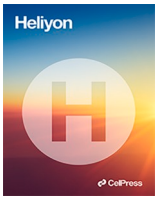
Heliyon 10 (2024) e38782

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Circulating levels of micronutrients and the risk of benign paroxysmal positional vertigo: A Mendelian randomization study

Jian Wang [*], Cheng Cao, Wen-Bo Jiang, Hong-Cun Sun, Tao Jiang, Jian-Dao Hu [**]

Department of Otorhinolaryngology Head and Neck Surgery, The Affiliated People's Hospital of Ningbo University, Ningbo, 315040, Zhejiang Province, China

A R T I C L E I N F O

Keywords:
BPPV
Micronutrients
Mendelian randomization analysis
Selenium
Folate

A B S T R A C T

Background: Benign paroxysmal positional vertigo (BPPV) is a typical vestibular disease characterized by recurrent episodes of vertigo. The role of micronutrients in BPPV pathogenesis has not been extensively studied, prompting this investigation into the relationship between circulating micronutrients and BPPV risk. This research aimed to explore the relationship between blood micronutrient levels and BPPV risk via Mendelian randomization (MR) analysis, a robust method for inferring causality from observational data.

Methods: A total of 15 circulating micronutrients were assessed for their association with BPPV risk. MR analysis was conducted via the following methods: MR–Egger, weighted median, simple model, inverse variance weighting (IVW), and weighted mode. Sensitivity analyses were performed to assess heterogeneity and pleiotropy. A multivariate MR analysis was also conducted, incorporating potential confounders such as trauma, chronic otitis media, hearing loss, peripheral atherosclerosis, ageing, and osteoporosis.

Results: MR analysis revealed an obvious association between selenium and BPPV risk (OR 1.074, 95 % CI 1.005 to 1.148; P = 0.035). Folate was negatively related (OR 0.694, 95 % CI 0.501 to 0.962, P = 0.028) but was excluded because of inconsistent OR values across methods. Sensitivity analysis supported the IVW results, and there was no evidence of significant heterogeneity among the selenium-related instrumental variables included in the study, nor was horizontal pleiotropy detected among the instrumental variables. Multivariate MR analysis confirmed that selenium was an independent risk factor for BPPV (OR 1.22, 95 % CI 1.059 to 1.406, P = 0.006), with no significant associations observed for other micronutrients or exposure factors.

Conclusion: This study provides evidence that blood selenium levels are positively associated with the risk of BPPV, suggesting a potential role for selenium in the pathogenesis of this disorder. These findings are robust to various sensitivity analyses and support the use of MR analysis to identify novel risk factors for BPPV. The identification of selenium as an independent risk factor for BPPV has implications for the development of preventive strategies and targeted interventions. It is necessary to analyse the biological mechanisms of this association and determine the therapeutic value of limiting selenium intake for BPPV to provide support for the treatment of such patients.

* Corresponding author.
** Corresponding author.
E-mail addresses: wangjian_nbu@163.com (J. Wang), hjd413@163.com (J.-D. Hu).

https://doi.org/10.1016/j.heliyon.2024.e38782
Received 9 May 2024; Received in revised form 20 September 2024; Accepted 30 September 2024
Available online 2 October 2024

1. Introduction

Benign paroxysmal positional vertigo (BPPV) is a typical vestibular disease, and according to clinical experience, the main symptom of such patients is sudden dizziness, which can have a very adverse impact on their lives [1]. Although many studies related to BPPV exist, the exact cause is not yet clear, and it is generally believed that its main influencing factors are genetic and environmental factors [2]. Some scholars have shown that the levels of circulating micronutrients play important roles in pathological processes, and research on these factors is constantly increasing [3–5].

Micronutrients are crucial for the physiological functions of the human body and are closely related to overall health. Research has shown that micronutrients play important roles in maintaining cell integrity and enzyme activity. When the contents of micronutrients are insufficient, various diseases can develop, such as cardiovascular disease and immune dysfunction [6–9]. Therefore, it is necessary to study the correlations between these substances and various physiological processes and determine their impact on the risk of BPPV to provide support for the treatment of this disease.

Many studies have investigated the relationship between micronutrient levels and BPPV risk, but no clear and consistent conclusions have been obtained yet [3–5]. Some scholars have reported a significant correlation between the two, but other studies have not yielded the same results. Gunizi H et al. reported that low copper and zinc levels reduced antioxidant activity and increased the incidence of BPPV and that serum oxidative stress and trace element levels played important roles in the pathophysiology of BPPV. The results of one systematic review and meta-analysis demonstrated a negative correlation between the serum vitamin D concentration and BPPV incidence. However, the serum homocysteine, vitamin B12, and folic acid levels in BPPV patients were not significantly different from those in normal controls [10–12]. The results obtained from observational studies have obvious limitations, which are influenced mainly by confusion and reverse causality, and the reliability of the results obtained under these factors is not high.

Mendelian randomization (MR) is a widely used instrumental variable method that can be utilized to determine the causal relationship between micronutrient levels and BPPV risk, providing support for pathological research on this disease [13]. The advantage of MR is that it can avoid the aforementioned limitations of traditional observational research and improve the reliability of the obtained results. Therefore, in the current research on the potential causal relationship between exposure and outcomes, MR methods have begun to receive attention, and the results obtained provide support for the development of relevant disease intervention strategies.

In recent years, many scholars have chosen the MR method to analyse the relationships between micronutrient levels and related diseases and have achieved a series of important results [14–17]. However, according to relevant information, research on the causal relationship of BPPV risk has not yet been conducted [18]. Therefore, in this context, this study analysed the correlation between trace nutrient levels and BPPV risk through MR methods and conducted causal relationship tests to provide support for case studies of this disease.

Genome-wide association studies (GWASs) refer to the identification of sequence variations, namely, single-nucleotide polymorphisms (SNPs), in the whole human genome to screen for disease-related SNPs. This research method involves identifying the genetic factors associated with complex diseases and fully revealing those related to the occurrence, development and treatment of diseases. In this study, a GWAS database was searched, and the collected data were analysed to identify genetic variations related to BPPV. Next, genetic variation was set as an instrumental variable to determine the causal relationships between micronutrient levels and BPPV risk. To improve the reliability of the obtained results, multiple sensitivity analyses were conducted, and multiple MR methods were used to test the validity to obtain more reliable results.

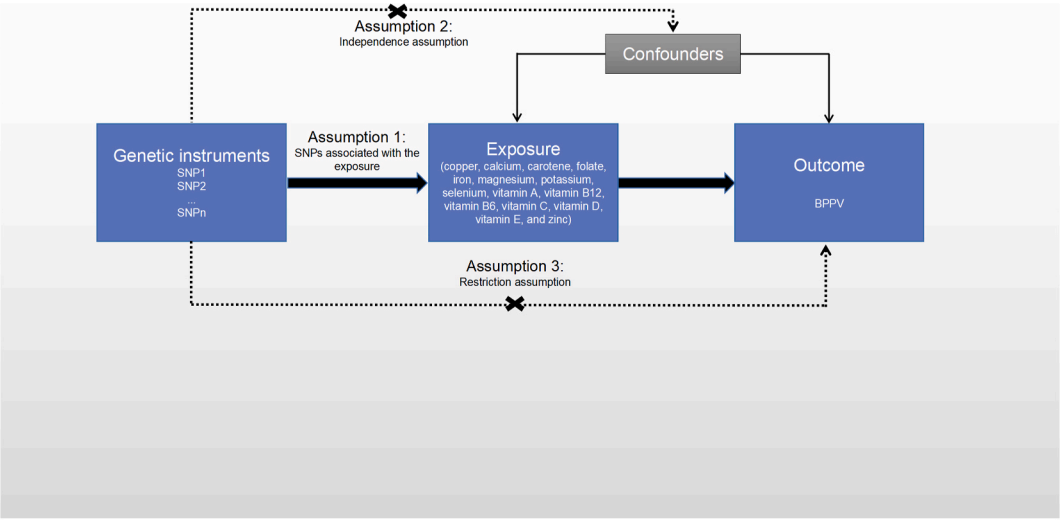


Fig. 1. Overview of the study design of the Mendelian randomization analyses. Abbreviations: SNP, single-nucleotide polymorphism; BPPV, benign paroxysmal positional vertigo.

2. Materials and methods

2.1. Study design

A summary diagram of the research design is shown in Fig. 1. In short, this study performed a two-sample MR analysis based on publicly available aggregated statistics from 22 GWASs: 15 trace elements and 6 confounders for exposure and 1 BPPV for results. To reduce bias caused by population distribution factors, only patients from the European region were included in the study, which was highly important for improving the reliability of the obtained results. The collected data are publicly available, and the relevant research also meets ethical and moral requirements.

2.2. Gene-level data on the association of micronutrients and BPPV

We searched the European descent GWAS database of individual genome-wide datasets (https://gwas.mrcieu.ac.uk/). A total of 15 potential micronutrients were identified: copper, calcium, carotene, folate, iron, magnesium, potassium, selenium, vitamin A, vB12, vB6, vC, vD, vitamin E, and zinc (ID numbers: ieu-a-1073, ukb-b-8951, ukb-b-16202, ukb-b-11349, ukb-b-20447, ukb-b-7372, ukb-b-17881, ieu-a-1077, ukb-b-9596, ukb-b-19524, ukb-b-7864, ukb-b-19390, ukb-b-18593, ukb-b-6888, and ieu-a-1079), 6 confusable factors: trauma exposure (GWAS identifier: ebi-a-GCST009982), chronic otitis media (GWAS identifier: ebi-a-GCST90018809), hearing loss (GWAS identifier: ebi-a-GCST90018857), peripheral atherosclerosis (GWAS identifier: finn-b-DM_PERIPHATHERO), ageing (GWAS identifier: finn-b-R18_SENILITY), osteoporosis (GWAS identifier: ukb-b-12141) and a BPPV event from a Finland database (https://storage.googleapis.finngen_R10_H8_BPV.gz).

2.3. Statistical power

This study included independent SNPs ($r2 < 0.001$ within a 10,000-kb window) that were strongly associated with the blood levels of each micronutrient [11]. To ensure valid instrumental variables, three basic assumptions must be met. There was a strong association between the selected instrumental variables (IVs) and exposure. IVs that met the exposure conditions did not have any confounding factors. The selected SNPs affected the results only through exposure. First, we obtained SNPs ($P \leq 5E{-}06$) that were strongly correlated with exposure and excluded weak instrumental variables with F statistics less than 10. Finally, we identified 6 SNPs related to serum copper, 6 SNPs related to serum selenium, 17 SNPs related to vitamin B6, 11 SNPs related to vitamin A, 13 SNPs related to vitamin D, 8 SNPs related to zinc, 6 SNPs related to serum selenium, 14 SNPS related to potassium, 8 SNPS related to vitamin B12, 19 SNPS related to calcium, 12 SNPS related to vitamin E, 17 SNPS related to magnesium, 10 SNPS related to vitamin C, 11 SNPS related to iron, 15 SNPS related to carotene, and 12 SNPS carotene-related SNPs for folate (Supplemental Material: Table 3). These SNPS served as IVs to explore potential causal associations between exposure and outcomes. For multivariate MR analysis, similar to the method above, SNPs of six clinically relevant confounders were obtained with more stringent P values ($P \leq 5E{-}08$).

2.4. MR analysis

The TwoSampleMR R package was applied for two-sample MR analysis of factors and outcomes [19]. Inverse variance weighting (IVW) was selected as the main method for data analysis. In addition, several auxiliary methods were applied, including MR–Egger, weighted median, and weighted mode, which can fully leverage the advantages of different methods and obtain more reliable results [20]. Comparative analysis revealed that the IVW method had high accuracy when all included SNPs met the variable assumption conditions. The main function of the MR–Egger method is to test for pleiotropy, but according to practical application experience, the estimation accuracy of this method is not high. The weighted median method also needs to satisfy the hypothesis of variable validity when estimating, resulting in more accurate results. Although the results obtained using the simple pattern method were incorrect, the stability of the validity test was high.

2.5. Sensitivity analyses

For an IV to be valid, it should meet the following three basic assumptions: the IV must be closely correlated with exposure, it must not influence confounders of exposure–outcome associations, and it must influence outcomes through risk factors alone. Horizontal pleiotropy SNPs with multiple effects may not meet the above assumptions. The MR–Egger, simple, and weighted model methods are typical sensitivity analysis methods used to clarify horizontal pleiotropy and are suitable when the number of genetic instruments is greater than 3. The MR–Egger model allows some SNPs to influence results by means other than exposure. If the intercept term is not equal to zero, this suggests that not all of the included tools are valid. The weighted median method determines the weighted median estimate according to the magnitude of the estimated genetic variation. Model-based approaches (i.e., simple and weighted models) assume that the most common causal effects are in accordance with true causal effects.

To assess whether differences in individual effect sizes between genetic tools are related to pleiotropic effects and not due to chance, we performed Cochran's Q test [21]. The test was performed when more variables were present, and $P < 0.05$ was regarded as significant in the heterogeneity test [22]. In addition, we performed a residual analysis of micronutrient levels >2 SNPs. This was done to check the robustness of the IVW results and to determine whether there were any specific SNPs driving the association.

2.6. Multivariate Mendelian randomization analysis

Multivariate MR was used to assess the presence of introduction-induced pleiotropy bias in other clinically common phenotypes [23]. As an extension of univariate MR, multivariate MR can collectively estimate the causal effects of different factors on the risk of benign paroxysmal vertigo. Because the onset of BPPV may be associated with risk factors such as trauma exposure, chronic otitis media, hearing loss, peripheral atherosclerosis, ageing, and osteoporosis, this study analysed these confounders using multivariate MR and investigated the direct effects of circulating trace elements on BPPV. The genetic variation of potential pleiotropic phenotypes was collected from the IEU Open GWAS. As previously mentioned, multivariate MR was used to evaluate the direct effect of circulating selenium on BPPV that was not mediated by other exposures. We extracted obvious SNPs ($P < 5 \times 10–8$) from the GWAS associated with multiple risk factors and then integrated them with an existing exposure tool variable (selenium). After excluding duplicate SNPs, we determined the effect of each SNP and the relevant standard error from the exposure and results. Weighted regression based on both IVW and MR–Egger methods was then used to determine causal relationships in multivariate MR.

2.7. Statistical analysis

We used the Mendelian Randomization and MRPRESSO packages in R software version 4.3.0 to perform TwoSampleMR 0.5.6 analysis to estimate the potential causal relationships between cyclic trace elements and BPPV occurrence. MR research is based on three core assumptions: the first hypothesis is that genetic variation as an instrumental variable should be closely related to exposure; the second hypothesis suggests that the genetic variation used should not be associated with any confounding factors; and the third hypothesis is that the selected gene variant will only affect the risk of the outcome through risk factors and not through other means. We primarily used IVW as the primary method for MR analysis, which provides a consistent estimate of the association between exposure and outcome risk when there is no pleiotropy. Cochran's Q statistics were used to assess the heterogeneity of individual SNPs. If there was no significant heterogeneity ($P < 0.05$), the fixed effect model was used. Otherwise, the random effects model was used. For the primary MR results, Bonferroni correction was used to determine the multiple test significance for each feature level. We also performed a sensitivity analysis to verify the robustness of the results. When the IVW effective value is greater than 50 %, the weighted median method can obtain a consistent estimate of the population effect and reduce the deviation of the causal effect estimate

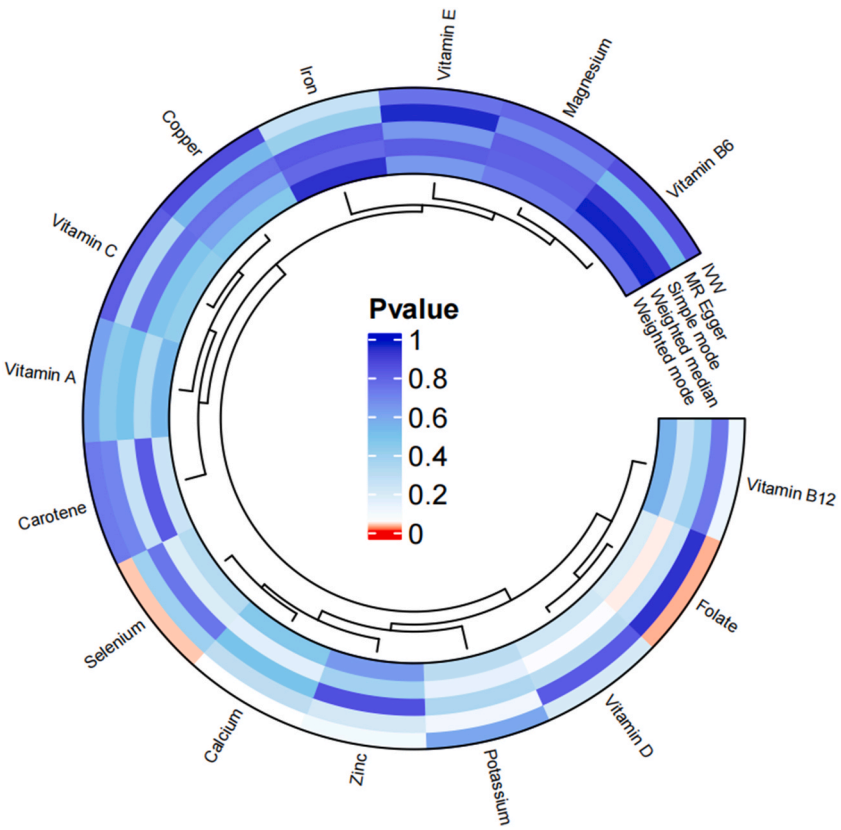


Fig. 2. Visualization of the effects of circulating micronutrient levels on the risk of BPPV by Mendelian randomization analysis. Legend: Circular graph of 5 Mendelian randomized causal analysis methods (MR Egger, weighted median, inverse variance weighted, and simple and weighted models). Red indicates $P < 0.05$, and blue indicates $P > 0.05$.

compared with the IVW method. In addition, the MR−Egger method was used to determine whether instrument SNPs had multiple effects. The intercept obtained from MR−Egger regression was used to measure directional pleiotropy. Considering that the trace element selenium may have been affected by traditional factors such as trauma, chronic otitis media, hearing loss, peripheral atherosclerosis, ageing, and osteoporosis, univariate MR analysis did not reflect the direct effects of trace elements on the incidence of BPPV, as these confounders could also influence BPPV risk. To determine whether the observed significant effect of the trace element selenium on BPPV was direct or indirect, we further performed a multivariate MR analysis, taking into account traditional risk factors for BPPV. Similarly, IVW and MR−Egger regression were used for analysis, and the intercept of MR−Egger regression was used to detect potential horizontal pleiotropy. All the statistical analyses were bilateral.

3. Results

3.1. MR analyses

After MR analysis, a statistically significant micronutrient–BPPV association was a gene prediction of blood selenium and folate levels and the risk of BPPV (Fig. 2). Among the 15 circulating micronutrients of interest, selenium and folate were significantly related to the risk of BPPV, with ORs of 1.074 (95 % CI 1.005 to 1.148, P = 0.035) and 0.694 (95 % CI 0.501 to 0.962, P = 0.028), respectively, via inverse variance weighting (SUPPLEMENTARY Fig. 1). However, depending on whether the OR values obtained by different methods (simple model, inverse variance weighting, and weighted model) were consistent (i.e., all were greater than or less than 1), folate was excluded, and selenium met these conditions (Fig. 3 and SUPPLEMENTARY Fig. 1). Little evidence was obtained that circulating concentrations of copper, calcium, carotene, iron, magnesium, potassium, zinc, vitamin A, vB12, vB6, vitamin C, vitamin D, and vE were related to any assessed risk of BPPV (SUPPLEMENTARY Fig. 1).

3.2. Sensitivity analyses

The results of IVW analysis were supported by the MR−Egger model-based sensitivity analysis results. In the primary MR analysis, no heterogeneity was found in the effects of selenium or folic acid on the risk of BPPV (P = 0.47, P = 0.31, Additional files: Table 1). The effects of vitamin D (P = 0.01), copper (P = 0.01) and calcium (P = 0.02) on BPPV were heterogeneous. For the other micronutrients, there was no heterogeneity (Additional Document: Table 1). According to the MR−Egger analysis results, there was no horizontal pleiotropy in the influence of all genes strongly associated with circulating trace elements on the risk of BPPV (P > 0.05) (Additional File: Table 2).

3.3. Multivariate Mendelian randomization analysis

Based on our clinical experience, we identified exposure factors that may be associated with the risk of BPPV: trauma, chronic otitis media, hearing loss, peripheral atherosclerosis, ageing, and osteoporosis. In addition, we performed a multivariate MR analysis of their associations with the risk of BPPV. We observed an OR of 1.22 (95 % CI 1.059 to 1.406, P = 0.006) for selenium, while the P values for the other exposure factors were greater than 0.05 (Fig. 4). These findings suggest that selenium is an independent risk factor for BPPV.

4. Discussion

BPPV is a brief episode of rotational vertigo caused by a change in head position and is the most common peripheral cause of vertigo. Its main clinical features are transient episodes of vertigo and nystagmus; patients can feel obvious rotation and shaking of both themselves and the surrounding environment, and symptoms can last for several days. BPPV is associated with a high incidence of inner ear vestibular disease, accounting for approximately 25 % of all vertigo cases, and is often observed in otolaryngology, neurology, internal medicine and emergency departments [24]. The pathogenesis of this disease involves a series of clinical manifestations caused by the loss of otoliths in the elliptical capsule to the semicircular canal or adhesions to the ampulla ridge and changes in body position, which can be divided into tubular lithiasis and crest lithiasis [25]. The 3 semicircular canals within the inner ear are involved, among which the posterior semicircular canal is the most affected, and the incidence of BPPV in the upper semicircular canal is the lowest. At present, the aetiology of BPPV is not completely clear, and it is generally believed that there are two categories:

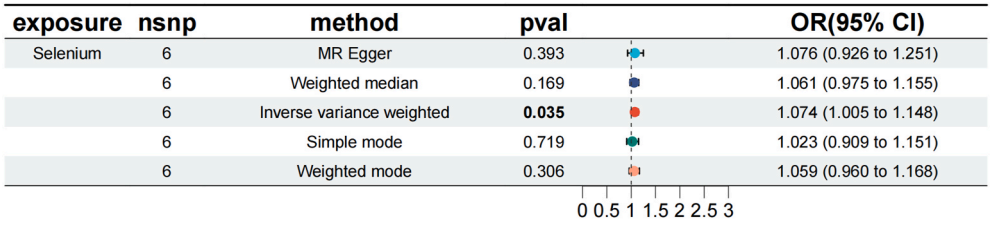


Fig. 3. Mendelian randomization analysis of the risk of BPPV according to the circulating level of the trace element selenium. Legend: Forest plots of 5 Mendelian randomized causal analysis methods.

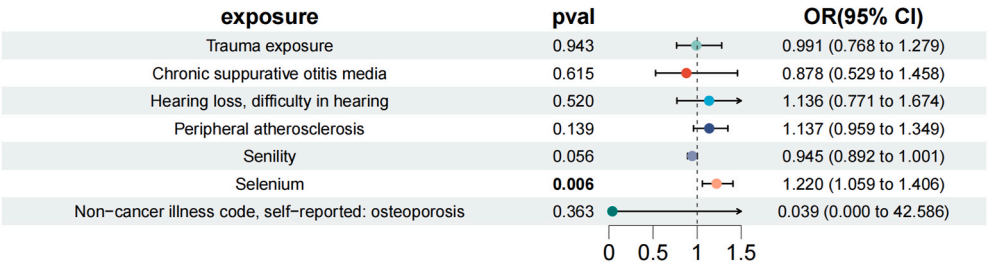


Fig. 4. Multivariate Mendelian randomization analysis of common clinical risk factors for BPPV risk. P < 0.05 indicates that selenium is an independent risk factor for BPPV.

idiopathic (primary) BPPV, with no clear aetiology and accounting for most cases of BPPV (50–70 % of all cases) [24]; and symptomatic (secondary) BPPV, which is secondary to head trauma and inner ear surgery. At present, the clinical treatment of this disease mostly involves the use of otolith manipulation resetting programs, but the disease still has a recurrent phenomenon; therefore, it is particularly important to actively search for the cause of BPPV and its risk factors.

According to previous reports, Vibert et al. studied the bone mineral density of BPPV patients and reported that the bone mineral density of elderly female BPPV patients was obviously lower than that of the control group, suggesting that the occurrence of BPPV in elderly women was related to osteoporosis and bone mass loss [26]. Giacomini et al. reported that taking contraceptives was associated with recurrent BPPV in women and speculated that oral contraceptives caused water and electrolyte disorders and carbohydrate or lipid metabolism disorders, which led to otolith loss [27]. Calcium and 25-hydroxyvitamin D (25(OH)D) metabolism in the inner ear may play important roles in otoconia formation and degeneration. Studies have shown that serum vitamin D is negatively correlated with the incidence of BPPV [11]. Earlier studies did not establish a link between low vitamin D levels and the occurrence of BPPV, but it was suggested that repeated BPPV episodes were linked to low vitamin D levels. In another systematic review, Lee et al. reported only weak evidence to support a relationship between BPPV and osteoporosis or low serum 25-hydroxyvitamin D levels [28]. Further prospective studies and more robust approaches are needed to clarify the link between BPPV and bone metabolic disorders. In this study, the Mendelian randomization method was used to take into account the interactions of many confounding factors rather than limiting calcium and vitamin D. Therefore, we hypothesized that circulating trace elements may be related to the incidence of BPPV and carried out relevant research and analysis.

If the causal relationship between circulating trace elements and BPPV is proven, it can be inferred that improving micronutrient status appropriately can effectively reduce the risk of BPPV occurrence for the population at risk. Furthermore, identifying specific micronutrients that are causally associated with BPPV risk could help inform targeted intervention strategies and personalized treatment approaches for individuals at high risk of developing BPPV. This study represents an important step towards understanding the role of nutrition in the aetiology of BPPV and may promote the development of novel prevention and treatment strategies for this common vertigo disorder.

This study utilized MR analysis to investigate the relationship between circulating micronutrient levels and BPPV risk, and our findings are beneficial for clarifying the potential roles of micronutrients, particularly selenium, in the aetiology of BPPV. Our MR analysis revealed a significant relationship between blood selenium levels and BPPV risk, with an odds ratio (OR) of 1.074 (95 % CI 1.005 to 1.148, P = 0.035). These findings suggest that higher selenium levels are associated with greater BPPV risk.

Selenium is an essential trace element and has many biological functions. Three selenium-dependent iodothyronine deiodinases (DIO1-3) catalyse the deiodination of the parathyroid hormone (T4) to produce T3, which is a key factor in the normal function of the thyroid gland (regulating the availability of local and circulating thyroid hormone) [29]. An appropriate thyroid hormone concentration is necessary for the proper development of some tissues, as demonstrated in people with cretinism, whose main characteristics are mental retardation and defects in bone development and maturation. Too much thyroid hormone may also lead to damage, which can be clarified by the failure of cochlear development in mice [30]. Bone is another organ that relies heavily on proper thyroid hormone levels, and a lack of Dio2 in mice markedly decreased bone stability [31]. Kaschin–Beck disease, a bone and joint disease, has been linked to selenium deficiency, although the link is still controversial [32]. Therefore, selenium may affect calcium homeostasis and metabolism (i.e., otolith loss) through thyroid hormones and thus affect the pathophysiological process of vertigo.

In addition, selenium-dependent glutathione peroxidase is a key factor in protecting cells from oxidative damage. In Fischer 344 standard model rats at 24 months of age, glutathione levels in the auditory nerve were significantly reduced by 86 % compared with those at 3 months of age [33]. Oxidative stress in the inner ear is thought to be another potential contributor to vertigo. In summary, an imbalance in selenium levels may affect calcium homeostasis through thyroxine or vestibular function through oxidative damage to the inner ear, resulting in vertigo symptoms.

Our analysis also revealed an inverse relationship between blood folate levels and the risk of BPPV, with an OR of 0.694 (P = 0.028). The IVW (inverse variance weighting) method was the main method for inferring causality from the MR data, the p value was less than 0.05. However, to obtain robust results, we require multiple methods to obtain consistent OR values. Folate was excluded from further analysis because of inconsistencies in the OR values obtained by different MR methods. Folate, a B vitamin, is crucial for DNA synthesis, repair, and methylation processes [34]. Although the exact mechanism linking folate to BPPV remains unclear, optimal folate status may protect against the development of BPPV through its role in maintaining genomic stability and regulating

neurotransmitter synthesis.

The robustness of our findings was supported by sensitivity analyses. The absence of heterogeneity in the effects of selenium and folic acid on the risk of BPPV (Cochran's Q $P = 0.47$, $P = 0.31$, respectively) suggests that our results are not driven by confounding factors or pleiotropic effects. However, heterogeneity was observed for vitamin D, copper, and calcium, indicating potential pleiotropic effects or unmeasured confounding factors in their associations with BPPV.

The aetiology and related risk factors for BPPV are still unclear, but the theories of otolith loss, semicircular canal calculus, ridge cap theory and inner ear circulation disturbance theory can partially reveal the pathogenesis of BPPV [18]. At present, it is generally accepted that when an otolith falls off into the semicircular canal or sticks to the ampulla ridge in the semicircular canal and stimulates inner ear hair cells when the head moves to a specific position, it can induce a short but strong sense of vertigo in affected patients. However, most primary BPPV cases have no clear aetiology, whereas most secondary BPPV cases have a clear aetiology, such as craniocerebral trauma, chronic otitis media, hearing loss, peripheral atherosclerosis, ageing and osteoporosis.

In a multivariate MR analysis, we explored the independent association of selenium with BPPV while adjusting for other clinical factors, such as trauma, chronic otitis media, hearing loss, peripheral atherosclerosis, ageing, and osteoporosis. The OR for selenium remained significant (1.22, 95 % CI 1.059 to 1.406, $P = 0.006$), suggesting that selenium is an independent risk factor for BPPV. This finding is consistent with the hypothesis that selenium may play a direct role in the development of BPPV, possibly through its effects on the vestibular system or through the modulation of thyroid function.

While this research helps clarify the associations between micronutrient levels and BPPV, several limitations need to be considered. First, a larger sample size of GWASs can reveal more SNPs associated with circulating trace elements, thereby increasing the proportion of variance interpretation and improving statistical power. Second, because the study was limited to Europeans, the results may not apply to the entire human population, and the conclusions should be extrapolated with caution. Third, while MR studies can provide important clues to the puzzle of possible causal effects of circulating trace elements on BPPV outcomes, MR findings should be interpreted in light of evidence from other sources, such as traditional observational and experimental studies.

In addition, a thorough analysis of the mechanism behind this correlation should also be conducted. For example, analysing the impact pathways and mechanisms of selenium and folic acid on BPPV risk provides support for optimizing intervention plans. Therefore, analysing the effects of these two substances on vestibular function and thyroid hormone levels can deepen research in this field.

In summary, this study revealed that selenium plays an important role in the pathological changes associated with BPPV and has a significant effect on its risk. Screening for circulating selenium levels in patients with a significant family history of inheritance, such as by controlling dietary intake, will help reduce the incidence of BPPV. In the future, it is necessary to analyse the impact mechanisms of these elements and provide support for the optimization of relevant intervention measures to better meet the prevention and treatment requirements of BPPV and help improve the health of such patients.

Funding

Not applicable.

Availability of data and materials

Data are provided within the article. We used the following web-based resource: IEU OpenGWAS (https://gwas.mrcieu.ac.uk/). The summary-level data for FinnGen can be obtained via (https://storage.googleapis.com/finngen-public-data-r10/summary_stats/finngen_R10_H8_BPV.gz). Data will be made available upon request.

Declarations

The study was approved by the ethics committee of the Affiliated People's Hospital of Ningbo University. Written informed consent from no person or animal was required for this study.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Jian Wang: Writing – original draft, Project administration, Data curation. **Cheng Cao:** Investigation. **Wen-Bo Jiang:** Formal analysis, Data curation. **Hong-Cun Sun:** Formal analysis, Data curation. **Tao Jiang:** Formal analysis, Data curation. **Jian-Dao Hu:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We would like to thank the researchers of the IEU OpenGWAS and FinnGen studies.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38782.

References

[1] T. Imai, H. Inohara, Benign paroxysmal positional vertigo, Auris Nasus Larynx 49 (5) (2022 Oct) 737–747.
[2] M. Gizzi, S. Ayyagari, V. Khattar, The familial incidence of benign paroxysmal positional vertigo, Acta Otolaryngol. 118 (6) (1998 Nov) 774–777.
[3] H.I. Shin, Y. Park, H.J. Lee, E.J. Jeon, Correlation between serum vitamin D level and benign paroxysmal positional vertigo recurrence, Auris Nasus Larynx 50 (5) (2023 Oct) 700–707.
[4] Y.Y. Ren, Y.J. Wang, J.L. Li, M. Liu, F. Xia, Low vitamin D and uric acid status in patients with benign paroxysmal positional vertigo, Sci. Prog. 106 (4) (2023 Oct-Dec) 368504231205397.
[5] G. Rhim, M.J. Kim, Vitamin D supplementation and recurrence of benign paroxysmal positional vertigo, Nutrients 16 (5) (2024 Feb 28) 689.
[6] X. Chen, Q. Cai, R. Liang, D. Zhang, X. Liu, M. Zhang, Y. Xiong, M. Xu, Q. Liu, P. Li, P. Yu, A. Shi, Copper homeostasis and copper-induced cell death in the pathogenesis of cardiovascular disease and therapeutic strategies, Cell Death Dis. 14 (2) (2023 Feb 11) 105.
[7] X. Fang, H. Ardehali, J. Min, F. Wang, The molecular and metabolic landscape of iron and ferroptosis in cardiovascular disease, Nat. Rev. Cardiol. 20 (1) (2023 Jan) 7–23.
[8] S.J. Wimalawansa, Infections and autoimmunity-the immune system and vitamin D: a systematic review, Nutrients 15 (17) (2023 Sep 2) 3842.
[9] C. Sîrbe, S. Rednic, A. Grama, T.L. Pop, An update on the effects of vitamin D on the immune system and autoimmune diseases, Int. J. Mol. Sci. 23 (17) (2022 Aug 29) 9784.
[10] H. Günizi, H.B. Savaş, An evaluation of trace elements and oxidative stress in patients with benign paroxysmal positional vertigo, PLoS One 18 (2) (2023 Feb 22) e0277960.
[11] H. Wood, K. Kluk, G. BinKhamis, Association between vitamin D deficiency and benign paroxysmal positional vertigo (BPPV) incidence and recurrence: a systematic review and meta-analysis, BMJ Open 14 (4) (2024 Apr 22) e077986.
[12] E. Aydın, S.T. Babakurban, O.N. Ozgirgin, L.N. Ozlüoğlu, The relationship of homocysteine, vitamin B12, folic acid levels with vertigo, Kulak Burun Bogaz Ihtis. Derg. 22 (4) (2012 Jul-Aug) 214–218.
[13] H.M. Flatby, A. Ravi, J.K. Damås, E. Solligård, T. Rogne, Circulating levels of micronutrients and risk of infections: a Mendelian randomization study, BMC Med. 21 (1) (2023 Mar 8) 84.
[14] S.S. Jeng, Y.H. Chen, Association of zinc with anemia, Nutrients 14 (22) (2022 Nov 20) 4918.
[15] J. Doroszkiewicz, J.A. Farhan, J. Mroczko, I. Winkel, M. Perkowski, B. Mroczko, Common and trace metals in alzheimer's and Parkinson's diseases, Int. J. Mol. Sci. 24 (21) (2023 Oct 29) 15721.
[16] M. Maywald, L. Rink, Zinc in human health and infectious diseases, Biomolecules 12 (12) (2022 Nov 24) 1748.
[17] S.J. Kurian, T. Baral, M.K. Unnikrishnan, R. Benson, M. Munisamy, K. Saravu, G.S. Rodrigues, M. Rao, A. Kumar, S.S. Miraj, The association between micronutrient levels and diabetic foot ulcer: a systematic review with meta-analysis, Front. Endocrinol. 14 (2023 Mar 29) 1152854.
[18] J. Chen, S. Zhang, K. Cui, C. Liu, Risk factors for benign paroxysmal positional vertigo recurrence: a systematic review and meta-analysis, J. Neurol. 268 (11) (2021 Nov) 4117–4127.
[19] L. Peng, W.P. Wen, Socioeconomic status and asthma: a bidirectional Mendelian randomization study, World Allergy Organ J 16 (6) (2023 Jun 15) 100790.
[20] J. Xu, S. Zhang, Y. Tian, H. Si, Y. Zeng, Y. Wu, Y. Liu, M. Li, K. Sun, L. Wu, B. Shen, Genetic causal association between iron status and osteoarthritis: a two-sample mendelian randomization, Nutrients 14 (18) (2022 Sep 6) 3683.
[21] S. Burgess, S.G. Thompson, Interpreting findings from Mendelian randomization using the MR-Egger method, Eur. J. Epidemiol. 32 (2017) 377–389.
[22] M.J. Shu, J.R. Li, Y.C. Zhu, H. Shen, Migraine and ischemic stroke: a mendelian randomization study, Neurol. Ther. 11 (2022) 237–246.
[23] D. Rasooly, G.M. Peloso, Two-sample multivariable mendelian randomization analysis using R, Curr Protoc 1 (12) (2021 Dec) e335.
[24] L. Power, K. Murray, D.J. Szmulewicz, Characteristics of assessment and treatment in benign paroxysmal positional vertigo (BPPV), J. Vestib. Res. 30 (1) (2020) 55–62.
[25] S.R. Cole, J.A. Honaker, Benign paroxysmal positional vertigo: effective diagnosis and treatment, Cleve. Clin. J. Med. 89 (11) (2022 Nov 1) 653–662.
[26] D. Vibert, M. Kompis, R. Häusler, Benign paroxysmal positional vertigo in older women may be related to osteoporosis and osteopenia, Ann. Otol. Rhinol. Laryngol. 112 (10) (2003) 885–889.
[27] P.G. Giacomini, B. Napolitano, M. Alessandrini, et al., Recurrent paroxysmal positional vertigo related to oral contraceptive treatment, Gynecol. Endocrinol. 22 (1) (2006) 5–8.
[28] A. Lee, F. Hassannia, M.J. Bergin, K. Al Zaabi, P. Misale, J.A. Rutka, The relationship between disorders of bone metabolism and benign paroxysmal positional vertigo: a systematic review, Ear Hear. 42 (6) (2021 Nov-Dec 01) 1462–1471.
[29] S. Mondal, K. Raja, U. Schweizer, G. Mugesh, Chemistry and biology in the biosynthesis and action of thyroid hormones, Angew Chem. Int. Ed. Engl. 55 (27) (2016 Jun 27) 7606–7630.
[30] L. Ng, A. Hernandez, W. He, T. Ren, M. Srinivas, M. Ma, V.A. Galton, D.L. St Germain, D. Forrest, A protective role for type 3 deiodinase, a thyroid hormone-inactivating enzyme, in cochlear development and auditory function, Endocrinology 150 (4) (2009 Apr) 1952–1960.
[31] J.H. Bassett, A. Boyde, P.G. Howell, R.H. Bassett, T.M. Galliford, M. Archanco, H. Evans, M.A. Lawson, P. Croucher, D.L. St Germain, V.A. Galton, G.R. Williams, Optimal bone strength and mineralization requires the type 2 iodothyronine deiodinase in osteoblasts, Proc. Natl. Acad. Sci. U. S. A. 107 (16) (2010 Apr 20) 7604–7609.
[32] R. Moreno-Reyes, C. Suetens, F. Mathieu, F. Begaux, D. Zhu, M.T. Rivera, M. Boelaert, J. Nève, N. Perlmutter, J. Vanderpas, Kashin-Beck osteoarthropathy in rural Tibet in relation to selenium and iodine status, N. Engl. J. Med. 339 (16) (1998 Oct 15) 1112–1120.
[33] J. Lautermann, S.A. Crann, J. McLaren, et al., Glutathione-dependent antioxidant systems in the mammalian inner ear: effects of aging, ototoxic drugs and noise, Hear. Res. 114 (1–2) (1997) 75–82.
[34] R. Spector, C.E. Johanson, The nexus of vitamin homeostasis and DNA synthesis and modification in mammalian brain, Mol. Brain 7 (2014 Jan 10) 3.