INPLASY

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Association between Zinc Status and Autism Spectrum Disorder in Children and Adolescents: A Meta-Analysis of Case-Control Studies

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ADMINISTRATIVE INFORMATION

INTRODUCTION

*R*eview question / Objective We aimed to conduct a meta-analysis to review and summarize the available evidence from observational studies and clarify the association between zinc and ASD.

Condition being studied Recent research highlights that autism spectrum disorder (ASD) is becoming more common in children and adolescents. ASD is a group of neuro-developmental disorders characterized by impaired social interaction, repetitive stereotyped behaviors, and narrowed interests. A systematic review found that the presence of ASD could lead to substantial health loss across the life cycle.
The prevalence of ASD among children is increasing every year, and the prevalence among children and adolescents in the US in 2014-2016 was 2.47%. A cross-sectional survey in 2019-2020 showed that the ASD prevalence among children and adolescents aged 3–17 years in the US was 3.4%. A national study in China found that the incidence of ASD in children aged 6–12 years was 0.70%.

Although many studies have shown that genetic, environmental, and immunological factors play an important role in the etiology of ASD, the exact mechanisms have not been fully elucidated. Research suggests that nutrients, as an important environmental factor, may be associated with ASD development. Eating-related problems are more common in children with ASD than in those without ASD. These problems are mainly in the form of fussy eating, preference for certain foods, and stereotyped eating behavior. Therefore, children with ASD are prone to have nutrient deficiencies. Zinc plays an important role in maintaining the normal structure and main functions of the central nervous system. Epidemiological investigations have shown that serum zinc levels were significantly lower in children with ASD than in those without ASD However, some studies found that the zinc levels were significantly higher in children with ASD than in the control group. Moreover, other studies did not find any association between zinc and ASD. Therefore, we aimed to conduct a meta-analysis to review and summarize the available evidence from observational studies and clarify the association between zinc and ASD.

METHODS

Search strategy We conducted this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Electronic searches of PubMed and Embase for English language literature were conducted up to July 13, 2023. In addition, we manually reviewed the list of references included in the article to avoid the potential omission of relevant articles. The search included a combination of MeSH words and free text words as follows: "Trace Elements," "Zinc," "Zinc levels" or "Trace Element" and "Autism," "Autism Spectrum Disorder," "ASD," or "Autistic Disorder."

Participant or population Autism spectrum disorder (ASD) in children and adolescents.

Intervention Not applicable.

Comparator Not applicable.

Study designs to be included case-control studies.

Eligibility criteria The inclusion criterion was case-control investigations involving children and adolescents aged 2–18 years. The diagnosis relied on either the Diagnostic and Statistical Manual of Mental Disorders or the International Classification of Diseases-10. The zinc concentrations in eligible ASD children were analyzed by measuring the zinc levels in biological specimens. All studies were required to provide comprehensive data. Reviews, animal experiments, meeting minutes, redundant literature, and studies involving additional psychiatric disorders were excluded.

Information sources We conducted this study in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Electronic searches of PubMed and Embase for English language literature were conducted up to July 13, 2023. In addition, we manually reviewed the list of references included in the article to avoid the potential omission of relevant articles. The search included a combination of MeSH words and free text words as follows: "Trace Elements," "Zinc," "Zinc levels" or "Trace Element" and "Autism," "Autism Spectrum Disorder," "ASD," or "Autistic Disorder."

Main outcome(s) Reviewers independently and redundantly extracted the following details from the studies: surname of the primary author, year of publication, geographical setting of the study, age of the participants, sample size, sample source, analytical method used to detect zinc, and zinc levels (mean ± standard deviation) in both the case and control groups.

Quality assessment / Risk of bias analysis The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of the case-control studies. In addition to the Comparability item, each item could receive 1 point (1 star), which ranges from 0 to 2 stars.

Strategy of data synthesis Statistical analysis was conducted using Stata 12.0 software (Stata Corporation LLC, College Station, USA). The association of zinc levels in the blood, hair, and urine with ASD was evaluated as a combination of standardized mean difference (SMD) and 95% confidence interval (CI). P-values 50% indicated substantial heterogeneity. Consequently, the random-effects model was employed to merge the data due to high heterogeneity.

Subgroup analysis Subgroup analysis and sensitivity analysis were also performed to investigate the sources of heterogeneity. The subgroup analysis stratified the studies based on the blood type (serum, plasma, and whole blood), continent of study (Europe and America, Russia, and Asia), year of study ($\leq$2010 and >2010), zinc measurement method (inductively coupled plasma-mass spectrometry [ICP-MS] and other methods), and NOS score ($\leq$6 and $\geq$7).

Sensitivity analysis Publication bias was assessed using funnel plot and Begg tests.

Country(ies) involved China (The Fourth Affiliated Hospital of China Medical University).

Keywords Zinc; Autism spectrum disorder; Children; Adolescents; Meta-analysis.

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