INPLASY

Folic acid and autism: Has what we know changed a decade later? An updated systematic review

INPLASY202430086
doi: 10.37766/inplasy2024.3.0086
Received: 21 March 2024
Published: 21 March 2024

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ADMINISTRATIVE INFORMATION

Support - Fundo de Incentivo à Pesquisa e Eventos (FIPE) of Hospital de Clínicas de Porto Alegre, Brazil.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202430086

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21March 2024 and was last updated on 21March 2024.

INTRODUCTION

Review question / Objective The systematic review will explore the relationship between maternal folic acid supplementation and the risk of Autism Spectrum Disorder (ASD) in their children, investigate studies of folic acid interventions in the therapeutic treatment of ASD patients and analyze the consumption of vitamins B6, folic acid and B12, as well as related biochemical markers, in ASD patients, with the aim of understanding the association between these nutrients and ASD.
1. Maternal supplementation and risk of ASD:
o Population: Mothers and their children.
o Intervention: Maternal folic acid supplementation.
o Comparison: Controls with typical development.
o Outcome: What is the risk of ASD associated with the use of folic acid before/during pregnancy?
2. Studies of interventions in patients with ASD:
o Population: Patients with ASD.
o Intervention: Folic acid therapy.
o Comparison: Placebo or standard treatment.
o Results: Does folic acid intervention improve ASD characteristics?
3. Intake and Biochemical Markers in ASD Patients:
o Population: ASD patients.
o Exposure: Intake and biochemical markers of vitamins B6, folic acid and B12, as well as homocysteine and methionine levels.
o Comparison: Controls with typical development.
o Results: What are the levels of nutritional and biochemical markers for vitamins B6, folic acid, B12, as well as homocysteine and methionine levels in patients with ASD?

Rationale Autism spectrum disorder (ASD) encompasses a complex array of neurological alterations that profoundly impact communication, social interaction, and behavior. This not only affects the lives of diagnosed individuals and their families but also has broader implications for society and healthcare systems. Understanding the multifaceted factors underlying this condition is

an ongoing endeavor, as it involves the intricate interplay between genetic and environmental influences.
Folic acid's significance in the development and maintenance of neurological health is widely acknowledged. The association between ASD and this vitamin has been the subject of investigation, with several recent studies addressing this topic. However, there remains a need to delve deeper into discussions regarding the potential relationship between the disorder and this micronutrient, as mentioned above.

Condition being studied Autism spectrum disorder.

METHODS

Search strategy ((Disorder, Autistic) OR (Disorders, Autistic) OR (Autism, Infantile) OR (Infantile Autism) OR (Autism) OR (Autisms) OR (Autism, Early Infantile) OR (Early Infantile Autism) OR (Infantile Autism, Early) OR (Autism Spectrum Disorders) OR (Disorder, Autism Spectrum) OR (Disorders, Autism Spectrum) OR (Spectrum Disorder, Autism) OR (Spectrum Disorders, Autism) OR (Autism Spectrum Disorder)) and ((Dietary Supplement) OR (Supplement, Dietary) OR (Supplements, Dietary) OR (Food Supplementation) OR (Supplementation, Food) OR (Nutraceuticals) OR (Nutraceutical) OR (Nutriceuticals) OR (Nutriceutical) OR (Neutraceuticals) OR (Neutraceutical) OR (Dietary Supplementation) OR (Dietary Supplementations) OR (Supplementation, Dietary) OR (Supplementations, Dietary) OR (Food, Supplemented) OR (Foods, Supplemented) OR (Supplemented Food) OR (Supplemented Foods) OR (Food Supplements) OR (Food Supplement) OR (Supplement, Food) OR (Supplements, Food) OR (Micronutrients) OR (Vitamins)).

Participant or population Children and adolescents diagnosed with autism spectrum disorder (using any recognized diagnostic criteria) and mothers who used folic acid supplementation during pregnancy.

Intervention The intervention involves maternal folic acid supplementation during pregnancy, and studies have explored its use in individuals with Autism Spectrum Disorder (ASD), with the goal of observing possible improvements in ASD symptoms.

Comparator Controls with typical development and/or using placebo.

Study designs to be included We will include randomized studies and non-randomized trials to assess the potential beneficial effects of folic acid treatments, along with observational studies, including cohort and case-control studies. Experimental studies, case reports, reviews, editorials and those not published in English will be excluded.Case-control studies, cross-sectional studies and randomized clinical trials.

Eligibility criteria Exclusion criteria encompass studies that do not report the relevant results, reviews, case reports, experimental studies, editorials, letters, comments, and publications not written in English.

Information sources PubMed (MEDLINE), Embase (Elsevier), Virtual Health Library (PAHO – WHO), EBSCO and CINAHL databases will be searched for all studies published between 2013 and 2024.

Main outcome(s) The risk of Autism Spectrum Disorder (ASD) associated with the use of folic acid before/during pregnancy, evaluate the possible improvement of ASD characteristics through folic acid intervention and evaluate the intake and levels of biochemical markers for vitamins B6, B9, B12, as well as homocysteine and methionine levels in individuals with ASD.

Additional outcome(s) Not applicable.

Data management The identification data of each study and their respective titles and abstracts will be recorded in an Excel spreadsheet. Two reviewers will independently assess the studies regarding the eligibility criteria of the systematic review. The agreement between the reviewers will be calculated by coefficient Kappa, and any disagreements will be resolved through consensus. Data related to the sample, including the total number and by diagnosis, age, gender, diagnostic criteria for ASD, country of origin and dates of data collection, will be recorded in a table. In addition, information on the study methodology will be included, such as the design and instruments used. The results regarding the intake of vitamin B6, folic acid, vitamin B12 and their biological markers, as well as serum levels of homocysteine and methionine, and the supplementation of children, adolescents and mothers will also be documented in different tables according to the nature of each study (intake/biochemical markers, maternal and ASD risk, and interventions).

Quality assessment / Risk of bias analysis The risk of bias assessments will be conducted on the

included studies after result extraction. The Jadad Scale will be employed for randomized clinical trials, assessing randomization processes, double-blinding, and participant withdrawals. For non-randomized studies, the Newcastle-Ottawa Scale will be utilized to evaluate case and control selection, comparability, and outcome assessment.

Strategy of data synthesis No minimum number of studies has been set for the systematic review, as long as they meet the established selection criteria. Our aim will be to cover all the studies that fit the proposed inclusion criteria, covering publications from 2013 to 2024. Information will be extracted from each study to document the authors, the year of publication, the characteristics of the research subjects, the study design and the results pertinent to the topics covered in this review. Data on other results will be disregarded. This approach will aim to be representative of knowledge production in the last decade related to the subject considered for this systematic review.

Subgroup analysis Not applicable.

Sensitivity analysis The quality of the included studies will be assessed using appropriate tools.

Language restriction Not published in English will be excluded.

Country(ies) involved Brazil.

Other relevant information None.

Keywords Autism spectrum disorder, Autistic disorder, folic acid, vitamin B12, vitamin B6, vitamins.

Dissemination plans Submit a paper with findings to a relevant journal.

Contributions of each author

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