Article

Genetic Causal Associations between Various Serum Minerals and Risk of Depression: A Mendelian Randomization Study

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Abstract

Background: Previous observational studies have discovered a connection between depression and mineral status. Confirming this potential connection is challenging due to confounding factors and potential reverse causality which is inherent in observational studies.

Materials and Methods: We performed a Mendelian randomization (MR) analysis to estimate the causal association of serum minerals with depression. Leveraging summary-level data on depression, a genome-wide association study (GWAS) was applied. The data on serum minerals were collected from the FinnGen Biobank database. MR assessments representing causality were produced by inverse-variance weighted approaches with multiplicative random and fixed effects.

Result: Sensitivity analyses were performed to validate the reliability of the results. A noteworthy correlation emerged between serum zinc levels and reduced risk of depression. An odds ratio (OR) of 0.917 for depression associated with a one standard deviation increase in serum zinc levels (OR = 0.968; 95% CI = 0.953–0.984, $p = 1.19 \times 10^{-4}$, random effects model inverse variance weighted (IVW)); (OR = 0.928; 95% CI = 0.634–1.358, $p = 0.766$, MR Egger). Sensitivity assessments supported this causation. However, the risk of depression did not exhibit an association with other minerals.

Conclusions: In summary, a higher zinc concentration is causally associated with a reduced depression risk. This MR outcome may assist clinicians in the regulation of specific mineral intake, particularly for high-risk patients with serum zinc deficiencies.

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Keywords

depression; serum; minerals; mendelian randomization; zinc; genetics

Introduction

Depression is a common disease of mood disorder that is characterized by constant melancholy, cognitive injury, and lack of interest. Severe depression often leads to thoughts about death, accompanied by self-abuse and even suicidal tendencies [1]. Depression influences many individuals, with more than 300 million individuals diagnosed with the disease each year [2]. The lifetime prevalence ranges from 15% to 18%, eventually impacting up to one-fifth of individuals worldwide [2]. Depression damages both mental and physical health. In 2019, depression ranked as the second leading cause of global disability [3], and it has become a public health problem whose prevalence will contribute to the global disease burden, which is expected to reach its peak by 2030 [2,3]. To reduce depression incidence, prevention plays a vital role. Therefore, it is important to identify the influencing factors and the molecular biomarkers of depression which may help to prevent the disease.

Several factors have been identified to be related to depression, including gender, genetics, childhood adversity, stress, and insufficient social support [3,4]. Essential minerals associate with metabolic pathways, influencing the

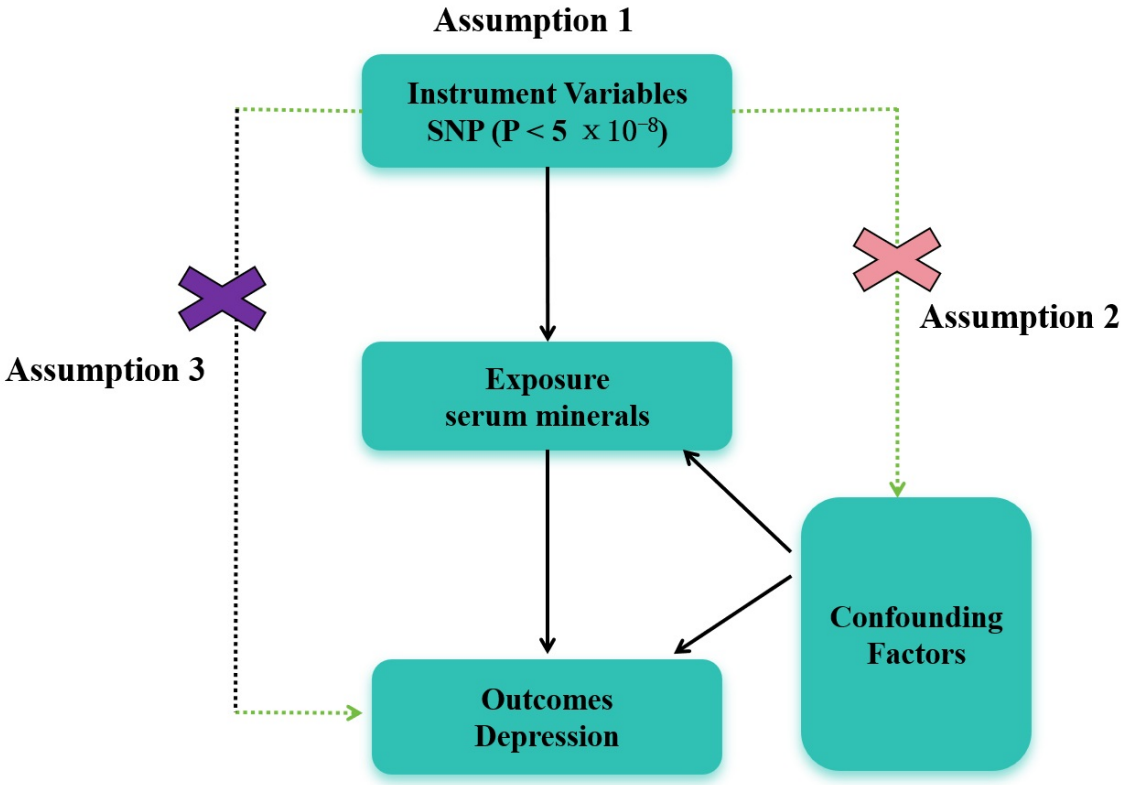

Fig. 1. Conceptual framework for the Mendelian randomization analysis of serum mineral levels and risk of depression. The three core assumptions were as follows: (1) the SNPs should be related to serum minerals, (2) the SNPs should be independent of the confounders, and (3) the SNPs could affect depression via serum minerals. SNPs, single nucleotide polymorphisms.

development and function of the nervous system [4]. An observational study has reported that certain elements may be risk factors for depressive disorders [5], prompting researchers to pay attention to the mineral concentrations that may be modified to prevent depression; however, this evidence is mostly derived from observational studies. Because of the underlying confounding factors and the reverse causality in observational trials [5], the causal association between mineral levels and depression risk remains unsubstantiated. Mendelian randomization (MR) is a statistical approach that assesses the causal relationship between exposures and outcomes. In an MR analysis, the instrumental variables of exposure are genetic variants [5]. MR can also eliminate residual confounding and reverse causality compared to observational studies because genetic variants are randomly allocated and retained at conception [6,7]. Furthermore, genotype cannot be altered by outcome. Therefore, MR analysis avoids reverse causality.

MR studies have not been used to explore whether serum minerals are related to depression risk. In this study, we selected single nucleotide polymorphisms (SNPs) from a publicly available genome-wide association study (GWAS) database to investigate the potential causality between serum minerals and depression risk using MR analysis.

Materials and Methods

Data Sources

We investigated the causal impact of serum minerals on depression risk using a two-sample MR design (Fig. 1). Several key assumptions were made as follows: assumption 1: the genetic instruments are directly associated with the exposure; assumption 2: the genetic instruments have no impact on the outcome and are independent of known and unknown confounders; and assumption 3: the genetic instruments are unrelated to the outcome and affect the outcome entirely through the exposure. The serum minerals included copper, iron, magnesium, zinc, phosphorus, calcium, selenium, chromium, cobalt, and molybdenum. The instrumental variables (IVs) for serum minerals were collected using PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and GWAS (https://www.ebi.ac.uk/gwas).

Due to a lack of genome-wide results, cobalt, chromium, and molybdenum were excluded [8,9]. This study finally included iron, copper, zinc, magnesium, calcium, phosphorus, and selenium [10–14]. Depression was the outcome of this study. The depression dataset was derived from a previous study (GWAS: ebi-a-GCST90018833; https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST90018833/), which provides summary values for depression. We also used data from published studies [15]. This study was approved by our institutional review board. This study did not require written informed consent.

SNP Selection

We collected SNPs for iron from 11 studies involving European populations, with an additional 8 cohorts providing replication data (up to 48,972 subjects) [10]. The SNPs for copper, zinc, and selenium were derived from a GWAS involving 2 Australian and British adult cohorts [11]. Typical SNPs for magnesium were obtained from approximately 2.5 million genotyped and imputed SNPs in 15,366 individuals of European ancestry from the international Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium [12]. The SNPs for phosphorus were sourced from a GWAS encompassing 16,264 individuals with European roots. These data were obtained from the Framingham Offspring Study, the Rotterdam Study, the Atherosclerosis Risk in Communities Study, and the Cardiovascular Health Analysis [13]. Serum calcium SNPs were extracted from a genome-wide association meta-analysis involving 39,400 participants across 17 population-based cohorts. Additionally, up to 21,679 additional individuals were examined to identify the 14 most strongly associated loci. This effort led to the discovery and replication of 6 new regions or 7 loci related to serum calcium [14].

Initially, candidate SNPs were selected based on *p*-values less than 5×10^{-8} and minor frequencies exceeding 1%. Furthermore, we verified the independence of the enrolled genetic variations by incorporating linkage disequilibrium SNPs (R2 <0.001 within a 1000 kb frame). Depression data were derived from a recent GWAS dataset (GWASID: ebi-a-GCST90018833) [16], encompassing 449,414 subjects (13,559 cases and 435,855 controls). Table 1 (Ref. [10–14]) provides detailed information on all SNPs used in this investigation.

Statistical Analysis

When the number of SNP-related exposure factors exceeded 3, this study employed 9 MR models to determine the causal associations. These models included simple mode, fixed-effect, random-effect inverse variance weighted (IVW), weighted mode, penalized weighted median, simple median, weighted median, and MR Egger. If the number of exposure factors was less than 3, only IVW (fixed effects and random effects) analyses were performed. Additionally, the Wald ratio approach was used to identify the causal effect of single SNP-related exposure factors. The primary method was IVW, providing a reliable causal estimate despite variability. Sensitivity analyses were conducted using a weighted median estimator and MR-Egger as the full instrumental parameters should adhere to the MR hypothesis in the IVW technique. The weighted median estimator obtains accurate causal estimates when the IV validity surpasses 50%. The MR-Egger evaluation is objective if the pleiotropic effects have no impact on the genetic instrument. Cochran's Q statistics and MR Egger intercepts were applied with IVW approaches to examine the heterogeneity and pleiotropy of specific SNPs. Pleiotropy effects were considered absent if the intercept did not substantially differ from 0 ($p > 0.05$) with Cochran's Q value estimating heterogeneity. The primary outcome was the IVW technique, with a multiplicative random effects model whenever the *p*-value was less than 0.05; otherwise, the fixed-effects IVW model was used. MR-Egger regression was employed to identify and adjust the pleiotropy to calculate a causal effect, and to assess the impact of directed horizontal pleiotropy on the outcome. A leave-one-out analysis validated the robustness of MR analysis outcomes in the presence of any outlier SNPs. Previous research established that a causal correlation was deemed significant if 3 criteria were met: (1) the *p*-value for IVW was less than 0.05; (2) the MR-Egger estimate, weighted median, and IVW all pointed in the same general direction; and (3) the *p*-value > 0.05 was obtained from the MR-Egger intercept test. All statistical analyses were conducted using the "TwoSampleMR" package within R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria). A statistically significant result was indicated by a two-tailed *p*-value less than 0.05.

Results

Results of Instrument Variable Selection

Five distinct SNPs were associated with magnesium, while five independent SNPs were identified for phosphorus. For selenium, 7 independent SNPs were recognized, and 3 independent SNPs were linked to iron. Additionally, 2 independent SNPs were associated with copper, 3 independent SNPs with zinc, and 7 independent SNPs with cal-

Table 1. Descriptions for data sources and exposure factors.

Exposure	GWAS	Race	Number of SNPs available	Sample size	Reference
Iron (Fe)	Benyamin *et al.*	Europeans	3	48,972	[10]
Copper (Cu)	Evans *et al.*	Australians	2	2603	[11]
Zinc (Zn)	Evans *et al.*	Australians	3	2603	[11]
Magnesium (Mg)	Meyer *et al.*	Europeans	5	15,366	[12]
Phosphorus (P)	Kestenbaum *et al.*	Europeans	5	16,264	[13]
Selenium (Se)	Evans *et al.*	Australians	7	5477	[11]
Calcium (Ca)	O'Seaghdha *et al.*	Europeans	7	39,400	[14]

GWAS, genome-wide association study.

cium, providing a diverse set of instrumental variables (IVs) (Table 2). Table 1 details the sources of the MR data.

Causal Association between Serum Minerals and Depression Risk

Fig. 2 illustrates the MR results between serum minerals and depression risk, while **Supplementary Fig. 1** demonstrates the association of each variant with serum minerals and depression risk. Zinc was demonstrated to be causally related to a lower risk of depression (odds ratio (OR) = 0.968; 95% CI = 0.953–0.984, $p = 0.0001$, IVW). Although IVW (fixed effects) indicated a significant relationship between serum iron and depression (OR = 0.868, 95% CI = 0.779–0.969, $p = 0.011$), the direction in simple mode and MR Egger was contrary to that of the other models (**Supplementary Fig. 2**). Therefore, the results did not support the causal association of serum iron with depression risk. Additionally, MR analysis consistently presented an insignificant causal impact of some serum minerals on depression risk, and they were as follows: calcium (OR = 0.976; 95% CI = 0.593–1.607, $p = 0.923$, IVW), serum magnesium (OR = 0.457; 95% CI = 0.101–2.070, $p = 0.309$, IVW), serum copper (OR = 1.031; 95% CI = 0.931–1.141, $p = 0.560$, IVW), serum selenium (OR = 0.992; 95% CI = 0.882–1.116, $p = 0.896$, IVW), and serum phosphorus (OR = 1.175; 95% CI = 0.862–1.602, $p = 0.308$, IVW). Table 1 provides additional MR model results of serum minerals. Table 2 presents heterogeneity results for selenium (IVW analysis: Q = 13.810, $p = 0.032$) and iron (IVW analysis: Q = 8.611, $p = 0.013$). MR Egger did not reveal any evidence of heterogeneity in all serum minerals ($p > 0.05$).

Sensitivity Analysis

Supplementary Fig. 2 illustrates that MR-Egger regression did not demonstrate a directional pleiotropic effect across the genetic variations (intercept = 0.128; $p = 0.389$). The findings of the leave-one-out sensitivity analysis exhibited that no one SNP was significantly responsible for the relationship between serum minerals and depression risk (**Supplementary Fig. 3**). The funnel plot revealed unapparent heterogeneity among the estimates, suggesting that no potential pleiotropic effects existed (**Supplementary Fig. 4**).

Discussion

This MR analysis examined the causal effect of 6 serum mineral levels on depression risk. This study discovered a negative causal effect of zinc levels on depression risk, with higher zinc levels potentially reducing depression risk. Sensitivity analyses robustly confirmed this finding. Other serum minerals, including calcium, copper, iron, magnesium, phosphorus, and selenium, were not identified to be associated with depression.

Numerous studies have emphasized the association between zinc and depression [17–20]. Zinc has regulatory effects on nerves. It impacts brain development and function, neurogenesis and transmission, cell metabolism, and endocrine functions [21,22]. Depressed patients are more likely to exhibit inadequate zinc levels compared to healthy individuals, making zinc a potential biological marker for depressive disorders [23,24]. Several studies have supported the efficacy of zinc supplementation as an adjunct to antidepressant therapy [25–27]. Siwek *et al.*'s [28] study showed that zinc supplementation can help reduce depression scores and facilitate the treatment of patients resistant to antidepressants. Yosaee *et al.* [20] included randomized controlled trials in a meta-analysis and provided additional evidence supporting the benefits of zinc supplementation on depressive symptoms, particularly in patients with mild-to-moderate depression. To date, the causal relationship between zinc and depression remains inconclusive, although our study indicated a significant causal association between zinc and depression. This finding supports the outcomes of previous studies reporting that zinc deficiency may increase the likelihood of developing depres-

Table 2. Characteristics of 32 SNPs and their genetic associations with serum minerals and depression risk.

Serum micronutrient	SNP	EAF	EA	OA	Serum micronutrient			Depression risk		
					Beta	SE	*p*	Beta	SE	*p*
Iron	rs1799945	0.828	C	G	–0.189	0.01	1.1×10^{-81}	0.0057	0.022	0.7968
Iron	rs1800562	0.0427	A	G	0.328	0.01	2.72×10^{-97}	0.0246	0.0365	0.501
Iron	rs855791	0.3877	A	G	–0.181	0.007	1.32×10^{-139}	0.0533	0.014	0.000138599
Copper	rs1175550	0.22	A	G	0.198	0.032	5.00×10^{-10}	0.0203	0.0156	0.1944
Copper	rs2769264	0.16	T	G	0.313	0.034	2.63×10^{-20}	–0.0022	0.0177	0.9027
Magnesium	rs11144134	0.08	T	C	0.011	0.001	8.00×10^{-15}	–0.0212	0.0286	0.4585
Magnesium	rs13146355	0.44	G	A	0.005	0.001	6.00×10^{-13}	–0.0166	0.0136	0.224
Magnesium	rs3925584	0.55	C	T	0.006	0.001	5.20×10^{-16}	0.0041	0.0135	0.7596
Magnesium	rs4072037	0.54	C	T	0.01	0.001	2.00×10^{-36}	–0.0094	0.0137	0.4913
Magnesium	rs448378	0.53	G	A	0.004	0.001	1.00×10^{-8}	0.0114	0.0138	0.4107
Phosphorus	rs1697421	0.49	G	A	0.05	0.005	1.00×10^{-27}	0.0231	0.0135	0.0871706
Phosphorus	rs17265703	0.85	G	A	0.036	0.006	4.00×10^{-9}	0.0024	0.0204	0.9050
Phosphorus	rs2970818	0.09	T	A	0.047	0.008	4.00×10^{-9}	–0.005	0.0285	0.8608
Phosphorus	rs9469578	0.92	T	C	0.059	0.009	1.00×10^{-11}	0.0035	0.0229	0.8785
Phosphorus	rs947583	0.29	T	C	0.035	0.005	3.00×10^{-12}	–0.0158	0.0176	0.3686
Zinc	rs1532423	0.37	G	A	0.178	0.026	6.00×10^{-11}	–0.0051	0.026	0.718701
Zinc	rs2120019	0.79	C	T	0.287	0.033	1.55×10^{-18}	–0.0125	0.033	0.438
Zinc	rs4826508	0.27	C	T	0.21	0.03	1.00×10^{-12}	–0.0034	0.030	0.820
Calcium	rs10491003	0.09	C	T	0.027	0.005	5.00×10^{-09}	0.0158	0.0225	0.4834
Calcium	rs1550532	0.31	G	C	0.018	0.003	8.00×10^{-11}	0.0099	0.0146	0.495801
Calcium	rs1570669	0.34	A	G	0.018	0.003	9.00×10^{-12}	0.0244	0.0139	0.0805694
Calcium	rs1801725	0.15	G	T	0.071	0.004	9.00×10^{-86}	–0.0029	0.0207	0.8893
Calcium	rs7336933	0.85	A	G	0.022	0.004	9.00×10^{-10}	–0.0247	0.0188	0.19
Calcium	rs7481584	0.70	A	G	0.018	0.003	1.00×10^{-10}	–0.0194	0.0157	0.2166
Calcium	rs780094	0.42	C	T	0.017	0.003	1.00×10^{-10}	–0.0116	0.0139	0.4066
Selenium	rs11951068	0.06	G	A	0.21	0.04	2.00×10^{-12}	0.002	0.0714	0.9781
Selenium	rs1789953	0.16	C	T	0.12	0.03	3.00×10^{-08}	–0.1074	0.1047	0.3048
Selenium	rs3797535	0.1	C	T	0.21	0.04	2.00×10^{-15}	0.0365	0.0469	0.4363
Selenium	rs567754	0.67	T	C	0.17	0.02	8.00×10^{-20}	–0.0162	0.0265	0.5409
Selenium	rs6586282	0.85	T	C	0.12	0.03	4.00×10^{-09}	–0.256	0.0928	0.00579602
Selenium	rs705415	0.88	T	C	0.23	0.04	5.00×10^{-10}	0.0386	0.0464	0.4055
Selenium	rs921943	0.29	C	T	0.25	0.02	9.00×10^{-28}	0.0268	0.0293	0.3606

Abbreviations: EA, effect allele; EAF, effect allele frequency; OA, other allele; SE, Standard Error.

sion, while quantitative zinc supplementation may help reduce depressive symptoms [29,30]. Several possible underlying mechanisms of zinc's protective impact on depression have been proposed. Synaptic zinc is generally regarded as an N-methyl-d-aspartate (NMDA) receptor antagonist. It therapeutically targets NMDA receptors to modulate excitatory amino acid (glutamatergic) and inhibitory (GABAergic) neurotransmission, producing an antidepressant-like effect [30,31]. According to an animal study, blocking NMDA receptors may reduce the protective benefits of zinc on depressive-related symptoms, further suggesting that NMDA receptors mediate the antidepressant properties of zinc [32].

Zinc transporters and receptors, such as Zinct-3 and GPR39 (G protein-coupled receptor 39), have been found to correlate with serotonin synthesis. Consequently, zinc supplementation may exert similar effects to antidepressants [33]. Another potential mechanism contributing to the antidepressant effects lies in its anti-inflammatory and antioxidant properties [23]. Depression is associated with increased inflammation and oxidative stress, and zinc, as an antioxidant and anti-inflammatory agent, may help alleviate these pathological processes, thereby improving depressive symptoms. Our findings offer evidence to support the zinc-related novel strategies for preventing and treating depression. Nevertheless, further studies are warranted.

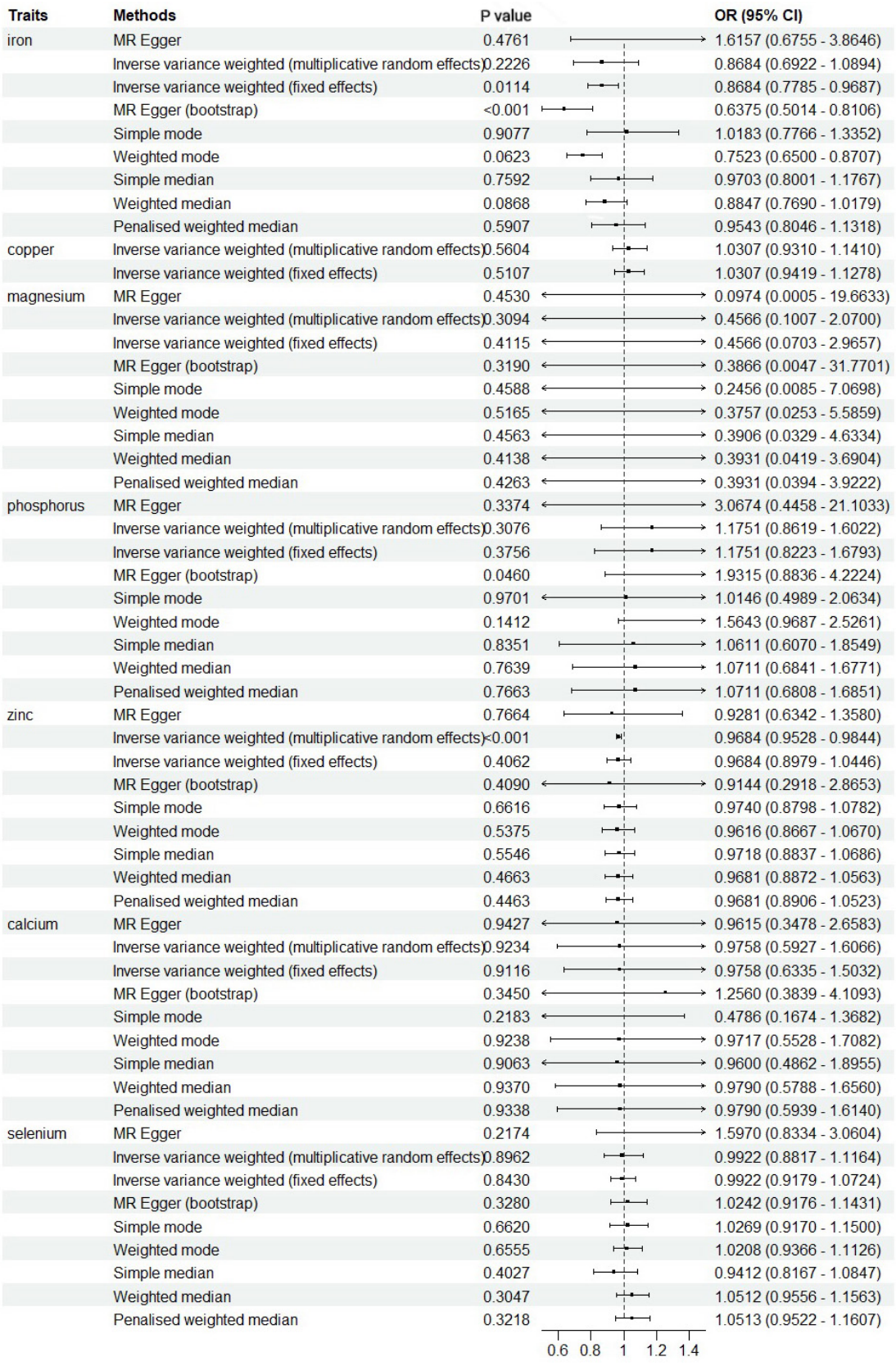

Fig. 2. Association of genetically-predicted serum mineral levels with depression risk. OR, odds ratio; CI, confidence interval.

Based on our findings, genetically-predicted serum concentrations of magnesium, calcium, copper, iron, and selenium were not found to be significantly associated with risk of depression. Prior researchers have presented inconsistent evidence on the roles of these essential elements in depression risk. Macro-minerals are essential for the function of the human body; for example, magnesium and calcium play crucial roles in nerve cell function [34]. Considering the connection between magnesium and limbic system function, magnesium may be involved in the development and progression of depression [35]. However, the effect of magnesium on depression is controversial in observational studies [36–38]. Previous studies have explored nerve signaling as a potential regulatory mechanism of magnesium in depression by blocking voltage-gating channels within the NMDA receptor. Magnesium deficiency may shift NMDA-coupled calcium channels toward the opening, leading to neurological dysfunction and neuronal damage [39–41].

Moreover, calcium influx has been considered a potential factor in affective disorders. Bowden *et al*. [42] observed a more significant reduction in plasma calcium levels in unipolar depression patients compared to healthy controls. Consequently, given the disrupted intracellular calcium dynamics in individuals with depression, regulating calcium levels with calcium channel blockers may have potential therapeutic benefits for depression-like symptoms [43]. However, our study lacks sufficient data to support a causal link between depression and genetically-predicted serum magnesium and calcium levels.

Copper works with multiple metalloenzymes as an electron donor or acceptor, playing a role in energy metabolism, neurobehavioral processes, and immune system function [44]. Maintaining copper homeostasis is fundamental for human health with deficiency or overload leading to problems. The effect of copper on depression is controversial. The participation of copper in the conversion of dopamine to norepinephrine suggests a potential role in depression development [45]. However, excessive copper can cause oxidative damage to cells and tissues due to redox activity [46]. Liu *et al*. [47] proposed that patients with major depressive disorders may have higher serum copper concentrations, which potentially results from neuronal dysfunction due to abnormal biochemical metabolite ratios. In our study, there was no evidence to suggest a causal role of genetically-predicted serum copper levels in depression. Therefore, the causality between serum copper levels and depression risk requires further studies.

Iron is an essential trace element in the body, crucial for oxygen transport and neurological function [48]. Some studies suggest that iron deficiency may be associated with the occurrence and severity of depression [49,50]. Iron deficiency can lead to anemia, which may increase the risk of depression [51,52]. Additionally, some research indicates that iron is involved in neurotransmitter synthesis and metabolism, which may also be related to the occurrence of depression [48].

Phosphorus is a vital component within cells, participating in biological processes such as energy metabolism and cellular signaling. Although there is currently no clear evidence of a direct association between phosphorus and depression, some studies suggest a potential relationship between dietary phosphorus intake and mental health [53–55]. For example, a high phosphorus diet may be associated with mood disorders, as it may influence neurotransmitter levels or other biological processes in the brain [56]. Conversely, selenium, an important antioxidant involved in immune system function and thyroid hormone synthesis, may be associated with an increased risk of depression. The antioxidant properties of selenium may help reduce oxidative stress-related damage to brain neurons, exerting a protective effect against depression [57].

There were several limitations in this study. First, although MR is a robust approach for estimating causality between serum zinc levels and depression risk, the results require further validation. Second, the robustness of the MR analysis heavily relies on the instrumental variables (IVs) to explain the exposure. Thus, a larger sample size is needed to provide a more accurate estimation of the genetic impact on serum minerals. Third, most participants were of European ancestry, and the outcomes of this study may not apply to other populations.

Overall, the relationship between serum levels of iron, phosphorus, and selenium and depression is not completely understood, and further investigation into their roles in the pathogenesis of depression is required.

Conclusions

In this study, zinc was demonstrated as a causally protective factor for depression risk. However, the causality of other serum minerals, including calcium, copper, iron, magnesium, phosphorus, and selenium, in depression was not supported by this MR analysis. Iron supplements may hold promise for depression prevention.

Institutional Review Board Statement

This study achieved summary data from GWAS and did not involve individual information. The relevant institutional review board approved all investigations that supplied data to this study.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article.

Author Contributions

YW, LL and DY co-designed the research study. YW and DY drafted the manuscript. YW and LL analyzed the data and drew the figures. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study did not involve individual information. The data in this study obtained from GWAS has been approved by informed consent.

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Conflict of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62641/aep.v52i3.1637

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