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Can we change the risk of autism?

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Autism spectrum disorders (ASD) are a group of neurodevelopmental disorders characterized by significant impairments in social interaction and communication and by repetitive, restrictive and stereotyped patterns of behavior.[1] The most serious of the conditions comprising ASD is autistic disorder (AD), as it is likely to have co-occurring intellectual disability and a range of medical, behavioral and psychiatric conditions.[1] The prevalence of ASD is estimated to be about 1% of children.[2] Because of temporal trends in autism prevalence and the clinical and behavioral challenges of the condition, understanding risk factors and determining potential causes, prevention, and treatment options are high priorities for researchers, parents, advocates, clinicians, and educators.

ASD is highly heritable; [3] however, the clinical presentation can vary widely between family members and among affected individuals. Genetic factors (*e.g.* fragile X syndrome, 15q11-13 duplications, and other *de novo* and inherited genetic variants) are the best studied risk factors for ASD that have thus far been identified.[3,4] Additionally some prenatal, obstetric and environmental exposures (*e.g.* parental age, prenatal drug exposure and infections) have been associated with increased risk for ASD.[5] The evidence to date suggests that ASD is a combination of multiple genetic and environmental risk factors leading to variable clinical presentations.[1,3,4,5] This heterogeneity is a major obstacle to researchers. Identified risk factors are implicated only in a minority of ASD cases, and the etiology of ASD remains largely unknown.

Given the interest in prenatal risk factors, some have hypothesized that nutritional exposures such as folic acid intake could increase the risk of autism.[6] ,[7] Folate and folic acid (a synthetic stable form of folate used in supplements and food fortification) are sources of one-carbon units essential for basic cellular processes including DNA replication and DNA, RNA, and protein methylation. Thus, it is biologically plausible that folic acid intake might impact innumerable conditions positivity or negatively depending on time and dose. Randomized controlled trials have found that periconceptional folic acid supplementation

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reduces the risk of neural tube birth defects up to 70% and have led to the recommendation that all women of childbearing age consume 400 μg/d folic acid.[8]

An earlier report of findings from the Norwegian Mother and Child Cohort Study (MoBa) found that periconceptional folic acid supplementation (4 weeks before to 8 weeks of gestation) was associated with a reduced risk of severe language delay in 3 year old children.[9] In this issue of *JAMA*, Suren and colleagues utilize the MoBa Autism Birth Cohort to report that periconceptional folic acid supplementation lowers the risk of AD in offspring.[10] Interestingly, several recent studies have pointed to improved neurodevelopmental outcomes in children of mothers having higher folate concentrations or receiving folic acid supplements. Follow-up of a cohort of Nepalese children whose mothers participated in a randomized controlled trial of prenatal and postnatal micronutrient supplementation found that aspects of intellectual functioning among offspring were positively associated with prenatal iron/folic supplements.[11] Follow-up of the Mysore Parthenon (Mysore, India) prospective birth cohort at age 9 to 10 years found that higher maternal plasma folate status during pregnancy was associated with better cognitive function scores.[12] Additionally, findings from a large multicenter case-control study, CHildhood Autism Risks from Genetics and Environment (CHARGE), suggested that maternal folate status during the periconceptional period was associated with a reduced risk of ASD.[13]

The cohort studied by Suren *et al.* has a number of positive characteristics such as prospective design, collection of supplement use with validated instruments during pregnancy, and active screening of children for autism and other neurodevelopmental disorders.[10] In any cohort study, however, selection bias, low participation, and unmeasured confounding are substantial concerns. The authors found limited evidence of selection bias by comparing MoBa to Norway's Medical Birth Registry data (AD risk in folic acid supplement users vs. non-users) and finding similar results. A potential source of unmeasured confounding is the comparison between those women who chose to take folic acid supplements before and during early pregnancy and those who did not take folic acid supplements either by choice or through lack of knowledge. To address this, the authors replicated their folic acid supplementation analysis with fish oil supplements, assuming that fish oil supplementation would be subject to similar unmeasured confounding. Additionally, they analyzed folic acid use at 22 weeks gestation. Neither of these secondary analyses found associations with AD or ASD (positive or negative) suggesting that the association found between AD risk reduction and periconceptional folic acid supplements is less likely to have been due to this type of unmeasured confounding.[10] Finally, the rates of AD and ASD are higher in the early birth cohort years vs. more recent years,[10] which presumably contributed to the lower than expected prevalence, additional years of follow-up might add additional ASD diagnoses and inform the findings.

Recently, Beaudet discussed the possibility of "preventable forms of autism" in response to the discovery of inborn errors of metabolism associated with autism.[14] Underlying genetic variation in children and/or their parents that could be ameliorated by folic acid supplementation might drive the observed reduction in risk seen by Suren and colleagues. This could include alterations in epigenetic regulator genes and their targets which have been previously been associated with a risk of ASD (*e.g. MeCP2*, 15q11-13 duplications,

PTEN, *CHD8*). [3,4] Impairment in folate metabolism, either due to undernutrition and/or genetic variation or both, could be an additional metabolic risk factor for autism that is potentially modifiable through nutritional intervention.

The finding that periconceptional supplement use might reduce the risk of autism is encouraging; however, it is important to confirm this finding in other population-based birth cohorts. In future studies, autism in children with co-morbid conditions (*e.g.* congenital anomalies, genetic disorders) should be explored in stratified analysis. Whereas folic acid supplement use in early pregnancy might be protective for AD, it is not clear that we can generalize to other neurodevelopmental outcomes or other populations. For example, Tamura *et al.* did not find an effect of folate status on mental and psychomotor development in a low SES population in the United States pre-folic acid fortification.[15] In all nutritional studies, timing, dose and especially the intake of other vitamins included in multivitamins are critical to consider. In Suren *et al*., with an intake of ~200-400μg/d (common doses in multivitamin and prenatal supplements in Norway), the risk reduction was limited to the periconceptional period.[10] This intriguing finding seems to be at odds with the continued increases in identified ASD diagnoses[2] seen in the US since the folic acid food fortification program began in 1998.[8] This may be attributable to changes in diagnosis and surveillance but may also reflect a concurrent real increase in the risk of ASD in the US attributable to yet to be described risk factors. In the US, the average daily consumption of folic acid is ~150μg/d[16] from folic acid food fortification. This level may be too low to contribute to a measureable decline in prevalence. Future studies should include other populations with different usual diets, supplementation recommendations, and voluntary and mandatory enriched cereal grain fortification programs.

It is reassuring that Suren and colleagues [10] found no association between folic acid supplementation and an increased risk for AD or ASD. This ensures that folic acid intake can continue to serve as a tool for the prevention of neural tube birth defects. The potential for a nutritional supplement to reduce the risk of AD is provocative and should be confirmed in other populations.

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