REVIEW ARTICLE

OPEN ACCESS

Association between serum copper and childhood asthma: A systematic review and meta-analysis

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KEYWORDS
asthma;
copper;
child;
meta-analysis

Abstract

Background: Asthma is a chronic respiratory disease with complex pathogenesis. Some studies suggest that certain trace metals may be associated with asthma. However, the relationship between serum copper (Cu) and childhood asthma remains unclear. This meta-analysis evaluates the association between Cu and childhood asthma.

Methods: Studies of multiple databases were searched from inception to 2024. We recorded the standardized mean difference (SMD), 95% confidence intervals (CIs), and other data. The analysis was performed using Stata 18.0 software. Two independent reviewers appraised methodological quality using the Newcastle–Ottawa Scale. Sensitivity analysis was used to test robustness. To evaluate publication bias, we used Begg's funnel plots and Egger's regression test.

Results: A total of 11 studies with a combined 1006 participants were included. There was no significant difference in the level of serum Cu between children with asthma cases and controls (SMD = −0.032, 95% CI: −0.291–0.228, *P* = 0.811). There was significant heterogeneity among the studies (I² = 73.5%, *P* < 0.0001). Subgroup analysis demonstrated that heterogeneity was not caused by the continent of origin, publication year, sample size, detection methods, and the mean age of participants. No publication bias was found.

Conclusion: There is no statistically significant association between serum Cu levels and childhood asthma. Further research, particularly large-scale prospective cohort studies, is needed to clarify this relationship.

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Introduction

Asthma is a chronic respiratory disease affecting 1-29% of the world's population.[1] Incidence in children aged < 5 years, 5-9 years, and 10-14 years are 1509.36, 980.25, and 586.95 per 100,000, respectively.[2] Globally, asthma rates in children continue to rise; asthma affected 262 million people in 2019.[3] The Global Initiative for Asthma (GINA) describes this condition as wheezing, difficulty breathing, cough, chest tightness, and variable expiratory airflow limitation.[1] The mechanisms of asthma are complex, which is mainly related to genetic, immune, and environmental factors, and inflammatory response. With the industrial process development, environmental pollution is constantly affecting human health, and a study suggesting that nutritional immunity also plays an important role in the function of lung immune cells.[4] Trace elements such as zinc (Zn),[5] nickel,[6] cobalt,[7] mercury,[8] and iron[9] have been proven to influence the pathogenesis of asthma.

The balance of Zn homeostasis is crucial during infection, as it can prevent Zn from invading microorganisms and also ensure the function of immune cells.[10] Zn deficiency leads to a decrease in the phagocytic ability of macrophages and increase in caspase-3 activation and in apoptosis of bronchial epithelial cells, thereby exacerbating airway inflammation.[11] Cellular Zn homeostasis is regulated by two families of Zn transporters: the solute carrier family 39A (SLC39A) importers and the SLC30A exporters.[11] Long-term nickel exposure leads to more nickel accumulation, passing through the blood-brain and peritoneal barriers, induce inflammatory responses and oxidative stress, and cause cell apoptosis.[12] Mercury toxicity increases the production of reactive oxygen species (ROS), triggers oxidative stress responses, and also causes immune dysfunction.[13] A study based on the National Health and Nutrition Examination Survey (NHANES) database shows that higher iron reserves were inversely associated with asthma and that lower systemic iron was associated with lower lung function.[14] In vitro macrophage iron loading assay showed that elevated iron levels promoted alternatively activated macrophages (M2) phenotype and inhibited lipopolysaccharide (LPS)-induced activated macrophage (M1) inflammation.[15] Inflammation and immune imbalance play an important role in the development of asthma.

However, the role of copper (Cu) in asthma is unclear and controversial, as Cu not only exerts antioxidant effects and promotes tissue repair,[16] but also activates mitogen-activated protein kinase (MAPK) or signal transducer and activator of transcription 6 (STAT6) signaling pathway, inducing oxidative stress and Th2 (Type 2 helper T cell)-mediated inflammation.[17,18] Cu is vital to plants and animals, and the human body contains about 150 mg.[19] Various studies have shown that it may be associated with cancer,[20] cardiovascular physiology and disease,[21] infectious diseases,[22] and allergic disease.[23] Cu strongly affects immunity and considered as a factor in asthma progression.[24] It could influence the secretion of cytokines and take part in the involvement of development and differentiation of immune cells.[25] The level of Cu may affect the function of oxidation-antioxidant systems.[26] Oxidative stress is an essential pathway to stimulate a respiratory disease like asthma.[27]

Some studies have revealed that both Cu deficiency and excess are associated with asthma; however, the association between the level of Cu and asthma and its mechanism require further investigation. In this study, we responded to this issue by performing a meta-analysis. The level of Cu may be a biomarker of the risk of childhood asthma.

Materials and Methods

Design and protocol registration

This study was conducted based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline,[28] and the protocol was registered in PROSPERO (ID: CRD42024505006).

Search strategy

We performed searches focusing on the association between serum Cu and childhood asthma in PubMed, Web of Science, Cochrane Library, Elsevier ScienceDirect, China National Knowledge Infrastructure, WANFANG Database, and China Science and Technology Journal Database from the building of database to 2024. The search terms used were: "copper" OR "cuprum" AND "asthma" OR "wheezing" OR "lung function". If the subjects were included in multiple studies, we included the most complete analysis. We also found other studies by researching the references. The search strategies for each database are shown in Table 1.

Inclusion and exclusion criteria

Studies were included if they met the following inclusion criteria: (1) the subjects were under 18 years old; (2) "asthma" or "wheezing" that meets GINA's diagnostic criteria[1]; (3) the reported level of serum Cu; (4) the availability of mean ± standard deviation (SD); and (5) a case-control study, cross-sectional studies, or randomized controlled trials and cohort study.

Studies were excluded if they (1) were duplicates; (2) were case reports, letters, commentaries, conferences, reviews, meta-analyses, or animal experiments; (3) did not include groups with asthma or wheezing; (4) did not report the level of serum Cu; and (5) were irrelevant literature, which is not related to the topic of our study or the population does not match.

Study selection

The study selection was independently conducted by two authors (Beilei Wang and Xingyue Su). Differences were settled by discussion.

Table 1 Search strategies used for online databases.

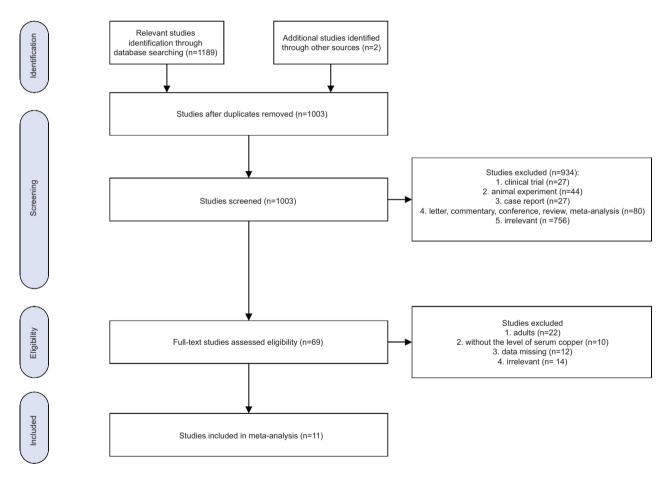| Database	Search strategies	Records
PubMed	("Asthma" (MeSH Terms) OR "wheeze" (Title/Abstract) OR "wheezing" (Title/Abstract) OR "lung function" (Title/Abstract) AND ("copper" (Title/Abstract) OR "cuprum" (Title/Abstract)	132
Web of Science	AB = asthma OR wheeze OR wheezing OR lung function AND AB = copper OR cuprum	400
Cochrane Library	Asthma OR wheeze OR wheezing OR lung function in Title/Abstract Keyword AND copper OR cuprum in Title/Abstract Keyword—Word variations have been searched	22
Elsevier ScienceDirect	Title, abstract, keywords: asthma OR wheeze OR wheezing OR lung function AND copper OR cuprum	81
China National Knowledge Infrastructure	TS = asthma OR wheeze OR wheezing OR lung function AND TS = copper OR cuprum	5
WANFANG Database	TS = asthma OR wheeze OR wheezing OR lung function AND TS = copper OR cuprum	535
China Science and Technology Journal Database	TS = asthma OR asthmatic OR intractable asthma OR wheeze OR wheezing OR lung function AND TS = copper OR cuprum	14

Figure 1 Flowchart of studies selection. n = the number of studies.

Data extraction

The two authors independently read the articles and extracted the data. Author names, publication year, the number of asthma and controls, confounding factors (age, height, weight, and Body Mass Index [BMI]), area of the subjects, and method of tracing the serum Cu were extracted and collected.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality and risk of bias of the included studies. The NOS comprises eight domains assessing methodological quality, with each study receiving a summary score on a 9-point scale. Studies with a score of 7-9 were

considered high quality. Two independent authors performed the quality assessment.

Statistical analysis

The standardized mean difference (SMD) and 95% confidence intervals (CIs) were calculated using the Stata 18.0 software. We assessed the association between the level of Cu (estimated by mean ± SD) with childhood asthma. The Q statistic was used to evaluate the heterogeneity of SMDs among studies. The I^2 statistic was used to test inconsistencies between different studies. According to the continent of origin and the determination method, we carried out subgroups analysis. Publication bias was estimated by Begg's funnel plots and Egger's regression test. We performed sensitivity analysis to evaluate the stability of included studies.

Results

Study selection

We conducted research by using the search strategy in the database. The selection process is shown in Figure 1. A total of 1191 studies that met the inclusion criteria were obtained and excluded those based on the exclusion criteria. A total of 1003 articles remained after deleting 188 duplicate ones. After reading the title and abstract, 934 studies were excluded, among which 27 were clinical trials, 44 were animal experiment, 27 articles were case reports, and for other reasons as shown in Figure 1. Furthermore, 69 studies were fully read and 58 articles were removed. A total of 22 studies researched adults with asthma and 10 did not report the level of serum Cu. We could not find the data we needed from 12 studies that were excluded, and 14 were excluded because of irrelevance (not related to the topic of our study, the population does not match, etc.). Finally, 11 studies were included in the meta-analysis.

Studies' characteristics

Eventually, we included 11 studies published from 1987 to 2024 involving 1006 children. The characteristics of the included studies are summarized in Table 2. Seven articles were from Asia, two from Europe, and two from Africa. The methods of tracing serum Cu differed. Seven studies were performed by atomic absorption spectroscopy (AAS), two by inductively coupled plasma mass spectrometry (ICP-MS), and one by proton-induced X-ray fluorescence technique (PIXE). Part of the studies was adjusted for age, gender, height, weight, and BMI.

Quality assessment

Each star represents 1 point. A score of 0-3 points equated to a low-quality study, 4-6 points to a moderate quality study, and 7-9 points required for a study to be given a

score of high quality. The scoring system and the quality of the studies are shown in Table 3.

Association between serum Cu and childhood asthma

The combined SMDs of Cu between children with asthma cases and controls was −0.032 (95% CI: −0.291–0.228, $P = 0.811$) by using the random effects model (Figure 2). We used the Q test to evaluate the heterogeneity ($I^2 = 73.5\%$, $P < 0.0001$). The result was not statistically significant.

Subgroup analysis

Subgroup analysis was performed to estimate the significant factors influencing the heterogeneity sources. For the serum Cu, the subgroup analysis results demonstrated that heterogeneity was not caused by the continent of origin, publication year, sample size, detection methods, and the mean age of participants (Figure 3). Because there were many missing data on height, weight, or BMI, there was no way to use BMI for subgroup analysis.

Sensitivity analysis

To evaluate the stability of the included studies, we conducted sensitivity analysis. When the method of one-by-one elimination was applied, the overall results did not change; these stable results provided credibility to our study (Figure 4).

Publication bias

Publication bias was estimated by Begg's funnel plots and Egger's regression test. The results of both methods indicated no publication bias (Begg, $P = 0.436$; Egger, $P = 0.980$) (Figure 5).

Discussion

The mechanism of asthma is complex, and many factors such as genetic factors, environmental factors and immune regulation interact. The disturbance of trace elements is related to the onset of asthma.[24] In this study, a meta-analysis was conducted to investigate the association between serum Cu level and childhood asthma. There was no significant difference in the level of serum Cu between children with asthma cases and controls (SMD = −0.032, 95% CI: −0.291–0.228, $P = 0.811$).

The main pathophysiological features of asthma are airway inflammation, airway hyperresponsiveness, and airway remodeling. Cu exists in the human body in free form and also in the form of Cu-binding proteins. Cu exhibits dual roles in asthma pathogenesis and is a key cofactor for some antioxidant enzyme expression, such as Cu-Zn superoxide dismutase (Cu-Zn SOD), glutathione peroxidase, glutathione reductase, and so on. Cu-Zn SOD participates

Table 2 Characteristics of the studies included.

Study	Study design	Continent of origin	Case/Control Age	Case/Control n	Case/Control Serum Cu	Adjust for confounding factors	Method of testing
Di Toro et al., 1987[29]	CC	Europe	83/92 (months)	22/19	23.5 ± 0.8/20.3 ± 1.3 μmol/L	Age, weight, height	PIXE
Li et al., 1995[30]	CC	Asia	4.6/5.95 (years)	15/32	19.97 ± 4.15/22.18 ± 4.46 μmol/L	Age	AAS
Kocyigit et al., 2004[31]	CC	Asia	8.2/7.3 (years)	44/32	1400.08 ± 256.44/1337.84 ± 283.23 μg/L	Age, gender, weight, height	AAS
Guo et al., 2006[32]	CC	Asia	3.69/4.5 (years)	34/26	0.92 ± 0.2/11.15 ± 0.35 mL/L	Age	AAS
Peng et al., 2007[33]	CC	Asia	4.8/4.8 (years)	96/128	1.5 ± 0.7/1.4 ± 0.5 mg/L	Age, gender, BMI	AAS
Oluwole et al., 2014[34]	CC	Africa	13.57/13.30 (years)	37/30	50.2 ± 8.9/53.3 ± 9.5 μg/mL	Age, gender, BMI	AAS
Uysalol et al., 2014[35]	CS	Asia	17.48/18.05 (months)	73/75	1.3 ± 0.28/1.22 ± 0.29 mg/L	Age, gender, weight, height	AAS
Mohammad M et al., 2016[36]	CC	Africa	7.8/7.7 (years)	30/15	122 ± 31.5/103.3 ± 21.1 (μg/dL)	Age, gender	ICP-MS
Yalçın et al., 2021[37]	CC	Asia	7.7/7.8 (years)	17/26	1.13 ± 0.19/1.05 ± 0.17 mg/L	Age, gender, weight, height, BMI	AAS
Podlecka et al., 2022[23]	CC	Europe	9-12/9-12 (years)	40/40	96.67 ± 17.43/104.59 ± 16.77 mg/L	Age, gender, BMI	AAS
Srivastava et al., 2023[38]	CS	Asia	8.75/9.04 (years)	100/75	115.22 ± 21.92/125.25 ± 31.99 μg/dL	Age, weight, height, BMI	ICP-MS

CC = Case control, CS = Cross sectional study, BMI = Body mass index, ICP-MS = inductively coupled plasma mass spectrometry, AAS = atomic absorption spectroscopy, PIXE = proton-induced X-ray fluorescence technique.

Table 3 Risk of bias among the included studies.

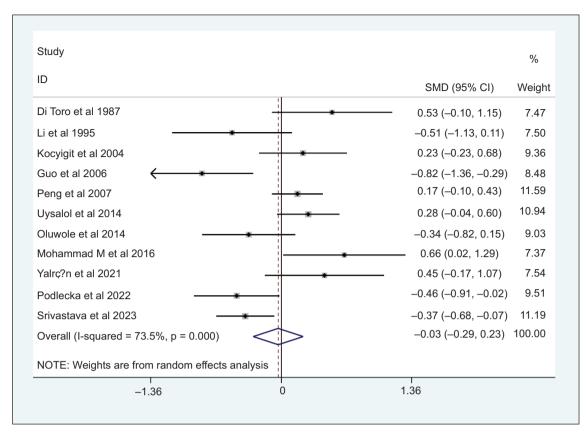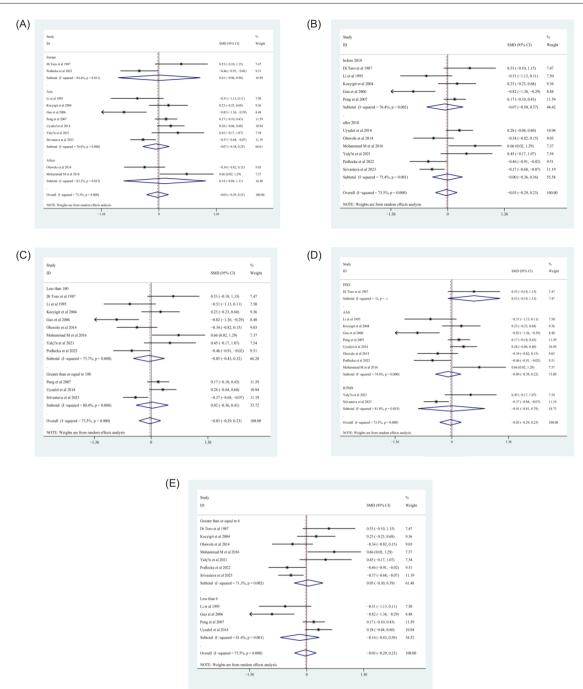| Studies	Selection Is the case definition adequate?	Selection Representativeness of the cases	Selection Selection of controls	Selection Definition of controls	Comparability Comparability of cases and controls on the basis of the design or analysis	Exposure Ascertainment of exposure	Exposure Same method of ascertainment for cases and controls	Exposure Nonresponse rate
Di Toro et al., 1987	★	★	★	★	★★	★	★	Not assessed
Li et al., 1995	★	★	★	★	★	★	★	Not assessed
Kocyigit et al., 2004	★	★	★	★	★	★	★	Not assessed
Guo et al., 2006	★	★	★	★	★	★	★	Not assessed
Peng et al., 2007	★	★	★	★	★★	★	★	Not assessed
Oluwole et al., 2014	★	★	★	★	★	★	★	
Uysalol et al., 2014	★	★	★	★	★	★	★	Not assessed
Mohammad et al., 2016	★	★	★	★	★	★	★	
Yalçın et al., 2021	★	★	★	★	★★	★	★	★
Podlecka et al., 2022	★	★	★	★	★★	★	★	★
Srivastava et al., 2023	★	★	★	★	★	★	★	★

Figure 2 Differences in the level of serum Cu between asthma cases and controls. Note: The combined SMDs of Cu between children with asthma cases and controls was −0.032 (95% CI: −0.291–0.228, *P* = 0.811) by using the random effect model.

in redox reactions and used to convert the radical superoxide into molecular oxygen and hydrogen peroxide.[16] Ceruloplasmin (Cp) is the main carrier protein for Cu, acting as a free radical scavenger and a component of antioxidant defense.[24] Therefore, Cu deficiency may lead to reduced antioxidant stress ability and exacerbate airway inflammation; however, Cu can increase the production of ROS.[39] Excessive ROS production exceeds the ability to neutralize the antioxidant defense system, leading to oxidative stress response.[40] Oxidative stress plays an important role in promoting the development of asthma. Increased ROS can lead to direct oxidative damage of bronchial epithelial cells and also promote the release of cytokines and proinflammatory mediators, thereby increasing the secretion of mucus and causing airway inflammation.[41] Cu can stimulate interleukin-6 (IL-6) production, a key regulator of specific markers of allergic airway inflammation, which may promote goblet cell hyperplasia and mucus secretion.[42] Cu effects some classic pathways in asthma and can activate the MAPK signaling pathway.[17,18] Cu may activate the transforming growth factor-β1-mediated Smad pathway, which is related to airway remodeling,[43] and also activates phosphatidylinositol 3-kinase (PI3K) and the PI3K-Akt (protein kinase B) signal transduction pathway.[44] Phosphorylated PI3K/Akt activates phospholipase C, leading to the phosphorylation and activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB).[45,46]

Some studies have pointed out that asthma is characterized by a lower level of Cu than healthy subjects.[23,32,34] Children with asthma have an increased inflammatory response and oxidative stress.[47] To resist this stress, trace elements are redistributed and then the liver accelerates the synthesis and release of Cp (ceruloplasmin), which may cause Cu to be consumed or redistributed. It also plays a role in the innate immune response to infections by reducing the survival of pathogens in host cells.[48] Therefore, low Cu levels may be associated with increased susceptibility to infection, promoting airway inflammation.

On the contrary, most researchers have demonstrated that an asthma group shows a higher Cu level than controls.[49,50] High serum copper levels may aggravate asthma through several mechanisms. Gagliardo had found that in severe asthmatics, the NF-κB signaling pathway showed a greater activation status.[51] Another study found a significantly increased Cu in uncontrolled asthma than in controls.[52] In addition, excess Cu can induce programmed cell death through the mitochondrial pathway,[53] leading to the shedding of airway epithelial cells and promoting inflammation; therefore, higher Cu levels may promote oxidative stress and mediate airway inflammation, contributing to the aggravation of asthma.

In addition, some studies have suggested that serum Cu levels are not associated with asthma. A two-center study has evaluated participants with uncontrolled, partially

Figure 3 Subgroup analysis of the relationship between the level of Cu and the risk of asthma. (A) continent of origin, (B) publication year, (C) sample size, (D) detection methods, and (E) the mean age of participants. The subgroup analysis results demonstrated that heterogeneity was not caused by the continent of origin, publication year, sample size, detection methods, and the mean age of participants.

controlled, and controlled asthma according to GINA guidelines; results showed no significant differences in Cu levels between groups.[38] A study from Toronto found no significant association between Cu and the risk of asthma.[54]

Our analysis did not find significant differences in serum Cu levels between children with asthma and healthy controls. There was high heterogeneity among the studies (I^2 = 73.5%, $P < 0.0001$). We explored multiple possible sources

of heterogeneity in our subgroup analysis. However, it was found that variables such as continent of origin, publication year, sample size, detection methods, and the mean age of participants could not explain the main source of heterogeneity.

Owing to some missing data, such as weight and BMI, analysis of some subgroups could not be completed. Trace elements can be collected from hair, nail, urine, sputum,
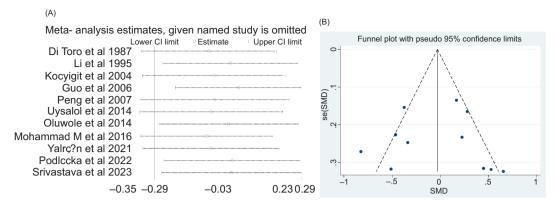
Figure 4 Sensitivity analysis (A) and funnel plot (B) of included studies.
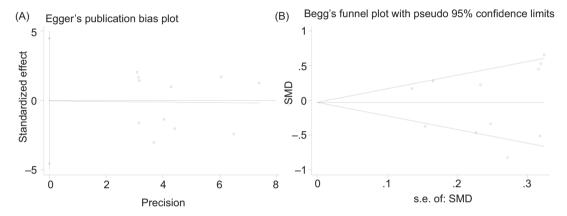

Figure 5 The test for publication bias. (A) Egger's regression test and (B) Begg's funnel plots.

and others sources, but we researched only the serum. Moreover, different asthma subtypes may have different Cu metabolism characteristics, but we did not explore subtypes. In addition, asthma severity, atopic status, nutritional status, environmental exposures, or dietary Cu intake may also have an impact on serum Cu; however, due to the lack of effective data from the included literature, further research will be conducted in the future. Most of the studies we included were case-control studies with small sample sizes. Future large sample, multicenter, longitudinal cohort studies are needed to fully explore the association between serum Cu levels and the risk of childhood asthma. In the future, we can explore the correlation between different severity and different types of asthma and serum Cu levels. Perhaps genes involved in Cu metabolism are also involved.

Conclusions

There is no statistically significant association between the level of serum Cu and childhood asthma. Subgroup analysis showed that the continent of origin, year of publication, sample size, assay methods, and mean age of participants were not major sources of heterogeneity. The relationship between Cu and asthma needs to be confirmed by prospective cohort studies with large samples.

Authors Contribution

Beilei Wang contributed to designing, selecting and assessing the quality of the studies, acquisition of data, analysis and interpretation of data and writing the manuscript. Xingyue Su contributed to the selecting and assessing the quality of the studies, acquisition of data and date analysis. Xiang Ma contributed to designing, interpreting results and reviewing the manuscript.

Conflicts of interest

The authors declare no potential conflicts of interest.

Funding

manuscript; and the decision to submit the manuscript for publication.

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