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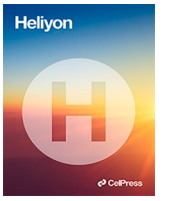

Review article

Selenium deficiency in inflammatory bowel disease: A comprehensive meta-analysis

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A R T I C L E I N F O

Keywords:
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Selenium
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A B S T R A C T

Background: Micronutrient deficiencies, particularly selenium, are common in Inflammatory Bowel Diseases and may influence disease progression and severity. Various studies have investigated blood selenium levels in patients with inflammatory bowel disease, but these studies have shown considerable heterogeneity and are generally limited by small sample sizes. Therefore, this study aims to clarify the selenium status in patients with inflammatory bowel disease compared to controls and to explore the potential of selenium supplementation as a therapeutic option.
Method: A comprehensive search of online databases from January 1980 to December 2023 was conducted, focusing on studies related to selenium levels in patients with inflammatory bowel disease. The relationship between blood selenium concentrations in inflammatory bowel disease patients and controls was pooled using a random-effects model.
Results: From the 1853 references screened, 20 studies were selected based on the inclusion criteria, involving 1792 inflammatory bowel disease patients (including both Crohn's disease and ulcerative colitis cases) and 1648 controls. The meta-analysis demonstrated that inflammatory bowel disease patients have significantly lower selenium levels compared to the control group. This trend was consistent across subgroups differentiated by study characteristics such as design, geographical location, selenium detection methods, types of samples analyzed, and age categories of participants, with particularly notable deficiencies observed in patients with Crohn's disease. The robustness of these findings was supported by sensitivity analysis, and tests for publication bias indicated no significant skewing of results.
Conclusion: The analysis confirms that inflammatory bowel disease patients, especially those with Crohn's disease, have significantly lower levels of selenium compared to controls, suggesting that that selenium supplementation may serve as a valuable adjunct to the therapeutic regimen for managing inflammatory bowel disease, particularly in patients identified with selenium insufficiency.

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1. Introduction

Inflammatory Bowel Diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic immune-mediated conditions characterized by a pattern of chronic relapsing and remitting inflammation within the gastrointestinal tract [1]. CD is known for its potential to affect any area of the gastrointestinal tract, presenting segmental, asymmetrical, and transmural inflammation. Conversely, UC is typically characterized by continuous inflammation that begins in the rectum and extends to more proximal segments of the colon [2,3]. The pathogenesis of IBD involves a multifaceted interplay between genetic susceptibility, environmental factors, and dysregulated immune responses [4]. In CD, an abnormal Th1 and Th17 cell-mediated immune response drives intestinal inflammation, with the IL-23/Th17 axis emerging as a critical pathway [5]. In contrast, UC involves both Th2 and Th17 cell-driven immune responses [6]. The imbalance between pro-inflammatory and anti-inflammatory cytokines, as well as the dysregulation of T cell subsets, particularly Th1, Th17, and regulatory T cells (Tregs), contributes to the chronic inflammation and tissue damage observed in IBD [7]. As a consequence of the chronic inflammatory state and alterations in intestinal absorption, micronutrient deficiencies are frequently observed in patients with IBD [8,9]. These deficiencies not only serve as indicators of complicated disease progression but also contribute to increased morbidity. Such nutritional inadequacies can exacerbate the severity of IBD and negatively impact the overall health and quality of life of affected individuals [10].

Selenium (Se), an essential trace element in humans, has gained recognition for its role in modulating inflammatory signaling pathways involved in the pathogenesis of IBD. The physiological functions of selenium are primarily mediated through its incorporation into selenoproteins, where it exists as the amino acid selenocysteine. These selenoproteins, numbering 25 in humans, play crucial roles in protecting against oxidative damage, regulating immune function, and inhibiting inflammatory responses [11]. Selenium supplementation can reduce intestinal inflammation by activating the Nrf2 and NF-κB signaling pathways [12] while selenium deficiency elevates the expression of pro-inflammatory cytokines, including COX-2, PTGE, TNF-α in gastrointestinal tissues [13]. Selenium supplementation also promotes the expression of tight junction proteins, such as ZO-1 and Occludin [14], which are essential for strengthening intestinal barrier function. Concurrently, selenium has been observed to inhibit oxidative stress and T-cell differentiation, thereby promoting the repair and reconstruction of the intestinal barrier [15–17]. These findings underscore the multifaceted role of selenium in gut health and its potential value in the prevention and treatment of intestinal diseases, particularly IBD.

The chronic inflammation in the gastrointestinal tract and dietary restrictions common in IBD often lead to nutrient deficiencies, including selenium [10]. Various studies have investigated blood selenium levels in IBD patients, but these studies show considerable heterogeneity and are generally limited by small sample sizes. Some studies have found that selenium deficiency is common in IBD patients [18–20], but others have found that there is no significant difference in blood selenium levels between IBD patients [21–23], including UC and CD, and controls. Therefore, we conducted a meta-analysis of the existing data to analyze the relationship between blood selenium concentrations in IBD patients and controls, to provide additional insights into the treatment and rehabilitation of IBD.

2. Materials and method

2.1. Search strategy

We conducted a comprehensive search of online databases for relevant studies published from January 1980 to December 2023. The databases included Pubmed, Web of Science, Embase and Scopus. Search terms used were: "selenium," "inflammatory bowel disease," "Crohn's disease," and "ulcerative colitis." These terms were combined using Boolean operators like 'AND' and 'OR' to refine the search results.

2.2. Inclusion and exclusion criteria

The articles were included if they met the following four criteria: (1) IBD patients were diagnosed based on a combination of clinical symptoms, endoscopic findings of mucosal inflammation and ulcerations, radiological evidence of intestinal inflammation, and histopathological features of chronic inflammation on biopsy specimens; (2) studies included case groups and control groups; (3) reported the number of cases and controls, mean and standard deviation (SD) or median and interquartile range (IQR) of blood selenium. The exclusion criteria were the following: (1) review articles, case reports, letters or posters, conference abstracts, or animal experiments; (2) duplicate publications or studies with no extractable data [24].

2.3. Data abstraction and quality assessment

Two investigators independently screened the titles and abstracts of all correlative studies, and reviewed the full texts of the included study carefully. For each included study, the following essential information was extracted by two reviewers independently: name of the first author, year of publication, study design, sample type, detection assay, region, age, sex, mean with SD (or median with IQR) of the blood selenium concentration (Table 1). The quality of the studies included in the meta-analysis was evaluated the Newcastle-Ottawa Quality Assessment Scale (NOS) and Agency for Healthcare Research and Quality (AHRQ). Cross-sectional studies use AHRQ to assess literature quality, and cohort studies as well as case-control studies use NOS to evaluate literature quality [25,26]. In cases where two researchers could not reach a consensus, we escalated the matter to include additional team members. A third researcher was consulted to offer an objective evaluation, and their input was crucial in shaping the final decision. A detailed quality

Table 1
Characteristics of studies included in the meta-analysis.

Study	Design	Region	Method	Sample type	Disease	Participants number	Age			Selenium level		
						CD/UC/CON	CD	UC	CON	CD	UC	CON
Amerikanou C et al., 2022	Cross-section	Europe	ICP-MS	Plasma	CD/UC	76/39/38	38.7 ± 14.0 [1]	39.3 ± 11.8 [1]	33.0 ± 12.2 [1]	50 ± 39 [1] μg/L	44 ± 41 [1] μg/L	77 ± 30 [1] μg/L
Brown S et al., 2022	Cross-section	Oceania	NR	Serum	CD	30/–/27	13.15 ± 6.36 [1]	–	13.2 ± 7.78 [1]	1.15 ± 0.18 [1] μmol/L	–	1.17 ± 0.28 [1] μmol/L
Ishihara J et al., 2021	retrospective cohort	Asia	AAS	Serum	CD/UC	98/118/43	13 (4–16) [2]	11 (1–16) [2]	11 (0–15) [2]	12.6(5.5–21.9) [2] μg/dL	14.6(4.7–23.1) [2] μg/dL	15.7(9.9–18.9 [2] μg/dL
Piątek Guziewicz A et al., 2021	Cross-section	Europe	AAS	Serum	IBD	IBD:32/30	IBD:41 ± 15.2 [1]		39.1 ± 11.8 [1]	IBD:0.9 ± 0.24 [1]μmol/L		0.93 ± 0.19 [1] μmol/L
Stojsavljević A et al., 2021	Cross-section	Europe	ICP-MS	Serum	CD	84/–/84	39 ± 14 [1]	–	42 ± 11 [1]	61.8 ± 14.4 [1] ng/g	–	83.0 ± 36.0 [1] ng/g
Barros SÉL et al., 2020	Cross-section	Europe	ICP-OES	plasma	CD	47/–/25	18-59 [3]	–	18-59 [3]	59.89 ± 5.58 [1] μg/L	–	81.50 ± 15.43 [1] μg/L
Stochel-Gaudyn A et al., 2019	Cross-section	Europe	HG-AFS	Serum	CD/UC	14/27/20	10.4 ± 5.50 [1]	12.1 ± 4.10 [1]	11	45.1 ± 15.0 [1] μg/L	42.7 ± 10.7 [1] μg/l	45.1 ± 13.4 [1] μg/L
Cho JM et al., 2018	retrospective cohort	Asia	ICP-MS	Serum	CD/UC	49/16/29	14.4 (5.0–17.4) [2]	14.2 (9.9–17.4) [2]	13.6 (4.8–17.1) [2]	87.5 (63.0–106.0) [2] μg/L	94.5 (63.0–131.0) [2] μg/L	90.0 (65.0–131.0) [2] μg/L
Anjali et al., 2015	Case-control	Asia	AAS	Serum	CD/UC	9/92/50	IBD:19–50 [3]			11.62 ± 1.24 [1] μg/dL	12.34 ± 1.81 [1] μg/dL	13.65 ± 1.90 [1] μg/dL
Gentschew L et al., 2012	Case-control	Oceania	NR	Serum	CD	351/–/853	NR	–	NR	101.8 ± 19.11 [1] ng/ml	–	111.1 ± 29.50 [1] ng/ml
Sikora SK et al., 2011	Case-control	North America	ICP-MS	Serum	CD/UC	81/73/64	11.85 ± 3.10 [1]	10.65 ± 4.27 [1]	10.69 ± 4.55 [1]	1.57 ± 0.23 [1] μmol/L	1.66 ± 0.32 [1] μmol/L	1.67 ± 0.21 [1] μmol/L
Poursadegh F et al., 2008	Cross-section	Asia	AAS	Serum	UC	–/56/56	–	36 ± 12.46 [1]	33.2 ± 8.7 [1]	–	81.85 ± 6.4 [1] μg/L	108.4 ± 12.98 [1] μg/L
Andoh A et al., 2005	Cross-section	Asia	AAS	Serum	CD/UC	37/34/20	31.4 ± 6.5 [1]	34.4 ± 14.5 [1]	32.4 ± 6.5 [1]	9.2 ± 2.3 [1] μg/dL	13.3 ± 2.6 [1] μg/dL	13.2 ± 2.1 [1] μg/dL
Kuroki F et al., 2003	Cross-section	Asia	AAS	Serum	CD	53/–/21	29.8 ± 11.7 [1]/30.6 ± 10.4 [1]	–	30.0 ± 6.3 [1]	8.50 ± 3.29 [1] μg/dL	–	11.8 ± 1.4 [1] μg/dL
Geerling BJ et al., 2000	Case-control	Europe	ETAAS	Serum	CD/UC	23/46/(23/46)	30.1 ± 10.2 [1]	37.8 ± 14.7 [1]	35.4 ± 13.7 [1]	0.92 ± 0.16 [1] μmol/L	0.91 ± 0.18 [1] μmol/L	0.99 ± 0.16/ 1.00 ± 0.17 [1] μmol/L

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Table 1 (*continued*)

Study	Design	Region	Method	Sample type	Disease	Participants number	Age			Selenium level		
						CD/UC/CON	CD	UC	CON	CD	UC	CON
Reimund JM et al., 2000	Cross-section	Europe	GF-AAS	plasma	CD	26/–/15	44 (22–75) [2]	–	39.5 (20–74) [2]	53.5 ± 16.32 [1] μg/L	–	79 ± 8.52 [1] μg/L
Geerling BJ et al., 1998	Cross-section	Europe	ETAAS	Serum	CD	32/–/32	40.0 (34.3–54.0) [4]	–	43.8 ± 13.5 [1]	0.86 ± 0.14 [1] μmol/L	–	1.03 ± 0.15 [1] μmol/L
Ringstad J et al., 1993	Case-control	Europe	ETAAS	Serum	CD/UC	47/117/123	31.3 ± 17.1 [1]	34.4 ± 18.6 [1]	32.7 ± 15.3 [1]	1.28 ± 0.21 [1] μmol/L	1.38 ± 0.20 [1] μmol/L	1.42 ± 0.15 [1] μmol/L
Rannem T et al., 1992	Cross-section	Europe	Fluorometry	Plasma	CD/UC	66/–/41	36 (21–65) [2]	–	34 (24–56) [2]	0.83 (0.08–1.64) [2] μmol/L	–	1.11 (0.75–1.86) [2] μmol/L
Penny WJ et al., 1983	Case-control	Europe	Fluorometry	Whole blood	CD and UC	70/50/58	44 ± 14 [1]	45.5 ± 12.4 [1]	44 ± 14 [1]	1.73 ± 4.98 [1] μmol/L	1.77 ± 32.9 [1] μmol/L	1.85 ± 3.77 [1] μmol/L

Abbreviations: CD (Crohn's disease), UC (ulcerative colitis), IBD (inflammatory bowel disease), CON (controls), AAS (Atomic Absorption Spectrometry), ETAAS (Electrothermal Atomic Absorption Spectroscopy), GFAAS (Graphite Furnace Atomic Absorption Spectrometry), ICP-MS (Inductively Coupled Plasma Mass Spectrometry), ICP-OES (Inductively Coupled Plasma Optical Emission Spectrometer), NR (not reported) [1]. mean (standard deviation) [2], median (range) [3], range [4], median (IQR).

assessment using NOS and AHRQ is presented in Supplementary Tables S1–S3.

2.4. Statistical analysis

All statistical analysis were conducted using the statistical software Stata (version 11.0). We converted median values to means and standard errors (SE) to standard deviations (SD) [19]. By presenting the differences in means relative to variability, we removed the heterogeneous effects of both unit and assay. Since different measurement indices adopted in the various studies using different tools, standardized mean difference (SMD) with 95 % confidence interval (CI) were used for reporting outcomes, and I^2 for assessing heterogeneity. To pool the results of the included articles, which contained variation between studies, we used a random effects model. In a random-effects meta-analysis, we typically assume that the true effects are normally distributed rather than fixed values. A sensitivity analysis was also performed to examine the effect of the omission of a single trial on the overall risk estimation. In addition, to assess potential publication bias, we used Begg's funnel plot and Egger's linear regression test. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Study characteristics

Our comprehensive literature search yielded a total of 1853 related references. After the removal of 95 duplicates, we preliminarily selected 1758 studies based on their abstracts. Further scrutiny of these studies led to the assessment of 52 full-text articles for eligibility, out of which only 20 met our inclusion criteria and were included in the meta-analysis [18–23,27–40]. The process of literature search and selection is detailed in a flow diagram presented in Fig. 1 [41].

The analysis encompassed a diverse array of study designs: 12 case-sectional studies, 6 case-control studies, and 2 retrospective cohort studies. The participant pool consisted of 1893 patients in total, with 1193 diagnosed with CD, 668 with UC, and 32 with unclassified IBD, alongside 1698 control subjects. Geographically, the studies were spread across various regions, with eleven conducted in Europe, six in Asia, two in Oceania, and one in North America, as detailed in Table 1.

3.2. Meta-analysis of the blood selenium levels in IBD patients compared to controls

A total of 20 studies investigated the differences in blood selenium between 1893 IBD patients and 1698 controls. The pooled blood selenium values were significantly lower in IBD patients than in controls (SMD = −0.64, 95%CI: −0.83 to −0.45, $P < 0.001$). A considerable degree of heterogeneity was observed among the studies ($I^2 = 86.0$ %, $P < 0.001$) (Fig. 2).

Next, the studies were categorized into three groups based on the specific type of IBD: (1) patients with only UC, (2) patients with only CD, and (3) patients from studies that did not specify the type of IBD. In the subgroup analysis, eighteen studies involving 1193 CD patients and 1566 controls revealed that blood selenium levels were significantly lower in CD patients (SMD = −0.77, 95 % CI: −1.00 to −0.54, $P < 0.001$) (Fig. 2). Similarly, ten studies focusing on 668 UC patients and 537 controls found that UC patients had significantly lower blood selenium levels compared to controls (SMD = −0.47, 95 % CI: −0.85 to −0.08, $P = 0.017$) (Fig. 2).

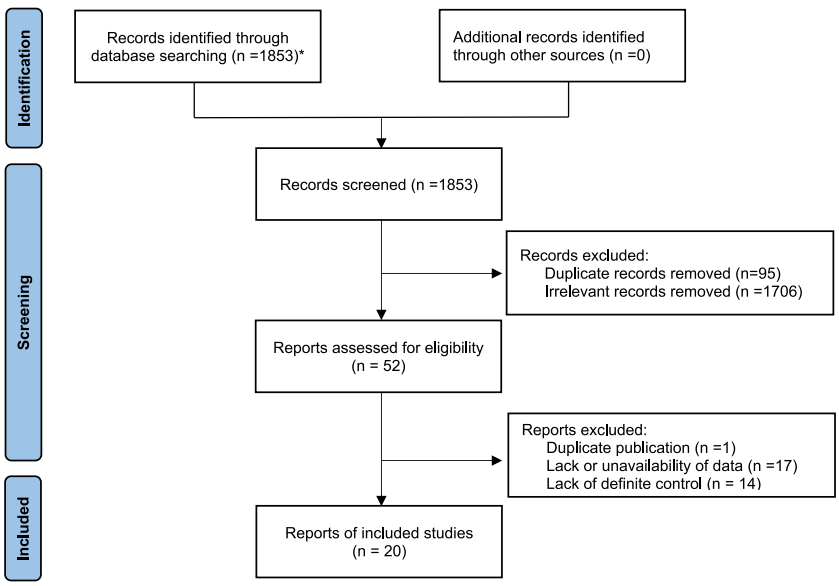

Fig. 1. Literature screening flow diagram.
*Databases searched and literature detected are as follows: PubMed (n = 277), Web of Science (n = 431), Embase (n = 928), and Scopus (n = 217).

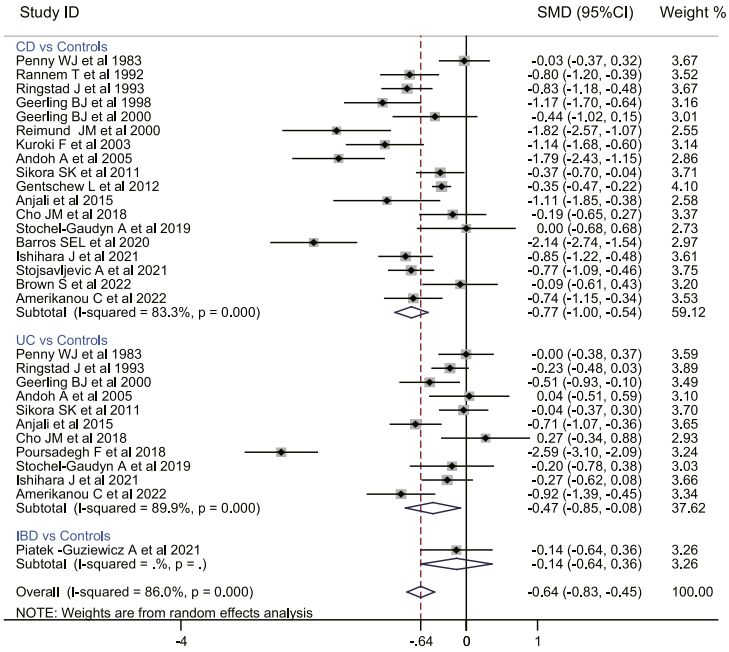

Fig. 2. The forest plot of blood concentrations of selenium between IBD patients and controls (CD: Crohn's disease; UC: Ulcerative colitis; IBD: Unclassified inflammatory bowel disease; SMD: standard mean difference).

3.3. Subgroup analysis

Due to the high level of heterogeneity observed in our initial analysis, we performed detailed subgroup analyses for both UC and CD groups. These analyses were tailored to account for various influential factors, including study design, geographic region of the patients, methods used for selenium detection, types of biological samples analyzed, and the maturity of the participants.

Firstly, our subgroup analysis focused on the selenium detection methods used in the studies, which were divided into three categories: Atomic Absorption Spectrometry (AAS), Inductively Coupled Plasma Mass Spectrometry (ICP-MS), and other methods. The mean selenium levels measured by these methods were as follows: AAS (CD: 96.36 ± 28.64 μg/L, UC: 116.05 ± 27.67 μg/L, Control: 105.40 ± 16.91 μg/L), ICP-MS (CD: 97.25 ± 28.57 μg/L, UC: 99.97 ± 30.33 μg/L, Control: 102.21 ± 19.15 μg/L), and other methods (CD: 96.52 ± 13.08 μg/L, UC: 105.73 ± 16.64 μg/L, Control: 107.37 ± 8.73 μg/L). (Table 3). The analysis indicated significantly lower blood selenium values across all methods for the CD group. This was observed in the AAS group, the ICP-MS group, and the other group (Table 2, Fig. 3A). Conversely, in the UC group, only the AAS group had a significant difference in blood selenium levels. No significant differences in blood selenium levels were observed between the detection methods, either ICP-MS or other (Table 2, Fig. 3B).

Secondly, we compared serum, plasma and whole blood selenium levels in patients with CD and UC. The mean selenium levels in these sample types were as follows: serum (CD: 104.97 ± 21.86 μg/L, UC: 113.93 ± 26.57 μg/L, Control: 108.16 ± 11.14 μg/L), plasma (CD: 57.36 ± 28.99 μg/L, UC: 44.00 ± 41.00 μg/L, Control: 81.87 ± 23.09 μg/L), and whole blood (CD: 136.60 ± 18.95 μg/L, UC:139.76 ± 18.95 μg/L, Control: 146.08 ± 18.95 μg/L). (Table 3). The results indicated that serum and plasma selenium levels were significantly lower in both the CD and UC groups. However, the differences in whole blood selenium values did not reach statistical significance in either group (Table 2, Fig. 4A and B)

Thirdly, concerning the study designs, a significant difference in blood selenium levels was observed between CD patients and controls in cross-sectional studies and case-control studies. However, retrospective cohort studies did not show a significant difference. In the UC group, a significant difference in blood selenium levels was observed between UC patients and controls in case control studies, but no significant differences in blood selenium levels were found between the cross-sectional studies and the retrospective cohort studies (Table 2, Fig. 5A and B).

Fourthly, the studies were categorized by geographic regions, including Asia, Europe, and other areas. The analysis revealed that blood selenium levels in CD patients were significantly lower compared to controls in Asia, Europe, and other regions. In contrast, for UC patients, the selenium values did not demonstrate statistical significance in Asia and other regions. However, a notable decrease in selenium levels was observed in the European group (Table 2, Fig. 6A and B).

Lastly, among the 18 studies reporting on blood selenium levels in CD patients, 5 focused on children (under 18 years old), 12 on adults (18 years old and above), and 1 study did not specify the age of participants. Notable differences in selenium levels were observed both in children and in adults with CD. For UC, 11 studies reported selenium level indices, which included 7 studies involving

Table 2
Results of subgroup analysis.

Subgroup		Studies(n)	Sample size	I [2] (%)	SMD(95%CI)	p-value
Study type						
Case-control	CD	6	581	65.6	−0.45(-0.69,-0.21)	<0.001
	UC	5	378	64.1	−0.29(-0.55,-0.04)	0.025
Cross-section	CD	10	465	81.5	−1.02(-1.39,-0.65)	<0.001
	UC	4	156	94.9	−0.92(-2.09,0.24)	0.121
Retrospective cohort	CD	2	147	79.2	−0.54(-1.18,0.11)	0.105
	UC	2	134	55.1	−0.06(-0.57,0.45)	0.818
Region						
Europe	CD	9	438	74.6	−0.71(-1.00,-0.41)	<0.001
	UC	5	279	61.5	−0.36(-0.64,-0.07)	0.016
Asia	CD	5	246	77.5	−0.98(-1.48,-0.49)	<0.001
	UC	5	316	94.8	−0.66(-1.54,0.23)	0.145
Other	CD	4	509	91.3	−0.68(-1.25,-0.10)	0.021
	UC	1	73	–	−0.04(-0.37,0.30)	0.831
Method						
ICP-MS	CD	5	360	69.9	−0.43(-0.72,-0.13)	0.005
	UC	3	128	83.4	−0.24(-0.90,0.42)	0.473
AAS	CD	8	325	56.9	−1.09(-1.37,-0.80)	<0.000
	UC	6	463	93.5	−0.70(-1.31,-0.09)	0.024
Other	CD	5	508	89.8	−0.66(-1.23,-0.10)	0.022
	UC	2	77	0.0	−0.06(-0.38,0.25)	0.698
Sample type						
Serum	CD	13	908	77.1	−0.67(-0.90,-0.44)	<0.001
	UC	9	579	91.1	−0.47(-0.92,-0.02)	0.040
Plasma	CD	4	215	85.1	−1.33(-1.99,-0.66)	<0.001
	UC	1	39	–	−0.92(-1.39,-0.45)	<0.001
Whole blood	CD	1	70	–	−0.03(-0.37,0.32)	0.880
	UC	1	50	–	−0.00(-0.38,0.37)	0.985
Maturity						
Adults(≥18 years old)	CD	12	570	81.5	−1.02(-1.34,-0.70)	<0.001
	UC	7	434	92.9	−0.69(-1.26,-0.13)	0.015
Children(<18 years old)	CD	5	272	56.5	−0.35(-0.65,-0.04)	0.025
	UC	4	234	0.0	−0.11(-0.32,0.10)	0.326

n: number; I^2: percentage of total variation across studies; P-value: an independent variable would be significant (<0.05) or not significant (≥0.05) in the model; CI: confidence interval; AAS: Atomic Absorption Spectrometry; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; Other: other region/methods; NR not reported.

Table 3
Selenium values for different sample types and measurement methods.

	CD			UC			Control		
	Mean (μg/L)	SD (μg/L)	Sample size	Mean (μg/L)	SD (μg/L)	Sample size	Mean (μg/L)	SD (μg/L)	Sample size
Method									
AAS	96.36	28.64	325	116.05	27.67	463	105.40	16.91	427
ICP-MS	97.25	28.57	360	99.97	30.33	128	102.21	19.15	273
Other Method	96.52	13.08	508	105.73	16.64	77	107.37	8.73	1088
Sample type									
serum	104.97	21.86	908	113.93	26.57	579	108.16	11.14	1491
plasma	57.36	28.99	215	44.00	41.00	39	81.87	23.09	119
whole blood	136.60	18.95	70	139.76	18.95	50	146.08	18.95	58

Abbreviations: CD (Crohn's disease), UC (ulcerative colitis), SD (standard deviation), AAS (Absorption Spectrometry), ICP-MS (Inductively Coupled Plasma Mass Spectrometry).

adults and 4 involving children. In the UC adult's group, the analysis showed a slight, yet statistically significant, difference. Conversely, in the children group, no significant difference in selenium levels was observed (Table 2, Fig. 7A and B).

3.4. Sensitivity analysis

In our meta-analysis, a sensitivity analysis was conducted to assess the robustness of the results regarding blood selenium levels in patients with IBD. This analysis involved sequentially omitting each study and recalculating the pooled SMD for the remaining studies. The results indicated that the pooled SMD remained stable and did not show any material change when any single study was excluded (Supplementary Fig. S1A). This consistency in the findings suggests a high level of reliability in our meta-analysis results. Similarly, when conducting sensitivity analyses separately for the CD and UC groups, the outcomes mirrored those of the overall IBD analysis,

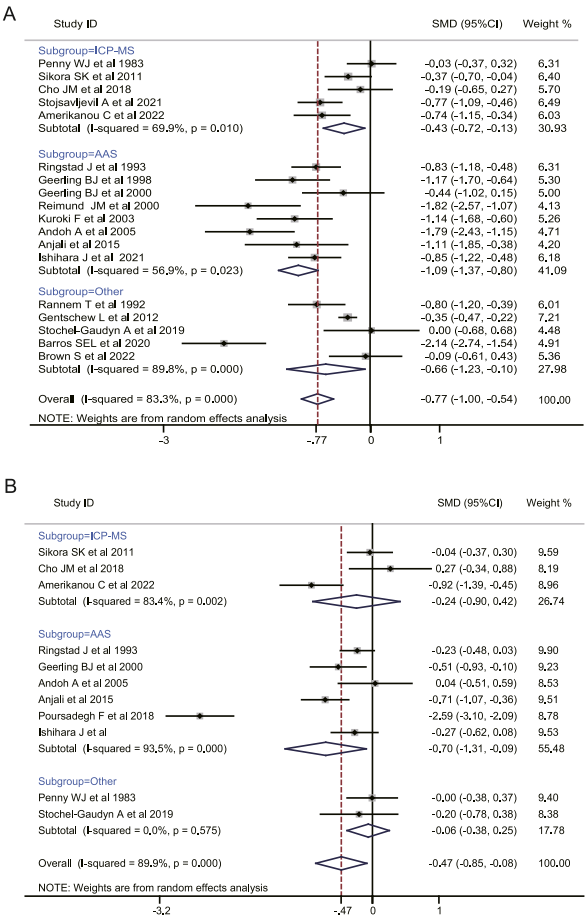

Fig. 3. Subgroup analysis of selenium blood concentrations in CD and UC patients compared with controls for the three detection methods.
(A) CD patients vs controls; (B) UC patients vs controls.
(AAS: Atomic Absorption Spectrometry; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; SMD: standard mean difference; CI: Confidence Interval).

further confirming the robustness of our results across different IBD subtypes (Supplementary Figs. S1B and S1C).

3.5. Publication bias

To assess for publication bias in our meta-analysis, we employed both Begg's and Egger's tests. For the IBD group, the results from these tests indicated no significant evidence of publication bias (Begg's test: P = 0.064; Egger's test: P = 0.051) (Supplementary Fig. S2A). Similarly, in the UC group, the tests also suggested an absence of publication bias (Begg's test: P = 0.640; Egger's test: P = 0.508) (Supplementary Fig. S2B). However, an asymmetry was noted in the funnel plot for blood selenium values between CD patients and controls, with Begg's test yielding a P-value of 0.069 and Egger's test a P-value of 0.016 (Supplementary Fig. S2C). To address this, a trim-and-fill analysis was conducted. After one iteration of the data, the results remain stable (SMD = −0.464, 95 % CI: −0.368 to −0.584) (Supplementary Fig. S2D). This suggests that the overall findings of our meta-analysis are robust, despite the initial asymmetry in the funnel plot, and that there is no significant publication bias in these studies.

4. Discussion

In this study, we aimed to clarify the selenium status in IBD patients compared to controls. We found that both CD and UC patients exhibit significantly lower mean selenium levels than the control populations. Subgroup analyses, based on various factors like study designs, patient regions, detection methods, sample types, and participant ages, revealed consistent findings in the CD group across different subgroups. However, the results for the UC group only showed significant differences in certain subgroups, such as the adult patient group, case-control study groups, European group, and serum and plasma sample groups. Blood selenium levels differed between CD and UC patients, possibly due to the differing sites of inflammation. UC primarily affects the colon, while CD can involve the entire gastrointestinal tract. It is worth noting that there are fewer and smaller studies on UC compared to CD. Therefore, our analysis

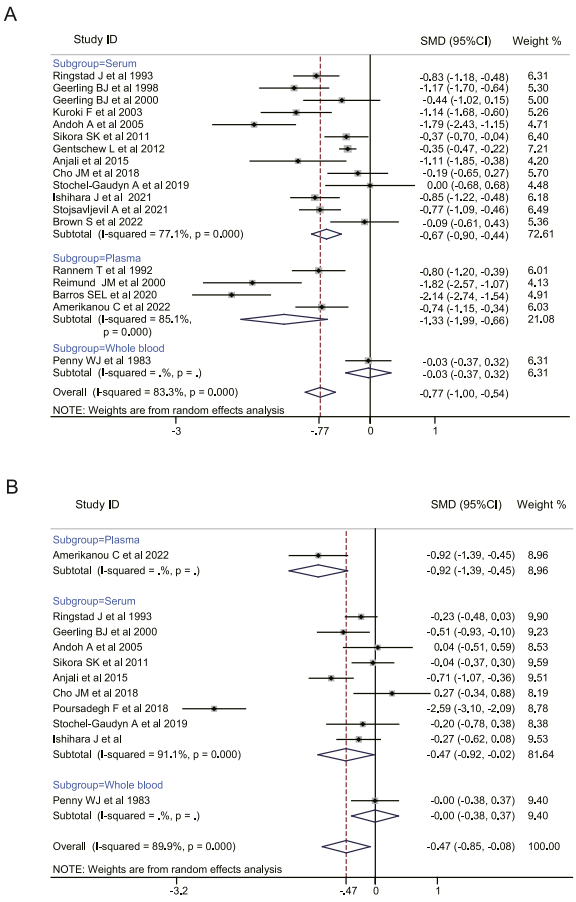

Fig. 4. Subgroup analysis of selenium blood concentrations in CD and UC patients compared with controls for the three types of biological samples analyzed.
(A) CD patients vs controls; (B) UC patients vs controls.
(SMD: standard mean difference; CI: Confidence Interval).

indicates a significant downregulation of selenium in IBD patients. This finding suggests that integrating selenium status evaluation and targeted supplementation into IBD management strategies may provide a valuable adjunct to existing therapies, ultimately improving patient care and outcomes.

One of the key strengths of this meta-analysis lies in its inclusion of a large and diverse subject pool, encompassing both CD and UC patients. This comprehensive approach allowed for a thorough examination of the associations between IBD and selenium levels. Additionally, the capability to conduct subgroup analyses based on varying study designs, patient regions, detection methods, sample types, and participant ages enriched the depth and specificity of our findings. Our sensitivity analysis further validated the robustness of the results, showing no significant change in the pooled Standardized Mean Difference when each study was sequentially excluded. Thus, this meta-analysis provides valuable insights into the relationship between selenium levels and IBD.

We observed a general trend of selenium deficiency in IBD patients, which could be due to impaired intestinal absorption, chronic bleeding, insufficient intake, and disease-related intestinal inflammation. While some subgroup analyses yielded contrary results, it's important to note the limited number of studies in these subgroups. For instance, the analysis of the whole blood group was based on a single study, while only two publications contributed to the retrospective cohort group. Therefore, future research should focus on standardizing detection samples and methods to enhance comparability and reliability of results. Uniform methodologies across studies will not only improve the accuracy of meta-analyses but also allow for more definitive conclusions about selenium status and its clinical implications in IBD. This approach is vital in addressing the current gaps in our understanding and effectively determining the potential role of selenium supplementation as a therapeutic measure for IBD patients.

The relationship between blood selenium levels and disease activity in patients with IBD remains not fully elucidated. In the present meta-analysis, we were unable to perform subgroup analyses based on disease activity due to the lack of comprehensive data on disease severity in most of the included studies. Among the literature included in our analysis, only one study specifically investigated the difference in plasma selenium levels between active and remission phases in 47 patients with CD (20 active and 27 in remission) and 25 healthy controls [20]. Although the mean plasma selenium levels were lower in patients with active disease compared to those in

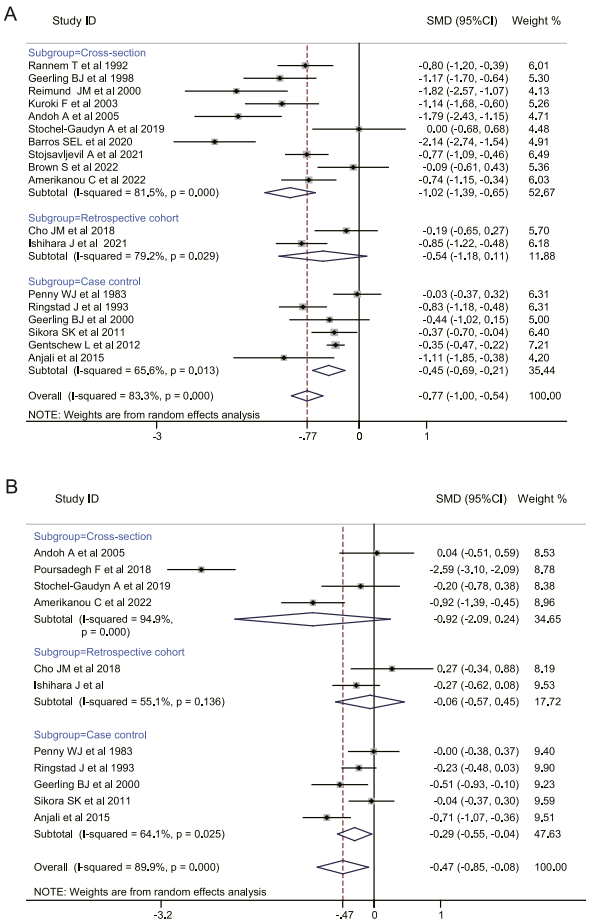

Fig. 5. Subgroup analysis of selenium blood concentrations in CD and UC patients compared with controls for the three study designs.
(A) CD patients vs controls; (B) UC patients vs controls.
(SMD: standard mean difference; CI: Confidence Interval).

remission, the difference did not reach statistical significance, possibly due to the high degree of within-sample variability.

The causative relationship between selenium deficiency and IBD pathogenesis remains uncertain. This deficiency may be attributed to factors such as impaired intestinal absorption, chronic bleeding, insufficient intake, and disease-related intestinal inflammation [42]. It is unclear whether selenium deficiency is a consequence of IBD or a contributing factor to its pathogenesis. However, selenium may be an important mediator in the pathogenesis of CD and UC, there are reports that in animal models, selenium deficient mice had exacerbated colitis after DSS injury, resulting in a pro-tumorigenic microenvironment with increased cytokines, oxidative stress, and DNA damage [43], and the absence of selenoproteins can enhance intestinal inflammation [44]. Moreover, a multi-omics analysis indicated that selenium supplementation mitigated the symptoms and onset of CD and inhibited Th1 cell differentiation via cellular scavenging of reactive oxygen species mediated by selenoprotein W (SELW) [45]. This suggests that selenium deficiency, or the absence of selenoproteins, might amplify intestinal inflammation.

Selenium deficiency has been associated with various symptoms and health problems, including weakened immune system, increased susceptibility to infections, elevated oxidative stress and inflammation, muscle weakness, fatigue, cardiovascular problems such as cardiomyopathy, mood disorders like depression and anxiety, cognitive decline, neurological symptoms, and thyroid dysfunction [46]. Considering the significantly lower selenium levels observed in IBD patients, especially those with CD, it is plausible that these individuals may be at a higher risk of developing selenium deficiency-related symptoms. Furthermore, given the crucial role of selenium in maintaining immune function and regulating inflammation, selenium deficiency may exacerbate IBD symptoms and contribute to disease progression.

In light of these potential consequences, monitoring selenium levels and initiating selenium supplementation in IBD patients with confirmed deficiency may be beneficial, even in the absence of overt selenium deficiency symptoms. By correcting selenium deficiency before symptoms manifest, clinicians may be able to prevent the development of associated health problems and potentially improve IBD outcomes. However, it is important to note that further research is needed to establish the optimal timing, dosage, and duration of selenium supplementation in IBD patients, as well as to evaluate the long-term effects of such interventions on disease course and patient well-being.

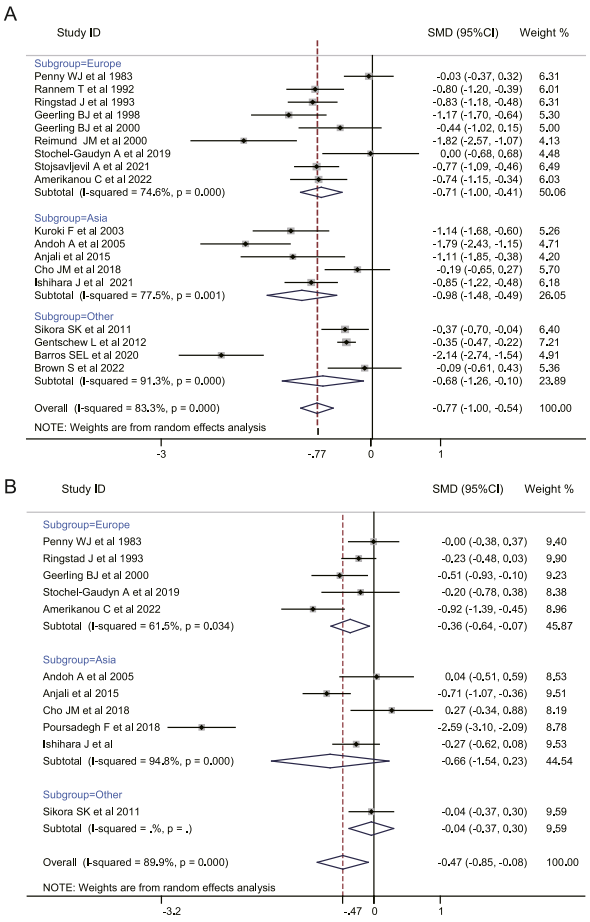

Fig. 6. Subgroup analysis of selenium blood concentrations in CD and UC patients compared with controls for the three geographical regions of the patients.
(A) CD patients vs controls; (B) UC patients vs controls.
(SMD: standard mean difference; CI: Confidence Interval).

5. Limitation

There are several limitations to this study. Firstly, the absence of subgroup analyses based on gender, season, race, or disease activity was a notable gap, primarily due to the lack of sufficient data in these categories. Secondly, while the funnel plots did not indicate significant publication bias, the potential for bias cannot be entirely ruled out. This concern arises particularly from the exclusion of some relevant studies that lacked control groups, possibly skewing the overall analysis. Lastly, the variability in diagnostic standards for IBD across different countries and study periods introduced an element of inconsistency. This lack of a unified diagnostic criterion could have potentially increased the false positive rate, thereby impacting the reliability of our conclusions.

6. Conclusion

The meta-analysis provides strong evidence that patients with IBD, particularly those with CD, have significantly lower blood selenium levels compared to controls. These findings suggest the importance of screening for selenium deficiency among IBD patients and highlight the potential benefits of selenium supplementation as an adjunct therapy in the management of IBD, especially in cases where selenium levels are found to be deficient. However, further research is needed to elucidate the precise causal relationship between selenium deficiency and IBD pathogenesis, as well as to determine the most effective strategies for selenium supplementation.

CRediT authorship contribution statement

Sishuo Liu: Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation. **Tingting Lin:** Data curation. **Wenguang Wang:** Methodology, Data curation. **Fangyuan Jing:** Writing – review & editing. **Jinghao Sheng:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

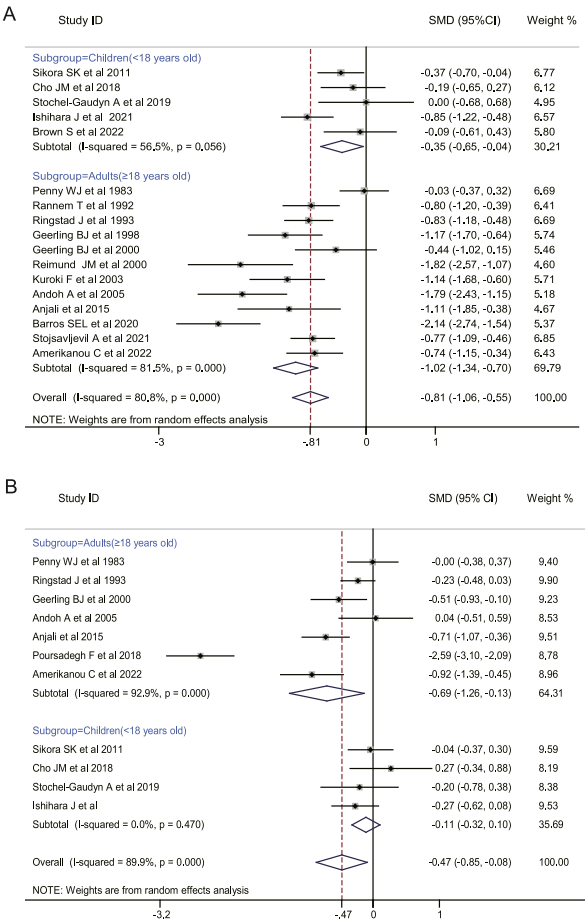

Fig. 7. Subgroup analysis of selenium blood concentrations in CD and UC patients compared with controls for the maturity of the participants. (A) CD patients vs controls; (B) UC patients vs controls.
(SMD: standard mean difference; CI: Confidence Interval).

Data availability

The data supporting the findings of this study are available within the article and its supplementary materials. Any additional data or materials can be requested from the corresponding author.

Abbreviations

Abbreviation	Full Name
AAS	Atomic Absorption Spectrometry
AHRQ	Agency for Healthcare Research and Quality
CD	Crohn's Disease
CI	Confidence Interval
CON	Controls
DSS	Dextran sulfate
ETAAS	Electrothermal Atomic Absorption Spectroscopy
GFAAS	Graphite Furnace Atomic Absorption Spectrometry
I [2]	Inconsistency Index
IBD	Inflammatory Bowel Diseases
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
ICP-OES	Inductively Coupled Plasma Optical Emission Spectrometer
IQR	Interquartile Range
NOS	Newcastle-Ottawa Quality Assessment Scale
NR	Not Reported
SD	Standard Deviations
Se	Selenium
SE	Standard Errors

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Abbreviation	Full Name
SELW	Selenoprotein W
SMD	Standardized Mean Difference
UC	Ulcerative Colitis

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Declaration of competing interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40139.

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