

Folic Acid Overconsumption May Contribute to Diabetes

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A [study](#) recently published in *Frontiers in Endocrinology* by researchers from the [Diabetes Research Institute at the University of Miami](#), discusses that folic acid overconsumption may be linked to the development of type 1 and type 2 diabetes.

What It Is

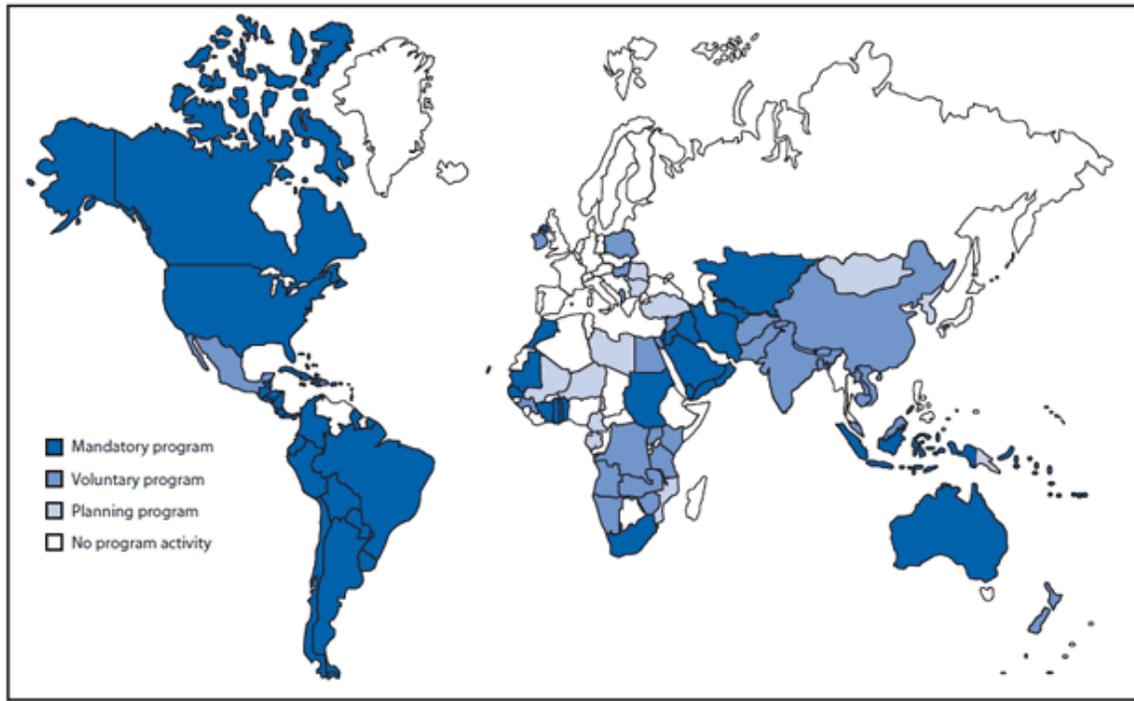
Folate (vitamin B9) is naturally found in foods such as leafy green vegetables, lentils, and nuts. The vitamin is very important for many biological functions, including cell growth, the immune response, and embryonic development.



Importantly, it is known that low folate levels can increase the risk of certain birth defects, in particular, neural tube defects. Thus, women who are pregnant, or are planning to become pregnant, are advised to take vitamins containing at least 400 micrograms of folic acid. Folic acid is the synthetic form of folate and can be metabolized, unless there are specific mutations in genes that encode the necessary enzymes

Image credit: iStockPhoto

In addition, since it was established that many people are deficient in micronutrients, the mandated fortification of wheat flour with folic acid has been in effect since the mid-1990s. This was done with the particular intention of combating birth defects. In fact, the prevalence of neural tube defects has decreased since the mandate.



Countries (N = 53) with regulations for fortification of wheat flour with folic acid*, by program status — worldwide, June 2010; * The World Health Organization recommends adding 1–5 ppm of folic acid to fortified wheat flour, depending on the average per capita wheat flour availability (g/day). Additional information is available [here](#)

Image credit: [The Centers for Disease Control and Prevention](#)

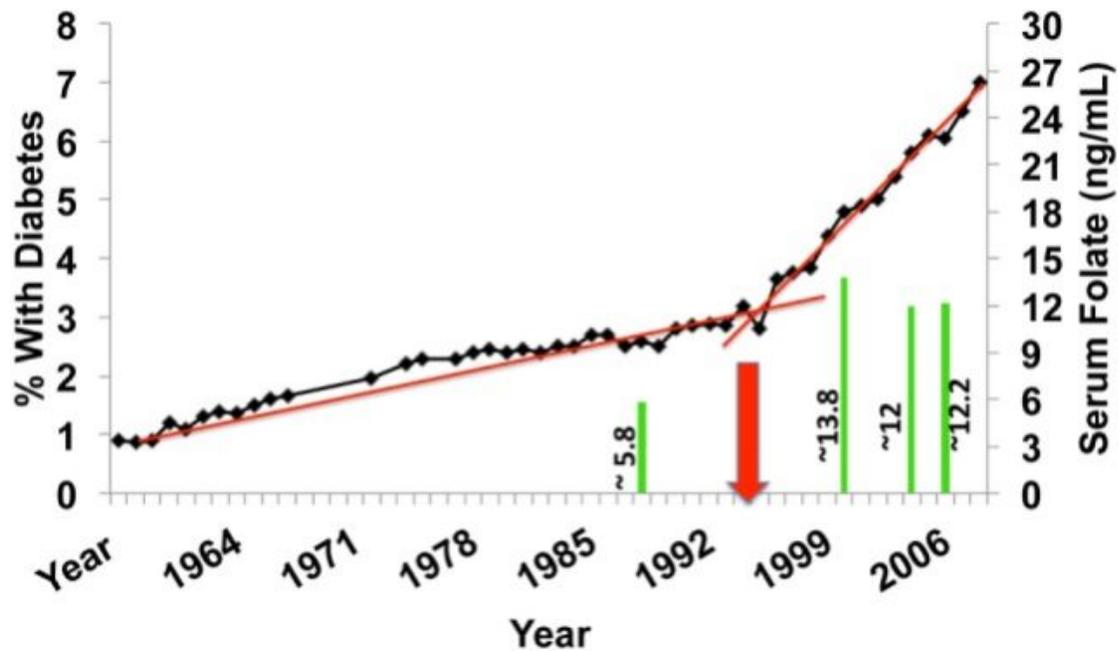
Emerging Concerns

After the introduction of mandatory folic acid fortification on a global scale, follow-up studies determined that the serum folate levels in the population have risen sharply, and are well above the recommended levels. Furthermore, substantial levels of unmetabolized folic acid were discovered. The physiological consequences of this remain to be fully elucidated, but many researchers are questioning whether mandatory fortification could have detrimental health effects.

Because the folate signaling pathway participates in many physiological processes, it is reasonable to consider the potential effects of folic acid overconsumption. Recent studies have highlighted the potential risks pertaining to the development of [inflammation, obesity](#), and even [certain cancers](#).

The Diabetes Connection

[Dr. Chris Fraker](#) is currently investigating whether folic acid plays a role in the development of diabetes. Diabetes incidence has been on the rise, more steeply since the folic acid fortification mandate of the mid-1990s, as depicted in the [recent publication](#).



U.S. incidence of diabetes over the past 50 years (type 1 diabetes and T2D) expressed as % of total population. The red arrow depicts the initiation point of mandatory fortification of flour products with folic acid. The green bars are measurements of serum folate levels from NHANES subjects of the corresponding years.

Numerous complex processes participate in the development of autoimmunity, and it is well-established that type 1 diabetes is caused by a combination of genetic and environmental factors. One of the known environmental factors is infection by certain viruses.

It has been noted that an improper immune response to particular viral infections can promote autoimmunity and type 1 diabetes. Interestingly, natural killer (NK) cells, which act to recognize and clear infections early on in the immune response, have been recently highlighted as important players.

NK cells act to sense infection and can relay stimulatory or suppressive signals to other immune cells. In this regard, aberrant NK cell signaling can promote the development of autoimmunity, although their role in the development of type 1 diabetes remains to be fully elucidated.

Strikingly, it [has been shown](#) that NK cells in the pancreases of diabetic mice preceded infiltration by T cells. In addition, a [study](#) investigating the cell population in the post-mortem pancreases of type 1 diabetics found NK cells in the absence of T cells. Preliminary research by the Fraker lab indicates that NK cells in patients with type 1 diabetes are dysfunctional as compared to the control subjects.

Importantly, the researchers hypothesize that dysfunctions in folate metabolism that arise from folic acid overconsumption may play a role. In the first step of a complicated metabolic process, folic acid and folate must first be converted to dihydrofolate by DHFR. However, this step of folic acid conversion occurs very slowly in comparison to that of folate.

In support of their theory, the scientists note that “high levels of folic acid and variations in DHFR activity could result in high levels of UMFA [unmetabolized folic acid] that could

adversely modulate NK cell and, furthermore, other immune cell activity. In support of this, malarial infection in mice fed a high folic acid (HFA) diet was associated with decreased NK cell activity, NK cell numbers, and survival; this was not observed in mice fed a control diet.”

When it comes to the potential effects of folic acid on the development of type 2 diabetes, Dr. Fraker notes that their preliminary research using mice and rat cells suggests that “folic acid negatively affects glucose metabolism and confers a phenotype of insulin resistance”.

Thus, in the pathogenesis of type 1 diabetes, an excess of folic acid may compromise NK cell function, increasing the likelihood of aberrant cell signaling that contributes to viral-induced autoimmunity. In the case of type 2 diabetes, folic acid is suspected to increase insulin resistance.

Further Investigation Is Warranted

In the quest to identify potential environmental triggers of diabetes, folic acid has taken center stage in Dr. Fraker’s research. “We believe that this metabolic factor may be actually causing a weakening, a general weakening, of people’s immune systems. In the person which has a genetic susceptibility, [it] may lead to the development of not only diabetes but other autoimmune conditions.” Dr. Fraker explains.

The effects of mass folic acid fortification and supplementation have resulted in an unprecedented increase in serum folate concentration and detectable levels of unmetabolized folic acid. The consequences of this remain to be fully investigated. While the theories proposed by the researchers are mainly based on associations and preliminary research, it is clear that the subject warrants further investigation.