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Association between Serum Selenium Level and the Presence of Diabetes Mellitus: A Meta-Analysis of Observational Studies

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Background: Epidemiological studies have suggested an association between selenium (Se) and diabetes mellitus (DM). However, different studies have reported conflicting results. Therefore, we performed a comprehensive meta-analysis to clarify the impact of Se on DM.

Methods: We searched the PubMed database for studies on the association between Se and DM from inception to June 2018.

Results: Twenty articles evaluating 47,930 participants were included in the analysis. The meta-analysis found that high levels of Se were significantly associated with the presence of DM (pooled odds ratios [ORs], 1.88; 95% confidence interval [CI], 1.44 to 2.45). However, significant heterogeneity was found ($I^2 = 82\%$). Subgroup analyses were performed based on the Se measurement methods used in each study. A significant association was found between high Se levels and the presence of DM in the studies that used blood (OR, 2.17; 95% CI, 1.60 to 2.93; $I^2 = 77\%$), diet (OR, 1.61; 95% CI, 1.10 to 2.36; $I^2 = 0\%$), and urine (OR, 1.49; 95% CI, 1.02 to 2.17; $I^2 = 0\%$) as samples to estimate Se levels, but not in studies on nails (OR, 1.24; 95% CI, 0.52 to 2.98; $I^2 = 91\%$). Because of significant heterogeneity in the studies with blood, we conducted a sensitivity analysis and tested the publication bias. The results were consistent after adjustment based on the sensitivity analysis as well as the trim and fill analysis for publication bias.

Conclusion: This meta-analysis demonstrates that high levels of Se are associated with the presence of DM. Further prospective and randomized controlled trials are warranted to elucidate the link better.

Keywords: Antioxidants; Diabetes mellitus; Selenium; Trace elements

INTRODUCTION

Selenium (Se) is an integral component of selenocysteine, a major structural amino-acid of selenoproteins [1]. In addition to its anti-oxidant and anti-inflammatory effects, Se is also involved in the synthesis of DNA and thyroid hormone [1]. The

cytoprotective properties of selenoproteins have garnered much interest leading to the discovery of selenoenzymes such as glutathione peroxidase (GPx), thioredoxin reductase (TrxR), and iodothyronine deiodinases (IDDs) [2]. GPx, which is one of the most well-studied selenoprotein family members, functions as a part of a defense mechanism to protect polyunsatu-

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rated fatty acids from the damaging effects of free radicals and inhibits the production of proinflammatory cytokines, reactive oxygen species, and reactive nitrogen species [3].

Due to the anti-oxidative and anti-inflammatory properties of Se, numerous studies have assessed the relationship between Se levels and conditions commonly known to be associated with increased oxidative stress and inflammation such as cardiovascular and neurodegenerative diseases, diabetes mellitus (DM), and cancer [4-6]. The association between Se and DM is one of the most vigorously investigated [7,8]. Studies have mainly been conducted based on the assumption that Se may be protective against DM [9]. Oxidative stress and inflammation have been reported to be involved in the onset and progression of diabetes [10,11]. Consistent with these findings, supplementation of antioxidants including Se has been shown to delay the onset of DM [6]. Moreover, data from isolated rat adipocytes show that Se in the form of selenate can act as an insulin mimetic [12,13]. Several cell and animal studies have suggested that Se plays a crucial role in controlling glucose homeostasis [14-17]. Moreover, epidemiological studies have evaluated the effects of Se on DM, but the conclusions have been conflicting [18-23]. Some studies report that Se is positively associated with DM [18-20] while others indicate a negative or no association [21-23]. Although there has been a meta-analysis including five observational studies [7], many additional studies have been published since then [18,19,24,25]. Hence, an updated meta-analysis to review the recent data is warranted to understand better and clarify the role of Se in DM. Therefore, we performed an updated meta-analysis by a comprehensive investigation of the literature with conflicting conclusions.

METHODS

Search strategy
The literature search was performed in accordance with the general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary Table 1). Two independent investigators (S.M. and J.K.) searched the PubMed and Embase databases and selected articles using a combination of terms "diabetes mellitus" and "selenium." Only articles published in English, before June 30, 2018, were included.

Study selection
The literature search yielded 2,085 potentially relevant articles,

of which 1,734 were screened for further review after excluding duplicate studies. If studies had multiple reports, the latest or the complete article was enrolled. All articles were electronically downloaded and screened for inclusion using a two-step method. After evaluation of the titles and abstracts according to predefined criteria, 1,696 articles were excluded if: (1) the studies had a different topic of interest; (2) there was no information on Se and DM; or (3) the study was published as an abstract, expert opinion, conference article, or review. Subsequently, the full texts of 38 selected articles were reviewed by two independent investigators (S.M. and J.K.), and any disagreement was resolved by a third investigator (J.M.Y.). A total of 20 articles were finally selected for the meta-analysis (Fig. 1).

Assessment of bias risk
Three researchers independently assessed the methodological quality of the included articles using the Newcastle-Ottawa Scale (NOS) for case control studies [26]. Nine items were used
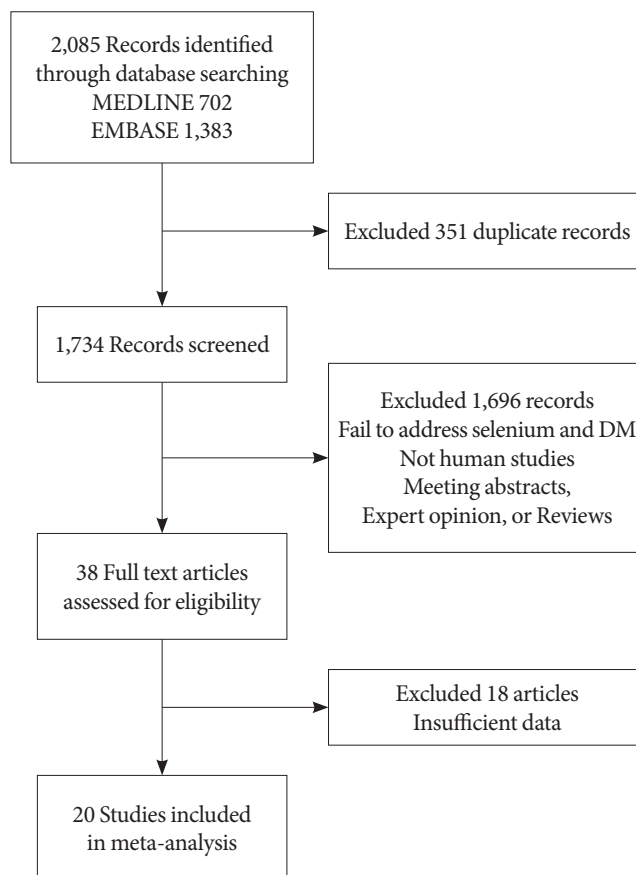
Fig. 1. Representation of the search strategy. DM, diabetes mellitus.

to assess the quality, and all articles scored 6 to 8 (Supplementary Table 2). We concluded that the quality of these cross-sectional studies did not affect the quality of our meta-analysis.

Data extraction

The following variables were independently extracted by the two investigators based on the same rules: first author, publication year, country, number of study participants, mean age, number of men and women, characteristics of study participants including coexisting diseases, the mean or median concentration of Se, and number of DM.

Data analyses and statistical methods

We calculated the pooled odds ratio (OR) with 95% confidence intervals (CIs) for the highest and lowest quantiles of Se using the Mantel-Haenszel method. The Higgins' I^2 statistic was used to test for heterogeneity. When I^2 was ≤50%, the included studies were considered to have little heterogeneity, and a fixed-effects model was used. However, I^2 >50% indicated heterogeneity and a random-effects model was used. Subgroup and sensitivity analyses were used to determine the cause of heterogeneity. The potential for publication bias was assessed by funnel plot analysis. To examine the strength of the outcome, we conducted a sensitivity analysis to estimate the effects of the remaining studies without the larger one. All statistical analyses were calculated using the statistical program R (R version 3.1.0, 2014, www.r-project.org).

Ethical statement

This article does not contain examinations performed on human participants. Then, ethical approval was not necessary.

RESULTS

Characteristics of selected studies

Twenty articles were included in the meta-analysis [18-25,27-38], and their main characteristics are summarized in Table 1. In total, 47,930 participants were enrolled, and 6,347 of them had DM. Sample sizes of these studies ranged from 128 to 8,876 participants. In these studies, Se concentrations were measured in the blood (n=13), nails (n=3), and urine (n=2). Two studies estimated Se intake from a food diary survey.

Se and DM

The meta-analysis found that high levels of Se were significantly

associated with the presence of DM (OR, 1.88; 95% CI, 1.44 to 2.45). However, there was significant heterogeneity (I^2=82%) (Fig. 2), and the funnel plot analysis showed significant publication bias (Supplementary Fig. 1). In the sensitivity analysis, the pooled OR changed little after omitting each study (Supplementary Fig. 2), and the heterogeneity ranged from 1.99 to 2.31, remaining statistically significant. A subgroup analysis based on the methods used for Se measurements, showed a significant association between high Se levels and DM in the studies on blood (OR, 2.17; 95% CI, 1.60 to 2.93; I^2=77%), dietary intake (OR, 1.61; 95% CI, 1.10 to 2.36; I^2=0%), and urine (OR, 1.49; 95% CI, 1.02 to 2.17; I^2=0%). However, studies on Se in the nails failed to show a significant association with DM (OR, 1.24; 95% CI, 0.52 to 2.98; I^2=91%). Because a significant heterogeneity was found in studies with blood, we conducted a sensitivity analysis and tested the publication bias. Sensitivity analysis found three outlier studies [34-36]. After omitting these studies, the estimated pooled OR was 1.64 (95% CI, 1.34 to 2.02) with no significant heterogeneity (I^2=40.3%). Since the funnel plot was asymmetric, publication bias was adjusted using the trim-and-fill method by adding two estimated missing studies, which produced significant results (OR, 1.82; 95% CI, 1.31 to 2.53). Because of the heterogeneity in Se levels in each study, we conducted a subgroup analysis based on the mean or median blood Se levels, using 100 μg/L as the cut-off value. The pooled OR was 2.17 (95% CI, 1.37 to 3.44; I^2=82%) in studies with mean Se <100 μg/L and 2.17 (95% CI, 1.40 to 3.39; I^2= 76%) in studies with mean Se ≥100 μg/L. A meta-regression analysis showed no significant effects of the mean Se levels (P=0.91) (Supplementary Fig. 3). The subgroup analysis using cut-off levels of Se of the highest group showed similar results (Table 2).

DISCUSSION

This meta-analysis of 20 observational studies showed that higher concentrations of Se were significantly associated with the presence of DM. Although significant heterogeneity was detected, the results did not change after adjustment by subgroup analysis, sensitivity analysis, and trim and fill analysis for publication bias.

DM is characterized by peripheral insulin resistance, with defects in insulin-secretion, which can be of varying degrees of severity. Although the mechanisms that underlie insulin resistance and diabetes are not fully understood, several studies

Table 1. Summary of the 20 observational studies included in the present meta-analysis

Study	Location	Design	Study population	No. of subjects	No. of DM (%)	Age, yr, mean or median	Selenium concentration, mean or median	Selenium measurement	Selenium classification
Yuan et al. (2018) [24]	China	Cross-sectional	Population based	2,078	1,039 (50) 1:1 match	Controls: 62.8 Cases: 62.9	Controls: 61.7 Cases: 64.3	Blood, μg/L	Quartile
Kohler et al. (2018) [18]	USA	Cross-sectional	Population based	1,727	172 (10)	63.1	139.8	Blood, μg/L	Tertile
Li et al. (2017) [19]	China	Cross-sectional	Population based	551	122 (22.1)	66.4	16.4	Blood, μg/L	Tertile
Galan-Chilet et al. (2017) [25]	Spain	Cross-sectional	Population based	1,452	120	49	84.2	Blood, μg/L	Tertile
Hansen et al. (2017) [22]	Norway	Cross-sectional	Population based	883	128	Controls: 61.4 Cases: 65.2	Controls: 101.4[a] Cases: 101.2[a]	Blood, μg/L	Quartile
Zhang et al. (2017) [27]	China	Cross-sectional	Population based	1,837	510	Controls: 55.2 Cases: 57.7	Controls: 200 Cases: 210	Blood, μg/L	Quartile
Skalnaya et al. (2017) [28]	Russia	Cross-sectional	Population based Menopausal women	128	64 (50) 1:1 match	Controls: 56.7 Cases: 55.8	Controls: 110.2 Cases: 126.8	Blood, μg/L	Median
Lu et al. (2016) [29]	Taiwan	Cross-sectional	Hospital, 40 yr or older	847	303 (35.8) 1:2 match	63.9	86.7[a]	Blood, μg/L	Quartile
Alehagen et al. (2016) [30]	Sweden	Cross-sectional	Population based 70–80 yr	668	146	NA	67.1	Blood, μg/L	Quartile
Gao et al. (2014) [23]	Sweden	Cohort	Population based	1,539	53 (for 10 yr)	49.7	75.6	Blood, μg/L	Tertile
Stranges et al. (2011) [31]	Italy	Cross-sectional	Population based	445	13	50.9	77.5	Blood, μg/L	Tertile
Laclaustra et al. (2009) [20]	USA	Cross-sectional	Population based	917	121	54.2	137.1	Blood, μg/L	Quartile
Bleys et al. (2007) [32]	USA	Cross-sectional	Population based	8,876	1,379	Controls: 42.8 Cases: 58.3	Controls: 125.7 Cases: 126.5	Blood, μg/L	Quintile
Su et al. (2016) [33]	China	Cross-sectional	Population based 65 yr or older	1,856	163	73.8	0.461[a]	Nail, μg/g	Quartile
Vinceti et al. (2015) [34]	Italy	Cross-sectional	Population based Women, 35–70 yr	621	226	Controls: 50.9 Cases: 51.2	0.57	Nail, μg/g	Quartile
Park et al. (2012) [21]	USA	Cohort	Population based Nurses, 30–55 yr Health professional, 40–75 yr	Men: 3,535 Women: 3,630	780	Men: 59.6 Women: 52.6	Men: 0.84 Women: 0.77	Nail, μg/g	Quintile
Liu et al. (2016) [35]	China	Cross-sectional	The coke oven workers	1,493	102	Controls: 41.8 Cases: 47	Controls: 10 Cases: 11.5	Urine, μg/L	Tertile
Feng et al. (2015) [36]	China	Cross-sectional	Population based	2,242	218	53	7.42[a]	Urine, μg/L	Quartile
Wei et al. (2015) [37]	China	Cross-sectional	Population based 40 yr or older	5,423	525	Controls: 52.9 Cases: 54.7	Controls: 43.2 Cases: 46.8	Intake, μg/day	Quartile
Stranges et al. (2010) [39]	Italy	Cohort	Population based Healthy women, 34–70 yr	7,182	253	Controls: 47.1 Cases: 51.2	Controls: 56.8 Cases: 60.9	Intake, μg/day	Quintile

DM, diabetes mellitus; NA, not available.
[a] Median.
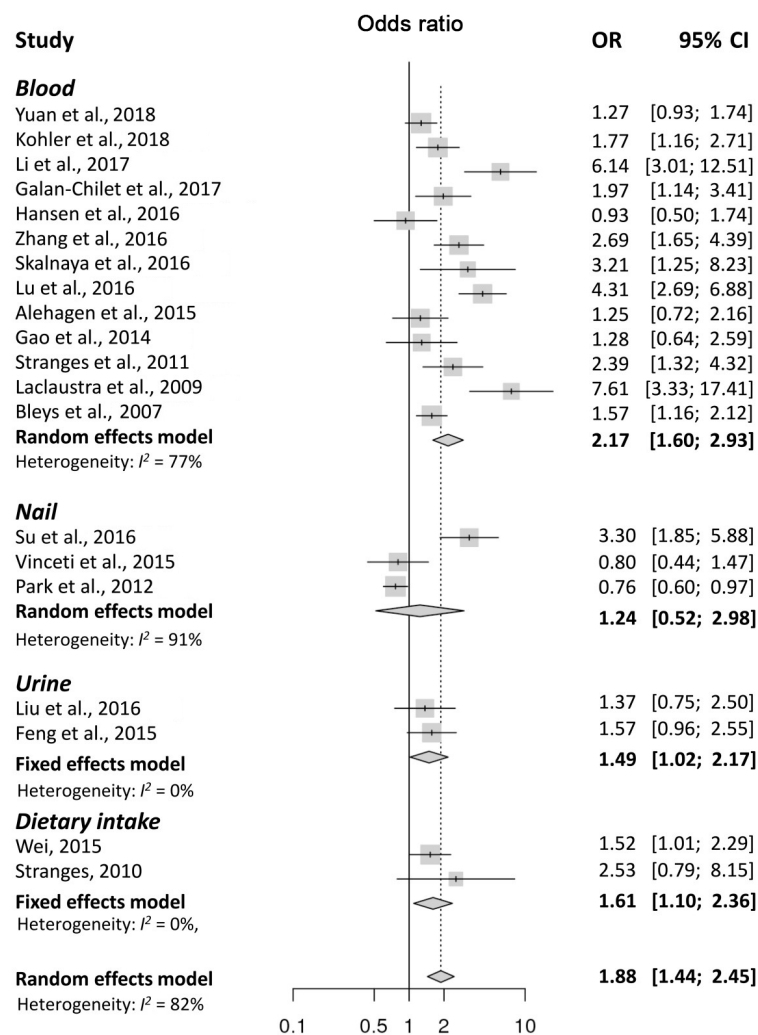
Fig. 2. Forest plots summarizing the odds ratio (OR) of the association between Se levels and the presence of diabetes mellitus. CI, confidence interval.

Table 2. The OR of the association between Se levels and the presence of DM by cut-off levels of Se of the highest group

Cut-off value of Se level of highest group	No. of studies	OR (95% CI)	Heterogeneity (I^2), %
<100 µg/L	6	1.90 (1.23–2.93)	74
100–120 µg/L	2	4.06 (2.67–6.18)	0
>120 µg/L	4	2.46 (1.48–4.10)	79

OR, odds ratio; Se, selenium; DM, diabetes mellitus; CI, confidence interval.

point to the role of oxidative stress in the onset and progression of DM [10]. Therefore, Se which has been long touted for its antioxidant properties was believed to prevent the onset of DM by counteracting oxidative stress [9]. Although earlier studies

have shown the insulin-mimetic and anti-diabetic effects of Se [16,39], recent experimental studies have revealed an unexpected association between high Se intake and insulin resistance or DM [40-44]. High Se exposure led to insulin resistance in rodents and pigs [45]. Although the mechanism underlying the diabetogenic effects of Se remains unclear, the high Se exposure might affect the expression of key regulators of glycolysis and gluconeogenesis. This action might potentially be mediated by the selenoprotein GPx-1 [45], as demonstrated by studies showing that overexpression of GPx-1 causes insulin resistance [46]. In skeletal muscles of pigs, high Se exposure led to an increase in GPx activity and expression of both forkhead box O1 and peroxisomal proliferator-activated receptor-γ coactivator 1α genes. It also led to a decrease in the

expression of the gene for the glycolytic enzyme pyruvate kinase [44].

A number of human studies have been conducted to evaluate the effects of Se on DM, but the conclusions have been inconsistent. Although previous meta-analyses showed a modest association between Se and DM, they included only five observational studies [7]. Therefore, this meta-analysis is noteworthy since it demonstrates an association between Se and the presence of DM based on a number of observational studies in large populations, providing significant epidemiological evidence to support the results of previous experimental studies.

Although our findings suggest that there is a significant association between increased exposure to Se and DM, data from clinical trials of Se supplementation have not been conclusive. The first large randomized trial was the Nutritional Prevention of Cancer (NPC) Trial, in which 200 μg Se per day or a matched placebo was administered to evaluate whether it could reduce the risk of non-melanoma skin cancer. Stranges et al. [47] performed the secondary analyses with the NPC data and showed an increased risk of DM among those in the Se intervention group compared to those in the placebo group. In contrast to the NPC trial, the Se and Vitamin E Cancer Prevention Trial (SELECT), the largest prostate cancer prevention trial with 35,533 participants showed no significant increase in the risk for DM after supplementation with 200 μg/day of Se compared to placebo [48]. However, in a subgroup analysis with the elderly aged >63 years, a significantly increased risk for DM was reported [49]. Mao et al. [8] on the other hand, showed no association between Se supplementation (200 μg/day) and the risk for DM in their meta-analysis with four randomized controlled trial studies.

The considerable strengths of this study are that a number of observational studies with large populations were included, and predefined subgroup analyses could be performed. However, the present study has some limitations. First, since most of the included studies were cross-sectional studies, further prospective studies will be needed to clarify the relationship between Se and the risk for DM. Second, the differences in age, sex ratio and Se concentrations between different studies could induce a bias. In addition, the different methods used for measuring Se levels could also have contributed to the bias. Third, because we compared the highest quantile of Se to the lowest quantile in each study, there might be great heterogeneity among the cases and control groups between different studies.

In conclusion, this meta-analysis demonstrates that high levels of Se are associated with the presence of DM. Although the mechanism remains unclear, our findings could have implications for nutritional supplementation in clinical settings. Further prospective and randomized controlled trials are warranted to elucidate the link between Se and DM better.

SUPPLEMENTARY MATERIALS

Supplementary materials related to this article can be found online at https://doi.org/10.4093/dmj.2018.0123.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

Conception or design: J.K., J.M.Y., S.M.
Acquisition, analysis, or interpretation of data: J.K., J.M.Y., S.M.
Drafting the work or revising: J.K., S.M.
Final approval of the manuscript: J.K., H.S.C., M.K.C., Y.K.R., H.J.Y., J.H.P., D.S.K., J.M.Y., S.M.

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Supplementary Table 1. PRISMA checklist

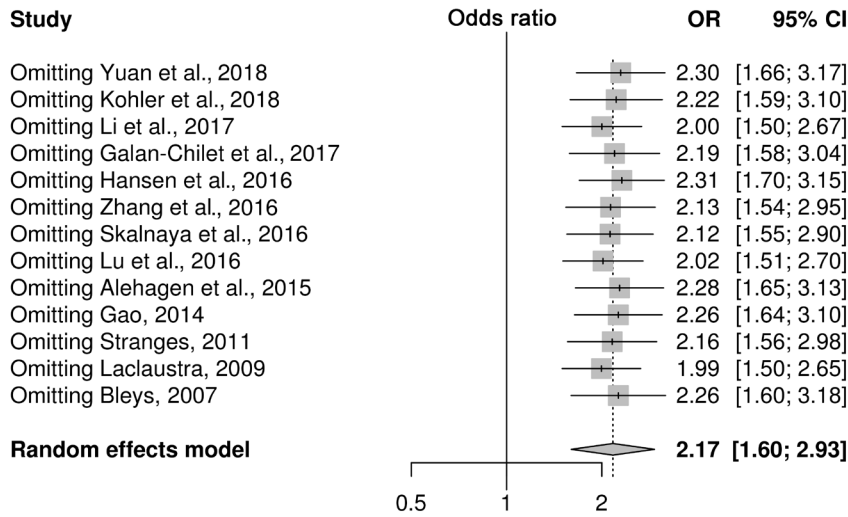| Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4–5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6–7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6, Fig. 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6–7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6, Supplementary Table 2
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8, Fig. 1

(*Continued to the next page*)

Supplementary Table 1. Continued

| Section/topic	#	Checklist item	Reported on page #
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Supplementary Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8–9, Fig. 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8–9, Fig. 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8–9, Supplementary Fig. 1, Supplementary Fig. 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8–9, Fig. 1, Supplementary Fig. 1
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11–12
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; NA, not available.

**Supplementary Table 2.** Quality assessment of included studies

Study	Adequate case definition	Represent-ativeness of the cases	Selection of controls	Definition of controls	Comparability	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate	Total
Yuan et al. (2018) [24]	*	*	*	*	**	*	*		8
Kohler et al. (2018) [18]	*	*	*	*	**	*	*		8
Li et al. (2017) [19]	*	*	*	*	**	*	*		8
Galan-Chilet et al. (2017) [25]	*	*	*	*	**	*	*		8
Su et al. (2016) [33]	*	*	*	*	**	*	*		8
Hansen et al. (2017) [22]	*	*	*	*	**	*	*		8
Zhang et al. (2017) [27]	*	*	*	*	**	*	*		8
Skalnaya et al. (2017) [28]	*	*	*	*	**	*	*		8
Lu et al. (2016) [29]	*			*	**	*	*		6
Liu et al. (2016) [35]	*			*	**	*	*		6
Feng et al. (2015) [36]	*	*	*	*	**	*	*		8
Wei et al. (2015) [37]	*	*	*	*	**	*	*		8
Alehagen et al. (2016) [30]	*	*	*	*		*	*		6
Vinceti et al. (2015) [34]	*	*	*	*	**	*	*		8
Gao et al. (2014) [23]	*	*	*	*	**	*	*		8
Park et al. (2012) [21]	*	*	*	*	**	*	*		8
Stranges et al. (2011) [31]	*	*	*	*		*	*		6
Stranges et al. (2010) [39]		*	*		**	*	*		6
Laclaustra et al. (2009) [20]	*	*	*	*	**	*	*		8
Bleys et al. (2007) [32]	*	*	*	*	**	*	*		8

Study	Odds ratio	OR	95% CI
Omitting Yuan et al., 2018		2.30	[1.66; 3.17]
Omitting Kohler et al., 2018		2.22	[1.59; 3.10]
Omitting Li et al., 2017		2.00	[1.50; 2.67]
Omitting Galan-Chilet et al., 2017		2.19	[1.58; 3.04]
Omitting Hansen et al., 2016		2.31	[1.70; 3.15]
Omitting Zhang et al., 2016		2.13	[1.54; 2.95]
Omitting Skalnaya et al., 2016		2.12	[1.55; 2.90]
Omitting Lu et al., 2016		2.02	[1.51; 2.70]
Omitting Alehagen et al., 2015		2.28	[1.65; 3.13]
Omitting Gao, 2014		2.26	[1.64; 3.10]
Omitting Stranges, 2011		2.16	[1.56; 2.98]
Omitting Laclaustra, 2009		1.99	[1.50; 2.65]
Omitting Bleys, 2007		2.26	[1.60; 3.18]
Random effects model		2.17	[1.60; 2.93]

0.5   1   2

Supplementary Fig. 1. Sensitivity analysis of the meta-analysis of studies comparing odds ratio (OR) of diabetes mellitus between the high and low selenium groups. CI, confidence interval.

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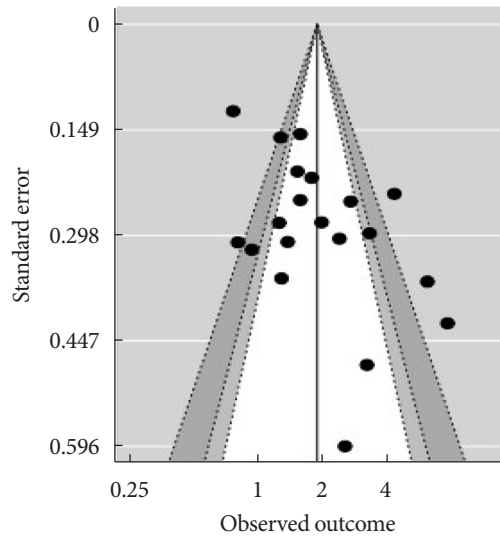
Supplementary Fig. 2. Funnel plot for publication bias in studies comparing odds ratio of diabetes mellitus between the high and low selenium groups.
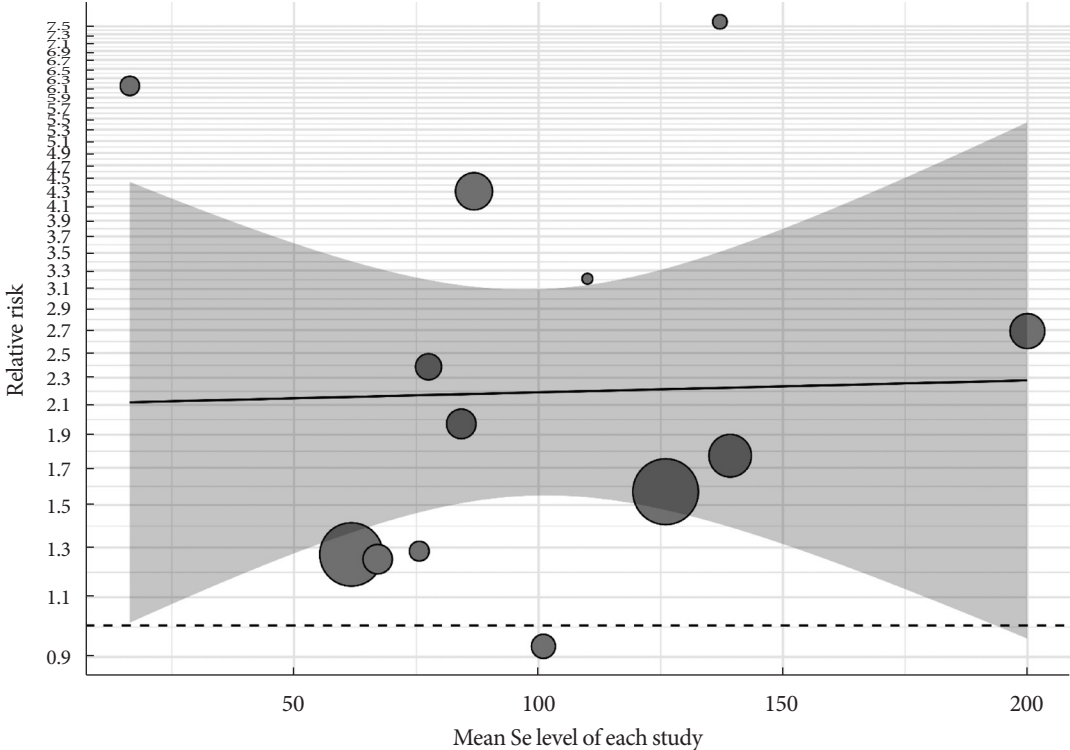
Supplementary Fig. 3. Meta-regression analysis based on the mean selenium (Se) level for each study.