BMC Endocrine Disorders

RESEARCH

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The association of selenium exposure with the odds of metabolic syndrome: a dose-response meta-analysis

Rongrong Yuan[1], Yu Zhang[2] and Jiakai Han[1*]

Abstract

Background Selenium is a key regulator of metabolic homeostasis. It has been proposed that exposure to selenium might be associated with metabolic syndrome (MetS). However, the results are contradictory. This meta-analysis was carried out to analyze the relationships between selenium levels in biological samples and odds of Mets.

Methods We searched Scopus and PubMed databases up until September 2024 to identify relevant studies. Odds ratio (OR) and 95% confidence interval was used to pool the data using a random effects model.

Results The meta-analysis encompassed 18 observational studies involving 21,481 participants. It found that higher selenium exposure was related to an elevated likelihood of MetS (OR = 1.30, 95% CI = 1.12–1.51), even after controlling for covariates, such as smoking, age, alcohol consumption, and physical activity. Heterogeneity was significant among the studies ($I^2 = 88.9\%$, $P = 0.001$). While elevated serum selenium levels linked to a higher odds of MetS, no such relationship was observed for selenium in urine or toenails. Subgroup analyses indicated that this association was evident only in females (OR = 2.0, 95% CI = 1.17–1.43) and particularly pronounced in individuals aged ≥ 50 years. A dose-response relationship was identified, showing a 6% increase in MetS odds for each additional 10 µg/L of serum selenium, with the odds rising non-linearly when serum levels surpassed 80 µg/L.

Conclusions This study suggests that selenium may associated with the odds of MetS, following a dose-response relationship.

Keywords Selenium, Dose-response, Metabolic syndrome, Meta-analysis

Background

Metabolic syndrome (MetS) is a multifaceted condition characterized by a combination of metabolic disturbances, including abdominal obesity, hypertension, impaired glucose regulation, and abnormal lipid levels [1]. Affecting approximately 20-25% of the global population, MetS remarkably increases the odds of type 2 diabetes, cardiovascular diseases, kidney failure, and overall mortality [2, 3]. It is also linked to heightened odds of developing reproductive disorders, nonalcoholic steatohepatitis, and various cancers [4, 5]. Although the precise etiology of MetS remains largely unclear, it is recognized

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to arise from a complex interplay of genetic, metabolic, and environmental factors, such as unhealthy dietary patterns [6–8]. As lifestyle and dietary patterns shift in tandem with the growing obesity epidemic, the prevalence of MetS is rapidly growing [9]. Therefore, preventing MetS is essential, making the identification of its risk factors critically important.

Oxidative stress plays a leading role in the pathophysiology of MetS, either prompting or exacerbating the mechanisms associated with its pathology [10]. Selenium, an essential trace element primarily sourced from the diet, contributes to the preservation of redox balance and endocrine and metabolic processes [11]. Recent studies have indicated a correlation between circulating selenium levels and metabolic risk factors, such as glycemic indices [12] and lipid profiles [13]. Selenium is crucial for human health due to its incorporation into selenoproteins, which are vital for antioxidant defense, insulin function, and thyroid hormone metabolism [14]. It is a key component of glutathione peroxidase (GSH-PX), which protects the body from oxidative damage by reducing lipid peroxidation and preserving the integrity and functionality of cell membranes [15].

Given the roles of selenium-dependent enzymes in oxidative stress and metabolic pathways, there has been significant interest in exploring the relationship between selenium exposure and MetS. However, the association of selenium levels in various biological samples, such as serum, urine, and nails, with MetS remains debated, with studies yielding inconsistent results. Some research indicates that elevated selenium levels may be linked to an increased odds of MetS [16, 17], while other studies suggest a protective effect or no significant association [18]. This could stem from the differences in study designs, types of samples collected, population characteristics, and the methodologies used to measure selenium exposure. This meta-analysis aimed to comprehensively synthesize the existing literature on the relationship between selenium concentrations in various biological samples and the odds of developing MetS to determine whether selenium exposure can be regarded as a modifiable risk factor for MetS and identify any potential dose-response relationships.

Methods

Information sources and search strategy

The meta-analysis was performed following the guidelines established by the PRISMA [19]. Relevant publications were recruited by searching the Scopus and PubMed databases up until September 2024, utilizing the following keywords: ("Selenium"[Mesh]) OR selenium OR selenite OR seleno OR selenious acid) AND ("Metabolic Syndrome"[Mesh] OR Metabolic Syndrome). The search was restricted to English-language articles. Furthermore, we manually reviewed the reference lists of eligible studies and relevant reviews to uncover any further qualifying studies. In cases where clarification was required or additional data were not present in the published manuscripts, the authors of the included studies were contacted directly. All literature was organized using EndNote X7 software. Two authors independently assessed the titles and abstracts of each article to determine their relevance, eligibility for inclusion, data extraction, and quality evaluation. Any disagreements were settled by consulting a third author.

Eligibility criteria

Studies were included if they satisfied the predefined inclusion criteria based on the PICO framework, which were as follows: (1) the population consisted of individuals at risk of MetS, (2) the exposure involved selenium levels in various biological samples, (3) the controls were individuals with the lowest selenium exposure, (4) the outcome measured was the odds of MetS, and (5) the studies were observational in design, encompassing cohort, case-control, and cross-sectional studies. Additionally, to qualify for inclusion, the studies had to provide risk estimates for the relationship between selenium concentrations in biological samples and MetS. We excluded animal studies, those with irrelevant exposures or outcomes, clinical trials, reviews, letters, protocols, short combinations, and editorials.

Data extraction

Data was gathered from each included study using a standardized protocol and reporting form, which encompassed the following information: country, first author's name, publication year, sample size, number of patients with MetS, definition of MetS, method of selenium measurement, study design, mean age and gender of participants, and the covariates adjusted for in the analyses.

Quality assessment

Two investigators (RY and YZ) independently measured the quality of the eligible publications with the use of the Newcastle-Ottawa Scale (NOS) [20], which assesses various domains, including selection, comparability, and assessment of exposure and outcome. The final quality scores were determined by the total number of criteria met, classified as follows: 7–9 asterisks (high quality), 4–6 asterisks (medium quality), and 1–3 asterisks (low quality).

For cross-sectional studies, a modified version of NOS was used according to the previous studies [21]. The NOS had the following domains to assess the quality of cohort studies: representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, demonstration that the outcome of interest was not

present at the start of the study, study controls for the main covariate, study controls for any additional factors, assessment of outcome, adequacy of follow-up duration for outcomes occurrence, and loss-to-follow up. For case-control studies, NOS had the following domains: selection of cases and controls, sample size, comparability of cases and controls, ascertainment of exposures, study controls for the main covariate, study controls for any additional factor, ascertainment of the outcome, and statistical test. For cross-sectional studies, NOS had the following domains: representativeness of the sample, sample size, non-respondents, ascertainment of exposure, study controls for the main covariate, study controls for any additional factor, ascertainment of the outcome, and statistical test [21] (Table S1).

Statistical analysis

The odds ratio (OR) and 95% confidence intervals (CI), adjusted for a comprehensive set of covariates, were utilized as the effect size to pool the data. In instances where the study did not directly report risk estimates, we estimated the unadjusted ORs using the raw data provided. To evaluate heterogeneity across the articles, Cochran's Q test and the I^2 statistic were employed, categorizing heterogeneity as low (0–25%), moderate (25–50%), or high (>50%) [22, 23]. A random-effects model was implemented for data pooling. Publication bias was examined using Egger's statistics and funnel plots, with a p-value < 0.05 showing statistically significant [24, 25]. Sensitivity analyses were conducted by sequentially excluding individual studies to evaluate the reliability of the results. Subgroup analyses utilizing random-effects models were performed based on sample size, gender, age, quality of study, source of population, geographic region, definitions of MetS, and methods of selenium assessment to explore potential sources of heterogeneity. Additionally, meta-regression analysis was executed to determine if pooled estimates were influenced by participants' age.

The analysis of linear dose-response relationship was conducted using varying cut-off points for categories in each study to calculate the (OR and 95%CI for MetS associated with every 10 μg/L increment in serum selenium levels. This was performed through generalized least squares for trend estimation, following the methodologies proposed by Greenland and Longnecker [26] and Orsini [27]. The median serum selenium within each category was utilized as the corresponding dose. The relationship between selenium concentration and MetS odds was delineated for each distribution of cases and controls according to this method. Studies that failed to quantify the number of cases and controls within each category or that reported selenium concentrations with OR and 95% CI for fewer than three categories were removed from this dose–response analysis. Furthermore, we evaluated a non-linear dose–response curve relating serum selenium concentration to the summary OR and 95% CI for MetS. A restricted cubic spline model featuring four knots at the 5th, 35th, 65th, and 95th percentiles of selenium concentration was employed. Both linear and non-linear models were derived by testing the null hypothesis, with the spline coefficients set to zero [28]. All statistical analyses were done with the use of Stata version 14 (Stata Corp, College Station, TX), with significance for pooled estimates established at $p < 0.05$.

Results

Study characteristics

Our preliminary literature review identified 667 publications. After removing 73 duplicates and 558 irrelevant studies, we conducted a full-text screening of 36 potentially relevant articles. Ultimately, 18 studies were excluded for failing to meet al.l eligibility criteria, as illustrated in Fig. 1. The meta-analysis included 18 studies [9, 11, 16–18, 29–41], comprising 9 case-control studies, 8 cross-sectional studies, and one cohort study. The sample sizes of these studies ranged from 145 to 3,272 participants, totaling 21,481 individuals. Among these, there were 6,231 cases of MetS. One study focused exclusively on women [39], three on men [9, 29, 31], while five provided separate results for both genders [9, 16, 17, 30, 40]; the remaining studies presented combined data. Out of the included studies, 15 evaluated serum selenium levels [9, 11, 16–18, 29–31, 33, 35, 36, 38–41], two examined urinary selenium [32, 37], and one assessed toenail selenium concentrations [34]. Measurement techniques varied: 11 studies utilized inductively coupled plasma mass spectrometry (ICP-MS), four employed atomic absorption spectrometry, one used spectrofluorimetry, and another utilized neutron activation analysis; one study did not specify the method of selenium assessment. Participants' mean ages ranged from 15.3 ± 2.6 to 73.4 ± 5.74 years. MetS was defined using the National Cholesterol Education Program Expert Panel and Adult Treatment Panel (III NCEP-ATP III) in 5 studies, IDF in 5 studies, Chinese criteria in 5 studies, The Joint Interim Statement in one study, and one study did not report the criteria used to define MetS. According to the Newcastle-Ottawa Scale (NOS), the quality of the included studies ranged from low to high, with scores between 3 and 9 (Table S1). Detailed characteristics of each study are summarized in Table 1.

Meta-analysis

The forest plot depicting the pooled association between selenium concentrations and MetS odds is shown in Fig. 2. The pooled odds ratio (OR) was calculated at 1.30 (95% CI = 1.12–1.51) for higher versus lower selenium

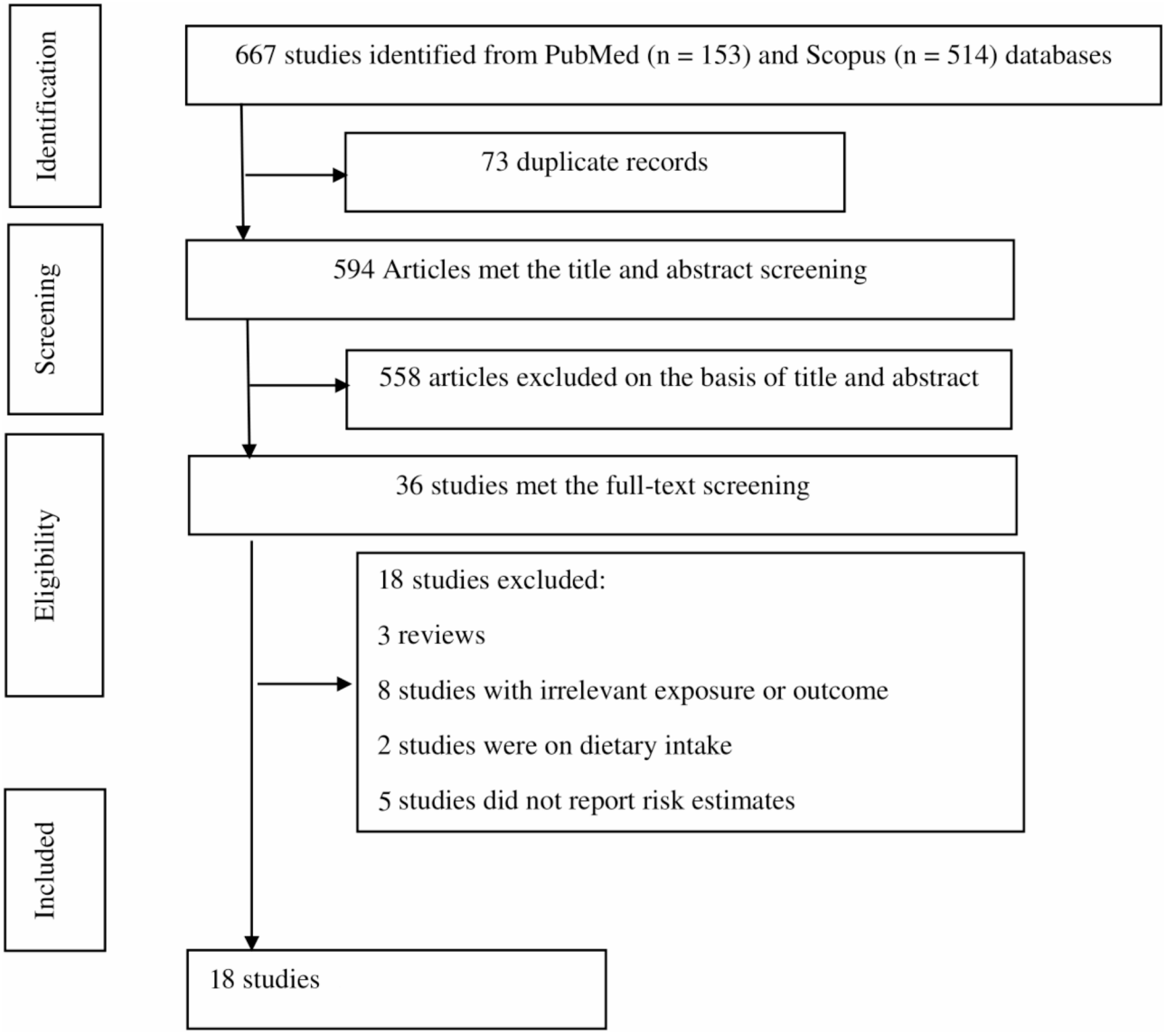

Fig. 1 Flow diagram of study selection

concentrations, indicating significant heterogeneity among the studies (I^2 = 88.9%, P = 0.001) (Fig. 2). The results of subgroup analyses are presented in Table 2. The results were supported by hospital-based studies and studies with a low risk of bias. Subgroup analyses revealed the increased odds of MetS in females (OR = 2.0, 95% CI = 1.17–1.43), but not in males. Elevated serum selenium levels were associated with increased odds of MetS; however, no such association was found for urinary or toenail selenium concentrations. This association was particularly evident among individuals aged ≥ 50 years and in studies employing the NCEP-ATP III and Chinese definitions for MetS, as well as within Asian populations and those measuring selenium via ICP-MS or atomic absorption spectrometry. In subgroup analyses adjusting for covariates, higher selenium levels were linked to increased odds of MetS when controlling for at least one potential covariate or when age was accounted for; however, associations remained unchanged when not adjusted for energy intake, body mass index (BMI), or education level. The relationship did not vary significantly in the stratified analysis according to the adjustment for alcohol consumption, sex, physical activity level, and smoking status among participants (Table 2).

A total of seven studies [9, 11, 17, 33, 36, 40, 41] provided data for dose-response meta-analysis. The OR for MetS was found to be 1.06 (95% CI = 1.003–1.12) per 10 μg/L increase in serum selenium concentration (Fig. 3). Notably, a direct nonlinear association between serum selenium concentration and MetS odds was observed (P < 0.001) (Fig. 4), indicating that the odds of MetS ascended when serum selenium surpassed 80 μg/L.

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

Study	Year	Country	Type of study	Cases with MetS	Total sample size	Mean age	Population	MetS definition	Selenium measurement	Gender (%males)	Sample type	Adjustment
Huang	2021	China	Cross-sectional	628	2109	60.18 ± 11.77	Community-based	IDF	ICP-MS	Both (42.3%)	Urine	Age, gender, and BMI
Feng	2020	China	Cohort	254	1970	41.8 ± 10.2	Community-based	Chinese criteria	ICP-MS	Male	Serum	Age, smoking, alcohol drinking, physical activity, education status, and family history
Arnaud	2010	France	Cross-sectional	293	1902	49.1 ± 7.5	Community-based, diabetic-free population	IDF	Atomic absorption spectrometry	Both (66%)	Serum	Age, group, social status, physical activity, energy intake, alcohol consumption, smoking and hormonal status
Lu	2019	Taiwan	Case-control	709	1165	64.9 ± 10.3	Hospital-based	NCEP-ATP III	ICP-MS	Both (36%)	Serum	Age, gender, current smoking status, current drinking status, physical activity, BMI, and HOMA-IR
Schneider-Matyka	2023	Poland	Case-control	72	390	52.59 ± 5.05	Community-based	IDF	Spectrofluorimetry	Female	Serum	NR
Fang	2018	China	Case-control	125	698	65.35 ± 7.86	Community-based	Chinese criteria	Atomic absorption spectrometry	Both (36%)	Serum	Smoking habit, alcohol consumption, physical activity and medication use at baseline
Guo	2019	China	Cross-sectional	80	145	39 ± 12	Hospital-based	NCEP-ATP III	ICP-MS	Male	Serum	Age
Deng	2023	China	Cross-sectional	278	1451	NR	Community-based	NR	NR	Male	Serum	NR
Jang	2018	Republic of Korea	Cross-sectional	40	500	≥ 35	Community-based	NCEP-ATP III	Neutron activation analysis	Both (NR)	Toenail	Age, sex, education level, smoking status, physical activity level, alcohol consumption status and total energy intake, family history of diabetes, hypertension and cardiovascular disease
Ma	2020	China	Cross-sectional	526	3272	58.14 ± 10.49	Community-based	NCEP-ATP III	ICP-MS	Both (26.4%)	Urine	Age, BMI, gender, race, education, smoking status, drinking status, traffic time, passive smoke status, city, medications, diet frequency, and physical activity status
Zhou	2020	China	Case-control	1279	2558	55.56 ± 10.46	Community-based	The Joint Interim Statement	ICP-MS	Both (64%)	Serum	Sex, age, BMI, smoking, drinking, physical activity, and education level
Pang	2024	China	Cross-sectional	395	852	72.86 ± 5.87	Community-based	NR	ICP-MS	Both (36.7%)	Serum	Gender, waistline, eGFR, age, smoke, drink, serum creatinine, health satisfaction
Kelishadi	2014	Iran	Case-control	160	320	15.3 ± 2.6	Community-based	NCEP-ATP III	Atomic absorption spectrometry	Both (nr)	Serum	Age and sex

Table 1 (continued)

Study	Year	Country	Type of study	Cases with MetS	Total sample size	Mean age	Population	MetS definition	Selenium measurement	Gender (%males)	Sample type	Adjustment
Lu	2016	Taiwan	Case-control	418	847	65.2 ± 9.6	Hospital-based, patients with diabetes mellitus	IDF	ICP-MS	Both (64%)	Serum	NR
Huang	2022	China	Cross-sectional	149	1277	62.51 ± 8.44	Hospital-based	Chinese criteria	ICP-MS	Both (44.3%)	Serum	Age, sex, smoking, drinking status and eGFR
Yuan	2015	China	Case-control	204	408	64.0 ± 6.4	Community-based	Chinese criteria	Atomic absorption spectrometry	Both (44.1%)	Serum	Gender and age
Guo	2023	China	Case-control	292	584	73.4 ± 5.74	Community-based	Chinese criteria	ICP-MS	Both (32.2%)	Serum	Age, sex, smoking status, drinking status.
Zhang	2020	China	Case-control	428	1033	60.1 ± 5.8	Community-based	IDF	ICP-MS	Both (49.2%)	Serum	Education level, smoking status, alcohol intake status, BMI, physical activity, family history of disease.

NR: not reported, MetS: metabolic syndrome, BMI: body mass index, NCEP-ATP III: the National Cholesterol Education Program Expert Panel and Adult Treatment Panel III, IDF: International Diabetes Federation, ICP-MS: Inductively coupled plasma mass spectrometry, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, eGFR: estimate glomerular filtration rate

Meta-regression and sensitivity analysis

The meta-regression analysis indicated that pooled effect sizes were unaffected by sample size, participant age, or publication year. Sensitivity analyses confirmed that no individual study significantly affected the pooled effect sizes, indicating the reliability of the findings.

Publication bias

A significant publication bias was detected ($P = 0.007$) (Fig. 5). However, following a trim-and-fill analysis to adjust for this bias, the pooled effect size remained unchanged, suggesting that publication bias had a negligible impact on the results.

Discussion

This analysis identified a direct relationship between serum selenium levels and the odds of MetS in females, particularly among older individuals (≥ 50 years), while no such association was observed in males. The relationship remained significant even after controlling for covariates such as age, smoking habits, alcohol intake, and levels of physical activity. Specifically, a dose-response relationship was identified, indicating a 6% rise in MetS odds for every 10 μg/L increase in serum selenium concentration. Notably, this association exhibited a non-linear trend, with the likelihood of MetS increasing when serum selenium levels exceeded 80 μg/L.

The overall results of this study align with several previous observational studies that reported positive correlations between serum selenium levels and MetS [16, 40]. It has been observed that individuals with MetS have higher serum selenium levels compared to healthy controls [40]. Furthermore, serum selenium levels have been positively linked to various components of MetS, including insulin resistance, fasting glucose, obesity, and triglycerides [17]. The dual function of selenium as an essential nutrient and a possible risk factor for metabolic disorders has been previously proposed. Numerous studies highlight this contradiction, indicating that while selenium is vital for various physiological functions, including antioxidant defense and thyroid hormone metabolism, excessive selenium exposure may be linked to adverse health outcomes. For instance, some research suggests that selenium deficiency is associated with metabolic disorders due to oxidative stress and impaired signaling pathways, while other studies indicate that high serum selenium levels correlate with a heightened risk of these same conditions. Recent studies indicate that elevated blood selenium concentrations may adversely impact cardiovascular metabolic risk factors [13] and type 2 diabetes (T2DM) [42]. Elevated serum selenium levels have been correlated with increased concentrations of total cholesterol, low-density lipoprotein-cholesterol (LDL-c), high-density lipoprotein-cholesterol (HDL-c) triglyceride

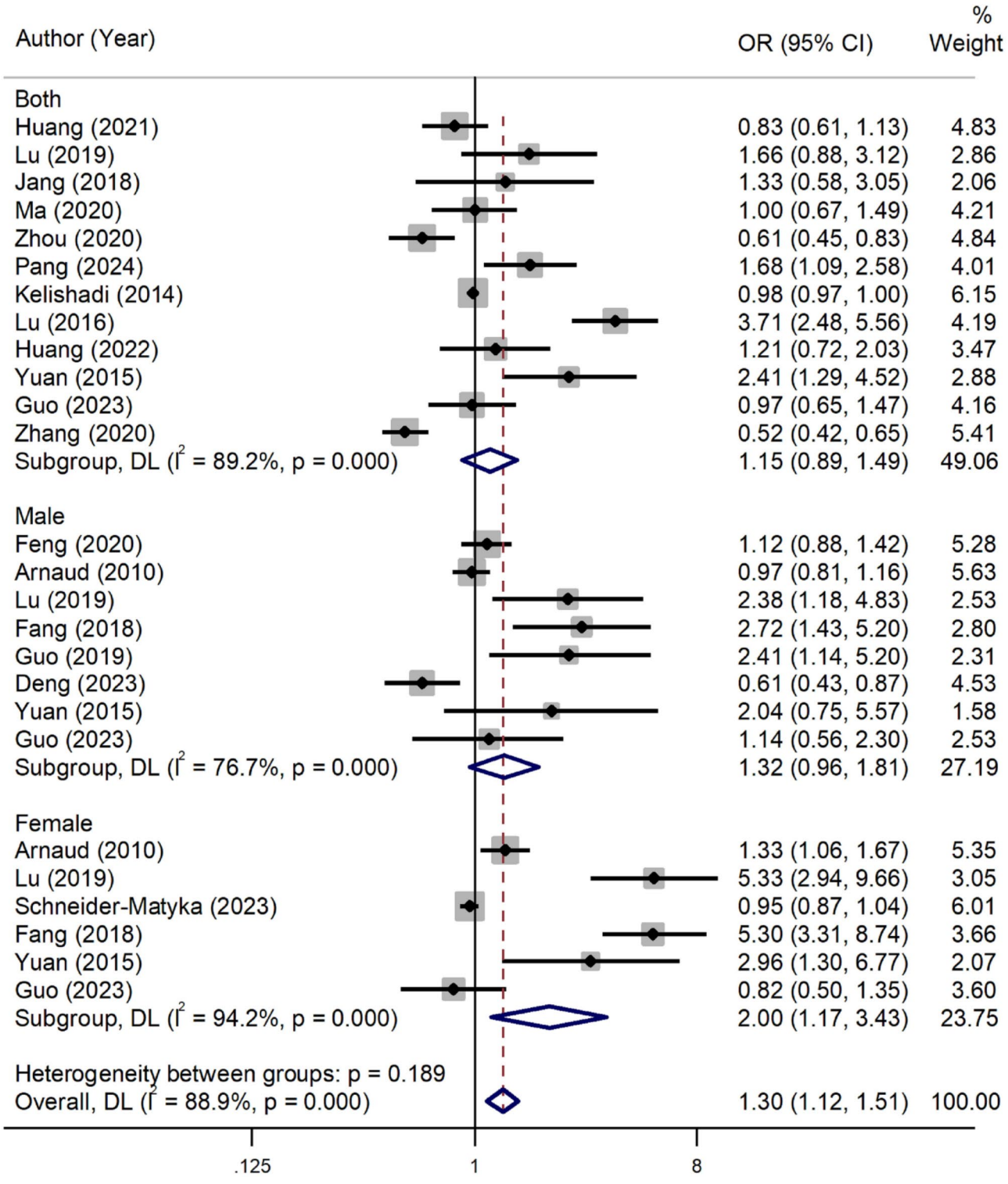

Fig. 2 Meta-analysis of the association between selenium levels and metabolic syndrome for the highest compared with the lowest exposure

(TG), and increased odds of dyslipidemia [43]. High serum selenium levels are associated with impaired fasting glucose and elevated fasting serum glucose [44]. While deficiency of selenium might be a risk factor for the development of high blood pressure [45], chronic overexposure to environmental selenium may increase blood pressure [46]. Moreover, a significant association between adiposity indices and selenium status has been

Table 2 Overall and subgroup analyses for the association between selenium levels and the odds of metabolic syndrome

Hormones	Subgroups	Studies (effect sizes)	Test of effect	Test of heterogeneity	
			OR (95%CI)	I^2 (%)	*P*
Overall		18 (26)	1.10 (1.03–1.17)	87.3	0.001
Population	Community-based	14 (20)	1.09 (0.95–1.25)	86.3	0.001
	Hospital-based	4 (6)	2.49 (1.57–3.96)	73.7	0.002
Quality of studies	Low risk of bias	13 (21)	1.36 (1.12–1.66)	88.2	0.001
	High risk of bias	5 (5)	1.29 (0.86–1.99)	92.8	0.001
Gender of participants	Both	12 (12)	1.02 (0.96–1.08)	85.6	0.001
	Male	8 (8)	1.32 (0.96–1.81)	76.7	0.001
	Female	6 (6)	2.00 (1.17–3.43)	94.2	0.001
MetS definition	NCEP-ATP III	5 (7)	1.75 (1.10–2.80)	86.9	0.001
	IDF	5 (6)	1.25 (0.91 to 1.72)	91.8	< 0.000
	Chinese criteria	5 (10)	1.69 (1.14 to 2.50)	82.4	< 0.000
	JIS	1 (1)	0.61 (0.45 to 0.83)	0.0	< 0.000
	NR	2 (2)	1.00 (0.37 to 2.71)	92.1	< 0.000
Sample size	≥ 1000 participants	9 (12)	1.16 (0.90 to 1.50)	84.6	< 0.000
	< 1000 participants	9 (14)	1.65 (1.34 to 2.05)	89.8	< 0.000
Age of participant	≥ 50 years	12 (19)	1.64 (1.23 to 2.20)	89.5	< 0.000
	< 50 years	4 (5)	1.10 (0.94 to 1.28)	70.3	0.009
	NR	2 (2)	0.82 (0.39 to 1.72)	65.1	0.090
Study type	Case-control	9 (16)	1.66 (1.33 to 2.06)	91.5	< 0.000
	Cohort	1 (1)	1.12 (0.88 to 1.42)	0.0	< 0.000
	Cross- sectional	8 (9)	1.09 (0.88 to 1.36)	69.4	0.001
Geographical region	Asian	16 (23)	1.52 (1.21 to 1.90)	88.7	< 0.000
	Non- Asian	2 (3)	1.05 (0.88 to 1.25)	72.7	0.026
Selenium assessment	ICP-MS	11 (15)	1.41 (1.03 to 1.93)	86.0	< 0.000
	Atomic absorption spectroscopy	4 (8)	1.80 (1.30 to 2.49)	91.2	< 0.000
	Spectrofluorimetry	1 (1)	0.95 (0.87 to 1.04)	0.0	< 0.000
	Neutron activation analysis	1 (1)	1.33 (0.58 to 3.05)	0.0	< 0.000
	NR	1 (1)	0.61 (0.43 to 0.87)	0.0	< 0.000
Sample type	Serum	15 (23)	1.43 (1.22 to 1.68)	89.0	< 0.000
	Urine	2 (2)	0.89 (0.70 to 1.14)	0.0	0.469
	Toenail	1 (1)	1.33 (0.58 to 3.05)	0.0	< 0.000
Adjustment for any covariates	Yes	15 (23)	1.42 (1.19 to 1.70)	85.4	< 0.000
	No	3 (3)	1.27 (0.58 to 2.82)	95.9	< 0.000
Adjustment for age	Yes	13 (20)	1.26 (1.08 to 1.47)	78.5	< 0.000
	No	5 (6)	1.94 (0.92 to 4.10)	96.1	< 0.000
Adjustment for sex	Yes	10 (16)	1.39 (1.09 to 1.77)	81.0	< 0.000
	No	8 (10)	1.46 (1.09 to 1.96)	92.1	< 0.000
Adjustment for smoking	Yes	11 (17)	1.44 (1.11 to 1.87)	85.4	< 0.000
	No	7 (9)	1.27 (1.03 to 1.56)	89.0	< 0.000
Adjustment for alcohol drinking	Yes	11 (17)	1.44 (1.11 to 1.87)	85.4	< 0.000
	No	7 (9)	1.27 (1.03 to 1.56)	89.0	< 0.000
Adjustment for total energy intake	Yes	2 (3)	1.14 (0.88 to 1.48)	58.1	0.11
	No	16 (23)	1.42 (1.20 to 1.67)	88.7	< 0.000
Adjustment for BMI	Yes	5 (7)	1.42 (0.80 to 2.50)	90.0	< 0.000
	No	13 (19)	1.38 (1.18 to 1.61)	87.4	< 0.000
Adjustment for education	Yes	5 (5)	0.93 (0.65 to 1.32)	71.3	0.10
	No	13 (21)	1.49 (1.26 to 1.75)	89.0	< 0.000
Adjustment for physical activity	Yes	8 (12)	1.63 (1.15 to 2.30)	89.7	0.001
	No	10 (14)	1.22 (1.03 to 1.43)	83.7	0.001

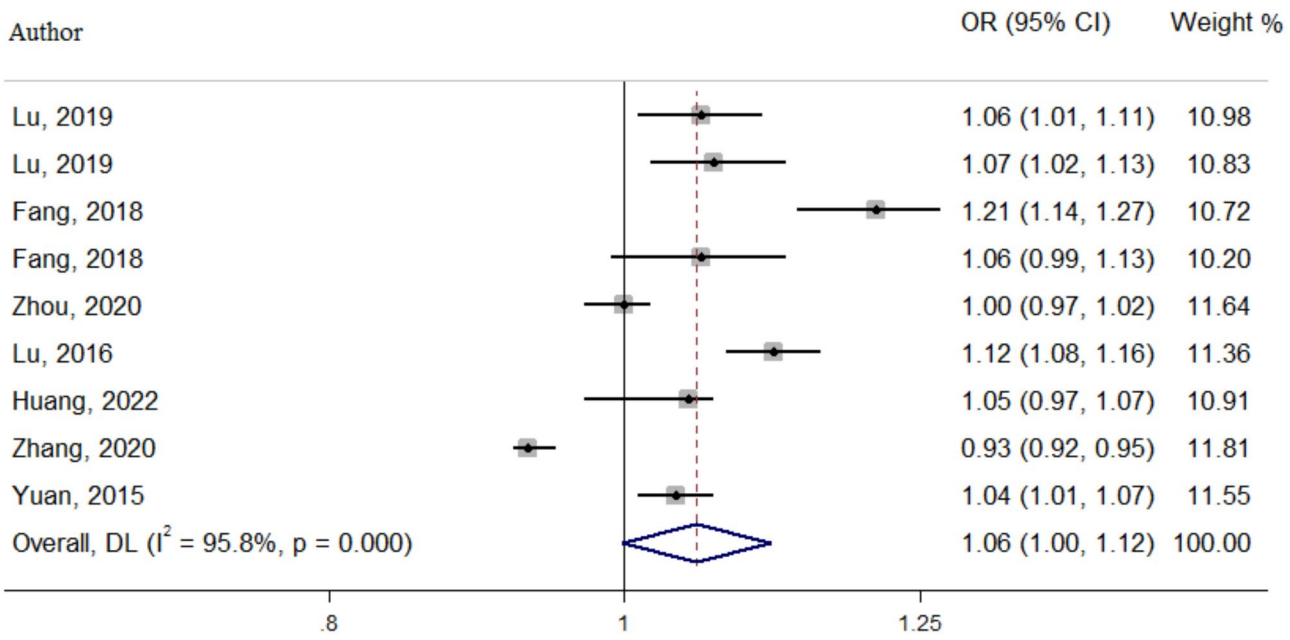

Fig. 3 Linear dose-response meta-analysis of the association between serum selenium levels and metabolic syndrome per 10 μg/L increment in selenium levels

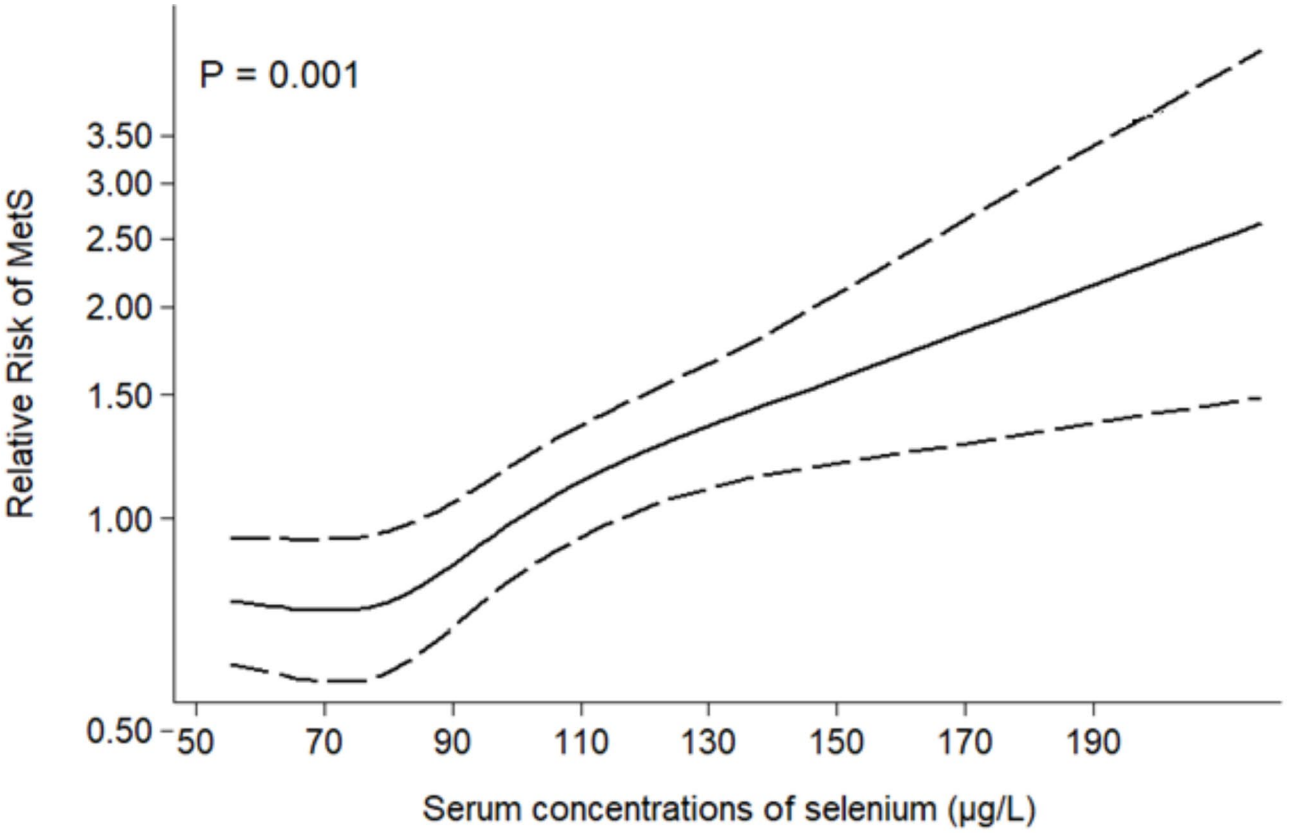

Fig. 4 Non-linear dose-response meta-analysis of the association between serum selenium levels and metabolic syndrome

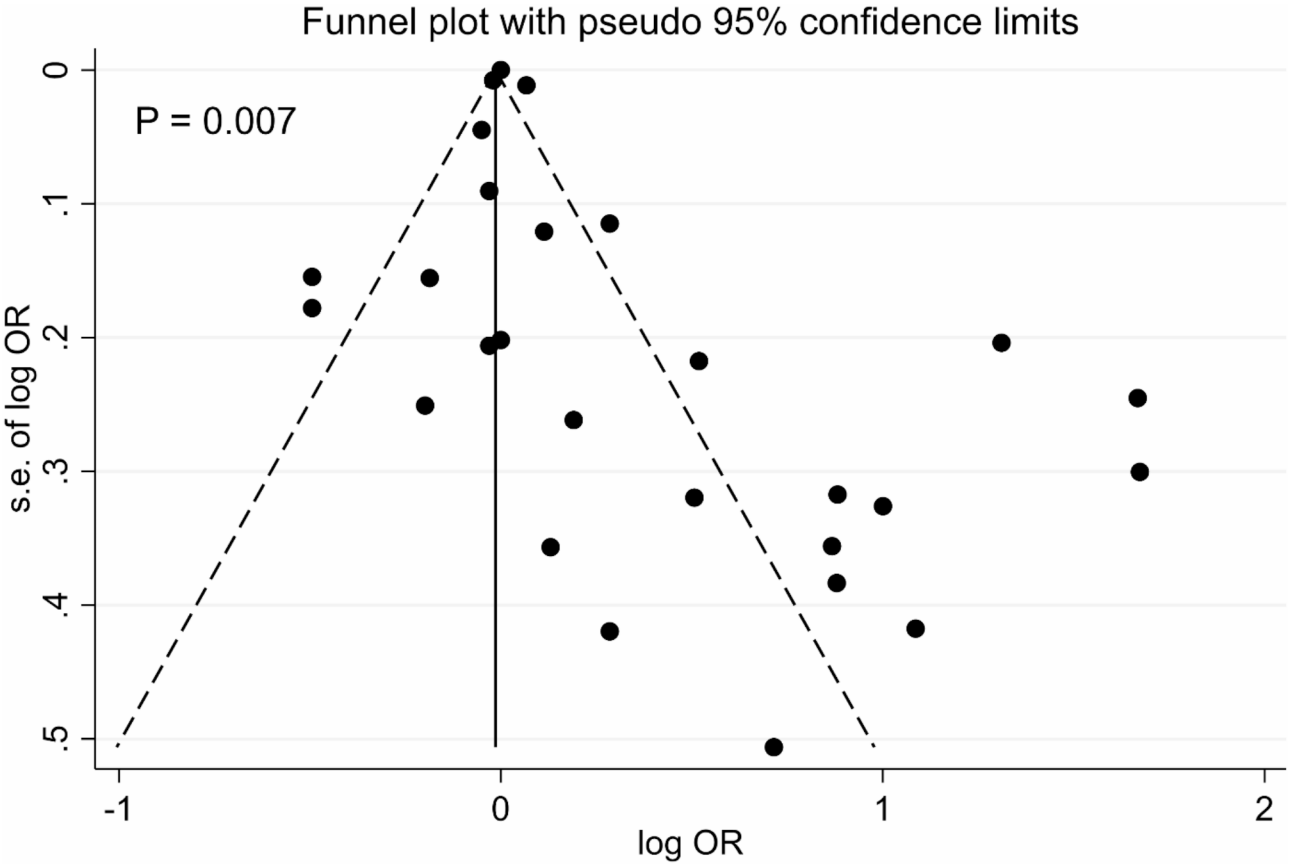

Fig. 5 Funnel plot for publication bias

suggested [47]. In contrast, reduced levels of selenium in urine and nails can be found in overweight or obese individuals [48].

In our study, we further identified the dose-response relationship between selenium and MetS, particularly in certain demographics such as females and older adults. These findings highlight the role of serum selenium as a biomarker for assessing MetS odds. The findings can inform public health policies aimed at addressing nutritional deficiencies or excesses in selenium, particularly in populations at higher odds for MetS. Identifying individuals with elevated selenium levels may help in early intervention strategies aimed at reducing MetS prevalence. Given the dose-response relationship observed, healthcare providers may consider monitoring selenium levels in patients at odds for MetS. This could lead to tailored dietary or supplementation recommendations to optimize selenium intake and potentially mitigate the associated risks. Given the potential risks associated with excessive selenium intake, public health policies may need to emphasize balanced dietary sources of selenium rather than high-dose supplementation. Future research should further explore the mechanisms behind this association and consider the implications for dietary guidelines to mitigate the risk of MetS while ensuring adequate selenium levels for overall health.

Supporting our findings, previous research has highlighted significant sex-specific effects of selenium on MetS odds, with associations observed either exclusively in females or showing a stronger correlation in females compared to males [17, 49]. The observed sex-specific differences could stem from a complex interplay of hormonal influences, metabolic processes, nutritional requirements, genetic factors, and age-related changes. Estrogen and other sex hormones may modulate how selenium affects metabolic processes. In females, estrogen can influence insulin sensitivity, adiposity, and lipid metabolism, potentially enhancing the impact of selenium on these pathways [50]. This hormonal interaction may explain why higher selenium levels are more strongly associated with MetS in women compared to men, who may not experience the same hormonal effects [17, 49]. Research indicates that selenium is more closely related to adiposity and lipid metabolism in females [49]. Differences in dietary patterns and nutritional needs between sexes could influence serum selenium levels and their health implications [51]. Women may require different amounts of selenium for optimal metabolic function compared to men [52], leading to differing associations

with MetS. Females often present with different comorbid conditions associated with MetS compared to males [53]. The interaction between selenium levels and these conditions may vary by sex [54], influencing how each gender responds to changes in selenium status. The study highlights that the association is particularly pronounced in older individuals (≥ 50 years). Age-related hormonal changes in women, such as menopause, can alter metabolic processes and potentially enhance the impact of selenium on MetS odds [55]. Additionally, biosynthesis of selenoenzymes and selenoproteins displays sex-specific differences in a dose-dependent manner [56]. In animal studies, the overexpression of glutathione peroxidase 1 (GPx1) in the context of hyperinsulinemia was observed exclusively in male mice [57], while GPx1 expression in the liver was found to be higher in female-derived cells compared to those from males [58]. Additionally, increased levels of selenoprotein P and insulin resistance were noted solely in female mice [59]. In human genetic studies, the England SELGEN study indicated that women exhibited higher expression levels of GPx1 and selenoprotein P genes associated with obesity [60]. Conversely, GPx1 polymorphisms were linked to a greater incidence of MetS in men within a Japanese adult cohort [61]. Furthermore, in a Finnish cohort, variations in the selenoprotein S gene locus were associated with the odds of cardiovascular disease exclusively in females [62]. These factors could explain the gender-specific relationship observed in our study. However, the underlying mechanisms warrant further investigation.

The relation of selenium to MetS could be mediated through mechanisms involving insulin resistance, lipid metabolism, adiposity, and hormonal regulation. Selenium plays a critical role in insulin signaling pathways, which are essential for glucose metabolism [63]. Elevated selenium levels have been associated with increased insulin resistance, increased triglycerides, and altered lipid profiles, particularly in females [17], which are the components of MetS. The direct effects of elevated blood selenium levels on glucose intolerance and dyslipidemia are mediated by various mechanisms, including the mevalonate pathway (which plays a role in the synthesis of selenoproteins and cholesterol), the regulation of lipoprotein synthesis by selenoprotein P, and the influence of selenium compounds, particularly GPx1, on protein tyrosine phosphatase 1B [13, 16]. Excess selenium disrupts the redox-methylation balance through the methionine-homocysteine cycle, resulting in excessive expression of GPx1 [64, 65]. Animal studies have shown that overexpression of GPx1 is linked to insulin resistance, hyperglycemia, and obesity [66]. In vitro and in vivo experiments suggest that selenoprotein P interferes with insulin signaling in the liver and muscle by reducing the phosphorylation of insulin receptors and protein kinase B (Akt) in response to insulin, while also decreasing insulin sensitivity by lowering phosphorylation of AMP-activated protein kinase (AMPK) [67, 68]. This disruption contributes to insulin resistance (IR) and the development of MetS. Regarding adiposity, serum selenium has been reported to have an inverse relationship with body mass index (BMI) in both men and women; however, it was associated with body fat percentage only in women according to the third NHANES study [69]. Such fat accumulation can exacerbate metabolic disturbances and increase the likelihood of developing MetS. Additionally, overexpression of GPx1 has been linked to the onset of insulin resistance and obesity [66], further promoting MetS development. A recent study indicated that a genetic variant of selenoprotein P is associated with glutathione peroxidase 1 (GPX1) activity and fasting insulin levels, suggesting that this mechanism may also play a role in the development of MetS [70]. Selenium may also influence the expression and activity of peroxisome proliferator-activated receptor gamma (PPAR-γ), a key regulator of glucose and lipid metabolism. Changes in PPAR-γ activity due to high selenium levels could affect metabolic processes and contribute to insulin resistance and dyslipidemia [39]. Furthermore, chronic overexposure to selenium may increase blood pressure, another component of MetS [46].

To our knowledge, this is the first meta-analysis exploring the link between selenium exposure across various biological samples and MetS. The strengths of the study include its dose-response analysis and subgroup evaluations across different factors while accounting for covariate effects on the findings. However, several limitations exist. First, most studies included were cross-sectional or case-control in design, preventing the establishment of causality and making it difficult to determine if elevated serum selenium levels in women with MetS are a cause or a consequence of metabolic abnormality. Future research should focus on prospective cohort studies to clarify the relationship between selenium concentrations and MetS. Additionally, the results for some subgroup analyses, such as urinary and toenail selenium concentrations were limited by the small number of studies available, warranting cautious interpretation of these results. Nonetheless, serum selenium remains a reliable measure of selenium status and is a standard method used in epidemiological investigations [71]. Moreover, significant heterogeneity was found across studies; we identified that variations in sample type, participant demographics (age and gender), study design, geographic location, definitions of MetS, methods for assessing selenium levels, sample sizes, and the level of adjustments for covariates contributed to this heterogeneity. Morovere, the test for publication bias indicated that some smaller studies may have been overlooked. The search was restricted to English-language

articles and some studies in other languages may be ignored. Lastly, we did not investigate the association of selenium exposure with individual components of MetS. Of the included studies, only a few studies provided risk estimates for specific components of MetS. Future studies could benefit from stratified analyses by MetS components to better understand these relationships and their implications for public health.

Conclusions

In conclusion, this meta-analysis revealed that higher serum concentrations of selenium are directly related to the elevated odds of MetS in females, exhibiting a dose-response relationship even after adjusting for covariates such as age, alcohol consumption, physical activity level, and smoking status. However, no significant association was found in males. Prospective cohort studies are required to confirm these findings and to clarify the mechanisms underlying these associations.

Abbreviations

MetS	Metabolic syndrome
OR	Odds ratio
GSH-PX	Glutathione peroxidase
NOS	Newcastle-Ottawa Scale
CI	Confidence intervals
ICP-MS	Inductively coupled plasma mass spectrometry
III NCEP-ATP III	National Cholesterol Education Program Expert Panel and Adult Treatment Panel
BMI	Body mass index
T2DM	Type 2 diabetes
GPx1	Glutathione peroxidase 1
AMPK	AMP-activated protein kinase
PPAR-γ	Peroxisome proliferator-activated receptor gamma

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12902-025-01858-8.

Supplementary Material 1

Acknowledgements
Not applicable.

Author contributions
This article was put forward by RY and JH performed data collection, data analysis, and article preparation. YZ and JH performed the analysis and collation of the literature. RY conceived of the study idea and article review. All authors read and approved the fnal manuscript.

Funding
Kaifeng Science and Technology Development Program, Project No. 2403029.

Data availability
The datasets used and/or analysed during the current study are available from the correspondingauthor on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
Kaifeng Science and Technology Development Plan in 2024 (Key science and technology projects)-2403029.

Received: 20 October 2024 / Accepted: 27 January 2025
Published online: 25 February 2025

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