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A Mendelian randomization study of the effect of selenium on autoimmune thyroid disease

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Abstract. – OBJECTIVE: The impact of selenium on autoimmune thyroid disease (AITD) is a subject of ongoing debate. This study aimed to analyze the causal correlations of selenium with autoimmune thyroiditis (AIT), autoimmune hyperthyroidism (AIH), and Graves' disease (GD) by Mendelian randomization (MR).

MATERIALS AND METHODS: Single nucleotide polymorphisms related to selenium, AIT, AIH, and GD were sourced from the IEU Open GWAS project and FinnGen. Exposure-outcome causality was assessed using inverse variance weighted, MR-Egger, and weighted median. Horizontal pleiotropy was examined using the MR-Egger intercept, heterogeneity was evaluated with Cochran's Q test, and the robustness of the results was confirmed via leave-one-out sensitivity analysis.

RESULTS: The MR analysis revealed that selenium did not exhibit a causal relationship with AIT (OR 0.993, 95% CI 0.786 to 1.108, *p*=0.432), AIH (OR 1.066, 95% CI 0.976 to 1.164, *p*=0.154), or GD (OR 1.052, 95% CI 0.984 to 1.126, *p*=0.138). Moreover, the MR-Egger intercept and Cochran's Q test demonstrated the absence of horizontal pleiotropy or heterogeneity in these results (*p*>0.05). Sensitivity analysis affirmed the robustness of these results.

CONCLUSIONS: This MR analysis concluded that selenium was not linked to AIT, AIH, or GD risk. Therefore, indiscriminate selenium supplementation is not advisable for AITD patients without concurrent selenium deficiency.

Key Words:
Selenium, Autoimmune thyroid disease, Autoimmune thyroiditis, Autoimmune hyperthyroidism, Graves' disease, Mendelian randomization.

Introduction

Autoimmune thyroid disease (AITD) is a chronic disease characterized by thyroid dysfunction and abnormal immune function[1], primarily encompassing Hashimoto's thyroiditis (HT) and Graves' disease (GD)[2]. HT, characterized by thyroid follicular cell damage and resulting hypothyroidism, is the most prevalent form of autoimmune thyroiditis (AIT)[3]. GD, the most common cause of hyperthyroidism, is characterized by thyroid cell hyperplasia and hyperthyroidism[4]. The pathogenesis of AITD remains unclear, but it is generally attributed to the infiltration of the thyroid gland by activated T and B lymphocytes and the production of autoimmune thyroid antibodies such as thyroid peroxidase antibodies (TPOAb), thyroglobulin antibodies (TGAb), and thyrotropin receptor antibody (TRAb)[5]. Epidemiological evidence indicates a gradual rise in the incidence of autoimmune endocrine diseases, including AITD[6]. The prevalence of HT has been reported to range from approximately 7.5% to 11.4% in low- and middle-income populations[7]. GD typically manifests between the ages of 30 and 60, with a prevalence of 3.0% in women and 0.5% in men[8]. The primary treatments for AITD include levothyroxine, antithyroid drugs, radioactive iodine, and surgery[9]. Although these treatments alleviate clinical symptoms in AITD patients, they do not fully reverse the disease process[9]. Therefore, it is necessary to find drugs with adjuvant therapeutic effects to further improve the prognosis of AITD patients.

As an essential trace element, selenium exists in the body mainly in two organic forms: seleno-amino acids selenocysteine and selenomethionine[10]. Previous studies[11-13] have demonstrated selenium's utility in the adjuvant treatment for a variety of diseases, including epilepsy, prostate cancer, and immunodeficiency disorders. As the study progressed, selenium deficiency was re-

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ported as a potential risk factor for HT and GD[14]. Furthermore, when combined with antithyroid drugs or thyroid hormones, selenium has shown[15] the ability to suppress autoimmune reactions and reduce autoimmune thyroid antibody levels. Nevertheless, some researchers[16,17] disagree, proposing that selenium supplementation offers no significant benefit to patients with HT or GD. The association between selenium and AITD remains controversial, and the existence of a causal relationship is not definitively established.

Mendelian randomization (MR) is a method that uses genetic variants to predict causal links between exposure factors and outcome variables18. This study employs MR to investigate the causal correlations of selenium with AIT, autoimmune hyperthyroidism (AIH), and GD from genetic variants.

Materials and Methods

Study Design

MR relies on three fundamental assumptions[19,20]: (1) The relevance assumption: the single nucleotide polymorphisms (SNPs) are closely related to exposure factors. (2) The independence assumption: SNPs are independent of confounding factors. (3) The exclusion restriction assumption: SNPs do not influence the outcome variable through pathways other than the exposure factor. The MR design for selenium and AITD is shown in Figure 1.

Data Sources

Data for selenium were sourced from IEU Open GWAS project (available at: gwas.mrcieu.ac.uk/), and data for AIT, AIH, and GD were sourced from FinnGen (available at: www.finngen.fi/en/). All data were retrieved from publicly available databases, obviating the need for additional ethical approval.

Selection of Genetic Instrument Variables

First, SNPs closely linked to exposure factors were identified using a significance threshold of $p<5\times10^{-5}$ to fulfill the relevance assumption. Second, SNPs underwent further screening based on $R^2<0.001$ and kb=10,000 to mitigate potential biases arising from linkage disequilibrium. Third, referring to PhenoScanner (available at: www.phenoscanner.medschl.cam.ac.uk) and related literature, SNPs potentially associated with AITD were removed to fulfill the independence assumption.

Statistical Analysis

The study adhered to the STROBE-MR[21]. The "TwoSampleMR (0.5.7)" package of R 4.3.1 (Vienna, Austria) was used to perform the two-sample MR analysis, and inverse variance weighted (IVW), MR-Egger, and weighted median were used as analysis methods. Among them, IVW is the primary analysis method, which offers unbiased causal estimation without horizontal pleiotropy and is the most informative.

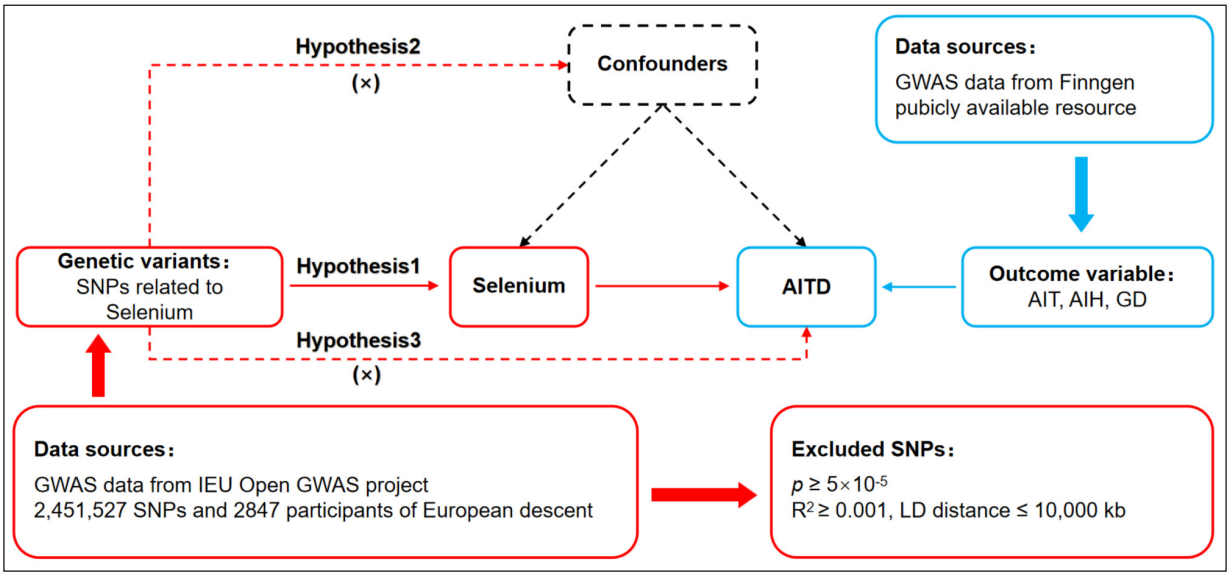

Figure 1. MR design for causal analysis of selenium and AITD. AITD, autoimmune thyroid disease; AIT, autoimmune thyroiditis; AIH, autoimmune hyperthyroidism; GD, Graves' disease.

MR-Egger and weighted median were used as secondary analysis methods. MR-Egger provides valid causal estimates in cases involving pleiotropy, and the weighted median is less sensitive to outliers and measurement errors. $p<0.05$ was defined as a statistical significance.

When harmonizing the allelic orientations of exposure SNPs and outcome SNPs, mismatched SNPs were excluded based on the effect of allele frequency. Outlier SNPs ($p<1.0$) were identified and removed using MR-Pleiotropy RESidual Sum and Outlier. Subsequently, the remaining SNPs were utilized for two-sample MR analysis. Additionally, horizontal pleiotropy was evaluated using MR-Egger's intercept analysis, with $p\geq0.05$ indicating the absence of horizontal pleiotropy, aligning with assumption 3. Heterogeneity was assessed using Cochran's Q, with $p\geq0.05$ signifying the absence of heterogeneity. The leave-one-out sensitivity analysis was used to assess the robustness of the results.

Results

GWAS Data for Selenium

The data for selenium were sourced from the IEU Open GWAS project, encompassing 2,874 individuals of European descent (Dataset ID: ieu-a-1075). This database provided 261 SNPs strongly associated with selenium. After eliminating the effects of linkage disequilibrium and confounding effects, a total of 44 SNPs were included, as shown in **Supplementary Table I.** After removing mismatched and outlier SNPs, the final included SNPs were presented in **Supplementary Table II, III, IV**.

GWAS Data for AITD

Data on AIT were retrieved from FinnGen, which comprised 321,192 Europeans (Dataset ID: finngen_R9_E4_THYROIDITAUTOIM). Additionally, data on AIH were sourced from the same database, including 281,683 Europeans (Dataset ID: finngen_R9_AUTOIMMUNE_HYPERTHYROIDISM). For GD, data were obtained from the FinnGen database, including 377,277 Europeans (Dataset ID: finngen_R9_E4_GRAVES_STRICT), as detailed in Table I.

Two-Sample MR Analysis Results

MR was employed to assess potential causal correlations of selenium with AIT, AIH, and GD. The forest plot of the MR analysis is depicted in Figure 2, and the scatter plot of the MR analysis is provided in **Supplementary Figure 1**. Results of MR-Egger's intercept analysis are exhibited in **Supplementary Table V**. Results of heterogeneity analysis are presented in **Supplementary Figure 2** and **Supplementary Table VI**. Additionally, leave-one-out sensitivity analysis is depicted in **Supplementary Figure 3**.

AIT

All three analytical methods consistently revealed no significant causal relationship between selenium and AIT: IVW (OR 0.993, 95% CI 0.786 to 1.108, $p=0.432$), MR-Egger (OR 1.267, 95% CI 0.878 to 1.827, $p=0.214$), and weighted median (OR 1.077, 95% CI 0.837 to 1.387, $p=0.563$). Intercept analysis demonstrated no evidence of horizontal pleiotropy ($p=0.804$), and Cochran's Q test did not detect significant heterogeneity ($p=0.320$). Sensitivity analysis suggested the robustness of these results.

AIH

Across all three analytical methods, no significant causal relationship between selenium and AIH was observed: IVW (OR 1.066, 95% CI 0.976 to 1.164, $p=0.154$), MR-Egger (OR 1.043, 95% CI 0.856 to 1.270, $p=0.682$), and weighted median (OR 1.094, 95% CI 0.963 to 1.243, $p=0.167$). Intercept analysis revealed no horizontal pleiotropy ($p=0.076$), and Cochran's Q test did not detect significant heterogeneity ($p=0.276$). Sensitivity analysis provided further support for the robustness of these findings.

GD

All three methods indicated no significant causal relationship between selenium and GD: IVW

Table I. Details of the GWAS studies included in the Mendelian randomization.

Year	Trait	Population	Sample size	Web source
2013	Selenium	European	2,874	gwas.mrcieu.ac.uk/
2023	Autoimmune thyroiditis	European	321,192	www.finngen.fi/en/
2023	Autoimmune hyperthyroidism	European	281,683	www.finngen.fi/en/
2023	Graves' disease	European	377,277	www.finngen.fi/en/

Exposure	Outcome	MR method	Forest plot	OR	95%CI	*p* value
Selenium	Autoimmune thyroiditis	IVW		0.993	0.786 to 1.108	0.432
		MR Egger		1.267	0.878 to 1.827	0.214
		Weighted median		1.077	0.837 to 1.387	0.563
	Autoimmune hyperthyroidism	IVW		1.066	0.976 to 1.164	0.154
		MR Egger		1.043	0.856 to 1.270	0.682
		Weighted median		1.094	0.963 to 1.243	0.167
	Graves' disease	IVW		1.052	0.984 to 1.126	0.138
		MR Egger		1.089	0.938 to 1.265	0.271
		Weighted median		1.085	0.980 to 1.201	0.114
			0.600 0.800 1.000 1.200 1.400 1.600 1.800 2.000			

Figure 2. Forest plot of MR analysis on the causal relationship between selenium and AITD. AITD, autoimmune thyroid disease; AIT, autoimmune thyroiditis; AIH, autoimmune hyperthyroidism; GD, Graves' disease.

(OR 1.052, 95% CI 0.984 to 1.126, p=0.138), MR-Egger (OR 1.089, 95% CI 0.938 to 1.265, p=0.271), and weighted median (OR 1.085, 95% CI 0.980 to 1.201, p=0.114). Intercept analysis found no evidence of horizontal pleiotropy (p=0.618), and Cochran's Q test did not identify significant heterogeneity (p=0.946). Sensitivity analysis consistently affirmed the robustness of these results.

Discussion

AITD is an autoimmune disease characterized by the presence of thyroid-specific autoantibodies in the serum and lymphocytic infiltration[22,23], including HT and GD[14]. HT is the most common form of AIT and represents the primary etiology of acquired hypothyroidism, and its specific antibodies are TPOAb and TGAb[24,25]. GD is an AITD characterized by diffuse enlargement of the thyroid gland and hyperthyroidism, and its specific antibody is TRAb[26,27]. Measurement of autoimmune antibody titers, such as TPOAb, TGAb, and TRAb, plays a crucial role in assessing disease activity in AITD[28]. Selenium supplementation has been reported[15,29] to enhance the prognosis of AITD patients by diminishing autoimmune thyroid antibody levels through attenuating oxidative stress. However, some studies[30] noted no significant association between selenium deficiency and AITD. The association between selenium and AITD remains controversial, and their causal relationship remains to be further elucidated. To better understand the correlation between selenium and AITD, this study employed MR to investigate the potential causal correlations of selenium with AIT, AIH, and GD.

The study findings indicated the absence of significant causal relationships of selenium with AIT, AIH, or GD. Sensitivity analysis further confirmed the robustness of the MR analysis. Given that the entire dataset of the study was derived from European populations, the results primarily elucidate the impact of selenium on the risk of AIT, AIH, and GD in European populations. It was reported[31] that differences in soil selenium levels result in lower dietary selenium intake in the European region than in the United States and lower dietary selenium intake in Eastern Europe than in Western Europe. The regional differences in selenium intake might be an essential factor influencing the study results.

This MR analysis revealed no causal relationship between selenium and GD or AIH. GD has attracted great interest from researchers since it is a common type of AITD and the most significant cause of hyperthyroidism. Serum selenium levels in Iranian patients with GD and Graves orbitopathy (GO) were not substantially different from those of healthy people, according to a cross-sectional study[32]. Serum selenium levels in GD patients did not differ significantly from those in healthy individuals in Poland, where selenium deficiency is common, and small-dose supplementation (42±14 g/day) did not affect serum total selenium levels, selenoprotein P, and glutathione peroxidase 3 activity[33]. Leo et al[34] conducted a 90-day study in GD patients with adequate serum selenium and found that serum selenium

had no significant effect on hyperthyroidism in the short term. Gorini et al[35] stated that the influence of selenium on GD patients is linked to their baseline selenium levels and that selenium supplementation is not beneficial in patients with adequate serum selenium. This evidence implies that selenium deficiency is not a common manifestation among all GD patients, and selenium supplementation appears to be of no benefit in GD patients without selenium deficiency.

However, it was reported[36] that selenium supplementation improved hyperthyroidism in selenium-deficient GD patients. In a 6-month clinical trial, Xu et al[16] demonstrated that selenium augmented the efficacy of methimazole in lowering FT3, FT4, and TRAb, as well as elevated TSH levels. Furthermore, selenium supplementation potentially enhanced the prognosis of GO patients with serum selenium deficiency[37]. Marcocci et al[38] discovered that selenium reduced ocular symptoms, slowed disease progression, and improved the quality of life in mild GO patients. An earlier study[33] indicated that low-dose selenium supplementation (42±14 g/day) did not significantly affect serum total selenium levels in Polish GD patients. However, another Polish study[39] showed that 100 g/day of selenium elevated serum total selenium levels and selenoprotein P concentration. These studies[33,39] suggest that high-dose selenium supplementation benefits selenium-deficient GD patients, but this benefit appears limited. A meta-analysis[40] revealed that while selenium supplementation reduced TRAb levels and improved thyroid function, this effect diminished after nine months. Kahaly et al[41] also reported that sodium selenite supplementation did not decrease recurrence rates in GD patients. These pieces of evidence suggest that it is unclear whether selenium supplementation has any long-term benefit. In summary, selenium supplementation lacks efficacy in GD patients without selenium deficiency and may be effective in those with selenium deficiency. However, its benefits are constrained by factors such as dosage and treatment duration.

This MR analysis found no causal relationship between selenium and AIT. Although prior research[42] has demonstrated a lower prevalence of HT in selenium-sufficient regions compared to selenium-deficient areas, the effectiveness of selenium supplementation in HT patients remains controversial. These contradictory findings are related to various factors, such as the preparation of selenium, the treatment duration of selenium, whether LT4 is used, and the auto-antibody levels of patients.

First, different selenium preparations have different effects on HT patients. Krysiak and Okopien[43] reported significant reductions in interferon (IFN)-γ and tumor necrosis factor (TNF)-α levels after six months of continuous selenomethionine supplementation in AIT patients with normal thyroid function. Pilli et al[44] reported similar results, though they found the benefit was temporary. However, Karanikas et al[45] observed that three months of continuous sodium selenite supplementation did not enhance TPOAb levels or cytokines such as IFN-γ, interleukin (IL)-4, TNF-α, and TNF-β in selenium-deficient AIT patients.

Second, the duration of selenium supplementation influences the efficacy of treating HT. A meta-analysis[46] that included 16 controlled trials showed that serum TPOAb and TGAb decreased at three months in AIT patients treated with selenium alone, but there were no significant differences from the control group at six and 12 months. Anastasilakis et al[47] and Esposito et al[48] also reported that TPOAb levels and thyroid function in AIT patients were comparable to those in the placebo group after six months of selenium supplementation. In contrast, Kong et al[49]'s meta-analysis indicated that three months of selenium supplementation failed to reduce TPOAb levels in HT patients, while six months of selenium supplementation effectively reduced TPOAb and TGAb levels in HT patients. Although these studies point to different optimal treatment durations for selenium, they reflect the fact that treatment duration has a potential impact on outcomes.

Third, the combination of other drugs will affect the efficacy of selenium. A meta-analysis[46] indicated that a 12-month selenium supplementation lowered TPOAb and TGAb levels in AIT patients receiving LT4 treatment, but no such benefit was observed in AIT patients not treated with LT4. Winther et al[50]'s meta-analysis also indicated that selenium supplementation did not significantly impact TSH levels in chronic AIT patients who were not treated with levothyroxine. These findings suggest that selenium supplementation alone appears to be ineffective, highlighting the potential therapeutic value of combining selenium with levothyroxine.

Fourth, the effect of selenium supplementation is also linked to baseline TPOAb levels in AIT patients. TPOAb levels have been reported[51] to be negatively correlated with serum selenium levels in HT patients, suggesting that patients with higher TPOAb titers are associated with more severe selenium deficiency. A meta-analysis[49] showed

that AIT patients with TPOAb>1,000 IU/mL had significant reductions in TPOAb and TGAb levels after three months of selenium supplementation, whereas AIT patients with TPOAb<1,000 IU/mL did not derive such benefits. This phenomenon is because patients with high TPOAb titers have lower selenium levels, and thus, selenium supplementation is more effective. In summary, the controversy over the causal relationship between selenium and AIT may be attributed to variables including the preparation of selenium, the treatment duration of selenium, whether LT4 is used, and the auto-antibody levels of patients. There is insufficient evidence to support that selenium has an absolute benefit in patients with AIT[52].

Our study has certain limitations. First, since GWAS only includes some types of AITD, only AIT, AIH, and GD were analyzed by MR in this study, potentially limiting the generalizability of our findings. Second, our data originated from European populations, limiting the applicability of our results to other ethnic groups. Third, the results could not be analyzed for the effect of selenium-related factors on outcome variables. Consequently, the influence of factors such as selenium preparations, dosage, treatment duration, and its combination with LT4 on AITD remains unclear. Considering these limitations, we expect that future research will enhance our understanding. First, investigate the impact of selenium on different ethnicities and types of AITD, thus providing more comprehensive data for MR. Second, stratified trials that control for relevant variables should be conducted to explore the specific effects of selenium preparations, dosage, treatment duration, and its combination with LT4 on patients with different types of AITD.

Conclusions

This MR analysis suggests that selenium is not associated with the risk of AIT, AIH, and GD. Consequently, blind selenium supplementation is not recommended for AITD patients without selenium deficiency. Further investigation into the causal relationship and mechanism between selenium and AITD is warranted for future studies.

Data Availability

The original data presented in this study are included in the manuscript and supplementary material. For more information, contact the corresponding author.

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Ethics Approval

Due to the fact that the data for this study is sourced from publicly available databases, ethical approval is not applicable.

Informed Consent

Due to the fact that the data for this study is sourced from publicly available databases, informed consent is not applicable.

Conflict of Interest

The authors declared that there are no conflicts of interest in this study.

Author's Contributions

Design: Can Hu, Yunfeng Yu, Yaoyao Li. Conduct/data collection: Keke Tong, Xinyu Yang, Siyang Bai. Analysis: Gang Hu, Jingyi Wu. Writing manuscript: Can Hu, Yunfeng Yu, Rong Yu, Yaoyao Li.

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