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Causal associations between gut microbiota and type 2 diabetes mellitus subtypes: a mendelian randomization analysis

Zhichao Ruan[1], Jiangteng Liu[1] and Jinxi Zhao[1*]

Abstract

Purpose To investigate the causal relationships between gut microbiota and novel adult-onset type 2 diabetes mellitus(T2DM) subtypes.

Methods We conducted Mendelian randomization (MR) analyses using genome-wide association data from European populations. Initial MR analyses examined associations between gut microbiota and four T2DM subtypes, followed by validation analyses using type 1 diabetes mellitus(T1DM) and T2DM GWAS data. We also performed bidirectional MR analyses and tested for heterogeneity and pleiotropy across all analyses.

Results Our MR analyses revealed distinctive associations between gut microbiota and T2DM subtypes: six bacterial taxa with severe insulin-deficient diabetes (SIDD), four with severe insulin-resistant diabetes (SIRD), eight with mild obesity-related diabetes (MOD), and eight with mild age-related diabetes (MARD). These associations were distinct from T1DM findings. Six bacterial taxa were validated in T2DM analyses, with four showing directionally consistent effects: Class *Clostridia* (OR = 0.57, $P = 0.045$) and Order *Clostridiales* (OR = 0.57, $P = 0.045$) were associated with reduced MOD risk, while species *Catus* (OR = 1.80, $P = 0.007$) was associated with increased MOD risk, and genus *Holdemania* (OR = 2.51, $P = 0.004$) was associated with increased SIRD risk. No significant heterogeneity or pleiotropy was observed across analyses.

Conclusions Our MR analyses reveal novel causal relationships between gut microbiota and adult-onset T2DM subtypes, though further validation studies are warranted.

Keywords Gut microbiota, Type 2 diabetes mellitus, Mendelian randomization, Genetic variants

Introduction

Type 2 diabetes mellitus (T2DM) represents a growing global health challenge, with prevalence figures in the hundreds of millions and projections indicating continued escalation [1]. Conventionally, diabetes is categorized into type 1 diabetes mellitus (T1DM), latent autoimmune diabetes in adults (LADA), T2DM, gestational diabetes, and other specific types [2]. However, mounting evidence suggests substantial heterogeneity within T2DM, stemming from distinct pathophysiological mechanisms, clinical characteristics, and complication risks [2–5]. This heterogeneity poses challenges for targeted prevention and management of complications. In 2018, a novel classification system based on six variables was proposed to stratify newly diagnosed adult-onset diabetes into five subtypes: severe autoimmune diabetes (SAID, encompassing T1DM and LADA) and four T2DM variants—severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), mild obesity-related diabetes (MOD), and mild age-related diabetes (MARD)

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[6]. This classification has since been validated across multiple international cohorts [7–9], revealing significant differences in clinical manifestations, complications, and genetic architecture among subtypes [6, 10].

The gut microbiota, comprising approximately 40 trillion bacteria and their collective genome, represents a complex ecosystem within the human intestine [11]. Through the production of various small molecule metabolites, the gut microbiota has been implicated in several systemic diseases, including metabolic disorders, cardiovascular diseases, and cancer [12–15]. While interest in the gut microbiota-diabetes relationship continues to grow, its associations with the newly defined adult-onset diabetes subtypes remain unexplored.

Evidence supporting a causal role for gut microbiota in diabetes pathogenesis continues to accumulate. Studies have documented significant alterations in gut microbial composition among individuals with diabetes compared to non-diabetic controls [16–18]. Gut microbial metabolites, particularly short-chain fatty acids (SCFAs), demonstrate regulatory effects on glucose homeostasis and insulin sensitivity [19, 20]. Furthermore, experimental studies show that fecal microbiota transplantation and probiotic interventions can improve glucose tolerance and insulin resistance [21, 22], suggesting that gut microbiota may influence diabetes development through modulation of host metabolism, immunity, and endocrine function.

The distinct pathophysiological mechanisms underlying different diabetes subtypes suggest potential differential impacts of gut microbiota. For instance, while SIDD primarily manifests as insulin deficiency due to pancreatic β-cell dysfunction, SIRD is characterized by peripheral insulin resistance [6]. Research indicates that specific gut microbes may contribute to insulin resistance by affecting gut permeability and inflammatory responses, while others influence β-cell function through regulation of insulin secretion-related hormones, such as glucagon-like peptide-1 (GLP-1) [23, 24]. These findings suggest that distinct alterations in gut microbiota might drive the development of different diabetes subtypes.

Mendelian randomization (MR)offers a robust approach to inferring causal relationships by utilizing genetic variants as instrumental variables [25]. By leveraging genetic variation randomly allocated at conception, MR minimizes confounding and reverse causality biases inherent in observational studies [26]. This approach, conceptually analogous to randomized controlled trials, is particularly well-suited for investigating the complex gut microbiota-diabetes relationship by using microbiome-associated genetic variants to evaluate causal effects independent of traditional confounders.

Materials and methods

Study design

This two-sample MR study followed the STROBE-MR guidelines for strengthening reporting [27]. We conducted MR analyses utilizing published genome-wide association study (GWAS) summary statistics for gut microbiota and six diabetes phenotypes: SIDD, SIRD, MOD, MARD—as well as T1DM and overall T2DM (Fig. 1).

Data sources

Data sources are detailed in Table 1. For T1DM, we utilized GWAS data from the recently released Finnish database (R12 version, November 2024), which included 4,721 T1DM cases [28]. T2DM data were derived from three major GWAS datasets of European ancestry: DIAbetes Genetics Replication and Meta-analysis (DIAGRAM), Genetic Epidemiology Research on Aging (GERA), and the full cohort release of the UK Biobank (UKB), collectively comprising 62,892 T2DM cases [29].

GWAS summary statistics for Novel adult-onset T2DM subtypes were obtained from a Swedish study that classified subtypes based on autoimmunity, age, BMI, HbA1c, β-cell function, and insulin resistance at diabetes diagnosis [6, 10]. The sample sizes for this Swedish study included SIDD ($n=3,937$), SIRD ($n=3,874$), MOD ($n=4,118$), and MARD ($n=5,605$).

For gut microbiota data, we utilized the Dutch Microbiome Project (DMP), a comprehensive GWAS involving 7,738 individuals of European descent [30]. This large-scale study employed shotgun metagenomic sequencing of fecal samples to identify gut microbiome composition and correlate genetic variants with taxa and pathway abundance. The analysis encompassed 207 distinct taxa across five taxonomic levels: 5 phyla, 10 orders, 13 families, 26 genera, and 105 species, representing the most extensive collection of species-level gut microbiota data currently available.

All the data used for this research is publicly accessible from the respective GWAS. Given that we utilized anonymized, summary-level data available in the public domain, ethical approval was not required for this study.

Instrumental variable (IV) selection

For forward MR analyses, We extracted exposure-related single nucleotide polymorphisms (SNPs) from the gut microbiota GWAS using the following selection criteria: a significance threshold of $P<1\times10^{\wedge}-5$ and effect allele frequency (EAF) >0.01. For reverse MR analyses examining the four T2DM subtypes, we applied a more stringent significance threshold of $P<5\times10^{\wedge}-6$.

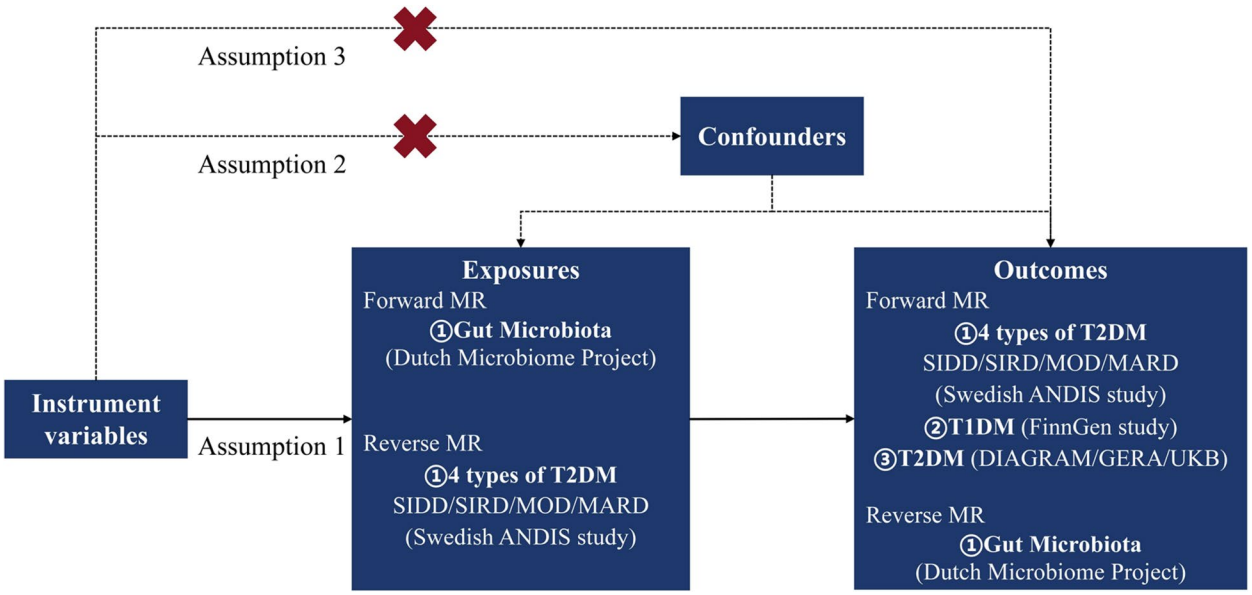

Fig. 1 Diagram for key assumptions of mendelian randomization analyses

Table 1 Detailed information for the GWAS data

Phenotype	PMID	Year	Sample size	Cases/Controls	Ancestry
T1DM	36,829,046	2023	408,210	4,721/403,489	European
T2DM	30,054,458	2018	659,316	62,892/596,424	European
SIDD	34,737,425	2021	3,937	1,193/2,744	European
SIRD	34,737,425	2021	3,874	1,130/2,744	European
MOD	34,737,425	2021	4,118	1,374/2,744	European
MARD	34,737,425	2021	5,605	2,861/2,744	European
Gut microbiota	35,115,690	2022	7,738	/	European

T1DM Type 1 diabetes mellitus, *T2DM* Type 2 diabetes mellitus, *SIDD* Severe insulin-deficiency diabetes, *SIRD* Severe insulin-resistant diabetes, *MOD* Mild obesity-related diabetes, *MARD* Mild age-related diabetes

We performed Linkage disequilibrium (LD) pruning (European ancestry; kb = 10,000; r2 < 0.001). The retained SNPs were merged with diabetes subtype data, excluding palindromic variants. Outliers were identified and filtered out using MR-PRESSO [31], while variants indicating reverse causation were removed following MR Steiger analysis [32]. To mitigate weak instrument bias, only SNPs with *F*-statistic > 10 (calculated using the formula $F = \beta\text{^}2/\text{SE}\text{^}2$) were retained as instruments for MR analyses [33].

Statistical analysis

The primary analysis utilized inverse variance weighted (IVW) regression under a random-effects model. To ensure robust causal estimates when the IVW assumptions were violated, we supplemented this with four additional MR methods: MR-Egger regression, weighted median estimation, weighted mode estimation, and simple mode estimation [34]. To enhance the reliability of our analyses, we excluded exposures with only one associated SNP. We assessed heterogeneity and pleiotropy across several analyses. The MR Egger intercept test evaluated pleiotropy, with $P > 0.05$ indicating no significant bias. We further gauged heterogeneity using MR Egger and IVW to calculate Cochran's Q statistic across SNPs, with $P > 0.05$ suggesting negligible heterogeneity [31, 35]. A significant causal effect was concluded if: IVW $P < 0.05$; $\geq$ 4 of 5 MR methods showed consistent direction of effect; and no significant heterogeneity/pleiotropy was detected.

All statistical analyses were performed using R (version 4.4.2). The MR analyses were facilitated by tools such as Two sample MR (version 0.6.8) [36], and MRPRESSO (version 1.0) [31].

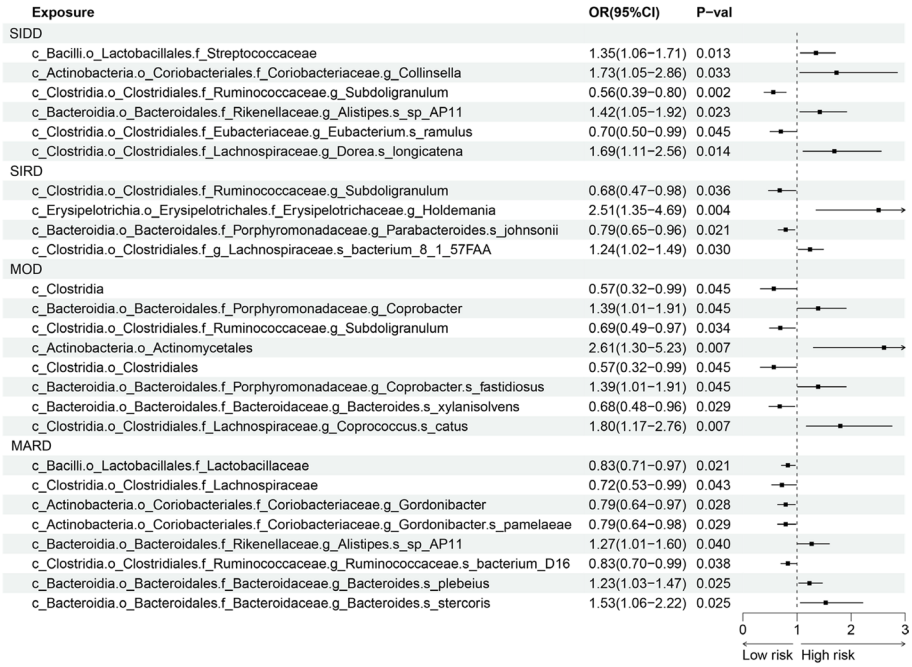

Fig. 2 Forest plot of mendelian randomization analysis of gut microbiota and T2DM subtypes

Results

Mendelian randomization analysis of gut microbiota on four T2DM subtypes

Multiple gut microbial taxa demonstrated significant causal associations with specific T2DM subtypes (Fig. 2; Supplementary Table 1).

For SIDD, positive risk associations were identified with species *Alistipes sp_AP11* (OR = 1.42, 95% CI: 1.05–1.92, *P* = 0.023), species *longicatena* (OR = 1.69, 95% CI: 1.11–2.56, *P* = 0.014), Family *Streptococcaceae*(OR = 1.35, 95% CI: 1.06–1.71, *P* = 0.013), and genus *Collinsella*(OR = 1.73, 95% CI: 1.05–2.86, *P* = 0.033). Conversely, species *ramulus* (OR = 0.70, 95% CI. 0.50–0.99, *P* = 0.045) and genus *Subdoligranulum*(OR = 0.56, 95% CI. 0.39–0.80, *P* = 0.002)showed protective effects against SIDD.

For SIRD, species *Bacterium_8_1_57FAA* (OR = 1.24, 95% CI: 1.02–1.49, *P* = 0.030) and genus *Holdemania*(OR = 2.51, 95% CI: 1.35–4.69, *P* = 0.004)showed positive risk associations. Protective effects were observed for species *johnsonii* (OR = 0.79, 95% CI: 0.65–0.96, *P* = 0.021) and genus *Subdoligranulum*(OR = 0.68, 95% CI: 0.47–0.98, *P* = 0.036),conferred protection against SIRD.

For MOD, risk-increasing associations were found with species *catus* (OR = 1.80, 95% CI: 1.17–2.76, *P* = 0.007), species *fastidiosus* (OR = 1.39, 95% CI: 1.01–1.91, *P* = 0.045), genus *Coprobacter*(OR = 1.39, 95% CI: 1.01–1.91, *P* = 0.045), and Order *Actinomycetales*(OR = 2.61, 95% CI: 1.30–5.23, *P* = 0.007). Protective associations were identified for species *xylanisolvens* (OR = 0.68, 95% CI: 0.48–0.96, *P* = 0.029), Class *Clostridia*(OR = 0.57, 95% CI: 0.32–0.99, *P* = 0.045),genus *Subdoligranulum*(OR = 0.69, 95% CI: 0.49–0.97, *P* = 0.034),and Order *Clostridiales*(OR = 0.57, 95% CI: 0.32–0.99, *P* = 0.045).

For MARD, positive risk associations were observed with species *Alistipes sp_AP11* (OR = 1.27, 95% CI: 1.01–1.60, *P* = 0.04), species *plebeius* (OR = 1.23, 95% CI: 1.03–1.47, *P* = 0.025), and species *stercoris* (OR = 1.53, 95% CI: 1.06–2.22, *P* = 0.025). Protective effects were found for species *pamelaeae* (OR = 0.79, 95% CI: 0.64–0.98, *P* = 0.029), species *Bacterium_D16* (OR = 0.83, 95% CI: 0.70–0.99, *P* = 0.038), Family *Lactobacillaceae*(OR = 0.83, 95% CI: 0.71–0.97, *P* = 0.021),_Family *Lachnospiraceae*(OR = 0.72, 95% CI: 0.53–0.99, *P* = 0.043), and genus *Gordonibacter*(OR = 0.79, 95% CI: 0.64–0.97, *P* = 0.028).

Figure 3 illustrates the taxonomic relationships between the identified gut microbiota and their associations with the four T2DM subtypes.

Mendelian randomization analysis of gut microbiota with T1DM and T2DM

Our MR analyses identified distinct associations between gut microbiota and diabetes types: eight microbial taxa were associated with T1DM, while twenty taxa showed significant associations with T2DM (detailed results in Supplementary Table 1). Through intersection analysis, we found that the microbial associations with T2DM

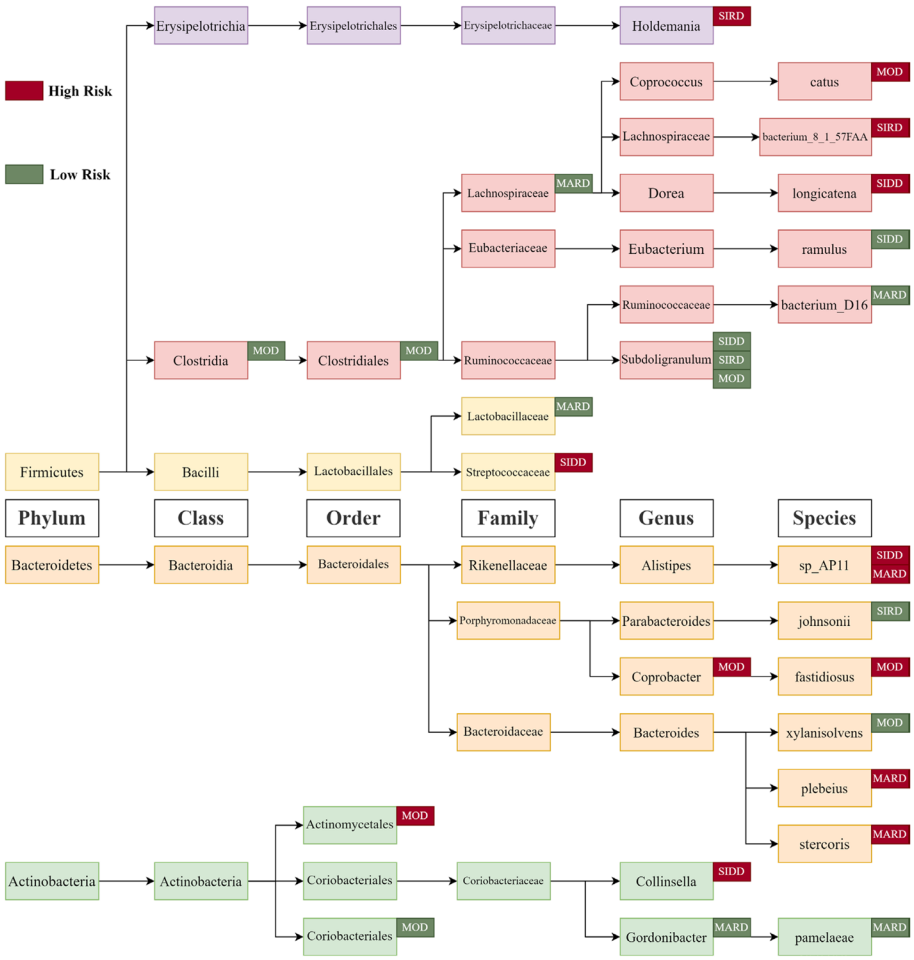

Fig. 3 Taxonomic network visualization of gut microbiota associated with T2DM subtypes identified through mendelian randomization

subtypes were distinct from those with T1DM, showing no overlap. However, six microbial taxa showed consistent associations between T2DM subtypes and overall T2DM. Of these, five were associated with MOD: Class *Clostridia*, Order *Clostridiales*, species *catus*, genus *Coprobacter*, and species *fastidiosus*. One taxon, genus *Holdemania*, showed consistent association with SIRD (Figs. 4 and 5).

Reverse mendelian randomization analysis

We conducted reverse MR analyses using the four T2DM subtypes as exposures against their significantly associated gut microbial taxa. The results revealed bidirectional causal relationships only for SIDD with species *sp. AP11* and species *ramulus* (detailed results in Supplementary Table 2).

Robustness analysis

As shown in Table 2, our comprehensive MR analyses demonstrated robust findings without significant heterogeneity or pleiotropy. MR-Egger regression results indicated no horizontal pleiotropy across all MR analyses. Q statistics from IVW showed no significant heterogeneity in all MR analyses.

Discussion

Our MR study has uncovered novel causal relationships between specific gut microbiota and distinct T2DM subtypes, including SIDD, SIRD, MOD, and MARD. The analysis revealed distinctive associations between gut microbiota and T2DM subtypes: six bacterial taxa with SIDD, four with SIRD, eight with MOD, and eight with MARD. These associations were distinct from T1DM findings. Six bacterial taxa were validated in T2DM analyses, with four showing directionally consistent effects: Class *Clostridia* and Order *Clostridiales* were associated with reduced MOD risk, while species *Catus* was associated with increased MOD risk, and genus *Holdemania* was associated with increased SIRD risk. No significant heterogeneity

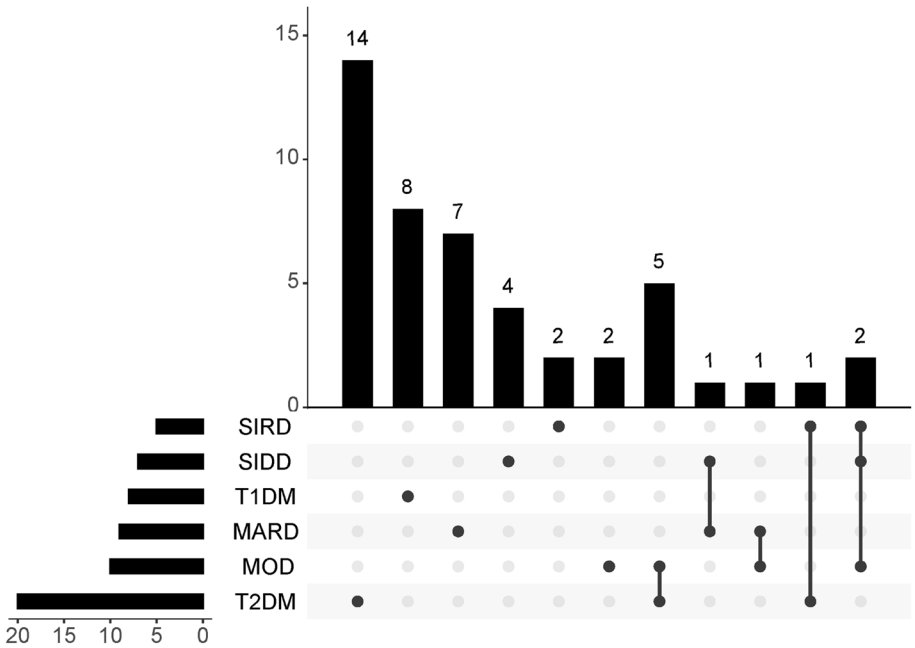

Fig. 4 UpSet plot of gut microbiota associations across six diabetes phenotypes

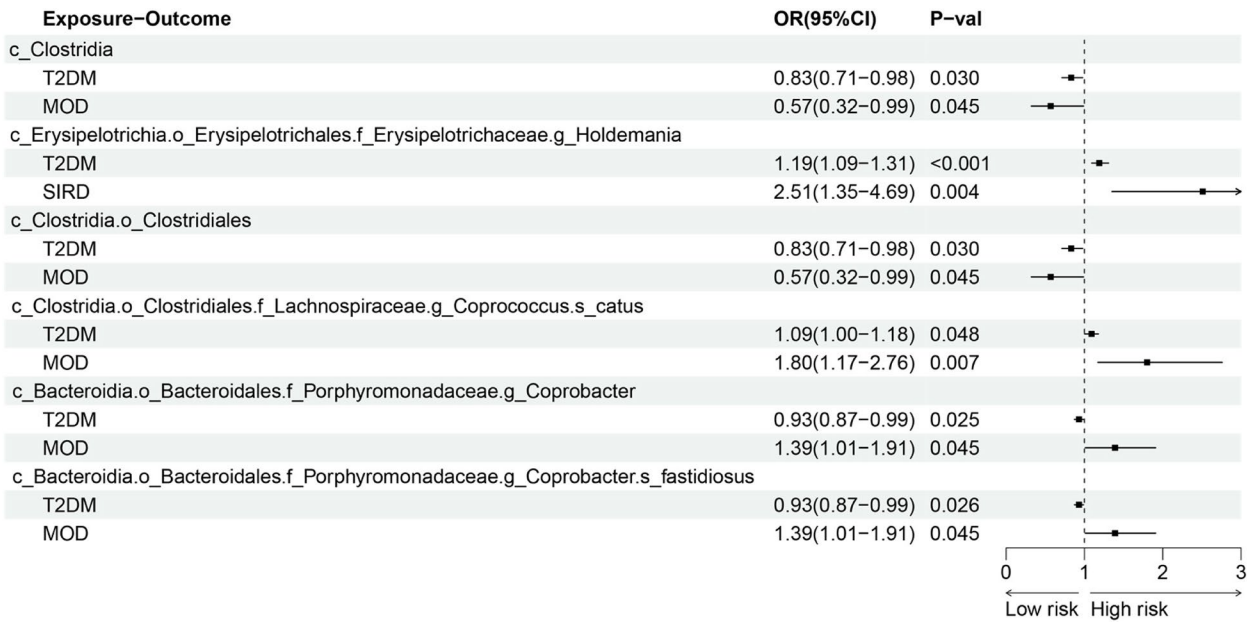

Fig. 5 Forest plot of shared gut microbial taxa between type 2 diabetes mellitus and its subtypes

or pleiotropy was observed across analyses.We have identified specific microbiota with altered risks for these subtypes, which could be potential targets for precision diabetes management through microbiome modulation. The relationships between certain taxa and diabetes subtype heterogeneity are nuanced, and specific microorganisms may have protective or deleterious effects depending on the subtype.

Previous MR studies have explored causal relationships between gut microbiota and T2DM, though without examining specific T2DM subtypes, thus overlooking the heterogeneous effects of gut microbiota.For instance,

Table 2 The results of the heterogeneity and pleiotropy analysis

Outcome	Exposure	Pleiotropy test			Heterogeneity test	
		Intercept	SE	*P* Value	Q	*P* Value
SIDD	Family *Streptococcaceae*	-0.07	0.08	0.405	9.76	0.779
SIDD	Genus *Collinsella*	-0.07	0.14	0.629	4.45	0.487
SIDD	Genus *Subdoligranulum*	0.1	0.08	0.243	9.78	0.712
SIDD	Species *sp_AP11*	0.03	0.12	0.78	4.49	0.722
SIDD	Species *ramulus*	0.01	0.12	0.967	2.79	0.903
SIDD	Species *longicatena*	-0.46	0.45	0.347	4.19	0.758
SIRD	Genus *Subdoligranulum*	-0.01	0.08	0.941	9.03	0.771
SIRD	Genus *Holdemania*	/	/	/	0.11	0.737
SIRD	Species *johnsonii*	0.04	0.12	0.741	6.46	0.596
SIRD	Species *bacterium_8_1_57FAA*	0	0.08	0.996	8.66	0.732
MOD	Class *Clostridia*	-0.04	0.1	0.693	1.85	0.763
MOD	Genus *Coprobacter*	-0.18	0.14	0.244	5.76	0.451
MOD	Genus *Subdoligranulum*	0.01	0.08	0.87	6.96	0.904
MOD	Order *Actinomycetales*	/	/	/	2.01	0.157
MOD	Order *Clostridiales*	-0.04	0.1	0.694	1.85	0.763
MOD	Species *fastidiosus*	-0.17	0.13	0.251	5.75	0.452
MOD	Species *xylanisolvens*	-0.03	0.08	0.755	4.67	0.862
MOD	Species *catus*	0.15	0.11	0.262	2.53	0.773
MARD	Family *Lactobacillaceae*	0.06	0.07	0.442	3.12	0.959
MARD	Family *Lachnospiraceae*	-0.05	0.08	0.552	9.65	0.472
MARD	Genus *Gordonibacter*	-0.11	0.16	0.556	3.65	0.302
MARD	Species *pamelaeae*	-0.11	0.16	0.547	3.67	0.299
MARD	Species *sp_AP11*	0.07	0.09	0.48	6.29	0.506
MARD	Species *bacterium_D16*	0.16	0.09	0.13	5.97	0.426
MARD	Species *plebeius*	0.02	0.08	0.793	2.61	0.856
MARD	Species *stercoris*	-0.11	0.18	0.585	2.07	0.723

SIDD Severe insulin-deficiency diabetes, *SIRD* Severe insulin-resistant diabetes, *MOD* Mild obesity-related diabetes, *MARD* Mild age-related diabetes. Pleiotropy cannot be calculated with less than 2 SNPS

while a prior MR study linked genus *Allisonella* and family *Coriobacteriaceae* to increased T2DM risk, our subtype-specific analysis revealed that species *Alistipes sp_AP11* within *Allisonella* raised SIDD/MARD risk, while *Gordonibacter pamelaeae* of *Coriobacteriaceae* protected against MARD [37]. Similarly, Zhang et al. [38] identified family *Lactobacillaceae* as protective against T2DM; our findings further specified this protection was primarily associated with MARD, suggesting particular relevance for age-related diabetes.The study also showed that species *faecis* in the genus *bacteroides* has a protective effect against type 2 diabetes.

Members of the genus *Bacteroides* are potential colonizers of the colon and account for a major fraction of the gut bacteriome.Previous studies have shown that genus *Bacteroides* can be beneficial or harmful to humans, depending on the environment [39]. For the study of genus *Bacteroides* and T2DM, different studies have produced opposite results [40]. The relationship between genus *Bacteroides* and diabetes is particularly complex. we discovered species *plebeius* and *stercoris* elevated MARD risk, though species *xylanisolvens* lowered MOD risk. species *xylanisolvens* may reduce the risk of MOD by activating the fatty acid G protein-coupled bile acid receptor GPBAR1 (TGR5) and upregulating the expression of uncoupling protein UCP-1, leading to increased thermogenesis in white adipose tissue [41]. Some studies have shown that species *xylanisolvens* can metabolize xylan S32 into monosaccharides and oligosaccharides, producing beneficial SCFAs and folate, which contribute to human health. As a potential probiotic, species *xylanisolvens* has demonstrated beneficial effects in metabolic disorders such as non-alcoholic fatty liver disease (NAFLD), suggesting common mechanistic pathways with MOD pathophysiology [42].

Our phylogenetic analysis revealed significant associations between microbial taxa across different taxonomic levels (phylum, class, order, family, genus, and

species) and distinct T2DM subtypes. From an evolutionary perspective, microorganisms sharing the same phylogenetic branch demonstrated consistent risk patterns across diabetes subtypes. For instance, within the Firmicutes lineage, Class *Clostridia*, Order *Clostridiales*, and Genus *Subdoligranulum* all exhibited protective effects against MOD. Similarly, Genus *Gordonibacter* and its species *pamelaeae* both showed protective associations with MARD. These consistent patterns among phylogenetically related taxa suggest shared functional characteristics that may influence diabetes pathophysiology through common biological mechanisms.

To validate our findings, we conducted separate MR analyses comparing gut microbiota associations with recent T1DM GWAS data and a large European T2DM meta-GWAS. This comparative approach, analyzing both general diabetes types without subtype stratification, allowed us to distinguish whether observed associations were driven by subtype-specific effects or broader diabetes pathophysiology, thereby enhancing the reliability of our results.Several key taxa emerged from our comparative analyses. Order *Clostridiales* showed a protective effect against MOD, likely mediated through SCFA production, particularly butyrate. These SCFAs improve insulin sensitivity and glucose control through modulation of host metabolism and immune function, while also promoting weight reduction—aligning with the obesity-related characteristics of MOD [43] species *catus*, a member of the phylum *Firmicutes*, demonstrated consistent associations with diabetes risk across studies. Previous research has identified this species as a key microbial signature distinguishing diabetic individuals from controls [44], with elevated abundance observed in obese individuals with poor glycemic control [45, 46]. The association between genus *Holdemania* and SIRD aligns with previous metabolic syndrome research, where genus *Holdemania* abundance decreased following syndrome resolution. This connection is particularly relevant given that insulin resistance is a hallmark of both metabolic syndrome and SIRD [47]. An intriguing finding emerged regarding species *fastidiosus*, which showed opposing effects in T2DM versus MOD. As a relatively newly characterized gut microorganism (named in 2013), further research is needed to determine whether these contrasting effects stem from host environmental factors or other mechanisms [48].

Although some associations were not validated in the general T2DM analysis, they remain potentially significant. Notably, genus *Subdoligranulum* demonstrated protective effects against multiple subtypes (MOD, SIDD, and SIRD). This aligns with population cohort studies showing negative correlations between genus *Subdoligranulum* abundance and obesity, suggesting beneficial effects on glucose and lipid metabolism [49].

SIDD patients characteristically exhibit systemic inflammation and impaired β-cell function [6]. Our finding linking species *longicatena* to increased SIDD risk aligns with its known role in modulating inflammatory pathways [50]. This connection is supported by studies showing species *longicatena's* involvement in insulin resistance-related inflammatory pathways following bariatric surgery [51]. Similarly, the protective association we observed between species *ramulus* and SIDD corresponds with clinical observations showing altered species *ramulus* abundance following GLP-1 treatment, which improved endothelial function [52]. These findings suggest that GLP-1's therapeutic effects may be partially mediated through modifications of gut microbiota composition.

Species *pamelaeae* has been identified as a nonsporulating, anaerobic, Gram-positive, nonmotile coccobacillus [53]. Prior studies also support connections between species *pamelaeae* and diabetes. This bacterium plays a role in metabolizing dietary compounds like imidazole propionate, which associates with T2DM development, highlighting a potential link between its metabolic activities and diabetes progression [54]. Additionally, species *pamelaeae* can biotransform ellagitannins, impacting metabolic diseases [55]. With growing interest in probiotics for glycemic control, the ability of species *pamelaeae* to produce diabetes-protective urolithin has been noted [56, 57]. Our findings further emphasize the role of aging in this association.

To our knowledge, this is the first study examining links between gut microbes and the novel diabetes classification system. Using GWAS data, we explored complex causal relationships between species-level gut flora and five diabetes subtypes. Our analysis provides preliminary evidence informing targeted prevention and management efforts based on microbiome-subtype interplay. Several methods were employed to improve result robustness by mitigating bias and pleiotropy. However, some limitations exist. First, the European population limits generalizability to other ethnicities, Second, despite using different validation cohorts, the inherent variability in gut microbiota composition across populations and the generally low reproducibility of microbiome studies may restrict the external validity of our results. Third, despite our comprehensive methodological approach, the possibility of residual biases cannot be completely eliminated. Finally, as an initial screening study, statistical power and sample size limitations should be considered when interpreting our findings.

Conclusions

In summary, our MR analysis revealed several potential causal associations between specific gut microbiota and distinct T2DM subtypes, demonstrating differential microbial signatures across SIDD, SIRD, MOD, and MARD. We identified specific taxa with subtype-specific effects, including protective associations of Class *Clostridia* and Order *Clostridiales* against MOD, and risk associations of genus *Holdemania* with SIRD. These preliminary findings may contribute to our understanding of diabetes heterogeneity and its relationship with the gut microbiome. Further validation across diverse populations and investigation of underlying mechanisms through clinical trials will be essential to establish the clinical relevance of these associations.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01863-x.

Supplementary Material 1.

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Authors' contributions
All authors contributed to the conception and design of the study. Material preparation, data collection, and analysis were conducted by Zhichao Ruan and Jinxi Zhao. The initial draft of the manuscript was written by Zhichao Ruan, and all authors provided feedback on previous versions. Jiangteng Liu contributed to revising the manuscript. All authors reviewed and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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