The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations

O'Mahoney, Lauren L ; Routen, Ash ; Gillies, Clare; Ekezie, Winifred ; Welford, Anneka; Zhang, Alexa ; Karamchandani, Urvi ; Simms-Williams, Nikita; Cassambai, Shabana ; Ardavani, Ashkon ; Wilkinson, Thomas J ; Hawthorne, Grace ; Curtis, Ffion ; Kingsnorth, Andrew P ; Almaqhawi, Abdullah ; Ward, Thomas ; Ayoubkhani, Daniel ; Banerjee, Amitava; Calvert, Melanie; Shafran, Roz

DOI:
10.1016/j.eclinm.2022.101762

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
O'Mahoney, LL, Routen, A, Gillies, C, Ekezie, W, Welford, A, Zhang, A, Karamchandani, U, Simms-Williams, N, Cassambai, S, Ardavani, A, Wilkinson, TJ, Hawthorne, G, Curtis, F, Kingsnorth, AP, Almaqhawi, A, Ward, T, Ayoubkhani, D, Banerjee, A, Calvert, M, Shafran, R, Stephenson, T, Sterne, JAC, Ward, H, Evans, RA, Zaccardi, F, Wright, S & Khunti, K 2023, 'The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: a systematic review and meta-analysis', *EClinicalMedicine*, vol. 55, 101762. https://doi.org/10.1016/j.eclinm.2022.101762

The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis

Lauren L. O'Mahoney,[a] Ash Routen,[a] Clare Gillies,[a,b] Winifred Ekezie,[a] Anneka Welford,[a] Alexa Zhang,[c] Urvi Karamchandani,[d] Nikita Simms-Williams,[e] Shabana Cassambai,[a] Ashkon Ardavani,[a] Thomas J. Wilkinson,[a] Grace Hawthorne,[a] Ffion Curtis,[a] Andrew P. Kingsnorth,[a] Abdullah Almaqhawi,[f] Thomas Ward,[g] Daniel Ayoubkhani,[b,h] Amitava Banerjee,[i,j] Melanie Calvert,[e,k,l] Roz Shafran,[c] Terence Stephenson,[c] Jonathan Sterne,[m] Helen Ward,[d] Rachael A. Evans,[g,n] Francesco Zaccardi,[a,b] Shaney Wright,[o] and Kamlesh Khunti[a,*]

[a]Diabetes Research Centre, University of Leicester, Leicester, UK
[b]Leicester Real World Evidence Unit, Diabetes Research Centre, University of Leicester, Leicester, UK
[c]Great Ormond Street Institute of Child Health, University College London, London, UK
[d]Faculty of Medicine, School of Public Health, Imperial College London, London, UK
[e]Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[f]Department of Family and Community Medicine, College of Medicine, King Faisal University, Al Ahsa, Saudi Arabia
[g]Department of Respiratory Sciences, University of Leicester, Leicester, UK
[h]Office for National Statistics, Government Buildings, Newport, UK
[i]Faculty of Population Health Sciences, Institute of Health Informatics, University College London, London, UK
[j]Department of Population Science and Experimental Medicine, University College London, London, UK
[k]NIHR Birmingham Biomedical Research Centre and NIHR Applied Research Collaboration West Midlands, University Hospital Birmingham and University of Birmingham, Birmingham, UK
[l]Birmingham Health Partners Centre for Regulatory Science and Innovation and Centre for Patient Reported Outcomes Research, University of Birmingham, Birmingham, UK
[m]Population Health Sciences, Bristol Medical School, University of Bristol, Bristol, UK
[n]NIHR Leicester Biomedical Research Centre, Respiratory Department, University Hospitals of Leicester NHS Trust, Leicester, UK
[o]Patient Partner, UK

eClinicalMedicine
2023;55: 101762

Published Online
https://doi.org/10.1016/j.eclinm.2022.101762

Summary

Background The aim of this study was to systematically synthesise the global evidence on the prevalence of persistent symptoms in a general post COVID-19 population.

Methods A systematic literature search was conducted using multiple electronic databases (MEDLINE and The Cochrane Library, Scopus, CINAHL, and medRxiv) until January 2022. Studies with at least 100 people with confirmed or self-reported COVID-19 symptoms at ≥28 days following infection onset were included. Patient-reported outcome measures and clinical investigations were both assessed. Results were analysed descriptively, and meta-analyses were conducted to derive prevalence estimates. This study was pre-registered (PROSPERO-ID: CRD42021238247).

Findings 194 studies totalling 735,006 participants were included, with five studies conducted in those <18 years of age. Most studies were conducted in Europe (n = 106) or Asia (n = 49), and the time to follow-up ranged from ≥28 days to 387 days. 122 studies reported data on hospitalised patients, 18 on non-hospitalised, and 54 on hospitalised and non-hospitalised combined (mixed). On average, at least 45% of COVID-19 survivors, regardless of hospitalisation status, went on to experience at least one unresolved symptom (mean follow-up 126 days). Fatigue was frequently reported across hospitalised (28.4%; 95% CI 24.7%–32.5%), non-hospitalised (34.8%; 95% CI 17.6%–57.2%), and mixed (25.2%; 95% CI 17.7%–34.6%) cohorts. Amongst the hospitalised cohort, abnormal CT patterns/x-rays were frequently reported (45.3%; 95% CI 35.3%–55.7%), alongside ground glass opacification (41.1%; 95% CI 25.7%–58.5%), and impaired diffusion capacity for carbon monoxide (31.7%; 95% CI 25.8%–3.2%).

Interpretation Our work shows that 45% of COVID-19 survivors, regardless of hospitalisation status, were experiencing a range of unresolved symptoms at ~ 4 months. Current understanding is limited by heterogeneous study design, follow-up durations, and measurement methods. Definition of subtypes of Long Covid is unclear, subsequently hampering effective treatment/management strategies.

*Corresponding author.
E-mail address: kk22@leicester.ac.uk (K. Khunti).

Funding No funding.

Keywords: Long Covid; Meta analyses; COVID-19

Research in context

Evidence before this study

Previous systematic reviews and meta-analyses have reported that patients globally suffer from a heterogeneous range of common ongoing symptoms including fatigue, malaise, altered smell and taste, breathlessness, and cognitive impairments. In this systematic review and meta-analysis, we searched MEDLINE, The Cochrane Library, Scopus, CINAHL, and medRxiv up to January 2022 for eligible studies. Studies with at least 100 people with confirmed or self-reported COVID-19 symptoms at ≥28 days following infection onset were included. The overall quality rating of included studies was poor (n = 14), fair (n = 62), or good (n = 118). Results were analysed descriptively, and random effects meta-analyses were conducted to derive prevalence estimates.

Added value of this study

This systematic review and meta-analysis provides the most comprehensive and contemporary review to date. To the best of our knowledge, no recent large-scale meta-analysis has reported both symptomology and abnormal/impaired investigation prevalence in a general population post SARS-CoV-2, both elements combined could be fundamental in identifying the mechanistic underpinning and subsequent clinical management of Long Covid. We included both hospitalised and non-hospitalised populations and excluded specialist study populations, such as patients treated in a specialist respiratory clinic, which may bias general population symptom prevalence estimates.

Implications of all the available evidence

Moving forward, harmonisation of data collection tools will be fundamental to improving the clinical utility of findings from systematic reviews of Long Covid. It is clear that given the high prevalence of persistent symptoms after 12 weeks (nearly 1 in 2 people) that healthcare services and policy need to prioritise Long Covid care, and in addition understand different sub-types of Long Covid to permit stratified healthcare and ensure services are not overwhelmed in future.

Introduction

As of July 2022, over 500 million confirmed cases of coronavirus disease 2019 (COVID-19) have been documented worldwide, leading to more than 6.3 million deaths.[1] The term Long Covid has since become internationally recognised within the literature, along with a range of other descriptors for prolonged or residual COVID-19 symptoms, including 'post-acute sequelae of COVID-19', 'ongoing COVID-19', 'chronic Covid syndrome', 'long-haul covid', and 'post-COVID-19'.[2] Like the condition itself, existing definitions of Long Covid are heterogeneous, and there is, as yet, no unified definition of Long Covid, and various descriptors exist based on the duration of symptoms, clustering or groups of symptoms, or a combination of both.

The number of people living with Long Covid worldwide is unknown, but the UK Office for National Statistics (ONS) estimated that 1.8 million people in the UK (2.8% of the population) were reporting COVID-19 symptoms lasting more than 4 weeks as of May 2022 (point in time prevalence estimate).[3] In the United States data from the Centre for Disease Control and Prevention estimated 7.5% of adults were still experiencing persistent symptoms three or more months after their initial COVID-19 diagnosis.[4]

A number of systematic reviews have reported patients globally suffering from a heterogeneous range of common ongoing symptoms (in some cases over 60 physical and psychological symptoms[5]), including fatigue, malaise, altered smell and taste, breathlessness, and cognitive impairments.[5–9] There is also concerning data of single or multiple organ impairment, even in low-risk individuals.[10,11] However, previous reviews have either focused largely on hospitalised populations,[5,7] are limited to studies with follow-up to ~ eight months, are published prior to March 2021 [5,7], and have included specialist study populations such as patients treated in a specialist respiratory clinic which may bias general population symptom prevalence estimates. Although more recent reviews and meta-analyses of the global burden of Long Covid are comprehensive, they are also somewhat limited by only including studies with a sample size of ≥323, again not excluding specialist study populations, and not including clinical investigations.[12] In addition to patient-reported outcome measures, clinical investigations can offer further insight into the mechanistic underpinning and

subsequent clinical management of Long Covid. To the best of our knowledge, no recent large-scale meta-analysis has reported both symptomology and abnormal/impaired investigation prevalence in a general population post SARS-CoV-2.

A greater understanding of Long Covid symptomology will provide important information to inform the identification, management and treatment of this condition. Therefore, the aim of this review is to systematically synthesise the global evidence base on the prevalence and symptomology of Long Covid in a general post COVID-19 population.

Methods

Search strategy and selection criteria

This systematic review and meta-analyses were conducted in accordance with Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) guidelines (supplemental file, Table S1) and was pre-registered at http://www.crd.york.ac.uk as CRD42021238247. We searched the following databases from 31st December 2019 (when the Wuhan Municipal Health Commission, China, first reported a cluster of cases of pneumonia in Wuhan, Hubei Province) to 21st January 2022: MEDLINE, The Cochrane Library, Scopus, CINAHL, and medRxiv. Pre-determined search terms and strategy are provided; see supplemental file, Table S2.

Studies were considered eligible if they included at least 100 people who previously had COVID-19 (either self-diagnosed or confirmed by a PCR, antigen or antibody test) and ongoing symptoms for a minimum of 28 days. We chose this definition of Long Covid to align with the comprehensive national data on Long Covid the ONS/NHS have been recording on "ongoing symptoms of COVID" from 4 to 12 weeks. All included studies must have reported the frequency of at least one symptom or clinical investigation; interventions, serology, histopathology, and clinical biomarkers were beyond the scope of this study. Exclusion criteria included: studies that failed to report if patients were hospitalised or not, those where the duration of follow-up could not be determined, case studies, and those where all patients were not assessed for a minimum of 28 days. We report outcomes reported in five or more studies across hospitalised, non-hospitalised, and mixed cohorts. As we were aiming to assess prevalence of Long Covid symptoms in a general population post-COVID-19, studies recruiting sub-groups of patients were excluded for example requiring critical care, specialist respiratory clinics, Long Covid groups, pregnant women, and health care workers to reduce selection bias. Titles, abstracts, and full-text articles identified through database searches were screened independently by two reviewers to determine whether they met the eligibility criteria using the online collaborative software Covidence (Melbourne, Australia). Disagreements were resolved by consensus of a third reviewer.

Data analysis

Data extraction was performed independently by one reviewer using a pre-specified and piloted data extraction form with a second reviewer checking for accuracy independently of the first. Fields included: study details, population demographics, frequency of relevant outcomes, COVID-19 context (e.g., hospitalisation status, time to follow-up). Two reviewers independently assessed the quality of the included studies. The study quality assessment tools of the National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) for quality assessment of observational cohort and cross-sectional studies and case series studies were used to assess the quality of included studies.[13] An overall quality rating of good, fair, or poor was determined for each study. Publication bias was assessed for the outcome 'one or more symptoms at follow-up' by hospital status using Egger's test.

Due to the multi-system nature of Long Covid we have presented prevalence of symptoms data by hospitalisation status and by the following systems/groupings: (i) systemic, (ii) pain, (iii) cardiopulmonary, (iv) gastrointestinal, (v) upper respiratory, (vi) neurological and neuromuscular, (vii) physiological and social, (viii) neurocognitive, abnormal imaging result, abnormal lung function, and (ix) other; see supplemental file, Figs. S1–S11.

Estimated symptom prevalence was pooled across studies. Random effects meta-analyses were used to allow for between study heterogeneity, and pooled prevalence was estimated using the inverse of the logit function. Hospitalised, non-hospitalised, and mixed populations were analysed separately. For studies reporting results for both hospitalised and non-hospitalised cohorts and the number of participants in each group was >100, the data were analysed separately. Where data results were presented separately by hospitalisation status, but with fewer than 100 participants in either group, the data was combined and categorised as mixed. Between study heterogeneity was quantified using the I-squared statistic,[14] and the heterogeneity was explored using sub-group and meta-regression techniques, where appropriate, to assess the impact of study level characteristics on the estimated prevalence of 'at least one symptom at follow-up'. A sensitivity analysis assessing the impact of study quality was also carried out for this outcome by removing studies categorised as poor quality, and recalculating the estimated pooled prevalence.

Role of the funding source

There was no funding source for this study.

Results

In total, 18,932 titles were identified through database searches, of which 194 were included in this review (Fig. 1). A total of 735,006 participants were included in this analysis with the number of people assessed at follow-up ranging from 100 to 437,943. Median age of the cohorts ranged from 3 to 74 years, with five studies conducted in those <18 years of age. Studies were conducted in Europe (n = 106), Asia (n = 49), North America (n = 26), South America (n = 5), Africa (n = 4), Oceania (n = 2), and across multiple continents (n = 2). Time to follow-up ranged from '>28 days' to 387 days. For study and participant characteristics of included studies; see supplemental file, Table S3. This analysis includes data from hospitalised (n = 122), non-hospitalised (n = 18), and hospitalised and non-hospitalised combined (mixed) (n = 54) patients. Of note, for 144 (74%) of the 194 studies included,

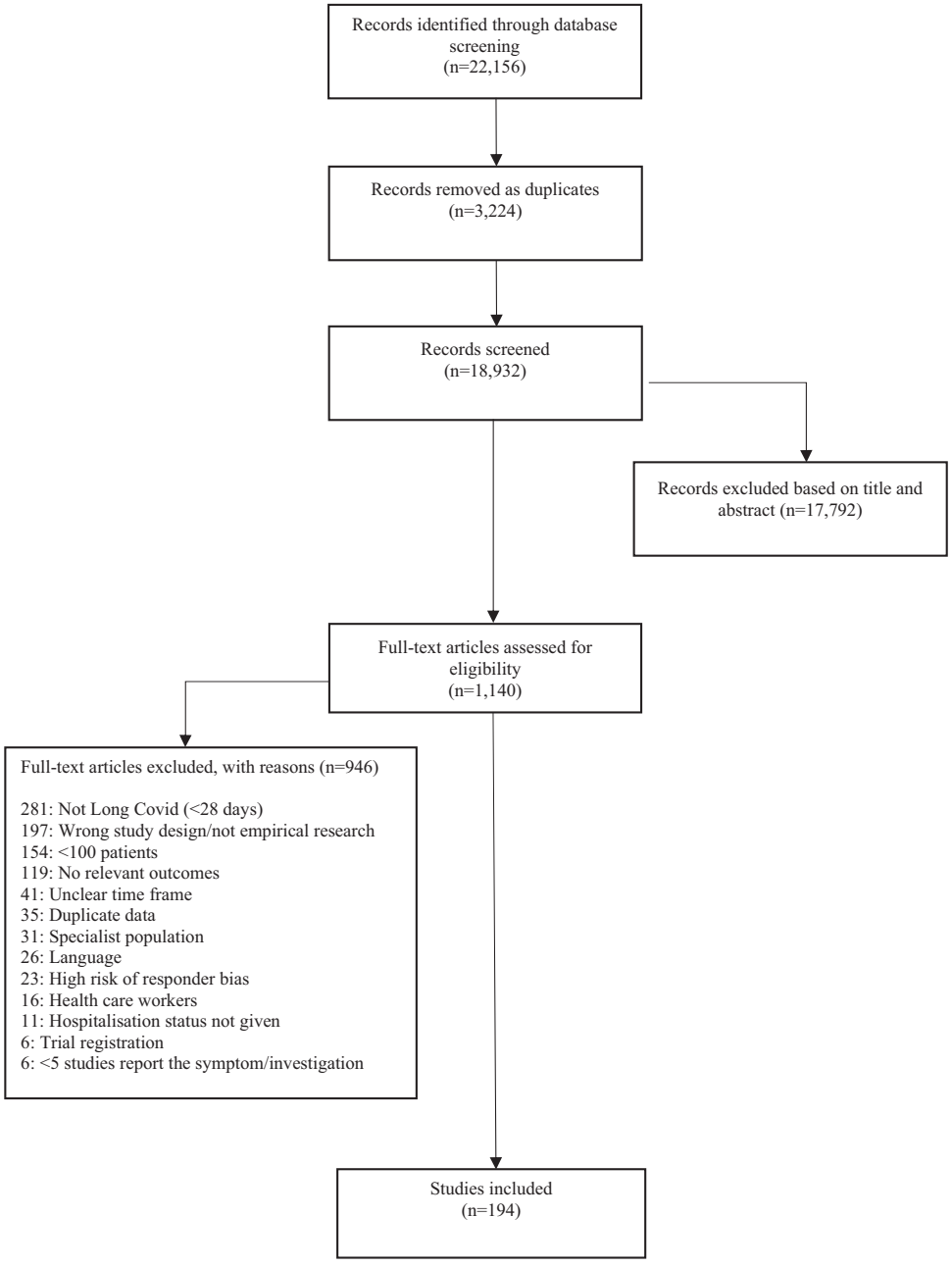

Fig. 1: PRISMA flow diagram. Delineation of study selection.

ethnicity/race of the populations was not reported. The overall quality rating of included studies was poor (n = 14), fair (n = 62), or good (n = 118); see supplemental file, Tables S4–S6. Publication bias was not found to be statistically significant for the outcome 'one of more symptoms at follow –up, with p-values from the Egger's test of 0.097, 0.277 and 0.892 for the sub-groups of hospitalised, non-hospitalised, and mixed respectively.

With an average study follow-up time of 126 days, the pooled prevalence of COVID-19 survivors experiencing at least one unresolved symptom, regardless of hospitalisation status, was 45%. Ranked symptom prevalence is presented by hospitalisation status: hospitalised (Fig. 2), non-hospitalised (Fig. 3), and mixed (Fig. 4). In the hospitalised group, 46 symptoms and 12 investigations were reported (Fig. 2). Amongst hospitalised patients, the pooled prevalence of COVID-19 survivors experiencing at least one symptom at a mean follow-up of 126 days was 52.6% (95% CI 43.5%–61.6%; 48 studies). The five most prevalent symptoms reported were fatigue (28.4%; 95% CI 24.7%–32.5%; 70 studies), pain/discomfort (27.9%; 95% CI 21.2%–35.6%; 10 studies), impaired sleep (23.5%; 95% CI 18.1%–29.8%; 34 studies), breathlessness (22.6%; 95% CI 18.3%–27.4%; 70 studies), and impaired usual activity (22.3%; 95% CI 14.2%–33.39%; 10 studies). Among patients from the hospitalised cohort who underwent clinical investigations, there were lasting changes in lung structure/function at follow-up. Of investigations, abnormal CT patterns/x-rays were frequently reported (pooled prevalence of 45.3%; 95% CI 3.3%–55.7%; 13 studies), alongside ground glass opacification (41.1%; 95% CI 25.7%–58.5%; 10 studies), and impaired diffusion capacity for carbon monoxide (31.7%; 95% CI 25.8%–38.2%; 13 studies). In addition to ground glass opacification, fibrotic changes (26%), reticular patterns (12%), and consolidations (2%) were also reported (see Fig. 2). Functionally, total lung capacity (TLC) (26%), forced expiratory volume in 1 s (FEV_1) (10%), forced vital capacity (FVC) (9%), and exercise capacity (19%) were also impaired in a proportion of the participants. See Fig. 2 for all symptom and investigation prevalence estimates in hospitalised study populations.

In the non-hospitalised group, the pooled prevalence of COVID-19 survivors experiencing at least one symptom at follow-up was 34.5% (95% CI 21.9%–49.7%; 11 studies). Although the overall number of studies reporting each symptom across cohorts was ≥5, the number of studies within the non-hospitalised cohort was often less. The most frequent symptoms amongst non-hospitalised patients where more than one study was included in the analysis were fatigue (34.8%; 95% CI 17.6%–57.2%; 12 studies), breathlessness (20.4%; 95% CI 13.9%–29.1%; 9 studies), muscle pain/myalgia (17.0%; 95% CI 5.0%–44.2%; 9 studies), affected sleep (15.3%, 95% CI 3.8%–45.4%; 9 studies), and loss of sense of smell (12.7%; 95% CI: 9.5, 16.7). For non-hospitalised patients, the variability in estimated prevalence between studies was high. See Fig. 3 for all symptom and investigation prevalence estimates in non-hospitalised study populations.

In the mixed group of hospitalised and non-hospitalised patients, the pooled prevalence of COVID-19 survivors experiencing at least one symptom at follow-up was 37.8% (95% CI 31.8%–44.2%; 36 studies). The most frequently described symptoms were fatigue (25.2%; 95% CI 17.7%–34.6%; 33 studies), breathlessness (18.2%; 95% CI 12.6%–25.6%; 26 studies), impaired usual activity (14.9%; 95% CI 6.7%–29.9%; 5 studies), loss of sense of taste (14.9%; 95% CI 6.7%–29.9%; 9 studies), and loss of sense of smell (14.1%; 95% CI 4.9%–34.5%; 14 studies). See Fig. 4 for all symptom and investigation prevalence estimates in mixed hospitalised and non-hospitalised study populations.

Between studies heterogeneity was high for the majority of meta-analyses, ranging from 2 to 99.9%, and reasons for this were explored with meta-regression and sub-group analyses. Meta-regression showed no association between the study level characteristics of average age (mean or median), % male, or average follow-up time (mean or median); and estimated prevalence of 'one or more symptom' in the study cohort (Table 1). The prevalence estimate for one symptom at a mean follow-up of 126 days, regardless of hospitalisation status, was 44.8% (95% CI 38.6%–51.2%). A comparison of the prevalence of 'one or more symptoms' in a hospitalised population across continents showed the pooled prevalence was higher in Europe, compared to both North America and Asia (estimated pooled prevalence estimates for Europe of 62.7% (95% CI 56.5%–68.5%), North America 38.9% (95% CI 24.0%–56.3%), Asia 40.9% (95% CI 34.5%–47.7%), and Other 24.8% (95% CI 2.0%–84.1%); with this difference being statistically significant between Europe and Aisa (Supplemental Table S7). Moreover, categorising follow-up time to either <12 weeks and ≥12 weeks showed no statistically significant difference, although in all categories (hospitalised, non-hospitalised, or mixed), the estimated pooled prevalence was numerically reduced in studies with longer follow-up by an estimated 3.72, 7.57 and 10.61 percentage points, respectively (Tables 2 and 3). See Supplemental Table S8 for prevalence estimates of at least one symptom at various follow-up time points. The sensitivity analyses which removed studies categorised as being of poor quality, also showed no significant change in the estimated prevalence of the outcome at least one symptom at follow-up (Supplementary Table S9).

Discussion

We report (using 194 studies including 735,006 participants) on the prevalence and symptomology of Long

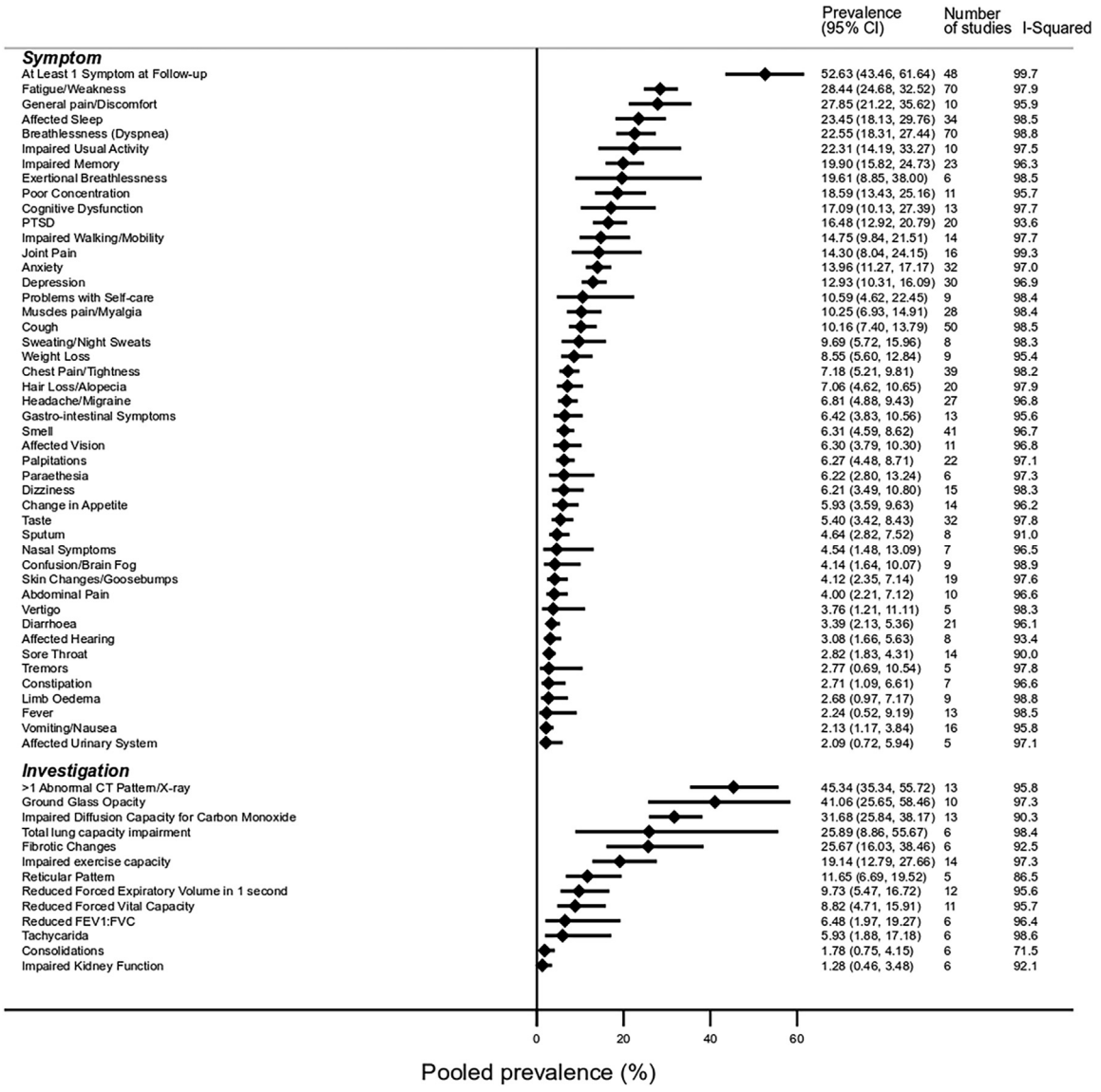

Fig. 2: Prevalence of symptoms (ranked) in the hospitalised population. In total 46 symptoms and 12 investigations were reported. PTSD, Post-traumatic stress disorder; FEV1:FVC, ratio of the forced expiratory volume in the first 1 s to the forced vital capacity of the lungs.

Covid in a general (i.e., non-specialist clinic or vulnerable/at-risk population) population post-COVID-19. This systematic review shows that at an average follow-up time of 126 days, 45% of COVID-19 survivors, regardless of hospitalisation status, go on to experience at least one unresolved symptom. In addition, the prevalence of ongoing symptoms appears to be higher in post-hospitalised cohorts compared to non-hospitalised populations.

Fatigue, disturbed sleep, and breathlessness were highly prevalent symptoms reported across hospitalised, non-hospitalised, and mixed cohorts. Amongst the hospitalised cohort, several clinical investigations showed lasting changes in lung structure/function at follow-up. Our updated findings correspond with previous research that reports Long Covid as a complex, multifaceted condition involving a range of symptoms affecting multiple systems.[5,7,8] Changes in pulmonary function are similar to those observed following other viral infections including SARS and MERS.[15] Even when excluding studies with less than 100 patients and those in specialist populations, variability in estimated prevalence between studies remained high, particularly in the non-hospitalised cohort. In addition to varying study designs, different follow-up measurement tools and a wide range of follow-up durations, observed

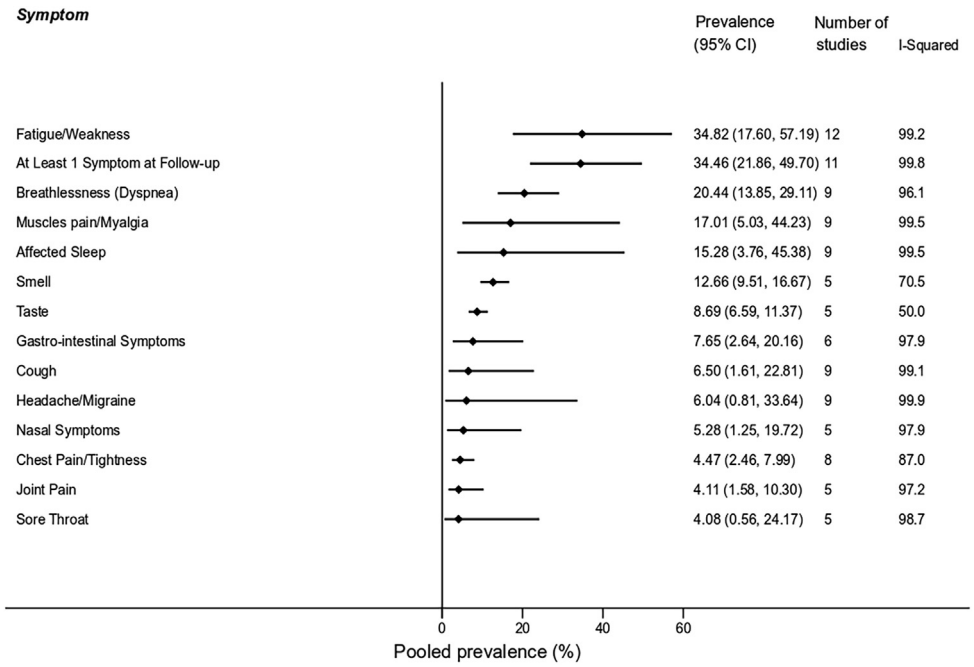

Fig. 3: Prevalence of symptoms (ranked) in the non-hospitalised population. In total 14 symptoms were reported.

heterogeneity between studies may be explained by the lack of standardised data collection tools, particularly in studies of non-hospitalised populations. This emphasizes the need for tools to harmonise data collection, such as the Symptom Burden Questionnaire™ which comprehensively assesses a wide range of symptoms highlighted by existing literature and co-production with patients, researchers and clinicians.[16] Without future studies using tools to harmonise data collection, the variability in estimated prevalence between studies is likely to remain high making data difficult to interpret. Future research should aim to map symptom classifications onto a core outcome set[17] for Long Covid to help harmonise findings. The reasons as to why so many patients are experiencing Long Covid remains unknown; proposed physiological mechanisms underpinning the persistent symptoms include: organ damage, inflammation, altered immune status and psychological effects.[18]

Meta-regression analyses of 'one or more symptoms' showed no association with age, sex, or average follow-up time. Previous meta-analyses have reported the risk of Long Covid is higher in females.[12] Regional differences showed the pooled prevalence of Long Covid was significantly higher in Europe compared to both North America and Asia, whereas previously systematic reviews have reported the highest prevalence in Asia.[12]

Differences in the summary statistic (i.e., estimated odds ratio/incidence etc), significant levels of heterogeneity across stratified meta-analyses, and exclusion of specialist clinics could be partly responsible for the differences in geographical findings across reviews and a lack of difference by sex in the present review. In addition, this may reflect the poor specificity of 'at least symptom' as a measure of Long Covid rather than homogeneity in Long Covid prevalence between men and women. Symptoms such as headache and tiredness are common in the general population at any given time, irrespective of age, sex, etc. Long Covid is typically characterised by relapsing and remitting symptoms,[19–21] and so the use of a single symptom over a period of time may be too crude an outcome for detecting group differences.

This systematic review intended to assess the prevalence and symptomology of Long Covid among hospitalised and non-hospitalised patients when stratified by age, sex, ethnicity, and deprivation, as originally outlined in the PROSPERO protocol. Unfortunately, only 26% (50/194 studies) of included studies reported ethnicity/race, none of which reported outcomes by ethnic group, and indices of deprivation were not reported in any of the included studies. This highlights the need for future Long Covid research to report outcomes by ethnicity (particularly given the disproportionate impact of acute COVID-19 on ethnic minorities[22,23]) and other-underserved groups or regions (e.g. Africa). As well as heterogeneity in prevalence estimates between studies, there is considerable variance within and between reported symptoms that will also likely be a function of variable study design, follow-up

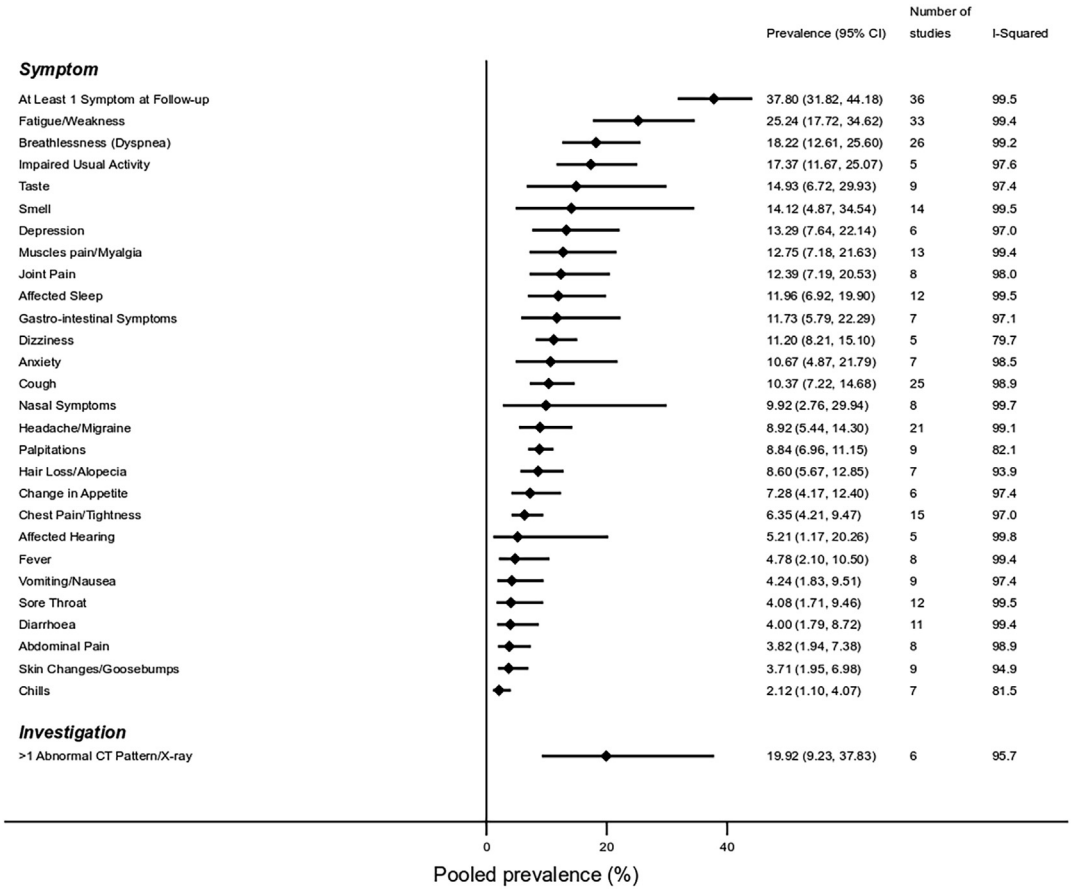

Fig. 4: Prevalence of symptoms (ranked) in the mixed (hospitalised and non-hospitalised) population. In total 28 symptoms and 1 investigation were reported. CT, Computed tomography.

durations, and symptoms measurement methods employed. For the general reader and the wider medical community, it makes the reported prevalence estimates hard to interpret without an appreciation and close reading of the methodological complexity that characterises current Long Covid research. As longer term-data from larger well designed prospective cohort studies become available, and population level routine data sources are explored and improved,[24,25] a clearer picture of the natural history and long-term sequelae after COVID-19 may emerge.

There are a number of strengths to this review. First it is the most comprehensive and contemporary review to date, systematically synthesising the global evidence on the prevalence and symptomology of Long Covid in a general population. In addition, we adhered to key guidelines on the development, conduct and reporting of reviews (PRISMA) guidelines, and pre-registered the review protocol on PROSPERO. There are however several limitations to this review, and the studies it includes, that require highlighting. First, the symptom data included in this review were collected from a wide range of self-report tools, limiting the standardisation of reporting. This may be related to the limited number of symptom burden assessment tools available during the early phases of the COVID-19 pandemic. Second, as other reviews have noted,[7] there is no unified consensus on the definition of Long Covid, in particular with time components of continuing symptoms ranging from 4 to 12 weeks following infection onset.

We chose to include studies with a minimum follow-up of 28 days, resulting in the synthesis of data collected from a wide range of follow-up periods (>28 days–387 days). Third, only a small number of included studies (22/194 studies) had control/comparator groups. Without a control group, it is hard to make comparison on the burden of Long Covid and symptom profiles between SARS-CoV-2 test positive and test negative individuals, as some reported Long Covid symptoms are non-specific and prevalent in the general population, and some individuals may experience symptoms due to comorbidities or due to broader impacts of the pandemic. Fourth, while we excluded studies recruiting from specific Long COVID-related clinics and aimed for

	Hospitalisation status	Regression coefficient (95%CI)	p-value	n
Age	Hospitalised	0.52 (−0.11, 1.17)	0.102	34
	Non-hospitalised	0.09 (−1.58, 1.75)	0.902	9
	Mixed	−0.49 (−1.22, 0.23)	0.170	24
% Male	Hospitalised	−0.58 (−1.34, 0.18)	0.132	37
	Non-hospitalised	−0.95 (−2.02, 0.13)	0.077	9
	Mixed	−0.33 (−0.98, 0.32)	0.308	30
Follow-up time	Hospitalised	0.01 (−0.05, 0.07)	0.676	42
	Non-hospitalised	0.03 (−0.21, 0.28)	0.679	5
	Mixed	−0.07 (−0.19, 0.05)	0.240	26

n, number of studies.

Table 1: **Meta-regression analyses assessing the impact of study level characteristics on the estimated prevalence of 'at least one symptom at follow-up' showed no association.**

inclusive samples, it is possible that people with persistent symptoms are more likely to respond to requests for follow-up surveys or visits, which would tend to overestimate the prevalence of Long COVID.

A further limitation of the evidence base within our review is the geographical homogeneity of the included studies. The majority of included data derive from Europe (n = 106 studies, 55%), with ≤5 studies per continent on Long Covid prevalence in Africa, Oceania, and South America. There is a need for more work to define the burden and long-term effects of COVID-19 in regions with a high density of low and middle income countries, such as Africa,[26] to ensure resources are appropriately targeted and utilised, and culturally appropriate intervention strategies are developed. As of July 2022, over 12 billion vaccine doses have been administered globally[1]; however, assessing the impact of vaccination status on Long Covid prevalence was beyond the scope of the current review. Future reviews should seek to investigate the prevalence of Long Covid across vaccination status and different variants of SARS-CoV-2.

This systematic review provides the most contemporary and comprehensive estimates on the prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations. It is evident that a large proportion of patients (45% at an average 126 days) are still experiencing a range of unresolved symptoms, with fatigue, disturbed sleep, and breathlessness highly prevalent symptoms reported across hospitalised, non-hospitalised, and mixed cohorts. Due to the heterogeneity of included study designs, populations, and methodology, our prevalence estimates and identification of long-term health effects should be interpreted with caution. Nevertheless, it is clear that a large proportion of patients appear to experience unresolved symptoms, of which there are many, with heterogeneity in number and severity experienced.

Moving forward, harmonisation of data collection tools will be fundamental to improving the clinical utility of findings from Long Covid systematic reviews. It is clear that given the high prevalence of persistent symptoms after 12 weeks (nearly 1 in 2 people) that healthcare services and policy need to prioritise Long Covid care, and in addition understand different subtypes of Long Covid to permit stratified healthcare and ensure services are not overwhelmed in future.

Contributors

LLO, AR, DA, AB, MC, RS, TS, JS, HW, RAE, and KK conceptualised the study. LLO, AR, WE, AW, AZ, UK, NS-W, SC, AA, TJW, GH, FC, APK, AA, and TW performed data curation. CG and FZ carried out the statistical analyses and accessed and verified the underlying study data. LLO wrote the first draft of the report with input from AR. All authors acquired the data. SW reviewed the final draft as a patient and public representative. All authors critically revised the manuscript for intellectual content. All authors had full access to the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declaration of interests

This work was supported by National Institute for Health Research (NIHR) ARC East Midlands. AB is PI of the NIHR funded STIMULATE-ICP study (COV-LT2-0043) and has also received other research funding from Astra Zeneca, NIHR, BMA, UK Research and Innovation (UKRI) and EU. MC is Director of the Birmingham Health Partners Centre for Regulatory Science and Innovation, Director of the Centre for the Centre for Patient Reported Outcomes Research and is a NIHR Senior Investigator. MC receives funding from the NIHR, UKRI, NIHR Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre, NIHR ARC West Midlands, UK SPINE, European Regional Development Fund–Demand Hub and Health Data Research UK at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Innovate UK (part of UKRI), Macmillan Cancer Support, UCB Pharma, Janssen, GSK and Gilead. She is senior author of the Symptom Burden Questionnaire™ for Long COVID. MC has received personal fees from Aparito Ltd, CIS Oncology, Takeda, Merck, Daiichi Sankyo, Glaukos, GSK and the Patient-Centered Outcomes Research Institute (PCORI) outside the submitted work. In addition, a family member owns shares in GSK. TS and RS receive funding from the NIHR, and by the UKRI who have awarded funding grant number COVLT0022. All research at

Great Ormond Street Hospital NHS Foundation Trust and UCL Great Ormond Street Institute of Child Health is made possible by the NIHR Great Ormond Street Hospital Biomedical Research Centre. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. HW is an NIHR Senior Investigator Award, and acknowledges support from the NIHR Imperial Biomedical Research Centre, Health Data Research UK, NIHR Applied Research Collaborative North West London, and the Wellcome Trust. KK is Chair of the Ethnicity Subgroup of the UK Scientific Advisory Group for Emergencies (SAGE) and Member of SAGE and also Chair of the National Long Covid working group which reports to the Chief Medical Officer. TW receives funding from the NIHR, the views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. JS receives funding from the NIHR and UKRI.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2022.101762.

References

1 WHO. WHO Coronavirus (COVID-19) dashboard. https://covid19.who.int/; 2021. Accessed January 18, 2022.

2 WHO. *A clinical case definition of post COVID-19 condition by a Delphi consensus*. 2021:2021.

3 Office for National Statistics. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 6 May 2022. https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/6may2022; 2022. Accessed May 4, 2022.

4 National Centre for Health Statistics. Nearly one in five American adults who have had COVID-19 still have "Long COVID". https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/20220622.htm; 2022. Accessed September 27, 2022.

5 Michelen M, Manoharan L, Elkheir N, et al. Characterising long COVID: a living systematic review. *BMJ Global Health*. 2021;6(9):e005427.

6 Aiyegbusi OL, Hughes SE, Turner G, et al. Symptoms, complications and management of long COVID: a review. *J R Soc Med*. 2021;114(9):428–442.

7 Groff D, Sun A, Ssentongo AE, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: a systematic review. *JAMA Netw Open*. 2021;4(10):e2128568.

8 Lopez-Leon S, Wegman-Ostrosky T, Perelman C, et al. More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis. *medRxiv*. 2021. https://doi.org/10.1101/2021.01.27.21250617.

9 Nasserie T, Hittle M, Goodman SN. Assessment of the frequency and variety of persistent symptoms among patients with COVID-19: a systematic review. *JAMA Netw Open*. 2021;4(5):e2111417.

10 Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open*. 2021;11(3):e048391.

11 Iacobucci G. Long covid: damage to multiple organs presents in young, low risk patients. *BMJ*. 2020;371:m4470.

12 Chen C, Haupert SR, Zimmermann L, Shi X, Fritsche LG, Mukherjee B. Global prevalence of post COVID-19 condition or long COVID: a meta-analysis and systematic review. *J Infect Dis*. 2022;226(9):1593–1607.

13 National Heart Lung, and Blood Institute. Study quality assessment tools. https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools; 2021. Accessed October 2021.

14 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557–560.

15 Huntley CC, Patel K, Bil Bushra S-ES, et al. Pulmonary function test and computed tomography features during follow-up after SARS, MERS and COVID-19: a systematic review and meta-analysis. *ERJ Open Res*. 2022;8(2):00056-2022.

16 Hughes SE, Haroon S, Subramanian A, et al. Development and validation of the symptom burden questionnaire for long covid (SBQ-LC): rasch analysis. *BMJ*. 2022;377:e070230.

17 Munblit D, Nicholson T, Akrami A, et al. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. *Lancet Respir Med*. 2022;10(7):715–724.

18 Raveendran AV, Jayadevan R, Sashidharan S. Long COVID: an overview. *Diabetes Metabol Syndr: Clin Res Rev*. 2021;15(3):869–875.

19 Ziauddeen N, Gurdasani D, O'Hara ME, et al. Characteristics and impact of long covid: findings from an online survey. *PLoS One*. 2022;17(3):e0264331.

20 National Institute for Health and Care Research. A dynamic review of the evidence around ongoing Covid 19 symptoms (often called Long Covid). https://evidence.nihr.ac.uk/themedreview/living-with-covid19/; 2021. Accessed June 2021.

21 Davis HE, Assaf GS, McCorkell L, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. *EClinicalMedicine*. 2021;38:101019.

22 Parolin Z, Lee EK. The role of poverty and racial discrimination in exacerbating the health consequences of COVID-19. *The Lan Reg Health Americas*. 2022;7:100178.

23 Tai DBG, Shah A, Doubeni CA, Sia IG, Wieland ML. The disproportionate impact of COVID-19 on racial and ethnic minorities in the United States. *Clin Infect Dis*. 2020;72(4):703–706.

24 Routen A, O'Mahoney L, Ayoubkhani D, et al. Understanding and tracking the impact of long COVID in the United Kingdom. *Nat Med*. 2021;28(1):11–15.

25 Walker AJ, MacKenna B, Inglesby P, et al. Clinical coding of long COVID in English primary care: a federated analysis of 58 million patient records in situ using OpenSAFELY. *Br J Gen Pract*. 2021;71(712):e806–e814.

26 Iwu CJ, Iwu CD, Wiysonge CS. The occurrence of long COVID: a rapid review. *Pan Afr Med J*. 2021;38:65.