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# Long COVID prevalence and risk factors in adults residing in middle- and high-income countries: secondary analysis of the multinational Anti-Coronavirus Therapies (ACT) trials

Lucas Etienne Hermans ,[1] Sean Wasserman,[2,3] Lizhen Xu,[4] John Eikelboom[5]

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For numbered affiliations see end of article.

**Correspondence to**
Dr Sean Wasserman;
swasserm@sgul.ac.uk

## ABSTRACT

**Background** During the recent COVID-19 pandemic, reports of long-term persistence or recurrence of symptoms after SARS-CoV-2 infection emerged, which are now collectively referred to as 'long COVID'. Most descriptions of long COVID originate from patients residing in high-income countries. We set out to characterise long COVID in a large-scale clinical trial that was conducted in low-middle, high-middle and high-income countries.

**Methods** The Anti-Coronavirus Therapies trials enrolled 6528 adult patients with symptomatic COVID-19 in Argentina, Brazil, Canada, Colombia, Ecuador, Egypt, India, Nepal, Pakistan, Philippines, Russia, Saudi Arabia, South Africa and the United Arab Emirates. Long COVID was defined as the presence of patient-reported symptoms at 180 days after enrolment. Multivariable logistic regression was used to evaluate associations of baseline characteristics with long COVID.

**Results** Of 4697 included participants, 1181 (25.1%) reported long COVID symptoms. The most frequently reported symptoms were sleeping disorders (n=601; 12.8%), joint pain (n=461; 9.8%), fatigue (n=410; 8.7%) and headaches (n=382; 8.1%). Long COVID prevalence was higher in participants from lower middle-income compared with high-income countries (29.8% (850/2854) vs 14.4% (102/706); adjusted OR (aOR) 1.53 (1.10 to 2.14); p=0.012). Prevalence also varied between participants of different ethnic backgrounds and was highest (36.1% (775/2145)) for patients of Arab/North African ethnicity. Patients requiring inpatient admission were at increased risk of long COVID (aOR: 2.04 (1.63 to 2.54); p<0.001). Other independent predictors of long COVID were male sex, older age and hypertension. Vaccination, prior lung disease, smoking and diabetes mellitus conferred protective effects.

**Conclusion** Symptoms of long COVID are reported in a quarter of cases of symptomatic COVID-19 in this study and were significantly more prevalent in participants from countries with lower income status and in patients of Arab/North African ethnicity. Research to further assess the health burden posed by long COVID in low- and middle-income countries is urgently needed.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long COVID is a syndrome of persistent or recurring symptoms, occurring at least 3 months after SARS-CoV-2.
⇒ Prevalence is estimated at around 10%, but prevalence estimates vary widely.

### WHAT THIS STUDY ADDS

⇒ This systematically studied long COVID across a substantial number of countries across the globe using standardised methods.
⇒ Potential long COVID symptoms were reported by a quarter of patients with previous symptomatic COVID-19 in this cohort.
⇒ This study shows that long COVID symptoms were more frequently present in patients from countries with lower income levels and in patients of Arab or North African ethnicity.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study emphasises that the morbidity burden conferred by long COVID may fall disproportionately on countries with the least capacity to carry it, and frequently affects individuals that are likely to be under-represented in interventional studies that are being conducted in the global North.
⇒ This study highlights the need for global and inclusive research on long COVID, and the development of interventions for long COVID that are globally applicable.

## INTRODUCTION

During the pandemic of SARS-CoV-2, reports of long-term persistence or recurrence of symptoms after SARS-CoV-2 emerged, which are now collectively referred to as 'long COVID'. The WHO defines long COVID as symptoms lasting for at least 2 months and present at least 3 months after probable or confirmed SARS-CoV-2 infection.[1] According to recent estimates, long COVID affects

approximately 10% of patients with previous SARS-CoV-2 infection.[2 3]

Over 100 different putative symptoms of long COVID have been reported in the literature, varying in severity from mild to profoundly debilitating.[4 5] Investigators have attempted to identify those symptoms that are specifically associated with previous SARS-CoV-2 infection.[6] Recent work has shown that long COVID symptoms cluster together in reproducible clinical subphenotypes, potentially driven by different pathophysiological mechanisms.[7] While the aetiology of long COVID remains to be elucidated, several risk factors have been consistently reported, including female sex, higher COVID-19 symptom severity, cardiovascular and respiratory comorbidities and smoking.[8–10] A recent meta-analysis has shown that vaccination for SARS-CoV-2 is protective against long COVID.[11]

Most of the evidence on long COVID has been generated from patients in high-income countries. We set out to characterise the prevalence and symptomatology of long COVID and risk factors for the syndrome in a large-scale international clinical trial that was conducted in low-middle, high-middle and high-income countries.

## METHODS

### Design

This study is a secondary analysis of data collected in the Anti-Coronavirus Therapies (ACT) trials. The ACT trials were two international multicentre parallel group 2×2 factorial trials, respectively enrolling 3917 outpatients and 2749 inpatients with symptomatic COVID-19. Both trials compared colchicine and usual care versus usual care alone. The outpatient trial further compared aspirin 100 mg daily and usual care versus usual care, and the inpatient trial compared the combination of aspirin 100 mg daily and rivaroxaban 2.5 mg two times per day and usual care versus usual care.[12] In both trials, none of the tested interventions were shown to be of benefit in reducing the primary outcome.[13 14]

### Participants

The trials were performed in Argentina, Brazil, Canada, Colombia, Ecuador, Egypt, India, Nepal, Pakistan, Philippines, Russia, Saudi Arabia, South Africa and the United Arab Emirates. For the outpatient trial, patients were eligible for inclusion if they were symptomatic with laboratory-confirmed COVID-19 and within 7 days (ideally 72 hours) of diagnosis or worsening clinically (but not requiring hospitalisation). Patients above 30 years of age were eligible, and those below 70 years had to have at least one additional risk factor for disease progression, including male sex, body mass index of at least 30 kg/m², chronic cardiovascular, respiratory, or renal disease, active cancer or diabetes. For the inpatient trial, patients were eligible for inclusion if they were symptomatic with laboratory-confirmed COVID-19 disease and aged 18 or older. Patients were eligible for recruitment within 72 hours of their admission to the hospital or, in patients already hospitalised, within 72 hours of clinical worsening (eg, requiring ventilation).

Exclusion criteria for both trials included advanced kidney or liver disease, pregnancy or breastfeeding, and the presence of a medical indication or contraindication to the trial interventions.

Full inclusion and exclusion criteria are available from the study protocols, which are available online.[12]

### Data collection

Assessment of patient symptoms was performed in both trials using a questionnaire at enrolment, and subsequently at day 8, 45 and 180 after enrolment. The questionnaire could be completed either in-person or telephonically. Symptoms that were assessed in both trials were fever, cough, muscle pain, sore throat, shortness of breath with activities of daily living, loss of smell or taste, diarrhoea, fatigue, conjunctivitis, headaches, sleeping disorder, palpitations, altered concentration, memory impairment and joint pain. Patients enrolled in Argentina did not complete the questionnaire and are not included in these analyses. Study questionnaires are available in online supplemental file 1.

Based on published data, we included the following as symptoms of long COVID[6]: muscle pain, shortness of breath with activities of daily living, anosmia/ageusia, diarrhoea, fatigue, headaches, sleeping disorder, palpitations, altered concentration, memory impairment and joint pain. We defined long COVID as the presence of at least one long COVID-associated symptom at 180 days after enrolment.

Vaccination status was assessed at enrolment. Participants were labelled as vaccinated if they had received a vaccine prior to the index episode of symptomatic acute COVID-19. Partially vaccinated was defined as having received only one dose of a vaccine of which the initial package insert recommended a two-dose vaccination schedule prior to enrolment.

### Patient involvement

As a result of restrictions on social gatherings during the COVID-19 pandemic, and due to the urgent need for trial evidence during the pandemic, it was not feasible to obtain patient or stakeholder input for the ACT trials protocols in a timely manner.

### Statistical analysis

Univariable analyses were performed by comparing the baseline characteristics between the two groups defined by the presence of long COVID symptoms (day 180) (table 1). Categorical variables were compared using Pearson's $\chi^2$ test. Continuous variables were compared using a t-test. A multivariate logistic regression was then used to analyse the joint relationship between the multiple explanatory variables and the response variable (ie, long COVID at day 180). Adjusted ORs (aORs), along with the 95% CIs and p values were reported.

**Table 1** Baseline characteristics according to the presence or absence of long COVID at day 180

| | Total | Long COVID (day 180) | | P value |
|---|---|---|---|---|
| | | Yes | No | |
| Participants | 4697 | 1181 | 3516 | |
| Age (years), mean±SD | 45.9±13.4 | 48.0±14.1 | 45.2±13.1 | <0.001 |
| Males, n (%) | 2828 (60.2%) | 609 (51.6%) | 2219 (63.1%) | <0.001 |
| Ethnicity, n (%) | | | | <0.001 |
| Arab/North African | 2145 (45.7%) | 775 (65.6%) | 1370 (39.0%) | |
| White European | 805 (17.1%) | 197 (16.7%) | 608 (17.3%) | |
| Latin American | 398 (8.5%) | 59 (5.0%) | 339 (9.6%) | |
| South Asian | 960 (20.4%) | 113 (9.6%) | 847 (24.1%) | |
| Other | 389 (8.2%) | 37 (3.1%) | 351 (9.9%) | |
| Country income status, n (%) | | | | <0.001 |
| High income | 706 (15.0%) | 102 (8.6%) | 604 (17.2%) | |
| Upper middle income | 1137 (24.2%) | 229 (19.4%) | 908 (25.8%) | |
| Lower middle income | 2854 (60.8%) | 850 (72.0%) | 2004 (57.0%) | |
| Smoking, n (%) | | | | 0.009 |
| Never | 3432 (73.1%) | 900 (76.2%) | 2532 (72.0%) | |
| Former | 442 (9.4%) | 89 (7.5%) | 353 (10.0%) | |
| Current (within 1 year of quitting) | 823 (17.5%) | 192 (16.3%) | 631 (17.9%) | |
| Diabetes mellitus, n (%) | 737 (15.7%) | 193 (16.3%) | 544 (15.5%) | 0.477 |
| Hypertension, n (%) | 1075 (22.9%) | 318 (26.9%) | 757 (21.5%) | <0.001 |
| Dyslipidaemia, n (%) | 375 (8.0%) | 115 (9.7%) | 260 (7.4%) | 0.010 |
| Cardiovascular disease, n (%) | 212 (4.5%) | 80 (6.8%) | 132 (3.8%) | <0.001 |
| Peripheral artery disease, n (%) | 36 (0.8%) | 13 (1.1%) | 23 (0.7%) | 0.128 |
| Lung disease, n (%) | 310 (6.6%) | 54 (4.6%) | 256 (7.3%) | 0.001 |
| Kidney disease, n (%) | 100 (2.1%) | 11 (0.9%) | 89 (2.5%) | <0.001 |
| Immunosuppressed, n (%) | 84 (1.8%) | 4 (0.3%) | 80 (2.3%) | <0.001 |
| Cancers, n (%) | 20 (0.4%) | 6 (0.5%) | 14 (0.4%) | 0.616 |
| Vaccination status, n (%) | | | | <0.001 |
| Confirmed not vaccinated | 3444 (73.3%) | 1037 (87.8%) | 2407 (68.5%) | |
| Partially vaccinated | 303 (6.5%) | 37 (3.1%) | 266 (7.6%) | |
| Fully vaccinated | 931 (19.8%) | 106 (9.0%) | 825 (23.5%) | |
| Unknown | 19 (0.4%) | 1 (0.1%) | 18 (0.5%) | |
| Participant type, n (%) | | | | 0.731 |
| Inpatient | 1119 (23.8%) | 277 (23.5%) | 842 (23.9%) | |
| Outpatient | 3578 (76.2%) | 904 (76.5%) | 2674 (76.1%) | |
| Treatment, n (%) | | | | 0.626 |
| ASA in ASA trial+colchicine in COL trial | 1175 (25.0%) | 287 (24.3%) | 888 (25.3%) | |
| ASA in ASA trial+control in COL trial | 1176 (25.0%) | 300 (25.4%) | 876 (24.9%) | |
| Control in ASA trial+colchicine in COL trial | 1173 (25.0%) | 285 (24.1%) | 888 (25.3%) | |
| Control in ASA trial+control in COL trial | 1173 (25.0%) | 309 (26.2%) | 864 (24.6%) | |

Percentages are calculated out of patients randomised. For continuous variables, t-test was used; for categorical variables, $\chi^2$ was used.

## RESULTS

### Participant characteristics

Data from 4697 trial participants with questionnaire data at 180 days was available for analysis, of whom 3578 (76.2%) were outpatients. The mean age of participants was 45.9 (SD: 13.4), and 2828 (60.2%) participants were male. The majority of participants (60.8%, n=2854) resided in lower middle-income countries, followed by

Table 2 Summary of long COVID symptoms at follow-up visits

| | Total | | | |
|---|---|---|---|---|
| | Baseline | Day 8 | Day 45 | Day 180 |
| Patients with data, N | 2596 | 2723 | 3124 | 4697 |
| Muscle pain, n (%) | 1699 (65.4%) | 591 (21.7%) | 159 (5.1%) | 130 (2.8%) |
| Shortness of breath on usual activities of daily living, n (%) | 1066 (41.1%) | 616 (22.6%) | 177 (5.7%) | 126 (2.7%) |
| Loss of sense of smell or taste, n (%) | 1316 (50.7%) | 740 (27.2%) | 210 (6.7%) | 100 (2.1%) |
| Diarrhoea, n (%) | 645 (24.8%) | 289 (10.6%) | 73 (2.3%) | 43 (0.9%) |
| Fatigue, n (%) | 1533 (59.1%) | 1188 (43.6%) | 623 (19.9%) | 410 (8.7%) |
| Headaches, n (%) | 1274 (49.1%) | 496 (18.2%) | 196 (6.3%) | 382 (8.1%) |
| Sleeping disorder, n (%) | 704 (27.1%) | 644 (23.7%) | 449 (14.4%) | 601 (12.8%) |
| Palpitations, n (%) | 309 (11.9%) | 183 (6.7%) | 77 (2.5%) | 42 (0.9%) |
| Concentration impairment, n (%) | 254 (9.8%) | 160 (5.9%) | 127 (4.1%) | 126 (2.7%) |
| Memory impairment, n (%) | 176 (6.8%) | 133 (4.9%) | 168 (5.4%) | 143 (3.0%) |
| Joint pain, n (%) | 869 (33.5%) | 561 (20.6%) | 430 (13.8%) | 461 (9.8%) |
| Overall | | | | |
| Any symptoms listed above, n (%) | 2421 (93.3%) | 1913 (70.3%) | 1229 (39.3%) | 1181 (25.1%) |
| With one symptom, n (%) | 298 (11.5%) | 515 (18.9%) | 456 (14.6%) | 424 (9.0%) |
| With two symptoms, n (%) | 289 (11.1%) | 456 (16.7%) | 366 (11.7%) | 352 (7.5%) |
| With ≥3 symptoms, n (%) | 1834 (70.6%) | 942 (34.6%) | 407 (13.0%) | 405 (8.6%) |

Percentages for symptoms are calculated based on the number of patients with data in each group.

24.2% (n=1137) residing in higher middle-income countries and 15.0% (n=706) residing in high-income countries. Participants were mostly of Arab/North African ethnicity (n=2145; 45.7%) or South Asian ethnicity (n=960; 20.4%). Current or past smoking was reported by 26.9% (n=1265) of participants. The most frequently recorded comorbidities were hypertension (22.9%; n=1075), diabetes mellitus (15.7%; n=737) and dyslipidaemia (8.0%; n=375). Partial or complete vaccination was reported by 26.3% (n=1234) of participants at the time of enrolment (table 1).

### Long COVID prevalence and symptomatology

Long COVID symptoms at 180 days after enrolment were reported in 1181 (25.1%) participants. Prevalence was 25.3% (904/3578) in outpatients and 24.8% (277/1119) in inpatients (table 1). At 45 days after enrolment, symptoms were reported in 39.3% (1229/3124) of cases, and symptom prevalence was 41.0% (993/2422) in outpatients and 33.6% (236/702) in inpatients (online supplemental file 2A,B).

Most frequently reported symptoms at day 180 were sleeping disorders (n=601; 12.8%), joint pain (n=461; 9.8%), fatigue (n=410; 8.7%) and headaches (n=382; 8.1%) (table 2). In most cases, more than one symptom was reported (n=757; 16.1%) (table 2). Symptom reporting frequencies were comparable between inpatients and outpatients with long COVID (online supplemental file 2A,B).

Subanalysis of symptomatology by age group revealed that symptoms suggestive of comorbidities were more frequently present in the upper age tertile (eg, fatigue, joint pain, shortness of breath, concentration impairment and memory impairment). Subanalysis by country income level and ethnicity did not reveal a particular symptom pattern for any specific group (online supplemental file 2C–E).

### Risk factors for long COVID

In multivariable analysis, male sex was associated with a reduced risk of long COVID (aOR: 0.81 (0.68 to 0.95); p=0.009), and more advanced age was associated with an increased risk of long COVID (aOR: 1.02 (1.02 to 1.03); p<0.001). Participants from lower middle-income countries more frequently reported symptoms than patients in upper middle-income countries and high-income countries (29.8% (850/2854) vs 20.1% (229/1137) vs 14.4% (102/706)). Participants from lower middle-income countries remained at increased risk of long COVID compared with patients from high-income countries in multivariable analysis (aOR: 1.53 (1.10 to 2.14); p=0.012). Prevalence varied between participants of different ethnic backgrounds, between 11.8% (113/960) for patients of South Asian ethnicity and 36.1% (775/2145) for patients of Arab/North African ethnicity (aOR: 0.18 (0.14 to 0.23); p<0.001; for South Asian vs Arab/North African ethnicity) (table 3).

Patients who were hospitalised with COVID-19 had an increased risk of long COVID compared with

**Table 3** Multivariable analysis

| | Overall (N=4697) | Long COVID at day 180 | | Unadjusted OR (95% CI) | Adjusted OR (95% CI) | P value* |
|---|---|---|---|---|---|---|
| | | Yes (N=1181) | No (N=3516) | | | |
| Age, mean (SD) | 45.9 (13.4) | 48.0 (14.1) | 45.2 (13.1) | 1.02 (1.01 to 1.02) | 1.02 (1.02 to 1.03) | <0.001 |
| Male sex | 2828 (60.2%) | 609 (51.6%) | 2219 (63.1%) | 0.62 (0.54 to 0.71) | 0.81 (0.68 to 0.95) | 0.009 |
| Ethnicity | | | | | | |
| Arab/North African | 2145 (45.7%) | 775 (65.6%) | 1370 (39.0%) | *reference* | *reference* | |
| White European | 805 (17.1%) | 197 (16.7%) | 608 (17.3%) | 0.57 (0.48 to 0.69) | 0.77 (0.48 to 1.24) | 0.285 |
| Latin American | 398 (8.5%) | 59 (5.0%) | 339 (9.6%) | 0.31 (0.23 to 0.41) | 0.39 (0.22 to 0.68) | <0.001 |
| South Asian | 960 (20.4%) | 113 (9.6%) | 847 (24.1%) | 0.24 (0.19 to 0.29) | 0.18 (0.14 to 0.23) | <0.001 |
| Other | 389 (8.3%) | 37 (3.1%) | 352 (10.0%) | 0.19 (0.13 to 0.26) | 0.15 (0.10 to 0.23) | <0.001 |
| Country income status | | | | | | |
| High-income | 706 (15.0%) | 102 (8.6%) | 604 (17.2%) | *reference* | *reference* | |
| Upper middle-income | 1137 (24.2%) | 229 (19.4%) | 908 (25.8%) | 1.49 (1.16 to 1.93) | 0.95 (0.64 to 1.40) | 0.780 |
| Lower middle-income | 2854 (60.8%) | 850 (72.0%) | 2004 (57.0%) | 2.51 (2.01 to 3.14) | 1.53 (1.10 to 2.14) | 0.012 |
| Smoking | | | | | | |
| Never | 3432 (73.1%) | 900 (76.2%) | 2532 (72.0%) | *reference* | *reference* | |
| Former | 442 (9.4%) | 89 (7.5%) | 353 (10.0%) | 0.71 (0.56 to 0.91) | 0.76 (0.57 to 0.99) | 0.045 |
| Current (within 1 year of quitting) | 823 (17.5%) | 192 (16.3%) | 631 (17.9%) | 0.86 (0.72 to 1.02) | 0.79 (0.64 to 0.98) | 0.030 |
| Diabetes mellitus | 737 (15.7%) | 193 (16.3%) | 544 (15.5%) | 1.07 (0.89 to 1.28) | 0.74 (0.60 to 0.92) | 0.006 |
| Hypertension | 1075 (22.9%) | 318 (26.9%) | 757 (21.5%) | 1.34 (1.15 to 1.56) | 1.31 (1.07 to 1.59) | 0.009 |
| Dyslipidaemia | 375 (8.0%) | 115 (9.7%) | 260 (7.4%) | 1.35 (1.07 to 1.70) | 1.16 (0.85 to 1.59) | 0.351 |
| Cardiovascular disease | 212 (4.5%) | 80 (6.8%) | 132 (3.8%) | 1.86 (1.40 to 2.48) | 1.22 (0.83 to 1.79) | 0.322 |
| Lung disease | 310 (6.6%) | 54 (4.6%) | 256 (7.3%) | 0.61 (0.45 to 0.82) | 0.46 (0.33 to 0.63) | <0.001 |
| Kidney disease | 100 (2.1%) | 11 (0.9%) | 89 (2.5%) | 0.36 (0.19 to 0.68) | 0.62 (0.31 to 1.27) | 0.191 |
| Immunosuppressed | 84 (1.8%) | 4 (0.3%) | 80 (2.3%) | 0.15 (0.05 to 0.40) | 0.38 (0.13 to 1.15) | 0.086 |
| Cancer | 20 (0.4%) | 6 (0.5%) | 14 (0.4%) | 1.28 (0.49 to 3.33) | 0.99 (0.35 to 2.84) | 0.991 |
| Vaccination status | | | | | | |
| Confirmed not vaccinated | 3444 (73.3%) | 1037 (87.8%) | 2407 (68.5%) | *reference* | *reference* | |
| Partially vaccinated | 303 (6.5%) | 37 (3.1%) | 266 (7.6%) | 0.32 (0.23 to 0.46) | 0.50 (0.34 to 0.73) | <0.001 |
| Fully vaccinated | 931 (19.8%) | 106 (9.0%) | 825 (23.5%) | 0.30 (0.24 to 0.37) | 0.34 (0.27 to 0.43) | <0.001 |
| Unknown | 19 (0.4%) | 1 (0.1%) | 18 (0.5%) | 0.13 (0.02 to 0.97) | 0.19 (0.02 to 1.46) | 0.109 |
| Patient type | | | | | | |
| In | 1119 (23.8%) | 277 (23.5%) | 842 (23.9%) | 0.97 (0.83 to 1.14) | 2.04 (1.63 to 2.54) | <0.001 |
| Out | 3578 (76.2%) | 904 (76.5%) | 2674 (76.1%) | *reference* | *reference* | |
| Treatment | | | | | | |
| ASA in ASA trial+colchicine in COL trial | 1175 (25.0%) | 287 (24.3%) | 888 (25.3%) | 0.90 (0.75 to 1.09) | 0.92 (0.75 to 1.12) | 0.413 |
| ASA in ASA trial+control in COL trial | 1176 (25.0%) | 300 (25.4%) | 876 (24.9%) | 0.96 (0.80 to 1.15) | 0.97 (0.79 to 1.18) | 0.737 |
| Control in ASA trial+colchicine in COL trial | 1173 (25.0%) | 285 (24.1%) | 888 (25.3%) | 0.90 (0.74 to 1.08) | 0.89 (0.73 to 1.08) | 0.275 |
| Control in ASA trial+control in COL trial | 1173 (25.0%) | 309 (26.2%) | 864 (24.6%) | *reference* | | |

*P value for adjusted OR.

outpatients (aOR: 2.04 (1.63 to 2.54); p<0.001). Vaccination conferred a protective effect when compared with unvaccinated participants (aOR: 0.34 (0.27 to 0.43); p<0.001 for fully vaccinated individuals and aOR: 0.50 (0.34 to 0.73); p<0.001 for partially vaccinated individuals) (table 3). Stratified presentation of baseline study characteristics by vaccination status is available in online supplemental file 3.

Several comorbidities were associated with long COVID. Hypertension conferred an increased risk (aOR: 1.31 (1.07 to 1.59); p=0.009), whereas diabetes mellitus (aOR: 0.74 (0.60 to 0.92); p=0.006), and the presence of lung disease (aOR: 0.46 (0.33 to 0.63); p<0.001) conferred a decreased risk of long COVID. Other recorded comorbidities, dyslipidaemia, cardiovascular disease, kidney disease, immunosuppression and cancer were not significantly associated with long COVID. Smokers had a marginally reduced risk for long COVID (aOR: 0.79 (0.64 to 0.98); p=0.030) (table 3). Randomised treatment did not affect the prevalence of long COVID (table 3).

In subanalysis of inpatient and outpatient groups, the increased risk of long COVID is in females and hypertensive patients in the subanalysis of inpatients but not outpatients. The increased risk of long COVID in patients residing in lower middle-income countries was only significant in outpatients. The protective effects conferred by prior lung disease, current smoking and diabetes were only significant in outpatients. The effects of ethnicity, former smoking and prior vaccination against SARS-CoV-2 remained largely consistent between inpatients and outpatients (online supplemental file 4A,B).

## DISCUSSION

This study is the first to systematically assess long COVID symptoms in various high-income and middle-income countries. Symptoms of long COVID were reported in a quarter of the cases after symptomatic COVID-19 in this study. We demonstrated that the burden of long COVID varies between participants of different ethnic backgrounds, and that participants from lower middle-income countries are at an increased risk compared with those from high-income countries. This study further adds to a growing body of evidence indicating that disease severity and vaccination status are important predictors of the risk of long COVID.

Estimates for the prevalence of long COVID symptoms vary widely.[15] While long COVID symptoms in low- and middle-income countries remain understudied, prevalence estimates ranging between 2% and 66.7% have been reported.[16 17] Differences in study design and patient selection may explain the variability in reported prevalence and preclude the accurate estimation of the true burden of long COVID.[15] This study systematically assessed symptoms of long COVID in a multinational trial conducted mainly in middle-income countries. This RCT applied the same inclusion and exclusion criteria across settings and revealed considerable variation in long COVID prevalence between ethnicities and a higher prevalence in lower middle-income settings.

The increased risk of long COVID for participants residing in lower middle-income countries, the lowest stratum of country income level represented in this cohort—Egypt, India, Nepal, Pakistan and the Philippines—is a concerning signal. Given the significant variability in symptom reporting between participants of different ethnicities, with very high rates of long COVID reported by participants of Arab/North African ethnicity, this variable was included in the logistic regression model. While ethnicity did attenuate the effect of country income level on the outcome, a statistically significant risk remained. The increased risk for long COVID in lower middle-income countries may reflect underlying health disparities between these and high-income countries. The encountered variability in the prevalence of long COVID among different ethnical groups encountered in this study may be the result of underlying environmental or genetic variation. Alternatively, they may be explained by cultural and linguistic differences, resulting in differential subjective symptom reporting rates.

In addition to a negative impact on quality of life and potential negative longer-term health effects, preliminary research indicates that a diagnosis of long COVID is associated with significantly increased immediate healthcare costs.[18] Our results thus suggest that the burden to health and healthcare-related costs may fall disproportionately on countries with the least capacity to carry them, and most frequently affect individuals that may be underrepresented in clinical trials of interventions aimed to combat long COVID.

This study also provides new insights into risk factors for long COVID. Findings that female sex and older age predict long COVID are in line with most other reports,[19] with the exception of one large propensity-matched case–control study of outpatients in the USA, which demonstrated a decreased risk with age in corrected analysis.[9 19] We were unable to replicate these findings in a separate analysis of outpatients. Hospitalisation with COVID-19 was the strongest predictor of risk for subsequent long COVID symptoms which reflects the well-described association between the severity of the initial COVID-19 episode and long COVID.[19 20]

While the presence of comorbidities likely plays a role in the aetiology of long COVID, pathogenetic mechanisms are not yet fully elucidated. This study demonstrated an association between hypertension and long COVID symptoms, but not with other cardiovascular risk factors or chronic kidney disease (CKD). These findings seem to partly align with the most comprehensive systematic review and meta-analysis on comorbidity risk factors for long COVID to date, which likewise shows an absence of association for CKD, and a small risk increase for ischaemic heart disease.[19] However, this review did not perform a meta-analysis for hypertension as a risk factor due to the low number of available studies.[19] Interestingly, several smaller studies have now shown an

increased risk of long COVID in hypertensive patients. Of six studies showing such effects, two were performed in sub-Saharan Africa,[21 22] two in Middle Eastern countries,[23 24] one in Russia[25] and one in Sweden.[26] The present study is the largest to date, showing an association between hypertension and long COVID. While the preponderance of evidence for this association in the literature seems to originate from African and Middle Eastern settings, the association was consistently encountered in participants from all ethnicities in this study. It has been suggested that the association may be due to overlapping pathophysiological pathways of SARS-CoV-2 infection and hypertension involving endothelial and cardiomyocyte damage, but further research is needed to prove this.[27]

This study revealed the protective effects of current smoking and pre-existing lung disease on long COVID, contradicting most of the available literature, which suggests strong correlations between pre-existing lung disease and long COVID and a small but significantly increased risk conferred by active smoking.[19] Likewise, diabetes mellitus was associated with a weak protective effect in this study, contradicting some of the available evidence, but concurring with a small study from Saudi Arabia showing a similar effect.[24]

The strongest protective factor for long COVID symptoms in this study was vaccination prior to presentation with acute COVID-19. Patients who were vaccinated had a threefold reduced risk of long COVID symptoms. These findings build on the large body of evidence that COVID-19 vaccination is an efficacious preventative tool for long COVID symptoms, and further support the value of vaccination for COVID-19.[11]

## Strengths and weaknesses

This study contributes a relatively large sample of prospectively collected data to the available literature on the epidemiology of long COVID. Strengths of the study include the prospective nature of data collection and the systematic assessment of long COVID symptoms through a structured questionnaire. The study design allowed for the study of long COVID across different geographical areas with equal patient inclusion and exclusion criteria, minimising the differences between populations. Several weaknesses of the study should be mentioned. The study did not assess long COVID symptom severity or metrics of quality of life at the 180-day timepoint, which would have enabled us to study the clinical impact of long COVID. Despite correction for measured covariables, residual confounding of the observed statistical correlations cannot be excluded due to the observational nature of this analysis. Despite the large number of countries and clinical centres that participated in the analysis, the findings may not be representative of individuals and regions that were not included. Reporting bias may have influenced the results of this study, as the primary outcome was based on self-reported symptoms.

## Final conclusion

Data from this large multi-country RCT identified long COVID symptoms in a quarter of patients with symptomatic COVID-19, and demonstrates independent risk increases for long COVID in patients from lower middle-income countries, patients who required admission for COVID-19 and patients who were unvaccinated for COVID-19. Research to further assess the health burden posed by long COVID to populations and regions outside the global North is urgently needed.

**Author affiliations**
[1]Internal Medicine, Groote Schuur Hospital, Cape Town, Western Cape, South Africa
[2]Infection and Immunity Research Institute, St George's University of London, London, UK
[3]Wellcome Discovery Research Platforms in Infection, Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Cape Town, South Africa
[4]Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada
[5]Department of Medicine, McMaster University Faculty of Health Sciences, Hamilton, Ontario, Canada

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**Disclaimer** The lead author affirms that this manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants. The ACT clinical trials were performed across 136 clinical sites in 15 countries. Each participating centre obtained local institutional review board or ethical committee approval. The details of the participating clinical sites and institutional review boards are available in the appendix of the paper describing the primary study outcomes: Eikelboom *et al*.[13 14] The appendix is available at https://doi.org/10.1016/S2213-2600(22)00298-3. Participants gave informed consent to participate in the study before taking part.

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**Data availability statement** Data are available upon reasonable request. Study materials including the protocol and statistical analysis plan are available online. Individual participant data will not be made publicly available. The ACT Trials Steering Committee will consider reasonable requests for specific additional

analyses on a cost recovery basis (waived for low-income and middle-income countries).



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**ORCID iD**

Lucas Etienne Hermans http://orcid.org/0000-0002-8741-5852

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