Postprint: Mendelian Randomization Study of the Causal Association Between Gut Microbiota and Insomnia

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Abstract

Background With the increasing incidence of insomnia, it severely affects patients' mental status and work performance. Gut microbiota is considered a risk factor for insomnia; however, relevant evidence remains relatively scarce, making it difficult to accurately understand the relationship between the two.

Objective To explore the causal relationship between gut microbiota and insomnia using two-sample Mendelian randomization as the research method.

Methods Summary statistics for gut microbiota were obtained from the largest available genome-wide association study meta-analysis conducted by the MiBioGen consortium (n=18,340). Based on preset thresholds, single nucleotide polymorphisms (SNPs) significantly associated with the relative abundance of 196 gut microbial taxa were extracted as instrumental variables (IVs). Summary statistics for insomnia were derived from UK Biobank (n=462,341). Inverse variance weighted method (IVW), MR-Egger regression, weighted median method (WME), weighted mode method (WM), among others, were employed to examine the causal relationship between gut microbiota and insomnia, with IVW as the primary method. Results were evaluated based on effect estimates of odds ratio (OR) and 95% confidence interval (CI). Sensitivity analysis, heterogeneity test, pleiotropy test, and outlier test (MR-PRESSO) were combined to verify the stability and reliability of the results. Reverse Mendelian randomization analysis was further performed on microbial taxa found to be causally associated with insomnia.

Results IVW results showed that genus_{Roseburia} (OR=0.787, 95%CI: 0.671-0.923, PFDR=0.016), genus_{Erysipelatoclostridium} (OR=0.880, 95%CI: 0.794-0.976, PFDR=0.077), genus_{Paraprevotella} (OR=0.891, 95%CI: 0.801-0.991, PFDR=0.083), genus_{Ruminococcaceae} UCG014 (OR=0.818, 95%CI: 0.697-0.961, PFDR=0.072), family_{Pasteurellaceae}

(OR=0.897, 95%CI: 0.814-0.988, PFDR=0.081), and order_{Pasteurellales} (OR=0.897, 95%CI: 0.814-0.988, PFDR=0.094) were associated with insomnia. No pleiotropy or significant heterogeneity was detected among the IVs. According to reverse Mendelian randomization analysis results, insomnia had no significant causal effect on gut microbiota.

Conclusion The abundance of six gut microbial taxa—genus_{Roseburia}, genus_{Erysipelatoclostridium}, genus_{Paraprevotella}, genus_{Ruminococcaceae} UCG014, family_{Pasteurellaceae}, and order_{Pasteurellales}—was negatively correlated with the risk of insomnia; that is, reduced abundance increases the risk of insomnia, serving as protective factors for insomnia.

Full Text

Title: Exploring the Causal Relationship Between Gut Microbiota and Insomnia Through Mendelian Randomization

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Abstract

Background: As the prevalence of insomnia continues to rise, it seriously affects patients' mental and work status. Gut microbiota is considered a risk factor for insomnia, but current evidence remains relatively scarce, making it difficult to accurately understand the relationship between the two.

Objective: This study employed two-sample Mendelian randomization (TSMR) to explore the causal relationship between gut microbiota and insomnia.

Methods: Summary statistics for gut microbiota were obtained from the largest available genome-wide association study (GWAS) meta-analysis conducted by the MiBioGen consortium (n=18,340). Single nucleotide polymorphisms (SNPs) significantly associated with the relative abundance of 196 gut microbial taxa were extracted as instrumental variables (IVs) according to predefined thresholds. Summary statistics for insomnia were derived from the UK Biobank (n=462,341). Inverse variance weighting (IVW), MR-Egger regression, weighted median (WME), and weighted mode (WM) methods were used to detect causal relationships between gut microbiota and insomnia, with IVW as the primary approach. Results were assessed using odds ratios (OR) and 95% confidence intervals (CI). Sensitivity analysis, heterogeneity testing,

pleiotropy testing, and outlier detection (MR-PRESSO) were performed to verify the stability and reliability of results. Reverse Mendelian randomization analysis was conducted on microbial taxa showing causal relationships with insomnia.

Results: IVW results revealed that *genus_{Roseburia}* (OR=0.787, 95%CI: 0.671-0.923, PFDR=0.016), *genus_{Erysipelatoclostridium}* (OR=0.880, 95%CI: 0.794-0.976, PFDR=0.077), *genus_{Paraprevotella}* (OR=0.891, 95%CI: 0.801-0.991, PFDR=0.083), *genus_{Ruminococcaceae} UCG014* (OR=0.818, 95%CI: 0.697-0.961, PFDR=0.072), *family_{Pasteurellaceae}* (OR=0.897, 95%CI: 0.814-0.988, PFDR=0.081), and *order_{Pasteurellales}* (OR=0.897, 95%CI: 0.814-0.988, PFDR=0.094) were associated with insomnia. No evidence of genetic pleiotropy or significant heterogeneity was found among the IVs. Reverse MR analysis indicated no significant causal effect of insomnia on gut microbiota.

Conclusion: The abundance of six gut microbial taxa—*genus_{Roseburia}*, *genus_{Erysipelatoclostridium}*, *genus_{Paraprevotella}*, *genus_{Ruminococcaceae} UCG014*, *family_{Pasteurellaceae}*, and *order_{Pasteurellales}*—is negatively correlated with insomnia risk. Decreased abundance of these taxa increases insomnia risk, suggesting they may be protective factors against insomnia.

Keywords: intestinal flora; insomnia; Mendelian randomization; causal association

Introduction

Insomnia is a common clinical condition characterized by difficulty falling asleep or frequent nighttime awakenings [1]. Approximately 10-20% of adults suffer from insomnia, with 50% experiencing chronic progression. It is estimated that about one-fifth of the global population has insomnia [2]. Gut microbiota (GM) constitutes a dynamic and complex ecological bacterial community [3]. Accumulating evidence indicates that GM dysbiosis is closely associated with insomnia, and maintaining a balanced microbial population plays an important role in sleep regulation [4]. Previous studies have shown that intestinal bacteria can affect the nervous, immune, metabolic, and endocrine systems through the brain-gut-microbiota axis (BGM axis), leading to sleep abnormalities [5]. For instance, Petra et al. [6] demonstrated that gut microbiota can regulate the synthesis of neuroactive molecules such as acetylcholine, catecholamine, GABA, histamine, melatonin, and serotonin, which are crucial for normal sleep. Additionally, research has shown that the composition and structure of GM in insomnia patients differ significantly from healthy individuals [7]. However, the specific gut microbial taxa and serum metabolites associated with insomnia remain largely unknown.

Mendelian randomization (MR) is a method that utilizes genetic variants as

instrumental variables (IVs) to estimate causal relationships between exposures and disease outcomes [8]. Since genotype allocation from parents to offspring is random, MR can be considered an alternative to randomized controlled trials (RCTs) [9], and associations between genetic variants and outcomes are not confounded by common environmental factors, establishing a reasonable causal sequence [10]. MR has been widely used to explore causal relationships between GM and various diseases, including metabolic diseases [11] and autoimmune diseases [12]. This study used GWAS summary statistics from MiBioGen and UK Biobank to conduct two-sample Mendelian randomization (TSMR) analysis, evaluating the causal relationship between GM and insomnia and identifying relevant microbial taxa.

Study Design

This study employed TSMR to investigate the causal association between GM (exposure) and insomnia (outcome). The inverse-variance weighted (IVW) method served as the primary analysis, supplemented by sensitivity analysis, heterogeneity testing, pleiotropy testing, and outlier detection (MR-PRESSO) to verify result reliability. MR analysis requires three key assumptions: (1) relevance: IVs must be strongly associated with the exposure; (2) independence: IVs should not be associated with the outcome through confounders; and (3) exclusion restriction: IVs affect the outcome only through the exposure, not directly [Figure 1: see original paper].

Data Sources

Single nucleotide polymorphisms (SNPs) associated with GM were selected as IVs. Summary data for these SNPs came from the MiBioGen consortium, which analyzed 16S rRNA gene sequencing data from 18,340 participants of diverse ethnicities and nationalities (72.3% European, with the remainder from the Middle East, East Asia, Hispanic/Latino Americans, and African Americans) [13]. Genetic data for insomnia were obtained from UK Biobank through the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/) (GWAS ID: ukb-b-3957), comprising 462,341 healthy European participants with 9,851,867 SNPs.

Instrumental Variable Selection

After removing 15 unknown genera, this study included 196 gut microbial taxa spanning 9 phyla, 16 classes, 20 orders, 32 families, and 119 genera. SNPs were selected using the following criteria: (1) SNPs with significance threshold $P<1.0\$\times10\^{}\{-5\}\$$ at genetic loci were selected as potential IVs [11]; (2) linkage disequilibrium threshold was set at $r^2<0.001$; (3) clumping window size was set to 10,000 kb to ensure SNP independence. Data for selected SNPs were then extracted from the outcome dataset. To assess weak instrument bias, F-statistics were calculated as $F=\beta^2/SE^2$ [14], where β is the effect size and SE is standard error. $F>10$ indicated no significant weak instrument bias [15], and all SNPs in this study met this criterion.

Statistical Methods

Analyses were performed using R (version 4.3.1) with TwoSampleMR (version 0.5.7) and MR-PRESSO (version 1.0) packages. IVW was the primary method for calculating ORs and 95%CIs to assess potential causal associations between microbial abundance and insomnia risk. MR-Egger regression, weighted median (WME), and weighted mode (WM) served as complementary methods. When IVW P<0.05 and effect directions were consistent across MR-Egger, WME, and WM, the association was considered relatively stable [9].

The MR-Egger intercept test identified horizontal pleiotropy; an intercept close to zero or non-significant indicated absence of pleiotropy [16]. MR-PRESSO detected potential outliers and re-analyzed causality after removing them (P<0.05) [17]. Leave-one-out sensitivity analysis assessed each SNP' s influence by sequentially removing individual SNPs and recalculating combined effects [18]. Heterogeneity was measured using Cochran' s Q test, with IVW Q statistics quantifying heterogeneity among IVs (P<0.05 indicated significant heterogeneity). False discovery rate (FDR) correction was applied to limit false positives, with PFDR<0.1 considered statistically significant [10,19]. Taxa with P<0.05 but PFDR$ $0.1 were considered potentially associated.

To evaluate bidirectional causality, reverse MR analysis was conducted on microbial taxa showing significant or potential causal relationships in the forward analysis, using identical methods and settings [Figure 2: see original paper].

Results

Instrumental Variables

After excluding 15 unknown genera, 196 gut microbial taxa were included. A total of 2,774 SNPs associated with gut microbiota were obtained after screening, all with F-statistics >10, eliminating weak instrument bias.

MR Analysis

Four TSMR methods were employed, with IVW as the primary approach and FDR correction applied . IVW results identified six gut microbial taxa significantly associated with insomnia (PFDR<0.1). At the genus level, *genus_{Roseburia}* (OR=0.787, 95%CI=0.671-0.923, PFDR=0.016), *genus_{Erysipelatoclostridium}* (OR=0.880, 95%CI=0.794-0.976, PFDR=0.077), *genus_{Paraprevotella}* (OR=0.891, 95%CI=0.801-0.991, PFDR=0.083), and *genus_{Ruminococcaceae} UCG014* (OR=0.818, 95%CI=0.697-0.961, PFDR=0.072) were negatively associated with insomnia risk. Additionally, *family_{Pasteurellaceae}* (OR=0.897, 95%CI=0.814-0.988, PFDR=0.081) and *order_{Pasteurellales}* (OR=0.897, 95%CI=0.814-0.988, PFDR=0.094) also showed protective effects against insomnia. As shown in

[Figure 3: see original paper], effect directions were consistent across all four TSMR methods, confirming these six taxa as protective factors for insomnia.

Furthermore, *class_{Bacteroidia}*, *genus_{Intestinibacter}*, *genus_{Ruminococcaceae} UCG003*, *order_{Bacteroidales}*, *order_{Desulfovibrionales}*, *phylum_{Euryarchaeota}*, and *phylum_{Lentisphaerae}* showed IVW $P<0.05$, but associations were no longer significant after FDR correction ($PFDR>0.1$), suggesting potential but inconclusive relationships.

Quality Control

Leave-one-out analysis showed no substantial differences between combined effects after sequentially removing individual SNPs and total effects [Figure 4: see original paper]. MR-PRESSO analysis detected no outliers ($P>0.05$) . Additionally, Cochran' s Q test and Egger-intercept test both yielded $P>0.05$, indicating no significant heterogeneity or pleiotropy among IVs.

Reverse MR Analysis

Reverse MR analysis of 13 microbial taxa (2 phyla, 1 class, 3 orders, 1 family, 6 genera) showing significant or potential causal relationships in forward analysis revealed no significant causal effect of insomnia on gut microbiota ($P>0.05$).

Discussion

This study using MiBioGen and UK Biobank GWAS data identified that decreased abundance of *genus_{Roseburia}*, *genus_{Erysipelatoclostridium}*, *genus_{Paraprevotella}*, *genus_{Ruminococcaceae} UCG014*, *family_{Pasteurellaceae}*, and *order_{Pasteurellales}* is causally associated with increased insomnia risk.

Recent research suggests GM is associated with insomnia. Choi et al. [20] found that gut microbiota exhibits circadian rhythms that interact with host circadian rhythms. Teichman et al. [21] confirmed that short-chain fatty acids (SCFAs) derived from gut microbiota (primarily acetate, propionate, and butyrate) can alter circadian rhythms and affect clock gene expression, linking GM to sleep-wake cycles. The brain-gut-microbiota (BGM) axis has been proposed as a key pathway through which intestinal bacteria participate in insomnia pathogenesis [5]. This complex bidirectional communication system, composed of neural, immune, metabolic, and endocrine pathways, tightly connects the gut and brain, allowing inflammatory factors, gut metabolites, hormones, neurotransmitters, and the vagus nerve to influence sleep [22]. Potential mechanisms include:

1. **Hypothalamic-pituitary-adrenal (HPA) axis:** Probiotic bacteria can regulate HPA axis-related stress responses [23], while HPA axis activation increases intestinal permeability and cortisol release [24], generating inflammatory factors that disrupt sleep [25].

2. **Neurotransmitters:** Insomnia is closely linked to neurotransmitters like GABA and serotonin (5-HT), which positively regulate sleep. *Lactobacillus* and *Bifidobacterium* can produce GABA and promote 5-HT conversion, indicating GM can influence sleep through neurotransmitter modulation [26-27].
3. **Immune system:** Interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) signaling in the central nervous system (CNS) regulates sleep-wake behavior [28], and chronic insomnia patients show elevated IL-1β levels [29]. Gut dysbiosis can damage intestinal barriers and mediate inflammatory responses affecting the CNS.
4. **Metabolites:** GM-derived metabolites, particularly SCFAs produced during fermentation, serve as important sleep signals by reducing inflammation and enhancing gut barrier function [5,30]. Reduced SCFA production due to dysbiosis may increase insomnia risk.
5. **Vagus nerve:** The vagus nerve represents a major signaling pathway between the brain and gut microbiota [31], with probiotics shown to modulate sleep by increasing GABA receptor expression in mice [32].

Clinical studies have demonstrated altered GM composition in insomnia patients. Xu et al. [7] found significantly reduced Firmicutes/Bacteroidetes ratios in insomnia patients, with Bacteroidetes as the dominant taxon. Zhou et al. [33] reported decreased Bacteroidaceae, Ruminococcaceae, and Bacteroides, but increased Prevotellaceae and *Prevotella* in insomnia patients.

Our study identified six microbial taxa as protective factors against insomnia (all OR<1), with *genus_{Roseburia}* being most significant (PFDR<0.05). This genus comprises obligate Gram-positive anaerobes that produce butyrate, an anti-inflammatory SCFA shown to promote non-rapid eye movement sleep in rodents [34-35]. Reduced *Roseburia* abundance may impair butyrate production and disrupt sleep. *Ruminococcaceae UCG014* belongs to Peptococcaceae, a family previously found reduced in insomnia patients [33]. *Paraprevotella*, established in 2009, is phylogenetically similar to *Prevotella* but with distinct secreted peptidase families [36-37]. While *Prevotella* abundance increases in insomnia [33], our findings suggest *Paraprevotella* is protective, indicating different pathogenic mechanisms despite similarities.

Taxa showing potential associations (P<0.05 but PFDR>0.1) included *class_{Bacteroidia}*, *genus_{Intestinibacter}*, *genus_{Ruminococcaceae} UCG003*, *order_{Bacteroidales}*, *order_{Desulfovibrionales}*, *phylum_{Euryarchaeota}*, and *phylum_{Lentisphaerae}*. Previous studies found reduced *Intestinibacter* in major depressive disorder patients with sleep disturbances [38] and associations between high-quality sleep and *Lentisphaerae* in older adults [39].

Strengths and Limitations

This study' s strengths include using MR to establish causality, large sample sizes minimizing confounding, and MR-PRESSO/Egger intercept tests to detect pleiotropy. Limitations include: (1) inability to explore species-level relation-

ships due to genus-level resolution of exposure data; (2) use of SNPs below traditional GWAS significance threshold (P<5$×10^{-8}$) for sensitivity analysis, requiring FDR correction to limit false positives; and (3) European ancestry of study populations, limiting generalizability to Asian populations.

In conclusion, this Mendelian randomization study identified causal relationships between six gut microbial taxa and insomnia, with increased abundance of these taxa reducing insomnia risk. These findings provide new insights for insomnia diagnosis and treatment, though further large-scale RCTs are needed to elucidate protective mechanisms.

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