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Gut microbiota and risk of polycystic ovary syndrome: Insights from Mendelian randomization

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ABSTRACT

Background: Polycystic ovary syndrome (PCOS) is a multifaceted endocrine and metabolic syndrome with complex origins and pathogenesis that has not yet been fully elucidated. Recently, the interconnection between gut microbiota and metabolic diseases has gained prominence in research, generating new insights into the correlation between PCOS and gut microbiota composition. However, the causal link between PCOS and gut microbiota remains relatively unexplored, indicating a crucial gap in current research.

Methods: We conducted a two-sample Mendelian randomization analysis using summary statistics obtained from the MiBioGen Consortium's extensive genome-wide association studies (GWAS) meta-analysis, focusing on the gut microbiota. Summary statistics for PCOS were acquired from the FinnGen Consortium R7 release data. Various statistical approaches, including inverse variance weighted, MR-Egger, maximum likelihood, weighted model, and weighted median, have been employed to investigate the causal association between the gut microbiota and PCOS. Additionally, we performed a reverse causal analysis. Cochran's Q statistic was used to assess the heterogeneity of the instrumental variables. Regarding the relationships between PCOS and specific genera within the gut microbiota, a significance level of $P < 0.05$ was observed, but only when $q \geq 0.1$.

Results: Our analysis revealed that specific microbial genera, namely Bilophila ($P = 4.62 \times 10^{-3}$), Blautia ($P = 0.02$), and Holdemania ($P = 0.04$), displayed a protective effect against PCOS. Conversely, the presence of the Lachnospiraceae family of bacteria was associated with a detrimental effect on PCOS ($P = 0.04$). Furthermore, reverse Mendelian randomization analysis confirmed the significant influence of Lachnospiraceae on PCOS. No significant variations in instrumental variables or evidence of horizontal pleiotropy were observed.

Conclusions: The results revealed a definitive causal link between PCOS and the presence of Bilophila, Blautia, Holdemania, and Lachnospiraceae in the gut microbiota. This discovery could provide pivotal insights, leading to novel preventive and therapeutic approaches for PCOS.

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1. Introduction

PCOS is a prevalent hormonal disorder that affects approximately 5–10 % of women in their reproductive years [1]. It carries a significant risk of infertility, obesity, and insulin resistance [2]. Additionally, PCOS is closely associated with an increased susceptibility to conditions such as diabetes, metabolic syndrome, endometrial cancer, cerebrovascular diseases, and other ailments [3]. Consequently, PCOS not only has detrimental effects on the physical and mental health of women in their reproductive years but also exacerbates the worldwide economic burden associated with healthcare expenditures. Current understanding suggests that PCOS is a multifactorial disease involving various factors such as genetics, inflammation, gut microbiota, endocrine hormones, and insulin resistance [4,5]. Notably, investigation of the gut microbiota in patients with PCOS has garnered significant attention in recent years, revealing its pivotal role in the development and progression of the condition [6]. Recent studies have increasingly emphasized the robust association between PCOS and the gut microbiome, encompassing factors such as insulin resistance, metabolic syndrome, and hyperandrogenemia [7]. Potential mechanisms by which the gut microbiota may modulate PCOS progression include short-chain fatty acids (SCFAs), the gut-brain axis, and the liver-ovary axis [8].

A clinical study comparing patients with PCOS with healthy controls revealed an imbalance in the composition of the intestinal microbiome. Patients with PCOS exhibit reduced levels of Faecalibacterium, Bifidobacterium, and Blautia genera, while the abundances of Parabacteroides and Clostridium are increased [9]. Similarly, in a study involving a letrozole-induced PCOS mouse model, hyperandrogenemia was observed to diminish the diversity and quantity of bacteria in the large intestines of mice [10]. Although the association between changes in the gut microbiota and PCOS has been established, there remains a lack of consensus regarding the specific bacteria that are most influential in PCOS, and the exact causal relationship between the two remains unclear [11]. Consequently, it is crucial to undertake comprehensive research to investigate and elucidate the causal connection between gut microbiota and PCOS.

Mendelian randomization (MR) is an analytical technique utilized in epidemiology to strengthen causal inference in associations between exposure and outcome using genetic variants as instruments [12]. This strategy is not prone to confounding because genetic variants are randomly distributed during conception; thus, they are not associated with environmental or self-selected factors that may confound the analysis. In addition, MR has the potential to reduce reverse causality because fixed alleles are not influenced by disease onset or progression.

The increase in large-scale GWAS focusing on the gut microbiome and its links to diverse diseases has led to the widespread adoption of MR in research. This approach has been extensively employed to investigate the relationship between gut microbiota and various health conditions, including cancers, metabolic disorders, and mental disorders [13]. Recent MR analysis has indicated that several factors, such as obesity, fasting insulin, male-pattern balding, menopause timing, and depression, may potentially contribute to the development of PCOS [14]. However, there have been no MR reports on the causal relationship between PCOS and the gut

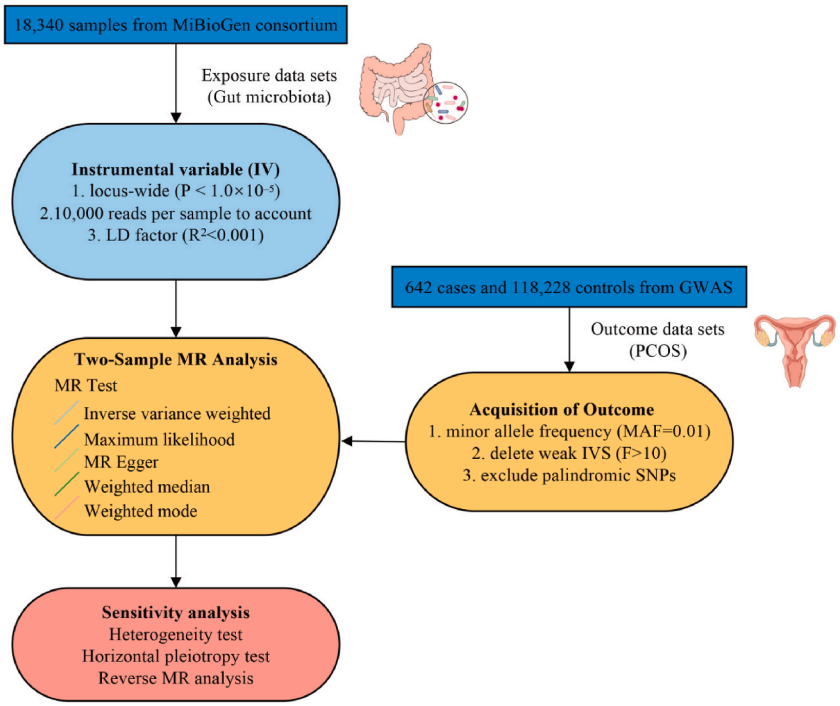

Fig. 1. The flowchart of the study. Furthermore, we performed a reverse MR analysis in the same way, with PCOS as the exposure and gut microbiota as the outcome. It was designed to investigate whether PCOS causes imbalances in the specific gut microbiota. IV, instrumental variable; LD factor, linkage disequilibrium factor; MR Egger, Mendelian randomization-Egger; SNPs, single nucleotide polymorphisms.

microbiota. Although prior observational research has shown a connection between gut microbiota and the onset and progression of PCOS, the causal relationship remains unclear. Therefore, through rigorous dual sample MR analysis, this study aims to reveal the complex causal relationship between gut microbiota composition and the development of PCOS, explore the potential impact of gut microbiota, and provide new insights for the treatment and prevention of PCOS.

2. Materials and methods

2.1. Study setting and design

We performed a two-sample MR study utilizing data sourced from the publicly available GWAS catalog to explore the causal relationship between the gut microbiome and PCOS (http://www.ebi.ac.uk/gwas). Fig. 1 provides a comprehensive overview of the study design.

2.2. Gut microbiota sample

Summary statistics of the gut microbial taxa were obtained through a multi-ethnic GWAS meta-analysis comprising 18,340 individuals from 24 cohorts, primarily of European origin [15]. Microbial composition was analyzed by targeting three variable regions of the 16S rRNA gene, with all datasets normalized to 10,000 reads per sample to account for variations in sequencing depth. Direct taxonomic binning was utilized for taxonomic classification, with only taxa present in over 10 % of the samples in each cohort considered, to assess the impact of host genetics on the abundance of gut bacterial taxa. The study-wide thresholds included a minimum sample size of 3000 individuals and their presence in at least three cohorts [16]. At the genus level, 131 genera with a mean abundance greater than 1 % were identified, including 12 unknown genera [15]. As a result, 119 genus-level taxa were analyzed in the current study.

2.3. PCOS sample

The study population for our research comprised Finnish adult female participants whose genetic information was derived from the GWAS available in the FinnGen Consortium R7 release [17]. FinnGen, a collaborative public–private research initiative, integrates imputed genotype data from both newly collected and existing samples in Finnish biobanks. This data is combined with digital health record information from Finnish health registries. The FinnGen consortium's reputation for data quality and adherence to rigorous research standards made it a suitable and reliable source for our study.

A meticulous screening process was applied to identify individuals meeting specific study criteria with PCOS diagnoses established using the Rotterdam criteria, the National Institutes of Health (NIH) criteria, or self-reported medical diagnoses as primary diagnostic standards. Following adjustments for age, sex, technical covariates, and genetic principal components, our analysis meticulously examined 642 cases of PCOS alongside 118,228 controls.

2.4. Instrumental variable (IV)

The IV method was introduced as an alternative statistical approach to investigate the causality of associations between exposure and outcome, effectively controlling for potential confounding variables. Originating from econometrics nearly a century ago, this concept was later embraced by the field of medical statistics [18]. To select the IVs, the following criteria were applied: (1) single nucleotide polymorphisms (SNPs) meeting the locus-wide significance threshold ($P < 1.0 \times 10^{-5}$) for each genus were chosen as potential instrumental variables [14]; (2) The reference panel for LD calculation was the European samples data from the 1000 Genomes project, and only the SNPs with the lowest P-values were kept among those that had $R^2 < 0.001$; (3) SNPs with a minor allele frequency (MAF) of $\leq$0.01 were excluded; and (4) In the presence of palindromic SNPs, the alleles on the forward strand were determined based on the allele frequency information.

In MR studies, the variance (R^2) represents the proportion of exposure variability that can be explained by each genetic instrument [19]. In a previous study, the R^2 value for the gut microbiome was calculated using the following formula:

$$R^2 = \frac{2 \times EAF \times (1 - EAF) \times \beta^2}{2 \times EAF \times (1 - EAF) \times \beta^2 + 2 \times EAF \times (1 - EAF) \times N \times se^2}$$

Here, EAF stands for the effect allele frequency, and se and beta represent the estimated effect and standard error (SE) of the SNP on a specific gut microbiome. N indicates the sample size [20]. In addition, we employed the following formula to calculate the F-statistics, which are used to assess the presence of weak instrument bias: $F = R^2 \times \frac{N-2}{1-R^2}$, with N representing the sample size [20]. If the F-statistic associated with the analysis exceeded 10, it indicated the absence of a significantly weak instrumental bias. The power of MR estimates was computed using the Stephen Burgess Online calculator tool [20].

2.5. Statistical analysis

2.5.1. Method of Mendelian randomization

This study used multiple approaches, including inverse-variance weighted (IVW) [21], MR-Egger regression [22], maximum likelihood (ML) [23], weighted median [24], and weighted mode [25], to investigate a possible causal link between gut microbiota and PCOS.

IVW combined the Wald estimates of each SNP using a meta-analysis to estimate the overall effect of the gut microbiota on PCOS. The IVW is unbiased when there is no horizontal pleiotropy [26].

The MR-Egger regression uses the instrument strength independent of the direct effect (InSIDE) assumption to assess the presence of pleiotropy by estimating the intercept term. A zero-intercept term in the MR-Egger regression indicates the absence of horizontal pleiotropy, which is consistent with the IVW [22].

The ML method is similar to IVW but assumes no heterogeneity or horizontal pleiotropy. If these assumptions hold, the ML results are unbiased and the standard errors are smaller than those of the IVW [23].

The weighted median method can accurately estimate causal associations even in the presence of up to 50 % of invalid instrumental variables [25].

The weighted-mode method estimate has proven to be more potent in identifying causal effects when the InSIDE hypothesis is breached. It exhibits diminished bias and lower type I error rates compared with the MR-Egger regression, as evidenced by prior research findings [25].

2.5.2. Sensitivity analysis

Cochran's Q test was used to evaluate heterogeneity between the two samples. The MR-Egger intercept was used to detect potential pleiotropy among the SNPs. An intercept greater than 0 indicated the presence of horizontal pleiotropy, suggesting that the outcome persisted even in the absence of exposure factor interference. To identify potential heterogeneous SNPs, we performed a "leave-one-out" analysis by excluding each instrumental SNP in turn. Furthermore, reverse MR analysis was performed on all bacteria to assess the causal link between the gut microbiota and PCOS. The methods and settings used were consistent with those employed in the forward MR analysis.

2.5.3. Statistical significance

All statistical analyses were performed using the R version. TwosampleMR (version 0.5.6) and q-value R packages were used to conduct MR analyses. For associations between PCOS and genera of gut microbiota, $P < 0.05$ was suggestive, but only if $q \geq 0.1$.

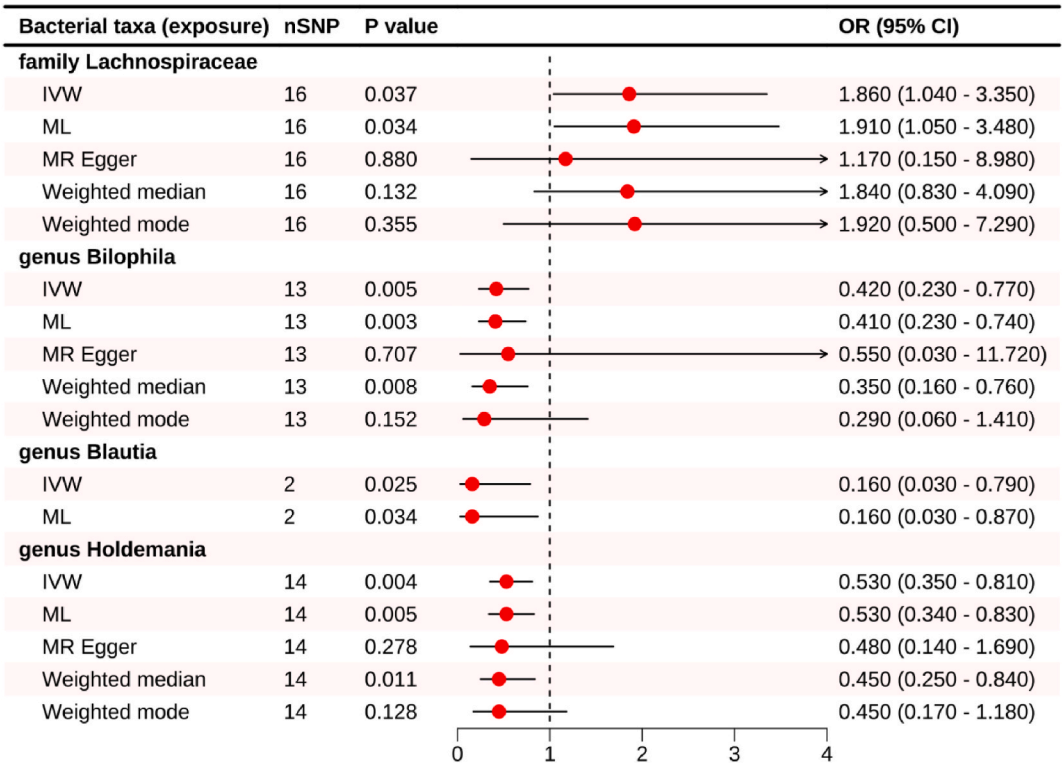

Fig. 2. Forest plot of the associations that were consistent across MR analyses.

2.6. Ethics approval and consent to participate

This study utilized published studies and consortia that offered publicly accessible summary statistics (GWAS). All original studies included in this review were approved by the relevant ethical review boards, and informed consent was obtained from all participants. Furthermore, no individual-level data were used in this study, eliminating the need for approval from a new ethical review board.

3. Results

3.1. Selection of IVs

We incorporated 45 SNPs as IVs at a significance level of $P < 1.0 \times 10^{-5}$. For all five causal associations examined, the F-statistics of these instrumental variables surpassed 10, indicating effective mitigation of bias arising from weak instruments (see Table S3). Furthermore, the Cochran's IVW Q test results showed no significant heterogeneity among the IVs.

3.2. Causal impact of gut microbiota on PCOS

Figs. 2 and 3 demonstrate the association of four bacterial genera (Bilophila, Blautia, Holdemania, and Lachnospiraceaefamily) with PCOS observed using at least one MR method. Based on the IVW estimates, certain bacteria exhibited either protective or harmful effects against PCOS. Specifically, Bilophila (OR = 0.42, 95 % CI:0.23–0.77, $P = 4.62 \times 10^{-3}$), Blautia (OR = 0.16, 95 % CI:0.03–0.79, P = 0.02), and Holdemania (OR = 0.53, 95 % CI:0.35–0.81, $P = 3.55 \times 10^{-3}$) genera were found to be protective against PCOS, while the Lachnospiraceae family (OR = 1.86, 95 % CI:1.04–3.35, P = 0.04) was associated with a harmful effect on PCOS.

3.3. Sensitivity analysis

We conducted heterogeneity testing using the IVW and MR-Egger methods, and the results revealed no heterogeneity among the instruments (Q pval >0.05; see Table S1). The intercepts from the MR-Egger regression did not deviate significantly from 0, suggesting the absence of horizontal pleiotropy (P > 0.05). Additionally, the robustness of our MR findings was confirmed through a leave-one-out analysis (Fig. 4).

3.4. Reverse MR analysis

According to the findings presented in Fig. 5 and Table S4, the reverse MR analysis indicated an association between PCOS and two

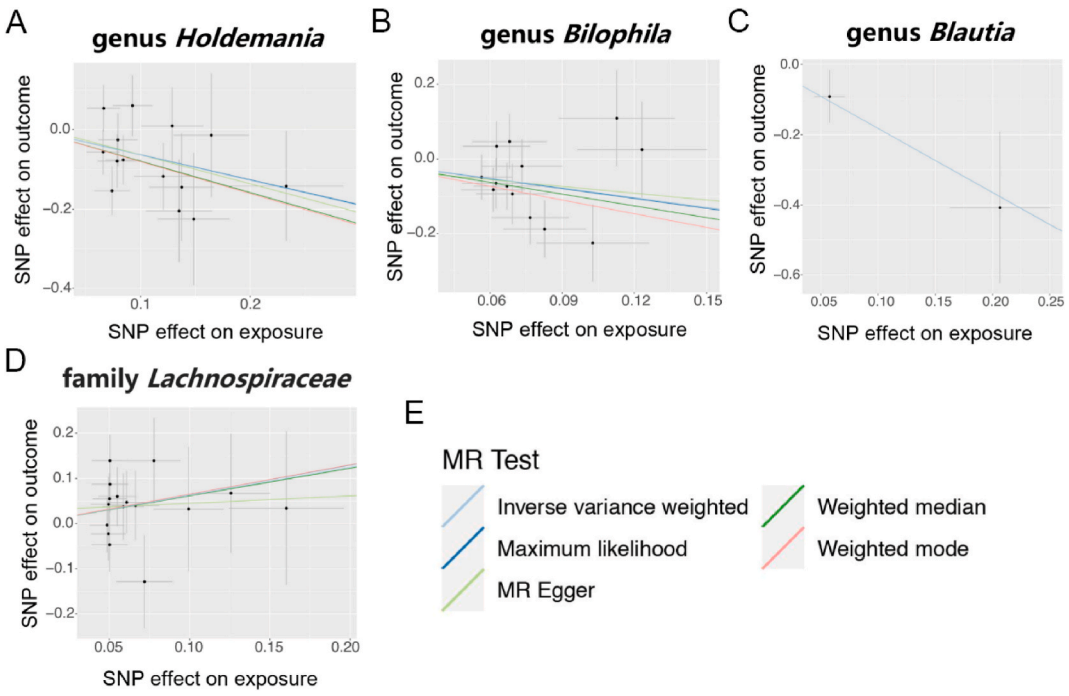

Fig. 3. Gut microbiota and PCOS: scatter plots. (A) Causal effect of genus Holdemania on PCOS; (B) Causal effect of genus Bilophila on PCOS; (C) Causal effect of genus Blautia on PCOS; (D) Causal effect of family Lachnospiraceae on PCOS; (E) Application of five MR analysis methods.

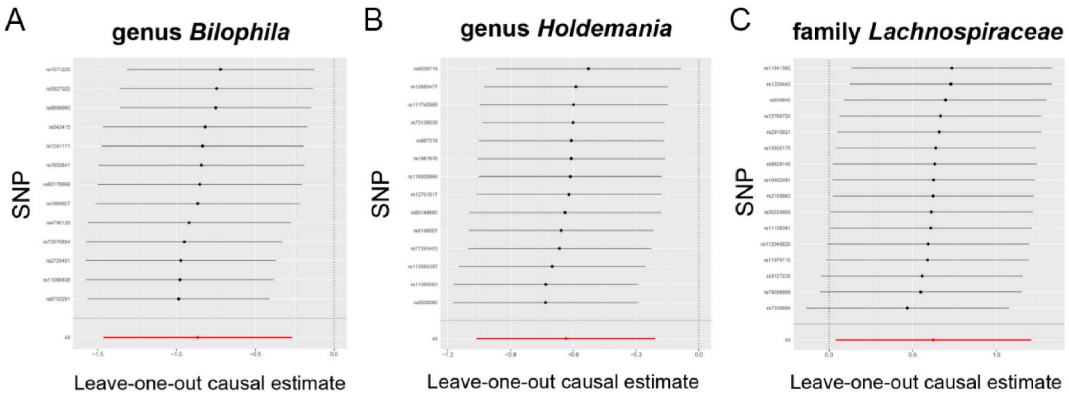

Fig. 4. Gut microbiota and PCOS: leave-one-out plots. (A) Leave-one-out analysis for genus Bilophila on PCOS; (B) Leave-one-out analysis for genus Holdemania on PCOS; (C) Leave-one-out analysis for family Lachnospiraceae on PCOS.

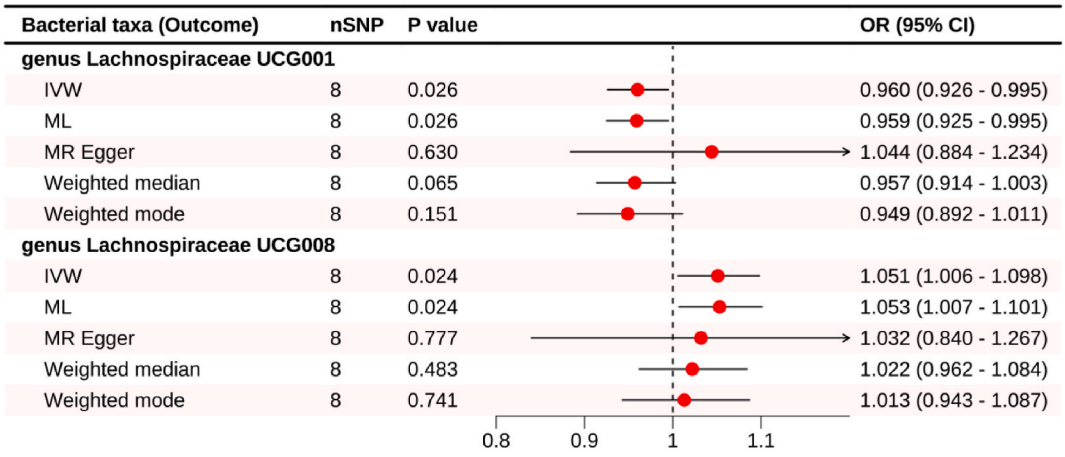

Fig. 5. Forest plot of the associations that were consistent across reverse MR analyses.

bacterial genera: Lachnospiraceae UCG001 (OR = 0.96, 95 % CI:0.93–1.00, P = 0.03) and Lachnospiraceae UCG008 (OR = 1.05, 95 % CI:1.01–1.10, P = 0.02). Additionally, sensitivity analysis, as shown in Table S2, did not reveal any signs of pleiotropy or heterogeneity (Q pval >0.05; P > 0.05).

4. Discussion

In this study, we used summary statistics of the gut microbiota obtained from the MiBioGen consortium's extensive GWAS meta-analysis. Our objective was to conduct a two-sample MR analysis and investigate the causal relationship between the gut microbiota and PCOS. Our findings revealed that certain microbial genera, namely Bilophila, Blautia, and Holdemania, exhibited a protective effect against PCOS. Conversely, the Lachnospiraceae family of bacteria was associated with detrimental effects in PCOS.

Blautia, belonging to the Bacillota and Leptospiraceae families, encompass a group of bacteria. As a prominent genus within the intestinal microbiota, Blautia plays a significant role in metabolic disorders, inflammatory conditions, and biotransformation processes [27,28]. Multiple studies have consistently shown a decreased abundance of Blautia in the gut microbiota of individuals with PCOS [29], diabetes, and obesity [30], which is consistent with our findings. Furthermore, Blautia has been correlated with clinical markers related to lipid and glucose metabolism, indicating its involvement in these physiological processes [31]. Additionally, these bacteria are recognized for their contribution to food digestion and the generation of beneficial metabolites such as SCFAs [32]. Bilopheles are typically not classified as conventional probiotics [33]. They are generally considered secondary members of the gut microbiota with relatively low abundance and limited distribution. Some Bilophela strains produce hydrogen sulfide (H_2S) during their metabolic processes, and high concentrations of H_2S can have detrimental effects on intestinal health [34]. Consequently, the presence of Bilophela bacteria may be associated with the development of specific intestinal conditions, such as inflammatory bowel disease and colitis [35]. Despite not being commonly recognized as a probiotic, our research revealed a protective role for Bilophela in PCOS. This finding is intriguing because it emphasizes the intricate nature of the gut microbiota and its significance in human health. The genus Holdemania comprises various strains, some of which have been identified in the human gut [36]. However, our current understanding

of Holdemania remains limited. Holdemania is believed to play a role in the breakdown and fermentation of sugars, leading to the production of beneficial metabolic byproducts such as SCFAs [37]. Furthermore, there is a negative correlation between Holdemania and impaired lipid metabolism.

Our study revealed a significant effect of the Lachnospiraceae family on PCOS. Consistent with our findings, recent research has demonstrated a notable increase in the levels of Lachnospiraceae UCG-008 and Lachnospiraceae NK4A136 in a PCOS-IR rat model when administered a combination of letrozole sodium carboxymethyl cellulose (CMC-na) solution and a high-fat emulsion [38]. Focusing on the Bilophila family, the pathogen Wadsworthia has been identified as being associated with the early stages of the inflammatory response and is closely linked to the development of various inflammatory diseases. Importantly, the level of Wadsworthia is higher in mice transplanted with fecal bacteria from PCOS patients than in those transplanted with healthy fecal bacteria, indicating that Wadsworthia may contribute to the pathogenesis of PCOS through inflammation [35]. However, it is crucial to acknowledge that we should not generalize the effects of the Lachnospiraceae family, and instead consider the significance of differences at the genus level and potentially even strain levels.

The gut microbiota plays a complex role in influencing PCOS, and our Mendelian randomization analysis has identified four key mechanisms through which the gut microbiota primarily impacts PCOS: increased androgen levels, insulin resistance, chronic inflammation, and metabolic syndrome. SCFAs, including acetate, propionate, and butyrate, are important byproducts of microbial metabolism in the human gut [39]. Our study revealed associations between PCOS and specific gut microbial taxa such as Blautia and Holdemania, which are SCFA producers. Research suggests that Reduced SCFA levels may contribute to the development of insulin resistance, a critical factor in PCOS progression [40]. SCFAs have the potential to alleviate insulin resistance by activating G-protein-coupled receptors in enteroendocrine cells, thereby regulating the secretion of glucagon-like peptides (GLP), ghrelin, and peptide YY (PYY) [40,41]. Furthermore, gut microbiota can influence sex hormones in PCOS, as elevated androgen levels are associated with metabolic dysfunction in women with PCOS. Additionally, chronic inflammation is often observed in individuals with PCOS, and inflammatory factors like TNF-α, IL-6, and IL-17 have been implicated in its development [42,43]. Wadsworthia, a member of the family Lachnospiraceae, is associated with chronic inflammation [44]. Based on our MR study, a hypothetical diagram depicting the mechanism of action between the gut microbiota and PCOS is shown in Fig. 6.

Although current research primarily focuses on the regulatory role of the gut microbiota in PCOS [6,11], our study revealed intriguing findings regarding the gut microbiota genera Lachnospiraceae UCG001 and Lachnospiraceae UCG008 in relation to PCOS. These genera demonstrated a reverse causal relationship with PCOS. Furthermore, evidence suggests an association between PCOS and dysbiosis of the gut microbiota. PCOS is closely associated with insulin resistance and metabolic disturbances. Insulin resistance can disrupt the gut environment and affect the ecological balance and functionality of the microbiota [45]. Several studies have indicated a correlation between insulin resistance and dysbiosis of the gut microbiota, which may contribute to gut microbiota imbalances in individuals with PCOS [46,47]. Furthermore, there may be a connection between hyperandrogenism and imbalance in the gut microbiota, referred to as "dysbiosis," in individuals with PCOS [48]. Additionally, it is important to consider that dietary habits and lifestyle changes commonly observed in patients with PCOS can influence the gut microbiota [49]. Poor dietary choices and unhealthy lifestyle practices may contribute to dysbiosis of the gut microbiota, thereby exacerbating the pathological processes associated with PCOS.

In terms of contribution, this study brings novel insights into the association between specific gut microbiota components and PCOS, shedding light on potential causal relationships. While the study does not specifically address developing countries, its significance lies in establishing a foundation for further research in diverse populations. By identifying specific gut microbiota elements linked to PCOS, this study paves the way for targeted interventions and therapies, potentially benefiting individuals in various geographical and socioeconomic contexts.

5. Strengths and limitations

This study had several noteworthy strengths. First, a meticulous MR analysis was performed to ascertain the causal relationship between gut microbiota and female reproductive disorders, which eliminated the possibility of confounding variables and reversed

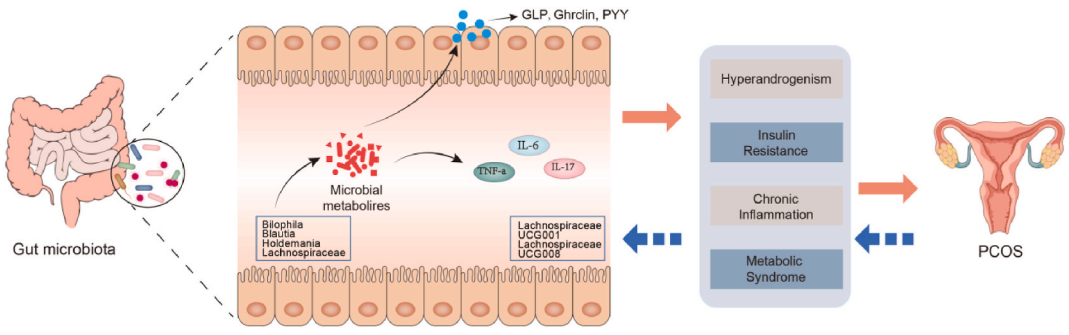

Fig. 6. The internal relationship between gut microbiota and PCOS. PCOS: polycystic ovary syndrome, GLP: glucagon-like peptides; PYY: peptide YY; TNF-α; tumor necrosis factor-α, IL-6: interleukin-6, IL-17: interleukin-17.

causation in causal inference. Furthermore, genetic variants of the gut microbiota were extracted from the largest available GWAS meta-analysis, guaranteeing the robustness of the instruments used in the MR analysis. Additionally, a two-sample MR design was implemented, and exposure and outcome summary-level data that did not overlap were used to circumvent potential sources of bias [8].

Despite the numerous strengths of this study, several limitations warrant consideration when interpreting the results. Firstly, the GWAS data used for our PCOS study is predominantly derived from individuals of European ancestry. While a significant portion of the gut microbiota GWAS data originates from European ancestry, a minor segment stems from other ethnic populations. This diversity in data sources could introduce bias into our results. Additionally, because this genus had the lowest taxonomic level in the exposure dataset, further exploration of the causal association between female reproductive disorders and gut microbiota at the species level was restricted. To perform sensitivity analysis and identify horizontal pleiotropy, additional genetic variations must be incorporated as instrumental variables, because the SNPs utilized in the analysis did not reach the conventional GWAS significance threshold ($P < 5 \times 10^{-8}$).

6. Conclusions

In summary, the findings of this two-sample MR study suggest a causal association between PCOS and Bilophila, Blautia, Holdemania, and Lachnospiraceae.

7. Recommendation

To gain a deeper understanding of the impact of the gut microbiota on PCOS and its specific mechanism, further randomized controlled trials are warranted.

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Consent for publication

Not applicable.

Data availability statement

Data included in article/supplementary material/referenced in article.

Additional information

No additional information is available for this paper.

CRediT authorship contribution statement

Jing-wei Li: Conceptualization, Writing - original draft. **Yu-zhi Chen:** Data curation. **Yu Zhang:** Data curation. **Li-hua Zeng:** Software. **Kai-wei Li:** Supervision. **Bao-zhen Xie:** Visualization. **Song-ping Luo:** Conceptualization, Funding acquisition. **Jie Gao:** Conceptualization, Funding acquisition, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Songping Luo reports financial support was provided by National Natural Science Foundation of China. 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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available.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22155.

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