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Polygenic risk of Major Depressive Disorder as a risk factor for Venous Thromboembolism

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Abstract:
Major depessive disorder (MDD), bipolar disorder (BD) and schizophrenia (SCZ) are accompanied by an increased risk of cardiovascular diseases including venous thromboembolism (VTE). Reasons for this are complex, and include obesity, smoking and use of hormone and psychotropic medications. Genetic studies increasingly provide evidence of shared genetic risk of psychiatric and cardiometabolic illness. This study aimed to determine whether genetic predisposition to MDD, BD or SCZ was associated with an increased risk of VTE. Genetic correlations using the largest genome-wide genetic meta-analyses summary statistics for MDD, BD and SCZ (Psychiatric Genetics Consortium) and a recent genome-wide genetic meta-analysis of VTE (INVENT consortium) demonstrated a positive association between VTE and MDD but not BD or SCZ. The same summary statistics were used to construct polygenic risk scores for MDD, BD and SCZ in UK Biobank participants of self-reported white British ancestry. These were assessed for impact on self-reported VTE risk (10786 cases, 285124 controls), using logistic regression, in sex-specific and sex-combined analyses. We identified significant positive associations between polygenic risk for MDD and risk of VTE in men, women and sex-combined analyses, independent of known risk factors. Secondary analyses demonstrated that this association was not driven by those with lifetime experience of mental illness. Meta-analyses of individual data from six additional independent cohorts replicated the sex-combined association. This report provides evidence for shared biological mechanisms leading to MDD and VTE, and suggests that, in the absence of genetic data, family history for MDD might be considered when assessing risk of VTE.

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Short title: Genetics of depression and risk of thromboembolism

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Data Sharing Statement

UKB data is accessed via an application to the central UKB team. Summary statistics for psychiatric disorders are available from the Psychiatric Genetics Consortium website (https://pgc.unc.edu/). Summary statistics from the INVENT consortium GWAS are available through application to the INVENT

consortium. All other enquiries should be addressed to Dr Rona J Strawbridge, Rona.Strawbridge@glasgow.ac.uk.

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Abstract

Major depessive disorder (MDD), bipolar disorder (BD) and schizophrenia (SCZ) are accompanied by an increased risk of cardiovascular diseases including venous thromboembolism (VTE). Reasons for this are complex, and include obesity, smoking and use of hormone and psychotropic medications. Genetic studies increasingly provide evidence of shared genetic risk of psychiatric and cardiometabolic illness. This study aimed to determine whether genetic predisposition to MDD, BD or SCZ was associated with an increased risk of VTE. Genetic correlations using the largest genome-wide genetic meta-analyses summary statistics for MDD, BD and SCZ (Psychiatric Genetics Consortium) and a recent genome-wide genetic meta-analysis of VTE (INVENT consortium) demonstrated a positive association between VTE and MDD but not BD or SCZ. The same summary statistics were used to construct polygenic risk scores for MDD, BD and SCZ in UK Biobank participants of self-reported white British ancestry. These were assessed for impact on self-reported VTE risk (10786 cases, 285124 controls), using logistic regression, in sex-specific and sex-combined analyses. We identified significant positive associations between polygenic risk for MDD and risk of VTE in men, women and sex-combined analyses, independent of known risk factors. Secondary analyses demonstrated that this association was not driven by those with lifetime experience of mental illness. Meta-analyses of individual data from six additional independent cohorts replicated the sex-combined association. This report provides evidence for shared biological mechanisms leading to MDD and VTE, and suggests that, in the absence of genetic data, family history for MDD might be considered when assessing risk of VTE.

Key points

- Genetic regulation of MDD and VTE were correlated
- Genetic predisposition to MDD was associated with increased risk of VTE

Introduction

Individuals with severe mental illness (SMI, schizophrenia (SCZ), bipolar disorder (BD) and major depressive disorder (MDD)) have an increased risk of several metabolic and cardiovascular diseases [1], including venous thromboembolism (VTE) [2,3].

A systematic review demonstrated the increased risk of VTE in psychotic disorders, depression and bipolar disorder [4]., with a shift in the balance of pro- and anti-coagulation signals resulting in hypercoagulability being proposed as a mechanism [2]. Smoking, obesity, pregnancy and exogenous hormones have pro-coagulation effects, with ABO blood group also influencing coagulation potential. Individuals with SMI have an increased burden of VTE risk factors, such as obesity, smoking [2] and sedentary behavior [5] with anti-psychotic and anti-depressant medication and immobility (for example during catatonia or sedation) [2] also increasing the risk. Further evidence of increased thrombotic risk includes altered levels of procoagulant factors in SMI patients: altered serotonin, which is a key component of MDD and an activator platelets [3], elevated D dimer, which is a marker of prothrombotic events, elevated coagulation Factor VIII in first-episode psychosis patients [3], and reduced anticoagulant protein S levels observed in SCZ[3]. Platelets are particularly interesting, as they demonstrate functional similarities with neurons [6], and their levels or activity have been shown to be altered in MDD [6] and by serotonin-affecting anti-depressant medication [7].

Psychiatric Genetics Consortium has collated large enough sample sizes that genome-wide association studies (GWAS) have identified risk variants for SCZ[8], BD[9] and MDD[10]. In parallel, GWAS of endophenotypes/characteristic features of SMI (such as anhedonia [11] or mood instability [12]), which cross diagnostic barriers and can be assessed in sub-clinical and clinical participants, have also identified associated genetic variants.

There is growing evidence from genetic studies that SMI and cardiometabolic diseases (including obesity [13], type 2 diabetes [14] and coronary artery disease [15]) share some pathological mechanisms. Some genetic overlap in regulation of MDD and platelet phenotypes have been demonstrated, specifically platelet count, mean platelet volume and platelet distribution width [16]. The aim of this study was to build on this work, specifically to determine whether genetic regulation of psychiatric disorders and VTE were correlated, and whether genetic predisposition to psychiatric disorders influenced risk of VTE in the large population-based UK Biobank. Replication analyses were conducted in case-control studies of VTE.

Methods

Genetic correlation analyses

Linkage disequilibrium (LD) score regression (using LDSC)[17] was used to assess the genome-wide genetic overlap of VTE [18] and MDD [10], BD [9] or SCZ [8]. Summary statistics for genome-wide association study (GWAS) meta-analyses of psychiatric illnesses were downloaded from the Psychiatric Genetics Consortium website (https://www.med.unc.edu/pgc/), and those for GWAS meta-analyses for VTE were provided by the INVENT consortium [19] Summary statistics from GWAS of research domain criteria (RDoC) traits of relevance to MDD, BD and SCZ were also considered, namely anhedonia [11], neuroticism[20] and mood instability [21]. Of note, mood instability is part of the neuroticism score.

Discovery study population and phenotypes

The UK Biobank study (UKB) has been described in detail [22,23]. All participants gave their written informed consent, and this study was conducted the UKB's generic approval from the NHS National Research Ethics Service (approval letter dated 29 June 2021, Ref 21/NW/0157).

Briefly, approximately 500,000 volunteers were assessed at 22 centers across the UK between 2006 and 2010. At baseline, individuals underwent physical assessment and blood sampling and completed extensive questionnaires on personal and family medical history, lifestyle and diet. VTE cases were defined as self-reported DVT and/or PE (data field #6152). Controls were defined as those answering "none of the above". Ever smoking (#20116) was defined as current and former smokers versus never smokers. Use of oral contraceptives and hormone replacement therapy were self-reported (#6153). Individuals with missing data or reporting "don't know" or "prefer not to answer" to any of these questions were excluded. Father, mother and sibling illness, including MDD, was also recorded (#20107, 20110 and 20111 respectively). A subset of individuals (N~150,000) also completed a detailed follow-up questionnaire on mental health, enabling assessment of lifetime history of MDD, BD, and psychiatric medication use[24]. A broader category, including individuals with lifetime history of any mental illness was also constructed [24]. Family history of MDD was defined as first degree relatives (parents and siblings) with MDD. Data on family history of BD or SCZ was not available.

Genotyping, imputation and genetic quality control

DNA was extracted from stored blood samples and genotyping, imputation and standard quality control procedures were conducted centrally by the UKB, as previously described [22,23]. Unrelated individuals of self-reported white British ancestry (confirmed using genetic data centrally by the UKB team) were included in this study. Additionally, participants were excluded if they were missing more than 10% of their genetic data, had purported sex chromosome aneuploidy, were heterozygosity outliers (as defined by UKB) or their self-reported sex did not match their genetically determined sex. Genetic principal components (PGCs) were calculated centrally by the UKB team.

Genotyped construction of ABO blood groups

ABO blood groups (A, AB, B and O) were defined as per Garvert et al [25], using genetic variants rs505922, rs8176746 and rs8176747.

Polygenic risk scores (PRS)

PRS_{SCZ}, PRS_{BD} and PRS_{MDD} were based on GWAS meta-analysis results from the Psychiatric Genetics consortium for SCZ [8], BD [9] and MDD [10] respectively (although the summary stats used excluded UKB data). PRS were calculated by summing the number of risk-increasing alleles for each individual. There is no consensus on whether it is better to calculate a PRS with fewer, strongly associated genetic variants (specific, but often low statistical power), or all variants across the genome (greater statistical power but a mixture of strongly associated and non-associated variants), or an intermediate approach. We used LDpred [26] to calculate PRS weighted by their effect sizes, including all variants across the genome, as this approach provides more comparable power across the PRS for SCZ, BD and MDD (which have 108, 30 and 44 significant loci, respectively). LDpred [26] considers LD patterns, based upon a reference panel of

1000 UKB participants that were not used in these analyses but passed the genetic QC above. These weighted PRS were scaled so that the mean =0 and standard deviation = 1.

Discovery statistical analyses in UKB

Logistic regression was used to assess the association of PRS_{MDD}, PRS_{BD} and PRS_{SCZ} with VTE. The primary analysis (Model 1) was consistent with models used for previous genetic studies of VTE [18], specifically, age, sex, population structure (PGCs 1-8) and technical covariates (genotyping chip) were adjusted for. Multiple testing correction was made for the three PRS being analysed, therefore $p<0.0167$ was considered significant. Statistical analyses were conducted in STATA 16.1 (StataCorp, Texas, USA). Secondary analyses were used to assess the stability of the associations when additional covariates were included: Model 2: Model 1 plus ABO blood group; Model 3: Model 2 plus BMI, ever smoking and any anti-psychotic medication. PE and DVT were also analysed separately. Additional secondary analyses were conducted, replacing the PRS_{MDD} with family history, whereby cases were those with at least one first degree relative (parents or siblings) with MDD and controls were those where no first-degree relatives had MDD.

Sensitivity analyses were conducted: Firstly, individuals with any self-reported lifetime experience of mental illness were excluded [24]. Secondly, sex-specific analyses were conducted, using the models described above and Model 4 in women only, where covariates were as for Model 3 plus use of exogenous hormones (hormone replacement therapy and oral contraceptives).

Replication cohorts

RETROVE: RETROVE is a prospective case–control study that includes 400 consecutive patients with VTE (cancer-associated thrombosis was excluded) and 400 healthy control volunteers [27]. All individuals were ≥18 years. Diagnosis was confirmed with Doppler ultrasonography, tomography, magnetic resonance, arteriography, phlebography or pulmonary gammagraphy. Blood samples from patients were taken ≥6 months after thrombosis to minimize the influence of the acute phase. None of the participants was using oral anticoagulants, heparin, or antiplatelet therapy at the time of blood collection. Controls were selected according to the age and sex distribution of the Spanish population (2001 census). All individuals were genotyped using Infinium Global Screening Array-24 v3.0 kit from Illumina and imputed using the Haplotype Reference Consortium panel. Written informed consent was obtained for all participants and all procedures were approved by the Institutional Review Board of the Hospital de la Santa Creu I Sant Pau (Barcelona).

GWAS meta-analysis summary statistics from the Psychiatric Genetics consortium for SCZ [8], BD [9] and MDD [10] were used as base data to generate PRS for replication analysis in RETROVE data (target data). Before downstream analyses, both base data and target data were quality controlled for file transfer, genome build, standard GWAS quality control metrics, mismatching SNPs, ambiguous SNPs, duplicated SNPs, sex check, sample overlap and relatedness. We computed PRS from base and target data using LDPred. The impact of PRS on VTE was tested using logistic regression adjusted for age, sex, and PGCs 1-20. Statistical analyses were performed using R (3.5).

EOVT: The Early Onset Venous Thrombosis study is a case-control sample of 339 VTE patients and 1327 healthy French persons from the Suvimax study [28]. Patients were selected for having documented idiopathic isolated PE or DVT at age <50 years in absence of acquired risk factors (including surgery, hospitalisation, pregnancy, puerperium, oral contraception, cancer, and autoimmune disease); at the time of VTE and thrombophilia defects (including Antithrombin, Protein C, or Protein S deficiencies, and homozygosity for FV Leiden or FII-20210A). Controls were healthy individuals of European ancestry with no chronic conditions and no regular medicine. Genome wide genotyping and quality control procedures have been previously described [19,28,29].

MARTHA: The MARseille THrombosis Association Study (MARTHA) study is a sample of 1542 VTE patients and 1110 healthy individuals[28]. VTE patients were unrelated individuals recruited at the Thrombophilia center of La Timone hospital (Marseille) with a history of a first VTE documented by venography, Doppler ultrasound, angiography and/or ventilation/perfusion lung scan. Patients were free of thrombophilia defects (as in EOVT) and free of any chronic conditions. Controls were 1110 health individuals from the 3C study. Detailed description of these samples as well as of their typing for genome wide polymorphisms has already been extensively described [19,29].
FARIVE: The Facteurs de Risques et de Récidives de la Maladie Thromboembolique Veineuse (FARIVE) study is a multicenter case-control study composed of 607 patients with a documented episode DVT and/or PE and 607 healthy individuals [28]. Patients were included if they fulfilled the criteria of a first VTE event, ≥18 years old and without active cancer or recent history (within 5 years) of malignancy. Controls were matched to cases for age, sex and center, and did not have any history of arterial/venous thrombosis or cancer, liver or kidney failure. A description of the study can be found in [28] and the genotyping procedures and quality controls is available in [30]

For EOVT, FARIVE, and MARTHA PRS calculation was performed using PRSice-2 (P+T method), with p thresholds of 5x10-5, 0.05 and 1.0, linkage disequilibrium cut-off of r2+0.1 and a window of 500Mb.

HVH: The Heart and Vascular Health (HVH) study is a population-based case-control study of risk factors for cardiovascular outcomes set at Group Health (GH), now Kaiser Permanente Washington, in western Washington State. Methods for HVH have been described previously [18,31,32]. For this analysis, VTE cases and controls were utilized; women aged 18-89 were eligible as a VTE case if they experienced a DVT and/or PE between 1995 and 2010, and men aged 30-89 were eligible as a case if they experienced a DVT and/or PE between 2002 and 2010. VTE events were verified by trained medical records abstractors from a review of the complete GH medical record, and controls with no prior history of VTE were selected to meet the same age and identification year as VTE cases. All study participants were GH members and provided a venous blood sample for DNA extraction. Study approval was granted by the human subjects committee at GH, and informed consent was provided by all study participants.

Two batches of genotyping were completed at the General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai: HVH1, using the Illumina 370CNV BeadChip system, and HVH3, using Illumina Omni Express. The PRS were created using LDPred2-auto [33] using the HM3+ SNPs recommended and LD for HVH.

Replication PRS and analyses

Analyses were consistent with discovery analyses model 1, specifically age, sex and population structure and any technical variables as covariates. Due to the smaller sizes of the replication cohorts, sex-specific analyses were not conducted.

Meta-analyses

Inverse variance-weighted meta-analyses were conducted using STATA 17 (STATA Corp), with Cochran's Q and I2 being used to assess between study heterogeneity. Meta-analyses were conducted on VTE, as well as DVT and PE separately.

Results

Genome-wide genetic correlation of psychiatric traits and VTE

Genome-wide genetic correlation analyses identified a significant overlap for VTE and MDD (Table 1), but not for VTE with BD or SCZ. We further explored the shared genetic correlations between VTE and endophenotypes of MDD, BD and SCZ (Table 1), which demonstrated significant correlations with anhedonia and mood instability. These findings consistently suggest that increased genetic liability to increased anhedonia, mood instability and risk of MDD are accompanied by an increased risk of VTE.

Discovery dataset: UKB

Characteristics of UKB are presented in Table 2. In men, 4440 VTE cases were reported, of which the majority were DVT (78.4%), and 13.4% reported both DVT and PE. In women there were 6346 VTE cases reported, with 79.1 % being DVT, and 9.1% reported both DVT and PE. At recruitment, cases were older (59.2 vs 56.8 years) and more overweight (29.3 vs 27.3 Kg/m2) than the controls. Of note, age of diagnosis was at least 10 years before recruitment into the the study (43.1 years and 45.8 years for PE and DVT respectively). Prior VTE is a contraindication for oral contraceptives and hormone replacement therapy, which (as well as the increased age) likely contributes to the reduced prevalence in the case group at recruitment. The frequency of ever smoking was higher in the cases compared to controls (50.3% vs 45.6%).

Primary analyses: Impact of psychiatric PRS on VTE risk

As most genetic analyses of VTE are conducted in sex-combined analyses (for increased statistical power), our primary analyses were conducted on sex-combined data (Table 3). The PRS_{MDD} was significantly, positively associated with risk of VTE (Model 1: Odds ratio (95% confidence interval) (OR (95% CI)) for 1 SD increase 1.08 (1.06-1.10) p<0.001), and secondary analyses demonstrated that this was irrespective of the covariates included. Despite the non-significant genetic correlations, for completeness, we also tested PRS_{BD} and PRS_{SCZ} for association with VTE. The PRS_{BD} was also significantly and positively associated with VTE in the sex combined analyses (Model 1: (OR (95%CI)) 1.03 (1.01-1.06) p=0.002), again with secondary analyses demonstrating that this is irrespective of which covariates were included. The PRS_{SCZ} demonstrated no effect on risk of VTE (Model 1: (OR (95%CI)) 1.00 (0.97-1.02) p=0.688). As the mood instability, anhedonia and neuroticism GWAS were conducted in UKB/included UKB, we were unable to explore the impact of these traits using PRS as we have for MDD, BD and SCZ.

Sensitivity analyses: sex-specific results

As there is a sex-difference in risk of VTE [34], sex-stratified analyses were conducted as sensitivity analyses (Table 3). Whilst there are sex differences in MDD as well, it is currently not possible to construct sex-specific PRS_{MDD} due to a lack of sex-specific MDD GWAS meta-analyses. The PRS_{MDD} was significantly and positively associated with risk of VTE in both men and women (Model 1: (OR (95%CI)) 1.07 (1.03-1.10) p<0.001 and 1.09 (1.06-1.12) p<0.001, respectively). Secondary analyses demonstrated that this was irrespective of the covariates included. Inclusion of a sex by PRS_{MDD} interaction term demonstrated a non-significant result (Models 1-3, p=0.049-0.190). The PRS_{BD} demonstrated a nominal positive association with VTE in women, irrespective of the covariates used (Model 1: (OR (95%CI)) 1.04 (1.01-1.07) p=0.013). No association was observed between PRS_{BD} and VTE in men. However, there was no evidence for a sex-PRS_{BD} interaction (models 1-3, p=0.573-0.599). The PRS_{SCZ} showed no significant association with VTE in men or in women, however opposite effects directions were noted. This was confirmed with a sex by PRS_{SCZ} interaction being observed (Models 1-3 p=0.004-0.005).

Secondary analyses: exclusion of individuals with self-reported mental illness

To assess whether the associations of PRS_{BD} and PRS_{MDD} were being driven by individuals with lifetime experience of psychiatric conditions, analyses were also conducted excluding all individuals who self-reported any mental illness (broad definition [24]). Demographics of those without mental illness were consistent with those observed in the entire cohort (STable 1), with VTE cases being older (59.4 vs 56.8 years), having a higher BMI (29.1 vs 27.2 kg/m2) and being more likely to smoke (49.3 vs 45.0%) than the controls. Sex-combined results were similar to those in the main analyses (STable 2), with PRS_{BD} and PRS_{MDD} being associated with increased risk of VTE (Model 1: (OR (95%CI)) 1.04 (1.01-1.06) p=0.004 and 1.06 (1.04-1.09) p<0.001, respectively).

Sensitivity analyses: family history instead of PRS_{MDD}

As genetic data is not currently clinically available, we compared whether family history might confer similar information to PRS_{MDD}. Therefore, a further sensitivity analysis replaced PRS_{MDD} with family history (first degree relatives) of MDD. Similar results were observed, where family history of MDD was associated with increased risk of VTE (STable 3). The stronger effects observed using family history are expected as family history includes environmental and behavioral patterns as well as genetics, whilst PRS_{MDD} only reflects genetic variation effects. Family history of BD or SCZ were not available.

Replication of psychiatric PRS on VTE risk: replication, sex-combined

Descriptive statistics of the replication studies are presented in STable 4. Analysis of the replication studies was restricted to sex-combined analyses (Model 1). Individual cohort results are presented in STable 5. Meta-analyses of replication cohorts demonstrated a significant positive effect of PRS_{MDD} on VTE risk (Figure 1A), with consistent results being observed when the discovery and replication results were combined (Figure 1B). In contrast, no association was observed for PRS_{BD} which demonstrated very high heterogeneity between studies (SFigure 1 A and B). No association was observed for PRS_{SCZ}. In order to explore the heterogeneity, we conducted meta-analyses of DVT and PE separately (this was not possible in RETROVE). PRS_{MDD} was positively associated with DVT in all cohorts (SFigure 2A), whilst there

was still some variability in associations between PRS_{MDD} and PE. Mixed null results were observed for PRS_{BD} or PRS_{SCZ} and DVT or PE (SFigure 2 C-F).

Discussion

This study demonstrated that genetic regulation of VTE overlaps with that for MDD and that increased genetic predisposition (as measured using PRS) to MDD was associated with increased risk of VTE, which was independent of major clinical risk factors and not driven by individuals with lifetime experience of self-reported mental illness. No associations were observed for BD or SCZ.

For clinical context, the risks of VTE (also in UKB) associated with monogenic thrombophilia variants as well as a PRS based on the largest GWAS of VTE (PRS_{VTE}) to date have been described [35]. Compared to our PRS_{MDD} (VTE OR=1.08), the risk of VTE associated with carriers of one or two F5 R534Q alleles (OR=2.21 and 7.3, respectively), one or two F2 G20210A alleles (OR=1.74 and 3.31 respectively) or one allele of each (OR=3.94) was much higher [35]. Similarly, the top decile of PRS_{VTE} had a greater impact on VTE risk (OR=2.35) [35].

MDD, BD and SCZ share some symptoms and some genetic regulation, therefore it was interesting that the genetic correlation observed between VTE and MDD was not also observed for BD and SCZ. This could be due to the sample size and power of the underlying GWAS studies (MDD is more prevalent than SCZ or BD). As anhedonia is a key feature of MDD, it was reassuring that the VTE-anhedonia genetic correlation was consistent with that for MDD. The greater strength of the correlation might reflect a less heterogeneous phenotype used in the GWAS of anhedonia compared to the notoriously heterogeneous MDD diagnosis. It should be noted that the moderate regression coefficients are likely to be underestimated, as the VTE analyses is a trans-ancestry analysis (European and African ancestry), whereas the MDD, anhedonia and mood instability analyses are European ancestry only. Whilst rare variants associated with monogenic thrombophilias are more common in the African ancestry compared to European, they are likely excluded from the European GWAS (due to very low minor allele frequency). Furthermore, differences in LD structure, allele frequencies and effect sizes between the European MDD and European/African VTE analyses would bias results towards the null (smaller regression coefficients), rather than causing inflation/false positive effects.

The stronger association with DVT than PE likely reflects sample size of these diagnoses (especially in the replication cohorts), as the genetic correlation between DVT and PE has been shown to be very high [35] and a systematic review of VTE in psychiatric disorders [4] provided no evidence for a differential effect of phenotypic MDD on risk of DVT vs PE. Thus, any differences in associations between PRS_{MDD} and DVT and PE would probably reflect differential effects of environmental risk factors or the interaction between genetic and environmental risk factors.

Sex-specific analyses demonstrated a significant association between PRS_{BD} and VTE in men but not women, however this was not possible to replicate the smaller size of the replication datasets precluded the use of stratified analyses. In addition, the GWAS of BD is the smallest of the psychiatric traits, which

limits the power to detect genetic associations with BD. When bigger GWAS of BD are available, it would be worth reassessing the association between PRS_{BD} and VTE, especially considering sex-specific effects.

The stability of the association between PRS_{MDD} and VTE in UKB irrespective of covariates used suggests that the PRS_{MDD} represents an independent mechanism, not captured by existing risk factors. Future work should consider whether the association between MDD-PRS and VTE occurs via risk factors such as immobilisation, hospitalisation, surgery and cancer and the UK Biobank study does have data on these variables, but as their timing in relation to the VTE event is unclear, therefore attempting to consider them here could provide misleading results. Further work is required to identify the mechanism(s) through which PRS_{MDD} promotes VTE. Whether the relationship between PRS_{MDD} and VTE is causal is an obvious question, however, assumptions underlying Mendelian randomisation methods mean that using genetic variation associated with a binary trait is not recommended [36]. Future work should investigate continuous measures of relevance to MDD to address this question.

Family history of MDD being associated with increased risk of VTE has important implications for translation to clinical practice. Genetic data is not available for clinical purposes, however asking a patient about MDD in their first-degree relatives is feasible in a clinical setting. Family history encompasses environmental as well as genetic risk factors, meaning that the larger effects observed for family history are unsurprising. Additional research is required to assess whether inclusion of family history of MDD into VTE risk prediction models would be of benefit. The same analyses were not possible for BD and SCZ as family history of these was not collected.

A strength of this study is that results are consistent between the population-based UKB study which used self-report of VTE and six clinical studies with more rigorous case-control definitions, with the meta-analysis of the clinical studies (Figure 1A) demonstrating that the association is not being driven by UKB alone. Furthermore, whilst UKB has a well recognised healthy participant bias [37], the six replication cohorts were collected from three different countries worldwide, with differing clinical inclusion and exclusion criteria, and differing burdens of risk factors such as non-O blood group, BMI, smoking, anti-psychotic medication and exogenous hormones. This consistency suggests that the observed association is robust. Limitations of this study include the fact that the discovery case-control status relied upon self-report. Whilst not perfect, previous studies have demonstrated that self-report of VTE is reliable and provides similar findings to those more rigorously defined [38]. In addition, the retrospective nature of the discovery data is challenging, as covariates such as smoking and BMI were recorded at recruitment, not at the time of the diagnosis, so this study assumes that these variables have not changed over time, which might not be valid. Finally, PRS do not generalise well to additional ancestry groups (outwith that of the GWAS upon which they are based), which hinders our assessment of this association in non-white British ancestry individuals in UKB.

In summary, here we present evidence that genetic predisposition to MDD is an independent risk factor for VTE. Further work is required to understand the mechanisms underlying the association between predisposition to MDD and VTE. Similar results were observed when considering family history (first

degree relatives) of MDD, instead of PRS_{MDD}, therefore, in the absence of GWAS data for individuals, considering family history of mental illness could be considered when assessing risk of VTE.

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Authorship Contributions:

RJS, JW, NQL, SS, JAB performed analyses.
RJS, JW, DAT and MS-L interpreted results.
BC, NG, provided phenotypic coding.
RB provided statistical advice.
JMS, JCS, NLS, DAT, PM oversaw individual study design and recruitment.
RJS conceived the study.
All authors critically revised and approved the manuscript.

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References

1. De Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011;10(1):52-77.

2. Chow V, Reddel C, Pennings G, et al. Global hypercoagulability in patients with schizophrenia receiving long-term antipsychotic therapy. *Schizophr Res*. 2015;162(1-3):175-182.
3. Hoirisch-Clapauch S, Nardi AE, Gris JC, Brenner B. Coagulation and mental disorders. *Rambam Maimonides Med J*. 2014;5(4):e0036.
4. Kowal C, Peyre H, Amad A, et al. Psychotic, Mood, and Anxiety Disorders and Venous Thromboembolism: A Systematic Review and Meta-Analysis. *Psychosom Med*. 2020;82(9):838-849.
5. Schuch F, Vancampfort D, Firth J, et al. Physical activity and sedentary behavior in people with major depressive disorder: A systematic review and meta-analysis. *J Affect Disord*. 2017;210:139-150.
6. Izzi B, Tirozzi A, Cerletti C, et al. Beyond Haemostasis and Thrombosis: Platelets in Depression and Its Co-Morbidities. *Int J Mol Sci*. 2020;21(22).
7. Grech J, Chan MV, Ochin C, et al. Serotonin-Affecting Antidepressant Use in Relation to Platelet Reactivity. *Clin Pharmacol Ther*. 2022;111(4):909-918.
8. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature*. 2014;511(7510):421-427.
9. Stahl EA, Breen G, Forstner AJ, et al. Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nat Genet*. 2019;51(5):793-803.
10. 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(5):668-681.
11. Ward J, Lyall LM, Bethlehem RAI, et al. Novel genome-wide associations for anhedonia, genetic correlation with psychiatric disorders, and polygenic association with brain structure. *Transl Psychiatry*. 2019;9(1):327.
12. Ward J, Strawbridge RJ, Bailey MES, et al. Genome-wide analysis in UK Biobank identifies four loci associated with mood instability and genetic correlation with major depressive disorder, anxiety disorder and schizophrenia. *Transl Psychiatry*. 2017;7(11):1264.
13. Milaneschi Y, Simmons WK, van Rossum EFC, Penninx BW. Depression and obesity: evidence of shared biological mechanisms. *Mol Psychiatry*. 2019;24(1):18-33.
14. Cao H, Chen J, Meyer-Lindenberg A, Schwarz E. A polygenic score for schizophrenia predicts glycemic control. *Transl Psychiatry*. 2017;7(12):1295.
15. Jackson CA, Kerssens J, Fleetwood K, Smith DJ, Mercer SW, Wild SH. Incidence of ischaemic heart disease and stroke among people with psychiatric disorders: retrospective cohort study. *Br J Psychiatry*. 2020;217(2):442-449.
16. Gialluisi A, Izzi B, Di Castelnuovo A, et al. Revisiting the link between platelets and depression through genetic epidemiology: new insights from platelet distribution width. *Haematologica*. 2020;105(5):e246-e248.
17. Bulik-Sullivan B, Finucane HK, Anttila V, et al. An atlas of genetic correlations across human diseases and traits. *Nat Genet*. 2015;47(11):1236-1241.
18. Lindstrom S, Wang L, Smith EN, et al. Genomic and transcriptomic association studies identify 16 novel susceptibility loci for venous thromboembolism. *Blood*. 2019;134(19):1645-1657.
19. Germain M, Chasman DI, de Haan H, et al. Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism. *Am J Hum Genet*. 2015;96(4):532-542.
20. Smith DJ, Escott-Price V, Davies G, et al. Genome-wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. *Mol Psychiatry*. 2016;21(6):749-757.
21. Ward J, Tunbridge EM, Sandor C, et al. The genomic basis of mood instability: identification of 46 loci in 363,705 UK Biobank participants, genetic correlation with psychiatric disorders, and association with gene expression and function. *Mol Psychiatry*. 2020;25(11):3091-3099.
22. Sudlow C, Gallacher J, Allen N, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. *PLoS Med*. 2015;12(3):e1001779.

23. Matthews PM, Sudlow C. The UK Biobank. *Brain*. 2015;138(Pt 12):3463-3465.
24. 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: a reanalysis. *BJPsych Open*. 2020;6(2):e18.
25. Garvert L, Baune BT, Berger K, et al. The association between genetically determined ABO blood types and major depressive disorder. *Psychiatry Res*. 2021;299:113837.
26. Vilhjalmsson BJ, Yang J, Finucane HK, et al. Modeling Linkage Disequilibrium Increases Accuracy of Polygenic Risk Scores. *Am J Hum Genet*. 2015;97(4):576-592.
27. Vazquez-Santiago M, Vilalta N, Cuevas B, et al. Short closure time values in PFA-100(R) are related to venous thrombotic risk. Results from the RETROVE Study. *Thromb Res*. 2018;169:57-63.
28. Tregouet DA, Heath S, Saut N, et al. Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. *Blood*. 2009;113(21):5298-5303.
29. Germain M, Saut N, Greliche N, et al. Genetics of venous thrombosis: insights from a new genome wide association study. *PLoS One*. 2011;6(9):e25581.
30. Munsch G, Proust C, Labrouche-Colomer C, et al. *preprint*.
31. Psaty BM, Heckbert SR, Koepsell TD, et al. The risk of myocardial infarction associated with antihypertensive drug therapies. *JAMA*. 1995;274(8):620-625.
32. Smith NL, Hindorff LA, Heckbert SR, et al. Association of genetic variations with nonfatal venous thrombosis in postmenopausal women. *JAMA*. 2007;297(5):489-498.
33. Privé F, Albiñana C, Pasaniuc B, Vilhjálmsson BJ. Inferring disease architecture and predictive ability with LDpred2-auto. *BioRxiv*. preprint.
34. Roach RE, Venemans A, Cannegieter SC, Lijfering WM. Differential risks in men and women for first and recurrent venous thrombosis: the role of genes and environment: reply. *J Thromb Haemost*. 2015;13(5):886-887.
35. Ghouse J, Tragante V, Ahlberg G, et al. Genome-wide meta-analysis identifies 93 risk loci and enables risk prediction equivalent to monogenic forms of venous thromboembolism. *Nat Genet*. 2023;55(3):399-409.
36. Burgess S, Labrecque JA. Mendelian randomization with a binary exposure variable: interpretation and presentation of causal estimates. *Eur J Epidemiol*. 2018;33(10):947-952.
37. Keyes KM, Westreich D. UK Biobank, big data, and the consequences of non-representativeness. *Lancet*. 2019;393(10178):1297.
38. Hinds DA, Buil A, Ziemek D, et al. Genome-wide association analysis of self-reported events in 6135 individuals and 252 827 controls identifies 8 loci associated with thrombosis. *Hum Mol Genet*. 2016;25(9):1867-1874.

Figure Legends

Figure 1: Meta-analyses results of A) PRS-MDD in replication cohorts and B) PRS-MDD in discovery and replication cohorts. Where: Effect, odds ratio; 95%CI, 95% confidence interval; weight, relative weight in the analyses, based on sample size; I^2, measure of heterogeneity; p, p-value for heterogeneity measure.

Tables

Table 1: Genetic correlation between VTE and psychiatric illnesses and related endophenotypes

Source	Psychiatric traits	rg	se	p	P_corr
PGC meta-analysis	MDD	0.179	0.044	**4.36E-05**	**1.31E-04**
PGC meta-analysis	BD	0.056	0.032	0.0770	1.39E-01
PGC meta-analysis	SCZ	-0.031	0.038	0.4128	4.13E-01
UKB	anhedonia	0.234	0.043	**4.04E-08**	**3.64E-07**
UKB	mood instability	0.186	0.037	**3.72E-07**	**1.67E-06**
UKB	neuroticism	0.071	0.046	1.24E-01	1.39E-01

Where: PGC, Psychiatric Genetics Consortium; UKB, UK Biobank GWAS; rg, regression coefficient; se, standard error; P_corr, FDR-corrected Pvalue; SCZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder.

Table 2: Characteristics of the UK Biobank study

	Men		Women		Combined	
	cases	controls	cases	controls	cases	controls
N (% male)	4440 (100)	135222 (100)	6346 (0)	149902 (0)	10786 (41.2)	285124 (47.4)
Age (years)	59.5 (7.4)	57.0 (8.1)	59.1 (7.3)	56.6 (7.9)	59.2 (7.4)	56.8 (8.0)
BMI (Kg/m2)	29.5 (5.1)	27.8 (4.2)	27.3 (5.4)	26.9 (5.0)	29.3 (5.7)	27.3 (4.7)
Ever Smoker	2608 (59.0)	69459 (51.6)	2790 (44.2)	60051 (40.2)	5398 (50.3)	129510 (45.6)
Oral contraceptives			58 (0.9)	3586 (2.4)	58 (0.9)	3586 (2.4)
HRT			394 (6.3)	10224 (6.9)	394 (6.3)	10224 (6.9)
PE	1558 (35.1)		1910 (30.1)		3468 (32.2)	
Age at PE diagnosis	48.8 (12.1)		43.4 (13.2)		45.8 (13.0)	
DVT	3479 (78.4)		5017 (79.1)		8496 (78.8)	
Age at DVT diagnosis	48.4 (11.9)		39.3 (13.7)		43.0 (13.8)	
DVT and PE	597 (13.4)		581 (9.1)		1178 (10.9)	
MDD	177 (4.2)	6184 (4.8)	531 (8.8)	12977 (9.1)	708 (6.9)	19161 (7.1)
BD	18 (0.4)	602 (0.5)	32 (0.5)	617 (0.4)	50 (0.5)	1219 (0.4)
GAD	56 (7.7)	1908 (6.4)	189 (17.6)	3615 (11.4)	245 (13.6)	5523 (9.0)

Where: BMI, Body mass index; HRT, hormone replacement therapy; PE, pulmonary embolism; DVT, deep vein thrombosis; MDD, major depressive disorder; BD, bipolar disorder; GAD, generalised anxiety disorder. Continuous variables are presented as mean (standard deviation) and categorical variables are presented as N (%).

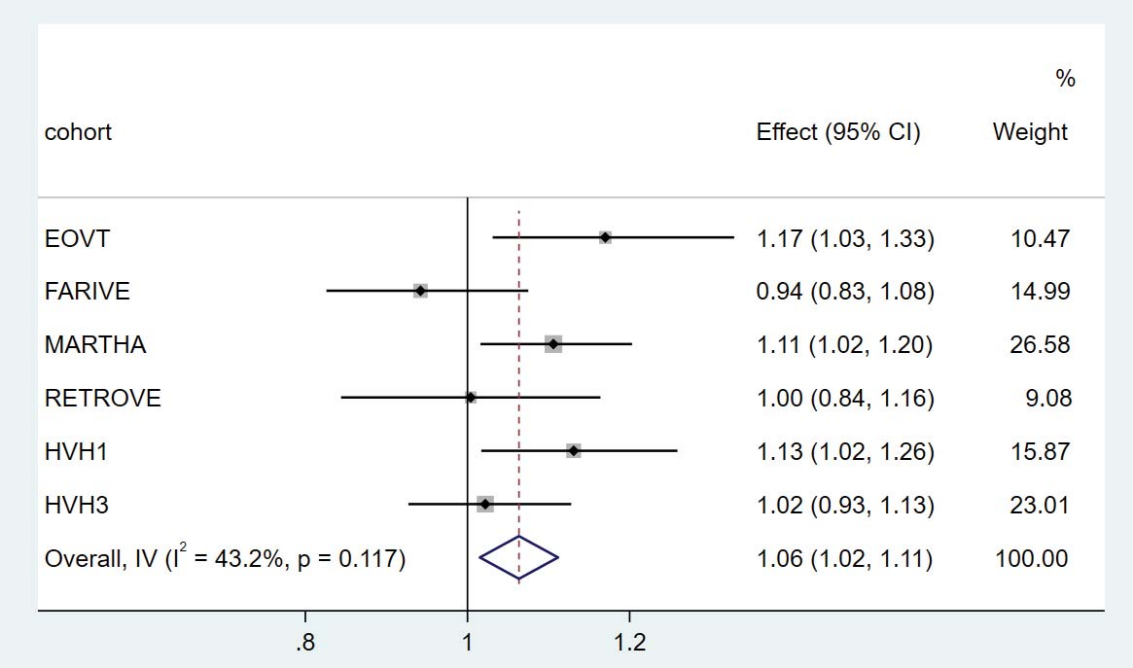
Table 3: Associations between PRS of SCZ, BD and MDD and risk of VTE in UKB

		sex-combined					men					women				
PRS	Model	R2*	OR	CI	P	N	R2*	OR	CI	P	N	R2*	OR	CI	P	N
SCZ	1	0.013	1.00	0.97-1.02	0.688	241483	0.011	0.96	0.93-1.00	0.028	114854	0.012	1.02	0.99-1.05	0.182	126629
	2	0.017	1.00	0.98-1.02	0.818	241470	0.017	0.97	0.93-1.00	0.049	114850	0.015	1.02	0.99-1.05	0.164	126620
	3	0.034	1.00	0.98-1.03	0.787	232482	0.033	0.97	0.93-1.00	0.072	111361	0.033	1.03	0.99-1.06	0.057	121121
	4											0.033	1.03	1.00-1.06	0.058	120685
BD	1	0.013	1.03	1.01-1.06	**0.002**	241483	0.010	1.03	1.00-1.07	0.069	114854	0.012	1.04	1.01-1.07	**0.013**	126629
	2	0.017	1.04	1.01-1.06	**0.002**	241470	0.017	1.03	1.00-1.07	0.058	114850	0.015	1.04	1.01-1.07	**0.012**	126620
	3	0.034	1.04	1.01-1.06	**0.002**	232482	0.030	1.03	1.00-1.07	0.073	111361	0.033	1.04	1.01-1.07	**0.011**	121121
	4											0.033	1.04	1.01-1.07	**0.012**	120685
MDD	1	0.014	1.08	1.06-1.10	**<0.001**	284866	0.012	1.07	1.03-1.10	**<0.001**	135152	0.014	1.09	1.06-1.12	**<0.001**	149714
	2	0.019	1.08	1.06-1.10	**<0.001**	284788	0.018	1.07	1.03-1.10	**<0.001**	135123	0.017	1.09	1.06-1.12	**<0.001**	149665
	3	0.036	1.07	1.04-1.09	**<0.001**	274064	0.034	1.05	1.02-1.09	**0.004**	130864	0.035	1.07	1.04-1.11	**<0.001**	143200
	4											0.035	1.07	1.04-1.11	**<0.001**	142542

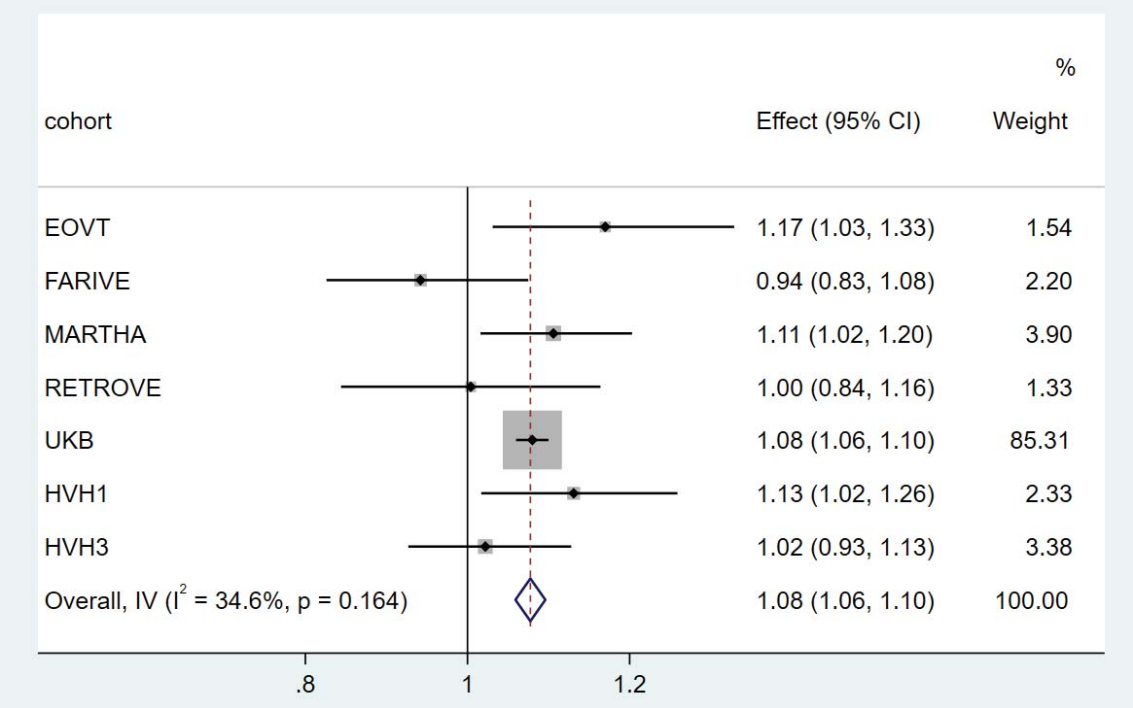
Where: R2*, Pseudo R2; OR, odds ratio; CI, 95% confidence interval; SCZ, schizophrenia; BD, bipolar disorder; MDD, major depressive disorder.
Model 1: age, principle genetic components 1-8 (PGC1-8) and genotyping chip; Model 2: Model 1 plus blood group; Model 3: model 2 plus BMI, ever smoking and any anti-psychotic medication; Model 4 (women only), model 3 plus exogenous hormones (hormone replacement therapy and oral contraceptives)

Figure 1

A)


cohort
Effect (95% CI)
%
Weight
EOVT
1.17 (1.03, 1.33)
10.47
FARIVE
0.94 (0.83, 1.08)
14.99
MARTHA
1.11 (1.02, 1.20)
26.58
RETROVE
1.00 (0.84, 1.16)
9.08
HVH1
1.13 (1.02, 1.26)
15.87
HVH3
1.02 (0.93, 1.13)
23.01
Overall, IV (I^2 = 43.2%, p = 0.117)
1.06 (1.02, 1.11)
100.00
.8
1
1.2

B)


cohort
Effect (95% CI)
%
Weight
EOVT
1.17 (1.03, 1.33)
1.54
FARIVE
0.94 (0.83, 1.08)
2.20
MARTHA
1.11 (1.02, 1.20)
3.90
RETROVE
1.00 (0.84, 1.16)
1.33
UKB
1.08 (1.06, 1.10)
85.31
HVH1
1.13 (1.02, 1.26)
2.33
HVH3
1.02 (0.93, 1.13)
3.38
Overall, IV (I^2 = 34.6%, p = 0.164)
1.08 (1.06, 1.10)
100.00
.8
1
1.2