Review

Folic acid and autism: What do we know?

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Autism spectrum disorders (ASD) consist in a range of neurodevelopmental conditions that share common features with autism, such as impairments in communication and social interaction, repetitive behaviors, stereotypies, and a limited repertoire of interests and activities. Some studies have reported that folic acid supplementation could be associated with a higher incidence of autism, and therefore, we aimed to conduct a systematic review of studies involving relationships between this molecule and ASD. The MEDLINE database was searched for studies written in English which evaluated the relationship between autism and folate. The initial search yielded 60 potentially relevant articles, of which 11 met the inclusion criteria. The agreement between reviewers was $\kappa = 0.808$. The articles included in the present study addressed topics related to the prescription of vitamins, the association between folic acid intake/supplementation during pregnancy and the incidence of autism, food intake, and/or nutrient supplementation in children/adolescents with autism, the evaluation of serum nutrient levels, and nutritional interventions targeting ASD. Regarding our main issue, namely the effect of folic acid supplementation, especially in pregnancy, the few and contradictory studies present inconsistent conclusions. Epidemiological associations are not reproduced in most of the other types of studies. Although some studies have reported lower folate levels in patients with ASD, the effects of folate-enhancing interventions on the clinical symptoms have yet to be confirmed.

Keywords: Autistic disorder, Folic acid, Vitamins

Introduction

The term autism spectrum disorders (ASD) is used to describe a range of neurodevelopmental conditions that share common features with autism, such as impairments in communication and social interaction,[1] repetitive behaviors, stereotypies, and a limited repertoire of interests and activities.[2,3] The most recent *Diagnostic and Statistical Manual of Mental Disorders* (DSM-V) explains the difficulties associated with the distinction between diagnostic criteria pertaining to communication deficits and impaired social skills, as these symptoms overlap significantly in individuals with a diagnosis of ASD.[1]

Although the etiology of autism is unclear, there is evidence to suggest that a strong genetic component and the exposure to several environmental factors may be involved in the pathogenesis of the disorder. Current epidemiological studies, such as the *Childhood Autism Risks from Genetics and the Environment* (CHARGE) project, investigate the role of environmental and genetic susceptibility factors as the underlying causes of autism.[4,5] Prenatal exposure to teratogens,[6] alcohol,[7] and infectious microorganisms[8] have already been established in the literature as factors associated with an increased incidence of autism.

Folic acid supplementation in pregnancy, as well as the dietary and blood folate levels of children with autism, has also been indicated as environmental contributors to the incidence of ASD.[9,10] Plasma folate concentration is an important determinant of the homocysteine concentration level, and an inverse correlation between these levels and folate intake has been consistently reported in the literature.[11] Recent studies indicate that children with autism have higher serum homocysteine levels[9,10] in comparison to controls[12] or reference values.[13] Furthermore, besides folate, vitamin B12 is essential for homocysteine

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metabolism. The B complex vitamins also play a major role in the synthesis and remethylation of this compound to methionine.[11]

Since 1992, the United States Public Health Service has recommended that women of childbearing age ingest 400 μg of folic acid daily. Although folic acid supplementation in women has been found to be inversely associated with the risk of having children with ASD,[14] it is interesting to note that, a decade after the implementation of this prophylactic action, the incidence of autism was found to have increased dramatically.[15]

A recent analysis of the autism incidence rates drawn from the Rochester Epidemiological Project, the percentage of prescribed prenatal vitamins containing 1 mg folic acid, and the percentage of prescription pediatric vitamins with any folic acid obtained from Physicians' Desk References revealed an association between the increased incidence of autism and the prevalence of folic acid supplementation.[16] However, the authors of the study highlighted that their data did not prove that prenatal exposure to folic acid was involved in the pathogenesis of autism, but only suggested that this possibility should be thoroughly investigated in future studies. On the other hand, a study of five children with autism who presented a central nervous system folate deficiency identified no mutations in these individuals' folate transporter or folate enzyme genes.[17] To investigate the possibility that folic acid supplementation could consist in a risk factor in the pathogenesis of autism, we aimed to perform a systematic review of studies of the relationship between this molecule and ASD.

Methods

Search strategy

The MEDLINE database was independently searched by two reviewers (K.C. and L.S.K.). The search was limited to studies published from January 2003 to July 2013, and was performed using the following search terms and strings: ((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)). The articles retrieved were screened based on their titles and abstracts, and those who met inclusion criteria underwent a full-text analysis. Kappa coefficients were calculated to assess the agreement rate between the two reviewers. Any disagreements were resolved by a third reviewer (I.S.P.).

Inclusion and exclusion criteria

Articles were considered eligible when they presented data regarding the association between ASD and folic acid in humans. All the studies whose results were not explicitly stated, as well as reviews, editorials, comments, and publications written in languages other than English were excluded.

Data extraction

Data extraction was performed by two reviewers (K.C. and L.S.K.), who assessed each article independently, and was verified by the principal investigator (I.S.P.). The data extracted from each article included its authors, publication year, characteristics of the studied population, and outcomes. The present analysis only considered the most relevant outcomes for the topic of study, excluding all data regarding other outcomes.

Results

Selection and characterization of the studies included

The method used in the present review is summarized in Fig. 1. A total of 60 potentially relevant articles were retrieved in the initial search, of which 47 were excluded based on title or abstract analysis. The inter-reviewer agreement was $\kappa = 0.808$. Thirteen[9,10,12–14,16–23] articles were selected for full-text analysis, after which 2 articles[17,20] were excluded for not addressing the relationship between autism and folic acid, which resulted in 11 articles meeting the inclusion criteria.

Study characteristics

Articles included in the present study addressed topics related to vitamin prescription,[16] the association between folic acid intake/supplementation during pregnancy and the incidence of autism,[9,14,21] food intake, and/or nutrient supplementation in children/adolescents with autism,[9,12,13,18,19,22,23] evaluation of serum nutrient levels, and nutritional interventions in children/adolescents with ASD.[12,13,19] These data were extracted and articles were classified into the

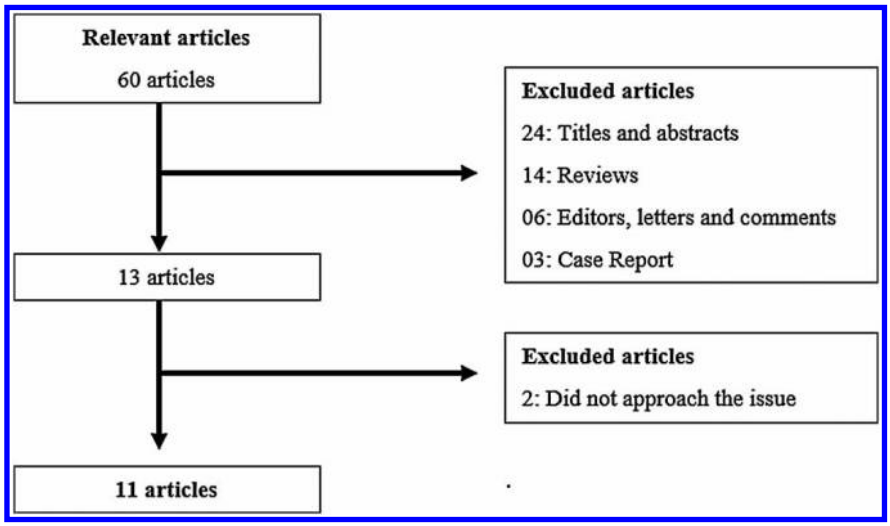

Figure 1 Flowchart of the study selection. Articles were considered eligible when data regarding the association between ASD and folic acid in humans were presented. Studies whose results were not explicitly stated, reviews, editorials, comments, and publications written in languages other than English were excluded. Sixty potentially relevant articles were retrieved in the initial search, of which 47 were excluded based on title or abstract analysis. Thirteen articles were selected for full-text analysis, after which two articles were excluded for not addressing the relationship between autism and folic acid. Eleven articles met the inclusion criteria.

following three categories, according to their main topic of study: gestational period, folic acid, and risk of autism (Table 1); vitamin consumption and serum levels implicated in homocysteine metabolism (Table 2); and intervention studies (Table 3).

Discussion

Recent studies indicate that children with autism present higher serum levels of homocysteine[9,10] in comparison to controls[12] or reference values.[13] Serum levels of folate and vitamin B12 may be diminished[9,10] or normal[13] in patients with autism. This could be associated with the lower folate intake presented by these patients,[9,23] since <50% of them reach the *Dietary Reference Intake* for folate.[22] It has also been found that B12 intake is decreased in children[9] with autism and that the percentage of children with intakes lowers than the *estimated average requirements* (EARs) increases with age.[18] On the other hand, there are also reports of children with autism consuming adequate or even high amounts of folate and vitamins B12 and B6 in comparison to controls.[18,22] Folate levels may be influenced by recent food intake; however, the studies that reported lower serum folate levels in patients with autism[10,24] specified that patients fasted before examination, which suggests that findings regarding folate levels were likely to be accurate.

The controversial results regarding the association between vitamin intake, serum vitamin levels, and the presence of autism could also be attributed to the different methods used to evaluate vitamin intake. Three authors used the 72-hour dietary recall method.[18,22,23] One of them presented atypical results, showing that folate consumption was adequate or above the upper intake levels in patients with ASD.[18] A food frequency questionnaire (FFQ), which is considered a better dietary assessment method, was also applied in one of the studies. In addition to assessing folate consumption, the study evaluated vitamin B12 intake, and showed that individuals with ASD had a low consumption of both nutrients.[9]

Folic acid supplementation in autistic children with low 5MTHF (L-5-methyltetrahydrofolate) levels in cerebrospinal fluid has been found to lead to the normalization of folate levels, and to relieve symptoms of ASD.[13] The same supplementation schedule was associated with B12 vitamin supplements, leading individuals with ASD to present folate levels comparable to those presented by controls[12] or reference values.[13] Consumption or supplementation of vitamins B6 and B12, associated with folic acid supplementation, also reduced homocystinuria in patients with autism.[19] The effect of folate-enhancing interventions on symptoms of autism may be a promising area of study, since only one of the aforementioned investigations identified such an association, while the remaining two only reported the contribution of folate supplementation to the normalization or reduction of homocysteine levels.

Supplementation with B vitamins led to similar benefits in terms of clinical symptoms.[25] Vitamin B supplementation is a common treatment method, since it is difficult to reach adequate vitamin B intake levels exclusively through diet, even in the general population.[26] This is aggravated by the food selectivity observed in patients with autism,[27,28]

Table 1 Serum homocysteine, methionine, vitamin B12 and folate levels, and vitamin B6, B12, and folic acid intake in autistic children and adolescents

Reference	Population	Methods	Results
Xia *et al.*[23]	$n = 111$ Chinese children with autism (2–9 years) who attended the Child Development and Behavior Research Center (Harbin Medical University) from (2007 to 2009). 89.2% males 10.8% females	Folate intake: 3-day food record based on parental interviews (2 weekdays and 1 weekend day)	Children with autism had inadequate folic acid intake, and consumed only 20.0% of RNI (Reference Nutrient Intake) for this nutrient
Ali *et al.*[10]	80 children (3–5 years), 40 with autism and 40 control subjects from Sultan Qaboos University Hospital (2009–2010)	Serum homocysteine and folate measures	Mean serum homocysteine levels were higher in children with autism (20.1 ± 3.3 μmol/l) as compared to age- and gender-matched healthy controls (9.64 ± 2.1 μmol/l) ($P < 0.01$, Student's unpaired *t*-test) Serum homocysteine levels in children with autism were also much higher than normal reference values (5–15 μmol/l)[5] Serum levels of folate (1.8 ± 0.4 vs. 6.1 ± 0.6 μg/l) and vitamin B12 (191.1 ± 0.9 vs. 288.9 ± 1.3 pg/ml) were significantly lower in children with autism as compared to controls ($P < 0.05$, Student's unpaired *t*-test) Serum folate and vitamin B12 levels were lower in Omani children with autism than normal children ($P < 0.05$, Student's unpaired *t*-test)
Hyman *et al.*[18]	$n = 252$ participants (2–11 years) (2009–2011) from Autism Treatment Network (ATN) sites in the USA 86% males 14% females	Folate intake: 3-day food record based on parental interviews (food, beverages, and supplements)	Folate intake from food alone observed in children with ASDs was above UL standards Children with ASDs did not consume insufficient folic acid Specific age groups consumed excessive amounts of folate The percentage of children with nutrient intake below EAR increased with age for vitamins B12 and folate
Soden *et al.*[22]	$n = 25$ patients (10–18 years) from two child development clinics in the USA 80.8% males 19.2% females 6 Asperger disorder 9 Autistic disorder 11 Pervasive developmental disorder (PDD-NOS)	Folate intake: food records (72 hours) and food selectivity reported though parental interviews (food, beverages, and supplements)	Fewer than half of participants met DRI for folate Nutrient intake (% of DRI): For folate: mean: 98.9; SD: 69.6; range: 9.4–277.6 For B12: mean: 199.1; SD: 117.4; range: 35.7–489.1 For B6: mean: 145.5; SD: 113.0; range: 20.0–582.7
Al-Farsi *et al.*[9]	$n = 80$ Omani children (3–5 years) (2009–2010) with ($n = 40$) and without ($n = 40$) diagnosed ASDs. 50% females and 50% males in both groups	Folate intake: dietary questionnaire completed through parental interviews	Children with ASD had consistently lower dietary ($P = 0.04$, Mann–Whitney test) and serum ($P = 0.001$, Mann–Whitney test) folate levels Children with ASD had consistently lower dietary ($P = 0.02$, Mann–Whitney test) and serum ($P = 0.001$, Mann–Whitney test) vitamin B12 levels Children with ASD had significantly increased homocysteine levels (68%; $P = 0.004$, Mann–Whitney test), whereas the level of methionine was 15% lower than normal values ($P = 0.05$, Mann–Whitney test) Mothers of children with autism tend to have higher and folic acid supplementation during pregnancy, as well as a higher consumption of fortified flour and bread

UL, upper intake levels; DRI, dietary reference intake.

Table 2 Folinic acid and B12 interventions in patients with autism

Reference	Population	Methods	Results
Ramaekers *et al.*[13]	$n = 25$ patients with early onset low-functioning autism (2.8–12.3 years) associated with one or more of the major features of childhood-onset brain folate deficiency; four of whom fulfilled diagnostic criteria for Kanner syndrome	Patients with low CSF 5MTHF levels were given oral folinic acid supplementation starting at a dose of 1 mg/kg/day. 5MTHF was measured through a lumbar puncture performed 3–6 months following start of treatment. If CSF 5MTHF levels had not normalized, the dose of folinic acid was increased up to 2–3 mg/kg/day, divided in two doses	Routine blood counts, serum vitamin B12, homocysteine, and amino acid levels were within the normal range in all patients CSF 5MTHF was low in 23 of 25 patients. CSF folate levels were low in 19 of the 23 patients with low 5MTHF Oral folinic acid supplements led to the normalization of CSF 5MTHF levels and partial or complete clinical recovery after 12 months
James *et al.*[12]	$n = 40$ children with autism (4.8 ± 0.8 years) 82% males 18% females Control group with 42 children with mean age (4.5 ± 0.9 years)	Children were treated with 75 μg/kg methylcobalamin (2 times/week) and 400 μg folinic acid (2 times/day) for 3 months	Methionine transmethylation metabolite levels significantly differed between children with autism and control children ($P < 0.005$, paired Student's *t*-test) at baseline with the exceptions of homocysteine levels The 3 months intervention did not lead to significant alterations in methionine, SAM, and SAH concentrations, even though methylcobalamin and folinic acid provide methyl groups for the methionine cycle
Kałuzna-Czaplińska *et al.*[19]	$n = 51$ Polish children (4–11 years) in a medical center (Navicula Centre in Lodz, Poland); 30 children with autism and 21 typically developing children Typically developing children 4.76% females 95.24% males Children with autism: 90% males 10% females	Each child underwent urine homocysteine level assessments twice: (1) before vitamin supplementation (2) 3 months after receiving either folic acid and vitamins B6 and B12 (24 autistic children) or vitamins B6 and B12 alone (6 autistic children) Children received daily supplementation with vitamins B6, B12, and folic acid in the following doses: 200 mg, 1.2 μg, and 400 μg, respectively	Levels of urinary homocysteine were significantly higher in children with autism before vitamin supplementation compared with both autistic children after vitamin supplementation and non-autistic children ($P < 0.05$, Scheffe test) Supplementation with vitamins B6 and B12 together with folic acid seems to be more effective in lowering the levels of urinary homocysteine than the supplementation with vitamins B6 and B12 alone

CSF, cerebrospinal fluid; 5MTHF, 5-methyltetrahydrofolate; SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine.

which may lead to poor dietary variety and increase the likelihood of nutrient deficiency.

Folic acid supplementation in women also had an inverse association with subsequent risk of the presence of ASD 4 weeks prior to the eighth week of gestation, although this association was lost after 22 weeks of gestation.[14] Similarly, Schmidt *et al.*[21] reported that mothers of children with autism ingested low amounts of folic acid during gestation, while mothers of typically developing met the guidelines for folic acid supplementation ($\geq$600 μg/day) during pregnancy. However, in contrast, other studies have also found that mothers of autistic children tend to have folic acid supplementation in pregnancy and consume elevated amounts of the nutrient.[9] Although only the results of this retrospective study and the results of epidemiological studies have shown associations between high folate intake and incidence of autism,[15,16] these have not yet been confirmed in studies with other designs. This suggests a need for new and more effective research to clarify these inconclusive findings. In regards to children supplementation and risk of autism, the epidemiological correlations found are not strong.[16]

The genotype of the mother and/or child was also found to play a role in the association between folate acid consumption and reduced risk of autism. This association was found to be significant when the mother and/or child had the *MTHFR* 677 C > T polymorphism, which affects the functioning of the enzyme methylenetetrahydrofolate reductase.[21]

With regard to dietary habits in children with autism, the studies were insufficient to identify a dietary pattern or possible nutritional deficits in this population. Most studies point to a possible role of homocysteine metabolism in the pathophysiology of this disorder, rather than an inadequate consumption of macro and micronutrients.

Recently, Anjos *et al.*[29] argued that the current evidence of the association between gestational nutrition and brain development points to folate as a credible positive influence on the developmental process.

Table 3 Studies with mothers and folic acid

Reference	Population	Methods	Results
Schmidt *et al.*[21]	$n = 837$ children with autism (1–2 years) intellectual disability, or developmental delays, and typically developing controls recruited from the general population through the CHARGE study (2003–2009) 18.4% females 81.6% males ASD: $n = 429$ (51.2%) DD: $n = 130$ (15.5%) TD: $n = 278$ (33.2%)	Folic acid intake: food records (multivitamins, prenatal vitamins, folic acid-specific vitamins, cereals, and other supplements) constructed based on parental telephone interviews	The mean daily folic acid intake in the 3 months before pregnancy tend to be lower in mothers of children with DD (399.7 ± 46.8 μg) than in mothers of children with TD (494.0 ± 36.6 μg), although levels were not significantly lower than those of mothers of children with ASD Mean estimated daily folic acid intake was higher in mothers of children with TD than in mothers of children with ASD throughout the entire period of study, with the greatest difference observed in the first month of pregnancy ($P < 0.01$, Chi-square test) The percentage of women who took supplemental folic acid at levels ≥600 μg/day during first month of pregnancy was higher among mothers of children with TD (68.5%) than in mothers of children with ASD (53.9%; $P = 0.001$, Chi-square test) or DD (54.4%; $P = 0.02$, Chi-square test) After adjustments, the association between ≥600 μg folic acid/day supplementation and reduced risk of ASD remained significant (OR = 0.61; 95% CI = 0.41–0.89, logistic regression odds ratio). The risk of ASD decreased as maternal folic acid intake increased during first month of pregnancy ($P = 0.001$, logistic regression odds ratio)
Surén *et al.*[14]	Children (3.3–10.2 years) (1999–2009) from the MoBa study A total of 270 children (0.32%) in the study sample had been diagnosed with ASDs: 114 (0.13%) with autistic disorder 56 (0.07%) with Asperger syndrome −100 (0.12%) with PDD-NOS (pervasive developmental disorder – not otherwise specified)	Folic acid intake: food record (vitamins, minerals, and other supplements) conducted from 4 weeks before to 8 weeks after the start of pregnancy, and FFQ completed in week 22	AD was present in 0.10% of children whose mothers took folic acid (OR = 0.61; 95% CI = 0.41–0.90, logistic regression odds ratio) and in 0.21% of children whose mothers did not take folic acid An inverse association was found between folic acid use and the presence of ASD in early pregnancy, although this relationship was absent in mid-pregnancy, as evidenced by the comparison between mothers who took ≥400 μg/day folic acid in week 22 of pregnancy (OR = 0.96; 95% CI = 0.60–1.55, logistic regression odds ratio) vs. mothers who took <400 μg/day of supplements at that time (OR = 1.02; 95% CI = 0.62–1.67, logistic regression odds ratio) There was no apparent association between daily maternal folate intake in week 22 (diet + supplements combined) and subsequent risk of AD in children
Al-Farsi *et al.*[9]	$n = 80$ Omani children (3–5 years) (2009–2010) with ($n = 40$) and without ($n = 40$) diagnosed ASDs. 50% females and 50% males in both groups	Acid folic intake: Reduced Dietary Questionnaire through parental interview	Mothers of children in the case group tend to have higher folic acid supplementation during pregnancy and a higher intake of fortified flour and bread

Continued

Table 3 ***Continued***

Reference	Population	Methods	Results
Beard *et al.*[16]	$n = 100\,000$ children in USA, from the Rochester Epidemiological Project (1976–1997)	Published autism incidence rates from the Rochester Epidemiological Project. Percent of prescription prenatal vitamins containing 1 mg folic acid and the percent of prescription pediatric vitamins with any folic acid from Physicians' Desk References for roughly the same time period	An increased incidence of autism was found to be associated with an increase in the % of prescribed prenatal vitamins with 1 mg folate over the study period (Pearson's Chi-squared test 0.87; 95% CI = 0.19–0.99) The increase in the incidence of autism was weakly associated with the % of prescribed pediatric vitamins with any folic acid over the study period (Pearson's Chi-squared test 0.62; 95% CI = −0.38 to 0.95)

ASD, autism spectrum disorder; DD, developmental delay; TD, typical development.

However, further investigations are still required to determine optimal supplementation strategies, and to investigate their long-term effects on child neurodevelopment. Given the known role of folate in neurodevelopment, these issues are of utmost importance, and recent studies of large cohorts of mothers and children may be the first step towards the understanding of the relationship between folic acid supplementation and autism.[29]

In summary, studies regarding the consumption and concentration of vitamins in patients with autism and their mothers are still inconclusive, mainly due to the discrepant methods used in the studies presented and the inconsistency of the results. Regarding our main issue, namely the effect of folic acid supplementation, especially in pregnancy, the few and contradictory studies present inconsistent conclusions. Epidemiological associations are not reproduced in most of the other types of studies. Although some studies have reported lower folate levels in patients with ASD, the effects of folate-enhancing interventions on the clinical symptoms have yet to be confirmed. The reduced number of studies is insufficient to a complete understanding about these topics. There is a need for large controlled prospective studies assessing serum levels and folic acid intake in autistic patients, the effects of folic acid supplementation on clinical symptoms in individuals with autism, as well the association between folate levels and supplementation during pregnancy (including supplemental folic acid levels and gestational age) and subsequent child outcomes. These questions should be the main focus of future research, combined with the search for mechanisms of action of folic acid ASDs.

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Contributors

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Conflicts of interest

None.

Ethics approval

Provided by Hospital de Clínicas de Porto Alegre.

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