A validation of the diathesis-stress model for depression in Generation Scotland.

Running title: **The diathesis-stress model for depression in Generation Scotland.**

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ABSTRACT

Depression has well-established influences from genetic and environmental risk factors. This has led to the *diathesis-stress* theory, which assumes a multiplicative gene-by-environment interaction (GxE) effect on risk. Recently, *Colodro-Conde et al.* empirically tested this theory, using the polygenic risk score for major depressive disorder (PRS, genes) and stressful life events (SLE, environment) effects on depressive symptoms, identifying significant GxE effects with an additive contribution to liability.

We have tested the *diathesis-stress* theory on an independent sample of 4 919 individuals.

We identified nominally significant positive GxE effects in the full cohort (R^2 = 0.08%, p = 0.049) and in women (R^2 = 0.19%, p = 0.017), but not in men (R^2 = 0.15%, p = 0.07). GxE effects were nominally significant, but only in women, when SLE were split into those in which the respondent plays an active or passive role (R^2 = 0.15%, p = 0.038; R^2 = 0.16%, p = 0.033, respectively). High PRS increased the risk of depression in participants reporting high numbers of SLE ($p = 2.86 \times 10^{-4}$). However, in those participants who reported no recent SLE, a higher PRS appeared to increase the risk of depressive symptoms in men (β = 0.082, p = 0.016) but had a protective effect in women (β = -0.061, p = 0.037). This difference was nominally significant (p = 0.017).

Our study reinforces the evidence of additional risk in the aetiology of depression due to GxE effects. However, larger sample sizes are required to robustly validate these findings.

63 **INTRODUCTION**

64 Stressful life events (SLE) have been consistently recognized as a determinant of
65 depressive symptoms, with many studies reporting significant associations between
66 SLE and major depressive disorder (MDD)[1-7]. Some studies suggest that severe
67 adversity is present before the onset of illness in over 50% of individuals with
68 depression[8] and may characterize a subtype of cases[9]. However, some individuals
69 facing severe stress never present symptoms of depression[10]. This has led to a
70 suggestion that the interaction between stress and an individual's vulnerability, or
71 *diathesis*, is a key element in the development of depressive symptoms. Such
72 vulnerability can be conceived as a set of biological factors that predispose to illness.
73 Several *diathesis-stress* models have been successfully applied across many
74 psychopathologies[11-15].

75 The *diathesis-stress* model proposes that a latent *diathesis* may be activated by stress
76 before psychopathological symptoms manifest. Some levels of *diathesis* to illness are
77 present in everybody, with a threshold over which symptoms will appear. Exceeding
78 such a threshold depends on the interaction between *diathesis* and the degree of
79 adversity faced in SLE, which increases the liability to depression beyond the combined
80 additive effects of the *diathesis* and stress alone[11]. Genetic risk factors can, therefore,
81 be conceived as a genetic *diathesis*. Thus, this genetically driven effect produced by
82 the *diathesis-stress* interaction can be seen as a gene-by-environment interaction
83 (GxE).

84 MDD is characterized by a highly polygenic architecture, composed of common
85 variants with small effect and/or rare variants[16]. Therefore, interactions in depression
86 are also expected to be highly polygenic. In recent years, with the increasing success of

87 genome-wide association studies, GxE studies in depression have shifted towards
88 hypothesis-free genome-wide and polygenic approaches that capture liability to
89 depression using genetic data[17-25]. Recent advances in genomics and the massive effort
90 from national institutions to collect genetic, clinical and environmental data on large
91 population-based samples now provide an opportunity to empirically test the
92 *diathesis-stress* model for depression. The construction of polygenic risk scores (PRS)
93 offers a novel paradigm to quantify genetic *diathesis* into a single genetic measure,
94 allowing us to study GxE effects with more predictive power than any single variant[26-
95 29]. PRS are genetic indicators of the aggregate number of risk alleles carried by an
96 individual weighted by their allelic effect estimated from genome-wide association
97 studies. This polygenic approach to assessing the *diathesis-stress* model for depression
98 has been tested using either childhood trauma[17,19,25] or adult SLE[18,23,25] as measures of
99 environmental adversity.
100 Recently, Colodro-Conde *et al.*[23] provided a direct test of the *diathesis-stress* model for
101 recent SLE and depressive symptoms. In this study, Colodro-Conde *et al.* used PRS
102 weighted by the most recent genome-wide meta-analysis conducted by the Psychiatric
103 Genetics Consortium (PGC; N = 159 601), and measures of three environmental
104 exposures: lack of social support, "personal" SLE, and "network" SLE. Colodro-Conde
105 *et al.* reported a significant additive risk on liability to depression due to a GxE effect in
106 individuals who combine a high genetic predisposition to MDD and a high number of
107 reported "personal" SLE, mainly driven by effects in women. A significant effect of
108 interaction was not detected in males. They found no significant interaction between
109 the genetic *diathesis* and "network" SLE or social support. They concluded that the
110 effect of stress on risk of depression was dependent on an individual's *diathesis,* thus

111 supporting the *diathesis-stress* theory. In addition, they suggested possible sex-specific
112 differences in the aetiology of depression. However, Colodro-Conde *et al.* findings
113 have not, to our knowledge, been independently validated.
114 In the present study we aim to test the *diathesis-stress* model in an independent
115 sample of 4 919 unrelated white British participants from a further longitudinal follow-
116 up from Generation Scotland and assess the differences between women and men,
117 using self-reported depressive symptoms and recent SLE.

118 **MATERIALS AND METHODS**

119 **Sample description**

120 Generation Scotland is a family-based population cohort recruited throughout
121 Scotland by a cross-disciplinary collaboration of Scottish medical schools and the
122 National Health Service (NHS) between 2006 and 2011[30]. At baseline, blood and
123 salivary DNA samples from Generation Scotland participants were collected, stored
124 and genotyped at the Wellcome Trust Clinical Research Facility, Edinburgh. Genome-
125 wide genotype data were generated using the Illumina HumanOmniExpressExome-8
126 v1.0 DNA Analysis BeadChip (San Diego, CA, USA) and Infinium chemistry[31]. The
127 procedures and further details for DNA extraction and genotyping have been
128 extensively described elsewhere[32,33]. In 2014, 21 525 participants from Generation
129 Scotland eligible for re-contact were sent self-reported questionnaires as part of a
130 further longitudinal assessment funded by a Wellcome Trust Strategic Award
131 "STratifying Resilience and Depression Longitudinally" (STRADL)[34] to collect new and
132 updated mental health questionnaires including psychiatric symptoms and SLE
133 measures. 9 618 re-contacted participants from Generation Scotland agreed to provide
134 new measures to the mental health follow-up[34] (44.7% response rate). Duplicate
135 samples, those showing sex discrepancies with phenotypic data, or that had more than
136 2% missing genotype data, were removed from the sample, as were samples identified
137 as population outliers in principal component analysis (mainly non-Caucasians and
138 Italian ancestry subgroup). In addition, individuals with diagnoses of bipolar disorder,
139 or with missing SLE data, were excluded from the analyses. SNPs with more than 2% of
140 genotypes missing, Hardy-Weinberg Equilibrium test $p < 1 \times 10^{-6}$, or a minor allele
141 frequency lower than 1%, were excluded. Individuals were then filtered by degree of

142 relatedness (pi-hat < 0.05) using PLINK v1.9[35], maximizing retention of those
143 participants reporting higher numbers of SLE (see phenotype assessment below). After
144 quality control, the final dataset comprised 4 919 unrelated individuals of European
145 ancestry and 560 351 SNPs (mean age at questionnaire: 57.2, s.d. = 12.2, range 22-95;
146 *women*: *n* = 2 990 - 60.8%, mean age 56.1, s.d. = 12.4; *men*: *n* = 1 929 - 39.2%, mean
147 age 58.7, s.d. = 11.8). Further details on the recruitment procedure and Generation
148 Scotland profile are described in detail elsewhere[30,32,36-38]. All participants provided
149 written consent. All components of Generation Scotland and STRADL obtained ethical
150 approval from the Tayside Committee on Medical Research Ethics on behalf of the
151 National Health Service (reference 05/s1401/89). Generation Scotland data is available
152 to researchers on application to the Generation Scotland Access Committee
153 (access@generationscotland.org).
154

155 **Phenotype assessment**

156 Participant self-reported current depressive symptoms through the 28-item scaled
157 version of The General Health Questionnaire[39,40]. The General Health Questionnaire is
158 a reliable and validated psychometric screening tool to detect common psychiatric and
159 non-psychotic conditions (General Health Questionnaire Cronbach alpha coefficient:
160 0.82 – 0.86)[41]. This consists of 28 items designed to identify whether an individual's
161 current mental state has changed over the last 2 weeks from their typical state. The
162 questionnaire captures core symptoms of depression through subscales for severe
163 depression, emotional (e.g. anxiety and social dysfunction) and somatic symptoms
164 linked to depression. These subscales are highly correlated[42] and suggest an overall
165 general factor of depression[43]. Participants rated the 28 items on a four-point Likert

166 scale from 0 to 3 to assess its degree or severity[41] (e.g., *Have you recently felt that life*
167 *is entirely hopeless?* "Not at all", "No more than usual", "Rather more than usual",
168 "Much more than usual"), resulting on an 84-point scale depression score. The Likert
169 scale, which provides a wider and smoother distribution[41], could be more sensitive to
170 detect changes in mental status in those participants with chronic conditions or
171 chronic stress who may feel their current symptoms as "usual"[44], and to detect
172 psychopathology changes as response to stress. The final depression score was log
173 transformed to reduce the effect of positive skew and provide a better approximation
174 to a normal distribution. In addition, participants completed the Composite
175 International Diagnostic Interview–Short Form, which diagnoses lifetime history of
176 MDD according to DSM-IV criteria[45]. The depression score predicted lifetime history of
177 MDD (odd ratio = 1.91, 95% confidence intervals 1.80-2.02, $p = 1.55 \times 10^{-102}$, N = 8
178 994), with a 3.8-fold increased odd of having a lifetime history of MDD between
179 participants in the top and bottom deciles, thus supporting the usefulness of the
180 depression score in understanding MDD. For a better interpretation, we scaled the
181 depression score to a mean of 0 when required (Figure 3).
182 Data from a self-reported questionnaire based on the List of Threating Experiences[46]
183 was used to construct a measure of common SLE over the previous 6 months. The List
184 of Threatening Experiences is a reliable psychometric device to measure psychological
185 "stress"[47,48]. It consists of a 12-item questionnaire to assess SLE with considerable
186 long-term contextual effects (e.g., *Over last 6 months, did you have a serious problem*
187 *with a close friend, neighbour or relatives?*). A final score reflecting the total number of
188 SLE (TSLE) ranging from 0 to 12 was constructed by summing the "yes" responses.
189 Additionally, TSLE was split into two categories based on those items measuring SLE in

190 which the individual may play and active role exposure to SLE, and therefore in which
191 the SLE is influenced by genetic factors and thus subject to be "dependent" on an
192 individual's own behaviour or symptoms (DSLE; 6 items, e.g., *a serious problem with a*
193 *close friend, neighbour or relatives* may be subject to a respondent's own behaviour),
194 or SLE that are not influenced by genetic factors, likely to be "independent" on a
195 participant's own behaviour (ISLE; 5 items, e.g., *a serious illness, injury or assault*
196 *happening to a close relative* is potentially independent of a respondent's own
197 behaviour)[46,49]. The item "*Did you/your wife or partner give birth?"* was excluded from
198 this categorization. In addition, SLE reported were categorized to investigate the
199 *diathesis* effect at different levels of exposure, including a group to test the *diathesis*
200 effect when SLE is not reported. 3 levels of SLE reported were defined (0 SLE = "none",
201 1 or 2 SLE = "low", and 3 or more SLE = "high") to retain a large enough sample size for
202 each group to allow meaningful statistical comparison.
203
204 **Polygenic profiling & statistical analysis**
205 Polygenic risk scores (PRS) were generated by PRSice[50], whose functionality relies
206 mostly on PLINK v1.9[35], and were calculated using the genotype data of Generation
207 Scotland participants (i.e. target sample) and summary statistics for MDD from the
208 PGC-MDD2 GWAS release (July 2016, discovery sample) used by Colodro-Conde *et*
209 *al.*[23], with the added contribution from QIMR cohort and the exclusion of Generation
210 Scotland participants, resulting in summary statistics for MDD derived from a sample
211 of 50 455 cases and 105 411 controls.
212 Briefly, PRSice removed strand-ambiguous SNPs and clump-based pruned (r^2 = 0.1,
213 within a 10Mb window) our target sample to obtain the most significant independent

214 SNPs in approximate linkage equilibrium. Independent risk alleles were then weighted
215 by the allelic effect sizes estimated in the independent discovery sample and
216 aggregated into PRS. PRS were generated for eight *p* thresholds (*p* thresholds: $< 5 \times 10^{-8}$, $< 1 \times 10^{-5}$, < 0.001, < 0.01, < 0.05, < 0.1, < 0.5, <=1) determined by the discovery
217
218 sample and standardized (See Supplementary Table 1 for summary of PRS).
219 A genetic relationship matrix (GRM) was calculated for each dataset (i.e. *full cohort*,
220 *women* and *men*) using GCTA1.26.0[51]. Mixed linear models using the GRM were used
221 to estimate the variance in depression score explained by PRS, SLEs and their
222 interaction; and stratified by sex. 20 principal components were calculated for the
223 datasets.
224 The mixed linear model used to assess the effects of PRS is as follows:

$$Depression = \beta_0 + \beta_1 PRS + GRM + Covariates$$

225 Mixed linear models used to assess the effect of the stressors are as follows:

$$Depression = \beta_0 + \beta_1 TSLE + GRM + Covariates$$

$$Depression = \beta_0 + \beta_1 DSLE + GRM + Covariates$$

$$Depression = \beta_0 + \beta_1 ISLE + GRM + Covariates$$

226 Following Colodro-Conde *et al.*[23], covariates (i.e. age, age^2, sex, age-by-sex and age^2-
227 by-sex interactions, and 20 principal components) were regressed from PRS (PRS') and
228 SLE scores (i.e. TSLE', DSLE' and ISLE'; SLEs') before fitting models in GCTA to guard
229 against confounding influences on the PRS-by-SLEs interactions[52]. PRS' and SLEs' were
230 standardized to a mean of 0 and a standard deviation of 1. The Mixed linear models
231 (i.e. the *diathesis-stress* model) used to assess GxE effects are as follows:

$$Depression = \beta_0 + \beta_1 PRS' + \beta_2 TSLE' + \beta_3 PRS' x TSLE' + GRM + Covariates$$

$$Depression = \beta_0 + \beta_1 PRS' + \beta_2 DSLE' + \beta_3 PRS' x DSLE' + GRM + Covariates$$

$$Depression = \beta_0 + \beta_1 PRS' + \beta_2 ISLE' + \beta_3 PRS' x ISLE' + GRM + Covariates$$

Covariates fitted in the models above were age, age^2, sex, age-by-sex, age^2-by-sex and 20 principal components. Sex and its interactions (age-by-sex and age^2-by-sex) were omitted from the covariates when stratifying by sex. All parameters from the models were estimated using GCTA and the significance of the effect (β) from fixed effects assessed using a Wald test. The significance of main effects (PRS and SLEs) allowed for nominally testing the significance of interactions at *p*-threshold = 0.05. To account for multiple testing correction, a Bonferroni's adjustment correcting for 8 PRS and 3 measures of SLE tested (24 tests) was used to establish a robust threshold for significance at $p = 2.08 \times 10^{-3}$.

The PRS effect on depression score at different levels of exposure was further examined for the detected nominally significant interactions by categorizing participants on three groups based on the number of SLE reported (i.e. "none", "low" or "high"). Using linear regression, we applied a least squares approach to assess PRS' effects on the depression score in each SLE category. Further conservative Bonferroni correction to adjust for the 3 SLE categories tested established a threshold for significance of $p = 6.94 \times 10^{-4}$.

Differences on the estimated size of GxE effect between women and men were assessed by comparing a z-score to the standard normal distribution (α = 0.05, one-tailed). Z-scores were derived from GxE estimates (β) and standard errors (SE) detected in women and men as follows:

$$\mathrm{Z-score} = \frac{\beta_{women} - \beta_{men}}{\sqrt{SE(\beta_{women})^2 + SE(\beta_{men})^2}}$$

253 **RESULTS**

254 PRS for MDD significantly predicted the depression score across the whole sample (β =
255 0.080, s.e. = 0.014, p = 7.53 x 10^{-9}) explaining 0.64% of the variance at its best p-
256 threshold (p-threshold = 0.1; Figure 1a). Stratifying by sex, PRS significantly predicted
257 the depression score in both sexes, explaining 0.59% in men and 0.67% in women
258 (*men*: p-threshold = 0.1, β = 0.077, s.e. = 0.022, p = 2.09 x 10^{-4}; *women*: p-threshold =
259 0.1, β = 0.082, s.e. = 0.018, p = 4.93 x 10^{-6}; Figure 1a). Self-reported SLE over the last 6
260 months (TSLE, mean = 1.3 SLE, s.d. = 1.5) also significantly predicted depression score
261 for the whole sample and stratified by sex (*full cohort*: variance explained = 4.91%, β =
262 0.222, s.e. = 0.014, p = 9.98 x 10^{-59}; *men*: 4.19%, β = 0.205, s.e. = 0.021, p = 2.23 x 10^{-22};
263 *women*: 5.33%, β = 0.231, s.e. = 0.018, p = 7.48 x 10^{-38}; Figure 1b). Overall, significant
264 additive contributions from genetics and SLE in depression score were detected in all
265 participants and across sexes. There was no significant difference in the direct effect of
266 TSLE between women and men (p = 0.17). However, the variance in depression score
267 explained by the TSLE appeared to be lower than the variance explained by the
268 measure of personal SLE (PSLE) used in Colodro-Conde *et al.*[23] (12.9%). This may, in
269 part, be explained by different contributions of dependent and independent SLE items
270 screened in Colodro-Conde *et al.* compared to our study. Although questions about
271 dependent SLE (DSLE, mean = 0.4 SLE) represented over 28% of the TSLE-items
272 reported in our study, the main effect of DSLE explained approximately 93% of the
273 amount of variance explained by TSLE (*full cohort*: variance explained = 4.56%, β =
274 0.212, s.e. = 0.014, p = 1.73 x 10^{-54}; *men*: 3.74%, β = 0.193, s.e. = 0.021, p = 9.66 x 10^{-21};
275 *women*: 5.07%, β = 0.225, s.e. = 0.018, p = 8.09 x 10^{-35}; Figure 1b). Independent SLE
276 (ISLE, mean = 0.85 SLE), which represented over 69% of TSLE-items, explained

277 approximately 57% of the amount of variance explained by TSLE (*full cohort*: variance
278 explained = 2.80%, β = 0.167, s.e. = 0.014, $p = 1.32 \times 10^{-33}$; *men*: 2.44%, β = 0.156, s.e. =
279 0.022, $p = 2.88 \times 10^{-13}$; *women*: 3.02%, β = 0.174, s.e. = 0.018, $p = 5.20 \times 10^{-22}$; Figure
280 1b). To explore the contribution from each measure, we combined DSLE and ISLE
281 together in a single model. DSLE explained 3.34% of the variance of depressive score
282 compared to 1.45% of the variance being explained by ISLE, suggesting that DSLE have
283 a greater effect on liability to depressive symptoms than ISLE.
284 A *diathesis-stress* model for depression was tested to assess GxE effects. We detected
285 significant, albeit weak, GxE effects on depression score (Figure 2). The PRS interaction
286 with TSLE was nominally significant in the full cohort (β = 0.028, s.e. = 0.014, R^2 =
287 0.08%, $p = 0.049$) and slightly stronger in women (β = 0.044, s.e. = 0.018, R^2 = 0.19%, p
288 = 0.017; Figure 2a), compared to men in which the effect was not significant (β =
289 0.039, s.e. = 0.022, R^2 = 0.15%, $p = 0.07$). However, these results did not survive
290 correction for multiple testing ($p > 2.08 \times 10^{-3}$).
291 The best-fit threshold was much lower in women (p-threshold = 1×10^{-5}) compared to
292 the full sample (p-threshold = 0.01). The size of GxE across sexes at p-threshold = 1 x
293 10^{-5} were significantly different (GxE*sex $p = 0.017$), but not at the best p-threshold in
294 the full cohort (p-threshold = 0.01, GxE*sex $p = 0.32$; Figure 2a). In women, GxE effect
295 with DSLE predicted depression score (p-threshold = 1×10^{-5}; β = 0.039, s.e. = 0.019, R^2
296 = 0.15%, $p = 0.038$; Figure 2b and Supplementary Figure 2a), as did the GxE effect with
297 ISLE (p-threshold = 1×10^{-5}; β = 0.040, s.e. = 0.019, R^2 = 0.16%, $p = 0.033$; Figure 2c and
298 Supplementary Figure 2b). No significant interaction was detected in men (best-fit p-
299 threshold = 0.1) with either TSLE (β = 0.039, s.e. = 0.022, R^2 = 0.15%, $p = 0.072$; Figure

300 2a), DSLE (β = 0.024, s.e. = 0.022, R^2 = 0.06%, *p* = 0.28; Figure 2b) or ISLE (β = 0.043, s.e.
301 = 0.022, R^2 = 0.18%, *p* = 0.055; Figure 2c).
302 To examine these results further and investigate the *diathesis* effect at different levels
303 of stress, nominally significant GxE were plotted between PRS and categories of SLE
304 (i.e, "none", "low" and "high" SLE reported; Figure 3). Examining the interaction found
305 at the full cohort (PRS at PGC-MDD GWAS *p*-threshold = 0.01), we detected a
306 significant direct *diathesis* effect on the risk of depressive symptoms in those
307 participants reporting SLE, with a higher risk when greater numbers of SLE were
308 reported ("low" number of SLE reported: PRS' β = 0.043, s.e. = 0.021, *p* = 0.039; "high"
309 number of SLE reported: PRS' β = 0.142, s.e. = 0.039, *p* = 2.86 x 10^{-4}; see Table 1 and
310 Figure 3a). Whereas, in participants who reported no SLE over the preceding 6 months,
311 the risk of depressive symptoms was the same regardless of their *diathesis* risk
312 ("none" SLE reported: PRS' β = 0.021, s.e. = 0.022, *p* = 0.339). Stratifying these results
313 by sex, we found the same pattern as in the full cohort in women ("none": *p* = 0.687;
314 "low": *p* = 0.023; "high": *p* = 2 x 10^{-3}), but not in men ("none": *p* = 0.307; "low": *p* =
315 728; "high": *p* = 0.053; see Table 1 and Figure 3a). However, the lack of significant
316 *diathesis* effect in men may be due to their lower sample size and its corresponding
317 reduced power.
318 Examining the interaction with PRS (at PGC-MDD GWAS *p*-threshold = 1 x 10^{-5}) with
319 which a significant interaction was detected in women, we only detected a significant
320 *diathesis* effect on depression score when stratifying by sex in those participants who
321 did not reported SLE over the last 6 months (see Table 1). The *diathesis* effect was
322 positive in men (PRS' β = 0.082, s.e. = 0.034, *p* = 0.016, R^2 = 0.7%; Figure 3b), consistent
323 with the contribution of risk alleles. Conversely, the *diathesis* effect was negative in

324 women (PRS' β = -0.061, s.e. = 0.029, p = 0.037, R^2 = 0.4%; Figure 3b), suggesting a
325 protective effect of increasing PRS in those women reporting no SLE, and consistent
326 with the contribution of alleles to individual sensitivity to both positive and negative
327 environmental effects (i.e. "plasticity alleles" rather than "risk alleles")[53,54]. This PRS
328 accounted for the effect of just 34 SNPs, and the size of its GxE across sexes were
329 significantly different (GxE*sex p = 0.017; Figure 2a), supporting possible differences in
330 the underlying stress-response mechanisms between women and men.

331 **DISCUSSION**

332 The findings reported in this study support those from Colodro-Conde *et al.*[23], in an
333 independent sample of similar sample size and study design, and also supports
334 possible sex-specific differences in the effect of genetic risk of MDD in response to SLE.
335 Both Colodro-Conde *et al.* and our study suggest that individuals with an inherent
336 genetic predisposition to MDD, reporting high number of recent SLE, are at additional
337 risk of depressive symptoms due to GxE effects, thus validating the *diathesis-stress*
338 theory. We identified nominally significant GxE effects in liability to depression at the
339 population level (p = 0.049) and in women (p = 0.017), but not in men (p = 0.072).
340 However, these interactions did not survive multiple testing correction ($p > 2.08 \times 10^{-3}$)
341 and the power of both studies to draw robust conclusions remains limited[55]. With
342 increased power these studies could determine more accurately both the presence
343 and magnitude of a GxE effect in depression. To better understand the effect of PRS at
344 different levels of exposure to stress, we examined the nominally significant
345 interactions detected in the full sample by categorizing participants on three groups
346 based on the number of SLE reported (i.e. "none", "low" or "high"). We detected a
347 significant *diathesis* effect on risk of depression only in those participants reporting
348 SLE, but not in those participants that reported no SLE over the last 6 month.
349 Furthermore, the *diathesis* effect was stronger on those participants reporting a "high"
350 number of SLE (β = 0.142, $p = 2.86 \times 10^{-4}$) compared to those participants reporting a
351 "low" number of SLE (β = 0.043, p = 0.039). The former effect was robustly significant
352 and survived a conservative Bonferroni correction to adjust for multiple testing ($p <$
353 6.94×10^{-4}). This finding corroborates the *diathesis-stress* model for depression and
354 supports Colodro-Conde *et al.* results using an independent sample.

355 To investigate the relative contribution of the GxE to the variance of depression, we
356 examined in the full cohort the total variance of depression score explained by the PRS
357 main effect and the significant GxE effect jointly. Together, they explained 0.34% of
358 the variance, of which 0.07% of the variance of the depression score was attributed to
359 the GxE effect (*p*-threshold = 0.01; PRS $p = 1.19 \times 10^{-4}$, GxE $p = 0.049$; both derived
360 from the full diathesis-model with TSLE). This is lower than the proportion of variance
361 attributed to common SNPs (8.9%) in the full PGC-MDD analysis[16]. As Colodro-Conde *et*
362 *al.* noted, this result aligns with estimates from experimental organisms suggesting
363 that around 20% of the heritability may be typically attributed to the effects of GxE[56],
364 although it is inconsistent with the majority of human traits with the potential
365 exception of depression[57].
366 Consistent with PRS predicting "personal" SLE in Colodro-Conde *et al.,* PRS for MDD
367 predicted SLE in our study (see Supplementary Figure 1), although not at the *p*-
368 threshold at which significant GxE effects were detected. Genetic factors predisposing
369 to MDD may contribute to individuals exposing themselves to, or showing an increased
370 reporting of, SLE via behavioural or personality traits[58,59]. Such genetic mediation of
371 the association between depression and SLE would disclose a gene-environment
372 correlation (i.e. genetic effects on the probability of undergoing a SLE) that hinders to
373 interpret our findings as pure GxE effects[60,61]. To address this limitation and assess this
374 aspect, following Colodro-Conde *et al.*, we split the 12-items TSLE measure into SLE
375 that are either potentially "dependent" on a participant's own behaviour (DSLE;
376 therefore, potentially driven by genetic factors) or not ("independent" SLE; ISLE)[46,49].
377 DSLE are reported to be more heritable and have stronger associations with MDD than
378 ISLE[49,62,63]. In our sample, reporting DSLE is significantly heritable ($h^2_{SNP} = 0.131$, s.e. =

379 0.071, p = 0.029), supporting a genetic mediation of the association, whereas reporting
380 ISLE is not significantly heritable (h^2_{SNP} = 0.000, s.e. = 0.072, p = 0.5). Nominally
381 significant GxE effects were seen in women for both DSLE and ISLE, suggesting that
382 both GxE and gene-environment correlation co-occur. Colodro-Conde *et al*. did not
383 identify significant GxE using independent SLE as the exposure.
384 Between-sex differences on stress response could help to explain previous differences
385 seen between sexes in depression such as those in associated risk (i.e. approximately
386 1.5 - 2-fold higher in women), symptoms reported and/or coping strategies (e.g.,
387 whereas women tend to cope through verbal and emotional strategies, men tend to
388 cope by doing sport and consuming alcohol)[64-68]. This also aligns with an increased risk
389 associated with a lack of social support seen in women compared to men[23].
390 Furthermore, although we do not know whether participants experienced recent
391 events with positive effects, we saw a protective effect in those women who did not
392 experienced recent SLE (p = 0.037), suggesting that some genetic variants associated
393 with MDD may operate as "plasticity alleles" and not just as "risk alleles"[53,54]. This
394 effect was neutralized in the full cohort due to an opposite effect in men (p = 0.016),
395 but it is supported by previous protective effects reported when using a serotoninergic
396 multilocus profile score and absence of SLE in young women[69]. These findings would
397 be consistent with a differential-susceptibility model[70,71] of depression, also suggested
398 by the interaction effects seen between the serotonin transporter linked promoter
399 region gene (5-HTTLPR) locus and family support and liability to adolescent depression
400 in boys[72]. However, our results and the examples given are only nominally significant
401 and will require replication in larger samples. Robustly identified sex-specific

402 differences in genetic stress-response could improve personalized treatments and
403 therapies such as better coping strategies.
404 There are notable differences between our study and Colodro-Conde *et al.* to consider
405 before accepting our findings as a replication of Colodro-Conde *et al.* results. First,
406 differences in PRS profiling may have affected replication power. We used the same
407 equivalent PGC-MDD2 GWAS as discovery sample. However, whereas Colodro-Conde
408 *et al.* generated PRS in their target sample containing over 9.5M imputed SNP, in this
409 study we generated PRS in a target sample of over 560K genotyped SNPs (see
410 Supplementary table 1 for comparison). This potentially results in a less informative
411 PRS in our study, with less predictive power, although the variance explained by our
412 PRS was slightly larger (0.64% vs. 0.46%). The size of the discovery sample is key to
413 constructing an accurate predictive PRS, but to exploit the most of the variants
414 available may be an asset[55]. Secondly, different screening tools were used to measure
415 both current depression and recent environmental stressors across the two studies.
416 Both studies transformed their data, using item response theory or by log-
417 transformation, to improve the data distribution. However, neither study used
418 depression scores that were normally distributed. The scale of the instruments used
419 and their corresponding parameterization to test an interaction could have a direct
420 effect on the size and significance of their interaction[56,73]; so findings from GxE must
421 be taken with caution. Furthermore, although both screening methods have been
422 validated and applied to detect depressive symptoms, different questions may cover
423 and emphasise different features of the illness, which may result in different outputs.
424 The same applies to the measurement of environmental stressors in the two studies.
425 Both covering of a longer time-period and upweighting by "dependent" SLE items may

426 explain the increased explanatory power of "personal" SLE (12.9%) in Colodro-Conde
427 *et al*. to predict depression score compared to our "total" SLE measure (4.91%). Finally,
428 the unmeasured aspects of the exposure to SLE or its impact may also contribute to
429 lack of stronger replication and positive findings.

430 In conclusion, despite differences in the measures used across studies, we saw
431 concordance and similar patterns between our results and those of Colodro-Conde *et*
432 *al.*[23]. Our findings are consistent with Colodro-Conde *et al.* and, therefore, add validity
433 to the *diathesis-stress* theory for depression. Empirically demonstrating the *diathesis-*
434 *stress* theory for depression would validate recent[20-22,24] and future studies using a
435 genome-wide approach to identify genetic mechanisms and interactive pathways
436 involved in GxE underpinning the causative effect of "stress" in the development of
437 depressive symptoms and mental illness in general. This study adds to our
438 understanding of gene-by-environment interactions, although larger samples will be
439 required to confirm differences in *diathesis-stress* effects between women and men.

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454

455 **FINANCIAL DISCLOSURE**

456 The authors declare no conflict of interest.

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653 **FIGURE LEGENDS**

654 **Figure 1. a)** Association between polygenic risk scores (PRS) and depression score
655 (main effects, one-sided tests). PRS were generated at 8 *p*-threshold levels using
656 summary statistics from the Psychiatric Genetic Consortium MDD GWAS (released July
657 2016) with the exclusion of Generation Scotland participants. The depression score
658 was derived from The General Health Questionnaire. The Y-axis represents the % of
659 variance of depression score explained by PRS main effects. The full cohort (yellow)
660 was split into men (blue) and women (red). In Colodro-Conde *et al.,* PRS for MDD
661 significantly explained up to 0.46% of depression score in their sample (~0.39% in
662 women and ~0.70% in men). **b)** Association between reported number of SLE and
663 depression score (main effect, one-sided tests, results expressed in % of depression
664 score explained). SLE were self-reported through a brief life-events questionnaire
665 based on the List of Threating Experiences and categorized into: total number of SLE
666 reported (TSLE), "dependent" SLE (DSLE) or "independent" SLE (ISLE). The full cohort
667 (yellow) was split into men (blue) and women (red). In Colodro-Conde *et al.,*
668 "personal" SLE significantly explained up to 12.9% of depression score variance in their
669 sample (~11.5% in women and ~16% in men).

670 **Figure 2.** Association between GxE effect and depression score. The results represent
671 percentage of depression score explained by the interaction term (two-sided tests)
672 fitted in linear mixed models to empirically test the *diathesis-stress* model. Red
673 numbers show significant interactions *p*-values. *Shows significance of difference
674 between sexes when comparing the size of the estimated GxE effects. The full cohort
675 (yellow) was split into men (blue) and women (red). PRS were generated at 8 *p*-
676 threshold levels using summary statistics from the Psychiatric Genetic Consortium

677 MDD GWAS (released July 2016) with the exclusion of Generation Scotland
678 participants. The interaction effect was tested with **a)** the number of SLE reported
679 (TSLE), **b)** "dependent" SLE (DSLE) and **c)** "independent" SLE (ISLE). In Colodro-Conde *et*
680 *al.,* the variance of depression score explained in their sample by GxE was 0.12% (p = 7
681 x 10^{-3}). GxE were also significant in women (p = 2 x 10^{-3}) explaining up to 0.25% of
682 depression score variation, but not in men (p = 0.059; R^2 = 0.17%; negative/protective
683 effect on depression score).

684 **Figure 3.** Scatterplot of *diathesis-stress* interactions on depression score. Interactions
685 with PRS at which nominally significant GxE effects were detected in **a)** full cohort (p-
686 threshold = 0.01) and **b)** in women (p-threshold = 1 x 10^{-5}) are shown. At bottom, the
687 remaining samples (i.e., *full cohort*, *women* or *men*) at same p-threshold are shown for
688 comparison. The X-axis represents the direct effect of PRS (standard deviation from
689 the mean) based on **a)** p-threshold = 0.01 and **b)** p-threshold = 1 x 10^{-5}, using the total
690 number of SLE reported by each participant (dot) as environmental exposures at three
691 SLE levels represented by colours. Blue: 0 SLE, "no stress", n = 1 833/1 041/792; green:
692 1 or 2 SLE, "low stress", n = 2 311/1 459/852; red: 3 or more SLE, "high stress", n =
693 775/490/285; in the full cohort, women and men, respectively. Y-axis reflects the
694 depression score standardized to mean of 0 and standard deviation of 1. Lines
695 represent the increment in risk of depression under a certain degree of "stress"
696 dependent on a genetic predisposition (= *diathesis*).
697

Table 1. *Diathesis* effect on depression score under SLE categories. Reported values at *p*-thresholds where nominally significant GxE effects were detected.

PRS at *p* value threshold = 0.01									
Sample	***FULL COHORT**			**WOMEN**			**MEN**		
SLE category	**none**	**low**	**high**	**none**	**low**	**high**	**none**	**low**	**high**
N	1833	2311	**775**	1041	1459	490	792	852	285
Effect	0.021	0.043	**0.142**	0.0118	0.0617	0.1538	0.0346	0.0113	0.1227
s.e.	0.022	0.021	**0.039**	0.029	0.027	0.049	0.034	0.032	0.063
t	0.957	2.07	**3.644**	0.403	2.274	3.112	1.021	0.348	1.947
***p* value**	0.339	0.039	**2.86×10^{-4}**	0.687	0.023	0.002	0.307	0.728	0.053
CI (95%)	-0.022, 0.065	0.002, 0.084	**0.065, 0.218**	-0.046, 0.069	0.008, 0.115	0.057, 0.251	-0.032, 0.101	-0.052, 0.075	-0.001,0.247

PRS at *p* value threshold = 1×10^{-5}									
Sample	**FULL COHORT**			***WOMEN**			**MEN**		
SLE category	**none**	**low**	**high**	**none**	**low**	**high**	**none**	**low**	**high**
N	1833	2311	775	1041	1459	490	792	852	285
Effect	-0.0022	0.0032	0.0705	-0.061	0.014	0.078	0.082	-0.0176	0.0548
s.e.	0.022	0.021	0.04	0.029	0.027	0.049	0.034	0.033	0.07
t	-0.098	0.153	1.76	-2.086	0.541	1.609	2.416	-0.537	0.778
***p* value**	0.922	0.878	0.079	0.037	0.589	0.108	0.016	0.592	0.437
CI (95%)	-0.046, 0.041	-0.037, 0.044	-0.008, 0.149	-0.119, -0.004	-0.038, 0.066	-0.017, 0.174	0.015, 0.149	-0.082,0.047	-0.084, 0.193

*Sample where nominally significant GxE was detected. SLE categories (number of SLE reported): 0 SLE = "none", 1 or 2 SLE = "low", and 3 or more SLE = "high". In red, nominally significant effects. In **bold red**, robustly significant effect after conservative Bonferroni correction ($p < 6.94 \times 10^{-4}$).

Figure 1.

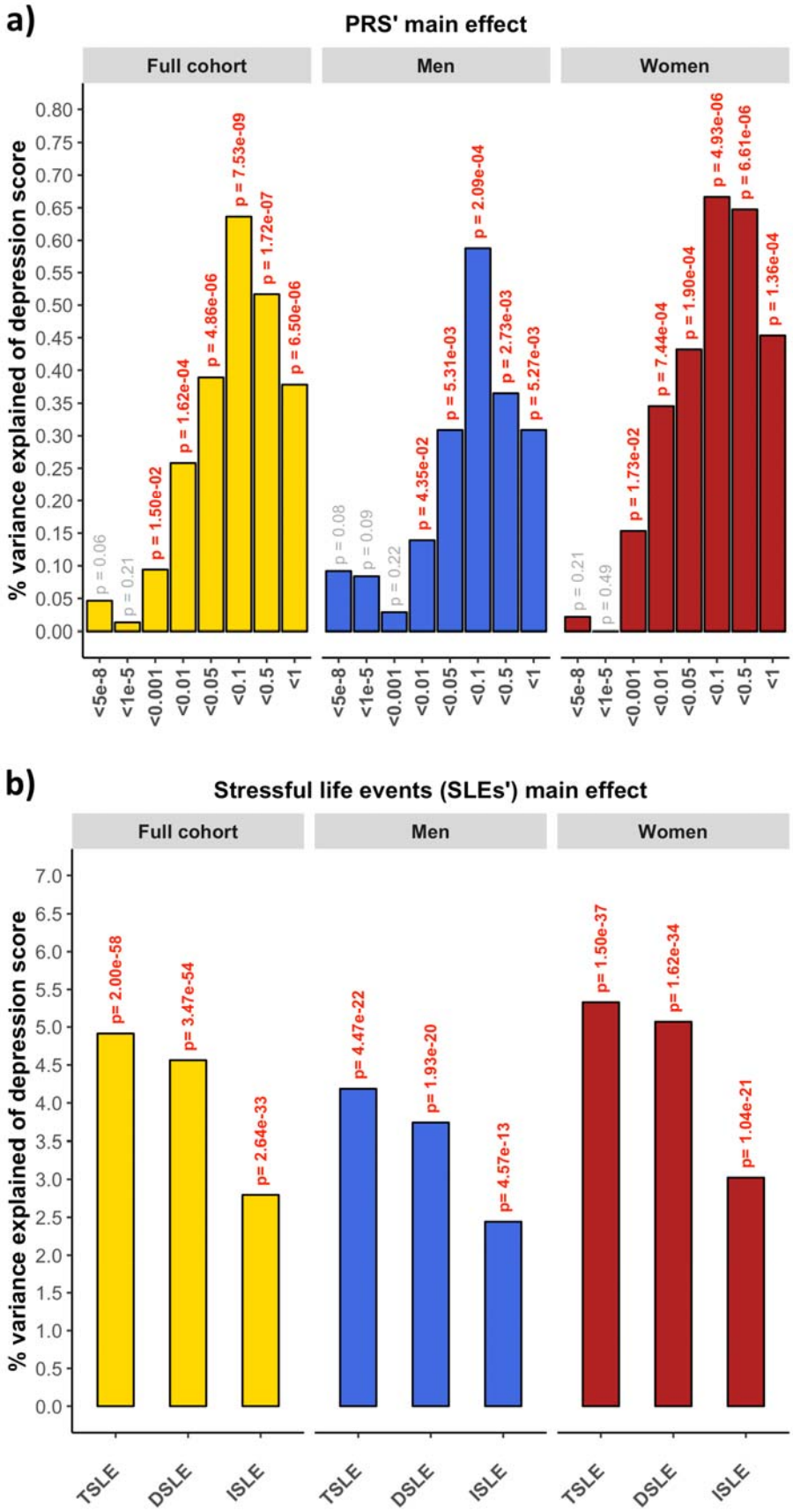

a)
PRS' main effect
Full cohort
Men
Women
% variance explained of depression score
0.00
0.05
0.10
0.15
0.20
0.25
0.30
0.35
0.40
0.45
0.50
0.55
0.60
0.65
0.70
0.75
0.80
p = 0.06
p = 0.21
p = 1.50e-02
p = 1.62e-04
p = 4.86e-06
p = 7.53e-09
p = 1.72e-07
p = 6.50e-06
p = 0.08
p = 0.09
p = 0.22
p = 4.35e-02
p = 5.31e-03
p = 2.09e-04
p = 2.73e-03
p = 5.27e-03
p = 0.21
p = 0.49
p = 1.73e-02
p = 7.44e-04
p = 1.90e-04
p = 4.93e-06
p = 6.61e-06
p = 1.36e-04
<5e-8
<1e-5
<0.001
<0.01
<0.05
<0.1
<0.5
<1
b)
Stressful life events (SLEs') main effect
Full cohort
Men
Women
% variance explained of depression score
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
p= 2.00e-58
p= 3.47e-54
p= 2.64e-33
p= 4.47e-22
p= 1.93e-20
p= 4.57e-13
p= 1.50e-37
p= 1.62e-34
p= 1.04e-21
TSLE
DSLE
ISLE

Figure 2.

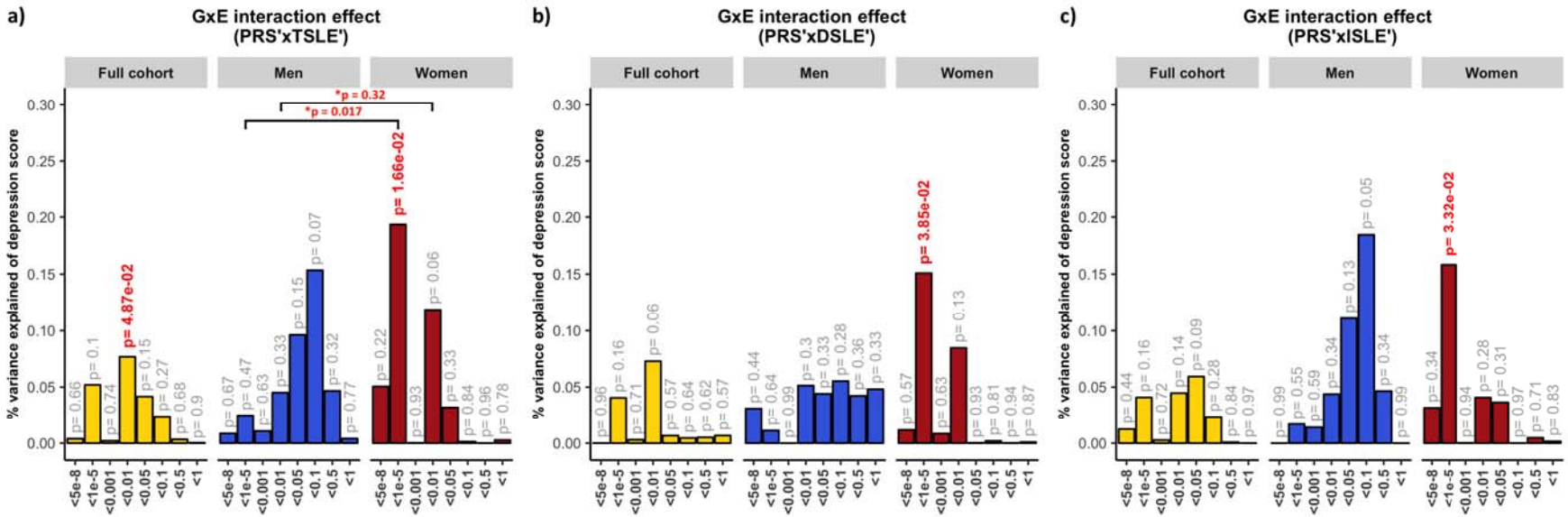
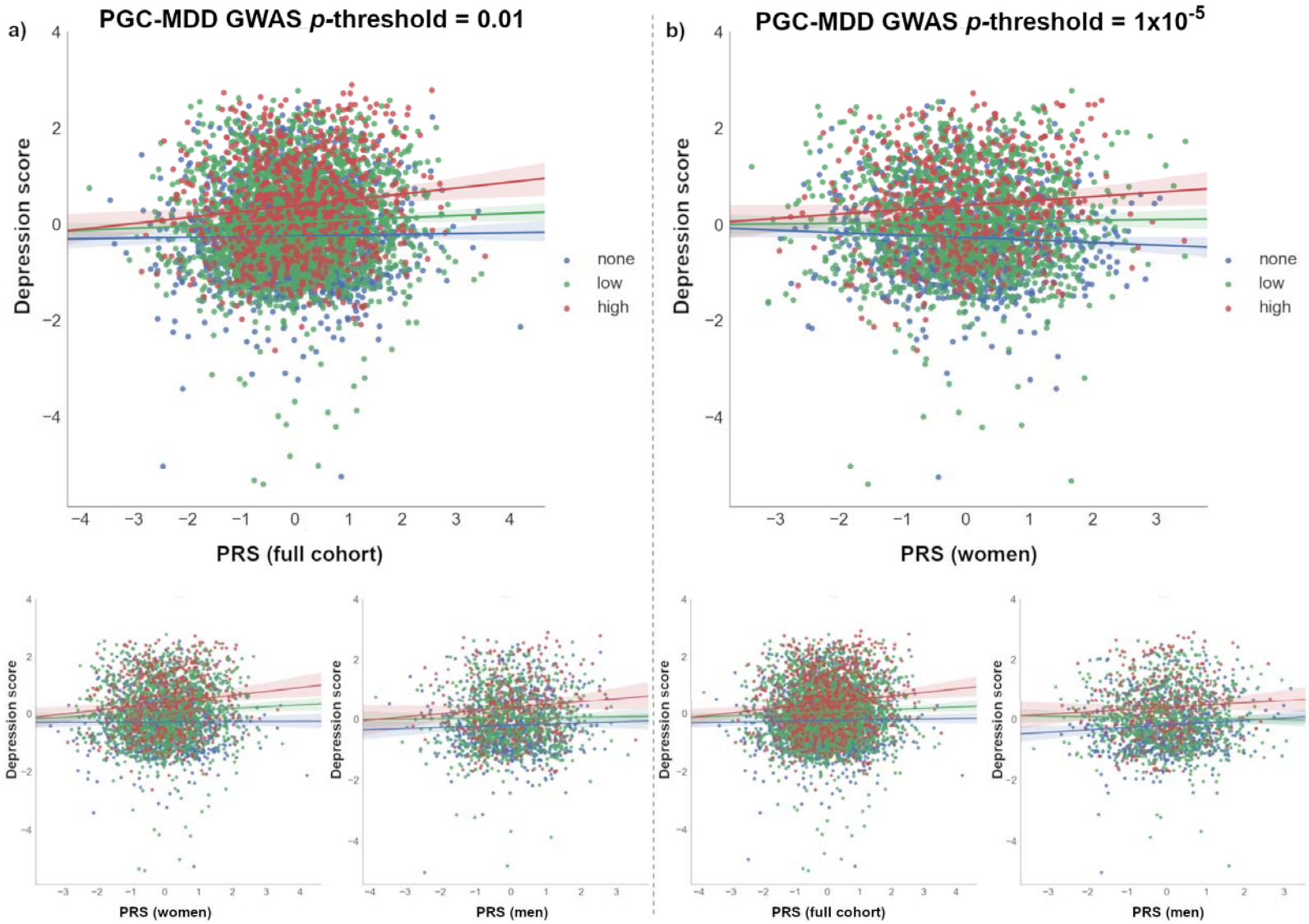

a)
GxE interaction effect
(PRS'xTSLE')
Full cohort
Men
Women
*p = 0.32
*p = 0.017
p= 4.87e-02
p= 1.66e-02
% variance explained of depression score
b)
GxE interaction effect
(PRS'xDSLE')
p= 3.85e-02
c)
GxE interaction effect
(PRS'xISLE')
p= 3.32e-02
<5e-8
<1e-5
<0.001
<0.01
<0.05
<0.1
<0.5
<1

Figure 3.


a)
PGC-MDD GWAS p-threshold = 0.01
Depression score
PRS (full cohort)
none
low
high
b)
PGC-MDD GWAS p-threshold = 1x10-5
Depression score
PRS (women)
none
low
high
Depression score
PRS (women)
Depression score
PRS (men)
Depression score
PRS (full cohort)
Depression score
PRS (men)