Identifying Potential Causal Risk Factors for Self-Harm: A Polygenic Risk Scoring and Mendelian Randomisation Approach

Kai Xiang Lim,[1] Frühling Rijsdijk,[1] Saskia P. Hagenaars,[1]
Adam Socrates,[1] Shing Wan Choi,[1,2] Jonathan R.I. Coleman,[1] Kylie P. Glanville,[1]
Cathryn M. Lewis,[1] Jean-Baptiste Pingault[1,3]

Affiliations:

1. Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK.
2. Icahn School of Medicine at Mount Sinai, New York City, USA.
3. Division of Psychology and Language Sciences, University College London, UK.

Abstract

Background. Multiple individual vulnerabilities and traits are phenotypically associated with suicidal and non-suicidal self-harm. However, associations between these risk factors and self-harm are subject to confounding. We implemented genetically informed methods to better identify individual risk factors for self-harm.

Methods. Using genotype data and online Mental Health Questionnaire responses in the UK Biobank sample (N = 125,925), polygenic risk scores (PRS) were generated to index 24 plausible individual risk factors for self-harm in the following domains: mental health vulnerabilities, substance use phenotypes, cognitive traits, personality traits and physical traits. PRS were entered as predictors in binomial regression models to predict self-harm. Multinomial regressions were used to model suicidal and non-suicidal self-harm. To further probe the causal nature of these relationships, two-sample Mendelian Randomisation (MR) analyses were conducted for significant risk factors identified in PRS analyses.

Outcomes. Self-harm was predicted by PRS indexing six individual risk factors, which are major depressive disorder (MDD), attention deficit/hyperactivity disorder (ADHD), bipolar disorder, schizophrenia, alcohol dependence disorder (ALC) and lifetime cannabis use. Effect sizes ranged from β = 0.044 (95% CI: 0·016 to 0·152) for PRS for lifetime cannabis use, to β = 0.179 (95% CI: 0·152 to 0·207) for PRS for MDD. No systematic distinctions emerged between suicidal and non-suicidal self-harm. In follow-up MR analyses, MDD, ADHD and schizophrenia emerged as plausible causal risk factors for self-harm.

Interpretation. Among a range of potential risk factors leading to self-harm, core predictors were found among psychiatric disorders. In addition to MDD, liabilities for schizophrenia and ADHD increased the risk for self-harm. Detection and treatment of core symptoms of these conditions, such as psychotic or impulsivity symptoms, may benefit self-harming patients.

Funding. Lim is funded by King's International Postgraduate Research Scholarship. Dr Pingault is funded by grant MQ16IP16 from MQ: Transforming Mental Health. Dr Coleman is supported by the UK National Institute of Health Research Maudsley Biomedical Research Centre. MRC grant MR/N015746/1 to CML and PFO'R. Dr Hagenaars is funded by the Medical Research Council (MR/S0151132). Kylie P. Glanville is funded by the UK Medical Research Council (PhD studentship; grant MR/N015746/1). This paper represents independent research part-funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Research in Context

Evidence before this study

A search was conducted on PubMed for literature from inception until 1st May 2019 using terms related to suicidal self-harm (SSH) and non-suicidal self-harm (NSSH), as well as polygenic risk scores (PRS), ("self-harm"[All Fields] OR "self-injurious"[All Fields] OR "self-mutilation"[All Fields] OR "suicide"[All Fields]) AND ("polygenic"[All Fields] OR "multifactorial inheritance"[All Fields]). Similar search was done for Mendelian Randomisation (MR), replacing "multifactorial inheritance" and "polygenic" with "Mendelian Randomisation/Randomization". Evidence was included only if the study had used PRS or MR method to predict self-harm phenotypes using risk factors of self-harm. Ten papers for PRS and no paper for MR were identified.

There were mixed results for PRS studies. PRS for MDD predicted SSH in two studies but not in another two studies. PRS for depressive symptoms predicted SSH but not NSSH. PRS for schizophrenia predicted SSH in one but not in another two studies. PRS for bipolar disorder predicted SSH in one study but did not predict SSH nor NSSH in another two studies.

Added value of this study

By using a large population-based sample, we systematically studied individual vulnerabilities and traits that can potentially lead to self-harm, including mental health vulnerabilities, substance use phenotypes, cognitive traits, personality traits and physical traits, summing up to 24 PRS as genetic proxies for 24 risk factors. We conducted MR to strengthen causal inference. We further distinguished non-suicidal self-harm (NSSH) and suicidal self-harm (SSH).

Apart from PRS for schizophrenia, MDD and bipolar disorder, novel PRS were also identified to be associated with self-harm, which are PRS for attention-deficit hyperactivity disorder (ADHD), cannabis use and alcohol dependence. A larger sample size allowed us to confirm positive findings from the previously mixed literature regarding the associations between PRS for MDD, bipolar disorder, and schizophrenia with self-harm. Multivariate analyses and MR analyses strengthened the evidence implicating MDD, ADHD and schizophrenia as plausible causal risk factors for self-harm.

Implications of all the available evidence

Among the 24 risk factors considered, plausible causal risk factors for self-harm were identified among psychiatric conditions. Using PRS and MR methods and a number of complementary analyses provided higher confidence to infer causality and nuanced insights into the aetiology of self-harm. From a clinical perspective, detection and treatment of core symptoms of these conditions, such as psychotic or impulsivity symptoms, may prevent individuals from self-harming.

Introduction

Self-harm is a complex trait that refers to any act of self-injury and self-poisoning carried out by an individual, regardless of intention or motivation.[1] Being a broadly defined term, it can be further categorised into suicidal self-harm (SSH) and non-suicidal self-harm (NSSH), i.e. with or without intention of suicide. According to a meta-analysis, the cross-national prevalence rate for NSSH peaks during adolescence (17.3%), and decreases among adults (5.5%).[2] For SSH, the cross-national prevalence rate is also the highest among adolescents (9.7%)[3] and drops among adults (2.7%).[4] Recently, both SSH and NSSH were included in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as separate conditions for further study.[5] The distinction between SSH and NSSH may facilitate investigations of the aetiology and heterogeneity of self-harm.

A range of individual vulnerabilities and traits can potentially lead to self-harm, such as psychiatric illnesses,[6] substance use,[7–9] cognitive abilities,[10] personality traits[11] and physical traits.[12] Although associations between these risk factors and self-harm have been shown in numerous observational studies, causality is difficult to infer reliably. Genetically informed designs can help in strengthening causal inference.[13] A polygenic risk score (PRS) is a single individual-level score computed in a given trait, weighted using summary statistics from an independent genome-wide association study (GWAS) for that particular trait. A PRS for an individual risk factor (e.g. schizophrenia) can be regarded as a genetic proxy for this risk factor.[14] To illustrate, if schizophrenia is causally related to self-harm, a PRS for schizophrenia should also be associated with self-harm. A significant association between the PRS for schizophrenia and self-harm can be regarded as an initial indication of a possible causal relationship between the two. The PRS approach can be construed as a first step in a series of genetically informed methods to investigate the aetiology of complex phenotypes, with follow-up steps including Mendelian Randomization (MR) discussed below.[14–16]

In previous studies, a PRS for major depressive disorder (MDD) was found to be associated with SSH in two clinical samples[17,18] and one non-clinical sample.[19] However, this was not replicated in a family-based sample.[20] A PRS for depressive symptoms predicted SSH but not NSSH in a twin sample.[21] On the other hand, a PRS for schizophrenia was positively associated with SSH among offspring of suicide attempters,[20] and a population sample,[22] but not in another clinical sample.[23] A PRS for bipolar disorder predicted SSH in one clinical sample[24] but did not predict SSH nor NSSH among offspring of suicide attempters,[20] and relatives of bipolar disorder patients.[25]

The aforementioned PRS studies with mixed results were limited in several ways. Firstly, these studies focused on PRS for psychiatric disorders or psychiatric symptoms, and did not include potential risk factors from other domains, such as substance use[7–9] , cognitive abilities,[10] personality traits[11] and physical traits.[12] Secondly, with two exceptions,[21,25] none of the studies had investigated SSH and NSSH simultaneously. Thirdly, these studies have a mixture of clinical and non-clinical samples with varying sample sizes ranging from 224 individuals[23] to 10,408 individuals,[18] making any comparison difficult. In addition, none of these studies have implemented multivariate analyses including multiple PRS to better estimate their unique effect.

A caveat of the PRS method is its proneness to unmediated (or horizontal) pleiotropy, arising from the inclusion of many thousands of genetic variants.[14] Unmediated pleiotropy exists when a genetic variant associated with an exposure causes the outcome through an alternative pathway, instead of via the exposure. Unmediated pleiotropy can generate associations between PRS and outcome in the absence of a causal relationship between the risk factors indexed by the PRS, and the outcome. Mendelian Randomisation (MR) can more stringently address unmediated pleiotropy and further strengthen causal inference. In MR, individual genetic variants associated with an exposure of interest are used as instrumental variables to infer causality between exposure and outcome. A number of complementary analyses, further detailed in the methods section, can be implemented to account for pleiotropy.[16] To date, there is no published MR study which focuses on any risk factor of self-harm.

The current study will address the aforementioned limitations by systematically using 24 PRS as proxies for risk factors from different domains to predict both NSSH and SSH, using a population-based sample of 125,925 individuals. We will conduct follow-up MR analyses to strengthen causal inference.

Methods

Participants

The participants of the current study are a subset of the UK Biobank (http://www.ukbiobank.ac.uk). A total of 157,358 participants completed an online mental health questionnaire (MHQ) in a period from July 2016 to July 2017, which included questions regarding their lifetime symptoms of mental disorders.[26] The participants were also genotyped. After the quality control (QC) process (see genotyping and QC details in supplementary materials), the final sample size was 125,925 individuals (56.2% females). Their ages ranged from 48 to 82 years, with a mean of 65.88 (*SD* = 7.69) years.

UK Biobank received ethical approval from the Research Ethics Committee (REC reference 11/NW/0382). The current study was conducted under the UK Biobank application 18177. Data analysis was conducted from March 2018 to June 2019.

Defining self-harm phenotypes

To know whether the participants have ever-self-harmed, participants were asked "Have you deliberately harmed yourself, whether or not you meant to end your life?" To ascertain whether their self-harm episodes were NSSH or SSH, they were asked "Have you harmed yourself with the intention to end your life?". In both questions, responses of "Prefer not to answer" (0.43%) were recoded as missing values. A flowchart depicting exclusion of participants and the number of participants who answered each question is shown in Figure 1.

Statistical Analyses

All statistical analyses were conducted in Linux environment using R version 3.5.0.[27]

PRS analyses

PRS of UK Biobank participants were generated using PRSice-2[28] based on their genotype data and 24 publicly available summary data from GWAS (see Table 1) selected based on the following criteria. First, we selected GWAS indexing individual vulnerabilities and traits that can potentially increase the risk of self-harm, including mental health vulnerabilities (e.g. MDD),[29] cognitive abilities (e.g. education attainment),[30] personality traits (e.g.

neuroticism),[31] substance use phenotypes (e.g. cannabis use),[32] and physical traits (e.g. BMI).[12] Second, we selected GWAS which only included participants of European ancestry and did not include UK Biobank participants (to avoid overlapping between discovery sample size and target sample). Finally, we excluded GWAS with effective sample sizes less than N = 15,000 to limit the use of underpowered PRS.

Each participant had 24 PRS, which were each calculated as the sum of alleles associated with their respective phenotypes, weighted by their effect sizes with *p*-values less than a threshold $p_T < 0.3$ (selecting and reporting results from a single threshold allowed us to limit multiple testing, as done in previous PRS studies).[22,33] Clumping was used to remove SNPs in linkage equilibrium ($r^2 < 0.1$ within a 250 kb window). All PRS in the final analytical sample were standardised.

Single PRS Binomial Logistic Regression

For each PRS, a binomial logistic regression was conducted to test whether it predicted self-harm (i.e. “Self-harmed” versus “Never self-harmed”).

Multiple PRS Binomial Logistic Regression

All PRS significantly associated with self-harm in single PRS binomial logistic regressions were then jointly modelled in a multivariate binomial logistic regression model to assess their unique effects.

Multinomial Logistic Regressions

To investigate whether each PRS differentially predicted NSSH versus SSH, we fitted a series of multinomial logistic regression models. We first compared each of the NSSH and SSH groups to the never self-harmed group (i.e. "Never self-harmed" as the reference group). We then directly compared NSSH and SSH by testing a model with "NSSH" as the reference group.

Covariates and multiple testing

All regression models were controlled for sex, age and population stratification (by including assessment centre, genotyping batch and the first 6 principal components as covariates in the models). To control for multiple testing in single PRS binomial and multinomial regressions, we employed the false discovery rate (FDR) method[34] which controls the expected proportion of false positives among the rejected hypotheses. We used $q < .05$ as the significance threshold.

MR analyses

All MR analyses were conducted using R package TwoSampleMR.[35] Risk factors for which their PRS significantly predicted self-harm were selected for follow-up MR analyses. For self-harm in UK Biobank sample as the outcome for MR analyses, we obtained GWAS summary statistics from Neale Lab (http://www.nealelab.is/uk-biobank). SNPs of the exposures which passed the p-value threshold of $p < 5E-5$ were selected as instrumental variables for MR analyses. A liberal threshold was used to ensure that enough variants were available for all risk factors, including those with few genome-wide significant SNPs (e.g. ADHD). The strategy entails potential weak instrument bias. In two-sample MR, the resulting bias is towards the null, making estimates more conservative (see below how this was dealt with).[36] Clumping of SNPs with $r^2 < .001$ within 250 kb was applied. SNPs in exposures and outcomes were harmonized by flipping alleles where possible, and we use allele frequencies to infer strands of ambiguous SNPs. Non-inferable SNPs with minor allele frequency > 0.42 were discarded.

We selected four MR methods which have different strengths and limitations. We conducted univariable MR using:

(i) Inverse variance weighted (IVW) method, which is the most powerful method but cannot account for directional pleiotropy;[37]

(ii) Robust Adjusted Profile Score (RAPS) method, which is used to account for the selection of weak instruments;[33]

(iii) Weighted median method, as it is more robust to directional pleiotropy than IVW and is more robust to individual genetic variants with outlying causal estimates than IVW and MR-Egger;[38] and

(iv) MR-Egger regression method, whereby significance of its intercept term can inform on the presence of directional pleiotropy.[39]

In addition, MR Steiger filtering[40] was implemented to address the possibility of reverse causation (i.e. self-harm causing the putative risk factor). For each SNP, we expect that the effect size for the association with the exposure should be larger than the effect size for the association with the outcome. This is because the effect on the outcome is hypothesised to be indirect through the exposure. As such, all SNPs for which the effect size of the association with the outcome was larger than the one with the exposure were filtered out before reimplementing MR. Finally, similar to PRS analyses, exposures which were significant in univariable MR were assessed for their independent effect in a multivariable MR model using the IVW method.

For PRS analyses, we conducted further complementary analyses excluding cases with MDD and schizophrenia diagnoses to investigate the effect of genetic liability on self-harm with the influence of diagnoses excluded. We also calculated risk ratios for medicated and non-medicated cases compared to those with median PRS in the general population (see supplementary materials for definitions of cases and medication). We created a quantile plot separating the participants into three groups: general population (in 20 quantiles), medicated cases and unmedicated cases, and calculated the risk ratios of these groups for self-harm relative to the group in the population with median PRS.

Results

Descriptive statistics

Figure 1 shows the number of participants who: never self-harmed, self-harmed, engaged in SSH, and engaged in NSSH. Table 2 shows the gender proportion, and mean age of each subgroup.

PRS analyses

Single PRS binomial logistic regression

Table 1 and Figure 2 show results from 24 single PRS binomial logistic regression tests, using each PRS as a predictor variable. Out of the 24 PRS, 10 PRS were significant predictors of self-harm at the nominal level ($p < 0.05$). After applying FDR correction, 6 PRS had *q*-value < .05. In order of decreasing effect sizes, they are PRS for: MDD, schizophrenia, ADHD, bipolar disorder, alcohol dependence disorder (ALC), and lifetime cannabis use, with effect sizes ranging from β = 0·179 (95% CI: 0·152 to 0·207) for MDD, to β = 0·044 (95% CI: 0·016 to 0·072) for lifetime cannabis use. Figure S3 shows the pseudo R^2 plots of these 6 PRS in accounting for the variance in self-harm.

Multiple PRS binomial logistic regression

In the multiple PRS model, all PRS except the PRS for ALC had an independent effect of self-harm as shown in Table 1 and Figure 2. By controlling for the effects of other PRS, effect sizes of these PRS have diminished slightly compared to those in single PRS binomial logistic regression, ranging from β = 0·144 (95% CI: 0·115 to 0·173) for MDD to β = 0·031 (95% CI: 0·002 to 0·060) for bipolar disorder. These PRS were weakly correlated, ranging from r = 0.01 (between bipolar disorder and ADHD) to r = 0.22 (between schizophrenia and bipolar disorder; see Table S3 for all correlations), suggesting that multicollinearity was not an issue.

Single PRS multinomial logistic regression

Table S1 shows results from 24 multinomial logistic regression tests, using PRS as predictor variable for three possible outcomes: “Never self-harmed”, “NSSH” and “SSH”. When “Never self-harmed” was used as the reference group, PRS for bipolar disorder, lifetime cannabis use and extreme BMI predicted SSH but not NSSH, with q < .05. However, when “NSSH” was set as the reference group in order to directly compare NSSH versus SSH, none of the PRS significantly distinguished between NSSH versus SSH.

MR analyses

Table 3 shows the results from MR analyses. ADHD, ALC, bipolar disorder, lifetime cannabis use, MDD and schizophrenia were exposures in 6 separate univariable MR analyses, with self-harm as the outcome. Out of these 6 exposures, MDD, ADHD and schizophrenia had MR estimates with *p*-values < .05. For other exposures, none of their MR estimates had *p* < .05.

For MDD, despite having the strongest IVW (β =0·008, 95% CI: 0·005 to 0·011, p = 2·84E-08), MR RAPS (β =0·008, 95% CI: 0·005 to 0·011, p = 1·24E-07), and weighted median (β = 0·006, 95% CI: 0·001 to 0·011, p = 0·013) estimates among the three exposures, the MR Egger estimate was not significant. On the other hand, all MR estimates for ADHD and schizophrenia were significant.

The significance of intercept terms in MR-Egger test indicates the presence of pleiotropy. Out of the 6 exposures in MR-Egger test, none of the intercept terms were significant, except for MDD (p = 0·023). MR Steiger directionality tests could only be applied to test the direction of causality between ADHD, MDD and schizophrenia with self-harm because the summary statistics for other exposures did not contain information about allele frequencies, which are needed for the test. MR Steiger directionality test showed that all SNPs of MDD, schizophrenia and ADHD are more predictive of the respective exposures than self-harm, suggesting that reverse causation unlikely explained our findings.

When ADHD, MDD and schizophrenia were included as exposures in multivariable IVW MR analysis, only MDD (β = 0.011, 95% CI: 0·007 to 0·015, p = 1·04E-12) and schizophrenia (β = 0·002, 95% CI: 4·00E-05 to 0·004, p = 0·002) remained as independent predictors of self-harm. Due to the potential presence of pleiotropy between MDD and self-harm, another multivariable IVW MR model was conducted with only ADHD and schizophrenia as exposures. Both ADHD (β = 0.003, 95% CI: 0.001 to 0.005, p = 2.21E-04) and schizophrenia (β = 0.003, 95% CI: 0.002 to 0.004, p = 7.60E-07) were significant predictors in this model.

In PRS complementary analyses which excluded cases, PRS for MDD and schizophrenia still predicted self-harm in a healthy, screened cohort, indicating that genetic liabilities can predict self-harm when influence of diagnoses is excluded (See Table S2). In the quantile plot, cases for schizophrenia and MDD appear to be at much larger risk for self-harm than the rest of the population. Medicated MDD cases were at higher risk of self-harm than non-medicated MDD cases, which was not the case for schizophrenia (See Figure 3).

Discussion

To our knowledge, this is the first study using multiple PRS as genetic proxies to systematically investigate a range of individual vulnerabilities and traits as risk factors for self-harm in a large population sample. In PRS analyses, we identified 6 risk factors (i.e. MDD, schizophrenia, ADHD, bipolar disorder, ALC, and lifetime cannabis use) which predicted self-harm. Five among six (except for ALC) remained significant in a multiple PRS regression. We found no evidence of differential prediction for SSH versus NSSH. In follow-up MR analyses, MDD, schizophrenia and ADHD emerged as plausible causal risk factors for self-harm, despite evidence of unmediated pleiotropy for MDD. We discuss in turn: (1) insights into the aetiology of self-harm, and (2) clinical implications.

Insights into the aetiology of self-harm

Results from our PRS methods corroborated previous observational findings where MDD,[6] schizophrenia,[41] ADHD,[42] bipolar disorder,[6] and ALC[8] were phenotypically associated with self-harm. Our results are also consistent with positive associations found in PRS studies for MDD,[17,19,43] schizophrenia,[20] and bipolar disorder[24]. Previous mixed findings for these PRS may have stemmed from lack of power, as sample sizes for those studies varied widely. The current study adds lifetime cannabis use, ADHD, and ALC as novel PRS associated with self-harm. However, when controlling for other PRS, the PRS for ALC did not significantly predict self-harm. This finding may suggest that the genetic liability for ALC does not independently predict self-harm when the effect of genetic liability for MDD, bipolar disorder, schizophrenia, ADHD and lifetime cannabis are accounted for. For example, ALC may be a marker for a true predictor such as impulsivity which is more efficiently captured in the PRS for ADHD.[44] . Alternatively, null findings for ALC can also plausibly be due to a lack of power compared to other polygenic scores. Hence, we cannot completely rule out that the PRS for ALC has an independent effect on self-harm and the corresponding causal effect of ALC on self-harm.

Most of the PRS which predicted self-harm in the current study relate to psychiatric conditions, which confirms the prominence of psychiatric conditions in the aetiology of self-harm.[45] Beyond psychiatric conditions, cognitive traits, physical traits, and personality traits were not found to be associated with self-harm using PRS approach, although previous observational findings found significant phenotypic associations for these three domains.[10–12] The absence of significant findings in this case is unlikely to be solely due to lack of power, given that GWAS for some of these traits are more powerful than GWAS for psychiatric conditions (e.g. BMI and education attainment). These findings suggest that these traits and vulnerabilities are unlikely to have (strong) causal effects on self-harm.

Our MR analyses provided further support for the role of MDD, ADHD, and schizophrenia in the aetiology of self-harm. An intriguing finding is the presence of significant pleiotropy in the case of MDD. Rather than signifying that MDD does not have a causal effect on self-harm, this may reflect a possible measurement issue. Indeed, one of the diagnostic criteria for MDD is related to having suicidal thoughts and attempts, which could artificially introduce a pleiotropic effect.[5] To deal with this issue, future studies may rely on a GWAS for MDD excluding the diagnostic criteria related to suicidal thoughts and attempts. This might also explain why, in multivariate MR, the effect of ADHD was no longer significant – as we partially controlled for self-harm – whereas it was significant when only considering ADHD and schizophrenia.

The current study found mixed results for whether there are distinct aetiologies for SSH and NSSH. Most PRS which predicted self-harm also predicted both SSH and NSSH, except bipolar disorder, lifetime cannabis use and extreme BMI, which only predicted SSH but not NSSH from those who never self-harmed. However, in a formal test comparing NSSH and SSH, the estimates of these three risk factors were not significantly different between NSSH and SSH. Hence, our findings do not provide evidence for marked differences in aetiology between SSH and NSSH.

Clinical implications

The current study suggests that individual vulnerabilities and traits underlying self-harm most likely relate to psychiatric conditions such as MDD and schizophrenia, rather than to other domains such as personality traits. Hence, treatments focusing on the core symptoms of these psychiatric conditions are important in preventing or addressing the risk of self-harm. Findings from PRS analyses suggest that genetic liabilities for these conditions increase the likelihood of self-harm even in those not clinically diagnosed. This may suggest that subthreshold symptoms of these core psychiatric conditions may increase the risk of self-harm. Clinicians may want to systematically test for such symptoms in self-harming patients. Future investigations may test whether drugs for such core conditions may be repurposed for treating self-harming patients, with either full blown or subthreshold conditions. For example, prescription of methylphenidate for ADHD treatment was found to be associated with reduction of suicide attempt risk.[46] As a note of caution, treated schizophrenia cases were not at less risk of self-harm than non-treated patients whereas treated MDD patients were at substantial higher risk for self-harm. This could be due to treated patients having more severe symptoms than untreated patients, or it could be due to adverse effects of medication, in particular in the case of MDD where suicidality might be an adverse effect of antidepressant treatment.[47]

Limitations

In order to avoid the overlapping of discovery and target sample, we excluded GWAS which contain UK Biobank sample, resulting in selecting older GWAS for generating PRS in some cases. This might have led to non-significant findings due to lack of power. The results should be generalised with caution because UK Biobank is not representative of the UK population as they are more educated, older, wealthier, and healthier.[48] The questions asked in MHQ were retrospective and their formulation led to an exclusive dichotomy between NSSH or SSH, whereby some might have engaged in both NSSH and SSH at different times.

Conclusion

Among 24 PRS used as genetic proxies for vulnerabilities and traits possibly associated with self-harm, we found that PRS for MDD, schizophrenia, ADHD, bipolar disorder, ALC and cannabis were statistically significant. After a series of complementary analyses to further strengthen the causal inference, schizophrenia survived as the most plausible causal risk factor, followed by MDD and ADHD. Detection and treatment of core symptoms of these conditions, such as psychotic or impulsivity symptoms, may benefit self-harming patients.

References

1 Hawton K, Harriss L, Hall S, Simkin S, Bale E, Bond A. Deliberate self-harm in Oxford, 1990-2000: A time of change in patient characteristics. *Psychol Med* 2003; **33**: 987–95.

2 Swannell S V., Martin GE, Page A, Hasking P, St John NJ. Prevalence of nonsuicidal self-injury in nonclinical samples: Systematic review, meta-analysis and meta-regression. *Suicide Life-Threatening Behav* 2014; **44**: 273–303.

3 Evans E, Hawton K, Rodham K, Psychol C, Deeks J. The Prevalence of Suicidal Phenomena in Adolescents: A Systematic Review of Population-Based Studies. *Suicide Life-Threatening Behav* 2005; **35**: 239–50.

4 Nock MK, Borges G, Bromet EJ, *et al.* Cross-national prevalence and risk factors for suicidal ideation, plans and attempts. *Br J Psychiatry* 2008; **192**: 98–105.

5 American Psychiatric Association. Diagnostic and statistical manual of mental disorders (DSM-5®). Washington, DC: Author, 2013.

6 Vaughn MG, Salas-Wright CP, DeLisi M, Larson M. Deliberate self-harm and the nexus of violence, victimization, and mental health problems in the United States. *Psychiatry Res* 2015; **225**: 588–95.

7 Borges G, Bagge CL, Orozco R. A literature review and meta-analyses of cannabis use and suicidality. *J Affect Disord* 2016. DOI:10.1016/j.jad.2016.02.007.

8 Darvishi N, Farhadi M, Haghtalab T, Poorolajal J. Alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: A meta-analysis. *PLoS One* 2015; **10**: 1–14.

9 Evins AE, Korhonen T, Kinnunen TH, Kaprio J. Prospective association between

tobacco smoking and death by suicide: A competing risks hazard analysis in a large twin cohort with 35-year follow-up. *Psychol Med* 2017; **47**: 2143–54.

10 Rehkopf DH, Buka SL. The association between suicide and the socio-economic characteristics of geographical areas: A systematic review. *Psychol Med* 2006; **36**: 145–57.

11 Brezo J, Paris J, Turecki G. Personality traits as correlates of suicidal ideation, suicide attempts, and suicide completions: A systematic review. *Acta Psychiatr Scand* 2006; **113**: 180–206.

12 Perera S, Eisen RB, Dennis BB, *et al.* Body Mass Index Is an Important Predictor for Suicide: Results from a Systematic Review and Meta-Analysis. *Suicide Life-Threatening Behav* 2016; **46**: 697–736.

13 Pingault JB, O'Reilly PF, Schoeler T, Ploubidis GB, Rijsdijk F, Dudbridge F. Using genetic data to strengthen causal inference in observational research. Nat. Rev. Genet. 2018; **19**: 566–80.

14 Gage SH, Davey Smith G, Ware JJ, Flint J, Munafò MR. G = E: What GWAS Can Tell Us about the Environment. *PLoS Genet* 2016; **12**: 1–13.

15 Pingault J-B, Cecil C, Murray J, Munafo M, Viding E. Causal inference in psychopathology: A systematic review of Mendelian randomisation studies aiming to identify environmental risk factors for psychopathology. 2016.

16 Pingault J-B, O'Reilly PF, Schoeler T, Ploubidis GB, Rijsdijk F, Dudbridge F. Using genetic data to strengthen causal inference in observational research. *Nat Rev Genet* 2018; : 1.

17 Mullins N, Perroud N, Uher R, *et al.* Genetic relationships between suicide attempts,

suicidal ideation and major psychiatric disorders: A genome-wide association and polygenic scoring study. *Am J Med Genet Part B Neuropsychiatr Genet* 2014; **165**: 428–37.

18 Mullins N, Bigdeli TB, Børglum AD, *et al.* GWAS of Suicide Attempt in Psychiatric Disorders and Association With Major Depression Polygenic Risk Scores. *Am J Psychiatry* 2019; : appi.ajp.2019.1.

19 Levey DF, Polimanti R, Cheng Z, *et al.* Genetic associations with suicide attempt severity and genetic overlap with major depression. *Transl Psychiatry* 2019; **9**: 22.

20 Sokolowski M, Wasserman J, Wasserman D. Polygenic associations of neurodevelopmental genes in suicide attempt. *Mol Psychiatry* 2016; **21**: 1381–90.

21 Maciejewski DF, Renteria ME, Abdellaoui A, *et al.* The Association of Genetic Predisposition to Depressive Symptoms with Non-suicidal and Suicidal Self-Injuries. *Behav Genet* 2017; **47**: 3–10.

22 Laursen TM, Trabjerg BB, Mors O, *et al.* Association of the polygenic risk score for schizophrenia with mortality and suicidal behavior - A Danish population-based study. *Schizophr Res* 2017; **184**: 122–7.

23 Bani-Fatemi A, Tasmim S, Wang KZ, Warsh J, Sibille E, De Luca V. No interaction between polygenic scores and childhood trauma in predicting suicide attempt in schizophrenia. *Prog Neuro-Psychopharmacology Biol Psychiatry* 2019; **89**: 169–73.

24 Wiste A, Robinson EB, Milaneschi Y, *et al.* Bipolar polygenic loading and bipolar spectrum features in major depressive disorder. *Bipolar Disord* 2014; **16**: 608–16.

25 Wilcox HC, Fullerton JM, Glowinski AL, *et al.* Traumatic Stress Interacts With Bipolar Disorder Genetic Risk to Increase Risk for Suicide Attempts. *J Am Acad Child*

Adolesc Psychiatry 2017; **56**: 1073–80.

26 Davis KAS, Coleman JRI, Adams M, *et al.* Mental health in UK Biobank: development, implementation and results from an online questionnaire completed by 157 366 participants. *BJPsych Open* 2018; **4**: 83–90.

27 R Core Team. R: A language and environment for statistical computing. 2017. https://www.r-project.org/.

28 Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. *Bioinformatics* 2015; **31**: 1466–8.

29 Wray NR, Ripke S, Mattheisen M, *et al.* Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 2018; **50**: 668–81.

30 Rietveld CA, Esko T, Davies G, *et al.* Common genetic variants associated with cognitive performance identified using the proxy-phenotype method. *Proc Natl Acad Sci U S A* 2014; **111**: 13790–4.

31 van den Berg SM, de Moor MHM, McGue M, *et al.* Harmonization of Neuroticism and Extraversion phenotypes across inventories and cohorts in the Genetics of Personality Consortium: an application of Item Response Theory. *Behav Genet* 2014; **44**: 295–313.

32 Stringer S, Minică CC, Verweij KJH, *et al.* Genome-wide association study of lifetime cannabis use based on a large meta-analytic sample of 32 330 subjects from the International Cannabis Consortium. *Transl Psychiatry* 2016; **6**: e769.

33 Hodgson K, Coleman JR, Hagenaars SP, *et al.* Cannabis use, depression and self-harm: phenotypic and genetic relationships. *bioRxiv* 2019; : 549899.

34 Benjamini Y, Hochberg Y. Controlling the False Discovery Rate : A Practical and Powerful Approach to Multiple Testing. *J R Stat Soc* 1995; **57**: 289–300.

35 Hemani G, Zheng J, Elsworth B, *et al.* The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018; **7**. DOI:10.7554/eLife.34408.

36 Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in Mendelian randomization studies. *Hum Mol Genet* 2018; **27**: R195–208.

37 Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet Epidemiol* 2013; **37**: 658–65.

38 Bowden J, Davey Smith G, Haycock PC, Burgess S. Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. *Genet Epidemiol* 2016; **40**: 304–14.

39 Bowden J, Smith GD, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015; **44**: 512.

40 Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. *PLoS Genet* 2017; **13**. DOI:10.1371/journal.pgen.1007081.

41 Angelakis I, Gooding P, Tarrier N, Panagioti M. Suicidality in obsessive compulsive disorder (OCD): A systematic review and meta-analysis. *Clin Psychol Rev* 2015; **39**: 1–15.

42 James A, Lai FH, Dahl C. Attention deficit hyperactivity disorder and suicide: a review of possible associations. *Acta Psychiatr Scand* 2004; **110**: 408–15.

43 Mullins N, Bigdeli TB, Borglum A, *et al.* Genome-wide association study of suicide

attempt in psychiatric disorders identifies association with major depression polygenic risk scores. *bioRxiv* 2018; : 416008.

44 Khemiri L, Kuja-Halkola R, Larsson H, Jayaram-Lindström N. Genetic overlap between impulsivity and alcohol dependence: a large-scale national twin study. *Psychol Med* 2016; **46**: 1091–102.

45 Franklin JC, Ribeiro JD, Fox KR, *et al.* Risk Factors for Suicidal Thoughts and Behaviors: A Meta-Analysis of 50 Years of Research. 2016. DOI:10.1037/bul0000084.

46 Liang SH-Y, Yang Y-H, Kuo T-Y, *et al.* Suicide risk reduction in youths with attention-deficit/hyperactivity disorder prescribed methylphenidate: A Taiwan nationwide population-based cohort study. *Res Dev Disabil* 2018; **72**: 96–105.

47 Braun C, Bschor T, Franklin J, Baethge C. Suicides and Suicide Attempts during Long-Term Treatment with Antidepressants: A Meta-Analysis of 29 Placebo-Controlled Studies Including 6,934 Patients with Major Depressive Disorder. *Psychother Psychosom* 2016; **85**: 171–9.

48 Fry A, Littlejohns TJ, Sudlow C, *et al.* Comparison of Sociodemographic and Health-Related Characteristics of UK Biobank Participants with Those of the General Population. *Am J Epidemiol* 2017; **186**: 1026–34.

49 Middeldorp CM, Hammerschlag AR, Ouwens KG, *et al.* A Genome-Wide Association Meta-Analysis of Attention-Deficit/Hyperactivity Disorder Symptoms in Population-Based Pediatric Cohorts. *J Am Acad Child Adolesc Psychiatry* 2016; **55**: 896-905.e6.

50 Demontis D, Walters RK, Martin J, *et al.* Discovery of the first genome-wide significant risk loci for attention deficit/hyperactivity disorder. *Nat Genet* 2019.

DOI:10.1038/s41588-018-0269-7.

51 Walters RK, Polimanti R, Johnson ECEO, *et al.* Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci* 2018; **21**: 1656–69.

52 Otowa T, Hek K, Lee M, *et al.* Meta-analysis of genome-wide association studies of anxiety disorders. *Mol Psychiatry* 2016; **21**: 1391–9.

53 Psychiatric GWAS Consortium Bipolar Disorder Working Group. Large-scale genome-wide association analysis of bipolar disorder identifies a new susceptibility locus near ODZ4. *Nat Genet* 2011; **43**: 977–83.

54 Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**: 421–7.

55 The Tobacco and Genetics Consortium. Genome-wide meta-analyses identify multiple loci associated with smoking behavior. *Nat Genet* 2010; **42**: 441–7.

56 Schumann G, Liu C, O'Reilly P, *et al.* KLB is associated with alcohol drinking, and its gene product β-Klotho is necessary for FGF21 regulation of alcohol preference. *Proc Natl Acad Sci* 2016; **113**: 14372–7.

57 de Moor MHM, Costa PT, Terracciano A, *et al.* Meta-analysis of genome-wide association studies for personality. *Mol Psychiatry* 2012; **17**: 337–49.

58 van den Berg SM, de Moor MHM, Verweij KJH, *et al.* Meta-analysis of Genome-Wide Association Studies for Extraversion: Findings from the Genetics of Personality Consortium. *Behav Genet* 2016; **46**: 170–82.

59 Pappa I, St Pourcain B, Benke K, *et al.* A genome-wide approach to children's aggressive behavior: The EAGLE consortium. *Am J Med Genet Part B Neuropsychiatr*

Genet 2016; **171**: 562–72.

60 Tielbeek JJ, Johansson A, Polderman TJC, *et al.* Genome-Wide Association Studies of a Broad Spectrum of Antisocial Behavior. *JAMA psychiatry* 2017; **74**: 1242–50.

61 van der Valk RJP, Kreiner-Møller E, Kooijman MN, *et al.* A novel common variant in DCST2 is associated with length in early life and height in adulthood. *Hum Mol Genet* 2015; **24**: 1155–68.

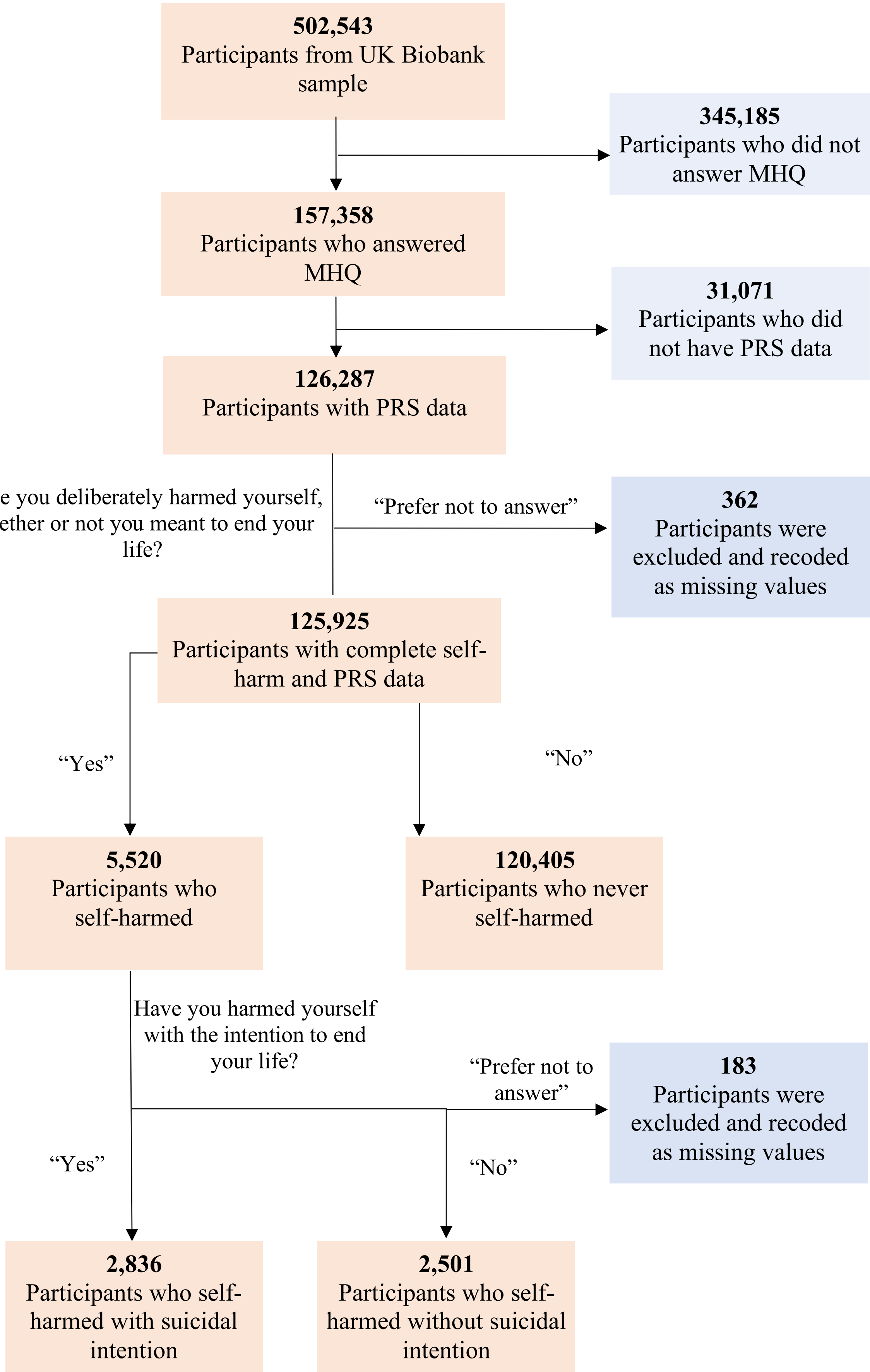
62 Horikoshi M, Yaghootkar H, Mook-Kanamori DO, *et al.* New loci associated with birth weight identify genetic links between intrauterine growth and adult height and metabolism. *Nat Genet* 2013; **45**: 76–82.

63 Wood AR, Esko T, Yang J, *et al.* Defining the role of common variation in the genomic and biological architecture of adult human height. *Nat Genet* 2014; **46**: 1173–86.

64 Berndt SI, Gustafsson S, Mägi R, *et al.* Genome-wide meta-analysis identifies 11 new loci for anthropometric traits and provides insights into genetic architecture. *Nat Genet* 2013; **45**: 501–12.

65 Locke AE, Kahali B, Berndt SI, *et al.* Genetic studies of body mass index yield new insights for obesity biology. *Nature* 2015; **518**: 197–206.

1 **Figures and Tables**



2 Figure 1. Flowchart showing the number of participants at each stage.

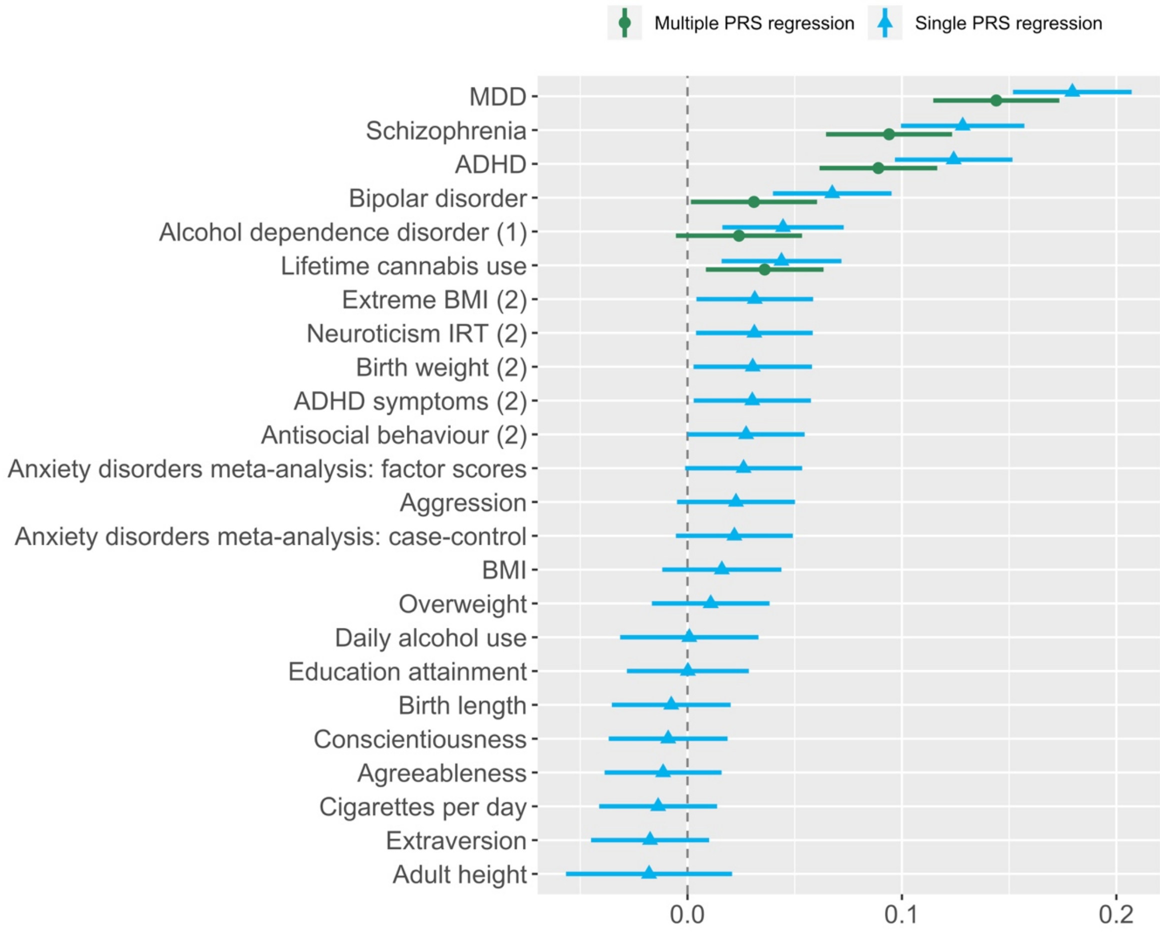


Figure 2. Estimates from single PRS regression and multiple PRS regression in decreasing effect sizes. (1) indicates not significant in multiple PRS regression. (2) indicates not significant after FDR correction.

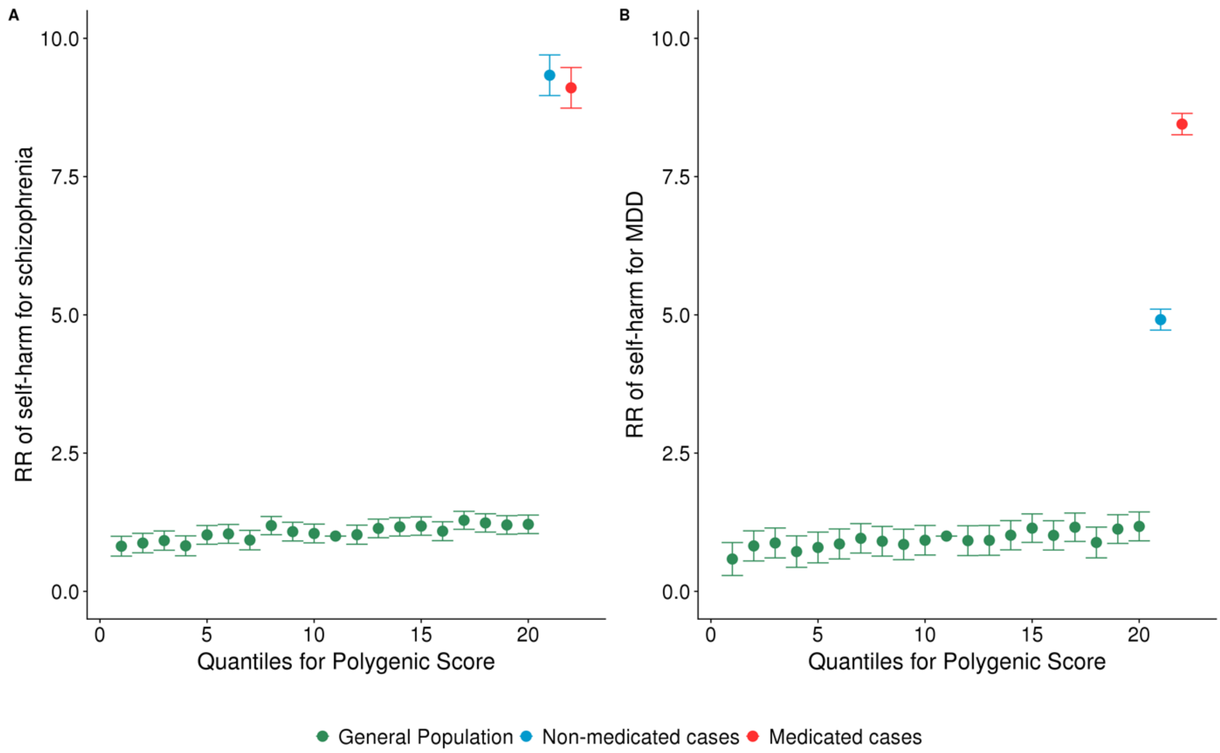


Figure 3. Relative risks of general population, non-medicated cases and medicated cases in self-harming compared to those with median PRS (11th quantile) in schizophrenia (A) and MDD (B). Out of 177 schizophrenia cases in the final analytical sample, 89 (50·3%) of them were medicated. Out of 34,680 MDD cases in the final analytical sample, 7,852 (22·6%) of them were medicated.

Table 1. Single and multiple PRS prediction of self-harm.

Traits/disorders	Discovery Sample size	Single PRS binomial model β	95% CI	p-value	q-value	Multiple PRS binomial model β	95% CI	p-value
Mental health vulnerabilities								
ADHD symptoms[49]	17,666	0·030	0·003, 0·058	0·030	0·074	-		-
ADHD[50]	49,017*	0·124	0·097, 0·152	6·69E-19	**8·02E-18**	0·089	0·062, 0·116	**4·24E-10**
Alcohol dependence disorder[51]	42,803*	0·045	0·016, 0·073	2·03E-03	**0·008**	0·024	-0·005, 0·053	0·101
Anxiety disorders meta-analysis: factor scores[52]	18,186	0·026	-0·001, 0·053	0·060	0·121	-		-
Anxiety disorders meta-analysis: case-control[52]	17,310*	0·022	-0·005, 0·049	0·116	0·199	-		-
Bipolar disorder[53]	16,544*	0·067	0·040, 0·095	1·74E-06	**1·05E-05**	0·031	0·002, 0·060	**0·033**
MDD[29]	124,331*	0·179	0·152, 0·207	5·52E-37	**1·33E-35**	0·144	0·115, 0·173	**3·99E-23**
Schizophrenia[54]	75,846*	0·128	0·100, 0·157	2·43E-18	**1·94E-17**	0·094	0·065, 0·123	**6·99E-10**
Substance use phenotypes								
Lifetime cannabis use[32]	31,933*	0·044	0·016, 0·072	0·002	**0·008**	0·036	0·009,0·063	**0·013**
Cigarettes per day[55]	38,181	-0·014	-0·041, 0·014	0·329	0·465	-	-	-
Daily alcohol use[56]	70,460	0·001	-0·031, 0·033	0·959	0·991	-	-	-
Cognitive trait								
Education attainment[30]	106,736	1·69E-04	-0·028, 0·029	0·991	0·991	-	-	-
Personality traits								
Conscientiousness[57]	17,375	-0·009	-0·037, 0·019	0·524	0·599	-	-	-
Extraversion[58]	63,030	-0·017	-0·045, 0·010	0·214	0·343	-	-	-

Neuroticism: Item Response Theory (IRT)[31]	63,661	0·031	0·004, 0·058	0·025	0·074	-	-	-
Agreeableness[57]	17,375	-0·011	-0·039, 0·016	0·414	0·523	-	-	-
Aggression[59]	18,988	0·023	-0·005, 0·050	0·107	0·198	-	-	-
Antisocial behaviour[60]	16,400	0·027	6·46E-05, 0·055	0·049	0·108	-	-	-
Physical traits								
Birth length[61]	28,459	-0·008	-0·035, 0·020	0·592	0·646	-	-	-
Birth weight[62]	26,836	0·030	0·003, 0·058	0·031	0·074	-	-	-
Adult height[63]	253,288	-0·018	-0·057, 0·021	0·365	0·486	-	-	-
Overweight[64]	154,206*	0·011	-0·017, 0·038	0·440	0·527	-	-	-
Extreme BMI[64]	16,067*	0·031	0·004, 0·059	0·024	0·074	-	-	-
BMI[65]	322,154	0·016	-0·012, 0·044	0·259	0·388	-	-	-

Note: Sample size with asterisks (*) are GWAS with case-control samples, and the effective sample sizes are calculated using the formula $\text{Neffective}=4/(1/\text{Ncases}+1/\text{Ncontrols})$ whenever possible. The *p*-values or *q*-values in bold are those that met the nominal $p < \cdot 05$ or corrected $q < \cdot 05$ thresholds.

Table 2. Descriptive statistics for each subgroup of self-harm related phenotypes.

Subgroup of sample	Female (%)	Mean age (years)	SD of age (years)
Full analytical sample	56·2	65·9	7·7
Self-harmed	69·4	62·3	7·5
SSH	68·0	63·1	7·4
NSSH	70·5	61·4	7·5
Never self-harmed	55·6	66·1	7·7

Table 3. Univariable and multivariable MR analyses

Exposure	Univariable MR						Multivariable MR				
	method	nsnp	b	LowCI	UpCI	pval	nsnp	b	lowCI	UpCI	p-value
ADHD	IVW	244	0·003	0·001	0·005	**0·001**	1206	0·001	-0·001	0·003	0·269
	MR RAPS		0·003	0·001	0·005	**0·001**					
	Weighted median		0·003	2·83E-04	0·005	**0·028**					
	MR Egger		0·006	0·001	0·011	**0·031**					
	MR Egger intercept		-2·57E-04	-6·88E-04	1·74E-04	0·243					
Alcohol dependence disorder	IVW	86	0·001	-4·50E-04	0·003	0·157	-	-	-	-	-
	MR RAPS		0·001	-4·57E-04	0·003	0·150					
	Weighted median		0·001	-0·001	0·004	0·332					
	MR Egger		0·001	-0·002	0·005	0·465					
	MR Egger intercept		-1·88E-05	-5·85E-04	5·48E-04	0·948					
Bipolar disorder	IVW	77	0·001	-0·001	0·003	0·310	-	-	-	-	-
	MR RAPS		0·001	-0·001	0·003	0·355					
	Weighted median		1·27E-04	-0·002	0·003	0·922					
	MR Egger		3·22E-04	-0·008	0·008	0·936					
	MR Egger intercept		8·31E-05	-9·39E-04	1·11E-03	0·874					
Lifetime cannabis use	IVW	85	-2·07E-04	-0·002	0·001	0·787	-	-	-	-	-
	MR RAPS		-2·85E-04	-0·002	0·001	0·730					
	Weighted median		-0·001	-0·004	0·001	0·314					
	MR Egger		-0·002	-0·006	0·001	0·171					
	MR Egger intercept		3·62E-04	-1·38E-04	8·61E-04	0·160					
MDD	IVW	239	0·008	0·005	0·011	**2·84E-08**	1206	0·011	0·007	0·015	**1·04E-12**
	MR RAPS		0·008	0·005	0·011	**1·24E-07**					
	Weighted median		0·006	0·001	0·011	**0·013**					

	MR Egger		0·002	-0·004	0·008	0·463					
	MR Egger intercept		4·20E-04	6·06E-05	7·80E-04	**0·023**					
Schizophrenia	IVW	1003	0·003	0·002	0·004	**1·54E-09**	1206	0·002	4·00E-05	0·004	**0·002**
	MR RAPS		0·003	0·002	0·004	**2·89E-09**					
	Weighted median		0·003	0·002	0·005	**1·80E-05**					
	MR Egger		0·004	0·001	0·007	**0·009**					
	MR Egger intercept		-4·84E-05	-2·42E-04	1·45E-04	0·625					

Note. The *p*-values in bold are those that met the p <·05 threshold.