



The Association of Essential Micronutrients in Serum with Immune-Mediated Inflammatory Diseases: A Cross-Sectional Study from NHANES

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Abstract: Background: Immune-mediated inflammatory diseases (IMIDs) occur when the immune system attacks the body's own tissues, affecting approximately 8% of the global population. Objective: This study investigated the serum levels of a few redox-relevant essential micronutrients, aiming to explore their relationships with the prevalence of IMIDs and to identify the serum concentration ranges associated with the lowest observed prevalence of IMIDs. Methods: A cross-sectional study was conducted using NHANES 2013–2014 data, comprising 1493 participants. IMIDs were defined as the presence of asthma, celiac disease, psoriasis, or psoriatic/rheumatoid arthritis. Weighted binary logistic regression evaluated the association between serum selenium, vitamin D, and the zinc-to-copper ratio with the prevalence of IMIDs. We identified the serum-selenium quartile associated with the lowest observed prevalence of IMIDs in this dataset using quartile-based and threshold analyses, adjusting for smoking status, alcohol consumption, diabetes, and cancer history. Results: Higher serum selenium levels were significantly associated with a lower prevalence of IMIDs (OR: 0.627, 95% CI: 0.402–0.977). In contrast, no significant associations were observed for vitamin D or zinc-to-copper ratio. Quartile analysis revealed that individuals in the second quartile of serum selenium (1.51–1.65 $\mu\text{mol/L}$) had the lowest observed prevalence of IMIDs (18.85%), with significantly lower odds of IMIDs compared to the lowest (OR: 0.659, 95% CI: 0.447–0.971). However, sufficiency levels of vitamin D and the zinc-to-copper ratio were not significantly associated with a lower prevalence. Conclusion: The inverse association between higher serum selenium (1.51–1.65 $\mu\text{mol/L}$) and IMIDs was statistically significant in crude and partially-adjusted models but was attenuated and non-significant in the primary fully-adjusted weighted model. These findings suggest a potential observational link between selenium status and the prevalence of IMIDs that warrants further investigation.

Keywords: immune-mediated inflammatory diseases; essential micronutrients; NHANES; selenium; vitamin D; zinc-to-copper ratio

1. Introduction

Immune-mediated inflammatory diseases (IMIDs) represent a growing global health challenge, affecting millions of individuals worldwide. Conditions such as asthma, psoriasis, celiac disease and rheumatoid arthritis (RA) are among the most common. IMIDs affect 7.6–9.4% people globally [1,2]. In the United States, approximately 3% of the population, or nearly 10 million people, are estimated to live with IMIDs [3], leading to significant morbidity, diminished quality of life, and escalating healthcare costs [4]. IMIDs occur when the immune system mistakenly attacks the body's own tissues, resulting in cytotoxic reactions and chronic inflammation [5]. Current treatments primarily rely on immunosuppressive agents and anti-inflammatory strategies. However, these therapies are often expensive and come with considerable drawbacks, including drug intolerance, hypersensitivity reactions, and increased risk of infections and malignancies [6–9]. Consequently,



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there is a growing interest in identifying dietary components with anti-inflammatory and antioxidant properties as alternative or complementary interventions.

Essential micronutrients, including vitamins, zinc, copper, and selenium, are critical for their anti-inflammatory and antioxidant functions and must be obtained through the diet [10]. These micronutrients play vital roles in every stage of the immune response, including barrier defense, innate immunity, and adaptive immunity [11]. Although the mechanisms and etiology of IMIDs are complex, there is increasing evidence suggesting that micronutrients—such as selenium, vitamin D, zinc, and copper—may influence the onset and progression of these conditions. Exploring their potential in mitigating IMIDs risk offers a promising venue for research and clinical application.

Selenium (Se) is an essential micronutrient known for its unique biochemistry and its critical role in regulating immune function and protecting against oxidative stress through its incorporation into selenoproteins [12]. Numerous studies have suggested that selenium deficiency is associated with an increased risk of IMIDs [13–15]. This deficiency has also been linked to the pathogenesis of celiac disease, psoriasis, RA, and asthma, with possible mechanisms involving heightened oxidative stress [16,17].

Vitamin D (Vit. D), a fat-soluble vitamin primarily obtained through sun exposure and dietary sources, is another key nutrient. Calcitriol, the active form of vitamin D, binds to vitamin D receptor on T cells, B cells, and dendritic cells, influencing their function and enhancing immunological tolerance [18]. Strong evidence links vitamin D deficiency with an increased risk of IMIDs. For example, low vitamin D levels have been associated with higher incidence and severity of RA [19,20]. Additionally, vitamin D deficiency may contribute to the onset and aggravation of asthma, psoriasis, and celiac diseases [21].

Zinc (Zn) and copper (Cu) are essential trace elements with crucial roles in the immune system, and their imbalance has been implicated in the development of IMIDs. Zinc is recognized for its immunomodulatory functions, particularly in the regulation of various immune cells [22]. Zinc deficiency can lead to immune dysfunction and the development of IMIDs such as RA and celiac disease [23]. Conversely, elevated copper levels are linked with inflammation and oxidative stress, which are common contributors to the development of IMIDs [24]. An imbalance in the zinc-to-copper ratio (Zn/Cu ratio) has been observed in individuals with IMIDs conditions such as RA and systemic lupus erythematosus (SLE), highlighting the importance of maintaining proper zinc and copper homeostasis to mitigate immune dysfunction [25].

Despite evidence supporting the roles of these nutrients in IMIDs, there remains a need for comprehensive epidemiological studies to better understand their roles in the occurrence and development of these conditions. The National Health and Nutrition Examination Survey (NHANES) provides valuable datasets for such investigations. NHANES is a program designed to assess the nutritional status and health of the U.S. population through a combination of interviews, physical examinations, and laboratory tests [26]. The extensive data collected by NHANES, including information on dietary intake, serum nutrient levels, and health outcomes, offer a unique opportunity to explore the relationship between selenium, vitamin D, the zinc-to-copper ratio, and IMIDs, with a particular focus on psoriatic/rheumatoid arthritis, celiac disease, psoriasis, and asthma.

Current guidelines increasingly recognize selenium and other micronutrients as crucial for immune function. The Recommended Dietary Allowance (RDA) for selenium, set by organizations like the National Institutes of Health (NIH), is aimed at maintaining optimal immune function, particularly in reducing oxidative stress and inflammation [27]. While no specific guidelines exist for IMIDs prevention, emerging research suggests that maintaining adequate serum selenium levels may offer protective effects against these conditions.

Using NHANES data, this study aims to explore the effects of selenium, vitamin D, and the zinc-to-copper ratio, and their recommended therapeutic ranges, on the prevalence of asthma, psoriasis, psoriatic/rheumatoid arthritis, and celiac disease. Our objective is to elucidate the potential roles of these micronutrients by examining their relationship with IMIDs outcomes. Specifically, we investigated whether higher nutrient levels are associated with lower prevalence of certain IMIDs. Confirming these relationships could improve understanding of nutritional epidemiology of IMIDs and inform future prospective and interventional studies.

This study offers two primary contributions: first, it enables head-to-head comparison of the relative strength of associations across three key immune-related micronutrients in the same population; second, it provides population-level dose–response evidence that complements existing mechanistic research. Our findings may inform the design of future nutritional intervention studies, and generate testable hypotheses regarding the role of micronutrient status in immune-mediated inflammatory conditions.

2. Methods

2.1. Study Population

The study used data from the 2013–2014 cycle of the National Health and Nutrition Examination Survey (NHANES), a nationally representative cross-sectional survey conducted by the National Center for Health Statistics (NCHS) of the U.S. Centers for Disease Control and Prevention (CDC). NHANES employs a multistage, stratified probability sampling design to recruit participants representative of the civilian non-institutionalized population of the United States. The survey integrates three core components: household interviews, standardized physical examinations, and laboratory biomarker testing, providing comprehensive data on demographic characteristics, lifestyle factors, disease status, and nutritional biomarkers. The NHANES survey protocol was reviewed and approved by the NCHS Research Ethics Review Board, and all participants provided written informed consent [28]. The 2013–2014 cycle was selected for the present analysis because it contains complete laboratory measurements of all target micronutrients (selenium, copper, zinc, and vitamin D) and standardized questionnaire data on immune-mediated inflammatory conditions, making it the most suitable publicly available NHANES cycle for this research question. A total of 1493 participants with complete serum micronutrient and IMIDs data were included. Individuals with missing data, minors, and pregnant participants were excluded. Demographic information, laboratory test results, and IMIDs status were collected and analyzed for this cohort (Figure 1).

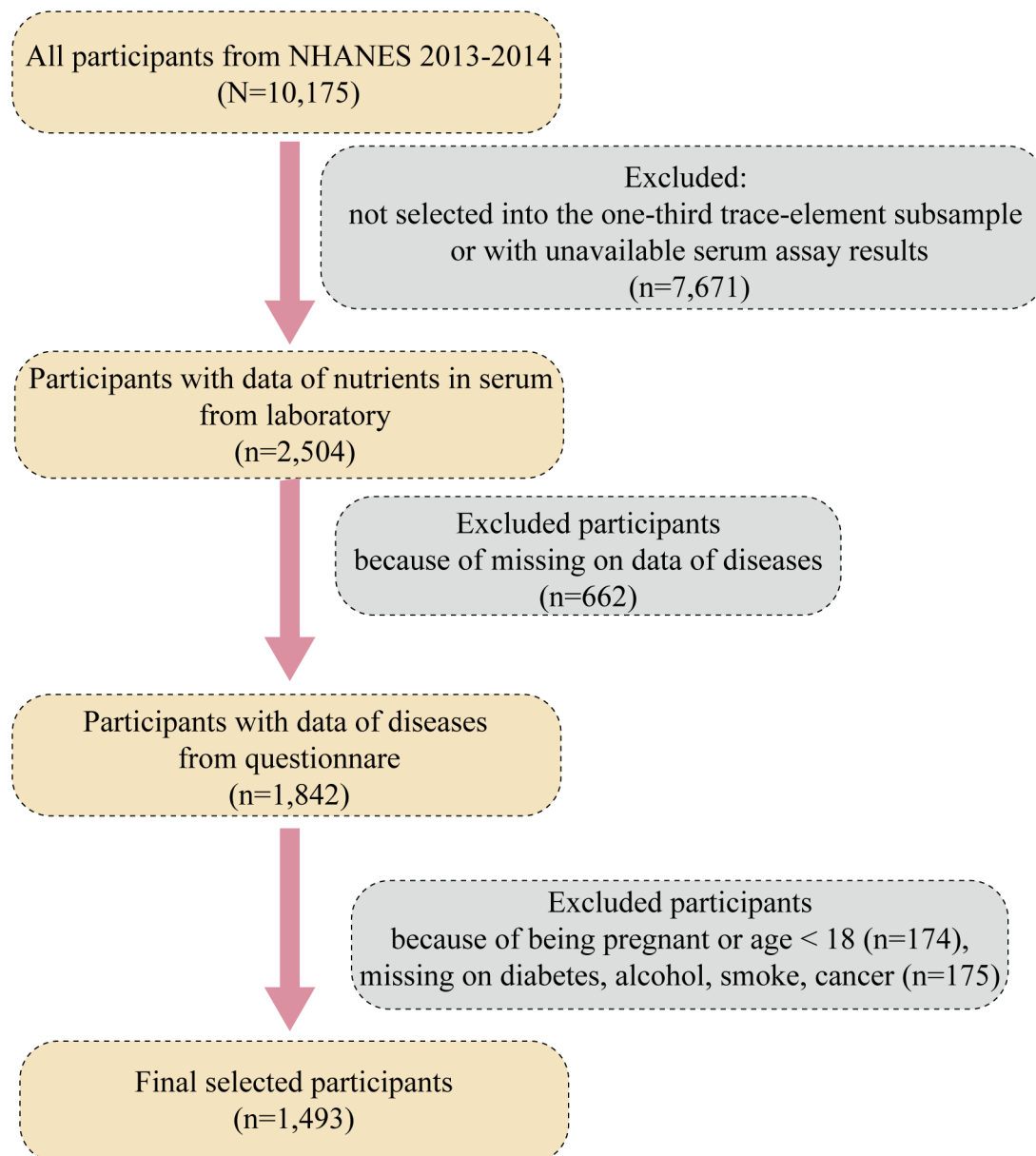


Figure 1. Flowchart of participant selection from NHANES 2013–2014.

2.2. Essential Micronutrients in Serum

Serum levels were determined through real-time detection methods, making them a more reliable indicator of potential regulatory roles. Serum specimens for trace-element measurements were stored at -70°C to preserve specimen integrity, while specimens for vitamin-D assays were stored at -30°C , consistent with NHANES laboratory protocols. Inductively Coupled Plasma Dynamic Reaction Cell Mass Spectrometry (ICP-DRC-MS) was used to measure serum copper, selenium, and zinc levels. The serum samples were diluted in a 1:1:28 ratio with water, using gallium (Ga) as an internal standard to ensure measurement accuracy. Ultra-High-Performance Liquid Chromatography-Tandem Mass Spectrometry (UHPLC-MS/MS) was employed to quantify 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ concentrations. Serum total 25-hydroxyvitamin D (25[OH]D; NHANES variable name: VID_H) represents the sum of 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ and excludes the C3-epimer, following NHANES laboratory documentation. All detection processes were conducted by trained professionals under stringent quality control protocols.

Serum selenium levels were analyzed and stratified into quartiles to account for geographic variations in threshold [29]. As copper and zinc can influence each other's absorption, the zinc-to-copper (Zn/Cu) ratio was used as an alternative marker, although a standardized reference range for this ratio has yet to be established [30,31]. The Zn/Cu ratio was analyzed as a continuous variable. Vitamin D levels were classified as severe deficient if they fell below 30 nmol/L, consistent with established guidelines [32].

2.3. Immune-Mediated Inflammatory Diseases Survey

IMIDs include RA, the spondyloarthritis disease spectrum, connective tissue disorders, cutaneous inflammatory conditions, inflammatory bowel disease, asthma and autoimmune neurological diseases such as multiple sclerosis [33]. Data on IMIDs were obtained from the Medical Conditions section of the NHANES survey, based on the “Medical Conditions” questionnaire from the National Health Interview Survey (NHIS). The 2013–2014 cycle database includes conditions such as psoriasis, asthma, celiac disease, and rheumatoid/psoriatic arthritis, representative of IMIDs. Participants diagnosed with any of these conditions were classified as having an IMID.

2.4. Covariables

Confounders were prespecified a priori based on published epidemiological and immunological evidence. A directed acyclic graph (DAG) was constructed to formalize causal assumptions and identify potential back-door confounding paths for the association between serum selenium and prevalence of IMIDs (Figure 2) [34]. Covariates included immune-related data collected by NHANES, such as smoking status, alcohol consumption, diabetes, and cancer history. Smoking status was categorized as nonsmokers (fewer than 100 cigarettes in their lifetime) and smokers, while alcohol consumption was classified as non-drinkers (fewer than 12 alcoholic beverages per year) and drinkers. Diabetes status was defined as nondiabetics (no diabetes diagnosis, glycosylated hemoglobin $< 6.5\%$, and fasting blood glucose $< 126\text{ mg/dL}$) or diabetics. Cancer history was categorized as ever diagnosed with cancer or not.

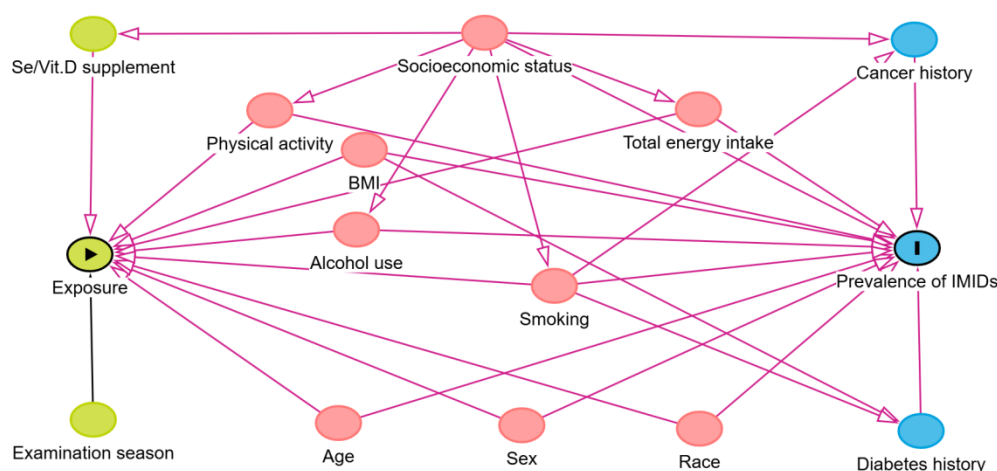


Figure 2. Directed acyclic graph (DAG) of hypothesized causal pathways between serum selenium and the prevalence of IMIDs. Arrows denote pre-specified causal assumptions based on published evidence. Serum selenium is the exposure and the prevalence of IMIDs is the outcome. The diagram highlights potential confounders including demographic, socioeconomic and lifestyle factors. Diabetes and cancer could be confounders or conditions associated with IMIDs, although their temporal relationships with IMIDs cannot be determined using

cross-sectional NHANES data. The core exposure variable **Exposure** consists of three serum biomarkers: serum selenium (Se) level, serum vitamin D (Vit. D) level, and serum zinc-to-copper ratio (Zn/Cu).

Given the cross-sectional nature of the NHANES dataset, temporal ordering cannot be definitively established for diabetes and cancer history. These comorbidities may operate as confounders, whereby shared prior lifestyle factors influence both micronutrient status and the prevalence of IMIDs. However, reverse causality is also plausible: pre-existing IMID and chronic inflammatory states may lead to subsequent diabetes or cancer. To address this ambiguity, our primary fully-adjusted model retained diabetes and cancer history as covariates. Some variables are not applicable to this NHANES cycle and therefore cannot be included in the regression model, despite being identified as potential confounding factors in our DAG.

2.5. Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation (Mean $\pm$ SD), and categorical variables as number of cases (n) and percentages (%). A weighted analysis was performed using the 2-year Subsample A weight (WTS2YR), masked variance pseudo-PSU (SDMVPSU), and masked variance pseudo-stratum (SDMVSTRA) from NHANES. Weighted logistic regression was used to examine the relationship between serum micronutrient levels and the prevalence of IMIDs. Model 1 performed no covariate adjustment at all; Model 2 partially adjusted exploratory model, adjusted only for demographic covariates (age, sex, race); Model 3 incorporated all potentially relevant covariates: age, sex, race, smoking, alcohol consumption, diabetes, and cancer status. Restricted Cubic Spline (RCS) regression with 4 knots (5th, 35th, 65th, and 95th percentiles) was used to explore potential non-linear relationships between serum levels and the prevalence of IMIDs. Serum nutrient levels were also stratified by deficiency status or quartiles for further analysis. Probability of IMIDs occurrence at various concentrations of each essential micronutrient was calculated using the weighted data, provided they showed statistical significance. All statistical analyses were conducted using R software (Version 4.3.2) and RStudio (2023.06.2 Build 561), and visualizations were created with Adobe Illustrator (Version 2020, San Jose, CA, USA).

3. Results

3.1. Population Characteristics

A total of 1493 participants were included in this study (Figure 1). The unweighted characteristics of the study population are summarized in Table 1, with additional weighted information presented in Table 2. Of these, 323 participants were diagnosed with IMIDs, 42.72% of whom were male. Among the 1170 participants without IMIDs, 47.95% were males. The age distribution was similar between those with and without IMIDs. Regarding race, 55.42% of participants with IMIDs identified as Non-Hispanic White, and 44.58% as belonging to other racial groups. Conversely, among participants without IMIDs, 42.74% identified as Non-Hispanic White, and 57.26% as belonging to other racial groups.

Table 1. Characteristics of the study population.

Characteristics	With IMIDs (n = 323)	Without IMIDs (n = 1170)	Total (n = 1493)	p-Value
Sex n (%)				0.0036
Male	138 (42.72)	561 (47.95)	699 (46.82)	
Female	185 (57.28)	609 (52.05)	794 (53.18)	
Age n (%)				0.3802
18–39 years	123 (38.08)	418 (35.73)	541 (36.24)	
40–59 years	99 (30.65)	407 (34.79)	506 (33.89)	
60–80 years	101 (31.27)	345 (29.49)	446 (29.87)	
Race n (%)				<0.0001
Non-Hispanic White	179 (55.42)	500 (42.74)	679 (45.48)	
Other	144 (44.58)	670 (57.26)	814 (54.52)	
Diabetes n (%)				0.0885
Yes	50 (15.48)	175 (14.96)	225 (15.07)	
No	273 (84.52)	995 (85.04)	1268 (84.93)	
Cancer n (%)				0.3135
Yes	35 (10.84)	103 (8.80)	138 (9.24)	
No	288 (89.16)	1067 (91.20)	1355 (90.76)	
Alcohol n (%)				0.2327
Yes	246 (76.16)	850 (72.65)	1096 (73.41)	
No	77 (23.84)	320 (27.35)	397 (26.59)	
Smoke n (%)				0.0053
Yes	162 (50.15)	483 (41.28)	645 (43.20)	
No	161 (49.85)	687 (58.72)	848 (56.80)	

Table 2. Characteristics of the weighted study population.

Characteristics	With IMIDs (n = 43,239,490)	Without IMIDs (n = 149,581,155)	Total (n = 192,820,645)
Sex n (%)			
Male	18,888,243 (43.68%)	78,418,939 (52.43%)	97,307,182 (50.47%)
Female	24,351,247 (56.32%)	71,162,216 (47.57%)	95,513,463 (49.53%)
Age n (%)			
18–39 years	17,090,876 (39.53%)	53,074,369 (35.48%)	70,165,245 (36.39%)
40–59 years	13,385,757 (30.96%)	58,375,226 (39.03%)	71,760,983 (37.22%)
60–80 years	12,762,857 (29.52%)	38,131,560 (25.49%)	50,894,417 (26.39%)
Race n (%)			
Non-Hispanic White	31,801,826 (73.55%)	98,485,004 (65.84%)	130,286,830 (67.57%)
Other	11,437,663 (26.45%)	51,096,151 (34.16%)	62,533,814 (32.43%)
Diabetes n (%)			
Yes	5,046,312 (11.67%)	17,612,733 (11.77%)	22,659,045 (11.75%)
No	38,193,178 (88.33%)	131,968,422 (88.23%)	170,161,600 (88.25%)
Cancer n (%)			
Yes	5,077,300 (11.74%)	15,507,813 (10.37%)	20,585,113 (10.68%)
No	38,162,190 (88.26%)	134,073,342 (89.63%)	172,235,532 (89.32%)
Alcohol n (%)			
Yes	34,715,464 (80.29%)	117,647,294 (78.65%)	152,362,758 (79.02%)
No	8,524,026 (19.71%)	31,933,861 (21.35%)	40,457,887 (20.98%)
Smoke n (%)			
Yes	21,994,595 (50.87%)	61,877,531 (41.37%)	83,872,126 (43.50%)
No	21,244,895 (49.13%)	87,703,624 (58.63%)	108,948,519 (56.50%)

Among the participants with IMIDs, 15.48% had also been diagnosed with diabetes, compared to 14.96% of those without IMIDs. The prevalence of cancer was slightly higher in participants with IMIDs (10.84%) than in those without (8.80%). In terms of alcohol consumption, 76.16% of patients reported consuming alcohol, compared to 72.65% of participants without the composite outcome. Smoking was more common among participants with IMIDs, with 50.15% identified as smokers, compared to 41.28% of participants without IMIDs.

3.2. The Association between Micronutrients with the Prevalence of IMIDs

First, we performed Spearman correlation analysis to assess pairwise interrelationships among serum selenium, total 25-hydroxyvitamin D, and the zinc-to-copper ratio. All pairwise correlation coefficients were weak ($|r| < 0.2$). Selenium exhibited weak positive correlations with vitamin D ($r = 0.065$, $p = 0.012$) and the zinc-to-copper ratio ($r = 0.175$, $p < 0.001$), whereas no statistically significant correlation was observed between vitamin D and the zinc-to-copper ratio ($r = 0.025$, $p = 0.329$). The low magnitude of pairwise correlations supports the simultaneous inclusion of these three biomarkers in multivariable regression models. Pairwise correlation coefficients and corresponding p -values are provided in Table 3. The association between Se, vitamin D, and the Zn/Cu ratio with the prevalence of IMIDs were analyzed using weighted logistic regression. In the covariate unadjusted model, serum selenium was significantly inversely associated with the prevalence of IMIDs (OR: 0.561, 95% CI: 0.361–0.873). However, neither vitamin D (OR: 1.003, 95% CI: 0.996–1.010) nor the Zn/Cu ratio (OR: 0.761, 95% CI: 0.298–1.948) showed significant associations (Figure 3A).

Table 3. Pairwise Spearman correlation coefficients among serum selenium, total vitamin D, and zinc-to-copper ratio.

Variable	Serum Se r (p)	Serum Vit. D r (p)	Serum Zn/Cu Ratio r (p)
Serum Se	—	0.065 ($p = 0.012$)	0.175 ($p < 0.001$)
Serum Vit. D	0.065 ($p = 0.012$)	—	0.025 ($p = 0.329$)
Serum Zn/Cu ratio	0.175 ($p < 0.001$)	0.025 ($p = 0.329$)	—

After adjusting for demographic covariates such as age, sex, race, Se remain significantly associated with a lower prevalence of IMIDs (OR: 0.627, 95% CI: 0.402–0.977). Vitamin D (OR: 1.000, 95% CI: 0.992–1.009) and the Zn/Cu ratio (OR: 0.925, 95% CI: 0.335–2.554) continued to show no significant association (Figure 3B). Furthermore, after adjustment for all covariates, serum Se, vitamin D, and Zn/Cu ratio no longer exhibited a significant inverse association with the prevalence of IMIDs (Figure 3C). RCS analysis demonstrated a linear relationship between serum Se levels and the prevalence of IMIDs in both the unadjusted model (p -value for nonlinear = 0.546) (Figure 4A) and the adjusted model (p -value for nonlinear = 0.434) (Figure 4B). Overall, selenium showed an inverse association with the prevalence of IMIDs in the model without any covariate adjustment.

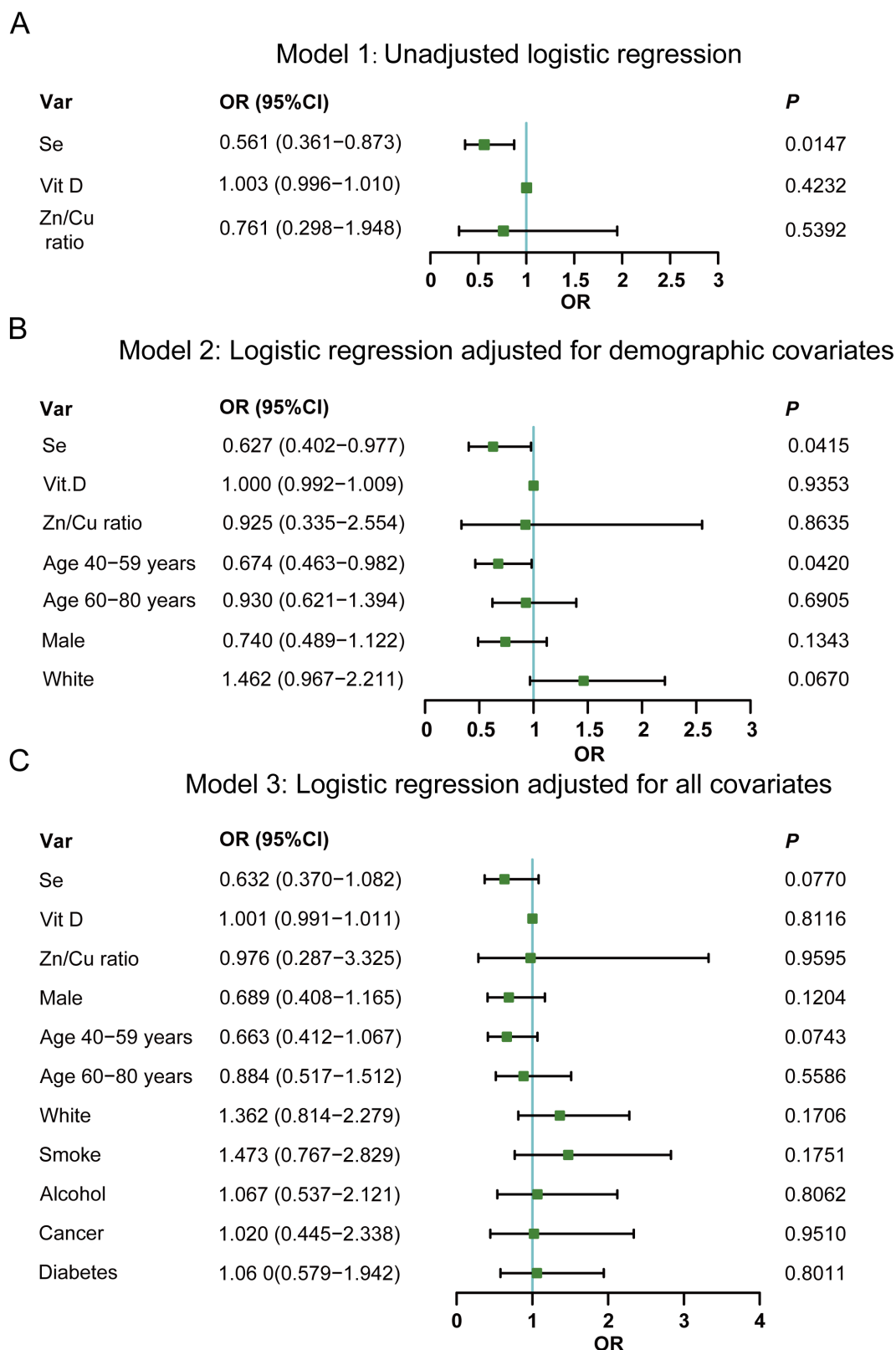


Figure 3. Odds ratios for the association between essential micronutrients and the prevalence of IMIDs estimated using weighted logistic regression models. **(A)** Unadjusted model. **(B)** Adjusted model using age, sex, race. **(C)** Adjusted model using sex, age, race, smoking status, alcohol consumption, diabetes, and cancer history. Each circle represents the odds ratio (OR), and horizontal lines represent 95% confidence intervals. ORs were estimated per 1 $\mu\text{mol/L}$ increment in serum selenium, per 1 nmol/L increment in total 25(OH)D, and per one-unit increment in Zn/Cu ratio, respectively. These exposure increments differ across biomarkers; therefore, effect sizes cannot be directly compared visually across rows. IMIDs, immune-mediated inflammatory diseases; OR, odds ratio.

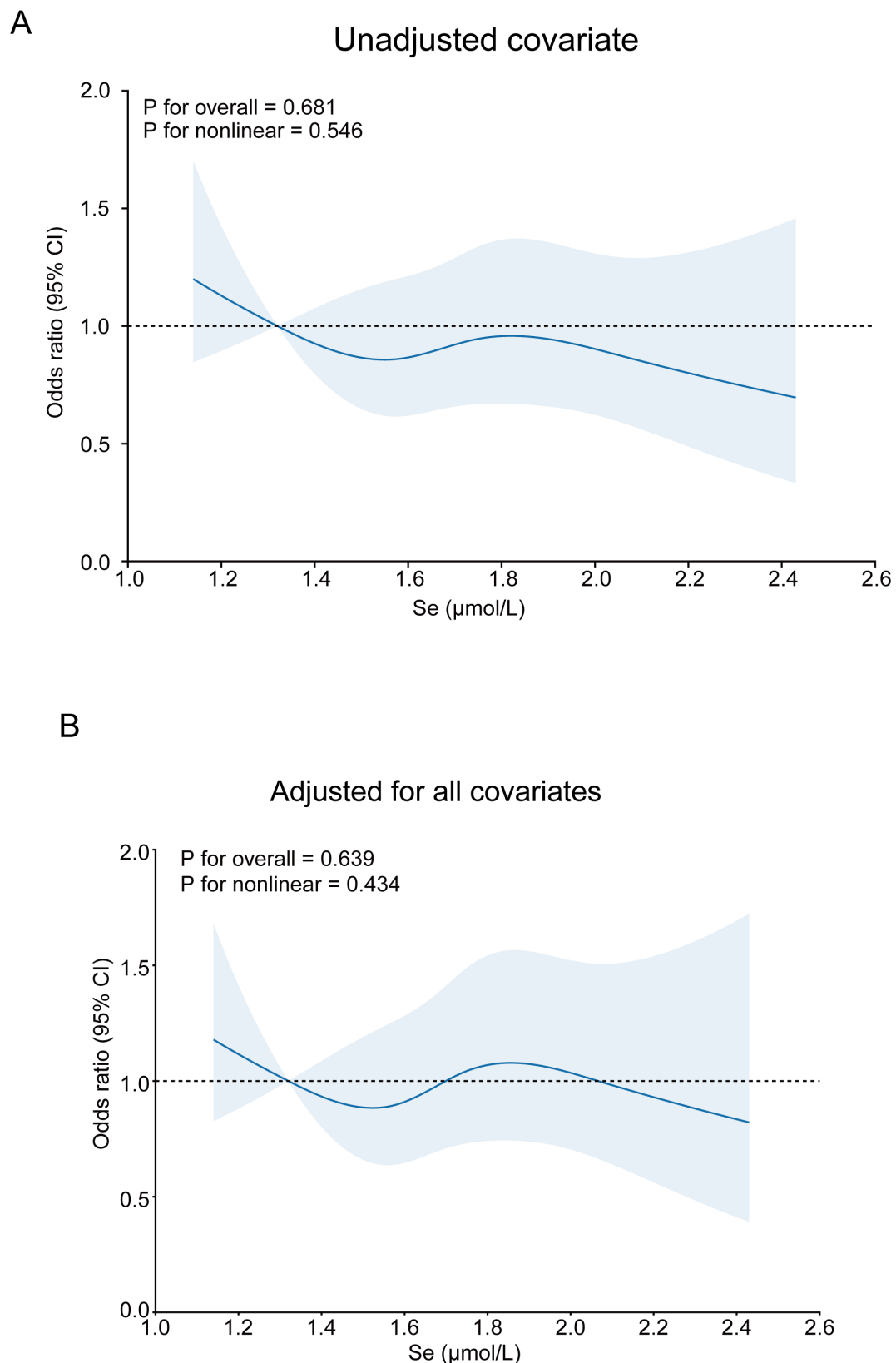


Figure 4. The RCS analysis of the association between Se levels and the prevalence of IMIDs. **(A)** Unadjusted model. **(B)** Adjusted model using sex, age, race, smoking status, alcohol consumption, diabetes, and cancer history.

3.3. Serum Concentration Strata in Relation to the Prevalence of IMIDs

To identify serum concentration ranges of essential micronutrients corresponding to the lowest observed prevalence of IMIDs, serum vitamin D levels were categorized as deficiency (<30 nmol/L) or sufficiency (≥ 30 nmol/L). Serum Se levels were stratified into quartiles, and the composition of participants at each level is presented in Table 4, with additional weighted data in Table 5. Weighted logistic regression analysis revealed that

Serum selenium concentrations of 1.51–1.65 $\mu\text{mol/L}$ were associated with the lowest observed prevalence of IMIDs, and the association was statistically significant (OR: 0.632, 95% CI: 0.438–0.913) (Figure 5A). Notably, descriptive analysis showed that the crude proportion of participants with selenium levels $> 1.8 \mu\text{mol/L}$ was slightly higher among participants with IMIDs (27.55%) than among those without IMIDs (24.53%). However, this minor difference in unadjusted proportions should not be interpreted as evidence of an association between higher selenium concentrations and IMIDs. It is primarily driven by the uneven distribution of confounding factors (including age, race, and smoking status) across selenium strata. In all regression models, the highest selenium quartile consistently had an odds ratio below 1.0 (ranging from 0.7 to 0.8) compared with the lowest quartile, confirming that higher selenium levels were not associated with higher prevalence of IMIDs after statistical adjustment for confounders. After adjusting for demographic covariates, Se levels in the 1.51–1.65 $\mu\text{mol/L}$ range (OR: 0.659, 95% CI: 0.447–0.971) continued to demonstrate the same significant association (Figure 5B). Consistent with the above results, after adjusting for all covariates, Se still exhibited an inverse association with the prevalence of IMIDs, yet the association was no longer statistically significant (Figure 5C). Notably, sufficient serum vitamin D status was inversely associated with the prevalence of IMIDs (Figure 6). Sensitivity analysis was performed by excluding diabetes and cancer history from the fully-adjusted model to assess whether the findings were sensitive to adjustment for these health conditions, given the cross-sectional nature of the study. The effect estimates for serum selenium (both continuous and quartile-based analyses) were nearly identical between the primary fully-adjusted model and the sensitivity model. For continuous serum selenium (per 1 $\mu\text{mol/L}$ increment), the OR was 0.632 (95% CI 0.370–1.082) in the primary model and 0.635 (95% CI 0.389–1.036) in the sensitivity model. Point estimates and confidence intervals for selenium quartiles also remained consistent across models. Full results of the sensitivity analysis are presented in Table 6, indicating that our main findings were robust to the exclusion of diabetes and cancer history. We further conducted exploratory disease-specific weighted logistic regression analyses to examine the associations of serum selenium quartiles with the prevalence of specific IMIDs, including asthma, psoriasis, and autoimmune arthritis. Celiac disease was not analyzed separately due to an extremely small number of cases (<20), which would result in insufficient statistical precision and unreliable estimates. As shown in Table 7, no statistically significant associations were observed between serum selenium quartiles and the prevalence of any specific IMIDs after adjustment for sex, race, and smoking status. For asthma, the second quartile of selenium showed a non-significant inverse trend (OR: 0.648, 95% CI: 0.408–1.031; $p = 0.0636$) compared with the lowest quartile. For psoriasis and autoimmune arthritis, no consistent dose–response trends were identified. The lack of significant subtype-specific findings may be largely attributed to the reduced sample size and statistical power in stratified analyses.

Table 4. Distribution of essential micronutrients in the study population.

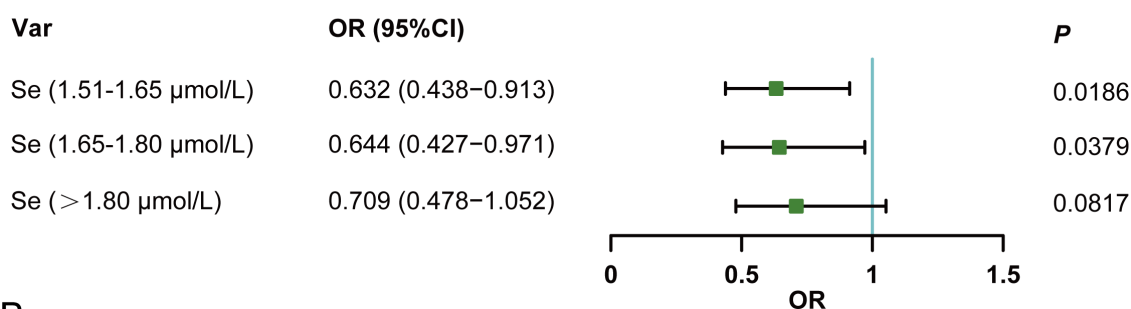
Essential Micronutrients	With IMIDs (n = 323)	Without IMIDs (n = 1170)	Total (n = 1493)
Serum Se concentration n (%)			
<1.51	86 (26.63)	275 (23.50)	361 (24.18)
1.51–1.65	78 (24.15)	322 (27.52)	400 (26.79)
1.66–1.80	70 (21.67)	286 (24.44)	356 (23.84)
>1.80	89 (27.55)	287 (24.53)	376 (25.18)
Serum Vit. D concentration n (%)			
<30	27 (8.36)	86 (7.35)	113 (7.57)
≥ 30	296 (91.64)	1084 (92.65)	1380 (92.43)
Serum Zn/Cu ratio (Mean $\pm$ SD)	0.70 $\pm$ 0.21	0.71 $\pm$ 0.22	0.71 $\pm$ 0.22

Table 5. Distribution of essential micronutrients in the weighted study population.

Essential Micronutrients	With IMIDs (n = 43,239,490)	Without IMIDs (n = 149,581,155)	Total (n = 192,820,645)
Serum Se concentration n (%)			
<1.51	13,568,975 (31.38%)	34,676,325 (23.18%)	48,245,300 (25.02%)
1.51–1.65	10,530,198 (24.35%)	42,576,447 (28.46%)	53,106,645 (27.54%)
1.66–1.80	9,236,303 (21.36%)	36,633,042 (24.49%)	45,869,345 (23.79%)
>1.80	9,904,014 (22.91%)	35,695,341 (23.86%)	45,599,355 (23.65%)
Serum Vit. D concentration n (%)			
<30	3,006,230 (6.95%)	6,753,769 (4.52%)	9,759,999 (5.06%)
≥ 30	40,233,260 (93.05%)	142,827,386 (95.48%)	183,060,646 (94.94%)
Serum Zn/Cu ratio			
Mean $\pm$ SD	0.72 $\pm$ 0.23	0.71 $\pm$ 0.21	0.72 $\pm$ 0.23

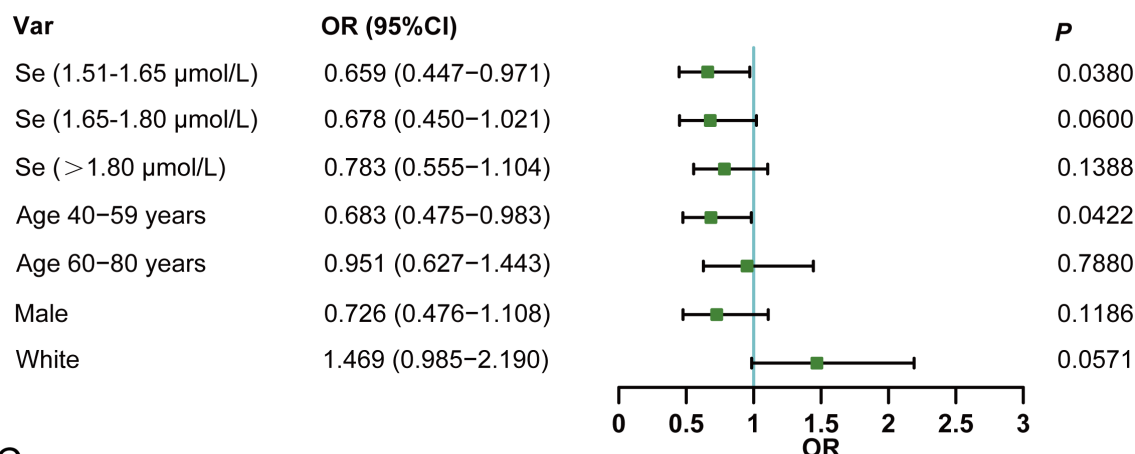
A

Model 1: Unadjusted logistic regression



B

Model 2: Logistic regression adjusted for demographic covariates



C

Model 3: Logistic regression adjusted for all covariates

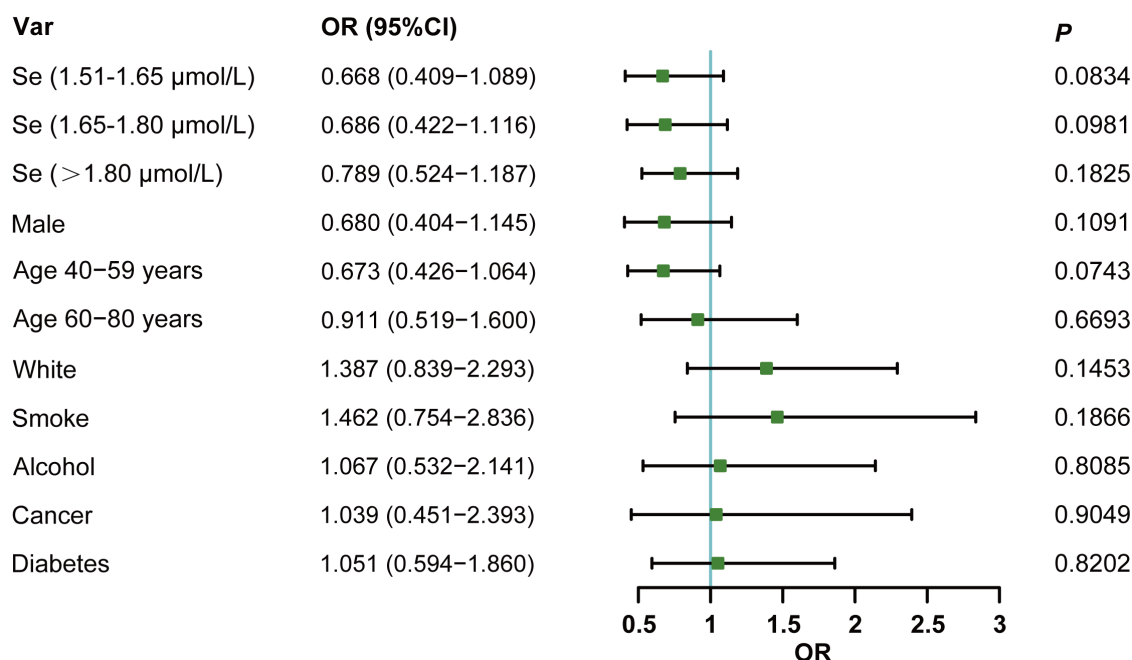


Figure 5. Odds ratios for the association between serum Se quartiles and the prevalence of IMIDs estimated using weighted logistic regression models. (A) Unadjusted model. (B) Adjusted model using age, sex, race. (C) Adjusted model using sex, age, race, smoking status, alcohol consumption, diabetes, and cancer history. ORs are relative to the lowest selenium quartile (<1.51 $\mu\text{mol/L}$, reference group).

Table 6. Odds ratios (95% confidence intervals) for the association between serum selenium and the prevalence of IMIDs in the primary fully-adjusted model and sensitivity model excluding diabetes and cancer history.

Variable	Primary Fully-Adjusted Model OR (95% CI)	Sensitivity Model (Excluding Diabetes and Cancer) OR (95% CI)
Continuous Se (per 1 µmol/L)	0.632 (0.370–1.082)	0.635 (0.389–1.036)
Se quartile 1.51–1.65 µmol/L	0.668 (0.409–1.089)	0.670 (0.437–1.026)
Se quartile 1.66–1.80 µmol/L	0.686 (0.422–1.116)	0.686 (0.448–1.049)
Se quartile >1.80 µmol/L	0.789 (0.524–1.187)	0.789 (0.543–1.146)

Table 7. Disease-specific weighted logistic regression analyses of serum selenium quartiles in relation to the prevalence of specific IMIDs.

Serum Selenium Quartiles (µmol/L)	Asthma (n = 241) OR (95% CI)	Psoriasis (n = 41) OR (95% CI)	Autoimmune Arthritis (n = 69) OR (95% CI)
<1.51 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
1.51–1.65	0.648 (0.408–1.031)	0.519 (0.206–1.305)	2.115 (0.544–8.223)
1.66–1.80	0.659 (0.389–1.116)	0.732 (0.29–1.846)	2.277 (0.743–6.979)
>1.80	0.843 (0.522–1.362)	0.487 (0.097–2.45)	1.971 (0.615–6.313)

Model adjusted for sex, race, and smoking status. Disease-specific subgroup analyses were exploratory in nature. The statistical power was limited by the small case count of specific IMIDs, and the results should be interpreted with caution.

Adjusted for significant covariates

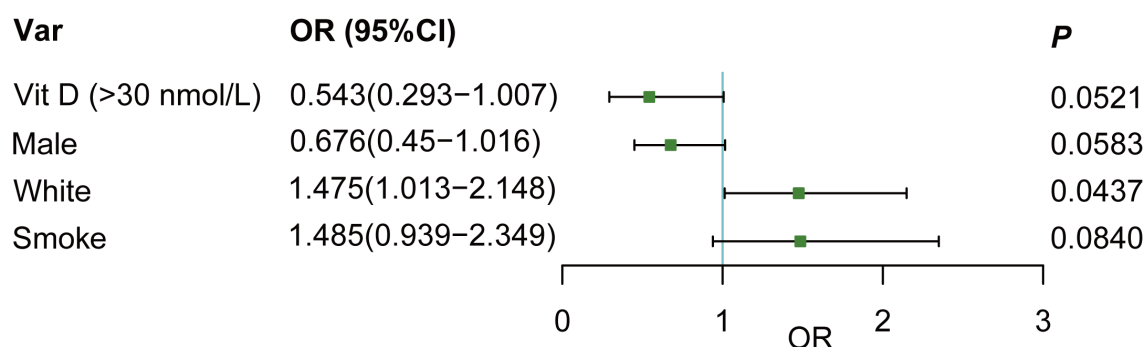


Figure 6. Odds ratios for the association between serum 25-hydroxyvitamin D (sufficient vs. insufficient) and the prevalence of IMIDs estimated using weighted logistic regression models. Model adjusted for sex, race, and smoking status.

3.4. Probability of Disease Occurrence in Stratified Analysis

Given the observed inverse association between serum selenium and IMIDs, the prevalence of IMIDs was further estimated based on Se concentration quartiles. In the analysis without covariates, the probability of IMIDs was 27.89% for serum Se concentrations below 1.51 µmol/L, 19.83% for concentrations between 1.51–1.65 µmol/L, 20.14% for concentrations between 1.66–1.80 µmol/L, and 21.72% for concentrations exceeding 1.80 µmol/L (Figure 7A). When demographic covariates were included, the probabilities were 26.80%, 18.85%, 18.88%, and 20.59%, respectively, for the same quartiles (Figure 7B). Finally, after all covariates were incorporated, the corresponding probabilities for the four quartiles were 26.83%, 18.97%, 19.06%, and 20.72%, respectively (Figure 7C).

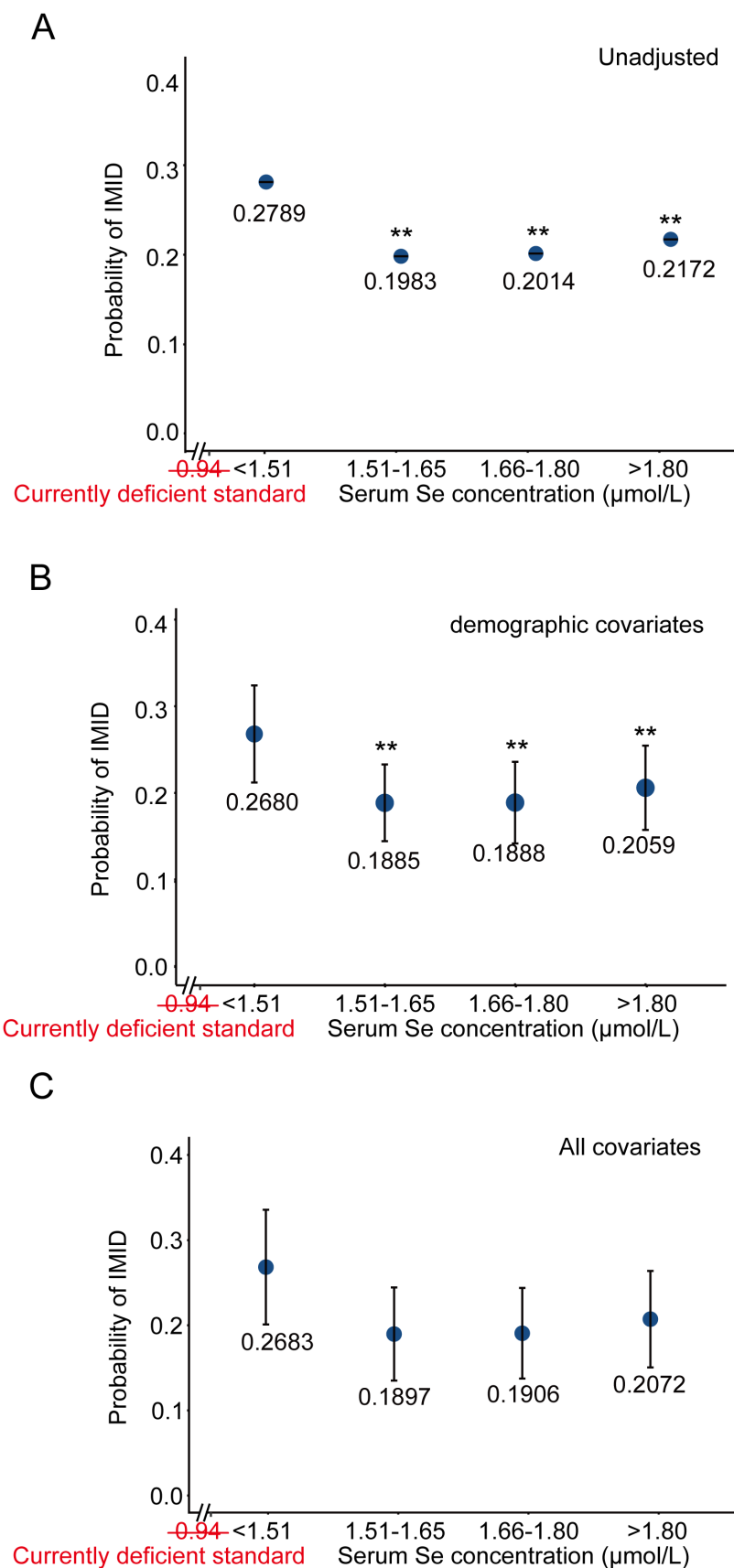


Figure 7. The model-based predicted prevalence of IMIDs in each Se quartiles. **(A)** Unadjusted model. **(B)** Adjusted model using sex, age, race. **(C)** Adjusted model using sex, age, race, smoking status, alcohol consumption, diabetes, and cancer history. Vertical bars denote standard deviation (SD). * $p < 0.05$, ** $p < 0.01$.

While higher selenium levels were associated with lower odds of IMIDs, descriptive prevalence was slightly elevated in the highest selenium quartile relative to the second quartile with the lowest observed prevalence. However, restricted cubic spline analyses did not provide statistical evidence for a non-linear dose-response relationship.

4. Discussion

IMIDs arise when the immune system malfunctions and mistakenly attacks the body's own tissues and organs [35]. While current treatments including recently emerged antibody drugs are clinically effective, they often come with substantial financial costs and potential side effects [36–38]. Given the strong connection between nutrition and immune function, identifying nutritional correlates of IMIDs that may inform future prevention and management strategies is crucial.

In this study, we employed weighted binary logistic regression to explore the association between serum levels of essential micronutrients and the prevalence of IMIDs. Additionally, we identified data-derived nutrient concentration ranges associated with the lowest observed weighted prevalence of these conditions within this dataset, generating population-level observational evidence to inform future research on nutritional correlates of IMIDs. Our results indicate that elevated serum Se levels are associated with a lower prevalence of IMIDs, with the most pronounced inverse association observed at serum selenium concentrations of 1.51–1.65 $\mu\text{mol/L}$. Of note, the significant inverse association persisted after adjusting for demographic covariates with baseline intergroup differences, whereas further adjustment for all relevant covariates slightly attenuated the statistical significance. Such fluctuations suggest that multi-dimensional demographic, lifestyle, and clinical characteristics jointly influence the correlation between serum Se status and IMIDs. Nevertheless, the overall inverse trend remained consistent across different analytical models, and the identified optimal Se concentration range still offers important observational evidence for understanding the nutritional correlates of IMIDs in general populations.

Despite this, other essential micronutrients may also be associated with IMIDs. Recent studies have shown that vitamin D deficiency is common in individuals with IMIDs conditions such as systemic lupus erythematosus and RA [39–41]. Prospective studies indicate that vitamin D supplementation may help reduce the risk of several IMIDs [42]. In animal models, vitamin D can ameliorate systemic lupus erythematosus by up-regulating miR-126a-5p to target GSK-3 β [43], and it has also demonstrated improvements in conditions like autoimmune encephalomyelitis and autoimmune thyroiditis in mice [44,45].

Similarly, redox-relevant trace elements such as zinc and copper are essential for numerous biological functions. Metal ions can compete mutually for absorption [30], which is why the Zn/Cu ratio is often used to assess nutritional status. Evidence suggests that serum zinc levels are reduced, while copper levels are elevated in patients with RA [46].

Selenium, well-known for its anti-inflammatory, antioxidant, and thyroid-regulating properties, plays a critical role in maintaining human health. Low selenium status has been associated with increased mortality and weakened immunity function, while higher selenium levels correlate with a reduced risk of cancer and enhanced resistance to viral infections [29]. In our study, selenium was the only micronutrient showing a significant inverse association with the prevalence of IMIDs in unadjusted and partially adjusted models. These findings highlight that lower serum selenium status was associated with higher odds of prevalent IMIDs in this study population. It is important to note that selenium status varies considerably across geographic regions, with differing thresholds required to define deficiency (Table 8) [47–53]. This underscores the need for updated, region-specific criteria for assessing selenium sufficiency. Our quantile analysis identified serum selenium concentrations between 1.51 and 1.65 $\mu\text{mol/L}$ as the interval with the lowest observed prevalence corresponding to the lowest observed prevalence of IMIDs. Based on our analysis, this range corresponds to the lowest prevalence of IMIDs conditions, reinforcing the potential relevance of adequate selenium status in immune-mediated inflammatory conditions.

Selenium exerts its biological effects in both organic and inorganic forms [54], influencing multiple systems, including the central nervous system, male reproductive system, endocrine system, muscle function, cardiovascular system, and immune system [55]. Previous studies have found a positive correlation between serum selenium levels and selenoproteins, which serve as biomarkers for autoimmune thyroiditis [14] and RA [56]. Animal studies have further demonstrated that selenium supplementation can alleviate symptoms of systemic lupus erythematosus and extend lifespan by inhibiting the activation, differentiation, and maturation of B cells and macrophages [57]. However, excessive selenium intake can be toxic. For example, a clinical trial reported an increased risk of all-cause mortality with high selenium intake (300 $\mu\text{g/d}$) [58]. Our findings align with these observations, emphasizing that while higher serum selenium status was observationally associated with lower prevalence of IMIDs, excessive intake could be detrimental. This underscores the importance of tailored selenium supplementation, particularly in regions where selenium deficiency is prevalent, such as northeast to south-central

China, Central Serbia, Poland, and Ethiopia [59–62]. In such areas, dietary intake should be augmented through selenium-containing supplements or selenium-rich foods, including sea salts, selenium-enriched eggs, giblets, selenium-enriched yeast, bread, mushrooms, garlic, asparagus, and kohlrabi [63], to support optimal immune function. Conversely, in regions with abundant selenium, such as Wyoming, North and South Dakota in the USA, Enshi in China, and parts of Ireland, Colombia and Venezuela [60], it is essential to avoid excessive intake to prevent toxicity and associated adverse effects.

Table 8. Selenium levels (dietary intake and blood) guidelines of different organization.

Parameters	Institute	Basis	Reference
Dietary selenium intake (µg/day)			
50–200 for adults	WHO	Estimated Safe and Adequate Daily Dietary Intake proposed in 1980	[47]
70 for men 65 for women	Australian dietary guidelines	Recommendation of respective institutions in Australia and New Zealand	[48]
45–55 for adults 20–30 for children 60 for pregnancy 70 for lactation	Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds	Animal models, intervention studies and observational studies	[49]
70 for men 60 for women 10–15 for infants 75 for lactation	Nutrition societies of Germany, Austria and Switzerland	The saturation of selenoprotein P in plasma	[50]
Selenium in blood (µmol/L)			
Healthy range: 0.9–1.65	Eastbourne District General Hospital & Conquest Hospital	Ratified by Clinical Biochemistry Team	[51]
Deficiency: <0.94	Cantonal Hospital Aarau	Laboratory	[52]
Deficiency: <0.75	CHU de Grenoble	A European group of scientists	[53]

The strengths of this study include its representative population sample and the systematic evaluation of multiple redox-relevant essential micronutrients, as well as the exploration of serum concentration ranges associated with the lowest observed prevalence of IMIDs. However, it is important to acknowledge several limitations. First, as a cross-sectional study based on the NHANES database, our findings can only demonstrate observational associations and cannot establish causal relationships between micronutrient status and IMIDs. Further prospective cohort studies and mechanistic experiments are warranted to validate our findings. Second, the relatively modest sample size limits the statistical precision of effect estimates, particularly for disease-specific subgroup analyses. Celiac disease was not analyzed separately due to an extremely small case count (<20). For other subtypes including asthma, psoriasis, and autoimmune arthritis, the reduced number of cases further diminished the statistical power to detect potential subtype-specific associations. Accordingly, all disease-specific results presented in this study should be interpreted as exploratory and hypothesis-generating rather than conclusive evidence.

Third, some variables such as disease status and lifestyle factors were collected via self-report, which may introduce recall bias and misclassification to a certain extent. Fourth, we did not conduct dedicated analyses exploring pairwise correlations between IMIDs and other prevalent chronic conditions such as obesity, dyslipidaemia and ventilatory dysfunction. Finally, regional differences in dietary patterns, selenium nutritional status, and disease prevalence may limit the generalizability of our findings to populations outside the United States.

Moreover, we adopted a complete-case analysis by excluding participants with missing data, which might cause potential selection bias. Multiple statistical tests across different models and micronutrient analyses might inflate the risk of type I error, and the findings should be interpreted as exploratory. Furthermore, small sample sizes in certain disease subgroups might reduce statistical precision, even though NHANES survey weights were strictly applied in our analysis.

5. Conclusions

In summary, our study systematically evaluated the associations of three redox-relevant essential micronutrients with the prevalence of IMIDs in a nationally representative sample of US adults. Serum selenium showed a trend toward an inverse association with the prevalence of IMIDs: the association was statistically significant in the crude unadjusted model and in the model adjusted for demographic covariates, but was attenuated and no longer statistically significant in the fully adjusted model accounting for additional lifestyle and

comorbidity covariates. Serum selenium concentrations in the range of 1.51–1.65 $\mu\text{mol/L}$ corresponded to the lowest observed prevalence of IMIDs. No statistically significant associations were observed for vitamin D or the zinc-to-copper ratio in either crude or adjusted models.

These findings provide population-level observational clues for the potential link between selenium status and IMIDs, and generate testable hypotheses for subsequent research. Our results underscore the need for further large-scale prospective cohort studies and mechanistic investigations to clarify the role of selenium in immune function and the development of immune-mediated inflammatory conditions.

Author Contributions: The authors' responsibilities were as follows—S.T.: Data curation, formal analysis, visualization, writing—original draft, writing—review & editing; M.A.A.: Formal analysis, writing—original draft; B.W.: Data curation; X.Z.: Writing—review & editing; J.W.: Methodology, validation, supervision, writing—review & editing; J.Q.: Resources; Q.Z.: Conceptualization, supervision, project administration, resources, writing—review & editing. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: The NHANES survey protocol was reviewed and approved by the NCHS Research Ethics Review Board, and all survey participants provided written informed consent. This study is a secondary analysis of publicly released de-identified NHANES datasets. Since all personal identifiers were removed from the publicly available data, no further ethics approval or participant informed consent was needed for the current analysis.

Data Availability Statement: Data described in the article, code book are publicly and freely available without restriction at <https://www.cdc.gov/nchs/nhanes/index.htm>. Custom analytic code used in the present study is available from the corresponding author upon reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies: No AI tools were utilized for this paper.

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