

NEWS

Flurry of studies hint at folic acid's protective role in autism

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Folic acid, a B vitamin, may lower autism risk and ease features of the condition, according to findings from five unrelated studies published over the past few months.

Three of the studies suggest that prenatal supplements of folic acid offset autism risk associated with in utero exposure to epilepsy drugs or toxic chemicals^{1,2,3}. The supplements are also known to prevent birth defects.

Another study found that people with autism and their immediate family members are more likely than controls to carry immune molecules that could block folate's passage into the brain⁴.

"These studies are particularly of interest because they suggest that people could potentially modify their risk of having a child with autism, even in the face of certain adverse exposures or conditions," says **Kristen Lyall**, assistant professor in the Modifiable Risk Factors Program at the A.J. Drexel Autism Institute in Philadelphia, who was not involved in any of the studies.

A fifth study reported results from a small clinical trial suggesting that folinic acid — a form of folic acid — can ease language and communication difficulties in people with autism⁵.

"It isn't enough to say that kids with [autism] should be taking folinic acid, necessarily, but it is enough to motivate a larger study," says **Jeremy Veenstra-VanderWeele**, professor of psychiatry at Columbia University, who was not involved in the trial.

Medication risk:

In one of the three studies on prenatal supplements, researchers looked at folic acid's effects on the known autism risk in children exposed to epilepsy drugs in utero¹. How these medications, such as valproic acid, boost autism risk is unclear, but many of them interfere with folic acid's metabolism and absorption from the gut into body tissues.

The researchers reviewed medical data for 104,946 births in Norway between 1999 and 2008. They focused on 288 women who took epilepsy drugs during their 328 pregnancies.

When the women were 17 to 30 weeks pregnant, they reported their intake of folic acid supplements. And when their children were 18 and 36 months old, they completed questionnaires assessing autism traits in the children.

Of the 288 women, 260 reported that they took folic acid from 4 weeks before to 12 weeks after conception — a key period for brain development.

Of the 68 children whose mothers did not take folic acid, 11 (32 percent) showed autism traits at age 18 months; 9 of the children (26 percent) showed these traits at 36 months. By comparison, 15 of the 18-month-olds (9 percent) and 8 of the 36-month-old children (6 percent) of women who took folic acid showed autism traits.

The researchers adjusted for differences in the women's age, income, education level, smoking,

alcohol use, prior pregnancies and features of depression.

Children whose mothers did not take folic acid were nearly sixfold as likely to show autism traits at 18 months, and nearly eightfold as likely at 36 months, as those whose mothers took the supplements, the researchers found.

“We argue that all women that use anti-epilepsy drugs should use folic acid supplements regularly, even if they are not planning to get pregnant,” says study investigator **Marte Bjørk**, a neurologist at Haukeland University Hospital in Bergen, Norway.

Pesticide protection:

The two other studies on supplements looked at births in California between 1997 and 2008. When the children were between ages 2 and 5, the mothers reported their intake of folic acid and other vitamins — from supplements and food — during pregnancy.

In one of these studies, the researchers explored whether folic acid mitigates autism risk from pesticides².

They surveyed the mothers to gauge prenatal exposure to insecticides in the home for 296 children with autism and 220 controls. They also estimated prenatal exposure to pesticides based on proximity of the children’s homes to farms that use these chemicals.

Among women with above-average folic acid intake, those exposed to pesticides are about 1.3 to 1.9 times as likely to have a child with autism as women with no exposure. Women with below-average folic acid intake and exposure to pesticides have about twofold the risk.

In the other study of California births, researchers estimated prenatal exposure to five types of air pollutants³. The study included 346 children with autism and 260 controls.

Above-average folic acid intake does not have a statistically significant effect on autism risk from most types of air pollutants — a risk that is **far from established** — the researchers reported. But it is linked to a slightly lower autism risk from exposure to one air pollutant: nitrogen dioxide. The study controlled for the child’s year of birth, the mother’s intake of other vitamins and minerals, and socioeconomic status.

Still, the study investigators and experts not involved in the work caution that the study is small.

What’s more, researchers still need to figure out how folic acid might mitigate the risk of autism associated with medications, pesticides or air pollution, given that these risk factors are likely to have diverse biological effects.

“If folate does make the effects of those things smaller on the brain, I think an interesting question to try to answer is, ‘What exactly is folate doing?’” says **Heather Volk**, assistant professor of mental health at Johns Hopkins University in Baltimore, who co-led the California studies.

Treatment hint:

The immune molecules study points to one possible mechanism. In that work, researchers screened blood samples from 82 children with autism and 52 controls for antibodies that react with a folate receptor⁴. Some of these antibodies prevent folic acid’s passage across the placenta and from the blood to the brain.

The researchers found that 62 of the children with autism are positive for these antibodies compared with 15 of the controls. Up to 75 percent of the parents and siblings of people with autism also carry the antibodies. (The researchers did not study the families of the controls.) This finding suggests that the antibodies are heritable risk factors for autism.

Pregnant women who make these antibodies may be able to mitigate this risk by taking folic acid or other forms of folate that pass into the womb or brain via a different mechanism, the researchers say.

Supplements may also benefit children with autism who carry the antibodies. In a small clinical trial, researchers randomly assigned 23 nonverbal children with autism to take folic acid daily for 12 weeks, and 25 nonverbal children with autism to take a placebo. None of the researchers, participants or caregivers knew who received the supplement.

The children who took folic acid showed more improvement in verbal communication, as measured by standardized tests, than those who took the placebo. The improvement was greatest in the children who test positive for folate receptor antibodies. The findings hint at a therapy for autism but warrant replication in a larger sample.

Together, the flurry of studies may largely serve to underscore the existing recommendation that women who are pregnant or planning to become pregnant should take folic acid supplements. Women should stick to the recommended dose, however.

“There’s some data that too much folate might be a problem,” says **Kimford Meador**, professor of neurology at Stanford University in California, who was not involved in any of the studies.

Future studies of folic acid and autism need to better control for dietary factors besides folic acid, Lyall says. The next step, she says, is to examine the links between autism risk and prenatal intake of numerous nutrients, including other B vitamins.

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