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

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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 interaction. 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.

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

73 previously as a proxy measure of stress-sensitivity [36]. Neuroticism is thought to mediate or
74 interact with the effects of adverse life events on risk of depression [5, 37]. It has a
75 substantial stable component [38], however, there is evidence for change, as well as stability,
76 across the life span [2-4, 39]. Individual differences in neuroticism are enduringly influenced
77 by both genetic and environmental factors [40]. Whereas the stable component of
78 neuroticism is strongly determined by genetics, change in neuroticism score is attributed to
79 the effects of unshared environment [39]. Persistent change in neuroticism score has been
80 shown in response to life events [2-4]. Negative life events lead to small persistent increases
81 in neuroticism over time [3]. Recent stressful life events (β = 0.14 95%CI 0.13 - 0.15, p <
82 0.001) have a stronger effect than distant stressful life events suggesting a reduction of effect
83 over time [3]. Long-lasting increases in neuroticism associated with distant negative life
84 events are mediated by depression [4].
85 Major depressive disorder (MDD) is a complex disorder influenced by both genetic
86 contributions and environmental risk factors, with heritability estimates from twin and family
87 studies of between 31-42% [41, 42]. Confirmed environmental risk factors for MDD include
88 maternal infections, childhood maltreatment and negative life events [5-7, 43, 44]. However,
89 few genetic studies have such information and even fewer prospective studies exist.
90 Incorporation of stressful life events has been shown to improve the ability to predict
91 MDD [45, 46] and, although stress is an environmental risk factor, it may have an
92 independent genetic contribution to risk of depression [46-50].
93 These studies suggest that a genetic variable derived from the difference in neuroticism
94 levels seen in individuals with MDD compared to controls may allow us to identify genetic
95 loci important for stress-sensitivity. We sought to identify the genetic underpinnings of
96 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, PCs 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 pi-hat < 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_{cases} = 7,834, $n_{controls}$ = 15,258, n_{female} = 11,510, n_{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 $p < 1x10^{-6}$ were exclude. Finally, individuals were removed based on relatedness (pi-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_{female} = 3,476, n_{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

166 **Neuroticism score (EPQN)**

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

173

174 **MDD diagnoses**

175 In UKB depressive symptoms were assessed by items relating to the lifetime experience of
176 minor and major depression [60], items from the Patient Health Questionnaire [65] and items
177 on help-seeking for mental health [63]. Controls were defined as those who a) answered
178 "No" to the question "Ever depressed for a whole week" or b) who reported symptoms but
179 duration was too short (< 2 weeks) or who did not report having seen a GP or psychiatrist for
180 nerves, anxiety, tension or depression. In our unrelated sample, 7,834 participants were
181 diagnosed with MDD (with single, moderate or recurrent episodes) and 15,258 were controls
182 (N = 23,092).

183 In GS:SFHS, participants who answered yes to either of two screening questions were
184 assessed for psychiatric, mood state/psychological distress, personality and cognitive
185 assessment by trained researchers using the Structured Clinical Interview for DSM-IV Non-
186 Patient Version (SCID) [66]. In our unrelated GWIS sample (N = 7,155), 2,010 had a lifetime
187 diagnosis of MDD and 5,145 were controls.

188

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 allele 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:

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

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

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

Or, it can be modelled as a whole as:

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

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,

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

209 $\hat{\beta}_{SS}$ is therefore defined as the effect size reflecting the genetic stress-sensitivity effect on
210 MDD cases compared to controls (S1 Fig).
211

212 **Stress-sensitivity GWIS, main additive effect GWASs, meta-analysis and gene-**
213 **set analysis.**

214 For GWIS and subsequent analyses, sample specific covariates were applied as
215 follows: *UKB.* All phenotypes were adjusted for centre, array and batch as random effects
216 prior to analyses. Analyses were adjusted for age, sex and 15 informative principal
217 components (PCs; UKB Data Dictionary items #22009.01 to #22009.15) as fixed effects to
218 take account of possible population stratification. *GS:SFHS.* All the analyses were adjusted for
219 age, sex and 20 PCs.
220 GWAS for MDD and neuroticism, using logistic and linear models of additive allelic effects
221 respectively, were conducted on the same sample sets for comparison and generation of
222 matched PRS using PRSice-2 [67].
223 Results from the GWIS of UKB and GS:SFHS were combined in a sample size weighted meta-
224 analysis performed using METAL [68]. While the use of standard error weighting is more
225 common, the different diagnostic scheme and MDD prevalence between the two cohorts
226 (GS:SFHS; 12.2%, UKB: 25.8%) [57, 63] may indicate systematic differences in the
227 measurement of MDD. Generalized gene-based analysis of the meta-analysis was performed
228 using MAGMA [69] implemented through FUMA [70] (http://fuma.ctglab.nl). Briefly, SNP
229 summary statistics were mapped to 17,931 protein-coding genes. Individual SNP *p* values
230 from a gene were combined into a gene test-statistic using a SNP-wise model and a known

231 approximation of the sampling distribution used to obtain a gene-based *p* value. Genome-
232 wide significance was defined at $p = 0.05/17{,}931 = 2.79\text{x}10^{-6}$.
233

234 **LD Score regression**

235 The summary statistics from the meta-analysis were used to examine the genetic
236 overlap between the polygenic architecture of stress-sensitivity, MDD and neuroticism. LD
237 score regression was used to derive the genetic correlations (r_G) between these traits [71, 72]
238 using meta-analysed GWAS and GWIS summary statistics. SNP-based heritability was also
239 estimated using LD score regression, which only requires summary statistics from single-SNP
240 analyses.
241

242 **Pathway, functional and gene expression analyses**

243 Lead SNPs, independently associated with the phenotype, were identified using PLINK
244 1.90 by clumping (*p* threshold < $2\text{x}10^{-5}$; LD r2 > 0.1; physical kb threshold = 500kb; 1000
245 Genomes Project Phase 1 CEU, GBR, TSI genotype data), and analysed using DEPICT [73].
246 Further detail is given in 'DEPICT analyses' in S1 Supporting Information.
247 Genes associated with lead SNPs were investigated for evidence of: phenotypic association in
248 the NCBI dbGaP database of genotypes and phenotypes [74]
249 (https://www.ncbi.nlm.nih.gov/gap/phegeni), regulatory DNA elements in normal cell lines
250 and association with expression quantitative trait loci (eQTLs) using the RegulomeDB
251 database [75] (http://www.regulomedb.org) and the Genotype-Tissue Expression (GTEx)
252 Portal [76] (http://www.gtexportal.org).
253

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.

278 Cross-validation was performed using UKB as target sample and GS:SFHS as discovery
279 sample. Additional analyses using PRS_D and PRS_N weighted by PGC2 MDD [42] and GPC
280 neuroticism [77] summary statistics were also tested. MDD status on UKB was adjusted by
281 centre, array and genotyping batch as random effects and scaled (between 0 and 1) prior to
282 analysis, giving a quasi-binomial distribution of MDD status on UKB. Models implemented on
283 UKB (quasi-binomial regression) were adjusted by sex, age and 15 PCs. Nagelkerke's R^2
284 coefficients were estimated to quantify the proportion of MDD liability explained at the
285 observed scale by each model and converted into R^2 coefficients at the liability scale
286 (prevalence: 12.2% in GS:SFHS [57] and 25.8% in UKB [63]) using Hong Lee's
287 transformation [79] available from GEAR: GEnetic Analysis Repository [80].
288

289 **Using stress-sensitivity to stratify depression**

290 GS:SFHS MDD cases (n_{cases} = 2,016; n_{female} = 1,345, n_{male} = 671) have data available on
291 MDD course (single or recurrent), age of onset (*n* = 1,964) and episode count (*n* = 2,016), as
292 well as on neuroticism (*n* = 2,010). In addition, a subset were evaluated by Mood Disorder
293 Questionnaire [81] (MDQ; *n* = 1,022) and Schizotypal Personality Questionnaire [82] (SPQ; *n* =
294 1,093). The reduced sample number of MDQ and SPQ reflects the later addition of these
295 questionnaires to the study and does not reflect a particular subgroup of GS:SFHS.
296 Difference in PRS_{SS} and PRS_D between MDD cases and controls on GS:SFHS were tested using
297 a Student's two sample t-test (two tailed). Cases of MDD on GS:SFHS with data available on
298 each trait analyzed were stratified by quintiles based on PRS_{SS} and PRS_D (5x5 groups). Post
299 hoc, the effects on each trait of quintiles based on PRS_{SS} and its interaction effect with
300 quintiles based on PRS_D were assessed using linear regression models adjusting by sex and
301 age in an attempt to identify a characteristic subtype of MDD patients with differential

302 stress-sensitivity levels. The same analysis was reproduced using PRSs as continuous
303 variables.
304

305 Results

306 We confirmed the elevated neuroticism score in MDD cases in our samples.
307 Individuals with a diagnosis of MDD had significantly higher EPQN scores compared to
308 healthy controls (all $p < 1.9.x10^{-279}$) in both GS:SFHS ($mean_{controls} = 3.16$; $mean_{cases} = 6.42$) and
309 UKB ($mean_{controls} = 2.79$; $mean_{cases} = 5.64$). Neuroticism levels differ significantly between
310 males and females. To control for this and any age/polygenic effects, which may account for
311 differences in the prevalence of MDD, we created a matched set of cases and controls. The
312 difference in neuroticism levels between cases and controls remained significant after
313 matching for PGC PRS_D, sex and age. (GS:SFHS: $mean_{controls} = 3.51$; UKB: $mean_{controls} = 2.97$; all
314 $p < 2.7x10^{-158}$; S1 Table).
315

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

317 No SNPs were associated with stress-sensitivity at the genome-wide significant
318 threshold ($p < 5x10^{-8}$, Fig 1). However, 14 SNPs from 8 loci achieved suggestive *p* value ($p <$
319 $1x10^{-5}$) ranging between $p = 8.9x10^{-6}$-$5.1x10^{-7}$ (Meta-analysis: Table 1; UKB and GS:SFHS: S2
320 and S3 Tables; Meta-analysis QQ-plot with λ: S2 Fig; UKB and GS:SFHS QQ-plots: S3 Fig).
321 Traits with prior evidence of association with the nearest genes to the 8 lead SNPs were
322 identified using dbGap and are shown in S4 Table. Comparison between the SNP association
323 profile along the genome between stress-sensitivity GWIS and MDD GWAS meta-analyses is
324 shown in Miami plots filtering for the most significant stress-sensitivity or MDD SNPs ($p <$

325 0.001; Meta-analysis: Fig 2; UKB and GS:SFHS: S4 Fig). No SNP with a *p*-value < 0.01 had a
326 corresponding p-value in the alternate trait, suggesting that different variants contribute to
327 depression and stress-sensitivity. Gene-based test identified *ZNF366* as the only gene
328 achieving genome-wide significance (p = 1.48×10^{-7}; Bonferroni-corrected significance
329 threshold $p < 2.79 \times 10^{-6}$; S5 Table and S5 Fig). Using summary statistics from meta-analysis
330 GWIS results, stress-sensitivity SNP-based heritability was estimated from LD score
331 regression at 5.0% (h^2 = 0.0499, s.e. = 0.017, p = 1.67×10^{-3}). Conversely, the SNP-based
332 heritability for MDD and neuroticism were estimated at 9.6% (h^2 = 0.0962, s.e. = 0.0179, p =
333 3.87×10^{-8}) and 10.1% (h^2 = 0.1006, s.e. = 0.0076, p = 3.47×10^{-40}) respectively, using summary
334 statistics from the meta-analysed GWAS of UKB and GS:SFHS.
335
336 **Fig 1. Manhattan plots showing stress-sensitivity associations.**
337 Manhattan plots of the GWIS from (A) UKB, (B) GS:SFHS and (C) sample size weighted meta-
338 analysis of UKB and GS:SFHS. The x-axis is chromosomal position and y-axis is the *p* value (-
339 log10 *p* value) of association with stress-sensitivity effect. Suggestive genome-wide
340 significance threshold (p = 1×10^{-5}) is shown by solid line at y = 5. Genes or closest gene up-
341 and down-stream from SNP position (/) are annotated. "-": No gene within 100kb of the SNP.
342
343 **Fig 2. Miami plots showing comparison between association profile between stress-**
344 **sensitivity GWIS and MDD GWAS.**
345 Miami plots from meta-analysis filter at p = 1×10^{-3}: (A) filtering for stress-sensitivity *p* values
346 (•), (B) filtering for MDD *p* values (×). The x-axis is chromosomal position and y-axis is the *p*
347 value (-log10 *p* value) of association with stress-sensitivity (up; red dots) and MDD *p* value

348 (down; blue crosses). Dot line: genome-wide suggestive threshold (p = 1x10^{-5}) at the filtered

349 effect; dashed lines: p = 0.01 and 0.05 at unfiltered effect.

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

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

[a]Effect direction in GS:SFHS and UK Biobank. [b,c,d]Significances of: [b]GWIS stress-sensitivity effect; [c]SNP main effect on neuroticism derived from GWAS meta-analysis of EPQN between UK Biobank and Generation Scotland; [d]SNP main effect on MDD derived from GWAS meta-analysis of MDD between UK Biobank and Generation Scotland. [e]Position of the SNP respect to closest gene transcripts within 100kb (including UTRs) from 5 prime (5') or 3prime (3').

350 LD score regression was performed to obtain genetic correlations between stress-sensitivity,
351 MDD and neuroticism. As previously shown, there was a significant genetic correlation
352 between MDD and neuroticism (r_G = 0.637, s.e. = 0.0704, p = 1.39x10^{-19}). However, we found
353 no evidence for a genetic correlation between stress-sensitivity and MDD (rG = -0.099, s.e. =
354 0.182, p = 0.585) or between stress-sensitivity and neuroticism (r_G = 0.114, s.e. = 0.107, p =
355 0.285).
356

357 Pathway enrichment, functional annotation and gene expression 358 analyses

359 Lead SNPs from the GWIS meta-analysis were investigated using DEPICT. No gene
360 showed statistically significant links to stress-sensitivity at a DEPICT false discovery rate (FDR)
361 < 0.05. No significant result was found for either gene set analysis or tissue enrichment
362 analysis at FDR < 0.05. Evidence of regulatory elements on normal cell lines/tissues was
363 identified for 5 of the 12 lead SNPs (i.e. rs3762096, rs10987199, rs2221540, rs246565,
364 rs319924). Two lead SNPs were associated with eQTLs: rs319924 (an intronic SNP in *EYS*) and
365 rs9509508 (an intronic SNP in *LATS2*) and potentially regulate *LGSN/RP3-407E4.3* (p =
366 6.31x10^{-12}/ p = 1.15x10^{-5}) and *LATS2* (p = 3.74x10^{-8}), respectively.
367

368 Polygenic risk scores for stress-sensitivity predict MDD liability

369 PRS were used to investigate whether common variants affecting stress-sensitivity
370 predict MDD risk. We generated PRS (PRS_{SS}) for stress-sensitivity based on the summary
371 statistics from the GWIS. After 10,000 permutations, PRS_{SS} significantly predicted MDD risk in
372 GS:SFHS using weights from the larger UKB summary data (Empirical-p = 0.04; p = 5.2x10^{-3}; β

373 = 0.078, s.e. = 0.028; best-fit *p* threshold = 0.005; S6 Table). On the liability scale, the MDD
374 variance explained in GS:SFHS by PRS_{SS} was modest (R^2 = 0.195%). This was less than
375 predicted by PRS weighted by the genetic main effects of MDD or neuroticism (PRS_D: R^2 =
376 0.368%; PRS_N: R^2 = 0.459%; Table 2 and S6 Table). However, this association was not cross-
377 validated in UKB using summary data from the smaller GS:SFHS GWIS (Empirical-*p* = 0.68; *p* =
378 0.23; β = 0.004, s.e. = 0.003; best-fit *p* threshold = 0.005; PRS_{SS} R^2 = 0.013%; S6 Table), likely
379 due to lack of power as a result of the small discovery sample size. PRS_D (R^2 = 0.204%) and
380 PRS_N (R^2 = 0.166%) derived from GS:SFHS also significantly predicted MDD in UKB (Table 2
381 and S6 Table).

382 **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	$1.5x10^{-36}$	-

[a]major depressive disorder, [b]neuroticism score, [c]combined effect fitting all 3 PRS weighted by all the effects (i.e. stress-sensitivity, MDD and EPQN), [d]Nagelkerke's R^2 at observed scale, [e]R^2 on the liability scale.

383 Due to the known genetic correlations between MDD, neuroticism and stressful life events [21],
384 models jointly fitting the effects of multiple PRS were analysed. Multiple regression analyses in
385 GS:SFHS showed that, compared to PRS_D effects alone, stress-sensitivity effect derived from the
386 UKB GWIS effects significantly explains an additional 0.195% (a predictive improvement of 53.1%,
387 $p = 5.1x10^{-3}$; PRS_D: β = 0.112, s.e. = 0.029; PRS_{SS} : β = 0.078, s.e. = 0.028). The inclusion of PRS_{SS} in
388 the full model, where PRS_{SS} was fitted along with both PRS_D and PRS_N weighted by GWAS summary
389 statistics derived from UKB remained significant; explaining an additional 0.172% (a predictive
390 improvement of 24.6%, $p = 8.5x10^{-3}$; PRS_D: β = 0.093, s.e. = 0.029; PRS_N: β = 0.107, s.e. = 0.030;
391 PRS_{SS}: β = 0.073, s.e. = 0.028). In models fitting PRS_D and PRS_N, the variances explained were non-
392 additive, demonstrating the partial overlap between MDD risk prediction from PRS_D and PRS_N main
393 additive effects. This is consistent with the known genetic correlation between these two traits. An
394 overlap was not seen between the variance explained by PRS_{SS} effect and the variance explained
395 by PRS_D and/or PRS_N. Multiple regression analyses fitting PRS_D and PRS_N derived from worldwide
396 consortiums (Fig 3) showed that the increased sample size from GWAS used to derive PRS_D
397 resulted in an increment of MDD variance explained in GS:SFHS by PRS_D (from 0.368% to 1.378%).
398 However, there was no change in the proportion of the variance explained by the PRS_{SS} in the full
399 model (PRS_{SS} $p = 3.5x10^{-3}$). These results suggest that PRS_{SS} explains a proportion of MDD risk not
400 accounted for by PRS_D or PRS_N at current sample sizes. However, these findings were not cross-
401 validated in UKB using PRS_{SS} derived from GS:SFHS GWIS, likely due to lack of power as a result of
402 the small discovery sample size (S6 Fig).
403
404 **Fig 3. MDD is best predicted using multiple PRS.**
405 MDD risk explained (R^2 coefficient (%); top bar values) on the liability scale by each PRS in GS:SFHS;
406 weighted by GWAS main additive and GWIS stress-sensitivity effects independently and combined.

407 (A) Using summary statistics from UKB as discovery sample. There is an increment on MDD risk
408 prediction from adding PRS_{SS} to PRS_D model of 53.1% and 24.6% when combining PRS_{SS} with both
409 MDD and neuroticism PRS. (B) Replication of fitting PRS_D and PRS_N using summary statistics from
410 worldwide consortiums (i.e. PGC &GPC). Significance codes: *p* values *** < 0.001 < ** < 0.01 < * <
411 0.05 < • < 0.1; derived from likelihood ratio tests. *SS* stands for stress-sensitivity.
412

413 Using stress-sensitivity to stratify MDD in GS:SFHS

414 MDD cases show significantly higher PRS_{SS} ($p = 2x10^{-3}$) and PRS_D ($p = 1.8x10^{-4}$) than
415 controls. Association between MDD-related traits and stress-sensitivity risk quintiles was assessed
416 on MDD cases in order to identify a subgroup of MDD patients, perhaps defining a characteristic
417 aetiological subtype of MDD. However, stratification analysis failed, and no quintile based on PRS_{SS}
418 nor its interaction with quintiles based on PRS_D showed statistically significant effects on any trait
419 analyzed. Individuals with high PRS_{SS} were not significantly different from other cases for sex, MDD
420 course, age of onset or episode count, nor neuroticism, mood disorder or schizotypal personality
421 scores ($p > 0.05$; S7 table). Results remained non significant when PRSs were fitted as continuous
422 variables ($p > 0.05$).

423 # Discussion

424 The existence of genetic variants affecting an individual's risk of depression in response to
425 stress has been predicted previously [46, 49, 50] and is consistent with the departure from a
426 simple additive genetic model seen in twin-studies of recurrent depressive disorder [83]. Through
427 international research efforts such as the PGC and UK Biobank, there are ever-increasing sample
428 sizes available for understanding the genetics of MDD. These resources are beginning, and will
429 continue to, identify genome-wide significant loci [42, 84, 85]. However, the lack of environmental
430 data and/or their reliability, makes the study of genetic individual's response to their negative
431 effects, and their contribution to the onset of MDD and other stress-related disorders, difficult. As
432 a way to address this limitation, we generated a proxy for stress-sensitivity through modelling the
433 interaction between SNP allele and MDD status on neuroticism score in a GWIS approach. Thus,
434 we sought to identify the genetic underpinnings of individual's sensitivity to stress response
435 (stress-sensitivity) through those variants that contribute to higher neuroticism levels only in
436 individuals with a lifetime diagnosis of MDD but not in healthy controls.
437 We performed a GWIS to identify loci showing differential effects on neuroticism scores in
438 individuals with and without MDD (so called stress-sensitivity proxy). No SNPs reached genome-
439 wide significance, but 14 SNPs from 8 loci reached suggestive significance levels (see S4 Table for
440 prior evidence of associated phenotypes). Enrichment analysis showed no evidence for
441 enrichment of specific pathways or tissues. The top two loci, *PTP4A1-PHF3-EYS* and *ZNF366* have
442 been previously associated with alcohol dependence [86-90], alcohol intake (dbGaP: phs000342)
443 and glucocorticoid receptor function [91-93]. The most significant SNP in this study, rs319924, is
444 an intronic variant in *EYS* that is a potential eQTL for *LGSN* [76], a gene previously associated with
445 male-specific depression [94]. This is of particular interest given previous studies linking alcohol

446 consumption, stress and the risk of depression [95-100]. However, findings should be interpreted
447 with caution, as these loci did not reach genome-wide significance at current sample size.
448 Evidence of an eQTL effect was predicted for a lead SNP in *LATS2*, a positive regulator of histone
449 methyltransferase activity [101] a process important in anxiety-related behaviours [102]. The prior
450 association of the top two loci in this study with alcohol related-phenotypes suggests that genes
451 involved in the sensitivity to stress may mediate the effects of stress on alcohol consumption.
452 Some *PHF3* paralogs have been shown to be linked with depression and modulate stress
453 response [103, 104].
454 Gene-based analysis identified a genome-wide significant association between *ZNF366* and stress-
455 sensitivity. *ZNF366* (also known as *DC-SCRIPT*) is a corepressor of transcription found in nuclear
456 receptor complexes including the glucocorticoid receptor. *ZNF366* represses glucocorticoid
457 receptor-mediated transcription in monocyte-derived dendritic cells [91]; and may act through
458 histone deacetylases to modulate immune response [92]. There is evidence from a large-scale
459 mRNA display study that *PHF3*, in the region underlying the most significant peak in the single SNP
460 analysis, may also interact, directly or indirectly, with the glucocorticoid receptor (IntAct
461 database [93]) but this has not been confirmed. These results reinforce the hypothesis that our
462 proxy for stress-sensitivity truly reflects the genetic architecture of sensitivity to respond to stress.
463 We estimated a significant lower bound on common SNP-based heritability for stress-sensitivity of
464 5%. Whilst the known genetic overlap between MDD and neuroticism was detectable, the lack of
465 genetic correlation with stress-sensitivity, reinforced by results from multiple regression analyses,
466 indicated a lack of significant overlap in the genetics factors underpinning stress-sensitivity and
467 MDD or neuroticism. This analysis may be limited by our sample size, although using the largest
468 available meta-analyses of MDD and neuroticism [42, 77] did not decrease the proportion of
469 liability explained by the PRS_{SS}. We note, that as such meta-analyses increase in size it is likely, as

470 with the effects of smoking in schizophrenia [105, 106], that the indirect genetic effects of the
471 environment on the risk of depression will be detected by GWAS. However, through studies such
472 as ours, or similar, the mechanism for the effect of the risk alleles may be clarified.
473 Further, we show that such genetic information in stress-sensitivity could significantly improve the
474 proportion of liability to MDD predicted by PRS based only on additive genetic effects on MDD
475 identified by large GWAS. The summary results from the GWIS were used to derive a PRS
476 reflecting the genetic difference in stress-sensitivity. This variable significantly predicted liability to
477 MDD in GS:SFHS ($p = 5.2x10^{-3}$, Empirical-p = 0.04 after 10,000 permutations), although this finding
478 could not be replicated in UKB (Empirical-p = 0.68), likely due to lack of power. This is consistent
479 with the expectation that the larger the discovery sample (i.e. UKB), the greater the accuracy of
480 the weighting and the more predictive the PRS [107]. Multiple regression models in GS:SFHS
481 suggest that inclusion of PRS weighted by stress-sensitivity significantly improves MDD prediction
482 over use of either MDD and/or neuroticism weighted PRS alone (improvement in full model p =
483 $8.5x10^{-3}$). However, we were unable to identify a subgroup of MDD cases with higher PRS_{ss}. The
484 polygenic interaction approach used in our study may, therefore, improve the interpretation of
485 both positive and negative findings from GWAS studies (i.e. pathways and mechanisms involved,
486 lack of replication, or negative findings in variants mediating environmental effects). Added to
487 paralleling recent developments in GWAS analyses, it may maximize our power to detect gene-by-
488 environment effects in this heterogeneous disorder.
489 Future studies will be required to further investigate the effects of adverse life events in
490 individuals with high or low polygenic risk scores for stress-sensitivity. However, the methodology
491 presented allows addressing the genetic response to negative outcomes via proxy in the absence
492 of prospective environmental data.

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

Acknowledgments

We thank all participants from UK Biobank, including families, volunteers, technicians and scientist who helped collect the samples and prepare the data. Analyses were performed under UK Biobank project 4844. We are grateful to all the families who took part in Generation Scotland, the general practitioners and the Scottish School of Primary Care for their help in recruiting them, the whole Generation Scotland team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists, healthcare assistants and nurses. We acknowledge the Genetics Core Laboratory at the Wellcome Trust Clinical Research Facility, Edinburgh to carry out the genotyping of the Generation Scotland samples. We gratefully acknowledge the Psychiatric Genomics Consortium MDD Working Group, which depends on the contributions of many parties.

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Supporting information

S1 Supporting Information.

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.

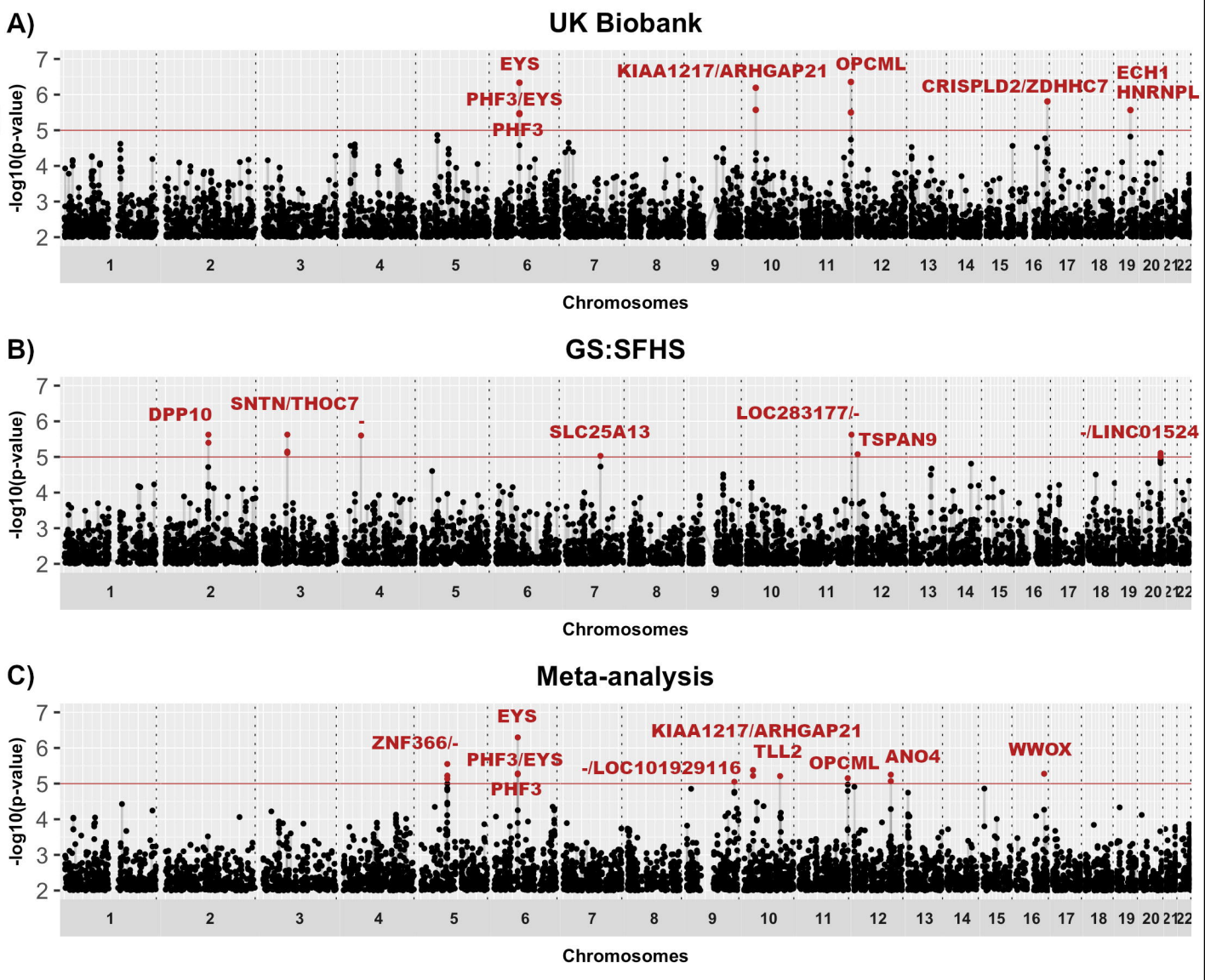
S2 Fig. QQ plot from stress-sensitivity meta-analysis. QQ plot of GWIS from sample size weighted meta-analysis (λ = 0.997; s.e. = 1.05×10^{-5}). All SNPs wit $p < 2 \times 10^{-5}$, p threshold (dot line) where some SNPs start to deviate from null distribution going outside 95% confidence intervals (grey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

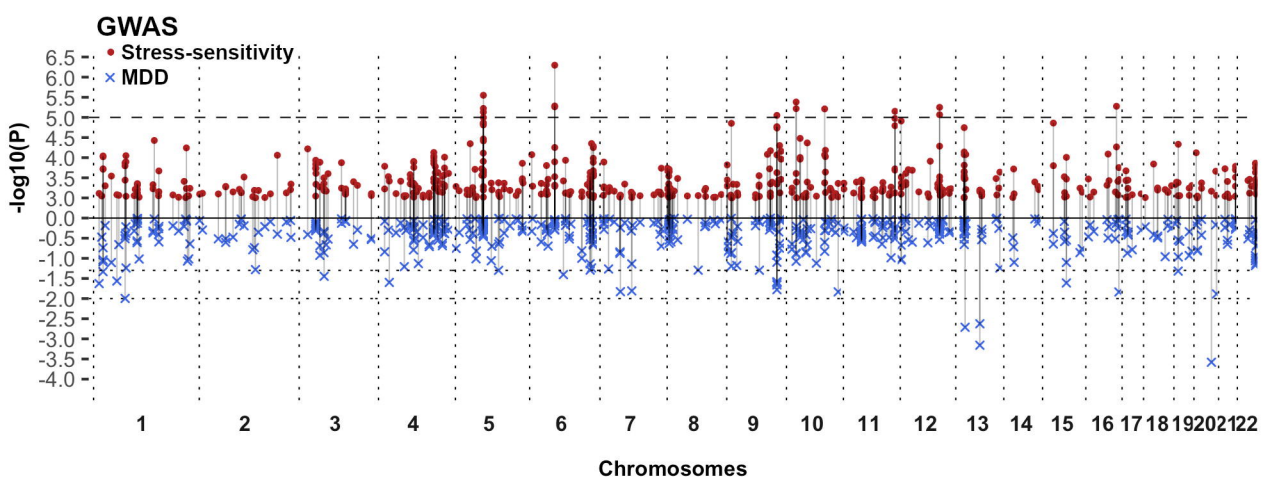
S3 Fig. QQ plots of GWIS *p* values. QQ plots of GWIS from (A) UKB (λ = 1.014; s.e.= 1.027×10^{-5}), (B) GS:SFHS (λ = 0.997; s.e. = 7.989×10^{-6}). The 95% confidence interval is shaded in grey.

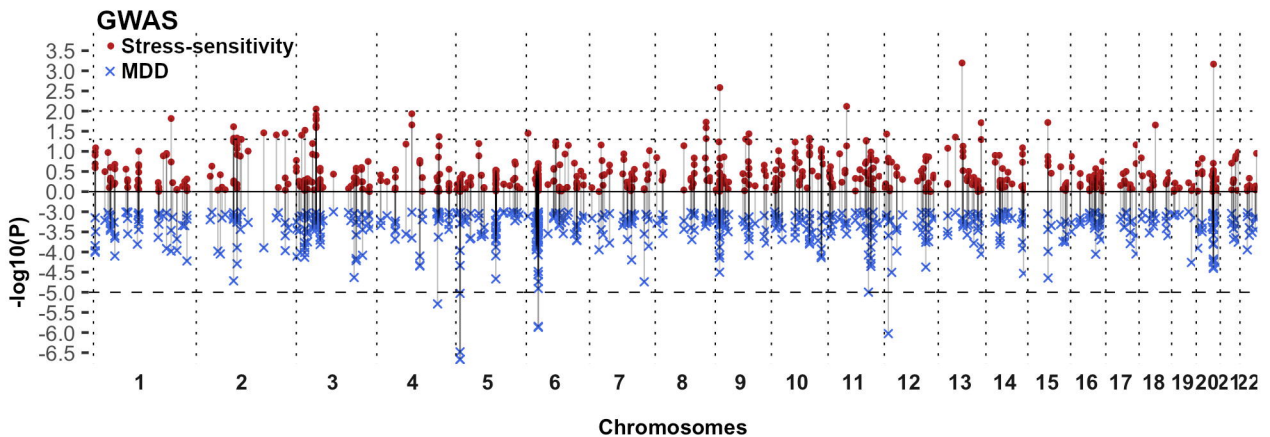
S4 Fig. Miami plots on UK Biobank and Generation Scotland: Scottish Family Health Study. Miami plots showing comparison between association profile between SS and MDD main additive effects. Miami plots from (A) UKB filtering for SS *p* values (top) and MDD *p* values (bottom), (B) GS:SFHS filtering for 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 (-log10 *p*) of association with (up; red

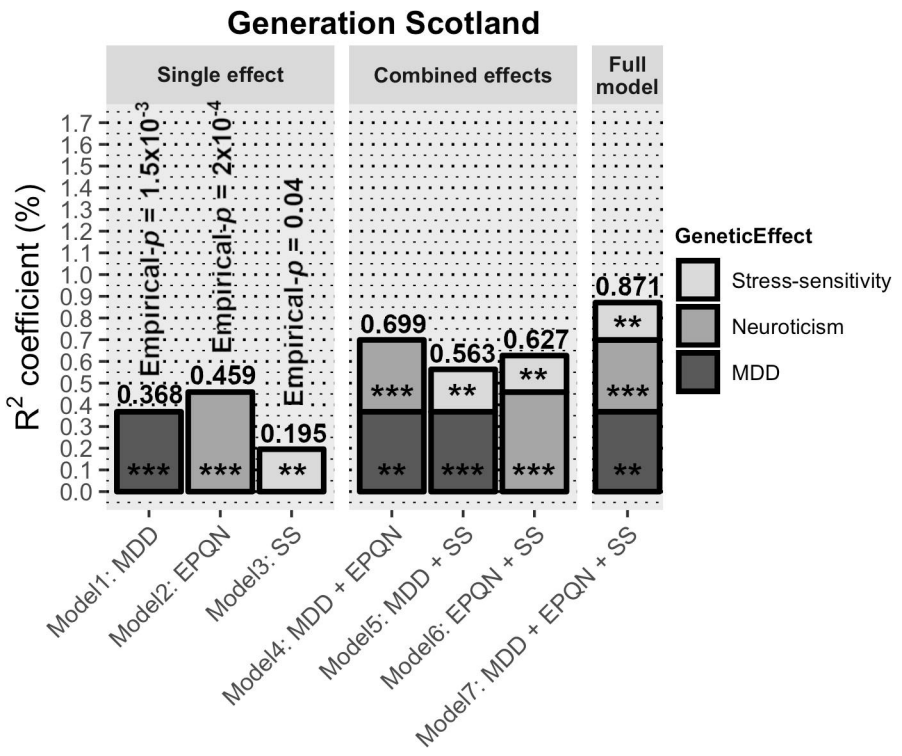
898 dots) SS effect and (down; blue dots) MDD. Dot line: genome-wide suggestive threshold (p = 1x10^{-}
899 ^{5}) at the filtered effect; dashes lines: p value = 0.01 and 0.05 at compared effect.
900
901 **S5 Fig. Manhattan plot of the gene-based test for stress-sensitivity.** Manhattan plot showing
902 gene-based association of stress-sensitivity. The x-axis is base-paired chromosomal position and y-
903 axis is the significance (-$\log_{10}$ p value) of association with SS effect. Genome-wide significance
904 threshold showed by red dashed line was defined at p = 0.05/17,931 = 2.79x10^{-6}.
905
906 **S6 Fig. PRS profiling predicting MDD in UK Biobank.** MDD risk explained (R^2 coefficient (%); top
907 bar values) on the liability scale by each PRS in UKB; weighted by GWAS main additive and GWIS
908 stress-sensitivity effects independently and combined. (A) Using summary statistics from GS:SFHS
909 as discovery sample. (B) Replication fitting PRS_D and PRS_N using summary statistics from worldwide
910 consortiums (i.e. PGC & GPC). Significance codes: p values *** < 0.001 < ** < 0.01 < * < 0.05;
911 derived from likelihood ratio tests. *SS* stands for stress-sensitivity.
912
913 **S1 Table. EPQN comparison between MDD cases and healthy controls.**
914
915 **S2 Table. Top 10 SNPs from GWIS on UK Biobank.**
916
917 **S3 Table. Top 10 SNPs from GWIS on Generation Scotland: Scottish Family Health Study.**
918
919 **S4 Table. Traits with significant evidence of association with closest gene to suggestive stress-**
920 **sensitive hits.** The closest genes to SNPs associated with stress-sensitivity at suggestive
921 significance levels have prior evidence of association in dbGAP with a wide range of

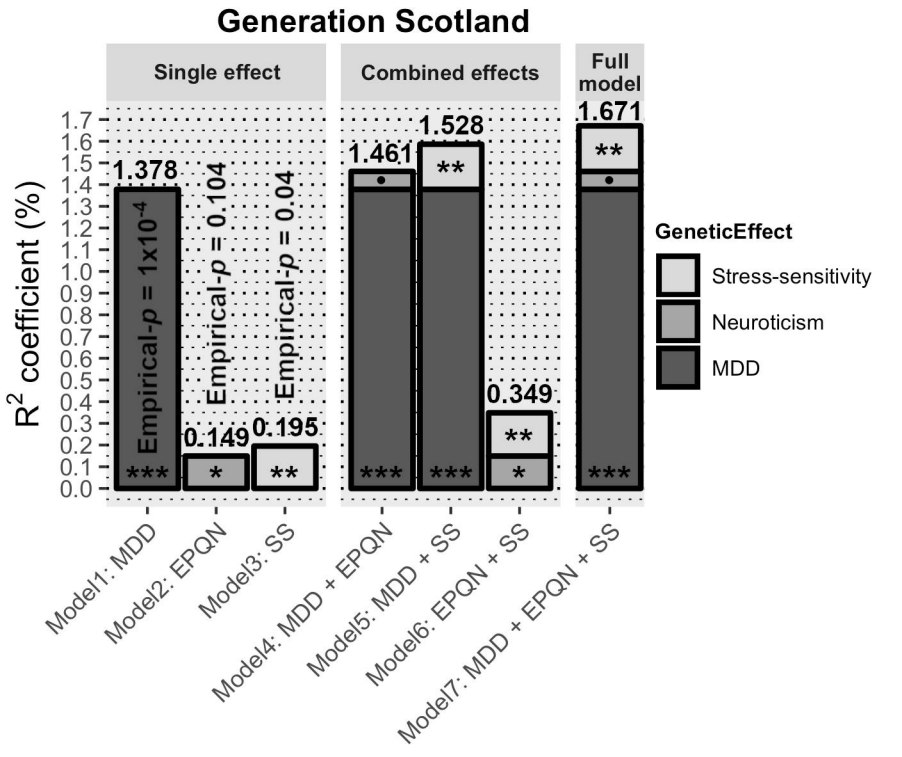
922 neuropsychiatric traits such as schizophrenia, bipolar disorder, attention deficit disorder with
923 hyperactivity, mental competency, intuition, sleep or alcohol drinking.
924
925 **S5 Table. Top 25 hits from gene-based analysis of GWIS meta-analysis.**
926
927 **S6 Table. : Summary results from polygenic risk score (PRS) analysis using PRSice-2.**
928
929 **S7 Table. MDD stratification.**


A)
UK Biobank
-log10(p-value)
EYS
PHF3/EYS
PHF3
KIAA1217/ARHGAP21
OPCML
CRISPLD2/ZDHHC7
ECH1
HNRNPL
Chromosomes
B)
GS:SFHS
-log10(p-value)
DPP10
SNTN/THOC7
-
SLC25A13
LOC283177/-
TSPAN9
-/LINC01524
Chromosomes
C)
Meta-analysis
-log10(p-value)
ZNF366/-
EYS
PHF3/EYS
PHF3
-/LOC101929116
KIAA1217/ARHGAP21
TLL2
OPCML
ANO4
WWOX
Chromosomes


GWAS
Stress-sensitivity
MDD
-log10(P)
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
0.0
-0.5
-1.0
-1.5
-2.0
-2.5
-3.0
-3.5
-4.0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosomes


GWAS
Stress-sensitivity
MDD
-log10(P)
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-3.0
-3.5
-4.0
-4.5
-5.0
-5.5
-6.0
-6.5
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Chromosomes


Generation Scotland
Single effect
Combined effects
Full model
R2 coefficient (%)
Empirical-p = 1.5x10-3
Empirical-p = 2x10-4
Empirical-p = 0.04
0.368
0.459
0.195
0.699
0.563
0.627
0.871
GeneticEffect
Stress-sensitivity
Neuroticism
MDD
Model1: MDD
Model2: EPQN
Model3: SS
Model4: MDD + EPQN
Model5: MDD + SS
Model6: EPQN + SS
Model7: MDD + EPQN + SS


Generation Scotland
Single effect
Combined effects
Full model
R2 coefficient (%)
Empirical-p = 1x10-4
Empirical-p = 0.104
Empirical-p = 0.04
1.378
0.149
0.195
1.461
1.528
0.349
1.671
GeneticEffect
Stress-sensitivity
Neuroticism
MDD
Model1: MDD
Model2: EPQN
Model3: SS
Model4: MDD + EPQN
Model5: MDD + SS
Model6: EPQN + SS
Model7: MDD + EPQN + SS