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Potential mechanisms of gut microbiota influence on different types of vertigo: a bidirectional Mendelian randomization and mediation analysis

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Abstract

Background The relationship between gut microbiota and vertigo, specifically Benign Paroxysmal Vertigo (BPV) and Vertigo of Central (VC), remains underexplored.

Aim and hypotheses This study aims to investigate the causal relationships between gut microbiota and two types of vertigo, BPV and VC. Additionally, the study seeks to explore the mediation effects of metabolic, inflammatory, and psychological factors on these relationships. We hypothesize that specific taxa of gut microbiota have a causal effect on the risk of developing BPV and VC. The mediation effects of HbA1c, obesity, major depression, and interleukin-18 levels significantly influence the relationships between gut microbiota and vertigo.

Method Utilizing a bidirectional two-sample Mendelian randomization approach, this study investigated causal associations between gut microbiota and the two types of vertigo. A network MR assessed mediation effects of HbA1c, major depression, obesity, and interleukin-18 levels, with data sourced from several consortia, including MiBioGen.

Results Distinct gut microbiota displayed varying influences on BPV and VC risks. A total of ten taxa affect BPV. Among these, two taxa have an odds ratio (OR) greater than 1, including one class, one order. Conversely, eight taxa have an OR less than 1, encompassing four families, three genera, and one order. The OR for these taxa ranges from 0.693 to 0.930, with p-values between 0.006 and 0.048. For VC, eight taxa were found to have an impact. Five of these taxa exhibit an OR greater than 1, including four genera and one phylum. The OR for these taxa ranges from 1.229 to 2.179, with p-values from 0.000 to 0.046. The remaining three taxa have an OR less than 1, comprising one family and two genera, with an OR range of 0.445 to 0.792 and p-values ranging from 0.013 to 0.050. The mediation analysis for BPV shows that major depression, obesity, and HbA1c are key mediators between specific taxa and BPV. Major depression mediates 28.77% of the effect of *family Rhodospirillaceae* on BPV. Obesity mediates 13.90% of the effect of *class Lentisphaeria/order Victivallales*. HbA1c mediates 11.79% of the effect of *genus Bifidobacterium*, 11.36% of *family Bifidobacteriaceae/order Bifidobacteriales*. For VC, interleukin-18 levels and major depression are significant mediators.

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Interleukin-18 levels mediate 6.56% of the effect of *phylum Actinobacteria*. Major depression mediates 6.51% of the effect of *genus Alloprevotella*.

Conclusion The study highlights potential causal links between gut microbiota and vertigo, emphasizing metabolic and psychological mediators. These insights underscore the therapeutic potential of targeting gut health in vertigo management.

Keywords HbA1c, Interleukin-18, Gut microbiota, Major depression, Mendelian randomization, Mediation analysis, Obesity, Vertigo

Background

Vertigo is a common clinical symptom characterized by the sensation of spinning or having one's surroundings spin about them. This symptom can be associated with several diseases, including but not limited to Meniere's disease, vestibular neuritis, and Benign Paroxysmal Vertigo (BPV) [1]. BPV is the most common cause of peripheral vertigo, accounting for over half of all cases. According to various estimates, a minimum of 20% of patients presenting with vertigo have BPV [2]. Approximately 80% of vertigo cases are peripheral, whereas about 20% are categorized as Vertigo of Central (VC) [3]. Vertigo and other vestibular disorders can significantly impact an individual's quality of life, causing issues with balance, spatial orientation, and daily activities [4]. The management of vertigo can be challenging due to its multifactorial nature. Current treatment strategies primarily focus on symptomatic relief, with canalith repositioning maneuvers being the mainstream treatment for conditions like BPV. However, the recurrence rate of vertigo after treatment is high, leading to increased patient anxiety and decreased quality of life [5].

Recent research has begun to explore the potential role of the gut microbiota in the development and management of vertigo. The gut microbiota, the diverse community of microorganisms residing in our gut, has been found to play a crucial role in human health and disease. It is involved in various physiological processes, including metabolism, immune function, and even the modulation of the central nervous system through the gut-brain axis [6, 7]. In the context of vertigo, certain gut microbiota, such as *Bifidobacterium*, have been associated with metabolic disorders like Type 2 diabetes mellitus, which can indirectly influence the development and severity of vertigo [8, 9]. Moreover, alterations in gut microbiota composition have been observed in mice with vestibular deficits [10]. However, despite these promising findings, the exact mechanisms through which the gut microbiota influences vertigo remain largely unknown. Further research is needed to elucidate these mechanisms and to explore the potential of microbiota-targeted interventions for the prevention and treatment of vertigo.

Mendelian randomization (MR) is a method of using measured variation in genes of known function to examine the causal effect of a modifiable exposure on disease in non-experimental studies [11]. It has been used in recent years to infer causality from publicly available genome-wide association study (GWAS) summary statistics. In the context of vertigo, MR studies can provide valuable insights into the potential causal relationships between gut microbiota and vertigo. We will use MR to explore the causal relationship between 211 gut microbiota and vertigo.

Research has consistently linked psychological, inflammatory, and metabolic factors to vertigo. Studies indicates a higher prevalence of depression and anxiety among patients with vestibular dysfunctions [12, 13], with further studies suggesting that individuals with depressive disorders are at an elevated risk of developing BPV [14]. This relationship underscores the psychological impact of gut microbiota imbalances, leading us to select major depression as a potential mediator. Concurrently, inflammatory markers like interleukin-1β and IL-6 have been associated with vertigo symptoms [15, 16], highlighting the interleukin pathways as significant contributors to vertigo's etiology. Additionally, a pivotal study examining various metabolites, such as high-density lipoprotein, cholesterol, low-density lipoprotein cholesterol, serum uric acid, and HbA1c, found that particularly lower levels of HbA1c were independently associated with BPV [17]. The study emphasized the metabolic influence on vertigo and supporting the inclusion of HbA1c as a mediator to explore glucose metabolism's impact as modulated by gut microbiota. We also investigated potential mediators that could influence the relationship between gut microbiota and vertigo, including HbA1c, obesity, major depression, and interleukin levels.

Method

Study design

In our research, we utilized a two-sample Mendelian randomization methodology [18] to explore the potential causal associations between gut microbiota and two distinct types of vertigo: BPV and VC. To further delve into the mediating effects of potential factors such as HbA1c, major depression, obesity, and interleukin-18 levels, we implemented a two-step (network) MR approach [19]. A simple flow chart of the study design is shown in Fig. 1A,

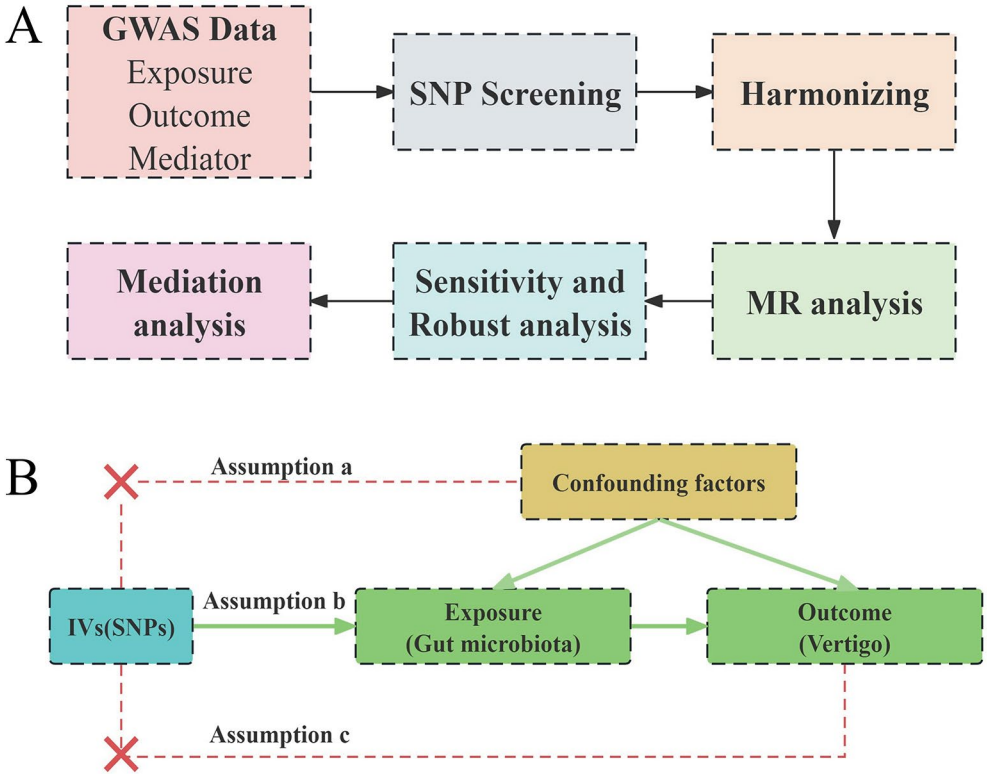

Fig. 1 Mendelian Randomization flow chart and assumptions. (**A**) Simple flow chart for MR analysis and mediation analysis. (**B**) In the depicted MR model, three core assumptions are illustrated: (a) Independence from confounding, ensuring that the genetic variants are not correlated with any confounders of the exposure-outcome relationship; (b) Instrument-exposure association, where genetic variants are strongly associated with the exposure; (c) No horizontal pleiotropy, stipulating that the genetic variants influence the outcome solely through the exposure, without any other pathways

and detailed processes and explanations can be found in the Supplemental text.

Data sources

Our study leveraged data from various cohorts and consortia to delve into the associations between gut microbiota and several health outcomes, including vertigo. The gut microbiota data integral to our study was derived from the MiBioGen consortium [20]. The MiBioGen consortium is a comprehensive repository, having meticulously curated and analyzed genome-wide genotypes in conjunction with 16S fecal microbiome data. This extensive dataset encompasses 18,340 individuals spanning across 24 distinct cohorts. Notably, a significant portion of this dataset, specifically 14,306 individuals, originates from 18 cohorts of European descent. The consortium has undertaken rigorous adjustments to ensure data consistency and reliability, including accounting for variables such as age and sex, as well as genetic principal components. Furthermore, to mitigate technical discrepancies, the consortium has also adjusted for technical covariates.

Interleukin-18 levels data was obtained from a meta-analysis encompassing 13 cohorts, resulting in a sample size of 21,758 participants [21]. From this, ninety proteins successfully passed the quality control (QC) criteria and were subsequently available for the GWAS meta-analysis. Data pertaining to HbA1c levels were sourced from the Within Family GWAS consortium, comprising 17,724 participants. Obesity data was informed by a collaborative meta-analysis of fourteen studies of European ancestry [22]. This included 5,530 cases (individuals with a body mass index (BMI) ≥ 95th percentile) and 8,318 controls (individuals with a BMI < 50th percentile). Major depression data relied on a meta-analysis of the two most extensive genome-wide association studies available: UK Biobank and PGC [23]. This meta-analysis, which excluded overlapping samples and data from 23andMe, encompassed 170,756 cases and 329,443 controls. Data specific to vertigo was extracted from the Round 9 FinnGen dataset [24]. Within this dataset, there are 8,280 cases and 359,094 controls for BPV, and 14,918 cases and 359,094 controls for VC. All the database sources used are listed in Supplemental Table 1.

SNP selection

In our endeavor to investigate the potential causal links between gut microbiota and vertigo, we utilized the technique of MR analysis. This approach involves the use of genetic variants as instrumental variables (IVs). The effectiveness of an MR analysis is dependent on three

fundamental assumptions (Fig. 1B) [25]: a)IVs are not correlated with any confounders; b)There exists a robust association between IVs and the exposure; c)The impact of IVs on the outcome is solely via the exposure.

Our first step involved the selection of single nucleotide polymorphisms (SNPs) from the GWAS summary data for exposures. These exposures demonstrated a genome-wide significant association ($p<5e{-}8$) with the traits, and were thus used as IVs. Due to the sparse pool of IVs, we adjusted the significance threshold to 5e-5 to maintain a minimum of 10 SNPs, thereby preventing inaccuracies due to a scarcity of significant genetic variants [26].

In the mediation analysis, the significance thresholds were set as follows: major depression $P<5e{-}8$, obesity $P<5e{-}5$, HbA1c $P<5e{-}7$, interleukin-18 levels $P<5e{-}6$. For the Reverse analysis, the outcome $P<5e{-}5$. Next, we applied linkage disequilibrium clumping to filter out certain undesirable SNPs ($r^2<0.01$, window size > 10,000 kb) [27]. After this, we harmonized the exposure and outcome datasets and removed palindromic SNPs with allele frequencies nearing 0.5. The selected SNPs are detailed in Supplemental Table 2.

To ascertain the robustness of genetic instruments for exposures, we calculated the F statistic using the formula [28]: $F=R^2 \times [(N-1-k) / k] / (1-R^2)$, where R^2 represents the cumulative explained variance in the selected SNPs, N is the sample size, and k is the number of SNPs in the analysis. An F statistic exceeding 10 indicates sufficient strength to circumvent the issue of weak instrument bias in the two-sample model.

Statistical analysis strategy

We carried out bidirectional two-sample MR analyses to evaluate the relationship between gut microbiota and vertigo. Our primary analysis utilized an inverse variance-weighted (IVW) meta-analysis approach, a robust method for MR analysis [29]. To increase the robustness of the results, we conducted sensitivity analyses using the weighted median (WM) [30] and MR-Egger regression approaches [31]. The potential impact of directional pleiotropy was assessed by testing the intercept value of the MR-Egger regression [32]. MR PRESSO also test pleiotropy and outliers. Heterogeneity was assessed using Cochran's Q test [33]. Futhermore, we use LDtrait tool find potiental SNP association with confounders [34].

In instances of heterogeneity, we opted for a random-effects IVW for the primary analysis. The mediation effect uses a Network Mendelian randomization [19] method involving several key steps. First, MR analysis is conducted to estimate the effect of gut microbiota on the mediator, represented by Beta(A). Next, MR analysis estimates the effect of the mediator on vertigo, represented by Beta(B). A third MR analysis estimates the direct effect of gut microbiota on vertigo, represented by Beta(C). For the mediation effect to be considered valid, both Beta(A) and Beta(B) must be significant. The mediation effect is then calculated as the product of Beta(A) and Beta(B). Finally, the mediation proportion, which represents the proportion of the total effect mediated through the specified mediator, is calculated as the product of Beta(A) and Beta(B) divided by Beta(C). To minimize the false discovery rate in our analysis, we employed the Benjamini-Hochberg method (FDR) for multiple testing corrections [35], establishing a significance threshold of $P_{FDR} < 0.05$. Additionally, we identified taxa that reached significance ($P<0.05$) but did not achieve significance after FDR adjustment ($P_{FDR} > 0.05$) as potentially causal associations.

For statistical analyses, we used R software (version 4.3.1) and specifically utilized packages 'TwoSampleMR' (version 0.5.7) for conducting Mendelian Randomization analyses. For visualization, we employed Python 3.11, utilizing libraries Matplotlib and Seaborn to create detailed and informative plots. These tools allowed for rigorous and reproducible analyses consistent with current best practices in the field.

Result

Differential influence of gut microbiota on two types of vertigo

We excluded 30 taxa of unknown significance, focusing our MR analysis on 191 taxa, including 9 phyla, 19 orders, 30 families, 16 classes, and 117 genera. In this MR study, we applied a multipronged approach to investigate the associations between the abundance of different gut microbiota and two types of vertigo: BPV and VC. The fixed-effects IVW method was employed as the primary analysis to estimate the causal effects. In cases where the results indicated significant heterogeneity, a random-effects IVW was used. When significant pleiotropy was detected, the MR-Egger method was utilized to provide more robust estimations. As shown in Fig. 2, the abundance of various gut microbiota could influence the risk of these vertigo types differently. For BPV, an increase in the abundance of the *phylum Lentisphaerae*, *class Lentisphaeria*, and the order Victivallales was associated with a higher risk. In contrast, a higher abundance of *families Bifidobacteriaceae*, *Christensenellaceae*, *Rhodospirillaceae*, *Rikenellaceae*, and *genera Bifidobacterium*, *Blautia*, *Enterorhabdus*, along with the *order Bifidobacteriales*, was associated with a lower risk. For VC, a rise in the abundance of the *genera Alloprevotella*, *Intestinibacter*, *Methanobrevibacter*, *Roseburia*, *Sutterella*, and the *phylum Actinobacteria* indicated a higher risk, whereas an increase in the *family Christensenellaceae* and the *genera Holdemanella*, and *Sellimonas* suggested a lower risk.

After adjusting for FDR, our analysis reveals that the genus Roseburia remains significantly associated with

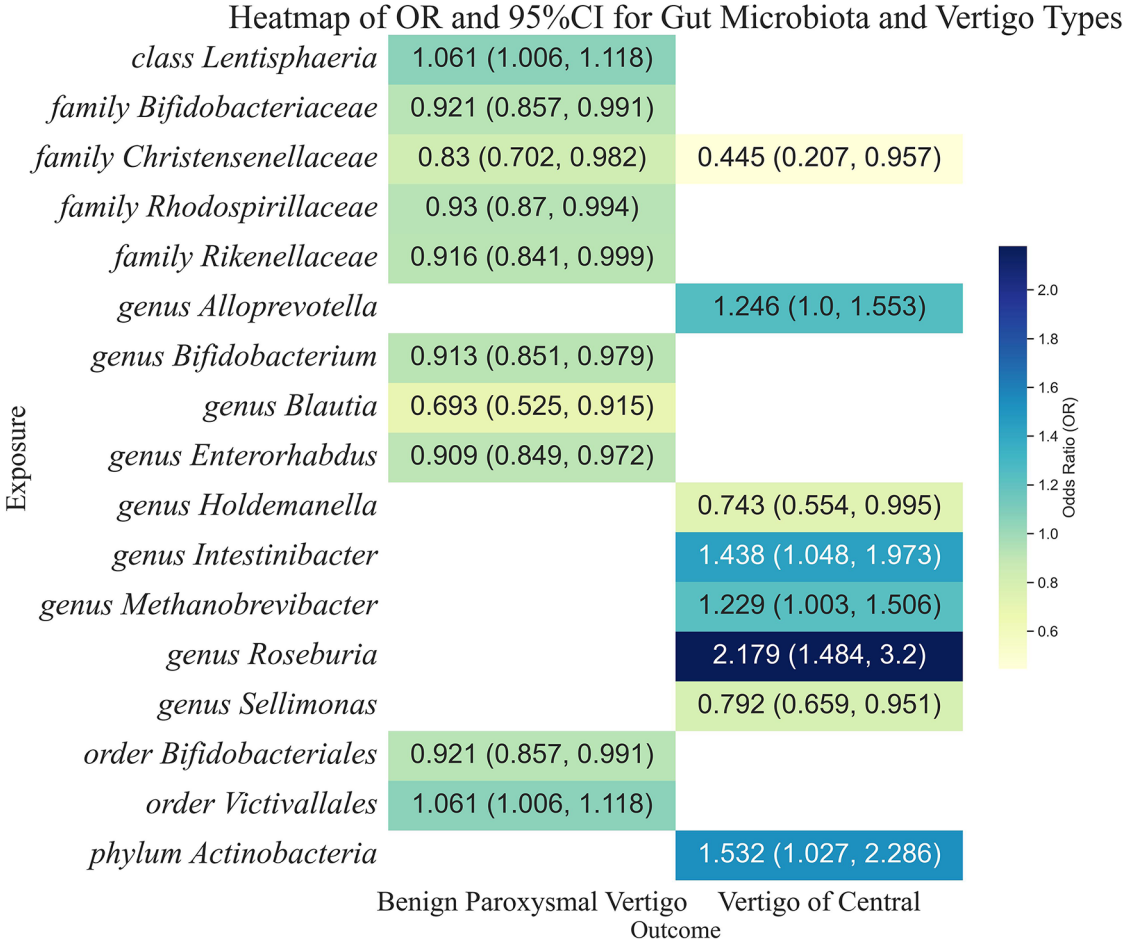

Fig. 2 MR analysis heatmap for gut microbiota abundance, benign paroxysmal vertigo, vertigo of central

VC, with an FDR-adjusted p-value of 8.31e-3. Similarly, significant associations are maintained for Enterorhabdus (P_{FDR} = 3.19e-2), Blautia (P_{FDR} = 4.37e-2), and Bifidobacterium (P_{FDR} = 4.47e-2) with BPV. Additionally, associations where the FDR-adjusted p-values exceed 0.05 but the nominal p-values are below 0.05 are considered suggestive, indicating potential trends that warrant further investigation.

To increase the robustness of our study, we also conducted a series of additional analyses (Supplemental Table 3). Notably, most of the WM and MR-Egger analyses showed the same direction to the IVW analysis, further strengthening the findings. We found no outliers in these results, adding to the consistency and reliability of the associations. Further, the intercept and global tests demonstrated no significant pleiotropy (Supplemental Table 4), indicating that our selected genetic variants are unlikely to affect the outcomes through pathways other than through the microbiota under investigation. However, using LDtrait, we identified 22 unique SNPs (Supplemental Table 5) associations with potential confounders. Excluding the phylum Lentisphaerae, which showed no association with BPV, and the genus Sutterella, which exhibited no association with VC after the confounding SNPs were removed, all other results remained significant (Supplemental Table 6). This methodology further support the robustness of our findings. Interestingly, in reverse MR analysis, VC have a higher level of *genus Roseburia* (Supplemental Table 7).

This heatmap illustrates the association between various taxa of gut microbiota and two types of vertigo: BPV and VC. The color gradient (from yellow to blue) represents the magnitude of the OR, with more yellow colors indicating lower odds and more blue colors indicating higher odds. OR and 95% confidence intervals (CI) are displayed in each cell. When OR>1, the presence of the specific gut microbiota taxa is associated with an increased risk of vertigo; When OR<1, gut microbiota taxa is associated with an decreased risk of vertigo.

Metabolic and psychological factors in gut microbiota-vertigo association

In the subsequent analysis, we evaluated potential mediating factors of vertigo that could be influenced by gut microbiota, using a stepwise method. These factors included HbA1c, major depression, obesity, and interleukin-18 levels. The initial Mendelian randomization analysis was performed between the gut microbiota and these selected mediators.

Our results demonstrated that certain microbiota were significantly associated with different potential mediators (Fig. 3). The abundance of the *genus Bifidobacterium* and the *family Bifidobacteriaceae*, as well as the *order Bifidobacteriales*, were negatively associated with HbA1c levels, suggesting that an increase in these microbiota might lead to a decrease in HbA1c levels. Similarly, the *family Rhodospirillaceae* was negatively associated with major depression. Conversely, positive associations were found between the *genus Alloprevotella* and major depression, the *order Victivallales* and *class Lentisphaeria* with obesity, and the *phylum Actinobacteria* with interleukin-18 levels. Subsequently, we conducted Mendelian randomization analyses between these mediators and the vertigo types (Fig. 4). Our findings indicated that major depression, obesity, HbA1c were positively associated with BPV, implying that higher levels of these factors might increase the risk of this type of vertigo. Similarly, for VC, interleukin-18 levels, and major depression showed positive associations. The robustness of these findings was verified using similar approaches as before (Supplemental Table 8). Specifically, when pleiotropy was detected in the case of the *family Rhodospirillaceae* with major depression (Supplemental Table 8), we used the MR-Egger method to provide a robust estimation.

Figure 3 illustrates the influence of different gut microbiota taxa on various health mediators from a Mendelian randomization study. Each line corresponds to a different taxon (labeled on the y-axis) and its effect size (beta coefficient) on a specific health mediator, indicated by color: "HbA1c" (sky blue), "Major depression" (red), "Obesity" (green), and "Interleukin-18 levels" (salmon). The horizontal lines represent the 95% confidence intervals for each effect size, showing the statistical uncertainty of these estimates. A dotted line at x=0 indicates no effect. When Beta>1, the presence of the specific gut microbiota taxa is associated with an increased level or risk of mediators; When Beta<1, gut microbiota taxa is associated with an decreased level or risk of mediators.

Figure 4 illustrates the influence of different mediators on two types vertigo from a Mendelian randomization study. Each line corresponds to different mediators (labeled on the y-axis) and its OR on a specific vertigo. The horizontal lines represent the 95% confidence intervals for each OR value, showing the statistical uncertainty of these estimates. A dotted line at x=1 indicates no effect. When OR>1, the presence of the specific

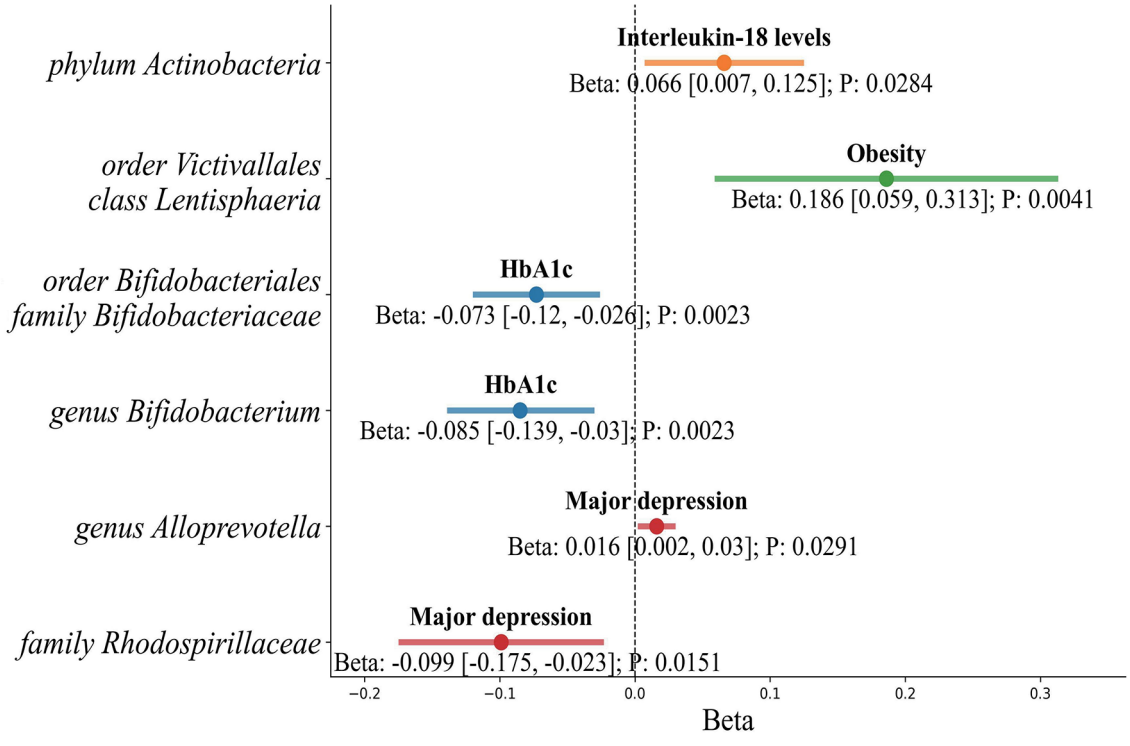

Fig. 3 Forest plot for gut microbiota effect on mediators

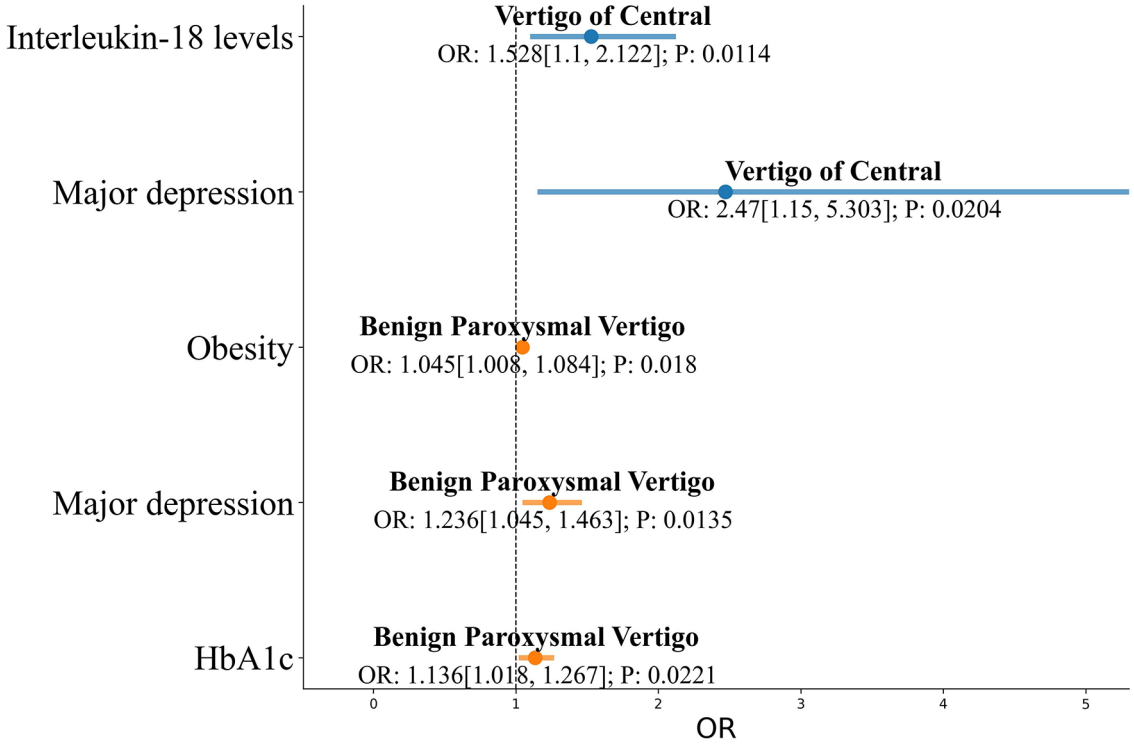

Fig. 4 Forest plot for mediator effect on vertigo

Table 1 Mediation effect between gut microbiota and vertigo

Benign Paroxysmal Vertigo (Outcome)						
Exposure	Mediator	Total effect	BetaA	BetaB	Mediation effect	Mediation effect proportion
family Rhodospirillaceae	Major depression	-0.073	-0.099	0.212	-0.021	28.77%
class Lentisphaeria/ order Victivallales	Obesity	0.059	0.186	0.044	0.008	13.90%
genus Bifidobacterium	HbA1c	-0.092	-0.085	0.127	-0.011	11.79%
family Bifidobacteriaceae/ order Bifidobacteriales	HbA1c	-0.082	-0.073	0.127	-0.009	11.36%
Vertigo of Central (Outcome)						
Exposure	Mediator	Total effect	BetaA	BetaB	Mediation effect	Mediation effect proportion
phylum Actinobacteria	Interleukin-18 levels	0.427	0.066	0.424	0.028	6.56%
genus Alloprevotella	Major depression	0.220	0.016	0.904	0.014	6.51%

mediators is associated with an increased risk of vertigo; When OR < 1, mediators is associated with an decreased risk of vertigo.

Mediating effects

We found that several health and metabolic factors mediate the relationship between gut microbiota and two types of vertigo, BPV and VC. For BPV (Table 1), a significant proportion of the total effect of the *family Rhodospirillaceae* (approximately 29%), the *class Lentisphaeria* (around 14%), the *order Victivallales* (about 14%), the *genus Bifidobacterium* (around 12%), the *family Bifidobacteriaceae* (approximately 11%), the *order Bifidobacteriales* (about 11%) on vertigo is mediated through major depression, obesity, and HbA1c. This suggests that these health factors may play a crucial role in the relationship between these gut microbiota and BPV.

Similarly, for VC, a notable proportion of the total effect of the *phylum Actinobacteria* (around 7%) and the *genus Alloprevotella* (approximately 7%) on vertigo is mediated through interleukin-18 levels and major depression respectively. This indicates that these health factors could be significant mediators in the relationship between these gut microbiota and VC.

Discussion

Our study unveils compelling evidence underpinning the intricate relationship between gut microbiota and vertigo. For BPV, we found that an increased risk was associated with a higher abundance in 1 class, and 1

order. Conversely, a decreased risk was linked to elevated abundance in 4 families and 4 genera. Regarding VC, an increased risk was tied to a rise in 1 phylum and 4 genera, while a decreased risk was correlated with increased levels in 1 family and 2 genera. Our findings suggest that the gut ecosystem may play a pivotal role in various neurological manifestations. Not only do we identify specific gut microbiota that have causal relationships with BPV and VC, but we also reveal key mediators in this process, including major depression, obesity, HbA1c levels, and interleukin-18 levels.

The gut-brain axis is a bidirectional communication network that links the enteric and central nervous systems [36]. This network is not only anatomical but it extends to include endocrine, humoral, metabolic, and immune routes of communication as well. Notably, our mediation analysis illuminates the significance of metabolic and psychological factors. Major depression's role, both as a potential consequence of altered gut microbiota and as a risk factor for vertigo, underscores the interconnectedness of mental health, gut health, and neurological disorders. The positive association between HbA1c levels and BPV hints at a potential metabolic pathway, suggesting that glycemic control may have implications beyond diabetes management. Furthermore, the link between obesity and BPV reiterates the systemic impact of gut microbiota, emphasizing the need for holistic approaches in health management. The association of interleukin-18 levels, an inflammatory marker, with VC, also hints at potential inflammatory pathways influenced by gut health.

Our findings, which link specific gut microbiota with vertigo types, are supported and further illuminated by existing literature. In particular, our observation of the *genus Bifidobacterium* being associated with HbA1c levels aligns with a prior randomized clinical trial suggesting that *Bifidobacterium* can lower HbA1c levels [37]. These associations underscore the intricate interplay between gut microbiota and metabolic parameters. Another intriguing observation from our study pertains to the abundance of *Bifidobacteriaceae* during early pregnancy. Higher levels of HbA1c among pregnant women were found to be associated with a reduced abundance of this family. Interestingly, in healthy controls, *Bifidobacteriaceae* was found to be more abundant. This suggests that *Bifidobacteriaceae* might play a protective role, especially in metabolic conditions like diabetes, during crucial periods such as pregnancy [38]. The case of the *genus Blautia* is especially fascinating. Previous research reported a decrease in *Blautia* levels, juxtaposed with an increase in *Bacteroides*, post-bariatric surgery [39]. This shift in bacterial abundance is pertinent given that the *Blautia/Bacteroides* ratio has been positively correlated with BMI in previous studies. A cross-sectional study involving Japanese adults identified the *Blautia* genus, particularly *B. wexlerae*, as a bacterium inversely correlated with obesity and type 2 diabetes mellitus [40]. This association was further strengthened by experimental evidence demonstrating that oral administration of *Blautia wexlerae* in mice could elicit metabolic alterations and anti-inflammatory responses, thereby mitigating high-fat diet-induced obesity and diabetes. Such findings emphasize the potential therapeutic implications of modulating gut microbiota in metabolic disorders. While existing literature primarily focuses on the correlated relationship between gut microbiota and metabolites or metabolic diseases, these studies fall short of confirming a causal relationship. Our study addresses this gap by utilizing a two-sample Mendelian randomization approach to establish causal links between specific gut microbiota and vertigo. Additionally, we have identified key mediators—major depression, obesity, HbA1c levels, and interleukin-18 levels—that partially mediate this process. By confirming the causal influence of certain gut microbiota on vertigo, our research adds a new dimension to the current understanding, emphasizing the multifaceted nature of the gut-brain axis. This approach not only strengthens the evidence for the role of gut microbiota in vertigo but also highlights the importance of metabolic and psychological factors in this relationship. These insights extend beyond correlation, providing a deeper understanding of the mechanisms involved and suggesting potential therapeutic avenues for targeting gut microbiota to manage vertigo and related conditions.

The etiology of vertigo remains multifaceted, with inflammation and immune dysregulation being pivotal players. Our findings hint at the probable mediating role of gut microbiota in vertigo's pathogenesis, possibly by modulating systemic inflammation and immune responses [41]. The neuroprotective and anti-neuroinflammatory properties attributed to Bifidobacterium echo the broader understanding of its potential beneficial impact on the nervous system [42]. Concurrently, Christensenellaceae might exert its neuroprotective effects by modulating metabolic pathways, further emphasizing the intricate links between metabolism, inflammation, and nervous system health [43]. Recent insights into post-SARS-CoV-2 sequelae have highlighted the persistence of inflammatory processes, especially within the olfactory system [44]. Chronic inflammation in this system, as evidenced in animal models like hamsters, could potentially mirror some neuropsychiatric manifestations observed in humans post-COVID, including depression and anxiety [45]. This post-viral inflammatory state, coupled with the observed alterations in gut microbiota post-SARS-CoV-2 infection, suggests a complex interplay between systemic inflammation, gut dysbiosis, and neurological symptoms. The noted decrease in protective microbial

taxa, such as Bifidobacterium bifidum and Akkermansia muciniphila, post-SARS-CoV-2 infection, further accentuates the potential role of gut microbiota in modulating systemic inflammation and its consequent neurological manifestations [46]. Another study found that patients with neuroinfections, including viral encephalitis/meningitis and bacterial meningitis, had a different gut microbiome compared to healthy controls. Bacterial taxa such as Clostridium, Anaerostipes, Lachnobacterium, Lachnospira, and Roseburia were decreased in patients with neuroinfection. The cause of these differences is unclear, but it could be due to inflammation accompanying the disease, the effect of diet modification, or hospitalization [47].

Our study's multifaceted design, employing various sensitive analyses, underscores the rigor and reliability of our findings. The alignment of results from the WM and MR-Egger methods with the primary IVW method further attests to the robustness of our conclusions. Additionally, our adoption of the MR-PRESSO technique to identify and rectify potential outliers and pleiotropy fortified our findings against bias. Although we did not detect any pleiotropy, the use of the LDtrait tool to remove confounding SNPs showed that the phylum Lentisphaerae and the genus Sutterella no longer maintained an association with vertigo. Consequently, we decided to exclude these two results to ensure the robustness of our findings. Another noteworthy aspect of our research is our ability to highlight specific genera that demonstrated pronounced associations with vertigo, even if some of these relationships still keep statistical significance post adjustment for multiple testing. To maximize the discovery of significant results, we keep these result wich P value <0.05, but it did not have significant p value after FDR adjust. These remain essential preliminary insights that could point towards specific biological interactions. The consistency in the ethnic background of both our exposure and outcome populations, being predominantly of European descent, also ensures reduced potential bias from population stratification.

However, our study is not without its limitations. The most significant constraint is the predominance of European population data, which may impart a certain bias and restrict the generalizability of our findings to other ethnic groups. Additionally, the lack of individual-level data prevented us from exploring intricate relationships, including potential non-linear correlations among microbiota, mediators, and vertigo. As a result, certain patterns such as U-shaped or J-shaped associations might have been overlooked.

Conclusion

Our study provides compelling evidence emphasizing the pivotal role of gut microbiota in influencing vertigo's pathogenesis. The intricate relationships between specific microbial taxa and types of vertigo, along with the mediating roles of metabolic and psychological factors, highlight the multifaceted nature of the gut-brain axis. The associations between gut microbiota and metabolic parameters, such as HbA1c levels and obesity, underscore the broader implications of gut health in systemic conditions. Furthermore, the potential protective roles of specific bacteria, such as Bifidobacterium, hint at novel therapeutic avenues for metabolic and neurological conditions. The intricate interplay between gut microbiota, systemic inflammation, and neurological symptoms, accentuates the need for holistic approaches to understanding and managing neurological conditions.

Future research

To further our understanding and devise effective interventions, several avenues of research beckon attention. Firstly, longitudinal studies are crucial to establish causality between gut microbiota alterations and neurological outcomes. This should be complemented with deeper dives into the mechanistic pathways of microbial influence. The therapeutic potential of probiotics or fecal microbiota transplants, inspired by the protective roles of certain bacteria, needs rigorous clinical trial evaluations. Concurrently, the impact of diet, medication, and other lifestyle factors on gut microbiota composition should be probed. Integrating this knowledge with multi-omics data can offer comprehensive insights into host-microbiome interactions. Through these focused research endeavors, we can better harness the potential of gut microbiota modulation in health and disease management.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-024-03805-x.

Supplementary Material 1

Supplementary Material 2

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Author contributions

Qiongwen Rong (QWR), Hao Chen (HC), Yibin Chen (YBC), Changxuan Li(CXL) conceptualized and designed the study. QWR, HC, and YBC were responsible for data collection and organization. Data analysis was performed by CXL. The manuscript was drafted by QWR, HC, and YBC. Minghui Xu (MHX), Ruixue Chen (RXC), CXL revised the manuscript. All authors reviewed, provided input, and approved the final version of the manuscript.

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Data availability
The current study utilized summary statistics for gut microbiota is accessed through this link: https://gwas.mrcieu.ac.uk/datasets/ (Accsession number: ebi-a-GCST90016908 to ebi-a-GCST90017118). Major depression (ieu-b-102), obesity (ebi-a-GCST001475), IL-18 (ebi-a-GCST90012024), HbA1c (ieu-b-4841) are accessed through this link: https://gwas.mrcieu.ac.uk/datasets/ . Vertigo of Central is accessed through https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_H8_VERTIGO.gz/. Benign Paroxysmal Vertigo is accessed through https://storage.googleapis.com/finngen-public-data-r9/summary_stats/finngen_R9_H8_BPV.gz/. Direct links of all data have been put in the Supplemental Table 1.

Declarations

Ethics approval and consent to participate
The data used in this paper are publicly available, ethically approved, and the subjects have given their informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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