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Review

Selenium intake and metabolic syndrome: A systematic review

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SUMMARY

Background & aims: Metabolic syndrome is a multi-causal disease. Its treatment includes lifestyle changes with a focus on weight loss. This systematic review assessed the association between Selenium intake and metabolic syndrome.

Methods: Data were collected mainly from four databases: PubMed, CENTRAL (Cochrane), Scopus and Web of Knowledge. Keywords related to metabolic syndrome, selenium, as well as metabolic syndrome features were searched. This review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. A systematic review protocol was registered at PROSPERO (n. 42016046321). Two reviewers independently screened 2957 abstracts. Six studies were included to perform data extraction with standardized spreadsheets. The risk of bias was assessed by using specific tools according to the design of the relevant studies. An assessment was carried out based on the appropriateness of the study reports accordingly to STROBE and the CONSORT-based checklist for each study design.

Results: Three studies found no association between Selenium intake and metabolic syndrome; two of them found an inverse association; and one study found a direct association between Selenium intake and metabolic syndrome. One study also showed an inverse association between Selenium intake and the prevalence of high waist circumference, high diastolic blood pressure, and hyperglycaemia in women.

Conclusions: Overall, based on the argumentation and results of this study, it is possible to conclude that Selenium intake and metabolic syndrome are not clearly associated in adults and elderly.

1. Introduction

Metabolic Syndrome (MetS) is a clustering of multiple risk factors for cardiovascular disease, type 2 diabetes mellitus (T2DM), and all-cause mortality [1,2]. MetS is considered a state of chronic inflammation, composed by excessive body weight, central obesity, dyslipidaemia, hypercoagulable state, endothelial dysfunction, high blood pressure, hyperglycaemia, insulin resistance, and chronic stress [3]. MetS prevalence varies between 11.6% and 62.5% around the world [4].

MetS has been extensively studied in international context, using different diagnostic criteria. These criteria vary according to the clinical features used to evaluate patients and/or according to reference cut-offs [5]. The National Cholesterol Education Programme – Adult Treatment Panel III criteria (NCEP-ATP III) are defined by: elevated waist circumference (WC $\geq$ 102 cm in men and $\geq$80 cm in women), high triglycerides blood concentration ($\geq$1.694 mmol/L or 150 mg/dL), low HDL-c blood concentration (<1.036 mmol/L or 40 mg/dL in men and <1.295 mmol/L or 50 mg/dL in women), high blood pressure (systolic blood pressure/diastolic blood pressure $\geq$130/85 mmHg), and high fasting blood glucose (>6.111 mmol/L or 110 mg/dL) [6]. In the same way, the International Diabetes Federation (IDF) uses the same criteria. However, for IDF, WC is a necessary factor for the diagnosis, with different reference cut-offs according to the ethnic group: for

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Europeans, Sub-Saharan Africans and Arabs it is ≥94 cm for men, and ≥80 cm for women; for South Asians, Chinese, Japanese and South and Central Americans it is ≥90 cm for men, and ≥80 cm for women [2]. Another frequently used criteria is the American Heart Association (AHA) Guidelines, which consider the same clinical features; however, the elevated WC is defined as ≥102 cm for men and ≥88 cm for women, whereas the high fasting blood glucose is defined as >100 mg/dL or 5.556 mmol/L [7].

MetS is a multi-causal disease determined by genetic and environmental factors, such as smoking, physical activity, stress, and food consumption [3]. The increase of both energy intake and sedentary lifestyle promotes overweight, obesity, and, consequently, a proinflammatory state [8,9]. Thus, MetS treatment includes lifestyle changes to weight loss and, if appropriate, the use of drugs [1,10].

Selenium (Se) is an essential mineral with these properties. It is incorporated into several selenoproteins and has various effects acknowledged in literature, such as the prevention of viral mutations, maintenance of intestinal mucosal integrity, antioxidant activity, thyroid hormone activation, inflammatory response regulation, cellular differentiation in immunological system, sperm motility and viability, glucose metabolism, and insulin sensitivity [11,12]. Despite the fact there is a gap when it comes to knowledge related to Se metabolism, that is, how it affects our biological functions [12], Se deficiency has been pointed out as an important factor for non-communicable disease development [11].

Although the relationship between Se and metabolic syndrome has been explored in literature, studies usually investigate the association between MetS and Se blood concentration, not considering Se intake. In this way, this systematic review aims to evaluate the association between Se intake or supplementation and MetS.

2. Methods

This systematic review was consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [13]. A systematic review protocol was registered at PROSPERO (www.crd.york.ac.uk/PROSPERO/) under the number 42016046321. PICO/PECO criteria (population, intervention/exposure, comparison, and outcome) and research questions used to determine key words and search strategy are shown in Table 1.

2.1. Search strategy

The literature search was conducted on August 19, 2016 using four different databases, and updated on February 7, 2017: PUBMED (via PubMed; National Library of Medicine, Bethesda, Maryland); The Cochrane Central Register of Controlled Trials (CENTRAL) (via Cochrane Library; Wiley Online Library, New York, USA); Science Direct (via Scopus, Elsevier, Philadelphia, USA); and Web of Knowledge (via Web of Science, Thomson Reuters, New York, USA). Search strategy was defined according to database orientations for the use of Booleans operators, parenthesis, quotation marks, and asterisk ("Metabolic syndrome" OR "Metabolic X Syndrome" OR "Metabolic Cardiovascular Syndrome" OR "Syndrome X") AND (Selenium) AND (Cholesterol OR HDL OR "high density lipoprotein" OR circumference OR obesity OR Triglyceride* OR Triacylglycerol OR Hypertension OR "Blood pressure" OR Hyperglycaemia OR "Blood Glucose" OR Insulin OR HOMA OR diabetes OR "Fat mass" OR "Body fat"). No filters were added for the search.

Table 1
PICO/PECO criteria description and research question defined to systematic review.

Parameter	Description
Population	Individuals with metabolic syndrome, both male and female, no age restriction
Intervention/exposure	Selenium intake from both dietary intake and/or oral supplementation
Comparison	Non-exposed group or group that did not receive intervention or placebo
Outcome	Changes in metabolic syndrome diagnosis and/or related parameters (HDL-c, waist circumference, triglycerides, blood pressure, and glycaemia)
Research question	What are the association between selenium intake and metabolic syndrome?

The search results were exported from the databases in .enl format to be included in a specific library in the reference manager software *EndNote® version X7* (Thomson Reuters, New York, USA).

Reference lists of all studies included in this systematic review were screened for relevant studies not found by the search strategy, as well as reviews about the theme [14–16].

2.2. Selection criteria

Duplicate and triplicate articles were excluded using *EndNote®*. When available information on titles and abstracts were not enough, full-text articles were read. The inclusion criteria included: observational and interventional studies; individuals with MetS defined by any diagnostic criteria; studies that assessed Se intake or Se supplementation; the presence of MetS and, if available, its parameters (HDL-c, waist circumference, triglycerides, blood pressure, and glycaemia) as outcomes.

2.3. Data extraction

Eligible articles [17–22] were exhaustively read by two independently reviewers (A.R. and G.R.) to allow adequate data extraction. The following data were extracted: local, period of data collection, study design, sample size and losses, intervention/exposure characteristics, patients' age and sex, MetS diagnostic criteria, dietary intake assessment tool, follow-up period, confounders variables, and main results. In observational studies, the mean related to Se intake and standard deviation were annotated when available.

Extracted outcome data were diagnosis of MetS (Yes or No), WC, systolic blood pressure, diastolic blood pressure, triglycerides, fasting blood glucose and HDL-c. The corresponding authors of the studies included in this systematic review were contacted by electronic mail to request unpublished data of interest, when necessary. Extracted data were organized via *Microsoft Excel®* spreadsheets by both reviewers and crosschecked.

2.4. Critical appraisal

Two reviewers (A.R. and G.R.) independently conducted a risk of bias assessment and the assessment of the appropriateness of study reports according to the STROBE and CONSORT.

Three different tools were used to assess the risk of bias due to differences in the study designs (see Supplementary file 1). Cross-sectional studies were evaluated using the Agency for Healthcare Research and Quality (AHRQ) tool [23]. Case–control studies were evaluated using the ROBINS-I tool for non-randomized studies. Intervention studies were evaluated using the Cochrane handbook for systematic reviews of interventions [24].

We assessed the appropriateness of study reports according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [25] and to the CONSORT-based checklist [26]. Two different tools were used to evaluate the quality of reporting because of differences in the study designs (see Supplementary file 2). Cross-sectional and case–control studies were evaluated using the first one, whereas prevention trials were evaluated using the latter. These tools are composed by 32 (cross-sectional), 33 (case–control), and 37 questions (trial), thus enabling an analysis of the study report, session-by-session.

Any disagreements between reviewers in the critical appraisal were solved by discussion until they reached a consensus.

3. Results

3.1. Selected articles

A total of 2957 studies were found by the above mentioned search strategy. Out of these, a total of 123 duplicate/triplicate articles were excluded. After reading titles and abstracts, fourteen full-text articles were assessed for eligibility (A.R. and M.A.A.) and cross-checked. Any inter-reviewer disagreement was solved by consensus and/or with an opinion of a third reviewer (R.F.). In the end, six articles [17–22] that investigated Se intake or supplementation in MetS subjects were included in this systematic review (Fig. 1).

3.2. Study features and subject characteristics

The description of the studies and their participant characteristics are summarized in Table 2. They were published between

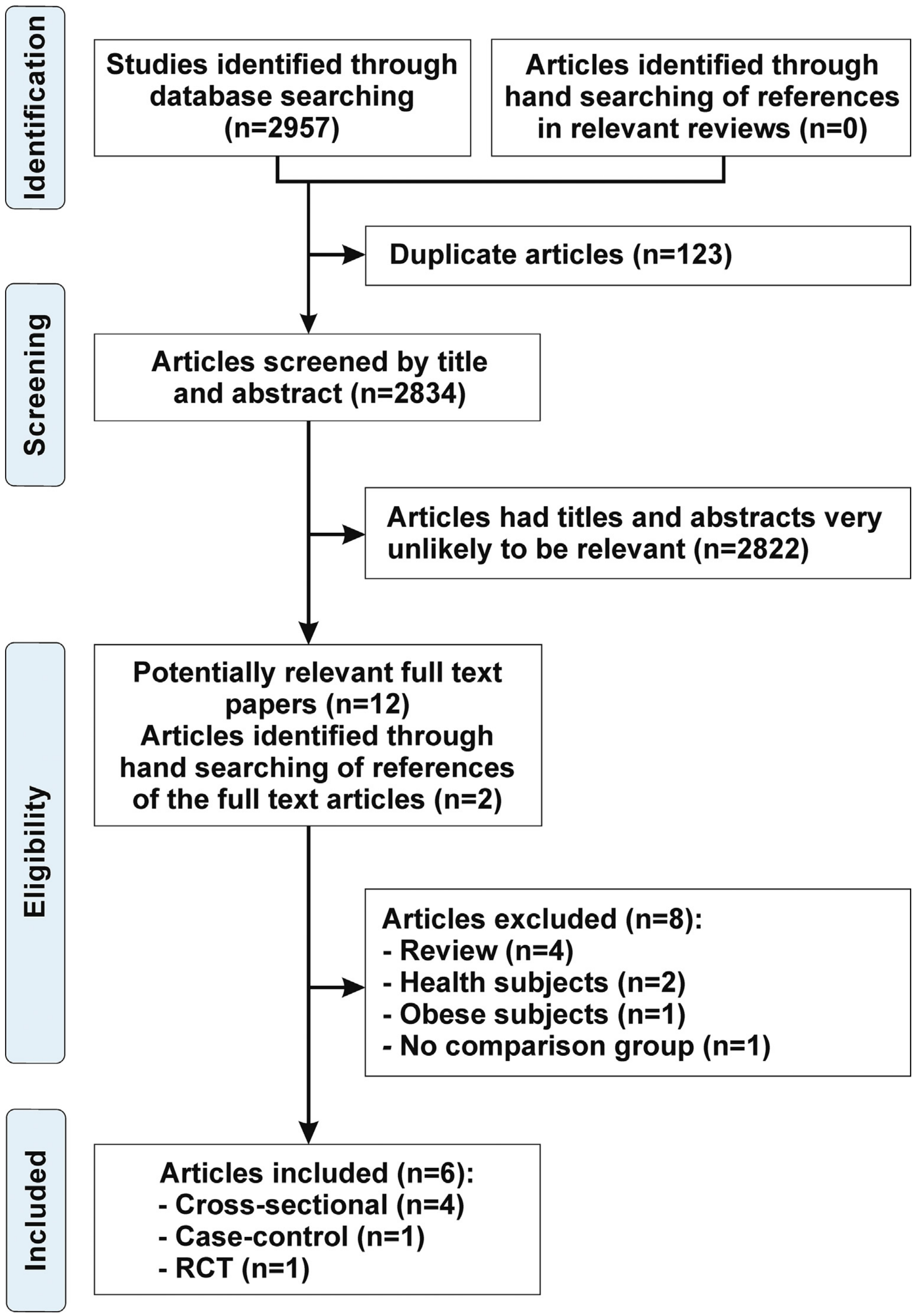

Fig. 1. PRISMA flow chart of literature selection process.

Table 2
Characteristics of studies included in this review.

Study-year	Country	Study design/quality report score (%)	Age (*years*)	Sample size *n total* (*n MetS subjects*)	MetS criteria	Food intake assess tool	Se intake (μg) (*Mean* ± *SD*)	Confounders/adjust variables	Main results
Czernichow et al. (2009) [18]	France	Double-blind RCT[a]/(54.3)	35–60	5220 (263)	NCEP-ATP III	–	[b]	Age, sex, educational level, smoking status, physical activity, and alcohol consumption	↔ MetS
Bian et al. (2013) [17]	China	Case–control/(62.1)	30–70	258 (123)	NCEP-ATP III	24 hR/7 days	MetS 58.9 ± 23.8 non-MetS 57.9 ± 17.5	Age, gender, educational level, smoking status, physical activity level. and BMI	↔ MetS
Li et al. (2013) [20]	China	Cross-sectional/(31.0)	18–65	550 (221)	NCEP-ATP III	FD/3 days	MetS 38.4 ± 25.7 non-MetS 43.1 ± 30.7	Age and sex	↔ MetS
Motamed et al. (2013) [21]	Iran	Cross-sectional/(42.9)	35–65	3630 (1699)	IDF	24 hR/1 day	Men MetS 32.9 ± 42.17 non-MetS 33.6 ± 31.63 Women MetS 31.8 ± 24.5 non-MetS 32.5 ± 24.5	Age, sex, physical activity level, smoking status, past-medical history, energy intake, and BMI	↓ MetS
Wei et al. (2015) [22]	China	Cross-sectional/(44.4)	18–84	2069 (351)	AHA	SQFFQ	MetS 48.5 ± 29.8 non-MetS 47.0 ± 27.6	Age, sex, smoking status, alcohol drinking, nutritional supplementary, activity level, dietary energy intake, fibre intake and protein intake	↓ MetS ↓ WC ↓ high DBP ↓ hyperglycaemia
Khayyatzadeh et al. (2016) [19]	Iran	Cross-sectional/(32.1)	35–65	5764 (3300)	IDF	24hR/1 day	[c]	Age, energy intake, marital status, education, smoking status, and physical activity	↑ MetS

Abbreviations: NCEP-ATP III, National Cholesterol Education Program's – Adult Treatment Panel III; IDF, International Diabetes Federation; AHA, American Heart Association; 24 hR, 24-hour dietary recall; FD, food diary; SQFFQ, semi-quantitative food frequency questionnaire; MetS, Metabolic Syndrome; non-MetS, non-Metabolic Syndrome; BMI, body mass index; WC, waist circumference; DBP, diastolic blood pressure. The presented value for quality report score corresponds to the proportion (%) of "yes" attributed for the applicable requirements; - represents unavailable data; ↔ represents no significant difference between groups; ↓represents significantly lower outcome prevalence between groups; ↑represents significantly higher outcome prevalence between groups.

[a] Randomized double-blind placebo-controlled primary prevention trial with duration of 7.5 years.

[b] Supplementation dose of Selenium (in a combination of antioxidants) = 100 μg.

[c] Unavailable data. In this study, selenium was included in a dietary nutrient pattern characterized by cooper, selenium, vitamin A, riboflavin and vitamin B12.

2009 and 2016: one was developed in France [18], three developed in China [17,20,22] and two developed in Iran [19,21]. Four studies have a cross-sectional design [19–22], one have a case–control design [17] and one was a primary prevention trial [18]. All studies included adults (age greater than 18y) of both sexes, and two of them [17,22] included elderly too (age greater than 65y). The estimated average ages of participants of the observational studies [17,19–22] were 52.0y for MetS subjects, and 50.7y for non-MetS ones. In the prevention trial [18], the mean ages were 57.2 ± 5.8y for MetS subjects and 55.5 ± 6.2y for non-MetS subjects. In total, 17,491 participants were included in this review (5220 from the prevention trial, 258 from the case–control study, and 12,013 from the cross-sectional studies). The majority of participants were women (56.7%).

The prevention trial did not perform an assessment of dietary intake. Two cross-sectional studies [19,21] used one 24-h dietary recall to assess the food intake; one [20] used three day food diary; and the last one [22] used a semi-quantitative food frequency questionnaire. The case–control study [17] used 24-h dietary recalls during 7 days.

Two cross-sectional studies [19,20] did not present rates of losses and/or their reasons. For the other studies [17,18,21,22], the rates of losses ranged between 4.5% and 15.2% due to missing data.

When it comes to exclusion criteria, missing data was mentioned in three studies [17,18,22]. Two cross-sectional studies [19,21] pointed pregnancy, lactation, cardiovascular disease or diabetes as exclusion criteria, while the use of dietary supplement was mentioned in three studies [19–21]. One of the cross-sectional studies [21] pointed out extreme outliers for any variables (below centile 3 or above centile 97) and total daily energy intake less than 800 or more than 4200 Kcal as exclusion criteria. In the prevention trial [18], participants with MetS at the baseline were excluded, since the study was looking for new cases of MetS.

The main outcome reported by the studies was MetS, and one study [22] presented also its features: WC, systolic blood pressure, diastolic blood pressure, triglycerides, HDL-c and fasting blood glucose. All the observational studies [17,19–22] reported significant differences in MetS features between groups (MetS *vs* non-MetS). Differences in body mass index (BMI) [17,19–22], age [19,21,22], weight [19,21], sex [19], physical activity [21], smoking status and educational level [17] and some nutrient intake (energy [17,20], total fat [17,20], carbohydrates [20], cholesterol [17], vitamin E [17,21], vitamin C [20], thiamine [21], magnesium [17], zinc [20], copper [20], and sodium [17]) were reported too. In the prevention trial [18], a significant difference in physical activity between groups at baseline (placebo *versus* intervention) was reported.

Information about the amount of Se intake was made available in four studies [17,20–22], whereas the trial [18] made reference to serum Se at baseline. Mean Se intake ranged between 31.8 ± 24.5 μg and 58.9 ± 23.8 μg in MetS subjects and between 32.5 ± 24.5 μg and 57.9 ± 17.5 μg in non-MetS subjects. Serum Se was 1.11 ± 0.2 μmol/L in placebo group and 1.12 ± 0.19 μmol/L in intervention group [18]. One study [20] adjusted the analysis according to age and sex only. All the other five studies [17–19,21,22] adjusted the analysis also for physical activity level and smoking status. Other adjustments made for the variables used concerned educational level [17–19], energy intake [19,21,22], alcohol consumption [18,22], BMI [17,21], past medical history [21], nutritional supplementary, fibre and protein intake [22], and marital status [19].

Three different MetS criteria were considered in this systematic review: NCEP-ATP III [17,18,20], IDF [19,21], and the American Heart Association criteria [22]. In total, 5957 subjects were diagnosed with MetS (34.1%). Out of these, 3230 were women (54.2% of MetS subjects).

The prevalence/incidence of MetS and the population of the studies characteristics in terms of MetS features are presented in Table 3.

3.3. *Assessment of risk of bias and of the appropriateness of study reports according to reporting guidelines*

The summaries of risk of bias from three different tools are presented in Fig. 2 and were appropriated for each study design.

All studies were deemed at low or unclear risk of selection bias, since the prevention trial [18] provided specified method of randomization; however, it was unclear about allocation concealment. Observational studies applied uniform inclusion/exclusion criteria to both Mets and non-Mets groups. Nevertheless, one of the cross-sectional studies [20] was classified as to present moderate risk when it comes to controlling confounders variables. In the cross-sectional studies, only one [20] presented unclear risk of attrition bias. The others [19,21,22] were evaluated as high risk of attrition bias, once they did not appropriately present how missing data were handled. All cross-sectional studies [19–22] were unclear in explaining the measures of confounding variables.

CONSORT checklist and STROBE Statement were applied in order to perform the assessment of appropriateness of study reports according to the relevant guidelines, and the percentages of agreement are shown in Table 2. According to the CONSORT checklist [26] (see Supplementary file 2), included prevention trial [18] met 54.3% of the applicable requirements. The article did not identify the study design in the title and did not give enough detailed information to allow replication of the intervention. However, outcome measures were completely pre-specified. This report did not explain the sample size determination; it, however, adequately displays how statistical methods were used and adjusted. On the other hand, results were clearly presented and made distinction between pre-specified analyses and exploratory ones. Trial limitations and external validity of the results were discussed, even though sources of funding and other support – including the role of funders – were not presented.

According to the STROBE-Statement for case–control studies [25] (see Supplementary file 2), the included case–control study [17] met 62.1% of the applicable requirements. The article identifies the study design in the title and presents an adequate scientific background in the introduction, even though it did not present any study hypotheses. Data related to the source of variables were presented; however, the choice of potential confounders and/or effect modifiers was not justified. Study limitations and generalizability of the results were discussed; funding sources were presented; they, however, did not include the role of such funders.

According to the STROBE-Statement for cross-sectional studies [25] (see Supplementary file 2), two studies [21,22] fulfilled 40% or more of the applicable requirements. All studies explained adequately the scientific background and rationale for the investigation reported, even though none stated the study hypotheses.

Table 3
Characteristics of the studies population according to metabolic syndrome diagnosis.

Study-year	MetS[a] (%)	Waist circumference (cm) (*Mean ± SD*)		Systolic blood pressure (mmHg) (*Mean ± SD*)		Diastolic blood pressure (mmHg) (*Mean ± SD*)		Triglycerides (mmol/L) (*Mean ± SD*)		HDL-c (mmol/L) (*Mean ± SD*)		Fasting blood glucose (mmol/L) (*Mean ± SD*)		Body Mass Index (kg/m²) (*Mean ± SD*)	
		MG	n-MG	MG	n-MG	MG	n-MG	MG	n-MG	MG	n-MG	MG	n-MG	MG	n-MG
Czernichow et al. (2009) [18]	Placebo group 5.1 Intervention group 4.9	97.7 ± 9.7	80.9 ± 10.9	137.0 ± 13.0	127.8 ± 14.5	86.1 ± 8.5	81.2 ± 9.1	1.81 (1.72,1.9)[b]	0.88 (0.87,0.89)[b]	1.1 ± 0.2	1.7 ± 0.4	5.7 ± 1.6	5.0 ± 0.5	29.6 ± 4.3	24.0 ± 3.3
Bian et al. (2013) [17]	[c]	88.0 ± 9.6	81.2 ± 8.2	144.0 ± 16.0	118.0 ± 14.4	87.0 ± 9.3	75.0 ± 9.5	2.7 ± 1.8	1.1 ± 0.9	1.3 ± 0.2	1.4 ± 0.3	6.9 ± 1.8	5.5 ± 1.5	28.2 ± 3.0	23.3 ± 2.7
Li et al. (2013) [20]	40.2	93.0 ± 7.8	83.6 ± 8.7	135.0 ± 16.2	123.0 ± 15.3	88.6 ± 9.6	81.6 ± 10.3	2.1 ± 1.3	1.2 ± 0.8	1.3 ± 0.5	1.4 ± 0.3	5.7 ± 2.0	4.9 ± 1.3	26.9 ± 3.2	24.1 ± 4.1
Motamed et al. (2013) [21]	46.8	Men 101.8 ± 6.9 Women 100.2 ± 10.7	Men 89.5 ± 10.8 Women 91.9 ± 12.6	Men 128.9 ± 17.1 Women 128.9 ± 20.3	Men 118.8 ± 15.5 Women 114.5 ± 14.8	Men 85.2 ± 10.5 Women 83.3 ± 12.1	Men 78.4 ± 10.2 Women 74.9 ± 9.9	Men[b] 2.0 (1.6,2.7) Women[b] 1.9 (1.3,2.4)	Men[b] 1.2 (0.9,1.7) Women[b] 1.2 (0.8,1.4)	Men 0.9 ± 0.2 Women 1.1 ± 0.2	Men 1.0 ± 0.2 Women 1.2 ± 0.3	Men 4.9 ± 1.3 Women 4.9 ± 1.3	Men 4.5 ± 0.8 Women 4.4 ± 0.3	Men 28.8 ± 3.3 Women 30.1 ± 4.3	Men 25.5 ± 3.2 Women 29.9 ± 7.9
Wei et al. (2015) [22]	17.0	90.8 ± 7.8	82.5 ± 8.4	137.5 ± 16.2	123.6 ± 16.4	87.0 ± 10.9	78.1 ± 11.4	3.1 ± 2.3	1.6 ± 1.4	1.2 ± 0.3	1.6 ± 0.4	6.6 ± 1.9	5.5 ± 1.3	26.9 ± 3.1	24.0 ± 3.0
Khayyatzadeh et al. (2016) [19]	57.3	101.1 ± 9.7	91.5 ± 11.6	130.3 ± 19.3	116.4 ± 16.9	84.1 ± 11.5	76.1 ± 11.0	1.9 (1.4,2.5)[b]	1.1 (0.8,1.5)[b]	1.0 ± 0.2	1.1 ± 0.3	5.6 ± 2.5	4.6 ± 1.4	29.9 ± 4.1	26.6 ± 4.4

Abbreviations: MG, MetS Groups; n-MG, non-MetS Group.
[a] Prevalence for cross-sectional studies; incidence for the trial.
[b] Geometric means and 95% Confidence intervals in parentheses due to skewed distribution.
[c] Unavailable data due to case–control design.

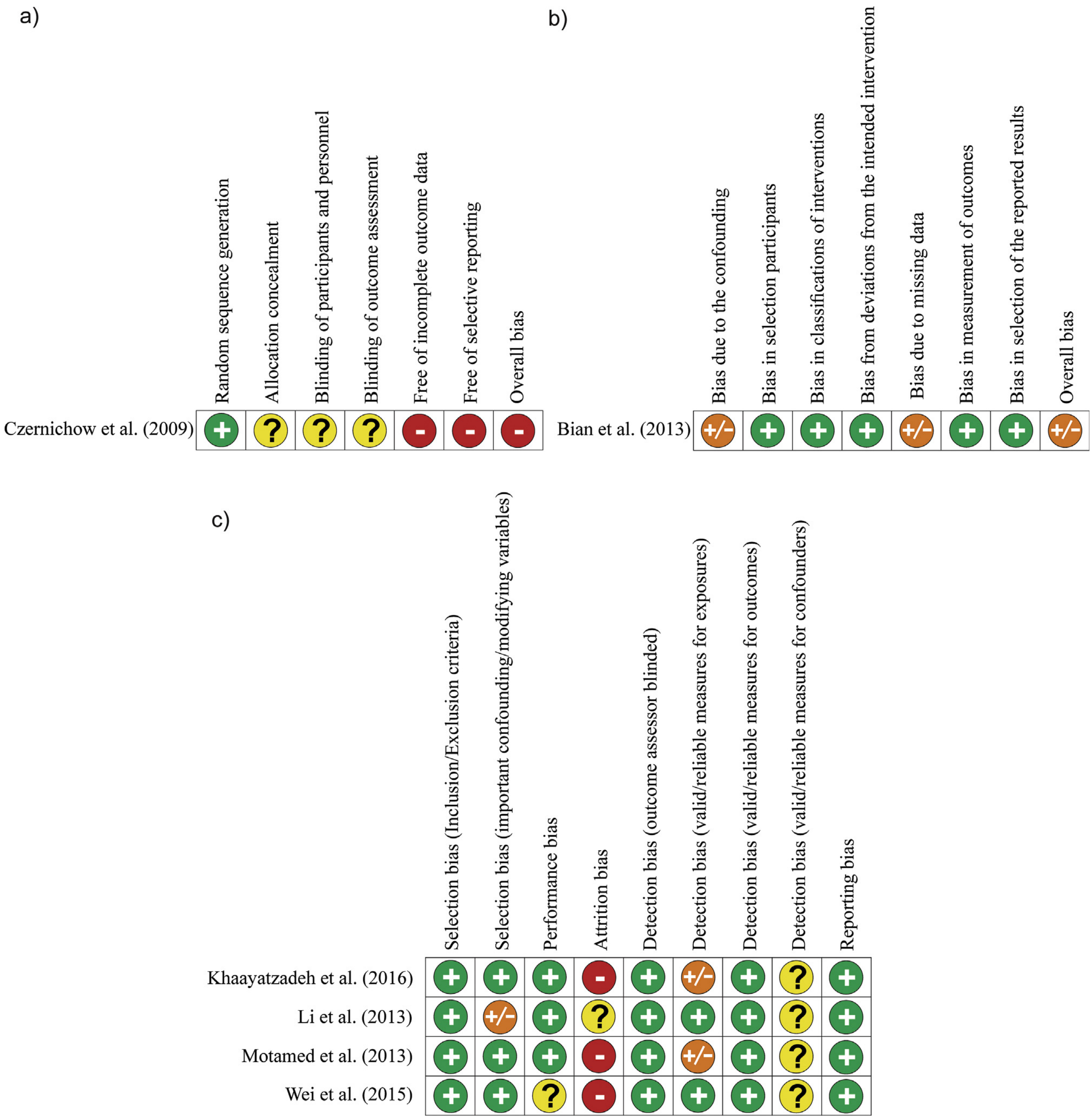

Fig. 2. Summary of risk of bias according to study design: a) the Cochrane Collaboration tool for the prevention trial; b) the ROBINS-I tool for the case–control study; c) the AHRQ tool for the cross-sectional studies. *Legend*: (+) Low risk (+/−) Moderate risk (−) High risk (?) Unclear risk.

When it comes to variables, only one article [20] did not describe the statistical adjustment adequately; two of them [21,22] did not mention potential confounders. All studies presented how quantitative variables were handled in the Methods section, and the characteristics of the participants are shown in the Results section. However, none of them made use of a flow diagram. All studies presented an overall interpretation of the results interpretation and only one [19] pointed out the external validity of the results.

3.3.1. Outcomes in observational studies

Both the case–control [17] and a cross-sectional study [20] observed no association between Se intake and MetS prevalence. Two studies [21,22] found an inverse association between Se intake and MetS prevalence; the last one [19] found a direct association between women intake of a nutrient pattern containing Se and MetS prevalence. One study [22] showed also an inverse association between Se intake and the prevalence of high WC, high diastolic blood pressure, and hyperglycaemia.

3.3.2. Outcomes in the primary prevention trial

The prevention trial [18] found no association between Se supplementation (in a combination of antioxidants at nutritional doses) and MetS incidence.

4. Discussion

The aim of this systematic review was to evaluate the association between Se intake or supplementation and the MetS. This section considered the relationship between Se and each MetS features, tools for food intake evaluation, presence and availability of Se in food sources, Se status in human body, confounding variables to consider in statistical models about MetS, our recommendations for future study methods and reports, and strengths and limitations of the current systematic review.

4.1. Selenium and metabolic syndrome features

Se is an essential mineral for maintenance of overall health [27]. Its role in human body has been studied, especially for the thyroid function, T2DM, hypertension, obesity, inflammation, reproductive system, cancer and cardiovascular disease. To the best of our knowledge, this is the first systematic review examining the relationship between Se intake or supplementation and MetS as main outcome.

Obesity is considered the main feature of MetS [2], once it is an important risk factor for hypertension, dyslipidaemia, and hyperglycaemia [9]. A cross-sectional study developed in Great Britain found inverse association between whole-blood Glutathione peroxidase (GPx) activity, central obesity (WC values), and general adiposity (BMI values) [28]; the same happened for a study conducted in the United States, which found inverse association between serum Se and BMI [29]. These findings are supported by a hypothesis which says that Se deficiency may lead to inflammatory diseases – obesity included [27].

Some studies showed a direct association between serum Se and hypertension [30,31]. On the other hand, a prospective analysis of data collected in Belgium concluded that low serum Se was associated with hypertension in men [32]. This is sustained by the hypothesis that the Se antioxidant function may prevent or reduce the oxidative stress process in hypertension [33].

Concerning dyslipidaemia, some studies pointed a direct association between serum Se and total cholesterol [29,34,35], LDL-c [29,34], non-HDL-c [35], HDL-c [29,34], and triglycerides [29]. Results of the Young Finns Study show positive association between serum Se and total cholesterol, HDL-c and LDL-c in cross-sectional analysis, but not in longitudinal ones [36]. In trials, Se supplementation alone [37,38] or with others antioxidants agents [39] had three different results: a direct association with hypertriglyceridemia in men and hypercholesterolemia in women [39]; no significant effect on lipid profile [37]; an inverse association between total cholesterol and non-HDL-c; and a direct association with HDL-c [38]. A possible explanation for these findings is an evidence of interdependence between the metabolic pathways of Se and lipoproteins. Lipoprotein receptors bind selenoproteins and could make easier Se transporting and retaining in the human body [40,41].

The link between Se and T2DM is still unclear [27]. Some studies found a direct association between them, where high serum Se [42,43] or Se intake [44] were associated with high prevalence of T2DM. High serum Se could deplete Chromium, leading to lipolysis, and increase the generation of reactive oxygen species, impairing insulin signalling [45]. This is a possible explanation for a direct association between both Se and T2DM. On the other hand, another study [46] found an inverse association between serum Se and hyperglycaemia, and two experimental studies [47,48] and a meta-analysis [49] found no association between Se and diabetes risk or prevention. Another review proposed that both low and high serum Se may increase the risk of T2DM [50].

Individuals with MetS usually present a pro-thrombotic, inflammatory status [7], with oxidative stress playing an important role in the development of chronic diseases [51]. Central obesity may be seen as a starting point for MetS, leading to insulin resistance and other hormonal and cytokines action diseases, which are produced by the adipose tissue. An example is the Tumour Necrosis Factor Alfa (TNF-α), which reduces the expression of insulin receptors and glucose transporters, thus leading to insulin resistance and hyperglycaemia. Resistin is also increased, what decreases glucose tolerance and insulin sensibility. On the other hand, adiponectin is reduced in central obesity and leads to an increase in triglycerides and insulin resistance. With an increase in angiotensin II, nitric oxide formation is inhibited and may lead to a stiffening in the blood vessels muscles. Once insulin resistance is installed, free fatty acids are increased in blood and liver, stimulating LDL-c and triglycerides production, thus leading to HDL-c reduction. On the other hand, Se – being a GPx component – may, then, develop an antioxidant role, decomposing lipid peroxides; when connected to free radicals, Se can block the nuclear transcription factor kappa-beta (NF-$\kappa\beta$), thus leading to inflammation reduction, as well as reduction of the vascular cell adhesion molecule; while inhibiting TNF-α, Se can also play a role in the reduction of the vascular cell adhesion molecule and triglycerides, thus increasing insulin reception, glucose transportation, and HDL-c [52–57].

4.2. Evidence of included articles

All studies included in this systematic review were published after 2009, which demonstrates an increase of interest in this field. Five of the six included articles were conducted in Asia (three from Oriental Asia [17,20,22] and two from Western Asia [19,21]). In this way, the results generalization for worldwide population needs to be carefully evaluated. Asian population tend to have a diverse lifestyle compared to Western population, characterized by reduced fat and meat intake, and increased physical activity [58,59]. However, the intake of energy, meat, and vegetables has been increasing since the 1970s, especially in China [60]. Furthermore, Se content in food is directly affected by Se variability in soil around the world [61].

Most of the studies included in this systematic review has a cross-sectional design [19–22] and one study has a case–control design [17]. In general, these observational studies require less financial, personnel, and time resources. Therefore, their results and conclusions need to be interpreted with caution – especially in terms of causality [62] – and should preferably be complemented by longitudinal studies.

Three different tools were used for assessing food intake in four different ways: 24-h dietary recalls repeated over 7 days [17], 24-h dietary recall applied once [19,21], food diary repeated over 3 days (including two weekdays and one weekend) [20] and a semi-quantitative food frequency questionnaire validated by comparison with a 24-h dietary recall for similar population [22]. A systematic review that analysed dietary assessment methods for Se intake [63] showed that food frequency questionnaire was the most common method to assess dietary mineral intake, validated by comparison with dietary records or 24-h recalls. The food frequency questionnaire was considered an acceptable tool for assessing mineral intake [63]. However, the correlation coefficient obtained for Se was not satisfactory, as it ranged from 0.3 to 0.5, being considered just acceptable. In this way, authors highlight the need for studies using biomarkers to validate Se intake assessment tool.

The studies included in our systematic review did not present and/or explain their losses. The articles mentioning losses [17,18,21,22] did not explain how the missing data were handled and considered in the analysis and interpretation of the results. Were missing data balanced between groups? Could missing data impute a clinically relevant bias on the effect estimate? Could it be possible to impute missing data? If yes, could they have been imputed using appropriated methods? These points are important to reduce attrition bias [24] and allow for a clear conclusion.

Only one study [22] presented MetS features as outcomes. MetS is a complex health condition, comprising, at least, three of five metabolic disorders interacting with each other. Several studies have looked for association between Se and some MetS features in different health conditions [49,64–69]. However, it is important to evaluate the association between Se intake and each MetS feature separately, especially in MetS subjects, to better understand the association with Se in this specific population.

The Se estimated average requirement is 45 μg/d for male and female over 18y [70]. For the German, Austrian, and Swiss Nutrition Societies, the reference values for Se intake are 70 μg/d for men and 60 μg/d for women [71]. Two included studies [20,21] found mean Se intake lower than the estimated average requirement, while two other studies [17,22] found mean Se intake higher than recommended. Se intake below 40 μg/d, as showed by Motamed et al. [21] and Li et al. [20] for MetS subjects, could be associated to a reduction in the GPx activity; however, it may not present clinical symptoms [72]. For Chinese with low Se status, a total daily intake of 49 μg seems to improve the selenoprotein P activity [73]. This value was reached by only one Chinese study [17] out of three [20,22]. Se intake above tolerable upper intake levels (UL: 400 μg/d) was not reported in the included articles. Average Se intake varies around the world, ranging from 200 to 350 μg/d in Venezuela, to 18–53 μg/d in Turkey [61]. Average Se intake was estimated at 93 μg/d for American women, 134 μg/d for American men and 40 μg/d for Europeans [74]. In some Chinese areas, Se deficiency is endemic, with a Se intake lower than 12 μg/d [75]. The variation of Se intake across regions reflects, among other factors, different Se content in soil around the world, which affects Se content in water and food [61,76], as well.

Se concentration in soil depends on some geological factors, such as pH and the types of rocks that form them. Alkaline lands, with rocks composed by volcanoes, coal, limestone (chalk), and pyrite tend to be rich in Se [76,77]. It seems that oceans are important sources of Se, thus, near ocean areas have higher Se concentration [78]. In this way, the use of local tools to inform food nutrient contents is recommended, in order to reduce the discrepancies in Se amount. Among the five included articles that reported food intake assess, only the Chinese ones [17,20,22] made reference to the use of a local food composition table.

The Se form affects its bioavailability and its use by the human body. Only one study [18] included in this article presented an interventional approach, by applying a combination of antioxidants containing 100 μg of Se: selenium-enriched yeast. This is an organic form of Se – an edible yeast product with a high concentration of intracellular Se [79]. Organic Se sources are considered the most bio available for human consumption [80]. The other articles studies included in this systematic review with an observational design. Food intake was evaluated, even though they did not mention the food which contributed the most to the total Se intake. In this way, it was not possible to determine the exact amount of each Se form consumed by the subjects of such studies.

All studies included in this systematic review analysed Se intake [17,19–22] or supplementation [18] along with other nutrients. Four studies [17,20–22] presented data related to Se intake alone, even though the methods used to assess food intake observed the diet as a whole. One observational study [19] evaluated Se intake in a dietary nutrient pattern characterized by copper, Se, vitamin A, riboflavin, and vitamin B12. It is important to highlight that, although synergistic physiological actions between Se and vitamin E are stated [81], Khayyatzadeh et al. did not find Se and vitamin E as following the same dietary nutrient pattern. Finally, the prevention trial [18] randomly offered a combination of oxidants (including vitamin C, vitamin E, β-carotene, zinc, and Se) and/or placebo. People do not eat nutrients separately; instead, they have a combination of foods resulting in an intake of nutrients. In terms of Se, it interacts with other nutrients, such as methionine, protein, and other antioxidants (e.g. zinc and vitamins E, A, and C) – thus increasing Se absorption – as well as sulphur and toxic metals (e.g. mercury and arsenic) [82], which can reduce Se bioavailability [82,83]. In this way, even though the results presented by some studies [17,20–22] included in this review did not directly address others nutrients, it is important to mention that they are involved in the whole diet evaluated.

Serum Se was reported only in the prevention trial [18]. Some biomarkers respond to Se intake changes, as plasma Se, erythrocyte Se, whole-blood Se, plasma selenoprotein P, and measures of GPx activity [84]. Although plasma GPx activity is a better biomarker for Se requirement to optimize selenoproteins activity [84], Se plasma is a better reflection of the Se intake, once it bears no saturation point [73]. Plasma selenoprotein P also is a good indicator of Se status, as its concentration reduces in the face of a low intake of Se [41]. Since the methods used to assess food intake and to estimate nutrient intake have their weaknesses, to associate them with an evaluation of Se status may improve the reliability of the results.

The relevant studies included in this review made use of different variables in order to analyse adjustment. There are important confounding factors in MetS studies given the multicausality of chronic non-communicable diseases [9,85]. These confounders were partially observed by the authors of such studies. Only three studies [17–19] made use of socio-economic factors in statistical models, such as educational level and marital status. It is a fact that socioeconomic factors influence the environment in which people live, affecting their habits and, consequently, their health [9,86]. Therefore, such factors also affect the way people eat, move, exercise, work, and sleep. Eating habits, physical activity, sedentary lifestyle, and sleep duration can be considered risk factors to obesity, hyperglycaemia, and dyslipidaemia [2,9,87–94]. Only one study [20] did not consider physical activity in the models and three [19,21,22] considered intake variables, such as protein, fibre, and energy. None of the studies included in this systematic review considered sleep duration as a confounding variable. Combined with obesity, smoking status, and alcohol consumption, these variables may also be seen as risk factors for developing hypertension [2,9,95–97]. One study [20] did not consider smoking status in its statistical model; two studies took obesity (BMI values) [17,21] and alcohol consumption [18,22] into consideration. These are non-individual variables, which interact with each other.

On the other hand, sex and age, which are personal factors associated to MetS [2,98,99], were considered by all included studies. Although most studies adjusted the analyses for some important variables, statistical models which contemplate different factors of disease determination can be improved by applying a conceptual hierarchical framework. Being so, such models would take into consideration the inter-relationship between variables and allow them to be organized at different levels [100]. None of the studies made use of a multilevel approach in their statistical analyses.

It is worth mentioning the fact that all the studies used in this review evaluated MetS by using three different criteria and were are accepted worldwide; therefore, they were defined in the systematic review protocol as inclusion criteria. The range of MetS prevalence found in the observational studies complies with the prevalence variation around the world, as comparable in Table 4.

Two studies [21,22] found inverse association between Se intake and MetS; one [22] of them also found that this association was connected with the prevalence of high WC, high diastolic blood pressure, and hyperglycaemia.

It is worth mentioning the importance of presenting all data related to MetS and its features in order to better understand the

Table 4
Metabolic syndrome prevalence around the world and in the studies included in this systematic review.

Study local, year	Range of Metabolic syndrome prevalence (%)
Studies included in this systematic review	17.0–57.3
Asia–Pacific, 2017 [4]	11.9–37.1
United States, 2015 [105]	13.5–36.0
Europe, 2014 [106]	11.6–26.3
Brazil, 2013 [107]	14.9–65.3
Africa, 2012 [108]	12.5–62.5
Latin America, 2011 [109]	18.8–43.3
Gulf Cooperation Council Countries, 2010 [110]	13.5–40.5

outcomes of a study. Some systematic reviews published after 2012 investigated Se supplementation and/or its status, along with cardiovascular diseases, T2DM, hypertension, and/or obesity; however, they did not consider MetS subjects. Although some studies found no association between Se concentration and obesity in children [101] and adults [102], a systematic review of observational studies concluded that Se status is lower in obese than in non-obese subjects [68]. Ress et al. [103] found a statistically significant reduction in non-HDL-c concentrations with Se supplementation. Nevertheless, the study points out that these potential benefits are for Se-depleted populations only. Wang et al. [66] found a positive association between serum Se and T2DM only in a range between 97.5 and 132.5 μg/L. Equally, Zhang et al. [67] found a benefit effect for cardiovascular disease only in a range between 55.0 and 145.0 μg/L of Se. These results show that both low and high concentrations of Se could be associated with a high prevalence of the diseases studied in the research.

One study [19] found a direct association between Se intake (in a nutrient pattern) and MetS prevalence in women only. Other published systematic reviews studies included in this systematic review presented a direct association between Se supplementation and/or status and their outcome of interest (MetS features, hypertension, T2DM, and cardiovascular disease). However, none of these reviews succeeded to find direct association between Se and their results [14,49,64,65,67,69].

Three studies [17,18,20] included in this review found no association between Se intake or supplementation and MetS. Fortmann et al. [64] found no association between Se supplementation and cardiovascular diseases, as well as Schwingshackl et al. [65]. Another published systematic review did not succeed to find an association neither between Se supplementation and T2DM [49,103], or serum Se and hypertension [69].

The main explanation for this inconsistency of results is the U-shaped performance between Se and cardiometabolic outcomes. This behaviour indicates that both Se-depleted and Se-replete individuals may, eventually, suffer health damages [11,76,104]. However, published studies are likely to only evaluate the association between MetS and Se status, not considering Se intake.

4.3. Recommendations for future studies

Further studies are indispensable to discover the real effects of Se intake in MetS and its features. With the desire to contribute to improve the methodological quality of various studies to come, a summary of a few points discussed in this paper is highlighted as follows:

Even though prospective studies are the most desired, all types of research need to be carefully planned based on validity methods for specific study populations, independently of the design. All study choices must have a solid base on literature, which has to be reported in the article. In order to support the writing of reports, manuscripts should be prepared in accordance with specific guidelines for study design, such as CONSORT or STROBE. It is also important to consider using conceptual frameworks (hierarchical or not) to lay out the research choices, thus making it easier to build a statistical model. In the results section, it is crucial to present all relevant data in a clear, organized way – the same applies for all individuals and groups. For instance, studies may present mean and standard deviation of Se intake for all participants and each subgroup analysed, as well as the prevalence of MetS and secondary outcomes. In addition, they may present mean and standard deviation (or similar measures) for each MetS feature (WC, systolic blood pressure, diastolic blood pressure, triglycerides, HDL-c, and glycaemia), categorized in groups. This standardization may allow for future meta-analyses. In order to minimize the weaknesses in dietary intake assessment tools, authors should be encouraged to perform data validation. The authors of this review would like to recommend assessing both Se intake and its status.

Finally, no studies made a comparison between MetS and non-MetS groups of children and adolescents. In this way, there is a gap that needs to be bridged, so that researchers are able to reach a higher level of understanding in this area.

4.4. Limitations and strengths of the study

This review has a few limitations worth pointing out. Firstly, the studies included in this systematic review have different designs – mostly observational – which makes it impossible to reach a conclusion when it comes to the directionality of the associations. Secondly, even in studies with equal designs, the controlled variables were different and important confounders were left out in some of the studies considered here. Furthermore, the majority of them were conducted in Asia, which limits the understanding concerning Se intake and MetS in other continents. Also, different MetS criteria were applied, which may impute discrepancies in terms incidence/prevalence of MetS. In addition, only one study presented MetS features as outcomes; therefore, most results were restricted to the Syndrome.

Looking on a better side, this review is in accordance with the PRISMA statement. The search was conducted by using several databases and, after the selection process, other eligible articles were searched in reference lists of the studies included in this review in order to minimize publication bias. Furthermore, the search was updated prior to this submission. Studies conducted with healthy subjects or ill individuals – even though MetS features were investigated in them – were not included in this review, once it was only relevant to know the effects of Se intake in subjects with MetS. Even though few studies were included in this systematic review, most of them were conducted by using a large sample, totalizing 17,941 subjects. In addition, we would like to propose improvements for future studies based on the findings of this review.

5. Conclusion

In summary, available evidences in literature are controversial when it comes to the association between Se intake and MetS. It can either be the result of various study designs, or the use of different diagnostic criteria, tools for evaluation of the dietary intake, confounding variables chosen to adjust the analysis, and different populations.

Based on the results and argumentation presented in this review, it is possible to conclude that Se intake and MetS are not clearly associated in adults and elderly. Therefore, there is no consensus in recommending Se intake as to improve MetS for age groups. To deepen research on this matter, it is crucial for further studies to follow pre-established protocols, describe methods in detail, and present – in a complete and clear way – their results, thus bringing more reliable and precise conclusions to the field.

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Conflict of interest

The authors have no relevant interests to declare.

Author contributions

A.R., R.F., G.R., E.B.S.M.T. and F.A.G.V. designed the research; A.R., R.F., G.R., M.A.A., L.P.B., E.B.S.M.T. and F.A.G.V. conducted the research; A.R. contributed to drafting the manuscript. All authors contributed to the critical review of the intellectual content. All authors read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.02.021.

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