

RESEARCH ARTICLE

Genome-wide interaction study of a proxy for stress-sensitivity and its prediction of major depressive disorder

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Data Availability Statement: Summary statistics generated (i.e. GWIS from Generation Scotland, GWIS from UK Biobank, and meta-analysed GWIS have been added as supplementary data and uploaded in bioRxiv (DOI: [10.1101/194290](https://doi.org/10.1101/194290)). This data is also available under requests at the Institute of Genetics and Molecular Medicine (IGMM) by contacting Dr. Pippa Thomson (pippa.thomson@ed.ac.uk). Data from the samples used in this study (Generation Scotland and UK Biobank)

Abstract

Individual response to stress is correlated with neuroticism and is an important predictor of both neuroticism and the onset of major depressive disorder (MDD). Identification of the genetics underpinning individual differences in response to negative events (stress-sensitivity) may improve our understanding of the molecular pathways involved, and its association with stress-related illnesses. We sought to generate a proxy for stress-sensitivity through modelling the interaction between SNP allele and MDD status on neuroticism score in order to identify genetic variants that contribute to the higher neuroticism seen in individuals with a lifetime diagnosis of depression compared to unaffected individuals. Meta-analysis of genome-wide interaction studies (GWIS) in UK Biobank (N = 23,092) and Generation Scotland: Scottish Family Health Study (N = 7,155) identified no genome-wide significance SNP interactions. However, gene-based tests identified a genome-wide significant gene, *ZNF366*, a negative regulator of glucocorticoid receptor function implicated in alcohol dependence ($p = 1.48 \times 10^{-7}$; Bonferroni-corrected significance threshold $p < 2.79 \times 10^{-6}$). Using summary statistics from the stress-sensitivity term of the GWIS, SNP heritability for stress-sensitivity was estimated at 5.0%. In models fitting polygenic risk scores of both MDD and neuroticism derived from independent GWAS, we show that polygenic risk scores derived from the UK Biobank stress-sensitivity GWIS significantly improved the prediction of MDD in Generation Scotland. This study may improve interpretation of larger genome-wide association studies of MDD and other stress-related illnesses, and the understanding of the etiological mechanisms underpinning stress-sensitivity.

is third-party data that comes from consortiums with their own Data Access Committee. Data is available from the MRC IGMM Institutional Data Access / Ethics Committee for researchers who meet the criteria for access to confidential data. Generation Scotland data is available to researchers on application to the Generation Scotland Access Committee (access@generationscotland.org). UK Biobank data is available to researchers on application via the UK Biobank Resource Access Management System (access@ukbiobank.ac.uk). The managed access process ensures that approval is granted only to research that comes under the terms of participant consent.

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Introduction

Stressful life events are known to increase liability to mental illness and disease-related traits [1] including neuroticism [2–4], major depressive disorder (MDD) [5–7], autoimmune diseases [8] and some cancers [9, 10]. A greater understanding of the causal mechanism by which negative events affect disease risk or outcome may be beneficial in identifying individuals for targeted support. However, it has been proposed that sensitivity to stress may be an important predictor of response to stress [11, 12]. In particular, the effect on an individual may result more from the perceived stress than the event itself, and may be dependent on individual differences in stress-sensitivity [13–18]. Studies of 5-HTT and twin studies suggest that stress-sensitivity may, at least in part, be heritable [19–22]. Despite a complex interaction between MDD, neuroticism and stress, multivariate structural equation models have confirmed a genetic effect on perceived stress, overlapping that on MDD or neuroticism, but with a specific genetic component [21]. The inter-relatedness of these traits may offer an approach to identify the genetic variation that affects an individual's stress-sensitivity, and improve genetic prediction of an individual's liability to negative outcomes. By modelling the interaction between SNP allele and MDD status on neuroticism score through genome-wide interaction studies (GWIS), we sought to investigate the genetics of stress-sensitivity.

The personality trait neuroticism is moderately heritable (30–50% estimates from twin studies) [23–26], is higher in individuals with depression compared to controls [27, 28] and is known to have shared genetic aetiology with depression [29–32]. Neuroticism is strongly correlated with measures of sensitivity to punishment but not reward [33], positively correlated with perceived personal relevance of a stressor [34, 35] and has been used previously as a proxy measure of stress-sensitivity [36]. Neuroticism is thought to mediate or interact with the effects of adverse life events on risk of depression [5, 37]. It has a substantial stable component [38], however, there is evidence for change, as well as stability, across the life span [2–4, 39]. Individual differences in neuroticism are enduringly influenced by both genetic and environmental factors [40]. Whereas the stable component of neuroticism is strongly determined by genetics, change in neuroticism score is attributed to the effects of unshared environment [39]. Persistent change in neuroticism score has been shown in response to life events [2–4]. Negative life events lead to small persistent increases in neuroticism over time [3]. However, recent stressful life events ($\beta = 0.14$ 95%CI 0.13–0.15, $p < 0.001$) have a stronger effect than distant stressful life events suggesting a reduction of effect over time [3]. Long-lasting increases in neuroticism associated with distant negative life events are mediated by depression [4].

Major depressive disorder (MDD) is a complex disorder influenced by both genetic contributions and environmental risk factors, with heritability estimates from twin and family studies of between 31–42% [41, 42]. Confirmed environmental risk factors for MDD include maternal infections, childhood maltreatment and negative life events [5–7, 43, 44]. However, few genetic studies have such information and even fewer prospective studies exist. Incorporation of stressful life events has been shown to improve the ability to predict MDD [45, 46] and, although stress is an environmental risk factor, it may have an independent genetic contribution to risk of depression [46–50].

These studies suggest that a genetic variable derived from the difference in neuroticism levels seen in individuals with MDD compared to controls may allow us to identify genetic loci important for stress-sensitivity. We sought to identify the genetic underpinnings of individual's sensitivity to stress response (stress-sensitivity) by identifying variants that contribute to the higher neuroticism levels seen in individuals with a lifetime diagnosis of MDD. Further, polygenic risk scores (PRS) derived from this stress-sensitivity variable may improve prediction of MDD over that based on MDD or neuroticism PRS alone.

Using unrelated individuals from two large population-based samples, UK Biobank (UKB; $N = 23,092$) and Generation Scotland: Scottish Family Health Study (GS:SFHS; $N = 7,155$), we sought to identify genes involved in stress-sensitivity by performing GWIS for the interaction between MDD status and SNP allele on neuroticism score. We identified a gene significantly associated with stress-sensitivity and show that a PRS derived from the interaction term of the GWIS, significantly predicts liability to depression independently of the PRS for MDD and/or neuroticism.

Materials and methods

UK Biobank (UKB) participants

UKB is a major national health resource that aims to improve the prevention, diagnosis and treatment of a wide range of illnesses. It recruited more than 500,000 participants aged from middle to older age who visited 22 assessment centres across the UK between 2006 and 2010. Data were collected on background and lifestyle, cognitive and physical assessments, sociodemographic factors and medical history. The scientific rationale, study design, ethical approval, survey methods, and limitations are reported elsewhere [51, 52]. UKB received ethical approval from the NHS National Research Ethics Service North West (Research Ethics Committee Reference Number: 11/NW/0382). All participants provided informed consent. The present study was conducted on genome-wide genotyping data available from the initial release of UKB data (released 2015). Details of sample processing specific to UKB project are available at <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583> and the Axiom array at http://media.affymetrix.com/support/downloads/manuals/axiom_2_assay_auto_workflow_user_guide.pdf. UKB genotyping and the stringent QC protocol applied to UKB data before it was released can be found at <http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580>. SNPs genotyped on GS:SFHS were extracted from the imputed UKB genotype data [53] (imputed by UKB using a merged panel of the UK10K haplotype reference panel and the 1000 Genomes Phase 3 reference panel) with quality > 0.9 was hard-called using PLINK v1.9 [54]. Individuals were removed based on UKB genomic analysis exclusion (UKB Data Dictionary item #22010), non-white British ancestry (#22006: genetic ethnic grouping; from those individuals who self-identified as British, principal component analysis was used to remove outliers), high genotype missingness (#22005), genetic relatedness (#22012; no pair of individuals have a KING-estimated kinship coefficient > 0.0442), QC failure in UK BiLEVE study (#22050 and #22051: UK BiLEVE Affymetrix and UK BiLEVE genotype quality controls for samples) and gender mismatch (#22001: genetic sex). Further, from the initial release of UKB data and using PLINK \hat{p} < 0.05 , individuals who were also participants of GS:SFHS and their relatives were excluded to remove any overlap of individuals between discovery and target samples. A dataset of 109,283 individuals with 557,813 SNPs remained for further analysis, aged 40–79 (57,328 female, 51,954 male; mean age = 57.1 years, s.d. = 7.99), of which 109,282 had data available for neuroticism score and 23,092 had data available on MDD status ($n_{\text{cases}} = 7,834$, $n_{\text{controls}} = 15,258$, $n_{\text{female}} = 11,510$, $n_{\text{male}} = 11,582$; mean age = 57.7 years, s.d. = 8.04). Thus, the final dataset comprised 23,092 unrelated individuals.

Generation Scotland Scottish Family Health Study (GS:SFHS) participants

GS:SFHS is a family-based genetic epidemiology study which includes 23,960 participants from ~7,000 Scottish family groups collected by a cross-disciplinary collaboration of Scottish medical schools and the National Health Service (NHS) from Feb 2006 to Mar 2011. Participants were interviewed and clinically assessed for a wide range of health-related traits (including high-fidelity phenotyping for Major Depressive Disorder and related endophenotypes),

environmental covariates and linked to routine health records [55, 56]. All components of GS:SFHS obtained ethical approval from the Tayside Committee on Medical Research Ethics on behalf of the NHS (Research Ethics Committee Reference Number: 05/S1401/89) and participants provided written consent. The protocol for recruitment is described in detail in previous publications [57, 58]. GS:SFHS genotyping and quality control is detailed elsewhere [59]. Briefly, individuals with more than 2% missing genotypes and sex discrepancies were removed, as well as population outliers. SNPs with genotype missingness $> 2\%$, minor allele frequency $< 1\%$ and a Hardy-Weinberg Equilibrium test $p < 1 \times 10^{-6}$ were excluded. Finally, individuals were removed based on relatedness ($\pi\text{-hat} < 0.05$), maximizing retention of case individuals, using PLINK v1.9 [54]. Genome-wide SNP data for further analysis comprised 7,233 unrelated individuals genotyped for 560,698 SNPs ($n_{\text{female}} = 3,476$, $n_{\text{male}} = 3,757$; PLINK v1.9 [54]), aged 18–92 (mean age = 50.4 years, s.d. = 12.06) of which: 7,190 had clinical data on MDD; 7,196 individuals had data on neuroticism; and 7,155 had data on both neuroticism and MDD.

Phenotype assessment

Neuroticism score (EPQN). Participants in both UKB and GS:SFHS cohorts were assessed for neuroticism using 12 questions from the Eysenck Personality Questionnaire-Revised Short Form's Neuroticism Scale (EPQN) [60–63]. Neuroticism can be scored by adding up the number of “Yes” responses on EPQN. This short scale has a reliability of more than 0.8 [64]. EPQN distributions were found to be sufficiently “normal” after assessment for skewness and kurtosis to be analysed using linear regression (both coefficients were between -1 and 1).

MDD diagnoses. In UKB, the MDD phenotype was derived following the definitions from Smith et al. [63] Current and previous depressive symptoms were assessed by items relating to the lifetime experience of minor and major depression [60], items from the Patient Health Questionnaire [65] and items on help-seeking for mental health [63]. Using a touchscreen questionnaire, participants were defined as probable cases if they i) answered “Yes” to the question “Ever depressed for a whole week” (UKB field: 4598), plus at least 2 weeks duration (UKB field: 4609), or ii) did report having seen a GP or psychiatrist for nerves, anxiety, tension or depression (UKB fields: 2090 and 2010) and reported symptoms (UKB field: 4631) with at least 2 weeks duration (UKB field: 5375). In our unrelated sample, 7,834 participants were diagnosed with MDD (with single, moderate or recurrent episodes) and 15,258 were controls ($N = 23,092$).

In GS:SFHS, participants took in-person clinical visits where they were screened for a history of psychiatric and emotional disorders (i.e., psychiatric, mood state/psychological distress, personality and cognitive assessment) by trained researchers using the Structured Clinical Interview for DSM-IV Non-Patient Version (SCID) [66], which is internationally validated to identify episodes of depression. Those participants that were positive in the initial screening continue through clinical interview and were administered the mood sections of the SCID. The SCID elicited the presence or absence of a lifetime history of MDD, age of onset and number of episodes. Participants fulfilling the criteria for at least one major depressive episode within the last month were defined as current MDD cases. Participants who were screened positive for Bipolar I Disorder were excluded. Those participants who were negative during the initial screening or did not fulfilled criteria for MDD were assigned as controls. Further details regarding the diagnostic assessment are reported elsewhere [56, 57]. All interviewers were trained for the administration of the SCID. Inter-rater reliability for the presence or absence of a lifetime diagnosis of major depressive disorder was good (Kappa = 0.86,

$p < 0.001$, 95%CI 0.7 to 1.0). In our unrelated GWIS sample ($N = 7,155$), 2,010 had a lifetime diagnosis of MDD and 5,145 were controls.

Statistical methods

GWIS and derivation of a genetic stress-sensitivity effect. The effect size of an stress-sensitivity effect (β_{SS}) was derived by performing a GWIS for the effect of the MDD status and SNP allele on EPQN (dependent variable) in both UKB and GS:SFHS cohorts using PLINK 1.90 (PLINK-command—gxe; fitting MDD diagnosis as a binary “group” effect) [54]. PLINK-command—gxe estimates the difference in allelic association with a quantitative trait (EPQN) between two groups (MDD cases vs. controls) producing effect estimates on each group and a test of significance for the interaction between SNP allele and MDD status. The interaction p value reflects the difference between the regression coefficient of the allelic effect in a linear model for EPQN in MDD cases (β_A) and the same regression coefficient in a linear model for EPQN in controls (β_B). The stress-sensitivity interaction effect was defined as the difference in allelic effect between MDD cases and control groups.

Considering one SNP, the effect it confers to EPQN can be modelled by MDD status (control = 0, MDD case = 1) as follows:

$$\begin{cases} MDD = 0; EPQN = \beta_0 + \beta_B SNP + \beta_{0c} COV + \epsilon \\ MDD = 1; EPQN = \beta_1 + \beta_A SNP + \beta_{1c} COV + \epsilon \end{cases}$$

This is equivalent to modelling the effect on MDD cases as follows:

$$\begin{cases} MDD = 0; EPQN = \beta_0 + \beta_B SNP + \beta_{0c} COV + \epsilon \\ MDD = 1; EPQN = \beta_1 + \beta_B SNP + (\beta_A - \beta_B) SNP + \beta_{1c} COV + \epsilon \end{cases}$$

Or, it can be modelled as a whole as:

$$EPQN = \beta_0 + \beta_2 MDD + \beta_B SNP + (\beta_A - \beta_B) SNP * MDD + \beta_{0c} COV + \beta_{2c} COV * MDD + \epsilon$$

Where COV stands for covariates, β_2 stands for $\beta_1 - \beta_0$, and β_{2c} stands for $\beta_{1c} - \beta_{0c}$.

Thus, the interaction effect (β_{SS}) can be estimated as the difference in allelic effect on EPQN between MDD cases (β_A) and controls (β_B) as follows,

$$\hat{\beta}_{SS} = \hat{\beta}_A - \hat{\beta}_B$$

$\hat{\beta}_{SS}$ is therefore defined as the effect size reflecting the genetic stress-sensitivity effect on MDD cases compared to controls (S1 Fig).

Stress-sensitivity GWIS, main additive effect GWASs, meta-analysis and gene-set analysis. For GWIS and subsequent analyses, sample specific covariates were applied as follows: UKB. All phenotypes were adjusted for centre, array and batch as random effects prior to analyses. Analyses were adjusted for age, sex and 15 informative principal components (PCs; UKB Data Dictionary items #22009.01 to #22009.15) as fixed effects to take account of possible population stratification. GS:SFHS. All the analyses were adjusted for age, sex and 20 PCs.

GWAS for MDD and neuroticism, using logistic and linear models of additive allelic effects respectively, were conducted on the same sample sets for comparison and generation of matched PRS using PRSice-2 [67].

Results from the GWIS of UKB and GS:SFHS were combined in a sample size weighted meta-analysis performed using METAL [68]. While the use of standard error weighting is more common, the different diagnostic scheme and MDD prevalence between the two cohorts

(GS:SFHS; 12.2%, UKB; 25.8%) [57, 63] may indicate systematic differences in the measurement of MDD. Generalized gene-based analysis of the meta-analysis was performed using MAGMA [69] implemented through FUMA [70] (<http://fuma.ctglab.nl>). Briefly, SNP summary statistics were mapped to 17,931 protein-coding genes. Individual SNP p values from a gene were combined into a gene test-statistic using a SNP-wise model and a known approximation of the sampling distribution used to obtain a gene-based p value. Genome-wide significance was defined at $p = 0.05/17,931 = 2.79 \times 10^{-6}$.

LD Score regression. The summary statistics from the meta-analysis were used to examine the genetic overlap between the polygenic architecture of stress-sensitivity, MDD and neuroticism. LD score regression was used to derive the genetic correlations (r_G) between these traits [71, 72] using meta-analysed GWAS and GWIS summary statistics. SNP-based heritability was also estimated using LD score regression, using the summary statistics from single-SNP analyses.

Pathway, functional and gene expression analyses. Lead SNPs, independently associated with the phenotype, were identified using PLINK 1.90 by clumping (p threshold $< 2 \times 10^{-5}$; LD $r^2 > 0.1$; physical kb threshold = 500kb; 1000 Genomes Project Phase 1 CEU, GBR, TSI genotype data), and analysed using DEPICT [73]. Further detail is given in 'DEPICT analyses' in [S1 Supporting Information](#).

Genes associated with lead SNPs were investigated for evidence of: phenotypic association in the NCBI dbGaP database of genotypes and phenotypes [74] (<https://www.ncbi.nlm.nih.gov/gap/phegeni>), regulatory DNA elements in normal cell lines and association with expression quantitative trait loci (eQTLs) using the RegulomeDB database [75] (<http://www.regulomedb.org>) and the Genotype-Tissue Expression (GTEx) Portal [76] (<http://www.gtexportal.org>).

Polygenic profiling. PRS were produced using PRSice-2 [67], permuted 10,000 times and standardized to a mean of 0 and a standard deviation of 1. Using GWIS summary statistics, we created PRS for stress-sensitivity (PRS_{SS}) by weighting the sum of the reference alleles in an individual by the stress-sensitivity effect (β_{SS}). Additional PRS were generated weighting by MDD main additive effects (PRS_D) and neuroticism main additive effects (PRS_N) using GWAS summary statistics from GS:SFHS or UKB. In addition, PRS_D and PRS_N were also generated using summary statistics from the most recent Psychiatric Genetic Consortium (PGC) MDD meta-analysis [42] (excluding GS:SFHS, and UKB individuals when required; $N = 155,866$ & $138,884$) and the Genetics of Personality Consortium (GPC) neuroticism meta-analysis [24, 77] ($N = 63,661$). Generalized linear models were implemented in R 3.1.3 [78]. The direct effect of PRS_{SS} (model 1), PRS_D (model 2) and PRS_N (model 3) on MDD risk were assessed in independent logistic regression models on GS:SFHS (target cohort) using GWAS and GWIS statistics from UKB (the largest cohort) as the discovery sample to weight PRS. Multiple regression models fitting both PRS_D and PRS_N (model 4) and fitting each of them separately with PRS_{SS} (models 5 and 6) were also calculated. Finally, full additive multiple regression models fitting PRS weighted by all three effects (full model) was assessed using both PRS_{SS}, PRS_D and PRS_N at their best-fit in independent models. Further, results were also assessed using PRS_D and PRS_N weighted by PGC2 MDD [42] and GPC neuroticism [77] summary statistics. Further detail is given in 'Polygenic Profiling' in [S1 Supporting Information](#). All models were adjusted by sex, age and 20 PCs. A null model was estimated from the direct effects of all covariates on MDD. 10,000 permutations were used to assess significance of each PRS. The predictive improvement of combining the effects of multiple PRS over a single PRS alone was tested for significance using the likelihood-ratio test.

Cross-validation was performed using UKB as target sample and GS:SFHS as discovery sample. Additional analyses using PRS_D and PRS_N weighted by PGC2 MDD [42] and GPC

neuroticism [77] summary statistics were also tested. MDD status on UKB was adjusted by centre, array and genotyping batch as random effects and scaled (between 0 and 1) prior to analysis, giving a quasi-binomial distribution of MDD status on UKB. Models implemented on UKB (quasi-binomial regression) were adjusted by sex, age and 15 PCs. Nagelkerke's R^2 coefficients were estimated to quantify the proportion of MDD liability explained at the observed scale by each model and converted into R^2 coefficients at the liability scale (prevalence: 12.2% in GS:SFHS [57] and 25.8% in UKB [63]) using Hong Lee's transformation [79] available from GEAR: GENetic Analysis Repository [80].

Using stress-sensitivity to stratify depression. GS:SFHS MDD cases ($n_{\text{cases}} = 2,016$; $n_{\text{female}} = 1,345$, $n_{\text{male}} = 671$) have data available on MDD course (single or recurrent), age of onset ($n = 1,964$) and episode count ($n = 2,016$), as well as on neuroticism ($n = 2,010$). In addition, a subset were evaluated by Mood Disorder Questionnaire [81] (MDQ; $n = 1,022$) and Schizotypal Personality Questionnaire [82] (SPQ; $n = 1,093$). The reduced sample number of MDQ and SPQ reflects the later addition of these questionnaires to the study and does not reflect a particular subgroup of GS:SFHS.

Difference in PRS_{SS} and PRS_{D} between MDD cases and controls on GS:SFHS were tested using a Student's two sample t-test (two tailed). Cases of MDD on GS:SFHS with data available on each trait analyzed were stratified by quintiles based on PRS_{SS} and PRS_{D} (5x5 groups). Post hoc, the effects on each trait of quintiles based on PRS_{SS} and its interaction effect with quintiles based on PRS_{D} were assessed using linear regression models adjusting by sex and age in an attempt to identify a characteristic subtype of MDD patients with differential stress-sensitivity levels. The same analysis was reproduced using PRSs as continuous variables.

Results

We confirmed the elevated neuroticism score in MDD cases in our samples. Individuals with a diagnosis of MDD had significantly higher EPQN scores compared to healthy controls (all $p < 1.9 \times 10^{-279}$) in both GS:SFHS (mean_{controls} = 3.16; mean_{cases} = 6.42) and UKB (mean_{controls} = 2.79; mean_{cases} = 5.64). Neuroticism levels differ significantly between males and females. To control for this and any age/polygenic effects, which may account for differences in the prevalence of MDD, we created a matched set of cases and controls. The difference in neuroticism levels between cases and controls remained significant after matching the controls for PGC PRS_{D} , sex and age. (GS:SFHS: mean_{controls} = 3.51; UKB: mean_{controls} = 2.97; all $p < 2.7 \times 10^{-158}$; S1 Table).

Meta-analysis of stress-sensitivity in UKB and GS:SFHS

No SNPs were associated with stress-sensitivity at the genome-wide significant threshold ($p < 5 \times 10^{-8}$, Fig 1). However, 14 SNPs from 8 loci achieved suggestive p value ($p < 1 \times 10^{-5}$) ranging between $p = 8.9 \times 10^{-6}$ – 5.1×10^{-7} (summary statistics available in S1–S3 Files; Meta-analysis: Table 1; UKB and GS:SFHS: S2 and S3 Tables; Meta-analysis QQ-plot with λ : S2 Fig; UKB and GS:SFHS QQ-plots: S3 Fig). Traits with prior evidence of association with the nearest genes to the 8 lead SNPs were identified using dbGap and are shown in S4 Table. Comparison between the SNP association profile along the genome between stress-sensitivity GWIS and MDD GWAS meta-analyses is shown in Miami plots filtering for the most significant stress-sensitivity or MDD SNPs ($p < 0.001$; Meta-analysis: Fig 2; UKB and GS:SFHS: S4 Fig). No SNP with a p -value < 0.01 had a corresponding p -value in the alternate trait, suggesting that different variants contribute to depression and stress-sensitivity. Gene-based test identified *ZNF366* as the only gene achieving genome-wide significance ($p = 1.48 \times 10^{-7}$; Bonferroni-corrected significance threshold $p < 2.79 \times 10^{-6}$; S5 Table and S5 Fig). Using summary statistics

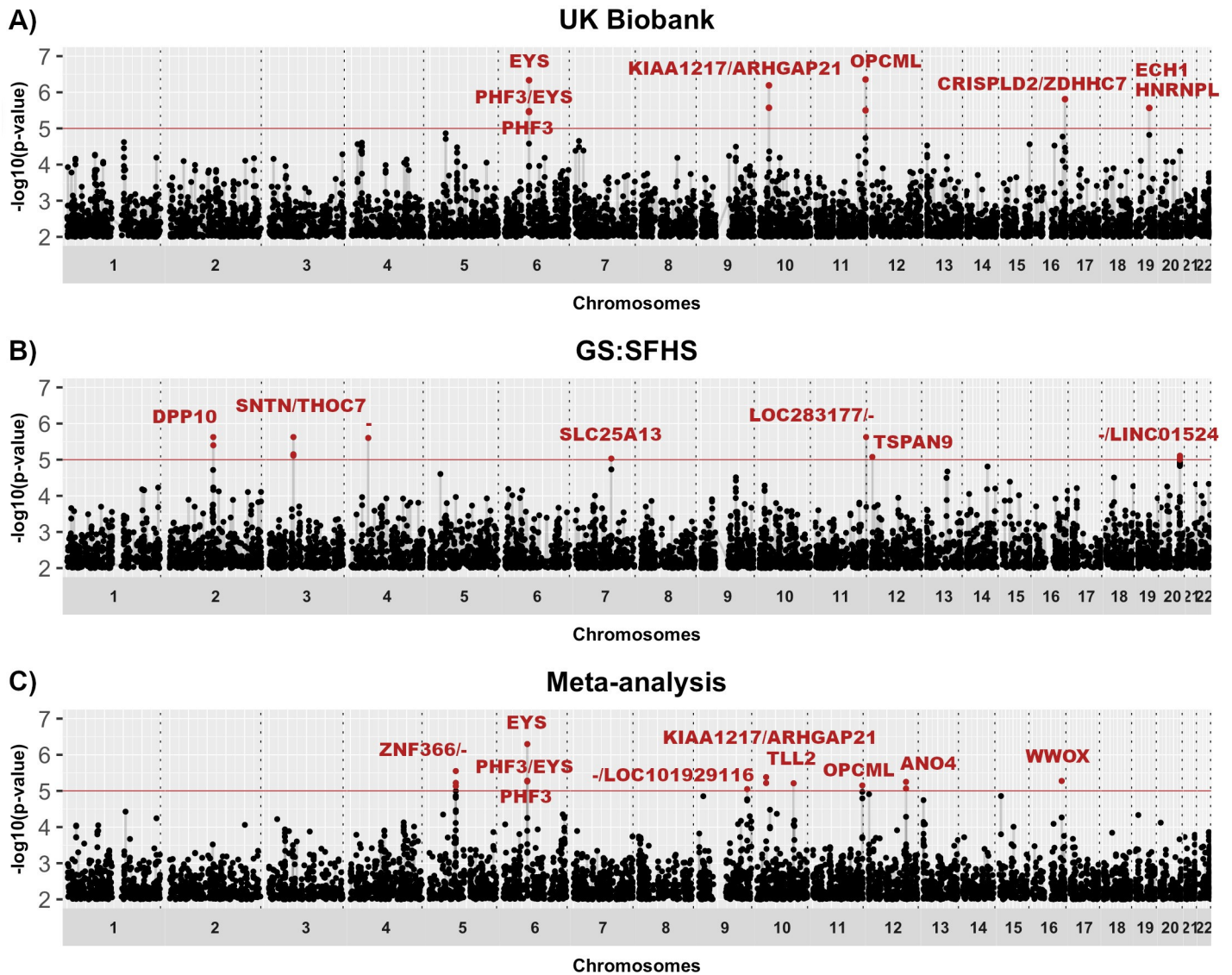


Fig 1. Manhattan plots showing stress-sensitivity associations. Manhattan plots of the GWIS from (A) UKB, (B) GS:SFHS and (C) sample size weighted meta-analysis of UKB and GS:SFHS. The x-axis is chromosomal position and y-axis is the p value ($-\log_{10} p$ value) of association with stress-sensitivity effect. Suggestive genome-wide significance threshold ($p = 1 \times 10^{-5}$) is shown by solid line at $y = 5$. Genes or closest gene up- and down-stream from SNP position (/) are annotated. “-“: No gene within 100kb of the SNP.

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from meta-analysis GWIS results, stress-sensitivity SNP-based heritability was estimated from LD score regression at 5.0% ($h^2 = 0.0499$, $s.e. = 0.017$, $p = 1.67 \times 10^{-3}$). Conversely, the SNP-based heritability for MDD and neuroticism were estimated at 9.6% ($h^2 = 0.0962$, $s.e. = 0.0179$, $p = 3.87 \times 10^{-8}$) and 10.1% ($h^2 = 0.1006$, $s.e. = 0.0076$, $p = 3.47 \times 10^{-40}$) respectively, using summary statistics from the meta-analysed GWAS of UKB and GS:SFHS.

Pathway enrichment, functional annotation and gene expression analyses

Lead SNPs from the GWIS meta-analysis were investigated using DEPICT. No gene showed statistically significant links to stress-sensitivity at a DEPICT false discovery rate (FDR) < 0.05. No significant result was found for either gene set analysis or tissue enrichment analysis

Table 1. Top 25 SNPs from meta-analysis of GWISs.

Rank	CHR	SNP	BP	A1	Z-score	Effect ^a	<i>p</i> ^b	<i>p</i> (EPQN) ^c	<i>p</i> (MDD) ^d	GENE	POSITION ^e
1	6	rs319924	64487247	A	5.024	++	5.05x10 ⁻⁷	0.376	0.637	EYS	Intronic
2	5	rs246565	71809247	A	-4.684	—	2.82x10 ⁻⁶	0.248	0.589	ZNF366	5998bp 5'
3	10	rs2265265	24854876	A	4.604	++	4.15x10 ⁻⁶	0.035	0.084	KIAA1217 / ARHGAP21	18104bp 3' / 17662bp 3'
4	6	rs1057530	64427095	A	-4.556	—	5.21x10 ⁻⁶	0.636	0.840	PHF3/EYS	1677bp 3' / 2781bp 3'
5	16	rs7199110	78790765	A	-4.553	—	5.29x10 ⁻⁶	0.661	0.741	WVOX	Intronic
6	6	rs10485358	64386060	A	-4.546	—	5.46x10 ⁻⁶	0.390	0.902	PHF3	Intronic
7	12	rs10778077	101193988	A	4.54	++	5.62x10 ⁻⁶	0.614	0.430	ANO4	Intronic
8	5	rs13358894	71803446	A	4.527	++	5.99x10 ⁻⁶	0.257	0.651	ZNF366	197bp 5'
9	10	rs2256220	24856314	A	-4.524	—	6.06x10 ⁻⁶	0.134	0.129	KIAA1217 / ARHGAP21	19542bp 3' / 16224bp 3'
10	10	rs3762096	98136250	A	-4.521	—	6.15x10 ⁻⁶	0.437	0.149	TLL2	Intronic
11	11	rs2221540	132716369	A	-4.492	—	7.05x10 ⁻⁶	0.468	0.364	OPCML	Intronic
12	5	rs10043659	71781839	A	4.483	++	7.37x10 ⁻⁶	0.339	0.808	ZNF366	Intronic
13	12	rs10778078	101195088	A	-4.45	—	8.58x10 ⁻⁶	0.599	0.456	ANO4	Intronic
14	9	rs10987199	128968987	A	-4.442	—	8.91x10 ⁻⁶	0.199	0.026	LOC101929116	63416bp 3'
15	5	rs10042132	71789021	A	-4.416	—	1.01x10 ⁻⁵	0.418	0.538	ZNF366	Intronic
16	11	rs10894606	132671611	A	-4.404	—	1.06x10 ⁻⁵	0.438	0.587	OPCML	Intronic
17	12	rs7295089	2440464	A	4.372	++	1.23x10 ⁻⁵	0.266	0.212	CACNA1C	Intronic
18	5	rs9293292	71696942	A	-4.351	—	1.36x10 ⁻⁵	0.126	0.731	PTCD2/ZNF366	41762bp 3' / 42292bp 3'
19	15	rs3097437	27872136	A	4.346	++	1.38x10 ⁻⁵	0.970	0.226	GABRG3	93762bp 3'
20	9	rs1999377	11919732	A	4.344	++	1.40x10 ⁻⁵	0.436	0.064	-	Intragenic
21	5	rs6862221	71754962	A	4.342	++	1.41x10 ⁻⁵	0.543	0.823	ZNF366	Intronic
22	5	rs9293289	71683885	A	-4.323	—	1.54x10 ⁻⁵	0.395	0.510	PTCD2/ZNF366	28705bp 3' / 55349bp 3'
23	11	rs4575282	132719646	A	-4.313	—	1.61x10 ⁻⁵	0.598	0.514	OPCML	Intronic
24	9	rs2417008	128970219	A	-4.3	—	1.71x10 ⁻⁵	0.208	0.026	LOC101929116	62184bp 3'
25	9	rs7021461	128972210	A	4.299	++	1.72x10 ⁻⁵	0.202	0.025	LOC101929116	60193bp 3'

^aEffect direction in GS:SFHS and UK Biobank.

^{b,c,d}Significances of

^bGWIS stress-sensitivity effect

^cSNP main effect on neuroticism derived from GWAS meta-analysis of EPQN between UK Biobank and Generation Scotland

^dSNP main effect on MDD derived from GWAS meta-analysis of MDD between UK Biobank and Generation Scotland.

^ePosition of the SNP respect to closest gene transcripts within 100kb (including UTRs) from 5 prime (5') or 3prime (3').

LD score regression was performed to obtain genetic correlations between stress-sensitivity, MDD and neuroticism. As previously shown, there was a significant genetic correlation between MDD and neuroticism ($r_G = 0.637$, $s.e. = 0.0704$, $p = 1.39 \times 10^{-19}$). However, we found no evidence for a genetic correlation between stress-sensitivity and MDD ($r_G = -0.099$, $s.e. = 0.182$, $p = 0.585$) or between stress-sensitivity and neuroticism ($r_G = 0.114$, $s.e. = 0.107$, $p = 0.285$).

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at $FDR < 0.05$. Evidence of regulatory elements on normal cell lines/tissues was identified for 5 of the 12 lead SNPs (i.e. rs3762096, rs10987199, rs2221540, rs246565, rs319924). Two lead SNPs were associated with eQTLs: rs319924 (an intronic SNP in *EYS*) and rs9509508 (an intronic SNP in *LATS2*) and potentially regulate *LGSN/RP3-407E4.3* ($p = 6.31 \times 10^{-12}$ / $p = 1.15 \times 10^{-5}$) and *LATS2* ($p = 3.74 \times 10^{-8}$), respectively.

Polygenic risk scores for stress-sensitivity predict MDD liability

PRS were used to investigate whether common variants affecting stress-sensitivity predict MDD risk. We generated PRS (PRS_{SS}) for stress-sensitivity based on the summary statistics from the GWIS. After 10,000 permutations, PRS_{SS} significantly predicted MDD risk in GS: SFHS using weights from the larger UKB summary data (Empirical- $p = 0.04$; $p = 5.2 \times 10^{-3}$; $\beta =$

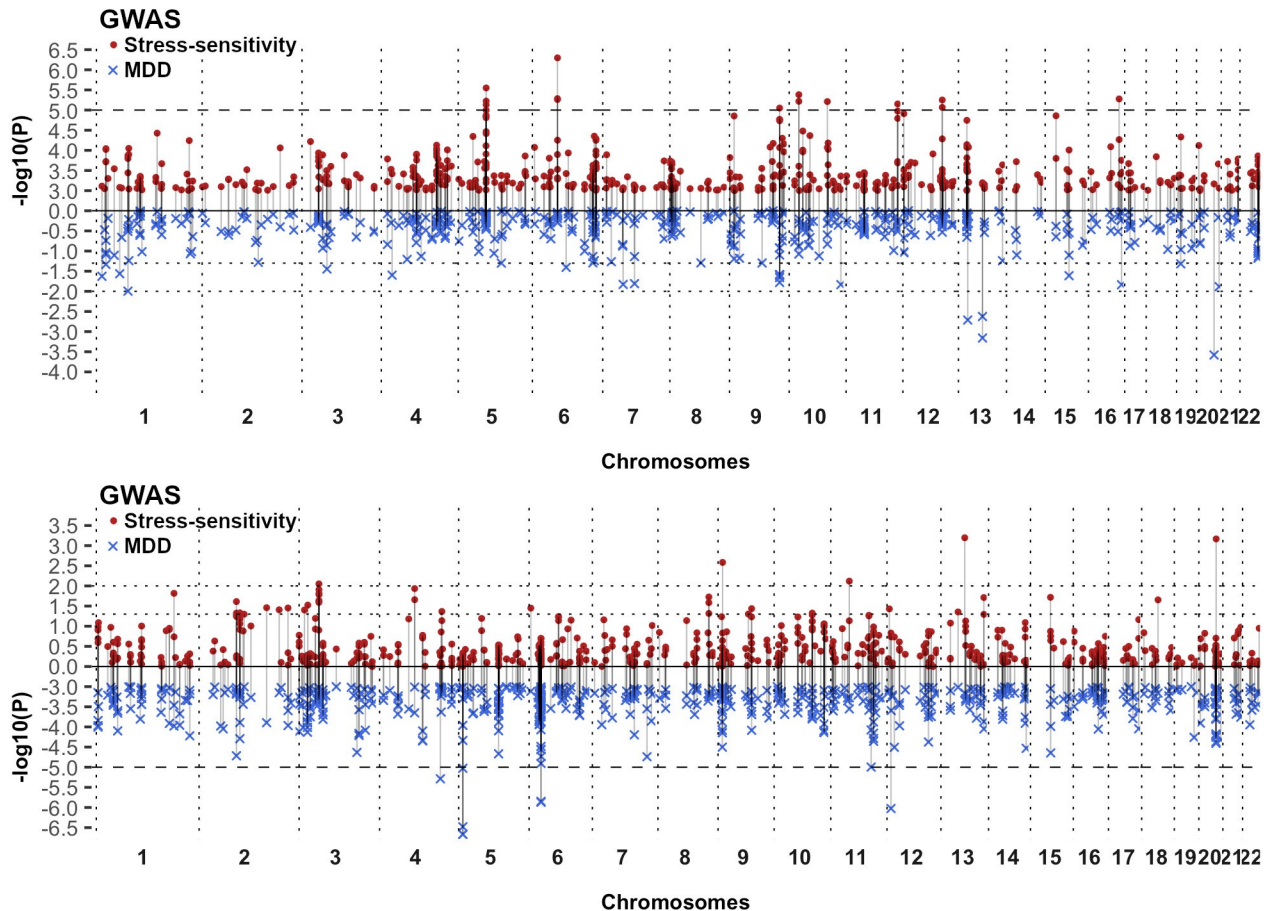


Fig 2. Miami plots showing comparison between association profile between stress-sensitivity GWIS and MDD GWAS. Miami plots from meta-analysis filter at $p = 1 \times 10^{-3}$: (A) filtering for stress-sensitivity p values (\bullet), (B) filtering for MDD p values (\times). The x-axis is chromosomal position and y-axis is the p value ($-\log_{10} p$ value) of association with stress-sensitivity (up; red dots) and MDD p value (down; blue crosses). Dot line: genome-wide suggestive threshold ($p = 1 \times 10^{-5}$) at the filtered effect; dashed lines: $p = 0.01$ and 0.05 at unfiltered effect.

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0.078, s.e. = 0.028; best-fit p threshold = 0.005; [S6 Table](#)). On the liability scale, the MDD variance explained in GS:SFHS by PRS_{SS} was modest ($R^2 = 0.195\%$). This was less than predicted by PRS weighted by the genetic main effects of MDD or neuroticism (PRS_D: $R^2 = 0.368\%$; PRS_N: $R^2 = 0.459\%$; [Table 2](#) and [S6 Table](#)). However, this association was not cross-validated in UKB using summary data from the smaller GS:SFHS GWIS (Empirical- $p = 0.68$; $p = 0.23$; $\beta = 0.004$, s.e. = 0.003; best-fit p threshold = 0.005; PRS_{SS} $R^2 = 0.013\%$; [S6 Table](#)), likely due to lack of power as a result of the small discovery sample size. PRS_D ($R^2 = 0.204\%$) and PRS_N ($R^2 = 0.166\%$) derived from GS:SFHS significantly predicted MDD in UKB ([Table 2](#) and [S6 Table](#)).

Due to the known genetic correlations between MDD, neuroticism and stressful life events [21], models jointly fitting the effects of multiple PRS were analysed. Multiple regression analyses in GS:SFHS showed that, compared to PRS_D effects alone, the stress-sensitivity effect derived from the UKB GWIS effects significantly explains an additional 0.195% (a predictive improvement of 53.1%, $p = 5.1 \times 10^{-3}$; PRS_D: $\beta = 0.112$, s.e. = 0.029; PRS_{SS}: $\beta = 0.078$, s.e. = 0.028). The inclusion of PRS_{SS} in the full model, where PRS_{SS} was fitted along with both PRS_D and PRS_N weighted by GWAS summary statistics derived from UKB remained significant; explaining an additional 0.172% (a predictive improvement of 24.6%, $p = 8.5 \times 10^{-3}$; PRS_D:

Table 2. MDD risk prediction at best fits.

UKB predicting on GS:SFHS						
Weighted effect	Best fit threshold	# SNPs	R ² (%) ^d	R ² (%) ^e	p	Empirical-p
Stress-sensitivity	0.005	1,626	0.141	0.195	5.2x10 ⁻³	0.0399
MDD ^a	0.1	22,771	0.265	0.368	1.3x10 ⁻⁴	0.0015
EPQN ^b	0.4	65,276	0.330	0.459	1.8x10 ⁻⁵	0.0002
MDD ^a + EPQN ^b	-	-	0.503	0.699	8.0x10 ⁻⁷	-
joint models ^c	-	-	0.627	0.871	1.2x10 ⁻⁷	-
PGC2 & GPC predicting on GS:SFHS						
PGC2 MDD ^a	1	92,248	0.993	1.378	1.4x10 ⁻¹³	≤0.0001
GPC EPQN ^b	0.01	3,521	0.108	0.149	0.014	0.1038
PGC2 MDD + GPC EPQN ^b	-	-	1.052	1.461	1.7x10 ⁻¹³	-
joint models ^c	-	-	1.203	1.671	1.6x10 ⁻¹⁴	-
GS:SFHS predicting on UKB						
Weighted effect	Best fit threshold	# SNPs	R ² (%) ^a	R ² (%) ^b	p	Empirical-p
Stress-sensitivity	0.005	1,526	0.008	0.013	0.231	0.6841
MDD ^a	0.03	7,725	0.130	0.204	1.6x10 ⁻⁶	≤0.0001
EPQN ^b	0.05	12,296	0.106	0.166	1.6x10 ⁻⁵	0.0005
MDD ^a + EPQN ^b	-	-	0.197	0.309	2.8x10 ⁻⁸	-
joint models ^c	-	-	0.206	0.322	6.6x10 ⁻⁸	-
PGC2 & GPC predicting on UKB						
PGC2 MDD ^a	0.5	64,113	0.919	1.440	3.4x10 ⁻³⁷	<0.0001
GPC EPQN ^b	0.03	8,761	0.066	0.104	6.5x10 ⁻⁴	0.006
PGC2 MDD ^a + GPC EPQN ^b	-	-	0.950	1.488	2.9x10 ⁻³⁷	-
joint models ^c	-	-	0.958	1.501	1.5x10 ⁻³⁶	-

^amajor depressive disorder

^bneuroticism score

^ccombined effect fitting all 3 PRS weighted by all the effects (i.e. stress-sensitivity, MDD and EPQN)

^dNagelkerke's R² at observed scale

^eR² on the liability scale.

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β = 0.093, s.e. = 0.029; PRS_N: β = 0.107, s.e. = 0.030; PRS_{SS}: β = 0.073, s.e. = 0.028). In models fitting PRS_D and PRS_N, the variances explained were non-additive, demonstrating the partial overlap between MDD risk prediction from PRS_D and PRS_N main additive effects. This is consistent with the known genetic correlation between these two traits. An overlap was not seen between the variance explained by PRS_{SS} effect and the variance explained by PRS_D and/or PRS_N. Multiple regression analyses fitting PRS_D and PRS_N derived from worldwide consortiums (Fig 3) showed that the increased sample size from GWAS used to derive PRS_D resulted in an increment of MDD variance explained in GS:SFHS by PRS_D (from 0.368% to 1.378%). However, there was no change in the proportion of the variance explained by the PRS_{SS} in the full model (PRS_{SS} p = 3.5x10⁻³). These results suggest that PRS_{SS} explains a proportion of MDD risk not accounted for by PRS_D or PRS_N at current sample sizes. However, these findings were not cross-validated in UKB using PRS_{SS} derived from GS:SFHS GWIS, likely due to lack of power as a result of the small discovery sample size (S6 Fig).

Using stress-sensitivity to stratify MDD in GS:SFHS

MDD cases show significantly higher PRS_{SS} (p = 2x10⁻³) and PRS_D (p = 1.8x10⁻⁴) than controls. Association between MDD-related traits and stress-sensitivity risk quintiles was assessed

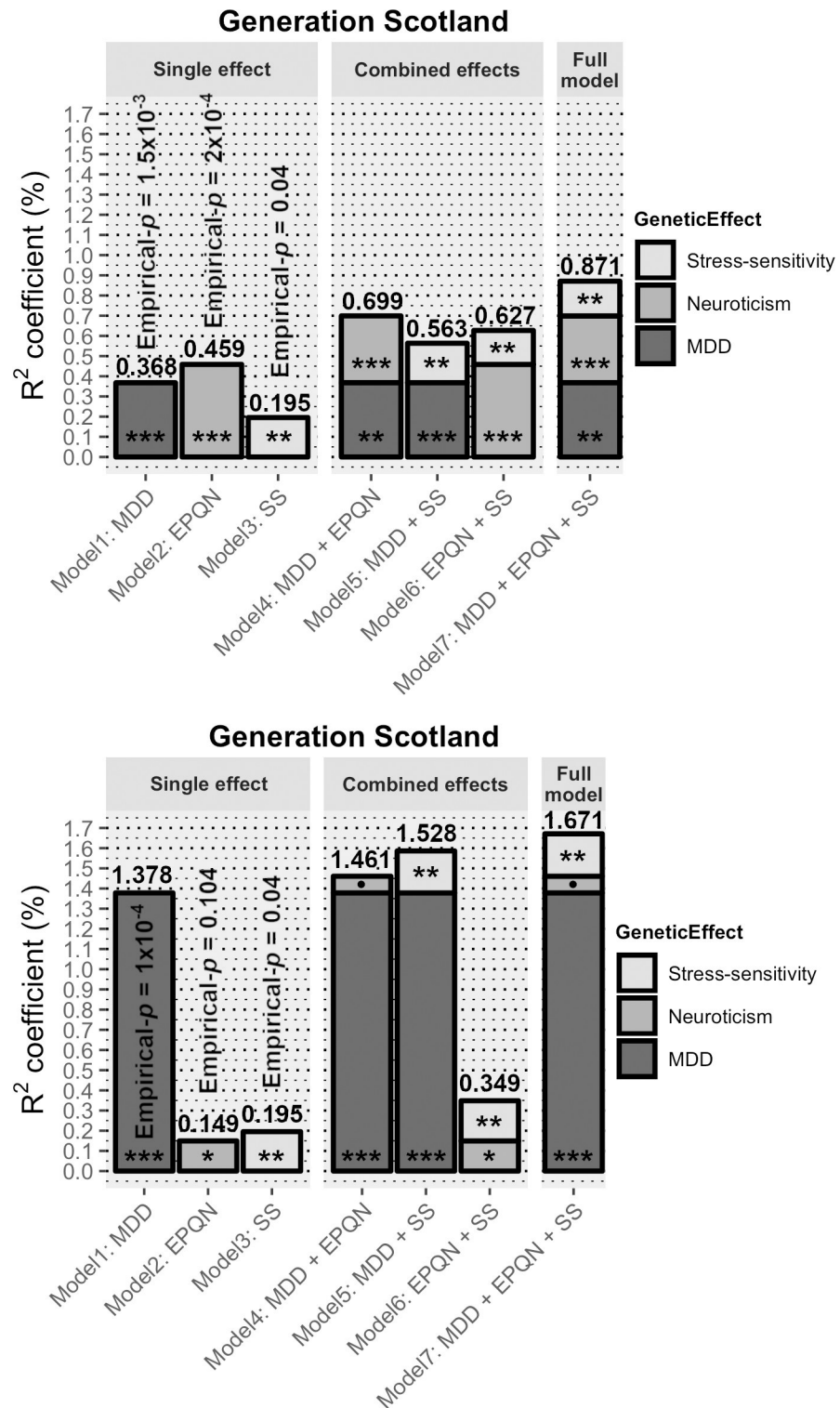


Fig 3. MDD is best predicted using multiple PRS. MDD risk explained (R^2 coefficient (%); top bar values) on the liability scale by each PRS in GS:SFHS; weighted by GWAS main additive and GWIS stress-sensitivity effects independently and combined. (A) Using summary statistics from UKB as discovery sample. There is an increment on MDD risk prediction from adding PRS_{SS} to PRS_D model of 53.1% and 24.6% when combining PRS_{SS} with both MDD and neuroticism PRS. (B) Replication of fitting PRS_D and PRS_N using summary statistics from worldwide consortiums (i.e. PGC & GPC). Significance codes: p values *** < 0.001 < ** < 0.01 < * < 0.05 < • < 0.1; derived from likelihood ratio tests. SS stands for stress-sensitivity.

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on MDD cases in order to identify a subgroup of MDD patients, perhaps defining a characteristic aetiological subtype of MDD. However, stratification analysis failed, and no quintile based on PRS_{SS} nor its interaction with quintiles based on PRS_D showed statistically significant effects on any trait analyzed. Individuals with high PRS_{SS} were not significantly different from other cases for sex, MDD course, age of onset or episode count, nor neuroticism, mood disorder or schizotypal personality scores ($p > 0.05$; [S7 Table](#)). Results remained non significant when PRSs were fitted as continuous variables ($p > 0.05$).

Discussion

The existence of genetic variants affecting an individual's risk of depression in response to stress has been predicted previously [[46](#), [49](#), [50](#)] and is consistent with the departure from a simple additive genetic model seen in twin-studies of recurrent depressive disorder [[83](#)]. Through international research efforts such as the PGC and UK Biobank, there are ever-increasing sample sizes available for understanding the genetics of MDD. These resources are beginning, and will continue to, identify genome-wide significant loci [[42](#), [84](#), [85](#)]. However, the lack of environmental data and/or their reliability, makes the study of genetic individual's response to their negative effects, and their contribution to the onset of MDD and other stress-related disorders, difficult. As a way to address this limitation, we generated a proxy for stress-sensitivity through modelling the interaction between SNP allele and MDD status on neuroticism score in a GWIS approach. Thus, we sought to identify the genetic underpinnings of individual's sensitivity to stress response (stress-sensitivity) through those variants that contribute to higher neuroticism levels only in individuals with a lifetime diagnosis of MDD but not in healthy controls.

We performed a GWIS to identify loci showing differential effects on neuroticism scores in individuals with and without MDD (so called stress-sensitivity proxy). No SNPs reached genome-wide significance, but 14 SNPs from 8 loci reached suggestive significance levels (see [S4 Table](#) for prior evidence of associated phenotypes). Enrichment analysis showed no evidence for enrichment of specific pathways or tissues. The top two loci, *PTP4A1-PHF3-EYS* and *ZNF366* have been previously associated with alcohol dependence [[86–90](#)], alcohol intake (dbGaP: phs000342) and glucocorticoid receptor function [[91–93](#)]. The most significant SNP in this study, rs319924, is an intronic variant in *EYS* that is a potential eQTL for *LGSN* [[76](#)], a gene previously associated with male-specific depression [[94](#)]. This is of particular interest given previous studies linking alcohol consumption, stress and the risk of depression [[95–100](#)]. However, findings should be interpreted with caution, as these loci did not reach genome-wide significance at current sample size. Evidence of an eQTL effect was predicted for a lead SNP in *LATS2*, a positive regulator of histone methyltransferase activity [[101](#)] a process important in anxiety-related behaviours [[102](#)]. The prior association of the top two loci in this study with alcohol related-phenotypes suggests that genes involved in the sensitivity to stress may mediate the effects of stress on alcohol consumption. Some *PHF3* paralogs have been shown to be linked with depression and modulate stress response [[103](#), [104](#)].

Gene-based analysis identified a genome-wide significant association between *ZNF366* and stress-sensitivity. *ZNF366* (also known as *DC-SCRIPT*) is a corepressor of transcription found in nuclear receptor complexes including the glucocorticoid receptor. *ZNF366* represses glucocorticoid receptor-mediated transcription in monocyte-derived dendritic cells [[91](#)]; and may act through histone deacetylases to modulate immune response [[92](#)]. There is evidence from a large-scale mRNA display study that *PHF3*, in the region underlying the most significant peak in the single SNP analysis, may also interact, directly or indirectly, with the glucocorticoid receptor (IntAct database [[93](#)]) but this has not been confirmed. These results reinforce the

hypothesis that our proxy for stress-sensitivity truly reflects the genetic architecture of sensitivity to respond to stress.

We estimated a significant lower bound on common SNP-based heritability for stress-sensitivity of 5%. Whilst the known genetic overlap between MDD and neuroticism was detectable, the lack of genetic correlation with stress-sensitivity, reinforced by results from multiple regression analyses, indicated a lack of significant overlap in the genetics factors underpinning stress-sensitivity and MDD or neuroticism. This analysis may be limited by our sample size, although using the largest available meta-analyses of MDD and neuroticism [42, 77] did not decrease the proportion of liability explained by the PRS_{SS}. We note, that as such meta-analyses increase in size it is likely, as with the effects of smoking in schizophrenia [105, 106], that the indirect genetic effects of the environment on the risk of depression will be detected by GWAS. However, through studies such as ours, or similar, the mechanism for the effect of the risk alleles may be clarified.

Further, we show that such genetic information in stress-sensitivity could significantly improve the proportion of liability to MDD predicted by PRS based only on additive genetic effects on MDD identified by large GWAS. The summary results from the GWIS were used to derive a PRS reflecting the genetic difference in stress-sensitivity. This variable significantly predicted liability to MDD in GS:SFHS ($p = 5.2 \times 10^{-3}$, Empirical- $p = 0.04$ after 10,000 permutations), although this finding could not be replicated in UKB (Empirical- $p = 0.68$), likely due to lack of power. This is consistent with the expectation that the larger the discovery sample (i.e. UKB), the greater the accuracy of the weighting and the more predictive the PRS [107]. Multiple regression models in GS:SFHS suggest that inclusion of PRS weighted by stress-sensitivity significantly improves MDD prediction over use of either MDD and/or neuroticism weighted PRS alone (improvement in full model $p = 8.5 \times 10^{-3}$). However, we were unable to identify a subgroup of MDD cases with higher PRS_{SS}. The polygenic interaction approach used in our study may, therefore, improve the interpretation of both positive and negative findings from GWAS studies (i.e. pathways and mechanisms involved, lack of replication, or negative findings in variants mediating environmental effects). Added to paralleling recent developments in GWAS analyses, it may maximize our power to detect gene-by-environment effects in this heterogeneous disorder.

Future studies will be required to further investigate the effects of adverse life events in individuals with high or low polygenic risk scores for stress-sensitivity. However, the methodology presented allows addressing the genetic response to negative outcomes via proxy in the absence of prospective environmental data.

Here we identify an independent set of risk variants for an individual's response to negative outcomes and show that incorporating information across many loci provides clear and replicable evidence for a genetic effect of stress-sensitivity on MDD risk; identifying a potential genetic link with alcohol intake. These results require further study, but may inform treatment of comorbid alcohol dependency and depression.

Supporting information

S1 Supporting Information.

(DOCX)

S1 File. GWIS summary statistics from Generation Scotland.

(CSV)

S2 File. GWIS summary statistics from UK Biobank.

(CSV)

S3 File. GWIS summary statistics from meta-analysis.
(CSV)

S1 Fig. Genetic stress-sensitivity effect representation. Genetic stress-sensitivity effect on MDD (β_{SS}) is defined as the difference between the regression coefficient in MDD cases (β_A) and the regression coefficient in controls (β_B) from linear models regressed on EPQN, adjusted by covariates. *A1*: allele 1. *A2* allele 2.
(TIFF)

S2 Fig. QQ plot from stress-sensitivity meta-analysis. QQ plot of GWIS from sample size weighted meta-analysis ($\lambda = 0.997$; s.e. = 1.05×10^{-5}). All SNPs with $p < 2 \times 10^{-5}$, p threshold (dot line) where some SNPs start to deviate from null distribution going outside 95% confidence intervals (grey shadow), were selected to perform DEPICT analyses to assess pathway and functional genomic analyses. 27 top variants from 12 independent loci were selected.
(TIFF)

S3 Fig. QQ plots of GWIS p values. QQ plots of GWIS from (A) UKB ($\lambda = 1.014$; s.e. = 1.027×10^{-5}), (B) GS:SFHS ($\lambda = 0.997$; s.e. = 7.989×10^{-6}). The 95% confidence interval is shaded in grey.
(TIFF)

S4 Fig. Miami plots on UK Biobank and Generation Scotland: Scottish Family Health Study. Miami plots showing comparison between association profile between SS and MDD main additive effects. Miami plots from (A) UKB filtering for SS p values (top) and MDD p values (bottom), (B) GS:SFHS filtering for SS p values (top) and MDD p values (bottom). Filter at $p = 1 \times 10^{-3}$. The x-axis is base-paired chromosomal position and y-axis is the significance ($-\log_{10} p$) of association with (up; red dots) SS effect and (down; blue dots) MDD. Dot line: genome-wide suggestive threshold ($p = 1 \times 10^{-5}$) at the filtered effect; dashes lines: p value = 0.01 and 0.05 at compared effect.
(TIFF)

S5 Fig. Manhattan plot of the gene-based test for stress-sensitivity. Manhattan plot showing gene-based association of stress-sensitivity. The x-axis is base-paired chromosomal position and y-axis is the significance ($-\log_{10} p$ value) of association with SS effect. Genome-wide significance threshold showed by red dashed line was defined at $p = 0.05/17,931 = 2.79 \times 10^{-6}$.
(TIFF)

S6 Fig. PRS profiling predicting MDD in UK Biobank. MDD risk explained (R^2 coefficient (%); top bar values) on the liability scale by each PRS in UKB; weighted by GWAS main additive and GWIS stress-sensitivity effects independently and combined. (A) Using summary statistics from GS:SFHS as discovery sample. (B) Replication fitting PRS_D and PRS_N using summary statistics from worldwide consortiums (i.e. PGC & GPC). Significance codes: p values *** < 0.001 < ** < 0.01 < * < 0.05; derived from likelihood ratio tests. SS stands for stress-sensitivity.
(TIFF)

S1 Table. EPQN comparison between MDD cases and healthy controls.
(XLSX)

S2 Table. Top 10 SNPs from GWIS on UK Biobank.
(XLSX)

S3 Table. Top 10 SNPs from GWIS on Generation Scotland: Scottish Family Health Study.
(XLSX)

S4 Table. Traits with significant evidence of association with closest gene to suggestive stress-sensitive hits. The closest genes to SNPs associated with stress-sensitivity at suggestive significance levels have prior evidence of association in dbGAP with a wide range of neuropsychiatric traits such as schizophrenia, bipolar disorder, attention deficit disorder with hyperactivity, mental competency, intuition, sleep or alcohol drinking.
(XLSX)

S5 Table. Top 25 hits from gene-based analysis of GWIS meta-analysis.
(XLSX)

S6 Table. Summary results from polygenic risk score (PRS) analysis using PRSice-2.
(XLSX)

S7 Table. MDD stratification.
(XLSX)

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