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Review Article

Lower circulating zinc and selenium levels are associated with an increased risk of asthma: evidence from a meta-analysis

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Abstract

Objective: Previous studies evaluating the associations of circulating Zn and Se levels with asthma have produced inconsistent results. Therefore, we conducted a meta-analysis to summarize and quantitatively synthesize the evidence from observational research.

Design: Meta-analysis.

Setting: We searched PubMed, Web of Science and Scopus databases up to May 2019 for relevant available articles. Random-effects model was adopted to estimate the pooled standardized mean difference (SMD) with 95 % CI. Meta-regression analysis and 'leave-one-out' sensitivity analysis were used to assess heterogeneity.

Participants: The meta-analysis focused on general populations.

Results: A total of twenty-six studies for Zn and forty studies for Se were included in the meta-analysis. The overall analyses identified that asthma patients had lower Zn (SMD = −0·40; 95 % CI −0·77, −0·03; I^2 = 94·1 %) and Se (SMD = −0·32; 95 % CI −0·48, −0·17; I^2 = 90·9 %) levels in serum or plasma compared with healthy controls. After removing the studies that contributed to the heterogeneity, the pooled SMD were −0·26 (95 % CI −0·40, −0·13; I^2 = 37·42 %) for Zn and −0·06 (95 % CI −0·13, 0·02; I^2 = 43·54 %) for Se.

Conclusions: Lower circulating Zn and Se levels might be associated with an increased risk of asthma.

Keywords
Asthma
Meta-analysis
Selenium
Zinc

Asthma is a common chronic disease, characterized by airway constriction, inflammation, bronchial hyper-responsiveness as well as recurrent coughing, wheezing, dyspnoea and chest tightness[1]. The rise in prevalence and medical costs of asthma are a major public health burden in both developed and developing counties[1–3]. It is generally thought that antioxidants play a vital role in maintaining the health of the airways, thus being associated with asthma[4]. Enzymatic antioxidants, including superoxide dismutase and glutathione peroxidase, require Cu, Zn, Se and others to catalyse the conversion of oxygen radicals into hydrogen peroxide and then to water and oxygen[5]. Therefore, the concentration of these trace elements in serum or plasma might change the efficiency of the antioxidant system and further impact the inflammation and hyper-responsiveness status of the respiratory tract.

Higher level of Cu in asthma patients than in healthy controls has been well documented by previous studies[6]. However, the observational studies on the associations of circulating Zn and Se levels with asthma have drawn conflicting conclusions. Some of them reported significantly lower levels of Zn[7,8] and Se[9–11] in asthma patients than in controls, while others found no significant difference[5,12–16] and a few suggested the opposite association[13,17].

Given that individual studies may have insufficient power to obtain a definitive conclusion, we performed the current meta-analysis to: (i) assess the associations of circulating Zn and Se levels with asthma; (ii) explore the

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potential between-study heterogeneity; and (iii) investigate the potential publication bias.

Materials and methods

We referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[18] for reporting the current meta-analysis.

Literature search and selection

A literature search from inception to May 2019 was conducted for relevant available articles published from three databases: PubMed, Web of Science and Scopus. Studies were limited to human studies in the English language. The search process was conducted using the following keywords: (microelement OR trace element OR selenium OR zinc) AND (asthma OR wheeze OR airway inflammation OR respiratory symptoms OR respiratory disease OR airway obstruction). Moreover, we reviewed the reference lists of retrieved articles to search for further relevant studies. The detailed steps for the literature search are shown in Fig. 1.

Inclusion criteria

To be included in the meta-analysis, studies had to meet the following criteria: (i) observational study design; (ii) the cases were asthma patients who were diagnosed according to the Global Initiative for Asthma (GINA) guidelines[19]; (iii) the controls were healthy people without any respiratory disease; and (iv) data for the level of Zn or Se in serum or plasma were presented as means and standard deviations (or data were available to calculate them). The following exclusion criteria were also used: (i) reviews; (ii) participants were pregnant women or professional groups; and (iii) samples were infants' umbilical cord blood.

If data were duplicated in more than one study, we included the one that was most recently published and/or had the largest number of cases. Two investigators searched for the articles and reviewed all possible studies independently. If the eligibility of an article was controversial, it was resolved by consensus.

Data extraction

The following data were extracted from each study independently by two investigators: the first author's name, publication year, country where the study was performed,

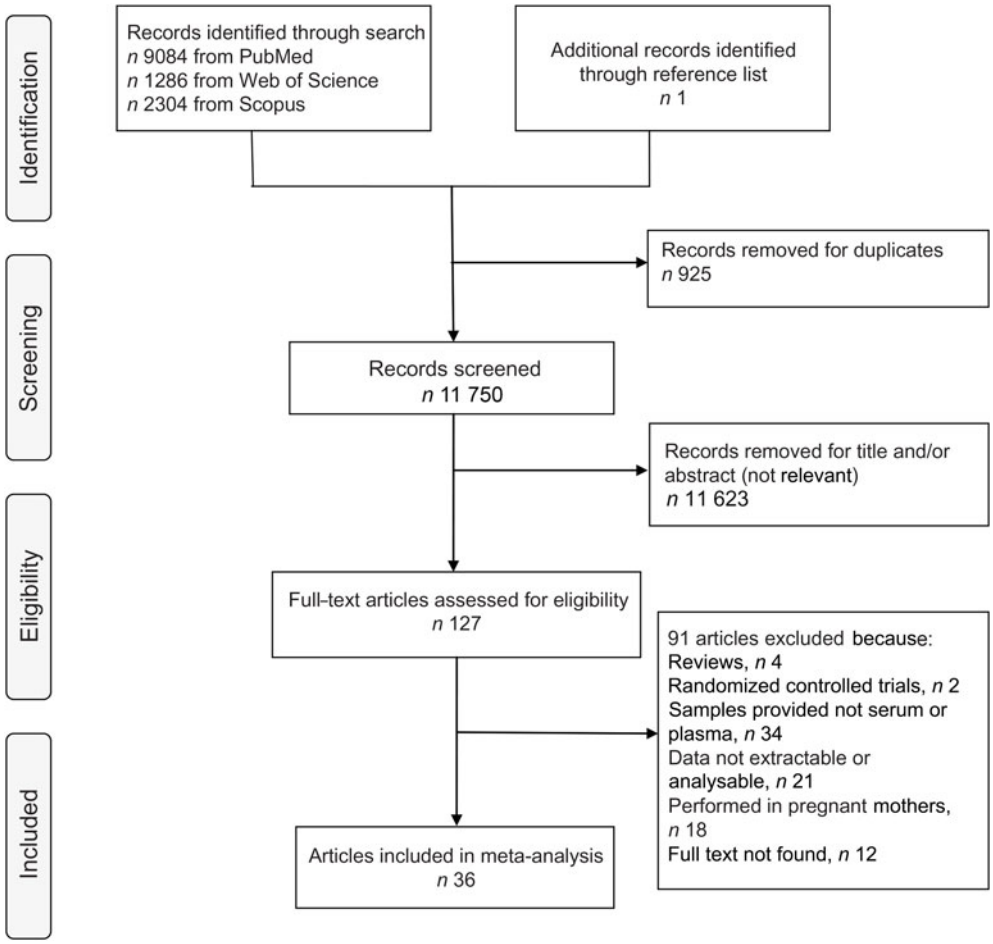

Fig. 1 Flow diagram of the literature search for observational studies on circulating zinc and selenium levels and asthma

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study type, the number of cases and controls, mean and standard deviation for level of Zn or Se, data units, sample type, treatment status in the case group, average age for the case and control groups, as well as matching of potential confounders. If the standard error of the mean was provided in a study, the standard deviation was calculated by the following formula: $\text{SEM} = \text{SD}/\sqrt{n}$.

The quality of the included literature was assessed by the Agency for Healthcare Research and Quality (AHRQ) methodology checklist for cross-sectional studies and by the Newcastle–Ottawa Scale (NOS) for case–control studies, respectively[20].

Statistical analyses

All statistical analyses were performed using standardized mean difference (SMD) with 95 % CI to assess the strength of the association of circulating Zn and Se levels with asthma. The SMD is the ratio of the mean difference to the pooled standard deviation by using the random-effects model. The I^2 statistic was used to evaluate the heterogeneity among the studies, with I^2 values of 25, 50 and 75 % representing low, moderate and high heterogeneity, respectively[21]. We conducted meta-regression and subgroup analyses to explore potential sources of heterogeneity. A sensitivity analysis[22] was performed to evaluate the key studies that have substantial impact on the between-study heterogeneity. An influence analysis was also performed in which one study at a time was removed and the rest were analysed to evaluate whether the results could have been affected markedly by a single study. Egger's regression asymmetry test and visual inspection were used to evaluate the potential effects of small studies[23]. In the presence of a potential small-study effect, we used the trim-and-fill technique to assess its influence on results[24], with the assumption that this effect was mainly due to publication bias. All statistical analyses were performed with the statistical software package Stata version 15.0. All reported probabilities (P values) were two-sided, with $P < 0{\cdot}05$ considered statistically significant.

Results

A total of 9084 articles from PubMed, 1286 articles from Web of Science, 2304 articles from Scopus and one article from the reference lists were identified. After exclusion of duplicate and non-relevant articles, 127 articles were reviewed in full. Another ninety-one articles were excluded for other reasons (Fig. 1) and thirty-six eligible articles were finally included in the meta-analysis. If one article reported two separate results according to sex[25,26] or asthma classification[7,27] or treatment status[28], then it was considered as two studies. A pooled analysis of Se conducted in fourteen European centres was considered as fourteen studies in data extraction[29]. Thus, twenty-two articles with twenty-six studies provided results for Zn level[5,7,8,10,12–17,25–27,30–38] and twenty-four articles with forty studies provided results for Se level[5,9–11,13,16,25,28,29,31,32,35,37–48]. The detailed characteristics of the included studies are shown in the online supplementary material, Supplemental File S1 for Zn and Supplemental File S2 for Se.

The quality assessment showed that the NOS score ranged from 6 to 8 for the case–control studies. The quality score of the AHRQ methodology checklist ranged from 7 to 10 for the cross-sectional studies. The detailed quality assessment is shown in the online supplementary material, Supplemental File S3 and Supplemental File S4, respectively.

Quantitative synthesis

The main results are summarized in Table 1.

Zinc

A total of twenty-six studies involving 1027 cases and 2150 controls were included in the Zn meta-analysis. The overall result suggested lower Zn level in the asthma group than in the control group (SMD = −0·40; 95 % CI −0·77, −0·03; $Z = 2{\cdot}13$, P for $Z = 0{\cdot}033$; $I^2 = 94{\cdot}1$ %, P for $I^2 < 0{\cdot}001$; Fig. 2). In subgroup analysis, the pooled measures did not change materially in studies conducted in Africa (SMD = −1·01; 95 % CI −1·99, −0·03), studies conducted in adults (SMD = −0·66; 95 % CI −1·21, −0·12), studies with case–control design (SMD = −0·47; 95 % CI −0·85, −0·09) and studies with treatment in patients (SMD = −0·67; 95 % CI −1·35, 0·00).

Selenium

A total of forty studies involving 3138 cases and 33 534 controls were included in the Se meta-analysis. The overall result showed lower Se level in the asthma group than in the control group (SMD = −0·32; 95 % CI −0·48, −0·17; $Z = 4{\cdot}04$, P for $Z < 0{\cdot}001$; $I^2 = 90{\cdot}9$ %, P for $I^2 < 0{\cdot}001$; Fig. 3). In subgroup analysis, the pooled measures did not change materially in studies conducted in Europe (SMD = −0·22; 95 % CI −0·40, −0·04), studies conducted in adults (SMD = −0·33; 95 % CI −0·56, −0·10) and children (SMD = −0·40; 95 % CI −0·74, −0·06), studies with case–control design (SMD = −0·41; 95 % CI −0·67, −0·14), studies with samples of serum (SMD = −0·39; 95 % CI −0·63, −0·15) and plasma (SMD = −0·28; 95 % CI −0·49, −0·06), studies with treatment in patients (SMD = −0·39; 95 % CI −0·64, −0·15), as well as studies with age-matched design (SMD = −0·39; 95 % CI −0·69, −0·10).

Sources of heterogeneity, sensitivity analysis and publication bias

Strong evidence of heterogeneity among studies was demonstrated for the associations of these trace elements with asthma. However, subgroup analysis and univariate

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Table 1 Subgroup analyses of studies on the associations of zinc and selenium levels with asthma

	Zn					Se				
	n	SMD	95 % CI	I^2 (%)	*P**	*n*	SMD	95 % CI	I^2 (%)	*P**
Overall	26	−0·40	−0·77, −0·03	94·1		40	−0·32	−0·48, −0·17	90·9	
Continent										
Europe	12	−0·06	−0·60, 0·49	93·5	0·13	25	−0·22	−0·40, −0·04	73·8	0·96
Asia	6	−0·36	−0·76, 0·04	81·5		7	−0·84	−1·73, 0·05	96·0	
Africa	8	−1·01	−1·99, −0·03	96·8		2	−0·61	−2·99, 1·76	98·5	
Oceania	–	–	–	–		3	−0·26	−0·52, 0·01	0·0	
North America	–	–	–	–		3	−0·02	−0·10, 0·06	61·3	
Mean age (years)										
Adults	15	−0·66	−1·21, −0·12	94·6	0·89	25	−0·33	−0·56, −0·10	93·1	0·91
Children	9	0·01	−0·61, 0·63	95·0		9	−0·40	−0·74, −0·06	87·3	
Others	2	−0·41	−0·89, 0·08	50·8		6	−0·25	−0·45, −0·05	32·5	
Study type										
Case–control	18	−0·47	−0·85, −0·09	90·7	0·69	33	−0·41	−0·67, −0·14	91·0	0·33
Cross-sectional	8	−0·26	−1·10, 0·59	96·9		7	−0·06	−0·16, 0·04	59·8	
Sample										
Serum	20	−0·37	−0·81, 0·07	95·2	0·83	17	−0·39	−0·63, −0·15	95·0	0·75
Plasma	6	−0·50	−1·01, 0·01	76·6		23	−0·28	−0·49, −0·06	78·8	
Treatment										
Yes	9	−0·67	−1·35, 0·00	92·2	0·37	12	−0·39	−0·64, −0·15	68·3	0·46
No	8	−0·50	−1·53, 0·54	97·2		4	−0·64	−1·79, 0·51	94·5	
N/A	9	−0·11	−0·47, 0·25	87·0		24	−0·26	−0·45, −0·06	92·9	
Match										
Age	11	−0·24	−0·58, 0·09	85·6	0·63	28	−0·39	−0·69, −0·10	92·0	0·60
N/A	15	−0·53	−1·19, 0·13	96·0		12	−0·18	−0·32, −0·04	76·6	

SMD, standardized mean difference; N/A, not applicable.
**P* value from meta-regression.

meta-regression analysis suggested that continent, age, study design, sample type, treatment in patients and age-matched design had no significant impact on between-study heterogeneity (Figs 2 and 3, Table 1). In the influence analysis, all of the point estimates lay within the 95 % CI of the combined analysis, indicating that no individual study had an excessive influence on the pooled measure for Zn or Se. Visual inspection of the funnel plot and Egger's test suggested that there was a potential small-study effect ($P = 0·036$ for Zn, $P = 0·024$ for Se).

Considering the unexplained heterogeneity and potential small-study effect, sensitivity analysis using $I^2 > 50$ % as the criterion was conducted to assess the robustness of conclusion. Six and seven studies contributed to the high heterogeneity of Zn[7,8,10,17,25,38] and Se[10,11,35,38,42,45,47], respectively. After excluding these studies, low heterogeneity and robust results without small-study effect were found for Zn (SMD = −0·26; 95 % CI −0·40, −0·13; $I^2 = 37·42$ %; *P* for Egger's test = 0·400). However, the pooled SMD for Se had no statistical significance (SMD = −0·06; 95 % CI −0·13, 0·02; $I^2 = 43·54$ %; *P* for Egger's test = 0·382). After running the trim-and-fill technique, no trimming was performed for Zn or Se.

Discussion

The current meta-analysis based on observational evidence, including 3177 participants for Zn and 36 672 participants for Se, indicated that asthma patients had lower circulating Zn and Se levels compared with healthy controls. Significant differences were found in most subgroup analyses by study characteristics and population characteristics. Different from our conclusion, the most recent meta-analysis by Mao *et al.*[6] including twelve studies for Zn and eighteen studies for Se reported no significant differences in Zn and Se between asthma patients and controls. Considering the small effects of Zn and Se on asthma, our meta-analysis that included a larger number of studies could enhance the test power to obtain a definitive conclusion and conduct subgroup analyses.

According to previous literatures, diet and supplements are the main sources of Zn exposure in the general population, accounting for 90–95 %[49]. Meanwhile, an experimental study showed that restriction of dietary Se and supplements could decrease the Se level in plasma[50]. In addition, accumulating evidence suggests that deficiency in dietary antioxidants such as Zn and Se might increase the risk of asthma[51,52]. The mechanisms underlying the associations of Zn and Se with asthma are still not fully understood. Zn is known to exhibit powerful antioxidant activity in the lungs and several body organs[15], and is one of the components of superoxide dismutase. It is possible that the absence of Zn can disturb the imbalance between type 1 and type 2 T-helpers[53], which leads to increased inflammation and eosinophilia. This is the same mechanism as for allergic airway hypersensitivity[54]. In addition, the increase of

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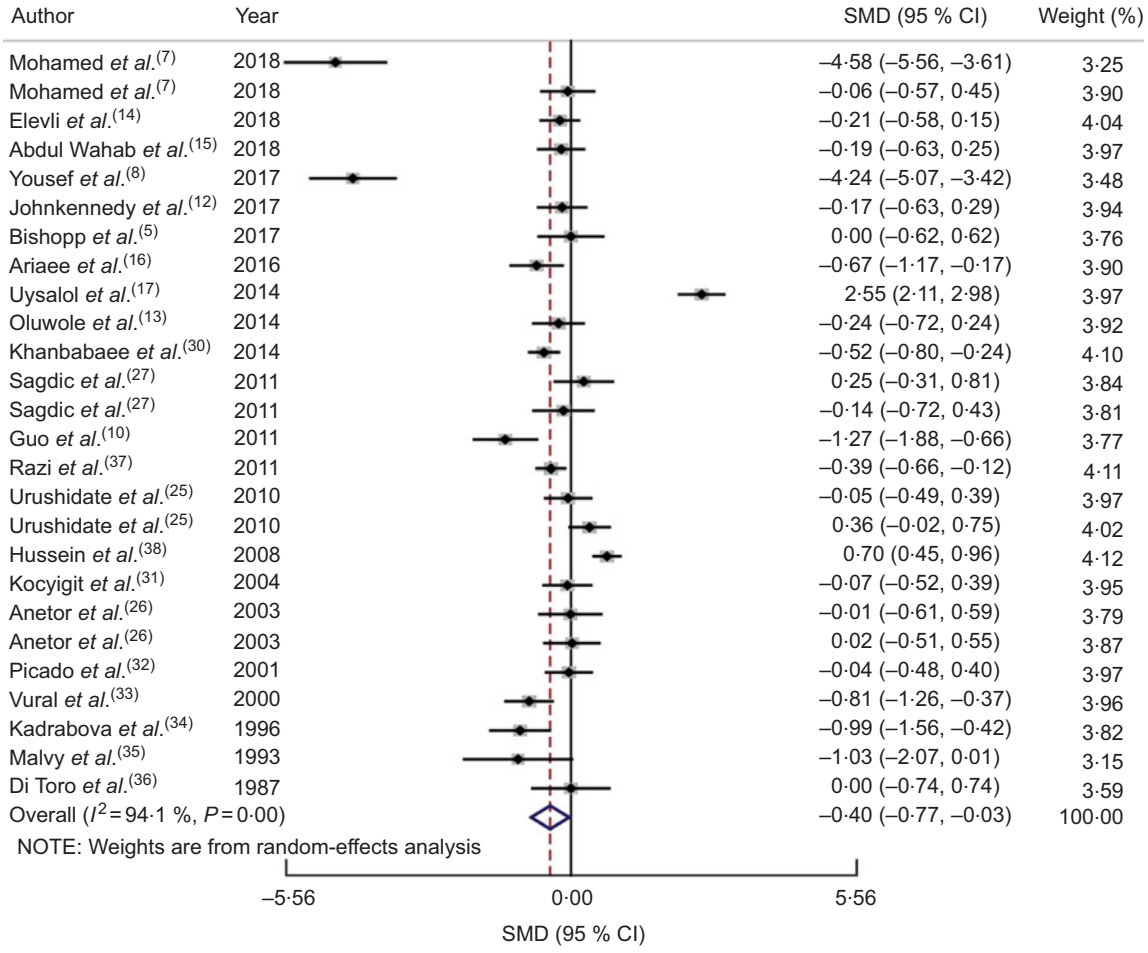

Fig. 2 (colour online) Forest plot of standardized mean difference (SMD) with corresponding 95 % CI of studies on the association between zinc level and asthma. The study-specific effect and 95 % CI are represented by the solid diamond and horizontal line, respectively; the size of the grey square is positively proportional to the weight assigned to each study in the meta-analysis. The centre of open the diamond and the vertical dashed line represent the pooled SMD, and the width of the open diamond represents the pooled 95 % CI

Cu:Zn can be occasionally seen in inflammatory disease. It has been postulated that the increase in serum Cu might be associated with decrease in serum Zn. The changes in these levels will affect enzyme activity and further implicitly cause inflammation by decreasing the capacity of the antioxidant system[17]. Se is necessary for the adequate function of the glutathione peroxidase, which is an important antioxidant to prevent the airway from being damaged by reactive oxygen species[29].

Between-study heterogeneity is common in meta-analysis[55]. In the present study, high heterogeneities were found for both element analyses. Subgroup analyses and meta-regressions with the covariates of several study and population characteristics did not successfully explain the heterogeneity. The further 'leave-one-out' sensitivity analyses using $I^2 > 50\,\%$ as the criterion suggested that six studies[7,8,10,17,25,38] in Zn analysis and seven studies[10,11,35,38,42,45,47] in Se analysis contributed to the high between-study heterogeneities. After excluding these studies, no significant association of Se with asthma was found, which needs to be confirmed. However, the significant difference in Zn between cases and controls was still found, supporting the robustness of conclusions of the current meta-analysis. In 'leave-one-out' sensitivity analysis, the reasons for excluding these studies may be the low quality assessment score, the small sample size and the sample sources mostly from hospitals.

The visual inspection of funnel plots and Egger's test showed funnel plot asymmetry for both trace elements. After running the trim-and-fill technique, no trimming was performed for Zn or Se. This might indicate that the asymmetric funnel patterns of Zn and Se were not caused by the small-study effect. The causes of funnel plot asymmetry or other shapes might be heterogeneity, reporting bias and chance[56]. When we excluded the studies that contributed to the high between-study heterogeneity assessed by the sensitivity analysis, no significant small-study effect was found. This further demonstrated that the funnel plot asymmetry might be caused by heterogeneity.

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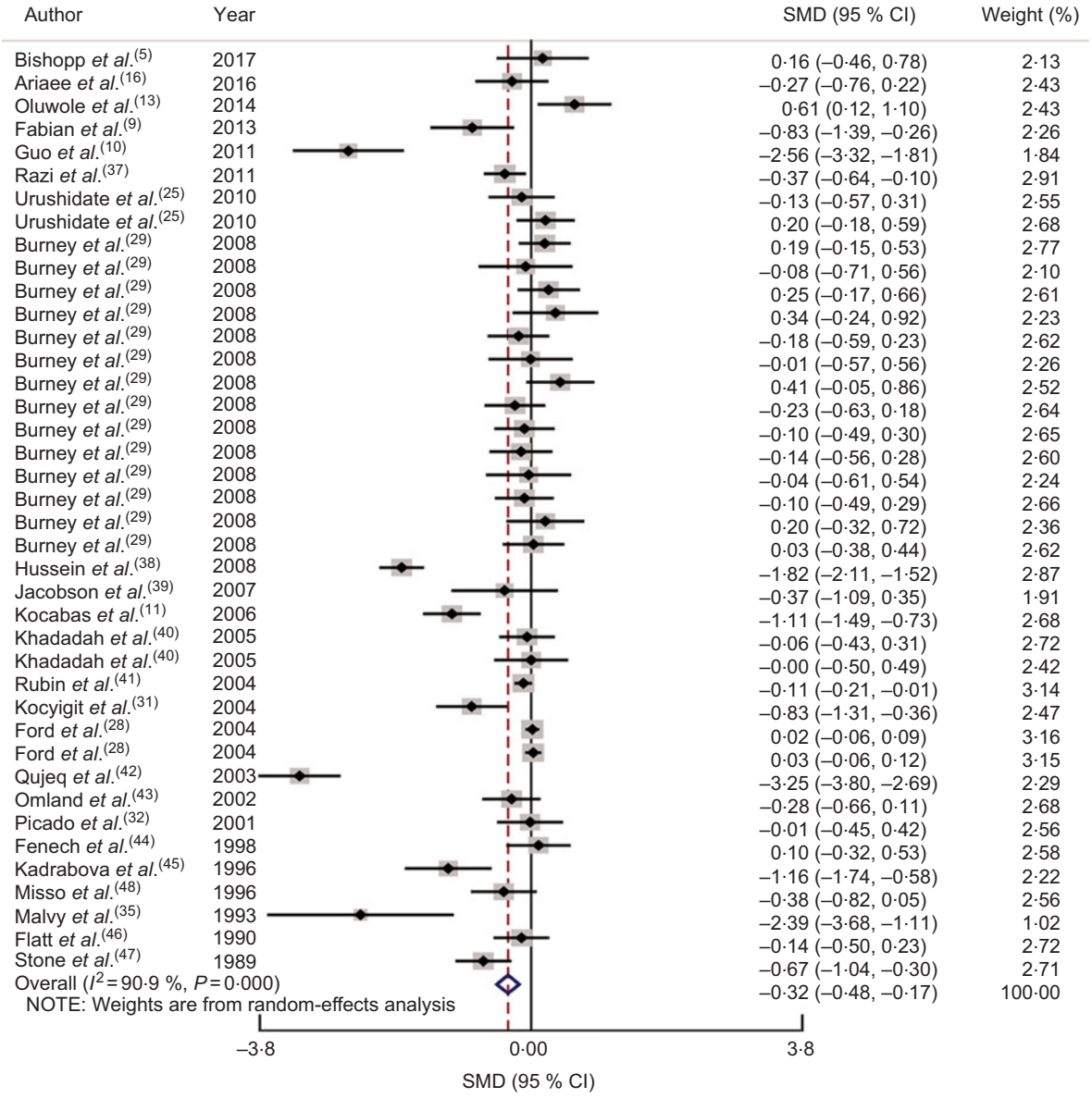

Fig. 3 (colour online) Forest plot of standardized mean difference (SMD) with corresponding 95 % CI of studies on the association between selenium level and asthma. The study-specific effect and 95 % CI are represented by the solid diamond and horizontal line, respectively; the size of the grey square is positively proportional to the weight assigned to each study in the meta-analysis. The centre of open the diamond and the vertical dashed line represent the pooled SMD, and the width of the open diamond represents the pooled 95 % CI

In addition to the large number of studies involved, another major strength of the current meta-analysis should be considered. To address the issue of inconsistency of measurement conditions and units for trace elements in different studies, we estimated the pooled SMD by using a random-effects model, which could draw more convincing results. Nevertheless, as a meta-analysis of published observational studies, our findings have several limitations. First, high between-study heterogeneity was discovered in each trace element analysis, but it was not explained by subgroup analysis or meta-regression. The lack of relevant study-level covariates in the reported articles precluded a more accurate assessment for sources of the heterogeneity. For example, most included studies[8,11,12,14–17,39] did not report stratified results according to asthma classification. Second, although the results in most subgroup analyses did not change materially compared with the overall analysis, the sensitivity analysis showed that the result for Se was not robust. Third, we were unable to explore the dose–response relationship between circulating Zn and Se levels and asthma or the association of Cu:Zn with the risk of asthma, due to the limited data availability. Fourth, confounders adjusted for in the involved studies were different, which might affect the observed associations. Finally, after hard work searching, we were unable to find the full text for twelve articles. Nine of them were

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conference papers and the other three were too old to be well preserved. Those missing articles would definitely have an impact on the overall results.

Conclusion

The current meta-analysis provides evidence that lower circulating Zn and Se levels are associated with an increased risk of asthma. This finding might contribute to the understanding of the pathogenesis of asthma. Considering the important role of diet and supplements in determining circulating Zn and Se levels, attention should be paid to daily intake of Zn and Se in the prevention of asthma. More large observational studies are required to confirm the association between Se level and asthma.

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Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1017/S1368980019003021

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