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Maternal prenatal folic acid supplementation is associated with a reduction in development of autistic disorder

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Surén P, Roth C, Bresnahan M, Haugen M, Hornig M, Hirtz D, et al. Association between maternal use of folic acid supplements and risk of autism spectrum disorders in children. *JAMA*. 2013;309:570-77.

Question What is the association of prenatal folic acid supplementation in pregnant women with subsequent development of autism spectrum disorders (ASDs; autistic disorder, Asperger syndrome, pervasive developmental disorder–not otherwise specified [PDD-NOS]) in their children?

Design Population-based, prospective Norwegian Mother and Child Cohort Study.

Setting Norway.

Participants 109 000 children born from 1999 to 2009 and their mothers.

Intervention The exposure of primary interest was use of folic acid from 4 weeks before to 8 weeks after the start of pregnancy, defined as the first day of the last menstrual period before conception.

Outcomes Specialist-confirmed diagnosis of ASD.

Main Results At the end of follow-up, 270 children in the study sample had been diagnosed with ASDs: 114 with autistic disorder, 56 with Asperger syndrome, and 100 with PDD-NOS. In children whose mothers took folic acid, 0.10% (64/61 042) had autistic disorder, compared with 0.21% (50/24 134) in those unexposed to folic acid. The adjusted OR for autistic disorder in children of folic acid users was 0.61 (95% CI, 0.41–0.90). No association was found with Asperger syndrome or PDD-NOS, but power was limited. Similar analyses for prenatal fish oil supplements showed no such association with autistic disorder, even though fish oil use was associated with the same maternal characteristics as folic acid use.

Conclusions Use of prenatal folic acid supplements around the time of conception was associated with a lower risk of autistic disorder in this cohort. Although these findings cannot establish causality, they do support prenatal folic acid supplementation.

Commentary The report by Suréen et al utilizes the Norwegian Mother and Child Cohort Study (MoBa) Autism Birth Cohort to report that periconceptional folic acid supplementation (4 weeks before to 8 weeks after conception) lowers the risk of autistic disorder, but not other ASDs. These findings are consistent with findings from recent studies

from Asia, Europe, and North America, suggesting that children of mothers with higher blood folate concentrations or mothers receiving folic acid supplements had improved neurodevelopmental outcomes.[1–4] It is unclear whether these findings have clinical implications in the US. We already know that periconceptional intake of folic acid will reduce a woman's risk of a neural tube birth defect-affected pregnancy. This knowledge has led to the existing recommendation in the US that women capable of becoming pregnant consume 400 μg/day of folic acid. This report may motivate more women to consume supplements before and during early pregnancy. Elsewhere in the world, these findings could be influential in establishing supplementation programs designed to increase folic acid intake, thus, preventing neural tube birth defects and possibly ASDs. The MoBa birth cohort has several advantages that are beneficial for examining this type of association. These include a prospective study design, collection of supplement-use data with validated instruments during pregnancy, and active screening of children for autism. In addition, the authors were able to address concerns about selection bias and unmeasured confounders that are potentially serious concerns inherent in any cohort study. To evaluate selection bias, the authors compared their results with Norway's Medical Birth Registry and found similar results, suggesting that those women who chose to participate in MoBa were similar to women who did not participate. Unmeasured confounding could have been a problem in MoBa because women who chose to take folic acid supplements before and during early pregnancy were compared with those who did not take folic acid supplements either by choice or lack of knowledge. To assess this potential confounder, the authors replicated their folic acid supplementation analysis with fish oil supplements, assuming that fish oil supplementation would be subject to similar unmeasured confounding. They also analyzed folic acid use at 22 weeks' gestation. Neither of these secondary analyses identified associations with ASDs, suggesting that unmeasured confounding was less likely to explain the association. The etiologies of ASDs are unknown, but are thought to be a combination of multiple genetic and environmental risk factors. Identified risk factors account for only a small portion of children with autistic disorder. The potential for folic acid to prevent autistic disorder likely will generate new avenues of research, which may yield new prevention strategies. However, these findings need to be confirmed in other population-based birth cohorts.

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