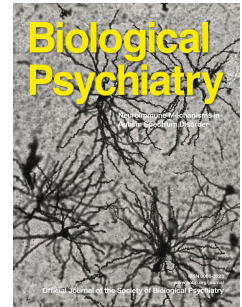


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Dissecting the shared genetic architecture of suicide attempt[†] psychiatric disorders and known risk factors

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Dissecting the shared genetic architecture of suicide attempt, psychiatric disorders and known risk factors

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Running title: ISGC GWAS of suicide attempt

Keywords: Genome-wide association study; suicide attempt; suicide; polygenicity; pleiotropy; genetic correlation

Abstract**Background**

Suicide is a leading cause of death worldwide, and non-fatal 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. The GWAS of SA was conditioned on psychiatric disorders using GWAS summary statistics via mtCOJO, 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, 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, smoking, and insomnia. SA showed strong genetic correlation with psychiatric disorders, particularly major depression, and also with smoking, pain, risk-taking, 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 non-psychiatric 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.

Introduction

Suicide is a worldwide public health problem, accounting for almost 800,000 deaths per year (1). Non-fatal suicide attempt (SA), defined as self-injurious behavior with 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 0.5-5% 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 17-55% (24–26). Several genome-wide association studies (GWAS) of SA have reported significant 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 which is partially distinct from that of psychiatric disorders (25). Consistent with this, one GWAS of SA which 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 6,500 cases from clinical cohorts of MDD, bipolar disorder and schizophrenia cases, within the Psychiatric Genomics Consortium (31). In a “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 due to limited statistical power, or different study designs which 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 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, 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 between 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, Supplementary Note) including cohorts 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 non-fatal SA (16 cohorts) or died by suicide (2 cohorts). A non-fatal 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 non-suicidal 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 the Supplementary Note and Supplementary Table 1.

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, since 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 non-suicidal 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 Supplementary Note).

Genotyping, quality control and imputation

Cohorts were required to have at least 200 cases prior to quality control (QC) for inclusion. Samples underwent standard genotyping, QC and imputation, performed by the collaborating research teams using comparable procedures (details per cohort available in Supplementary Note). Briefly, samples were genotyped on microarrays with the exception of the CONVERGE study, that used low-coverage sequencing. Standard parameters were used to retain individuals and SNPs after QC 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 Psychiatric Genomics Consortium (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.

Genome-wide association studies and meta-analysis

GWAS were performed in each cohort separately and procedures are outlined in the Supplementary Note. GWAS 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 LD 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 ($P < 0.05$), were corrected for confounding by multiplying the standard error per SNP by the square root of the intercept (34). A trans-ancestry meta-analysis was conducted using an inverse variance-weighted fixed effects model in METAL (35), implemented using the Rapid Imputation for COnsortias PIpeLIine (RICOPILI) (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 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 3,000 kilobase (kb) window, based on the LD structure of the Haplotype Reference Consortium European ancestries reference panel v1.0 (37).

Statistical conditioning on psychiatric disorders

The results of the SA-EUR meta-analysis were conditioned on the genetics of MDD using mtCOJO (multi-trait-based conditional & joint analysis using GWAS summary data) (38), implemented in GCTA software (39). mtCOJO38 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), since 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 (Mb) 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 bipolar disorder (BIP) (43) and schizophrenia (SCZ) (44) were additionally included as exposure traits.

LD Score regression (LDSC)

LDSC (34) was used to estimate the phenotypic variance in SA explained by common SNPs (SNP-heritability, h_{SNP}^2) from GWAS summary statistics. h_{SNP}^2 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

towards risk-taking behavior, using the largest available GWAS summary statistics (Bonferroni-corrected significance threshold $P < 0.0042$, 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_g s of SA-EUR and SA-EUR|MDD with 768 other non-overlapping human diseases and traits were calculated on LD Hub (46) (Bonferroni-corrected significance threshold $P < 6.51 \times 10^{-5}$). Traits were pre-categorized 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 (PRS) for SA were tested for association with SA or death by suicide versus controls in seven 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. PRS were generated using PRS-CS (52), 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 (52). 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 (53) 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. PRS 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 PRS generated from the SA-EUR|MDD GWAS results, excluding each PGC cohort in turn. Analyses performed are summarized in Table S2 (Bonferroni-corrected significance threshold $P < 3.12 \times 10^{-3}$, adjusting for 16 tests).

Results

SA shows significant SNP-heritability and association with polygenic risk scores

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. SA h_{SNP}^2 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). PRS for SA were tested in seven target cohorts (Table S2). SA PRS were significantly associated with SA in the PGC MDD, BIP and SCZ cohorts, with a phenotypic variance explained (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). PRS 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 rg between the University of Utah suicide death GWAS and a meta-analysis of the non-fatal SA cohorts in our study was 0.77 (SE=0.08, $P=3.08 \times 10^{-20}$). Examining the performance of SA PRS across ancestry, showed a significant association with SA in the CONVERGE EAS cohort, although with a lower variance explained ($R^2=0.25\%$, $P=3.06 \times 10^{-3}$). Analyses in two 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).

GWAS of SA identifies locus with stronger effect on SA than psychiatric disorders

The primary SA GWAS identified two genome-wide significant loci ($P < 5 \times 10^{-8}$) (Table S3). The most strongly associated locus was in an intergenic region on chromosome 7 (index SNP rs62474683, OR 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). The second genome-wide significant locus was in the MHC (index SNP rs71557378, OR 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). Both loci were also genome-wide significant in the SA-EUR meta-analysis, with the same effect sizes (Table S4). 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, OR A allele = 1.06 [1.04-1.08], $P=1.33 \times 10^{-8}$) (Figure 1a). Figures S4-5 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, OR 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).

Examination of the chromosome 7 locus in published GWAS results using the Open Targets Genetics web portal (59), indicated smaller and non-significant effects on all psychiatric disorders (Figure 1b). However, the SA-index SNP has been implicated at genome-wide significance in lifetime smoking index (57) (accounts for duration and amount of smoking), and propensity towards risk-taking behavior (56), although with smaller effect sizes than on SA (Figure 1b, Table S5-6). Pairwise GWAS analysis (see Supplementary Note) 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). 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, Table S5-6). The SA-index SNP has also been implicated in self-harm ideation (60), although not at genome-wide significance, and with a smaller effect size than on SA (Figure 1b).

MAGMA (48) enrichment analyses performed on the primary SA GWAS (see Supplementary Note), showed significant enrichment of SA associations in seven genes (Table S8), including *BTN2A1* which is a brain-expressed gene (61) 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), or in the set of genes expressed in any of the 54 tissues from the Genotype-Tissue Expression (GTEx) project (Table S10). Examining individual genes, a transcriptome-wide association study (see Supplementary Note) found five genes for which SA risk alleles were significantly associated with brain gene expression: *ERC2*, *RP11-266A24.1*, *TIAF1*, *BACE2*, *NUFIP2* ($P<4.28\times 10^{-6}$) (Table S11). 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_{SNP}^2 based on the SA-EUR GWAS was 7.5% (SE=0.006, $P=3.02\times 10^{-40}$) on the liability scale (Table S12). Conditioning SA-EUR on MDD resulted in a 45% decrease in the h_{SNP}^2 of SA to 4.1% (SE=0.005, $P=1.20\times 10^{-16}$) on the liability scale (Table S12). Conditioning on BIP and SCZ in addition to MDD did not further change the h_{SNP}^2 estimate ($h_{SNP}^2=4.1\%$, SE=0.005, $P=1.20\times 10^{-16}$). The SA-EUR|MDD results showed comparable h_{SNP}^2 and complete rg with a direct GWAS of SA within psychiatric diagnosis (Supplementary Note), 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 rg with 11 traits or disorders tested, most strongly with self-harm ideation (rg=0.82, SE=0.07, $P=3.57\times 10^{-36}$) and MDD (rg=0.78, SE=0.04, $P=4.11\times 10^{-106}$) (Figure 2, Table S13). Moderate genetic correlations were also observed between SA and SCZ, attention-deficit/hyperactivity disorder (ADHD), BIP, post-traumatic stress disorder (PTSD) and alcohol dependence (rgs 0.45-0.74) (Figure 2, Table S13).

To investigate whether these genetic correlations were mediated by MDD, we estimated rg 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 (ASD) and Tourette syndrome (Figure 2, Table S13). As expected, the rg with MDD significantly decreased after conditioning ($P=8.4\times 10^{-22}$ block jackknife), as did the rgs with self-harm ideation, PTSD and ASD (Figure 2, Table S13). The remaining psychiatric disorders did not show significant differences in rg after conditioning on MDD, after Bonferroni correction. Since conditional analysis only removes SNP effects on SA mediated by MDD, the remaining rg between SA-EUR|MDD and MDD (rg=0.53, SE=0.06, $P=8.9\times 10^{-19}$) indicates pleiotropic SNP effects.

Substantial shared genetic architecture of SA and non-psychiatric risk factors not mediated by MDD

To assess the shared genetic architecture of SA, psychiatric, and non-psychiatric phenotypes, we calculated genetic correlations of SA with 768 non-overlapping phenotypes (46). There were 198 phenotypes which showed a significant r_g with SA-EUR, 133 of which were in one of the pre-defined SA risk categories (Figure 3a, Table S14). The most significant genetic correlations were predominantly with traits related to depressive symptoms, smoking, and socioeconomic status. Examining phenotypes in the risk categories after conditioning on MDD, 110 phenotypes retained a significant r_g with SA-EUR|MDD (Table S14). 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, and determine that genetic liability to SA not mediated by psychiatric disorders is shared with the genetic architecture of non-psychiatric 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 does not clearly link this variant to any gene, with the nearest gene being a long non-coding RNA (*LINC01392*) 149 kb away. The index SNP (rs62474683) is a methylation quantitative trait locus (mQTL), with the SA risk allele associated with decreased methylation of a nearby DNA methylation site (probe cg04544267) in blood (62). 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 (56), smoking (57), and insomnia (63). While variants in the MHC also reached genome-wide significance for SA, this effect did not remain after conditioning on MDD, suggesting 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 (64).

Our GWAS results provide robust evidence of the h_{SNP}^2 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_{SNP}^2 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, GWAS 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 (Supplementary Note).

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 PTSD, ADHD, 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 (65,66), and accordingly genetic overlap between SA and related disorders is anticipated. Our findings suggest that many pleiotropic genetic variants increase risk for SA directly, independent of their effects on psychiatric disorders.

Significant genetic overlap was found between SA and many non-psychiatric traits, including smoking, lower socioeconomic status, pain, lower educational attainment, reproductive traits, risk-taking, 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 non-psychiatric traits remained unchanged by conditioning. This suggests 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 (67–69) 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 (70). Our GWAS included both non-fatal 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 amongst 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 International Suicide Genetics Consortium 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.

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Disclosures

In the past 3 years, Dr. Kessler was a consultant for Datastat, Inc, Sage Pharmaceuticals, and Takeda. Drs. Kranzler and Gelernter are named as inventors on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018. Dr. Kranzler 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 three years by AbbVie, Alkermes, Dicerna, Ethypharm, Indivior, Lilly, Lundbeck, Otsuka, Pfizer, Arbor, and Amygdala Neurosciences. Dr. Li is an employee of Janssen Research & Development, LLC, and shareholder in Johnson & Johnson, the parent company of the Janssen companies. Dr. Li 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 three years for research or professional service, and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest. Dr. Stein 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. Dr. Stein has stock options in Oxeia Biopharmaceuticals and Epivario. Dr. Grabe 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. Dr. Andreassen is a consultant for HealthLytix, and received speaker's honorarium from Lundbeck and Sunovion. Dr Power is employed by and holds shares in BioMarin Pharmaceuticals. Michael O'Donovan and Michael Owen are supported by a collaborative research grant from Takeda Pharmaceuticals. That support did not contribute to the work described in this manuscript. Eugenio H Grevet. has served in the speakers' bureau and the advisory board of Takeda (former Shire do Brasil) Pharmaceutical. Josep Antoni Ramos-Quiroga 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. Christian Fadeuilhe has received fees to give talks for Shire, Ferrer, Italfarmaco and Otsuka in the last 5 years. He also received travel awards (air tickets + hotel) for taking part in psychiatric meetings from Janssen-Cilag, Rubió, Shire, Lundbeck, Otsuka and Ferrer. Vanesa Richarte 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. Miguel Casas 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.

Data availability

The policy of the International Suicide Genetics Consortium is to make genome-wide summary results publicly available. Summary statistics will be made available online upon publication. This study included some publicly available datasets accessed through dbGaP (PGC bundle phs001254) and the Haplotype Reference Consortium reference panel v1.0 (<http://www.haplotype-reference-consortium.org/home>). Databases used: Open Targets Genetics web portal <https://genetics.opentargets.org> LDHub <http://ldsc.broadinstitute.org> FUMA <https://fuma.ctglab.nl>

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Figure legends

Figure 1: Genome-wide significant locus contributes to suicide attempt 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 grey points in the background depict the results of European-only suicide attempt meta-analysis (SA-EUR) and the colored points in the foreground depict the results after conditioning these results on major depressive disorder (SA-EUR|MDD). The horizontal line shows the genome-wide significance threshold ($P < 5.0 \times 10^{-8}$). MHC - major histocompatibility complex b) Forest plot: The points indicate the log odds ratio of the A allele at rs62474683 (SA-index SNP 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 (LD) with the index SNP is shown instead (rs12666306 A allele, LD $r^2 = 0.94$ with rs62474683 A allele).

Figure 2: Substantial genetic correlation of suicide attempt with psychiatric traits or disorders before and after conditioning suicide attempt on major depressive disorder

SA-EUR denotes the European-only suicide attempt meta-analysis and SA-EUR|MDD denotes these results after conditioning on major depressive disorder. 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. MDD-major depressive disorder, SCZ-schizophrenia, ADHD-attention-deficit/hyperactivity disorder, BIP-bipolar disorder, PTSD-post-traumatic stress disorder, AN-anorexia nervosa, AlcUse Disorder P-Alcohol Use Disorders Identification Test-P (AUDIT-P, measure of problematic consequences of drinking), ASD-autism spectrum disorder, OCD-obsessive compulsive disorder.

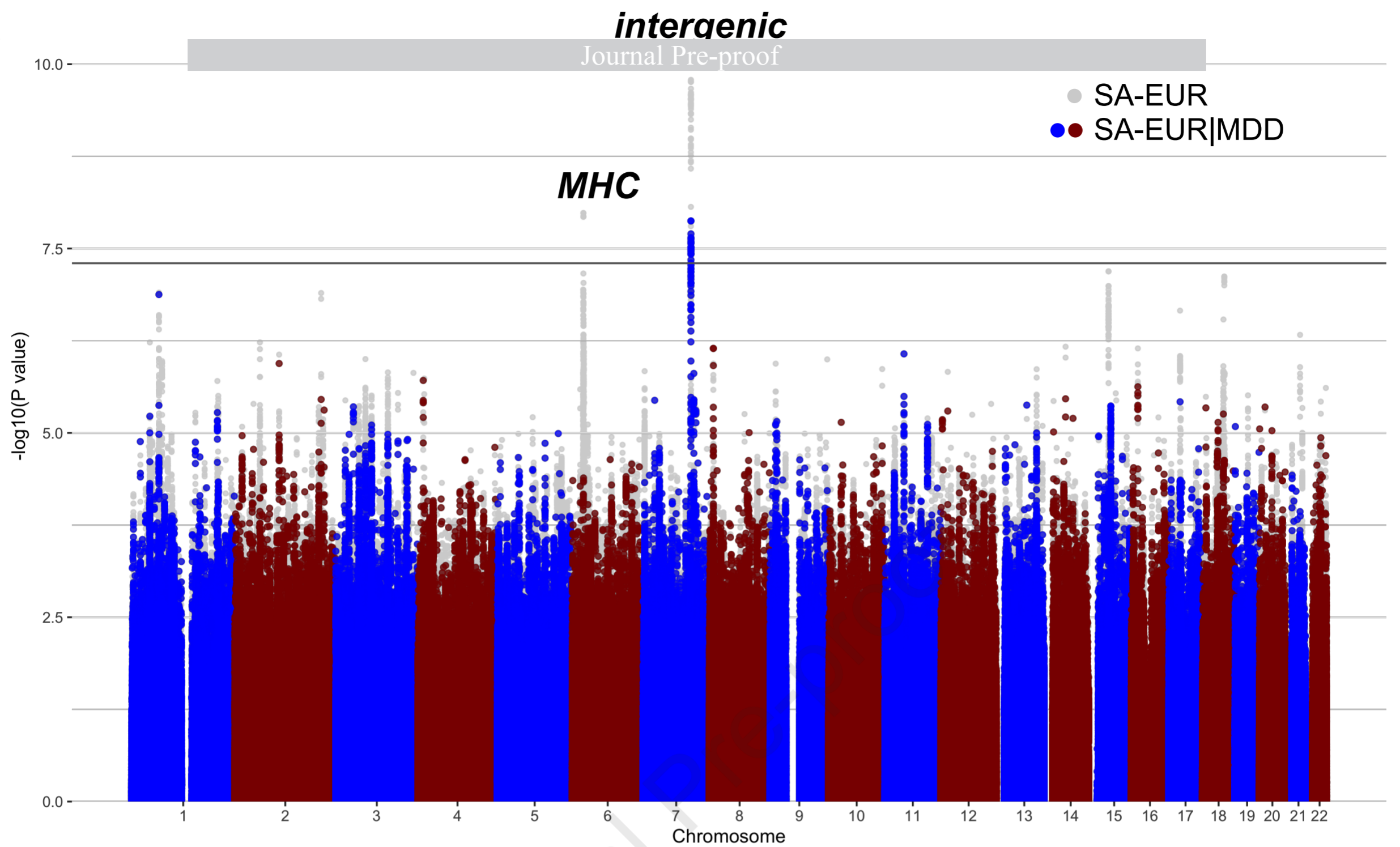
Figure 3: Conditioning suicide attempt on major depressive disorder reduces genetic correlation with psychiatric phenotypes but has limited effect on other traits

a) Comparison of significant genetic correlations with the European-only suicide attempt meta-analysis (SA-EUR) versus genetic correlations with SA-EUR conditioned on MDD (SA-EUR|MDD). Data include 198 significant genetic correlations after Bonferroni correction ($P < 0.05/768 = 6.51 \times 10^{-5}$) annotated by risk category. b) Top 30 phenotypes with the most significant genetic correlations with SA-EUR before (in gray) and after conditioning on MDD (SA-EUR|MDD) (in red). Full genetic correlation results, including standard errors, are provided in Table S14.

Tables

| 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) | 1,528 | 16,626 |
| Psychiatric Genomics Consortium BIP (EUR) | 3,214 | 17,642 |
| Psychiatric Genomics Consortium SCZ (EUR) | 1,640 | 7,112 |
| Psychiatric Genomics Consortium ED (EUR) | 170 | 5,070 |
| Army STARRS (EUR) | 670 | 10,637 |
| German Borderline Genomics Consortium (EUR) | 481 | 1,653 |
| UK Biobank (EUR) | 2,433 | 334,766 |
| iPSYCH (EUR) | 7,003 | 52,227 |
| Janssen (EUR) | 255 | 1,684 |
| Yale-Penn (EUR) | 475 | 1,817 |
| GISS Ukraine (EUR) | 660 | 660 |
| Columbia University (EUR) | 577 | 1,233 |
| Australian Genetics of Depression Study and QSkin Study (EUR) | 2,792 | 20,193 |
| University of Utah (EUR) | 4,692 | 20,702 |
| Japan (EAS) | 746 | 14,049 |
| CONVERGE (EAS) | 1,148 | 6,515 |
| Grady Trauma Project (admixed AA) | 669 | 4,473 |
| Yale-Penn (admixed AA) | 629 | 2,902 |
| Total | 29,782 | 519,961 |

SA - suicide attempt, MDD - major depressive disorder, BIP - bipolar disorder, SCZ - schizophrenia, ED - eating disorder, EUR - European ancestry, EAS - East Asian ancestry, AA - African American ancestry.

A**B**