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Breakfast skipping is linked to a higher risk of major depressive disorder and the role of gut microbes: a mendelian randomization study

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Abstract

Background Observational studies have indicated that breakfast skipping and gut microbiome dysbiosis are associated with a higher risk of major depressive disorder (MDD). However, it remains unknown whether the alteration of gut microbes is implicated in the associations between breakfast skipping and MDD.

Methods Leveraging genome-wide association studies (GWAS) on breakfast skipping, gut microbes, and MDD, we conducted a two-step Mendelian randomization (MR) study to determine the causal associations between breakfast skipping (*N* = 193,860) and MDD (*N* = 1,815,091), and evaluate the role of gut microbes (*N* = 18,340). Genetic variants with a P-value less than 5E-08 were selected as instrumental variables (IVs). The false discovery rate (FDR) method was employed to correct the P-values for multiple tests in gut microbes.

Results Breakfast skipping was associated with an increased risk of MDD (odds ratio [OR] = 1.36, 95%CI = 1.12–1.65, *P* = 0.002), but no effect of MDD on breakfast skipping was observed (β per doubling odds of MDD =-0.001, 95%CI=-0.024 to 0.023, *P* = 0.957). After adjusting for multiple comparisons, the MR analysis provided little evidence for an association between breakfast skipping and the abundance of any gut microbes (P_{FDR}>0.05). Among the 21 gut microbes with IVs available, only the abundance of Class Actinobacteria was causally associated with a reduced risk of MDD (OR = 0.85, 95%CI = 0.75–0.97, P_{FDR}=0.015).

Conclusions Our findings demonstrated that breakfast skipping was associated with an increased risk of MDD, but provided little evidence supporting the role of the abundance of gut microbes in it. Further efforts with a large sample size are warranted to clarify the findings.

Keywords Breakfast skipping, Microbiome, Major depressive disorder, Mendelian randomization

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Introduction

Major depressive disorder (MDD) is a prevalent mental health condition that affects a substantial portion of the global population [1, 2]. It causes pain for the individual, lowers quality of life, and places a heavy strain on healthcare systems [3]. Thus, identifying the risk factors and underlying mechanisms contributing to the development of MDD is crucial for effective prevention of MDD. Dietary behaviors have been identified as modifiable factors that influence gut microbial composition and subsequently impact mental health [4]. One prevalent dietary behavior of interest is breakfast skipping, characterized by omitting the morning meal [5]. Breakfast skipping has been associated with an increased risk of MDD [6–8], but the underlying mechanisms linking breakfast skipping to MDD risk remain poorly understood.

In recent years, there has been a growing recognition of the bidirectional communication between the gut microbiota and the brain, known as the gut-brain axis [9, 10]. The gut microbiota, a diverse community of microorganisms residing in the gastrointestinal tract, has been implicated in various aspects of mental health [11, 12]. It is reported that alterations in gut microbial composition have been associated with the susceptibility to MDD [13–15]. Previous studies showed that gut microbes were able to influence various physiological processes, including neurotransmitter production, immune response, and inflammation, all of which are implicated in the development and progression of MDD [16, 17]. Given that dietary behavior plays a vital role in regulating gut microbiota composition, we hypothesize that gut microbes may mediate the relationship between breakfast skipping and MDD risk. Therefore, investigating the role of gut microbial composition in linking breakfast skipping and MDD risk is of great interest, which will contribute to the understanding of the mechanisms underlying the association between dietary behaviors, gut microbes, and mental health outcomes.

To explore the above hypothesis, we employed a Mendelian randomization (MR) study design, which allows for causal inference by leveraging genetic variants as instrumental variables (IVs) [18]. The use of MR reduces confounding and reverse causation biases that commonly occur in observational studies [18]. By utilizing IVs associated with breakfast skipping, gut microbes, and MDD, we aimed to evaluate the causal effect of breakfast skipping on MDD risk and explore the role of gut microbial composition in it.

Methods

Study design and data collection

This study employed a MR design to investigate the causal relationship between breakfast skipping, gut microbial composition, and the risk of MDD in the European population. The MR analysis adhered to the STROBE-MR guideline for the MR study (Additional file 1) [19, 20]. MR utilizes genetic variants randomly allocated to offspring as IVs to estimate the causal effect of an exposure on an outcome, minimizing biases introduced by confounding and reverse causation [18]. Summary-level data on breakfast skipping, MDD, and gut microbial abundance were obtained from the latest published large-scale population-based genome-wide association studies (GWAS) (Additional file 2: Table S1). The summary statistics of breakfast skipping frequency were from the latest GWAS based on the UK Biobank participants of European descent (N=193,860) [21]. Breakfast skipping was assessed using self-report questionnaires according to their reported frequency of breakfast cereal consumption through the use of the Oxford WebQ, a web-based 24-hour diet recall [21]. Briefly, participants were asked if they ate any breakfast cereal the previous day. Responses were categorized as "breakfast skipping" if always "No", "sometimes breakfast skipping" if sometimes "Yes", and "breakfast consumers" if always "Yes". Summary-level data on MDD was from the latest GWAS meta-analysis by the Psychiatric Genomics Consortium (PGC) with up to 1,815,091 individuals of multiple ancestries [22]. The diagnosis of MDD was determined using the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria. For gut microbiome composition, the summary statistics were from the GWAS meta-analysis on 24 cohorts by MiBioGen consortium with 18,340 individuals of multiple ancestries with 13,266 Europeans [23]. Gut microbial abundance was assessed through the collection and analysis of fecal samples via sequencing of microbial 16 S rRNA regions [23].

Genetic instrumentation selection

Single nucleotide polymorphisms (SNPs) associated with breakfast skipping, MDD, and gut microbes were identified from GWAS and used as IVs in this MR analysis. As we previously described [24], three assumptions should be fulfilled for the selected IVs (Fig. 1): (1) IVs are associated with breakfast skipping, MDD, and gut microbes (P<5E-08) (Relevance assumption); (2) there are no common causes or confounders of the IVs and outcome (Independence assumption); (3) IVs are not associated with outcome independent of the exposure (Exclusivity assumption). Additionally, to achieve a sufficient number of IVs for gut microbes, we also set the threshold to 5E-06 for selecting IVs associated with gut microbes as a complementary sensitivity analysis. IVs were clumped according to the 1000 Genomes Project linkage disequilibrium (LD) structure (r^2<0.01 within 1000 kb, European). Moreover, an SNP absent in corresponding GWAS summary statistics would be replaced with an overlapping proxy SNP in LD (r^2=0.8). Finally, the Steiger

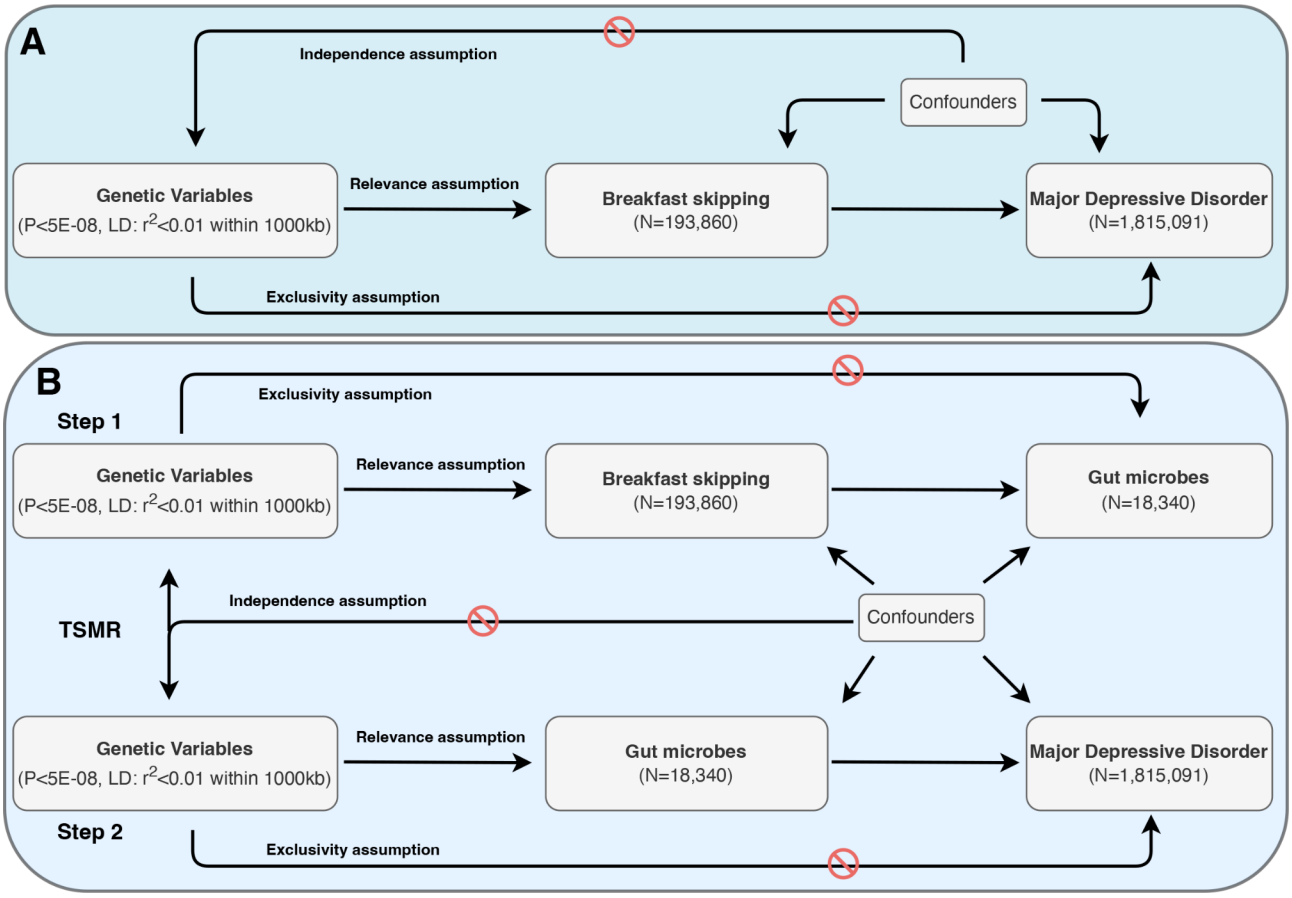

Fig. 1 The flowchart for this Mendelian randomization analysis. Two-sample Mendelian randomization (MR) analysis assesses the effect of breakfast skipping on MDD (**A**). Two-step Mendelian randomization (TSMR) evaluates the effect of breakfast skipping on gut microbes (Step 1) and the effect of gut microbes on major depressive disorder (MDD) (Step 2) (**B**). Red signs mean that genetic variants are not associated with confounders and outcomes. LD, linkage disequilibrium

filtering test was also conducted to identify the SNPs explaining more variance in the outcome than the exposure, which were removed from the IVs. The F-statistic was calculated for each SNP, with values less than 10 indicating weak instrumentality. Meanwhile, palindromic SNPs with intermediate allele frequencies were removed during the harmonization stage. Detailed information on the IVs corresponding to each exposure (breakfast skipping, MDD, and gut microbes) is provided in Additional file 2: Table S2.

Mendelian randomization analysis

The MR analysis was conducted to estimate the causal effect of breakfast skipping on the risk of MDD and evaluate the potential role of gut microbial composition. We performed a two-step MR (TSMR) analysis as follows: (1) estimation of the associations between breakfast skipping and MDD using bidirectional MR; (2) estimation of the causal effect of breakfast skipping on gut microbes; (3) estimation of the associations between gut microbes and MDD (Fig. 1). The inverse variance weighted (IVW) or Wald ratio method was used as the main analytical approach to assess the causal estimates. The effect size, including odd ratio (OR) for binary outcome (MDD) and β coefficients for continuous outcome (gut microbes and breakfast skipping), represented the change in the outcome per standard deviation (SD) or unit increase in the corresponding exposure. As described previously [25], to interpret the findings from the binary exposure (MDD), the original MR estimates were multiplied by 0.693 ($\log_e 2$) to represent the change in breakfast skipping per doubling of the odds of MDD. To evaluate the robustness of the estimates, we conducted various sensitivity analyses using other methods, including MR-Egger, weighted median, and weight mode. Leave-one-out analysis was performed to evaluate the robustness of MR results by sequentially removing one SNP at a time. MR-Pleiotropy RESidual Sum and Outlier (MR-PRESSO) test and MR-Egger intercept test were employed to identify the outliers and evaluate the potential pleiotropic effects of the IVs [26, 27]. The Cochran Q test was performed to assess the heterogeneity. Additionally, since datasets for

both breakfast skipping and MDD had samples from the UK Biobank, there was the possibility of sample overlap between breakfast skipping and MDD, which may raise the risk of overfitting bias [28, 29]. Thus, we also used the MR for causal inference accounting for pleiotropy and sample structure (MR-APSS) approach [30], which took sample overlap and population structure into consideration in two-sample MR analysis, to re-estimate the causal effect of breakfast skipping on MDD. The Mendelian randomization analysis was conducted using the TwoSampleMR package (version 0.5.7) and MR-APSS (version 0.0.0.9) in R software (version 4.3.2) [31]. To account for multiple comparisons in gut microbes, the false discovery rate (FDR) method was utilized to adjust the P-values for each taxonomic level.

Results

Using the P-value threshold of 5E-08, there were six IVs available for breakfast skipping as exposure. Using the IVW method, higher breakfast skipping frequency was associated with an increased risk of MDD (odds ratio [OR] per unit increase=1.36, 95%CI=1.12–1.65, *P*=0.002). Similar results with the same trend were obtained using other approaches (Fig. 2A), but little evidence for a causal effect of MDD on breakfast skipping was observed (β per doubling odds of MDD=-0.001, 95%CI=-0.024 to 0.023, *P*=0.957) (Fig. 2B), as illustrated in the scatter plot (Fig. 3A, B). Leave-one-out analysis showed that no single SNP was driving the estimated bias between breakfast skipping and MDD (Fig. 3C, D). There were no heterogeneity, pleiotropy, and outliers observed in the Cochran Q test, MR-Egger intercept, and MR-PRESSO RSSobs test between breakfast skipping and MDD, but heterogeneity and outliers were found between MDD and breakfast skipping (Table 1). The MR-PRESSO test consistently showed that there was little evidence for a causal effect of MDD on breakfast skipping after correcting outliers (β per doubling odds of MDD=0.005, 95%CI=-0.017 to 0.028, *P*=0.629). Due to potential sample overlap (UK Biobank) between breakfast skipping and MDD, we used the MR-APSS approach to re-estimate the causal effect of breakfast skipping on MDD, showing that breakfast skipping remained associated with an increased risk of MDD (OR per unit increase=1.16, 95%CI=1.09–1.23, *P*=0.012). However, the MR-APSS result was attenuated compared to the main finding using the IVW approach.

For the associations between breakfast skipping and gut microbes, our data showed that breakfast skipping was not associated with the abundance of any gut microbes after adjusting for multiple tests (P_{FDR}>0.05). The gut microbes with raw P-value less than 0.1 for MR estimates were Phylum *Verrucomicrobia* (β=0.87, 95%CI=-0.04-1.78, P_{raw}=0.061), Class *Negativicutes* (β=0.58, 95%CI=-0.003 to 1.17, P_{raw}=0.051), Order *Selenomonadales* (β=0.58, 95%CI=-0.003 to 1.17, P_{raw}=0.051), Genus *ErysipelotrichaceaeUCG003* (β=-0.71, 95%CI=-1.36 to -0.06, P_{raw}=0.031), and Genus *RuminococcaceaeUCG004* (β=0.67, 95%CI=-0.07 to 1.42, *P*=0.076) (Fig. 4A). Full details on the causal estimates between breakfast skipping and all gut microbes with different approaches were presented in Additional file 2: Table S3. There were no heterogeneity, pleiotropy, and outliers observed in the Cochran Q test, MR-Egger intercept, and MR-PRESSO

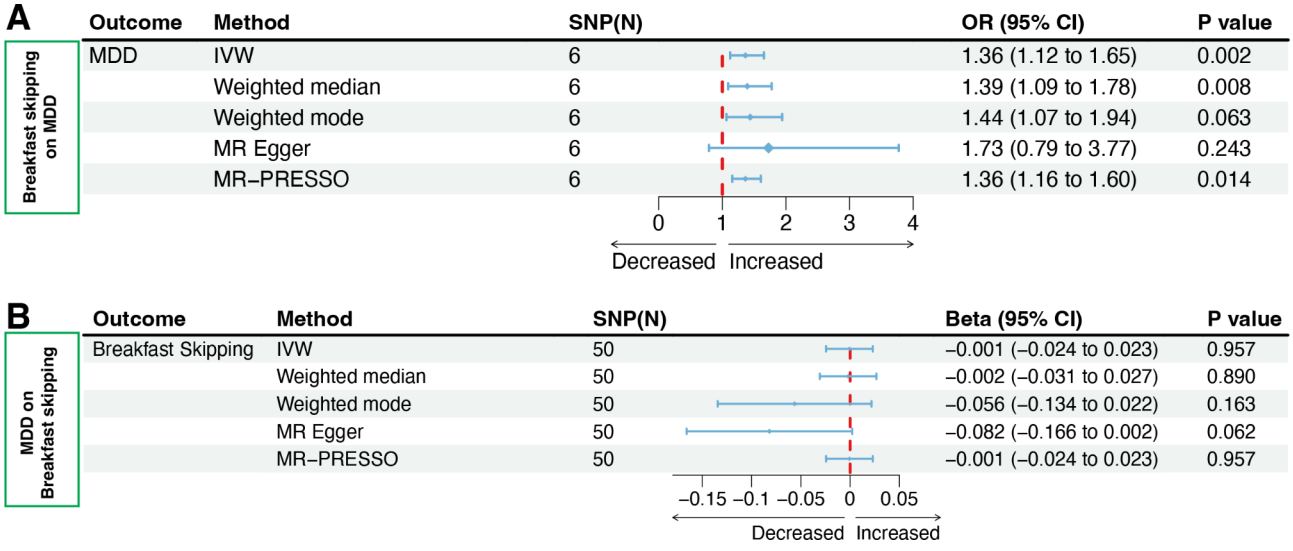

Fig. 2 Bi-directional Mendelian randomization analysis between breakfast skipping and major depressive disorder. Using a P-value threshold of 5E-08, genetic predisposition to higher breakfast skipping frequency was associated with an increased major depressive disorder (MDD) (**A**). OR represented the risk change of MDD per unit increase in breakfast skipping. However, MDD was not linked with the susceptibility to breakfast skipping (**B**). Beta (β) coefficients represented the change in breakfast skipping per doubling odds of MDD. SNP, single nucleotide polymorphism; N, number

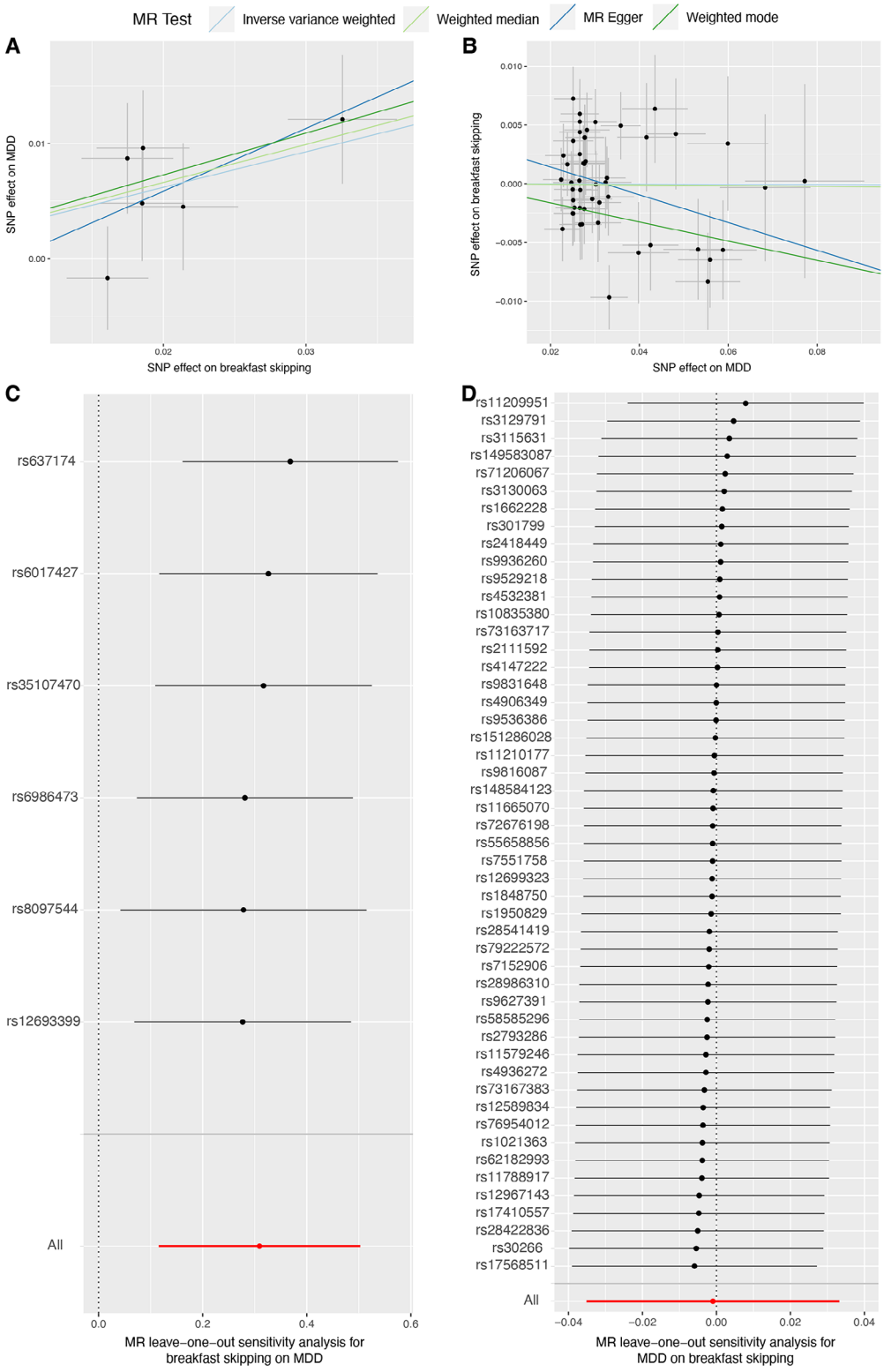

Fig. 3 Scatter plots and leave-one-out plots for Mendelian randomization analysis between breakfast skipping and major depressive disorder. Bi-directional Mendelian randomization (MR) analysis using IVW, weighted median, weighted mode, and MR–Egger to evaluate the causal relationship between breakfast skipping and MDD. **A** showed the SNPs' effect on breakfast skipping and major depressive disorder (MDD). **B** showed the SNPs' effect on MDD and breakfast skipping. Leave-one-out analysis plots for breakfast skipping on MDD (**C**) and MDD on breakfast skipping (**D**). SNP, single nucleotide polymorphism; IVW, inverse-variance weighted; MR, Mendelian randomization

Table 1 Pleiotropy and heterogeneity analysis for breakfast skipping and major depressive disorder

Exposure	Outcome	SNP (*N*)	Cochran Q (*P*)		Intercept-Egger (*P*)	MR-PRESSO RSSobs (*P*)
			MR-Egger	IVW		
Breakfast skipping	Major depressive disorder	6	3.20 (0.524)	3.58 (0.611)	-0.005 (0.573)	4.83 (0.647)
Major depressive disorder	Breakfast skipping	50	68.67 (0.027)	74.22 (0.012)	0.004 (0.054)	77.74 (0.012)

Note MR_PRESSO, Mendelian Randomization Pleiotropy RESidual Sum and Outlier; SNP, single nucleotide polymorphism; P, P value; N, number

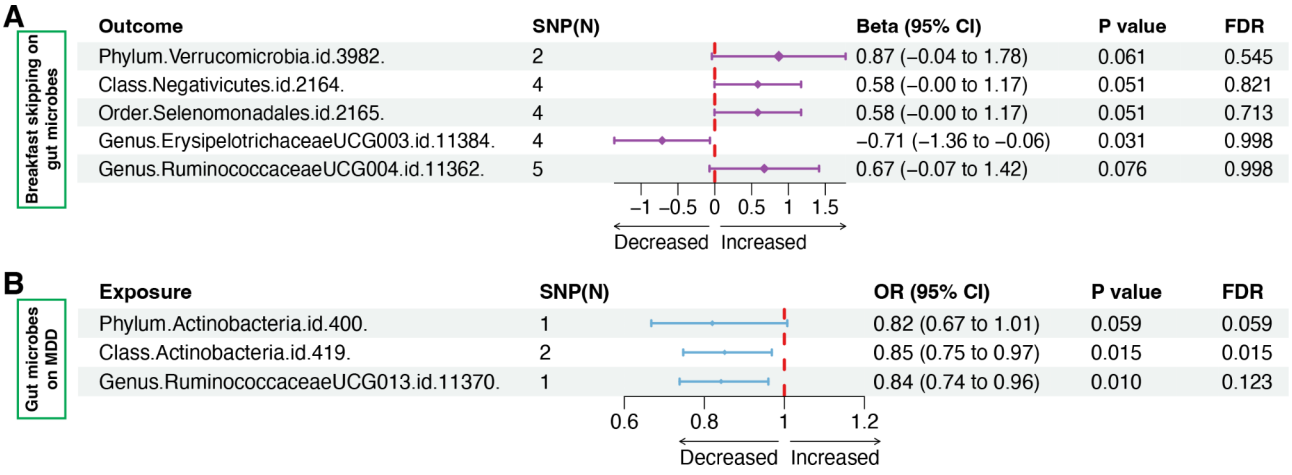

Fig. 4 Causal effects of breakfast skipping on gut microbe and gut microbes on major depressive disorder. **A** showed the causal effect of breakfast skipping on the abundance of five gut microbes with a P value less than 0.1. Beta (β) coefficients represented the change in gut microbes per unit increase in breakfast skipping. **B** showed the causal effect of the abundance of 3 gut microbes on the risk of major depressive disorder (MDD) with a P value less than 0.1. OR represented the risk change of MDD per standard deviation (SD) increase in corresponding gut microbes. SNP, single nucleotide polymorphism; OR, odds ratio; FDR, false discovery rate; N, number

RSSobs test between breakfast skipping and gut microbes (Additional file 2: Table S4).

For the associations between gut microbes and MDD, there were 21 gut microbes with IVs available passing the genome-wide threshold (P<5E-08). Among them, only bacteria within Class *Actinobacteria* were associated with a decreased risk of MDD (OR per SD increase=0.85, 95%CI=0.75–0.97, P_{FDR}=0.015) (Fig. 4B). There were two other gut microbes, including Phylum *Actinobacteria* (OR per SD increase=0.82, 95%CI=0.67–1.01, P_{raw}=0.059) and Genus *RuminococcaceaeUCG013* (OR per SD increase=0.84, 95%CI=0.74–0.96, P_{raw}=0.010), with a raw P-value less than 0.1 for MR estimates (Fig. 4B). Completed information on the causal estimates between all gut microbes and MDD was provided in Additional file 2: Table S5. Due to having less than four IVs available for each gut microbe, the MR-PRESSO RSSobs test and MR-Egger intercept test were not performed (Additional file 2: Table S6). Except for Class *Actinobacteria*, there was potential heterogeneity observed in the Cochran Q test (Additional file 2: Table S6). The sensitivity MR analysis using P<5E-06 as the threshold showed that none of the 21 gut microbes were associated with the risk of MDD (Additional file 3: Figure S1).

Discussion

The relationship between either breakfast skipping or gut microbes and MDD has been widely explored, but the interactive effect of breakfast skipping and gut microbes on MDD remained largely unknown. The present MR study showed that breakfast skipping was associated with an increased risk of MDD, but did not find a potential role of gut microbes in it.

Numerous observational studies have indicated that breakfast skipping was associated with depressive symptoms and a higher risk of mood disorders [7, 32–35]. Consistently, an MR investigation by Dashti et al. showed that breakfast skipping was causally associated with depressive symptoms, such as frequent feelings of disinterest and depression/hopelessness experienced in the past two weeks [21, 36]. MDD, on the other hand, is a clinical diagnosis characterized by a persistent and severe form of depression, typically involving more than five depressive symptoms that cause significant distress or impairment, lasting for at least two weeks [22]. However, the causal association between breakfast skipping and MDD was not well determined. Moreover, since patients with MDD might had lower appetite for food intake, it remained unknown whether the association between breakfast skipping on MDD resulted from reverse causation [37, 38]. Our bidirectional MR analysis demonstrated a causal effect of breakfast skipping on the risk of

MDD, but not MDD on breakfast skipping. These findings indicate the impact of breakfast skipping on MDD was not due to reverse causation and eating breakfast could reduce the risk of MDD.

Our MR study showed that breakfast skipping was not associated with the abundance of gut microbes after adjustment of multiple comparisons. However, it is worth noting that the results of this MR study showed that breakfast skipping was potentially linked to a reduced abundance of Genus *ErysipelotrichaceaeUCG003* (Praw = 0.031), which belongs to the Family *Erysipelotrichaceae*. Previous studies have indicated that Family *Erysipelotrichaceae* was implicated in gastrointestinal inflammation-related disorders, such as inflammatory bowel diseases (IBD) and dysbiosis [39], which was tightly associated with the risk of depression [40, 41]. However, due to no IVs available for Genus *ErysipelotrichaceaeUCG003*, we could not determine its causal effect on the risk of MDD in this MR study. Future studies should focus on longitudinal investigations and experimental models to establish causal relationships between them.

The results of this MR study showed that Class *Actinobacteria* was the only one causally associated with a decreased risk of MDD, which was consistent with the findings from a previous MR study using a different GWAS dataset on MDD [14]. Indeed, a recent cross-sectional study indicated that the abundance of Class *Actinobacteria* was negatively associated with the severity of depression [42]. Although there was little evidence for a causal effect of breakfast skipping on Class *Actinobacteria*, the MR estimates showed that breakfast skipping was linked to a reduced abundance of Class *Actinobacteria*. These findings suggest that Class *Actinobacteria* might be also implicated in the impact of breakfast skipping on MDD. Thus, further gut microbiome GWAS with larger sample sizes are encouraged to validate the effect of Class *Actinobacteria* and Genus *ErysipelotrichaceaeUCG003* on MDD and delineate the specific mechanisms by which they might contribute to the effect of breakfast skipping on MDD pathophysiology.

Some potential limitations should be addressed here. First, there were only 211 gut microbes at different taxonomy levels with summary-level data available in the GWAS from the MiBioGen consortium, we are not able to investigate the causal effect of breakfast skipping on other gut microbes. Second, since only 21 gut microbes with IVs passed a genome-wide P-value threshold ($P < 5e\text{-}08$), the role of other gut microbes in MDD was not analyzed in this MR study. Studies with larger sample sizes are warranted to further determine the association between gut microbes and MDD. Third, the results of sensitivity analysis using a lenient P-value threshold of 5E-06 for gut microbes did not replicate the findings in the main analysis using 5E-08 as the threshold. The potential reasons contributed to the above inconsistent findings might be due to the violation of the relevance and exclusivity assumption for the MR study when using $P < 5E\text{-}06$ as the threshold. Fourth, there might be sample overlapping between breakfast skipping and MDD. Despite the results from the MR-APSS approach consistently showing that breakfast skipping was associated with an increased risk of MDD, we could not fully exclude the risk of overfitting bias due to the sample overlapping. Fifth, it is worth noting that breakfast skipping defined in the original GWAS by Dashti et al. primarily captured the behavior of skipping breakfast cereal. Since breakfast cereal consumption is not a common practice across cultures, relying on this proxy may introduce bias and limit the generalizability of the findings to diverse populations. Finally, since the findings of this MR study are based on samples from multiple ancestries for gut microbes and MDD, the genetic differences between populations might lead to population stratification and heterogeneous associations, which might confound the results. Thus, it still needs to further validate the above association in specific racial groups.

In conclusion, the present MR investigation shows that breakfast skipping causally increases the risk of MDD. However, combining the current GWAS data on human gut microbiome, our findings do not observe a potential role of intestinal microbes in the impact of breakfast skipping on the susceptibility to MDD. Further research with larger sample sizes is warranted to validate the role of gut microbes in linking breakfast skipping and MDD.

Abbreviations

DSM	Diagnostic and Statistical Manual of Mental Disorders
FDR	False Discovery Rate
GWAS	Genome-Wide Association Studies
IBD	Inflammatory Bowel Diseases
IVW	Inverse Variance Weighted
IVs	Instrumental Variables
LD	Linkage Disequilibrium
MDD	Major Depressive Disorder
METTL4	Methyltransferase Like 4
MR	Mendelian Randomization
MR-PRESSO	MR-Pleiotropy RESidual Sum and Outlier
OR	Odds Ratio
PGC	Psychiatric Genomics Consortium
SNPs	Single Nucleotide Polymorphisms
TSMR	Two-step Mendelian Randomization

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

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Author contributions
XG, WL, and RL conceived and designed the study. XG, WL, and CH collected and analyzed the data. XG and WL drafted the manuscript. RL revised the manuscript. All authors reviewed and approved the final manuscript.

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Data availability
The GWAS summary statistics data of breakfast skipping, gut microbes, and major depressive disorder used in this study are all publicly available. All R scripts used in the MR analysis are available from the authors upon request.

Declarations

Ethical approval
There were no patients directly involved in the overall process of our study. This study was performed based on publicly available data and no ethical approval was required.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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