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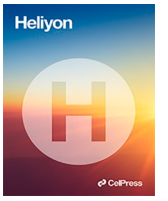

Research article

Causal relationship between gut microbiota and autoimmune thyroiditis: A mendelian study

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ABSTRACT

Background: Autoimmune thyroiditis (AIT), also known as Hashimoto's thyroiditis (HT) or chronic lymphocytic thyroiditis, is a prevalent autoimmune disorder. Despite its high prevalence, the pathogenesis of AIT remains unclear. Previous studies have suggested a potential association between gut microbiota and AIT. However, whether this relationship is causal or coincidental remains uncertain. To address this gap in knowledge, our study aimed to investigate the potential causal association between gut microbiota and AIT using the two-sample Mendelian randomization (MR) method.

Methods: Summary-level gut microbiota data comprising 211 taxa (131 genera, 35 families, 20 orders, 16 classes, and 9 phyla) were obtained from the comprehensive MiBioGen study. Genetic associations with 22 gastrointestinal diseases were extracted from the UK Biobank, FinnGen study, and various extensive GWAS studies. A meticulous MR analysis was conducted to evaluate the causal relationship between genetically predicted gut microbiota and these gastrointestinal diseases. Sensitivity analyses and tests for heterogeneity were systematically performed to validate the reliability of our findings.

Results: Six gut microbiota species showed significant associations with AIT according to the IVW method. Among them, the following exhibited negative associations with AIT: family Alcaligenaceae, family Pasteurellaceae (ID: 3689), family Peptococcaceae, genus Lachnospira, genus Victivallis, and order Pasteurellales (ID: 3688). No evidence of pleiotropy or heterogeneity was detected.

Conclusion: The MR analysis uncovered a causal relationship at the genetic prediction level between specific gut microbiota and AIT. These findings offer novel insights into the mechanisms governing the development of AIT mediated by gut microbiota. This knowledge could inform the design of future interventions, potentially involving microbiome-related strategies, to address the mechanisms associated with AIT development.

1. Introduction

Autoimmune thyroiditis (AIT), also known as Hashimoto's thyroiditis (HT) or chronic lymphocytic thyroiditis, is a prevalent autoimmune disorder with an annual prevalence ranging from 0.3 to 1.5 cases per 1000 individuals [1]. While the clinical

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presentations of HT and chronic lymphocytic thyroiditis differ, both conditions share common immune-mediated mechanisms of pathogenesis, and there are instances where they can transition from one to the other [2]. In general, the onset of AIT is initiated by the breakdown of immune tolerance towards thyroid-specific self-antigens, influenced by genetic predisposition, environmental factors, gut microbiome composition, and immune responses [3]. Nonetheless, the specific risk factors and underlying pathogenesis of AIT still remain elusive.

Increasingly, there is compelling evidence indicating that modifications in gut microbiota composition play a pivotal role in the initiation and advancement of AIT in individuals. The alternations in gut microbiota composition, also known as dysbiosis, has also been documented in individuals with intestinal autoimmune diseases, as well as in those with type 1 diabetes mellitus, systemic sclerosis, and systemic lupus erythematosus [4]. A meta-analysis revealed that patients with HT showed significantly higher values of diversity indices [5]. The mechanism behind that, may be associated with gut microbiota metabolites. Metabolites produced by the gut microbiota, notably short-chain fatty acids (SCFAs), can serve as energy substrates for enterocytes. In conjunction with thyroid hormones, they facilitate the differentiation of intestinal epithelial cells and strengthen tight intercellular junctions [6], and therefore might influence thyroid function.

One promising approach to investigate the potential causal relationship between gut microbiota and AIT is Mendelian randomization (MR). In fact, MR has been used to investigate the relationship between gut microbiota and many diseases, like seven gastrointestinal diseases [7], periodontitis [8], and pancreatic cancer [9]. MR is a robust methodology that leverages genetic variants as instrumental variables to assess causality. By utilizing genetic variants strongly associated with a specific exposure as proxies, MR can provide more robust evidence for causal inference compared to traditional observational studies [10]. MR mitigates the impact of confounding and reverse causation, offering a unique opportunity to examine causal relationships systematically [11].

In the context of AIT, we aim to employ MR to explore the causal relationship between gut microbiota and AIT, and identify specific harmful or protective bacterial taxa AIT.

2. Materials and methods

2.1. Study design

In general, we conducted a two-sample MR study to assess the causal relationship between gut microbiota and AIT, as shown in Fig. 1.

The selection criteria for identifying instrumental variables (IVs) were as follows: a) Single nucleotide polymorphisms (SNPs) linked to each genus with locus-wide significance ($P < 1 \times 10^{-5}$) were considered as potential IVs; b) Data from the European samples within the 1000 Genomes Project served as the reference panel for calculating linkage disequilibrium (LD) among the SNPs. SNPs with an R^2 value of less than 0.001 (using a clumping window size of 10,000 kb) were further analyzed, and only those SNPs exhibiting the most significant *P*-values were retained for subsequent analysis; c) SNPs with an F statistic <10 should be excluded; d) In cases where palindromic SNPs were present, the alleles on the forward strand were determined using allele frequency information.

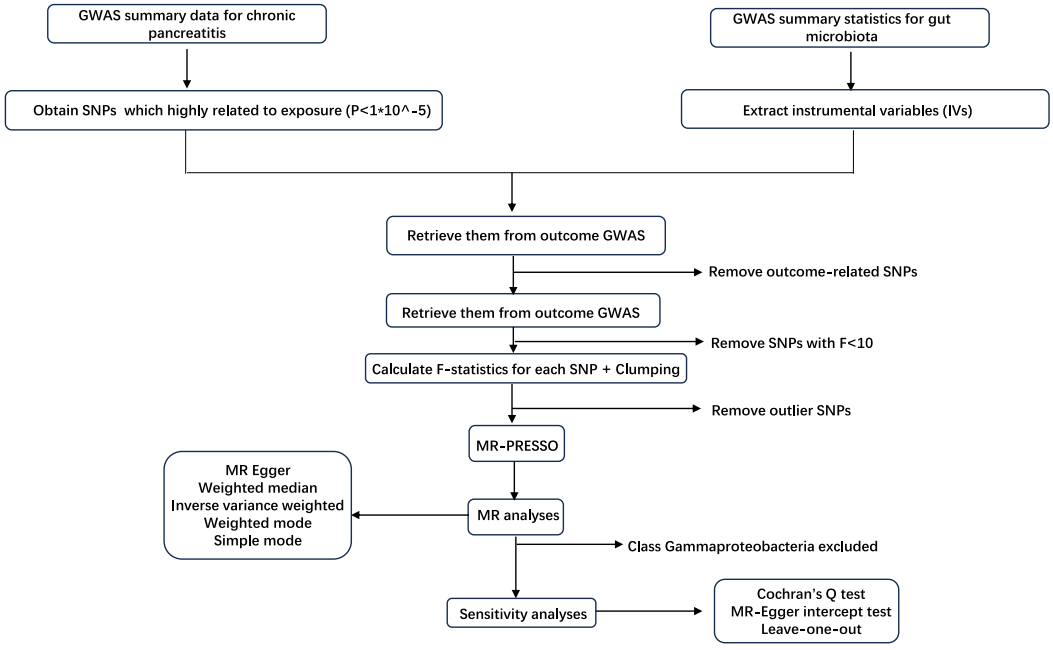

Fig. 1. The flowchart of the Mendelian randomization study revealing the causal relationship between gut microbiota and autoimmune thyroiditis.

2.2. Data sources

In this study, we employed the Genome-Wide Association Study (GWAS) dataset sourced from the MiBioGen consortium, encompassing a cohort of 18,340 participants, to scrutinize the exposure variable, gut microbiota [12]. This specific GWAS endeavor meticulously scrutinized a total of 211 gastrointestinal microbiota taxa through the utilization of the 16S ribosomal RNA sequencing technique.

For the outcome, AIT, the GWAS summary statistics consisting of 213,746 individuals, specifically 244 patients with AIT and 187,684 controls were from FinnGen database R8. Detailed information was listed in Table 1.

2.3. Statistical analysis

In our study, we initiated by harmonizing SNPs with identical alleles from the data source, followed by conducting a two-sample MR analysis. The primary analysis method employed for assessing the causal relationship between gut microbiota and AIT was the inverse Variance Weighted (IVW) method and MR Egger method. The IVW method integrates Wald estimates from each SNP through meta-analysis, providing a comprehensive estimation of the influence of gut microbiota on AIT. Its advantage lies in simultaneously considering the effects of multiple genotypes on the study factor, thereby enhancing the accuracy of causal inference. The IVW result remains unbiased in the absence of horizontal pleiotropy [13]. We utilized odds ratios (ORs) of the exponential β for categorical outcomes along with corresponding confidence intervals (CIs) to estimate effect sizes of causality. A significance threshold of $P < 0.05$ was applied. All the analyses were done by R package named "TwoSampleMR" within the environment of R 4.3.2.

To ensure the robustness and sensitivity of our findings, we also performed additional analyses, including MR-Egger, weighted median, simple mode, MR-PRESSO (Mendelian Randomization Pleiotropy Residual Sum and Outlier). The MR-Egger method is a commonly employed randomization pattern in Mendelian randomization, assessing the impact of a factor on a disease through a linear regression model. Egger regression is utilized to estimate bias and correct results, enhancing the accuracy of causal estimates [14]. The Weighted Median method is primarily applied to address biased samples, effectively mitigating sample bias and improving the reliability and accuracy of randomized experiments [15]. Both the simple mode and weighted mode are frequently implemented randomization patterns that eliminate interfering factors in experimental results by random grouping [16]. Heterogeneity was assessed using Cochrane's Q test calculated in the IVW methods while potential pleiotropy was evaluated and corrected using the MR-Egger intercept test. Cochran's Q test is employed as a method to evaluate heterogeneity among different IVs in a study. The p-value derived from Cochran's Q test is crucial in determining the presence or absence of significant heterogeneity. If the *P*-value is less than the pre-defined significance level (usually 0.05), it is indicative of significant heterogeneity among the IVs [17]. The "leave-one-out" method was employed to evaluate the causal genetic impact of potential outlier SNPs and to ascertain whether the exclusion of these SNPs influenced the MR estimates.

3. Results

Based on the criteria for selecting IVs, a total of 1050 SNPs were employed as IVs to investigate 210 bacterial genera ($P < 1 \times 10^{-5}$). The F-statistic for all IVs exceeded 10, signifying that the chosen SNPs exhibited robust IV effects, thus minimizing the potential for weak instrument bias.

As shown in Table 2, six bacterial genera were found to be significantly associated with AIT in at least IVW method. It is noteworthy that the MR Egger results for class.Gammaproteobacteria.id.3303, in contrast to the remaining four analytical methods, exhibited entirely divergent trends. Furthermore, the OR derived from their analyses showed significant discrepancies, leading to its exclusion, just as illustrated in Fig. 1. IVW estimates suggests family Alcaligenaceae (OR = 0.25, 95% CI: 0.09–0.74, P = 0.012), family Pasteurellaceae (OR = 0.50, 95% CI: 0.27–0.93, P = 0.026), family Peptococcaceae (OR = 0.35, 95% CI: 0.15–0.81, P = 0.014), genus Lachnospira (OR = 0.18, 95% CI: 0.04–0.90, P = 0.037), genus Victivallis (OR = 0.56, 95% CI: 0.33–0.96, P = 0.034), order Pasteurellales (OR = 0.50, 95% CI: 0.27–0.93, P = 0.026) all exhibited negative correlation to AIT (Fig. 2). The MR results were presented via scatter plots in Fig. 3 (A-F) to reveal the potential positive and negative associations between gut microbiota and AIT.

As shown in Table 3, there was no significant heterogeneity identified in AIT IVs by Cochrane's Q test, revealing that all *P*-values were over 0.05 both by IVW method and MR Egger method. The outcomes from the leave-one-out method indicated that certain individual SNPs might introduce bias in genetic prediction (Fig. 4A–F). Horizontal pleiotropy, which refers to the possibility of the IVs affecting outcomes through pathways other than the intended one, was evaluated using the MR Egger intercept method. The results revealed no indications of horizontal pleiotropy, suggesting that the chosen IVs were not significantly influencing outcomes through

Table 1
Details of the exposure and outcome.

Trait	Consortium	Samples	Link	Year
Exposure				
211 GM taxa	MiBioGen	/	https://mibiogen.gcc.rug.nl/	2021
Outcome				
Autoimmune thyroiditis	FinnGen	/	https://www.finngen.fi/en	2021

Table 2
Significant Mendelian randomization estimates of the associations from gut microbiota on autoimmune thyroiditis.

Taxa	Exposure	MR method	No. of SNP	OR	P value
Family	Alcaligenaceae.id.2875	MR Egger	11	0.057	0.285
		Weighted median	11	0.203	0.026
		Inverse variance weighted	11	0.254	0.012
		Simple mode	11	0.141	0.147
		Weighted mode	11	0.168	0.171
Family	Pasteurellaceae.id.3689	MR Egger	13	0.493	0.322
		Weighted median	13	0.509	0.122
		Inverse variance weighted	13	0.499	0.026
		Simple mode	13	0.816	0.792
		Weighted mode	13	0.891	0.876
Family	Peptococcaceae.id.2024	MR Egger	9	0.283	0.325
		Weighted median	9	0.408	0.102
		Inverse variance weighted	9	0.345	0.014
		Simple mode	9	0.408	0.307
		Weighted mode	9	0.422	0.273
Genus	Lachnospira.id.2004	MR Egger	5	0.037	0.588
		Weighted median	5	0.229	0.164
		Inverse variance weighted	5	0.182	0.037
		Simple mode	5	0.214	0.307
		Weighted mode	5	0.214	0.332
Genus	Victivallis.id.2256	MR Egger	10	0.323	0.623
		Weighted median	10	0.665	0.282
		Inverse variance weighted	10	0.558	0.034
		Simple mode	10	0.667	0.581
		Weighted mode	10	0.720	0.654
Order	Pasteurellales.id.3688	MR Egger	13	0.493	0.322
		Weighted median	13	0.509	0.146
		Inverse variance weighted	13	0.499	0.026
		Simple mode	13	0.816	0.800
		Weighted mode	13	0.891	0.880

Abbreviation: Mendelian randomization (MR), Single-nucleotide polymorphism (SNP), Odds ratio (OR).

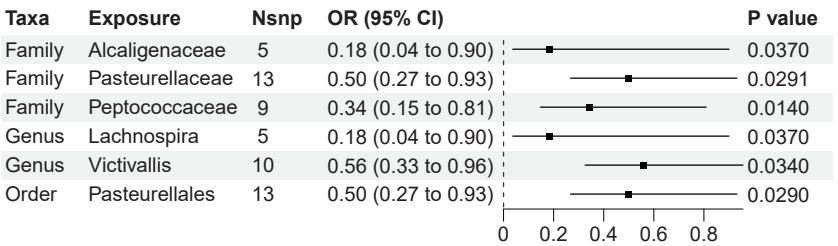

Fig. 2. Forrest plot for summary causal effects of gut microbiota on autoimmune thyroiditis risk based on inverse variance weighted MR method.

alternative pathways (Table 4).

4. Discussion

In our current investigation, we harnessed extensive GWAS summary-level data to undertake MR analysis, with the aim of assessing the potential causal relationship between gut microbiota and AIT. Our research findings indicate that various constituents of the gut microbiota have the potential to decrease the risk of AIT. Specifically, our study revealed that family Alcaligenaceae, family Pasteurellaceae, family Peptococcaceae, genus Lachnospira, genus Victivallis, order Pasteurellales exhibited an inverse association with the risk of AIT.

It is noteworthy that dietary constituents have the potential to impact AIT by influencing the gut microbiota. Specifically, the gut microbiota is known to contribute to the production of various metabolites, including short-chain fatty acids (SCFAs), which serve to mitigate bacterial translocation, uphold intestinal integrity, and curtail intestinal inflammation [18]. These SCFAs, such as acetate, propionate, and butyrate, have been shown to possess anti-inflammatory and antioxidant properties [19,20]. Butyrate exhibits multifaceted properties within the gastrointestinal milieu. It activates G-protein coupled receptors, namely GPR41 and GPR43, thereby modulating immune responses and dampening inflammation [21]. Furthermore, butyrate promotes the synthesis of antimicrobial peptides by intestinal epithelial cells, bolstering the innate immune system's ability to combat pathogenic microorganisms [22]. As previous studies reported, genus Lachnospiraceae, family Alcaligenaceae, family Pasteurellaceae and family Peptostreptococcaceae

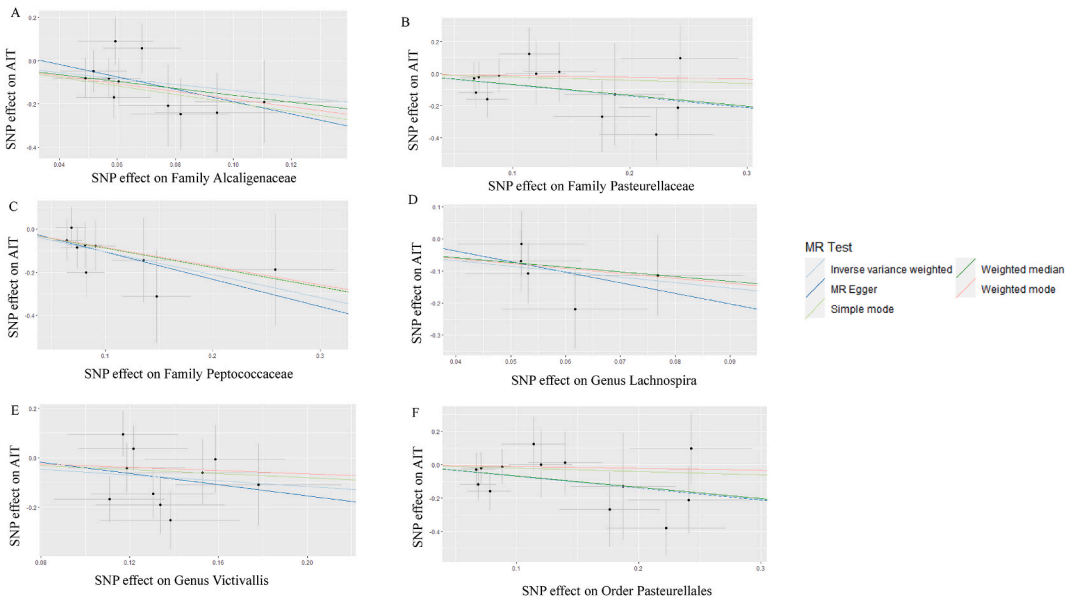

Fig. 3. Summary of scatter plots of potential associations between gut microbiota and autoimmune thyroiditis risk. (A) SNP effect on Family Alcaligenaceae; (A) SNP effect on Family Alcaligenaceae; (B) SNP effect on Family Pasteurellaceae; (C) SNP effect on Family Peptococcaceae; (D) SNP effect on Genus Lachnospira; (E) SNP effect on Genus Victivallis; (F) SNP effect on Order Pasteurellales.

Table 3
The heterogeneity results from the Cochran's Q test.

Taxa	Exposure	IVW		MR Egger	
		Q	P value	Q	P value
Family	Alcaligenaceae.id.2875	6.441	0.777	6.073	0.733
Family	Pasteurellaceae.id.3689	7.887	0.794	7.886	0.723
Family	Peptococcaceae.id.2024	2.454	0.964	2.422	0.933
Genus	Lachnospira.id.2004	1.462	0.833	1.375	0.711
Genus	Victivallis.id.2256	9.860	0.362	9.784	0.281
Order	Pasteurellales.id.3688	7.887	0.734	7.886	0.723

Abbreviation: Inverse variance weighted (IVW).

belong to SCFA-producing bacteria families [23]. Therefore, their negative association with AIT risk observed in this study suggests that SCFAs produced by certain gut bacteria may play a protective role in AIT pathogenesis [24], consistent with studies ever reported [25,26].

Our study offers several notable advantages. Firstly, it represents the inaugural MR analysis aimed at establishing a causal link between gut microbiota and AIT. This approach effectively mitigates the influence of confounding variables and offers potential candidate bacteria for subsequent functional investigations [27]. Additionally, our MR findings hold substantial implications for public health, as they complement prior research on the interplay between gut microbiota and AIT, offering a novel genetic perspective on their connection. From a disease prevention standpoint, the regulation of gut microbiota could potentially guide preventive strategies for AIT. Furthermore, on a diagnostic note, it underscores the importance of screening for AIT in individuals displaying gut microbiota irregularities.

However, there are notable limitations in our research that warrant attention. It is essential to consider these constraints when interpreting the data. Firstly, our study relied on summary statistics rather than raw data, which precluded the performance of subgroup analyses, such as gender-specific investigations within the AIT patient population. Secondly, due to a limited sample size and the limitations of microbiome GWAS, we could only classify gut microbiota at the genus level. Consequently, we were unable to delve deeper into the causal relationship between specific bacterial species and AIT. Thirdly, while the majority of participants in the GWAS meta-analysis of gut microbiota data were of European descent, potential confounding from demographic stratification remains, limiting the generalizability of our findings to non-European populations. Moreover, MR methods utilize genetic variations to address causal inference questions in epidemiology rather than genetic inquiries per se. In this two-sample MR analysis, we discussed the overall association between gut microbiota and DN but did not investigate the direct cause-and-effect relationship. Hence, further research is essential to uncover the precise mechanisms, targets, and pathways linking gut microbiota and AIT. Consequently, cautious interpretation of these findings is warranted.

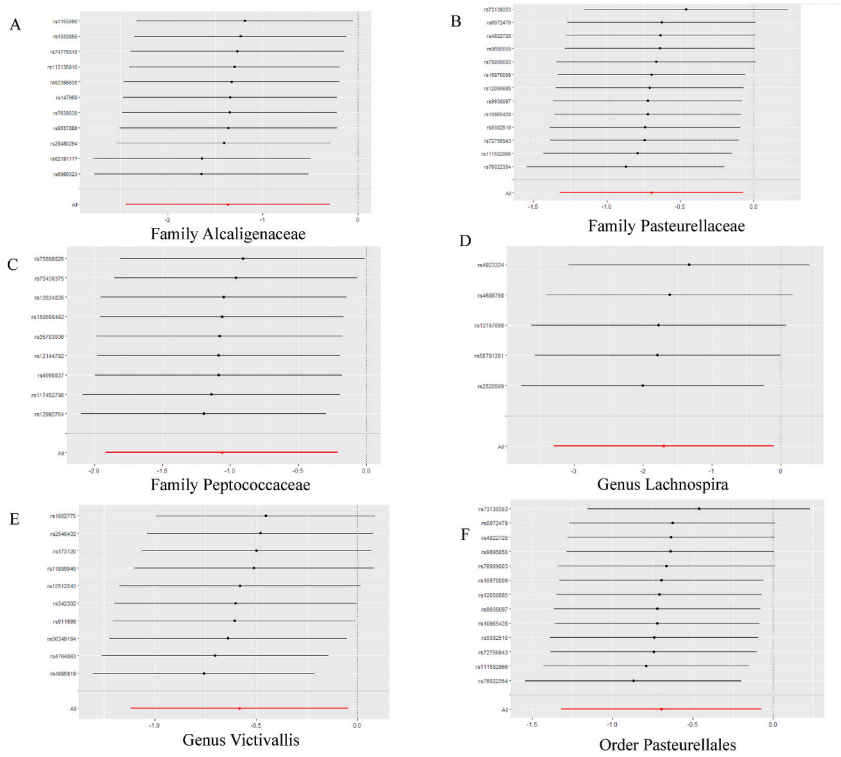

Fig. 4. Leave-one-out analysis of gut microbiota on autoimmune thyroiditis. (A) Family Alcaligenaceae; (B) Family Pasteurellaceae; (C) Family Peptococcaceae; (D) Genus Lachnospira; (E) Genus Victivallis; (F) Order Pasteurellales.

Table 4
Pleiotropy results from MR Egger intercept analysis.

Taxa	Exposure	Egger intercept	SE	P value
Family	Alcaligenaceae.id.2875	0.097	0.160	0.559
Family	Pasteurellaceae.id.3689	0.002	0.080	0.984
Family	Peptococcaceae.id.2024	0.020	0.108	0.862
Genus	Lachnospira.id.2004	0.093	0.314	0.787
Genus	Victivallis.id.2256	0.072	0.289	0.809
Order	Pasteurellales.id.3688	0.002	0.080	0.984

Abbreviation: standard error (SE).

5. Conclusion

In summary, this two-sample MR study found that family Alcaligenaceae, family Pasteurellaceae, family Peptococcaceae, genus Lachnospira, genus Victivallis, order Pasteurellales were negatively associated with AIT. The MR analysis revealed a genetic prediction-level causal relationship between specific gut microbiota and AIT, providing novel insights into the mechanisms underlying the development of AIT mediated by gut microbiota. Further RCT studies are needed to clarify the protective effect of probiotics on AIT and its specific mechanism.

Data availability statement

The raw data supporting the conclusions of this article can be found here: https://mibiogen.gcc.rug.nl/, https://r8.finngen.fi/. All data are uploaded in the supplementary data.

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Ethics approval

The study was conducted utilizing publicly accessible data derived from the MiBioGen and FinnGen studies, adhering to the principles outlined in the Helsinki Declaration of 1964 and its subsequent revisions. Ethical approval was obtained for both the MiBioGen and FinnGen studies, and all participants provided informed consent before their participation. The databases contain patient data that has been de-identified, ensuring the confidentiality of personal information.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Yujun Xiong: Writing – original draft, Software, Formal analysis, Data curation. **Xingyun Zhu:** Software, Methodology, Investigation. **Qingfeng Luo:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Qingfeng Luo reports financial support was provided by National Key R&D Program of China. Qingfeng Luo reports financial support was provided by CAMS Innovation Fund for Medical Sciences. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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