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MAJOR ARTICLE

Systematic Review of the Prevalence of Long COVID

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Background. Long COVID occurs in those infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) whose symptoms persist or develop beyond the acute phase. We conducted a systematic review to determine the prevalence of persistent symptoms, functional disability, or pathological changes in adults or children at least 12 weeks postinfection.

Methods. We searched key registers and databases from January 1, 2020 to November 2, 2021, limited to publications in English and studies with at least 100 participants. Studies in which all participants were critically ill were excluded. Long COVID was extracted as prevalence of at least 1 symptom or pathology, or prevalence of the most common symptom or pathology, at 12 weeks or later. Heterogeneity was quantified in absolute terms and as a proportion of total variation and explored across predefined subgroups (PROSPERO ID CRD42020218351).

Results. One hundred twenty studies in 130 publications were included. Length of follow-up varied between 12 weeks and 12 months. Few studies had low risk of bias. All complete and subgroup analyses except 1 had $I^2 \geq 90\%$, with prevalence of persistent symptoms range of 0%–93% (pooled estimate [PE], 42.1%; 95% prediction interval [PI], 6.8% to 87.9%). Studies using routine healthcare records tended to report lower prevalence (PE, 13.6%; PI, 1.2% to 68%) of persistent symptoms/pathology than self-report (PE, 43.9%; PI, 8.2% to 87.2%). However, studies systematically investigating pathology in all participants at follow up tended to report the highest estimates of all 3 (PE, 51.7%; PI, 12.3% to 89.1%). Studies of hospitalized cases had generally higher estimates than community-based studies.

Conclusions. The way in which Long COVID is defined and measured affects prevalence estimation. Given the widespread nature of SARS-CoV-2 infection globally, the burden of chronic illness is likely to be substantial even using the most conservative estimates.

Keywords. Long COVID; prevalence; SARS-CoV-2; systematic review.

Long COVID is the state of not fully recovering for many weeks, months, or years after contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The World Health Organization (WHO) defines post-COVID-19 condition (Long COVID) as the condition occurring in individuals with a history of probable or confirmed SARS-CoV-2 infection 3 months after the onset with symptoms that last at least 2 months, cannot be explained by an alternative diagnosis, and generally impacts everyday functioning [1]. These symptoms may be the same as the acute illness or new symptoms developing weeks or months after the acute phase. Clinical guidelines [2, 3] in the United Kingdom and the United States consider Long COVID as symptoms ongoing for 4 weeks or more.

Long COVID can occur across the spectrum of severity of initial infection [4]. A wide range of symptoms have been reported with exhaustion, breathlessness, muscle aches, cognitive dysfunction, headache, palpitations, dizziness, and chest tightness or heaviness among the most common [5, 6]. Patients are still struggling to access adequate recognition, support, medical assessment, and treatment [7, 8].

Studies assessing the prevalence of Long COVID have produced wide-ranging results due to varying settings, case definitions, population denominators, and methods of ascertainment. This is exemplified in the UK Office for National Statistics (ONS) estimates of Long COVID during 2020–2021 where 3 different approaches were used resulting in 3 different

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estimates: approach 1 estimated 5.0% prevalence based on respondents reporting any of 12 common symptoms at 12–16 weeks after infection; approach 2 estimated 3.0% prevalence based on respondents reporting any of 12 common continuous symptoms at least 12 weeks after infection; and approach 3 estimated 11.7% prevalence based on respondents describing themselves as having Long COVID [9].

For the purposes of this review, we define Long COVID as persistent (constant, fluctuating or relapsing) symptoms and/or functional disability and/or the development of new pathology after SARS-CoV-2 infection for equal to or more than 12 weeks from onset of symptoms or from time of diagnosis, in people in whom the infection is self-described, clinically diagnosed, and/or diagnosed through a laboratory test.

We aimed to systematically collate, appraise, and synthesize studies that describe the prevalence of Long COVID and to characterize its typology including patient demographics, symptoms/function disability, and pathology.

METHODS

Search Strategy and Selection Criteria

Included study designs were cohort, cross-sectional, and case control studies with an estimate of the denominator where participants were followed-up/assessed at a minimum of 12 weeks postinfection. Studies were restricted to those published in English between January 1, 2020 and November 2, 2021, including peer-reviewed articles, online reports, letters, and preprints. Only studies with a sample size of 100 or more participants (at the time of follow-up assessment if longitudinal study) were included (50 or more per subgroup).

Studies of adults and children with a confirmed or probable SARS-CoV-2 infection in any age group (as defined by each study) were included. The control group in studies that included one comprised individuals with a confirmed or probable case of SARS-CoV-2 infection (as defined by the study) who had recovered (duration as defined by study as long as under 12 weeks from symptom onset or confirmation of infection) and had no new pathology attributed to SARS-CoV-2 infection. Studies that compared population-based prevalence as the control arm were excluded from the control analysis.

Community-based, hospital-based, and mixed studies were all included, apart from studies that only reported outcomes for critically ill patients admitted to intensive care, because this review did not aim to estimate delayed recovery after intensive care unit (ICU) admission (post-ICU syndrome). Patients who were not hospitalized within 2 weeks of symptom onset but were subsequently hospitalized were counted as nonhospitalized for the purpose of this review.

A systematic search was conducted using MEDLINE (Ovid), Embase (Ovid), the Cochrane COVID-19 Study register (covid-19.cochrane.org; includes Cochrane Central Register of Controlled Trials [CENTRAL]), WHO International Clinical Trials Registry Platform [ICTRP], medRxiv, Cochrane CENTRAL, MEDLINE [PubMed], ClinicalTrials.gov, and the WHO Global research on coronavirus disease [COVID-19]) database [10]. The initial search was run on November 13, 2020 and updated on November 2, 2021, both by VL. An example of the search strategy applied to Medline is provided in the Supplementary Material; it was adapted for other databases as needed.

The screening management software Covidence was used to screen for eligibility. All articles were screened independently by 2 reviewers at each stage (title, abstract, and full text) with any discrepancies resolved by NAA. This review is reported in line with PRISMA guidelines [11]. The protocol was published on the international prospective register of international reviews, PROSPERO (CRD42020218351): https://www.crd.york.ac.uk/prospero/display_record.php? RecordID=218351.

Data Analysis

Data for each study were extracted independently by 2 of 4 reviewers (MW, DCG, CC, NZ). Any discrepancies were resolved by consensus between the 2 reviewers for each study or by a third reviewer (NAA). In instances in which multiple publications were identified as originating from the same study, all data were extracted but each data point was only used once in the analysis. In addition to excluding duplicate reports, or duplicate results from the same study, several general decisions were made to cope with multiple publications from the same study, either focusing on different lengths of follow-up, different timepoints, or different subgroups. These were guided by the following principles: (1) avoiding double counting individuals; (2) using the most appropriate outcome, for example, general Long COVID definition, in the broadest group such as the widest population, largest sample, most recent update; and (3) unless stratifying by length of follow-up, taking the earliest and/or most complete follow-up as the main result.

The primary outcome is Long COVID, defined as nonrecovery from COVID-19, according to symptoms, functional ability, or pathology. The SARS-CoV-2 infection can be confirmed, probable, or suspected with prolonged symptoms (including but not limited to those explicitly defined as "new onset"), functional disability, or pathology for equal to or more than 12 weeks from onset of symptoms or positive test date (as defined by the study). Secondary outcomes included the demographics of people with Long COVID in relation to each study's denominator, prevalence of specific persistent or relapsing symptoms, prevalence of functional disability, and the characterization of post-COVID-19 pathology.

A Long COVID-specific risk of bias tool was developed, based on the Newcastle-Ottawa scale, but it was tailored to the relevant sources of bias. The domains used are reported in Supplementary Table 3. Risk of bias was particularly assessed

in relation to the denominator, how the symptoms were assessed (active or passive elicitation of the symptoms), and hospital stay. Subgroup analysis by risk of bias was performed. In studies where follow up was measured posthospital admission or discharge, symptom onset was estimated to have been 7 or 14 days before discharge, respectively, and estimated as 21 days if follow up was measured from a postinfection negative test.

The prevalence was extracted as cumulative incidence. In extracting the prevalence of persistent symptoms, we used either prevalence of at least 1 symptom or pathology, or the prevalence of the most common symptom/pathology, depending on the data reported by the study. Data for each symptom was extracted separately in studies that reported on the prevalence of individual symptoms but did not provide an overall estimate of prevalence of Long COVID. We used the symptom with the highest estimate as our best estimate of overall prevalence, although it is likely to be an underestimate of actual prevalence. In studies with controls, the prevalence of the same symptom was used for comparison. In instances in which length of follow-up varied between study participants, we report a measure of average (eg, mean or median) length of follow-up, or the midpoint of the reported range.

All analysis was conducted in Stata version 17 [12]. The distribution, prevalence estimates, numerators, denominators, and assessment time points in different populations was qualitatively summarized. We used random-effects meta-analysis on the logit of the proportions to ensure estimates and confidence limits did not go below 0% or over 100%, transforming back to the original scale for presentation.

The heterogeneity was quantified both in absolute terms (range of individual study estimates) and as a proportion of total variation (I^2), and this was explored across predefined subgroups described below. In a variation to our protocol, we present pooled estimates (PEs) alongside 95% prediction intervals (PIs) to evaluate and incorporate uncertainty in the analysis, as recently recommended for prevalence studies, where true between-study heterogeneity is expected [13, 14]. Heterogeneity was explored by stratifying on predefined subgroups: outcome type (pathology, symptom, functional status), geographical region (China, Europe, North America, Mixed, and other), source of sample (community, healthcare workers, outpatients, hospital inpatients), length of follow-up, study design, confirmed diagnosis, and other risk of bias domains. We also stratified by severity score based on the WHO Clinical Progression Scale (CPS) (Supplementary Methods). Potential small study effects such as publication bias were investigated using contour-enhanced funnel plots and Egger's test of funnel plot asymmetry.

Patient Consent Statement

In this systematic review, we analyzed publicly available data included in published scientific papers. Patient consent and ethical approval were not required.

RESULTS

Literature Search

In our search, we found 11 518 studies in total. After deduplication and title and abstract screening, 457 full-text studies were assessed for eligibility. Using handsearching, we sourced an additional 9 studies and 130 publications in total were included, 120 of these were discrete studies (Figure 1). Twenty-four studies were conducted in China (including Hong Kong), 66 in Europe, 14 in North America, and 16 in various other countries [9, 15–143]. Reasons for exclusion are listed in Supplementary Table 1.

Table 1 summarizes the included studies' key characteristics and primary outcome for the first follow-up. Study design was reported as described by each study or designated based on study description if not explicitly stated. Most studies were in adults and included patients who were hospitalized in the acute phase (24 studies with <10% of the sample hospitalized in the acute phase). However, hospitalization did not always correspond with disease severity, probably due to local diagnostic, treatment, and containment policies. Most studies used polymerase chain reaction (PCR) testing to identify COVID-19 cases at baseline. However, most did not perform COVID-19 diagnostic tests at follow up and therefore did not consider the impact of reinfection on their results. Of the included studies, 21 were community-based studies, 17 were in outpatient settings, 3 were from social media, and 8 were healthcare worker-based studies.

Prevalence Estimates

The prevalence of Long COVID for studies with more than 12 weeks from infection ranged between 0% and 93% (PE, 42.1%; 95% PI, 6.8%–87.9%) (Figure 2). For all complete and subgroup analyses except one, I^2 was >75%. All subgroup analysis results including PEs and PIs can be found in Supplementary Table 4.

Seventy-three included studies had a follow up of 12 weeks to 5 months (PE, 39.8%; PI, 5.1%–89.1%), 49 had a follow up of 6–11 months (PE, 44.9%; PI, 8%–88.4%), and 12 had a follow up of 12 months or more (PE, 48.5%; PI, 12.7%–86%). We recognize that most were not within-study comparisons, but longer follow-up times showed higher pooled estimates (Supplementary Figure 1).

Hospitalization and severity of acute infection were key factors influencing Long COVID prevalence estimates. The prevalence range in analyses in which less than 10% of the participants were hospitalized was 0% to 67% ($n = 24$) (PE, 26.4%; PI, 2.6%–82.8%), but in studies in which all participants were hospitalized for acute COVID-19 ($n = 65$), the prevalence range was 5% to 93% (PE, 47.5%; PI, 8.3%–90.0%) (Supplementary Figure 2). Thirty-one studies had 10% or more of their sample admitted to intensive care unit ICU during their acute COVID-19 illness with a Long COVID

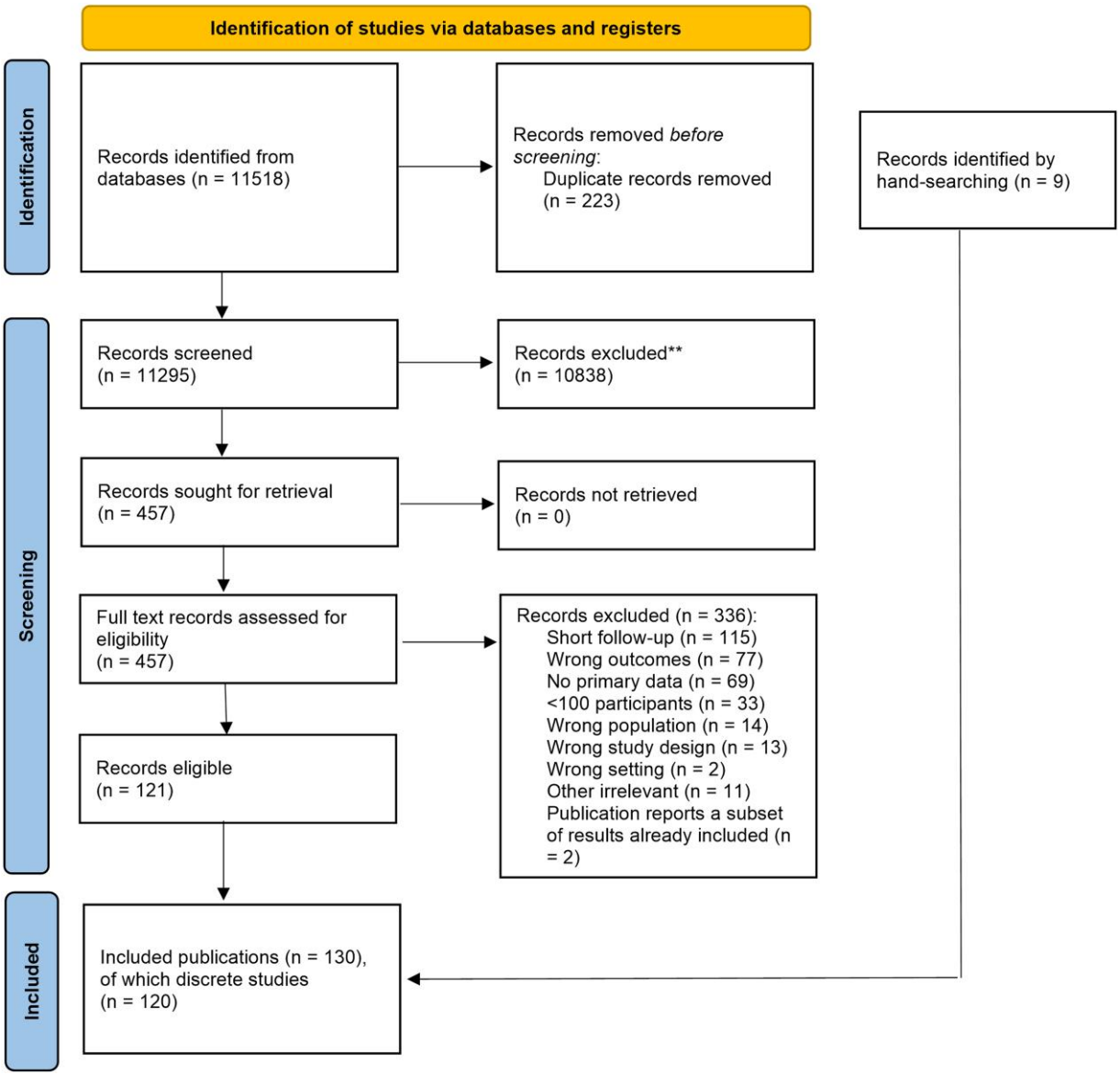

Figure 1. Study selection.

prevalence estimate of 48.8% (PI, 5.7%–93.7%) compared with PE 34.9% (PI, 5.2%–84%, $n = 48$) in studies with <5% of their samples admitted to ICU (Supplementary Figure 3). Studies including more hospitalized participants or more patients in ICU tended to report higher prevalence estimates (Supplementary Table 4). Likewise using the WHO CPS, we found that studies including those with ambulatory mild disease ($n = 38$) generally reported lower prevalence estimates (PE, 23.5%; PI, 1.6%–85.7%) than those with hospitalized severe disease who needed oxygen by noninvasive ventilation or high flow ($n = 27$) (PE, 54.8%; PI, 7.7%–94.7%) (Supplementary Figure 4).

The prevalence of not returning to full health/fitness after at least 12 weeks from infection ranged between 8% and 70% (PE, 34.5%; PI, 4.3%–85.9%; $n = 10$) (Supplementary Figure 5). The prevalence of lower quality of life after at least 12 weeks was 31% ($n = 2$) (Supplementary Figure 6). With regard to individual symptoms, common symptoms reported included fatigue (PE, 21.6%; PI, 2.5%–74.7%; $n = 72$) followed by breathing problems (PE, 14.9%; PI, 1.6%–64.9%; $n = 78$), sleep problems (PE, 13.2%; PI, 1.2%–64.9%; $n = 42$), tingling or itching (PE, 11.3%; PI, 0.7%–69.5%; $n = 14$), and joint/muscle aches and pains (PE, 10.6%; PI, 1.0%–57.5%; $n = 61$) (Figure 3). With regard to pathology, lung pathology was the most common (PE, 38.9%; PI, 3.4%–91.9%, $n = 26$) followed by heart (PE, 6.0%; PI, 0.1%–79.3%; $n = 12$) or neurological pathology (PE, 5.3%; PI, 0.5%–36.5%; n = 11) (Figure 3 and Supplementary Figures 7–40).

Table 1. Study characteristics and primary outcome at first follow-up.

	Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
1.	Abdelrahman et al [15]	Egypt	Prospective cohort	172	…	Hospitalized patients and nonhospitalized	41.8/17.6	65.7	"Tested positive"	12.8% hospitalized (including 4% ICU)	240–300 (range) after "improvement of acute COVID-19"	61.0%
2.	Al-Aly et al [16]	USA	Cohort with controls	60 255	4 526 737 without COVID-19 and not hospitalized	Nonhospitalized	61 (4872)	12.1	"Positive test"	…	126[c]	2.9%
2a.	Al-Aly et al [16]	USA	Cohort with controls	11 800	11 868 hospitalized with seasonal influenza	Hospitalized patients	70 (61–76)	5.8	PCR confirmed	26.3% ICU	150[c]	9.2%
3.	Aminian et al [18]	USA	Retrospective	2839	…	Hospitalized patients	52.7/20.1	52.3	PCR confirmed	ICU excluded	243[c]	44.2%
4.	Arnold et al [144]	UK	Prospective cohort	110	…	Hospitalized patients	60 (46–73)	44.0	PCR confirmed or clinico-radiological	Mixed	90[c]	73.6%
5.	Augustin et al [20]	Germany	Longitudinal prospective cohort	442	…	Nonhospitalized patients	43 (31–54)	52.3	PCR confirmed	97.5% mild	131[c]	27.8%
6.	Ayoubkhani et al [21]	UK	Observational retrospective matched cohort (with controls)	47 780	47 780 matched for age, sex	Hospitalized patients	64.5/19.2	45.1	Laboratory confirmed or clinical diagnosis	9.9% ICU	140[e]	21.5
7.	Baricich et al [22]	Italy	Cross-sectional	204	…	Hospitalized patients	57.9/12.8	40.0	"Confirmed diagnosis"	13% ICU	124.7[e]	32.4%
8.	Becker et al [23]	USA	Cross-sectional	740	…	Hospitalized patients, outpatients and ER attendees	49 (38–59)	63.0	Tested positive or antibody positive	…	228[b]	24.1%
9.	Bellan et al [24]	Italy	Prospective cohort	238	…	Hospitalized patients	61 (50–71)	40.3	PCR confirmed bronchial swab, serological testing, or suggestive CT	27.7% did not require oxygen 11.8% ICU	91–121[e]	53.8%
10.	Blanco et al [25]	Spain	Prospective	100	…	Hospitalized patients	54.9/10.3	36.0	PCR confirmed	47% severe	104[c]	52.0%
11.	Bliddal et al [26]	Denmark	Cohort	129	…	Nonhospitalized patients	44.8 (13.6)	70.0	PCR confirmed	Nonhospitalized	90[b]	40.3%

Table 1. Continued

	Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
12.	Blomberg et al [17]	Norway	Prospective cohort with controls	312	60 seronegative household contacts	Hospitalized patients and nonhospitalized	46 (30–58)	51.0	"Tested positive"	2% asymptomatic,78% symptomatic in community, 21% hospitalized	152–213 (range) after illness	60.6%
13.	Boscolo-Rizzo et al [27]	Italy	Prospective	304	…	Community	47 (n/a)	60.9	PCR confirmed	Mild-to-moderate (home-isolated)	365[b]	53.0%
14.	Carrillo-Garcia et al [28]	Spain	Longitudinal observational	165	…	Hospitalized older adult patients	88.5/6.7	69.1	PCR confirmed and suspected cases (clinical, imaging and laboratory results)	…	3 months posthospital discharge	66.2%
15.	Caruso et al [29]	Italy	Prospective	118	…	Hospitalized patients with interstitial pneumonia	65/12	53.0	PCR confirmed	Moderate to severe	6 months posthospital admission	77.1%
16.	Caspersen et al [30]	Norway	Matched cohort	774	72 953	Community (MoBa: population-based pregnancy cohort study)	25+	58.0	PCR confirmed	…	334–365 (range) after infection	16.5%
17.	Castro et al [31]	USA	Retrospective cohort	5571	30 193 hospitalized COVID-19 negative patients	Hospitalized patients	63 (50–76)	47.0	PCR confirmed	13% ICU	91–150 days posthospital admission	10.9%
18.	Chai et al [32]	China	Multicenter ambidirectional cohort	546	–***	Hospitalized cancer and noncancer patients	65 (59–70)	51.0	PCR confirmed	24% severe	370[d]	28.6%
19.	Cirulli et al [33]	USA	Prospective longitudinal	357	…	Community	…	…	PCR confirmed	…	90[b]	14.8%
20.	Clavario et al [34]	Italy	Prospective cohort	200	…	Hospitalized patients	58.8 (51.6–66.0)	43.0	PCR confirmed	89% required at least oxygen support	107[f]	80.0%
21.	Cristillo et al [35]	Italy	Cohort*	101	…	Hospitalized patients	63.6/12.9	27.7	"Hospitalized for COVID-19"	hospitalized for mild to moderate COVID	6 months posthospital discharge	49.5%
22.	Diaz-Fuentes et al [36]	USA	Retrospective cohort	111	…	Hospitalized patients and nonhospitalized	60/13.9	53.1	Positive nasal swab	Mixed	12 weeks postinfection	79.3%
23.	Domenech-Montoliu et al [37]	Spain	Prospective cohort	483	…	Community	37.2/17.1	62.1	Laboratory confirmed	11.2% asymptomatic	7 months postinfection	53.4%
24.	Erol et al [38]	Turkey	Cohort	121	95 randomly selected from non-COVID patients attending the ward	Hospitalized and nonhospitalized children	9.2 (10.9–17.9)	46.2	"Tested positive"	22.3% hospitalized	5.6 months postinfection	37.2%

Table 1. Continued

	Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
25.	Evans et al (PHOSP-COVID study) [39] (¥)	UK	Prospective longitudinal cohort	804	…	Hospitalized patients	58.0/12.6	39.0	PCR confirmed or clinician diagnosed	Mixed	365[f]	48.8%
26.	Evans et al (PHOSP-COVID study) [40] (¥)	UK	Prospective longitudinal cohort	1077	…	Hospitalized patients	57.9/13	35.7	Confirmed or clinician-diagnosed	Mixed	176[f]	92.6%
27.	Fernandez-de-Las-Penas et al [43] (∞)	Spain	Multicenter observational	1142	…	Hospitalized patients	61/17	47.5	PCR confirmed	7% ICU	210[e]	81.4%
28.	Fernandez-de-Las-Penas et al [41] (∞)	Spain	Multicenter observational	1142	…	Hospitalized patients	61/17	47.4	PCR confirmed	7% ICU	210[e]	49.6%
29.	Fernandez-de-Las-Penas et al [42] (∞)	Spain	Multicenter cohort	1950	…	Hospitalized patients	61/16	46.9	PCR confirmed	6.6% ICU	340[e]	81.2%
30.	Frija-Masson et al [44]	France	Retrospective	137	…	Not stated	59 (50–68)	49.0	PCR confirmed	90.5% required respiratory support	3 months postsymptom onset	75.2%
31.	Froidure et al [45]	Belgium	Single-center cohort	107	…	Hospitalized patients	60 (53–68)	41.0	PCR confirmed	Severe and critical	103[c]	68.2%
32.	Fu et al [46]	China	Cross-sectional	199	…	Hospitalized patients	18+	53.3	Not stated	2.5% ICU	6 months posthospital discharge	10.1%
33.	Gaber et al [47]	UK	Cross-sectional	138	…	98% nonhospitalized healthcare workers	…	92.0	83% PCR confirmed 17% no laboratory confirmation	2% hospitalized	4 months postinfection	44.2%
34.	Garcia-Abellan et al [48]	Spain	Prospective longitudinal	116	…	Hospitalized patients	64 (54–76)	39.7	PCR confirmed	14% ICU	180[b]	24.1%
35.	Garratt et al [49] (■)	Norway	Cross-sectional survey of a geographical cohort	447	Norwegian general population norms	Community	49.5/15.3	56.0	PCR confirmed	Nonhospitalized	117.5[c]	35.3%
36.	Gonzalez-Hermosillo et al [50]	Mexico	Prospective longitudinal	130	…	Hospitalized patients	51/14	34.6	PCR confirmed	Moderate to severe	3 months posthospital discharge	91.5%
37.	Han et al [51]	China	Prospective longitudinal	114	…	Hospitalized patients	54/12	30.0	PCR confirmed	Severe	175[b]	62.3%
38.	Havervall et al [52]	Sweden	Cohort with controls	323	1072 seronegative	Health care workers	43 (33–52)	83.0	Seropositive	mild/moderate (severe excluded)	122[b]	21.4%
39.	Huang et al [53] (Ω)	China	Ambidirectional cohort	1655	…	Hospitalized patients	57 (47–65)	48.0	Laboratory confirmed	68% required oxygen therapy 4% ICU	186[c]	76.4%

Table 1. Continued

	Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
40.	Huang et al [54] (Ω)	China	Ambidirectional cohort with controls	1227	3383 community dwelling without SARS-CoV-2 infection, 1164 matched pairs	Hospitalized patients	59 (49–67)	47.0	Laboratory confirmed	4% ICU	185[c]	68.0%
41.	Jacobson et al [55]	USA	Cohort*	118	…	Hospitalized patients and nonhospitalized	43.3/14.4	46.6	PCR confirmed	18.6% hospitalized 9.3% ICU	119.3[c]	66.9%
42.	Kashif et al [56]	Pakistan	Cohort*	242	…	Hospitalized patients and nonhospitalized	18–65	30.6	PCR confirmed	Mild	3 months posthospital discharge or visit	41.7%
43.	Kim et al [57]	S Korea	Cohort*	900	…	Hospitalized patients and nonhospitalized	31 (24–47)	69.7	PCR confirmed	12% moderate or severe	195[c]	65.7%
44.	Lemhofer et al [58]	Germany	Cross-sectional	365	…	Community	49.8/16.9	59.2	"Positively tested"	Mild and moderate	93.7%-more than 3 months postinfection	61.9%
45.	Li et al [59]	China	Cohort	289	…	Hospitalized patients	43.6/17.4	48.8	PCR confirmed	19.4% severe/critical	90–150 (range) postsymptom onset	59.9%
46.	Liao et al [60]	China	Cohort*	303	…	Hospitalized healthcare workers	39 (33–48)	80.5	"Infected with COVID-19'	62.7% critical/severe	395[f]	37.3%
47.	Liao et al [61]	China	Longitudinal cohort	142	…	Hospitalized patients	47.5 (36–57)	48.8	PCR confirmed	21.1% severe	90[f]	85.9%
48.	Liu et al [62]	China	Cross-sectional	1301	466 uninfected spouses who lived together	Hospitalized patients, elderly	68 (66–74)	53.3	"Diagnosis of COVID-19"	1.8% ICU	6 months posthospital discharge	28.7%
49.	Liyanage-Don et al [63]	USA	Cohort*	153	…	Hospitalized patients	54.5/16.7	39.9	"Hospitalized for COVID-19"	5.9% ICU	111[c]	64.7%
50.	Logue et al [64]	USA	Longitudinal prospective cohort (cross-sectional for controls*)	177	21, "healthy controls recruited via email and flyer advertisements"	Hospitalized and outpatients	48/15.2	57.1	laboratory-confirmed	6.2% asymptomatic, 84.7% mild illness, 9.0% moderate or severe disease	169[c]	30.0%
51.	Lucidi et al [65]	Italy	Observational retrospective	110	…	Not stated	41.4/12.3	63.6	"COVID-19 positive patients"	…	6.1 ± 1.1 months postinfection	36.4%
52.	Lui et al [66]	China (HK)	Prospective	204	…	Hospitalized patients	55 (44–63)	53.4	PCR confirmed	3.9% severe	89[d]	20.1%
53.	Maestre-Muniz et al [67]	Spain	Cross-sectional	543	…	Hospitalized patients and ER attendees	65.1/17.5	49.3	Laboratory confirmed	Mixed	12 months posthospital discharge	56.9%

Table 1. Continued

	Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
54.	Martinez et al [68]	Switzerland	Retrospective cohort	260	…	Healthcare workers	Mean range 30–39	75.4	'Positive test'	1.2% hospitalized	168[c]	26.5%
55.	Matteudi et al [69]	France	Prospective cohort	137	…	Hospitalized patients and outpatients, pediatric	9.3 (n/a)	…	PCR confirmed	27% asymptomatic	180[b]	16.8%
56.	Mazza et al [70]	Italy	Prospective cohort	226	…	Hospitalized patients and ER attendees	58.5/12.8	34.1	PCR confirmed	78% hospitalized	90.1[e]	35.8%
57.	Mechi et al [71]	Iraq	Single-center cross-sectional	112	…	Hospitalized patients and nonhospitalized	50.6/13.4	34.0	Laboratory confirmed	46.4% hospitalized	9 months after acute infection	82.1%
58.	Mei et al [72] (†)	China	Cohort*	4328	1500, random sample of general population	Hospitalized patients	59 (47–68)	54.1	Met relevant clinical criteria	Not defined	144[f]	14.2%
59.	Mei et al [73] (†)	China	Prospective cohort	3677	…	Hospitalized patients	59 (47–68)	55.5	PCR confirmed	33.7% severe, 2.6% critical	144[f]	26.5%
60.	Menges et al [74]	Switzerland	Population-based prospective cohort	431	…	Community	47 (33–58)	49.7	PCR confirmed	10.7% asymptomatic, 38.1% severe/very severe	220[c]	24.6%
61.	Milanese et al [75]	Italy	Prospective cohort	135	…	Hospitalized patients	59/11	33.0	Not stated	Moderate and severe	182[e]	47.4%
62.	Millet et al [76]	USA	Prospective cohort	173	…	Hospitalized patients and outpatients	51.5/n/a	50.6	PCR confirmed	…	12 months postdiagnosis	48.0%
63.	Mohiuddin Chowdhury et al [77]	Bangladesh	Prospective multicenter cross-sectional	313	…	Hospitalized patients and outpatients	37.7/13.7	19.8	PCR confirmed	Not critically ill (ICU/HDU)	140[g]	21.4%
64.	Munblit et al [78]	Russia	Longitudinal cohort	2649	…	Hospitalized patients	56 (46–66)	51.1	PCR confirmed and clinically diagnosed	2.6% severe	218[f]	57.9%
65.	Nabahati et al [79]	Iran	Prospective cross-sectional	173	…	Hospitalized patients	53.6/13.7	67.1	PCR confirmed	54% severe	90[e]	52.0%
66.	Nehme et al [80]	Switzerland	Prospective cohort	410	…	Outpatients	42.7/12.9	67.1	PCR confirmed	Mild and moderate	7–9 months postdiagnosis	39.0%
67.	Nguyen et al [81]	France	Cohort*	125	…	Hospitalized	36 (27–48))	55.0	PCR confirmed	Nonsevere	210[b]	24.0%
68.	Nunez-Fernandez et al [82]	Spain	Prospective cohort	200	…	Hospitalized patients	62 (n/a)	40.5	PCR confirmed	15.5% ICU	84[e]	29.0%
69.	O'Keefe et al [83]	USA	Cross-sectional	198	…	Outpatients	45/14	74.2	PCR confirmed	29.7% moderate, 1.1% severe	119[c]	39.9%

Table 1. Continued

	Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
70.	Office for National Statistics [9]	UK	Prospective cohort	21 374	…	Community	2+	52.3	PCR confirmed	…	12 weeks postinfection	11.7%
71.	Ong et al [84]	Singapore	Prospective longitudinal multicenter cohort	175	…	Hospitalized patients	44 (33–56)	24.6	PCR confirmed	30.1% severe	90[e]	7.4%
72.	Orru et al [85]	Italy	retrospective	152	…	Community via social media	…	…	Self-report	…	At least 3 months postinfection	74.3%
73.	Osmanov et al [86]	Russia	Prospective cohort	518	…	Hospitalized children	10.4 (3.0–15.2)	52.1	PCR confirmed	2.7% severe (NIV/IV or PICU)	256[f]	24.3%
74.	Peghin et al [87]	Italy	Bidirectional prospective cohort	599	…	Hospitalized patients and outpatients	53/15.8	53.4	NAAT for confirmed cases; laboratory, imaging or serology for suspected cases	Mixed	191[c]	40.2%
75.	Peluso et al [88]	USA	Cohort	143	…	Hospitalized patients and nonhospitalized	48 (37–57)	44.0	RNA-confirmed	Mixed	4 months posttest or first symptoms	62.2%
76.	Petersen et al [89]	Faroe Islands	Longitudinal	180	…	96% nonhospitalized patients	39.9/19.4	54.4	PCR confirmed	4.4% asymptomatic	125[b]	52.8%
77.	Qin et al [90]	China	Prospective cohort	647	…	Hospitalized patients	58/15	56.0	PCR confirmed	38% severe	3 months posthospital discharge	13.4%
78.	Qu et al [91]	China	Multicenter follow-up	540	…	Hospitalized patients	47.5 (37–57)	50.0	PCR confirmed	9.4% severe	3 months posthospital discharge	32.6%
79.	Radtke et al [92]	Switzerland	Longitudinal cohort	109	1246 seronegative	Community, children and adolescents	6–16	53.0	Antibody positive	No hospitalisation	84[b]	3.7%
80.	Rass et al [93]	Austria	Prospective observational cohort	135	…	Hospitalized and outpatients	56 (48–68)	39.0	PCR confirmed	23% severe (ICU), 53% moderate (hospitalized)	90[b]	60.7%
81.	Riestra-Ayora et al [94]	Spain	Prospective case-control	195	125 healthcare workers with negative PCR	Hospitalized and nonhospitalized healthcare workers	41.6/n/a	80.0	PCR confirmed	4.4% hospitalized	6 months postpositive test	26.7%
82.	Righi et al [95]	Italy	Prospective cohort	421	…	Hospitalized patients and outpatients	56 (45–66)	45.1	PCR confirmed	52% hospitalized, 20% ICU	84[b]	19.7%
83.	Roessler et al [96] *Split cohort (Adults)*	Germany	Matched cohort	145 184	…	Community	…	60.2	"Laboratory confirmed"	5.8% hospitalized, 2.1% intensive care or ventilation	>90[b]	9.2%

Table 1. Continued

	Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
83a.	Roessler et al [96] *Split cohort (Children)*	Germany	Matched cohort	11 950	…	Community, children	…	48.1	Laboratory confirmed	1% hospitalized, 0.4% ICU	>90[b]	6.1%
84.	Romero-Duarte et al [97]	Spain	Retrospective longitudinal observational follow-up	797	…	Hospitalized patients	63/14.4	46.3	PCR confirmed	10.8% ICU	6 months posthospital discharge	63.9%
85.	Sathyamurthy et al [98]	India	Single-center prospective cohort	279	…	Hospitalized older adult patients	71.0/5.6	36.2	PCR confirmed	41.6% severe to critical	90[e]	23.7%
86.	Seeβle et al [99]	Germany	Prospective cohort	146	…	Hospitalized and outpatients	57 (50–63)	57.0	PCR confirmed	15.6% mild, 55.2% moderate, 25.0% severe, 4.2% critical	140–154 (range) after symptom onset	73.3%
87.	Shang et al [100]	China	Cohort	796	…	Hospitalized patients	62 (51–69)	49.2	PCR confirmed	90.8% severe, 9.2% critical	6 months posthospital discharge	55.4%
88.	Sibila et al [101]	Spain	Prospective cohort	172	…	Hospitalized patients	56.1/19.8	43.0	Not stated	moderate and severe 43% ICU	101.5[e]	57.0%
89.	Sigfrid et al [102]	UK	Prospective cohort	327	…	Hospitalized patients	59.7 (51.7–67.7)	41.3	PCR confirmed or "clinically diagnosed highly suspected"	20.8% no O_2, 36.1% supplemental O_2, 15.0% noninvasive O_2, 28.1% mechanical ventilation	222[c]	93.3%
90.	Simani et al [103]	Iran	Cohort*	120	…	Hospitalized patients	54.6/16.9	33.3	Spiral chest CT scan or PCR confirmed	7.5% ICU	183[e]	10.0%
91.	Skala et al [104]	Czech Republic	Prospective cohort	102	…	Hospitalized patients and outpatients	46.7/n/a	53.9	PCR confirmed	14.7% hospitalized	3 months after testing positive	54.9%
92.	Skjorten et al [105]	Norway	Multicenter prospective cohort	126	…	Hospitalized patients	56.2/12.7	38.5	"Discharge diagnosis of COVID-19"	20% ICU	104[f]	46.8%
93.	Sonnweber et al [106]	Austria	Prospective observational	145	…	Hospitalized and outpatients	57/14	43.0	PCR confirmed	22% ICU	103[b]	54.9%
94.	Soraas et al [107] (π)	Norway	Cohort	651	5712 SARS-CoV-2-negative + 3342 randomly selected untested	Community	48.6/13.6	57	PCR confirmed	Nonhospitalized, mild	258[b]	51.9%
95.	Soraas et al [108] (π)	Norway	Prospective cohort	672	6006 SARS-COV-2-negative patients	Community	48.5/13.5	56.8	PCR confirmed	Nonhospitalized	126[b]	56.2%
96.	Stavem et al [109] (■)	Norway	Cross-sectional	451	…	Community survey	49.7/15.2	56.0	PCR confirmed	…	117[c]	41.0%
97.	Stavem et al [110] (■)	Norway	Cross-sectional mixed-mode	458	…	Community	49.5/15.3	56.0	PCR confirmed	…	117.5[c]	46.0%

Table 1. Continued

	Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
98.	Stephenson et al [111]	UK	Matched cohort	3065	3739 who tested negative	Community, adolescents	11–17	63.5	PCR confirmed	35.4% symptomatic	104[c]	66.5%
99.	Sudre et al [112]	UK, USA and Sweden	Prospective observational cohort	4182	4182, matched PCR negative***	Community	46.0/15.8	57.0	PCR confirmed	13.9% visited hospital	84[b]	2.6%
100.	Sykes et al [113]	UK	Cohort*	127	…	Hospitalized patients	59.6/14	34.3	PCR confirmed	87% required oxygen and/or respiratory support, 20% ICU	113[f]	59.1%
101.	Taboada et al [114]	Spain	Cross-sectional observational	183	…	Hospitalized patients	6.9/14.1	40.5	PCR confirmed	18.2% ICU	6 months posthospitalization	47.5%
102.	Taquet et al [116] (◊)	Primarily USA	Retrospective cohort with matching	236 379	105 579 diagnosed with flu, 236 038 with any other RTI including flu	healthcare organisations including hospitals, primary care, and specialist providers	46/19.7	55.6	"Confirmed diagnosis"	Mixed	180[b]	12.8%
103.	Taquet et al [115] (◊)	USA	Retrospective cohort	273 618	106 578 matched cohort with influenza and without a diagnosis of COVID-19 or positive test	Hospitalized patients and nonhospitalized	46.3/19.8	55.6	"Confirmed diagnosis", ICD-10 code	Mixed	90[b]	36.5%
104.	Tarsitani et al [117]	Italy	Cohort follow-up	115	…	Hospitalized patients	57 (48–66)	46.0	"Confirmed COVID-19"	23% ICU	3 months posthospital discharge	29.6%
105.	Tawfik et al [118]	Egypt	Retrospective cohort	120	…	Hospitalized and nonhospitalized healthcare workers	33.7/7.29	58.0	PCR confirmed	28.3% moderate, 10.0% severe	At least 3 months postpositive test	33.3%
106.	Taylor et al [119]	UK	Cohort*	545	…	Hospitalized patients	58.6/15.3	38.2	"Presumed and confirmed"	…	16 weeks posthospital discharge	47.9%
107.	Tempany et al [120]	Republic of Ireland	Cross-sectional*	217	…	Healthcare workers	20–69	80.0	PCR confirmed or antibody positive	…	At least 12 weeks postpositive test	53.5%
108.	The Writing Committee for the COMEBAC Study Group [121]	France	Prospective uncontrolled cohort	478	…	Hospitalized patients	60.9/16.1	42.1	PCR confirmed or by CT scan	29.7% ICU, remainder hospitalized	113[f]	51.0%

Table 1. Continued

Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
109. Tholin et al [122] (■)	Norway	Multicenter prospective cohort	683	…	Hospitalized patients and nonhospitalized	52.9/15.5	51.0	PCR confirmed, or discharge diagnosis of "confirmed or unconfirmed COVID-19'	Mixed	3 months after discharge (hospitalized), 4 months postsymptom onset (nonhospitalized)	1.8%
110. Tleyjeh et al [123]	Saudi Arabia	Prospective cohort	222	…	Hospitalized patients	52.5/14.0	23.0	PCR confirmed	Mixed 30.2% ICU	122[f]	56.3%
111. Todt et al [124]	Brazil	Single-center cohort	239	…	Hospitalized patients	53.6/14.9	40.2	PCR confirmed	69.7% severe	3 months posthospital discharge	40.2%
112. Tohamy et al [125]	Egypt	Retrospective comparative study with controls	100	100 randomly recruited from hospital registration system without COVID-19	Hospitalized and outpatients	55.5/6.2	43.0	PCR confirmed	25% moderate, 45% severe	3 months posthospital discharge	5.0%
113. Townsend et al [126]	Republic of Ireland	Cross-sectional*	128	…	Hospitalized and nonhospitalized	49.5/15	53.9	PCR confirmed	55.5% hospitalized	72[f]	57.8%
114. Trunfio et al [127]	Italy	Cross-sectional	168	…	Hospitalized patients and outpatients	56 (43–69)	42.0	PCR confirmed	63.7% hospitalized	194[c]	24.4%
115. Ursini et al [128]	Italy	Cross-sectional	616	…	Community via social media	45/12	77.4	Positive nasopharyngeal swab	10.7% hospitalized, 1.6% ICU	6 ± 3 months postpositive test	43.8%
116. Venturelli et al [129]	Italy	Cohort*	767	…	Emergency Department and hospitalized patients	63/13.6	32.9	PCR confirmed	88.4% admitted 8.6% ICU	105[c]	51.4%
117. Walle-Hansen et al [130]	Norway	Cohort	106	…	Hospitalized older adult patients	74.3/n/a	43.0	PCR confirmed	26% severe	186[f]	53.8%
118. Weng et al [131]	China	Retrospective	117	…	Hospitalized patients	…	44.4	PCR confirmed	28.2% severely ill	89.5[e]	44.4%
119. Whitaker et al [132]	UK	Random community-based survey (REACT-2)	76 155	…	Community	−18+	57.3	Self-reported	0.8% admitted to hospital	84[b]	37.7%
120. Xiong et al [133]	China	Ambidirectional cohort	162	…	Hospitalized healthcare workers	36 (31–43)	77.0	"Infected with COVID-19"	100% severe, 5% ICU	153[f]	70.4%
121. Xiong et al [134]	China	Longitudinal with controls	538	184, volunteers	Hospitalized patients	52 (41–62)	54.5	"confirmed"	5% critical, 33.5% severe	97[f]	49.6%

Table 1. Continued

Author	Country	Study Design (as Described by Study,* If Not Stated)	Denominator[a]	Controls N, Type	Setting	Age (Years) Mean/SD Median (IQR)	% Female	COVID-19 Diagnostic Method	Severity	Follow-up Time Days	Finding: %With at Least 1 Symptom or Pathology Remaining at Follow up
122. Yan et al [135]	China	Prospective observational	125	…	Mobile cabin hospital, adult males	35 (30–49)	0.0	"Diagnosed with COVID-19"	asymptomatic/mild symptoms	84[e]	0.0%
123. Yan et al [136]	China	Cohort	119	…	Hospitalized patients	53.0/12.2	59.0	PCR confirmed	24% severe	365[e]	39.5%
124. Yin et al [137]	China	Retrospective analysis	337	…	Hospitalized patients	53.5/14.8	49.5	PCR confirmed	12.8% severe, 3.6% ICU	203[b]	55.8%
125. Zayet et al [138]	France	Retrospective cohort	354	…	Hospitalized patients and outpatients	49.6/18.7	63.0	PCR confirmed	34.2% hospitalized, 5% ICU	289[b]	35.9%
126. Zhan et al [139]	China	Prospective cohort	121	…	Hospitalized patients	49 (40–57)	58.7	PCR confirmed	15.7% severe	348[c]	29.8%
127. Zhang et al [140]	China	Retrospective comparative	122	…	Hospitalized patients	51 (31.8–61.0)	50.3	PCR confirmed	mild cases excluded, only patients with pulmonary sequelae at discharge included	92[f]	54.9%
128. Zhang et al [141]	China	Cohort*	245	…	Hospitalized patients	43 (33–54)	43.8	Nucleic acid testing	9.3% severe/critical	90[e]	72.7%
129. Zhang et al [142]	China	Retrospective multicenter cohort	2433	…	Hospitalized patients	60 (49–68)	50.5	Laboratory confirmed	27.9% severe	364[f]	45.0%
130. Zhou et al [143]	China	Prospective cohort with controls	164	42 healthy controls —negative nucleic acid and antibody tests	Hospitalized patients	…	56.9	PCR and antibody test	54.6% severe	129[c] (severe cases) 125[c] (mild)	69.5%

Abbreviations: COVID, coronavirus disease 2019; CT, computerised tomography ; ER, emergency room; HDU, high dependency unit ; ICD, intensive care department ; ICU, intensive care unit; IV, intravenous; IQR, interquartile range; NAAT, nucleic acid amplification test; NIV, noninvasive ventilation; PCR, polymerase chain reaction; PICU, paediatric intensive care unit; RTI, respiratory tract infection; SARS-COV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; UK, United Kingdom.

NOTE: Papers coded with the following symbols are different publications from the same study data: Ω, ■, ◊, ¥, †, ∞, π.
* refers to those studies where study design was not explicitly stated so a design was designated based on the study description.
*** refers to studies where the relevant outcome data was not available for controls.

[a]Different denominators specific to each outcome have been used in cases where data are incomplete or where individual symptoms have different denominators.

[b]Mean number of days postsymptom onset or positive test.

[c]Median number of days postsymptom onset or positive test.

[d]Median number of days posthospital admission.

[e]Mean number of days posthospital discharge.

[f]Median number of days posthospital discharge.

[g]Mean number of days postnegative test after infection.

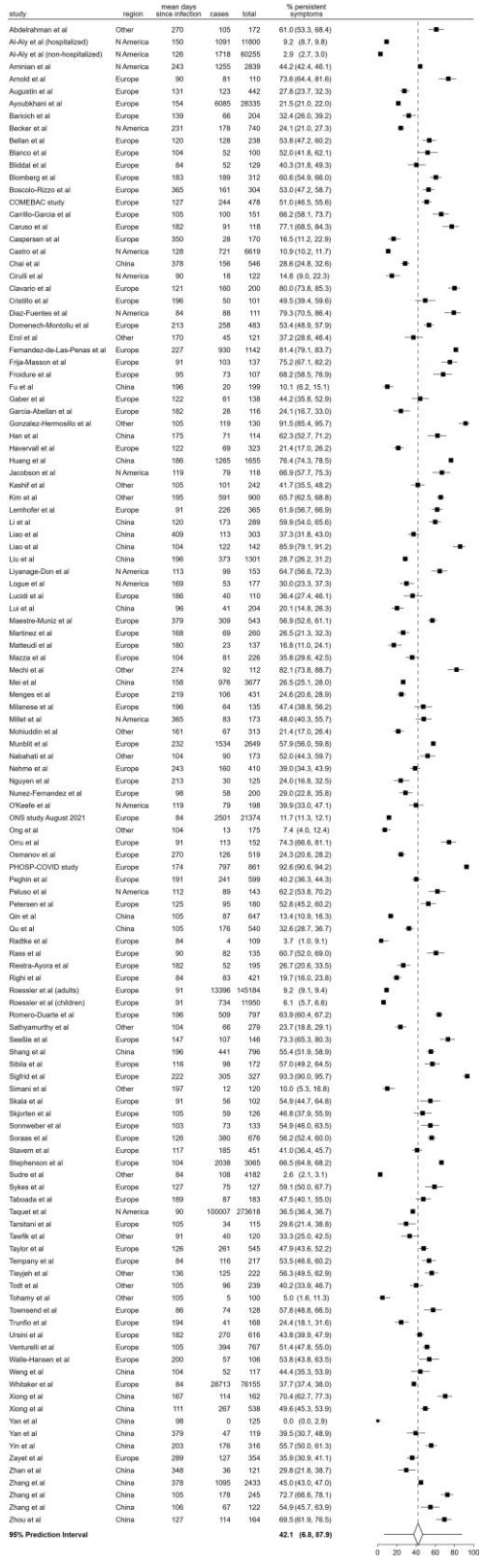

Figure 2. Forest plot of prevalence of Long COVID in the included studies, with 95% prediction intervals.

Pathology tended to be reported in only a small number of studies, with the exception of lung pathology, which was reported in 26 studies.

There were very few studies with a low risk of bias (Supplementary Table 2). Few studies used a sample that was representative of all COVID-19 cases in the population. Approximately half of the studies indicated that symptoms had not been present before infection, whereas the rest did not report ascertaining this. When stratifying by risk of bias, generally lower prevalence estimates were seen in studies with COVID-19 diagnoses confirmed for all participants, studies scored as having a representative sample, studies with an internal or external non-COVID-19 comparator, studies that assessed all participants in the same way, and studies based on community participants (Supplementary Figures 41 and 42).

Comorbidities, ethnicity, and other demographic data were not reported in all studies. Higher prevalence of Long COVID was observed in studies in which study samples had higher proportions of older people (<50 years PE 38.5%, PI 7.9%–82.1%; 50+ years PE 47.7%, PI 7.9%–90.6%), males (<50% female PE 45.6%, PI 5.5%–92.4%; 50%+ female PE 38.7%, PI 8.5%–81.2%), people of non-White ethnicity (<50% White ethnicity PE 56.3%, PI 22.3%–85.2%; 50%+ White ethnicity PE 37.6%, PI 1.7%–95.3%), diabetes (<10% pre-existing diabetes PE 35.4%, PI 5.7%–83.2%; 10%+ pre-existing diabetes PE 51.9%, PI 8.3%–92.8%), hypertension (<30% pre-existing hypertension PE 37.3%, PI 7.0%–82.5%; 30%+ pre-existing hypertension PE 58.5%, PI 16.9%–90.7%), cardiovascular disease (<10% pre-existing CVD PE 38.2%, PI 5.9%–85.9%; 10%+ pre-existing CVD PE 54.7%, PI 9.4%–93.4%), and other comorbidities including obesity, respiratory disease, liver disease, kidney disease, and immunological disorder or allergy (Supplementary Figure 43). Prevalence of Long COVID did not differ substantially with smoking status.

When subgrouping by study design, the range was 0% to 93% (PE, 41.3%; PI, 6.0%–88.6%) in cohort studies and 10% to 82% (PE, 45.9%; PI, 11.2%–85.1%) in cross-sectional studies (Supplementary Figure 50). Prevalence estimates derived from assessing Long COVID as self-reported symptoms and function ($n = 93$) on the whole tended to report higher prevalence (PE, 43.9%; PI, 8.2%–87.2%) than those that used clinical coding in healthcare records ($n = 9$) (PE, 13.6%; PI 1.2%–68%). However, studies that had dedicated pathology follow up of COVID-19 patients (for example, pulmonary function tests or scans with pathology discovered at follow up) tended to report the highest prevalence ($n = 20$) (PE, 51.7%; PI 12.3%–89.1%) (Figure 4). Studies that defined Long COVID as at least 1 of multiple symptom or pathology domains tended to report a slightly higher prevalence than those that assessed a single symptom/pathology domain (Supplementary Figure 44).

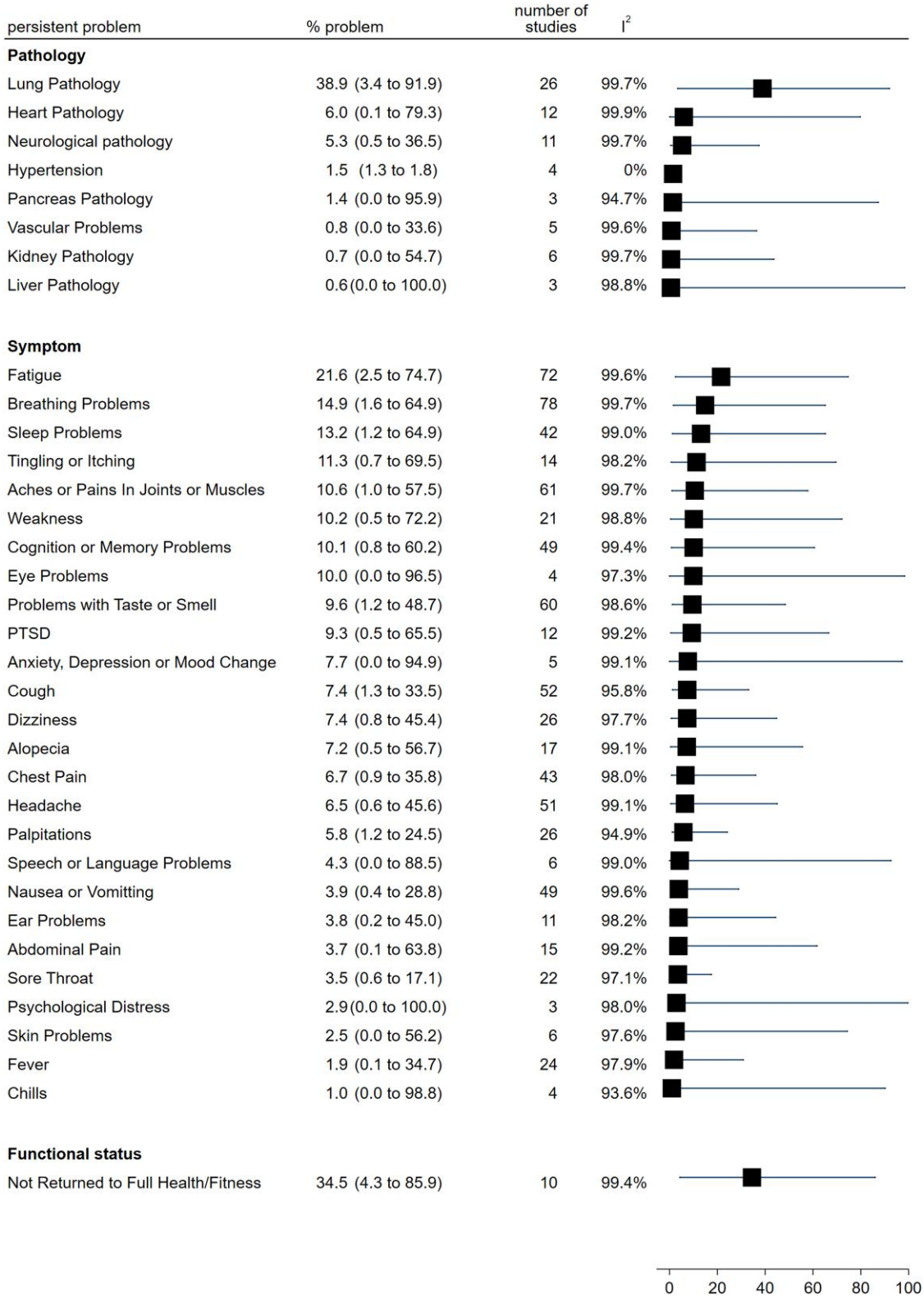

Figure 3. Forest plot of individual symptoms, pathology, and functional disability identified in the included studies, with 95% prediction intervals.

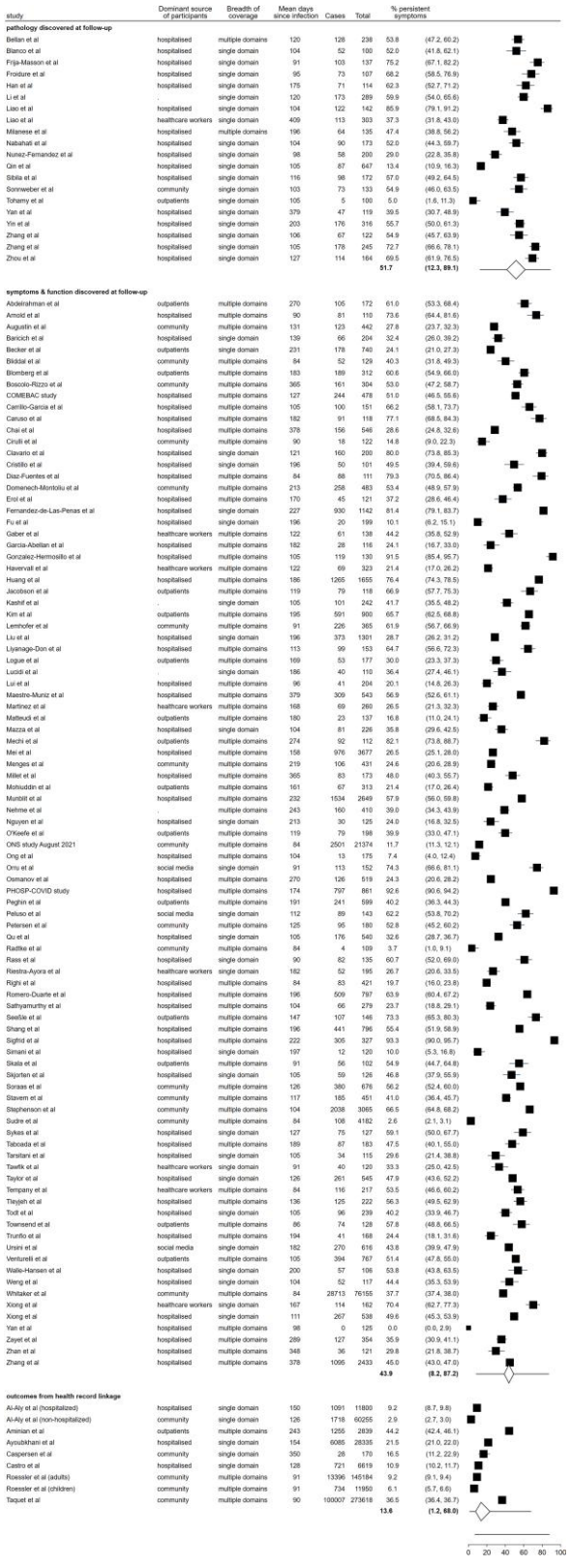

Figure 4. Forest plot of prevalence of Long COVID in the included studies by method of outcome assessment, with 95% prediction intervals.

Comparison to Controls

Twenty-four of the 130 publications included comparison to at least 1 group of controls (Supplementary Figure 45). The majority of studies used test-negative controls (antigen and antibody, with some matching), but others used untested controls. In community-based studies with controls, the relative risk ranged between 1.0 and 51.4 (pooled relative risk, 2.7; 95% PI, 0.2–39.4) and the absolute risk difference ranged between −1% and 35% (pooled risk difference, 10.1%; 95% PI, −12.7% to 32.8%) (Supplementary Figures 46 and 47). In community-based samples with controls and assessed as having a low risk of bias ($n = 4$), the pooled relative risk of experiencing symptoms/ill health after COVID-19 was 1.33 compared to controls (95% PI, 1.30. to 1.36; $I^2 = 28.1\%$) (Figure 5) and the absolute risk difference between cases and controls ranged between 1% and 9% (Supplementary Figure 48). There was no evidence of small-study effects such as publication bias (Supplementary Figure 49).

DISCUSSION

This systematic review—which included 120 studies assessing Long COVID symptoms, functional status, or pathology published up to November 2021—demonstrates substantial between-study heterogeneity and wide variation in prevalence estimates. This is due to differences in sources of study samples (community, outpatient clinic, occupational, hospitalized) and number of assessed symptoms and method of assessment (self-reported individual or collective symptoms, healthcare records, clinical investigations at follow up). The only PE with low between-study heterogeneity was a 33% (95% PI, 30%–36%) excess risk of experiencing prolonged symptoms in COVID-19 cases compared to controls in community-based studies with low risk of bias. Although studies that included controls showed, on the whole, lower net prevalence of Long COVID than studies that did not, the evidence from most of these studies is that COVID-19 is associated with a substantially higher risk of being ill 12 weeks after infection than those not infected.

In characterizing Long COVID, the review demonstrated higher prevalence estimates in study samples where a substantial proportion of included individuals were hospitalized during the acute phase of the infection and/or had severe acute disease. It is difficult to comment on prevalence difference by ethnicity, deprivation, or gender because although we conducted subgroup analyses by proportion of participants by gender or ethnicity in included studies, the difference between the prediction estimates may be related to other confounding factors, such as, for example, studies that included more males may indicate that they also include a high proportion of those who had

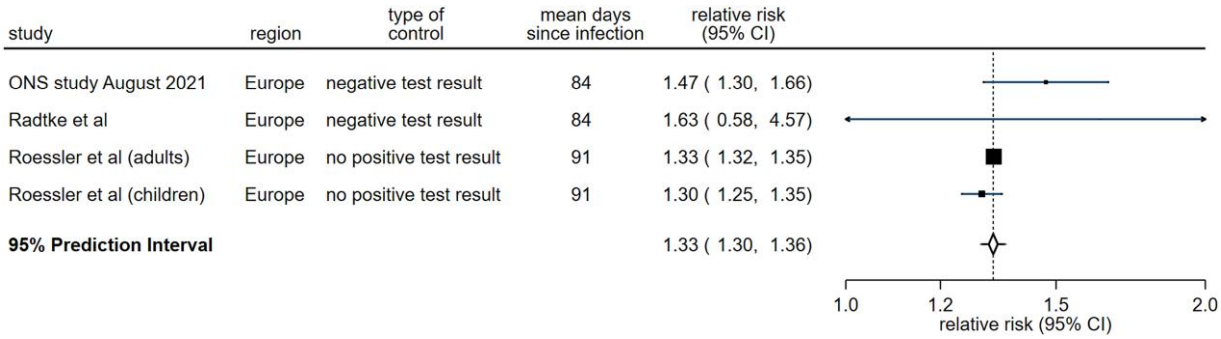

Figure 5. Forest plot of risk of Long COVID in included studies with community-based samples and controls assessed as having low risk of bias, with 95% prediction intervals.

severe acute illness [145]. Many studies did not report ethnicity or deprivation. These factors will be important to include in future studies if a comprehensive understanding of Long COVID and inequity is to be gained.

Long COVID's proposed pathophysiological mechanisms are multiple and potentially overlapping including persisting viral reservoirs, immune dysfunction, microclotting, and end-organ damage [146]. It is concerning that studies that specifically investigated for pathology tend to report higher prevalence estimates than those depending on healthcare records or even self-reporting of symptoms. The review found that Long COVID presents a significant burden of functional disability, symptoms, and pathology, with a pooled estimate of 34.5% of people not returning to full health/fitness after at least 12 weeks, and estimates of the most common symptoms/pathology including lung pathology (38.9%), fatigue (34.5%), breathing problems (14.9%), sleep problems (13.2%), and tingling or itching (11.3%). The paucity of long-term longitudinal studies after individuals' disease progression means it is difficult to comment on which symptoms are most persistent over time.

The UK's ONS produces population-level Long COVID prevalence estimates where the denominator is the whole population in the specific reported population group, for example, by age, sex, or occupation [147]. These fall out of our inclusion criteria. The ONS also produced prevalence estimates based on following up with those with confirmed SARS-CoV-2 infection, and we used the most recent estimate within the review's search period [9]. This study used multiple approaches including assessing individual symptoms compared to controls and asking participants whether they believe they have Long COVID. The latter approach, in the absence of a standardized method of assessment, may realistically be the best way to assess the presence of Long COVID because most people will take the combination of their symptoms, duration, fluctuation, effect on functional ability, and change from pre-COVID-19 health to shape their responses.

The lack of consensus on the precise definition of Long COVID plays an important part in the wide differences in prevalence assessments; however, we found that the way the question is specifically asked and the source of retrieved clinical information at follow up are likely to play a crucial role. The ONS study is an example of how different methods of assessment at time of follow up can produce substantially different Long COVID estimates [9]. This was illustrated by our analysis in which studies that asked about multiple symptoms/domains tended to report higher prevalence estimates than single-domain studies. Our analysis indicated higher prevalence estimates with longer follow-up time, although we recognize these were mostly not within-study comparisons. However, in 4 of 10 longitudinal studies, prevalence was higher at the time of the second follow up. These results could be explained by several factors, eg, by the episodic nature of Long COVID, whereby in the early stages people may believe they have recovered from their illness, but with passing time and phases of relapse and remittance, people may be more cautious about reporting they have recovered. People may also be developing new symptoms over time, or perhaps there is more study drop-out by people who believe they have recovered. Overall, however, the results indicate that, over time, prevalence does not substantially reduce.

Studies that used questionnaires/surveys to ask participants about their symptoms, health status, or quality of life tend to report higher prevalence estimates than those that recorded symptoms from healthcare records' clinical coding. This is manifested in the prevalence from Al-Aly et al [16] studies being on the lower side in our analysis because we only included those with symptoms rather than recorded post-COVID-19 pathology, and such symptoms are expected to be severe enough to prompt seeking medical help and being recorded in medical notes. Studies that had dedicated pathology follow up and discovery of COVID-19 patients tended to report the highest prevalence. This is possibly because, in addition to pathology that leads to recognizable signs and symptoms, specific medical investigations as part of the research protocol can pick up latent pathology that may not be accompanied by clinical manifestations.

Studies such as Al-Aly et al [16] that investigated medical diagnoses in the period after COVID-19, report cardiovascular, neurological, and other system-specific clinical sequelae, providing a substantial excess burden in those who survived the acute phase of COVID-19 [13]. However, there is no agreement yet as to whether these outcomes are classified as Long COVID. They are generally not recorded by symptom studies, and the WHO does not yet specifically include such outcomes within its clinical case definition of Post-COVID-19 Condition (also known as Long COVID) [1]. A specific pathology diagnosed after COVID-19 could have been triggered by the infection, but identification as such will depend on the extent of clinical investigations identifying and labeling specific pathology as opposed to differences in the disease manifestation themselves.

Other sources of heterogeneity between studies include study design with some including assessment at 1 point in time, whereas others were longitudinal where assessment of COVID-19 status was conducted before the development of Long COVID. This assessment itself varied in terms of using PCR or antigen testing or self-reporting of history of acute infection.

Ideally, excess absolute risk in comparison to controls is a good measure to estimate the burden of Long COVID. This is likely dependent on the approach to control selection, whether based on self-report of absence of infection history or laboratory results that are not accurate enough to ascertain the state of previous infection (antigen or antibody) and timing of assessment given the predominant episodic nature of Long COVID.

Few studies had a low risk of bias, which suggests there is a gap in the evidence base for strong studies of Long COVID prevalence. In terms of causal inference, many studies were liable to potential collider bias, which presented as selection bias caused by restricting analyses to people who were hospitalized, self-selected for PCR, or lateral flow tests based on symptoms, or simply volunteered their study participation [148]. Similarly, our exploration of potential sources of heterogeneity may be prone to table 2 fallacy in the original studies, where these subgroups do not derive from the focal research question, so these should be interpreted descriptively rather than causally [149].

The strengths of our review include comprehensive electronic searching for relevant studies and comprehensive assessment of risk of bias, data extraction, and checking with each of these processes being done independently by 2 authors. We also adapted the Newcastle-Ottawa scale (Supplementary Table 3) for this prevalence systematic review, which can be used by other researchers for risk assessment and/or to build high-quality study designs. The quality assessment criteria and process were discussed within the study team, which includes 2 authors with lived experience of Long COVID.

Our review was limited by the substantial between-study heterogeneity. We used the most common reported symptom estimate for studies and did not combine multiple individual symptoms into 1 overall estimate of prevalence of Long COVID. The symptom with the highest prevalence differed from study to study, so this may not be entirely comparable. We did not include more recent studies that assessed the prevalence of Long COVID after infection with different variants of SARS-CoV-2 and/or in double- or triple-vaccinated populations. Recent estimates point to a prevalence of 4%–5% of reporting Long COVID at 12 to 16 weeks after first confirmed SARS-CoV-2 infection depending on variant, with no evidence of difference between variants among those who are triple vaccinated when infected [150]. In those double-vaccinated group, the prevalence of persistent symptoms was approximately 10% compared to 15% of unvaccinated controls [151].

We extracted estimates of "new-onset" Long COVID/symptoms where possible. In instances in which the proportion is of a symptom-like fatigue, for example, we picked the one quoted as new-onset fatigue if available, or we downgraded quality because it was not possible to ascertain that the symptom is "new" after infection. Because Long COVID is a novel condition, prevalence of the condition is considered equivalent to cumulative incidence. When comparing with controls, we estimated cumulative incidence from reported absolute risk, when appropriate. When reporting risk ratio, we included incidence rate ratio and hazard ratios, but we did not consider the odds ratio an adequate approximation because of the high potential prevalence in some populations.

CONCLUSIONS

We know that significant numbers of people experience ill health after SARS-CoV-2 infection. Long COVID has an impact on society, particularly in places with continuing waves of infection. By reviewing how different research approaches attempted to quantify the population burden of Long COVID, our findings provide insight into how to get more accurate estimates of prevalence and severity. With quantification of prevalence and the associated inequity, we can understand the investment needed for prevention, diagnosis, and treatment as well as the policy decisions needed to resource healthcare and social care services both adequately and equitably, and to mitigate the wider social and economic impact of Long COVID.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. NAA, DCG, RT, AA, VL, and MW conceptualized and designed the study. MW drafted the protocol and search strategy with input from all coauthors. VL conducted the search. All authors contributed to screening the articles. MW, DCG, NZ, RT, and CC extracted and assessed the data for quality. NAA, MW, DCG, NZ, and CC contributed to the process of checking and verifying the extracted data. DCG planned and conducted the statistical analyses and produced the forest plots. MW, DCG, NZ, and NAA interpreted the data and drafted the manuscript. All authors reviewed the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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Potential conflicts of interest. DCG is a coinvestigator on the NIHR-funded LOCOMOTION study. NAA has lived experience of Long COVID, is a coinvestigator on the NIHR-funded STIMULATE-ICP and HI-COVE studies, has contributed in an advisory capacity to World Health Organization (WHO) and the European Union Commission's Expert Panel on effective ways of investing in health meetings in relation to post-COVID-19 condition, and has acted as a collaborator on some of the UK's Office for National Statistics outputs on the prevalence of Long COVID. AA has lived experience of Long COVID, is a co-founder of the Patient-Led Research Collaborative, and has contributed in an advisory capacity to National Institutes of Health, Centers for Disease Control and Prevention, and WHO. All authors: No reported conflicts of interest.

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