Covid-19: Metformin reduces the risk of developing long term symptoms by 40%, study finds

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Metformin—a cheap, safe, and widely available diabetes drug—could reduce the incidence of long covid if given during the acute phase of covid-19, a new study indicates.[1]

A two week course of metformin given within three days of testing positive for SARS-CoV-2 led to 40% fewer long covid diagnoses over the following 10 months compared with people who had taken placebo, according to a randomised controlled trial.

The authors of the study, published in *Lancet Infectious Diseases*, caution that the trial did not look at whether metformin would be effective as a treatment for those who already have long covid.

The 1126 people included in the trial had tested positive for SARS-CoV-2 in the previous three days but had no known previous covid infection. They were not admitted to hospital for covid-19 but were at higher risk of developing severe covid-19 as they were overweight or obese. The median age of participants was 45 years; 44% were male and 56% were female.

Participants were randomly allocated to receive placebo or metformin which was titrated over six days from 500 mg to 1000 mg. They were asked whether a medical provider had given them a diagnosis of long covid in follow-up surveys on days 180, 210, 240, 270, and 300. The study authors said that this method of ascertaining long covid was chosen as the definition of long covid rapidly changed over the study period.

The cumulative incidence of long covid by day 300 was 6.3% (35 of 564) in participants given metformin compared with 10.4% (58 of 562) in those receiving placebo (hazard ratio 0.59, 95% confidence interval 0.39-0.89; P=0.012). When metformin was started within three days of symptom onset, its effect was potentially greater (hazard ratio 0.37 (95% CI 0.15-0.95) than in those who started metformin four days or longer after symptom onset (HR 0.64, 0.40-1.03).

Other arms of the trial looked at ivermectin and fluvoxamine and found that neither decreased the risk of long covid.

The study is the first to suggest that drugs given during the acute phase of covid-19 may be able to reduce the risk of long covid. Symptoms of long covid are wide ranging and fluctuating and can include breathlessness, chronic fatigue, "brain fog," anxiety, and stress. Currently there are no proven treatments or ways to prevent long covid, other than reducing the risk of infection in the first place.

According to the latest data from the Office for National Statistics an estimated 1.9 million people living in private households in the UK (2.9%) were experiencing self-reported long covid as of 5 March 2023.[2] This was defined as symptoms continuing for more than four weeks after the first confirmed or suspected covid-19 infection that were not explained by something else.

"Long covid is a significant public health emergency that may have lasting physical health, mental health, and economic impacts, especially in socioeconomically marginalised groups," said lead study author Carolyn Bramante, from the University of Minnesota Medical School. "There is an urgent need to find potential treatments and ways to prevent this disease. Our study showed that metformin, a drug that is safe, low cost, and widely available, substantially reduces the risk of being diagnosed with long covid if taken when first infected with the coronavirus."

Jeremy Faust from Harvard Medical School, who was not involved in the research, said the findings, if confirmed, are "profound and potentially landmark." Writing in a linked comment, he said, "This is the first high quality evidence from a randomised controlled trial to show that the incidence of long covid can be reduced by a medical intervention, metformin—an inexpensive treatment with which clinicians have ample experience."[3]

The mechanism of action by which metformin might reduce the incidence of long covid remains unclear. "Previous studies have found that metformin stops the SARS-CoV-2 virus from replicating in the lab, which is consistent with predictions from our mathematical modelling of viral replication, so that might be what is causing the reduction in both severe covid-19 and long covid diagnoses seen in this trial," said co-author David Odde, a University of Minnesota biomedical engineer.

Limitations to the study include that the trial excluded those with a body mass index under 25 and those younger than 30 years and so it is not known if the findings could be generalised to those populations.

1   Bramante C, Buse J, Liebovitz D, etal. Outpatient treatment of covid-19 and incidence of post-covid-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial. *Lancet Infect Dis* 2023;(June). doi: 10.1016/S1473-3099(23)00299-2.

2   Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (covid-19) infection in the UK: 30 March 2023. www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/30march2023.

3   Faust J. The therapeutic validation of long covid. *Lancet Infect Dis* 2023;(June).
     doi: 10.1016/S1473-3099(23)00355-9.