

## Ask a Lurie Center Researcher: Can Low Folate Cause Autism?

Folate, a form of vitamin B9, is essential for early brain development, and its role in preventing serious birth defects like spina bifida is well known. But could it also influence the risk of autism spectrum disorder (ASD)? Recent research has begun to explore this complex relationship, uncovering potential links between folate metabolism, immune factors, and brain health. In this article, we'll explore what science currently tells us—and what it doesn't—about folate, autism, and the emerging evidence connecting the two.

### The role of folate in brain development

Folate is a key nutrient that helps our brains work properly by supporting DNA production and cell growth. It's especially important during pregnancy, as it plays a big role in the baby's brain and spinal cord development. Low maternal folate levels in early pregnancy have been associated with an increased incidence of serious birth defects, like neural tube defects.

While folate is found in foods like leafy greens, beans, and citrus fruits, health experts recommend that anyone planning to become pregnant take a daily supplement of folic acid (a synthetic form of folate) to ensure they get enough—usually 400-800 micrograms per day. To help even more, the U.S. and many other countries started adding folic acid to foods like flour and grains in the late 1990s <sup>1</sup>. This public health intervention has greatly reduced the number of babies born with neural tube defects <sup>2,3</sup>.

The benefits of folate go beyond preventing birth defects. Research suggests that getting enough folate during pregnancy may also lower the chances of a child developing autism spectrum disorder (ASD) <sup>4,5</sup> or schizophrenia <sup>1</sup> later in life, highlighting its broader protective effects on brain health <sup>6</sup>. Importantly, it's possible to ingest too much folate during pregnancy. Excess folate may also be associated with an increased likelihood of having a child with ASD <sup>7,8</sup>. It is important to follow recommended guidelines for supplementation as more is not necessarily better.



*Leafy greens, beans, citrus, and fortified foods are good sources of folate.*

## **Cerebral Folate Deficiency**

In most cases, sufficient dietary folate intake guarantees sufficient folate levels in the blood, but that doesn't always mean the brain is getting enough. A rare condition called Cerebral Folate Deficiency (CFD) syndrome is one example of this. People with CFD have normal folate levels in their blood, but not enough in their brain. This can lead to problems with brain development, intellectual disability, speech and language difficulties, epilepsy, and some traits associated with autism<sup>9,10</sup>. Since CFD and ASD share some similarities, scientists are exploring whether low folate levels in the brain could play a role in ASD. The standard treatment for CFD is to supplement with high doses of a special form of folate called leucovorin (folinic acid), but it doesn't always work for everyone. Researchers have also tested leucovorin as a possible treatment for ASD in a few clinical trials, which we will discuss below.



## **Folate transport in the body**

When we eat foods containing folate, it enters our bloodstream and travels to different parts of the body where it's needed. During pregnancy folate moves from the mother's blood into the baby's bloodstream through special folate receptors in the placenta. In a similar way, folate needs to pass from the blood into the brain, using folate receptors at the brain's protective barrier. However, this transport process doesn't always work perfectly. Some people have genetic changes in their folate receptors that make it harder for folate to reach the brain<sup>11-13</sup>. Other people have antibodies that mistakenly block folate receptors, preventing folate from getting into the brain<sup>9,10,14</sup>.

## **Could folate deficiency contribute to autism?**

There are multiple points during a baby's development at which folate deficiency may be associated with autism, including prenatally (i.e., during pregnancy) and postnatally (i.e., after birth and during development). Some research suggests that taking multivitamins or folate supplements during pregnancy might help lower the risk of autism, intellectual disability, and other brain-related conditions in children<sup>15</sup>. However, more studies are needed to confirm whether folate alone has this protective effect.

In the early 2000s, scientists discovered that some women with pregnancies affected by neural tube defects had folate receptor antibodies that blocked folate from reaching the baby's brain<sup>16</sup>. These same antibodies were later found in people with Cerebral Folate Deficiency syndrome<sup>17</sup>. More recently, studies have suggested that these antibodies are more prevalent in children with ASD than in typically developing children<sup>18</sup>. However, it remains unclear how this finding relates to the development of ASD.

## **Folic acid supplementation in individuals with ASD**

Researchers are still studying whether folic acid or folinic acid supplements can help people with ASD. Some early studies suggest they might improve certain symptoms, but more research is needed. One clinical trial comparing folinic acid to placebo (a pill with no active ingredient) in autistic children found an improvement in expressive language (i.e., the ability to verbally and nonverbally communicate thoughts, feelings, and ideas) in those receiving folinic acid <sup>19</sup>. Interestingly, the children who had higher levels of folate-blocking antibodies in their blood seemed to benefit the most from folinic acid. Another small study found that taking folic acid along with behavioral therapy helped improve language, expression, and communication skills <sup>20</sup>. However, other studies haven't found a clear link between folate levels in the blood or spinal fluid and ASD symptoms <sup>21,22</sup>. Scientists need to do more research to understand whether and how folate supplementation might help individuals with ASD.

### **Terminology**

**Folate:** the natural form of vitamin B9 found in foods. This is readily absorbed by the body.

**Folic Acid:** the synthetic form of folate used in supplements and fortified foods. The body needs to convert it to its active form in order for it to be metabolized.

**Folinic Acid:** also known as leucovorin, is an active form of folate that is readily usable by the body. This is used in certain medical treatments such as reducing side effects of chemotherapy, treating types of anemia, and treating cerebral folate deficiency.

## **The bottom line**

Some early research suggests that folic acid or folinic acid supplements might help improve certain symptoms in some individuals with ASD. However, these studies are small, and larger clinical trials are needed to determine whether these supplements truly make a difference, and who might benefit. For these reasons, there isn't enough scientific evidence to recommend folic or folinic acid supplements as a treatment for ASD at this time. With more research, these supplements could become a helpful option for some individuals in the future.

## **About the Author**



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