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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

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Declaration of interests

All other authors declare no competing interests.

See **Online** for appendix

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Summary

Background—Post-COVID-19 condition (also known as long COVID) is an emerging chronic illness potentially affecting millions of people. We aimed to evaluate whether outpatient COVID-19 treatment with metformin, ivermectin, or fluvoxamine soon after SARS-CoV-2 infection could reduce the risk of long COVID.

Methods—We conducted a decentralised, randomised, quadruple-blind, parallel-group, phase 3 trial (COVID-OUT) at six sites in the USA. We included adults aged 30–85 years with overweight or obesity who had COVID-19 symptoms for fewer than 7 days and a documented SARS-CoV-2 positive PCR or antigen test within 3 days before enrolment. Participants were randomly assigned via 2 × 3 parallel factorial randomisation (1:1:1:1:1:1) to receive metformin plus ivermectin, metformin plus fluvoxamine, metformin plus placebo, ivermectin plus placebo, fluvoxamine plus placebo, or placebo plus placebo. Participants, investigators, care providers, and outcomes assessors were masked to study group assignment. The primary outcome was severe COVID-19 by day 14, and those data have been published previously. Because the trial was delivered remotely nationwide, the a priori primary sample was a modified intention-to-treat sample, meaning that participants who did not receive any dose of study treatment were excluded. Long COVID diagnosis by a medical provider was a prespecified, long-term secondary outcome. This trial is complete and is registered with ClinicalTrials.gov, NCT04510194.

Findings—Between Dec 30, 2020, and Jan 28, 2022, 6602 people were assessed for eligibility and 1431 were enrolled and randomly assigned. Of 1323 participants who received a dose of study treatment and were included in the modified intention-to-treat population, 1126 consented for long-term follow-up and completed at least one survey after the assessment for long COVID at day 180 (564 received metformin and 562 received matched placebo; a subset of participants in the metformin *vs* placebo trial were also randomly assigned to receive ivermectin or fluvoxamine). 1074 (95%) of 1126 participants completed at least 9 months of follow-up. 632 (56·1%) of 1126 participants were female and 494 (43·9%) were male; 44 (7·0%) of 632 women were pregnant. The median age was 45 years (IQR 37–54) and median BMI was 29·8 kg/m^2 (IQR 27·0–34·2). Overall, 93 (8·3%) of 1126 participants reported receipt of a long COVID diagnosis by day 300. The cumulative incidence of long COVID by day 300 was 6·3% (95% CI 4·2–8·2) in participants

who received metformin and 10·4% (7·8–12·9) in those who received identical metformin placebo (hazard ratio [HR] 0·59, 95% CI 0·39–0·89; p=0·012). The metformin beneficial effect was consistent across prespecified subgroups. When metformin was started within 3 days of symptom onset, the HR was 0·37 (95% CI 0·15–0·95). There was no effect on cumulative incidence of long COVID with ivermectin (HR 0·99, 95% CI 0·59–1·64) or fluvoxamine (1·36, 0·78–2·34) compared with placebo.

Interpretation—Outpatient treatment with metformin reduced long COVID incidence by about 41%, with an absolute reduction of 4·1%, compared with placebo. Metformin has clinical benefits when used as outpatient treatment for COVID-19 and is globally available, low-cost, and safe.

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Introduction

Infection with SARS-CoV-2 can lead to post-COVID-19 condition, also known as long COVID.[1] Long COVID is heterogeneous, ranging from a single symptom to serious multiorgan involvement, and from mild and short-lived to chronically debilitating.[1,2] The US Centers for Disease Control and Prevention estimates that long COVID disproportionately affects people belonging to racial and ethnic minority populations.[1,3,4] Therefore, preventing long COVID is crucial.

Estimates on the prevalence of long COVID after SARS-CoV-2 infection differ. Early in the pandemic, symptoms beyond 4 weeks after infection were not fully recognised, and most trials did not follow participants for longer than 35 days. The proportion of adults with SARS-CoV-2 infection who are diagnosed with long COVID by medical providers remains poorly described. Previous efforts have tried to understand long COVID using electronic health record (EHR) data, but reliably capturing the condition is challenging.[5] A code for long COVID in the International Classification of Diseases 10th Edition was not added until October, 2021, and there are concerns about its sensitivity and specificity.

We aimed to evaluate whether outpatient COVID-19 treatment with metformin, ivermectin, or fluvoxamine soon after SARS-CoV-2 infection could reduce the risk of long COVID.

Methods

Study design

This investigator-initiated, randomised, quadruple-blind, placebo-controlled, phase 3 trial (COVID-OUT)[6] was conducted at six sites in the USA. The primary outcome was severe COVID-19 by day 14 after starting the study drug, and those data have been published previously.[6] A key secondary outcome was the incidence of long COVID; the trial included monthly follow-up for 300 days to assess the prespecified secondary hypothesis that early COVID-19 treatment with the study drugs would prevent long COVID.[6]

The trial was decentralised, with no in-person contact with participants. The protocol was approved by institutional review boards at each site, and Advarra (Columbia, MD, USA) centrally. Written informed consent was obtained from each participant. An independent data safety monitoring board provided oversight of safety and efficacy monitoring, and an independent monitor provided oversight of study conduct in compliance with the Declaration of Helsinki, Good Clinical Practice Guidelines, and local requirements.

Participants

Participants were recruited remotely with online advertising, patient portal messages, and health-system advertising at the six participating sites. The eligibility criteria have been published previously.[6] In brief, we included adults aged 30–85 years with overweight or obesity (by self-reported height and weight; BMI ≥25 kg/m^2 or ≥23 kg/m^2 for people identifying as Asian or Latino) who had COVID-19 symptoms for fewer than 7 days and a documented SARS-CoV-2 positive PCR or antigen test within 3 days before enrolment, with no known previous SARS-CoV-2 infection. We excluded people who were already taking one of the study medications or who had already received a COVID-19 treatment with Emergency Use Authorization by the US Food and Drug Administration. Use of home medications and treatments received after enrolment was recorded. Vaccination against SARS-CoV-2 was not an exclusion criterion.

Women who were pregnant or lactating were not excluded, which is noteworthy given that pregnant women with COVID-19 are at risk of poor outcomes and are excluded from 99% of non-obstetric clinical trials.[7,8] Women who were pregnant or lactating were randomly assigned (1:1) to receive metformin or placebo, and were not assigned to the fluvoxamine or ivermectin groups (due to less established safety data during pregnancy and lactation for these medications, whereas there is a large body of literature to support the safety of metformin during pregnancy and lactation).[9]

Because the study was done remotely, study drug products had to be posted. Thus, the a priori primary sample was a modified intention-to-treat population, which excluded participants who did not receive a dose of study drug (eg, due to delivery failure, hospitalisation before delivery of drug, or withdrawal of consent before they received the study drug).[6]

Randomisation and masking

The trial was designed to simultaneously assess three distinct oral medications (metformin, ivermectin, and fluvoxamine) using a 2 × 3 parallel treatment factorial design to efficiently share placebo controls in three separate randomised comparisons. Participants were randomly assigned with equal probability to each group that was open at the time of enrolment. Randomisation was stratified by study site and schedules were pre-generated using the mass-weighted urn design, which limits deviations from the targeted equal allocation, similar to permuted blocks.[10]

The trial opened with randomisation (1:1) to metformin or placebo on Dec 30, 2020. The factorial design opened on May 21, 2021, and participants were then randomly assigned (1:1:1:1:1:1) to receive metformin plus ivermectin, placebo plus ivermectin, metformin plus

fluvoxamine, placebo plus fluvoxamine, metformin plus placebo, or placebo plus placebo (figure 1; appendix pp 4–5).[6] The fluvoxamine group was closed on Jan 7, 2022, by the independent data and safety monitoring board. Enrolment ended on Jan 28, 2022, and all investigators except the unmasked statistician remained masked to group-level results until Feb 14, 2022 (the end of the follow-up period for the primary outcome). The 300-day follow-up ended on Nov 27, 2022. Quadruple blinding to individual treatment allocation remains intact, with investigators, outcome assessors, treating clinicians, and participants still masked.

Manufacturers provided placebo pills to exactly match each active treatment. Because two groups had two active medications, each participant received two types of pill to maintain masking in the factorial design: all participants received metformin or exact-matching metformin placebo; and a subset received fluvoxamine, ivermectin, or their exact-matching placebos (appendix p 4). The study medications were dispensed by the research pharmacy into pill boxes to ensure the participants took the correct number of each type of pill.[6] The pill boxes were wrapped in opaque tamper-resistant packaging.[6] As identical placebos were used, even if visualised, investigators and outcome assessors would not have been able to determine if these were active or placebo.[6] The pill boxes and opaque covering included the unique packet identifier.

At the time of randomisation, a newly enrolled study participant identifier was matched to a packet identifier by the randomisation programme. The treatment allocation was generated through a password-protected Shiny application and concealed from all members of the study team, except the statistician who developed the randomisation programme and the pharmacists who prepared the study drug.

Procedures

Pre-packaged pill boxes facilitated faster delivery to participants. Study medication was sent via same-day courier or overnight postage to participants, which meant the average time from consent to ingestion of the first dose of study drug was less than 1 day.

All study drugs were oral medications in tablet form. The metformin dose was titrated over 6 days: 500 mg on day 1, 500 mg twice daily on days 2–5, then 500 mg in the morning and 1000 mg in the evening up to day 14. The ivermectin dose was 390–470 μg/kg per day for 3 days (median 430 μg/kg per day). The fluvoxamine dose was 50 mg on day 1 followed by 50 mg twice daily up to day 14.

The active follow-up period for the trial was 28 days. Beginning at 60 days after randomisation, surveys were sent every 30 days up to day 300 (10 months) after randomisation, via automated email, text message, letter, or call, per patient preference. 10-month follow-up for long COVID was not in the original protocol because long COVID was not a known entity in late 2020. The prespecified secondary endpoint on long COVID was added to the protocol on April 23, 2021, and survey tools were institutional review board-approved in July, 2021 (appendix pp 17–18). Participants who were enrolled before the long COVID surveys were approved were contacted for reconsent to receive the long COVID surveys.

Outcomes

The primary outcome was severe COVID-19 by day 14 of study drug, which has been reported previously.[6] Severe COVID-19 was defined as meeting any one of the four components of the four-part binary composite outcome: hypoxaemia on home oximeter, emergency department visit, hospitalisation, or death due to COVID-19. Self-reported hypoxaemia was inaccurate.[6]

Understanding whether metformin, ivermectin, or fluvoxamine can reduce the risk of long COVID over long-term follow-up was a separate research question to whether they prevented severe COVID-19 in the first 2 weeks of infection. Long COVID diagnosed by a medical provider was the only prespecified clinical outcome in COVID-OUT beyond the acute infectious period (first 28 days). The primary method for ascertaining long COVID was participant-reported receipt of a long COVID diagnosis from a medical provider. Participants 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. If participants responded with yes, a calendar prompt asked them to provide the date this diagnosis was given, and these dates are represented in the cumulative incidence curves (figure 2; appendix p 16). Participants consented for medical record review so diagnoses could be confirmed in the EHR.

This method of ascertaining long COVID was chosen as an important balance of sensitivity and specificity because the definition of long COVID is rapidly changing, fluctuating symptoms are challenging to assess, and EHR codes have low specificity and sensitivity.[11] WHO outlines that long COVID can only be diagnosed when symptoms have no other explanation. We are therefore reliant on clinical judgement by medical professionals to make long COVID diagnoses, as they have the ability to exclude other causes. All health-care providers were masked to treatment allocation.

Statistical analysis

The 2 × 3 factorial design of distinct, parallel treatments allowed for the simultaneous evaluation of three comparisons that efficiently shared concurrently randomised controls. The comparison groups for each study drug consisted of participants who were assigned the active version of the drug versus those who were assigned to a masked control condition with a placebo instead of the active drug (appendix pp 4–5). By design, the active and control comparison groups had balanced numbers of participants receiving the active and placebo versions of the other study drugs. Correcting for multiple comparisons for a factorial design of distinct parallel treatments is not indicated.[12,13] Accordingly, factorial design trials often publish findings for individual medications separately.[14–16] Because the overall structure of this 2 × 3 factorial design meant that all participants received either metformin or exact-matching metformin placebo, and only a proportion received ivermectin, fluvoxamine, or their exact-matching placebos, we present the metformin versus matched placebo comparison in the main manuscript and the details of the fluvoxamine and ivermectin comparisons in the appendix. The sample size calculation was based on the primary outcome, which has been described in detail previously.[6] All analyses were done in the modified intention-to-treat population, which excluded participants who took no doses

of the study drug owing to shipping failure, hospitalisation, or no longer wanting to take the study drug at the time of delivery.

Reports of long COVID diagnosis by a medical provider were analysed using a time-to-event approach beginning from the date of randomisation. This approach appropriately accounted for participants who did not complete all the potential long COVID surveys, and thus were lost to follow-up before day 300. Each active study drug was compared against its placebo control using a log-rank test, with a two-sided p value of less than 0·05 as the criterion for statistical significance. To characterise the effect size for each study drug, Kaplan-Meier estimates of cumulative incidence of long COVID and absolute risk reduction were calculated in 60-day intervals. Unadjusted and adjusted hazard ratios (HRs) with 95% CIs were estimated using Cox proportional hazards models, with adjustments for other study drugs and baseline vaccination status as was prespecified in the protocol and statistical analysis plan. To assess the consistency of the treatment effect across subgroups, unadjusted HRs with 95% CIs were estimated for each subgroup, and a hypothesis test for the treatment by subgroup interaction was done. We also analysed long COVID incidence by dominant SARS-CoV-2 variant in the period in which randomisation occurred: the alpha variant (B.1.1.7)-dominant period (Dec 30, 2020–June 18, 2021), the delta variant (B.1.617.2)-dominant period (June 19–Dec 12, 2021), and the omicron variant (B.1.1.529)-dominant period (Dec 13, 2021–Jan 28, 2022).

Participants who did not report a diagnosis of long COVID and who completed the day 300 survey were censored on day 300, whereas participants who did not complete the day 300 survey were censored on the date of the last long COVID survey they completed. For participants who reported a diagnosis of long COVID, the date of diagnosis was recorded as the 15th day of the earliest month in which they reported receiving the diagnosis. For participants reporting an erroneous date (earlier than 15 days from their date of randomisation), their diagnosis date was recorded as the earliest date they completed a long COVID survey in which they reported the diagnosis.

This trial is complete and is registered with ClinicalTrials.gov, NCT04510194.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 30, 2020, and Jan 28, 2022, 6602 people were assessed for eligibility and 1431 were enrolled and randomly assigned (figure 1). Of the 1323 participants in the primary, modified intention-to-treat population, 1126 consented for long-term follow-up and completed at least one survey after the assessment for long COVID at day 180. (564 received metformin and 562 received matched placebo; 361 received ivermectin and 378 received matched placebo, and 297 received fluvoxamine and 298 received matched placebo; after the factorial design opened, each person in the trial contributed to two of the three [2 × 3] comparisons [appendix pp 4–5]). 632 (56·1%) of 1126 participants were

female and 494 (43·9%) were male; 44 (7·0%) of 632 women were pregnant (table). The median age was 45 years (IQR 37–54). Overall, 24 (2·1%) of 1126 participants identified as Native American, 42 (3·7%) as Asian, 83 (7·4%) as Black, 933 (82·9%) as White, and 77 (6·8%) as other or unknown race (these numbers sum to more than the total number of participants as some chose more than one category). The median BMI was 29·8 kg/m^2 (IQR 27·0–34·2), and 548 (48·7%) of 1126 participants had a BMI of greater than 30 kg/m^2. The median duration from symptom onset to study drug initiation was 5 days (IQR 4–6), and 519 (46·8%) of 1108 participants started study drug within 4 days after symptom onset. Overall, 619 (55·0%) of 1126 participants had received a primary SARS-CoV-2 vaccination series before enrolment, including 57 (5·1%) who had received an initial 2021 monovalent booster (table).

Overall, 1074 (95·4%) of 1126 participants completed at least 9 months of follow-up or reported a long COVID diagnosis. 28 (5·0%) of 564 participants who received metformin and 24 (4·3%) of 562 who received matched placebo were lost to follow-up before day 270. Adverse events did not significantly differ between the treatment groups.6

Overall, 93 (8·3%) of 1126 participants reported receipt of a long COVID diagnosis by day 300. Most long COVID diagnoses were made by primary care providers (72 [78%] of 93), followed by providers specialising in long COVID (four [4%]), other specialists (seven [8%]; three by cardiologists, one by neurologist, one by infectious disease specialist, one by otolaryngologist, and one by pulmonologist), emergency department doctors (three [3%]), hospital doctors (two [2%]), urgent care providers (two [2%]), and others (three [3%]; one by chiropractor, one by other unspecified, and one missing).

The cumulative incidence of long COVID by day 300 was 6·3% (95% CI 4·2–8·2) in participants who received metformin and 10·4% (7·8–12·9) in those who received matched placebo (HR 0·59, 95% CI 0·39–0·89; p=0·012; figure 2); the HR did not appreciably change when adjusted for the a priori baseline variables (vaccination status and receipt of other study medicines in the factorial randomisation; appendix p 9).

The effect of metformin to reduce the risk of long COVID was consistent across subgroups categorised by a priori baseline risk factors, including across SARS-CoV-2 dominant variants (figure 3). When metformin was initiated within fewer than 4 days after symptom onset, its effect to reduce the risk of long COVID was potentially greater (HR 0·37, 95% CI 0·15–0·95) than in those who started metformin 4 days or longer after symptom onset (HR 0·64, 0·40–1·03). Subgroup analyses should be interpreted with caution because of low power, multiple comparisons, and sparse data bias.[17]

Neither ivermectin nor fluvoxamine had a significant effect on the incidence of long COVID. The cumulative incidence of long COVID by day 300 was 7·7% (95% CI 5·0–10·4) in participants who received ivermectin and 8·1% (5·3–10·9) in those who received matched placebo (HR 0·95, 95% CI 0·57–1·59); the HR remained consistent across subgroups (appendix pp 10–11). The cumulative incidence of long COVID by day 300 was 10·1% (95% CI 6·6–13·5) in participants who received fluvoxamine and 7·5% (4·4–10·4) in those who received matched placebo (HR 1·36, 95% CI 0·78–2·35); the HR remained consistent

across subgroups (appendix pp 12–13). The HRs for ivermectin and fluvoxamine did not change when adjusted for vaccination status and receipt of metformin (appendix p 9).

In the comparison of participants who received metformin and placebo only versus those who received placebo only (ie, those who received no active ivermectin or fluvoxamine), the HR was 0·48 (95% CI 0·23–0·98; figure 3). The event rate in the ivermectin and fluvoxamine control groups was lower than the event rate in the metformin placebo group (appendix pp 11, 13), which was because about 50% of participants in the ivermectin and fluvoxamine control groups received active metformin. About 50% of participants in the active ivermectin and fluvoxamine groups also received active metformin, thereby facilitating the randomised evaluation of their effects. This is inherent to factorial designs as described in the appendix (p 4).

The mean incidence of long COVID was 7·9% (five of 63 participants) during the alpha-dominant period, 8·3% (66 of 800) during the delta-dominant period, and 8·4% (22 of 263) during the omicron-dominant period. The timing of long COVID diagnoses did not substantially change over the course of the trial, with a median time from randomisation to long COVID diagnosis of 138 days (IQR 74–142) during the alpha-dominant period, 138 days (89–180) during the delta-dominant period, and 122 days (73–171) during the omicron-dominant period. Participants who reported receiving a diagnosis of long COVID were more likely to report that their work or leisure was disrupted by at least one ongoing symptom after their COVID-19 infection (figure 4A). The relative average prevalence of all 38 symptoms was a median of 4·4 (IQR 3·6–5·5) times higher among participants who reported receiving a long COVID diagnosis than those who reported no long COVID diagnosis (figure 4B).

Overall, 69 (10·9%) of 632 female participants and 24 (4·9%) of 494 male participants had a diagnosis of long COVID by day 300. Among participants who had received at least the primary SARS-CoV-2 vaccine series, 41 (6·6%) of 619 reported a diagnosis of long COVID, compared with 52 (10·3%) of 507 who were unvaccinated. Among the 57 participants who had received a booster vaccination before enrolment, only one (1·8%) participant reported a diagnosis of long COVID (appendix p 15).

Discussion

In this investigator-initiated, decentralised, multicentre, randomised, quadruple-blind, placebo-controlled, phase 3 trial of outpatient treatment for COVID-19, treatment with metformin during acute COVID-19 infection reduced the risk of long COVID by day 300 by 41·3% compared with placebo, with an estimated cumulative incidence of 6·3% in the metformin group and 10·6% in the placebo group. This finding is consistent with the results for the primary outcome of the trial, in which metformin reduced the risk of emergency department visits, hospitalisations, and death due to COVID-19 by day 14 of study drug by 42·3% compared with placebo (odds ratio [OR] 0·58, 95% CI 0·35–0·94).[6,18] Participants who received metformin were also less likely to be hospitalised by day 28 than those who received placebo (eight [1·3%] of 596 *vs* 19 [3·2%] of 601; HR 0·42, 95% CI 0·18–0·95; appendix p 14). Ivermectin and fluvoxamine did not reduce the risk of long COVID in this

trial, and this finding was consistent with their lack of efficacy to reduce severe COVID-19 outcomes by day 14.[6]

Several factors could influence whether individuals receive a diagnosis of long COVID from a medical provider within 10 months of infection, such as access to medical care, competing demands, willingness to seek medical care for post-COVID-19 symptoms, and provider awareness of long COVID as a diagnosis. We would expect such factors to be equally distributed between treatment groups by the randomisation in this trial and so they were unlikely to influence our interpretation of treatment effects. Although some organisations define long COVID as symptoms lasting for beyond 4 weeks after infection,[1,19] seeking a diagnosis from a clinician is important to rule out other explanations and to thereby meet the WHO definition of long COVID (the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation).[20] Definition-driven sensitivity analyses were beyond the scope of this manuscript.

The reduction in severe COVID-19 outcomes in participants who received metformin in this trial is consistent with two other randomised trials that assessed metformin. The first trial (TogetherTrial)[21] assessed a metformin dose of 1500 mg per day with no dose titration, which would be expected to cause side-effects in a large proportion of people; this group was stopped early, with a substantial proportion of participants not tolerating metformin without dose titration. Thus, the per-protocol group might be particularly informative, and it showed a similar effect size (OR 0·61, 95% CI 0·27–1·38) in a sample size of 352 participants.[21] On the basis of the TogetherTrial, we would not recommend starting metformin without a multiple-day dose titration; we titrated over 6 days in this trial. Another randomised trial suggested a similar effect; however, the trial had only 20 participants.[22]

Although the effect sizes for metformin to reduce the risk of severe COVID-19 and long COVID were similar, the number of cases of long COVID was higher than the number of emergency department visits or hospitalisations for acute COVID-19 in this trial. This difference supports the current understanding that long COVID also occurs in people who did not have severe COVID-19.[23] The exact pathophysiology of long COVID is unknown but is likely to be multifactorial, including the inflammatory cascade during acute infection and persistent viral replication.[24] Mechanistic in-silico modelling predicts that translation of SARS-CoV-2 viral proteins is a particularly sensitive target for inhibition of viral replication,[25] and previous studies have shown that metformin is capable of suppressing protein translation via mammalian target of rapamycin (mTOR) inhibition.[25,26]

Experimentally, metformin has shown in-vitro activity at a physiologically relevant dose against SARS-CoV-2 in cell culture and in human lung tissue, ex vivo.[22,27–29] Larger effects for therapies started earlier in the course of infection support an antiviral mechanism. Both the health-care utilisation component of the primary outcome and subsequent development of long COVID were assessed by subgroup of initiation time from symptom onset. Participants who started metformin in fewer than 4 days after symptom onset were compared with those who started metformin 4 days or longer after symptom onset. The HRs showed a greater effect when metformin was started sooner, consistent with an antiviral

mechanism. The point estimate for the vaccinated subgroup showed a weaker effect than in the unvaccinated subgroup and its 95% CI crossed 1·00. However, subgroup analyses should be interpreted with caution, as this trial was not powered to detect an effect in subgroups. Further study is needed to understand the efficacy in people who have received SARS-CoV-2 vaccination.

In addition to in-vitro and in-vivo activity against SARS-CoV-2, metformin has been extensively studied for actions relevant to oxidative stress and inflammation.[30] These actions have been studied in the setting of SARS-CoV-2 infection as well. In human bronchial and lung epithelial cell lines infected with SARS-CoV-2, metformin restored autophagic flux, inhibited cleavage of caspase-1 by non-structural protein 6 (NSP6), and inhibited maturation and release of interleukin-1β and interleukin-18.[31] Metformin also prevented a senescent phenotype induced by SARS-CoV-2 infection in dopaminergic neurons in vitro, which could be relevant to neurocognitive sequelae of infection seen in long COVID.[32]

There were no issues with safety in this phase 3 trial of metformin in adults without diabetes.[6] Safety concerns for metformin have centred around a risk of lactic acidosis, but that historical concern was driven by evidence from other biguanides. Several large studies and Cochrane reviews have shown no increased risk of lactic acidosis, and have actually shown fewer cases of lactic acidosis, in people receiving metformin than in those not receiving metformin,[33] including in adults with heart failure.[34] Metformin has also been shown to be safe in adults with kidney disease and should not be withheld from people with glomerular filtration rates of greater than 30 mL/min per 1·73 m^2 (and perhaps even lower), because it has been shown to be associated with improved macrovascular outcomes in people with chronic kidney disease.[35]

Metformin treats diabetes largely by preventing hepatic gluconeogenesis, not by lowering blood glucose concentrations; therefore, the risk of hypoglycaemia is very low, including in people without diabetes. The safety of metformin has also been shown in children and in women who are lactating or pregnant.[9,36] Guidelines recommend that metformin should no longer be stopped upon hospital admission or for surgery.[37,38]

The COVID-OUT trial does not indicate whether metformin would be effective at preventing long COVID if started at the time of emergency department visit or hospitalisation for COVID-19, or whether metformin would be effective as a treatment in people who already have long COVID. The p value (0·012) for metformin to reduce the risk of long COVID was low enough that it would still be less than 0·05 after applying a Bonferroni correction for the multiple testing of the primary outcome and all four secondary clinical outcomes in this trial.[39] Future research directions include correlation with different and emerging definitions of long COVID, and clinical trials to assess the synergy of metformin with other treatments and in people with previous COVID-19.

This study has some limitations. There is selection bias in that individuals who choose to enrol in clinical trials and complete 10 months of follow-up surveys might not represent the general population affected by COVID-19 and long COVID. When the long COVID assessment was added to the trial, little was known about the best assessment tool for

incident long COVID in clinical trial participants. The use of a long COVID diagnosis based on the documented professional judgement of a medical provider, as well as the long duration of follow-up, should address some of the issues around the changing nature of this disease definition. Additionally, factors that might affect the receipt of a long COVID diagnosis by a medical provider would be expected to be evenly distributed between treatment groups in this randomised trial. The quadruple blinding also limits potential biases compared with observational cohorts or case-control studies that assess long COVID. The largest proportion of participants were enrolled within the delta-dominant period; however, the estimated benefit of metformin appeared to be consistent across variant periods, including the omicron-dominant period.

This trial excluded groups at low risk of severe COVID-19—adults with a normal BMI and those who were younger than 30 years—and whether these findings would be generalisable to those populations remains unknown. Additionally, it is unknown whether these findings would be generalisable to early outpatient treatment of SARS-CoV-2 in people with previous SARS-CoV-2 infection. The sample of participants in this trial was mostly White (83·2%), compared with 76% in the general population of the USA, and only 12·3% identified as Latino or Hispanic. As 56% of trial participants were female, sex was well balanced. This was also one of few randomised trials of outpatient COVID-19 treatment to enrol women who were pregnant.

In conclusion, early outpatient COVID-19 treatment with metformin decreased the subsequent risk of long COVID by 41·3% during 10-month follow-up. This finding is consistent with the 42·3% reduction in health-care utilisation for severe COVID-19 with metformin in the first 14 days of the trial. Fluvoxamine and ivermectin did not decrease the risk of long COVID, which was also consistent with the findings for severe COVID-19 outcomes by day 14. As the COVID-19 pandemic continues to evolve, all therapeutics require further prospective, interventional trials to assess long COVID incidence, including among people who have received vaccination and booster vaccination, and people with previous SARS-CoV-2 infection. Long COVID is an important public health emergency that might have lasting health, mental health, and economic sequelae, particularly in socioeconomically marginalised groups, and metformin is safe and widely available at low cost.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data sharing

A de-identified dataset with the variables used to create these analyses will be freely available at https://covidout.umn.edu within approximately 2 months of publication, for valid research questions with a clearly stated hypothesis. The protocol and statistical analysis plan have been published previously, are included in the appendix, and are also available on ClinicalTrials.gov.

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Research in context

Evidence before this study

Few randomised trials of outpatient treatment of COVID-19 have followed participants for 10 months to assess the effect of early treatments on the incidence of post-COVID-19 condition (also known as long COVID). Emerging clinical, observational, and preclinical data have shown that metformin inhibits SARS-CoV-2 and prevents severe COVID-19. We searched PubMed on July 1 and Aug 5, 2020, with no date or language restrictions, using the terms “metformin” and “COVID-19” and “clinical trial”; and “metformin” and “SARS-CoV-2” and “clinical trial”; similar searches were done using “ivermectin” and “fluvoxamine” on Jan 25, 2021. These searches did not identify any randomised trials of early treatment of SARS-CoV-2 infection with metformin, nor any phase 3 randomised trials with fluvoxamine or ivermectin. On March 1, 2023, we searched PubMed with the terms “clinical trial” and “COVID-19” and “SARS-CoV-2” and “randomized” and each medication individually. For ivermectin, placebo-controlled trials showed no clinical effect with 3 days of treatment (the TOGETHER trial in Brazil [400 μg/kg per day], the ACTIV-6 trial [300 μg/kg per day], de la Rocha and colleagues, and Rezai and colleagues [400 μg/kg per day]) nor with 1–2 days of treatment (Mirahmadizadeh and colleagues). For effect on viral load, Biber and colleagues showed lower viral load with ivermectin; Manomaipiboon and colleagues and the PLATCOV trial showed no benefit with ivermectin. For fluvoxamine, placebo-controlled trials showed no clinical effect with 50 mg twice daily (ACTIV-6) and clinical benefit with 100 mg twice daily (TOGETHER trial). For metformin, the TOGETHER trial showed no clinical or virological benefit with 1500 mg extended-release formulation with no titration but benefit in the per-protocol group; Ventura-López and colleagues found clinical and antiviral benefit in a phase 2b trial.

Added value of this study

To our knowledge, this is the first randomised, placebo-controlled, phase 3 trial to evaluate the effect of outpatient COVID-19 treatment on the incidence of long COVID. Additionally, this is one of the few COVID-19 treatment trials to include pregnant women. Metformin was shown to reduce the incidence of long COVID and is safe, inexpensive, widely available, and has few contraindications or medication interactions.

Implications of all the available evidence

People with long COVID frequently require continued medical treatment or are unable to work for 6 months or longer. Although disease prevention is a public health challenge, taking the next steps to implement metformin as a COVID-19 treatment to prevent long COVID is an urgent public health need.

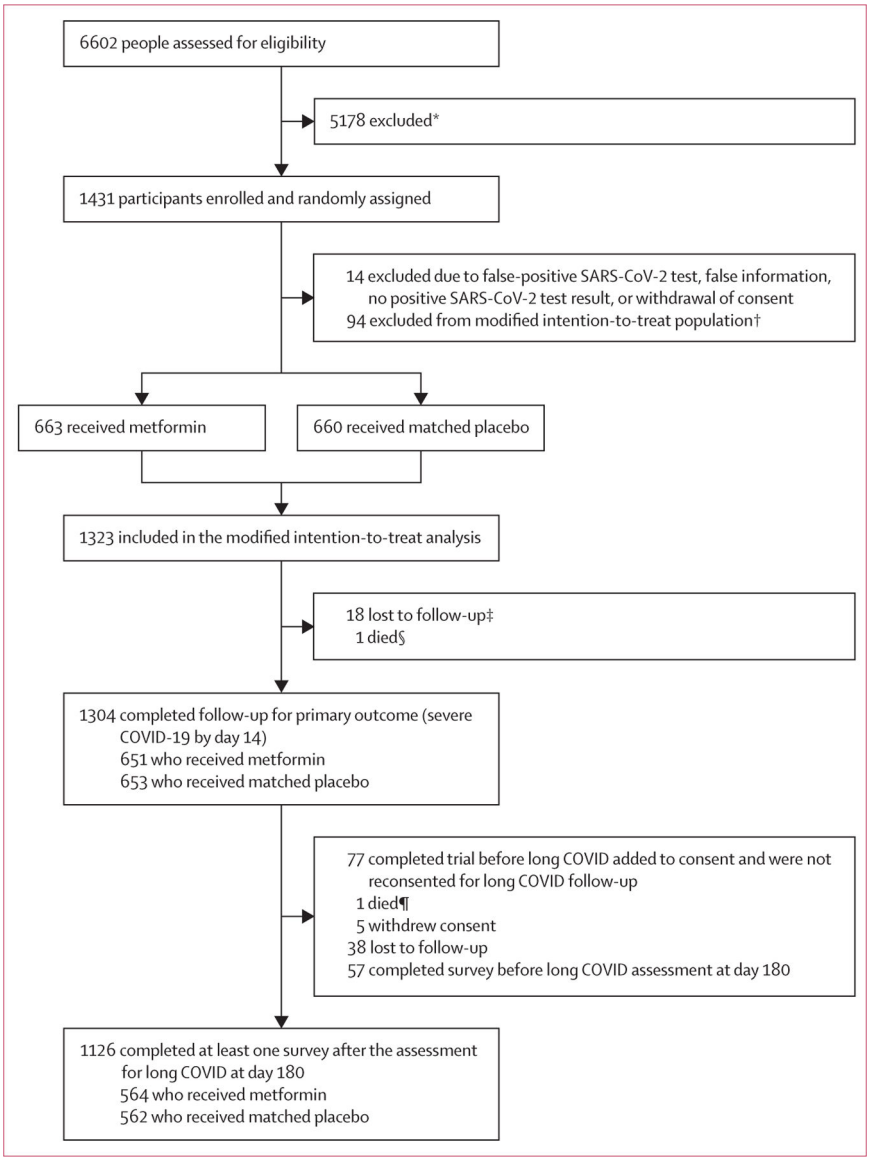

Figure 1: Trial profile

*Reasons for exclusion are provided in the appendix (p 6). †Further detailed in the appendix (p 5). ‡11 received metformin, seven received placebo. §Within 14 days, in the metformin plus ivermectin group. ¶Within 28 days, received placebo.

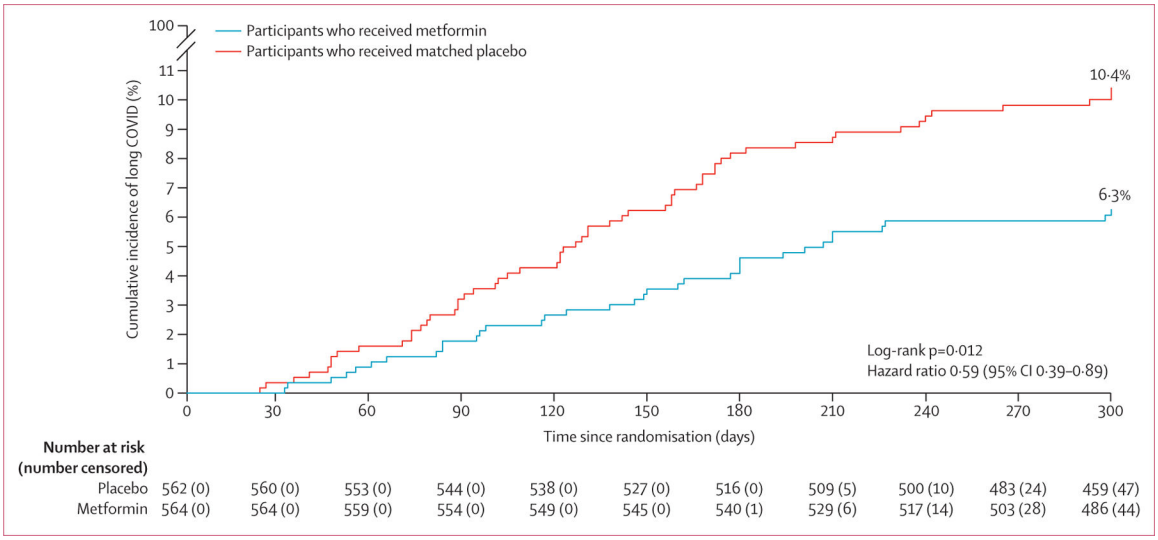

Figure 2: Cumulative incidence of post-COVID-19 condition (long COVID) diagnoses over 10 months after randomization

The absolute risk reduction for metformin compared with matched placebo was 4·1% (95% CI 0·9–7·4).

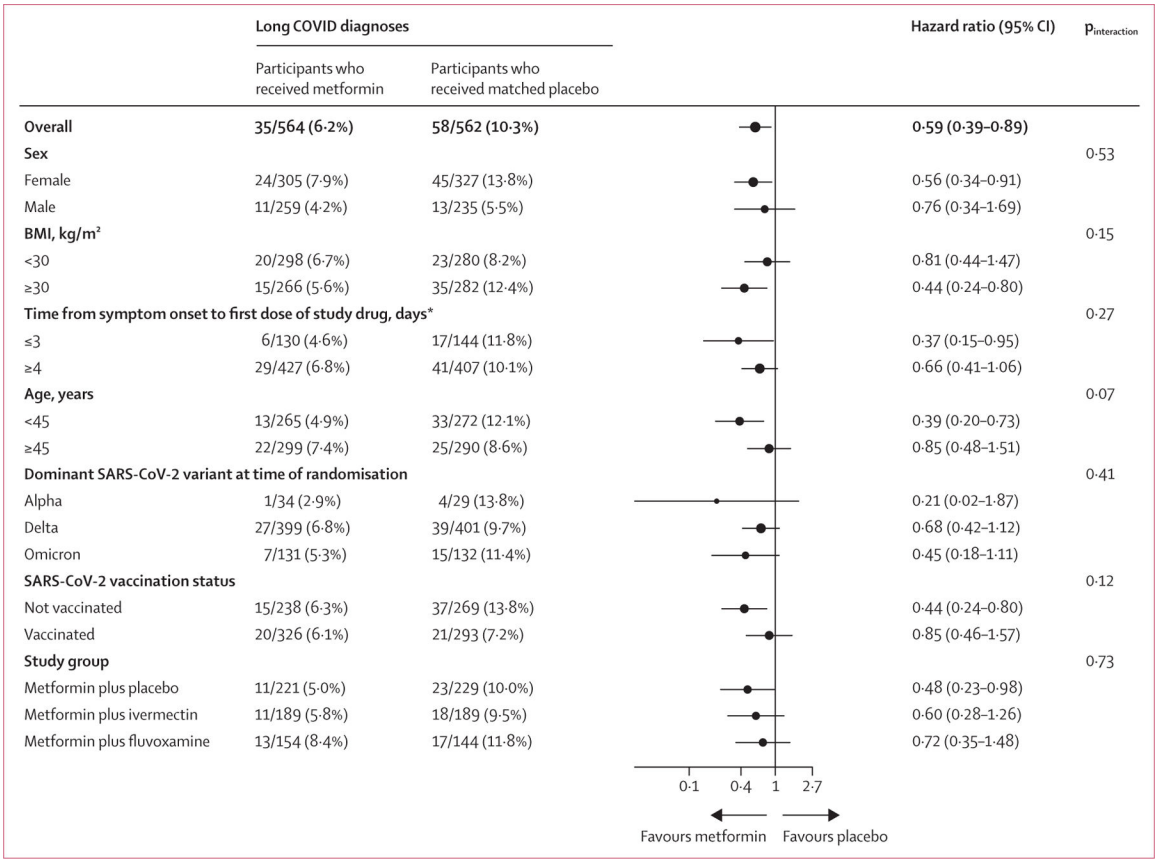

Figure 3: Incidence of post-COVID-19 condition (long COVID) diagnoses across prespecified subgroups

Error bars are 95% CIs. *For 18 (1·6%) of the 1126 participants, the timing of study drug initiation was not known.

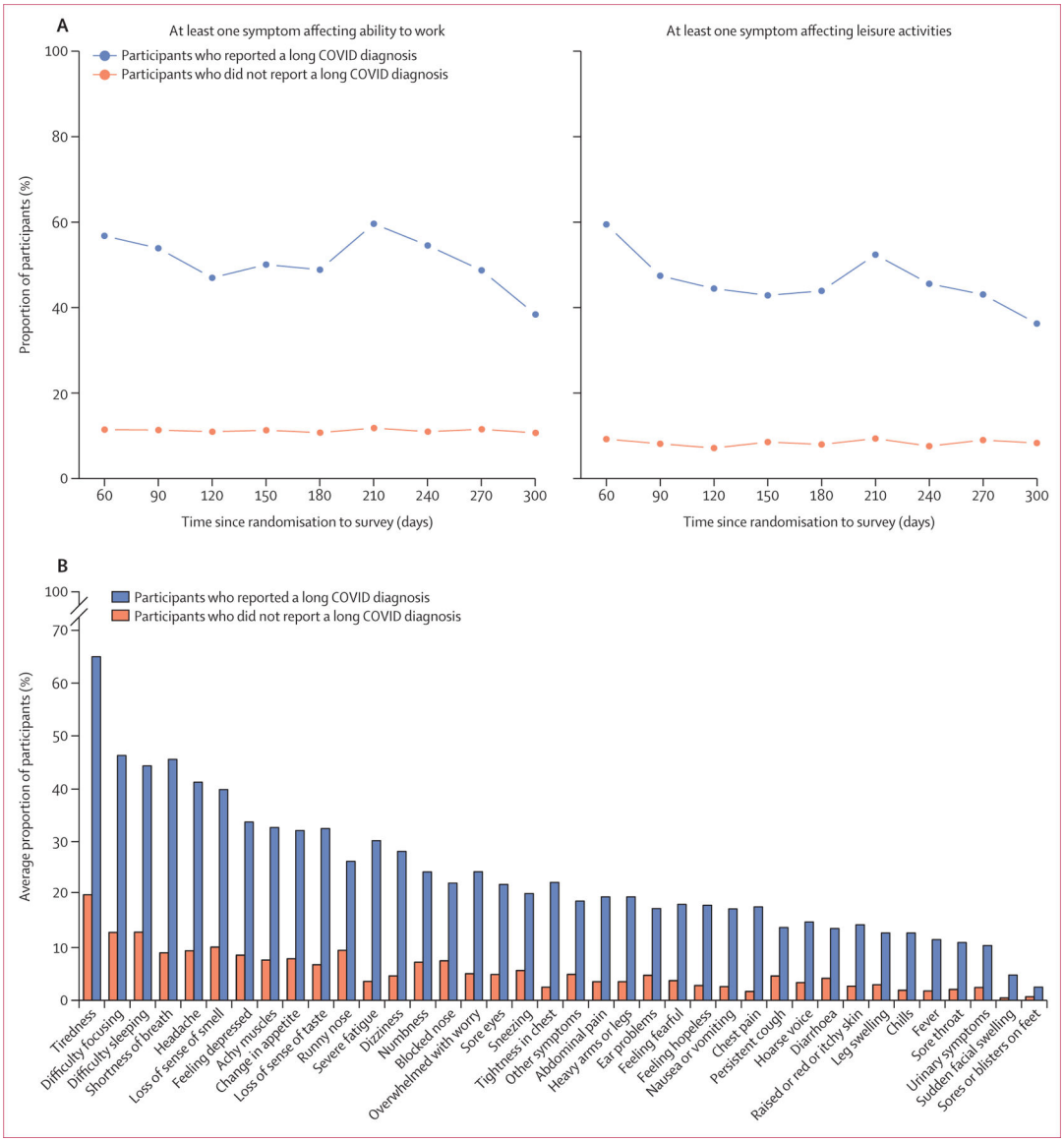

Figure 4: Symptomology by post-COVID-19 condition (long COVID) diagnosis status

(A) Proportion of participants with at least one symptom that affects their work or leisure activities. (B) Average proportion of participants reporting individual symptoms with and without a long COVID diagnosis. Symptom terms were as provided in the surveys sent every 30 days from day 30 to 300. Reported proportions are among participants with non-missing responses.

Table:

Baseline characteristics

	Participants who received metformin (n=564)	Participants who received matched placebo (n=562)
Age, years	46 (11)	46 (11)
Sex		
Female *	305 (54·1%)	327 (58·2%)
Male	259 (45·9%)	235 (41·8%)
Race †		
Native American	9 (1·6%)	15 (2·7%)
Asian	21 (3·7%)	21 (3·7%)
Black	43 (7·6%)	40 (7·1%)
White	469 (83·2%)	464 (82·6%)
Other or unknown	40 (7·2%)	37 (6·6%)
Ethnicity		
Hispanic or Latino ‡	66 (11·8%)	76 (13·7%)
BMI, kg/m^2		
Median (IQR)	29·7 (27·1–33·7)	30·0 (26·9–34·4)
≥30	266 (47·2%)	282 (50·3%)
Medical history		
Cardiovascular disease §	147 (26·1%)	138 (24·6%)
Type 2 diabetes	6 (1·1%)	11 (2·0%)
SARS-CoV-2 primary vaccination	326 (57·8%)	293 (52·1%)
First SARS-CoV-2 vaccine booster dose	30 (5·3%)	27 (4·8%)
Time from symptom onset to study drug initiation, days ¶		
Median (IQR)	5 (4–6)	5 (3–6)
Mean (SD)	4·8 (1·9)	4·7 (1·9)
≤3	130 (23·3%)	144 (26·1%)
SARS-CoV-2 dominant variant at time of randomisation		
Alpha	34 (6·0%)	29 (5·2%)
Delta	399 (70·7%)	401 (71·4%)
Omicron	131 (23·2%)	132 (23·5%)
Health-care insurance		
Private	358 (64·4%)	346 (62·6%)
Public Medicare	41 (7·4%)	38 (6·9%)
Public Medicaid	75 (13·5%)	97 (17·5%)
None	82 (14·7%)	72 (13·0%)

Data are mean (SD), n (%), or median (IQR).

* 44 (7·0%) of 632 women were pregnant.

† Numbers do not sum to the group totals as some participants chose more than one option.

‡ Data missing for nine participants.

[§]Hypertension, hyperlipidaemia, coronary artery disease, previous myocardial infarction, congestive heart failure, pacemaker, arrhythmia, or pulmonary hypertension.

[¶]For 18 (1·6%) of the 1126 participants, the timing of study drug initiation was not known.