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Review Article

Association between Maternal Selenium Exposure and Congenital Heart Defects in Offspring: A Systematic Review and Meta-Analysis

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Abstract

Background: The association between congenital heart defects (CHDs) and selenium (Se) is still unclear. We aimed to systematically review and quantitative analyze the potential relationship between maternal Se exposure and CHDs in the offspring.

Methods: PubMed, Embase, Web of Science and Scopus databases were searched from inception up to August 2021 for relevant studies. Methodological quality of the studies was assessed through Newcastle-Ottawa scale. The Standard mean difference (SMD) and corresponding 95% confidence interval (CI) were calculated to compare maternal Se levels between CHDs groups and control groups using a random-effects model.

Results: Four articles covering five studies were included in the systematic review, and three articles covering four studies were included in the meta-analysis. One study measured Se concentrations in maternal hair and found a positive correlation between high concentrations and increased risk of CHDs in offspring. However, one study on cord blood, and one on whole blood illustrated that Se exposure was associated with decreased risk of CHDs. There was no significant association found between serum Se levels and CHDs in two studies. Pooled results showed decreased Se levels in the circulation of mothers with CHDs offspring (SMD = -108.27, 95% CI: -192.72, -23.82), with statistically significant heterogeneity (I^2 = 99.8%, P < 0.001) but not in hair, as compared with controls.

Conclusion: Low maternal Se status may be associated with increased risk of CHDs in offspring. However, further larger-scale studies with strict and consistent design methods are still required to investigate this issue.

Keywords: Selenium; Metal exposure; Congenital heart defects; Offspring

Introduction

Congenital heart defects (CHDs) are defined as developmental abnormalities involving structures of the heart and great vessels, with an incidence rate ranging from approximately 6‰ to 10‰ (1).

The prevalence of CHDs continues to increase globally (2). Although CHDs are affected by both genetic and environmental factors (3, 4), the pathogenesis of CHDs is still unknown. Environmental factors such as maternal smoking (5), obesity (6), and exposure to certain toxic chemicals (7-9) have been proved to be risk factors of CHDs, whereas folic acid has been reported to have a protective effect on CHDs (10).

Selenium (Se) is an essential trace element in human body (11) and is a component of the 21st amino acid, selenocysteine (12), involved in regulating the activity of glutathione peroxidases (13), a group of antioxidant enzymes. Se deficiency is closely related to Keshan disease (14), an epidemic cardiomyopathy that was first found in China. Owing to the decreased antioxidative ability caused by Se deficiency, the myocardium is more vulnerable to oxidative stress (15). However, exposure to excess Se is also harmful to human health. Excessive intake of Se is associated with nail loss, neurological damage, tooth decay, and other clinical symptoms (16, 17). Excessive Se may cause genotoxicity and cytotoxicity in humans (18). Therefore, Se is considered a double-edged sword for human health.

However, the impact of Se on cardiac development remains unclear. There was no significant difference between Se concentrations in the hearts of infants who died from CHDs and those who died from other diseases (19). Elevated maternal Se concentrations during pregnancy were associated with decreased risk of CHDs in the offspring (20), while there was contradictory result (21). To the best of our knowledge, probably no systematic review or meta-analysis has explored this issue. Hence, we conducted a systematic review and meta-analysis of observational studies on the potential association between maternal Se exposure and CHDs in the offspring.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (22). We retrieved relevant studies from the PubMed, Embase, Web of Science and Scopus databases from inception up to August 2021. The following keywords were used in our literature search: "selenium" combined with "congenital heart defects" or "congenital heart diseases" or "heart abnormalities" or "heart malformations" or other similar strings (the details of search strategies used in the databases are shown in Supplemental Table 1) (Supplementary materials are not published and readers may contact the author if needed). The reference lists of relevant studies and review articles were manually searched for additional studies.

The following eligibility criteria were entailed: 1) original observational studies, including cross-sectional, case-control, and cohort studies; 2) studies that examined the association between maternal Se exposure (including Se concentrations in blood, hair, urine, and in other biomarkers that can reflect Se exposure concentrations) and CHDs or one of the CHDs subtypes in offspring; 3) Full-text articles published in English. Reviews, letters, comments, case reports, and conference abstracts were excluded.

Two reviewers (Z.P. and T.Z.) independently screened the titles and abstracts of all retrieved studies and conducted a full-text evaluation for future screen based on the eligibility criteria. Any discrepancies between the two reviewers were solved through discussion, and if no consensus was reached, a senior reviewer (N.Z.) was consulted.

Data extraction and quality assessment

Data extraction and quality assessment of the included studies were conducted by two reviewers (Z.P. and T.Z.), and the differences between the two reviewers were resolved through discussion. The following information was extracted from all eligible studies: name of the first author, publication year, country, study design, sample size, specimens, collection time, Se exposure concentrations, CHDs subtypes, and adjusted covariates.

We used the nine-star Newcastle-Ottawa Scale (NOS) to assess the methodological quality and

evaluate possible sources of bias in the included case-control and cohort studies, based on the three parts of the NOS, including selection, comparability, and outcomes (23). In this systematic review and meta-analysis, studies with scores ≥ 6 were defined to be high quality, studies with scores < 6 were considered of relatively low quality.

Statistical analysis

Statistical analysis was conducted using STATA 16.0 (StataCorp, College Station, TX, USA). The standard mean difference (SMD) and corresponding 95% confidence interval (CI) were calculated to evaluate maternal Se levels between CHDs groups and control groups. The pooled effect was considered significant at $P < 0.05$. If the studies provided data as median ± interquartile range (IQR) or median ± range, we used a standard method to estimate the mean ± standard deviation (SD) (24). Statistical heterogeneity was assessed using the I^2 statistic (25). If $P < 0.1$ or $I^2 > 50\%$, significant heterogeneity was considered, and we used a fixed-effects model in the meta-analysis; otherwise, the random-effects model was utilized.

Results

Study characteristics

A total of 186 articles were initially identified from the databases, including 23 articles from PubMed, 33 from Embase, 22 from Web of Science, and 107 from Scopus. We also identified one additional article from the reference lists of the relevant studies. After removing duplicates, 128 articles entered the screening stage, of which 119 articles did not meet the eligibility criteria and were excluded after screening the titles and abstracts. Nine articles remained for further eligibility assessment. After viewing full-text, we excluded two articles for no eligible data (26, 27), two for incompatible study designs (28, 29), and one for including biomarker that may not appropriately reflect maternal Se levels (*i.e.* Se concentrations in drinking water) (30). Four articles covering five studies were included in our systematic review (20, 21, 31, 32). For the meta-analysis, we excluded one article for no available effect size, and included three articles covering four studies (20, 21, 31). The flow diagram of study selection process is shown in Fig. 1.

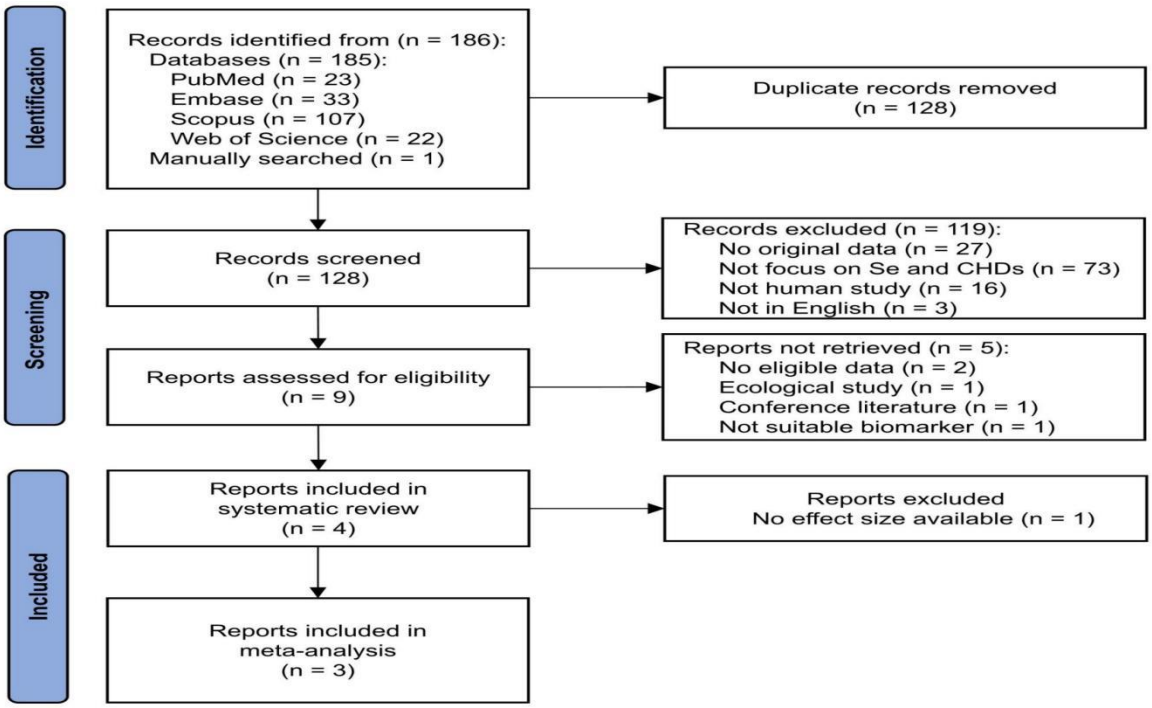

Fig. 1: Flow diagram of study selection

The characteristics of the four included articles are summarized in Table 1. Two articles were conducted in China (20, 21), one in Turkey (31), and one in Saudi Arabia (32). One study was a cohort study (32), and the remaining studies were case-control studies (20, 21, 31).

Table 1: Characteristics of studies included in the systematic review

Author & Year (Ref)	*Country*	*Study design*	*Sample size*	*Exposure biomarker*	*Collection time*	*Selenium levels*	*CHDs subtypes*	*Adjustment variables*	*Quality assessment †*
Guo et al. (2019) (20)	China	Case-control	Hair: 644 Cord blood: 316	Hair Cord blood	Hair: middle or late gestation (14th - 40th week) Cord blood: delivery	Hair: Mean (SD): 0.62 (0.21) ng/mg Median (IQR): case: 0.58 (0.5 - 0.73) ng/mg; control: 0.58 (0.5 - 0.71) ng/mg Cord blood: Mean (SD): 34.03 (14.35) ng/mL Median: case: 33.76 (16.43 - 36.36) ng/mL; control: 37.68 (27.49 - 47.30) ng/mL	SPD, CTD, LVOTO, RVOTO, APVR and other heart defects	Maternal age, gestational age, maternal education, landfill sites or factory distribution, folic acid supplementation, parental smoking, maternal pre-pregnancy BMI, lead and copper concentration in hair or cord blood.	High
Hammouda et al. (2013) (32)	Saudi Arabia	Prospective cohort	968	Serum	First-trimester	NA	PDA, ASD, VSD, COA, PH and other heart defects	NA	High
Ou et al. (2017) (28)	China	Case-control	219	Whole blood	Middle to late gestation (17th - 40th week)	Median (IQR): Case: 172.90 (153.87 - 192.23) µg/L Control: 186.47 (172.45 - 207.34) µg/L	SPD, CTD, LVOTO, RVOTO and other heart defects	Maternal age, parity, education, newborn gender, migrant, folic acid or multivitamin intake, cigarette smoking, maternal pre-pregnancy BMI, time of sample collection	High
Şahin et al. (2019) (31)	Turkey	Case-control	76	Serum	After birth (details are not available)	Mean (SD): Case: 61.8 (18.2) µg/L Control: 57.3 (20.6) µg/L	VSD, PS, PDA, PFO, ASD, TOF and other heart defects	NA	Low

Abbreviations: APVR, anomalous pulmonary venous return; ASD, atrial septal defect; BMI, body mass index; CHDs, congenital heart diseases; COA, coarctation of aorta; CTD, conotruncal defects; IQR, interquantile range; LVOTO, left ventricle outflow tract obstructions; NA, not available; PDA, patent ductus arteriosus; PFO, patent foramen ovale; PH, pulmonary hypertension; PS, pulmonary stenosis; RVOTO, right ventricle outflow tract obstructions; SD, standard deviation; SPD, septal defects; TOF, tetralogy of Fallot; USA, United States of America; VSD, ventricular septal defects.

† Quality assessment was conducted using the nine-star Newcastle-Ottawa Scale (NOS), studies with NOS scores ≥ 6 were high quality, and studies with NOS scores < 6 were relatively low quality

Two articles (20, 21) explored the association between maternal Se exposure and CHDs of different subtypes, including conotruncal defects (CTD), septal defects (SPD), right ventricle outflow tract obstructions (RVOTO), left ventricular outflow tract obstructions (LVOTO), and anomalous pulmonary venous return (APVR). The classification of CHDs subtypes was based on previous reports (33, 34). The average NOS score of the four included articles was 6. Based on the criteria for literature quality classification, three articles were considered to be of high quality (20, 21, 32), and one was deemed to be of relatively low quality (31). The details of methodological quality assessment of the case-control and cohort studies are presented in Supplemental Table 2 (Not published).

Assessment of Se exposure

Samples from maternal whole blood (21), maternal serum (31, 32), maternal hair (20), and umbilical cord serum (20) were used to assess Se concentrations in mothers. Se concentrations were analyzed during middle to late gestation (ranged from 14 - 40 weeks of gestation) in participants' hair by Guo et al. (20) and whole blood by Ou et al. (21). Hammouda et al. restricted the analysis of maternal serum samples to the first trimester (32). The maternal serum was collected after birth in Şahin et al.'s study, but the concrete sampling time was not recorded.

Systematic Review of Se exposure and CHDs

The study showed that the relationship between maternal Se exposure and CHDs in the offspring was inconsistent. Guo et al. explored the correlation between maternal hair Se and CHDs, and found that high maternal Se concentrations were associated with increased incidence of total CHDs in offspring (20). As for CHDs subtypes, Se exposure ≥ 0.884 mg/g increased the risk of CTD, SPD, RVOTO, LVOTO, and APVR compared to 0.423–0.884 mg/g (20).

Conversely, one study of whole blood reported that Se at the highest concentrations reduced the risk of total CHDs and CHDs subtypes, including CTD, SPD, and RVOTO, compared to the lowest exposure categories (21). The association between Se in cord serum and CHDs was also explored by Guo et al., and the results illustrated that Se exposure < 15.705 μg/L was associated with an approximate 4-fold greater risk of total CHDs (odds ratio (OR) = 4.14, 95% CI: 1.79, 9.56) when compared to a higher Se exposure concentration of 15.705 - 52.722 μg/L. The risk of SPD, CTD and LVOTO were also increased at lower Se concentrations compared to higher Se concentrations (20). Nevertheless, no significant association was found between serum Se levels and CHDs (31) (32).

Meta-analysis of maternal Se levels in CHDs vs. controls

We further assessed the difference in maternal Se concentrations between CHDs and control groups using quantitative analysis. The pooled results showed that Se levels were significantly decreased in mothers with CHDs offspring compared to controls (SMD = -36.31, 95% CI: -42.72, -29.89), with substantial heterogeneity (I^2 = 99.7%, P < 0.001; Fig. 2). Subgroup analysis subsequently showed decreased Se levels in the circulation of mothers with CHDs offspring (SMD = -108.27, 95% CI: -192.72, -23.82), with statistically significant heterogeneity (I^2 = 99.8%, P < 0.001). However, no significant difference in maternal hair Se levels were found between the CHDs and control groups.

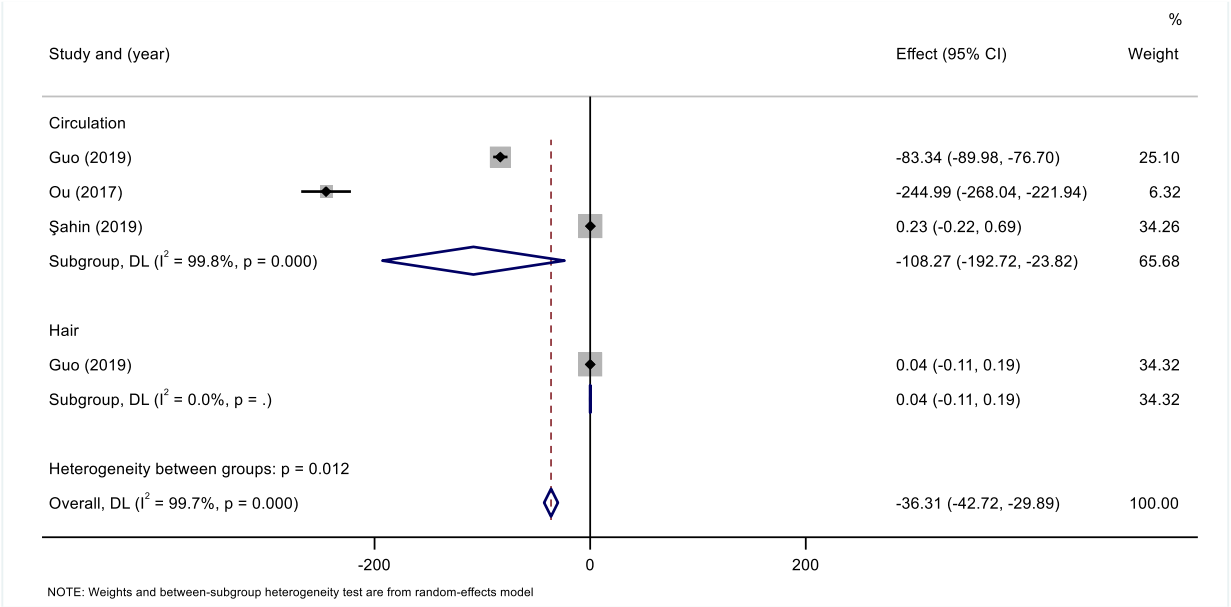

Fig. 2: Comparisons of maternal Se levels between CHDs and controls

Discussion

We conducted a systematic review and meta-analysis of current studies on the association between maternal Se exposure and CHDs in offspring. Four articles covering five studies were included in the systematic review, and three articles covering four studies were included in the meta-analysis. One study on maternal hair showed a positive correlation between high Se concentrations and CHDs in offspring (20). However, one study on whole blood (21) and one study on cord serum (20) illustrated that Se exposure decreased the risk of CHDs. Two studies demonstrated no significant association between Se exposure and CHDs (31, 32); however, these two studies were limited by small sample sizes. Furthermore, the results of this meta-analysis showed that Se levels were significantly decreased in the circulation of mothers with CHDs offspring, but not in hair, compared to controls. Due to the substantial heterogeneity among the included studies, the results should be interpreted with caution.

Dietary intake is the main source of Se in humans (35). However, considering the various dietary preferences and different sources of food, biomarkers are regarded as a more reliable method to evaluate Se status than dietary estimates (20, 36). Studies evaluating blood Se concentrations showed a protective role of Se on CHDs (20, 21); however, high Se concentrations in hair were associated with increased risk of CHDs (20). Furthermore, although a significant correlation has been found between blood and hair Se concentrations in some studies (37, 38), these two biomarkers may reflect Se concentrations in different status. Unusual consumption of Se-rich food may strongly influence blood Se concentrations, reflecting a higher variability of blood Se as a biomarker (37). In contrast, hair can provide an integrated measure that reflects total body intake compared to other common biomarkers (38). In addition, hair collected in different sections could reflect Se concentrations at different periods; hence, segmental analysis of hair is a potentially useful method to determine Se concentrations at different periods and to evaluate Se concentrations over a long period (38).

Significantly reduced Se concentrations in the second and third trimesters have been reported by Mihailović et al., which may indicate a dynamic change in Se status in mothers during pregnancy (39). Moreover, the susceptibility of fetal hearts varies during different periods of pregnancy. For example, the first trimester of pregnancy

is a critical period for cardiac development (40), during which the embryonic heart is more sensitive to exposure to certain medications and toxic substances (41). However, a comparison of the effects of maternal Se status during different pregnancy periods on CHDs could not be conducted because only one of the included study (32) explored Se concentrations in the first trimester and two studies (20, 21) collected samples during the middle to late gestation. The association between Se concentrations in different periods of pregnancy and CHDs should be further investigated to determine the critical time window during which Se levels affect cardiac development.

The effects of some essential trace elements on embryological cardiac development are double-sided. For example, zinc (Zn) and copper (Cu) are both critical to cardiac development, and a lack thereof may increase the incidence of CHDs (42, 43). However, excessive Zn and Cu can also induce abnormalities in embryonic hearts (44). Similarly, the possible duality of Se may explain the inconsistent results in this study. Hair Se concentrations were 0.423 - 0.884 ng/mg in the medium group of Guo et al.'s study, and these concentrations corresponded to relatively Se-sufficient concentrations according to Dinh et al. (45). Compared with the medium group, higher Se concentrations in hair were associated with greater risk of CHDs, which can be explained by excessive Se exerting toxicity on cardiac development (20). Conversely, a protective effect of Se was detected by Ou et al., which suggests that an appropriate elevation of Se concentrations in pregnant mothers may prevent the occurrence of CHDs (21). However, due to the limited data and various biomarkers in the included studies, it could not be established, which parameters of Se concentrations serve in protecting embryonic hearts and which induce heart abnormalities.

Our study has several strengths. First, it is the first comprehensive review of the current evidence on the relationship between Se exposure and CHDs through both qualitative and quantitative analysis. Second, most of the studies included in our meta-analysis had a relatively high methodological quality. Third, various biomarkers were used to evaluated maternal Se concentrations in the included studies, providing a broader insight on the possible association between Se and CHDs. However, several limitations should be identified. Due to the novelty of this subject, the number of relevant studies was small and only four articles were included in this review. Furthermore, although the pooled results showed deceased circulating Se levels in mothers with CHDs offspring, substantial heterogeneity could not be ruled out. However, owing to the limited number of included studies, we could not conduct a meta-regression to further determine the source of heterogeneity. It is speculated that tissue source, tissue collection time, and ethnicity may contribute to the heterogeneity. In addition, only articles in English were included in our study, which may have introduced language bias. Finally, it is not feasible to carry out a horizontal comparison of Se concentrations in samples from different regional sources, according to the available data.

Conclusion

Quantitative analysis showed that maternal Se levels were significantly deceased in the circulation, but not in hair of mothers with CHDs offspring compared to controls. Hence, low maternal Se status may be associated with an increased risk of CHDs in offspring. However, owing to the small number of included studies and the significant heterogeneity among these studies, the results should be interpreted with caution.

Further large-scale epidemiological studies with strict design methods are needed to explore the following problems: 1) to determine biomarkers that can accurately reflect the Se status in pregnant women; 2) to determine the association between Se status in different pregnancy periods and incidence of CHDs in offspring; and 3) to determine the effectiveness and safety of Se supplementation in pregnant women. Further laboratory research is also needed to clarify the role of Se in cardiac development.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Zijian Pan and Tong Zhu have contributed equally to this work and share first authorship.

Conflict of interest

The authors declare no conflict of interest.

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