Dissecting the shared genetic architecture of suicide attempt, psychiatric disorders and known risk factors — Source link ↗

Niamh Mullins, Jooeun Kang, Adrian I. Campos, Adrian I. Campos ...+324 more authors

Institutions: Icahn School of Medicine at Mount Sinai, Vanderbilt University Medical Center, QIMR Berghofer Medical Research Institute, University of Queensland ...+112 more institutions

Related papers:

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

- A genome-wide association study of total child psychiatric problems scores

- Genome-wide association study of suicide attempt in psychiatric disorders identifies association with major depression polygenic risk scores

- Not just one p: Multivariate GWAS of psychiatric disorders and their cardinal symptoms reveal two dimensions of cross-cutting genetic liabilities

- Polygenic risk of psychiatric disorders exhibits cross-trait associations in electronic health record data

Share this paper: 🔵 🐦 in ✉

View more about this paper here: https://typeset.io/papers/dissecting-the-shared-genetic-architecture-of-suicide-5f06o0pxjc

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

Word count: 3423

Authors

Niamh Mullins 1, 2, 251,*, Jooeun Kang 3, 251, Adrian I Campos 4, 5, Jonathan R I Coleman 6, 7, Alexis C Edwards 8, Hanga Galfalvy 9, 10, Daniel F Levey 11, 12, Adriana Lori 13, Andrey Shabalin 14, Anna Starnawska 15, 16, 17, 18, Mei-Hsin Su 19, Hunna J Watson 20, 21, 22, Mark Adams 23, Swapnil Awasthi 24, Michael Gandal 25, Jonathan D Hafferty 23, Akitoyo Hishimoto 26, Minsoo Kim 25, Satoshi Okazaki 27, Ikuo Otsuka 10, 27, Stephan Ripke 24, 28, 29, Erin B Ware 30, 31, Andrew W Bergen 32, 33, Wade H Berrettini 34, Martin Bohus 35, Harry Brandt 36, Xiao Chang 37, Wei J Chen 19, 38, 39, Hsi-Chung Chen 39, Steven Crawford 36, Scott Crow 40, Emily DiBlasi 14, Philibert Duriez 41, 42, Fernando Fernández-Aranda 43, Manfred M Fichter 44, 45, Steven Gallinger 46, Stephen J Glatt 47, Philip Gorwood 41, 42, Yiran Guo 37, Hakon Hakonarson 37, 48, Katherine A Halmi 49, Hai-Gwo Hwu 50, Sonia Jain 51, Stéphane Jamain 52, Susana Jiménez-Murcia 43, Craig Johnson 53, Allan S Kaplan 54, 55, 56, Walter H Kaye 57, Pamela K Keel 58, James L Kennedy 54, 55, 56, Kelly L Klump 59, Robert D Levitan 54, 55, 56, Dong Li 37, Shih-Cheng Liao 39, Klaus Lieb 60, Lisa Lilenfeld 61, Chih-Min Liu 39, Pierre J Magistretti 62, 63, Christian R Marshall 64, James E Mitchell 65, Eric T Monson 14, Richard M Myers 66, Dalila Pinto 1, 2, Abigail Powers 13, Nicolas Ramoz 42, Stefan Roepke 67, Alessandro Rotondo 68, Vsevolod Rozanov 69, 70, Stephen W Scherer 71, Christian Schmahl 35, Marcus Sokolowski 72, Michael Strober 73, 74, Laura M Thornton 22, Janet Treasure 75, 76, Ming T Tsuang 77, Maria C La Via 22, Stephanie H Witt 78, D Blake Woodside 55, 56, 79, 80, Zeynep Yilmaz 22, 81, 82, Lea Zillich 78, Rolf Adolfsson 83, Ingrid Agartz 84, 85, 86, Tracy M Air 87, Martin Alda 88, 89, Lars Alfredsson 90, 91, Ole A Andreassen 92, 93, Adebayo Anjorin 94, Vivek Appadurai 95, 96, María Soler Artigas 97, 98, 99, 100, Sandra Van der Auwera 101, M Helena Azevedo 102, Nicholas Bass 103, Claiton HD Bau 104, 105, Bernhard T Baune 106, 107, Frank Bellivier 108, 109, 110, 111, Klaus Berger 112, Joanna M Biernacka 113, Tim B Bigdeli 114, 115, Elisabeth B Binder 13, 116, Michael Boehnke 117, Marco Boks 118, Rosa Bosch 97, 98, 119, David L Braff 120, Richard Bryant 121, Monika Budde 122, Enda M Byrne 123, Wiepke Cahn 124, Miguel Casas 97, 98, 100, 119, Enrique Castelao 125, Jorge A Cervilla 126, Boris Chaumette 127, 128, 129, Sven Cichon 130, 131, 132, 133, Aiden Corvin 134, Nicholas Craddock 135, David Craig 136, Franziska Degenhardt 133, Srdjan Djurovic 137, 138, Howard J Edenberg 139, 140, Ayman H Fanous 114, 115, Jerome C Foo 141, Andreas J Forstner 130, 133, 142, Mark Frye 143, Janice M Fullerton 144, 145, Justine M Gatt 121, 146, Pablo V Gejman 147, 148, Ina Giegling 149, 150, Hans J Grabe 101, Melissa J Green 144, 151, Eugenio H Grevet 152, 153, Maria Grigoroiu-Serbanescu 154, Blanca Gutierrez 155, Jose Guzman-Parra 156, Steven P Hamilton 157, Marian L Hamshere 135, Annette Hartmann 149, Joanna Hauser 158, Stefanie Heilmann-Heimbach 133, Per Hoffmann 131, 132, 133, Marcus Ising 159, Ian Jones 135, Lisa A Jones 160, Lina Jonsson 161, René S Kahn 2, 118, John R Kelsoe 120, 162, Kenneth S Kendler 115, Stefan Kloiber 54, 159, 163, Karestan C Koenen 164, 165, 166, Manolis Kogevinas 167, Bettina Konte 149, Marie-Odile Krebs 127, 128, 129, Mikael Landén 161, 168, Jacob Lawrence 169, Marion Leboyer 108, 170, 171, Phil H Lee 28, 29, 172, Douglas F Levinson 173, Calwing Liao 174, 175, Jolanta Lissowska 176, Susanne Lucae 159, Fermin Mayoral 156, Susan L McElroy 177, Patrick McGrath 178, Peter McGuffin 7, Andrew McQuillin 103, Sarah Medland 179, Divya Mehta 180, 181, Ingrid Melle 92, 182, Yuri Milaneschi 183, Philip B Mitchell 151, Esther Molina 184, Gunnar Morken 185, 186, Preben Bo Mortensen 16, 81, 187, 188, Bertram Müller-Myhsok 116, 189, 190, Caroline Nievergelt 120, Vishwajit Nimgaonkar 191, Markus M Nöthen 133, Michael C O'Donovan 135, Roel A Ophoff 192, 193, Michael J Owen 135, Carlos Pato 194, 195, Michele T Pato 195, Brenda WJH Penninx 183, 183, Jonathan Pimm 103, Giorgio Pistis 125, James B Potash 196, Robert A Power 7, 197, 198, Martin Preisig 125, Digby Quested 199, Josep Antoni Ramos-Quiroga 97, 98, 100, 119, Andreas Reif 200, Marta Ribasés 97, 98, 99, 100, Vanesa Richarte 97, 98, 119, Marcella Rietschel 201, Margarita Rivera 7, 202, Andrea Roberts

203, Gloria Roberts 151, Guy A Rouleau 175, 204, Diego L Rovaris 205, Dan Rujescu 149, Cristina Sánchez-Mora 97, 98, 99, 100, Alan R Sanders 147, 148, Peter R Schofield 144, 145, Thomas G Schulze 122, 141, 206, 207, 208, Laura J Scott 117, Alessandro Serretti 209, Jianxin Shi 210, Stanley I Shyn 211, Lea Sirignano 141, Pamela Sklar 1, 2, 212, Olav B Smeland 92, 93, Jordan W Smoller 28, 166, 213, Edmund J S Sonuga-Barke 214, Gianfranco Spalletta 215, 216, John S Strauss 54, 163, Beata Świątkowska 217, Maciej Trzaskowski 123, Gustavo Turecki 218, Laura Vilar-Ribó 97, 100, John B Vincent 219, Henry Völzke 220, James TR Walters 135, Cynthia Shannon Weickert 151, Thomas W Weickert 151, Myrna M Weissman 221, 222, Leanne M Williams 223, Major Depressive Disorder Working Group of the PsychiatricGenomics Consortium, Bipolar Disorder Working Group of the Psychiatric Genomics Consortium, Eating Disorders Working Group of the Psychiatric Genomics Consortium, German Borderline Genomics Consortium, Naomi R Wray 123, 181, Clement Zai 54, Esben Agerbo 81, 187, 188, Anders D Børglum 15, 16, 17, 18, Gerome Breen 6, 7, Annette Erlangsen 18, 224, 225, 226, Tõnu Esko 227, 228, Joel Gelernter 11, 12, David M Hougaard 229, 230, Ronald C Kessler 231, Henry R Kranzler 232, Qingqin S Li 233, Nicholas G Martin 234, Andrew M McIntosh 23, Sarah E Medland 234, Ole Mors 188, 235, Merete Nordentoft 229, 236, Catherine M Olsen 237, David Porteous 238, Robert J Ursano 239, Danuta Wasserman 72, Thomas Werge 95, 96, 240, 241, David C Whiteman 237, Cynthia M Bulik 22, 168, 242, Hilary Coon 14, 243, Ditte Demontis 15, 16, 17, 18, Anna R Docherty 8, 14, Po-Hsiu Kuo 19, 39, Cathryn M Lewis 7, 244, J John Mann 245, Miguel E Rentería 4, 5, Daniel J Smith 246, Eli A Stahl 1, 2, 227, Murray B Stein 247, Fabian Streit 78, Virginia Willour 248, Douglas M Ruderfer 3, 249, 250,*

Abstract

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 are known to have a substantial genetic etiology, which is partially shared and partially distinct from that of related psychiatric disorders. 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 and conditioned the results on psychiatric disorders using GWAS summary statistics, to investigate their shared and divergent genetic architectures. Two loci reached genome-wide significance for SA: the major histocompatibility complex and an intergenic locus on chromosome 7, which remained associated after conditioning and has previously been implicated in risk-taking, smoking, and insomnia. SA showed strong genetic correlation with psychiatric disorders, particularly major depression, and also with smoking, lower socioeconomic status, pain, lower educational attainment, reproductive traits, risk-taking, sleep disturbances, and poorer overall general health. After conditioning, the genetic correlations between SA and psychiatric disorders decreased, whereas those with non-psychiatric traits remained largely unchanged. Our results identify a risk locus that contributes more strongly to SA than other phenotypes and suggest the existence of a shared genetic etiology between SA and known risk factors that is not mediated by psychiatric disorders.

Introduction

Suicide is a worldwide public health problem, accounting for close to 800,000 deaths per year[1]. Suicide attempt (SA), defined as non-fatal 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 0.5-5% worldwide[3]. There are several well established comorbidities and risk factors for SA, with the presence of a psychiatric disorder 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 such as childhood maltreatment[21], isolation[22], and stressful life events[23].

Both suicide and SA are moderately heritable, with estimates from genetic epidemiology studies in the range of 17-55%[24–26]. Several genome-wide association studies (GWAS) of SA have reported significant SNP-heritability estimates of ~4%, pointing to 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 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]. One GWAS of SA adjusted for the presence of a psychiatric disorder and estimated a SNP heritability of 1.9%[27], suggesting that the genetic etiology of SA is likely to comprise genetic variants which confer risk more strongly to SA than psychiatric disorders, as well as variants that confer risk more strongly to psychiatric disorders than SA.

Few genetic samples have been collected specifically for SA, with studies often relying on individuals ascertained for psychiatric disorders. For example, a large GWAS of SA included over 6,500 cases from clinical cohorts of depression, 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 have been 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 advance our understanding of the genetics of SA and dissect the contribution of genetic variation to SA versus psychiatric disorders.

Here, we present the first collaborative GWAS meta-analysis of SA from the International Suicide Genetics Consortium, including over 29,000 cases of suicide or SA from 15 institutes or consortia 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 known risk factors.

Methods

Cohorts and case definition

This study included 21 cohorts worldwide, many of which have been described previously (Table S1, Supplementary Note). These included cohorts ascertained for psychiatric disorders, including substance use (15 cohorts), studies of suicide or SA (4 cohorts), and population-based biobanks (2 cohorts). Cases were individuals who died by suicide (2 cohorts) or made a non-fatal suicide attempt (19 cohorts). A non-fatal suicide attempt was defined as a lifetime act of deliberate self-harm with intent to result in death. Information on SA was ascertained using structured clinical interviews for 15 cohorts, self-report questionnaires for 2 cohorts, and hospital records or International Classification of Diseases (ICD) codes for 2 cohorts. Cases of death by suicide (2 cohorts) 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 from the iPSYCH and Columbia University cohorts were also individuals who had died by suicide, determined using the Cause of Death Register in Denmark and The Columbia Classification Algorithm for Suicide Assessment respectively[33]. Individuals endorsing suicidal ideation only were not included as cases. There were 14 cohorts of European ancestry, 2 cohorts of admixed African American ancestry, and 5 cohorts of East Asian ancestry. All individual studies received institutional and ethical approval from their local institutional review board (Table S1). Detailed information on the ascertainment and case definition for each cohort is included in the Supplementary Note. Supplementary Table 1 contains an overview of cohort characteristics.

Control definition

For the primary GWAS, controls included all individuals with no evidence of SA, including those ascertained for having a psychiatric disorder. Controls from the general population were screened for the absence of SA if such information was available; however since the prevalence of SA in the general population is low (~2%)[3], some cohorts included unscreened controls. Amongst controls ascertained for having a psychiatric disorder, all were screened for the absence of lifetime SA. Controls from the general population were not screened for the absence of psychiatric disorders and no controls were screened for suicidal ideation. A GWAS of SA within psychiatric diagnosis was also conducted, where controls were individuals with the same psychiatric disorder as the SA cases in each cohort, and were all screened for the absence of lifetime SA. Cohorts were included in the GWAS of SA in the general population and/or the GWAS of SA within psychiatric diagnosis, depending on the characteristics of the controls available, and therefore there is some overlap of individuals and cohorts between the GWAS. The primary GWAS of SA included 29,782 cases and 519,961 controls from 18 cohorts and the GWAS of SA within psychiatric diagnosis included 14,847 cases and 69,951 controls from 13 cohorts (Table 1).

Genotyping, quality control and imputation

Cohorts were required to have a minimum of 200 cases prior to quality control for inclusion in the GWAS meta-analysis. Samples underwent standard genotyping, quality control and imputation, according to the local protocol for each study. Briefly, samples were genotyped on microarrays with the exception of one study (CONVERGE) that used low-coverage sequencing. Parameters used to retain individuals and SNPs

after quality control for missingness, relatedness and Hardy-Weinberg equilibrium are outlined in the Supplementary Note. Imputation was performed using the appropriate ancestry reference panels, resulting in > 7.7 million SNPs that were well-represented across cohorts. Full details of the genotyping, quality control and imputation for each cohort are available in the Supplementary Note. 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 remaining between any of the 21 cohorts after QC.

Genome-wide association study

GWAS were performed in each cohort separately by the collaborating research team and analysis procedures are outlined in the Supplementary Note. GWAS were conducted within ancestry group, covarying for genetic ancestry-informative principal components (PCs), 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 assess potential confounding from cryptic relatedness or population stratification[34]. For any studies with a significant intercept (P<0.05), the GWAS summary statistics were corrected for confounding by multiplying the standard error per SNP by the square root of the LDSC intercept[34]. A meta-analysis of GWAS summary statistics was conducted using an inverse variance-weighted fixed effects model (standard error) in METAL[35], implemented using the Rapid Imputation for COnsortias PIpeLIne (RICOPILI)[36], for the GWAS of SA in the general population, and the GWAS of SA within psychiatric diagnosis. The meta-analyses were performed across all cohorts regardless of ancestry. 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 imputation 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 (HRC) European ancestry reference panel v1.0[37].

mtCOJO

The results of the GWAS of SA 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]. mtCOJO[38] estimates the effect size of a SNP on an outcome trait (eg. SA) conditioned on exposure trait(s) (eg. MDD). It first uses the genome-wide significant SNPs for the exposure trait as instruments to estimate the effect of the exposure on the outcome, and then performs a genome-wide conditioning of the estimated effect from the exposure, resulting in conditioned effect sizes and P values for the outcome trait. We conditioned SA on MDD, since MDD is the most prevalent psychiatric disorder among individuals who die by suicide[40] and has the highest genetic correlation with SA among psychiatric disorders (rg=0.44)[28]. mtCOJO analysis was performed on the SA as the outcome trait. For this, GWAS summary statistics from the European-only subset of the SA meta-analysis were used (26,590 cases and 492,022 controls), since mtCOJO requires an ancestry-matched LD reference panel. The PGC MDD GWAS summary statistics (excluding 23andMe)[41]

were used for the exposure trait. mtCOJO is robust to overlap in samples contributing to the GWAS of the exposure and outcome. In the selection of SNPs as instruments, independence was defined as SNPs more than 1 megabase (Mb) apart or with an LD r^2 value < 0.05 based on the 1000 Genomes Project Phase 3 European reference panel[42]. To obtain at least 10 independent instruments for MDD, the genome-wide significance threshold was adjusted to P<5.0x10^{-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^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%, which is the middle of the range reported worldwide[3]. For the GWAS of SA within psychiatric diagnosis, h^2_{SNP} was calculated on the liability scale using a prevalence of SA in psychiatric populations ranging from 10-20%. LDSC bivariate genetic correlations attributable to genome-wide SNPs (rg) were estimated between all GWAS of SA and between each GWAS of SA and a range of psychiatric disorders, self-harm ideation and propensity towards risk-taking behavior (risk tolerance), using the largest available GWAS summary statistics (Table S11). The Bonferroni corrected significance threshold was P<0.0042, adjusting for 12 traits tested. The difference between the rg of SA before and after conditioning on MDD was tested for deviation from 0, using the block jackknife method, implemented by the LDSC software[45]. The rg of each SA GWAS with 768 other non-overlapping human diseases and traits was calculated on LD Hub (http://ldsc.broadinstitute.org)[46] (Bonferroni corrected significance threshold P<6.51x10^{-5} for each GWAS). Before analysis, traits were categorized manually into 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 (Table S12). A second reviewer validated the categories assigned to traits and their relevance to SA risk. Overlapping traits were appended.

Gene-based, gene-set and tissue-set enrichment analyses

P values quantifying the degree of association of genes and gene-sets with SA based on the GWAS of SA in the general population were generated using MAGMA (v1.08), implemented in FUMA (v1.3.6a) (https://fuma.ctglab.nl)[47,48]. Gene-based tests were performed for 18,517 genes and a Bonferroni correction was applied for the number of genes tested (P<2.70x10^{-6}). A total of 11,638 curated gene sets from MSigDB V7.0 were also tested for association with SA (Bonferroni-corrected significance threshold P<4.30x10^{-6}). Competitive gene-set tests were conducted correcting for gene size, variant density and LD within and between genes. Gene-sets including < 10 genes were excluded. Finally, tissue-set enrichment analyses were performed using MAGMA[48] implemented in FUMA[47], to test for enrichment of genetic associations with SA in genes expressed in 54 tissues from the Genotype-Tissue Expression (GTEx) project V8[49]. The significance threshold was P<9.26x10^{-4}, adjusting for the number of tissues tested.

Integrative eQTL analysis

A transcriptome-wide association study (TWAS) was conducted using FUSION software[50] and precomputed expression reference weights from PsychENCODE data[51]. The PsychENCODE Consortium has

conducted a genome-wide eQTL analysis using 1,321 brain samples, predominantly from the dorsolateral prefrontal cortex[51]. For genes with significant *cis*-SNP heritability (13,435 genes), a TWAS was performed to test whether SNPs influencing brain gene expression are also associated with SA, using the meta-analysis results from the GWAS of SA in the general population (Bonferroni corrected significance threshold $P<4.28x10^{-6}$).

Polygenic risk scoring analysis

Polygenic risk scores (PRS) for SA were tested for association with SA or death by suicide in independent target cohorts. The target cohorts used were PGC MDD, PGC BIP, PGC SCZ, CONVERGE (a cohort of East Asian ancestry), and the University of Utah cohort (a sample of individuals who died by suicide). The meta-analysis of SA was repeated excluding each of these cohorts in turn, to create independent discovery and target datasets. PRS were tested for association with SA versus controls in all five of the target samples. PRS were also tested for association with SA within psychiatric diagnosis in the PGC MDD, BIP and SCZ samples. Analyses in the PGC datasets were repeated using the PRS for SA in the general population generated from the GWAS results after conditioning on MDD. The Bonferroni corrected significance threshold is $P<3.57x10^{-3}$, correcting for 14 tests. The analyses performed are summarized in Table S2.

PRS analyses were performed using PRS-CS[52], a method which uses a Bayesian regression framework and places a continuous shrinkage prior on the effect sizes of all SNPs in the discovery GWAS summary statistics. Continuous shrinkage priors allow a specific amount of shrinkage to be applied to each SNP, which is adaptive to the strength of its association signal in the discovery GWAS and the LD structure from an external reference panel[52]. The 1000 Genomes European or East Asian reference panels[42], as appropriate, were used to estimate LD between SNPs. PRS were calculated for each individual in the target cohorts using standard procedures. PLINK 1.9[53] was used to weight all SNPs by their effect sizes calculated using PRS-CS and sum all SNPs into PRS for each individual in the target cohort. PRS were tested for association with case versus control status in the target cohort using a logistic regression model, covarying for PCs, genomic relatedness matrices or factors capturing site of recruitment or batch effects, as required. The amount of phenotypic variance explained by the PRS (R^2) was calculated on the liability scale, which accounts for the proportion of cases in the target sample and the proportion of cases in the population[54]. Calculations assumed a lifetime prevalence of SA in the general population of 2%[3] and a lifetime prevalence of SA in MDD, BIP, and SCZ of 16%, 37% and 36% respectively. These numbers represent the observed prevalence of SA in these disorders in the PGC cohorts.

Pairwise GWAS

Pairwise GWAS[55] was used to investigate genome-wide significant loci for SA and overlapping causal variants with propensity towards risk-taking behavior[56] and lifetime smoking index[57]. These phenotypes were chosen because they share genome-wide significant loci in the same region as the genome-wide significant locus on chromosome 7 in the GWAS of SA and SA conditioned on MDD. The genome-wide significant locus on chromosome 6 is in the major histocompatibility complex and due to the complex long-range LD of this region, it was not included for this analysis. Pairwise GWAS uses association statistics from two GWAS to estimate the probability that a genomic region 1) contains a genetic variant that influences only the first trait, 2) contains a genetic variant that influences only the second trait, 3) contains

a shared causal or pleiotropic variant, and 4) contains two independent variants in the same region, one influencing the first trait and the other influencing the second trait. The GWAS summary statistics from the European-only subset of the SA meta-analysis (26,590 cases and 492,022 controls) were used for Pairwise GWAS as the method requires an ancestry-matched LD reference panel. The genome was divided into approximately independent LD blocks based on patterns of LD in the European population in Phase 1 of the 1000 Genomes Project, as previously described[55]. We divided the 3 Mb-wide genome block containing the genome-wide significant locus for SA on chromosome 7 into two blocks to separate the two independent causal variants for risk-taking behavior in that region (rs8180817 and rs4275159, LD r^2=0.001)[56]. The fgwas package[58] was used to determine the baseline correlation between the two GWAS by extracting all genomic regions with a posterior probability of containing an association less than 0.2 and calculating the correlation in the Z-scores between the two GWAS. This summary statistic-level correlation was used as a correction factor to each Pairwise GWAS analysis.

Results

Study description and samples analyzed

We conducted a primary GWAS meta-analysis of SA (29,782 cases, 519,961 controls) from 18 cohorts (Table 1), which included both population-based and clinically ascertained samples for psychiatric disorders (see Methods). The majority (n=26,590) of cases were individuals of European ancestries but cases also included 1,894 individuals of East Asian ancestries and 1,298 individuals of admixed African American ancestries. Case definition was lifetime SA, with ~20% (n=5,438) of cases having died by suicide (see Methods). To investigate the shared and divergent genetic architectures of SA and psychiatric disorders, we performed two additional analyses. We conditioned our primary GWAS results using GWAS summary statistics for MDD, to remove the genetic effects mediated by MDD, the most commonly comorbid psychiatric disorder with SA. Furthermore, we conducted a GWAS of SA versus no SA among individuals with a psychiatric diagnosis in 14,847 cases and 69,951 controls from 13 cohorts.

SA shows significant SNP-heritability and polygenic risk association with death by suicide

In the primary GWAS of SA, h^2_{SNP} estimated using LDSC was 6.8% (SE=0.005, P=2.00x10^{-42}) on the liability scale. The genomic inflation factor (λ_{GC}) was 1.23, the LDSC intercept was 1.04 (SE=0.01, P=2.84x10^{-4}) and the LDSC attenuation ratio was 0.14 (SE=0.04), indicating that the majority of inflation of the GWAS test statistics was due to polygenicity. PRS for SA were tested in five target SA cohorts, which were each excluded in turn from the discovery GWAS to ensure independent discovery and target samples (Table S2). SA PRS were significantly associated with SA in the PGC MDD, PGC BIP and PGC SCZ cohorts, with a phenotypic variance explained (R^2) of 0.69% (P=7.17x10^{-15}), 0.68% (P=8.11x10^{-28}) and 0.88% (P=1.24x10^{-17}) respectively, on the 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=9.79x10^{-81}). The genetic correlation between the University of Utah GWAS of suicide death and SA from a meta-analysis of the remaining cohorts in our study was 0.77 (SE=0.08, P=1.54x10^{-20}). Examining the performance of SA PRS across ancestry showed a significant association with SA in the CONVERGE East Asian cohort, although with a lower variance explained (R^2=0.25%, P=3.06x10^{-3}) (Table S2).

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

The GWAS of SA identified two genome-wide significant loci (P<5x10^{-8}) (Figure 1a, Table S3). The locus most highly associated with SA was in an intergenic region on chromosome 7 (index SNP rs62474683, OR for A allele = 1.06 [1.04-1.08], P=1.91x10^{-10}, frequency in SA cases = 0.52). The second genome-wide significant locus was in the major histocompatibility complex (MHC) (index SNP rs71557378, OR for T allele = 1.10 [1.06-1.13], P=1.97x10^{-8}, frequency in SA cases = 0.91). After conditioning the genetic effects of SA (European-only subset) on the genetic effects of MDD using mtCOJO, only the chromosome 7 locus remained genome-wide significant (index SNP = rs62474683, OR for A allele = 1.06 [1.04-1.08], P=1.33x10^{-8}, Figure 1a). In the GWAS of SA within psychiatric diagnosis, this index SNP had a slightly smaller effect size on SA (index SNP = rs62474683, OR for A allele = 1.04 [1.01-1.07], P=0.007), but no SNPs reached genome-wide significance in this analysis. Examining the intergenic locus on chromosome 7 in published GWAS results using Open Targets Genetics web portal[59] (https://genetics.opentargets.org), showed smaller and non-significant effects on all psychiatric disorders tested (Figure 1b). However, the index SNP from our SA GWAS has been implicated at genome-wide significance in lifetime smoking index[57] (which 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 S4-5). Pairwise GWAS analysis on the genomic region containing the chromosome 7 locus indicated that the causal variant is most likely shared between SA and these phenotypes (lifetime smoking index: posterior probability = 0.997, risk-taking behavior: posterior probability = 1) (Table S13). Furthermore, a variant in high LD with the index SNP on chromosome 7 (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 S4-5). The index SNP for SA has also been implicated in self-harm ideation[60], although with a smaller effect size than on SA (Figure 1b).

Enrichment analyses using MAGMA[48] and the GWAS results for SA indicated significant enrichment of SA associations in 7 genes (Table S6), 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 (Table S7) or in the set of genes expressed in any of the 54 GTEx tissues tested (Table S8). Examining individual genes, our transcriptome-wide association study (TWAS) found 5 genes for which SA risk alleles were significantly associated with brain gene expression: *ERC2, RP11−266A24.1, TIAF1, BACE2, NUFIP2* (P<4.28x10^{-6}) (Table S9). None of the TWAS significant genes were located in genome-wide significant loci.

Table 1: Numbers of cases and controls for 21 cohorts in the International Suicide Genetics Consortium

Cohort	SA*		SA within psychiatric diagnosis*	
	Cases	Controls	Cases	Controls
Psychiatric Genomics Consortium MDD	1,528	16,626	1,677	8,793
Psychiatric Genomics Consortium BIP	3,214	17,642	3,214	5,408
Psychiatric Genomics Consortium SCZ	1,640	7,112	1,668	2,928
Psychiatric Genomics Consortium ED	170	5,070	198	583
Army STARRs	670	10,637	376	3,447
German Borderline Genomics Consortium	481	1,653	481	144
UK Biobank	2,433	334,766	2,149	35,912
iPSYCH	7,003	52,227	-	-
Janssen	255	1,684	-	-
Yale-Penn	475	1,817	-	-
GISS Ukraine	660	660	-	-
Columbia University	577	1,233	-	-
Australian Genetics of Depression Study and QSkin Study	2,792	20,193	2,792	8,718
University of Utah	4,692	20,702	-	-
Japan (EAS)	746	14,049	-	-
CONVERGE (EAS)	1,148	6,515	1,148	1,183
Taiwan MDD (EAS)	-	-	222	318
Taiwan BIP (EAS)	-	-	235	397
Taiwan SCZ (EAS)	-	-	332	1,004
Grady Trauma Project (admixed AA)	669	4,473	355	1,116
Yale-Penn (admixed AA)	629	2,902	-	-
Total	29,782	519,961	14,847	69,951

SA - suicide attempt, MDD - major depressive disorder, BIP - bipolar disorder, SCZ - schizophrenia, ED - eating disorder, EAS - East Asian ancestry, AA - African American ancestry. All other samples are of European ancestries. *GWAS contain some overlapping individuals and cohorts.
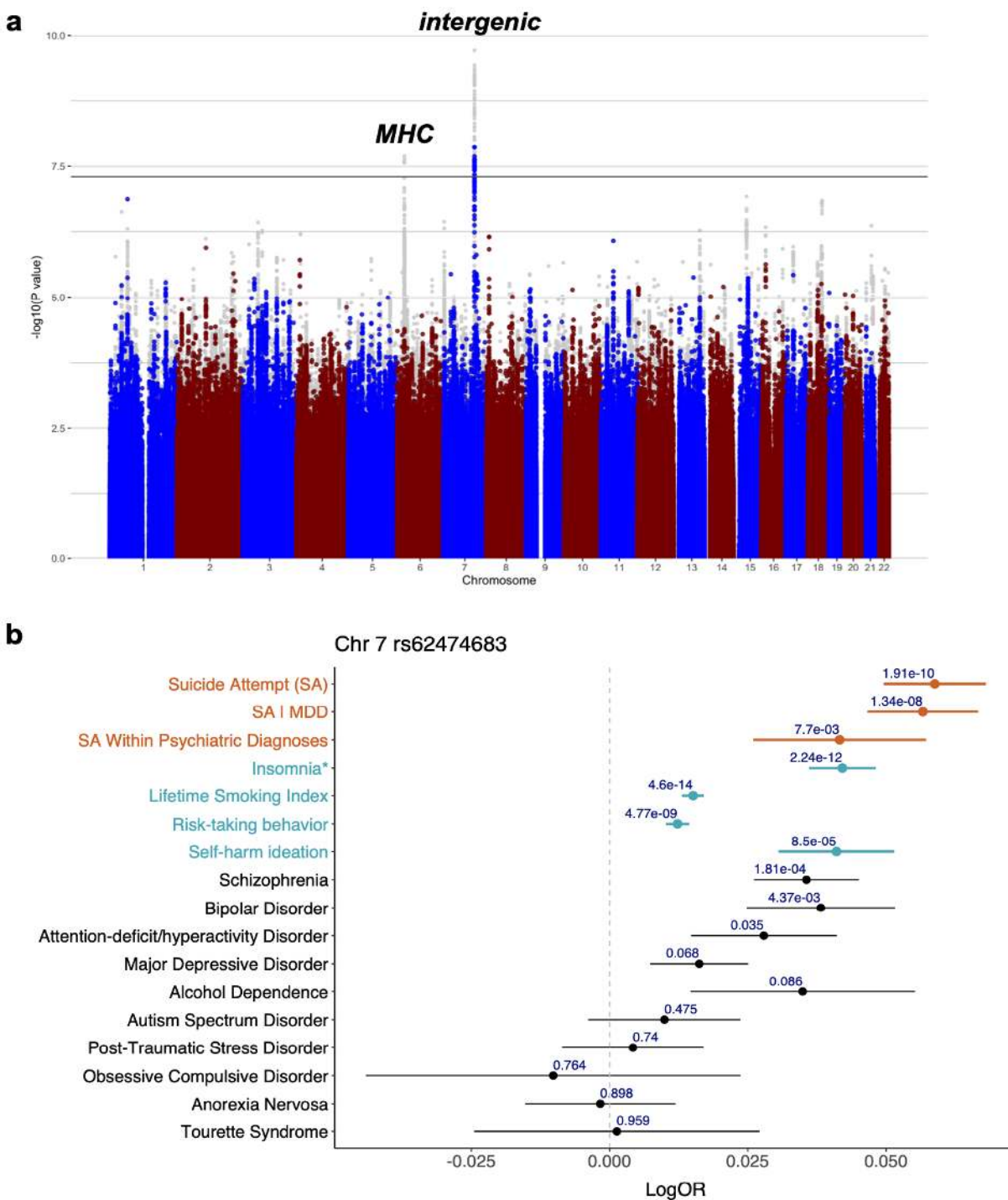
Figure 1: Genome-wide significant locus contributes to suicide attempt more strongly than psychiatric disorders and other traits

a) Manhattan plot: The *x*-axis shows genomic position and the *y*-axis shows statistical significance as −$\log_{10}$(P value). The grey points in the background depict the GWAS results for SA and the colored points in the foreground depict the results after conditioning SA on major depressive disorder (MDD), which was performed on the European meta-analysis results. The horizontal line shows the genome-wide significance threshold (P<5.0×10^{-8}). b) Forest plot: The points indicate the log odds ratio of the A allele at

rs62474683 (index SNP for SA 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 LD with the index SNP is shown instead (rs12666306 A allele, LD r^2=0.94 with SA index SNP).

Evidence for substantial proportion of SNP-heritability of SA not mediated by psychiatric disorders

We employed two approaches to assess the genetic architecture of SA after accounting for psychiatric disorders: 1) we statistically conditioned out genetic effects mediated by MDD and 2) we directly analyzed SA versus no SA among psychiatric disorder cases (see Methods). The statistical conditioning was performed on the European-only subset of the meta-analysis, in which the h^2_{SNP} of SA was 7.5% (SE=0.006, P=3.02x10^{-40}) on the liability scale (Table S10). Conditioning these SA GWAS results on MDD resulted in a 45% decrease in the h^2_{SNP} of SA to 4.1% (SE=0.005, P=1.20x10^{-16}) on the liability scale (Table S10). This conditioned estimate was comparable with estimates of the h^2_{SNP} of SA within psychiatric diagnosis, which ranged from 3.7% to 4.6%, using a prevalence of SA in psychiatric populations from 10-20% (P<1.35x10^{-3}). Conditioning SA on BIP and SCZ in addition to MDD did not change the h^2_{SNP} estimate (h^2_{SNP}=4.1%, SE=0.005, P=1.20x10^{-16}).

The genetic correlation between the GWAS of SA and SA within psychiatric diagnosis was 0.93 (SE=0.09, P=5.35x10^{-24}). PRS for SA were significantly associated with SA within psychiatric diagnosis in the PGC cohorts, with an R^2 of 0.43% (P=5.83x10^{-6}), 0.81% (P=2.33x10^{-11}) and 0.71% (P=5.78x10^{-6}) on the liability scale for SA in MDD, BIP and SCZ respectively (Table S2). After conditioning the GWAS of SA on MDD, the genetic correlation with the GWAS of SA within psychiatric diagnosis was not significantly different from 1 (rg=1.13, SE=0.13) (Table S10). After conditioning on MDD, PRS for SA remained significantly associated with SA within psychiatric diagnosis in the PGC cohorts, with slightly lower phenotypic variance explained (0.32%, 0.67% and 0.46% for SA in MDD, BIP and SCZ respectively), consistent with the reduction in h^2_{SNP} (Table S2).

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. SA showed a significant genetic correlation with 11 traits or disorders tested, most strongly with self-harm ideation (rg=0.81, SE=0.06, P=3.52x10^{-36}) and MDD (rg=0.78, SE=0.03, P=5.82x10^{-112}) (Figure 2, Table S11). Significant genetic correlations were also observed between SA and SCZ, attention-deficit/hyperactivity disorder (ADHD), BIP, post-traumatic stress disorder (PTSD) and alcohol dependency (rg=0.46-0.73) (Figure 2, Table S11).

To investigate whether these genetic correlations were mediated by the genetics of MDD, we estimated genetic correlations with the same traits and disorders after conditioning the GWAS of SA on MDD (SA|MDD). Genetic correlations with all psychiatric disorders remained significant after conditioning except for autism spectrum disorder (ASD) and Tourette syndrome (Figure 2, Table S11). As expected, the rg with MDD significantly decreased after conditioning (P=2.3x10^{-16} block jackknife), as well as the rg with self-harm ideation (P=1.3x10^{-4} block jackknife) and ASD (P=1.8x10^{-5} block jackknife) (Figure 2, Table S11).

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 genetic correlation between SA|MDD and MDD (rg=0.53, SE=0.06, P=8.9x10^{-19}) indicates pleiotropic SNP effects.

Examining the genetic correlations between SA within psychiatric diagnosis and psychiatric disorders, most genetic correlations were comparable to those observed with SA|MDD (Table S11). Genetic correlations of SA within psychiatric diagnosis and MDD (rg=0.52, SE=0.11, P=4.48x10^{-6}), ADHD (rg=0.60, SE=0.12, P=7.08x10^{-7}), and PTSD (rg=0.56, SE=0.19, P=3.41x10^{-3}) were significant after Bonferroni correction. As exceptions, BIP and SCZ had non-significant genetic correlations with SA within psychiatric diagnosis (SCZ: rg=-0.07, SE=0.075, P=3.24x10^{-1}, BIP: rg=-0.08, SE=0.10, P=4.38x10^{-1}). This is consistent with a previous report that BIP and SCZ cases who had attempted suicide did not have higher BIP or SCZ PRS, compared with cases who did not attempt suicide[31].
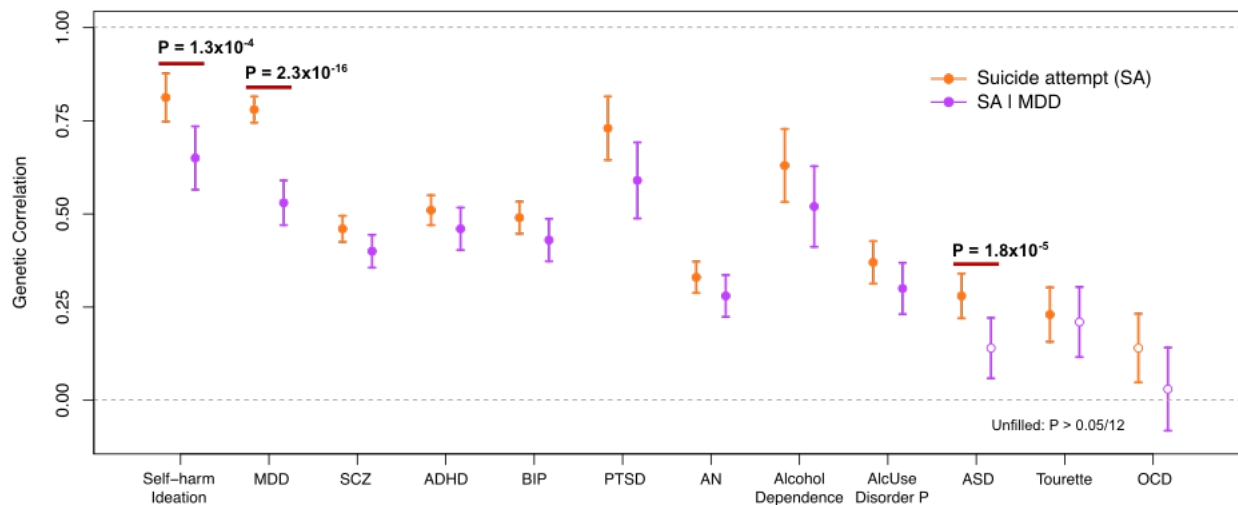
Figure 2: Substantial genetic correlation of suicide attempt with psychiatric traits or disorders before and after conditioning on major depressive disorder

Unfilled points indicate genetic correlations that did not pass the Bonferroni-corrected significance threshold P<4.17x10^{-3} (12 traits tested). Error bars represent the standard error. P values indicate significant differences in genetic correlation after conditioning, that pass the Bonferroni correction. SA|MDD-suicide attempt conditioned on major depressive disorder, 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.

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 our three GWAS (SA, SA|MDD and SA within psychiatric diagnosis) with 768 non-overlapping phenotypes[46]. We grouped 269 of these phenotypes into 15 categories of previously identified risk factors for SA[4,5,10] (see Methods). There were 194 phenotypes which showed a significant rg with SA, 133 of which were in one of the pre-defined SA risk categories (Figure 3a, Table S12). 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, 81 phenotypes retained a significant genetic correlation with SA (Table S12). Within the psychiatric risk category, there was an average decrease in the magnitude of genetic correlation of 33% with SA after conditioning, whereas the genetic correlation values in other risk categories were much less affected by conditioning (smoking: 3% decrease, education/cognition: 0.74% increase, alcohol: 12.5% decrease, and socioeconomic: 9.7% decrease) (Figure 3a). Genetic correlations of SA within psychiatric diagnosis were similar to those of SA|MDD: of the 39 phenotypes with significant genetic correlation after Bonferroni correction, 21 phenotypes were in the smoking, education/cognition or socioeconomic risk categories (Figure 3b, Table S12).
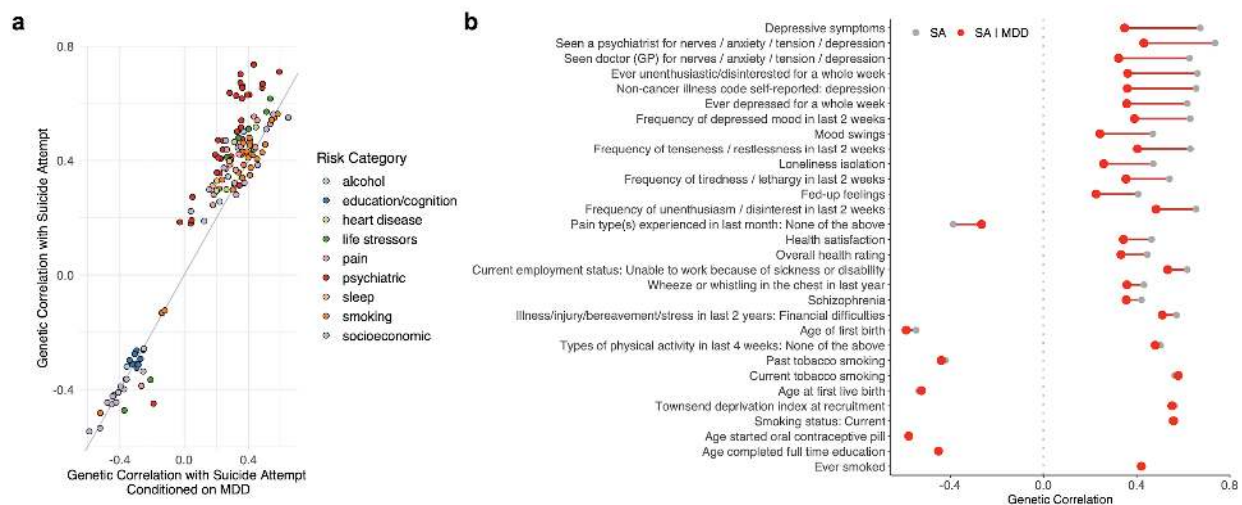
Figure 3: Conditioning suicide attempt on major depressive disorder reduces genetic correlation with psychiatric phenotypes but has limited effect on other traits

a) Comparison of significant genetic correlations with suicide attempt (SA) versus genetic correlations with SA conditioned on MDD (SA|MDD). Data include 133 significant genetic correlations after Bonferroni correction (P<0.05/768=6.51x10⁻⁵) annotated by risk category. b) Top 30 phenotypes with the most significant genetic correlations with SA before (in gray) and after conditioning on MDD (SA|MDD) (in red). Full genetic correlation results, including standard errors, are provided in Table S12.

Discussion

We present a GWAS of suicide attempt in over 29,000 cases, identifying 2 genome-wide significant loci, including one locus more strongly associated with SA than with psychiatric disorders or other related traits. We demonstrate that a substantial proportion of the SNP-heritability of SA is independent of psychiatric diagnosis, by conditioning our GWAS results on the genetics of MDD and by examining the genetics of SA among individuals with a psychiatric diagnosis. Finally, we determine that the genetic liability to SA not mediated by psychiatric disorders is shared with the genetic architecture of traits related to smoking, socioeconomic traits, and poorer overall health.

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 any common psychiatric disorder, remained genome-wide significant after conditioning on MDD and had a comparable effect size on SA within psychiatric diagnosis and self-harm ideation. Taken together, these results suggest that the genetic association with SA at this locus is not mediated through risk for psychiatric disorders. Current functional genomic data does not clearly link this variant to any gene, with the nearest gene being a long-non-coding RNA (*LINC01392*) located 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 previously been implicated at genome-wide significance in risk-taking behaviors[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 the GWAS results on MDD. Indeed, variants in the MHC have previously been associated with risk for a range of psychiatric disorders including MDD[64]. This suggests that the association between the MHC and SA may be pleiotropic or potentially a byproduct of psychiatric diagnosis. Further investigation is needed to determine causality or direction for both of these loci.

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% in the European-only subset). Importantly, conditioning on MDD resulted in a smaller but significant h^2_{SNP} estimate (4.1%), which was on par with estimates from the GWAS of SA within psychiatric diagnosis (h^2_{SNP} 3.7-4.6% on the liability scale, using a prevalence of SA in psychiatric populations from 10-20%). These results corroborate previous reports[25,27] of the independent genetic contribution to SA from genetic epidemiology studies and GWAS, and illustrate the importance of accounting for potential bias from the genetics of psychiatric disorders. Traditionally, GWAS of SA have sought to dissect this specific genetic component by conducting GWAS of SA within psychiatric diagnosis. More recently, a GWAS of SA in the iPSYCH Danish Registry took the approach of including a covariate for cases' psychiatric diagnoses[27]. Here, we found complete genetic correlation between the GWAS of SA after conditioning on MDD and the GWAS of SA within psychiatric diagnosis (rg=1.13, SE=0.13), thus demonstrating that comparable results can be achieved via a statistical genetics approach. Since conditioning only requires GWAS summary statistics, this approach is readily applicable to different types of cohort and circumvents the need for samples with specific psychiatric diagnoses, detailed phenotypic information or individual-level genotype data available.

SA showed substantial positive genetic correlation with many psychiatric disorders, the highest being with MDD (rg=0.78, SE=0.03), consistent with previous reports[28,29,31]. Genetic overlap was also particularly strong with PTSD, ADHD, SCZ, and BIP (rg=0.44-0.74). After conditioning on MDD, there was a modest decrease in the genetic correlation of SA with most psychiatric disorders, but only significant decreases were observed with MDD, ASD, and self-harm ideation. Notably, after conditioning, SA was still strongly genetically correlated with MDD (rg=0.53, SE=0.06, P=8.85x10^{-19}), representing pleiotropic effects between them. This genetic correlation would only be completely eliminated if all SNP effects on SA were mediated by MDD. Many studies have demonstrated extensive pleiotropy between psychiatric disorders[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. Examining the genetic liability to SA in a group of cases without psychiatric disorders would be a valuable future endeavor to corroborate these findings, however such individuals are a minority.

Genetic correlations were also examined between SA and 768 traits, with a focus on known risk factors and comorbidities. There was significant genetic correlation between SA and many other traits, including smoking, lower socioeconomic status, pain, lower educational attainment, reproductive traits, risk-taking behavior, sleep disturbances and poorer overall general health. While conditioning on MDD reduced the genetic correlations between SA and psychiatric disorders, in contrast, the genetic correlation of SA with most non-psychiatric traits remained unchanged. These results were largely corroborated using the GWAS of SA within psychiatric diagnosis, pointing to a consistent picture of shared genetic architecture between SA and these risk factors that is not a byproduct of psychiatric illness. There is substantial epidemiological literature on the relationship of risk factors including sleep disorders[12–15], smoking[18–20] and socioeconomic factors[67–69] on SA, but less on the role of genetics. We have not assessed any causal role between the genetic risk of these traits and SA, but additional work on this topic will provide important insights and potentially highlight opportunities for risk stratification.

This first collaborative study by the International Suicide Genetics Consortium is almost 5-fold larger than any previous GWAS of SA, providing a substantial increase in statistical power. Furthermore, we have assessed the specificity of our findings to SA using two approaches. Nevertheless, several limitations must be acknowledged. Cases were defined across cohorts using a variety of diagnostic interviews, self-report, or hospital records, which may result in heterogeneity in the phenotype definition. Standard diagnostic criteria for SA are lacking and here sample sizes prohibited calculating genetic correlations across pairs of cohorts. Our GWAS included both cases of non-fatal SA and death by suicide which are imperfectly although highly genetically correlated (rg=0.77 between the University of Utah GWAS of suicide death and a meta-analysis of the remaining cohorts in our study). There is potential for misclassification of controls in the GWAS of SA within psychiatric diagnosis, as some patients may go on to make a suicide attempt later in life. We examined the genetic correlation between our GWAS of SA and psychiatric disorders, using publicly available GWAS summary statistics, however we note that the prevalence of SA amongst the cases in these GWAS are 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 expansive data to stratify our analyses, to assess their possible contribution or confounding effects.

This work establishes the best-powered genetic analysis of SA to date. We identify SA risk loci and demonstrate a genetic component of SA that is not mediated through psychiatric disorders, but is shared with known risk factors. At present, PRS for SA do not have meaningful predictive utility and their premature use in either clinical or direct-to-consumer settings could be harmful. Dissecting the shared genetic architecture of SA, psychiatric disorders and other risk factors will be crucial to understanding the biological mechanisms of risk and assessing whether genetics can inform risk stratification or treatment.

Data availability

The policy of the International Suicide Genetics Consortium is to make genome-wide summary results public. Summary statistics will be made available online upon publication. This study included some publicly available datasets accessed through dbGaP - PGC bundle phs001254.v1.p1**.**

Affiliations

1, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, US

2, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, US

3, Division of Genetic Medicine, Department of Medicine, Vanderbilt Genetics Institute, Vanderbilt University Medical Center, Nashville, TN, US

4, Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

5, School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Brisbane, QLD, Australia

6, National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre at South London and Maudsley NHS Foundation Trust, King's College London, London, UK

7, Social Genetic and Developmental Psychiatry Centre, King's College London, London, UK

8, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US

9, Department of Biostatistics, Columbia University, New York, NY, US

10, Department of Psychiatry, Columbia University, New York, NY, US

11, Department of Psychiatry, Veterans Affairs Connecticut Healthcare Center, West Haven, CT, US

12, Division of Human Genetics, Department of Psychiatry, Yale University School of Medicine, New Haven, CT, US

13, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, US

14, Department of Psychiatry, University of Utah School of Medicine, Salt Lake City, UT, US

15, Centre for Genomics and Personalized Medicine, CGPM, Aarhus University, Aarhus, Denmark

16, Centre for Integrative Sequencing, iSEQ, Aarhus University, Aarhus, Denmark

17, Department of Biomedicine, Aarhus University, Aarhus, Denmark

18, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Aarhus University, Aarhus, Denmark

19, Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

20, School of Psychology, Curtin University, Perth, Western Australia, Australia

21, Division of Paediatrics, The University of Western Australia, Perth, Western Australia, Australia

22, Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

23, Division of Psychiatry, University of Edinburgh, Edinburgh, UK

24, Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin Berlin, Berlin, Germany

25, Department of Psychiatry and Biobehavioral Science, Semel Institute, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, US

26, Department of Psychiatry, Yokohama City University Graduate School of Medicine, Yokohama, Japan

27, Department of Psychiatry, Kobe University Graduate School of Medicine, Kobe, Japan

28, Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US

29, Analytical and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, US

30, Population Studies Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, US

31, Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI, US

32, BioRealm, LLC, Walnut, CA, US

33, Oregon Research Institute, Eugene, OR, US

34, Department of Psychiatry, Center for Neurobiology and Behavior, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, US

35, Department of Psychosomatic Medicine and Psychotherapy, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

36, The Center for Eating Disorders at Sheppard Pratt, Baltimore, MD, US

37, Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, PA, US

38, Center for Neuropsychiatric Research, National Health Research Institutes, Miaoli County, Taiwan

39, Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan

40, Department of Psychiatry, University of Minnesota, Minneapolis, MN, US

41, Hôpital Sainte Anne, GHU Paris Psychiatrie et Neurosciences, Paris, France

42, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, Université de Paris, Paris, France

43, Department of Psychiatry, University Hospital Bellvitge-IDIBELL and CIBEROBN, Barcelona, Spain

44, Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University (LMU), Munich, Germany

45, Schön Klinik Roseneck affiliated with the Medical Faculty of the University of Munich (LMU), Munich, Germany

46, Department of Surgery, Faculty of Medicine, University of Toronto, Toronto, Canada

47, Department of Psychiatry and Behavioral Sciences, SUNY Upstate Medical University, Syracuse, NY, US

48, The Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, US

49, Department of Psychiatry, Weill Cornell Medical College, New York, NY, US

50, Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan

51, Division of Biostatistics, Department of Family Medicine and Public Health, University of California San Diego, La Jolla, CA, US

52, Inserm U955, Institut Mondor de recherches Biomédicales, Laboratoire, Neuro-Psychiatrie Translationnelle, and Fédération Hospitalo-Universitaire de Précision Médecine en Addictologie et Psychiatrie (FHU ADAPT), University Paris-Est-Créteil, Créteil, France

53, Eating Recovery Center, Denver, CO, US

54, Centre for Addiction and Mental Health, Toronto, ON, Canada

55, Department of Psychiatry, University of Toronto, Toronto, Canada

56, Institute of Medical Science, University of Toronto, Toronto, Canada

57, Department of Psychiatry, University of California San Diego, San Diego, CA, US

58, Department of Psychology, Florida State University, Tallahassee, FL, US

59, Department of Psychology, Michigan State University, Lansing, MI, US

60, Department of Psychiatry and Psychotherapy, University Medical Center, Mainz, Germany

61, Department of Clinical Psychology, The Chicago School of Professional Psychology, Washington DC, Washington, DC, US

62, BESE Division, King Abdullah University of Science and Technology, Thuwal, Saudi Arabia

63, Department of Psychiatry, University of Lausanne-University Hospital of Lausanne (UNIL-CHUV), Lausanne, Switzerland

64, Department of Paediatric Laboratory Medicine, The Hospital for Sick Children, Toronto, Canada

65, Department of Psychiatry and Behavioral Science, University of North Dakota School of Medicine and Health Sciences, Fargo, ND, US

66, HudsonAlpha Institute for Biotechnology, Huntsville, AL, US

67, Department of Psychiatry, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, Berlin Institute of Health, Campus Benjamin Franklin, Berlin, Germany

68, Department of Psychiatry, Neurobiology, Pharmacology, and Biotechnologies, University of Pisa, Pisa, Italy

69, Department of Psychology, Saint-Petersburg State University, Saint-Petersburg, Russian Federation

70, Department of Borderline Disorders and Psychotherapy, V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology, Saint-Petersburg, Russian Federation

71, Department of Genetics and Genomic Biology, The Hospital for Sick Children, Toronto, Canada

72, National Centre for Suicide Research and Prevention of Mental Ill-Health (NASP), LIME, Karolinska Institutet, Stockholm, Sweden

73, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, LA, US

74, Department of Psychiatry and Biobehavioral Science, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, LA, US

75, Institute of Psychiatry, Psychology and Neuroscience, Department of Psychological Medicine, King's College London, London, UK

76, National Institute for Health Research Biomedical Research Centre, King's College London and South London and Maudsley National Health Service Foundation Trust, London, UK

77, Center for Behavioral Genomics, Department of Psychiatry, University of California, San Diego, San Diego, CA, US

78, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany

79, Centre for Mental Health, University Health Network, Toronto, Canada

80, Program for Eating Disorders, University Health Network, Toronto, Canada

81, National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark

82, Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

83, Department of Clinical Sciences, Psychiatry, Umeå University Medical Faculty, Umeå, Sweden

84, Department of Psychiatric Research, Diakonhjemmet Hospital, Oslo, Norway

85, Department of Clinical Neuroscience, Centre for Psychiatry Research, Karolinska Institutet, Stockholm, Sweden

86, NORMENT, Institute of Clinical Medicine, University of Oslo, Oslo, Norway

87, Discipline of Psychiatry, University of Adelaide, Adelaide, SA, Australia

88, Department of Psychiatry, Dalhousie University, Halifax, NS, Canada

89, National Institute of Mental Health, Klecany, CZ

90, Department of Clinical Neuroscience, Karolinska Institutet,, Sweden

91, Inst of Environmental Medicine, Karolinska Institutet,, Sweden

92, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway

93, NORMENT, University of Oslo, Oslo, Norway

94, Psychiatry, Berkshire Healthcare NHS Foundation Trust, Bracknell, UK

95, Institute of Biological Psychiatry, Copenhagen Mental Health Services, Copenhagen University Hospital, Copenhagen, Denmark

96, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Copenhagen, Denmark

97, Department of Psychiatry, Hospital Universitari Vall d'Hebron, Barcelona, Spain

98, Biomedical Network Research Centre on Mental Health (CIBERSAM), Instituto de Salud Carlos III, Madrid, Spain

99, Department of Genetics, Microbiology & Statistics, University of Barcelona, Barcelona, Spain

100, Psychiatric Genetics Unit, Group of Psychiatry, Mental Health and Addiction, Vall d'Hebron Research Institute (VHIR), Universitat Autònoma de Barcelona, Barcelona, Spain

101, Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany

102, Department of Psychiatry, University of Coimbra, Coimbra, Portugal

103, Division of Psychiatry, University College London, London, UK

104, Laboratory of Developmental Psychiatry, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil

105, Department of Genetics, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

106, Department of Psychiatry, Melbourne Medical School, University of Melbourne, Melbourne, Australia

107, Department of Psychiatry, University of Münster, Münster, Germany

108, Department of Psychiatry and Addiction Medicine, Assistance Publique - Hôpitaux de Paris, Paris, France

109, Paris Bipolar and TRD Expert Centres, FondaMental Foundation, Paris, France

110, UMR-S1144 Team 1: Biomarkers of relapse and therapeutic response in addiction and mood disorders, INSERM, Paris, France

111, Psychiatry, Université Paris Diderot, Paris, France

112, Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, Germany

113, Health Sciences Research, Mayo Clinic, Rochester, MN, US

114, Department of Psychiatry and Behavioral Sciences, State University of New York Downstate Medical Center, New York, NY, US

115, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US

116, Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, Germany

117, Center for Statistical Genetics and Department of Biostatistics, University of Michigan, Ann Arbor, MI, US

118, Psychiatry, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, Netherlands

119, Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain

120, Department of Psychiatry, University of California San Diego, La Jolla, CA, US

121, School of Psychology, University of New South Wales, Sydney, NSW, Australia

122, Institute of Psychiatric Phenomics and Genomics (IPPG), University Hospital, LMU Munich, Munich, Germany

123, Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, Australia

124, Department of Psychiatry, UMC Utrecht Hersencentrum Rudolf Magnus, Utrecht, Netherlands

125, Department of Psychiatry, Lausanne University Hospital and University of Lausanne, Lausanne, Vaud, Switzerland

126, Mental Health Unit, Department of Psychiatry, Faculty of Medicine, Granada University Hospital Complex, University of Granada, Granada, Spain

127, Institut de Psychiatrie, CNRS GDR 3557, Paris, France

128, Department of Evaluation, Prevention and Therapeutic innovation, GHU Paris Psychiatrie et Neurosciences, Paris, France

129, Team Pathophysiology of psychiatric diseases, Université de Paris, Institute of Psychiatry and Neuroscience of Paris (IPNP), INSERM U1266, Paris, France

130, Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Jülich, Germany

131, Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland

132, Department of Biomedicine, University of Basel, Basel, Switzerland

133, Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany

134, Neuropsychiatric Genetics Research Group, Dept of Psychiatry and Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland

135, Medical Research Council Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, Cardiff, UK

136, Department of Translational Genomics, University of Southern California, Pasadena, CA, US

137, Department of Medical Genetics, Oslo University Hospital, Oslo, Norway

138, NORMENT, KG Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen, Bergen, Norway

139, Department of Medical & Molecular Genetics, Indiana University, Indianapolis, IN, US

140, Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, IN, US

141, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

142, Centre for Human Genetics, University of Marburg, Marburg, Germany

143, Department of Psychiatry & Psychology, Mayo Clinic, Rochester, MN, US

144, Neuroscience Research Australia, Sydney, NSW, Australia

145, School of Medical Sciences, University of New South Wales, Sydney, NSW, Australia

146, University of New South Wales, Sydney, NSW, Australia

147, Department of Psychiatry and Behavioral Sciences, NorthShore University HealthSystem, Evanston, IL, US

148, Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, IL, US

149, Dept. of Psychiatry, Psychotherapy and Psychosomatics, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany

150, Department of Psychiatry, University of Munich, Munich, Germany

151, School of Psychiatry, University of New South Wales, Sydney, NSW, Australia

152, ADHD Outpatient Program, Adult Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS, Brazil

153, Department of Psychiatry, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil

154, Biometric Psychiatric Genetics Research Unit, Alexandru Obregia Clinical Psychiatric Hospital, Bucharest, Romania

155, Department of Psychiatry, Faculty of Medicine and Biomedical Research Centre (CIBM), University of Granada, Granada, Spain

156, Mental Health Department, University Regional Hospital. Biomedicine Institute (IBIMA), Málaga, Spain

157, Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, US

158, Department of Psychiatry, Laboratory of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland

159, Max Planck Institute of Psychiatry, Munich, Germany

160, Department of Psychological Medicine, University of Worcester, Worcester, UK

161, Department of Psychiatry and Neuroscience, University of Gothenburg, Gothenburg, Sweden

162, Institute for Genomic Medicine, University of California San Diego, La Jolla, CA, US

163, Department of Psychiatry, University of Toronto, Toronto, ON, Canada

164, Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US

165, Department of Epidemiology, Harvard TH Chan School of Public Health, Boston, MA, US

166, Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US

167, Center for Research in Environmental Epidemiology (CREAL), Barcelona, Spain

168, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

169, Psychiatry, North East London NHS Foundation Trust, Ilford, UK

170, INSERM, Paris, France

171, Faculté de Médecine, Université Paris Est, Créteil, France

172, Psychiatric and Neurodevelopmental Genetics Unit, Massachusetts General Hospital, Boston, MA, US

173, Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, US

174, Department of Human Genetics, McGill University, Montreal, QC, Canada

175, Montreal Neurological Institute and Hospital, Montreal, QC, Canada

176, Cancer Epidemiology and Prevention, M. Sklodowska-Curie Cancer Center and Institute of Oncology, Warsaw, Poland

177, Research Institute, Lindner Center of HOPE, Mason, OH, US

178, Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, US

179, Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia

180, School of Psychology and Counseling, Queensland University of Technology, Brisbane, QLD, Australia

181, Queensland Brain Institute, The University of Queensland, Brisbane, QLD, Australia

182, Division of Mental Health and Addiction, University of Oslo, Institute of Clinical Medicine, Oslo, Norway

183, Department of Psychiatry, Amsterdam UMC, Vrije Universiteit and GGZ inGeest, Amsterdam, Netherlands

184, Department of Nursing, Faculty of Health Sciences and Biomedical Research Centre (CIBM), University of Granada, Granada, Spain

185, Mental Health, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology - NTNU, Trondheim, Norway

186, Psychiatry, St Olavs University Hospital, Trondheim, Norway

187, Centre for Integrated Register-based Research, Aarhus University, Aarhus, Denmark

188, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research,, Denmark

189, Munich Cluster for Systems Neurology (SyNergy), Munich, Germany

190, University of Liverpool, Liverpool, UK

191, Psychiatry and Human Genetics, University of Pittsburgh, Pittsburgh, PA, US

192, Psychiatry, Erasmus University Medical Center, Rotterdam, Netherlands

193, Jane and Terry Semel Institute for Neuroscience and Human Behavior, Los Angeles, CA, US

194, College of Medicine Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, US

195, Institute for Genomic Health, SUNY Downstate Medical Center College of Medicine, Brooklyn, NY, US

196, Psychiatry, University of Iowa, Iowa City, IA, US

197, Genetics, BioMarin Pharmaceuticals, London, UK

198, St Edmund Hall, University of Oxford, Oxford, UK

199, Department of Psychiatry, University of Oxford, Oxford, UK

200, Department of Psychiatry, Psychosomatic Medicine and Psychotherapy, University Hospital Frankfurt, Frankfurt, Germany

201, Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, Germany

202, Department of Biochemistry and Molecular Biology II and Institute of Neurosciences, Biomedical Research Centre (CIBM), University of Granada, Granada, Spain

203, Department of Environmental Health, Harvard TH Chan School of Public Health, Boston, MA, US

204, Department of Neurology and Neurosurgery, McGill University, Faculty of Medicine, Montreal, QC, Canada

205, Instituto de Ciencias Biomedicas Departamento de Fisiologia e Biofisica, Universidade de São Paulo, São Paulo, SP, Brazil

206, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, US

207, Human Genetics Branch, Intramural Research Program, National Institute of Mental Health, Bethesda, MD, US

208, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Göttingen, Germany

209, Department of Biomedical and NeuroMotor Sciences, University of Bologna, Bologna, Italy

210, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, US

211, Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, US

212, Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY, US

213, Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US

214, Institute of Psychology, Psychiatry & Neuroscience, King's College London, London, UK

215, Menninger Department of Psychiatry and Behavioral Sciences, Baylor College of Medicine, Houston, Houston, TX, US

216, Laboratory of Neuropsychiatry, IRCCS Santa Lucia Foundation, Rome, Rome, Italy

217, Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland

218, Department of Psychiatry, McGill University, Montreal, QC, Canada

219, Molecular Brain Science, Centre for Addiction and Mental Health, Toronto, ON, Canada

220, Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, Germany

221, Columbia University College of Physicians and Surgeons, New York, NY, US

222, Division of Translational Epidemiology, New York State Psychiatric Institute, New York, NY, US

223, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA, US

224, Center of Mental Health Research, Australian National University, Canberra, Australia

225, Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, US

226, Danish Research Institute for Suicide Prevention, Mental Health Centre Copenhagen, Copenhagen, Denmark

227, Program in Medical and Population Genetics, Broad Institute, Cambridge, MA, US

228, Estonian Genome Center, Institute of Genomics, University of Tartu, Tartu, Estonia

229, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, Aarhus, Denmark

230, Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, Denmark

231, Department of Health Care Policy, Harvard Medical School, Boston, MA, US

232, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, US

233, Neuroscience, Janssen Research & Development, LLC, Titusville, NJ, US

234, Department of Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia

235, Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, Denmark

236, Mental Health Center Copenhagen, Copenhagen University Hospital, Copenhagen, Denmark

237, Department of Population Health, QIMR Berghofer Medical Research Institute, Herston, QLD, Australia

238, Institute for Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK

239, Department of Psychiatry, Uniformed University of the Health Sciences, Bethesda, MD, US

240, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

241, Lundbeck Foundation GeoGenetics Centre, GLOBE Institute, University of Copenhagen, Copenhagen, Denmark

242, Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, NC, US

243, Biomedical Informatics, University of Utah School of Medicine, Salt Lake City, UT, US

244, Department of Medical & Molecular Genetics, King's College London, London, UK

245, Departments of Psychiatry and Radiology, Columbia University, New York, NY, US

246, Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK

247, Department of Psychiatry and School of Public Health, University of California San Diego, La Jolla, CA, US

248, Department of Psychiatry, University of Iowa, Iowa City, IA, US

249, Department of Biomedical Informatics, Vanderbilt University Medical Center, Nashville, TN, US

250, Department of Psychiatry and Behavioral Sciences, Vanderbilt University Medical Center, Nashville, TN, US

251, These authors contributed equally

*Corresponding Authors

References

1. WHO | Suicide data. http://www.who.int/mental_health/prevention/suicide/suicideprevent/en/ (2019).

2. Centers for Disease Control and Prevention. Web-based Injury Statistics Query and Reporting System. *cdc.gov* https://www.cdc.gov/injury/wisqars/index.html.

3. Nock, M. K. *et al.* Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br. J. Psychiatry* **192**, 98–105 (2008).

4. Franklin, J. C. *et al.* Risk factors for suicidal thoughts and behaviors: A meta-analysis of 50 years of research. *Psychol. Bull.* **143**, 187–232 (2017).

5. Fazel, S. & Runeson, B. Suicide. *N. Engl. J. Med.* **382**, 266–274 (2020).

6. Arsenault-Lapierre, G., Kim, C. & Turecki, G. Psychiatric diagnoses in 3275 suicides: a meta-analysis. *BMC Psychiatry* **4**, 37 (2004).

7. Cavanagh, J. T. O., Carson, A. J., Sharpe, M. & Lawrie, S. M. Psychological autopsy studies of suicide: a systematic review. *Psychological Medicine* vol. 33 395–405 (2003).

8. Qin, P. The impact of psychiatric illness on suicide: differences by diagnosis of disorders and by sex

and age of subjects. *J. Psychiatr. Res.* **45**, 1445–1452 (2011).

9. Ribeiro, J. D. *et al.* Self-injurious thoughts and behaviors as risk factors for future suicide ideation, attempts, and death: a meta-analysis of longitudinal studies. *Psychological Medicine* vol. 46 225–236 (2016).

10. Ahmedani, B. K. *et al.* Major Physical Health Conditions and Risk of Suicide. *Am. J. Prev. Med.* **53**, 308–315 (2017).

11. Khazem, L. R. Physical disability and suicide: recent advancements in understanding and future directions for consideration. *Curr Opin Psychol* **22**, 18–22 (2018).

12. Bernert, R. A. & Nadorff, M. R. Sleep Disturbances and Suicide Risk. *Sleep Med. Clin.* **10**, 35–39 (2015).

13. Woznica, A. A., Carney, C. E., Kuo, J. R. & Moss, T. G. The insomnia and suicide link: toward an enhanced understanding of this relationship. *Sleep Med. Rev.* **22**, 37–46 (2015).

14. Pigeon, W. R., Pinquart, M. & Conner, K. Meta-analysis of sleep disturbance and suicidal thoughts and behaviors. *J. Clin. Psychiatry* **73**, e1160–7 (2012).

15. Bishop, T. M., Walsh, P. G., Ashrafioun, L., Lavigne, J. E. & Pigeon, W. R. Sleep, suicide behaviors, and the protective role of sleep medicine. *Sleep Med.* **66**, 264–270 (2020).

16. Qin, P., Agerbo, E. & Mortensen, P. B. Suicide risk in relation to family history of completed suicide and psychiatric disorders: a nested case-control study based on longitudinal registers. *The Lancet* vol. 360 1126–1130 (2002).

17. Chesney, E., Goodwin, G. M. & Fazel, S. Risks of all-cause and suicide mortality in mental disorders: a meta-review. *World Psychiatry* **13**, 153–160 (2014).

18. Poorolajal, J. & Darvishi, N. Smoking and Suicide: A Meta-Analysis. *PLoS One* **11**, e0156348 (2016).

19. Orri, M. *et al.* A genetically informed study on the association of cannabis, alcohol, and tobacco smoking with suicide attempt. *Molecular Psychiatry* (2020) doi:10.1038/s41380-020-0785-6.

20. Harrison, R., Munafò, M. R., Davey Smith, G. & Wootton, R. E. Examining the effect of smoking on suicidal ideation and attempts: triangulation of epidemiological approaches. *Br. J. Psychiatry* 1–7 (2020).

21. McMahon, K. *et al.* Childhood maltreatment and impulsivity as predictors of interpersonal violence, self-injury and suicide attempts: A national study. *Psychiatry Res.* **269**, 386–393 (2018).

22. Calati, R. *et al.* Suicidal thoughts and behaviors and social isolation: A narrative review of the literature. *J. Affect. Disord.* **245**, 653–667 (2019).

23. Liu, R. T. & Miller, I. Life events and suicidal ideation and behavior: a systematic review. *Clin. Psychol. Rev.* **34**, 181–192 (2014).

24. Voracek, M. & Loibl, L. M. Genetics of suicide: a systematic review of twin studies. *Wien. Klin. Wochenschr.* **119**, 463–475 (2007).

25. Brent, D. A. & Melhem, N. Familial transmission of suicidal behavior. *Psychiatr. Clin. North Am.* **31**, 157–177 (2008).

26. Fu, Q. *et al.* A twin study of genetic and environmental influences on suicidality in men. *Psychol. Med.* **32**, (2002).

27. Erlangsen, A. *et al.* Genetics of suicide attempts in individuals with and without mental disorders: a population-based genome-wide association study. *Mol. Psychiatry* (2018) doi:10.1038/s41380-018-0218-y.

28. Ruderfer, D. M. *et al.* Significant shared heritability underlies suicide attempt and clinically predicted probability of attempting suicide. *Mol. Psychiatry* (2019) doi:10.1038/s41380-018-0326-8.

29. Strawbridge, R. J. *et al.* Identification of novel genome-wide associations for suicidality in UK Biobank, genetic correlation with psychiatric disorders and polygenic association with completed suicide. *EBioMedicine* **41**, 517–525 (2019).

30. Docherty, A. R. *et al.* Genome-wide association study of suicide death and polygenic prediction of clinical antecedents. doi:10.1101/234674.

31. Mullins, N. *et al.* GWAS of Suicide Attempt in Psychiatric Disorders and Association With Major Depression Polygenic Risk Scores. *Am. J. Psychiatry* **176**, 651–660 (2019).

32. Kessler, R. C. & Bromet, E. J. The epidemiology of depression across cultures. *Annu. Rev. Public Health* **34**, 119–138 (2013).

33. Posner, K., Oquendo, M. A., Gould, M., Stanley, B. & Davies, M. Columbia Classification Algorithm of Suicide Assessment (C-CASA): Classification of Suicidal Events in the FDA's Pediatric Suicidal Risk Analysis of Antidepressants. *American Journal of Psychiatry* vol. 164 1035–1043 (2007).

34. Bulik-Sullivan, B. K. *et al.* LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat. Genet.* **47**, 291–295 (2015).

35. Willer, C. J., Li, Y. & Abecasis, G. R. METAL: fast and efficient meta-analysis of genomewide association scans. *Bioinformatics* **26**, 2190–2191 (2010).

36. Lam, M. *et al.* RICOPILI: Rapid Imputation for COnsortias PIpeLIne. *Bioinformatics* **36**, 930–933 (2020).

37. McCarthy, S. *et al.* A reference panel of 64,976 haplotypes for genotype imputation. *Nat. Genet.* **48**, 1279–1283 (2016).

38. Zhu, Z. *et al.* Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat. Commun.* **9**, 224 (2018).

39. Yang, J., Lee, S. H., Goddard, M. E. & Visscher, P. M. GCTA: a tool for genome-wide complex trait analysis. *Am. J. Hum. Genet.* **88**, 76–82 (2011).

40. Bachmann, S. Epidemiology of Suicide and the Psychiatric Perspective. *Int. J. Environ. Res. Public Health* **15**, (2018).

41. Wray, N. R. *et al.* Genome-wide association analyses identify 44 risk variants and refine the genetic

architecture of major depression. *Nat. Genet.* **50**, 668–681 (2018).

42. Consortium, T. 1000 G. P. & The 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature* vol. 526 68–74 (2015).

43. Stahl, E. A. *et al.* Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat. Genet.* **51**, 793–803 (2019).

44. Pardiñas, A. F. *et al.* Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat. Genet.* **50**, 381–389 (2018).

45. Hübel, C. *et al.* Genomics of body fat percentage may contribute to sex bias in anorexia nervosa. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **180**, 428–438 (2019).

46. Zheng, J. *et al.* LD Hub: a centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. *Bioinformatics* vol. 33 272–279 (2017).

47. Watanabe, K., Taskesen, E., van Bochoven, A. & Posthuma, D. Functional mapping and annotation of genetic associations with FUMA. *Nature Communications* vol. 8 (2017).

48. de Leeuw, C. A., Mooij, J. M., Heskes, T. & Posthuma, D. MAGMA: generalized gene-set analysis of GWAS data. *PLoS Comput. Biol.* **11**, e1004219 (2015).

49. Aguet, F. *et al.* The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Genetics* 1860 (2019).

50. Gusev, A. *et al.* Integrative approaches for large-scale transcriptome-wide association studies. *Nat. Genet.* **48**, 245–252 (2016).

51. Gandal, M. J. *et al.* Transcriptome-wide isoform-level dysregulation in ASD, schizophrenia, and bipolar disorder. *Science* **362**, (2018).

52. Ge, T., Chen, C.-Y., Ni, Y., Feng, Y.-C. A. & Smoller, J. W. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat. Commun.* **10**, 1776 (2019).

53. Chang, C. C. *et al.* Second-generation PLINK: rising to the challenge of larger and richer datasets. *Gigascience* **4**, 7 (2015).

54. Lee, S. H., Goddard, M. E., Wray, N. R. & Visscher, P. M. A Better Coefficient of Determination for Genetic Profile Analysis. *Genetic Epidemiology* vol. 36 214–224 (2012).

55. Pickrell, J. K. *et al.* Detection and interpretation of shared genetic influences on 42 human traits. *Nat. Genet.* **48**, 709–717 (2016).

56. Karlsson Linnér, R. *et al.* Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. *Nat. Genet.* **51**, 245–257 (2019).

57. Wootton, R. E. *et al.* Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. *Psychol. Med.* 1–9 (2019).

58. Pickrell, J. K. Joint analysis of functional genomic data and genome-wide association studies of 18 human traits. *Am. J. Hum. Genet.* **94**, 559–573 (2014).

59. Mountjoy, E. *et al.* Open Targets Genetics: An open approach to systematically prioritize causal variants and genes at all published human GWAS trait-associated loci. doi:10.1101/2020.09.16.299271.

60. Campos, A. I. *et al.* Genetic aetiology of self-harm ideation and behaviour. *Sci. Rep.* **10**, 9713 (2020).

61. GTEx Consortium *et al.* Genetic effects on gene expression across human tissues. *Nature* **550**, 204–213 (2017).

62. Min, J. L. *et al.* Genomic and phenomic insights from an atlas of genetic effects on DNA methylation. *Preprint at medRxiv* 2020.09.01.20180406 (2020).

63. Jansen, P. R. *et al.* Genome-wide analysis of insomnia in 1,331,010 individuals identifies new risk loci and functional pathways. *Nat. Genet.* **51**, 394–403 (2019).

64. Bergen, S. E. *et al.* Genome-wide association study in a Swedish population yields support for

greater CNV and MHC involvement in schizophrenia compared with bipolar disorder. *Molecular Psychiatry* vol. 17 880–886 (2012).

65. Brainstorm Consortium *et al.* Analysis of shared heritability in common disorders of the brain. *Science* **360**, (2018).

66. Cross-Disorder Group of the Psychiatric Genomics Consortium. Electronic address: plee0@mgh.harvard.edu & Cross-Disorder Group of the Psychiatric Genomics Consortium. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. *Cell* **179**, 1469–1482.e11 (2019).

67. Agerbo, E., Nordentoft, M. & Mortensen, P. B. Familial, psychiatric, and socioeconomic risk factors for suicide in young people: nested case-control study. *BMJ* **325**, 74 (2002).

68. Qin, P., Agerbo, E. & Mortensen, P. B. Suicide Risk in Relation to Socioeconomic, Demographic, Psychiatric, and Familial Factors: A National Register–Based Study of All Suicides in Denmark, 1981–1997. *American Journal of Psychiatry* vol. 160 765–772 (2003).

69. Lorant, V. *et al.* Socioeconomic inequalities in suicide in Europe: the widening gap. *Br. J. Psychiatry* **212**, 356–361 (2018).