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1 Genetic stratification of depression in UK Biobank

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## 41 **Abstract**

42 Depression is a common and clinically heterogeneous mental health disorder that is frequently  
43 comorbid with other diseases and conditions. Stratification of depression may align sub-diagnoses  
44 more closely with their underlying aetiology and provide more tractable targets for research and  
45 effective treatment. In the current study, we investigated whether genetic data could be used to  
46 identify subgroups within people with depression using the UK Biobank. Examination of cross-locus  
47 correlations were used to test for evidence of subgroups using genetic data from seven other complex  
48 traits and disorders that were genetically correlated with depression and had sufficient power ( $> 0.6$ )  
49 for detection. We found no evidence for subgroups within depression for schizophrenia, bipolar  
50 disorder, attention deficit/hyperactivity disorder, autism spectrum disorder, anorexia nervosa,  
51 inflammatory bowel disease or obesity. This suggests that for these traits, genetic correlations with  
52 depression were driven by pleiotropic genetic variants carried by everyone rather than by a specific  
53 subgroup.

## 54 **Introduction**

55 Depression is a common mental health disorder characterised by persistent feelings of sadness or a  
56 loss of interest in day-to-day activities lasting for at least a two-week period. These feelings can be  
57 accompanied by tiredness, changes in appetite, changes in sleep patterns, reduced concentration,  
58 feelings of worthlessness or hopelessness, and thoughts of self-harm or suicide. Zimmerman *et al.* <sup>1</sup>  
59 found that there were 170 different symptom profiles amongst 1 566 participants diagnosed with  
60 major depressive disorder from the Rhode Island MIDAS project. This variety of different symptom  
61 profiles suggest that depression is highly heterogeneous <sup>2</sup>. Depression is also comorbid with many  
62 diseases including cancer <sup>3</sup>, cardiovascular disease <sup>4</sup> and other psychiatric illnesses <sup>5</sup>. Stratification of  
63 depression, to address heterogeneity and comorbidity, may aid in providing valuable aetiological  
64 insights and improve treatment efficacy.

65 Studies aimed at stratifying depression have examined differences between melancholic and atypical  
66 depression<sup>6</sup>, differences between the sexes and recurrence of the disorder<sup>7</sup> and used data from other  
67 traits, such as neuroticism<sup>8</sup> and social contact<sup>9</sup> to stratify depression. Twin-based studies<sup>10</sup> and  
68 genome-wide association studies<sup>11, 12</sup> have shown depression to be heritable and genetically  
69 correlated with a number of other traits and disorders. This shared genetic component could be due  
70 to pleiotropic variants shared across all individuals but could also be as a result of a subgroup for the  
71 other trait within depression cases. For example, there is a genetic correlation of 0.33 (standard error  
72 = 0.03) between depression and bipolar disorder<sup>13</sup>. If this genetic correlation was due to pleiotropy,  
73 then several of the bipolar disorder variants would be carried by most depression cases. However, if  
74 this correlation was due to a subgroup, then a greater proportion of the bipolar disorder variants  
75 would only be carried by individuals in this subgroup. A subgroup could arise where there is a causal  
76 association, a shared molecular pathway, a misclassification between the traits, or an ascertainment  
77 bias in the diagnosis of depression.

78 For the current study, BUHMBOX (Breaking Up Heterogeneous Mixture Based On cross(X)-locus  
79 correlations)<sup>14</sup> was used to determine whether there was evidence of a subgroup within depression  
80 that was genetically more similar to other traits. BUHMBOX uses variants associated with a subgroup  
81 trait to calculate weighted pairwise correlations of risk allele dosages within depression cases and  
82 controls, adjusted for effect size and allele frequency. Where there is a subgroup amongst depression  
83 cases that carry a greater proportion of the risk alleles for the non-depression trait, there will be  
84 consistent positive pairwise correlations between those variants (as illustrated in Figure 1). BUHMBOX  
85 then calculates a *P*-value based on the likelihood of the observed pairwise correlations between  
86 variants.

87 Two definitions of depression were assessed in the UK Biobank<sup>15</sup>, one based on the Composite  
88 International Diagnostic Interview Short Form (CIDI-SF)<sup>16</sup> and the other based on a broader help-  
89 seeking definition (broad depression)<sup>12</sup>. Since many traits are genetically correlated with depression  
90<sup>13</sup>, a power calculation was performed to determine traits with sufficient power to detect a subgroup.

91 Power is determined by the number of depression cases, the size of any subgroup within depression  
92 cases, the number of associated variants tested from the subgroup trait and the effect sizes of these  
93 variants. We tested sufficiently-powered traits for evidence of a subgroup in depression cases using  
94 BUHMBOX v0.38<sup>14</sup>.

## 95 **Materials and Methods**

### 96 UK Biobank cohort

97 The UK Biobank is a population-based cohort of 501 726 individuals with imputed genome-wide data  
98 for 93 095 623 autosomal genetic variants<sup>15</sup>. A genetically homogeneous sample of 462 065  
99 individuals was identified using the first two principal components from a 4-means clustering  
100 approach. A total of 131 790 individuals were identified as being related up to the third degree (kinship  
101 coefficients > 0.044) using the KING toolset<sup>17</sup> and were removed from the sample. For these related  
102 individuals a genomic relationship matrix was calculated to enable the identification of one individual  
103 from each related group that could be reinstated. This allowed the reintroduction of 55 745 individuals  
104 providing an unrelated sample of 386 020 individuals.

### 105 UK Biobank depression phenotypes

106 Two depression phenotypes were assessed for evidence of subgroups in UK Biobank. Both phenotypes  
107 were restricted to only those individuals that had completed the online mental health questionnaire  
108 (n = 109 049). The first phenotype analysed was based on the Composite International Diagnostic  
109 Interview Short Form (CIDI-SF)<sup>18</sup> as used by Davis *et al.*<sup>16</sup> to provide a lifetime instance measure of  
110 depression in the UK Biobank. Davis *et al.*<sup>16</sup> provide a more in-depth description of this CIDI-SF  
111 phenotype, but in summary cases were defined as having:

- 112 • at least one core symptom of depression (persistent sadness (Data-Field: 20446) or a loss of  
113 interest (Data-Field: 20441)) for most or all days over a two-week period which were present  
114 “most of the day” or “all of the day”.

- 115       • plus at least another four non-core depressive symptoms with some or a lot of impairment  
116           experienced during the worst two-week period of depression or low mood.

117 The non-core depressive symptoms that were included in this assessment of the worst episode of  
118 depression were: Feelings of tiredness (Data-Field: 20449), Weight change (Data-Field: 20536), Did  
119 your sleep change? (Data-Field: 20532), Difficulty concentrating (Data-Field: 20435), Feelings of  
120 worthlessness (Data-Field: 20450), and Thoughts of death (Data-Field: 20437). Cases that self-  
121 reported another mood disorder were excluded. Controls were determined by not having at least one  
122 core symptom of depression or not endorsing at least another four non-core depressive symptoms if  
123 at least one core symptom was endorsed. This provided 25 721 CIDI-SF cases and 61 894 controls.

124 A second depression phenotype within the UK Biobank cohort was also examined using the broad  
125 depression definition from Howard *et al.*<sup>12</sup> with detailed information provided in that paper. In  
126 summary, cases had sought help for nerves, anxiety, tension or depression from either a general  
127 practitioner or a psychiatrist (Data-Field: 2090 and Data-Field: 2100), whereas controls had not. Cases  
128 were supplemented with an additional 132 individuals identified as having a primary or secondary  
129 International Classification of Diseases (ICD)-10 diagnosis of a depressive mood disorder from linked  
130 hospital admission records (Data-Field: 41202 and Data-Field: 41204). Participants identified with  
131 bipolar disorder, schizophrenia or personality disorder and those reporting a prescription for an  
132 antipsychotic medication were removed. This provided a total of 36 790 broad depression cases and  
133 70 304 controls. The phenotypic correlation between the CIDI-SF depression phenotype and the broad  
134 depression phenotype was 0.61 with the number of cases and controls shared across the two  
135 definitions shown in Supplementary Table 1.

### 136 Sensitivity analysis

137 To allow a direct comparison between the two definitions of depression, the main analysis was  
138 restricted to those UK Biobank participants that had completed the mental health questionnaire. To  
139 examine whether the full UK Biobank sample provided greater power for the detection of subgroups,

140 a sensitivity analysis was conducted using the broad depression phenotype (113 769 cases and 208  
141 811 controls).

142 Traits examined as subgroups within depression

143 We selected traits genetically correlated with depression (false discovery rate corrected,  $q < 0.01$ ) in  
144 Howard *et al.*<sup>13</sup> to test as subgroups within depression, which included anthropomorphic,  
145 autoimmune, life course, cardiovascular and other psychiatric traits. For each trait, there was a  
146 requirement that publicly available summary statistics were available and that the UK Biobank was  
147 not included in that study due to potential confounding effects (Supplementary Table 2).

148 The BUHMBOX power calculation test v0.1<sup>14</sup> was used to determine whether there was sufficient  
149 power to detect a subgroup for each depression correlated trait and to identify the optimum variant  
150 selection criterion ( $P < 5 \times 10^{-8}$ ,  $P < 10^{-6}$  or  $P < 10^{-4}$ ). The power calculation was conducted separately  
151 for the CIDI-SF depression phenotype and the broad depression phenotype. Variants from the  
152 summary statistics for each subgroup trait were examined in the UK Biobank. Variants that had a call  
153 rate less than 0.99, were out of Hardy-Weinberg equilibrium ( $P < 10^{-10}$ ), had a hard call threshold less  
154 than 0.25, or had a minor allele frequency less than 0.01 were excluded. BUHMBOX requires that all  
155 variants are available for all individuals and therefore individuals with a call rate less than 1 were  
156 removed. To identify independently segregating variants, clumping was conducted in PLINK v1.90b4  
157<sup>19</sup> using an  $r^2$  value of 0.01 across a 3Mb window in either CIDI-SF or broad depression control  
158 individuals, respectively.

159 For the power analysis the approach used in Han *et al.*<sup>14</sup> was followed, with 1 000 simulated iterations  
160 run for each trait, the proportion of individuals in the subgroup was set to the genetic risk score beta  
161 coefficient (which represents the upper bound of the heterogeneity proportion) and a nominal  
162 subgroup  $P$ -value of 0.05 was used. Power analyses were used to identify the optimum variant  
163 selection criterion that provided the greatest power for each subgroup trait. Where power was the  
164 same across variant selection criteria, the strictest variant selection criterion was selected as the

165 optimum. Variants with  $P < 10^{-4}$  were not publicly available for Squamous Cell Lung Cancer or Lung  
166 Cancer and so  $P < 10^{-5}$  was used instead. Only those traits that had a power  $> 0.6$  (using the optimum  
167 variant selection criterion) were selected to be tested for evidence of a subgroup within depression.  
168 A linear regression was used to examine the association between power and the heritability of each  
169 subgroup trait and the genetic correlation each subgroup trait shares with depression.

#### 170 Testing for subgroups within depression

171 For the traits that had power  $> 0.6$ , variants meeting the optimum variant selection criterion were  
172 extracted from the UK Biobank. The same quality control thresholds and method to identify  
173 independently segregating variants as used as previously in the power analysis were applied.  
174 BUHMBOX v0.38<sup>14</sup> was used to examine shared risk alleles for each subgroup trait within CIDI-SF  
175 depression and broad depression. BUHMBOX uses the positive correlations between risk allele  
176 dosages in cases to determine whether any sharing of risk alleles is driven by all individuals (whole-  
177 group pleiotropy) or by a subset of individuals (Figure 1). The likelihood of observing such positive  
178 correlations are used to determine the subgroup  $P$ -values.

179 Sex, age, genotyping array and the first 20 principal components were fitted as covariates in the  
180 subgroup analysis. Bonferroni correction was used to account for the multiple testing of subgroup  
181 traits, with  $P$ -values  $< 7.14 \times 10^{-3}$  (0.05/7) or  $< 0.01$  (0.05/5) deemed significant for CIDI-SF or broad  
182 depression, respectively. No multiple testing correction was applied for the two depression definitions  
183 analysed. In the sensitivity analysis, using the full UK Biobank sample, a  $P$ -value  $< 8.33 \times 10^{-3}$  (0.05/6)  
184 was deemed significant for broad depression.

#### 185 Code availability

186 The R code for BUHMBOX v0.38 and BUHMBOX power calculation test v0.1 are freely available and  
187 downloadable from <http://software.broadinstitute.org/mpg/buhmbox/>.

#### 188 Results



189 Power analyses of potential subgroups traits

190 To determine whether there was sufficient power ( $> 0.6$ ) to detect a subgroup and identify the  
191 optimum variant selection criterion ( $P < 5 \times 10^{-8}$ ,  $P < 10^{-6}$  or  $P < 10^{-4}$ ) for each trait the BUHMBOX  
192 power calculation test v0.1<sup>14</sup> was used. The genetic risk score beta coefficients, representing an upper  
193 bound for heterogeneity proportion, for each trait within either Composite International Diagnostic  
194 Interview Short Form (CIDI-SF) depression or broad depression are provided in Supplementary Table  
195 3. The results of the power analysis for detecting a subgroup for 25 available traits within the two  
196 depression definitions are provided in Table 1. Five traits had power  $> 0.6$  across both the CIDI-SF  
197 depression and broad depression definitions: bipolar disorder<sup>20</sup>, attention deficit/hyperactivity  
198 disorder<sup>21</sup>, autism spectrum disorder<sup>22</sup>, anorexia nervosa<sup>23</sup>, and inflammatory bowel disease<sup>24</sup>. There  
199 were two further traits, schizophrenia<sup>25</sup> and obesity<sup>26</sup>, that had power  $> 0.6$  for detection of a  
200 subgroup in CIDI-SF depression.

201 A linear regression of subgroup power on the heritability of each subgroup trait and the genetic  
202 correlation shared with depression revealed that heritability was positively associated with power  
203 (CIDI-SF depression  $P$ -value =  $5.32 \times 10^{-4}$ ; broad depression  $P$ -value =  $3.48 \times 10^{-4}$ ), but genetic  
204 correlation with depression was not associated with power (CIDI-SF depression  $P$ -value = 0.57; broad  
205 depression  $P$ -value = 0.21).

206 The sensitivity analysis, analysing broad depression in the full UK Biobank sample, provided a small  
207 increase in power for the majority of subgroups compared to broad depression amongst individuals  
208 who had completed the mental health questionnaire. Six traits had power  $> 0.6$ : bipolar disorder,  
209 attention deficit/hyperactivity disorder, autism spectrum disorder, anorexia nervosa, inflammatory  
210 bowel disease, and schizophrenia (Supplementary Table 4).

211 Testing for subgroups within depression

212 BUHMBOX v0.38<sup>14</sup> was used to test seven traits for evidence of a subgroup within CIDI-SF depression,  
213 five traits within broad depression and six traits in the sensitivity analysis. The results of the subgroup

214 for CIDI-SF and broad depression analyses are provided in Table 2 and the results of the sensitivity  
215 analysis are provided in Supplementary Table 5. None of the traits examined provided evidence of a  
216 genetic subgroup within depression ( $P > 0.05$ ) before correction for multiple testing.

## 217 **Discussion**

218 Depression is a heterogeneous mental health disorder and is comorbid with many other diseases and  
219 illnesses. Over the last few years, valuable progress has been made in understanding the underlying  
220 genetic architecture of depression <sup>11, 13, 27</sup>. Furthermore, stratifying depression using genetic data  
221 remains a key goal within the psychiatric genetics community <sup>28</sup> and should lead to improved  
222 classification of mental health conditions and more efficacious treatment for patients. Machine  
223 learning <sup>29, 30</sup> and polygenic risk score <sup>6, 31</sup> approaches offer possible methods for stratification in  
224 mental health. In the current study, we used BUHMBOX <sup>14</sup> to identify whether traits that were  
225 genetically correlated with depression were correlated due to a subgroup, i.e. the correlation was  
226 driven by a subset of depressed individuals who had a greater genetic loading for the trait. Evidence  
227 of a subgroup within depression may provide future opportunities for stratifying the disease.

228 To allow a direct comparison between stricter and broader definitions of depression two phenotypes  
229 were examined. For the subgroups examined across both definitions (and using the same variant  
230 selection criteria), CIDI-SF depression had greater upper bounds for the heterogeneity proportion for  
231 bipolar disorder, autism spectrum disorder and anorexia nervosa, whereas broad depression had a  
232 greater upper bound for the heterogeneity proportion for attention deficit/hyperactivity disorder. The  
233 heterogeneity upper bound was assessed using genetic risk scores, which suggests that a stricter  
234 definition of depression shared a larger genetic component with bipolar disorder, autism spectrum  
235 disorder and anorexia nervosa and the broader definition shared a genetic component with attention  
236 deficit/hyperactivity disorder. This supports the observations of Cai *et al.* <sup>32</sup> for bipolar disorder, autism  
237 spectrum disorder and attention deficit/hyperactivity disorder using genetic correlations (although  
238 they didn't assess anorexia nervosa). As there were no significant subgroups found within depression,

239 no firm conclusions can be drawn on the effectiveness of using stricter or broader definitions to  
240 stratify depression.

241 The lack of evidence for subgroups within depression for the seven traits examined with BUHMBOX,  
242 suggest that the previously reported genetic correlations<sup>13</sup> were the result of pleiotropy, i.e. a genetic  
243 variant is associated with multiple phenotypes. Pleiotropy can result from either horizontal pleiotropy  
244 (where a variant has direct effects on multiple phenotypes) or vertical pleiotropy (where a variant has  
245 an effect on a phenotype, then this phenotype influences further traits downstream)<sup>33</sup>. To assess the  
246 presence of vertical pleiotropy a technique known as Mendelian randomization<sup>34</sup> can be used. This  
247 technique has been applied previously to depression and the traits examined with BUHMBOX, and no  
248 evidence of vertical pleiotropy was found<sup>13</sup>. This indicates that the genetic correlations between  
249 depression and the seven traits examined as subgroups are likely due to horizontal pleiotropy. Gaining  
250 a greater understanding of the biological mechanisms associated with pleiotropic variants could be  
251 informative for improving our comprehension and treatment for both depression and the correlated  
252 traits.

253 A sensitivity analysis was conducted to investigate whether additional power for detection of  
254 subgroups within broad depression could be obtained by analysing the full UK Biobank sample (n =  
255 322 580) compared to the subsample that had completed the mental health questionnaire (n = 109  
256 049). Decreased power was observed for some subgroup traits using the full sample which was due  
257 to lower heterogeneity proportions (based on the genetic risk score beta coefficient) and fewer  
258 genetic variants available for analysis (as all variants are required to be known and so fewer were  
259 available in the full sample). For most subgroup traits greater power was available using the full  
260 sample, however most were still underpowered to run the subgroup analysis. Schizophrenia was the  
261 only subgroup trait that sufficiently increased in power to exceed the > 0.6 threshold, although no  
262 evidence of a subgroup was found. The average increase in power using the full sample compared to  
263 the mental health questionnaire subsample was only 0.06. However, larger genome-wide association  
264 studies of the currently underpowered traits could allow their re-examination as subgroups within

265 depression in the future. The power to detect a subgroup for a trait was also influenced by the trait's  
266 heritability, but not its genetic correlation with depression. Therefore, there is the potential to assess  
267 additional highly heritable traits where a feasible subgroup may exist within depression.

268 The limitations of the current study include selection bias, whereby particular individuals are more  
269 likely to participate in population-based cohorts or complete additional assessments, such as the  
270 online mental health questionnaire. Participants of the UK Biobank are healthier and from less  
271 deprived areas than the general population<sup>35</sup> and those that completed the mental health  
272 questionnaire had a lower genetic predisposition to severe depression than those who did not<sup>36</sup>. UK  
273 Biobank participants that had either a self-reported or a hospital diagnosis of schizophrenia or bipolar  
274 disorder were excluded in the current analysis, which may limit the potential for identifying subgroups  
275 for these disorders. Most of the traits that are genetically correlated with depression were not  
276 included in the subgroup analysis due to a lack of power ( $\leq 0.6$ ). As increasing large genome-wide  
277 association studies become available, a greater number of variants will meet the required selection  
278 criteria, allowing additional traits to be tested for evidence of a subgroup within depression.

279 Depression is both polygenic and heterogeneous and stratification of the disorder may lead to  
280 improvements in treatment outcomes. We examined 25 traits genetically correlated with depression  
281 using individuals that had completed the UK Biobank mental health questionnaire. There were seven  
282 traits sufficiently powered to be tested as subgroups within CIDI-SF depression and five traits tested  
283 as subgroups within broad depression, although none of these provided evidence for a genetic  
284 subgroup within depression. Alternative methodologies for stratification of depression could also be  
285 examined (i.e. polygenic risk scores and cluster analysis) along with consideration of other potential  
286 stratifiers (i.e. depression severity, depressive symptoms and antidepressant treatment response).

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302 Competing interests

303 Cathryn Lewis is a member of the Science Advisory Board for Myriad Neuroscience. Andrew McIntosh  
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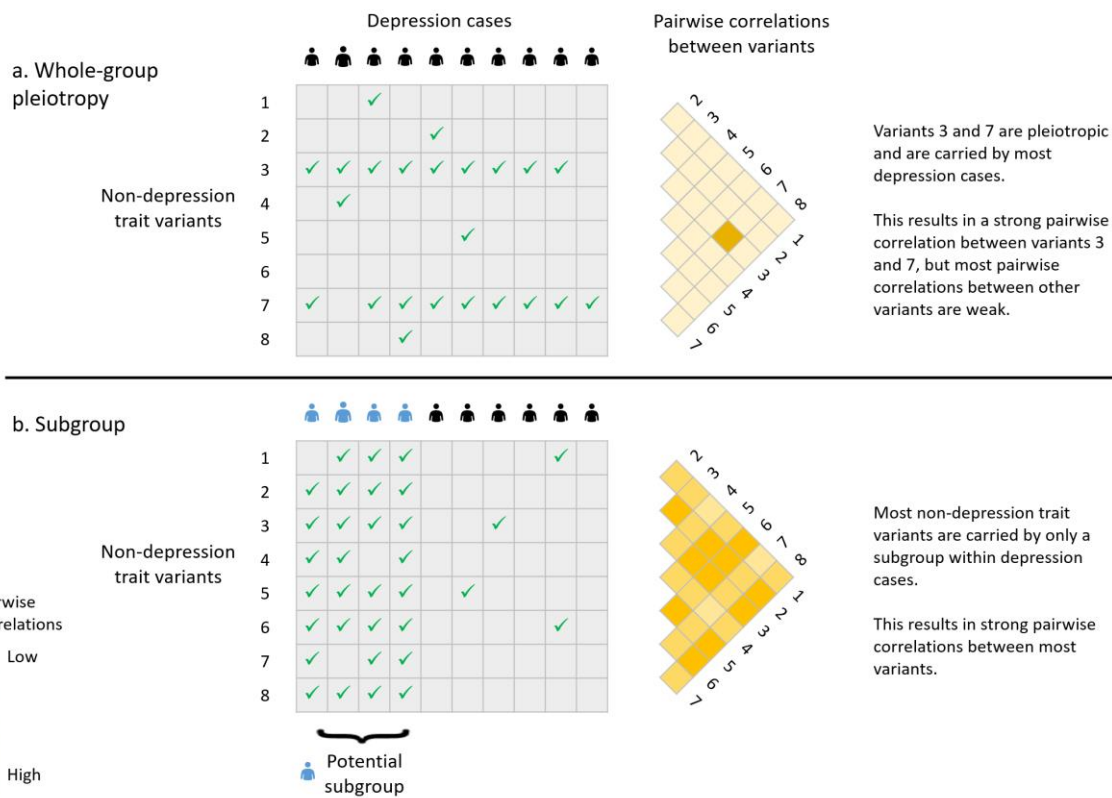
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439 Figure 1. Illustration of pairwise correlations between variants for (a) whole-group pleiotropy, where  
 440 most depression cases carry a few variants associated with a non-depression trait and (b) a subgroup  
 441 within depression cases (👤), where just the subgroup carry many of the non-depression trait variants.  
 442 A tick indicates a depression case individual is a carrier of that non-depression variant.

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451 **Tables**

452 Table 1. Power analysis for detecting a subgroup for 25 traits within either Composite International  
 453 Diagnostic Interview Short Form (CIDI-SF) depression or broad depression in the UK Biobank. PubMed  
 454 identifiers (PubMed ID) for the 25 traits are provided. Bold values indicate that power was > 0.6. The  
 455 optimum variant selection criterion that maximised power for the subgroup traits are provided.  
 456 †Variants with  $P < 10^{-4}$  were not publicly available for Squamous Cell Lung Cancer or Lung Cancer and  
 457 so variants with  $P < 10^{-5}$  were tested instead.

Subgroup trait	PubMed ID	CIDI-SF depression		Broad depression	
		Optimum variant selection criterion	Power	Optimum variant selection criterion	Power
Neuroticism	24828478	$< 10^{-4}$	0.137	$< 10^{-4}$	0.120
Schizophrenia	25056061	$< 10^{-6}$	<b>0.607</b>	$< 10^{-6}$	0.306
Bipolar Disorder	29906448	$< 10^{-4}$	<b>0.912</b>	$< 10^{-4}$	<b>0.727</b>
Attention Deficit/Hyperactivity Disorder	30478444	$< 10^{-4}$	<b>0.912</b>	$< 10^{-4}$	<b>0.992</b>
Autism Spectrum Disorder	30804558	$< 10^{-4}$	<b>1</b>	$< 10^{-4}$	<b>1</b>
Anorexia Nervosa	28494655	$< 10^{-4}$	<b>1</b>	$< 10^{-4}$	<b>1</b>
Triglyceride Level	24097068	$< 10^{-4}$	0.183	$< 5 \times 10^{-8}$	0.131
Coronary Artery Disease	26343387	$< 10^{-4}$	0.229	$< 5 \times 10^{-8}$	0.071
Crohn's Disease	26192919	$< 10^{-4}$	0.193	$< 10^{-4}$	0.271
Inflammatory Bowel Disease	28067908	$< 10^{-4}$	<b>0.706</b>	$< 10^{-6}$	<b>0.665</b>
Waist to Hip Ratio	25673412	$< 10^{-4}$	0.070	$< 5 \times 10^{-8}$	0.076
Body Fat Percentage	26833246	$< 10^{-6}$	0.057	$< 10^{-6}$	0.067
Waist Circumference	25673412	$< 10^{-4}$	0.107	$< 10^{-4}$	0.070
Overweight	23563607	$< 10^{-4}$	0.131	$< 5 \times 10^{-8}$	0.068
Obesity 1	23563607	$< 10^{-4}$	0.199	$< 10^{-6}$	0.089
Obesity 3	23563607	$< 10^{-4}$	<b>0.794</b>	$< 10^{-4}$	0.196
Body Mass Index	25673413	$< 10^{-4}$	0.101	$< 10^{-4}$	0.073
Age of Menarche	25231870	$< 10^{-4}$	0.451	$< 5 \times 10^{-8}$	0.081
Age of Natural Menopause	26414677	$< 10^{-4}$	0.407	$< 10^{-4}$	0.220
Years of Schooling	25201988	$< 10^{-4}$	0.105	$< 10^{-4}$	0.089
College Completion	25201988	$< 10^{-4}$	0.248	$< 10^{-4}$	0.160
Ever Smoked	20418890	$< 10^{-4}$	0.081	$< 10^{-4}$	0.134
Age of Smoking Initiation	20418890	$< 10^{-4}$	0.061	$< 10^{-4}$	0.062
Squamous Cell Lung Cancer†	28604730	$< 10^{-5}$	0.078	$< 5 \times 10^{-8}$	0.085
Lung Cancer†	28604730	$< 10^{-5}$	0.123	$< 10^{-6}$	0.137

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462 Table 2. Evidence of a subgroup from traits tested within either Composite International Diagnostic  
 463 Interview Short Form (CIDI-SF) depression or broad depression in the UK Biobank. The number of  
 464 individuals classified as depression cases and depression controls is provided. The number of variants  
 465 assessed and the genetic risk score beta coefficient (representing the upper bound of the  
 466 heterogeneity proportion) using the optimum variant selection criterion for that trait (as provided in  
 467 Table 1).

Depression definition	Subgroup trait	Variants	$\beta_{GRS}$	Depression cases / controls	Subgroup <i>P</i> -value
CIDI-SF	Schizophrenia	180	0.077	15 311 / 36 811	0.42
	Bipolar Disorder	436	0.062	8 140 / 19 466	0.62
	Attention Deficit/Hyperactivity Disorder	342	0.028	8 522 / 21 030	0.11
	Autism Spectrum Disorder	242	0.057	13 138 / 31 598	0.12
	Anorexia Nervosa	169	0.016	16 024 / 38 388	0.47
	Inflammatory Bowel Disease	954	$7.37 \times 10^{-3}$	2 186 / 5 265	0.46
	Obesity 3	61	0.038	22 096 / 53 312	0.55
Broad	Bipolar Disorder	435	0.041	11 531 / 22 186	0.60
	Attention Deficit/Hyperactivity Disorder	342	0.034	12 345 / 23 844	0.07
	Autism Spectrum Disorder	242	0.051	18 802 / 36 000	0.15
	Anorexia Nervosa	169	$7.87 \times 10^{-3}$	22 946 / 43 644	0.79
	Inflammatory Bowel Disease	219	$8.02 \times 10^{-3}$	22 738 / 43 355	0.64

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