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Mendelian randomization of serum micronutrients and osteoarthritis risk: focus on zinc

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Abstract

Background Osteoarthritis (OA) is an increasingly severe public health issue globally. Micronutrients are essential for maintaining normal physiological functions and metabolic balance; however, their relationship with OA is not fully understood.

Methods This study aimed to evaluate the potential causal relationships between 15 key micronutrients and the risk of OA using both two-sample and multivariate Mendelian randomization approaches. We gathered data from a large prospective cohort of genome-wide association studies on these micronutrients and OA. Comprehensive Mendelian randomization analyses were conducted using inverse variance weighting, MR Egger, weighted median, weighted models, and simple models. Through multivariate analyses, factors such as BMI and strenuous exercise were controlled to assess the independent associations between zinc and OA risk.

Results In the two-sample Mendelian randomization analysis, zinc was positively associated with OA risk (OR = 1.045, 95% CI: 1.009 to 1.082, $P = 0.015$). This association remained significant even after controlling for other confounding factors in multivariate analyses, indicating an independent effect of zinc. Other micronutrients, such as calcium, iron, and vitamin D, did not show significant associations with OA risk in this study.

Conclusion This study provides new evidence of a positive association between the micronutrient zinc and the risk of OA, emphasizing the importance of considering micronutrients in osteoarthritis prevention and treatment strategies. Future research should further validate these findings and explore the specific biological mechanisms by which zinc influences the risk of osteoarthritis.

Keywords Zinc, Osteoarthritis, Causality, Mendelian randomization, Multivariate analysis, Micronutrients

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Introduction

In the context of global aging populations, osteoarthritis (OA), a prevalent degenerative joint disease, has seen a rising incidence, becoming one of the leading causes of disability worldwide [1–3]. It is estimated that over 500 million individuals globally are affected by OA, significantly diminishing their quality of life and imposing substantial economic burdens on healthcare systems [4, 5]. The pathological characteristics of OA primarily manifest as cartilage degradation, osteophyte formation at the joint margins, and changes in synovial fluid, leading to joint pain, stiffness, and functional impairment [6]. Compared to 2020, the prevalence of OA is expected to significantly increase by 2050, with knee OA projected to rise by 74.9% (ranging from 59.4 to 89.9%) [7]. Despite the complex etiology involving genetics, mechanical stress, obesity, and age, our understanding of the pathogenesis, particularly at the molecular level, remains nascent [8].

The genetic basis of OA has been extensively studied, but environmental factors—especially the intake of trace nutrients—are equally crucial in the development and progression of the disease. While growing evidence suggests that trace nutrients may play important roles in OA, there remains a relative scarcity of causal research on their relationship with OA. Currently, there is still a lack of clarity regarding the specific mechanisms by which trace nutrients contribute to the pathogenesis of OA, particularly with regard to their causal role. This research aims to address this gap and further highlights the innovation and necessity of this tudy [9]. For instance, calcium and magnesium are fundamental elements for bone structure, with their deficiencies linked to increased risks of fractures and OA. Calcium aids in bone mineralization and maintaining bone density, reducing the occurrence of OA; magnesium, in addition to supporting bone health, may also help alleviate OA progression by affecting joint stability. Vitamins D, C, and E not only support immune functions but also regulate bone remodeling and joint inflammation through various mechanisms [10]. Vitamin D enhances bone health by regulating calcium absorption, while vitamins C and E reduce oxidative damage by neutralizing free radicals and protect joint cartilage. Zinc plays an important role in immune modulation and antioxidation, alleviating chronic inflammation and aiding cartilage repair. Studies show that zinc slows joint cartilage degeneration by modulating the immune system. Selenium has potent antioxidant effects, and research indicates that higher dietary selenium intake may be associated with increased OA risk. Excessive iron intake induces oxidative stress damage, leading to synovial impairment and worsening OA symptoms [11]. Folic acid may have a potential role in reducing joint inflammation, and its deficiency could result in degenerative changes in joints. Vitamin B12 deficiency is associated with OA, particularly in elderly patients. Vitamin B6 plays an important role in antioxidant and anti-inflammatory responses, helping control OA symptoms. Copper promotes connective tissue formation and may aid in joint repair for OA. Potassium, through its anti-inflammatory effect, has been shown to help slow OA progression. Vitamin A's importance for bone health has been established through research, and its deficiency may exacerbate OA symptoms. Vitamin K is essential for bone mineralization, and its deficiency may affect the bone health of OA patients. Beta-carotene, as an antioxidant, reduces joint inflammation and may slow OA progression. Sulfur contributes to cartilage composition and repair, potentially aiding in OA treatment. Phosphorus plays an important role in maintaining bone health, and its deficiency may exacerbate OA symptoms. Although the relationship between trace nutrients and OA has been widely discussed in epidemiological studies, inconsistencies still exist due to potential confounding factors and reverse causality. Therefore, further research is crucial to clarify the specific mechanisms of these trace nutrients in OA [12].

Despite widespread exploration in epidemiological studies, inconsistencies remain in the evidence linking trace nutrients to OA, due in part to potential confounders and reverse causality. Mendelian randomization (MR), an emerging epidemiological tool, offers a new perspective for exploring causal relationships in observational data [13, 14]. This method leverages genetic variations as instrumental variables, helping to address confounding and reverse causation issues commonly found in traditional observational studies. This study aims to comprehensively assess the potential causal relationships between 15 mainstream trace nutrients and OA using MR approaches. By analyzing data from large prospective cohorts and genome-wide association studies (GWAS), we will explore the genetic markers of these nutrients and their associations with OA risk. Furthermore, multivariable analysis methods will be employed to control for potential confounders, such as obesity and vigorous exercise, enhancing the accuracy of our causal inferences.

Our research not only promises to offer new insights into the etiology of OA but may also profoundly impact nutritional guidance, disease prevention, and public health policy formulation. By elucidating the causal relationships between trace nutrients and OA, our study aims to improve our understanding of the complex etiology of OA and provide a scientific basis for future prevention and treatment strategies.

Materials and methods

Research design

This study employs MR to explore the potential causal relationships between 15 trace nutrients and OA. Initially, genetic instrumental variables (SNPs) for these nutrients were extracted from published GWAS. These instruments were then used to perform a preliminary two-sample MR analysis to screen for trace nutrients significantly associated with OA risk. Subsequently, to control for confounders impacting OA, factors closely related to OA such as BMI and vigorous exercise were included in a multivariable Mendelian randomization analysis to exclude any additional effects of these factors on OA risk. The MR approach must meet three essential criteria [13]: (A) the genetic variants chosen as instrumental variables (IVs) should be closely associated with the 15 trace nutrients; (B) the genetic instruments should be unrelated to osteoarthritis outcomes and independent of potential confounders; (C) the genetic variants should be specifically associated with OA through trace nutrients and not via other pathways. Figure 1 presents our workflow diagram.

Data sources for GWAS

Data sources for 15 micronutrients

The comprehensive summary statistics for GWAS on trace nutrients provided by Ben Elsworth et al. [15] involved a majority of samples from a European cohort of 64,979 individuals, comprising 9,851,867 SNPs. This data includes 12 trace nutrients: calcium, carotene, folate, iron, magnesium, potassium, vitamins A, B12, B6, C, D, and E. The remaining three trace nutrients—copper, zinc, and selenium—derived their GWAS data from a cohort study by Evans et al. [16] involving 2,603 individuals with 2,543,646 SNPs. All subjects are from Europe and have undergone strict quality control. These data are stored in the IEU OpenGWAS database (https://gwas.mrcieu.ac.uk), with specific GWAS IDs provided in Supplementary Table 1.

The samples used in this study were obtained from large-scale genetic databases, specifically the UK Biobank and the IEU OpenGWAS platform. We primarily selected individuals of European ancestry to reduce population stratification bias. To ensure the reliability of our results, individuals with severe comorbidities or incomplete genetic data were excluded, and only those with complete genetic data and OA-related phenotype information were included in the final analysis.

Outcome data and confounders data

The summary data for SNP associations with OA originate from a study by Tachmazidou et al. [17] published in 2019, available in the IEU OPEN GWAS database under the ID ebi-a-GCST007090. This dataset is a meta-analysis from GWAS involving 343,442 individuals (24,955 OA patients and 318,169 controls) [18]. OA patients were diagnosed according to the International Classification of Diseases (ICD)-8, ICD-9, and ICD-10. All statistical data used are freely available in public databases, thus ethical approval was not required.

The GWAS for BMI includes data from 8,658 Europeans and 9,811,391 SNPs, available under the ID

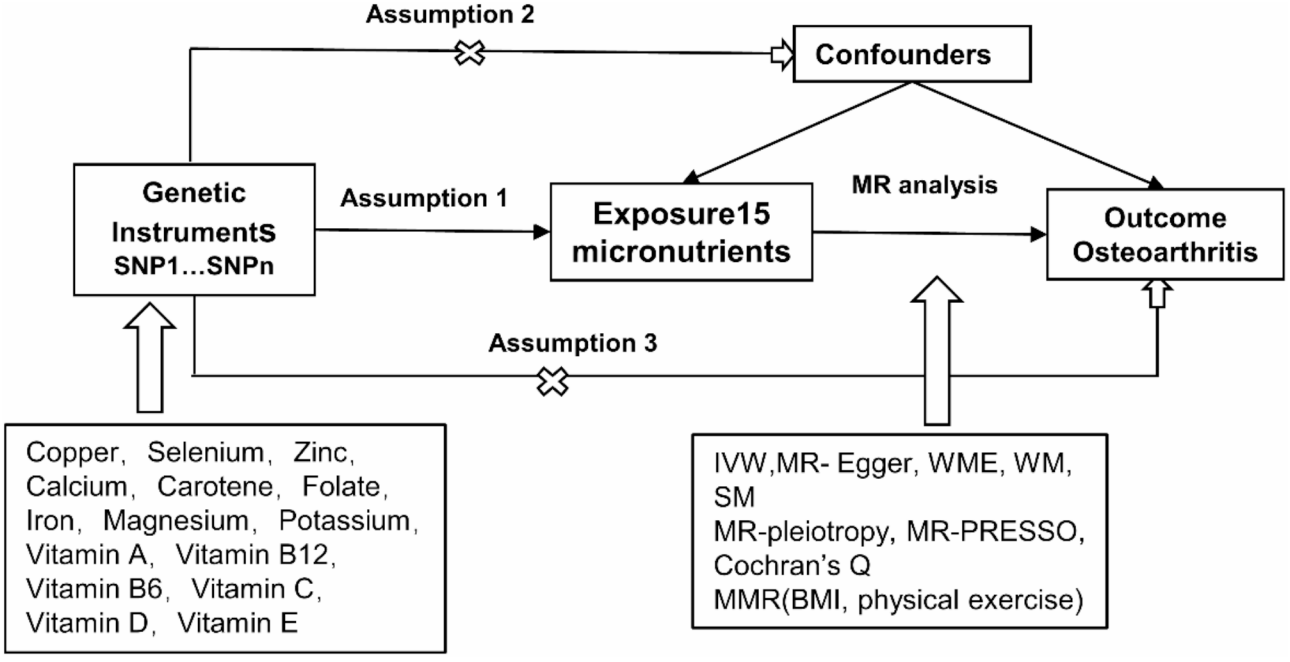

Fig. 1 Mendelian randomisation (MR) design flowchart

ukb-e-23104_CSA in the IEU OpenGWAS database. The GWAS data for vigorous exercise, under the ID ebi-a-GCST006100, includes 124,842 exercisers and 225,650 controls, comprising 11,807,536 SNPs. Although both the zinc exposure data and OA outcome data were derived from European populations, the datasets were independently collected, and the sample sources differed significantly in scope. Furthermore, our two-sample MR design, by utilizing independent datasets, further minimized the potential impact of sample overlap on the results.

Selection of instrumental variables

Initially, SNPs with a p-value below the genome-wide significance level (5×10^{-6}) were selected as IVs to obtain comprehensive results and enhance sensitivity to the instruments. Subsequently, all IVs underwent linkage disequilibrium clustering ($r^2 = 0.001$; distance = 10,000 kb) to minimize the impact of correlated SNPs. Additionally, the GWAS Catalog (https://www.ebi.ac.uk/gwas/) was used to filter for potential pleiotropic effects, excluding SNPs related to outcomes as detailed in Supplementary Table S3. The F-statistic [$R^2(N-2)/(1-R^2)$] was calculated to assess the strength of each instrument, where R^2 represents the proportion of variance explained by the genetic instruments and N is the effective sample size of the GWAS. SNPs with an F-statistic threshold greater than 10 were selected for subsequent MR analyses as they provide reliable estimates of genetic variation [19].

Mendelian randomization analysis

A two-sample MR analysis was conducted to investigate the causal relationships between 15 trace nutrients and OA. Methods included the weighted mode [20], inverse variance weighted test (IVW) [21], weighted median [22], and simple model. When horizontal pleiotropy is non-existent or balanced, the IVW method uses the variance of each instrumental variable to determine its weight, thereby reducing the influence of instruments with larger variances. This method assumes all instruments are valid and that there is no direct confounding between the instruments and the outcome variable, providing an unbiased estimate of the causal effects. MR Egger [23] combines traditional instrumental variable regression analysis with a quantile-based method. This approach detects and corrects potential issues with invalid instruments, such as measurement errors or correlations with confounders, making it an essential tool for sensitivity analysis. The weighted median method, by applying different weights to each estimate based on their variances, aims to provide a more robust causal estimate by reducing the impact of estimates with larger variances, allowing for up to half of the SNPs to be ineffective instruments or exhibit pleiotropy. Finally, the weighted model and simple model serve as supplementary methods to the IVW approach. If these five methods converge in the same direction, the results are deemed more reliable, thus studies that did not exhibit consistent direction across all methods were excluded (ensuring all effect values OR must be in the same direction). Cochran's Q test [24] was used to assess heterogeneity among the instruments. Additionally, MR pleiotropy residuals (MR-PRESSO) [25] and leave-one-out sensitivity analysis [26] were used for sensitivity analysis, ensuring the robustness and reliability of our final results.

Multivariate Mendelian randomisation analysis

As an extension of the two-sample MR, multivariable MR allows the estimation of the causal effects of various risk factors on OA susceptibility by incorporating all exposures into the same model [27]. To demonstrate the direct impact of the trace nutrient zinc on OA risk, independent of BMI and vigorous exercise, and not mediated by other exposures, we extracted significantly associated SNPs and combined them with existing exposure instrumental variables. After excluding these duplicate SNPs, the effects of each SNP and their respective standard errors were obtained from the exposure and outcome data. The core analytical method—the IVW method—was used to infer causal relationships in multivariable MR analysis.

Results

Selection of Ivs

Supplementary Table 4 presents comprehensive details of the SNPs related to the 15 trace nutrients, including β-values, standard errors, effect alleles, and other alleles. The range of F-statistics for the selected SNPs was between 20.87 and 84.68, supporting the absence of weak instrument bias.

Causal relationship between 15 micronutrients and OA

In our MR analysis, we assessed the potential causal relationships between 15 trace nutrients and the risk of OA. We employed methods such as IVW, MR Egger, Weighted Median Estimator (WME), Simple Mode (SM), and Weighted Mode (WM) to estimate the effect sizes of each nutrient, calculating the corresponding *P*-values and 95% confidence intervals (CIs). Trace nutrients like calcium, iron, folate, and copper showed *P*-values greater than 0.05, indicating no significant associations with OA risk. The results of the analysis for the 15 trace nutrients are displayed in Fig. 2. Among them, zinc and vitamin B6 were consistently significant across all five analytical methods, as illustrated in Fig. 3.

In the two-sample MR analysis, we found a significant positive association between zinc levels and OA risk. Specifically, for every standard deviation increase in serum zinc levels, the risk of OA increased by 3.66%

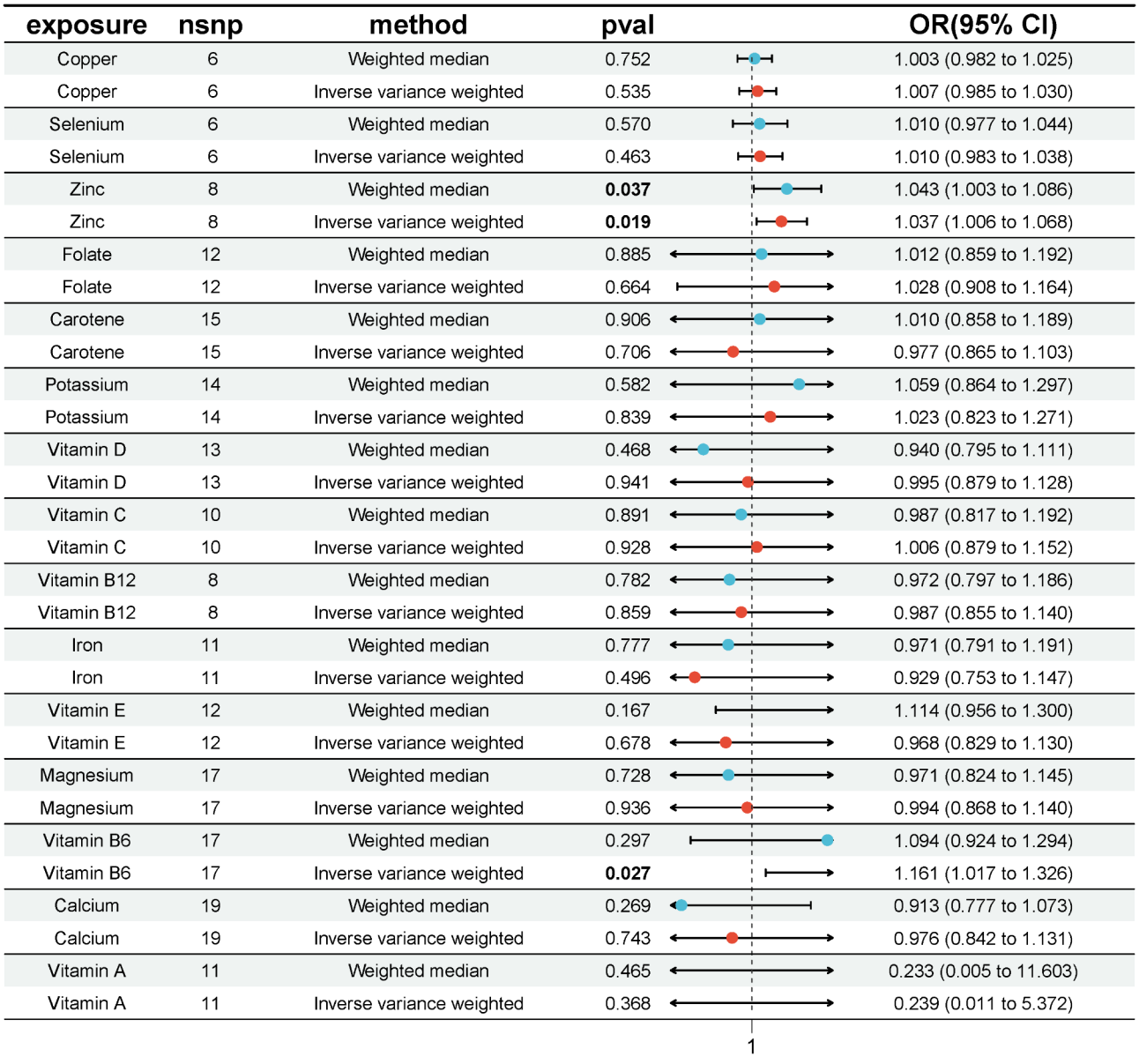

Fig. 2 Results of 15 micronutrients with OA MR analysis (IVW & WME)

(95% CI: 1.006 to 1.068, $P = 0.015$). The results from MR Egger, WME, IVW, SM, and WM were as follows: (OR = 1.067, 95% CI: 0.955–1.191, $P = 0.297$), (OR = 1.043, 95% CI: 1.003–1.086, $P = 0.037$), (OR = 1.036, 95% CI: 1.006–1.072, $P = 0.068$), (OR = 1.035, 95% CI: 0.970–1.105, $P = 0.336$), and (OR = 1.054, 95% CI: 1.006–1.105, $P = 0.064$), respectively. All methods produced OR values greater than 1, and outcomes that did not align in direction were excluded, ensuring minimal bias. Forest plots for these analyses are shown in Fig. 4. Additionally, vitamin B6 also exhibited a positive trend with OA risk, but was excluded due to inconsistent OR values across the five MR methods in MR Egger. Figure 5 presents the MR results for zinc and OA, including scatter plots, forest plots, funnel plots, and leave-one-out analysis. The MR-pleiotropy test, a principal tool for pleiotropy testing, showed that the pleiotropic results for zinc were not significant ($P > 0.05$), whereas for vitamin B6, significant pleiotropy was detected ($P = 0.018$), which is not permissible in MR analysis as it contradicts the three key assumptions of MR analysis. Therefore, vitamin B6 was not considered in the significant results analysis. Our analysis found no evidence of horizontal pleiotropy as indicated by the MR-Egger intercept term, which checks for biases due to SNPs affecting multiple traits ($P > 0.05$), suggesting that our MR results are not influenced by horizontal pleiotropy. The MR-PRESSO analysis, a main indicator of heterogeneity, also indicated no outlier

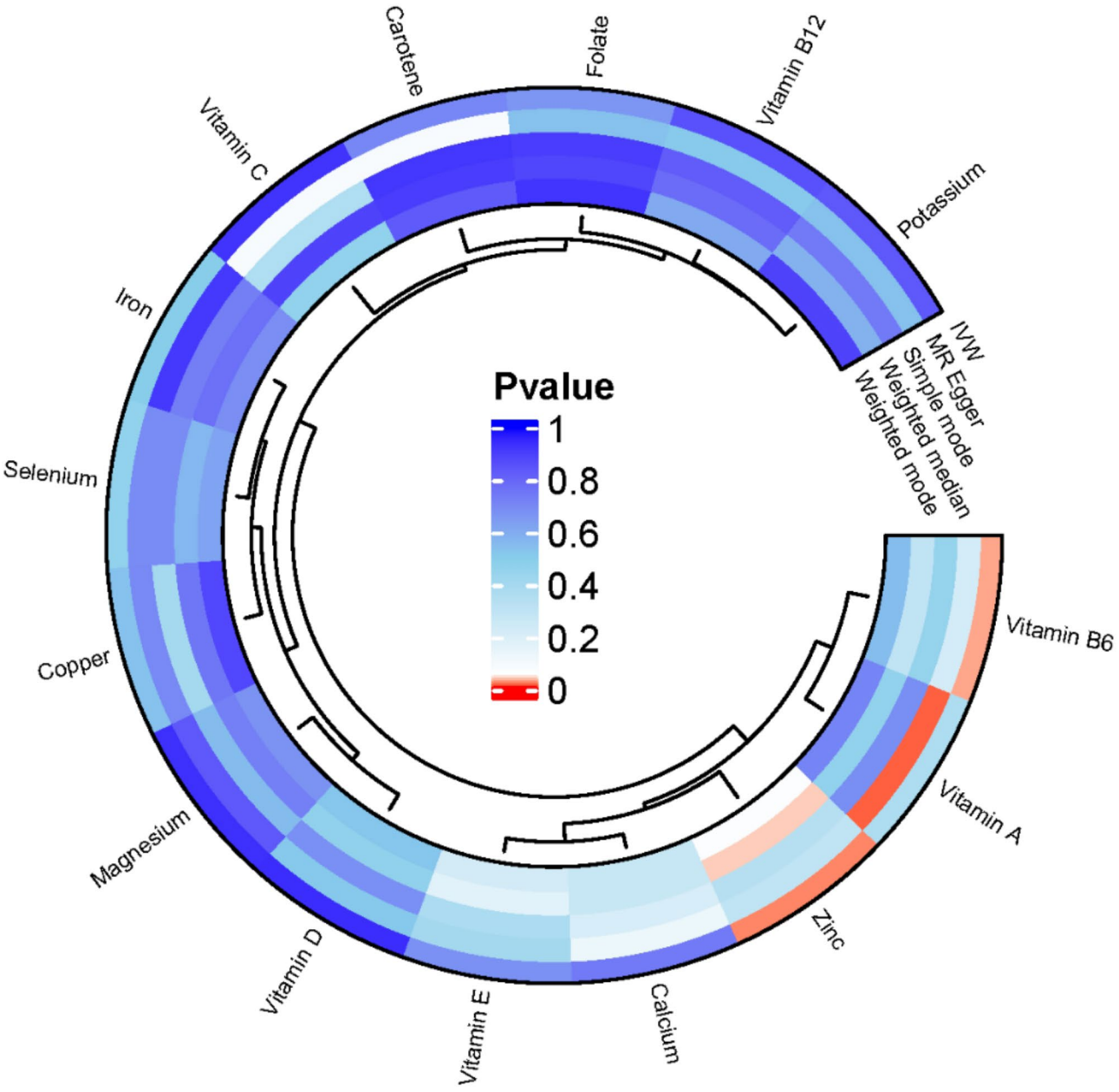

Fig. 3 Positive results in 15 micronutrients

presence. Leave-one-out sensitivity analysis revealed no single SNP driving the overall effect, and Cochran's Q test ($P = 0.36$) suggested no significant heterogeneity, further corroborating the robustness of our results.

Multivariate Mendelian randomisation analysis

In the multivariable analysis, we further controlled for the effects of BMI and vigorous exercise to assess the independent association between zinc and OA risk. After adjusting for these and other risk factors for osteoarthritis, the positive association between zinc and OA risk remained significant (IVW: OR = 1.050, 95% CI: 1.011 to 1.090), with significant results for BMI as well, confirming its reliability as a high-risk factor for osteoarthritis. These findings indicate that zinc's effect remains robust even when considering other relevant risk factors, and it is a significant risk factor for OA. Specific effect values are shown in Fig. 6. Our sensitivity analysis using Mr-pleiotropy as a pleiotropy assessment tool yielded negative results ($P = 0.333$), indicating that all instrumental variables selected for the three exposures were not influenced by horizontal pleiotropy.

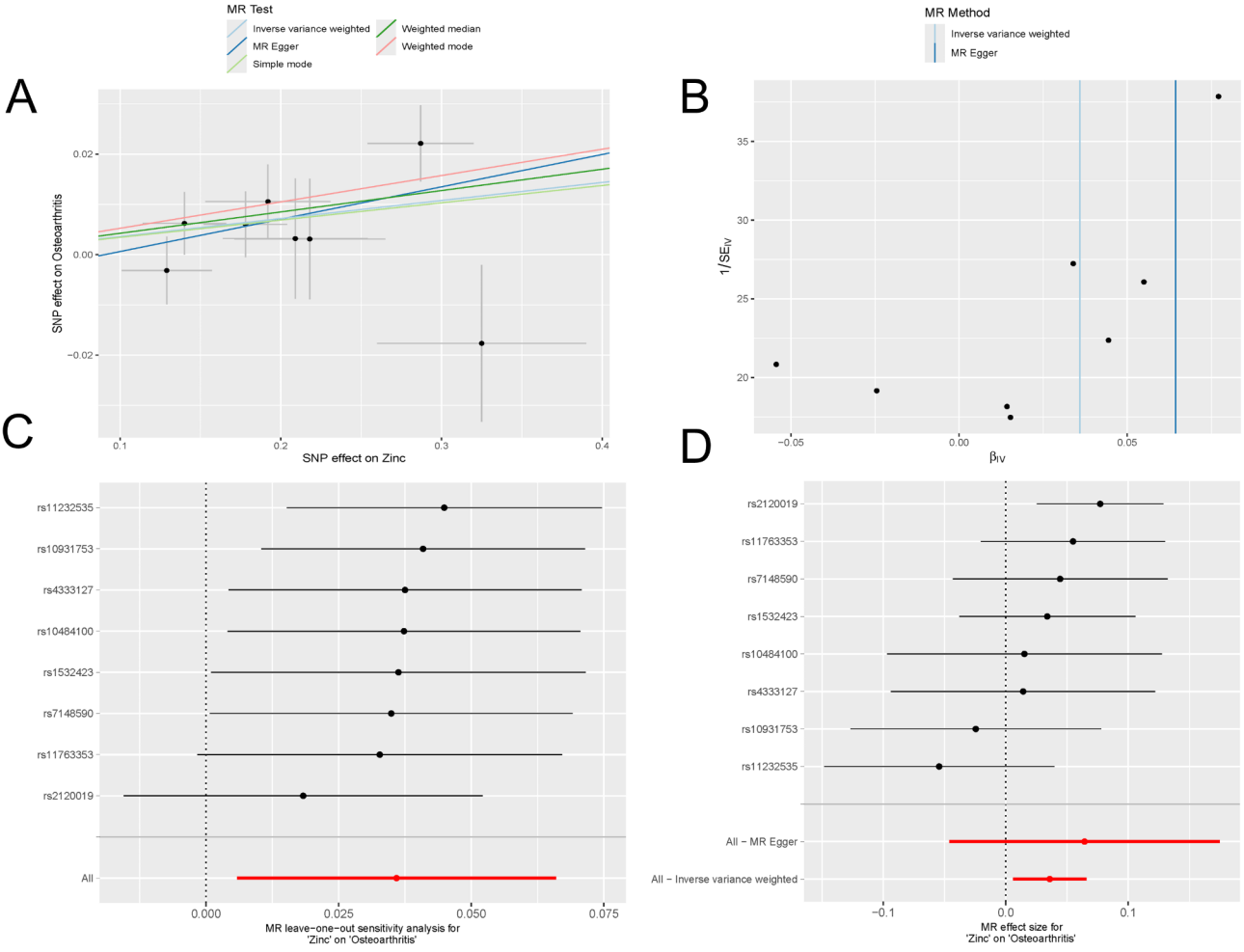

Fig. 4 Results of MR analyses of zinc versus OA, including **(A)** scatter plots, **(B)** forest plots, **(C)** leave-one-out method, **(D)** funnel plots

exposure	nsnp	method	pval	OR(95% CI)
Zinc	8	MR Egger	0.297	1.067 (0.955 to 1.191)
	8	Weighted median	**0.029**	1.043 (1.004 to 1.084)
	8	Inverse variance weighted	**0.019**	1.037 (1.006 to 1.068)
	8	Simple mode	0.314	1.035 (0.973 to 1.101)
	8	Weighted mode	0.084	1.054 (1.001 to 1.109)

Fig. 5 Results of five MR analyses between micronutrient zinc and OA

exposure	pval	OR(95% CI)
Strenuous sports	0.334	0.825 (0.559 to 1.219)
Zinc	**0.011**	1.050 (1.011 to 1.090)
Body mass index (BMI)	**0.030**	1.185 (1.092 to 1.282)

Fig. 6 Multivariate MR analysis to correct for the confounding effects of BMI and strenuous sports on the effects of zinc and OA

Discussion

This study employed Mendelian randomization to explore the potential causal relationships between 15 trace nutrients and OA. Our key finding is the positive association between zinc and OA risk, which remained robust across various sensitivity analyses. The subsequent multivariable MR analysis, accounting for factors such as BMI and vigorous exercise, affirmed the significant impact of zinc on OA risk. This insight enriches our understanding of zinc's role in the pathogenesis of OA and could influence future strategies for osteoarthritis prevention.

Both two-sample and multivariable MR analyses consistently showed that elevated serum zinc levels are significantly associated with increased OA risk, aligning with previous studies. For instance, Yang et al. [28] analyzed NHANES data from 2011 to 2016, including 4,200 participants, and found that zinc intake was independently associated with increased OA risk, consistent with our findings. Similar results were reported by Zhou et al. [29], where genetic predisposition to high zinc status was positively correlated with OA, with every standard deviation increase in zinc linked to higher odds of general OA (OR = 1.18, 95% CI: 1.05–1.31) and unspecified OA (OR = 1.21, 95% CI: 1.11–1.31). Their use of GWAS data from the UK, alongside our Finnish data, confirms the reliability of our research conclusions. Further studies on zinc homeostasis in osteoarthritis have found [30] that ZIP8, a zinc transporter, is significantly upregulated in chondrocytes from OA patients compared to normal cartilage cells. Inhibiting ZIP8 in mouse OA chondrocytes protected the cartilage from degeneration. This indicates that enhanced ZIP8 functionality aggravates the OA disease mechanism. Ovesen et al. [31] measured zinc status in 40 patients with either osteoarthritis or osteoporosis, finding significantly higher serum zinc levels in OA patients, which further suggests that elevated zinc levels are a risk factor for OA progression. Xing et al.'s study further emphasizes the potential link between OA and metabolic diseases, particularly the genetic relationship between knee OA and type 2 diabetes. This finding aligns with our study's positive correlation between zinc and OA risk, suggesting that metabolic dysregulation may play an important role in the development and progression of OA [32, 33].

Zinc, a vital trace nutrient, participates in various biological processes, including serving as a component of numerous enzymes, and in the synthesis of proteins, DNA, and RNA [34]. It has been shown to exhibit antioxidant and anti-inflammatory properties [35], including activating antioxidant pathways that clear harmful reactive oxygen species (ROS), thus protecting cartilage cells from oxidative damage [36]. Zinc also regulates cytokine expression, reducing the production of pro-inflammatory cytokines like IL-1β and TNF-α, thereby slowing OA progression. Unlike most previous studies, our Mendelian randomization approach provides a different answer: genetically predicted zinc is a risk factor for OA, which corroborates findings published in Cell by Kim et al. [37], who highlighted the critical role of the zinc-ZIP8-MTF1 axis in the pathogenesis of OA. Zinc, through the transporter ZIP8 and the transcription factor MTF1, regulates the degradation signaling cascade within chondrocytes, promoting the expression of matrix metalloproteinases (MMPs) such as collagen and proteoglycans, thus exacerbating cartilage degradation. High expression of ZIP8 in chondrocytes increases zinc intake, activating MTF1, which in turn triggers inflammatory responses and cartilage degradation. This process includes the release of pro-inflammatory cytokines like IL-1β, activating downstream NF-κB signaling pathways and increasing the expression of MMPs like MMP-13, which disrupt the extracellular matrix of cartilage cells. MMP-3 and MMP-13 play central roles in the destruction of cartilage structures, accelerating OA progression. Based on this, Lee et al. [38] expanded the study to explore the interaction between HIF-2α and the zinc-ZIP8-MTF1 axis in OA and its impact on disease progression. Specifically, HIF-2α activates the zinc-ZIP8-MTF1 axis, upregulating ZIP8 expression, increasing zinc ion influx, and activating the transcription factor MTF1 [39]. This activation not only enhances HIF-2α's regulatory effects on OA cartilage destruction but also synergistically promotes the expression of matrix-degrading enzymes. The reciprocal activation of the zinc-ZIP8-MTF1 axis by HIF-2α forms a positive feedback loop that further promotes the expression of matrix-degrading enzymes and OA cartilage destruction. Experimental OA models showing specific knockouts of HIF-2α, ZIP8, and MTF1 inhibited the OA disease process, confirming their key roles in OA pathogenesis. Gene chip analysis and various experimental methods, such as qRT-PCR, ChIP analysis, and fluorescence microscopy, have revealed the interaction mechanisms between HIF-2α and the zinc-ZIP8-MTF1 axis. These results not only provide a new perspective on the molecular mechanisms of osteoarthritis but also offer potential targets for future treatment strategies, particularly interventions targeting zinc ion metabolism and transport that may help control the progression of osteoarthritis.

While our findings support the positive correlation between zinc and OA risk, we also recognize the limitations of the MR approach. Firstly, the selection of genetic instrumental variables may be influenced by population structure, particularly in populations from different races and geographical regions; our GWAS data all originate from European populations, necessitating further validation in other populations. Secondly, the biological effects

of zinc may be influenced by interactions with other nutrients, which might not have been fully considered in our analysis. Additionally, the bioactivity of zinc may depend on its chemical form and bioavailability, which might not have been fully considered in our analysis.

Beyond the roles mediated via the zinc-ZIP8-MTF1 axis, zinc also directly contributes to osteoarthritis progression through mechanisms such as oxidative damage and apoptosis, which accelerate cartilage deterioration. Specifically, an increase in zinc ions enhances the expression of MMPs, speeding up cartilage breakdown [9], and triggers the Fenton reaction to produce more reactive ROS [29]. This not only escalates oxidative stress within cartilage cells, causing further damage [40], but also leads to a significant increase in cellular oxidative stress, worsening the damage to cartilage cells. Excess zinc ions catalyze the Fenton reaction with intracellular transition metals, transforming hydrogen peroxide into highly reactive hydroxyl radicals. These radicals are potent ROS that can damage essential biomolecules within cells, such as proteins, lipids, and nucleic acids, leading to cellular membrane permeability alterations, DNA damage, and loss of protein function, thereby triggering a cascade of cellular injuries [41, 42]. The accumulation of ROS also disrupts the cell's antioxidant defenses, diminishing the activity of enzymes like superoxide dismutase, glutathione peroxidase, and catalase, reducing the cell's ability to clear ROS and creating a vicious cycle that exacerbates oxidative stress. This oxidative environment not only damages the structural and functional integrity of cartilage cells but also activates inflammatory signaling pathways such as NF-κB and MAPKs, leading to overexpression of pro-inflammatory cytokines like IL-1β, TNF-α, and IL-6, which further intensifies the inflammatory and degradation processes in cartilage [37]. High levels of zinc disrupt normal mitochondrial functions, leading to mitochondrial membrane potential loss, significant increase in mitochondrial ROS [43], and chaos in cellular metabolism [44]. Furthermore, excessive zinc can trigger apoptosis by upregulating Bax and Bak, leading to the release of cytochrome C from mitochondria and activating the caspase cascade, resulting in programmed cell death of cartilage cells [45, 46]. This series of reactions not only weakens cartilage cell functions but also degrades the extracellular matrix, accelerating the degradation of cartilage tissue and playing a pivotal role in the progression of osteoarthritis [47, 48].

While our study results support a positive association between zinc and osteoarthritis risk, it is important to acknowledge the limitations of the Mendelian Randomization approach. First, the selection of genetic instrumental variables may be influenced by population structure, particularly in populations from different ethnicities and geographical regions. Our current GWAS data are based on individuals of European ancestry, and further validation in populations from Asia, Africa, and Latin America is essential to verify the robustness and applicability of our findings across different ethnic groups. Second, the biological effects of zinc may be influenced by interactions with other nutrients, which may not have been fully considered in our analysis. Additionally, the bioactivity of zinc could depend on its chemical form and bioavailability, which may not have been adequately addressed in our study.

Conclusion

This study systematically evaluated the potential causal relationships between 15 trace nutrients and the risk of OA using MR. After accounting for confounders such as BMI and hypertension, the results from multivariable MR remained significant. Our primary finding is a positive correlation between serum zinc and OA risk, which remained robust across multiple sensitivity analyses. This supports the potential role of zinc in the development of OA and offers a new perspective for future prevention and treatment strategies for the disease.

Our findings are consistent with some previous studies that have also identified a relationship between zinc and the risk of OA. While other trace nutrients did not show significant associations with OA risk in this study, our research highlights the importance of considering trace nutrients comprehensively in OA research. Overall, this study provides new insights into the role of the trace nutrient zinc in the development of osteoarthritis and offers new directions for future research and clinical applications. Our findings require further validation and exploration within a broader biological context.

Abbreviations

OA	Osteoarthritis
MR	Mendelian Randomization
GWAS	Genome-Wide Association Studies
SNP	Single Nucleotide Polymorphism
IV	Instrumental Variable
BMI	Body Mass Index
IVW	Inverse Variance Weighted
ZIP8	Zrt- and Irt-like Protein 8
MTF1	Metal Regulatory Transcription Factor 1
MMPs	Matrix Metalloproteinases
ROS	Reactive Oxygen Species
NF-κB	Nuclear Factor kappa-light-chain-enhancer of activated B cells
IL-1β	Interleukin 1 beta
TNF-α	Tumor Necrosis Factor alpha
HIF-2α	Hypoxia-Inducible Factor 2 alpha

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12937-025-01100-0.

Supplementary Material 1

Supplementary Material 2

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Author contributions
WZ and ZJ designed the study and reviewed the manuscript. LM and FH contributed to data collection and performed the data analysis. DC drafted the initial manuscript. EH and WY provided assistance during the revision process. All authors (WZ, ZJ, LM, DC, FH, EH, WY) revised the manuscript critically and approved the final version. Each author has participated sufficiently to take public responsibility for appropriate portions of the content.

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Data availability
The analyses in this study utilized publicly available datasets. These data can be accessed here: GWAS data for the 15 trace nutrients, BMI, and hypertension were sourced from IEU OpenGWAS. Specific IDs are listed in Supplementary Table 1. The GWAS data ID for OA is ebi-a-GCST007090.

Declarations

Ethics approval and consent to participate
Ethical approval was not required for this study involving human data, in accordance with local legislation and institutional requirements. Similarly, written informed consent to participate was not necessary from the participants or their legal guardians/next of kin, as per national legislation and institutional guidelines. These decisions were based on the fact that the study used de-identified, publicly available data sets where participants' privacy and confidentiality are inherently protected. institutional requirements.

Conflict of interest
The authors declare that this study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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