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1 **Reconsidering the reasons for heightened inflammation in major depressive disorder**

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29 *Key words:* Inflammation, major depressive disorder, body mass index, polygenic risk scores.

30

31 **Abstract**

32 **Background:** Increased circulating pro-inflammatory markers have repeatedly been associated
33 with major depressive disorder (MDD). However, it remains unclear whether inflammation
34 represents a causal mechanism for MDD, or whether the association is influenced by confounding
35 factors such as body mass index (BMI).

36 **Methods:** To better understand this complex relationship, we generated polygenic risk scores
37 (PRS) for MDD and BMI in a population cohort and attempted to isolate the impact these potential
38 risk factors have on adulthood inflammation. Peripheral blood samples were collected as part of the
39 South East London Community Health study, where we generated individualized PRS for MDD and
40 BMI and quantified inflammatory markers using multiplex ELISA-based technology. We performed
41 linear regressions to investigate the effects of PRS for MDD and BMI on inflammatory marker levels.

42 **Results:** Out of 35 inflammatory markers, we found a nominal effect of PRS for MDD on interleukin-
43 10. We also found a significant positive effect of BMI on nine inflammatory markers, of which the
44 two most strongly affected markers, interleukin-6 (IL-6) and C-reactive protein (CRP), were also
45 nominally predicted by BMI PRS.

46 **Limitations:** The study utilized a cross-sectional design with a moderately sized sample.

47 **Conclusions:** Our findings suggest there may not be a shared genetic mechanism contributing to
48 MDD and higher inflammatory marker levels. However, there may be shared genetic etiology
49 between BMI and adulthood levels of CRP and IL-6. Therefore, polygenic risk scores for BMI may
50 represent a useful indicator for heightened levels of inflammation in adulthood.

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71 1. Introduction

72 The total number of people with major depressive disorder (MDD) exceeded 300 million globally in 2015
73 and the World Health Organization (WHO) currently states that MDD is the single largest contributor to
74 global disability worldwide (Friedrich, 2017). The pathophysiology of MDD is not yet fully understood,
75 although numerous causal mechanisms have recently been proposed, with some studies suggesting
76 that MDD could manifest as a result of aberrant immune functioning in the body (Dantzer et al., 2008;
77 Harrison et al., 2009). According to this hypothesis, over-activation of inflammatory pathways can lead
78 to a systemic increase in peripheral immune modulators known as cytokines, which have been
79 associated with psychiatric symptoms in both humans and animal models (Dantzer et al., 2008; McNally
80 et al., 2008). This suggestion is corroborated by case-control studies demonstrating heightened
81 inflammation amongst MDD patients (Osimo et al., 2020), and in particular, those in an active episode
82 (Dahl et al., 2014) .

83 However, research investigating inflammation in the context of MDD is often confounded by a number
84 of extraneous factors. For example, an increase in circulating pro-inflammatory cytokines has also been
85 associated with increased body mass index (BMI), smoking and poor diet (Kantor et al., 2013; Lee et
86 al., 2013; Opel et al., 2015). These factors are highly prevalent in the MDD population (Kilian et al.,
87 2006) and their confounding effect was highlighted recently by our work revealing strong positive
88 associations between BMI and interleukin-6 (IL-6), C-reactive protein (CRP) and tumor necrosis factor
89 (TNF) levels, above-and-beyond the influence of MDD case control status or childhood maltreatment
90 effects (Palmos et al., 2019; Powell et al., 2018). Several other studies have also shown that high BMI
91 is associated with pro-inflammatory cytokine release and a state of chronic inflammation, which in turn
92 could lead to symptoms of MDD and inflammatory-related diseases such as cardiovascular disease
93 and arthritis (Anuradha et al., 2016; Borges et al., 2018; Rea et al., 2018). This association is likely due
94 to the correlation between BMI and abdominal fat levels, and in particular, the level of white adipose
95 tissue, which is known to exert a strong effect on hormone regulation and on the storage and release
96 of pro-inflammatory cytokines (Makki et al., 2013). Therefore, it is possible that BMI is a mediating factor
97 for increased inflammation in MDD and other inflammatory conditions, and further research into the
98 differential effects of MDD and BMI on circulating inflammatory markers could inform a more targeted
99 treatment for these conditions. For example, other fields have successfully demonstrated targeted anti-
100 inflammatory treatments, which could be repurposed in psychiatry for patients with inflammatory
101 subtypes of MDD (Durham et al., 2016).

102 When studying disease etiology, using genetic risk scores as a proxy for disease susceptibility in a
103 healthy population is one way to overcome the effect of confounding factors common in clinical cohorts
104 (Palmos et al., 2018). Genetic factors play a significant role in determining risk for MDD and adulthood
105 BMI, with studies reporting heritability estimates of around 40–50% and 41–85% respectively (Feng,
106 2016; Lohoff, 2010). MDD and BMI are both considered to be highly polygenic, meaning that many risk
107 variants of small effect size confer genetic risk. Individual variants may have little diagnostic value, but
108 by using summary statistics taken from mega-GWASs such as the ones carried out by the psychiatric
109 genomics consortium (PGC et al., 2017) or the genetic investigation of anthropometric traits consortium

110 (Locke et al., 2015), it is now possible to calculate polygenic risk scores (PRS) for MDD and BMI, for
111 any given individual (Euesden et al., 2015; Mullins et al., 2016; Wray et al., 2018).

112 In summary, current research suggests that although inflammation is associated with MDD, BMI is a
113 strong mediating factor for pro-inflammatory cytokine release and represents a potentially important
114 confounder. To investigate this in more detail, we tested for a shared genetic etiology between MDD
115 and inflammatory marker levels, and between BMI and inflammatory marker levels. We achieved this
116 by testing the effect of polygenic risk scores for MDD and BMI on levels of 35 inflammatory markers in
117 a largely disease-free population cohort. This allowed us to isolate the influence of genetic risk signals,
118 without confounding factors often present in clinical sample sets, such as medication use, higher
119 incidences of smoking, drug use, and various other factors known to be associated with MDD or obesity.
120 Our results indicate a far more important role for genetic risk for BMI than for MDD in explaining levels
121 of inflammatory markers in adulthood.

122 **2. Methods**

123 *2.1. The Sample*

124 Peripheral blood samples used in this study were collected by venipuncture as part of the South East
125 London Community Health Study (Hatch et al., 2012). SELCoH is a population study in London, UK,
126 investigating mental and physical health in the general population (Hatch et al., 2011). Participants have
127 so far received detailed phenotypic assessments as part of three separate phases. The first phase was
128 carried out to assess common mental and physical health disorders in South East London; the second
129 phase examined the roles of social context and policy in shaping patterns of health inequalities; and the
130 third phase included the collection of biological specimens including blood for DNA extraction and serum
131 separation. After collection, serum was stored at -80°C until required. Information relating to age, BMI
132 and smoking status was collected in conjunction with blood samples. Participants information can be
133 found in Table 1.

134

135 << Table 1 >>

136

137 *2.2. Ethics*

138 The SELCoH study received ethics approval from the King's College London research ethics
139 committee, reference PNM/12/13-152. Participation all provided written informed consent to taking part
140 in the study.

141 *2.3. Inflammatory Marker Quantification*

142 Upon use, serum was thawed at room temperature and 41 inflammatory markers were quantified
143 simultaneously using multiplex ELISA-based technology provided by the Meso Scale Discovery V-
144 PLEX Plus Human Biomarker 40-Plex kit, and a customized human duplex kit assaying brain-derived
145 neurotrophic factor (BDNF) and interferon-alpha (IFN- α). Note however, that interleukin-8 (IL-8) is

146 repeated twice on the 40-plex array (IL-8 and IL-8(HA)) alongside two different standard curves,
147 allowing for a very wide range of IL-8 levels to be detected. We only utilized data from IL-8 (not IL-
148 8(HA)) as our samples were detectable specifically within the range of this standard curve (0.0700 –
149 498 pg/mL). The 41 captured antibodies are etched to the bottom of five 96-well plates, each capturing
150 between 2 and 10 inflammatory markers. Seven-point standard curves were run in duplicate on each
151 plate in order to calculate absolute pg/mL values for the 80 samples assayed per plate, and a no-
152 template control was used to correct for background fluorescence. Plates were scanned on the
153 Mesoscale Scale Discovery MESO Quickplex SQ 120 reader at the MRC SGDP Centre, Institute of
154 Psychiatry, Psychology and Neuroscience, King's College London. Pilot studies revealed very high
155 intra-plate ($r > 0.99$) and inter-plate ($r > 0.97$) correlations, suggesting single measurements were
156 acceptably reliable using this methodology. Furthermore, known quantities within the standard curves
157 used on each plate, correlated very highly with quantities predicted by fluorescence intensity ($r > 0.99$).

158 *2.4. Genotyping & Quality Control (Target dataset)*

159 10 mL of blood was collected from subjects in tubes containing EDTA (BD Vacutainer; BD, NJ, USA)
160 and stored at -80°C . DNA was then extracted using a standard in-house protocol (Freeman et al., 2003)
161 and stored at -80°C . DNA samples were sent to the Affymetrix Research Services Laboratory in Santa
162 Clara, California, USA. Genotyping for SELCoH was assayed using the UK Biobank Axiom Array which
163 comprises of 820,967 genetic markers (Affymetrix, California, United States). Genotype data was put
164 through quality control measures as outlined previously (Coleman et al.), using PLINK v1.9 (Purcell et
165 al., 2007), as described previously (Palmos et al., 2019).

166 *2.5. Polygenic Risk Score Quantification*

167 *2.5.1. PRSice Software*

168 Individualized Polygenic Risk Scores (PRS) within our sample were calculated using PRSice, a PRS
169 quantification software (Euesden et al., 2015). The software uses summary results from previously
170 performed, well-powered GWAS (the base dataset) to generate PRS in our sample, SELCoH (the target
171 dataset). Briefly, PRSice works by first clumping SNPs in the genotype PLINK files corresponding to
172 the target dataset and removing those in high linkage disequilibrium, as this can falsely inflate polygenic
173 scores. Subsequently, within the target dataset the number of risk alleles at a particular SNP is
174 multiplied by that SNP's effect size (established in the base dataset), and then all the SNP information
175 is summed. Where previous work has already validated the optimal number of SNPs to include in a
176 PRS, the user can define which SNPs to include based on a p-value threshold in the base GWAS.
177 Alternatively, a user can include a phenotype file corresponding to their target dataset and PRSice can
178 automatically determine the best combination of SNPs from across a range of p-value thresholds (P_{τ}),
179 to predict the phenotype of interest.

180 For MDD PRS analyses, we set a $P_{\tau} = 0.1$, as defined by the recent Psychiatric Genomics Consortium
181 MDD GWAS (Wray et al., 2018), whereby we included all SNPs under this threshold from the base
182 dataset, to calculate polygenic risk scores in our target dataset. For BMI PRS analyses, because BMI
183 data was available from all participants as a continuous variable, we determined the optimal P_{τ} within

184 the SELCoH sample itself. We adjusted BMI for sex, age and ethnicity and tested the best combination
185 of SNPs (under different p-value thresholds), to predict BMI in our cohort, using BMI GWAS summary
186 statistics from the GIANT Consortium (Locke et al., 2015). We tested six p-value thresholds in total (P_T
187 = 0.05, $P_T = 0.1$, $P_T = 0.2$, $P_T = 0.3$, $P_T = 0.4$, $P_T = 0.5$), whilst covarying for seven population covariates
188 (PCs), using PRSice.

189 *2.5.2. Base Datasets*

190 The MDD base dataset (GWAS summary statistics) was obtained from the Psychiatric Genomics
191 Consortium (PGC), website (<https://www.med.unc.edu/pgc/results-and-downloads/downloads>) and
192 represents the largest GWAS for MDD to-date, consisting of 130,664 MDD cases and 330,470 controls
193 (Wray et al., 2018). The BMI base dataset was downloaded from the Genetic Investigation of
194 Anthropomorphic Traits (GIANT) Consortium website (the specific file is labelled BMI.SNPadjSMK)
195 (Locke et al., 2015).

196 *2.6. Statistical Analysis*

197 *2.6.1. Data Processing*

198 Standard curves were used to determine absolute quantities (pg/mL) of each inflammatory marker.
199 Absolute quantities (pg/mL) were then log-transformed to allow for parametric analyses. Subsequently,
200 data points were removed if they exceeded +/- 2 standard deviations from the mean. We also excluded
201 inflammatory markers where greater than 30% of the data was missing, leaving 35 inflammatory
202 markers (Powell et al., 2020).

203 *2.6.2. Major Depressive Disorder Analyses*

204 To test the association between genetic risk for MDD and inflammatory marker levels, we performed
205 linear regressions with log-protein levels as the dependent variable and a PRS for MDD as the
206 independent variable, alongside ethnicity, smoking, plate/batch effects, gender, age, BMI and seven
207 PCs as covariates. Multiple testing correction was performed using the Bonferroni method. Given a
208 sample size of 406, and an $\alpha = 0.0014$ ($0.05 / 35$), we had 80% power to detect medium effect sizes ρ
209 > 0.2 in our study.

210 *2.6.3. Body Mass Index Analyses*

211 First, we tested whether BMI correlated with inflammatory marker levels. Log-protein level was set as
212 the dependent variable and BMI was set as the independent variable, with gender, age, ethnicity,
213 smoking, plate/batch effects, and seven PCs as covariates. As above, we had 80% power to detect
214 medium effect sizes in our sample of $\rho > 0.2$. Next, for those markers significantly affected by BMI, we
215 determined if BMI PRS was also associated with levels of inflammatory markers by performing the same
216 regression, but instead of BMI as the independent variable we included PRS for BMI. Multiple testing
217 correction was performed using the Bonferroni method.

218 *2.6.4. Sensitivity Analyses*

219 We performed additional sensitivity analyses to verify the validity of our results. Given that inflammation
220 has been associated with depression and some individuals in our sample had self-reported depressive
221 symptoms, we first ran the same models as above with the inclusion of depression case/control status
222 and depression severity at the time of blood collection as covariates, for any significant associations.
223 Second, since BMI has previously been associated with depression risk, we ran a binary logistic
224 regression with PRS for BMI as the independent variable and depression case/control (0/1) status as
225 the dependent variable to test whether the genes responsible for BMI also predict depression diagnosis
226 in our sample. Finally, for IL-6 and CRP, we ran the same model as above and individually tested for
227 the potential mediating/confounding effect of physical illness (type-2 diabetes, arthritis, cardiovascular
228 disease, stroke, high blood pressure and cancer), socioeconomic factors (employment status,
229 educational attainment level) and antidepressant use, all of which were available within the SELCoH
230 study.

231 3. Results

232 3.1. *The effect of a polygenic risk for MDD on inflammatory marker levels*

233 The first part of our regression analyses investigated the effect of PRS for MDD on inflammatory marker
234 levels. Our findings revealed that higher polygenic risk for MDD correlates with higher IL-10 levels ($\beta =$
235 0.393 , $P = 0.016$, $R^2 = 0.02$); this finding did not survive multiple testing correction, see Figure 1. No
236 other inflammatory markers were found to be significant. See S1 in Supplementary Materials for a full
237 table of results.

238

239 <<<Figure 1>>>

240

241 3.2. *The effect of a polygenic risk for BMI on inflammatory marker levels*

242 To narrow down which inflammatory markers should be the focus of our BMI PRS analyses, we first
243 investigated the main effect of raw BMI scores on inflammatory marker levels. 15 inflammatory markers
244 showed a significant association; nine of which survived multiple testing correction ($P < 0.0014$), see
245 Figure 2(a). The optimal PRS for predicting BMI in SELCoH was defined by SNPs under $P_T = 0.2$ from
246 the GIANT GWAS ($N_{\text{SNPs}} = 24,507$, $R^2 = 0.063$, $P = 3.364 \times 10^{-7}$). We then outputted individualized PRS
247 for BMI and tested whether the inflammatory markers significantly affected by BMI also correlated with
248 PRS for higher BMI. Our results showed that PRS for higher BMI is positively associated with three
249 inflammatory markers, including Macrophage Inflammatory Protein (MIP)-1 β ($\beta = 0.228$, $P = 0.047$, R^2
250 $= 0.01$), IL-6 ($\beta = 0.302$, $P = 0.018$, $R^2 = 0.02$) and CRP ($\beta = 0.285$, $P = 0.018$, $R^2 = 0.01$), see Figure
251 2(b). These findings did not survive multiple testing correction (i.e. $p > 0.006$). See S2 in Supplementary
252 Materials for a full table of results.

253

254 <<<Figure 2>>>

255

256 *3.3. Sensitivity analyses*

257 The PRS for BMI did not significantly predict depression case/control status in a binary logistic
258 regression model ($P > 0.05$), suggesting that increased IL-6 and CRP levels via genetic risk factors for
259 BMI are independent of MDD diagnosis. In addition, we did not find a mediating/confounding effect of
260 depression severity, physical illness, socioeconomic status or antidepressant use on CRP or IL-6 ($P >$
261 0.05), suggesting that PRS for BMI is exerting an independent effect on CRP and IL-6 levels. Finally,
262 we did not find a mediating/confounding effect of depression severity, socioeconomic status or
263 antidepressant use on IL-6. We did observe a nominally significant effect of arthritis and stroke history
264 on IL-6 levels ($P < 0.05$), though these effects were independent of BMI, which remained significantly
265 associated with IL-6 ($P < 0.001$).

266

267 **4. Discussion**

268 The first aim of our study was to investigate whether genetic risk for MDD was associated with higher
269 levels of circulating pro-inflammatory cytokines. Given that numerous studies have reported BMI as a
270 major confounding factor when studying inflammation (Kantor et al., 2013; Palmos et al., 2019), our
271 second aim was to investigate whether a PRS for BMI was associated with pro-inflammatory cytokine
272 levels. Our findings revealed nominal effects of genetic risk for MDD on IL-10 levels, but no effect on
273 the levels of pro-inflammatory markers classically associated with MDD, such as IL-6 and CRP. We did
274 however find that both high BMI and a genetic risk for high BMI were associated with higher levels of
275 CRP and IL-6.

276 It is surprising that a genetic risk for MDD is not associated with adult levels of inflammatory markers,
277 given increased inflammation has been reported as a risk factor for developing MDD (Smith et al.,
278 2018), and non-human animal studies indicate a causal effect of increased inflammation on depression-
279 like phenotypes (O'Connor et al., 2009). A lack of significant associations in our study could relate to
280 the fact that BMI (as well as other factors) can have a very strong influence of inflammatory marker
281 levels in clinical sample sets, especially CRP and IL-6 (Powell et al., 2018). Indeed, BMI has been
282 shown to have a far stronger effect on inflammatory marker levels than MDD case/control status
283 (Palmos et al., 2019; Shelton et al., 2015), or in our case, than the genetic risk for MDD. This prompted
284 us to study the effects of BMI on inflammatory marker levels, and to test whether there is shared genetic
285 etiology between BMI and inflammatory marker levels.

286 We found strong effects of BMI on levels of two pro-inflammatory modulators commonly associated
287 with MDD (among other disease states), IL-6 and CRP (Khandaker et al., 2014; Smith et al., 2018;
288 Valkanova et al., 2013). This effect was also mimicked at the genetic level, whereby PRS for higher
289 BMI was nominally associated with higher levels of these markers. Studies have previously shown that
290 high BMI and larger abdominal adiposity is associated with increased circulating levels of IL-6 and CRP
291 (Khaodhjar et al., 2004; Rexrode et al., 2003), and that IL-6 and CRP gene polymorphisms are

292 associated with obesity (Todendi et al., 2015); but to our knowledge, this study is one of the first to
293 demonstrate a similar effect using BMI polygenic risk scores as predictors. Mechanistically, it is likely
294 that the increased levels of these inflammatory markers are due to an increase in adipose tissue in the
295 body, which is supported by studies investigating adipose tissue as an endocrine organ and a regulator
296 of inflammation (Ahima et al., 2000; Coppack, 2001; Juge-Aubry et al., 2005). Given that PRS can be
297 applied to people from a young age, our results suggest that PRS for BMI could represent a useful way
298 of identifying children at risk of increased adulthood inflammation and subsequent inflammatory related
299 conditions. In addition, these findings highlight the importance of studying BMI in the context of MDD
300 treatment, given that several studies have suggested that a reduction in BMI alone is associated with a
301 decrease in inflammation and that this decrease may lead to subsequent reduction in depression
302 symptoms, providing a valuable tool for clinical use (Miller et al., 2017; Powell et al., 2013; Shelton et
303 al., 2015; Shelton and Miller, 2011).

304 It is important to note that our study has a number of limitations. First, the study is of cross-sectional
305 design, meaning that we were unable to capture longitudinal changes in inflammatory marker levels. It
306 would be important to test how the penetrance of the PRS change over time, and whether the PRS for
307 MDD have stronger effects on inflammatory marker levels during development, or in conjunction with
308 environmental stress. Second, it's possible that a relatively rare 'inflammatory subtype' of depression
309 exists which is distinct from the more common causes of depression assayed in large GWAS
310 (Milaneschi et al., 2016). For instance, a recent study suggests that atypical depression with
311 neurovegetative symptoms may represent a subtype of depression with an inflammatory component
312 (Badini et al., 2020). Furthermore, it is well established that a high proportion of hepatitis sufferers
313 experience depression related to IFN- α treatment (Lotrich, 2009), and so we cannot rule out a causal
314 role for inflammation in rarer subtypes of MDD not captured by our PRS. Though, our results suggest
315 a major factor contributing to higher inflammation amongst the majority of MDD patients might be BMI.
316 This is also supported by meta-analyses which reveal that the effect size denoting the association
317 between IL-6 levels and MDD is five times higher when combining results from studies where BMI was
318 not adjusted (Howren et al., 2009). Third, the PRS for BMI may be inherently better at predicting
319 inflammatory marker expression compared to PRS for MDD because BMI is more heritable, and the
320 corresponding PRS explains more variance. Consequently, larger sample sets may allow us to detect
321 more subtle effects exerted by the PRS for MDD, which is not possible in this sample. Fourth, although
322 BMI is a commonly used measure, recent studies suggest waist-to-hip ratios, or dietary indexes in
323 conjunction with BMI can provide more accurate clinical utility (Kant and Graubard, 2005; Lam et al.,
324 2015). These measures may have even greater relevance to inflammatory cytokine levels and should
325 be considered in future studies. Finally, there may be other factors affecting inflammatory marker levels
326 which we were unable to account for in our study, including seasonality (Ter Horst et al., 2016), time of
327 day the blood was collected (Nakao, 2014) and effects of menstruation (O'Brien et al., 2007), which
328 could have increased heterogeneity and lowered our power to detect genetic effects.

329 Immune modulators such as pro-inflammatory cytokines are strongly associated with an increased risk
330 of psychiatric disorders such as MDD, as well as inflammatory conditions such as cardiovascular

331 disease (Dantzer et al., 2008; McNally et al., 2008 2019; Williams et al., 2019). Nevertheless, our study
332 is the first to demonstrate that genetic risk for MDD may not be responsible for increased inflammatory
333 marker levels in adulthood, rather a genetic risk for BMI may be associated with adulthood levels of
334 inflammatory markers instead. These findings suggest that genetic risk scores for BMI may be useful
335 in identifying individuals (including individuals with MDD), at risk for inflammatory-related conditions,
336 and allow for early intervention. Future replication in larger longitudinal samples are now needed to
337 assess the dynamic relationship between MDD, BMI and inflammation across the lifecourse, and to
338 discern the temporal ordering of effect.

339 **Appendix A. Supporting information**

340 Supplementary data associated with this article can be found in the submission folder.

341 **References**

- 342 Ahima, R. S. and J. S. Flier., 2000. Adipose Tissue as an Endocrine Organ. *Trends in Endocrinology &*
343 *Metabolism* 11: 327-332.
344
- 345 Anuradha, R., Munisankar, S., Bhootra, Y., Dolla, C., Kumaran, P., Babu, S., 2016. High body mass
346 index is associated with heightened systemic and mycobacterial antigen – Specific pro-inflammatory
347 cytokines in latent tuberculosis. *Tuberculosis* 101, 56-61.
- 348 Badini, I., Coleman, J.R.I., Hagenars, S.P., Hotopf, M., Breen, G., Lewis, C.M., Fabbri, C., 2020.
349 Depression with atypical neurovegetative symptoms shares genetic predisposition with immuno-
350 metabolic traits and alcohol consumption. *Psychol Med*, 1-11.
- 351 Borges, M.D., Franca, E.L., Fujimori, M., Silva, S.M.C., de Marchi, P.G.F., Deluque, A.L., Honorio-
352 Franca, A.C., de Abreu, L.C., 2018. Relationship between Proinflammatory Cytokines/Chemokines and
353 Adipokines in Serum of Young Adults with Obesity. *Endocrine, Metabolic & Immune Disorders - Drug*
354 *Targets* 18, 260-267.
- 355 Coleman, J.R.I., Euesden, J., Patel, H., Folarin, A.A., Newhouse, S., Breen, G., 2016. Quality control,
356 imputation and analysis of genome-wide genotyping data from the Illumina HumanCoreExome
357 microarray. *Briefings in Functional Genomics* 15, 298-304.
- 358 Dahl, J., Ormstad, H., Aass, H.C.D., Malt, U.F., Bendz, L.T., Sandvik, L., Brundin, L., Andreassen, O.A.,
359 2014. The plasma levels of various cytokines are increased during ongoing depression and are reduced
360 to normal levels after recovery. *Psychoneuroendocrinology* 45, 77-86.
- 361 Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., Kelley, K.W., 2008. From inflammation to
362 sickness and depression: when the immune system subjugates the brain. *Nature Reviews*
363 *Neuroscience* 9, 46-56.
- 364 Euesden, J., Lewis, C.M., O'Reilly, P.F., 2015. PRSice: Polygenic Risk Score software. *Bioinformatics*
365 31, 1466-1468.
- 366 Feng, R., 2016. How much do we know about the heritability of BMI? *The American Journal of Clinical*
367 *Nutrition* 104, 243-244.
- 368 Freeman, B., Smith, N., Curtis, C., Hockett, L., Mill, J., Craig, I.W., 2003. DNA from buccal swabs
369 recruited by mail: evaluation of storage effects on long-term stability and suitability for multiplex
370 polymerase chain reaction genotyping. *Behavior genetics* 33, 67-72.
- 371 Friedrich, M.J., 2017. Depression Is the Leading Cause of Disability Around the World. *JAMA* 317,
372 1517-1517.
- 373 Harrison, N.A., Brydon, L., Walker, C., Gray, M.A., Steptoe, A., Critchley, H.D., 2009. Inflammation
374 causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity.
375 *Biol Psychiatry* 66, 407-414.

- 376 Hatch, S.L., Frissa, S., Verdecchia, M., Stewart, R., Fear, N.T., Reichenberg, A., Morgan, C., Kankulu,
377 B., Clark, J., Gazard, B., Medcalf, R., Hotopf, M., Hotopf, M., 2011. Identifying socio-demographic and
378 socioeconomic determinants of health inequalities in a diverse London community: the South East
379 London Community Health (SELCoH) study. *BMC Public Health* 11, 861-861.
- 380 Hatch, S.L., Woodhead, C., Frissa, S., Fear, N.T., Verdecchia, M., Stewart, R., Reichenberg, A.,
381 Morgan, C., Bebbington, P., McManus, S., Brugha, T., Kankulu, B., Clark, J.L., Gazard, B., Medcalf, R.,
382 Hotopf, M., SELCoH Study Team, t.S.s., 2012. Importance of thinking locally for mental health: data
383 from cross-sectional surveys representing South East London and England. *PLoS one* 7, e48012.
- 384 Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1,
385 and IL-6: a meta-analysis. *Psychosom Med* 71, 171-186.
- 386 Kant, A.K., Graubard, B.I., 2005. A comparison of three dietary pattern indexes for predicting
387 biomarkers of diet and disease. *J Am Coll Nutr* 24, 294-303.
- 388 Kantor, E.D., Lampe, J.W., Kratz, M., White, E., 2013. Lifestyle factors and inflammation: associations
389 by body mass index. *PLoS One* 8, e67833.
- 390 Khandaker, G.M., Pearson, R.M., Zammit, S., Lewis, G., Jones, P.B., 2014. Association of serum
391 interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a
392 population-based longitudinal study. *JAMA psychiatry* 71, 1121-1128.
- 393 Khaodhriar, L., Ling, P.-R., Blackburn, G.L., Bistrrian, B.R., 2004. Serum Levels of Interleukin-6 and C-
394 Reactive Protein Correlate With Body Mass Index Across the Broad Range of Obesity. *Journal of*
395 *Parenteral and Enteral Nutrition* 28, 410-415.
- 396 Kilian, R., Becker, T., Kruger, K., Schmid, S., Frasch, K., 2006. Health behavior in psychiatric in-patients
397 compared with a German general population sample. *Acta Psychiatrica Scandinavica* 114, 242-248.
- 398 Lam, B.C.C., Koh, G.C.H., Chen, C., Wong, M.T.K., Fallows, S.J., 2015. Comparison of Body Mass
399 Index (BMI), Body Adiposity Index (BAI), Waist Circumference (WC), Waist-To-Hip Ratio (WHR) and
400 Waist-To-Height Ratio (WHtR) as predictors of cardiovascular disease risk factors in an adult population
401 in Singapore. *PLoS one* 10, e0122985-e0122985.
- 402 Lee, H., Lee, I.S., Choue, R., 2013. Obesity, Inflammation and Diet. *Pediatric Gastroenterology,*
403 *Hepatology & Nutrition* 16, 143.
- 404 Locke, A.E., Kahali, B., Berndt, S.I., Justice, A.E., Pers, T.H., Day, F.R., Powell, C., Vedantam, S.,
405 Buchkovich, M.L., Yang, J., Croteau-Chonka, D.C., Esko, T., Fall, T., Ferreira, T., Gustafsson, S.,
406 Kutalik, Z., Luan, J., Magi, R., Randall, J.C., Winkler, T.W., Wood, A.R., Workalemahu, T., Faul, J.D.,
407 Smith, J.A., Zhao, J.H., Zhao, W., Chen, J., Fehrmann, R., Hedman, A.K., Karjalainen, J., Schmidt,
408 E.M., Absher, D., Amin, N., Anderson, D., Beekman, M., Bolton, J.L., Bragg-Gresham, J.L., Buyske, S.,
409 Demirkan, A., Deng, G., Ehret, G.B., Feenstra, B., Feitosa, M.F., Fischer, K., Goel, A., Gong, J.,
410 Jackson, A.U., Kanoni, S., Kleber, M.E., Kristiansson, K., Lim, U., Lotay, V., Mangino, M., Leach, I.M.,
411 Medina-Gomez, C., Medland, S.E., Nalls, M.A., Palmer, C.D., Pasko, D., Pechlivanis, S., Peters, M.J.,
412 Prokopenko, I., Shungin, D., Stancakova, A., Strawbridge, R.J., Sung, Y.J., Tanaka, T., Teumer, A.,
413 Trompet, S., van der Laan, S.W., van Setten, J., Van Vliet-Ostaptchouk, J.V., Wang, Z., Yengo, L.,
414 Zhang, W., Isaacs, A., Albrecht, E., Arnlöv, J., Arscott, G.M., Attwood, A.P., Bandinelli, S., Barrett, A.,
415 Bas, I.N., Bellis, C., Bennett, A.J., Berne, C., Blagieva, R., Bluher, M., Bohringer, S., Bonnycastle, L.L.,
416 Botcher, Y., Boyd, H.A., Bruinenberg, M., Caspersen, I.H., Chen, Y.I., Clarke, R., Daw, E.W., de Craen,
417 A.J.M., Delgado, G., Dimitriou, M., Doney, A.S.F., Eklund, N., Estrada, K., Eury, E., Folkersen, L.,
418 Fraser, R.M., Garcia, M.E., Geller, F., Giedraitis, V., Gigante, B., Go, A.S., Golay, A., Goodall, A.H.,
419 Gordon, S.D., Gorski, M., Grabe, H.J., Grallert, H., Grammer, T.B., Grassler, J., Gronberg, H., Groves,
420 C.J., Gusto, G., Haessler, J., Hall, P., Haller, T., Hallmans, G., Hartman, C.A., Hassinen, M., Hayward,
421 C., Heard-Costa, N.L., Helmer, Q., Hengstenberg, C., Holmen, O., Hottenga, J.J., James, A.L., Jeff,
422 J.M., Johansson, A., Jolley, J., Juliusdottir, T., Kinnunen, L., Koenig, W., Koskenvuo, M., Kratzer, W.,
423 Laitinen, J., Lamina, C., Leander, K., Lee, N.R., Lichtner, P., Lind, L., Lindstrom, J., Lo, K.S., Lobbens,
424 S., Lorbeer, R., Lu, Y., Mach, F., Magnusson, P.K.E., Mahajan, A., McArdle, W.L., McLachlan, S.,
425 Menni, C., Merger, S., Mihailov, E., Milani, L., Moayyeri, A., Monda, K.L., Morken, M.A., Mulas, A.,
426 Muller, G., Muller-Nurasyid, M., Musk, A.W., Nagaraja, R., Nothen, M.M., Nolte, I.M., Pilz, S., Rayner,
427 N.W., Renstrom, F., Rettig, R., Ried, J.S., Ripke, S., Robertson, N.R., Rose, L.M., Sanna, S.,
428 Scharnagl, H., Scholtens, S., Schumacher, F.R., Scott, W.R., Seufferlein, T., Shi, J., Smith, A.V.,
429 Smolonska, J., Stanton, A.V., Steinthorsdottir, V., Stirrups, K., Stringham, H.M., Sundstrom, J., Swertz,
430 M.A., Swift, A.J., Syvanen, A.C., Tan, S.T., Tayo, B.O., Thorand, B., Thorleifsson, G., Tyrer, J.P., Uh,

- 431 H.W., Vandenput, L., Verhulst, F.C., Vermeulen, S.H., Verweij, N., Vonk, J.M., Waite, L.L., Warren,
 432 H.R., Waterworth, D., Weedon, M.N., Wilkens, L.R., Willenborg, C., Wilsgaard, T., Wojczynski, M.K.,
 433 Wong, A., Wright, A.F., Zhang, Q., LifeLines Cohort, S., Brennan, E.P., Choi, M., Dastani, Z., Drong,
 434 A.W., Eriksson, P., Franco-Cereceda, A., Gadin, J.R., Gharavi, A.G., Goddard, M.E., Handsaker, R.E.,
 435 Huang, J., Karpe, F., Kathiresan, S., Keildson, S., Kiryluk, K., Kubo, M., Lee, J.Y., Liang, L., Lifton, R.P.,
 436 Ma, B., McCarroll, S.A., McKnight, A.J., Min, J.L., Moffatt, M.F., Montgomery, G.W., Murabito, J.M.,
 437 Nicholson, G., Nyholt, D.R., Okada, Y., Perry, J.R.B., Dorajoo, R., Reinmaa, E., Salem, R.M.,
 438 Sandholm, N., Scott, R.A., Stolk, L., Takahashi, A., Tanaka, T., van 't Hooft, F.M., Vinkhuyzen, A.A.E.,
 439 Westra, H.J., Zheng, W., Zondervan, K.T., Consortium, A.D., Group, A.-B.W., Consortium, C.A.D.,
 440 Consortium, C.K., Gloc, Icbp, Investigators, M., Mu, T.C., Consortium, M.I., Consortium, P., ReproGen,
 441 C., Consortium, G., International Endogene, C., Heath, A.C., Arveiler, D., Bakker, S.J.L., Beilby, J.,
 442 Bergman, R.N., Blangero, J., Bovet, P., Campbell, H., Caulfield, M.J., Cesana, G., Chakravarti, A.,
 443 Chasman, D.I., Chines, P.S., Collins, F.S., Crawford, D.C., Cupples, L.A., Cusi, D., Danesh, J., de
 444 Faire, U., den Ruijter, H.M., Dominiczak, A.F., Erbel, R., Erdmann, J., Eriksson, J.G., Farrall, M., Felix,
 445 S.B., Ferrannini, E., Ferrieres, J., Ford, I., Forouhi, N.G., Forrester, T., Franco, O.H., Gansevoort, R.T.,
 446 Gejman, P.V., Gieger, C., Gottesman, O., Gudnason, V., Gyllenstein, U., Hall, A.S., Harris, T.B.,
 447 Hattersley, A.T., Hicks, A.A., Hindorf, L.A., Hingorani, A.D., Hofman, A., Homuth, G., Hovingh, G.K.,
 448 Humphries, S.E., Hunt, S.C., Hypponen, E., Illig, T., Jacobs, K.B., Jarvelin, M.R., Jockel, K.H.,
 449 Johansen, B., Jousilahti, P., Jukema, J.W., Jula, A.M., Kaprio, J., Kastelein, J.J.P., Keinanen-
 450 Kiukaanniemi, S.M., Kiemenev, L.A., Knekt, P., Kooner, J.S., Kooperberg, C., Kovacs, P., Kraja, A.T.,
 451 Kumari, M., Kuusisto, J., Lakka, T.A., Langenberg, C., Marchand, L.L., Lehtimaki, T., Lyssenko, V.,
 452 Mannisto, S., Marette, A., Matise, T.C., McKenzie, C.A., McKnight, B., Moll, F.L., Morris, A.D., Morris,
 453 A.P., Murray, J.C., Nelis, M., Ohlsson, C., Oldehinkel, A.J., Ong, K.K., Madden, P.A.F., Pasterkamp,
 454 G., Peden, J.F., Peters, A., Postma, D.S., Pramstaller, P.P., Price, J.F., Qi, L., Raitakari, O.T.,
 455 Rankinen, T., Rao, D.C., Rice, T.K., Ridker, P.M., Rioux, J.D., Ritchie, M.D., Rudan, I., Salomaa, V.,
 456 Samani, N.J., Saramies, J., Sarzynski, M.A., Schunkert, H., Schwarz, P.E.H., Sever, P., Shuldiner,
 457 A.R., Sinisalo, J., Stolk, R.P., Strauch, K., Tonjes, A., Tregouet, D.A., Tremblay, A., Tremoli, E., Virtamo,
 458 J., Vohl, M.C., Volker, U., Waeber, G., Willemssen, G., Witteman, J.C., Zillikens, M.C., Adair, L.S.,
 459 Amouyel, P., Asselbergs, F.W., Assimes, T.L., Bochud, M., Boehm, B.O., Boerwinkle, E., Bornstein,
 460 S.R., Bottinger, E.P., Bouchard, C., Cauchi, S., Chambers, J.C., Chanock, S.J., Cooper, R.S., de
 461 Bakker, P.I.W., Dedoussis, G., Ferrucci, L., Franks, P.W., Froguel, P., Groop, L.C., Haiman, C.A.,
 462 Hamsten, A., Hui, J., Hunter, D.J., Hveem, K., Kaplan, R.C., Kivimaki, M., Kuh, D., Laakso, M., Liu, Y.,
 463 Martin, N.G., Marz, W., Melbye, M., Metspalu, A., Moebus, S., Munroe, P.B., Njolstad, I., Oostra, B.A.,
 464 Palmer, C.N.A., Pedersen, N.L., Perola, M., Perusse, L., Peters, U., Power, C., Quertermous, T.,
 465 Rauramaa, R., Rivadeneira, F., Saaristo, T.E., Saleheen, D., Sattar, N., Schadt, E.E., Schlessinger, D.,
 466 Slagboom, P.E., Snieder, H., Spector, T.D., Thorsteinsdottir, U., Stumvoll, M., Tuomilehto, J.,
 467 Uitterlinden, A.G., Uusitupa, M., van der Harst, P., Walker, M., Wallaschofski, H., Wareham, N.J.,
 468 Watkins, H., Weir, D.R., Wichmann, H.E., Wilson, J.F., Zanen, P., Borecki, I.B., Deloukas, P., Fox, C.S.,
 469 Heid, I.M., O'Connell, J.R., Strachan, D.P., Stefansson, K., van Duijn, C.M., Abecasis, G.R., Franke, L.,
 470 Frayling, T.M., McCarthy, M.I., Visscher, P.M., Scherag, A., Willer, C.J., Boehnke, M., Mohlke, K.L.,
 471 Lindgren, C.M., Beckmann, J.S., Barroso, I., North, K.E., Ingelsson, E., Hirschhorn, J.N., Loos, R.J.F.,
 472 Speliotes, E.K., 2015. Genetic studies of body mass index yield new insights for obesity biology. *Nature*
 473 518, 197-206.
- 474 Lohoff, F.W., 2010. Overview of the genetics of major depressive disorder. *Current psychiatry reports*
 475 12, 539-546.
- 476 Lotrich, F.E., 2009. Major depression during interferon-alpha treatment: vulnerability and prevention.
 477 *Dialogues Clin Neurosci* 11, 417-425.
- 478 Makki, K., Froguel, P., Wolowczuk, I., 2013. Adipose tissue in obesity-related inflammation and insulin
 479 resistance: cells, cytokines, and chemokines. *ISRN Inflamm* 2013, 139239.
- 480 McNally, L., Bhagwagar, Z., Hannestad, J., 2008. Inflammation, glutamate, and glia in depression: a
 481 literature review. *CNS spectrums* 13, 501-510.
- 482 Milaneschi, Y., Lamers, F., Peyrot, W.J., Abdellaoui, A., Willemssen, G., Hottenga, J.-J., Jansen, R.,
 483 Mbarek, H., Dehghan, A., Lu, C., Boomsma, D.I., Penninx, B.W.J.H., Penninx, B.W.J.H., 2016.
 484 Polygenic dissection of major depression clinical heterogeneity. *Molecular Psychiatry* 21, 516-522.
- 485 Miller, A.H., Haroon, E., Felger, J.C., 2017. Therapeutic Implications of Brain-Immune Interactions:
 486 Treatment in Translation. *Neuropsychopharmacology* 42, 334-359.

- 487 Mullins, N., Power, R.A., Fisher, H.L., Hanscombe, K.B., Euesden, J., Iniesta, R., Levinson, D.F.,
 488 Weissman, M.M., Potash, J.B., Shi, J., Uher, R., Cohen-Woods, S., Rivera, M., Jones, L., Jones, I.,
 489 Craddock, N., Owen, M.J., Korszun, A., Craig, I.W., Farmer, A.E., McGuffin, P., Breen, G., Lewis, C.M.,
 490 2016. Polygenic interactions with environmental adversity in the aetiology of major depressive disorder.
 491 *Psychological Medicine* 46, 759-770.
- 492 Nakao, A., 2014. Temporal regulation of cytokines by the circadian clock. *J Immunol Res* 2014, 614529.
- 493 O'Connor, J.C., Lawson, M.A., Andre, C., Moreau, M., Lestage, J., Castanon, N., Kelley, K.W., Dantzer,
 494 R., 2009. Lipopolysaccharide-induced depressive-like behavior is mediated by indoleamine 2,3-
 495 dioxygenase activation in mice. *Mol Psychiatry* 14, 511-522.
- 496 O'Brien, S.M., Fitzgerald, P., Scully, P., Landers, A.M.T., Scott, L.V., Dinan, T.G., 2007. Impact of
 497 Gender and Menstrual Cycle Phase on Plasma Cytokine Concentrations. *Neuroimmunomodulation* 14,
 498 84-90.
- 499 Opel, N., Redlich, R., Grotegerd, D., Dohm, K., Heindel, W., Kugel, H., Arolt, V., Dannlowski, U., 2015.
 500 Obesity and major depression: Body-mass index (BMI) is associated with a severe course of disease
 501 and specific neurostructural alterations. *Psychoneuroendocrinology* 51, 219-226.
- 502 Osimo, E.F., Pillinger, T., Rodriguez, I.M., Khandaker, G.M., Pariante, C.M., Howes, O.D., 2020.
 503 Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166
 504 patients and 5,083 controls. *Brain, behavior, and immunity* 87, 901-909.
- 505 Palmos, A.B., Breen, G., Goodwin, L., Frissa, S., Hatch, S.L., Hotopf, M., Thuret, S., Lewis, C.M.,
 506 Powell, T.R., 2018. Genetic risk for psychiatric disorders and telomere length. *Frontiers in Genetics* 9.
- 507 Palmos, A.B., Watson, S., Hughes, T., Finkelmeyer, A., McAllister-Williams, R.H., Ferrier, N., Anderson,
 508 I.M., Nair, R., Young, A.H., Strawbridge, R., Cleare, A.J., Chung, R., Frissa, S., Goodwin, L., Hotopf,
 509 M., Hatch, S.L., Wang, H., Collier, D.A., Thuret, S., Breen, G., Powell, T.R., 2019. Associations between
 510 childhood maltreatment and inflammatory markers. *BJPsych Open* 5.
- 511 PGC, -M.D.D.W.G.o.t., Wray, N.R., Sullivan, P.F., 2017. Genome-wide association analyses identify
 512 44 risk variants and refine the genetic architecture of major depression. *bioRxiv*, 167577.
- 513 Powell, T.R., Duarte, R.R.R., Hotopf, M., Hatch, S.L., de Mulder Rougvie, M., Breen, G.D., Lewis, C.M.,
 514 Nixon, D.F., 2020. The behavioral, cellular and immune mediators of HIV-1 acquisition: New insights
 515 from population genetics. *Sci Rep* 10, 3304.
- 516 Powell, T.R., Gaspar, H.A., Chung, R., Keohane, A., Gunasinghe, C., Uher, R., Aitchison, K.J., Souery,
 517 D., Mors, O., Maier, W., Zobel, A., Rietschel, M., Henigsberg, N., Dernovsek, M.Z., Hauser, J., Frissa,
 518 S., Goodwin, L., Hotopf, M., Hatch, S.L., Collier, D.A., Wang, H., Breen, G., 2018. Assessing 42
 519 inflammatory markers in 321 control subjects and 887 major depressive disorder cases: BMI and other
 520 confounders and overall predictive ability for current depression. *bioRxiv*.
- 521 Powell, T.R., Tansey, K.E., Breen, G., Farmer, A.E., Craig, I.W., Uher, R., McGuffin, P., D'Souza, U.M.,
 522 Schalkwyk, L.C., 2013. ATP-binding cassette sub-family F member 1 (ABCF1) is identified as a putative
 523 therapeutic target of escitalopram in the inflammatory cytokine pathway. *J Psychopharmacol* 27, 609-
 524 615.
- 525 Purcell, S., Neale, B., Todd-Brown, K., Thomas, L., Ferreira, M.A.R., Bender, D., Maller, J., Sklar, P.,
 526 de Bakker, P.I.W., Daly, M.J., Sham, P.C., 2007. PLINK: A Tool Set for Whole-Genome Association
 527 and Population-Based Linkage Analyses. *The American Journal of Human Genetics* 81, 559-575.
- 528 Rea, I.M., Gibson, D.S., McGilligan, V., McNerlan, S.E., Alexander, H.D., Ross, O.A., 2018. Age and
 529 Age-Related Diseases: Role of Inflammation Triggers and Cytokines. *Frontiers in immunology* 9, 586.
- 530 Rexrode, K.M., Pradhan, A., Manson, J.E., Buring, J.E., Ridker, P.M., 2003. Relationship of total and
 531 abdominal adiposity with CRP and IL-6 in women. *Annals of Epidemiology* 13, 674-682.
- 532 Shelton, R.C., Falola, M., Li, L., Zajecka, J., Fava, M., Papakostas, G.I., 2015. The pro-inflammatory
 533 profile of depressed patients is (partly) related to obesity. *J Psychiatr Res* 70, 91-97.
- 534 Shelton, R.C., Miller, A.H., 2011. Inflammation in depression: is adiposity a cause? *Dialogues Clin
 535 Neurosci* 13, 41-53.

- 536 Smith, K.J., Au, B., Ollis, L., Schmitz, N., 2018. The association between C-reactive protein, Interleukin-
537 6 and depression among older adults in the community: A systematic review and meta-analysis.
538 *Experimental Gerontology* 102, 109-132.
- 539 Ter Horst, R., Jaeger, M., Smeekens, S.P., Oosting, M., Swertz, M.A., Li, Y., Kumar, V., Diavatopoulos,
540 D.A., Jansen, A.F.M., Lemmers, H., Toenhake-Dijkstra, H., van Herwaarden, A.E., Janssen, M., van
541 der Molen, R.G., Joosten, I., Sweep, F., Smit, J.W., Netea-Maier, R.T., Koenders, M., Xavier, R.J., van
542 der Meer, J.W.M., Dinarello, C.A., Pavelka, N., Wijmenga, C., Netea, R.A., Joosten, L.A.B., Netea,
543 M.G., 2016. Host and Environmental Factors Influencing Individual Human Cytokine Responses. *Cell*
544 167, 1111-1124 e1113.
- 545 Todendi, P.F., Klinger, E.I., Ferreira, M.B., Reuter, C.P., Burgos, M.S., Possuelo, L.G., Valim, A.R.,
546 2015. Association of IL-6 and CRP gene polymorphisms with obesity and metabolic disorders in children
547 and adolescents. *An Acad Bras Cienc* 87, 915-924.
- 548 Valkanova, V., Ebmeier, K.P., Allan, C.L., 2013. CRP, IL-6 and depression: A systematic review and
549 meta-analysis of longitudinal studies. *Journal of Affective Disorders* 150, 736-744.
- 550 Williams, J.W., Huang, L.H., Randolph, G.J., 2019. Cytokine Circuits in Cardiovascular Disease.
551 *Immunity* 50, 941-954.
- 552 Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J.,
553 Agerbo, E., Air, T.M., Andlauer, T.M.F., Bacanu, S.-A., Bækvad-Hansen, M., Beekman, A.F.T., Bigdeli,
554 T.B., Binder, E.B., Blackwood, D.R.H., Bryois, J., Buttenschøn, H.N., Bybjerg-Grauholm, J., Cai, N.,
555 Castelao, E., Christensen, J.H., Clarke, T.-K., Coleman, J.I.R., Colodro-Conde, L., Couvy-Duchesne,
556 B., Craddock, N., Crawford, G.E., Crowley, C.A., Dashti, H.S., Davies, G., Deary, I.J., Degenhardt, F.,
557 Derks, E.M., Direk, N., Dolan, C.V., Dunn, E.C., Eley, T.C., Eriksson, N., Escott-Price, V., Kiadeh,
558 F.H.F., Finucane, H.K., Forstner, A.J., Frank, J., Gaspar, H.A., Gill, M., Giusti-Rodríguez, P., Goes,
559 F.S., Gordon, S.D., Grove, J., Hall, L.S., Hannon, E., Hansen, C.S., Hansen, T.F., Herms, S., Hickie,
560 I.B., Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.-J., Hougaard, D.M., Hu, M., Hyde, C.L., Ising,
561 M., Jansen, R., Jin, F., Jorgenson, E., Knowles, J.A., Kohane, I.S., Kraft, J., Kretschmar, W.W., Krogh,
562 J., Kutalik, Z., Lane, J.M., Li, Y., Li, Y., Lind, P.A., Liu, X., Lu, L., MacIntyre, D.J., MacKinnon, D.F.,
563 Maier, R.M., Maier, W., Marchini, J., Mbarek, H., McGrath, P., McGuffin, P., Medland, S.E., Mehta, D.,
564 Middeldorp, C.M., Mihailov, E., Milaneschi, Y., Milani, L., Mill, J., Mondimore, F.M., Montgomery, G.W.,
565 Mostafavi, S., Mullins, N., Nauck, M., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H.,
566 Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E., Peyrot,
567 W.J., Pistis, G., Posthuma, D., Purcell, S.M., Quiroz, J.A., Qvist, P., Rice, J.P., Riley, B.P., Rivera, M.,
568 Saeed Mirza, S., Saxena, R., Schoevers, R., Schulte, E.C., Shen, L., Shi, J., Shyn, S.I., Sigurdsson,
569 E., Sinnamoni, G.B.C., Smit, J.H., Smith, D.J., Stefansson, H., Steinberg, S., Stockmeier, C.A., Streit,
570 F., Strohmaier, J., Tansey, K.E., Teismann, H., Teumer, A., Thompson, W., Thomson, P.A.,
571 Thorgeirsson, T.E., Tian, C., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D.,
572 Van der Auwera, S., van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T.,
573 Weinsheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., Arold,
574 V., Baune, B.T., Berger, K., Boomsma, D.I., Cichon, S., Dannlowski, U., de Geus, E.C.J., DePaulo,
575 J.R., Domenici, E., Domschke, K., Esko, T., Grabe, H.J., Hamilton, S.P., Hayward, C., Heath, A.C.,
576 Hinds, D.A., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.F.A., Magnusson,
577 P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., Müller-Myhsok, B.,
578 Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Penninx, B.W.J.H.,
579 Perlis, R.H., Porteous, D.J., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G.,
580 Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Winslow,
581 A.R., Lewis, C.M., Levinson, D.F., Breen, G., Børglum, A.D., Sullivan, P.F., 2018. Genome-wide
582 association analyses identify 44 risk variants and refine the genetic architecture of major depression.
583 *Nature Genetics* 50, 668-681.
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589 **Figure & Table Legends**

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591 **Table 1: Participant characteristics in the SELCoH sample.**

592

593 **Figure 1: The association between polygenic risk scores for MDD and inflammatory markers.**

594 This figure summarizes the linear associations between polygenic risk scores for MDD and 35
595 inflammatory markers. (a) A bar chart showing individual results from linear model with each
596 inflammatory marker displayed on the x-axis and the negative log-transformed p-value for each
597 inflammatory marker displayed on the y-axis. Nominally significant associations are represented by a
598 white bar. (b) A graphical representation of the nominally significant association between polygenic risk
599 scores for MDD and IL-10. Polygenic risk scores are displayed on the x-axis (adjusted for seven PCs)
600 and IL-10 levels are displayed on the y-axis (adjusted for age, sex, gender, ethnicity, BMI and smoking
601 status). The black line represented a line of best fit.

602

603 **Figure 2: The association between BMI, polygenic risk scores for BMI and inflammatory markers.**

604 This figure summarizes the linear associations between BMI, polygenic risk scores for BMI and 35
605 inflammatory markers. (a) A bar chart showing individual results from linear models with BMI as the
606 predictor, with each inflammatory marker displayed on the x-axis and log-transformed p-value for each
607 inflammatory marker displayed on the y-axis. Nominally significant associations are represented by a
608 white bar and the Bonferroni multiple testing correction threshold is displayed by the dotted line and an
609 asterisk. (b) A bar chart showing individual results from linear models with polygenic risk scores for BMI
610 as the predictor. BMI-associated inflammatory markers are displayed on the x-axis, and negative log-
611 transformed p-values for each inflammatory marker are displayed on the y-axis. Nominally significant
612 associations are represented by a white bar.

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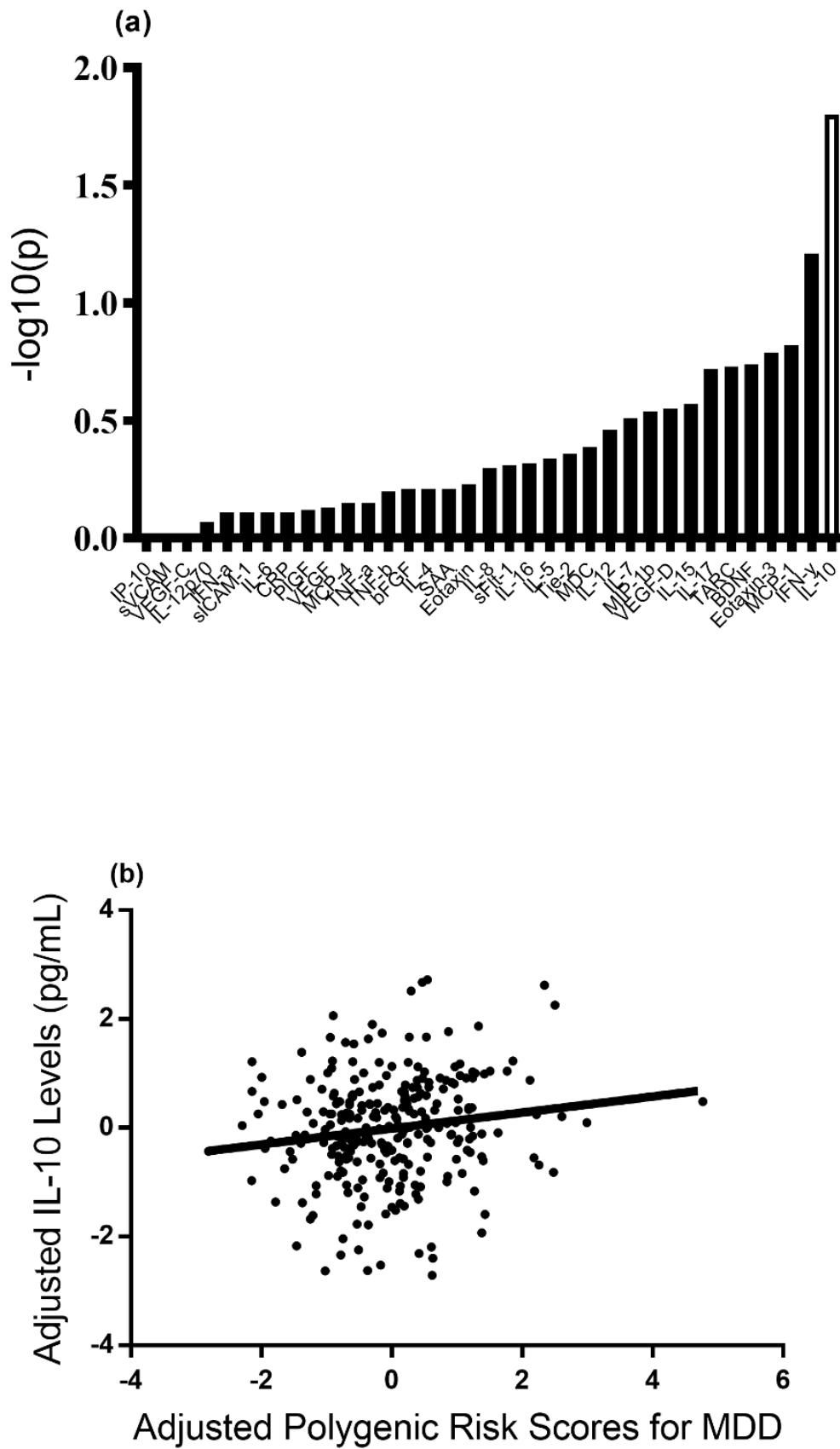
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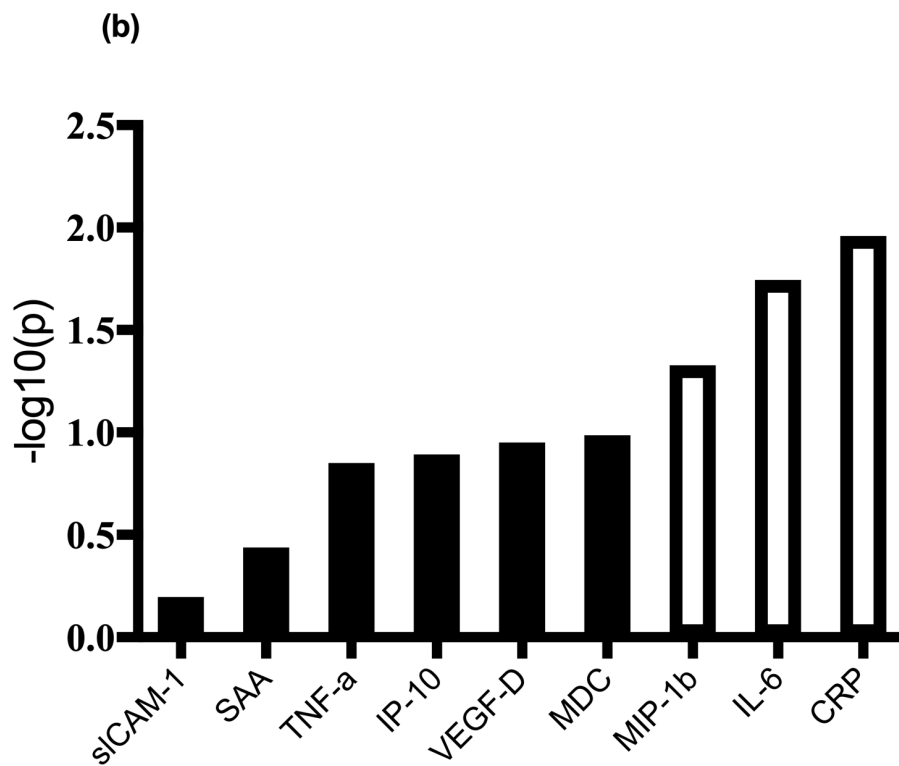
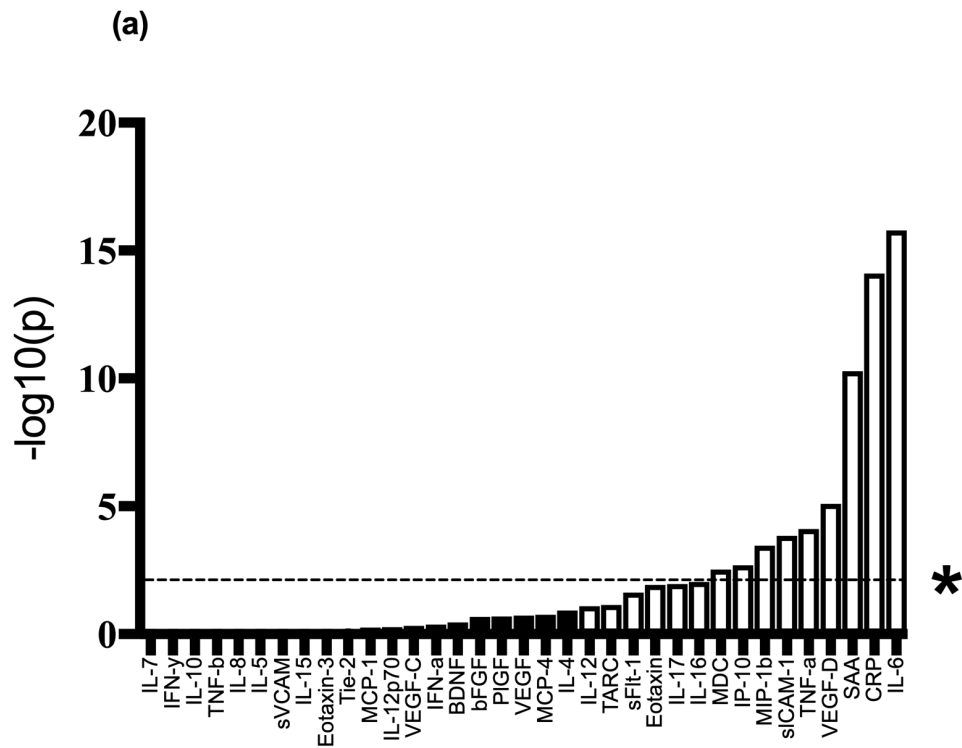
631 **Figure 1**



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634 **Figure 2**



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