

Amygdala responses to negative faces are not associated with depressive symptoms: cross-sectional data from 28 638 individuals in the UK Biobank cohort

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Supplemental analyses

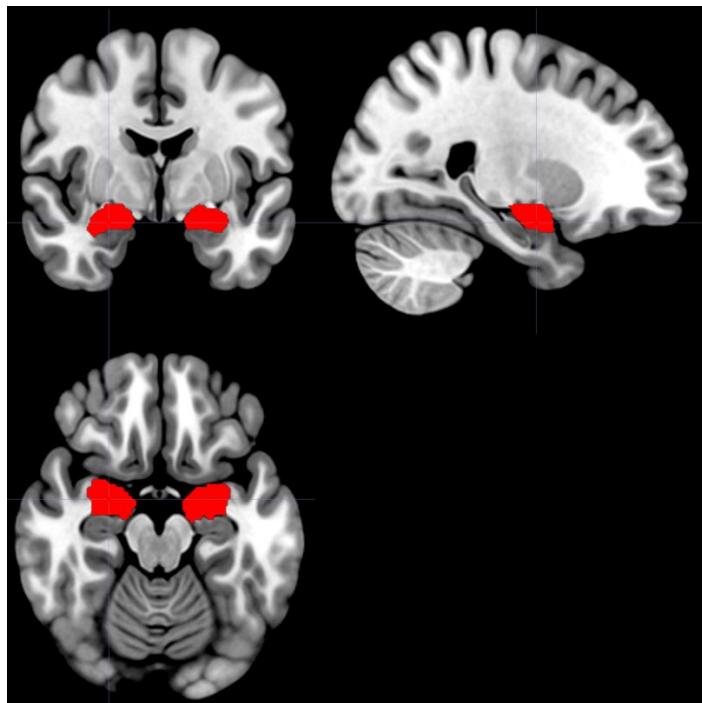
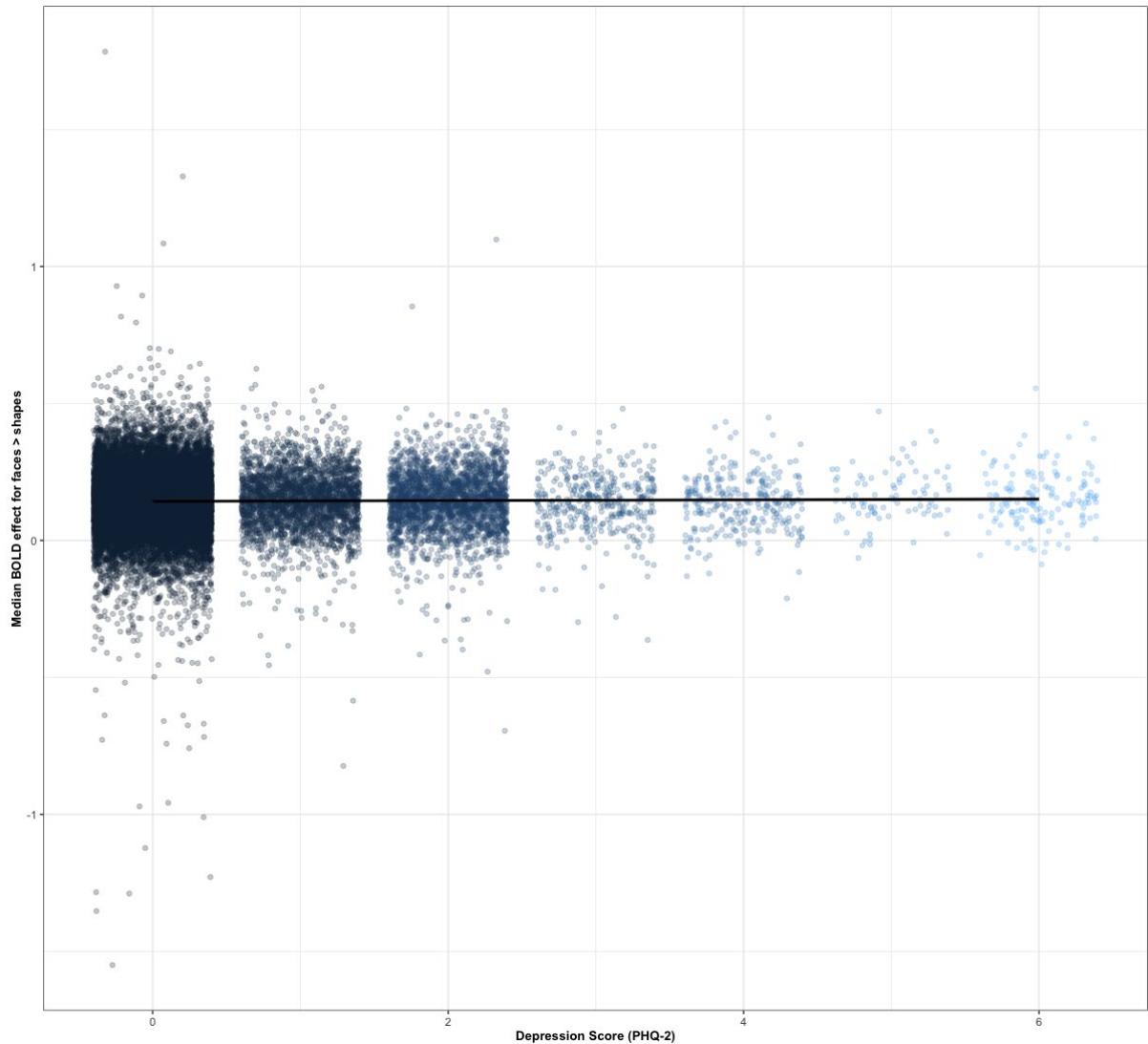


Figure 1. Amygdala mask overlaid on a T1 template in MRIcroGL

Analyses of mood and anhedonia depression items (analogous with the PHQ-2), supplemental table 1.

Predictor	Univariable analysis			Multivariable-adjusted		
	β -coefficient	se	p-value	β -coefficient	se	p-value
PHQ 2 analogue	0.0013	0.0007	0.0725	0.0001	0.0007	0.8548
Age	-0.0012	0.0001	< 0.0001	-0.0012	0.0001	< 0.0001
Sex	0.0080	0.0013	< 0.0001	0.0090	0.0014	< 0.0001
Townsend deprivation index	0.0008	0.0002	0.0025	0.0004	0.0003	0.0745
Attended college	0.0091	0.0013	< 0.0001	0.0083	0.0013	< 0.0001
Body Mass Index	0.0005	0.0002	0.0005	0.0004	0.0002	0.0051



Supplementary figure 2. Association between amygdala responses and mood/anhedonia items (PHQ-2)

Sensitivity analyses without zero values (N = 14905), supplemental table 2.

Predictor	Univariable analysis			Multivariable-adjusted		
	β -coefficient	se	p-value	β -coefficient	se	p-value
Depression score	0.0004	0.0005	0.3871	-0.0002	0.0005	0.6436
Age	-0.0012	0.0001	< 0.0001	-0.0012	0.0001	< 0.0001
Sex	0.0062	0.0018	0.0008	0.0070	0.0018	0.0002
Townsend deprivation index	0.0009	0.0003	0.0042	0.0006	0.0003	0.0566
Attended college	0.0085	0.0018	< 0.0001	0.0078	0.0018	< 0.0001
Body Mass Index	0.0005	0.0002	0.0054	0.0005	0.0002	0.0191

Sensitivity analysis comparing subjects with depression score 0 ($n = 13733$) with those with depression score 12 ($n = 68$)

Welch Two Sample t-test

$t = -0.27813$, $df = 67.707$, $p\text{-value} = 0.7818$

95 percent confidence interval: [-0.03110379, 0.02349440]

sample estimates:

mean of x mean of y

0.1425777 0.1463824

Sensitivity analysis comparing subjects with depression score 0 ($n = 13733$) with those with depression score > 6 ($n = 525$)

Welch Two Sample t-test

$t = 0.32365$, $df = 582.2$, $p\text{-value} = 0.7463$

95 percent confidence interval: [-0.007166031, 0.009993731]

sample estimates:

mean of x mean of y

0.1425777 0.1411638

Analysing self-reported depression diagnosis (previous or current) at any of the visits as a predictor of amygdala responses, supplemental table 3.

Predictor	Univariable analysis			Multivariable-adjusted		
	β -coefficient	se	p -value	β -coefficient	se	p -value
Depression diagnosis	0.0039	0.0023	0.0805	0.0023	0.0023	0.2993
Age	-0.0012	0.0001	< 0.0001	-0.0012	0.0001	< 0.0001
Sex	0.0080	0.0013	< 0.0001	0.0091	0.0014	< 0.0001
Townsend deprivation index	0.0008	0.0002	0.0025	0.0004	0.0002	0.0768
Attended college	0.0091	0.0013	< 0.0001	0.0083	0.0013	< 0.0001
Body Mass Index	0.0005	0.0002	0.0005	0.0004	0.0002	0.0060

Antidepressant use

Analysing current use of antidepressants as a predictor of amygdala responses (model including depression score), supplemental table 4.

Predictor	Univariable analysis			Multivariable-adjusted		
	β-coefficient	se	p-value	β-coefficient	se	p-value
Depression score	0.0006	0.0004	0.1206	-0.0001	0.0004	0.7256
Use of antidepressants	0.0010	0.0028	0.7087	0.0012	0.0029	0.6719
Age	-0.0012	0.0001	< 0.0001	-0.0012	0.0001	< 0.0001
Sex	0.0080	0.0013	< 0.0001	0.0090	0.0014	< 0.0001
Townsend deprivation index	0.0008	0.0002	0.0025	0.0005	0.0003	0.0694
Attended college	0.0091	0.0013	< 0.0001	0.0083	0.0013	< 0.0001
Body Mass Index	0.0005	0.0002	0.0005	0.0004	0.0002	0.0051

Analysing current use of antidepressants as a predictor of amygdala responses (model without depression score), supplemental table 5.

Predictor	Univariable analysis			Multivariable-adjusted		
	β-coefficient	se	p-value	β-coefficient	se	p-value
Use of antidepressants	0.0010	0.0028	0.7087	0.0010	0.0028	0.7208
Age	-0.0012	0.0001	< 0.0001	-0.0012	0.0001	< 0.0001
Sex	0.0080	0.0013	< 0.0001	0.0090	0.0014	< 0.0001
Townsend deprivation index	0.0008	0.0002	0.0025	0.0004	0.0002	0.0725
Attended college	0.0091	0.0013	< 0.0001	0.0083	0.0013	< 0.0001
Body Mass Index	0.0005	0.0002	0.0005	0.0004	0.0002	0.0054

Analyses stratified by age

To further control for the effect of age, we performed the main analyses stratified by age \leq or $>$ median (64), as well as an analysis of the interaction between age and depression score on their effect on amygdala responses.

Analysing depression score as a predictor of amygdala responses in younger participant (age \leq 64), N = 15421, supplemental table 6.

Predictor	Univariable analysis			Multivariable-adjusted		
	β-coefficient	se	<i>p</i> -value	β-coefficient	se	<i>p</i> -value
Depression score	0.0001	0.0005	0.8371	-0.0003	0.0005	0.5170
Age	-0.0014	0.0002	<0.0001	-0.0014	0.0002	<0.0001
Sex	0.0096	0.0018	<0.0001	0.0090	0.0018	<0.0001
Townsend deprivation index	0.0005	0.0003	0.0894	0.0003	0.0003	0.2826
Attended college	0.0070	0.0018	0.0001	0.0074	0.0018	<0.0001
Body Mass Index	0.0006	0.0002	0.0027	0.0006	0.0002	0.0038

Analysing depression score as a predictor of amygdala responses in older participant (age >64), N = 13217, supplemental table 7.

Predictor	Univariable analysis			Multivariable-adjusted		
	β-coefficient	se	<i>p</i> -value	β-coefficient	se	<i>p</i> -value
Depression score	-0.0001	0.0007	0.8765	0.0001	0.0007	0.8565
Age	-0.0008	0.0003	0.0059	-0.0008	0.0003	0.0049
Sex	0.0088	0.0021	<0.0001	0.0086	0.0021	<0.0001
Townsend deprivation index	0.0006	0.0004	0.1514	0.0006	0.0004	0.1405
Attended college	0.0099	0.0021	<0.0001	0.0094	0.0021	<0.0001
Body Mass Index	0.0003	0.0003	0.2044	0.0003	0.0003	0.2747

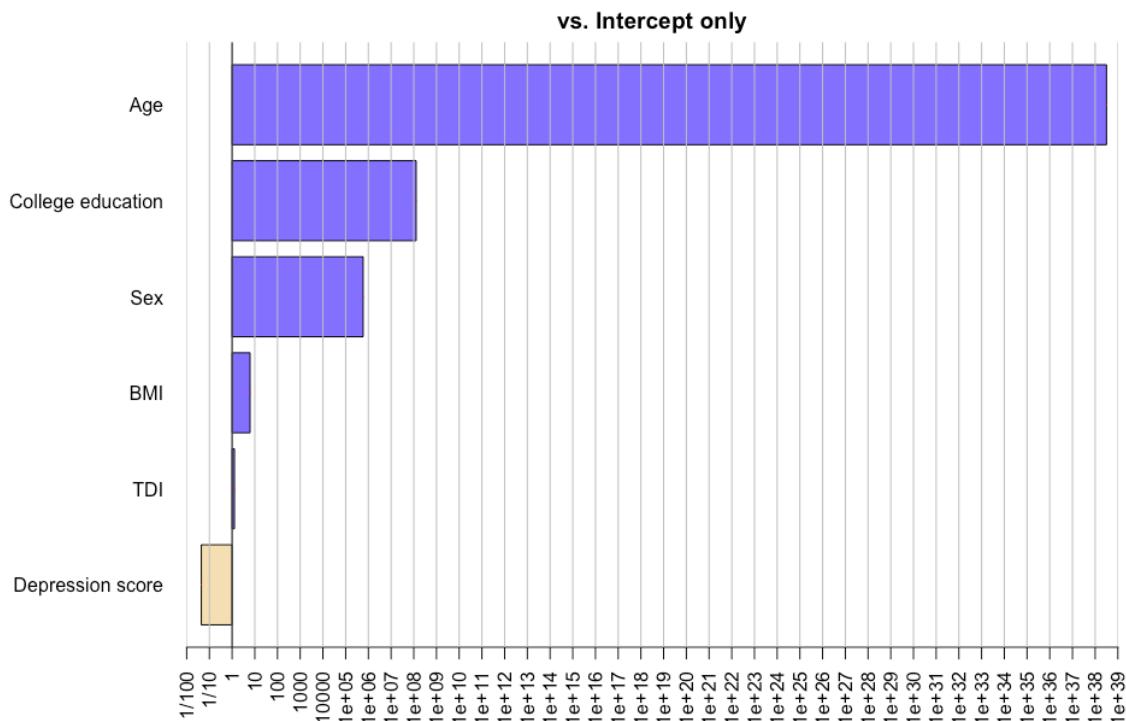
*Analysing depression score*Age group as a predictor of amygdala responses, N = 28638,
supplemental table 8.*

Predictor	Univariable analysis			Multivariable-adjusted		
	β -coefficient	se	p-value	β -coefficient	se	p-value
Depression score	0.0006	0.0004	0.1206	0.0001	0.0005	0.7964
Age group	-0.0154	0.0013	<0.0001	-0.0152	0.0016	<0.0001
Sex	0.0080	0.0013	<0.0001	0.0086	0.0014	<0.0001
Townsend deprivation index	0.0008	0.0002	0.0025	0.0005	0.0003	0.0336
Attended college	0.0091	0.0013	<0.0001	0.0086	0.0013	<0.0001
Body Mass Index	0.0005	0.0002	0.0005	0.0005	0.0002	0.0037
Depression score*Age Group	-0.0002	0.0008	0.8059	0.0000	0.0008	0.9783

Reviewer-suggested analyses

Presenting the main results using Bayesian statistics

As suggested by one reviewer, we here present the main results using Bayesian statistics. The plot below shows change in Bayes factor when each predictor is added to the model. Age, education, sex, BMI and socioeconomic status all contributed to a larger Bayes Factor (i.e. strengthen evidence in favour of an association), whereas adding depression score to the model leads to a decreased Bayes Factor (i.e. evidence against an association).



Supplementary figure 3. Change in Bayes Factor when adding predictors to the model.

Analysing a strictly defined depression definition as a predictor of amygdala responses ($N = 20159$), supplemental table 9.

As suggested during the review process, we here present explorative analyses using other indicators of depression. The predictor of interest here is a lifetime probable depressive episode according to a Composite International Diagnostic Interview, as part of a separate mental health follow-up in 2017, performed in a subset of participants as done by Cai et al (Cai et al., 2020). The diagnosis is based on DSM criteria and participants are classified as having had a probable episode of depression if reporting 1 or 2 cardinal depression symptoms AND a total of 5 symptoms as well as scoring “a lot impact of normal roles” during worst period of depression.

Predictor	Univariable analysis			Multivariable-adjusted		
	β -coefficient	se	p-value	β -coefficient	se	p-value
CIDI defined depression	0.0054	0.0022	0.0149	0.0034	0.0022	0.1317
Age	-0.0012	0.0001	<0.0001	-0.0012	0.0001	<0.0001
Sex	0.0072	0.0016	<0.0001	0.0090	0.0016	<0.0001
Townsend deprivation index	0.0007	0.0003	0.0149	0.0004	0.0003	0.1708
Attended college	0.0084	0.0016	<0.0001	0.0076	0.0016	<0.0001
Body Mass Index	0.0005	0.0002	0.0036	0.0004	0.0002	0.0222

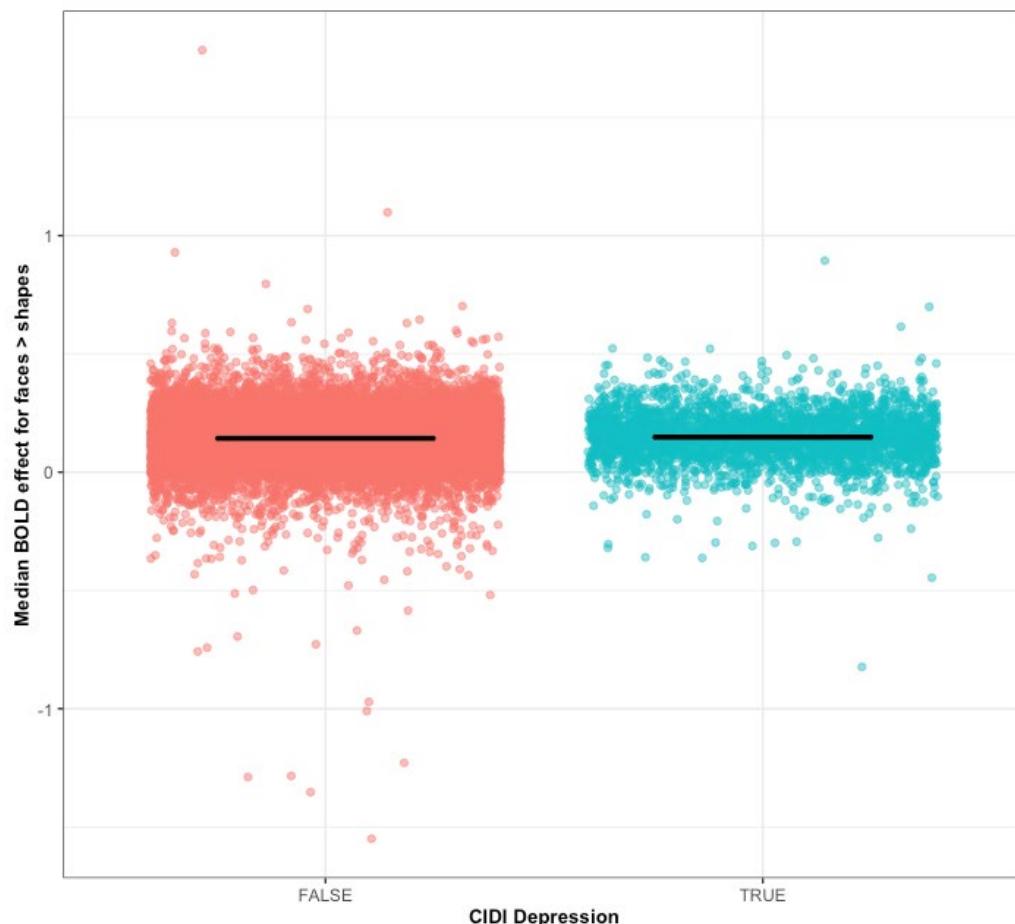


Figure 4. Amygdala responses in participants with a CIDI defined lifetime depression episode compared to those without

Predictors of depressive symptoms (including amygdala responses), supplemental table 10.

The main analyses in this report focus on depressive symptoms as a predictor of amygdala responses to negative faces. For completeness, we here report the opposite association (i.e. depression as the dependent variable and amygdala responses as a predictor). We also report associations between the demographic covariates and depression score.

Predictor	Univariable analysis			Multivariable-adjusted		
	β -coefficient	se	p-value	β -coefficient	se	p-value
Amygdala responses	0.1405	0.0905	0.1206	-0.0237	0.0888	0.7891
Age	-0.0356	0.0014	<0.0001	-0.0322	0.0014	<0.0001
Sex	-0.2739	0.0205	<0.0001	-0.2684	0.0203	<0.0001
Townsend deprivation index	0.0559	0.0038	<0.0001	0.0425	0.0038	<0.0001
Attended college	-0.1254	0.0205	<0.0001	-0.1012	0.0203	<0.0001
Body Mass Index	0.0464	0.0024	<0.0001	0.0443	0.0024	<0.0001

Sensitivity analyses removing participants with suspected dropout in the amygdala

When plotting the median BOLD effect for the faces-shapes contrast, we observed an ‘excess’ number of exact zero values (see Figure below). We further investigated this unusual pattern by consulting with colleagues who lead the UK Biobank imaging analysis team. Their view, consistent with ours, is that susceptibility artefacts may have led to a signal dropout in the amygdala ROI for some of these participants. Below, we present a sensitivity analysis for the main analyses where we exclude these data points ($N = 170$, 0.6 % of the sample). As can be seen from the table, the results are identical.

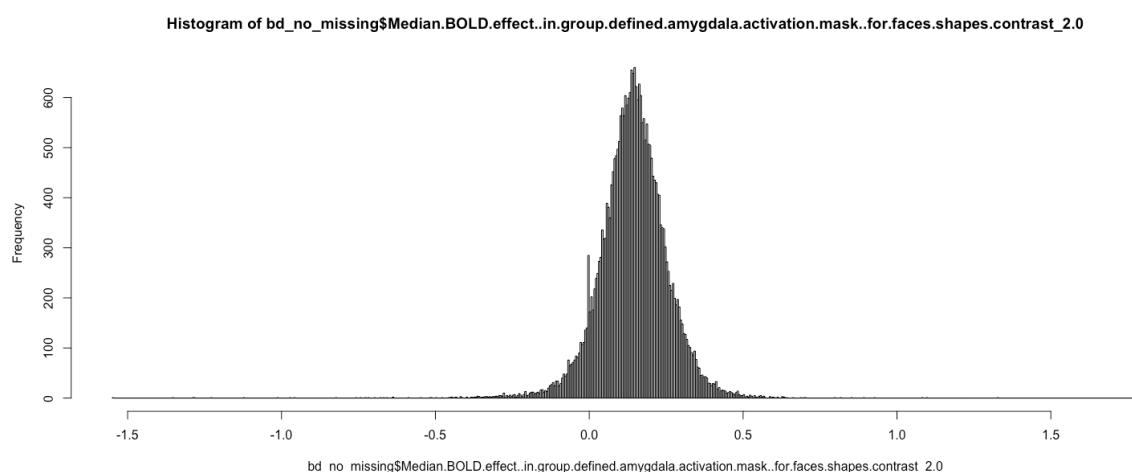


Figure 5. Distribution of the main dependent variable (BOLD effect for the faces > shapes contrast within the amygdala).

Supplemental table 11. Strength of univariable and multivariable-adjusted relationships in linear regression between depression score and amygdala responses to adverse emotional stimuli in UK Biobank participants. Participants with contrast value = 0 are removed

Predictor	Univariable analysis			Multivariable-adjusted		
	β-coefficient	se	p-value	β-coefficient	se	p-value
Depression score	0.0006	0.0004	0.1283	-0.0001	0.0004	0.7539
Age	-0.0012	0.0001	< 0.0001	-0.0012	0.0001	< 0.0001
Sex	0.0077	0.0013	< 0.0001	0.0088	0.0014	< 0.0001
Townsend deprivation index	0.0008	0.0002	0.0024	0.0005	0.0003	0.0655
Attended college	0.0091	0.0013	< 0.0001	0.0082	0.0013	< 0.0001
Body Mass Index	0.0005	0.0002	0.0011	0.0004	0.0002	0.0099

References

Cai N, Revez JA, Adams MJ, et al. (2020) Minimal phenotyping yields genome-wide association signals of low specificity for major depression. *Nature Genetics* 52(4). Springer US: 437–447.
 DOI: 10.1038/s41588-020-0594-5.