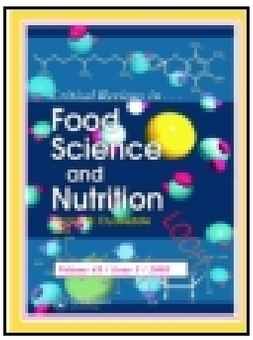

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REVIEW

Selenium status in the body and cardiovascular disease: a systematic review and meta-analysis

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ABSTRACT

Background: Both experimental and observational studies have provided conflicting evidence on the associations of selenium with incidence and mortality of cardiovascular disease (CVD). The aim of this study was to evaluate the association between selenium status in the body and incidence and mortality of CVD by performing a systematic review and meta-analysis of observational studies and randomized controlled trials. **Methods:** A systematic search for articles in MEDLINE (Ovid), Embase, Web of Science (Thomson Reuters) and Cochrane library (Wiley) was conducted. Thirteen of the 1811 articles obtained from the databases met our inclusion criteria and were considered in the final analysis. The effect sizes were presented as weighted relative risk (RR) and 95% confidence intervals (CIs) using random-effects model. To detect dose-response relationships, we used meta-regression. **Results:** Overall, there was a reduced risk of CVD incidence (RR = 0.66; 95% CI: 0.40–1.09) and mortality (RR = 0.69; 95% CI: 0.57–0.84) in physiologically high selenium status compared to low selenium status in the body. There was a 15% (RR = 0.85, 95% CI: 0.76–0.94) decreased risk of CVD incidence per 10 μg increment in blood selenium concentration. In addition, a statistically significantly nonlinear dose-response relationship was found between CVD mortality and increased blood selenium concentration with the lowest risk at the 30–35 μg increment in blood selenium. **Conclusions:** Physiologically high selenium levels in the body are associated with decreased risk for CVD incidence and mortality, however, people should be cautious about the potential harmful effects from excessive intake of selenium.

KEYWORDS
Cardiovascular disease; incidence; meta-analysis; mortality; selenium status

Introduction

Selenium is a natural element that is essential for normal human physiological processes in trace amounts. It is incorporated into the amino acid selenocysteine which is required in selenoproteins. In humans, twenty-five genes encoding for selenoproteins have been identified (Hatfield et al. 2016). Although the roles of most of the selenoproteins are not well understood, thioredoxin reductases and glutathione peroxidases (GPx) have been characterized as antioxidants, thyroid hormone deiodinases as thyroid hormone metabolism regulator, and Selenoprotein P as selenium transporter, transporting and delivering selenium in peripheral tissues (Papp et al. 2007; Rayman 2000).

Whereas overt selenium deficiency is rare, there are indications that selenium levels below the recommended daily intake (55 μg/day) are accompanied by low expression of selenoproteins, which could lead to deleterious health effects including cancer (Kuria et al. 2020; Hurst et al. 2010), cardiovascular disease (CVD) and immune dysfunction (Rayman 2000). Selenium deficiency has been associated with incidences of CVD for example Keshan disease that is characterized by cardiomyopathy, a disease that was endemic in some parts of China with low selenium soils (Chen 2012). Experiments that focused on selenium deficiency in the development of CVD indicated that cardiac pathologies may be due to increased oxidative stress and its sequelae (Venardos et al. 2007). Reactive oxygen species (ROS) generated during ischemia appeared to damage the myocardium and its blood vessels leading to poor post-ischemic recovery (Venardos et al. 2007). In animal experiments, selenium supplementation was used to reduce the production of ROS during ischemia and reperfusion injury by increasing the activity of GPx-1 (Venardos et al. 2004). Selenium supplementation has also been suggested to reduce

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mortality among people with very low selenium intake, as observed after supplementation for a period of four years (Alehagen et al. 2016).

Although the above observations indicate a relationship between suboptimal selenium intake and incidence of CVD, evidence on selenium having protective effects on CVD is still inconclusive. While some studies indicate that suboptimal selenium is an independent risk factor for myocardial infarction (MI; Salonen et al. 1982; Suadicani, Hein, and Gyntelberg 1992), others have not found this to be the case (Rayman 2000; Stranges et al. 2006). A study by Lubos et al. found an association of low selenium levels with increased risk of acute coronary syndrome but not with stable angina pectoris (Lubos et al. 2010), while another study by Vinceti et al suggests that chronic overexposure to environmental selenium may increase blood pressure (Vinceti et al. 2019). Evidence on the association between low selenium levels and increased mortality is also conflicting. While some studies indicate that selenium can reduce mortality (Alehagen et al. 2016), others have found no association (Stranges et al. 2006) or even indicate that selenium in certain levels could increase mortality (Bleys, Navas-Acien, and Guallar 2008). The objective of the present study was to examine if there is an association between selenium status in the body and CVD incidence and mortality by performing a systematic review and meta-analysis. The results are expected to be of importance for public health policies regarding dietary selenium intakes, especially in regions with low selenium soil levels.

Methods

Data sources and search strategy

To carry out the systematic review and meta-analysis, we used a protocol that was constructed in line with the standard criteria the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (Moher et al. 2009) (Supplementary material 1) and the Meta-analysis of Observational Studies in Epidemiology (Stroup et al. 2000) (Supplementary material 2). The study was registered in the international prospective register of systematic reviews PROSPERO (https://www.crd.york.ac.uk/prospero/) with registration number CRD42020161851. (The PROSPERO team has not checked eligibility of the published registration till the submission of the manuscript due to the COVID-19 emergency.)

A systematic search was carried out by two librarians from the Research Consultation Group of the University Library, Karolinska Insitutet, Sweden in MEDLINE (Ovid), Embase, and Web of Science core collection (Thomson Reuters) for observational studies that investigated selenium status in body and its associations with CVD incidence and mortality. In addition, another systematic search was done in Cochrane library (Wiley) for randomized controlled trials (RCTs) (Supplementary material 3). To minimize publication bias, we also searched for additional studies in gray literature sources which include Virtual Health Library (http://bvsalud.org/en/), NARCIS (https://www.narcis.nl/), Gray literature report (http://greylit.org/), and Open gray EU (http://opengrey.eu/).

The free text and the Medical Subject Headings terms used for the search included: selenium, body burden, body level, body status, CVD, coronary heart disease (CHD), MI, ischemic cardiovascular disease (ICD), cardiomyopathy, heart disease, incidence, mortality, blood, urine, toenail, feces, observational study, case control study, cohort, and clinical trial. We included all the observational studies and RCT, addressing selenium in human body and CVD incidence and mortality since the beginning of the databases to December 2018. Furthermore, a manual retrieval was performed afterwards to ensure inclusion of the latest literatures. To ensure inclusivity of all studies, no language limitations were imposed for literature searching, but for articles published in languages other than English or Chinese, only the abstracts were reviewed.

Inclusion and exclusion criteria

Inclusion criteria: (1) original studies on human; (2) selenium levels in blood, urine, feces or toenail has been measured in the study; (3) had incidence and/or mortality of all CVD or specific CVD as outcomes; (4) had at least two selenium dose groups; (5) reported risks as well as the associated 95% confidence intervals (CIs) or other data to estimate the standard deviation or standard error; (6) risk estimates reported had been adjusted for potential confounders.

Exclusion criteria: (1) narrative reviews, editorial papers, or methodological papers; (2) studies that evaluated selenium but could not reflect selenium status in the body; (3) studies that had not reported selenium doses; (4) studies that had no outcomes related to CVD incidence or mortality; (5) animal studies.

Data extraction

After the systematic search of the relevant articles in the databases, two investigators (A.K. and H.T.) embarked on screening and identification of potentially relevant abstracts independently. For any disagreements that occurred between the two investigators regarding the eligibility of a study, there was a through discussion or advising from an academic expert (M.L. or Y.C.). Later, articles for selected abstracts were downloaded and data extracted by A.K. and H.T. independently by use of a standardized form in Microsoft excel. Data extracted was compared and summarized to have one final document on which analysis was conducted. The information extracted included: name of the first author, study design, year of publication, duration of study, country that the study was conducted in, selenium measurement, sample type, selenium dose levels, sample size, CVD mortality and/or incidence cases of each selenium dose level, outcome ascertainment method, relative risk (RR) and the associated 95% CI, statistical analysis method used, and the confounders adjusted for in each study. For studies that reported several multivariable adjusted effect estimates,

we selected the effect estimate that had been adjusted for all the potential confounders.

Study quality assessment

To assess the quality of each observational study, we used the Newcastle-Ottawa scale which assesses the quality of non-randomized studies in meta-analysis (Bae 2016). In addition, the Cochrane collaboration's tool for assessing risk of bias in randomized trials was also used to assess the quality of RCT (Higgins et al. 2011) (Supplemental material 5). A.K. and M.L. assessed the quality of the articles independently then average scores were taken as the final quality assessment (Supplementary material 4).

Statistical analysis

In the pooled meta-analysis, hazard ratios, odds ratios or incidence rate ratios were used as RR because they approximate one another when event rates are small (Zhang and Yu 1998). To increase the power in our study, all CVD, including CHD, MI, and ICD, were combined and analyzed as CVD. RR for incidence and mortality were pooled and analyzed separately.

Statistical heterogeneity was investigated using I^2 statistics (Higgins et al. 2003). $I^2 > 30\%$ was considered moderate heterogeneity while $I^2 > 50\%$ was considered substantial heterogeneity. A p-value of heterogeneity <0.05 was considered statistically significant (Higgins and Green 2011). Random-effects model was used when heterogeneity presented among studies otherwise a fixed-effects model was used (DerSimonian and Laird 1986). The possibility of publication bias was assessed by the combination of Egger's test and visual inspection of funnel plots (Egger et al. 1997).

RR for the highest doses of selenium compared with the lowest doses in every study were pooled to investigate the effect of highest dose of selenium on CVD incidence or mortality. The influence analysis to investigate the influence of a single study on the overall risk was also performed as a sensitivity analysis.

To investigate if the effects of selenium on CVD incidence and mortality varied with selenium level and other variables, subgroup analysis was performed by study design, sample type, disease type, region of study conducted, and dose level of selenium in blood or toenail. To assess potential linear and nonlinear dose-response relationship between increment in selenium level and CVD incidence and mortality, meta-regression was performed. Restricted cubic splines were used to assess nonlinear dose-response relationship. All the analysis was performed in Stata 16.0 (StataCorp LLC, College Station, TX) and a two-sided p value <0.05 was considered statistically significant unless otherwise specified.

Results

Characteristics of the studies

One thousand eight hundred and eleven articles were obtained from all the databases, after removal of the duplicates, and 1258 articles remained after screening by title and abstarct. Of the 1258 articles remaining, 242 articles were considered relevant for the meta-analysis by more detailed review. Of the 242 downloaded full articles, 13 met our inclusion criteria. These included five cohort studies (Lubos et al. 2010; Alehagen et al. 2016; Eaton et al. 2010; Bleys, Navas-Acien, and Guallar 2008; Wei et al. 2004), five case-control studies (Salonen et al. 1982; Kardinaal et al. 1997; Yoshizawa et al. 2003; Yuan et al. 2017; Alissa et al. 2006), one nested case-control (Salvini et al. 1995) and two RCTs (Stranges et al. 2006; Alehagen, Aaseth, and Johansson 2015) (Figure 1).

Of the 13 articles included in the meta-analysis, seven addressed mortality (Alehagen et al. 2016; Salonen et al. 1982; Lubos et al. 2010; Bleys, Navas-Acien, and Guallar 2008; Eaton et al. 2010; Wei et al. 2004; Alehagen, Aaseth, and Johansson 2015), five addressed incidences (Kardinaal et al. 1997; Yoshizawa et al. 2003; Yuan et al. 2017; Alissa et al. 2006; Salvini et al. 1995) and one addressed both incidence and mortality (Stranges et al. 2006). Majority of the case-control studies addressed CVD incidences with only Salonen et al. addressing mortality. There was a total of 3258 cases of CVD incidence and 3592 cases of CVD mortality in a population of 41,739 (mean age = 58.5 years with a standard deviation of 5.8 years). Most studies measured selenium in blood (n = 11), and two studies measured selenium in toenail. No eligible studies measured selenium in urine or feaces. In total, 51 doses of body selenium were extracted (10 doses in toenail samples and 41 doses in blood samples). A more detailed summary of characteristics of the included studies is reported in the Supplemental Table S1.

Association between selenium status and CVD incidence and mortality

The funnel plot of RR for all included articles appears symmetric (Figure 2). Although one RR from Alissa's study show bias with other studies (Figure 2a and c), no statistically significant publication bias was found by Egger's test. There was no presence of publication bias for the studies that addressed either mortality or incidence as shown in the funnel plots (Figure 2).

Statistically significant heterogeneity was present among the RR on CVD incidence (I^2: 79.88%, $p = 0.01$). Although the overall heterogeneity by use of the I^2 statistic is low at 28%, the Q-statistic indicates a statistically significant heterogeneity ($p = 0.02$; Figure 3). Pooled RR of the highest selenium levels compared to the lowest selenium levels showed a non-statistically significant decrease in incidence of CVDs (RR = 0.66; 95% CI: 0.40–1.09; Figure 3) while for mortality the decrease was statistically significant (RR = 0.69; 95% CI: 0.57–0.84; Figure 3). The pooled RR for CVD mortality based on the fixed-effects model was also statistically significant (RR = 0.76; 95% CI: 0.67–0.87). Overall, there was a reduced risk of CVD incidence and mortality together in physiologically high body selenium status compared to low body selenium status (RR = 0.70; 95% CI: 0.61–0.81; Figure 3).

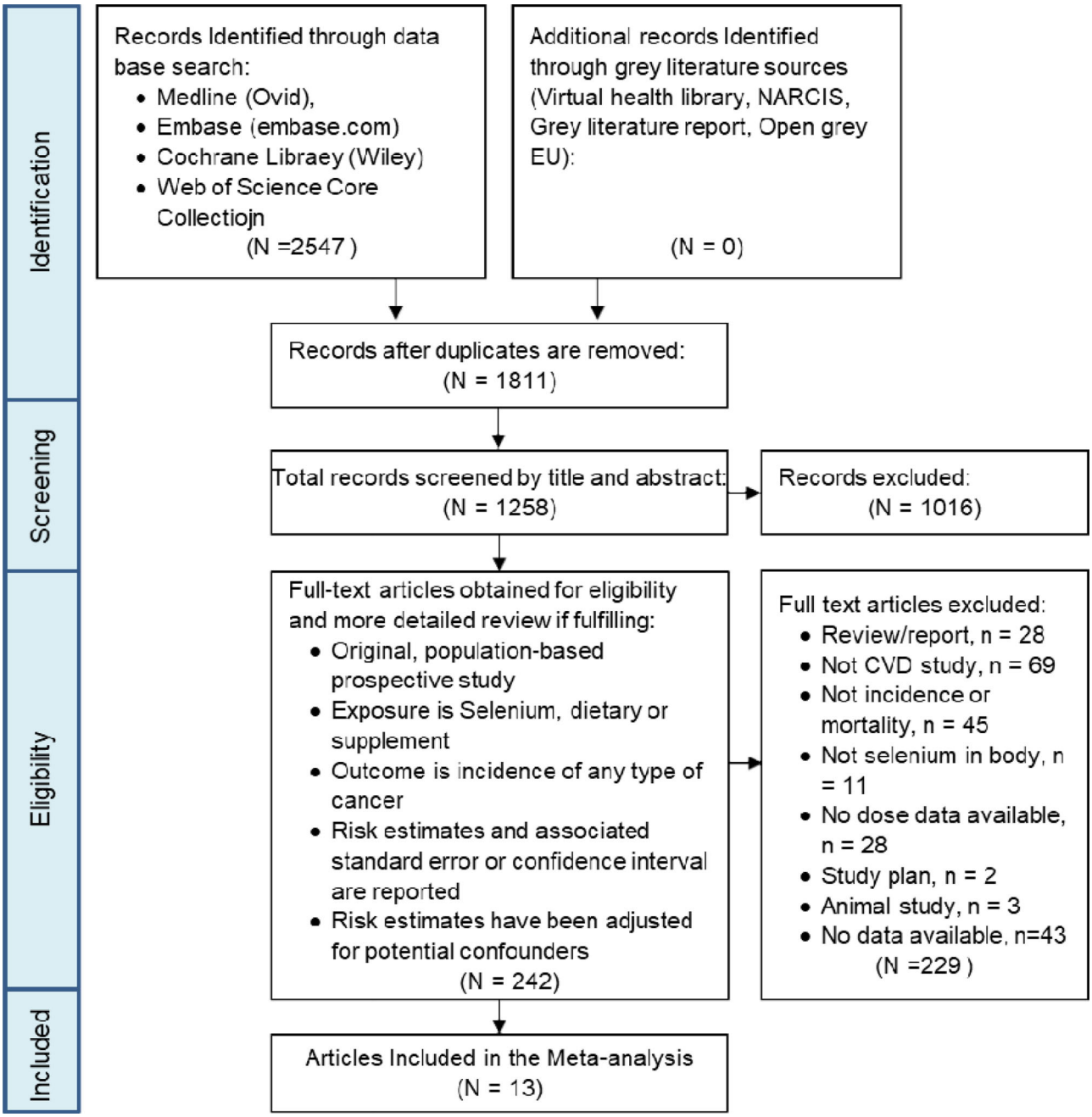

Figure 1. PRISMA flow diagram for screening and selection of articles on body selenium status and cardiovascular diseases incidence and mortality.

Subgroup analysis

Table 1 summarizes pooled results for subgroups by study design, sample type, specific disease, study region, and selenium dose. The RCT studies showed a statistically non-significantly decreased risk of physiologically high selenium body status in CVD mortality (RR = 0.84, 95% CI: 0.41–1.73) but null effect on CVD incidence (RR = 1.07, 95% CI: 0.81–1.42). The cohort studies showed a statistically significant decreased risk of physiologically high selenium body status for both CVD mortality and incidence with a RR of 0.75 (95% CI: 0.64–0.87) and of 0.80 (95% CI: 0.70–0.92), respectively. There was a statistically significantly decreased risk in CVD mortality in only one case-control study (RR = 0.45, 95% CI: 0.25–0.83) and a marginally statistically significant decrease in CVD incidence (RR = 0.86, 95% CI: 0.73–1.01). Toenail selenium showed a statistically non-significantly decreased risk in CVD incidence (RR = 0.89, 95% CI: 0.77–1.04) while blood selenium showed a statistically significantly decreased risk in both incidence (RR = 0.84, 95% CI: 0.71–0.99) and mortality (RR = 0.71, 95% CI: 0.60–0.85). Physiologically high body selenium status was associated with decreased mortality of both CHD (RR = 0.73, 95% CI: 0.59–0.91) and CVD (RR = 0.71, 95% CI: 0.55–0.91), and with decreased CHD incidence (RR = 0.83, 95% CI: 0.74–0.94), but showed no association with CVD incidence (RR = 1.07, 95% CI: 0.81–1.42). Reduced risk for CVD mortality was found in studies conducted in Asia (RR = 0.59, 95% CI: 0.45–0.79) and Europe (RR = 0.55, 95% CI: 0.45–0.68), while reduced risk for CVD incidence was only found in studies conducted in Europe (RR = 0.76, 95% CI: 0.61–0.94).

Table 1. Pooled RRs by study designs, sample type, disease, region of study conducted, and dose level of selenium in blood or toenail.

Outcome	Group variable	Subgroups	No. of doses	Pooled RR (95% CI)	I^2	p of I^2
Mortality	Study design	Case-control	1	0.45 (0.25–0.83)		
		RCT	5	0.84 (0.41–1.73)	72.63%	0.003
		Cohort*	12	0.75 (0.64–0.87)	39.14%	0.106
	Sample type	Blood	18	0.71 (0.60–0.85)	54.32%	0.003
		Toenail	0			
	Disease	CHD*	6	0.73 (0.59–0.91)	0.00%	0.575
		CVD	12	0.71 (0.55–0.91)	70.90%	0.000
	Region	Asia*	3	0.59 (0.45–0.79)	0.00%	0.553
		Europe*	8	0.55 (0.45–0.68)	0.00%	0.494
		US*	7	0.93 (0.82–1.05)	24.58%	0.241
	Dose level	Low (blood)*	2	0.46 (0.32–0.68)	0.00%	0.936
		Normal (blood)	16	0.75 (0.64–0.90)	49.95%	0.011
		Low (toenail)	0			
		High (toenail)	0			
Incidence	Study design	Case-control	13	0.86 (0.73–1.01)	47.76%	0.028
		RCT*	3	1.07 (0.81–1.42)	0.00%	0.587
		Cohort*	3	0.80 (0.70–0.92)	44.57%	0.165
	Sample type	Blood	11	0.84 (0.71–0.99)	29.82%	0.012
		Toenail*	8	0.89 (0.77–1.04)	10.68%	0.347
	Disease	CHD	16	0.83 (0.74–0.94)	18.23%	0.027
		CVD*	3	1.07 (0.81–1.42)	0.00%	0.587
	Region	Asia	4	0.52 (0.21–1.31)	97.23%	0.001
		Europe*	4	0.76 (0.61–0.94)	0.00%	0.650
		US*	11	1.02 (0.88–1.21)	0.00%	0.853
	Dose level	Low (blood)	1	0.92 (0.74–1.14)		
		Normal (blood)	10	0.82 (0.66–1.02)	37.39%	0.010
		Low (toenail)*	3	0.79 (0.62–1.00)	0.00%	0.647
		High (toenail)*	5	0.97 (0.80–1.19)	23.70%	0.263

RCT: Randomized controlled trial; CVD, cardiovascular diseases; CHD, coronary heart disease
*Fixed-effects model was used.

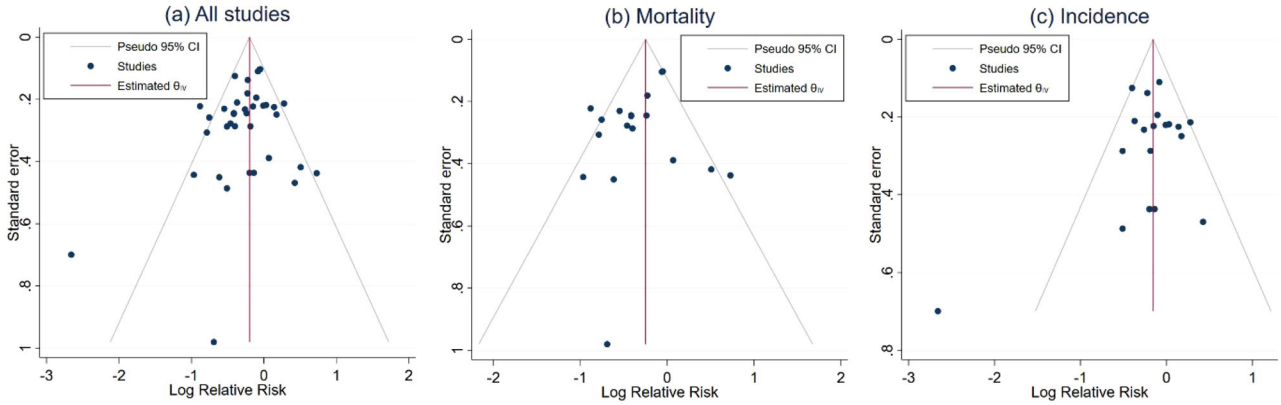

Figure 2. Funnel plot with pseudo 95% confidence limit.

The reference range of serum selenium concentration in adults is 70–150 μg/L (González et al. 2006), and the highest blood selenium concentration in our study is 150 μg/L. Therefore, we divided the doses into physiologically low and normal subgroups for blood sample. There are no specific reference values for toenail selenium available, therefore, we divided the doses into physiologically low- and high-level subgroups by their median for toenail samples. The stratified analysis by selenium doses shows that CVD mortality was reduced in both low (RR = 0.46, 95% CI: 0.31–0.68) and normal (RR = 0.75, 95% CI: 0.64–0.90) levels of blood selenium, compared to the lowest selenium levels in the included studies (Table 1). However, neither blood selenium nor toenail selenium are statistically significantly associated with CVD incidence in the stratified analysis by selenium dose level (Table 1).

Dose-response relationship between increment in body selenium and risk of CVD incidence and mortality

Meta-regression analysis revealed a statistically significant linear dose-response relationship between blood selenium concentration and CVD incidence. The risk of CVD incidence reduced 15% (RR = 0.85, 95% CI: 0.76–0.94) per 10 μg increment in blood selenium concentration (Table 2, Figure 4). No statistically significant dose-response relationship was found between blood selenium increment and the risk for CVD mortality, and between toenail selenium increment and risk for CVD incidence (Table 2).

Meta-regression analysis with restricted cubic splines indicated a statistically significantly non-linear dose-response relationship between the risk of CVD mortality and blood selenium increment. The risk for the CVD mortality was the lowest when blood selenium was increased between

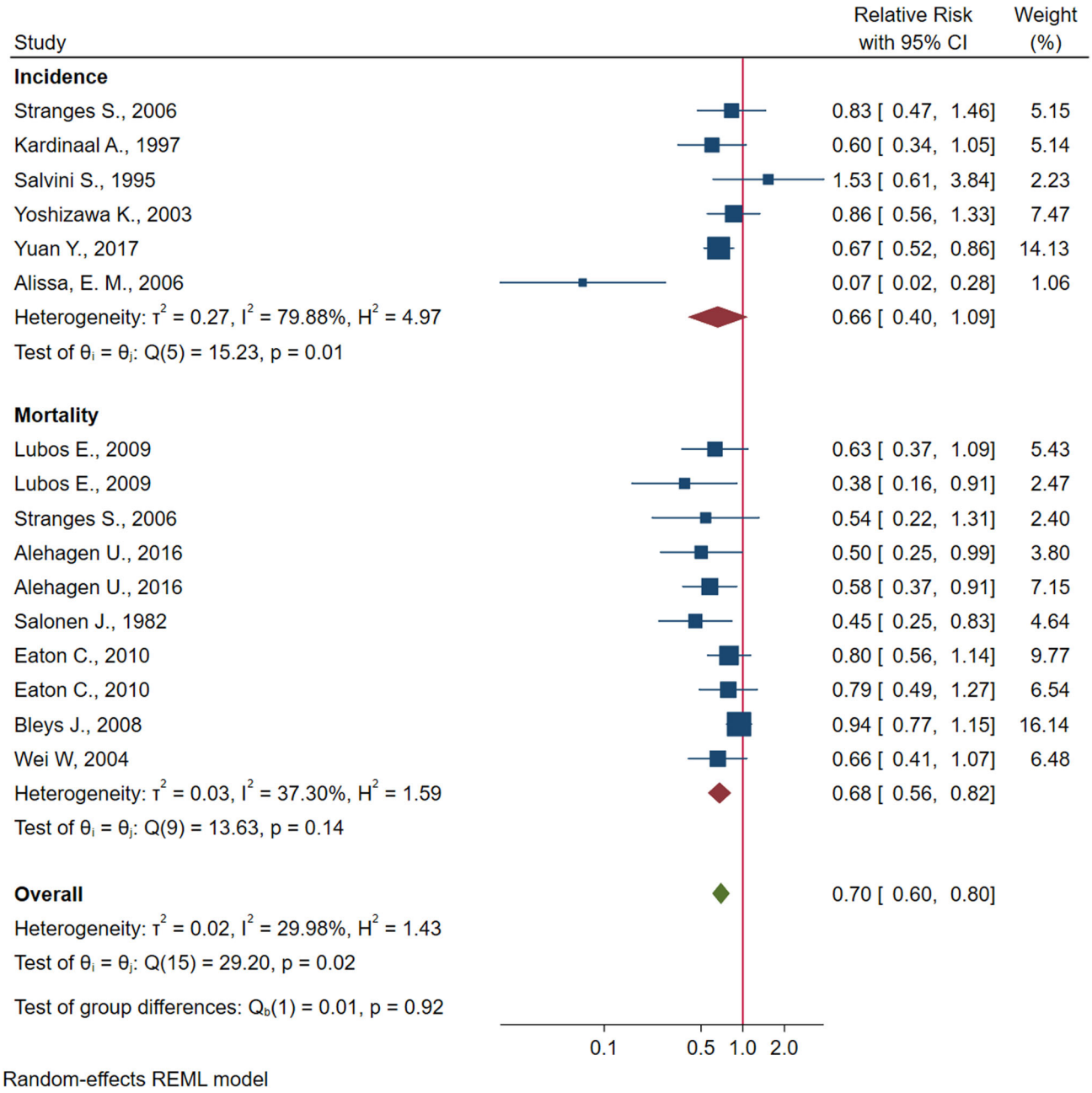

Figure 3. Pooled RRs of the highest concentrations compared to the lowest concentrations of selenium status in the body.

Table 2. Relative risk for mortality and incidence of cardiovascular diseases per unit* increase in selenium concentration.

	Sample type	Dose	RR (95% CI)	*p*
Mortality	Blood	18	0.93 (0.83–1.05)	0.240
	Toenail	0		
Incidence	Blood	11	0.85 (0.76–0.94)	0.003
	Toenail	8	0.54 (0.09–3.28)	0.438

*Units are10 μg/L for blood sample and 1 μg/g for toenail sample, respectively.

30–35 μg/L (Figure 5), then the risk of CVD mortality seemed to start increasing when blood selenium increased by 35 μg/L or more.

There was no statistically significantly non-linear dose-response relationship found between the risk of CVD incidence and increased toenail selenium (Figure 6) or blood selenium (data not shown).

Discussion

Selenium and CVD incidence and mortality

Selenium is an essential micronutrient for human and animals. The role of selenium has been attributed largely to its presence in selenoproteins. In the human genome, at least 25 selenoproteins in the form of the amino acid selenocysteine (Sec) have been identified. Incorporation of Sec into selenoproteins employs a unique mechanism that involves decoding of the umber mutation codon. Although the function of most selenoproteins is currently unknown; some of them (such as glutathione peroxidases, thioredoxin reductases, and iodothyronine deiodinases) are involved in oxidoreductions, redox signaling, antioxidant defense, thyroid hormone metabolism, and immune responses. Thus, they play important roles in human diseases such as cancer,

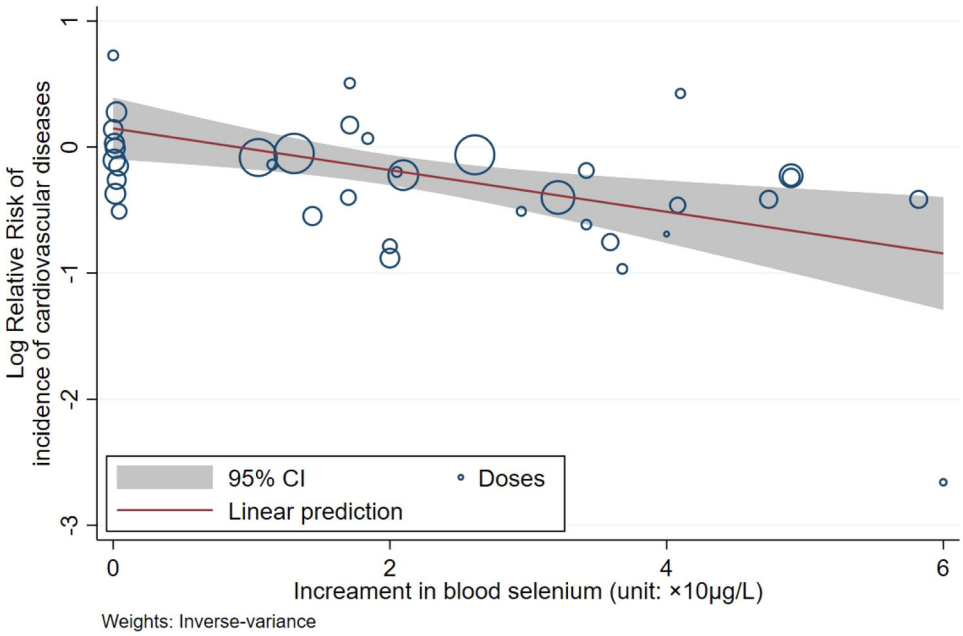

Figure 4. Association between log relative risk of incidence of cardiovascular diseases and increment in blood selenium concentration.

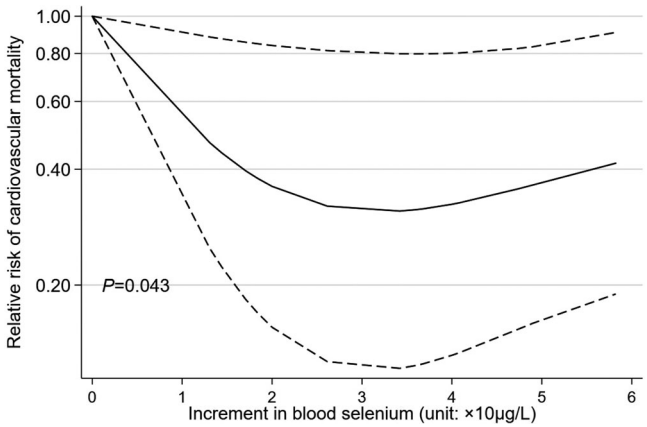

Figure 5. Association between the relative risk of cardiovascular mortality and increment in blood selenium concentration.

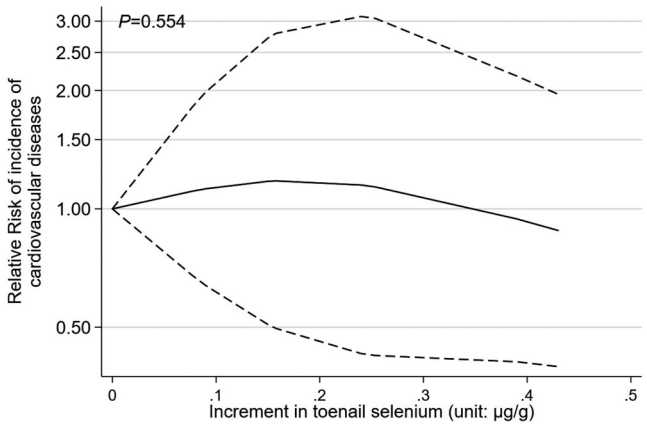

Figure 6. Association between the relative risk of incidence of cardiovascular diseases and increment in toenail selenium concentration.

Keshan disease, virus infections, male infertility, and abnormalities in immune responses and thyroid hormone function (Papp et al. 2007; Hatfield et al. 2016). Selenium has been associated with CVD due to its inclusion in antioxidant selenoenzymes such as GPx. The selenium-dependent enzymes play significant roles in protecting cells against oxidative damage from ROS and reactive nitrogen species (RNS) (Rayman 2000; Tinggi 2008). These reactive species are reduced to harmless products mostly water and alcohols by the GPx enzymes ensuring that cell membrane integrity is maintained, protects prostacyclin production, and reduces propagation of further oxidative damage to molecules like lipids that are associated with increased risk of CVDs (Nève 1996).

The findings in this study suggest that physiologically high selenium levels in body may be a protective factor for both incidence and mortality of CVD, which are consistent with the results of a previous meta-analysis on selenium and CHD that reported a 15% reduced risk of CHD among those with adequate selenium levels (Flores-Mateo et al. 2006). Alehagen et al. reported similar findings of reduced CVD mortality among those who were supplemented with selenium and coenzyme Q10 ten years after supplementation (Alehagen, Aaseth, and Johansson 2015). However, Bleys et al. reported that there was no association between serum selenium and CVD mortality. The inconsistency in the findings has been suggested to be due to a number of reasons. The major one is the difference in selenium soil concentration due to the geographical location. The protective effects of selenium are observed in regions with low selenium levels for example Keshan disease in China but not in regions with adequate intake like the United States (NPC and SELECT trials) (Huttunen 1997; Rayman 2012). In our stratified analysis by geographical regions, reduced risks of CVD mortality and/or CVD incidence were found in Asia and Europe, which are consistent with the protective effects of selenium found among populations with low selenium intake (<50 μg/L) or status (serum level <100 μg/L) (Kuria et al. 2020; Salonen et al. 1982; Alehagen, Aaseth, and Johansson 2015).

Among all the study designs, there was an overall statistically significantly decreased risk in CVD mortality, but no statistically significant decreased risk was found in CVD incidence (Figure 1). The statistically non-significant finding for CVD incidence might be due to the much larger heterogeneity among the studies on CVD incidence compared to those on CVD mortality ($I^2 = 80\%$ vs. 35%; Figure 1). In the results from the stratified analysis by study designs, only one dose from case-control studies was found for CVD mortality, therefore no pooled risk could be estimated. However, thirteen doses for CVD incidence indicated a marginally significant decrease in the risk (Table 1). The RCT included in the meta-analysis showed no effect of body selenium status on CVD incidence but showed a statistically non-significant decrease in CVD mortality. Although the hierarchy of evidence suggests that RCT may give the best evidence compared to observational studies (Petrisor and Bhandari 2007), in our meta-analysis, the trials either used elderly population (Alehagen, Aaseth, and Johansson 2015) or already sick population (Stranges et al. 2006) therefore limiting the generalizability of the findings. In contrast, in our meta-analysis, cohort studies showed statistically significantly decreased risks in both CVD incidence and mortality, which might be resulted from the high quality of the studies (Supplementary material 4) and/or control of relevant confounders in data analysis, however, the results should be interpreted carefully due to the inherent limitations of observational studies (Petrisor and Bhandari 2007). In general, our findings are in agreement with the meta-analysis on selenium and CHD that reported a non-significantly decreased risk among the included RCT but a significantly decreased risk among the observational studies (Flores-Mateo et al. 2006).

Taken together, the two different biospecimens (blood and toenail) used in this review to assess selenium status showed an overall decrease in risk for CVD incidence and mortality related to increased selenium values. Blood and toenail have been used routinely to assess selenium exposure in epidemiological studies. A study by Satia et al. described the relationship of the two biomarkers and reported a significant correlation in selenium concentration. The study concluded that both blood and toenail selenium levels reflected selenium exposure adequately (Satia et al. 2006). Low levels of blood and toenail selenium have been associated with increased inflammatory biomarkers that are risk factors of CVD (Satia et al. 2006; Xun et al. 2010).

An overall linear dose-response relationship between reduced CVD incidence and increment in blood selenium was observed in our study, however the result should be interpreted with caution due to the narrow safety margin of selenium (Stranges et al. 2006). In addition, the findings in this study report a statistically significantly non-linear dose-response relationship between blood selenium and CVD mortality beyond which the risk start increasing. This finding has been reported by several other studies including Kuria et al. leading to derivation of selenium daily requirements that have been shown to be between (50–300 µg/day) (Kuria et al. 2020; Hurst et al. 2013).

Our findings are consistent with previous meta-analyses that reported a 50% increase in selenium concentration in blood and toenails associated with a 24% decreased risk in coronary events (Flores-Mateo et al. 2006). In addition, the findings of our study also collaborates with the findings of Zhang et al., a meta-analysis that reported an association between physiologically higher levels of blood selenium with a 13% reduction in CVD risk (Zhang et al. 2016). A similar nonlinear dose-response relationship between blood selenium concentrations and CVD risk are found in both Zhang's meta-regression analysis and our analysis. However, the two previous meta-analyses did not separate the CVD risks by mortality and incidence, and no stratified analysis by potential confounders was presented in the two studies either. In contrast, our analysis provided more detailed subgroup analysis, which might reduce the heterogeneity raised by the potential confounding factors. Furthermore, our findings strengthen the evidence on the narrow safety margin of selenium as it has been shown in other studies (Klein et al. 2011; Stranges et al. 2006).

Strengths and limitations

The major strength of our study is that selenium was measured in blood or toenail instead of food frequency questionnaire. This avoids recall bias, and is more precise on selenium measurement and also indicates effects of long-term selenium exposure. The studies included in the meta-analysis were of medium or high-quality (see Supplementary material 4) and most of them were controlled for potential confounders, thus increasing the validity of the present study.

Although random-effects model was used to minimize the potential bias, heterogeneity is a major limitation in this study. Overall, statistically significant associations were found between selenium and CVD mortality, and between blood selenium and CVD incidence, but the evidence for the association between toenail selenium and CVD mortality and incidence is not sufficient. Besides, some studies have reported that selenium's protective effect is evident in some types of CVD, for example in ischemic/myocardial reperfusion but not in CVD in general. It was not possible to stratify our analysis to this level due to no detailed information available in the included studies. Limited by the available published data, our study might have underestimated the effects of body burden of selenium on CVD incidence or mortality.

Because the selenium concentrations were only measured at baseline, and the concentrations might have changed during the study period. This time-varying-confounding could bias the association toward an unknown direction, which is another limitation that we should bear in mind and investigate further in the future. We should also notice the enlarged weights for Lubos E, Alehagen U, and Eaton C's studies in the pooled RRs for CVD mortality and overall outcomes, because they appeared two times due to the different selenium concentrations in the subgroups with different clinical conditions. Therefore, the pooled RRs for CVD mortality and overall outcome might be over-weighted by the three studies. Furthermore, although we conducted subgroup analysis by study design, sample type, disease, and

study region, the source of heterogeneity still remains largely undetected. Thus, we must explain the results with caution.

Conclusion

We conclude that physiologically high selenium levels in blood and toenail is associated with decreased CVD incidence and mortality however the daily selenium intake should be within the recommended daily allowance (50–300 µg/day) to prevent the harmful effects of selenium that may occur at levels beyond 300 µg/day. There is need for further studies on specific types of CVD and selenium as some seem to be more associated with selenium than others. Further research using large RCT is also warranted to confirm the conclusion as the inconsistent findings between RCT and observational studies is still present in this meta-analysis.

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Disclosure statement

No conflict of interest was declared.

Author's contribution

This study was designed by Y.C. and J.A. A.K., H.T. and M.L. did the literature screening, data extraction and study quality assessment; Y.C. and A.K. performed statistical analysis and interpreted results. A.K. and Y.C. drafted the manuscript. All authors contributed to the manuscript writing, made critical revision, read, and approved the final manuscript. All authors had full access to all the data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviations

CHD	coronary heart disease
CI	confidence interval
CVD	cardiovascular disease
GPx	glutathione peroxidases
ICD	ischemic cardiovascular disease
MI	myocardial infarction
RCT	randomized controlled trial
ROS	reactive oxygen species
RR	relative risk

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References

Alehagen, U., J. Alexander, and J. Aaseth. 2016. Supplementation with selenium and coenzyme Q10 reduces cardiovascular mortality in elderly with low selenium status. A secondary analysis of a randomised clinical trial. *PLoS One* 11(7): e0157541. doi: 10.1371/journal.pone.0157541.

Alehagen, U., P. Johansson, M. Björnstedt, A. Rosén, C. Post, and J. Aaseth. 2016. Relatively high mortality risk in elderly Swedish subjects with low selenium status. *European Journal of Clinical Nutrition* 70 (1):91–6. doi: 10.1038/ejcn.2015.92.

Alissa, E. M., S. M. Bahjri, W. H. Ahmed, N. Al-Ama, and G. A. A. Ferns. 2006. Trace element status in saudi patients with established atherosclerosis. *Journal of Trace Elements in Medicine and Biology* 20 (2):105–14. doi: 10.1016/j.jtemb.2005.10.004.

Bae, J.-M. 2016. A suggestion for quality assessment in systematic reviews of observational studies in nutritional epidemiology. *Epidemiology and Health* 38:e2016014. doi: 10.4178/epih.e2016014.

Bleys, J., A. Navas-Acien, and E. Guallar. 2008. Serum selenium levels and all-cause, cancer, and cardiovascular mortality among US adults. *Archives of Internal Medicine* 168 (4):404–10. doi: 10.1001/archinternmed.2007.74.

Chen, J. 2012. An original discovery: Selenium deficiency and keshan disease (an endemic heart disease). *Asia Pacific Journal of Clinical Nutrition* 21 (3):320–6.

DerSimonian, R., and N. Laird. 1986. Meta-analysis in clinical trials. *Controlled Clinical Trials* 7 (3):177–88. doi: 10.1016/0197-2456(86)90046-2.

Eaton, C. B., A. R. Abdul Baki, M. E. Waring, M. B. Roberts, and B. Lu. 2010. The association of low selenium and renal insufficiency with coronary heart disease and all-cause mortality: NHANES III follow-up study. *Atherosclerosis* 212 (2):689–94. doi: 10.1016/j.atherosclerosis.2010.07.008.

Egger, M., G. D. Smith, M. Schneider, and C. Minder. 1997. Bias in meta-analysis detected by a simple, graphical test. *BMJ (Clinical Research Ed.)* 315 (7109):629–34. doi: 10.1136/bmj.315.7109.629.

Flores-Mateo, G., A. Navas-Acien, R. Pastor-Barriuso, and E. Guallar. 2006. Selenium and coronary heart disease: A meta-analysis. *The American Journal of Clinical Nutrition* 84 (4):762–73. doi: 10.1093/ajcn/84.4.762.

González, S., J. M. Huerta, S. Fernández, E. M. Patterson, and C. Lasheras. 2006. Food intake and serum selenium concentration in elderly people. *Annals of Nutrition & Metabolism* 50 (2):126–31. doi: 10.1159/000090633.

Hatfield, D. L., U. Schweizer, P. A. Tsuji, and V. N. Gladyshev. 2016. *Selenium: Its molecular biology and role in human health*. New York, NY: Springer.

Higgins, J. P. T., D. G. Altman, P. C. Gøtzsche, P. Jüni, D. Moher, A. D. Oxman, J. Savovic, K. F. Schulz, L. Weeks, J. A. C. Sterne, et al. 2011. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clinical Research ed.)* 343:d5928. doi: 10.1136/bmj.d5928.

Higgins, J. P. T., and S. Green. 2011. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. http://handbook.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm.

Higgins, J. P. T., S. G. Thompson, J. J. Deeks, and D. G. Altman. 2003. Measuring inconsistency in meta-analyses. *BMJ (Clinical Research ed.)* 327 (7414):557–60. doi: 10.1136/bmj.327.7414.557.

Hurst, R., C. N. Armah, J. R. Dainty, D. J. Hart, B. Teucher, A. J. Goldson, M. R. Broadley, A. K. Motley, and S. J. Fairweather-Tait. 2010. Establishing optimal selenium status: Results of a randomized, double-blind, placebo-controlled trial. *The American Journal of Clinical Nutrition* 91 (4):923–31. doi: 10.3945/ajcn.2009.28169.

Hurst, R., R. Collings, L. J. Harvey, M. King, L. Hooper, J. Bouwman, M. Gurinovic, and S. J. Fairweather-Tait. 2013. EURRECA—Estimating selenium requirements for deriving dietary reference values. *Critical Reviews in Food Science and Nutrition* 53 (10):1077–96. doi: 10.1080/10408398.2012.742861.

Huttunen, J. K. 1997. Selenium and cardiovascular diseases—An update. *Biomedical and Environmental Sciences: BES* 10 (2–3):220–6.

Kardinaal, A. F., F. J. Kok, L. Kohlmeier, J. M. Martin-Moreno, J. Ringstad, J. Gómez-Aracena, V. P. Mazaev, M. Thamm, B. C. Martin, A. Aro, et al. 1997. Association between toenail selenium and risk of acute myocardial infarction in European men. The EURAMIC Study. European Antioxidant Myocardial Infarction and

Breast Cancer. *American Journal of Epidemiology* 145 (4):373–9. doi: 10.1093/oxfordjournals.aje.a009115.

Klein, E. A., I. M. Thompson, C. M. Tangen, J. J. Crowley, M. S. Lucia, P. J. Goodman, L. M. Minasian, L. G. Ford, H. L. Parnes, J. M. Gaziano, et al. 2011. Vitamin E and the risk of prostate cancer: The Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA* 306 (14):1549–56. doi: 10.1001/jama.2011.1437.

Kuria, A., X. Fang, M. Li, H. Han, J. He, J. Olav Aaseth, and Y. Cao. 2020. Does dietary intake of selenium protect against cancer? A systematic review and meta-analysis of population-based prospective studies. *Critical Reviews in Food Science and Nutrition* 60 (4): 684–11. doi: 10.1080/10408398.2018.1548427.

Lubos, E., C. R. Sinning, R. B. Schnabel, P. S. Wild, T. Zeller, H. J. Rupprecht, C. Bickel, K. J. Lackner, D. Peetz, J. Loscalzo, et al. 2010. Serum selenium and prognosis in cardiovascular disease: Results from the AtheroGene Study. *Atherosclerosis* 209 (1):271–7. doi: 10.1016/j.atherosclerosis.2009.09.008.

Moher, D., A. Liberati, J. Tetzlaff, and D. G. Altman. 2009. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. *PLoS Medicine* 6 (7):e1000097. doi: 10.1371/journal.pmed.1000097.

Nève, J. 1996. Selenium as a risk factor for cardiovascular diseases. *Journal of Cardiovascular Risk* 3 (1):42–7.

Papp, L. V., J. Lu, A. Holmgren, and K. K. Khanna. 2007. From selenium to selenoproteins: Synthesis, identity, and their role in human health. *Antioxidants & Redox Signaling* 9 (7):775–806. doi: 10.1089/ars.2007.1528.

Petrisor, B. A., and M. Bhandari. 2007. The hierarchy of evidence: Levels and grades of recommendation. *Indian Journal of Orthopaedics* 41 (1):11–5. doi: 10.4103/0019-5413.30519.

Rayman, M. P. 2000. The importance of selenium to human health. *Lancet (London, England)* 356 (9225):233–41. doi: 10.1016/S0140-6736(00)02490-9.

Rayman, M. P. 2012. Selenium and human health. *The Lancet* 379 (9822):1256–68. doi: 10.1016/S0140-6736(11)61452-9.

Salonen, J. T., G. Alfthan, J. K. Huttunen, J. Pikkarainen, and P. Puska. 1982. Association between cardiovascular death and myocardial infarction and serum selenium in a matched-pair longitudinal study. *Lancet (London, England)* 320 (8291):175–9. doi: 10.1016/S0140-6736(82)91028-5.

Salvini, S., C. H. Hennekens, J. S. Morris, W. C. Willett, and M. J. Stampfer. 1995. Plasma levels of the antioxidant selenium and risk of myocardial infarction among U.S. physicians. *The American Journal of Cardiology* 76 (17):1218–21. doi: 10.1016/S0002-9149(99)80344-0.

Satia, J. A., I. B. King, J. Steven Morris, K. Stratton, and E. White. 2006. Toenail and plasma levels as biomarkers of selenium exposure. *Annals of Epidemiology* 16 (1):53–8. doi: 10.1016/j.annepidem.2005.02.011.

Stranges, S., J. R. Marshall, M. Trevisan, R. Natarajan, R. P. Donahue, G. F. Combs, E. Farinaro, L. C. Clark, and M. E. Reid. 2006. Effects of selenium supplementation on cardiovascular disease incidence and mortality: Secondary analyses in a randomized clinical trial. *American Journal of Epidemiology* 163 (8):694–9. doi: 10.1093/aje/kwj097.

Stroup, D. F., J. A. Berlin, S. C. Morton, I. Olkin, G. D. Williamson, D. Rennie, D. Moher, B. J. Becker, T. A. Sipe, and S. B. Thacker. 2000. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-Analysis Of Observational Studies in Epidemiology (MOOSE) Group. *JAMA* 283 (15):2008–12. doi: 10.1001/jama.283.15.2008.

Suadicani, P., H. O. Hein, and F. Gyntelberg. 1992. Serum selenium concentration and risk of ischaemic heart disease in a prospective cohort study of 3000 males. *Atherosclerosis* 96 (1):33–42. doi: 10.1016/0021-9150(92)90035-F.

Tinggi, U. 2008. Selenium: Its role as antioxidant in human health. *Environmental Health and Preventive Medicine* 13 (2):102–8. doi: 10.1007/s12199-007-0019-4.

Venardos, K., G. Harrison, J. Headrick, and A. Perkins. 2004. Selenium supplementation and ischemia-reperfusion injury in rats. *Redox Report: Communications in Free Radical Research* 9 (6):317–20. doi: 10.1179/135100004225006803.

Venardos, K. M., A. Perkins, J. Headrick, and D. M. Kaye. 2007. Myocardial ischemia-reperfusion injury, antioxidant enzyme systems, and selenium: A review. *Current Medicinal Chemistry* 14 (14): 1539–49. doi: 10.2174/092986707780831078.

Vinceti, M., R. Chawla, T. Filippini, C. Dutt, S. Cilloni, R. Loomba, A. Bargellini, N. Orsini, K. S. Dhillon, and P. Whelton. 2019. Blood pressure levels and hypertension prevalence in a high selenium environment: Results from a cross-sectional study. *Nutrition, Metabolism, and Cardiovascular Diseases: NMCD* 29 (4):398–408. doi: 10.1016/j.numecd.2019.01.004.

Wei, W.-Q., C. C. Abnet, Y.-L. Qiao, S. M. Dawsey, Z.-W. Dong, X.-D. Sun, J.-H. Fan, E. W. Gunter, P. R. Taylor, and S. D. Mark. 2004. Prospective study of serum selenium concentrations and esophageal and gastric cardia cancer, heart disease, stroke, and total death. *The American Journal of Clinical Nutrition* 79 (1):80–5. doi: 10.1093/ajcn/79.1.80.

Xun, P., K. Liu, J. S. Morris, M. L. Daviglus, J. Stevens, D. R. Jacobs, and K. He. 2010. Associations of toenail selenium levels with inflammatory biomarkers of fibrinogen, high-sensitivity C-reactive protein, and interleukin-6: The CARDIA Trace Element Study. *American Journal of Epidemiology* 171 (7):793–800. doi: 10.1093/aje/kwq001.

Yoshizawa, K., A. Ascherio, J. S. Morris, M. J. Stampfer, E. Giovannucci, C. K. Baskett, W. C. Willett, and E. B. Rimm. 2003. Prospective study of selenium levels in toenails and risk of coronary heart disease in men. *American Journal of Epidemiology* 158 (9): 852–60. doi: 10.1093/aje/kwg052.

Yuan, Y., Y. Xiao, W. Feng, Y. Liu, Y. Yu, L. Zhou, G. Qiu, H. Wang, B. Liu, K. Liu, et al. 2017. Plasma metal concentrations and incident coronary heart disease in Chinese adults: The Dongfeng-Tongji Cohort. *Environmental Health Perspectives* 125 (10):107007. doi: 10.1289/EHP1521.

Zhang, J., and K. F. Yu. 1998. What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 280 (19):1690–1. doi: 10.1001/jama.280.19.1690.

Zhang, X., C. Liu, J. Guo, and Y. Song. 2016. Selenium status and cardiovascular diseases: Meta-analysis of prospective observational studies and randomized controlled trials. *European Journal of Clinical Nutrition* 70 (2):162–9. doi: 10.1038/ejcn.2015.78.