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Research paper

Gut microbiota and major depressive disorder: A bidirectional Mendelian randomization

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ABSTRACT

Background: Observational studies showed an association between gut microbiota and depression, but the causality relationship between them is unclear. We aimed to determine whether there is a bidirectional causal relationship between the composition of gut microbiota and major depressive disorders (MDD) and explore the role of gut microbiota in decreasing the risk of MDD.

Methods: Our two-sample Mendelian randomization (MR) study acquired top SNPs associated with the composition of gut microbiota (n = 18,340) and with MDDs (n = 480,359) from publicly available genome-wide association studies (GWAS). The SNPs estimates were pooled using inverse-variance weighted meta-analysis, with sensitivity analyses—weighted median, MR Egger, and MR Pleiotropy Residual Sum and Outlier (PRESSO).

Results: The *Actinobacteria* class had protective causal effects on MDD (OR 0.88, 95%CI 0.87 to 0.9). The *Bifidobacterium* (OR 0.89, 95%CI 0.88 to 0.91) were further found to have similar effects as the *Actinobacteria* class. The genus *Ruminococcus1* had a protective effect on MDD (OR 0.88, 95%CI 0.76 to 0.99) while the *Streptococcaceae* family and its genus had an anti-protective effect on MDD (OR 1.07, 95%CI 1.01 to 1.13), but these findings were not supported by the MR-Egger analysis. Bidirectional MR showed no effect of MDD on gut microbiota composition.

Limitations: The use of summary-level data, the risk of sample overlap and low statistical power are the major limiting factors.

Conclusions: Our MR analysis showed a protective effect of *Actinobacteria*, *Bifidobacterium*, and *Ruminococcus* and a potentially anti-protective effect of *Streptococcaceae* on MDD pathogenesis. Further studies are needed to transform the findings into practice.

1. Introduction

Major depressive disorder, MDD, is a common illness that significantly restricts workability and diminishes the quality of life. It is reported that the overall 12-month prevalence of MDD is approximately 6 %, although it varies substantially across countries (Malhi and Mann, 2018). It is estimated that an additional 53 million (44·8 to 62·9) cases of major depressive disorder were added globally (an increase of 27·6 % [25·1 to 30·3]) owing to the COVID-19 pandemic (COVID-19 Mental Disorders Collaborators, 2021). The high and gradually increased prevalence of MDD urges the development of more treatment options for patients since current treatments are not all effective.

Gut microbiota composition is closely related to anxiety and depressive disorders, which was recently supported by at least two systematic reviews (Carlessi et al., 2021; Simpson et al., 2021). Several studies showed that rodents with gut microbiota dysbiosis presented with anxiety- and depressive-like behaviors (Mayer et al., 2015; Zhao et al., 2018; Zheng et al., 2016), and the abnormal behaviors normalized after bacterial probiotic administration (Tian et al., 2022). One study applied fecal microbiota transplantation from depressed patients to microbiota-depleted rats and induced depressive-like behaviors (Kelly et al., 2016).

Observational studies showed that patients with MDD had apparent alterations in gut microbiota compositions compared with healthy controls; however, it is unclear which specific bacterial taxa contribute to group differences (Huang et al., 2018; Sanada et al., 2020; Simpson

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et al., 2021). Although cumulating evidence suggests a correlation between gut microbiota composition and MDD, it is still unclear whether particular taxa of gut microbiota cause MDD. The observational studies focusing on gut microbiota diversity cannot make a causal inference (Simpson et al., 2021). Some experimental studies suggest that antidepressants worked by changing the composition of gut microbiota (Ait Chait et al., 2020; Lukić et al., 2019), indicating that specific taxa might play an essential role in modifying MDD pathogenesis. Based on the above findings, we hypothesized that changes in gut microbiota composition lead to MDD. Confirming whether the correlation is causal and which microbiota taxa were the most essential are critical to clinical practice in MDD management.

Mendelian randomization (MR) studies use genetic instruments, normally single nucleotide polymorphisms (SNPs), to detect the causal effects of exposures on outcomes. The MR studies are analogous to randomized controlled trials as there is an equal probability of either allele being randomly inherited to an individual (Emdin et al., 2017). Compared with observational studies like case-control studies, MR studies are less affected by confounding issues and capable of making causal inferences (Bowden and Holmes, 2019; Emdin et al., 2017).

We aimed to conduct an MR study first to verify the causal effect of gut microbiota taxa on the pathogenesis of MDD, and we secondly examined whether the causal effect was bidirectional.

2. Materials and methods

We acquired de-identified summary-level data from publicly available GWAS studies. The GWAS study providing the data on gut microbiota was conducted by the international MiBioGen consortium initiative (Kurilshikov et al., 2021; Wang et al., 2018), and the GWAS study providing the data on MDD was mainly conducted by the Psychiatric Genomics Consortium (PGC) (Wray et al., 2018). Ethical approval and consent to participate were acquired by each cohort included in the GWAS studies, and the summary-level data were released for analysis.

2.1. Gut microbiota

Genetic instruments of gut microbiota were obtained from a large-scale association study containing 24 cohorts (18,340 participants) (Kurilshikov et al., 2021). The included cohorts were conducted in the USA, Canada, Israel, South Korea, Germany, Denmark, the Netherlands, Belgium, Sweden, Finland, and the UK. Twenty cohorts included samples of single ancestry, and most of the participants were of European ancestry (16 cohorts, N = 13,266). Seventeen (n = 13,804) of the 24 cohorts included participants with mean ages ranging from 50 to 62 years. For each cohort, the quantitative microbiome trait loci (mbQTL) mapping analysis included only the taxa presented in >10 % of the samples, containing 211 taxa (131 genera, 35 families, 20 orders, 16 classes, and 9 phyla). The binary trait loci mapping (mbBTL) analysis included the taxa that presented in a percentage of 10 %–90 % in the included samples. The included cohorts all adjusted covariates for sex and age in their calculations. The summary-level statistics of the association study were openly available at the www.mibiogen.org website.

2.2. Major depressive disorder

Summary-level statistics were acquired from the largest publicly available GWAS meta-analysis for MDD, incorporating 29 cohorts with 480,359 participants (135,458 MDD cases and 344,901 controls) (Wray et al., 2018). The participants with MDD met one of the following diagnostic criteria: The Diagnostic and Statistical Manual of Mental Disorders (DSM), the Third or Fourth edition; the International Statistical Classification of Diseases and Related Health Problems (ICD), the ninth or tenth edition. The participants had a wide range of ages from 18 to 80 years, and the proportion of females was approximately 56 %.

2.3. Statistical analysis

All the analyses were performed in the R environment (www.r-project.org; version 4.1.1) and the R package TwosampleMR (version 0.56). The SNPs (genetic instruments) were identified in the GWASs with a p-value threshold of 5×10^{-8}, and these SNPs were further confirmed to be uncorrelated by a distance cut-off of 10,000 kilobases apart and a correlation index $R^2 \leq 0.001$.

The effect estimates and corresponding standard errors of the selected SNPs were acquired from the GWASs summary statistics of the gut microbiota composition and MDD. We harmonized the data from exposure (gut microbiota) and outcome (MDD), removing palindromic SNPs with intermediate allele frequencies. We performed an inverse-variance weighting (IVW) meta-analysis to combine the effect estimates of the exposure on the outcome, and the combined effect estimate βwas transformed into odds ratio (OR) by the formula—$\beta = \ln(OR)$. We calculated each microbiota taxa's effect size and corresponding standard error (SE) in the single-variable MR. We examined the heterogeneity of the IVW meta-analysis by using the Cochran's Q statistics, and a $p < 0.1$ would indicate significant heterogeneity in the SNP effect estimates.

Several sensitivity analyses were performed to avoid confounding issues. First, MR Egger analysis, a meta-regression of the SNP-outcome association estimates on the SNP-exposure association estimates, was performed to examine the confounding of directional pleiotropy. When the intercept of the MR-Egger analysis was close to zero, and the results were consistent between the IVW and the MR-Egger analysis, we assumed no directional pleiotropy. Second, we performed a weighted median analysis with greater robustness to individual genetic variants with strongly outlying causal estimates than the IVW and the MR-Egger methods (Bowden and Holmes, 2019). Third, we implemented the Mendelian Randomization Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test, which evaluates overall horizontal pleiotropy by comparing the observed distance of all the SNPs to the regression line (residual sum of squares) with the expected distance under the null hypothesis of no horizontal pleiotropy (Verbanck et al., 2018). We provided the results of the MR-PRESSO global test, and outlier-corrected estimates would be provided when there were indications of horizontal pleiotropy. Fourth, we performed a leave-one-outcome analysis to examine the influence of a single SNP on the overall causal effect. We did not perform multivariable MR analysis, since most SNPs were removed from the analysis due to LD with other variants or absence from the LD reference panel.

3. Results

We found that the Class *Actinobacteria* was negatively associated with MDD, suggesting a protective effect of the Class *Actinobacteria* on MDD (OR 0.89, 95%CI 0.87 to 0.9; p-value <0.0001; Table 1, Fig. 1-2). The MR Egger analysis showed similar findings (OR 0.80, 95%CI 0.70 to 0.90; p-value = 0.003), and the result suggested no directional horizontal pleiotropy (Egger intercept 0.01, p-value = 0.08). MR-PRESSO analysis showed no evidence of horizontal pleiotropy (observed residual sum of squares 79.08, p-value = 1). The Cochran's Q test showed no evidence of heterogeneity (Cochran's Q = 80.28, p-value = 1).

The Family *Bifidobacteriaceae*, a gut microbiota family belonging to the *Actinobacteria* Class, had also a protective effect on MDD (OR 0.89, 0.88 to 0.91; p-value <0.0001; Table 1, Figs. 1–2), which were consistent with previous studies (Barandouzi et al., 2020; Bastiaanssen et al., 2020; Knuesel and Mohajeri, 2021; Scriven et al., 2018; Tian et al., 2020). The MR Egger analysis showed similar results (OR 0.83, 95%CI 0.73 to 0.95; p-value = 0.007), and the result informed no directional horizontal pleiotropy (Egger intercept 0.007, p-value = 0.297). MR-PRESSO analysis showed no evidence of horizontal pleiotropy (observed residual sum of squares 69.91, p-value = 1). The Cochran's Q test showed no evidence of heterogeneity (Cochran's Q = 78.48, p-value = 1).

Table 1
Characteristics of the study population.

Exposure	Methods	Number of SNPs	Beta	SE	p-Value
Phylum_*Actinobacteria*	IVW	81	−0.17779	0.016818	4.03E-26
Class_*Actinobacteria*	IVW	266	−0.11836	0.008456	1.63E-44
Order_*Bifidobacteriales*	IVW	250	−0.11224	0.008341	2.84E-41
Family_*Bifidobacteriaceae*	IVW	250	−0.11224	0.008341	2.84E-41
Family_*Streptococcaceae*	IVW	17	0.069547	0.030505	0.022614
Genus_*Ruminococcustorques*	IVW	3	−0.12216	0.077397	0.114474
Genus_*Allisonella*	IVW	3	−0.05563	0.031369	0.076146
Genus_*Bifidobacterium*	IVW	249	−0.11143	0.008414	4.88E-40
Genus_*Enterorhabdus*	IVW	6	−0.05055	0.035255	0.151631
Genus_*Erysipelatoclostridium*	IVW	3	0.086373	0.055754	0.121335
Genus_*Ruminococcus1*	IVW	5	−0.13079	0.057771	0.023578
Genus_*Streptococcus*	IVW	63	0.020311	0.015569	0.192029
Genus_*Tyzzerella3*	IVW	3	0.069996	0.046088	0.128828
Phylum_*Actinobacteria*	MR Egger	81	−0.36806	0.18441	0.049392
Class_*Actinobacteria*	MR Egger	266	−0.22921	0.062812	0.000317
Order_*Bifidobacteriales*	MR Egger	250	−0.18173	0.067039	0.007182
Family_*Bifidobacteriaceae*	MR Egger	250	−0.18173	0.067039	0.007182
Family_*Streptococcaceae*	MR Egger	17	0.35033	1.91201	0.857074
Genus_*Ruminococcustorques*	MR Egger	3	−0.16924	4.27244	0.974795
Genus_*Allisonella*	MR Egger	3	−1.78875	6.780836	0.835804
Genus_*Bifidobacterium*	MR Egger	249	−0.19573	0.06637	0.003493
Genus_*Enterorhabdus*	MR Egger	6	−0.23662	2.09811	0.915639
Genus_*Erysipelatoclostridium*	MR Egger	3	3.379642	6.351142	0.68868
Genus_*Ruminococcus1*	MR Egger	5	0.139262	2.93173	0.965099
Genus_*Streptococcus*	MR Egger	63	0.952405	0.231976	0.000122
Genus_*Tyzzerella3*	MR Egger	3	0.012636	2.607364	0.996915

Abbreviation: Beta, The effect size of the exposure on MDD. IVW, inverse-variance weighted. MR, mendelian randomization. SE, standard errors. SNP, single nucleotide polymorphisms.

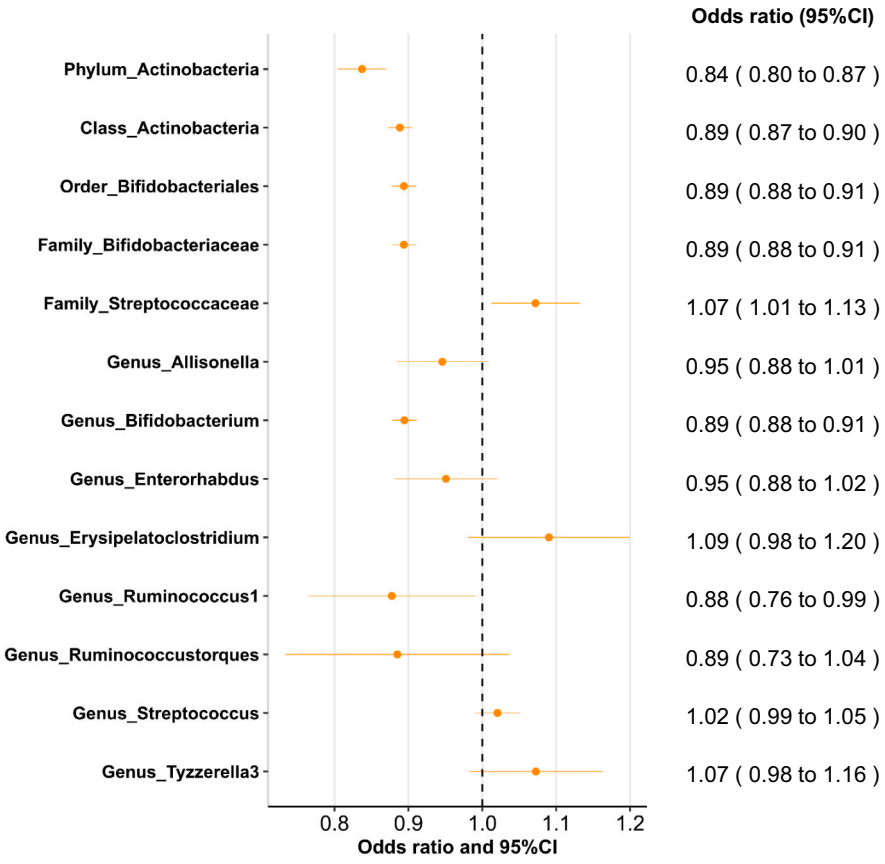

Fig. 1. Gut microbiota composition and major depressive disorder.
Annotation: This figure shows the effect size of each gut microbiota Phylum, Class, Order, Family, or Genus on the pathogenesis of major depressive disorder. An odds ratio value <1 indicated a protective causal effect, while a value >1 indicated an causal pathogenic impact. The results were generated through the inverse variance weighted analysis.

The Genus *Bifidobacterium*, belonging to the Family *Bifidobacteriaceae*, also showed protective causal effects on MDD (OR 0.89, 0.88 to 0.91; p-value <0.0001; Table 1, Figs. 1–2). The MR Egger analysis showed similar results (OR 0.82, 95%CI 0.72 to 0.94; p-value = 0.003), and the result informed no directional horizontal pleiotropy (Egger intercept 0.008, p-value = 0.201). MR-PRESSO analysis showed no

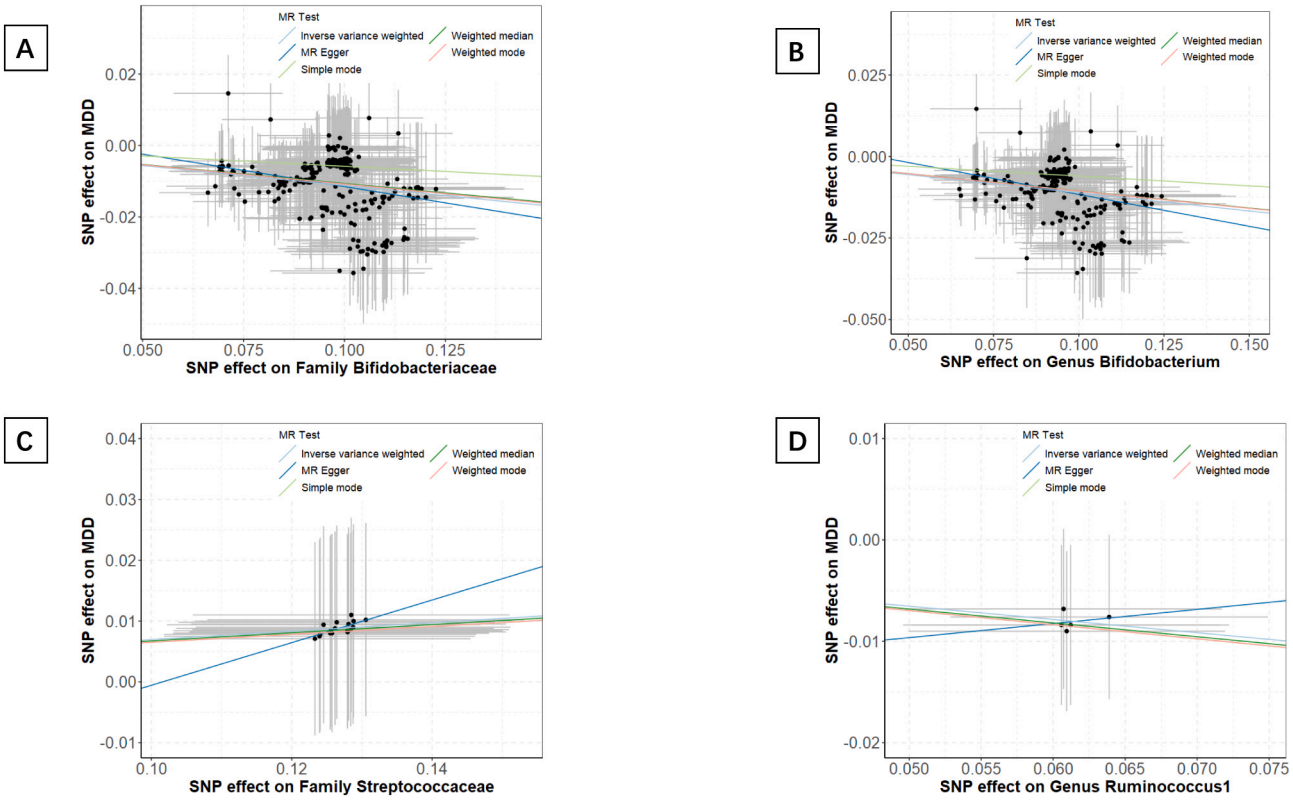

Fig. 2. Scatter plots of four taxa of gut microbiota associated with major depressive disorder.
Abbreviations: MDD, major depressive disorder. MR, mendelian randomization. SNP, single nucleotide polymorphisms.
Annotation: Scatter plots of the taxa-SNP associations (x-axis) versus the MDD-SNP associations (y-axis) were shown, with horizontal and vertical lines showing 95 % confidence intervals for each association. The MR analysis was performed primarily with the inverse variance weighted method and secondarily examined with the MR-Egger, the weighted median, and other methods. The lines that move obliquely upward from left to right show a positive correlation of the taxa with MDD, indicating a pathogenic causal effect. The lines that are inclined down indicate a protective causal effect.

evidence of horizontal pleiotropy (observed residual sum of squares 79.08, p-value = 1). The Cochran's Q test showed no evidence of heterogeneity (Cochran's Q = 69.39, p-value = 1).

The Genus *Ruminococcus1* was also found to be protective against MDD (OR 0.88, 0.78 to 0.98; p-value = 0.024; Table 1, Figs. 1–2) in the IVW analysis. However, the result was not supported in the MR-Egger analysis (OR 1.15, 95%CI 0 to 359.77; p-value = 0.965; Table 1).

The Family *Streptococcaceae* was positively associated with MDD (OR 1.07, 95%CI 1.01 to 1.14; p-value = 0.023; Table 1, Figs. 1–2). However, the result was not supported by the MR-Egger analysis (OR 1.42, 95%CI 0.03 to 60.21; p-value = 0.857). The analysis for its Genus *Streptococcus* had inconsistent findings. The IVW analysis showed no causal effect on MDD (OR 1.02, 95%CI 0.99 to 1.05; p-value = 0.192; Table 1, Fig. 1), but the MR-Egger analysis (OR 2.59, 95%CI 1.64 to 4.08; p-value = 0.0001) and the weighted median analysis (OR 1.06, 95%CI 1.02 to 1.10; p-value = 0.003) showed a positively causal effect on MDD.

4. Discussion

Our study found that the Class *Actinobacteria* and its Family *Bifidobacteriaceae* and Genus *Bifidobacterium* had a protective causal effect on the pathogenesis of MDD. The results were examined through several sensitivity analyses—MR-Egger analysis, weighted-median analysis, and MR-EXPRESSO analysis, which showed consistent findings. We also found a possible negative association of Genus *Ruminococcus1* and a possible positive association of the Family *Streptococcaceae* and its Genus *Streptococcus* with the pathogenesis of MDD. Still, the sensitivity analyses did not confirm these findings.

The *Actinobacteria* includes three main anaerobe families (*Bifidobacteriaceae*, *Propionibacteria*, and *Corynebacteria*). The *Bifidobacteriaceae family* and *Bifidobacterium* were found to be protective of MDD, and the mechanism of which is discussed in the next paragraph. A growing body of evidence suggests that activation of microglia-induced neuroinflammation plays a crucial role in the pathophysiology of depression (Cao et al., 2021; Klawonn et al., 2021; Liu et al., 2022). The short-chain fatty acids (SCFAs), the major metabolites that were normally derived from gut microbiome, reduced depressive-like behaviors in mice by suppressing suppress microglia activation and neuroinflammation (Tang et al., 2022). The *Actinobacteria* was associated with the increased production of SCFAs—mainly via the *Bifidobacteriaceae* family (Binda et al., 2018). The acetate, propionate, and butyrate are the major components of the SCFAs. Acetate was recently found as the essential microbiome-derived SCFA driving microglia maturation, and it could modulate microglial phagocytosis (Erny et al., 2021), which was acknowledged as an essential factor in developing depression. The butyrate, another component of SCFAs, was found to be negatively correlated with depressive-like behaviors, and its anti-depression effect might depend on increasing the level of brain-derived neuron factor (BDNF) in prefrontal cortex (Wei et al., 2014). In addition, butyrate also showed anti-inflammatory effects in microglia by reducing NF-κB signaling (Stilling et al., 2016).

Several previous experimental studies demonstrated that the intake of *Bifidobacterium* reversed depressive-like behavior (Guo et al., 2019; Han and Kim, 2019; Kosuge et al., 2021; Tian et al., 2020; Tian et al., 2019; Yang et al., 2017). These findings indicated the probability of developing treatments based on the changes in gut microbiota composition, and *Bifidobacterium* was a potential treatment target. A study in 2016 showed that individuals with MDD presented with a lower level of

Bifidobacterium (Aizawa et al., 2016), and a trial in 2022 showed that *Bifidobacterium breve* CCFM1025 induced relief in both psychometric and gastrointestinal symptoms (Tian et al., 2022). Our study result was consistent with the experimental studies showing the potential of *Bifidobacterium* served as a treatment option for MDD. One study adopted fMRI to explore how *Bifidobacterium* changed brain function in patients with depression, and the results showed that *Bifidobacterium* reduced responses to negative emotional stimuli in the amygdala and frontolimbic regions (Pinto-Sanchez et al., 2017). One pilot study, examining the effect of probiotic *Bifidobacterium* on anxiety and depression in patients with irritable bowel syndrome, found that *Bifidobacterium* decreased the depression score and improved depressive symptoms. Although the study was small-scale, it shed some light on drug development for depression. In future studies, large-scale randomized controlled trials are warranted to test the treatment effect of *Bifidobacterium* for patients with MDD, and the administration methods and optimal dose should also be further studied.

The mechanism of how *Bifidobacterium* improves depressive symptoms is still unclear. As mentioned above in the working mechanism of the *Actinobacteria*, *the* activation of microglia-induced neuroinflammation played an important role in MDD pathogenesis. *Bifidobacterium* could inhibit the NLRP3-mediated generation of IL-1β in microglia cells to reduce neuroinflammation (Westfall et al., 2018), and this anti-neuroinflammation effect might also be associated with deactivating microglial in the hippocampus and IL-6 and corticosterone in the blood. (Carlessi et al., 2021) Another study further demonstrated that *Bifidobacterium* inhibited hippocampal NF-κB activation, further supporting the neuroinflammation-suppression theory (Han and Kim, 2019). The anti-neuroinflammation effect of *Bifidobacterium* might first work through its metabolites—the SCFAs, as mentioned above. The SCFAs derived from *Bifidobacterium* lowered the intestinal pH, developed biological barriers, and secreted antimicrobial compounds to temper pathogenic bacteria, which helped to restore a normal brain-gut communication (Knuesel and Mohajeri, 2021; Liao et al., 2016). Secondly, it is hypothesized that *Bifidobacterium* might induce the cholinergic anti-inflammatory effect through activating vagus nerve function (Kobayashi et al., 2017). Another study showed that SCFAs could suppress food intake by activating vagal afferent neurons, and the authors of the article proposed that vagal afferents might serve to link intestinal information to the brain (Goswami et al., 2018).

The mechanism of how the Family *Streptococcaceae* and its Genus *Streptococcus* affect MDD is unknown since experimental studies are lacking. It was reported that, in a systematic review, 4 out of the 19 included studies showed that the Genus *Streptococcus* had a higher abundance in patients with MDD. Our MR analysis also showed a higher abundance of the Family *Streptococcaceae* or Genus *Streptococcus* was causally associated with MDD. The same dilemma was also encountered in discovering the mechanism of *Ruminococcus*, which was found inversely associated with MDD pathogenesis in our study. A recent case-control study had similar findings, showing that patients with anxiety and depression had a lower abundance of *Ruminococcus* (Zhu et al., 2021). *Ruminococcus* may involve in the pathogenesis of MDD by causing the lipid disturbance (especially phosphoethanolamine and glycerophosphorylcholine), and activating the NLRP3 inflammasome in the inferior frontal gyrus (Zhao et al., 2022). However, this assumption has not been examined. *In summary*, the role of Genus *Streptococcus* and *Ruminococcus* in the pathogenesis of MDD is unclear, which warrants further investigation.

It is noteworthy that sex-specific effects on gut microbiota might affect our findings. One study showed that gut microbiota contributed more to nervous feelings and anxious feelings in females than males (Qi et al., 2021). However, another study showed inconsistent findings. Using anti-microbial medication to alter gut microbiome composition, they found that males were more susceptible than females to microbial modulation of anxiety-like behavior, while females were more susceptible than males to microbial-modulation-induced impairments in aversive learning (Geary et al., 2021). Another study showed that gut microbiota, particularly members of *Ruminococcaceae*, might affect pubertal timing, possibly via regulating host sex-hormone levels. These findings suggested a need to use participant-level data to study the impact of the sex-specific effects on our study results, to further find out whether the change of microbiome composition has more impact on females.

Our study had several limitations. First, we used summary-level data for two-sample MR. Although this method increased statistical power and obtained interesting results, we could not adjust for important covariates like diet or medication usage. Second, the two GWASs adopted the meta-analytic method by pooling data from several cohorts. Although this method had better performance in acquiring the genetic characteristics of the general population, it might cause bias in sample overlapping. We checked the data source and found approximately 1000 samples in both GWASs from the UK population. However, the gut microbiota GWAS included adolescents while the MDD GWAS recruited adults, so we assumed they were independent samples. Third, MR analysis typically reveals a lifetime exposure, so the effect size of the exposure might be overestimated. The effect of exposures (e.g., *Bifidobacterium*) should be further examined in randomized controlled trials. Fourth, the two GWASs recruited participants who were mainly of European ancestry, so the results of our MR analysis might apply to the population with European ancestry. The generalization of the results to other ethnic groups should be cautious, and further studies are warranted. Fifth, null findings of other gut microbiota taxa might reflect low statistical power. The lack of statistical power might explain the inconsistent results between Family Streptococcaceae and its Genus Streptococcus, which should be further examined.

In conclusion, our MR study showed that the Family *Bifidobacteriaceae* and its Genus *Bifidobacterium* had protective causal effects on MDD, which were consistent with previous studies (Aizawa et al., 2016; Tian et al., 2022). In addition, our study also demonstrated that the *Actinobacteria* and *Ruminococcus* might have a protective effect while *Streptococcus* might have anti-protective effects on MDD pathogenesis, but these findings warrant further examination owing to the unclear mechanisms.

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Role of the funder/sponsor

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Data availability statement

All authors agree to share the study data after the publication of the article. The data will be acquired upon reasonable request.

CRediT authorship contribution statement

All authors had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. MC and HZ designed the study. CRX, YZS, and TCT acquired the study data. MC and HZ analyzed and interpreted the data. MC wrote the first draft of the manuscript. All authors revised the manuscript and

approved it for publication.

Conflict of interest

All authors have no conflicts of interest to report for this study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2022.08.012.

References

Ait Chait, Y., Mottawea, W., Tompkins, T.A., Hammami, R., 2020. Unravelling the antimicrobial action of antidepressants on gut commensal microbes. Sci. Rep. 10, 17878. https://doi.org/10.1038/s41598-020-74934-9.

Aizawa, E., Tsuji, H., Asahara, T., Takahashi, T., Teraishi, T., Yoshida, S., Ota, M., Koga, N., Hattori, K., Kunugi, H., 2016. Possible association of bifidobacterium and lactobacillus in the gut microbiota of patients with major depressive disorder. J. Affect. Disord. 202, 254–257. https://doi.org/10.1016/j.jad.2016.05.038.

Barandouzi, Z.A., Starkweather, A.R., Henderson, W.A., Gyamfi, A., Cong, X.S., 2020. Altered composition of gut microbiota in depression: a systematic review. Front. Psychiatry 11, 541. https://doi.org/10.3389/fpsyt.2020.00541.

Bastiaanssen, T.F.S., Cussotto, S., Claesson, M.J., Clarke, G., Dinan, T.G., Cryan, J.F., 2020. Gutted! Unraveling the role of the microbiome in major depressive disorder. Harv. Rev. Psychiatry 28, 26–39. https://doi.org/10.1097/HRP.0000000000000243.

Binda, C., Lopetuso, L.R., Rizzatti, G., Gibiino, G., Cennamo, V., Gasbarrini, A., 2018. Actinobacteria: a relevant minority for the maintenance of gut homeostasis. Dig. Liver Dis. 50, 421–428. https://doi.org/10.1016/j.dld.2018.02.012.

Bowden, J., Holmes, M.V., 2019. Meta-analysis and mendelian randomization: a review. Res. Synth. Methods 10, 486–496. https://doi.org/10.1002/jrsm.1346.

Cao, P., Chen, C., Liu, A., Shan, Q., Zhu, X., Jia, C., Peng, X., Zhang, M., Farzinpour, Z., Zhou, W., Wang, H., Zhou, J.-N., Song, X., Wang, L., Tao, W., Zheng, C., Zhang, Y., Ding, Y.-Q., Jin, Y., Xu, L., Zhang, Z., 2021. Early-life inflammation promotes depressive symptoms in adolescence via microglial engulfment of dendritic spines. Neuron 109, 2573–2589. https://doi.org/10.1016/j.neuron.2021.06.012 e9.

Carlessi, A.S., Borba, L.A., Zugno, A.I., Quevedo, J., Réus, G.Z., 2021. Gut microbiota-brain axis in depression: the role of neuroinflammation. Eur. J. Neurosci. 53, 222–235. https://doi.org/10.1111/ejn.14631.

COVID-19 Mental Disorders Collaborators, 2021. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. Lancet 398, 1700–1712. https://doi.org/10.1016/S0140-6736(21)02143-7.

Emdin, C.A., Khera, A.V., Kathiresan, S., 2017. Mendelian randomization. JAMA 318, 1925–1926. https://doi.org/10.1001/jama.2017.17219.

Erny, D., Dokalis, N., Mezö, C., Castoldi, A., Mossad, O., Staszewski, O., Frosch, M., Villa, M., Fuchs, V., Mayer, A., Neuber, J., Sosat, J., Tholen, S., Schilling, O., Vlachos, A., Blank, T., Gomez de Agüero, M., Macpherson, A.J., Pearce, E.J., Prinz, M., 2021. Microbiota-derived acetate enables the metabolic fitness of the brain innate immune system during health and disease. Cell Metab. 33, 2260–2276. e7. https://doi.org/10.1016/j.cmet.2021.10.010.

Geary, C.G., Wilk, V.C., Barton, K.L., Jefferson, P.O., Binder, T., Bhutani, V., Baker, C.L., Fernando-Peiris, A.J., Mousley, A.L., Rozental, S.F.A., Thompson, H.M., Touchon, J. C., Esteban, D.J., Bergstrom, H.C., 2021. Sex differences in gut microbiota modulation of aversive conditioning, open field activity, and basolateral amygdala dendritic spine density. J. Neurosci. Res. 99, 1780–1801. https://doi.org/10.1002/jnr.24848.

Goswami, C., Iwasaki, Y., Yada, T., 2018. Short-chain fatty acids suppress food intake by activating vagal afferent neurons. J. Nutr. Biochem. 57, 130–135. https://doi.org/10.1016/j.jnutbio.2018.03.009.

Guo, Y., Xie, J.-P., Deng, K., Li, X., Yuan, Y., Xuan, Q., Xie, J., He, X.-M., Wang, Q., Li, J.-J., Luo, H.-R., 2019. Prophylactic effects of bifidobacterium adolescentis on anxiety and depression-like phenotypes after chronic stress: a role of the gut microbiota-inflammation Axis. Front. Behav. Neurosci. 13, 126. https://doi.org/10.3389/fnbeh.2019.00126.

Han, S.-K., Kim, D.H., 2019. Lactobacillus mucosae and bifidobacterium longum synergistically alleviate immobilization stress-induced anxiety/depression in mice by suppressing gut dysbiosis. J. Microbiol. Biotechnol. 29, 1369–1374. https://doi.org/10.4014/jmb.1907.07044.

Huang, Y., Shi, Xing, Li, Z., Shen, Y., Shi, Xinxin, Wang, L., Li, G., Yuan, Y., Wang, J., Zhang, Y., Zhao, L., Zhang, M., Kang, Y., Liang, Y., 2018. Possible association of firmicutes in the gut microbiota of patients with major depressive disorder. Neuropsychiatr. Dis. Treat. 14, 3329–3337. https://doi.org/10.2147/NDT.S188340.

Kelly, J.R., Borre, Y., O' Brien, C., Patterson, E., El Aidy, S., Deane, J., Kennedy, P.J., Beers, S., Scott, K., Moloney, G., Hoban, A.E., Scott, L., Fitzgerald, P., Ross, P., Stanton, C., Clarke, G., Cryan, J.F., Dinan, T.G., 2016. Transferring the blues: depression-associated gut microbiota induces neurobehavioural changes in the rat. J. Psychiatr Res. 82, 109–118. https://doi.org/10.1016/j.jpsychires.2016.07.019.

Klawonn, A.M., Fritz, M., Castany, S., Pignatelli, M., Canal, C., Similä, F., Tejeda, H.A., Levinsson, J., Jaarola, M., Jakobsson, J., Hidalgo, J., Heilig, M., Bonci, A., Engblom, D., 2021. Microglial activation elicits a negative affective state through prostaglandin-mediated modulation of striatal neurons. Immunity 54, 225–234. https://doi.org/10.1016/j.immuni.2020.12.016 e6.

Knuesel, T., Mohajeri, M.H., 2021. The role of the gut microbiota in the development and progression of major depressive and bipolar disorder. Nutrients 14, 37. https://doi.org/10.3390/nu14010037.

Kobayashi, Y., Sugahara, H., Shimada, K., Mitsuyama, E., Kuhara, T., Yasuoka, A., Kondo, T., Abe, K., Xiao, J., 2017. Therapeutic potential of bifidobacterium breve strain A1 for preventing cognitive impairment in Alzheimer's disease. Sci. Rep. 7, 13510. https://doi.org/10.1038/s41598-017-13368-2.

Kosuge, A., Kunisawa, K., Arai, S., Sugawara, Y., Shinohara, K., Iida, T., Wulaer, B., Kawai, T., Fujigaki, H., Yamamoto, Y., Saito, K., Nabeshima, T., Mouri, A., 2021. Heat-sterilized bifidobacterium breve prevents depression-like behavior and interleukin-1β expression in mice exposed to chronic social defeat stress. Brain Behav. Immun. 96, 200–211. https://doi.org/10.1016/j.bbi.2021.05.028.

Kurilshikov, A., Medina-Gomez, C., Bacigalupe, R., Radjabzadeh, D., Wang, J., Demirkan, A., Le Roy, C.I., Raygoza Garay, J.A., Finnicum, C.T., Liu, X., Zhernakova, D.V., Bonder, M.J., Hansen, T.H., Frost, F., Rühlemann, M.C., Turpin, W., Moon, J.-Y., Kim, H.-N., Lüll, K., Barkan, E., Shah, S.A., Fornage, M., Szopinska-Tokov, J., Wallen, Z.D., Borisevich, D., Agreus, L., Andreasson, A., Bang, C., Bedrani, L., Bell, J.T., Bisgaard, H., Boehnke, M., Boomsma, D.I., Burk, R. D., Claringbould, A., Croitoru, K., Davies, G.E., van Duijn, C.M., Duijts, L., Falony, G., Fu, J., van der Graaf, A., Hansen, T., Homuth, G., Hughes, D.A., Ijzerman, R.G., Jackson, M.A., Jaddoe, V.W.V., Joossens, M., Jørgensen, T., Keszthelyi, D., Knight, R., Laakso, M., Laudes, M., Launer, L.J., Lieb, W., Lusis, A.J., Masclee, A.A.M., Moll, H.A., Mujagic, Z., Qibin, Q., Rothschild, D., Shin, H., Sørensen, S.J., Steves, C.J., Thorsen, J., Timpson, N.J., Tito, R.Y., Vieira-Silva, S., Völker, U., Völzke, H., Võsa, U., Wade, K.H., Walter, S., Watanabe, K., Weiss, S., Weiss, F.U., Weissbrod, O., Westra, H.-J., Willemsen, G., Payami, H., Jonkers, D.M.A. E., Arias Vasquez, A., de Geus, E.J.C., Meyer, K.A., Stokholm, J., Segal, E., Org, E., Wijmenga, C., Kim, H.-L., Kaplan, R.C., Spector, T.D., Uitterlinden, A.G., Rivadeneira, F., Franke, A., Lerch, M.M., Franke, L., Sanna, S., D'Amato, M., Pedersen, O., Paterson, A.D., Kraaij, R., Raes, J., Zhernakova, A., 2021. Large-scale association analyses identify host factors influencing human gut microbiome composition. Nat. Genet. 53, 156–165. https://doi.org/10.1038/s41588-020-00763-1.

Liao, Z.-L., Zeng, B.-H., Wang, W., Li, G.-H., Wu, F., Wang, L., Zhong, Q.-P., Wei, H., Fang, X., 2016. Impact of the consumption of tea polyphenols on early atherosclerotic lesion formation and intestinal bifidobacteria in high-fat-fed ApoE-/- mice. Front. Nutr. 3, 42. https://doi.org/10.3389/fnut.2016.00042.

Liu, Y., Hu, P., Zheng, Z., Zhong, D., Xie, W., Tang, Z., Pan, B., Luo, J., Zhang, W., Wang, X., 2022. Photoresponsive vaccine-like CAR-M system with high-efficiency central immune regulation for inflammation-related depression. Adv. Mater. 34, e2108525 https://doi.org/10.1002/adma.202108525.

Lukić, I., Getselter, D., Ziv, O., Oron, O., Reuveni, E., Koren, O., Elliott, E., 2019. Antidepressants affect gut microbiota and ruminococcus flavefaciens is able to abolish their effects on depressive-like behavior. Transl. Psychiatry 9, 133. https://doi.org/10.1038/s41398-019-0466-x.

Malhi, G.S., Mann, J.J., 2018. Depression. Lancet 392, 2299–2312. https://doi.org/10.1016/S0140-6736(18)31948-2.

Mayer, E.A., Tillisch, K., Gupta, A., 2015. Gut/brain axis and the microbiota. J. Clin. Invest. 125, 926–938. https://doi.org/10.1172/JCI76304.

Pinto-Sanchez, M.I., Hall, G.B., Ghajar, K., Nardelli, A., Bolino, C., Lau, J.T., Martin, F.-P., Cominetti, O., Welsh, C., Rieder, A., Traynor, J., Gregory, C., De Palma, G., Pigrau, M., Ford, A.C., Macri, J., Berger, B., Bergonzelli, G., Surette, M.G., Collins, S. M., Moayyedi, P., Bercik, P., 2017. Probiotic bifidobacterium longum NCC3001 reduces depression scores and alters brain activity: a pilot study in patients with irritable bowel syndrome. Gastroenterology 153, 448–459. https://doi.org/10.1053/j.gastro.2017.05.003 e8.

Qi, X., Guan, F., Cheng, S., Wen, Y., Liu, L., Ma, M., Cheng, B., Liang, C., Zhang, L., Liang, X., Li, P., Chu, X., Ye, J., Yao, Y., Zhang, F., 2021. Sex specific effect of gut microbiota on the risk of psychiatric disorders: a mendelian randomisation study and PRS analysis using UK biobank cohort. World J. Biol. Psychiatry 22, 495–504. https://doi.org/10.1080/15622975.2021.1878428.

Sanada, K., Nakajima, S., Kurokawa, S., Barceló-Soler, A., Ikuse, D., Hirata, A., Yoshizawa, A., Tomizawa, Y., Salas-Valero, M., Noda, Y., Mimura, M., Iwanami, A., Kishimoto, T., 2020. Gut microbiota and major depressive disorder: a systematic review and meta-analysis. J. Affect. Disord. 266, 1–13. https://doi.org/10.1016/j.jad.2020.01.102.

Scriven, M., Dinan, T.G., Cryan, J.F., Wall, M., 2018. Neuropsychiatric disorders: influence of gut microbe to brain signalling. Diseases 6, E78. https://doi.org/10.3390/diseases6030078.

Simpson, C.A., Diaz-Arteche, C., Eliby, D., Schwartz, O.S., Simmons, J.G., Cowan, C.S.M., 2021. The gut microbiota in anxiety and depression - a systematic review. Clin. Psychol. Rev. 83, 101943 https://doi.org/10.1016/j.cpr.2020.101943.

Stilling, R.M., van de Wouw, M., Clarke, G., Stanton, C., Dinan, T.G., Cryan, J.F., 2016. The neuropharmacology of butyrate: the bread and butter of the microbiota-gut-brain axis? Neurochem. Int. 99, 110–132. https://doi.org/10.1016/j.neuint.2016.06.011.

Tang, C.-F., Wang, C.-Y., Wang, J.-H., Wang, Q.-N., Li, S.-J., Wang, H.-O., Zhou, F., Li, J.-M., 2022. Short-chain fatty acids ameliorate depressive-like behaviors of high fructose-fed mice by rescuing hippocampal neurogenesis decline and blood-brain barrier damage. Nutrients 14, 1882. https://doi.org/10.3390/nu14091882.

Tian, P., Chen, Y., Zhu, H., Wang, L., Qian, X., Zou, R., Zhao, J., Zhang, H., Qian, L., Wang, Q., Wang, G., Chen, W., 2022. Bifidobacterium breve CCFM1025 attenuates major depression disorder via regulating gut microbiome and tryptophan metabolism: a randomized clinical trial. Brain Behav. Immun. 100, 233–241. https://doi.org/10.1016/j.bbi.2021.11.023.

Tian, P., O'Riordan, K.J., Lee, Y.-K., Wang, G., Zhao, J., Zhang, H., Cryan, J.F., Chen, W., 2020a. Towards a psychobiotic therapy for depression: bifidobacterium breve CCFM1025 reverses chronic stress-induced depressive symptoms and gut microbial abnormalities in mice. Neurobiol. Stress 12, 100216. https://doi.org/10.1016/j.ynstr.2020.100216.

Tian, P., Wang, G., Zhao, J., Zhang, H., Chen, W., 2019. Bifidobacterium with the role of 5-hydroxytryptophan synthesis regulation alleviates the symptom of depression and related microbiota dysbiosis. J. Nutr. Biochem. 66, 43–51. https://doi.org/10.1016/j.jnutbio.2019.01.007.

Verbanck, M., Chen, C.-Y., Neale, B., Do, R., 2018. Detection of widespread horizontal pleiotropy in causal relationships inferred from mendelian randomization between complex traits and diseases. Nat. Genet. 50, 693–698. https://doi.org/10.1038/s41588-018-0099-7.

Wang, J., Kurilshikov, A., Radjabzadeh, D., Turpin, W., Croitoru, K., Bonder, M.J., Jackson, M.A., Medina-Gomez, C., Frost, F., Homuth, G., Rühlemann, M., Hughes, D., Kim, H., Spector, T.D., Bell, J.T., Steves, C.J., Timpson, N., Franke, A., Wijmenga, C., Meyer, K., Kacprowski, T., Franke, L., Paterson, A.D., Raes, J., Kraaij, R., Zhernakova, A., 2018. Meta-analysis of human genome-microbiome association studies: the MiBioGen consortium initiative. Microbiome 6, 1–7. https://doi.org/10.1186/s40168-018-0479-3.

Wei, Y., Melas, P.A., Wegener, G., Mathé, A.A., Lavebratt, C., 2014. Antidepressant-like effect of sodium butyrate is associated with an increase in TET1 and in 5-hydroxymethylation levels in the Bdnf gene. Int. J. Neuropsychopharmacol. 18, pyu032. https://doi.org/10.1093/ijnp/pyu032.

Westfall, S., Lomis, N., Prakash, S., 2018. A novel polyphenolic prebiotic and probiotic formulation have synergistic effects on the gut microbiota influencing Drosophila melanogaster physiology. Artif. Cells Nanomed. Biotechnol. 46, 441–455. https://doi.org/10.1080/21691401.2018.1458731.

Wray, N.R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.M.F., Bacanu, S.-A., Bækvad-Hansen, M., Beekman, A.F.T., Bigdeli, T.B., Binder, E.B., Blackwood, D.R.H., Bryois, J., Buttenschøn, H.N., Bybjerg-Grauholm, J., Cai, N., Castelao, E., Christensen, J.H., Clarke, T.-K., Coleman, J.I.R., Colodro-Conde, L., Couvy-Duchesne, B., Craddock, N., Crawford, G.E., Crowley, C.A., Dashti, H.S., Davies, G., Deary, I.J., Degenhardt, F., Derks, E.M., Direk, N., Dolan, C.V., Dunn, E.C., Eley, T.C., Eriksson, N., Escott-Price, V., Kiadeh, F.H.F., Finucane, H.K., Forstner, A.J., Frank, J., Gaspar, H.A., Gill, M., Giusti-Rodríguez, P., Goes, F.S., Gordon, S.D., Grove, J., Hall, L.S., Hannon, E., Hansen, C.S., Hansen, T.F., Herms, S., Hickie, I.B., Hoffmann, P., Homuth, G., Horn, C., Hottenga, J.-J., Hougaard, D.M., Hu, M., Hyde, C.L., Ising, M., Jansen, R., Jin, F., Jorgenson, E., Knowles, J.A., Kohane, I.S., Kraft, J., Kretzschmar, W.W., Krogh, J., Kutalik, Z., Lane, J.M., Li, Yihan, Li, Yun, Lind, P.A., Liu, X., Lu, L., MacIntyre, D.J., MacKinnon, D.F., Maier, R.M., Maier, W., Marchini, J., Mbarek, H., McGrath, P., McGuffin, P., Medland, S.E., Mehta, D., Middeldorp, C.M., Mihailov, E., Milaneschi, Y., Milani, L., Mill, J., Mondimore, F.M., Montgomery, G.W., Mostafavi, S., Mullins, N., Nauck, M., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H., Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E., Peyrot, W.J., Pistis, G., Posthuma, D., Purcell, S.M., Quiroz, J.A., Qvist, P., Rice, J.P., Riley, B.P., Rivera, M., Saeed Mirza, S., Saxena, R., Schoevers, R., Schulte, E.C., Shen, L., Shi, J., Shyn, S.I., Sigurdsson, E., Sinnamon, G.B.C., Smit, J.H., Smith, D.J., Stefansson, H., Steinberg, S., Stockmeier, C.A., Streit, F., Strohmaier, J., Tansey, K.E., Teismann, H., Teumer, A., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Tian, C., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D., Van der Auwera, S., van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T., Weinsheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., eQTLGen, 23andMe, Arolt, V., Baune, B.T., Berger, K., Boomsma, D.I., Cichon, S., Dannlowski, U., de Geus, E.C.J., DePaulo, J.R., Domenici, E., Domschke, K., Esko, T., Grabe, H.J., Hamilton, S.P., Hayward, C., Heath, A.C., Hinds, D.A., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.F.A., Magnusson, P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., Müller-Myhsok, B., Nordentoft, M., Nöthen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Penninx, B.W.J.H., Perlis, R.H., Porteous, D.J., Potash, J.B., Preisig, M., Rietschel, M., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Völzke, H., Weissman, M.M., Werge, T., Winslow, A.R., Lewis, C.M., Levinson, D.F., Breen, G., Børglum, A.D., Sullivan, P.F., Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, 2018. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nat. Genet. 50, 668–681. https://doi.org/10.1038/s41588-018-0090-3.

Yang, C., Fujita, Y., Ren, Q., Ma, M., Dong, C., Hashimoto, K., 2017. Bifidobacterium in the gut microbiota confer resilience to chronic social defeat stress in mice. Sci. Rep. 7, 45942. https://doi.org/10.1038/srep45942.

Zhao, H., Jin, K., Jiang, C., Pan, F., Wu, J., Luan, H., Zhao, Z., Chen, J., Mou, T., Wang, Z., Lu, J., Lu, S., Hu, S., Xu, Y., Huang, M., 2022. A pilot exploration of multi-omics research of gut microbiome in major depressive disorders. Transl. Psychiatry 12, 8. https://doi.org/10.1038/s41398-021-01769-x.

Zhao, Z.-X., Fu, J., Ma, S.-R., Peng, R., Yu, J.-B., Cong, L., Pan, L.-B., Zhang, Z.-G., Tian, H., Che, C.-T., Wang, Y., Jiang, J.-D., 2018. Gut-brain axis metabolic pathway regulates antidepressant efficacy of albiflorin. Theranostics 8, 5945–5959. https://doi.org/10.7150/thno.28068.

Zheng, P., Zeng, B., Zhou, C., Liu, M., Fang, Z., Xu, X., Zeng, L., Chen, J., Fan, S., Du, X., Zhang, X., Yang, D., Yang, Y., Meng, H., Li, W., Melgiri, N.D., Licinio, J., Wei, H., Xie, P., 2016. Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol. Psychiatry 21, 786–796. https://doi.org/10.1038/mp.2016.44.

Zhu, J., Li, M., Shao, D., Ma, S., Wei, W., 2021. Altered fecal microbiota signatures in patients with anxiety and depression in the gastrointestinal cancer screening: a case-control study. Front. Psychiatry 12, 757139. https://doi.org/10.3389/fpsyt.2021.757139.