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ORIGINAL RESEARCH

Gut Microbiota, Immune Phenotypes, and Insomnia: A Two-Sample Mendelian Randomization Study

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Purpose: The microbiota-gut-brain axis offers a novel framework for understanding insomnia; however, the hypothesis that specific immune pathways mediate the causal effects of gut microbial taxa on insomnia requires supporting genetic evidence. This study aimed to explore the genetic evidence supporting the causal interplay between the gut microbiota, immune phenotypes, and insomnia using large-scale genetic data.

Patients and Methods: We employed two-sample bidirectional Mendelian Randomization (MR) using large-scale genome-wide association study (GWAS) summary statistics for gut microbiota, 731 immune cell phenotypes, and insomnia (FinnGen R12). Mediation analysis was conducted to quantify the specific indirect effects of immune cells.

Results: We found suggestive genetic evidence linking 13 gut microbial taxa to insomnia risk. Notably, a directional divergence was observed within the *Blautia* genus at the species level, where Blautia A sp900066355 showed a robust protective association (surviving FDR correction), whereas other species within the genus increased risk at a nominal significance level (uncorrected $P < 0.05$). Furthermore, 17 immune phenotypes were found to be associated with insomnia. Exploratory mediation analysis suggested that monocytic myeloid-derived suppressor cells (M-MDSCs) may mediate the pathway linking the uncultured bacterium CAG-177 to insomnia, accounting for 10.7% of the total effect.

Conclusion: This study provides preliminary genetic evidence linking specific gut microbial taxa and immune phenotypes to insomnia risk, with Blautia A sp900066355 demonstrating robust protective effects. As a secondary hypothesis-generating observation, we propose a preliminary hypothesis that the depletion of protective M-MDSCs, rather than solely pro-inflammatory activation, may contribute to insomnia pathogenesis. Given the borderline statistical significance of this mediation finding, drawing direct therapeutic implications is currently premature.

Keywords: insomnia, microbiota, immunity, inflammation, Mendelian randomization

Introduction

As the most prevalent sleep disorder, insomnia has become a growing public health concern due to its rising global prevalence. Clinically, it manifests not only as difficulty in initiating or maintaining sleep and reduced sleep quality,[1] but also as a systemic pathological condition. Insomnia elevates the risk of psychiatric disorders, such as depression and anxiety, and is closely linked to chronic somatic diseases, including cardiovascular disorders, metabolic dysfunction (eg., diabetes), and immune dysregulation.[2,3] Despite its substantial clinical burden, the underlying pathophysiological mechanisms of insomnia remain complex and incompletely understood, limiting the development of precise therapeutic strategies. Recently, the emergence of the "microbiota-gut-brain axis" (MGBA) has renewed interest in the bidirectional interactions between the gut ecosystem and the central nervous system, offering a novel framework for elucidating the biological basis of insomnia.[4]

Some observational studies have reported characteristic alterations in gut microbiota diversity and abundance among individuals with insomnia,[5,6] and clinical trials have suggested that microbiome remodeling through probiotics or fecal microbiota transplantation (FMT) may improve sleep parameters.[7,8] Similarly, animal studies have shown that drug-

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induced insomnia can alter gut microbiota composition.[9–11] However, these findings are largely descriptive. Furthermore, clinical insomnia is a highly heterogeneous phenotype, encompassing diverse manifestations, such as difficulties with sleep onset versus maintenance, which complicates the identification of unified pathological mechanisms. While previous Mendelian Randomization (MR) studies utilizing 16S rRNA data have explored this causal link at broader taxonomic levels, clarifying the high-resolution, species-level causal effects of the gut microbiota on insomnia and identifying specific effector pathways remain critical research gaps.

Immune modulation is believed to play a central role in the pathogenesis of insomnia.[12] Gut-associated lymphoid tissue (GALT), the body's largest immune reservoir, accounts for approximately 70% of the immune effector cells.[13] The gut microbiota can trigger local or systemic immune responses through metabolites or bacterial components, after which immune cells and their secreted cytokines (eg., IL-1β, TNF-α, IL-6) directly influence key sleep-regulatory brain regions via specific receptors.[14–18] Because broad inflammatory markers often lack specificity and are prone to confounding, high-resolution immune cell phenotypes offer a more precise, genetically robust proxy for mapping these complex neuroimmune interactions. Building upon this broad biological framework, we hypothesized that specific immune cell phenotypes may serve as measurable mediators of the relationship between genetically predicted gut microbial taxa and insomnia.

To overcome the confounding biases and reverse causality inherent in traditional epidemiology, we employed MR. Using single-nucleotide polymorphisms (SNPs) that are randomly assorted at conception as genetic instrumental variables (IVs), MR approximates the logic of a randomized experiment, enabling causal inference under specific assumptions.[19–21] We aimed to estimate the causal effect of genetically predicted gut microbial taxa on insomnia using two-sample bidirectional MR and to conduct mediation analysis further to dissect the specific role of immune cells in this relationship, thereby providing preliminary genetic insights and hypothesis-generating targets for future experimental investigation.

Materials and Methods

Study Design

This study was conducted and reported in accordance with the STROBE-MR guidelines.[22] The scientific validity of the MR analysis relies on three core assumptions: (1) Relevance: The selected instrumental variants (IVs) must be strongly associated with the exposure (gut microbiota and immune cells); (2) Independence: IVs must be independent of potential confounders; and (3) Exclusion restriction: IVs must influence the outcome (insomnia) only through the exposure, not via alternative pathways.[23] A flowchart of the study design is presented in Figure 1.

Data Sources

To minimize population stratification bias, all genome-wide association study (GWAS) summary statistics were strictly restricted to individuals of European ancestry. Gut microbiota data were obtained from a large metagenomic sequencing study by Qin et al,[24] which included 5,959 individuals and provided genetic association data for 473 microbial taxa at the phylum, class, order, family, genus, and species levels. In this dataset, microbial traits were quantified as inverse rank-normal transformed (IRNT) relative abundances. For immune phenotypes, we utilized summary statistics for 731 immune cell traits from Orrù et al[25] This dataset was based on 3,434 European individuals with no sample overlap with the outcome dataset, effectively avoiding participant overlap bias. Genetic association data for insomnia were obtained from FinnGen R12 (https://r12.finngen.fi/),[26] which is defined using the International Classification of Diseases (ICD) diagnostic framework. Cases were ascertained through Finnish national health registries based on physician-assigned ICD-10 codes F51.0 (Nonorganic insomnia) and G47.0 (Disorders of initiating and maintaining sleep). Because these diagnoses are derived from the electronic health records of individuals seeking medical care, the phenotype represents a clinical insomnia disorder rather than self-reported insomnia symptoms. This distinction is crucial because these two entities are known to possess distinct genetic architectures. The dataset comprised 6776 insomnia cases and 490,763 controls (totaling 497,539 European individuals), thereby ensuring robust statistical power. To mitigate the risk of sample overlap bias, we selected exposure and outcome datasets from distinct, geographically separated populations.

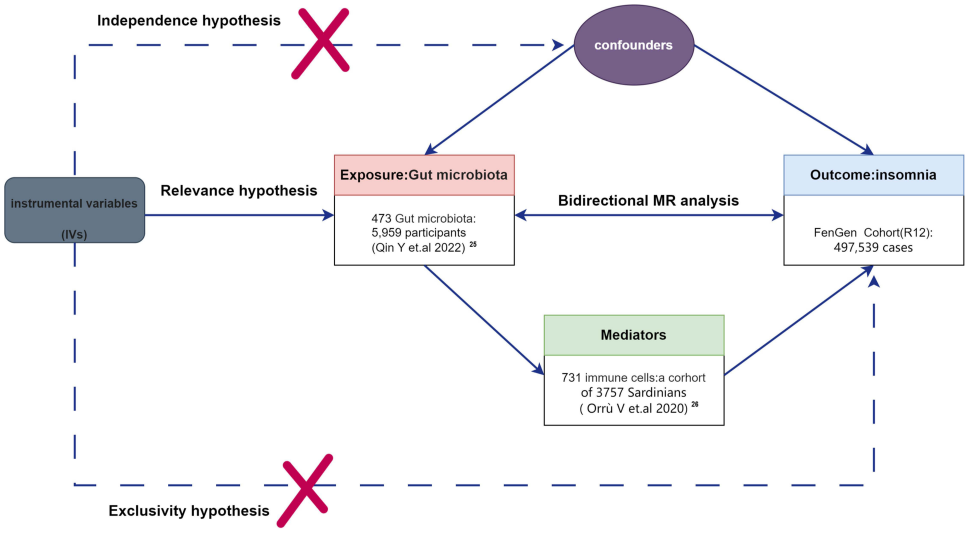

Figure 1 Study design flowchart.

Specifically, the gut microbiota data originated from the Dutch Microbiome Project (individuals from the northern Netherlands), the immune phenotype data were based on the SardiNIA project (individuals from Sardinia, Italy), and the outcome dataset (FinnGen R12) consisted exclusively of Finnish individuals. Because these represent three demographically non-intersecting cohorts, participant overlap bias is effectively avoided. Detailed information on the data sources is provided in Table S1. Ethical approval was waived because only publicly available summary statistics were used.

Instrumental Variable Selection

A rigorous and standardized multistep quality control procedure was applied to select robust genetic instruments. Given the specific nature of microbiome and immune trait data, strictly applying the traditional genome-wide significance threshold ($P < 5\times10^{-8}$) would result in an insufficient number of IVs (Table S13), compromising statistical power. Therefore, consistent with established practice in microbiome and immune-trait MR studies,[27] we adjusted the selection threshold for gut microbiota and immune cells to $P < 5\times10^{-6}$ to balance instrument quantity with statistical strength. To satisfy the independence assumption, linkage disequilibrium (LD) clumping was performed ($r2 < 0.001$ and 10,000 kb distance) to remove the linked SNPs. During harmonization, palindromic SNPs and variants with ambiguous allele frequencies were removed to ensure consistent alignment of the effect alleles between the exposure and outcome datasets. Instrument strength was assessed using F-statistic, and only SNPs with $F > 10$ were retained to avoid weak-instrument bias.[28]

MR Analysis Strategy

The inverse variance-weighted (IVW) meta-analysis method served as the primary statistical model for causal estimation. To bolster reliability, we performed cross-validation using the MR-Egger regression, weighted median, simple mode, and weighted mode methods. A nominally significant causal association was defined as $P < 0.05$ in the IVW analysis, with consistent effect directions (β) across complementary methods. To account for multiple testing across the numerous microbial and immune traits, we applied the Benjamini–Hochberg (FDR) correction. Findings with an uncorrected $P < 0.05$, but a $P\_FDR > 0.05$, were classified as "nominally significant" or "suggestive" causal associations.

Comprehensive sensitivity analyses were performed to assess reliability and exclude potential bias. First, heterogeneity among the IVs was evaluated using Cochran's Q statistic ($P < 0.05$).[29] Second, horizontal pleiotropy was monitored using the MR-Egger intercept and the MR-PRESSO global test; the latter also identified and removed outliers to correct the estimates.[30,31] Additionally, a leave-one-out analysis was performed by sequentially omitting single SNPs and repeating the IVW analysis to ensure that no single variant disproportionately influenced the overall result.[32]

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Furthermore, the MR Steiger filtering test was applied to all analyses to robustly confirm the correct causal directionality; this test verified our directional assumptions, and consequently, no SNPs were excluded due to reverse causation.

To delineate the "gut microbiota-immune-insomnia" pathway, we constructed a mediation analysis model by initially screening for gut microbiota and immune cells causally associated with insomnia that passed heterogeneity and pleiotropy tests and subsequently evaluated the causal effect of these gut microbes on the identified immune cells. The direction of the effects in the mediation model required logical consistency: if the total effect of microbiota on insomnia (β) is positive, the microbiota-immune (β1) and immune insomnia (β2) effects must have the same sign; if β is negative, β1 and β2 must have opposite signs. We calculated the mediation effects and confidence intervals using the Delta method and computed the mediation proportion as $((\beta1 \times \beta2)/\beta)$.[33] Statistical significance was defined as $P < 0.05$. Finally, to rule out reverse causality, we performed a reverse MR analysis treating insomnia as the exposure and gut microbiota/immune phenotypes as the outcomes using the same threshold ($P < 5\times10^{-6}$).

All statistical analyses were performed using R software (V.4.4.2), primarily utilizing the "TwoSampleMR" and "MR-PRESSO" packages.

Results

Selection and Strength of Genetic Instruments

Based on our strict quality control criteria, we identified 5,284 SNPs significantly associated with the gut microbiota (Table S2) and 11,198 SNPs associated with immune cell traits (Table S3). All selected instrumental variables exhibited F-statistics > 10. Specifically, the F-statistics for gut microbiota IVs ranged from 20.81 to 156.59 (mean: 23.88), and for immune cell IVs, it ranged from 20.87 to 3159.29 (mean: 43.25). These robust values confirm sufficient statistical power and minimize weak instrument bias.

Causal Effect of Gut Microbiota on Insomnia

Using IVW as the primary method, supported by consistent directional validation across secondary approaches, we found suggestive genetic evidence linking 13 gut microbial taxa to insomnia risk (Figure 2, Table S4). Notably, Blautia A sp900066355 demonstrated a robust protective effect against insomnia, which remained statistically significant after FDR correction (OR = 0.503, 95% CI = 0.368–0.688, $P < 0.001$, $P\_FDR < 0.05$). The remaining 12 taxa exhibited suggestive causal associations ($P < 0.05$, $P\_FDR > 0.05$). For instance, Treponemataceae (OR = 0.813, 95% CI = 0.669–0.988, P = 0.037) demonstrated protective effects against insomnia. Conversely, several taxa exhibited nominal pathogenic risk, most notably UBA7182 sp002491115 (OR = 1.730, 95% CI = 1.036–2.888, P = 0.036) and UBA9475 sp002161675 (OR = 1.585, 95% CI = 1.024–2.454, P = 0.039).

Causal Association Between Immune Phenotypes and Insomnia

An analysis of immune phenotypes revealed suggestive causal associations between the 17 immune cell traits and insomnia (Figure 3, Table S5). The results displayed a distinct polarization: 11 phenotypes showed positive associations with insomnia risk, with the $CD62L^{-}$HLA DR^{++} monocyte absolute count showing the largest risk-increasing estimate (OR = 1.153, 95% CI = 1.032–1.287, P = 0.011), implying that the activation of specific monocyte subsets contributes to insomnia pathophysiology. In contrast, six phenotypes showed protective associations, most notably FSC-A on plasmacytoid dendritic cells (OR = 0.943, 95% CI = 0.895–0.994, P = 0.028).

Sensitivity and Robustness Verification

Cochran's Q test indicated no significant heterogeneity among IVs for gut microbiota or immune traits ($P > 0.05$; Tables S6 and S7). Furthermore, the MR-Egger intercept analysis and MR-PRESSO global test detected no evidence of horizontal pleiotropy ($P > 0.05$), excluding interference from alternative pathways (specifically, for our primary robust finding *Blautia A sp900066355*: RSSobs = 8.058, P = 0.507; and for the mediation pathway CAG-177: RSSobs = 8.863, P = 0.484; M-MDSC: RSSobs = 16.808, P = 0.485). Leave-one-out analysis indicated that removing any single SNP did not substantially alter the causal estimates (Figure S1–S3), reinforcing the robustness of our MR findings.

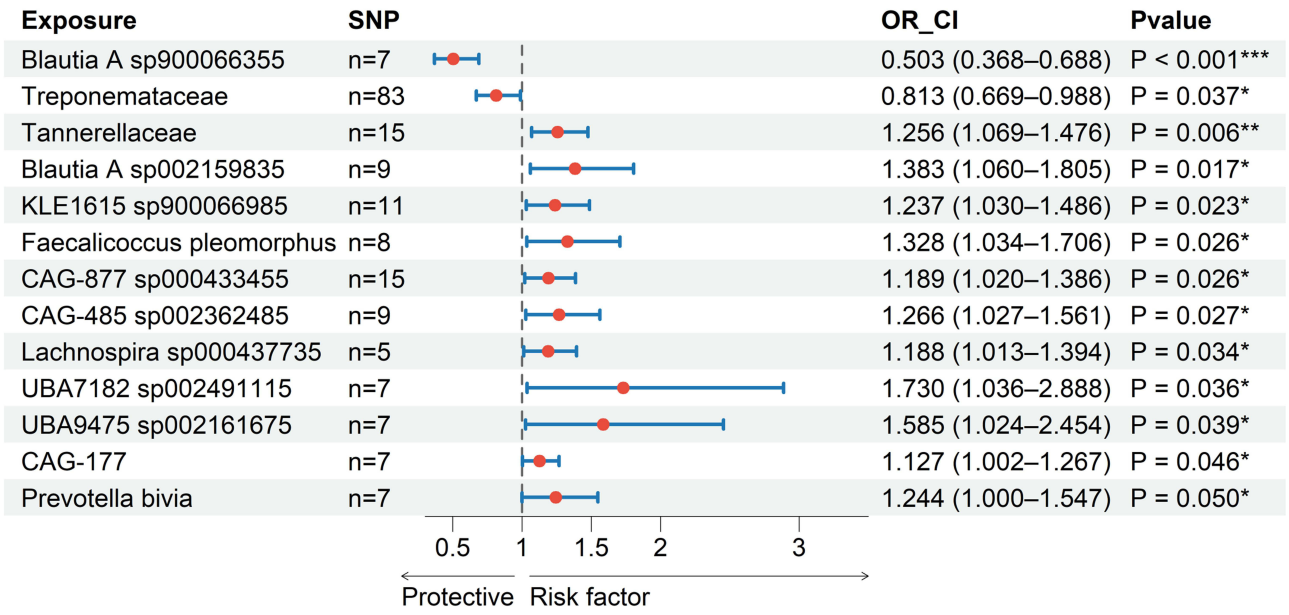

Figure 2 Mendelian randomization results of causal associations between gut microbiota and insomnia. *P <0.05, ***P <0.001.
Abbreviations: OR, odds ratio; CI, confidence interval.

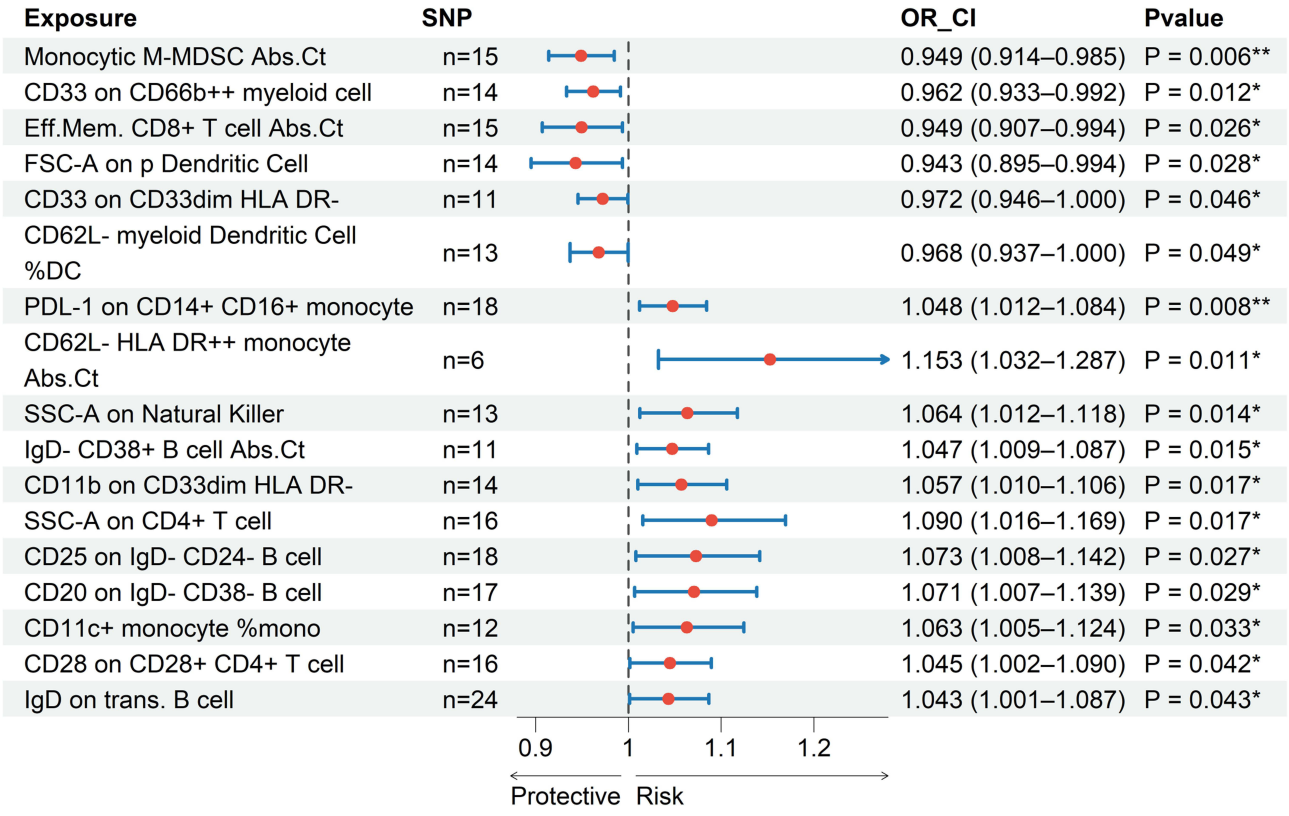

Figure 3 Mendelian randomization results of causal associations between immune cells and insomnia. *P <0.05, **P <0.01.
Abbreviations: OR, odds ratio; CI, confidence interval; M-MDSC, monocytic myeloid-derived suppressor cell; Abs.Ct, absolute count; Eff.Mem. CD8+ T cell, Effector Memory CD8+ T cell.

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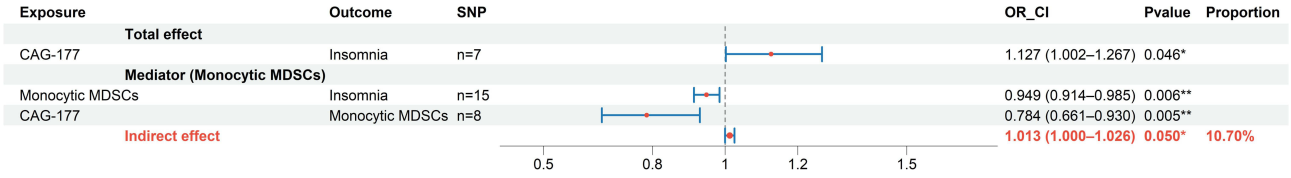

Figure 4 The results of the mediation analysis. *P <0.05, **P <0.01.
Abbreviations: OR, odds ratio; CI, confidence interval; M-MDSC, monocytic myeloid-derived suppressor cell.

Exploratory Mediation Analysis of Immune Phenotypes

To map the pathways linking the gut microbiota to insomnia, we conducted mediation modeling. We first evaluated the causal effects of insomnia-associated gut microbes on immune phenotypes (Table S10) by screening eight potential "Microbiota-Immune-Insomnia" pathways (Table S11). Our exploratory analysis suggested that the absolute count of monocytic myeloid-derived suppressor cells (M-MDSCs) may act as a statistical mediator in the pathway from CAG-177 to insomnia (OR = 1.013, 95% CI = 1.000–1.026, P = 0.050), with an estimated mediation proportion of 10.7% of the total effect. Notably, this P-value falls at the conventional significance boundary, and the confidence interval for the indirect effect includes the null, warranting cautious interpretation (Figure 4, Table S12). Reverse MR revealed no significant association of genetically predicted insomnia liability with CAG-177 or M-MDSCs (Tables S8 and 9), supporting the hypothesized directionality of this pathway.

Discussion

This study used two-sample bidirectional MR to systematically explore the causal relationships among gut microbial taxa, immune phenotypes, and insomnia risk. Beyond identifying 13 bacterial taxa with suggestive causal associations, our exploratory mediation analysis provides preliminary genetic insights into the potential mediating role of the "Microbiota-Immune-Central" axis in insomnia.

Among taxa with protective associations, Treponemataceae showed a suggestive causal protective effect on insomnia risk. Literature on the potential benefits of this family is limited, likely because its abundance has diminished in urban populations owing to dietary refinement and antibiotic exposure.[34] Functionally, Treponemataceae degrade dietary fibers to produce short-chain fatty acids (SCFAs),[35] which mitigate neuroinflammation-induced sleep disruption via systemic anti-inflammatory effects (eg., lowering IL-6 and TNF-α)[14,36,37] and enhance sleep by modulating neurotransmitter synthesis.[38] Therefore, we cautiously hypothesize that any potential protective association of Treponemataceae might involve SCFA-dependent pathways. However, given the limited literature on its role in modern populations, this mechanism remains speculative, and any therapeutic considerations are currently premature and require fundamental experimental validation.

An intriguing statistical observation in our MR analysis was the divergent directional effects within the Blautia genus. Although Blautia is generally considered a beneficial butyrate producer,[6,39,40] with butyrate enhancing NREM sleep via serotonin modulation and HPA axis regulation,[40–43] our data revealed divergent effects: Blautia A sp900066355 was protective, whereas Blautia A sp002159835 conferred a risk. While this statistical dichotomy aligns with the genomic evidence from Maturana et al[44] suggesting diverse lineages, our MR results alone cannot confirm differing metabolic functions in vivo. Therefore, this observed strain-level heterogeneity should be treated as a hypothesis-generating statistical finding rather than a confirmed biological discovery, highlighting a critical area for future functional validation.

The potential pathogenic mechanisms of the at-risk taxa identified in this study varied. Lachnospira, sometimes considered a potentially beneficial genus, has been positively associated with inflammatory bowel syndrome (IBS) symptom severity in observational studies.[45] Chassard et al observed that such functional dysbiosis can alter fermentation metabolites and increase gas production, leading to visceral hypersensitivity and bloating,[46,47] factors that may precipitate or exacerbate insomnia. Similarly, the Faecalicoccus pleomorphus family has been shown to drive high-fat diet (HFD)-induced obesity and metabolic dysfunction in animal models.[48] Given the tight coupling between bile acid metabolism and circadian gene expression,[49,50] Faecalicoccus may impair sleep by interfering with host lipid and bile

acid pools, thereby disrupting circadian signaling. Meanwhile, as Gram-negative bacteria, *Prevotella bivia* and *Tannerellaceae* possess cell walls rich in lipopolysaccharide, a potent immune activator; Tannerellaceae also exhibit immune-evasion mechanisms,[51] potentially sustaining a state of chronic low-grade inflammation that continuously disrupts central sleep regulation via the upregulation of pro-inflammatory cytokines such as IL-6.[52,53]

This study also highlights the contributions of uncultured or uncharacterized microbes (eg., UBA7182, UBA9475, and various CAG species) to insomnia mechanisms. These unassigned taxa, primarily within Oscillospiraceae and Lachnospiraceae, may disrupt gut-brain signaling through the synthesis of unknown neuroactive metabolic byproducts.[54–57] These findings suggest that the microbial contributions to insomnia risk may be broader than currently appreciated, and that these uncharacterized taxa warrant further investigation as potential targets for future research.

To clarify the pathways by which the gut microbiota influences insomnia, we focused on immune mediation. Our results are consistent with two broad immunological patterns: risk-increasing effects of activated immune phenotypes and protective effects of immunoregulatory phenotypes. On the one hand, activated phenotypes, specifically HLA-DR-high monocytes and differentiated B cells, were associated with increased insomnia risk. These associations are consistent with existing evidence that pro-inflammatory cytokines (eg., IL-1β, IL-6, TNF-α) can disrupt sleep homeostasis, though our MR analysis does not directly test this cytokine-mediated pathway.[52,58] On the other hand, M-MDSCs showed a nominally significant protective association with insomnia, consistent with their reported role in immune regulation via anti-inflammatory mediators.[59] Our exploratory mediation analysis suggested that M-MDSCs might be a node in the CAG-177-induced insomnia pathway (10.7% mediation). This suggests a preliminary hypothesis regarding the loss of protective immunosuppression. CAG-177, an anaerobic member of the Acutalibacteraceae family, has been suggested to influence the gut redox environment. One speculative hypothesis is that such changes could impair M-MDSC differentiation or function through metabolic interference (eg., altered SCFA synthesis or metabolite accumulation), potentially reducing their immunosuppressive capacity and thereby contributing to neuroinflammation. However, this proposed chain of events remains entirely hypothetical and is not directly tested by our MR analysis.

Our findings can be conceptually anchored within established frameworks of insomnia neurobiology, particularly the hyperarousal model and the neuroimmune basis of sleep regulation. In the hyperarousal model, chronic physiological and cortical arousal serve as core drivers of insomnia pathology. The immune associations we identified, including risk-increasing effects of HLA-DR-high monocytes and potential protective effects of M-MDSCs, are consistent with a model in which chronic, low-grade systemic inflammation may perpetuate the hyperarousal state. Specifically, microbiota-driven shifts toward these pro-inflammatory myeloid phenotypes can lead to the sustained central release of sleep-disrupting cytokines (eg., IL-1β and TNF-α), which directly sensitize central arousal networks and disrupt homeostatic sleep drive, thereby providing preliminary genetic evidence consistent with an immunogenetic component of the persistent arousal observed in clinical insomnia. However, we must strictly emphasize the exploratory nature of this mediation analysis as robust clinical implications and therapeutic speculations are currently premature. Future rigorous in vivo and in vitro experiments, along with larger independent cohorts, are necessary to validate this suggested pathway before specific interventions can be considered.

Compared to previous MR studies based on the 16S rRNA-based MiBioGen,[60–62] our study offers significant methodological advancements. First, we used a metagenomic sequencing dataset from Qin et al[24] This single-cohort design minimizes multicenter technical heterogeneity and improves detection power for low-abundance taxa, while also achieving species-level resolution. This enabled the precise dissection of functional heterogeneity within genera (eg., Blautia) and the identification of uncultured taxa (CAG and UBA species) invisible to traditional methods. Second, mediation analysis provided preliminary evidence for immune cells as a mechanistic bridge between the microbiome and insomnia, thus providing a new theoretical foundation for understanding the pathogenesis of insomnia.

This study has several limitations that must be carefully considered. The reliance on European ancestry cohorts and the lack of individual-level covariate data (eg., medication and lifestyle) restrict cross-population generalizability and preclude the exclusion of environmental confounders. Furthermore, the registry-based FinnGen insomnia phenotype aggregates heterogeneous clinical subtypes (eg., sleep onset versus maintenance difficulties), which may dilute subtype-specific causal pathways. Methodologically, our MR design assumes linear relationships, potentially overlooking complex nonlinear biological interactions, and our strict requirement for directional consistency across multiple estimators

may conservatively omit weak but genuine signals. From a genetic perspective, utilizing a relaxed instrumental variable threshold ($P < 5 \times 10^{-6}$) inherently increases the risk of LD confounding; however, because the absence of strong, locus-specific peaks precluded formal colocalization analyses, we cannot definitively rule out the influence of distinct but physically proximal causal variants. Additionally, the 731 evaluated immune traits include highly nested subpopulations with correlated genetic instruments, which precluded multivariable MR (MVMR) adjustment due to multicollinearity. Consequently, the individual immune associations should be interpreted as reflecting broader immunological patterns rather than independent causal mechanisms. Finally, the statistical power of this study was inherently constrained by the modest sample sizes of the exposure datasets (microbiota: n = 5,959; immune cells: n = 3,434). We explicitly acknowledge that no formal power calculations were performed and that these modest sample sizes may have limited our ability to reliably detect small mediation effects. This limited precision, compounded by rigorous FDR correction, explains why only Blautia A sp900066355 retained strict statistical significance, whereas the remaining associations, including the borderline exploratory mediation pathway involving CAG-177 and M-MDSCs, achieved only nominal significance. Consequently, these results should be interpreted as providing preliminary mechanistic insights rather than definitive confirmation, strictly serving as hypothesis-generating observations that warrant rigorous validation in experimental models and larger, independent clinical cohorts.

Conclusion

This study employed bidirectional MR and mediation analysis to explore the causal relationships among gut microbial taxa, immune cell phenotypes, and insomnia. Our primary finding was a directional divergence within the Blautia genus: Blautia A sp900066355 demonstrated a statistically significant protective association with insomnia that survived FDR correction. Through exploratory mediation analysis, we proposed a preliminary immune pathway whereby CAG-177 may contribute to insomnia by depleting protective M-MDSCs. These findings are consistent with the hypothesis that insomnia pathogenesis may involve not only pro-inflammatory immune activation but also a loss of protective immune regulation. However, as the mediation finding is strictly hypothesis-generating, any therapeutic speculations are premature. Future research should rigorously validate these preliminary pathways in experimental models before any clinical application can be considered.

Abbreviations

FMT, Fecal microbiota transplantation; GALT, Gut-associated lymphoid tissue; GWAS, Genome-wide association study; IBS, Inflammatory bowel syndrome; ICD, International Classification of Diseases; IRNT, Inverse rank-normal transformed; IVW, Inverse variance-weighted; LD, Linkage disequilibrium; MGBA, Microbiota-gut-brain axis; SCFA, Short-chain fatty acids; SNP, Single-nucleotide polymorphisms.

Data Sharing Statement

Data is provided within the paper and/or supplementary files. Any further requests can be directed to the corresponding author.

Ethics Approval and Informed Consent

The data used in this study are sourced from publicly available large-scale GWAS, with ethical approval and informed consent obtained in the original studies. According to the Measures for Ethical Review of Life Science and Medical Research Involving Human Subjects (Article 32, Items 1 and 2) issued in China on February 18, 2023, ethical review is exempted for research that uses legally obtained public data or anonymized information data, provided it causes no harm to human subjects and does not involve sensitive personal information or commercial interests. Therefore, the Ethics Committee of Shanghai YangZhi Rehabilitation Hospital granted an exemption from ethical approval for this study.

Author Contributions

Xiaofeng Jiang: Conceptualization, Methodology, Formal Analysis, Investigation, Data Curation, Writing – Original Draft; Bin Yu: Conceptualization, Methodology, Supervision, Project Administration, Funding Acquisition, Writing – Original Draft, Writing – Review & Editing.

All authors gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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