

High folic acid supplementation associated with higher rates of COVID-19 infections and mortality

August 31 2022, by Lisa Howard



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People in the United Kingdom with folic acid prescriptions were 1.5 times more likely to get COVID-19. They were also 2.6 times more

likely to die from COVID-19 compared to the control group. Those are the findings of a new study from UC Davis Health and the University of Alabama at Birmingham.

The research, published in the journal *BMJ Open*, also found that having a prescription for the antifolate drug methotrexate mitigated the negative impact of folic acid on COVID-19 when folic acid and methotrexate were given together.

The research team studied a large cohort of patients enrolled in the UK BioBank, a major biomedical database containing [health information](#) from half a million people.

"We examined whether COVID-19 diagnosis and death were related to the large doses of folic acid—five times the safe upper limit—prescribed to patients for a variety of medically approved indications. We found that the risk of becoming infected and dying from COVID-19 was significantly greater in the group treated with folic acid," said Ralph Green, an expert on B vitamins. Green is a distinguished professor in the UC Davis Department of Pathology and Laboratory Medicine and co-senior author of the study.

Folic acid and COVID-19

Folic acid is a synthetic form of vitamin B9, also known as [folate](#). Low levels of B9 are associated with [health conditions](#) such as an increased risk of heart disease, stroke and birth defects.

Folic acid is prescribed for several conditions, including [sickle cell disease](#), high-risk pregnancies, and people receiving anti-seizure medications. Folic acid is also prescribed to help offset some side effects for patients taking methotrexate.

Methotrexate is used to treat certain types of cancer and some autoimmune diseases. The drug is an "antifolate," meaning it interferes with folate, which cancer cells require for proliferation.

Green was inspired by research published last year in *Nature Communications* that suggested the SARS-CoV-2 virus, which causes COVID-19, hijacks the host's folate for viral replication. This suggests that the virus might be sensitive to both folate and folate inhibitors like

To find out if folic acid was associated with an increased risk of COVID-19 and if methotrexate was associated with a decreased risk, the researchers looked at folic acid and methotrexate prescription data from 2019 to 2021 in 380,380 participants in the UK Biobank.

They identified 26,033 individuals with COVID-19, of whom 820 died from COVID-19. People with a methotrexate prescription were diagnosed with COVID-19 at a similar rate to the general study population.

However, people with a folic acid prescription were diagnosed with COVID-19 infections at a higher rate (5.99%) and had a much higher COVID-19 mortality rate (15.97%) than the [control group](#).

"Our findings could have implications for patients who take supplementary folate to prevent complications of other pharmacological therapies," said Angelo L. Gaffo, co-senior author and an associate professor of medicine in the Division of Rheumatology at the University of Alabama at Birmingham. "Although taking folate in these cases is clearly indicated, clinicians should be cautious about excessive folate intake. Of course, our results will require replication."

The researchers note that due to the makeup of the UK BioBank data, the current findings are limited to people 45 years of age and older who

are predominantly from White European ethnicities of the UK population.

The study did not look at the serum folate levels of the participants. They note that further investigations are needed to explore the impact of folate status and folic acid intake on susceptibility to SARS-CoV-2 infection and its fatal complications.

"The defined safe upper limit of folic acid is one milligram. Until we have more information, it would be prudent to avoid extremely high doses of folic acid unless it is medically indicated. High [folic acid](#) would be of greater concern in unvaccinated individuals," Green said.

More information: Ruth Topless et al, Folic acid and methotrexate use and their association with COVID-19 diagnosis and mortality: a case–control analysis from the UK Biobank, *BMJ Open* (2022). [DOI: 10.1136/bmjopen-2022-062945](https://doi.org/10.1136/bmjopen-2022-062945)

Yuchen Zhang et al, SARS-CoV-2 hijacks folate and one-carbon metabolism for viral replication, *Nature Communications* (2021). [DOI: 10.1038/s41467-021-21903-z](https://doi.org/10.1038/s41467-021-21903-z)

Provided by UC Davis

Citation: High folic acid supplementation associated with higher rates of COVID-19 infections and mortality (2022, August 31) retrieved 21 July 2023 from <https://medicalxpress.com/news/2022-08-high-folic-acid-supplementation-higher.html>

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