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Causal relationship between gut microbiota and metabolic syndrome

A bidirectional Mendelian randomization study

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Abstract

Metabolic syndromes (MetS) are complex metabolic disorders, the pathogenesis of which has not been fully elucidated. In recent years, the association between the gut microbiota and MetS has attracted widespread attention, but the causal relationship remains unclear. We performed a 2-sample Mendelian randomization analysis (MR) to examine whether the gut microbiota is causally related to MetS and its components to find a basis for potential diagnostic or intervention approaches for MetS. We utilized summary statistics from whole-genome association analyses of gut microbiota from the MiBioGen consortium and obtained MetS-related data from the UK Biobank, IEU Open GWAS project, and The Meta-Analyses of Glucose and Insulin-related traits Consortium (MAGIC). MR analyses were performed using inverse variance weighted, MR-Egger, and weighted median. Sensitivity analyses were conducted to verify the robustness of the results. Among the 211 gut microbiota, we identified 8 that were significantly associated with the risk of MetS. Specifically, Lachnospiraceae (family), Veillonellaceae (family), Victivallaceae (family), Odoribacter (genus), and Olsenella (genus) may increase the risk of MetS, while Bifidobacteriaceae (family), Ruminococcaceae UCG-010 (genus), Actinobacteria (phylum) may decrease the risk of MetS. Additionally, we discovered that multiple microbiota are associated with various components of MetS, such as BMI, hypertension, and blood lipid levels. This study is the first to use MR methods to reveal the potential causal relationship between specific gut microbiota and MetS, providing a new perspective for understanding the pathogenesis of MetS, and offering important evidence for the development of gut microbiota-based prevention and treatment strategies for MetS.

Abbreviations: BMI = body mass index, CI = confidence interval, FBG = fasting blood glucose, GLP-1 = glucagon-like peptide-1, GWAS = genome-wide association studies, HDL-C = high-density lipoprotein cholesterol, IVs = instrumental variables, IVW = inverse variance weighted analysis, MAGIC = the meta-analyses of glucose and insulin-related traits consortium, MetS = metabolic syndromes, MR = Mendelian randomization analysis, MR-PRESSO = MR pleiotropy residual sum and outlier test, MRC-IEU = MRC integrative epidemiology unit, OR = odds ratio, SNP = single nucleotide polymorphism, TG = triglyceride, WM = weighted median.

Keywords: causal inference, gut microbiota, Mendelian randomization, metabolic syndrome, microbiome.

1. Introduction

MetS is a cluster of metabolic abnormalities primarily characterized by central obesity, hypertension, and dyslipidemia.[1,2] MetS not only significantly increases the risk of type 2 diabetes, cardiovascular diseases, and certain types of cancer but is also closely associated with higher mortality rates.[3,4] Statistics show that approximately 1-quarter of adults worldwide suffer from MetS, and in some developed and developing countries, this proportion even reaches 20% to 30%. More alarmingly, MetS is showing a trend towards younger populations, which undoubtedly puts immense pressure on the global public health system.[5,6] Therefore, gaining a deep understanding of the pathogenesis of MetS and finding effective early intervention strategies haves become focal points of current medical research.

In recent years, the relationship between gut microbiota and human health has attracted widespread attention. As the "second genome" of the human body, the gut microbiota plays a key role in the host's physiological metabolism, immune regulation, and the occurrence and development of diseases.[7–9]

The authors have no funding and conflicts of interest to disclose.

The datasets generated during and/or analyzed during the current study are publicly available.

As this study constitutes a secondary analysis of previously published data, it does not necessitate ethical approval. All the original studies incorporated into this research had received ethical approval.

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A growing body of evidence suggests a close link between gut microbiota and MetS.[10–12] Studies have found that the composition and diversity of the gut microbiota in patients with MetS are significantly different from those in healthy individuals, and the degree of gut microbiota dysbiosis is positively correlated with the severity of MetS.[13,14] Animal experiments further confirmed that transplanting the gut microbiota from conventional mice into germ-free mice can improve their metabolic status, while transplanting the gut microbiota from patients with MetS can cause mice to exhibit symptoms similar to MetS.[15,16]

Although these studies have provided important clues for understanding the relationship between gut microbiota and MetS, most are based on observational studies or animal experiments, which struggle to eliminate the influence of confounding factors and cannot determine the causal relationship between the 2. Traditional randomized controlled trials can address this issue, but they often face challenges in implementation such as high costs, long cycles, and difficulty in control.[17] Therefore, there is an urgent need for a more efficient and accurate research method to explore the causal relationship between gut microbiota and MetS.

Mendelian Randomization (MR) is a causal inference method based on genetic variation that has emerged recentiy years.[18] MR uses genetic variants associated with exposure factors as instrumental variables (IV), which can largely avoid the influence of confounding factors and reverse causality, and is hailed as the "natural randomized controlled trial."[19] With the accumulation of GWAS data, the MR method is playing an increasingly important role in etiological research on complex diseases.

Based on the above background, this study aimed to use the latest large-scale gut microbiota GWAS data and GWAS data of MetS and its components to explore the causal relationship between gut microbiota and MetS through 2-sample MR analysis. Our research hypothesis was that specific gut microbiota may affect the risk of MetS occurrence by influencing host metabolism. Through this study, we aimed to: 1) identify specific gut microbiota significantly associated with the risk of MetS; 2) explore the potential causal relationships between these microbiota and various components of MetS (such as BMI, blood pressure, and blood lipids); and 3) provide a scientific basis for the development of gut microbiota-based prevention and treatment strategies for MetS. This study will not only help to deepen our understanding of the interaction between gut microbiota and host metabolism, but also open up new avenues for the precise prevention and personalized treatment of MetS, which has important theoretical significance and potential clinical application value.

2. Materials and methods

2.1. Study design

This study aimed to comprehensively assess the causal relationship between the gut microbiota and MetS and its components

Table 1

Detailed information on genome-wide association studies data for metabolic syndrome and its components.

Exposure	PMID	Sample size	Sources	Website
MetS	31589552	291,107	UK Biobank	http://www.nealelab.is/uk-biobank
FBG	34059833	281,461	MAGIC	https://magicinvestigators.org/
Hypertension	34017140	407,746	MRC-IEU	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90013916/
BMI	35534559	99,998	MRC-IEU	https://gwas.mrcieu.ac.uk/datasets/ieu-b-4816/
HDL-C	35213538	115,082	MRC-IEU	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092822/
TG	35213538	115,082	MRC-IEU	https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90092992/

BMI = body mass index, FBG = fasting blood glucose, HDL-C = high-density lipoprotein cholesterol, MAGIC = the meta-analyses of glucose and insulin-related traits consortium, MetS = metabolic syndromes, MRC-IEU = MRC integrative epidemiology unit, TG = triglyceride.

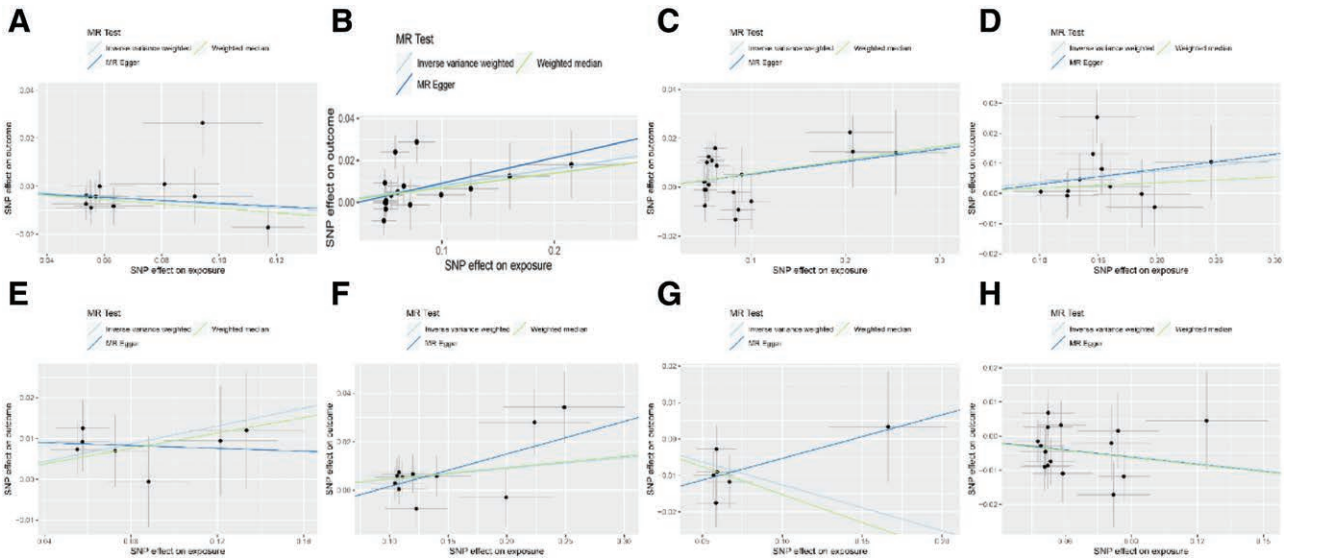

Figure 1. Scatter plot of positive results associated with metabolic syndromes. (A) Scatter plot of genus Bifidobacteriaceae (family); (B) scatter plot of genus Lachnospiraceae (family); (C) scatter plot of genus Veillonellaceae (family); (D) scatter plot of genus Victivallaceae (family); (E) scatter plot of genus Odoribactergenus (genus); (F) scatter plot of genus Olsenella (genus); (G) scatter plot of genus Odoribactergenus (genus); (F) scatter plot of genus Ruminococcaceae UCG-010 (genus); (H) scatter plot of genus Actinobacteria (phylum). MR = Mendelian randomization

using a 2-sample Mendelian Randomization (MR) approach. MR analysis utilizes genetic variants as IV, which can effectively avoid the influence of confounding factors and reverse causality in traditional observational studies. The 2-sample MR design was chosen because it allows us to use exposure (gut microbiota) and outcome (MetS) data from different populations, thereby increasing the sample size and statistical power.

The MR analysis in this study is based on 3 core assumptions: genetic variants are strongly associated with exposure; genetic variants are independent of confounding factors that affect the exposure and outcome; and genetic variants affect the outcome only through the exposure.[17,18] Each bacterial taxon in the gut microbiota is considered an independent exposure factor, with MetS and its components as the outcomes. GWAS summary data were used to conduct MR analysis to determine which bacterial taxa had a causal relationship with MetS.

2.2. Data sources

GWAS summary statistics for the gut microbiota were obtained from the MiBioGen consortium (https://mibiogen.gcc.rug.nl), which is the largest human gut microbiome genetics study to date, including 18,340 participants from 24 cohorts, with 78% being of European descent. We obtained data on 211 gut microbial classifications at 5 taxonomic levels.[19] After excluding 15 unknown bacterial genera and 1 duplicate bacterium, 195 taxa (including 9 phyla, 15 classes, 20 orders, 32 families, and 119 genera) were included in the MR analysis.[20]

The MetS GWAS data were obtained from the UK Biobank (https://www.ukbiobank.ac.uk), which contains whole-genome genotype data from 291,107 individuals.[21] Additionally, we conducted MR analysis for each MetS component. GWAS data for BMI, hypertension, triglycerides (TG), and high-density lipoprotein cholesterol (HDL-C) were obtained using the IEU Open GWAS project data platform, and fasting blood glucose GWAS data were obtained from MAGIC. Detailed information regarding the genetic IV used in this study is presented in Table 1.

2.3. Selection of IV

To ensure the authenticity and accuracy of the causal relationship between the gut microbiota and MetS and its components, we employed stringent inclusion and exclusion criteria to select SNPs closely associated with specific gut microbiota as IVs. For each bacterial taxon, we filtered SNPs through the following steps: Given the limited number of SNPs with genome-wide significance of $P < 5 \times 10^{-8}$, a more lenient genome-wide significance threshold was applied, that is, $P < 1 \times 10^{-5}$[22]; the aggregation distance between 2 SNPs was set to 10,000 kb, and the inter-SNP linkage disequilibrium correlation coefficient r2 threshold was set to 0.001; we calculated the *F*-statistic for each SNP and excluded those with $F < 10$ to avoid weak IV bias, where the formula for the *F*-statistic was $F = (\text{beta/se})^2$, with beta being the allelic effect size and setting the standard error[23]; palindrome SNPs were removed to prevent the impact of alleles on the causal relationship between gut microbial taxa and MetS and its components.

2.4. Statistical analysis

All statistical analyses were conducted using R software (version 4.3.2). We utilized the "Two Sample MR" package (version 0.5.8) within R for MR analysis. In the MR analysis, the effect size of each specific microbial group was evaluated using odds ratio (OR) and 95% confidence interval (95% CI). An OR value >1 indicates a positive correlation between exposure and outcome, indicating that an increase in the exposure factor increases the risk of the outcome. Conversely, when the OR value was < 1, an increase in the exposure factor decreased the risk of the outcome. A statistical significance level of $P < .05$ is considered evidence of a potential causal effect.

The primary analysis method in this study was the random-effects model of inverse variance weighted (IVW). IVW is a meta-analysis technique that combines ratio estimation with inverse variance weighting, ensuring the effectiveness of each IV and accounting for SNP heterogeneity. Therefore, when all the selected genetic variants are valid IVs, IVW provides the most

Table 2

The results on Mendelian randomization analysis of metabolic syndrome and gut microbiota.

Exposure	Method	Beta	SE	OR	*P*-value	95% CI
Bifidobacteriaceae (family)	IVW	−0.075	0.034	0.928	.028	0.868 to 0.992
	MR-Egger	−0.062	0.121	0.741	.621	0.741 to 1.192
	WM	−0.092	0.045	0.912	.040	0.835 to 0.996
Lachnospiraceae (family)	IVW	0.080	0.034	1.083	.017	1.014 to 1.157
	MR-Egger	0.122	0.083	1.130	.163	0.960 to 1.329
	WM	0.069	0.042	1.072	.102	0.986 to 1.165
Veillonellaceae (family)	IVW	0.053	0.025	1.055	.033	1.004 to 1.108
	MR-Egger	0.051	0.056	1.052	.372	0.944 to 1.174
	WM	0.056	0.037	1.057	.132	0.983 to 1.137
Victivallaceae (family)	IVW	0.037	0.018	1.038	.035	1.003 to 1.074
	MR-Egger	0.050	0.077	1.051	.535	0.903 to 1.223
	WM	0.018	0.023	1.018	.441	0.972 to 1.066
Odoribacter (genus)	IVW	0.109	0.045	1.115	.015	1.021 to 1.218
	MR-Egger	−0.018	0.145	0.982	.907	0.740 to 1.304
	WM	0.095	0.057	1.099	.099	0.982 to 1.230
Olsenella (genus)	IVW	0.045	0.019	1.046	.015	1.009 to 1.085
	MR-Egger	0.134	0.070	1.143	.090	0.996 to 1.313
	WM	0.047	0.025	1.048	.061	0.998 to 1.100
Ruminococcaceae UCG-010 (genus)	IVW	−0.126	0.048	0.882	.009	0.803 to 0.969
	MR-Egger	0.119	0.143	1.127	.452	0.851 to 1.492
	WM	−0.153	0.064	0.859	.018	0.757 to 0.974
Actinobacteria (phylum)	IVW	−0.067	0.032	0.935	.037	0.878 to 0.996
	MR-Egger	−0.071	0.128	0.932	.590	0.725 to 1.197
	WM	−0.069	0.043	0.933	.107	0.857 to 1.015

95% CI = 95% confidence interval, IVW = inverse variance weighted analysis, MR = Mendelian randomization, OR = odds ratio, SE = standard error, WM = weighted median.

accurate results.[24,25] Additionally, we employed the MR-Egger analysis and the weighted median (WM) method as robustness checks, complementing the results estimated by the IVW method. WM can provide a valid estimate of the causal relationship when at least 50% of SNPs are valid IVs.[26] When all SNPs are considered invalid IVs, MR-Egger analysis can provide a reliable estimate.[27]

2.5. Sensitivity analysis

To ensure the reliability and robustness of the causal relationship assessment results, we conducted a sensitivity analysies. Cochran *Q* test was used to assess the heterogeneity among the selected SNPs associated with each bacterial taxon, with $P < .05$ indicating significant heterogeneity among IVs. MR-Egger regression and MR-PRESSO analyses were used to test for horizontal pleiotropy among the SNPs included. If the *P*-value of the MR-Egger regression intercept is >.05, horizontal pleiotropy was not considered present. MR-PRESSO identifies and corrects for outliers in the IVs; if outliers are detected, they are removed, and the remaining IVs are re-analyzed to reduce the impact of horizontal pleiotropy on the causal estimates. Leave-one-out analysis was used to assess whether the overall causal effect was influenced by individual SNPs.[28]

3. Results

3.1. IVs from the positive MR analysis

After excluding SNPs in linkage disequilibrium, those with medium allele frequencies, palindrome SNPs, and removing IVs with outlier values, we identified the following strongly associated and independent SNPs from MetS and its components: MetS (96), BMI (92), hypertension (128), HDL-C (119), and TG (114). Notably, we were unable to identify any SNPs that were significantly associated with fasting glucose levels. The *F*-statistics for all IVs were >10, indicating no weak instrument bias.

Table 3

The results on Mendelian randomization analysis of body mass index and gut microbiota.

Exposure	Method	Beta	SE	OR	*P*-value	95% CI
Melainabacteria (class)	IVW	−0.069	0.071	0.933	.334	0.811 to 1.074
	MR-Egger	−0.098	0.207	0.907	.651	0.604 to 1.361
	WM	−0.047	0.092	0.954	.612	0.796 to 1.144
Bacteroidales S24-7 group (family)	IVW	−0.133	0.101	0.876	.188	0.719 to 1.067
	MR-Egger	−0.070	0.395	0.932	.868	0.430 to 2.023
	WM	−0.157	0.123	0.855	.203	0.671 to 1.088
Family XIII (family)	IVW	−0.012	0.16	0.988	.942	0.722 to 1.354
	MR-Egger	−0.489	0.572	0.626	.440	0.204 to 1.922
	WM	0.115	0.167	1.121	.491	0.809 to 1.554
Negativicutes (class)	IVW	0.283	0.137	1.327	.040	1.014 to 1.738
	MR-Egger	0.503	0.446	1.654	.288	0.691 to 3.962
	WM	0.411	0.164	1.508	.012	1.094 to 2.081
Clostridiales vadinBB60 group (family)	IVW	0.157	0.073	1.170	.032	1.013 to 1.350
	MR-Egger	0.497	0.210	1.645	.034	1.089 to 2.483
	WM	0.175	0.100	1.191	.081	0.979 to 1.449
Rikenellaceae (family)	IVW	−0.190	0.096	0.827	.047	0.689 to 0.992
	MR -Egger	−0.329	0.304	0.770	.294	0.397 to 1.306
	WM	−0.261	0.122	0.720	.032	0.607 to 0.978
Allisonella (genus)	IVW	0.160	0.065	1.173	.014	1.033 to 1.332
	MR-Egger	0.161	0.392	1.173	.705	0.544 to 2.531
	WM	0.160	0.079	1.175	.042	1.006 to 1.372
Collinsella (genus)	IVW	−0.356	0.129	0.701	.006	0.544 to 0.903
	MR-Egger	−0.446	0.479	0.493	.394	0.250 to 1.637
	WM	−0.212	0.169	0.118	.208	0.581 to 1.126
Enterorhabdus (genus)	IVW	−0.356	0.129	0.701	.006	0.544 to 0.903
	MR-Egger	−0.446	0.479	0.640	.394	0.250 to 1.637
	WM	−0.212	0.166	0.809	.201	0.584 to 1.119
Lachnospiraceae FCS020 group (genus)	IVW	0.242	0.100	1.274	.015	1.048 to 1.549
	MR-Egger	−0.225	0.224	0.799	.339	0.515 to 1.239
	WM	0.241	0.131	1.272	.065	0.985 to 1.644
Lachnospiraceae UCG-001 (genus)	IVW	0.242	0.100	1.274	.015	1.048 to 1.549
	MR-Egger	−0.225	0.224	0.799	.339	0.515 to 1.239
	WM	0.242	0.131	1.272	.066	0.984 to 1.645
Parabacteroides (genus)	IVW	−0.465	0.170	0.628	.006	0.451 to 0.876
	MR-Egger	−0.818	0.615	0.441	.254	0.132 to 1.473
	WM	−0.530	0.191	0.589	.006	0.405 to 0.856
Rikenellaceae RC9 gut group (genus)	IVW	−0.107	0.053	0.898	.013	0.809 to 1.000
	MR-Egger	−0.140	0.316	0.869	.670	0.468 to 1.616
	WM	−0.094	0.068	0.910	.165	0.796 to 1.040
Burkholderiales (order)	IVW	−0.243	0.113	0.784	.031	0.628 to 0.978
	MR-Egger	0.215	0.384	1.240	.589	0.585 to 2.631
	WM	−0.178	0.153	0.837	.245	0.619 to 1.130
Selenomonadales (order)	IVW	0.283	0.137	1.327	.040	1.014 to 1.738
	MR-Egger	0.503	0.446	1.654	.288	0.691 to 3.962
	WM	0.411	0.157	1.508	.009	1.108 to 2.054

95% CI = 95% confidence interval, IVW = inverse variance weighted analysis, MR = Mendelian randomization, OR = odds ratio, SE = standard error, WM = weighted median.

3.2. MR analysis

3.2.1. MetS and gut microbiota. Through MR analysis using the IVW method, we found that 8 gut microbial groups had a significant causal relationship with MetS ($P < .05$). These groups included 1 phylum, 4 families, and 3 genera (Fig. 1 and Table 2). Groups associated with an increased risk of MetS: Lachnospiraceae (family) (OR = 1.083, 95% C: 1.014–1.157), Veillonellaceae (family) (OR = 1.055, 95% CI: 1.004–1.108), Victivallaceae (family) (OR = 1.038, 95% CI: 1.003–1.074), Odoribacter (genus) (OR = 1.115, 95%C: 1.021–1.218), and Olsenella (genus) (OR = 1.046, 95% CI: 1.009–1.085). Groups were associated with a decreased risk of MetS:Bifidobacteriaceae (family) (OR = 0.928, 95%CI: 0.868–0.992), Ruminococcaceae UCG-010(genus) (OR = 0.882, 95% CI: 0.803–0.969), and Actinobacteria (phylum) (OR = 0.935, 95% CI: 0.878–0.996).

3.2.2. Components and gut microbiota. We further analyzed the causal relationships between the gut microbiota and each MetS component, with the main findings as follows:

BMI: Fifteen gut microbial groups showed significant causal relationships with BMI. Among them, 8 groups such as Melainabacteria (class) and Bacteroidales S2-7 group (family) were negatively correlated with BMI, while 7 groups such as Negativicutes (class) and Clostridiales vadinBB60 group (family) were positively correlated with BMI (Table 3).

Hypertension: Ten gut microbial groups were associated with the risk of hypertension. Seven groups, including Bifidobacteriaceae (family) and Clostridiales vadinBB60 group (family), may reduce the risk of hypertension, while 3 groups, such as Family XIII AD3011 group (genus), may increase the risk of hypertension (Table 4).

HDL-C: Ten gut microbial groups were associated with HDL-C level. Four groups, Melainabacteria (class), were negatively correlated with HDL-C, while 6 groups, such as Eubacterium fissicatena group (genus), were positively correlated with HDL-C (Table 5).

TG: Ten gut microbial groups were associated with TG levels. Five groups such as the Bacteroidales S24-7 group (family), were negatively correlated with TG, while 5 groups, such as Family XIII (family), were positively correlated with TG (Table 6).

Fasting glucose: No direct causal association was found between gut microbiota and fasting glucose levels.

3.2.3. Sensitivity analysis. The results of Cochran's Q test indicated no heterogeneity among all IVs; MR-Egger results showed no evidence of horizontal pleiotropy; the MR-PRESSO global test did not detect any outliers, as seen in Table 7–11; leave-one-out analysis showed that individual SNPs had a small impact on the overall outcome, as seen in Figures 2–6. A series of sensitivity analyses indicated that the results of this study are robust.

3.3. Strategies for gut microbiota to prevent and treat Met S

Based on the above findings, we propose the following intervention strategies to provide scientific evidence for the development of prevention and treatment strategies based on the gut microbiota:

3.3.1. Increasing the abundance of beneficial bacteria. Dietary Intervention: Increasing the intake of foods rich in dietary fiber, such as whole grains, vegetables, fruits, and legumes, can promote the growth of beneficial bacteria (such as Bifidobacteriaceae and Ruminococcaceae UCG-010). Bifidobacteriaceae can ferment dietary fiber to produce

Table 4

The results on Mendelian randomization analysis of hypertension and gut microbiota.

Exposure	Method	Beta	SE	OR	*P*-value	95% CI
Bifidobacteriaceae (family)	IVW	−0.073	0.026	0.929	.005	0.882 to 0.978
	MR-Egger	0.025	0.090	1.025	.791	0.859 to 1.223
	WM	−0.048	0.038	0.954	.212	0.885 to 1.027
Clostridiales vadinBB60 group (family)	IVW	−0.064	0.032	0.938	.048	0.881 to 0.999
	MR-Egger	0.049	0.088	1.050	.591	0.883 to 1.249
	WM	−0.031	0.328	0.970	.338	0.909 to 1.033
Eubacterium brachy group (family)	IVW	−0.042	0.017	0.959	.015	0.928 to 0.992
	MR-Egger	−0.141	0.061	0.868	.050	0.770 to 0.979
	WM	−0.039	0.022	0.962	.071	0.921 to 1.003
Blautia (genus)	IVW	−0.073	0.025	0.930	.005	0.884 to 0.978
	MR-Egger	0.023	0.055	0.977	.681	0.877 to 1.089
	WM	−0.053	0.035	0.949	.133	0.886 to 1.016
Family XIII AD3011 group (genus)	IVW	0.070	0.035	1.073	.046	1.001 to 1.149
	MR-Egger	−0.104	0.166	0.901	.544	0.652 to 1.248
	WM	0.042	0.037	1.043	.258	0.969 to 1.121
Rikenellaceae RC9 gut group (genus)	IVW	0.070	0.035	1.073	.046	1.001 to 1.149
	MR-Egger	−0.104	0.166	0.901	.544	0.651 to 1.248
	WM	0.042	0.038	1.043	.266	0.969 to 1.122
Subdoligranulum (genus)	IVW	−0.071	0.033	0.931	.029	0.874 to 0.993
	MR-Egger	−0.013	0.087	0.987	.889	0.832 to 1.171
	WM	−0.011	0.043	0.989	.804	0.910 to 1.076
Terrisporobacter (genus)	IVW	−0.080	0.033	0.923	.016	0.865 to 0.985
	MR-Egger	−0.152	0.095	0.859	.210	0.713 to 1.036
	WM	−0.089	0.038	0.914	.019	0.849 to 0.985
Bifidobacteriales (order)	IVW	−0.073	0.026	0.929	.005	0.882 to 0.978
	MR-Egger	0.025	0.09	1.025	.791	0.859 to 1.223
	WM	−0.048	0.039	0.954	.222	0.883 to 1.029
Burkholderiales (order)	IVW	0.096	0.045	1.101	.031	1.009 to 1.202
	MR-Egger	0.210	0.152	1.233	.201	0.916 to 1.661
	WM	0.050	0.049	1.051	.309	0.955 to 1.157

95% CI = 95% confidence interval, IVW = inverse variance weighted analysis, MR = Mendelian randomization, OR = odds ratio, SE = standard error, WM = weighted median.

short-chain fatty acids (SCFAs), which can regulate intestinal barrier function, improve glucose homeostasis, and enhance immune response, thereby reducing the risk of MetS.[29]

Probiotic Supplementation: The direct increase in the abundance of beneficial bacteria can be achieved by supplementing with specific probiotic strains, such as Bifidobacterium and Lactobacillus. These probiotics can improve the host's metabolic state by modulating the composition and function of the gut microbiota. For example, some studies have shown that Bifidobacterium supplementation can significantly improve insulin resistance and inflammatory status in obese patients.[30]

Prebiotic Supplementation: Prebiotics are nondigestible food components that selectively stimulate the growth of beneficial bacteria. For example, inulin and fructooligosaccharides can significantly increase the abundance of Bifidobacteriaceae and Actinobacteria, thereby helping to reduce the risk of MetS.[31]

3.3.2. Inhibiting the growth of harmful bacteria. Antibiotic therapy: In certain cases, the use of specific antibiotics can inhibit the growth of harmful bacteria (such as Lachnospiraceae and Olsenella). However, the use of antibiotics should be cautious to avoid negative impacts on the entire gut microbiota. Studies have shown that certain narrow-spectrum antibiotics can selectively reduce the abundance of harmful bacteria without significantly affecting beneficial bacteria.[29]

Phage therapy: Phages are viruses that specifically infect and lyse bacteria and can be used to selectively reduce the abundance of specific harmful bacteria. This method is highly specific and can minimize interference with beneficial bacteria. For example, phages targeting Lachnospiraceae can effectively reduce the abundance of this bacterial group, thereby reducing the risk of MetS.[32]

4. Discussion

This study employed a 2-sample Mendelian Randomization approach to systematically explore the causal relationship between the gut microbiota and MetS. The main findings include the following: 8 gut microbial groups were significantly associated with the risk of MetS; Bifidobacteriaceae, Ruminiclostridium UCG-010, and Actinobacteria may reduce the risk of MetS; Lachnospiraceae, Veillonellaceae, Ruminococcaceae, Prevotella, and Oscillibacter may increase the risk of MetS; and multiple gut microbial groups have causal associations with various components of MetS (such as BMI, blood pressure, and blood lipids). These results support the hypothesis that gut microbiota affects the development of MetS through its metabolic products and interactions with the host.

This study systematically investigates the potential causal relationships between gut microbiota and MetS and its components. The findings reveal that certain gut bacterial groups (such as Lachnospiraceae, Veillonellaceae, and Porphyromonadaceae) are causally associated with an increased risk of MetS, while others (such as Bifidobacteriaceae, Ruminococcaceae UCG-010, and Actinobacteria) appear to exert protective effects against MetS. These results suggest that the composition and function of gut microbiota may influence the development of metabolic syndrome through various mechanisms. Firstly, bacterial groups that produce SCFAs, such as Bifidobacteriaceae, Ruminococcaceae UCG-010, and Actinobacteria, may reduce the risk of MetS by modulating gut barrier function, glucose homeostasis, and immune responses. SCFAs, which are major metabolic products of dietary fiber fermentation by gut microbiota, can promote the secretion of glucagon-like peptide-1 (GLP-1) and peptide YY. This action increases satiety via the gut-brain axis, indirectly regulating appetite and energy intake.

Table 5

The results on Mendelian randomization analysis of high-density lipoprotein cholesterol and gut microbiota.

Exposure	Method	Beta	SE	OR	*P*-value	95% CI
Melainabacteria (class)	IVW	−0.039	0.013	0.962	.003	0.938 to 0.987
	MR-Egger	0.012	0.037	1.012	.754	0.942 to 1.087
	WM	−0.034	0.018	0.967	.053	0.934 to 1.000
Eubacterium fissicatena group (genus)	IVW	0.027	0.012	1.027	.023	1.004 to 1.051
	MR-Egger	0.71	0.064	1.074	.303	0.947 to 1.217
	WM	0.012	0.016	1.012	.438	0.981 to 1.045
Blautia (genus)	IVW	−0.039	0.02	0.961	.048	0.925 to 1.000
	MR-Egger	−0.069	0.044	0.933	.142	0.857 to 1.017
	WM	−0.038	0.025	0.962	.131	0.915 to 1.011
Collinsella (genus)	IVW	0.05	0.024	1.051	.034	1.004 to 1.101
	MR-Egger	0.107	0.091	1.113	.283	0.932 to 1.330
	WM	0.036	0.03	1.036	.24	0.976 to 1.100
Desulfovibrio (genus)	IVW	0.053	0.021	1.055	.009	1.013 to 1.098
	MR-Egger	−0.009	0.06	0.991	.89	0.882 to 1.115
	WM	0.038	0.024	1.039	.106	0.992 to 1.088
Lachnospiraceae NK4A136 group (genus)	IVW	0.041	0.018	1.042	.018	0.940 to 1.083
	MR-Egger	0.009	0.036	1.009	.809	0.995 to 1.093
	WM	0.042	0.024	1.043	.08	1.042 to 1.079
Parabacteroides (genus)	IVW	0.063	0.031	1.035	.045	1.001 to 1.131
	MR-Egger	0.138	0.099	1.148	.237	0.945 to 1.394
	WM	0.07	0.039	1.072	.074	0.993 to 1.157
Ruminococcaceae UCG-009 (genus)	IVW	−0.04	0.016	0.961	.012	0.931 to 0.991
	MR-Egger	−0.038	0.073	0.962	.611	0.834 to 1.111
	WM	−0.029	0.019	0.972	.139	0.935 to 1.009
Sutterella (genus)	IVW	−0.05	0.023	0.951	.028	0.910 to 0.995
	MR-Egger	−0.071	0.113	0.931	.541	0.747 to 1.161
	WM	−0.046	0.027	0.955	.094	0.905 to 1.008
Actinobacteria (phylum)	IVW	0.053	0.018	1.054	.003	1.018 to 1.092
	MR-Egger	0.125	0.071	1.133	.104	0.985 to 1.304
	WM	0.038	0.026	1.039	.144	1.039 to 1.093

95% CI = 95% confidence interval, IVW = inverse variance weighted analysis, MR = Mendelian randomization, OR = odds ratio, SE = standard error, WM = weighted median.

Moreover, SCFAs can enhance insulin sensitivity and modulate hepatic glucose metabolism to improve metabolic health.[33–36] For example, studies by Cani have shown that supplementation with Bifidobacterium can significantly improve insulin resistance and inflammatory status in obese children, further confirming the important role of SCFAs in metabolic regulation.[37] Secondly, certain gut microbial groups (such as Bifidobacterium and Firmicutes) can modulate the host's metabolic state by influencing bile acid metabolism. Joyce found that these microbial groups can convert primary bile acids into secondary bile acids, thereby activating the Takeda G protein-coupled receptor-5 receptor and promoting energy expenditure and secretion of GLP-1.[38] This process not only helps regulate lipid metabolism but may also reduce the risk of metabolic syndrome by improving insulin sensitivity.

Compared with previous observational studies, this study provides stronger evidence for causal inference using the Mendelian randomization method. For example, Ley et al previously reported a reduced abundance of Bifidobacterium in the gut of obese individuals but could not determine whether this was a causal or reverse causal relationship.[39] Our MR analysis directly supports the protective effect of Bifidobacteriaceae against MetS and identifies new microbial groups potentially associated with MetS risk, such as Veillonellaceae and

Table 6

The results on Mendelian randomization analysis of triglyceride and gut microbiota.

Exposure	Method	Beta	SE	OR	*P*-value	95% CI
Bacteroidales S24-7 group (family)	IVW	−0.041	0.019	0.960	.032	0.925 to 0.997
	MR-Egger	−0.119	0.084	0.888	.208	0.753 to 1.047
	WM	−0.059	0.026	0.942	.024	0.895 to 0.992
Family XIII (family)	IVW	0.059	0.023	1.031	.010	1.014 to 1.110
	MR-Egger	0.208	0.077	1.231	.026	1.057 to 1.434
	WM	0.048	0.030	1.049	.109	0.989 to 1.112
Clostridium sensu stricto1 (genus)	IVW	−0.046	0.023	0.955	.044	0.913 to 0.999
	MR-Egger	−0.082	0.051	0.921	.170	0.834 to 1.018
	WM	−0.049	0.029	0.952	.094	0.899 to 1.008
Coprobacter (genus)	IVW	0.041	0.014	1.042	.003	1.014 to 1.070
	MR-Egger	0.029	0.048	1.030	.552	0.938 to 1.131
	WM	0.047	0.019	1.048	.016	1.009 to 1.088
Coprococcus 2 (genus)	IVW	0.054	0.023	1.055	.020	1.008 to 1.104
	MR-Egger	−0.257	0.146	0.773	.130	0.581 to 1.030
	WM	0.053	0.030	1.054	.077	0.994 to 1.118
Gordonibacter (genus)	IVW	0.054	0.023	1.055	.020	1.008 to 1.104
	MR-Egger	−0.257	0.146	0.773	.130	0.580 to 1.030
	WM	0.053	0.030	1.054	.085	0.993 to 1.120
Lachnoclostridium (genus)	IVW	−0.080	0.039	0.924	.043	0.855 to 0.997
	MR-Egger	0.028	0.143	1.028	.851	0.776 to 1.360
	WM	−0.044	0.032	0.957	.166	0.898 to 1.019
Olsenella (genus)	IVW	0.025	0.011	1.025	.030	1.002 to 1.048
	MR-Egger	0.058	0.043	1.060	.207	0.975 to 1.153
	WM	0.020	0.016	1.020	.200	0.989 to 1.052
Ruminiclostridium 9 (genus)	IVW	−0.053	0.027	0.949	.050	0.900 to 1.000
	MR-Egger	−0.089	0.121	0.915	.485	0.722 to 1.159
	WM	−0.054	0.036	0.948	.138	0.882 to 1.017
Lactobacillales (order)	IVW	−0.076	0.026	0.927	.003	0.881 to 0.974
	MR-Egger	0.021	0.062	1.021	.737	0.904 to 1.155
	WM	−0.028	0.027	0.972	.290	0.922 to 1.025

95%CI = 95% confidence interval, IVW = inverse variance weighted analysis, MR = Mendelian randomization, OR = odds ratio, SE = standard error, WM = weighted median.

Table 7

The results of pleiotropy and heterogeneity for bacterial taxa associated with metabolic syndromes.

	Heterogeneity		Pleiotropy		
Exposure	*P*-val_Q from IVW	*P*-val_Q from MR-Egger	MR-Egger intercept	*P*-val from MR-Egger intercept	*P*-val from MR-PRESSO global test
Bifidobacteriaceae (family)	.525	.432	−0.001	.915	.318
Lachnospiraceae (family)	.284	.244	−0.003	.587	.146
Veillonellaceae (family)	.486	.419	0.000	.963	.612
Victivallaceae (family)	.589	.496	−0.002	.869	.595
Odoribacter (genus)	.921	.951	0.010	.398	.619
Olsenella (genus)	.539	.615	−0.012	.223	.555
Ruminococcaceae UCG-010 (genus)	.314	.608	−0.017	.147	.106
Actinobacteria (phylum)	.79	.726	0.000	.978	.762

IVW = inverse variance weighted analysis, MR = Mendelian randomization, MR-PRESSO = MR pleiotropy residual sum and outlier test.

Ruminococcaceae, offering new directions for research in this field.

This study provides a solid scientific basis for developing prevention and treatment strategies based on gut microbiota. A series of potentially pathogenic microbial groups (such as Lachnospiraceae and Porphyromonadaceae) and beneficial microbial groups (such as Bifidobacteriaceae and Actinobacteria) were identified, offering clear targets for targeted interventions. For example, increasing the abundance of beneficial bacteria or inhibiting the growth of harmful bacteria may become new strategies for the prevention and treatment of MetS. Moreover, the findings further reveal the potential role of gut microbiota in regulating components of MetS, such as hypertension, BMI, and dyslipidemia. For instance, the causal association between certain microbial groups and hypertension suggests that modulating the gut microbiota composition may help lower blood pressure. Similarly, microbial groups associated with BMI and dyslipidemia provide new ideas for developing interventions targeting these metabolic abnormalities. Previous studies have shown that dietary interventions, probiotic supplementation, and fecal microbiota transplantation can effectively modulate the composition and function of gut microbiota.[40] The findings of this study further support the potential value of these intervention measures, providing a theoretical basis for developing personalized prevention and treatment strategies based on gut microbiota.

Specifically, future research should focus on the functional characteristics of gut microbiota and combine them with the clinical manifestations of MetS patients to develop personalized dietary intervention plans and determine the appropriate dosage of specific microbial supplements. This microbiota function-oriented research paradigm not only offers the possibility of precision treatment for metabolic diseases but also brings new perspectives and insights to the entire field of metabolic disease research. Additionally, the Mendelian randomization analysis of MetS highlights the key role of genetic factors in

Table 8

The results of pleiotropy and heterogeneity for bacterial taxa associated with body mass index.

	Heterogeneity		Pleiotropy		
Exposure	***P*-val_Q from IVW**	***P*-val_Q from MR-Egger**	**MR-Egger intercept**	***P*-val from MR-Egger intercept**	***P*-val from MR-PRESSO global test**
Melainabacteria (class)	.958	.923	0.003	.886	.099
Bacteroidales S24-7 group (family)	.970	.928	−0.007	.878	.988
Family XIII (family)	.083	.080	0.032	.432	.195
Negativicutes (class)	.124	.097	−0.015	.614	.131
Clostridiales vadinBB60 group (family)	.559	.726	−0.032	.108	.987
Rikenellaceae (family)	.206	.173	0.010	.636	.141
Allisonella (genus)	.967	.918	−2.435	1.000	.262
Collinsella (genus)	.636	.512	0.007	.853	.431
Enterorhabdus (genus)	.636	.512	0.007	.853	.131
Lachnospiraceae FCS020 group (genus)	.243	.566	0.038	.046	.194
Lachnospiraceae UCG-001 (genus)	.243	.566	0.038	.046	.349
Parabacteroides (genus)	.223	.172	0.035	.58	.099
Rikenellaceae RC9 gut group (genus)	.950	.913	0.005	.92	.755
Burkholderiales (order)	.466	.519	−0.032	.025	.325
Selenomonadales (order)	.124	.097	−0.015	.614	.117

IVW = inverse variance weighted analysis, MR = Mendelian randomization, MR-PRESSO = MR pleiotropy residual sum and outlier test.

Table 9

The results of pleiotropy and heterogeneity for bacterial taxa associated with hypertension.

	Heterogeneity		Pleiotropy		
Exposure	***P*-val_Q from IVW**	***P*-val_Q from MR-Egger**	**MR-Egger intercept**	***P*-val from MR-Egger intercept**	***P*-val from MR-PRESSO global test**
Bifidobacteriaceae (family)	.679	.717	−0.007	.282	.357
Clostridiales vadinBB60 group (family)	.001	.003	−0.011	.197	.306
Eubacterium brachy group (family)	.325	.488	0.013	.129	.162
Blautia (genus)	.45	.449	−0.004	.335	.107
Family XIII AD3011 grou (genus)	.039	.048	0.014	.307	.837
Rikenellaceae RC9 gut group (genus)	.039	.048	0.014	.307	.005
Subdoligranulum (genus)	.313	.279	−0.004	.484	.195
Terrisporobacter (genus)	.214	.189	0.008	.48	.24
Bifidobacteriales (order)	.679	.717	−0.007	.282	.344
Burkholderiales (order)	.019	.019	−0.008	.455	.058

IVW = inverse variance weighted analysis, MR = Mendelian randomization, MR-PRESSO = MR pleiotropy residual sum and outlier test.

the pathogenesis of the disease, further emphasizing the importance of considering individual genetic background differences in the prevention and treatment of MetS. Therefore, advanced technologies such as genetic testing should be utilized to achieve more precise and personalized medical strategies to effectively address this complex disease.

This study use large-scale population data for MR analysis to explore the causal relationship between gut microbiota and metabolic syndrome, yielding reliable results without additional experimental costs. Moreover, using MR analysis to explore the causal relationship between MetS and gut microbiota can avoid biases caused by reverse causality and unknown confounding factors. However, our study does have some limitations. First, the use of GWAS data does not allow for the exploration of any potential nonlinear relationships or stratification effects due to differences in age, sex, body mass, and health status, which may introduce heterogeneity. Second, MR studies could not determine whether there was any overlap in the included GWAS summary data. We minimized the bias of participant overlap using the *F*-statistic ($F > 10$). Third, our analysis was conducted using only European data; therefore, further evidence is needed to generalize our conclusions to other populations. More cross-population studies on gut microbiota and MetS are needed in the future to further validate these findings. Lastly, the diversity of the adult gut microbiota is a complex and dynamically changing field, which not only becomes richer with age but is also deeply influenced by a variety of factors, including ethnicity, daily dietary habits, and individual lifestyle.[41] This dynamic variation may interfere with the accurate inference of the causal relationship between genetic variants and phenotypes in the MR analysis. Therefore, long-term follow-up studies are needed, and methods such as time-series analysis should be employed to accurately assess the temporal and cumulative effects of the gut microbiota, thereby strengthening the reliability of MR analysis.

Future research should delve deeper into the following areas: further elucidate the detailed molecular mechanisms by which specific gut microbial groups influence MetS; investigate how the interplay between host genetic factors and the gut microbiota collectively affects the risk of MetS; explore the modulatory effects of environmental and lifestyle factors (such as diet and exercise) on the gut microbiota-MetS relationship; conduct large-scale MR studies across different ethnicities to verify the universality of the results of this study; and design long-term longitudinal studies to assess the time-dependent impact of gut microbiota on the development of MetS.

5. Conclusion

In summary, this study has successfully utilized Mendelian randomization methods to uncover the potential causal links between specific gut microbiota and MetS, as well as its various components such as BMI, hypertension, and blood lipid levels.

Table 10

The results of pleiotropy and heterogeneity for bacterial taxa associated with high-density lipoprotein cholesterol.

	Heterogeneity			Pleiotropy	
Exposure	*P*-val_Q from IVW	*P*-val_Q from MR-Egger	MR-Egger intercept	*P*-val from MR-Egger intercept	*P*-val from MR-PRESSO global test
Melainabacteria (class)	.574	.711	−0.006	.177	.114
Eubacterium fissicatena group (genus)	.436	.384	−0.006	.502	.735
Blautia (genus)	.276	.252	0.003	.459	.127
Collinsella (genus)	.451	.386	−0.004	.539	.425
Desulfovibrio (genus)	.135	.157	0.007	.303	.886
Lachnospiraceae NK4A136 group (genus)	.297	.304	0.003	.324	.187
Parabacteroides (genus)	.236	.210	−0.008	.467	.579
Ruminococcaceae UCG-009 (genus)	.251	.188	0.000	.984	.126
Sutterella (genus)	.115	.081	0.001	.851	.679
Actinobacteria (phylum)	.471	.477	−0.005	.316	.179

IVW = inverse variance weighted analysis, MR = Mendelian randomization, MR-PRESSO = MR pleiotropy residual sum and outlier test.

Table 11

The results of pleiotropy and heterogeneity for bacterial taxa associated with triglyceride.

	Heterogeneity		Pleiotropy		
Exposure	*P*-val_Q from IVW	*P*-val_Q from MR-Egger	MR-Egger intercept	*P*-val from MR-Egger intercept	*P*-val from MR-PRESSO global test
Bacteroidales S24-7 group (family)	.401	.388	0.008	.378	.154
Family XIII (family)	.548	.841	−0.01	.077	.651
Negativicutes (class)	.404	.360	0.004	.462	.685
Clostridiales vadinBB60 group (family)	.698	.619	0.001	.804	.470
Rikenellaceae (family)	.447	.899	0.024	.075	.424
Allisonella (genus)	.447	.899	0.024	.075	.032
Collinsella (genus)	.000	.000	−0.007	.453	.980
Enterorhabdus (genus)	.589	.561	−0.005	.435	.564
Lachnospiraceae FCS020 group (genus)	.398	.310	0.003	.766	.232
Lachnospiraceae UCG-001 (genus)	.022	.062	−0.008	.113	.310

IVW = inverse variance weighted analysis, MR = Mendelian randomization, MR-PRESSO = MR pleiotropy residual sum and outlier test.

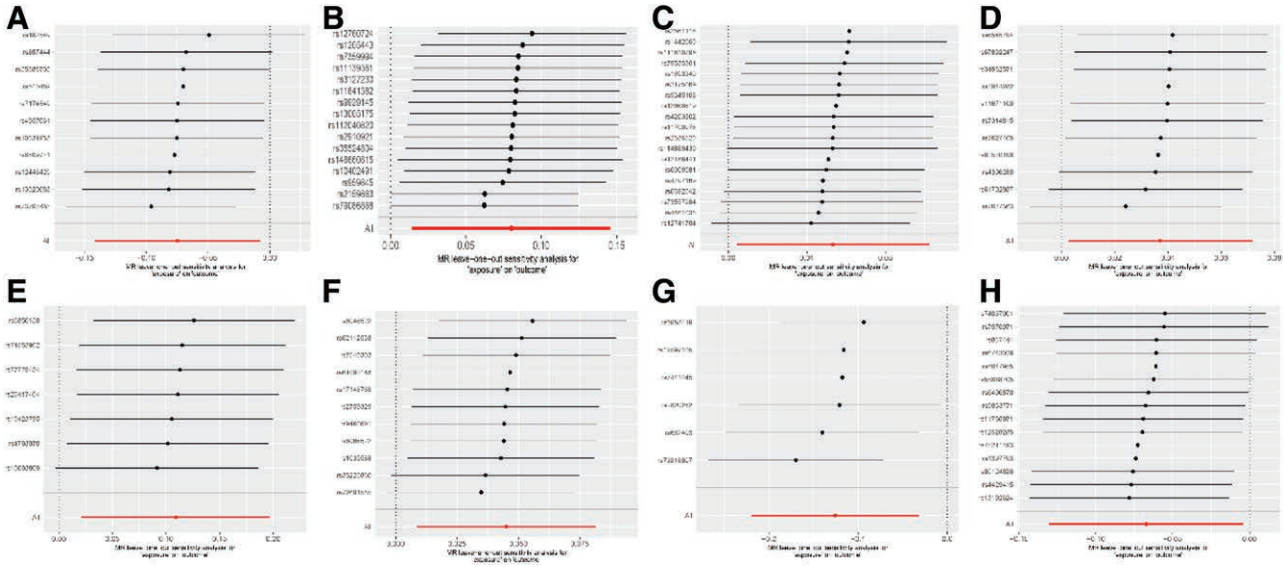

Figure 2. Leave-one-out plots. (A) leave-one-out plot of genus Bifidobacteriaceae (family) and MetS; (B) leave-one-out plot of genus Lachnospiraceae (family) and MetS; (C) leave-one-out plot of genus Veillonellaceae (family) and MetS; (D) leave-one-out plot of genus Victivallaceae (family) and MetS; (E) leave-one-out plot of genus Odoribacter (genus) and MetS; (F) leave-one-out plot of genus Olsenella (genus) and MetS; (G) leave-one-out plot of genus Odoribactergenus (genus) and MetS; (F) leave-one-out plot of genus Ruminococcaceae UCG-010 (genus) and MetS; (H) leave-one-out plot of genus Actinobacteria (phylum) and MetS. MetS = metabolic syndrome.

These findings not only deepen our understanding of the pathogenesis of MetS but also highlight the significant role of gut microbiota in metabolic health. By identifying specific microbiota that may increase or decrease the risk of MetS, we provide valuable insights for the development of novel diagnostic tools and targeted interventions based on gut microbiota modulation. Future research should focus on validating these results in diverse populations, elucidating the underlying molecular mechanisms, and exploring the combined effects of genetic and environmental factors. Overall, this study marks an important step towards precision medicine in the prevention and treatment of metabolic syndrome, offering a promising avenue for improving global metabolic health.

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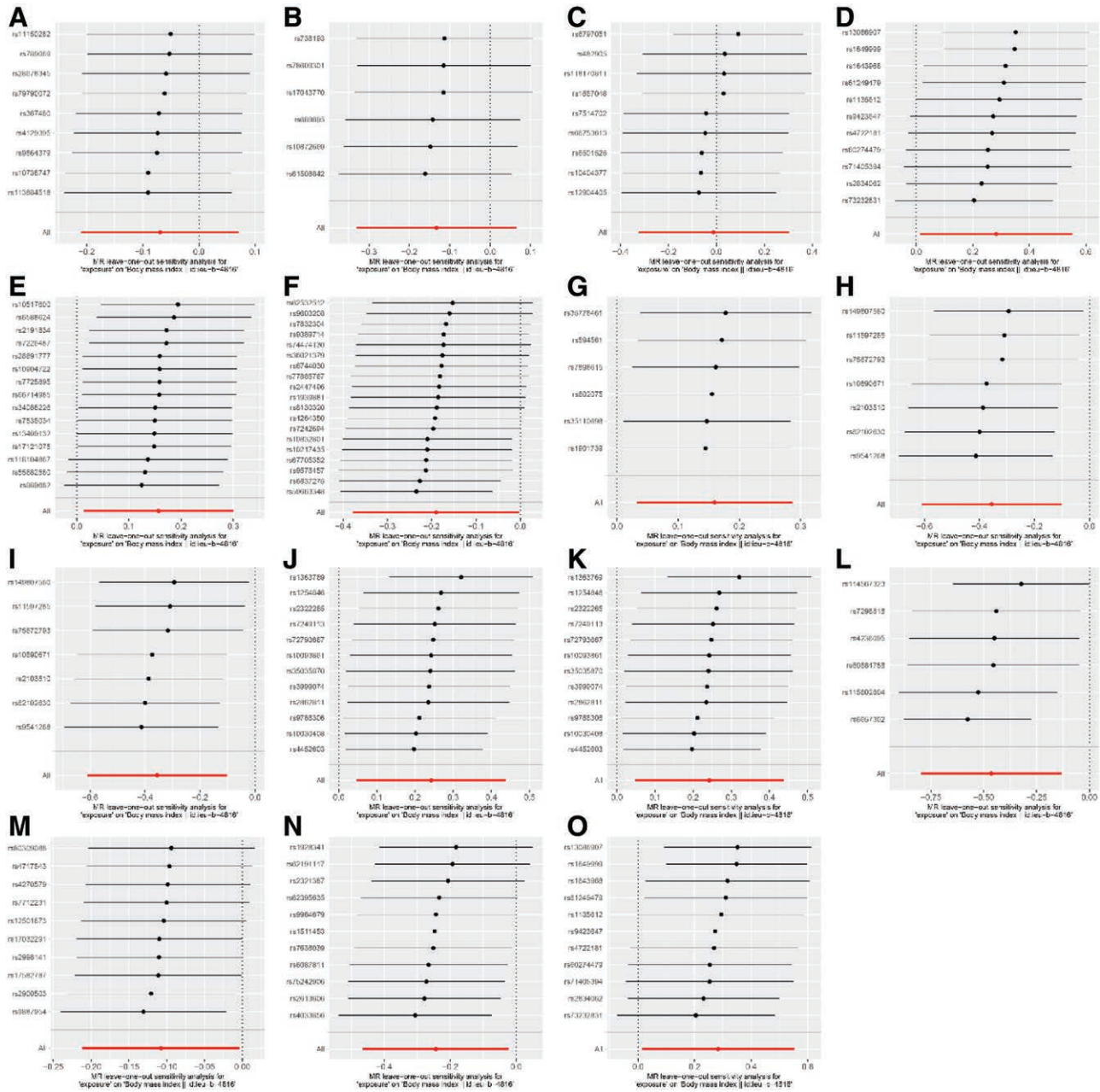

Figure 3. Leave-one-out plots. (A) leave-one-out plot of genus Melainabacteria (class) and BMI; (B) leave-one-out plot of genus Bacteroidales S24-7 group (Family) and BMI; (C) leave-one-out plot of genus Family XIII (family) and BMI; (D) leave-one-out plot of genus Negativicutes (class) and BMI; (E) leave-one-out plot of genus Clostridiales vadinBB60 group (family) and BMI; (F) leave-one-out plot of genus Rikenellaceae (family) and BMI; (G) leave-one-out plot of genus Allisonella (genus)and BMI; (H) leave-one-out plot of genus Collinsella (genus) and BMI; (I) leave-one-out plot of genus Enterorhabdus (genus) and BMI; (J) leave-one-out plot of genus Lachnospiraceae FCS020 group (genus) and BMI; (K) leave-one-out plot of genus Lachnospiraceae UCG-001 (genus) and BMI; (L) leave-one-out plot of genus Parabacteroides (genus) and BMI; (M) leave-one-out plot of genus Rikenellaceae RC9 gut group (genus) and BMI; (N) leave-one-out plot of genus Burkholderiales (order) and MetS; (O) leave-one-out plot of genus Selenomonadales (order) and BMI. BMI = body mass index, MetS = metabolic syndrome.

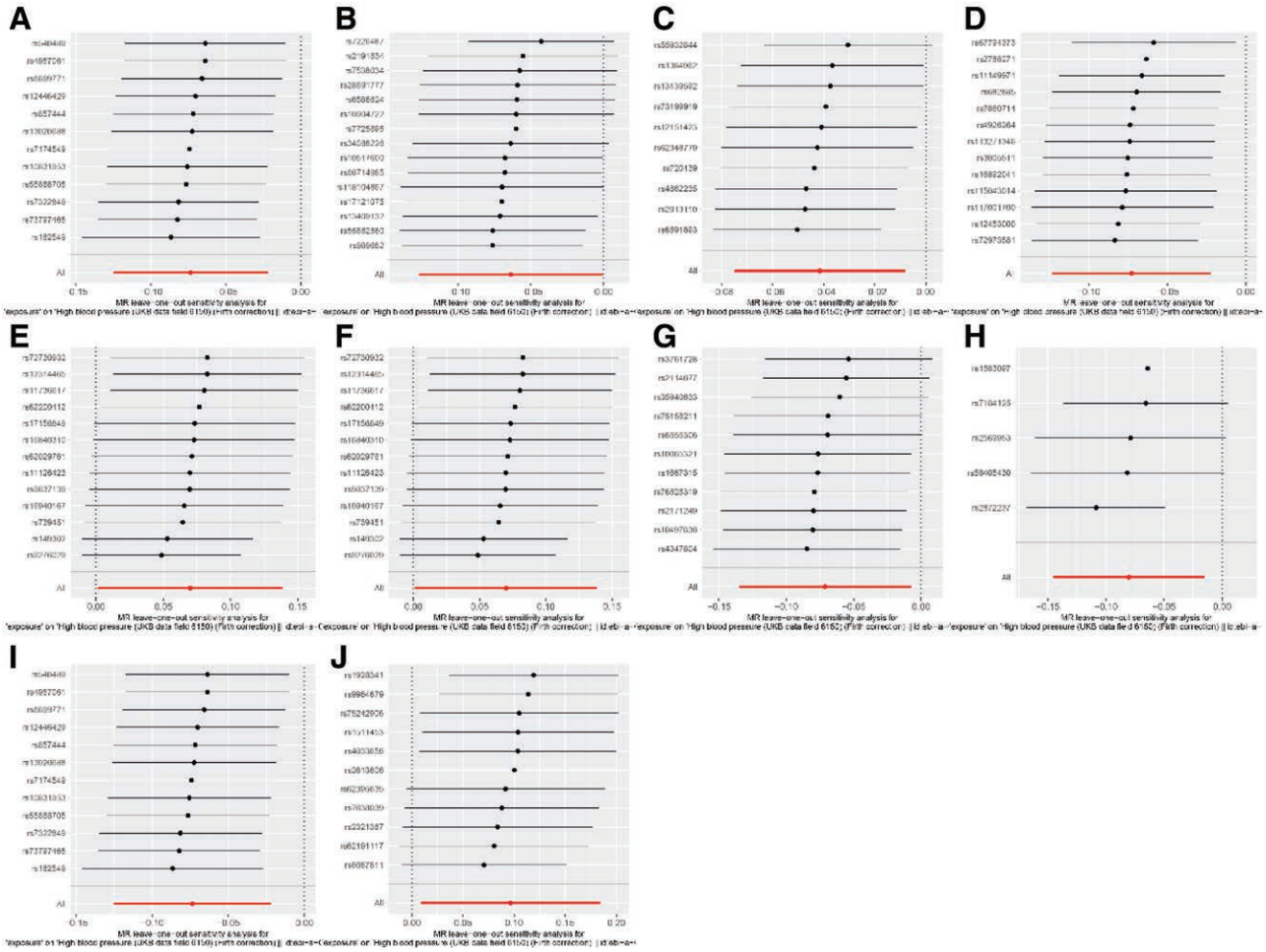

Figure 4. Leave-one-out plots. (A) leave-one-out plot of genus Bifidobacteriaceae (family) and hypertension; (B) leave-one-out plot of genus Clostridiales vadinBB60 group (family) and hypertension; (C) leave-one-out plot of genus Eubacterium brachy group (family) and hypertension; (D) leave-one-out plot of genus Blautia (genus) and hypertension; (E) leave-one-out plot of genus Family XIII AD3011 grou (genus) and hypertension; (F) leave-one-out plot of genus Rikenellaceae RC9 gut group (genus) and hypertension; (G) leave-one-out plot of genus Subdoligranulum (genus) and hypertension; (H) leave-one-out plot of genus Terrisporobacter (genus) and hypertension; (I) leave-one-out plot of genus Bifidobacteriales (order) and hypertension; (J) leave-one-out plot of genus Burkholderiales (order) and hypertension.

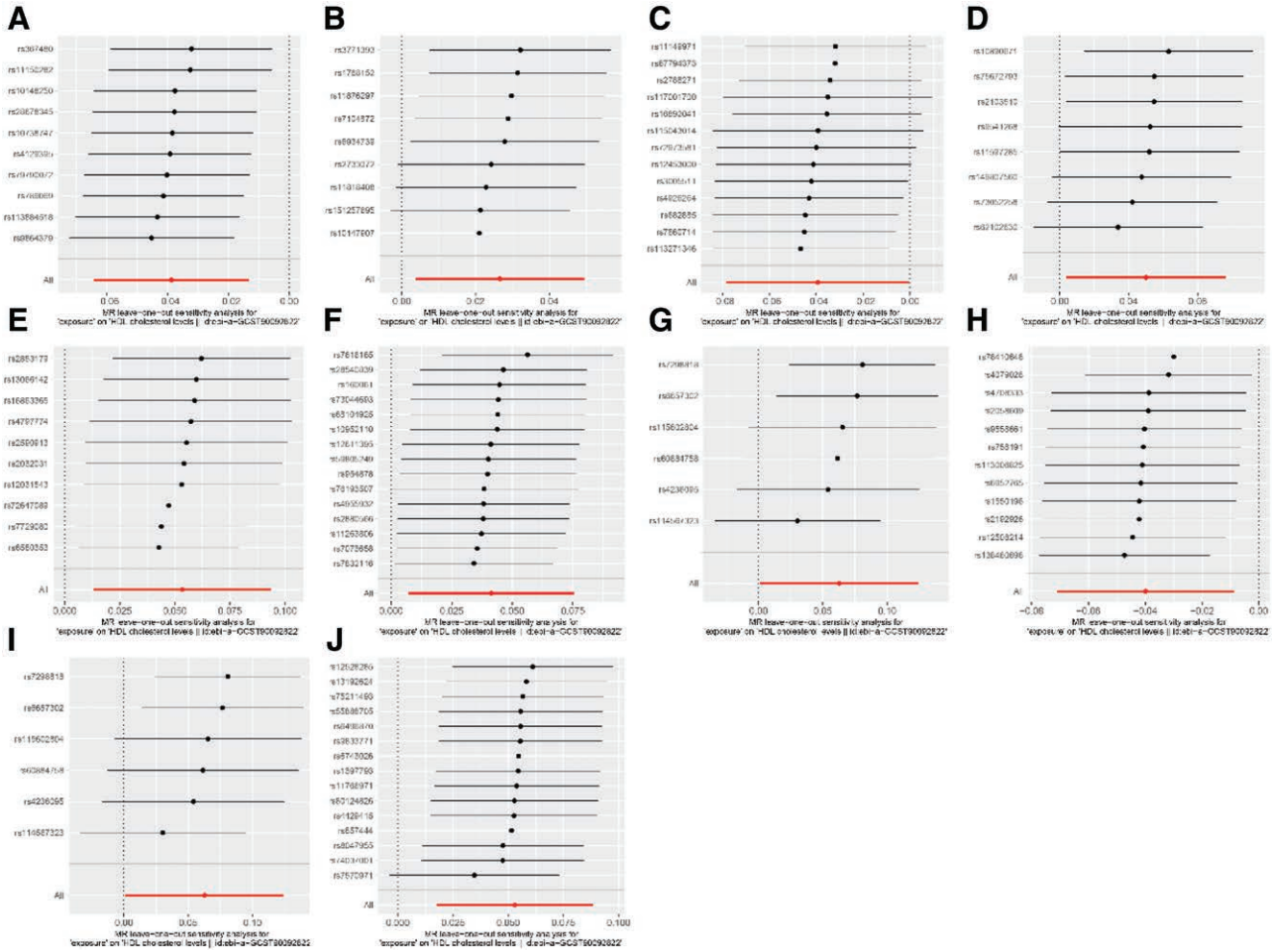

Figure 5. Leave-one-out plots. (A) leave-one-out plot of genus Melainabacteria (class) and HLD-C; (B) leave-one-out plot of genus Eubacterium fissicatena group (genus) and HLD-C; (C) leave-one-out plot of genus Blautia (genus) and HLD-C; (D) leave-one-out plot of genus Collinsella (=genus) and HLD-C; (E) leave-one-out plot of genus Desulfovibrio (genus) and HLD-C; (F) leave-one-out plot of genus Lachnospiraceae NK4A136 group (genus) and HLD-C; (G) leave-one-out plot of genus Parabacteroides (genus) and HLD-C; (H) leave-one-out plot of genus Ruminococcaceae UCG-009 (genus) and HLD-C; (I) leave-one-out plot of genus Sutterella (genus) and HLD-C; (J) leave-one-out plot of genus Actinobacteria (phylum) and HLD-C. HDL-C = high-density lipoprotein cholesterol.

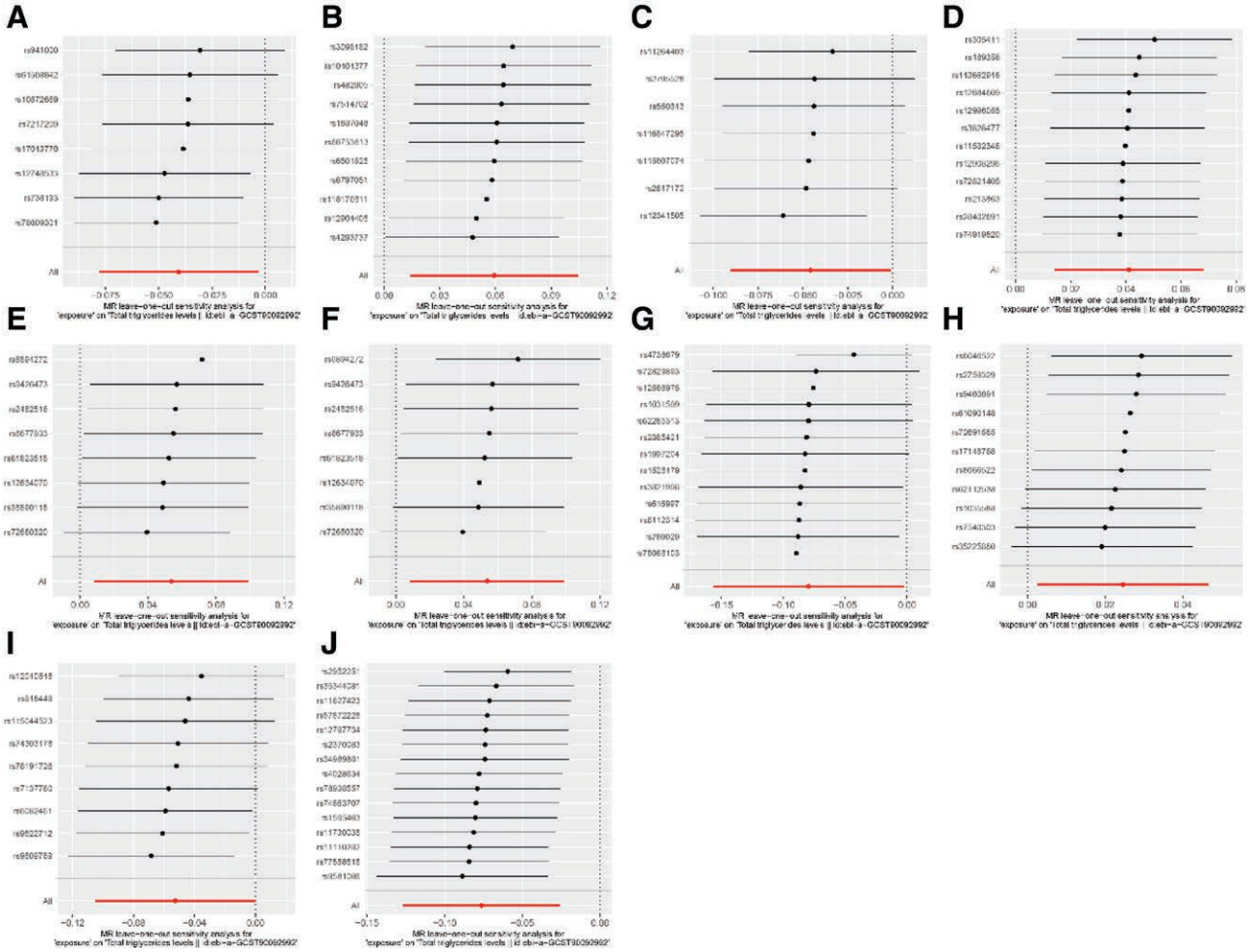

Figure 6. Leave-one-out plots. (A) leave-one-out plot of genus BacteroidalesS24-7group (family) and TG; (B) leave-one-out plot of genus Family XIII (family) and TG; (C) leave-one-out plot of genus Negativicutes (class) and TG; (D) leave-one-out plot of genus Clostridiales vadinBB60 grou p (family) and TG; (E) leave-one-out plot of genus Rikenellaceae (family) and TG; (F) leave-one-out plot of genus Allisonella (genus) and TG; (G) leave-one-out plot of genus Collinsella (genus) and TG; (H) leave-one-out plot of genus Enterorhabdus (genus)) and TG; (I) leave-one-out plot of genus Lachnospiraceae FCS020 group (genus) and TG; (J) leave-one-out plot of genus Lachnospiraceae UCG-001 (genus) and TG. TG = triglyceride.

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