EAS)	746	14,049
CONVERGE (EAS)	1148	6515
Grady Trauma Project (Admixed AA)	669	4473
Yale-Penn (Admixed AA)	629	2902
Total	29,782	519,961

AA, African American; Army STARRS, Army Study to Assess Risk and Resilience in Servicemembers; BIP, bipolar disorder; EAS, East Asian; ED, eating disorder; EUR, European; GISS, Genetic Investigation of Suicide and Suicide Attempt; MDD, major depressive disorder; SA, suicide attempt; SCZ, schizophrenia.

cohort. SNPs with a weighted minor allele frequency of <1%, weighted INFO score <0.6, or SNPs present in <80% of total effective sample size were removed from the meta-analysis results. A genome-wide significant locus was defined as the region around a SNP with $p < 5.0 \times 10^{-8}$ with linkage disequilibrium (LD) $r^2 > 0.1$, within a 3000 kb window, based on the LD structure of the Haplotype Reference Consortium European ancestries reference panel (version 1.0) (37).

Statistical Conditioning on Psychiatric Disorders

The results of the SA-EUR meta-analysis were conditioned on the genetics of MDD using multitrait-based conditional and joint analysis using GWAS summary data (mtCOJO) (38), implemented in the GCTA software package (39). mtCOJO (38) estimates the effect size of a SNP on an outcome trait conditioned on exposure trait(s). Genome-wide significant SNPs for the exposure are used as instruments to estimate the effect of the exposure on the outcome, and this effect is used to perform genome-wide conditioning, yielding conditioned effect sizes and *p* values for the outcome trait. We conditioned SA (outcome) on MDD (exposure), because MDD is the most prevalent psychiatric disorder among individuals who die by suicide (40) and has the highest genetic correlation with SA (28). The SA-EUR GWAS summary statistics were used as the outcome trait, because mtCOJO requires an ancestry-matched LD reference panel and GWAS summary statistics for the exposure trait. The PGC MDD GWAS results (excluding 23andMe) (41) were used as the exposure, and the results yielded GWAS summary statistics for SA conditioned on MDD (SA-EUR|MDD). mtCOJO is robust to sample overlap between the GWAS of the exposure and outcome. To select SNPs as instruments, independence was defined as SNPs more than 1 megabase apart or with LD $r^2 < 0.05$ based on the 1000 Genomes Project Phase 3 EUR reference panel (42). To obtain at least 10 independent instruments for MDD, the genome-wide significance threshold was adjusted to $p < 5.0 \times 10^{-7}$, leading to 15 SNPs used. In a further sensitivity analysis, GWAS summary statistics for BIP (43) and SCZ (44) were additionally included as exposure traits.

LD Score Regression

LDSC (34) was used to estimate the phenotypic variance in SA explained by common SNPs (SNP-heritability, h^2_{SNP}) from GWAS summary statistics. h^2_{SNP} was calculated on the liability scale assuming a lifetime prevalence of SA in the general population of 2% (middle of the range reported worldwide) (3). The bivariate genetic correlation attributable to genome-wide SNPs (r_g) was estimated between the SA-EUR and SA-EUR|MDD GWAS and a range of psychiatric disorders, self-harm ideation, and propensity toward risk-taking behavior, using the largest available GWAS summary statistics (Bonferroni-corrected significance threshold $p < .0042$, adjusting for 12 traits tested). Differences in r_g with SA-EUR versus SA-EUR|MDD were tested for deviation from 0, using the block jackknife method, implemented in LDSC software (45). The r_gs of SA-EUR and SA-EUR|MDD with 768 other nonoverlapping human diseases and traits were calculated on LD Hub (46) (Bonferroni-corrected significance threshold $p < 6.51 \times 10^{-5}$). Traits were precategorized manually into 15 risk factor groups previously ascribed to SA (4,5,10): autoimmune disease, neurologic disease, heart disease, hypertension, diabetes, kidney disease, cancer, alcohol use, smoking, pain, psychiatric, sleep, life stressors, socioeconomic, and education/cognition. There were 259 traits belonging to these categories, and a second reviewer validated the categories assigned to traits and their relevance to SA risk.

Polygenic Risk Scoring

Polygenic risk scores (PRSs) for SA were tested for association with SA or death by suicide versus controls in 7 target cohorts: PGC MDD, BIP and SCZ, CONVERGE (EAS ancestries), the University of Utah (suicide death cohort), Yale-Penn (AA ancestries), and Grady Trauma Project (AA ancestries). The primary SA GWAS meta-analysis was repeated excluding each cohort in turn, to create independent discovery datasets. PRSs were generated using PRS-CS (47), which uses a Bayesian regression framework to place continuous shrinkage priors on effect sizes of SNPs in the PRS, adaptive to the strength of their association signal in the discovery GWAS, and the LD structure from an external reference panel (47). The 1000 Genomes EUR, EAS, or African reference panels (42) were used to estimate LD between SNPs, as appropriate for each target cohort. PLINK 1.9 (48) was used to weight SNPs by their effect sizes calculated using PRS-CS and sum all SNPs into PRS for each individual in the target cohorts. PRSs were tested for association with case versus control status in the target cohort using a logistic regression model including covariates as per

the GWAS. The amount of phenotypic variance explained by the PRS (R^2) was calculated on the liability scale, assuming a lifetime prevalence of SA in the general population of 2% (3). Analyses in the PGC cohorts were repeated using PRSs generated from the SA-EUR|MDD GWAS results, excluding each PGC cohort in turn. Analyses performed are summarized in Table S2 in Supplement 2 (Bonferroni-corrected significance threshold $p < 3.12 \times 10^{-3}$, adjusting for 16 tests).

RESULTS

SA Shows Significant SNP-Heritability and PRS Associations

The primary SA GWAS included 29,782 cases and 519,961 controls from 18 cohorts (Table 1). Cases were predominantly of EUR ancestries (90%), with 6% of EAS ancestries and 4% of admixed AA ancestries. Case definition was lifetime SA, with ~20% of cases having died by suicide. The SNP-heritability (h^2_{SNP}) SA was 6.8% (SE = 0.005, $p = 2.00 \times 10^{-42}$) on the liability scale. The LDSC intercept was 1.04 (SE = 0.01, $p = 2.84 \times 10^{-4}$), and the attenuation ratio was 0.14 (SE = 0.04), indicating that the majority of GWAS test statistic inflation was due to polygenicity (Figure S1 in Supplement 1). PRSs for SA were tested in 7 target cohorts (Table S2 in Supplement 2). SA PRSs were significantly associated with SA in the PGC MDD, BIP, and SCZ cohorts, with a phenotypic explained variance (R^2) of 0.69% ($p = 7.17 \times 10^{-15}$), 0.68% ($p = 8.11 \times 10^{-28}$), and 0.88% ($p = 1.24 \times 10^{-17}$), respectively (liability scale). PRSs for SA were also associated with death by suicide in the University of Utah cohort, explaining slightly more phenotypic variance ($R^2 = 1.08\%$, $p = 9.79 \times 10^{-81}$). The r_g between the University of Utah suicide death GWAS and a meta-analysis of the nonfatal SA cohorts in our study was 0.77 (SE = 0.08, $p = 3.08 \times 10^{-20}$). Examining the performance of SA PRSs across ancestries showed a significant association with SA in the CONVERGE EAS cohort, although with a lower explained variance ($R^2 = 0.25\%$, $p = 3.06 \times 10^{-3}$). Analyses in 2 admixed AA cohorts showed variable results ($R^2 = 0.21\%$, $p = 5.28 \times 10^{-1}$ and $R^2 = 0.58\%$, $p = 3.44 \times 10^{-3}$, respectively) (Table S2 in Supplement 2).

GWAS of SA Identifies Locus With Stronger Effect on SA Than Psychiatric Disorders

The primary SA GWAS identified 2 genome-wide significant loci ($p < 5 \times 10^{-8}$) (Table S3 in Supplement 2). The most strongly associated locus was in an intergenic region on chromosome 7 (index SNP rs62474683, odds ratio A allele = 1.06 [1.04–1.08], $p = 1.91 \times 10^{-10}$, frequency in cases = 0.52, frequency in controls = 0.50, I^2 heterogeneity index = 0%) (forest plot Figure S2 in Supplement 1). The second genome-wide significant locus was in the major histocompatibility complex (MHC) (index SNP rs71557378, odds ratio T allele = 1.10 [1.06–1.13], $p = 1.97 \times 10^{-8}$, frequency in cases = 0.91, frequency in controls = 0.90, I^2 heterogeneity index = 46%) (forest plot Figure S3 in Supplement 1). Both loci were also genome-wide significant in the SA-EUR meta-analysis, with the same effect sizes (Table S4 in Supplement 2). In order to identify SA genetic effects not mediated by MDD, we conditioned the SA-EUR GWAS on the genetic effects of MDD via mtCOJO. After conditioning, only the chromosome 7 locus remained genome-wide significant (index SNP = rs62474683, odds ratio A allele = 1.06 [1.04–1.08], $p = 1.33 \times 10^{-8}$) (Figure 1A). Figures S4 and S5 in Supplement 1 show regional association plots of the loci before and after conditioning. The association of the chromosome 7 index SNP with SA was further replicated in the independent Million Veteran Program cohort (rs62474683, odds ratio A allele = 1.03 [1.01–1.07], $p = 3.27 \times 10^{-3}$), while the index SNP in the MHC was not associated with SA in this cohort (Table S4 in Supplement 2).

Examination of the chromosome 7 locus in published GWAS results using the Open Targets Genetics web portal (49) indicated smaller and nonsignificant effects on all psychiatric disorders (Figure 1B). Additionally, the SA-index SNP has been implicated at genome-wide significance in lifetime smoking index (50) (accounts for duration and amount of smoking) and propensity toward risk-taking behavior (51), although again with smaller effect sizes than on SA (Figure 1B; Tables S5 and S6 in Supplement 2). Pairwise GWAS analysis (see Supplement 1) of the genomic region containing the chromosome 7 locus suggested the existence of a single putative causal variant shared between SA and these phenotypes (lifetime smoking index: posterior probability = 0.99, risk-taking behavior: posterior probability = 1) (Table S7 in Supplement 2). Furthermore, a variant in high LD with the chromosome 7 index SNP (rs12666306, LD $r^2 = 0.94$) has a positive genome-wide significant effect on insomnia (reported in GWAS catalog, full summary statistics not available) (Figure 1B; Tables S5 and S6 in Supplement 2). The SA-index SNP has also been implicated in self-harm ideation (52), although not at genome-wide significance, and with a smaller effect size than on SA (Figure 1B).

MAGMA (53) enrichment analyses performed on the primary SA GWAS (see Supplement 1) showed significant enrichment of SA associations in 7 genes (Table S8 in Supplement 2), including *BTN2A1*, which is a brain-expressed gene (54) located within the MHC, that encodes a plasma-membrane protein. There was no enrichment of SA association signal in any of the biological gene sets tested (Table S9 in Supplement 2) or in the set of genes expressed in any of the 54 tissues from the Genotype-Tissue Expression project (Table S10 in Supplement 2). Examining individual genes, a transcriptome-wide association study (see Supplement 1) found 5 genes for which SA risk alleles were significantly associated with brain gene expression: *ERC2*, *RP11−266A24.1*, *TIAF1*, *BACE2*, and *NUFIP2* ($p < 4.28 \times 10^{-6}$) (Table S11 in Supplement 2). None of these genes were within genome-wide significant loci.

Evidence for Substantial Proportion of SNP-Heritability of SA Not Mediated by Psychiatric Disorders

h^2_{SNP} based on the SA-EUR GWAS was 7.5% (SE = 0.006, $p = 3.02 \times 10^{-40}$) on the liability scale (Table S12 in Supplement 2). Conditioning SA-EUR on MDD resulted in a 45% decrease in the h^2_{SNP} of SA to 4.1% (SE = 0.005, $p = 1.20 \times 10^{-16}$) on the liability scale (Table S12 in Supplement 2). Conditioning on BIP and SCZ in addition to MDD did not further change the h^2_{SNP} estimate ($h^2_{SNP} = 4.1\%$, SE = 0.005, $p = 1.20 \times 10^{-16}$). The SA-EUR|MDD results showed comparable h^2_{SNP} and complete r_g with a direct GWAS of SA within psychiatric diagnosis

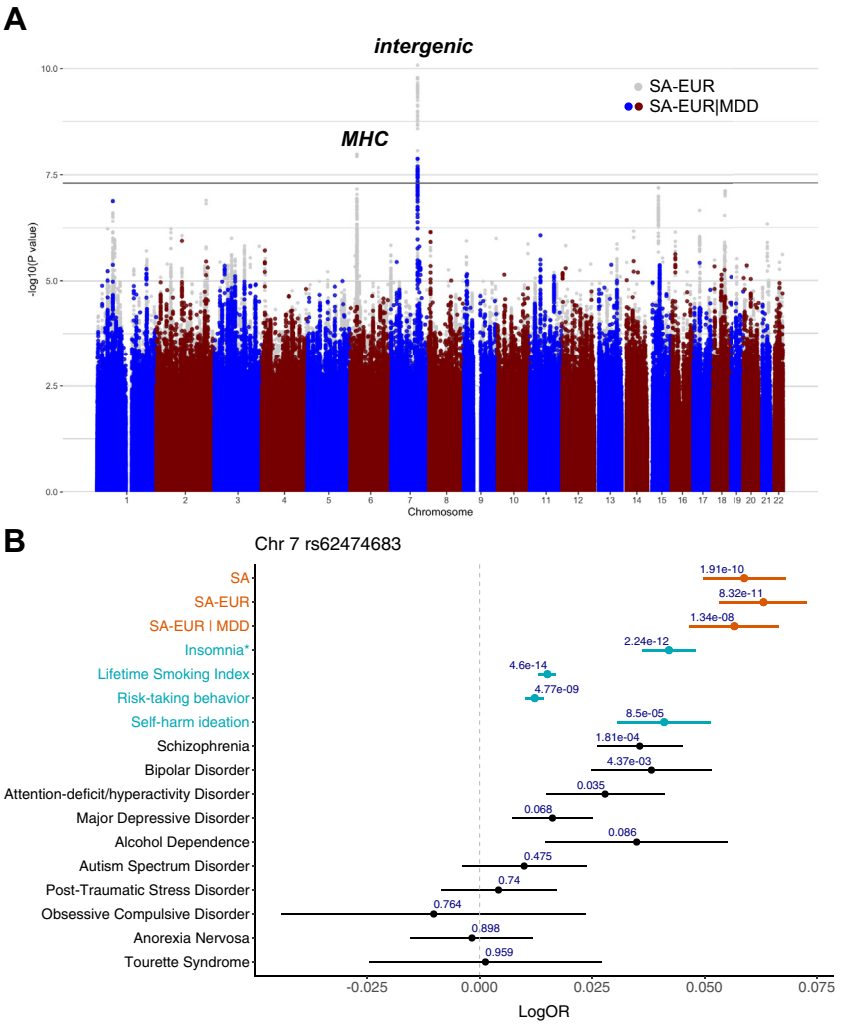


Figure 1. Genome-wide significant locus contributes to SA more strongly than psychiatric disorders and other traits. **(A)** Manhattan plot: the x-axis shows genomic position, and the y-axis shows statistical significance as $-\log_{10}(p \text{ value})$. The gray points in the background depict the results of SA-EUR, and the colored points in the foreground depict the results after conditioning these results on MDD (SA-EUR|MDD). The horizontal line shows the genome-wide significance threshold ($p < 5.0 \times 10^{-8}$). **(B)** Forest plot: the points indicate the log odds ratio of the A allele at rs62474683 (SA-index single nucleotide polymorphism on chromosome 7) on each phenotype, and the error bars show the standard error. The p value of association with each phenotype is shown above the error bars. *For insomnia, the effect size of a variant in high linkage disequilibrium with the index single nucleotide polymorphism is shown instead (rs12666306 A allele, linkage disequilibrium $r^2 = 0.94$ with rs62474683 A allele). MDD, major depressive disorder; MHC, major histocompatibility complex; OR, odds ratio; SA, suicide attempt; SA-EUR, European-only suicide attempt meta-analysis; SA-EUR|MDD, SA-EUR results after conditioning on MDD.

(Supplement 1), confirming the validity of the statistical conditioning approach to control for the genetic effects of psychiatric disorders.

Significant Genetic Overlap Between SA and Psychiatric Traits or Disorders

Genetic correlations were calculated to explore the genetic overlap between SA and 12 psychiatric traits or disorders before and after conditioning on MDD. The SA-EUR GWAS showed significant r_g with 11 traits or disorders tested, most strongly with self-harm ideation ($r_g = 0.82$, SE = 0.07, $p = 3.57 \times 10^{-36}$), MDD ($r_g = 0.78$, SE = 0.04, $p = 4.11 \times 10^{-106}$), and posttraumatic stress disorder ($r_g = 0.74$, SE = 0.09, $p = 5.29 \times 10^{-17}$) (Figure 2; Table S13 in Supplement 2). Moderate genetic correlations were also observed between SA and SCZ, attention-deficit/hyperactivity disorder, BIP, posttraumatic stress disorder, and alcohol dependence (r_gs 0.45–0.74) (Figure 2; Table S13 in Supplement 2).

To investigate whether these genetic correlations were mediated by MDD, we estimated r_g with the same traits and disorders using the SA-EUR|MDD results. Most genetic correlations with psychiatric disorders remained significant after conditioning, except for autism spectrum disorder and Tourette syndrome (Figure 2; Table S13 in Supplement 2). As expected, the r_g with MDD significantly decreased after conditioning ($p = 8.4 \times 10^{-22}$ block jackknife), as did the r_gs with self-harm ideation, posttraumatic stress disorder, and autism spectrum disorder (Figure 2; Table S13 in Supplement 2). The remaining psychiatric disorders did not show Bonferroni corrected significant differences in r_g after conditioning on MDD. Because conditional analysis only removes SNP effects on SA mediated by MDD, the remaining r_g between SA-EUR|MDD and MDD ($r_g = 0.53$, SE = 0.06, $p = 8.9 \times 10^{-19}$) indicates pleiotropic SNP effects.

Substantial Shared Genetic Architecture of SA and Nonpsychiatric Risk Factors Not Mediated by MDD

To assess the shared genetic architecture of SA, psychiatric, and nonpsychiatric phenotypes, we calculated genetic

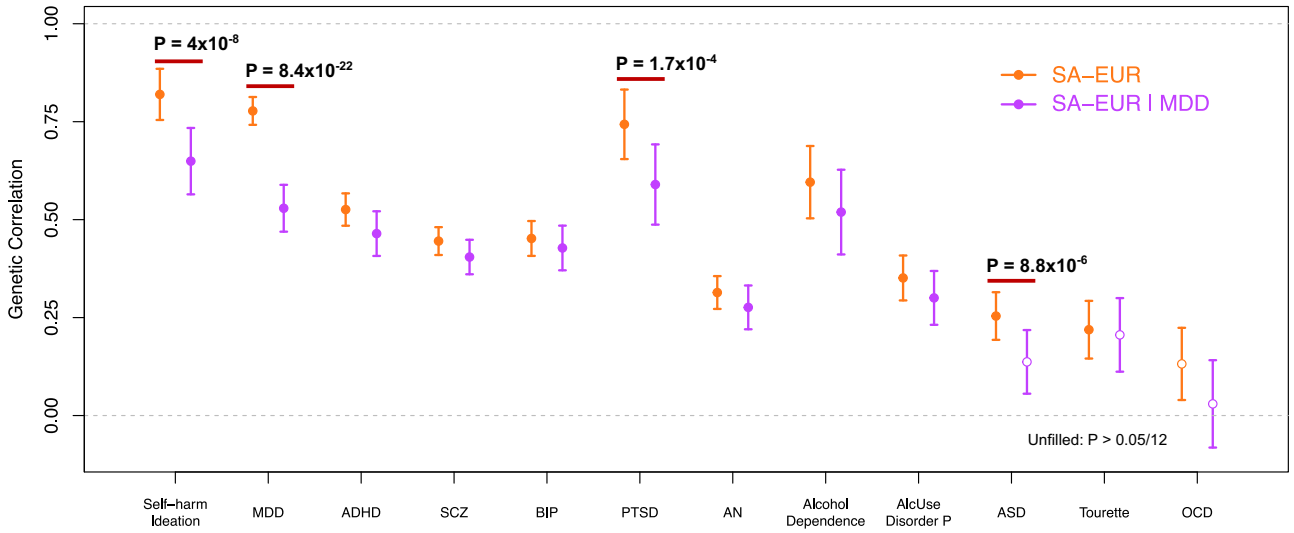


Figure 2. Substantial genetic correlation of SA with psychiatric traits or disorders before and after conditioning SA on MDD. Unfilled points indicate genetic correlations that did not pass the Bonferroni-corrected significance threshold ($p < 4.17 \times 10^{-3}$). Error bars represent the standard error. *p* values indicate significant differences in genetic correlation after conditioning that pass Bonferroni correction. ADHD, attention-deficit/hyperactivity disorder; AlcUse Disorder P, Alcohol Use Disorders Identification Test-P (measure of problematic consequences of drinking); AN, anorexia nervosa; ASD, autism spectrum disorder; BIP, bipolar disorder; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; PTSD, posttraumatic stress disorder; SA, suicide attempt; SA-EUR, European-only suicide attempt meta-analysis; SA-EUR|MDD, SA-EUR results after conditioning on MDD; SCZ, schizophrenia.

correlations of SA with 768 nonoverlapping phenotypes (46). There were 198 phenotypes that showed a significant r_g with SA-EUR, 133 of which were in one of the predefined SA risk categories (Figure 3A; Table S14 in Supplement 2). The most significant genetic correlations were predominantly with traits related to depressive symptoms, smoking, and socioeconomic status. On examining phenotypes in the risk categories after conditioning on MDD, 110 phenotypes retained a significant r_g with SA-EUR|MDD (Table S14 in Supplement 2). Within the psychiatric risk category, there was a 38% average decrease in the magnitude of genetic correlations with SA-EUR after conditioning, whereas the r_g values in other risk categories were much less affected by conditioning (smoking: 4.6% decrease, education/cognition: 3% decrease, alcohol: 14.5% decrease, and socioeconomic: 9.3% decrease) (Figure 3B).

DISCUSSION

We present a GWAS of SA in over 29,000 cases, identifying 2 genome-wide significant loci, including one more strongly associated with SA than psychiatric disorders or related traits. We demonstrate that a substantial proportion of the SNP-heritability of SA is independent of psychiatric diagnosis. Finally, we show that the genetic liability to SA not mediated by psychiatric disorders is shared with the genetic architecture of nonpsychiatric risk factors.

The locus most strongly associated with SA was in an intergenic region on chromosome 7. The index SNP had a larger effect on SA than on any common psychiatric disorder, remained genome-wide significant after conditioning on MDD, and replicated in an independent cohort from the Million Veteran Program. Taken together, these results suggest that the genetic association with SA at this locus is not mediated through risk for psychiatric disorders. Functional genomic data do not clearly link this variant to any gene, with the nearest gene being a long noncoding RNA (*LINC01392*) 149 kb away. The index SNP (rs62474683) is a methylation quantitative trait locus, with the SA risk allele associated with decreased methylation of a nearby DNA methylation site (probe cg04544267) in blood (55). However, this methylation site has not been linked to any gene transcript. Intriguingly, SA risk alleles at this locus have been implicated at genome-wide significance in risk-taking behavior (51), smoking (50), and insomnia (56). While variants in the MHC also reached genome-wide significance for SA, this effect did not remain after conditioning on MDD, suggesting that this association may be a byproduct of psychiatric diagnosis. Indeed, variants in the MHC have previously been associated with risk for a range of psychiatric disorders, including MDD (57).

Our GWAS results provide robust evidence of the h^2_{SNP} of SA, with an estimate of 6.8% on the liability scale (7.5% based on SA-EUR). Importantly, conditioning on MDD resulted in a smaller but significant h^2_{SNP} estimate (4.1%), corroborating previous reports (25,27) of the independent genetic contribution to SA, and illustrating the importance of accounting for potential confounding from the genetics of psychiatric disorders. Traditionally, GWASs have sought to dissect the specific genetic component of SA by studying SA within psychiatric diagnosis or covarying for cases' psychiatric diagnoses (27). Here, we demonstrate that statistical conditioning is an appropriate and easily applicable approach to control for the genetic effects of psychiatric disorders, producing equivalent results to a direct GWAS of SA within psychiatric diagnosis (Supplement 1).

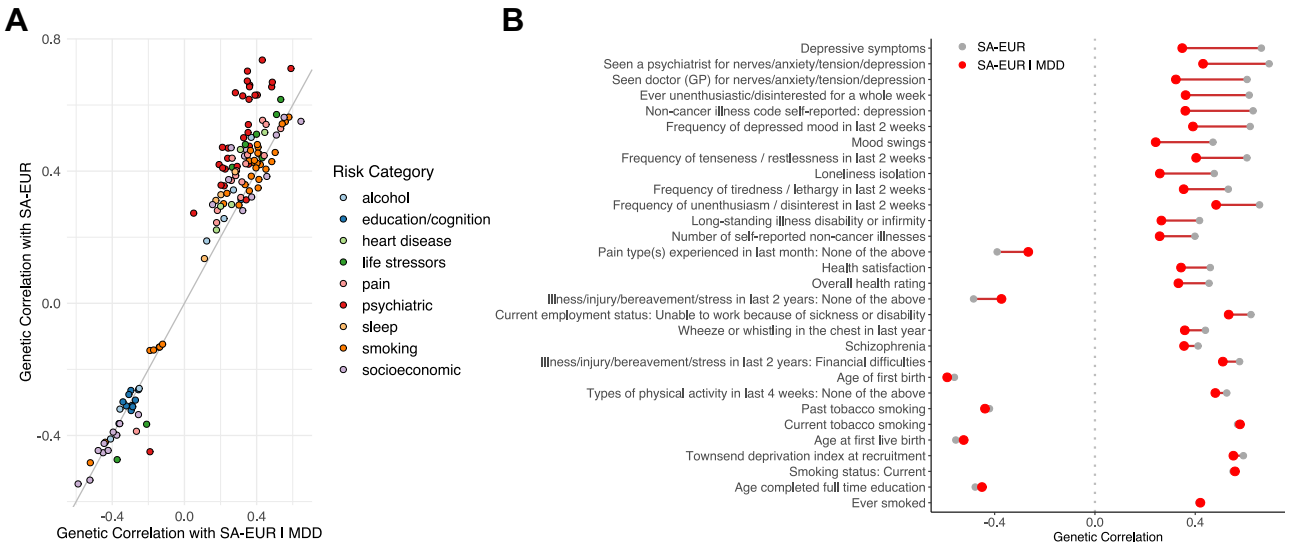


Figure 3. Conditioning SA on MDD reduces genetic correlation with psychiatric phenotypes but has limited effect on other traits. **(A)** Comparison of significant genetic correlations with the SA-EUR vs. genetic correlations with SA-EUR|MDD. Data include 198 significant genetic correlations after Bonferroni correction ($p < .05/768 = 6.51 \times 10^{-5}$) annotated by risk category. **(B)** Top 30 phenotypes with the most significant genetic correlations with SA-EUR before (gray) and after (red) conditioning on MDD (SA-EUR|MDD). Full genetic correlation results, including standard errors, are provided in Table S14 in Supplement 2. GP, general practitioner; MDD, major depressive disorder; SA, suicide attempt; SA-EUR, European-only suicide attempt meta-analysis; SA-EUR|MDD, SA-EUR results after conditioning on major depressive disorder.

SA showed substantial positive genetic correlation with many psychiatric disorders, the highest being with MDD (r_g = 0.78, SE = 0.03), consistent with previous reports (28,29,31). Genetic overlap was also particularly strong with posttraumatic stress disorder, attention-deficit/hyperactivity disorder, SCZ, and BIP (r_g = 0.44 − 0.74). After conditioning on MDD, there was a modest decrease in the genetic correlation of SA with most psychiatric disorders. Notably, SA remained strongly genetically correlated with MDD (r_g = 0.53, SE = 0.06, $p = 8.85 \times 10^{-19}$), representing pleiotropic effects between them. This genetic correlation would only be eliminated if all SNP effects on SA were mediated by MDD. Pleiotropy between psychiatric disorders is widespread (58,59), and accordingly, genetic overlap between SA and related disorders is anticipated. Our findings suggest that many pleiotropic genetic variants increase the risk for SA directly, independent of their effects on psychiatric disorders.

Significant genetic overlap was found between SA and many nonpsychiatric traits, including smoking, lower socioeconomic status, pain, lower educational attainment, reproductive traits, risk-taking behavior, sleep disturbances, and poorer overall general health. While conditioning SA on MDD reduced genetic correlations with psychiatric disorders, the genetic correlation of SA with most nonpsychiatric traits remained unchanged. This suggests a shared genetic architecture between SA and these risk factors that is not mediated by psychiatric illness. There is substantial epidemiological literature on the relationship between sleep disorders (12–15), smoking (18–20), and socioeconomic factors (60–62) and risk for SA but less on genetic overlap between them. We have not examined potential causal relationships between these risk factors and SA, but future Mendelian randomization studies that will become possible with further increases in the power of SA GWAS may highlight modifiable risk factors.

Several limitations of our study must be noted. Cases were defined using a variety of diagnostic interviews, self-report, or hospital records, which may result in phenotypic heterogeneity. However, suicidal intent was central to all phenotype definitions, and a previous study found 98% concordance between self-report of lifetime SA and face-to-face clinician interview (63). Our GWAS included both nonfatal SA and suicide death cases, and these phenotypes were highly but imperfectly genetically correlated (r_g = 0.77). Genetic correlations between SA and psychiatric disorders were examined using publicly available GWAS summary statistics; however, the prevalence of SA among the cases in these studies is unknown. Finally, population, demographic, and environmental factors are always present in genetic analyses, and while our sample is large and diverse, we did not have sufficient data to assess their possible contribution or confounding effects.

This first collaborative SA GWAS by the ISGC is almost 5-fold larger than previous studies, substantially improving statistical power. We identify a robustly associated SA risk locus and demonstrate genetic liability to SA that is not mediated through psychiatric disorders but is shared with known risk factors. We emphasize that genetic risk does not currently have meaningful predictive utility for SA, and its premature use in clinical or direct-to-consumer settings could be harmful. Future larger studies dissecting the genetic etiology of SA, psychiatric disorders, and other risk factors will provide further insights into the biological mechanisms of risk and assess potential clinical utility.

ACKNOWLEDGMENTS AND DISCLOSURES

Statistical analyses were carried out on the NL Genetic Cluster Computer (http://www.geneticcluster.org) hosted by SURFsara and the Mount Sinai high performance computing cluster (http://hpc.mssm.edu), which is supported by the Office of Research Infrastructure of the National Institutes of Health (Grant Nos. S10OD018522 and S10OD026880). This work was conducted in part using the resources of the Advanced Computing Center for Research and Education at Vanderbilt University, Nashville, TN. This work was funded by the National Institutes of Health (Grant Nos. R01MH116269 and R01MH121455 [to DMR]), NIGMS of the National Institutes of Health (Grant No. T32GM007347 [to JK]), and the Brain & Behavior Research Foundation (NARSAD Young Investigator Award No. 29551 [to NM]).

The content is solely the responsibility of the authors and does not necessarily represent the official views of any funding body.

We thank the participants who donated their time, life experiences, and DNA to this research, and the clinical and scientific teams that worked with them.

The International Suicide Genetics Consortium has made genome-wide summary results from this study available online (https://tinyurl.com/ISGC2021). This study included some publicly available datasets accessed through dbGaP (Psychiatric Genomics Consortium [PGC] bundle phs001254) and the Haplotype Reference Consortium reference panel v.1.0 (http://www.haplotype-reference-consortium.org/home). Databases used: Open Targets Genetics web portal (https://genetics.opentargets.org), LDHub (http://ldsc.broadinstitute.org), and FUMA (https://fuma.ctglab.nl).

In the past 3 years, RCK was a consultant for Datastat, Inc., Sage Pharmaceuticals, and Takeda. HRK and JG are named as inventors on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018. HRK is a member of an advisory board for Dicerna Pharmaceuticals and of the American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative, which was supported in the last 3 years by AbbVie, Alkermes, Dicerna, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, Pfizer, Arbor, and Amygdala Neurosciences. DL is an employee of Janssen Research & Development, LLC, and shareholder in Johnson & Johnson, the parent company of the Janssen companies. DL declares that, except for income received from her primary employer, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. MBS has in the past 3 years been a consultant for Actelion, Acadia Pharmaceuticals, Aptinyx, Bionomics, BioXcel Therapeutics, Epivario, GW Pharmaceuticals, Janssen, Jazz Pharmaceuticals, and Oxeia Biopharmaceuticals. MBS has stock options in Oxeia Biopharmaceuticals and Epivario. HJG has received travel grants and speaker honoraria from Fresenius Medical Care, Neuraxpharm, Servier, and Janssen-Cilag as well as research funding from Fresenius Medical Care. OAA is a consultant for HealthLytix and received speaker's honorarium from Lundbeck and Sunovion. RAP is employed by and holds shares in BioMarin Pharmaceuticals. MCO and MJO are supported by a collaborative research grant from Takeda Pharmaceuticals. That support did not contribute to the work described in this manuscript. EHG has served in the speakers' bureau and the advisory board of Takeda (former Shire do Brasil) Pharmaceutical. JAR-Q was on the speakers' bureau and/or acted as consultant for Eli Lilly, Janssen-Cilag, Novartis, Shire, Takeda, Bial, Shionogui, Lundbeck, Almirall, Braingaze, Sincrolab, Medice, and Rubió in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Takeda, Shionogui, Bial, Medice, and Eli Lilly. The Department of Psychiatry chaired by him received unrestricted educational and research support from the following companies in the last 5 years: Eli Lilly, Lundbeck, Janssen-Cilag, Actelion, Shire, Ferrer, Oryzon, Roche, Psious, and Rubió. VR was on the speakers' bureau and/or acted as consultant for Takeda and Rubió in the last 5 years. She also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Rubió, Shire, Takeda, and Lundbeck. MC was on the speakers' bureau and/or acted as consultant for Janssen-Cilag in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag. All other authors report no biomedical financial interests or potential conflicts of interest.

Full acknowledgments are available in Supplement 1.

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Received Jan 5, 2021; revised May 7, 2021; accepted May 26, 2021.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2021.05.029.

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