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

Aleix Arnau-Soler[1*], Mark J. Adams[2], Generation Scotland[&], Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium[¶], Caroline Hayward[3], Pippa A. Thomson[1*]

[1] Medical Genetics Section, Centre for Genomic and Experimental Medicine, MRC Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom

[2] Division of Psychiatry, Royal Edinburgh Hospital, University of Edinburgh, Edinburgh, United Kingdom

[3] Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom

* Corresponding authors

E-mail: Pippa.Thomson@ed.ac.uk (PT) or aleix.arnau.soler@igmm.ed.ac.uk (AAS)

[&]A collaboration between the University Medical School and NHS in Aberdeen, Dundee, Edinburgh and Glasgow, Scotland, United Kingdom.

[¶]Membership of the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium is provided in the S1 Supporting Information.

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.

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]. However, recent stressful life events ($\beta = 0.14$ 95%CI 0.13 - 0.15,
82 $p < 0.001$) have a stronger effect than distant stressful life events suggesting a reduction of
83 effect over time [3]. Long-lasting increases in neuroticism associated with distant negative
84 life 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

120 specific to UKB project are available at
121 http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155583 and the Axiom array at
122 http://media.affymetrix.com/support/downloads/manuals/axiom_2_assay_auto_workflow_
123 user_guide.pdf. UKB genotyping and the stringent QC protocol applied to UKB data before it
124 was released can be found at http://biobank.ctsu.ox.ac.uk/crystal/refer.cgi?id=155580. SNPs
125 genotyped on GS:SFHS were extracted from the imputed UKB genotype data [53] (imputed
126 by UKB using a merged panel of the UK10K haplotype reference panel and the 1000
127 Genomes Phase 3 reference panel) with quality > 0.9 was hard-called using PLINK v1.9 [54].
128 Individuals were removed based on UKB genomic analysis exclusion (UKB Data Dictionary
129 item #22010), non-white British ancestry (#22006: genetic ethnic grouping; from those
130 individuals who self-identified as British, principal component analysis was used to remove
131 outliers), high genotype missingness (#22005), genetic relatedness (#22012; no pair of
132 individuals have a KING-estimated kinship coefficient > 0.0442), QC failure in UK BiLEVE study
133 (#22050 and #22051: UK BiLEVE Affymetrix and UK BiLEVE genotype quality controls for
134 samples) and gender mismatch (#22001: genetic sex). Further, from the initial release of UKB
135 data and using PLINK pi-hat < 0.05, individuals who were also participants of GS:SFHS and
136 their relatives were excluded to remove any overlap of individuals between discovery and
137 target samples. A dataset of 109,283 individuals with 557,813 SNPs remained for further
138 analysis, aged 40-79 (57,328 female, 51,954 male; mean age = 57.1 years, s.d. = 7.99), of
139 which 109,282 had data available for neuroticism score and 23,092 had data available on
140 MDD status (n_{cases} = 7,834, $n_{controls}$ = 15,258, n_{female} = 11,510, n_{male} = 11,582; mean age = 57.7
141 years, s.d. = 8.04). Thus, the final dataset comprised 23,092 unrelated individuals.
142

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

186 In GS:SFHS, participants took in-person clinical visits where they were screened for a history
187 of psychiatric and emotional disorders (i.e., psychiatric, mood state/psychological distress,
188 personality and cognitive assessment) by trained researchers using the Structured Clinical

189 Interview for DSM-IV Non-Patient Version (SCID) [66], which is internationally validated to
190 identify episodes of depression. Those participants that were positive in the initial screening
191 continue through clinical interview and were administered the mood sections of the SCID.
192 The SCID elicited the presence or absence of a lifetime history of MDD, age of onset and
193 number of episodes. Participants fulfilling the criteria for at least one major depressive
194 episode within the last month were defined as current MDD cases. Participants who were
195 screened positive for Bipolar I Disorder were excluded. Those participants who were
196 negative during the initial screening or did not fulfilled criteria for MDD were assigned as
197 controls. Further details regarding the diagnostic assessment are reported elsewhere [56,
198 57]. All interviewers were trained for the administration of the SCID. Inter-rater reliability for
199 the presence or absence of a lifetime diagnosis of major depressive disorder was good
200 (Kappa = 0.86, $p < 0.001$, 95%CI 0.7 to 1.0). In our unrelated GWIS sample (N = 7,155), 2,010
201 had a lifetime diagnosis of MDD and 5,145 were controls.
202

203 ## Statistical Methods

204 ### GWIS and derivation of a genetic stress-sensitivity effect

205 The effect size of an stress-sensitivity effect (β_{SS}) was derived by performing a GWIS
206 for the effect of the MDD status and SNP allele on EPQN (dependent variable) in both UKB
207 and GS:SFHS cohorts using PLINK 1.90 (PLINK-command --gxe; fitting MDD diagnosis as a
208 binary "group" effect) [54]. PLINK-command --gxe estimates the difference in allelic
209 association with a quantitative trait (EPQN) between two groups (MDD cases vs. controls)
210 producing effect estimates on each group and a test of significance for the interaction
211 between SNP allele and MDD status. The interaction *p* value reflects the difference between

212 the regression coefficient of the allelic effect in a linear model for EPQN in MDD cases (β_A)
213 and the same regression coefficient in a linear model for EPQN in controls (β_B). The stress-
214 sensitivity interaction effect was defined as the difference in allele effect between MDD
215 cases and control groups.
216 Considering one SNP, the effect it confers to EPQN can be modelled by MDD status (control =
217 0, MDD case = 1) as follows:

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

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

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

219 Or, it can be modelled as a whole as:

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

220 Where *COV* stands for covariates, β_2 stands for $\beta_1 - \beta_0$, and β_{2c} stands for $\beta_{1c} - \beta_{0c}$.
221 Thus, the interaction effect (β_{SS}) can be estimated as the difference in allelic effect on EPQN
222 between MDD cases (β_A) and controls (β_B) as follows,

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

223 $\hat{\beta}_{SS}$ is therefore defined as the effect size reflecting the genetic stress-sensitivity effect on
224 MDD cases compared to controls (S1 Fig).
225

226 Stress-sensitivity GWIS, main additive effect GWASs, meta-analysis and gene-
227 set analysis.

228 For GWIS and subsequent analyses, sample specific covariates were applied as
229 follows: *UKB*. All phenotypes were adjusted for centre, array and batch as random effects
230 prior to analyses. Analyses were adjusted for age, sex and 15 informative principal

231 components (PCs; UKB Data Dictionary items #22009.01 to #22009.15) as fixed effects to
232 take account of possible population stratification. *GS:SFHS.* All the analyses were adjusted for
233 age, sex and 20 PCs.
234 GWAS for MDD and neuroticism, using logistic and linear models of additive allelic effects
235 respectively, were conducted on the same sample sets for comparison and generation of
236 matched PRS using PRSice-2 [67].
237 Results from the GWIS of UKB and GS:SFHS were combined in a sample size weighted meta-
238 analysis performed using METAL [68]. While the use of standard error weighting is more
239 common, the different diagnostic scheme and MDD prevalence between the two cohorts
240 (GS:SFHS; 12.2%, UKB: 25.8%) [57, 63] may indicate systematic differences in the
241 measurement of MDD. Generalized gene-based analysis of the meta-analysis was performed
242 using MAGMA [69] implemented through FUMA [70] (http://fuma.ctglab.nl). Briefly, SNP
243 summary statistics were mapped to 17,931 protein-coding genes. Individual SNP *p* values
244 from a gene were combined into a gene test-statistic using a SNP-wise model and a known
245 approximation of the sampling distribution used to obtain a gene-based *p* value. Genome-
246 wide significance was defined at $p = 0.05/17{,}931 = 2.79\text{x}10^{-6}$.
247

248 **LD Score regression**

249 The summary statistics from the meta-analysis were used to examine the genetic
250 overlap between the polygenic architecture of stress-sensitivity, MDD and neuroticism. LD
251 score regression was used to derive the genetic correlations (r_G) between these traits [71, 72]
252 using meta-analysed GWAS and GWIS summary statistics. SNP-based heritability was also
253 estimated using LD score regression, using the summary statistics from single-SNP analyses.
254

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

256 Lead SNPs, independently associated with the phenotype, were identified using PLINK
257 1.90 by clumping (*p* threshold < $2x10^{-5}$; LD r2 > 0.1; physical kb threshold = 500kb; 1000
258 Genomes Project Phase 1 CEU, GBR, TSI genotype data), and analysed using DEPICT [73].
259 Further detail is given in 'DEPICT analyses' in S1 Supporting Information.
260 Genes associated with lead SNPs were investigated for evidence of: phenotypic association in
261 the NCBI dbGaP database of genotypes and phenotypes [74]
262 (https://www.ncbi.nlm.nih.gov/gap/phegeni), regulatory DNA elements in normal cell lines
263 and association with expression quantitative trait loci (eQTLs) using the RegulomeDB
264 database [75] (http://www.regulomedb.org) and the Genotype-Tissue Expression (GTEx)
265 Portal [76] (http://www.gtexportal.org).
266

267 **Polygenic profiling**

268 PRS were produced using PRSice-2 [67], permuted 10,000 times and standardized to a
269 mean of 0 and a standard deviation of 1. Using GWIS summary statistics, we created PRS for
270 stress-sensitivity (PRS_{SS}) by weighting the sum of the reference alleles in an individual by the
271 stress-sensitivity effect (β_{SS}). Additional PRS were generated weighting by MDD main
272 additive effects (PRS_D) and neuroticism main additive effects (PRS_N) using GWAS summary
273 statistics from GS:SFHS or UKB. In addition, PRS_D and PRS_N were also generated using
274 summary statistics from the most recent Psychiatric Genetic Consortium (PGC) MDD meta-
275 analysis [42] (excluding GS:SFHS, and UKB individuals when required; N = 155,866 & 138,884)
276 and the Genetics of Personality Consortium (GPC) neuroticism meta-analysis [24, 77] (N =
277 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].

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

303 GS:SFHS MDD cases (n_{cases} = 2,016; n_{female} = 1,345, n_{male} = 671) have data available on
304 MDD course (single or recurrent), age of onset (*n* = 1,964) and episode count (*n* = 2,016), as
305 well as on neuroticism (*n* = 2,010). In addition, a subset were evaluated by Mood Disorder
306 Questionnaire [81] (MDQ; *n* = 1,022) and Schizotypal Personality Questionnaire [82] (SPQ; *n* =
307 1,093). The reduced sample number of MDQ and SPQ reflects the later addition of these
308 questionnaires to the study and does not reflect a particular subgroup of GS:SFHS.
309 Difference in PRS_{SS} and PRS_{D} between MDD cases and controls on GS:SFHS were tested using
310 a Student's two sample t-test (two tailed). Cases of MDD on GS:SFHS with data available on
311 each trait analyzed were stratified by quintiles based on PRS_{SS} and PRS_{D} (5x5 groups). Post
312 hoc, the effects on each trait of quintiles based on PRS_{SS} and its interaction effect with
313 quintiles based on PRS_{D} were assessed using linear regression models adjusting by sex and
314 age in an attempt to identify a characteristic subtype of MDD patients with differential
315 stress-sensitivity levels. The same analysis was reproduced using PRSs as continuous
316 variables.
317

318 # Results

319 We confirmed the elevated neuroticism score in MDD cases in our samples.
320 Individuals with a diagnosis of MDD had significantly higher EPQN scores compared to
321 healthy controls (all $p < 1.9.x10^{-279}$) in both GS:SFHS ($mean_{controls}$ = 3.16; $mean_{cases}$ = 6.42) and
322 UKB ($mean_{controls}$ = 2.79; $mean_{cases}$ = 5.64). Neuroticism levels differ significantly between
323 males and females. To control for this and any age/polygenic effects, which may account for
324 differences in the prevalence of MDD, we created a matched set of cases and controls. The

325 difference in neuroticism levels between cases and controls remained significant after
326 matching the controls for PGC PRS_D, sex and age. (GS:SFHS: $mean_{controls}$ = 3.51; UKB:
327 $mean_{controls}$ = 2.97; all $p < 2.7x10^{-158}$; S1 Table).
328

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

330 No SNPs were associated with stress-sensitivity at the genome-wide significant
331 threshold ($p < 5x10^{-8}$, Fig 1). However, 14 SNPs from 8 loci achieved suggestive *p* value ($p <$
332 $1x10^{-5}$) ranging between $p = 8.9x10^{-6}$-$5.1x10^{-7}$ (Meta-analysis: Table 1; UKB and GS:SFHS: S2
333 and S3 Tables; Meta-analysis QQ-plot with λ: S2 Fig; UKB and GS:SFHS QQ-plots: S3 Fig).
334 Traits with prior evidence of association with the nearest genes to the 8 lead SNPs were
335 identified using dbGap and are shown in S4 Table. Comparison between the SNP association
336 profile along the genome between stress-sensitivity GWIS and MDD GWAS meta-analyses is
337 shown in Miami plots filtering for the most significant stress-sensitivity or MDD SNPs ($p <$
338 0.001; Meta-analysis: Fig 2; UKB and GS:SFHS: S4 Fig). No SNP with a *p*-value < 0.01 had a
339 corresponding p-value in the alternate trait, suggesting that different variants contribute to
340 depression and stress-sensitivity. Gene-based test identified *ZNF366* as the only gene
341 achieving genome-wide significance ($p = 1.48x10^{-7}$; Bonferroni-corrected significance
342 threshold $p < 2.79x10^{-6}$; S5 Table and S5 Fig). Using summary statistics from meta-analysis
343 GWIS results, stress-sensitivity SNP-based heritability was estimated from LD score
344 regression at 5.0% (h^2 = 0.0499, s.e. = 0.017, $p = 1.67x10^{-3}$). Conversely, the SNP-based
345 heritability for MDD and neuroticism were estimated at 9.6% (h^2 = 0.0962, s.e. = 0.0179, $p =$
346 $3.87x10^{-8}$) and 10.1% (h^2 = 0.1006, s.e. = 0.0076, $p = 3.47x10^{-40}$) respectively, using summary
347 statistics from the meta-analysed GWAS of UKB and GS:SFHS.

348

349 **Fig 1. Manhattan plots showing stress-sensitivity associations.**

350 Manhattan plots of the GWIS from (A) UKB, (B) GS:SFHS and (C) sample size weighted meta-
351 analysis of UKB and GS:SFHS. The x-axis is chromosomal position and y-axis is the *p* value (-
352 log10 *p* value) of association with stress-sensitivity effect. Suggestive genome-wide
353 significance threshold ($p = 1x10^{-5}$) is shown by solid line at y = 5. Genes or closest gene up-
354 and down-stream from SNP position (/) are annotated. "-": No gene within 100kb of the SNP.

355

356 **Fig 2. Miami plots showing comparison between association profile between stress-**
357 **sensitivity GWIS and MDD GWAS.**

358 Miami plots from meta-analysis filter at $p = 1x10^{-3}$: (A) filtering for stress-sensitivity *p* values
359 (•), (B) filtering for MDD *p* values (×). The x-axis is chromosomal position and y-axis is the *p*
360 value (-log10 *p* value) of association with stress-sensitivity (up; red dots) and MDD *p* value
361 (down; blue crosses). Dot line: genome-wide suggestive threshold ($p = 1x10^{-5}$) at the filtered
362 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').

363 LD score regression was performed to obtain genetic correlations between stress-sensitivity,
364 MDD and neuroticism. As previously shown, there was a significant genetic correlation
365 between MDD and neuroticism (r_G = 0.637, s.e. = 0.0704, p = 1.39x10^{-19}). However, we found
366 no evidence for a genetic correlation between stress-sensitivity and MDD (rG = -0.099, s.e. =
367 0.182, p = 0.585) or between stress-sensitivity and neuroticism (r_G = 0.114, s.e. = 0.107, p =
368 0.285).
369

370 Pathway enrichment, functional annotation and gene expression
371 analyses

372 Lead SNPs from the GWIS meta-analysis were investigated using DEPICT. No gene
373 showed statistically significant links to stress-sensitivity at a DEPICT false discovery rate (FDR)
374 < 0.05. No significant result was found for either gene set analysis or tissue enrichment
375 analysis at FDR < 0.05. Evidence of regulatory elements on normal cell lines/tissues was
376 identified for 5 of the 12 lead SNPs (i.e. rs3762096, rs10987199, rs2221540, rs246565,
377 rs319924). Two lead SNPs were associated with eQTLs: rs319924 (an intronic SNP in *EYS*) and
378 rs9509508 (an intronic SNP in *LATS2*) and potentially regulate *LGSN/RP3-407E4.3* (p =
379 6.31x10^{-12}/ p = 1.15x10^{-5}) and *LATS2* (p = 3.74x10^{-8}), respectively.
380

381 Polygenic risk scores for stress-sensitivity predict MDD liability

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

386 = 0.078, s.e. = 0.028; best-fit *p* threshold = 0.005; S6 Table). On the liability scale, the MDD
387 variance explained in GS:SFHS by PRS_{SS} was modest (R^2 = 0.195%). This was less than
388 predicted by PRS weighted by the genetic main effects of MDD or neuroticism (PRS_D: R^2 =
389 0.368%; PRS_N: R^2 = 0.459%; Table 2 and S6 Table). However, this association was not cross-
390 validated in UKB using summary data from the smaller GS:SFHS GWIS (Empirical-*p* = 0.68; *p* =
391 0.23; β = 0.004, s.e. = 0.003; best-fit *p* threshold = 0.005; PRS_{SS} R^2 = 0.013%; S6 Table), likely
392 due to lack of power as a result of the small discovery sample size. PRS_D (R^2 = 0.204%) and
393 PRS_N (R^2 = 0.166%) derived from GS:SFHS significantly predicted MDD in UKB (Table 2 and S6
394 Table).

395 **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.

396 Due to the known genetic correlations between MDD, neuroticism and stressful life events [21],
397 models jointly fitting the effects of multiple PRS were analysed. Multiple regression analyses in
398 GS:SFHS showed that, compared to PRS_D effects alone, the stress-sensitivity effect derived from
399 the UKB GWIS effects significantly explains an additional 0.195% (a predictive improvement of
400 53.1%, $p = 5.1x10^{-3}$; PRS_D: β = 0.112, s.e. = 0.029; PRS_{SS} : β = 0.078, s.e. = 0.028). The inclusion of
401 PRS_{SS} in the full model, where PRS_{SS} was fitted along with both PRS_D and PRS_N weighted by GWAS
402 summary statistics derived from UKB remained significant; explaining an additional 0.172% (a
403 predictive improvement of 24.6%, $p = 8.5x10^{-3}$; PRS_D: β = 0.093, s.e. = 0.029; PRS_N: β = 0.107, s.e. =
404 0.030; PRS_{SS}: β = 0.073, s.e. = 0.028). In models fitting PRS_D and PRS_N, the variances explained were
405 non-additive, demonstrating the partial overlap between MDD risk prediction from PRS_D and PRS_N
406 main additive effects. This is consistent with the known genetic correlation between these two
407 traits. An overlap was not seen between the variance explained by PRS_{SS} effect and the variance
408 explained by PRS_D and/or PRS_N. Multiple regression analyses fitting PRS_D and PRS_N derived from
409 worldwide consortiums (Fig 3) showed that the increased sample size from GWAS used to derive
410 PRS_D resulted in an increment of MDD variance explained in GS:SFHS by PRS_D (from 0.368% to
411 1.378%). However, there was no change in the proportion of the variance explained by the PRS_{SS}
412 in the full model (PRS_{SS} $p = 3.5x10^{-3}$). These results suggest that PRS_{SS} explains a proportion of
413 MDD risk not accounted for by PRS_D or PRS_N at current sample sizes. However, these findings were
414 not cross-validated in UKB using PRS_{SS} derived from GS:SFHS GWIS, likely due to lack of power as a
415 result of the small discovery sample size (S6 Fig).
416
417 **Fig 3. MDD is best predicted using multiple PRS.**
418 MDD risk explained (R^2 coefficient (%); top bar values) on the liability scale by each PRS in GS:SFHS;
419 weighted by GWAS main additive and GWIS stress-sensitivity effects independently and combined.

420 (A) Using summary statistics from UKB as discovery sample. There is an increment on MDD risk
421 prediction from adding PRS_{SS} to PRS_D model of 53.1% and 24.6% when combining PRS_{SS} with both
422 MDD and neuroticism PRS. (B) Replication of fitting PRS_D and PRS_N using summary statistics from
423 worldwide consortiums (i.e. PGC &GPC). Significance codes: *p* values *** < 0.001 < ** < 0.01 < * <
424 0.05 < • < 0.1; derived from likelihood ratio tests. *SS* stands for stress-sensitivity.
425

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

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

436 # Discussion

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

459 consumption, stress and the risk of depression [95-100]. However, findings should be interpreted
460 with caution, as these loci did not reach genome-wide significance at current sample size.
461 Evidence of an eQTL effect was predicted for a lead SNP in *LATS2*, a positive regulator of histone
462 methyltransferase activity [101] a process important in anxiety-related behaviours [102]. The prior
463 association of the top two loci in this study with alcohol related-phenotypes suggests that genes
464 involved in the sensitivity to stress may mediate the effects of stress on alcohol consumption.
465 Some *PHF3* paralogs have been shown to be linked with depression and modulate stress
466 response [103, 104].
467 Gene-based analysis identified a genome-wide significant association between *ZNF366* and stress-
468 sensitivity. *ZNF366* (also known as *DC-SCRIPT*) is a corepressor of transcription found in nuclear
469 receptor complexes including the glucocorticoid receptor. *ZNF366* represses glucocorticoid
470 receptor-mediated transcription in monocyte-derived dendritic cells [91]; and may act through
471 histone deacetylases to modulate immune response [92]. There is evidence from a large-scale
472 mRNA display study that *PHF3*, in the region underlying the most significant peak in the single SNP
473 analysis, may also interact, directly or indirectly, with the glucocorticoid receptor (IntAct
474 database [93]) but this has not been confirmed. These results reinforce the hypothesis that our
475 proxy for stress-sensitivity truly reflects the genetic architecture of sensitivity to respond to stress.
476 We estimated a significant lower bound on common SNP-based heritability for stress-sensitivity of
477 5%. Whilst the known genetic overlap between MDD and neuroticism was detectable, the lack of
478 genetic correlation with stress-sensitivity, reinforced by results from multiple regression analyses,
479 indicated a lack of significant overlap in the genetics factors underpinning stress-sensitivity and
480 MDD or neuroticism. This analysis may be limited by our sample size, although using the largest
481 available meta-analyses of MDD and neuroticism [42, 77] did not decrease the proportion of
482 liability explained by the PRS_{SS}. We note, that as such meta-analyses increase in size it is likely, as

483 with the effects of smoking in schizophrenia [105, 106], that the indirect genetic effects of the
484 environment on the risk of depression will be detected by GWAS. However, through studies such
485 as ours, or similar, the mechanism for the effect of the risk alleles may be clarified.
486 Further, we show that such genetic information in stress-sensitivity could significantly improve the
487 proportion of liability to MDD predicted by PRS based only on additive genetic effects on MDD
488 identified by large GWAS. The summary results from the GWIS were used to derive a PRS
489 reflecting the genetic difference in stress-sensitivity. This variable significantly predicted liability to
490 MDD in GS:SFHS ($p = 5.2x10^{-3}$, Empirical-p = 0.04 after 10,000 permutations), although this finding
491 could not be replicated in UKB (Empirical-p = 0.68), likely due to lack of power. This is consistent
492 with the expectation that the larger the discovery sample (i.e. UKB), the greater the accuracy of
493 the weighting and the more predictive the PRS [107]. Multiple regression models in GS:SFHS
494 suggest that inclusion of PRS weighted by stress-sensitivity significantly improves MDD prediction
495 over use of either MDD and/or neuroticism weighted PRS alone (improvement in full model p =
496 $8.5x10^{-3}$). However, we were unable to identify a subgroup of MDD cases with higher PRS_{ss}. The
497 polygenic interaction approach used in our study may, therefore, improve the interpretation of
498 both positive and negative findings from GWAS studies (i.e. pathways and mechanisms involved,
499 lack of replication, or negative findings in variants mediating environmental effects). Added to
500 paralleling recent developments in GWAS analyses, it may maximize our power to detect gene-by-
501 environment effects in this heterogeneous disorder.
502 Future studies will be required to further investigate the effects of adverse life events in
503 individuals with high or low polygenic risk scores for stress-sensitivity. However, the methodology
504 presented allows addressing the genetic response to negative outcomes via proxy in the absence
505 of prospective environmental data.

506 Here we identify an independent set of risk variants for an individual's response to negative
507 outcomes and show that incorporating information across many loci provides clear and replicable
508 evidence for a genetic effect of stress-sensitivity on MDD risk; identifying a potential genetic link
509 with alcohol intake. These results require further study, but may inform treatment of comorbid
510 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 Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium**, which depends on the contributions of many parties: Naomi R Wray (Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU and Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU), Stephan Ripke (Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, MA, US, Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, DE and Medical and Population Genetics, Broad Institute, Cambridge, MA, US), Manuel Mattheisen (Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, SE, Department of Biomedicine, Aarhus University, Aarhus, DK, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK and iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK), Maciej Trzaskowski (Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD), Enda M Byrne (Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU), Abdel Abdellaoui (Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL), Mark J Adams (Division of Psychiatry, University of Edinburgh, Edinburgh, GB), Esben Agerbo (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK, Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK and National Centre for Register-Based Research, Aarhus University, Aarhus, DK), Tracy M Air (Discipline of Psychiatry, University of Adelaide, Adelaide, SA, AU), Till F M Andlauer (Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE and Munich Cluster for Systems Neurology (SyNergy), Munich, DE), Silviu-Alin Bacanu (Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US), Marie Bækvad-Hansen (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK and Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK), Aartjan T F Beekman (Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, NL), Tim B Bigdeli (Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US and Virginia Institute for Psychiatric and Behavior Genetics, Richmond, VA, US), Elisabeth B Binder (Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE and Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, US), Douglas H R Blackwood (Division of Psychiatry, University of Edinburgh, Edinburgh, GB), Julien Bryois (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE), Henriette N Buttenschøn (iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK and Department of Clinical Medicine, Translational Neuropsychiatry Unit, Aarhus University, Aarhus, DK), Jonas Bybjerg-Grauholm (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK and Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK), Na Cai (Human Genetics, Wellcome Trust Sanger Institute, Cambridge, GB and Statistical genomics and systems genetics, European Bioinformatics Institute (EMBL-EBI), Cambridge, GB), Enrique Castelao (Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, CH), Jane Hvarregaard Christensen (Department of Biomedicine, Aarhus University, Aarhus, DK, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK and iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK), Toni-Kim Clarke (Division of Psychiatry, University of Edinburgh,

Edinburgh, GB), Jonathan R I Coleman (MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB), Lucía Colodro-Conde (Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, AU), Baptiste Couvy-Duchesne (Centre for Advanced Imaging, The University of Queensland, Saint Lucia, QLD, AU and Queensland Brain Institute, The University of Queensland, Saint Lucia, QLD, AU), Nick Craddock (Psychological Medicine, Cardiff University, Cardiff, GB), Gregory E Crawford (Center for Genomic and Computational Biology, Duke University, Durham, NC, US and Department of Pediatrics, Division of Medical Genetics, Duke University, Durham, NC, US), Gail Davies (Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB), Ian J Deary (Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB), Franziska Degenhardt (Institute of Human Genetics, University of Bonn, Bonn, DE and Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE), Eske M Derks (Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, AU), Nese Direk (Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, NL and Psychiatry, Dokuz Eylul University School Of Medicine, Izmir, TR), Conor V Dolan (Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL), Erin C Dunn (Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US, Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US and Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US), Thalia C Eley (MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB), Valentina Escott-Price (Neuroscience and Mental Health, Cardiff University, Cardiff, GB), Farnush Farhadi Hassan Kiadeh (Bioinformatics, University of British Columbia, Vancouver, BC, CA), Hilary K Finucane (Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, US and Department of Mathematics, Massachusetts Institute of Technology, Cambridge, MA, US), Andreas J Forstner (Institute of Human Genetics, University of Bonn, Bonn, DE, Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE, Department of Psychiatry (UPK), University of Basel, Basel, CH and Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH), Josef Frank (Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE), Héléna A Gaspar (MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB), Michael Gill (Department of Psychiatry, Trinity College Dublin, Dublin, IE), Fernando S Goes (Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US), Scott D Gordon (Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU), Jakob Grove (Department of Biomedicine, Aarhus University, Aarhus, DK, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK and Bioinformatics Research Centre, Aarhus University, Aarhus, DK), Lynsey S Hall (Division of Psychiatry, University of Edinburgh, Edinburgh, GB and Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne, GB), Christine Søholm Hansen (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK and Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK), Thomas F Hansen (Danish Headache Centre, Department of Neurology, Rigshospitalet, Glostrup, DK, Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, DK and iPSYCH, The Lundbeck Foundation Initiative for Psychiatric Research, Copenhagen, DK), Stefan Herms (Institute of Human Genetics, University of Bonn, Bonn, DE, Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE and Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH), Ian B Hickie (Brain and Mind Centre, University of Sydney, Sydney, NSW, AU), Per Hoffmann (Institute of Human Genetics, University of Bonn, Bonn, DE, Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE and Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH), Georg Homuth (Interfaculty Institute for Genetics and Functional Genomics, Department of Functional Genomics, University Medicine and Ernst Moritz Arndt University Greifswald, Greifswald, Mecklenburg-Vorpommern, DE), Carsten Horn (Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences, Roche Innovation Center Basel, F. Hoffmann-La Roche Ltd, Basel, CH), Jouke-Jan Hottenga (Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL), David M Hougaard (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK and Center for Neonatal Screening, Department for Congenital Disorders, Statens Serum Institut, Copenhagen, DK), Marcus Ising (Max Planck Institute of Psychiatry,

605 Munich, DE), Rick Jansen (Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam,
606 NL), Eric Jorgenson (Division of Research, Kaiser Permanente Northern California, Oakland, CA, US), James A Knowles
607 (Psychiatry & The Behavioral Sciences, University of Southern California, Los Angeles, CA, US), Isaac S Kohane
608 (Department of Biomedical Informatics, Harvard Medical School, Boston, MA, US, Department of Medicine, Brigham
609 and Women's Hospital, Boston, MA, US and Informatics Program, Boston Children's Hospital, Boston, MA, US), Julia
610 Kraft (Department of Psychiatry and Psychotherapy, Universitätsmedizin Berlin Campus Charité Mitte, Berlin, DE),
611 Warren W. Kretzschmar (Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, GB), Jesper Krogh
612 (Department of Endocrinology at Herlev University Hospital, University of Copenhagen, Copenhagen, DK), Zoltán
613 Kutalik (Institute of Social and Preventive Medicine (IUMSP), University Hospital of Lausanne, Lausanne, VD, CH and
614 Swiss Institute of Bioinformatics, Lausanne, VD, CH), Yihan Li (Wellcome Trust Centre for Human Genetics, University
615 of Oxford, Oxford, GB), Penelope A Lind (Genetics and Computational Biology, QIMR Berghofer Medical Research
616 Institute, Herston, QLD, AU), Donald J MacIntyre Division of Psychiatry, Centre for Clinical Brain Sciences, University of
617 Edinburgh, Edinburgh, GB and Mental Health, NHS 24, Glasgow, GB), Dean F MacKinnon (Psychiatry & Behavioral
618 Sciences, Johns Hopkins University, Baltimore, MD, US), Robert M Maier (Queensland Brain Institute, The University of
619 Queensland, Brisbane, QLD, AU), Wolfgang Maier (Department of Psychiatry and Psychotherapy, University of Bonn,
620 Bonn, DE), Jonathan Marchini (Statistics, University of Oxford, Oxford, GB), Hamdi Mbarek (Dept of Biological
621 Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL), Patrick
622 McGrath (Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, US), Peter McGuffin
623 (MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB), Sarah E Medland
624 (Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Herston, QLD, AU), Divya Mehta
625 (Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU and School of Psychology and
626 Counseling, Queensland University of Technology, Brisbane, QLD, AU), Christel M Middeldorp (Dept of Biological
627 Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL, Child and
628 Youth Mental Health Service, Children's Health Queensland Hospital and Health Service, South Brisbane, QLD, AU and
629 Child Health Research Centre, University of Queensland, Brisbane, QLD, AU), Evelin Mihailov (Estonian Genome
630 Center, University of Tartu, Tartu, EE), Yuri Milaneschi (Department of Psychiatry, Vrije Universiteit Medical Center
631 and GGZ inGeest, Amsterdam, NL), Lili Milani (Estonian Genome Center, University of Tartu, Tartu, EE), Francis M
632 Mondimore (Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US), Grant W Montgomery
633 (Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU), Sara Mostafavi (Medical
634 Genetics, University of British Columbia, Vancouver, BC, CA and Statistics, University of British Columbia, Vancouver,
635 BC, CA), Niamh Mullins (MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London,
636 GB), Matthias Nauck DZHK (German Centre for Cardiovascular Research), Partner Site Greifswald, University Medicine,
637 University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE and Institute of Clinical Chemistry and
638 Laboratory Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE), Bernard Ng
639 (Statistics, University of British Columbia, Vancouver, BC, CA), Michel G Nivard (Dept of Biological Psychology &
640 EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL), Dale R Nyholt
641 (Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, QLD, AU), Paul F
642 O'Reilly (MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB), Hogni
643 Oskarsson (Humus, Reykjavik, IS), Michael J Owen (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff
644 University, Cardiff, GB), Jodie N Painter (Genetics and Computational Biology, QIMR Berghofer Medical Research
645 Institute, Herston, QLD, AU), Carsten Bøcker Pedersen (iPSYCH, The Lundbeck Foundation Initiative for Integrative
646 Psychiatric Research, DK, Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK and National
647 Centre for Register-Based Research, Aarhus University, Aarhus, DK), Marianne Giørtz Pedersen (iPSYCH, The Lundbeck
648 Foundation Initiative for Integrative Psychiatric Research, DK, Centre for Integrated Register-based Research, Aarhus
649 University, Aarhus, DK and National Centre for Register-Based Research, Aarhus University, Aarhus, DK), Roseann E.
650 Peterson (Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US and Virginia Institute for
651 Psychiatric & Behavioral Genetics, Virginia Commonwealth University, Richmond, VA, US), Erik Pettersson
652 (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE), Wouter J Peyrot
653 (Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, NL), Giorgio Pistis

654 (Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, CH), Danielle Posthuma (Clinical Genetics,
655 Vrije Universiteit Medical Center, Amsterdam, NL and Complex Trait Genetics, Vrije Universiteit Amsterdam,
656 Amsterdam, NL), Jorge A Quiroz (Solid Biosciences, Boston, MA, US), Per Qvist (Department of Biomedicine, Aarhus
657 University, Aarhus, DK, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK and iPSYCH, The
658 Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK), John P Rice (Department of Psychiatry,
659 Washington University in Saint Louis School of Medicine, Saint Louis, MO, US), Brien P. Riley (Department of
660 Psychiatry, Virginia Commonwealth University, Richmond, VA, US), Margarita Rivera (MRC Social Genetic and
661 Developmental Psychiatry Centre, King's College London, London, GB and Department of Biochemistry and Molecular
662 Biology II, Institute of Neurosciences, Center for Biomedical Research, University of Granada, Granada, ES), Saira
663 Saeed Mirza (Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, NL), Robert Schoevers (Department of Psychiatry,
664 University of Groningen, University Medical Center Groningen, Groningen, NL), Eva C Schulte (Department of
665 Psychiatry and Psychotherapy, Medical Center of the University of Munich, Campus Innenstadt, Munich, DE and
666 Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Campus
667 Innenstadt, Munich, DE), Ling Shen (Division of Research, Kaiser Permanente Northern California, Oakland, CA, US),
668 Jianxin Shi (Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, US), Stanley I Shyn
669 (Behavioral Health Services, Kaiser Permanente Washington, Seattle, WA, US), Engilbert Sigurdsson (Faculty of
670 Medicine, Department of Psychiatry, University of Iceland, Reykjavik, IS), Grant C B Sinnamon (School of Medicine and
671 Dentistry, James Cook University, Townsville, QLD, AU), Johannes H Smit (Department of Psychiatry, Vrije Universiteit
672 Medical Center and GGZ inGeest, Amsterdam, NL), Daniel J Smith (Institute of Health and Wellbeing, University of
673 Glasgow, Glasgow, GB), Hreinn Stefansson (deCODE Genetics / Amgen, Reykjavik, IS), Stacy Steinberg (deCODE
674 Genetics / Amgen, Reykjavik, IS), Fabian Streit (Department of Genetic Epidemiology in Psychiatry, Central Institute of
675 Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE), Jana
676 Strohmaier (Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty
677 Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE), Katherine E Tansey (College of Biomedical
678 and Life Sciences, Cardiff University, Cardiff, GB), Henning Teismann (Institute of Epidemiology and Social Medicine,
679 University of Münster, Münster, Nordrhein-Westfalen, DE), Alexander Teumer (Institute for Community Medicine,
680 University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE), Wesley Thompson iPSYCH, The Lundbeck
681 Foundation Initiative for Integrative Psychiatric Research, DK, Institute of Biological Psychiatry, Mental Health Center
682 Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, DK, Department of Psychiatry, University
683 of California, San Diego, San Diego, CA, US and KG Jebsen Centre for Psychosis Research, Norway Division of Mental
684 Health and Addiction, Oslo University Hospital, Oslo, NO), Pippa A Thomson (Medical Genetics Section, CGEM, IGMM,
685 University of Edinburgh, Edinburgh, GB), Thorgeir E Thorgeirsson (deCODE Genetics / Amgen, Reykjavik, IS), Matthew
686 Traylor (Clinical Neurosciences, University of Cambridge, Cambridge, GB), Jens Treutlein (Department of Genetic
687 Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University,
688 Mannheim, Baden-Württemberg, DE), Vassily Trubetskoy (Department of Psychiatry and Psychotherapy,
689 Universitätsmedizin Berlin Campus Charité Mitte, Berlin, DE), André G Uitterlinden (Internal Medicine, Erasmus MC,
690 Rotterdam, Zuid-Holland, NL), Daniel Umbricht (Roche Pharmaceutical Research and Early Development,
691 Neuroscience, Ophthalmology and Rare Diseases Discovery & Translational Medicine Area, Roche Innovation Center
692 Basel, F. Hoffmann-La Roche Ltd, Basel, CH), Sandra Van der Auwera (Department of Psychiatry and Psychotherapy,
693 University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE), Albert M van Hemert (Department of
694 Psychiatry, Leiden University Medical Center, Leiden, NL), Alexander Viktorin (Department of Medical Epidemiology
695 and Biostatistics, Karolinska Institutet, Stockholm, SE), Peter M Visscher (Institute for Molecular Bioscience, The
696 University of Queensland, Brisbane, QLD, AU and Queensland Brain Institute, The University of Queensland, Brisbane,
697 QLD, AU), Yunpeng Wang (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK,
698 Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark,
699 Copenhagen, DK and KG Jebsen Centre for Psychosis Research, Norway Division of Mental Health and Addiction, Oslo
700 University Hospital, Oslo, NO), Bradley T. Webb (Virginia Institute of Psychiatric & Behavioral Genetics, Virginia
701 Commonwealth University, Richmond, VA, US), Shantel Marie Weinsheimer (iPSYCH, The Lundbeck Foundation
702 Initiative for Integrative Psychiatric Research, DK and Institute of Biological Psychiatry, Mental Health Center Sct. Hans,

Mental Health Services Capital Region of Denmark, Copenhagen, DK), Jürgen Wellmann (Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, DE), Gonneke Willemsen (Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL), Stephanie H Witt (Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE), Yang Wu (Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU), Hualin S Xi (Computational Sciences Center of Emphasis, Pfizer Global Research and Development, Cambridge, MA, US), Jian Yang (Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU and Institute for Molecular Bioscience; Queensland Brain Institute, The University of Queensland, Brisbane, QLD, AU), Futao Zhang (Institute for Molecular Bioscience, The University of Queensland, Brisbane, QLD, AU), Volker Arolt (Department of Psychiatry, University of Münster, Münster, Nordrhein-Westfalen, DE), Bernhard T Baune (Discipline of Psychiatry, University of Adelaide, Adelaide, SA, AU), Klaus Berger (Institute of Epidemiology and Social Medicine, University of Münster, Münster, Nordrhein-Westfalen, DE), Dorret I Boomsma (Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL), Sven Cichon (Institute of Human Genetics, University of Bonn, Bonn, DE, Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, CH, Institute of Medical Genetics and Pathology, University Hospital Basel, University of Basel, Basel, CH and Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, DE), Udo Dannlowski (Department of Psychiatry, University of Münster, Münster, Nordrhein-Westfalen, DE), EJC de Geus (Dept of Biological Psychology & EMGO+ Institute for Health and Care Research, Vrije Universiteit Amsterdam, Amsterdam, NL and Amsterdam Public Health Institute, Vrije Universiteit Medical Center, Amsterdam, NL), J Raymond DePaulo (Psychiatry & Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US), Enrico Domenici (Centre for Integrative Biology, Università degli Studi di Trento, Trento, Trentino-Alto Adige, IT), Katharina Domschke (Department of Psychiatry and Psychotherapy, Medical Center, University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, DE), Tõnu Esko 5, (Estonian Genome Center, University of Tartu, Tartu, EE), Hans J Grabe (Department of Psychiatry and Psychotherapy, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE), Steven P Hamilton (Psychiatry, Kaiser Permanente Northern California, San Francisco, CA, US), Caroline Hayward (Medical Research Council Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, GB), Andrew C Heath (Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, US), Kenneth S Kendler (Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, US), Stefan Kloiber (Max Planck Institute of Psychiatry, Munich, DE, Department of Psychiatry, University of Toronto, Toronto, ON, CA and Centre for Addiction and Mental Health, Toronto, ON, CA), Glyn Lewis (Division of Psychiatry, University College London, London, GB), Qingqin S Li (Neuroscience Therapeutic Area, Janssen Research and Development, LLC, Titusville, NJ, US), Susanne Lucae (Max Planck Institute of Psychiatry, Munich, DE), Pamela AF Madden (Department of Psychiatry, Washington University in Saint Louis School of Medicine, Saint Louis, MO, US), Patrik K Magnusson (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE), Nicholas G Martin (Genetics and Computational Biology, QIMR Berghofer Medical Research Institute, Brisbane, QLD, AU), Andrew M McIntosh* (Division of Psychiatry, University of Edinburgh, Edinburgh, GB and Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, GB), Andres Metspalu (Estonian Genome Center, University of Tartu, Tartu, EE and Institute of Molecular and Cell Biology, University of Tartu, Tartu, EE), Ole Mors (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK and Psychosis Research Unit, Aarhus University Hospital, Risskov, Aarhus, DK), Preben Bo Mortensen (iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK, iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK, Centre for Integrated Register-based Research, Aarhus University, Aarhus, DK and National Centre for Register-Based Research, Aarhus University, Aarhus, DK), Bertram Müller-Myhsok (Department of Translational Research in Psychiatry, Max Planck Institute of Psychiatry, Munich, DE, Munich Cluster for Systems Neurology (SyNergy), Munich, DE and University of Liverpool, Liverpool, GB), Merete Nordentoft (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK and Mental Health Center Copenhagen, Copenhagen Universtity Hospital, Copenhagen, DK), Markus M Nöthen (Institute of Human Genetics, University of Bonn, Bonn, DE and Life&Brain Center, Department of Genomics, University of Bonn, Bonn, DE), Michael C O'Donovan (MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, GB), Sara A Paciga (Human

Genetics and Computational Biomedicine, Pfizer Global Research and Development, Groton, CT, US), Nancy L Pedersen (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE), Brenda WJH Penninx (Department of Psychiatry, Vrije Universiteit Medical Center and GGZ inGeest, Amsterdam, NL), Roy H Perlis (Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US and Psychiatry, Harvard Medical School, Boston, MA, US), David J Porteous (Medical Genetics Section, CGEM, IGMM, University of Edinburgh, Edinburgh, GB), James B Potash (Psychiatry, University of Iowa, Iowa City, IA, US), Martin Preisig (Department of Psychiatry, University Hospital of Lausanne, Prilly, Vaud, CH), Marcella Rietschel (Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE), Catherine Schaefer (Division of Research, Kaiser Permanente Northern California, Oakland, CA, US), Thomas G Schulze (Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Baden-Württemberg, DE, Institute of Psychiatric Phenomics and Genomics (IPPG), Medical Center of the University of Munich, Campus Innenstadt, Munich, DE, Department of Psychiatry and Behavioral Sciences, Johns Hopkins University, Baltimore, MD, US, Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Goettingen, Niedersachsen, DE and Human Genetics Branch, NIMH Division of Intramural Research Programs, Bethesda, MD, US), Jordan W Smoller (Department of Psychiatry, Massachusetts General Hospital, Boston, MA, US, Psychiatric and Neurodevelopmental Genetics Unit (PNGU), Massachusetts General Hospital, Boston, MA, US and Stanley Center for Psychiatric Research, Broad Institute, Cambridge, MA, US), Kari Stefansson (deCODE Genetics / Amgen, Reykjavik, IS and Faculty of Medicine, University of Iceland, Reykjavik, IS), Henning Tiemeier (Epidemiology, Erasmus MC, Rotterdam, Zuid-Holland, NL, Child and Adolescent Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL and Psychiatry, Erasmus MC, Rotterdam, Zuid-Holland, NL), Rudolf Uher (Psychiatry, Dalhousie University, Halifax, NS, CA), Henry Völzke (Institute for Community Medicine, University Medicine Greifswald, Greifswald, Mecklenburg-Vorpommern, DE), Myrna M Weissman (Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY, US and Division of Epidemiology, New York State Psychiatric Institute, New York, NY, US), Thomas Werge (iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK, Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Mental Health Services Capital Region of Denmark, Copenhagen, DK and Department of Clinical Medicine, University of Copenhagen, Copenhagen, DK), Cathryn M Lewis* (MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB and Department of Medical & Molecular Genetics, King's College London, London, GB), Douglas F Levinson (Psychiatry & Behavioral Sciences, Stanford University, Stanford, CA, US), Gerome Breen (MRC Social Genetic and Developmental Psychiatry Centre, King's College London, London, GB and NIHR BRC for Mental Health, King's College London, London, GB), Anders D Børglum (Department of Biomedicine, Aarhus University, Aarhus, DK, iSEQ, Centre for Integrative Sequencing, Aarhus University, Aarhus, DK and iPSYCH, The Lundbeck Foundation Initiative for Integrative Psychiatric Research, DK), Patrick F Sullivan (Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, SE, Genetics, University of North Carolina at Chapel Hill, Chapel Hill, NC, US and Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC, US). **PGC-MDD group Chairs*:** Catherine Lewis (cathryn.lewis@kcl.ac.uk) and Andrew McIntosh (andrew.mcintosh@ed.ac.uk).

789 # References

790 1. Monroe SM. Modern approaches to conceptualizing and measuring human life stress.
791 Annu Rev Clin Psychol. 2008;4:33-52. doi: 10.1146/annurev.clinpsy.4.022007.141207.
792 PubMed PMID: 17716038.
793 2. Jeronimus BF, Riese H, Sanderman R, Ormel J. Mutual reinforcement between
794 neuroticism and life experiences: a five-wave, 16-year study to test reciprocal causation.
795 Journal of personality and social psychology. 2014;107(4):751-64. doi: 10.1037/a0037009.
796 PubMed PMID: 25111305.
797 3. Riese H, Snieder H, Jeronimus BF, Korhonen T, Rose RJ, Kaprio J, et al. Timing of
798 Stressful Life Events Affects Stability and Change of Neuroticism. European Journal of
799 Personality. 2014;28(2):193-200. doi: 10.1002/per.1929.
800 4. Jeronimus BF, Ormel J, Aleman A, Penninx BW, Riese H. Negative and positive life
801 events are associated with small but lasting change in neuroticism. Psychol Med.
802 2013;43(11):2403-15. doi: 10.1017/S0033291713000159. PubMed PMID: 23410535.
803 5. Kendler KS, Kuhn J, Prescott CA. The interrelationship of neuroticism, sex, and stressful
804 life events in the prediction of episodes of major depression. Am J Psychiatry.
805 2004;161(4):631-6. doi: 10.1176/appi.ajp.161.4.631. PubMed PMID: 15056508.
806 6. Kessler RC. The effects of stressful life events on depression. Annu Rev Psychol.
807 1997;48:191-214. doi: 10.1146/annurev.psych.48.1.191. PubMed PMID: 9046559.
808 7. Tennant C. Life events, stress and depression: a review of recent findings. Aust N Z J
809 Psychiatry. 2002;36(2):173-82. doi: 10.1046/j.1440-1614.2002.01007.x. PubMed PMID:
810 11982537.
811 8. Porcelli B, Pozza A, Bizzaro N, Fagiolini A, Costantini MC, Terzuoli L, et al. Association
812 between stressful life events and autoimmune diseases: A systematic review and meta-
813 analysis of retrospective case-control studies. Autoimmun Rev. 2016;15(4):325-34. doi:
814 10.1016/j.autrev.2015.12.005. PubMed PMID: 26708168.
815 9. Lin Y, Wang C, Zhong Y, Huang X, Peng L, Shan G, et al. Striking life events associated
816 with primary breast cancer susceptibility in women: a meta-analysis study. J Exp Clin Cancer
817 Res. 2013;32(1):53. doi: 10.1186/1756-9966-32-53. PubMed PMID: 23941600; PubMed
818 Central PMCID: PMCPMC3751759.
819 10. Jafri SHR, Ali F, Mollaeian A, Hasan SM, Hussain R, Akkanti BH, et al. Major stressful life
820 events and risk of developing lung cancer. Journal of Clinical Oncology.
821 2017;35(15_suppl):1575-. doi: 10.1200/JCO.2017.35.15_suppl.1575.
822 11. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major
823 depression. Neuropsychopharmacology. 2004;29(10):1765-81. doi: 10.1038/sj.npp.1300506.
824 PubMed PMID: 15213704.
825 12. Bogdan R, Nikolova YS, Pizzagalli DA. Neurogenetics of depression: a focus on reward
826 processing and stress sensitivity. Neurobiol Dis. 2013;52:12-23. doi:
827 10.1016/j.nbd.2012.05.007. PubMed PMID: 22659304; PubMed Central PMCID:
828 PMCPMC3570616.
829 13. Lazarus RS, Folkman S. Transactional theory and research on emotions and coping.
830 European Journal of Personality. 1987;1(3):141-69. doi: 10.1002/per.2410010304.
831 14. Smith MA, Riccalton VC, Kelly-Hughes DH, Craw OA, Allen SF, O'Connor DB, et al. The
832 relationship between Type D personality and physical health complaints is mediated by
833 perceived stress and anxiety but not diurnal cortisol secretion. Stress. 2018:1-8. doi:
834 10.1080/10253890.2018.1435637. PubMed PMID: 29402161.

15. Herr RM, Barrech A, Riedel N, Gundel H, Angerer P, Li J. Long-Term Effectiveness of Stress Management at Work: Effects of the Changes in Perceived Stress Reactivity on Mental Health and Sleep Problems Seven Years Later. Int J Environ Res Public Health. 2018;15(2). doi: 10.3390/ijerph15020255. PubMed PMID: 29401657.
16. Moore RC, Eyler LT, Mausbach BT, Zlatar ZZ, Thompson WK, Peavy G, et al. Complex interplay between health and successful aging: role of perceived stress, resilience, and social support. Am J Geriatr Psychiatry. 2015;23(6):622-32. doi: 10.1016/j.jagp.2014.08.004. PubMed PMID: 25217186; PubMed Central PMCID: PMCPMC4329284.
17. Hayman LW, Jr., Lucas T, Porcerelli JH. Cognitive appraisal vs. exposure-based stress measures: links to perceived mental and physical health in low-income black women. J Nerv Ment Dis. 2014;202(11):807-12. doi: 10.1097/NMD.0000000000000198. PubMed PMID: 25275345.
18. Harris ML, Loxton D, Sibbritt DW, Byles JE. The influence of perceived stress on the onset of arthritis in women: findings from the Australian Longitudinal Study on women's health. Ann Behav Med. 2013;46(1):9-18. doi: 10.1007/s12160-013-9478-6. PubMed PMID: 23436274.
19. Caspi A, Hariri AR, Holmes A, Uher R, Moffitt TE. Genetic sensitivity to the environment: the case of the serotonin transporter gene and its implications for studying complex diseases and traits. Am J Psychiatry. 2010;167(5):509-27. doi: 10.1176/appi.ajp.2010.09101452. PubMed PMID: 20231323; PubMed Central PMCID: PMCPMC2943341.
20. Bleys D, Luyten P, Soenens B, Claes S. Gene-environment interactions between stress and 5-HTTLPR in depression: A meta-analytic update. J Affect Disord. 2018;226:339-45. doi: 10.1016/j.jad.2017.09.050. PubMed PMID: 29031184.
21. Rietschel L, Zhu G, Kirschbaum C, Strohmaier J, Wust S, Rietschel M, et al. Perceived stress has genetic influences distinct from neuroticism and depression. Behav Genet. 2014;44(6):639-45. doi: 10.1007/s10519-013-9636-4. PubMed PMID: 24366676.
22. Rietschel L, Streit F, Zhu G, McAloney K, Frank J, Couvy-Duchesne B, et al. Hair Cortisol in Twins: Heritability and Genetic Overlap with Psychological Variables and Stress-System Genes. Sci Rep. 2017;7(1):15351. doi: 10.1038/s41598-017-11852-3. PubMed PMID: 29127340; PubMed Central PMCID: PMCPMC5703444.
23. Glahn DC, Curran JE, Winkler AM, Carless MA, Kent JW, Jr., Charlesworth JC, et al. High dimensional endophenotype ranking in the search for major depression risk genes. Biol Psychiatry. 2012;71(1):6-14. doi: 10.1016/j.biopsych.2011.08.022. PubMed PMID: 21982424; PubMed Central PMCID: PMCPMC3230692.
24. van den Berg SM, de Moor MH, McGue M, Pettersson E, Terracciano A, Verweij KJ, et al. Harmonization of Neuroticism and Extraversion phenotypes across inventories and cohorts in the Genetics of Personality Consortium: an application of Item Response Theory. Behav Genet. 2014;44(4):295-313. doi: 10.1007/s10519-014-9654-x. PubMed PMID: 24828478; PubMed Central PMCID: PMCPMC4057636.
25. Wray NR, Birley AJ, Sullivan PF, Visscher PM, Martin NG. Genetic and phenotypic stability of measures of neuroticism over 22 years. Twin Res Hum Genet. 2007;10(5):695-702. doi: 10.1375/twin.10.5.695. PubMed PMID: 17903109.
26. Vukasovic T, Bratko D. Heritability of personality: A meta-analysis of behavior genetic studies. Psychol Bull. 2015;141(4):769-85. doi: 10.1037/bul0000017. PubMed PMID: 25961374.
27. Hirschfeld RM, Klerman GL. Personality attributes and affective disorders. Am J Psychiatry. 1979;136(1):67-70. doi: 10.1176/ajp.136.1.67. PubMed PMID: 758831.

883 28. Hirschfeld RM, Klerman GL, Clayton PJ, Keller MB, McDonald-Scott P, Larkin BH.
884 Assessing personality: effects of the depressive state on trait measurement. Am J Psychiatry.
885 1983;140(6):695-9. doi: 10.1176/ajp.140.6.695. PubMed PMID: 6846626.
886 29. Levinson DF. The genetics of depression: a review. Biol Psychiatry. 2006;60(2):84-92.
887 doi: 10.1016/j.biopsych.2005.08.024. PubMed PMID: 16300747.
888 30. Middeldorp CM, Cath DC, Van Dyck R, Boomsma DI. The co-morbidity of anxiety and
889 depression in the perspective of genetic epidemiology. A review of twin and family studies.
890 Psychol Med. 2005;35(5):611-24. PubMed PMID: 15918338.
891 31. Smith DJ, Escott-Price V, Davies G, Bailey ME, Colodro-Conde L, Ward J, et al. Genome-
892 wide analysis of over 106 000 individuals identifies 9 neuroticism-associated loci. Mol
893 Psychiatry. 2016;21(6):749-57. doi: 10.1038/mp.2016.49. PubMed PMID: 27067015; PubMed
894 Central PMCID: PMCPMC4879189.
895 32. Luciano M, Hagenaars SP, Davies G, Hill WD, Clarke TK, Shirali M, et al. Association
896 analysis in over 329,000 individuals identifies 116 independent variants influencing
897 neuroticism. Nat Genet. 2018;50(1):6-11. doi: 10.1038/s41588-017-0013-8. PubMed PMID:
898 29255261.
899 33. Smits DJM, Boeck PD. From BIS/BAS to the big five. European Journal of Personality.
900 2006;20(4):255-70. doi: 10.1002/per.583.
901 34. Schneider TR, Rench TA, Lyons JB, Riffle RR. The influence of neuroticism, extraversion
902 and openness on stress responses. Stress Health. 2012;28(2):102-10. doi: 10.1002/smi.1409.
903 PubMed PMID: 22281953.
904 35. Kim SE, Kim HN, Cho J, Kwon MJ, Chang Y, Ryu S, et al. Direct and Indirect Effects of
905 Five Factor Personality and Gender on Depressive Symptoms Mediated by Perceived Stress.
906 PLoS One. 2016;11(4):e0154140. doi: 10.1371/journal.pone.0154140. PubMed PMID:
907 27120051; PubMed Central PMCID: PMCPMC4847785.
908 36. Tak LM, Kingma EM, van Ockenburg SL, Ormel J, Rosmalen JG. Age- and sex-specific
909 associations between adverse life events and functional bodily symptoms in the general
910 population. J Psychosom Res. 2015;79(2):112-6. doi: 10.1016/j.jpsychores.2015.05.013.
911 PubMed PMID: 26052060.
912 37. Hovens JG, Giltay EJ, van Hemert AM, Penninx BW. Childhood Maltreatment and the
913 Course of Depressive and Anxiety Disorders: The Contribution of Personality Characteristics.
914 Depress Anxiety. 2016;33(1):27-34. doi: 10.1002/da.22429. PubMed PMID: 26418232.
915 38. Bazana PG, Stelmack RM. Chapter 8 - Stability of Personality Across the Life Span: A
916 Meta-Analysis. On the Psychobiology of Personality. Oxford: Elsevier; 2004. p. 113-44.
917 39. McGue M, Bacon S, Lykken DT. Personality Stability and Change in Early Adulthood.
918 Developmental Psychology. 1993;29(1):96-109.
919 40. Nivard MG, Middeldorp CM, Dolan CV, Boomsma DI. Genetic and Environmental
920 Stability of Neuroticism From Adolescence to Adulthood. Twin Res Hum Genet.
921 2015;18(6):746-54. doi: 10.1017/thg.2015.80. PubMed PMID: 26678053.
922 41. Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review
923 and meta-analysis. Am J Psychiatry. 2000;157(10):1552-62. doi:
924 10.1176/appi.ajp.157.10.1552. PubMed PMID: 11007705.
925 42. Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A, et al.
926 Genome-wide association analyses identify 44 risk variants and refine the genetic
927 architecture of major depression. Nat Genet. 2018;50(5):668-81. doi: 10.1038/s41588-018-
928 0090-3. PubMed PMID: 29700475; PubMed Central PMCID: PMCPMC5934326.
929 43. Loret de Mola C, de Franca GV, Quevedo Lde A, Horta BL. Low birth weight, preterm
930 birth and small for gestational age association with adult depression: systematic review and

931 meta-analysis. Br J Psychiatry. 2014;205(5):340-7. doi: 10.1192/bjp.bp.113.139014. PubMed
932 PMID: 25368358.
933 44. Peyrot WJ, Milaneschi Y, Abdellaoui A, Sullivan PF, Hottenga JJ, Boomsma DI, et al.
934 Effect of polygenic risk scores on depression in childhood trauma. Br J Psychiatry.
935 2014;205(2):113-9. doi: 10.1192/bjp.bp.113.143081. PubMed PMID: 24925986; PubMed
936 Central PMCID: PMCPMC4118052.
937 45. Mullins N, Power RA, Fisher HL, Hanscombe KB, Euesden J, Iniesta R, et al. Polygenic
938 interactions with environmental adversity in the aetiology of major depressive disorder.
939 Psychol Med. 2016;46(4):759-70. doi: 10.1017/S0033291715002172. PubMed PMID:
940 26526099; PubMed Central PMCID: PMCPMC4754832.
941 46. Colodro-Conde L, Couvy-Duchesne B, Zhu G, Coventry WL, Byrne EM, Gordon S, et al. A
942 direct test of the diathesis-stress model for depression. Mol Psychiatry. 2017. doi:
943 10.1038/mp.2017.130. PubMed PMID: 28696435.
944 47. Kendler KS, Baker JH. Genetic influences on measures of the environment: a systematic
945 review. Psychol Med. 2007;37(5):615-26. doi: 10.1017/S0033291706009524. PubMed PMID:
946 17176502.
947 48. Luciano M, Batty GD, McGilchrist M, Linksted P, Fitzpatrick B, Jackson C, et al. Shared
948 genetic aetiology between cognitive ability and cardiovascular disease risk factors:
949 Generation Scotland's Scottish family health study. Intelligence. 2010;38(3):304-13. doi:
950 http://dx.doi.org/10.1016/j.intell.2010.03.002.
951 49. Silberg J, Rutter M, Neale M, Eaves L. Genetic moderation of environmental risk for
952 depression and anxiety in adolescent girls. Br J Psychiatry. 2001;179:116-21. PubMed PMID:
953 11483472.
954 50. Kendler KS, Kessler RC, Walters EE, MacLean C, Neale MC, Heath AC, et al. Stressful life
955 events, genetic liability, and onset of an episode of major depression in women. Am J
956 Psychiatry. 1995;152(6):833-42. PubMed PMID: 7755111.
957 51. Biobank U. UK Biobank: protocol for a large-scale prospective epidemiological
958 resource 2010. Available from: http://www.ukbiobank.ac.uk/wp-
959 content/uploads/2011/11/UK-Biobank-Protocol.pdf.
960 52. Biobank U. UK Biobank ethics and governance framework, version 3.0 2007. Available
961 from: http://www.ukbiobank.ac.uk/wp-
962 content/uploads/2011/05/EGF20082.pdf?phpMyAdmin=trmKQlYdjjnQIgJ%2CfAzikMhEnx6.
963 53. Biobank U. Genotype imputation and genetic association studies of UK Biobank. 2015.
964 54. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MA, Bender D, et al. PLINK: a tool
965 set for whole-genome association and population-based linkage analyses. Am J Hum Genet.
966 2007;81(3):559-75. doi: 10.1086/519795. PubMed PMID: 17701901; PubMed Central PMCID:
967 PMCPMC1950838.
968 55. Amador C, Huffman J, Trochet H, Campbell A, Porteous D, Generation S, et al. Recent
969 genomic heritage in Scotland. BMC Genomics. 2015;16:437. doi: 10.1186/s12864-015-1605-
970 2. PubMed PMID: 26048416; PubMed Central PMCID: PMCPMC4458001.
971 56. Smith BH, Campbell A, Linksted P, Fitzpatrick B, Jackson C, Kerr SM, et al. Cohort
972 Profile: Generation Scotland: Scottish Family Health Study (GS:SFHS). The study, its
973 participants and their potential for genetic research on health and illness. Int J Epidemiol.
974 2013;42(3):689-700. doi: 10.1093/ije/dys084. PubMed PMID: 22786799.
975 57. Fernandez-Pujals AM, Adams MJ, Thomson P, McKechanie AG, Blackwood DH, Smith
976 BH, et al. Epidemiology and Heritability of Major Depressive Disorder, Stratified by Age of
977 Onset, Sex, and Illness Course in Generation Scotland: Scottish Family Health Study (GS:SFHS).
978 PLoS One. 2015;10(11):e0142197. doi: 10.1371/journal.pone.0142197. PubMed PMID:
979 26571028; PubMed Central PMCID: PMCPMC4646689.

58. Smith BH, Campbell H, Blackwood D, Connell J, Connor M, Deary IJ, et al. Generation Scotland: the Scottish Family Health Study; a new resource for researching genes and heritability. BMC medical genetics. 2006;7:74. doi: 10.1186/1471-2350-7-74. PubMed PMID: 17014726; PubMed Central PMCID: PMC1592477.
59. Kerr SM, Campbell A, Murphy L, Hayward C, Jackson C, Wain LV, et al. Pedigree and genotyping quality analyses of over 10,000 DNA samples from the Generation Scotland: Scottish Family Health Study. BMC Med Genet. 2013;14:38. doi: 10.1186/1471-2350-14-38. PubMed PMID: 23521772; PubMed Central PMCID: PMCPMC3614907.
60. Biobank U. Touchscreen questionnaire 2012. Available from: http://www.ukbiobank.ac.uk/wp-content/uploads/2011/06/Touch_screen_questionnaire. pdf?phpMyAdmin = trmKQlYdjjnQIgJ%2CfAzikMhEnx6.
61. Eysenck HJ ES. Manual of the Eysenck Personality Questionnaire. London: Hodder and Stoughton; 1975.
62. Kendler KS, Myers J. The genetic and environmental relationship between major depression and the five-factor model of personality. Psychol Med. 2010;40(5):801-6. doi: 10.1017/S0033291709991140. PubMed PMID: 19732485.
63. Smith DJ, Nicholl BI, Cullen B, Martin D, Ul-Haq Z, Evans J, et al. Prevalence and characteristics of probable major depression and bipolar disorder within UK biobank: cross-sectional study of 172,751 participants. PLoS One. 2013;8(11):e75362. doi: 10.1371/journal.pone.0075362. PubMed PMID: 24282498; PubMed Central PMCID: PMCPMC3839907.
64. Eysenck SBG, Eysenck, H.J. & Barrett, P. A revised version of the psychoticism scale. Personality and Individual Differences. 1985;6:21-9.
65. Spitzer RL, Kroenke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: the PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire. JAMA. 1999;282(18):1737-44. PubMed PMID: 10568646.
66. First MB SR, Gibbon M, Williams JB. Structured Clinical Interview for DSM-IV-TR Axis I Disorders. New York: New York State Psychiatric Institute; 2002.
67. Euesden J, Lewis CM, O'Reilly PF. PRSice: Polygenic Risk Score software. Bioinformatics. 2015;31(9):1466-8. doi: 10.1093/bioinformatics/btu848. PubMed PMID: 25550326; PubMed Central PMCID: PMCPMC4410663.
68. Willer CJ, Li Y, Abecasis GR. METAL: fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;26(17):2190-1. doi: 10.1093/bioinformatics/btq340. PubMed PMID: 20616382; PubMed Central PMCID: PMCPMC2922887.
69. de Leeuw CA, Mooij JM, Heskes T, Posthuma D. MAGMA: generalized gene-set analysis of GWAS data. PLoS Comput Biol. 2015;11(4):e1004219. doi: 10.1371/journal.pcbi.1004219. PubMed PMID: 25885710; PubMed Central PMCID: PMCPMC4401657.
70. Watanabe K, Taskesen E, van Bochoven A, Posthuma D. FUMA: Functional mapping and annotation of genetic associations. bioRxiv. 2017. doi: 10.1101/110023.
71. Bulik-Sullivan BK, Loh PR, Finucane HK, Ripke S, Yang J, Schizophrenia Working Group of the Psychiatric Genomics C, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;47(3):291-5. doi: 10.1038/ng.3211. PubMed PMID: 25642630; PubMed Central PMCID: PMCPMC4495769.
72. Bulik-Sullivan B, Finucane HK, Anttila V, Gusev A, Day FR, Loh PR, et al. An atlas of genetic correlations across human diseases and traits. Nat Genet. 2015;47(11):1236-41. doi: 10.1038/ng.3406. PubMed PMID: 26414676; PubMed Central PMCID: PMCPMC4797329.
73. Pers TH, Karjalainen JM, Chan Y, Westra HJ, Wood AR, Yang J, et al. Biological interpretation of genome-wide association studies using predicted gene functions. Nat

1028 Commun. 2015;6:5890. doi: 10.1038/ncomms6890. PubMed PMID: 25597830; PubMed
1029 Central PMCID: PMCPMC4420238.
1030 74. Mailman MD, Feolo M, Jin Y, Kimura M, Tryka K, Bagoutdinov R, et al. The NCBI dbGaP
1031 database of genotypes and phenotypes. Nat Genet. 2007;39(10):1181-6. doi:
1032 10.1038/ng1007-1181. PubMed PMID: 17898773; PubMed Central PMCID:
1033 PMCPMC2031016.
1034 75. Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M, et al. Annotation of
1035 functional variation in personal genomes using RegulomeDB. Genome research.
1036 2012;22(9):1790-7. doi: 10.1101/gr.137323.112. PubMed PMID: 22955989; PubMed Central
1037 PMCID: PMC3431494.
1038 76. Consortium GT. Human genomics. The Genotype-Tissue Expression (GTEx) pilot
1039 analysis: multitissue gene regulation in humans. Science. 2015;348(6235):648-60. doi:
1040 10.1126/science.1262110. PubMed PMID: 25954001; PubMed Central PMCID:
1041 PMCPMC4547484.
1042 77. Genetics of Personality C, de Moor MH, van den Berg SM, Verweij KJ, Krueger RF,
1043 Luciano M, et al. Meta-analysis of Genome-wide Association Studies for Neuroticism, and the
1044 Polygenic Association With Major Depressive Disorder. JAMA Psychiatry. 2015;72(7):642-50.
1045 doi: 10.1001/jamapsychiatry.2015.0554. PubMed PMID: 25993607; PubMed Central PMCID:
1046 PMCPMC4667957.
1047 78. Team RC. R: A language and environment for statistical computing. Vienna, Austria: R
1048 Foundation for Statistical Computing; 2015.
1049 79. Lee SH, Wray NR, Goddard ME, Visscher PM. Estimating missing heritability for disease
1050 from genome-wide association studies. Am J Hum Genet. 2011;88(3):294-305. doi:
1051 10.1016/j.ajhg.2011.02.002. PubMed PMID: 21376301; PubMed Central PMCID:
1052 PMCPMC3059431.
1053 80. Chen GB. Estimating heritability of complex traits from genome-wide association
1054 studies using IBS-based Haseman-Elston regression. Front Genet. 2014;5:107. doi:
1055 10.3389/fgene.2014.00107. PubMed PMID: 24817879; PubMed Central PMCID:
1056 PMCPMC4012219.
1057 81. Hirschfeld RM, Williams JB, Spitzer RL, Calabrese JR, Flynn L, Keck PE, Jr., et al.
1058 Development and validation of a screening instrument for bipolar spectrum disorder: the
1059 Mood Disorder Questionnaire. Am J Psychiatry. 2000;157(11):1873-5. doi:
1060 10.1176/appi.ajp.157.11.1873. PubMed PMID: 11058490.
1061 82. Raine A. The SPQ: a scale for the assessment of schizotypal personality based on DSM-
1062 III-R criteria. Schizophr Bull. 1991;17(4):555-64. PubMed PMID: 1805349.
1063 83. Polderman TJ, Benyamin B, de Leeuw CA, Sullivan PF, van Bochoven A, Visscher PM, et
1064 al. Meta-analysis of the heritability of human traits based on fifty years of twin studies. Nat
1065 Genet. 2015;47(7):702-9. doi: 10.1038/ng.3285. PubMed PMID: 25985137.
1066 84. consortium C. Sparse whole-genome sequencing identifies two loci for major
1067 depressive disorder. Nature. 2015;523(7562):588-91. doi: 10.1038/nature14659. PubMed
1068 PMID: 26176920; PubMed Central PMCID: PMCPMC4522619.
1069 85. Hyde CL, Nagle MW, Tian C, Chen X, Paciga SA, Wendland JR, et al. Identification of 15
1070 genetic loci associated with risk of major depression in individuals of European descent. Nat
1071 Genet. 2016;48(9):1031-6. doi: 10.1038/ng.3623. PubMed PMID: 27479909.
1072 86. Zuo L, Tan Y, Zhang X, Wang X, Krystal J, Tabakoff B, et al. A New Genomewide
1073 Association Meta-Analysis of Alcohol Dependence. Alcohol Clin Exp Res. 2015;39(8):1388-95.
1074 doi: 10.1111/acer.12786. PubMed PMID: 26173551.
1075 87. Cook MN, Baker JA, Heldt SA, Williams RW, Hamre KM, Lu L. Identification of candidate
1076 genes that underlie the QTL on chromosome 1 that mediates genetic differences in stress-

1077 ethanol interactions. Physiol Genomics. 2015;47(8):308-17. doi:
1078 10.1152/physiolgenomics.00114.2014. PubMed PMID: 25991709; PubMed Central PMCID:
1079 PMCPMC4525077.
1080 88. Zuo L, Wang K, Wang G, Pan X, Zhang X, Zhang H, et al. Common PTP4A1-PHF3-EYS
1081 variants are specific for alcohol dependence. Am J Addict. 2014;23(4):411-4. doi:
1082 10.1111/j.1521-0391.2013.12115.x. PubMed PMID: 24961364; PubMed Central PMCID:
1083 PMCPMC4111256.
1084 89. Zuo L, Zhang X, Deng HW, Luo X. Association of rare PTP4A1-PHF3-EYS variants with
1085 alcohol dependence. J Hum Genet. 2013;58(3):178-9. doi: 10.1038/jhg.2012.153. PubMed
1086 PMID: 23324950.
1087 90. Zuo L, Zhang CK, Wang F, Li CS, Zhao H, Lu L, et al. A novel, functional and replicable
1088 risk gene region for alcohol dependence identified by genome-wide association study. PLoS
1089 One. 2011;6(11):e26726. doi: 10.1371/journal.pone.0026726. PubMed PMID: 22096494;
1090 PubMed Central PMCID: PMCPMC3210123.
1091 91. Hontelez S, Karthaus N, Looman MW, Ansems M, Adema GJ. DC-SCRIPT regulates
1092 glucocorticoid receptor function and expression of its target GILZ in dendritic cells. J Immunol.
1093 2013;190(7):3172-9. doi: 10.4049/jimmunol.1201776. PubMed PMID: 23440419.
1094 92. Lopez-Garcia J, Periyasamy M, Thomas RS, Christian M, Leao M, Jat P, et al. ZNF366 is
1095 an estrogen receptor corepressor that acts through CtBP and histone deacetylases. Nucleic
1096 Acids Res. 2006;34(21):6126-36. doi: 10.1093/nar/gkl875. PubMed PMID: 17085477;
1097 PubMed Central PMCID: PMCPMC1693901.
1098 93. Miyamoto-Sato E, Fujimori S, Ishizaka M, Hirai N, Masuoka K, Saito R, et al. A
1099 comprehensive resource of interacting protein regions for refining human transcription factor
1100 networks. PLoS One. 2010;5(2):e9289. doi: 10.1371/journal.pone.0009289. PubMed PMID:
1101 20195357; PubMed Central PMCID: PMCPMC2827538.
1102 94. Aragam N, Wang KS, Pan Y. Genome-wide association analysis of gender differences in
1103 major depressive disorder in the Netherlands NESDA and NTR population-based samples. J
1104 Affect Disord. 2011;133(3):516-21. doi: 10.1016/j.jad.2011.04.054. PubMed PMID: 21621269.
1105 95. Fidalgo TM, da Silveira ED, da Silveira DX. Psychiatric comorbidity related to alcohol
1106 use among adolescents. Am J Drug Alcohol Abuse. 2008;34(1):83-9. doi:
1107 10.1080/00952990701764664. PubMed PMID: 18161646.
1108 96. Lopez B, Turner RJ, Saavedra LM. Anxiety and risk for substance dependence among
1109 late adolescents/young adults. J Anxiety Disord. 2005;19(3):275-94. doi:
1110 10.1016/j.janxdis.2004.03.001. PubMed PMID: 15686857.
1111 97. Low NC, Lee SS, Johnson JG, Williams JB, Harris ES. The association between anxiety
1112 and alcohol versus cannabis abuse disorders among adolescents in primary care settings. Fam
1113 Pract. 2008;25(5):321-7. doi: 10.1093/fampra/cmn049. PubMed PMID: 18753288.
1114 98. Rutledge PC, Sher KJ. Heavy drinking from the freshman year into early young
1115 adulthood: the roles of stress, tension-reduction drinking motives, gender and personality. J
1116 Stud Alcohol. 2001;62(4):457-66. PubMed PMID: 11523533.
1117 99. Schmidt NB, Buckner JD, Keough ME. Anxiety sensitivity as a prospective predictor of
1118 alcohol use disorders. Behav Modif. 2007;31(2):202-19. doi: 10.1177/0145445506297019.
1119 PubMed PMID: 17307935.
1120 100. Varlinskaya EI, Kim EU, Spear LP. Chronic intermittent ethanol exposure during
1121 adolescence: Effects on stress-induced social alterations and social drinking in adulthood.
1122 Brain Res. 2017;1654(Pt B):145-56. doi: 10.1016/j.brainres.2016.03.050. PubMed PMID:
1123 27048754; PubMed Central PMCID: PMCPMC5047849.
1124 101. Torigata K, Daisuke O, Mukai S, Hatanaka A, Ohka F, Motooka D, et al. LATS2 Positively
1125 Regulates Polycomb Repressive Complex 2. PLoS One. 2016;11(7):e0158562. doi:

1126 10.1371/journal.pone.0158562. PubMed PMID: 27434182; PubMed Central PMCID:
1127 PMCPMC4951031.
1128 102. Shen EY, Jiang Y, Javidfar B, Kassim B, Loh YE, Ma Q, et al. Neuronal Deletion of
1129 Kmt2a/Mll1 Histone Methyltransferase in Ventral Striatum is Associated with Defective
1130 Spike-Timing-Dependent Striatal Synaptic Plasticity, Altered Response to Dopaminergic
1131 Drugs, and Increased Anxiety. Neuropsychopharmacology. 2016;41(13):3103-13. doi:
1132 10.1038/npp.2016.144. PubMed PMID: 27485686; PubMed Central PMCID:
1133 PMCPMC5101561.
1134 103. Wong ML, Arcos-Burgos M, Liu S, Velez JI, Yu C, Baune BT, et al. The PHF21B gene is
1135 associated with major depression and modulates the stress response. Mol Psychiatry.
1136 2017;22(7):1015-25. doi: 10.1038/mp.2016.174. PubMed PMID: 27777418; PubMed Central
1137 PMCID: PMCPMC5461220.
1138 104. Walsh RM, Shen EY, Bagot RC, Anselmo A, Jiang Y, Javidfar B, et al. Phf8 loss confers
1139 resistance to depression-like and anxiety-like behaviors in mice. Nat Commun. 2017;8:15142.
1140 doi: 10.1038/ncomms15142. PubMed PMID: 28485378; PubMed Central PMCID:
1141 PMCPMC5436068.
1142 105. Gage SH, Jones HJ, Taylor AE, Burgess S, Zammit S, Munafo MR. Investigating causality
1143 in associations between smoking initiation and schizophrenia using Mendelian
1144 randomization. Sci Rep. 2017;7:40653. doi: 10.1038/srep40653. PubMed PMID: 28102331;
1145 PubMed Central PMCID: PMCPMC5244403.
1146 106. Hartz SM, Horton AC, Hancock DB, Baker TB, Caporaso NE, Chen LS, et al. Genetic
1147 correlation between smoking behaviors and schizophrenia. Schizophr Res. 2017. doi:
1148 10.1016/j.schres.2017.02.022. PubMed PMID: 28285025.
1149 107. Dudbridge F. Power and predictive accuracy of polygenic risk scores. PLoS Genet.
1150 2013;9(3):e1003348. doi: 10.1371/journal.pgen.1003348. PubMed PMID: 23555274;
1151 PubMed Central PMCID: PMCPMC3605113.
1152

1153

1154 # Supporting information

1155 **S1 Supporting Information.**

1156

1157 **S1 Fig. Genetic stress-sensitivity effect representation.** Genetic stress-sensitivity effect on MDD
1158 (β_{SS}) is defined as the difference between the regression coefficient in MDD cases (β_A) and the
1159 regression coefficient in controls (β_B) from linear models regressed on EPQN, adjusted by
1160 covariates. *A1*: allele 1. *A2* allele 2.

1161

1162 **S2 Fig. QQ plot from stress-sensitivity meta-analysis.** QQ plot of GWIS from sample size weighted
1163 meta-analysis (λ = 0.997; s.e. = 1.05×10^{-5}). All SNPs wit $p < 2 \times 10^{-5}$, p threshold (dot line) where
1164 some SNPs start to deviate from null distribution going outside 95% confidence intervals (grey
1165 shadow), were selected to perform DEPICT analyses to assess pathway and functional genomic
1166 analyses. 27 top variants from 12 independent loci were selected.

1167

1168 **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)
1169 GS:SFHS (λ = 0.997; s.e. = 7.989×10^{-6}). The 95% confidence interval is shaded in grey.

1170

1171 **S4 Fig. Miami plots on UK Biobank and Generation Scotland: Scottish Family Health Study.** Miami
1172 plots showing comparison between association profile between SS and MDD main additive effects.
1173 Miami plots from (A) UKB filtering for SS *p* values (top) and MDD *p* values (bottom), (B) GS:SFHS
1174 filtering for SS *p* values (top) and MDD *p* values (bottom). Filter at $p = 1 \times 10^{-3}$. The x-axis is base-
1175 paired chromosomal position and y-axis is the significance (-log10 *p*) of association with (up; red

1176 dots) SS effect and (down; blue dots) MDD. Dot line: genome-wide suggestive threshold (p = 1x10^{-}
1177 ^{5}) at the filtered effect; dashes lines: p value = 0.01 and 0.05 at compared effect.
1178
1179 **S5 Fig. Manhattan plot of the gene-based test for stress-sensitivity.** Manhattan plot showing
1180 gene-based association of stress-sensitivity. The x-axis is base-paired chromosomal position and y-
1181 axis is the significance (-$\log_{10}$ p value) of association with SS effect. Genome-wide significance
1182 threshold showed by red dashed line was defined at p = 0.05/17,931 = 2.79x10^{-6}.
1183
1184 **S6 Fig. PRS profiling predicting MDD in UK Biobank.** MDD risk explained (R^2 coefficient (%); top
1185 bar values) on the liability scale by each PRS in UKB; weighted by GWAS main additive and GWIS
1186 stress-sensitivity effects independently and combined. (A) Using summary statistics from GS:SFHS
1187 as discovery sample. (B) Replication fitting PRS_D and PRS_N using summary statistics from worldwide
1188 consortiums (i.e. PGC & GPC). Significance codes: p values *** < 0.001 < ** < 0.01 < * < 0.05;
1189 derived from likelihood ratio tests. *SS* stands for stress-sensitivity.
1190
1191 **S1 Table. EPQN comparison between MDD cases and healthy controls.**
1192
1193 **S2 Table. Top 10 SNPs from GWIS on UK Biobank.**
1194
1195 **S3 Table. Top 10 SNPs from GWIS on Generation Scotland: Scottish Family Health Study.**
1196
1197 **S4 Table. Traits with significant evidence of association with closest gene to suggestive stress-**
1198 **sensitive hits.** The closest genes to SNPs associated with stress-sensitivity at suggestive
1199 significance levels have prior evidence of association in dbGAP with a wide range of

1200 neuropsychiatric traits such as schizophrenia, bipolar disorder, attention deficit disorder with

1201 hyperactivity, mental competency, intuition, sleep or alcohol drinking.

1202

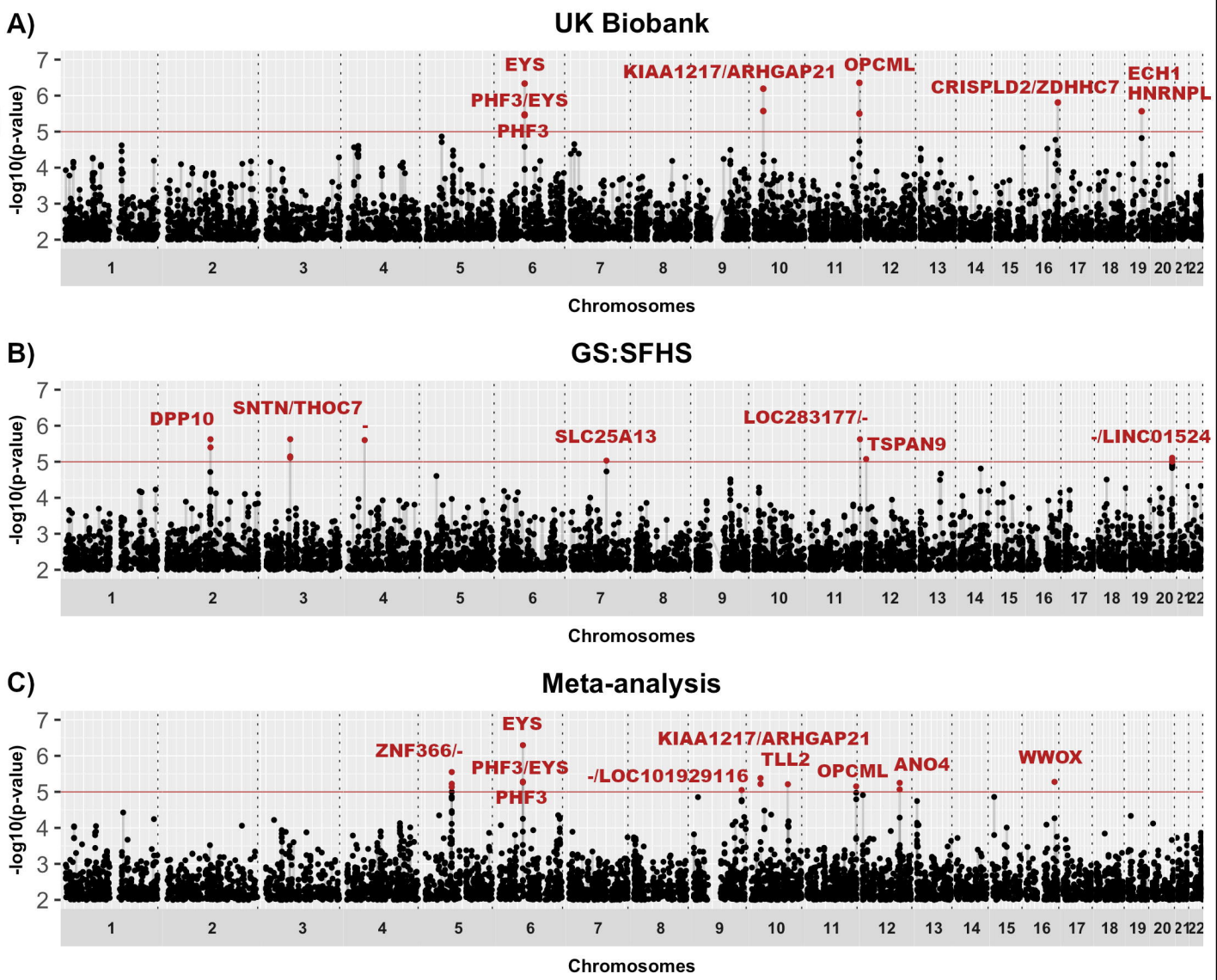
1203 **S5 Table. Top 25 hits from gene-based analysis of GWIS meta-analysis.**

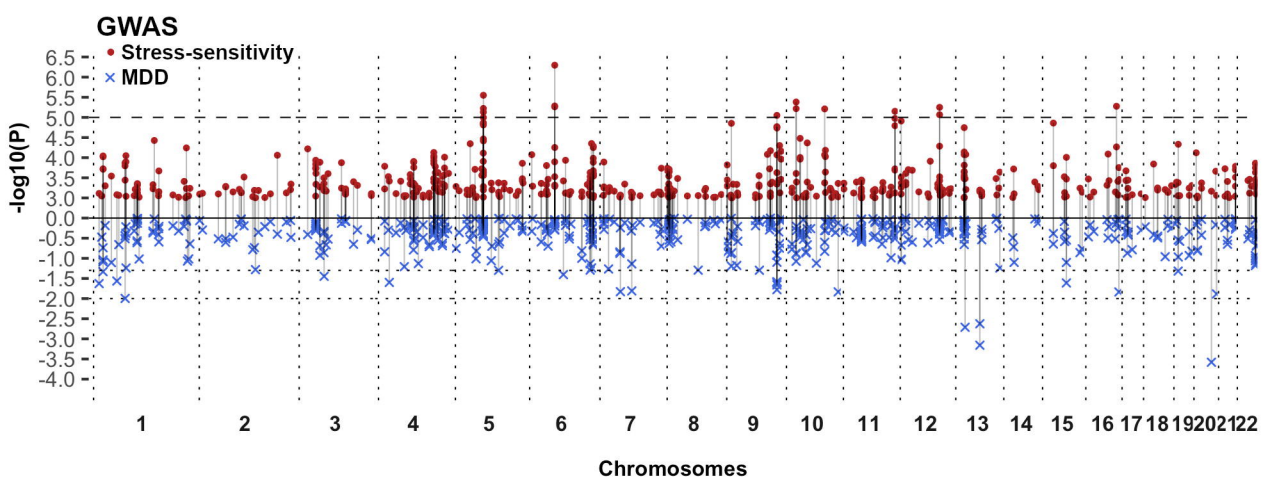
1204

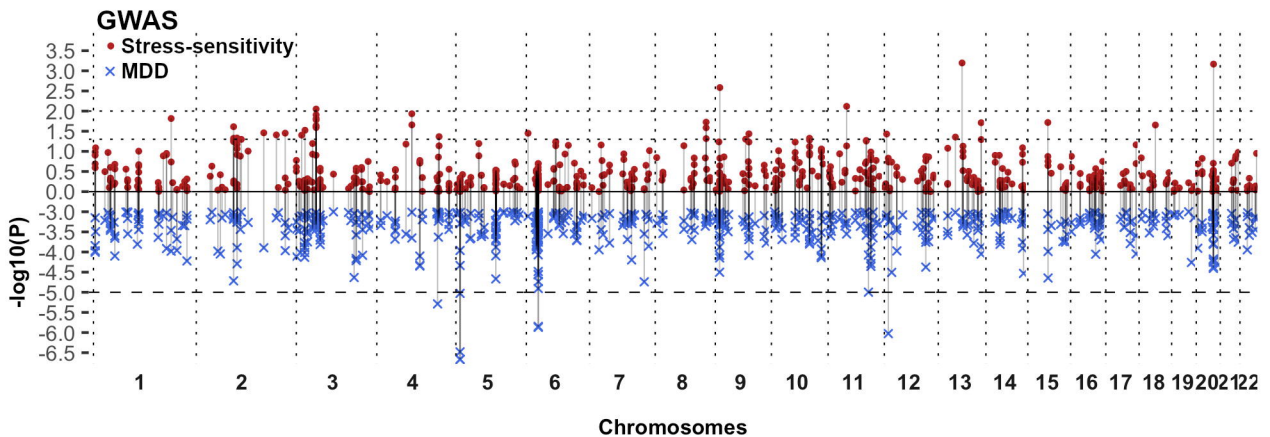
1205 **S6 Table. : Summary results from polygenic risk score (PRS) analysis using PRSice-2.**

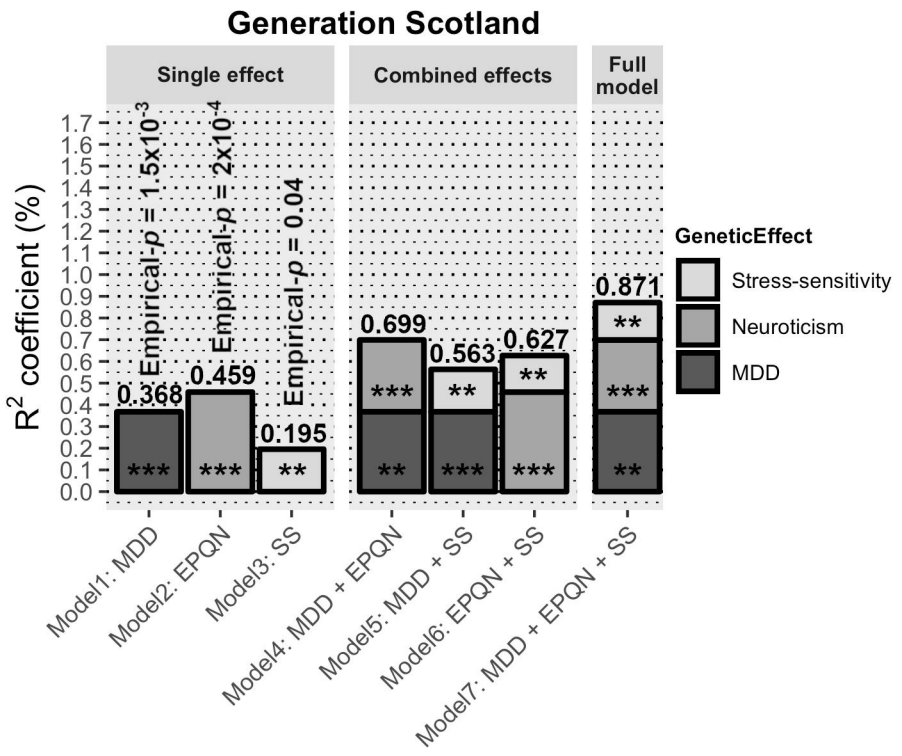
1206

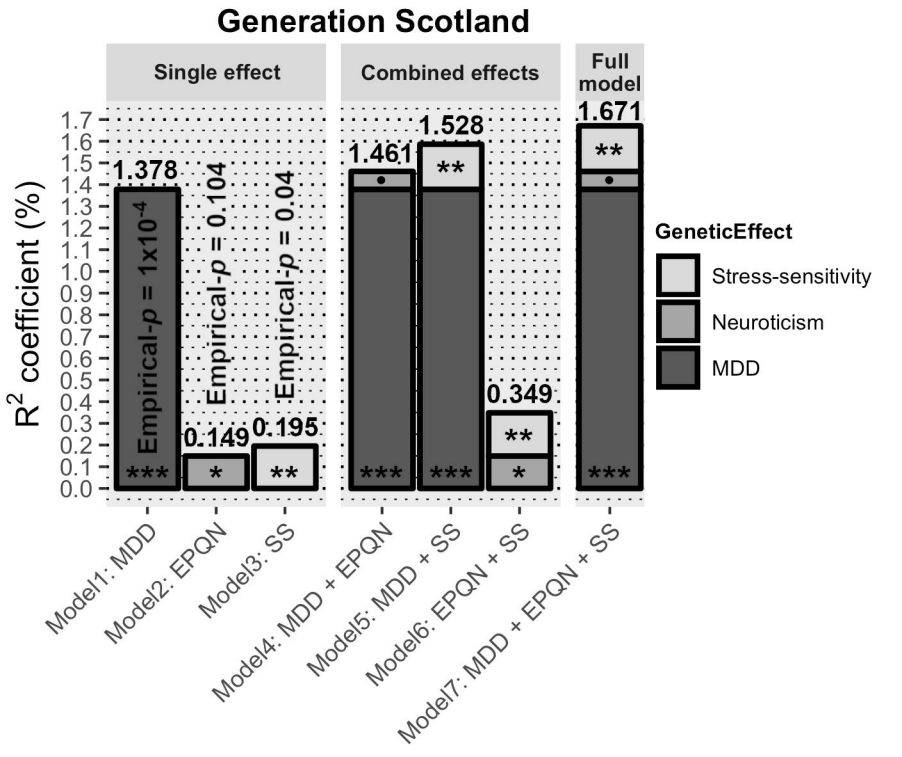
1207 **S7 Table. MDD stratification.**


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