Prevalence, risk factors and treatments for post-COVID-19 breathlessness: a systematic review and meta-analysis

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A sizable proportion of patients with COVID-19 experienced post-COVID breathlessness, and the prevalence estimate varied by population characteristics and methodological approaches. Further research on mechanisms and interventions for this sequela is needed. https://bit.ly/3P5ayv6

Cite this article as: Zheng B, Daines L, Han Q, *et al*. Prevalence, risk factors and treatments for post-COVID-19 breathlessness: a systematic review and meta-analysis. *Eur Respir Rev* 2022; 31: 220071 [DOI: 10.1183/16000617.0071-2022].

Received: 24 April 2022
Accepted: 4 July 2022

Abstract

Persistent breathlessness >28 days after acute COVID-19 infection has been identified as a highly debilitating post-COVID symptom. However, the prevalence, risk factors, mechanisms and treatments for post-COVID breathlessness remain poorly understood. We systematically searched PubMed and Embase for relevant studies published from 1 January 2020 to 1 November 2021 (PROSPERO registration number: CRD42021285733) and included 119 eligible papers. Random-effects meta-analysis of 42 872 patients with COVID-19 reported in 102 papers found an overall prevalence of post-COVID breathlessness of 26% (95% CI 23–29) when measuring the presence/absence of the symptom, and 41% (95% CI 34–48) when using Medical Research Council (MRC)/modified MRC dyspnoea scale. The pooled prevalence decreased significantly from 1–6 months to 7–12 months post-infection. Post-COVID breathlessness was more common in those with severe/critical acute infection, those who were hospitalised and females, and was less likely to be reported by patients in Asia than those in Europe or North America. Multiple pathophysiological mechanisms have been proposed (including deconditioning, restrictive/obstructive airflow limitation, systemic inflammation, impaired mental health), but the body of evidence remains inconclusive. Seven cohort studies and one randomised controlled trial suggested rehabilitation exercises may reduce post-COVID breathlessness. There is an urgent need for mechanistic research and development of interventions for the prevention and treatment of post-COVID breathlessness.

Introduction

Long-COVID or post-COVID syndrome, defined as ongoing otherwise unexplained symptoms lasting for over 4 weeks after getting COVID-19 [1], has become an urgent international health challenge. Persistent breathlessness is one of the most prevalent and debilitating symptoms experienced by COVID-19 survivors with long-COVID [2]. In this paper, we used the term post-COVID breathlessness to describe the experience of breathlessness >28 days following acute COVID-19 infection.

Several meta-analyses on post-COVID symptoms have found that between 24–37% of hospitalised and nonhospitalised patients with COVID-19 experienced short-term persistent breathlessness (2 weeks to 7 months post-COVID) [2–7]. However, most previous meta-analyses have not distinguished the

prevalence estimate of post-COVID breathlessness by different definitions of persistent breathlessness, initial severities of illness, follow-up lengths and demographic characteristics. With a fast-growing body of data on post-COVID breathlessness now becoming available, a detailed synthesis of longer-term follow-up data (especially 7–12 months post-COVID) is required to better understand the natural history of post-COVID breathlessness and provide evidence to guide ongoing healthcare provision.

Furthermore, there is an urgent need to better understand risk factors and characterise underlying mechanisms of post-COVID breathlessness. These important evidence gaps make it challenging to develop targeted interventions or rehabilitation therapies for at-risk or affected patients [8].

To inform these deliberations, we conducted a systematic review and meta-analysis to comprehensively evaluate the prevalence of post-COVID breathlessness across different populations, using differing criteria and methodological approaches, and investigate changes in prevalence over time. We also synthesised data from studies that examined risk factors, mechanisms and potential interventions for post-COVID breathlessness to inform strategies for prevention and clinical management of post-COVID breathlessness.

Methods

Registration and reporting

The study protocol is registered in PROSPERO with the registration number: CRD42021285733. The reporting of this study followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) reporting guideline [9].

Search strategy

We systematically searched PubMed and Embase databases to identify studies that reported data on persistent breathlessness in patients with COVID-19 published in English between 1 January 2020 and 1 November 2021. Studies were identified using search terms related to COVID-19, long-term follow-up and breathlessness (or dyspnoea). Detailed search strategies and procedures are presented in the supplementary material.

Inclusion/exclusion criteria

For the estimation of prevalence of post-COVID breathlessness in COVID-19 survivors, studies were included if they used a cohort, cross-sectional or case series design and reported data required for meta-analyses. To comply with this criterion of long-COVID symptoms [1] and our practical definition of post-COVID breathlessness, we only included studies with a mean/median follow-up time of >28 days after acute COVID-19 infection, symptom onset, initial COVID-19 diagnosis/positive test, or hospital discharge, depending on the follow-up time information provided by individual studies. Studies were excluded from meta-analysis if they did not report follow-up time, only recruited participants who had residual symptoms/complications following COVID-19 (*e.g.* all study participants were sufferers of post-COVID syndrome), or only recruited participants with a specific comorbidity. We also excluded studies with ⩽50 COVID-19 survivors because of concerns regarding the precision and potential bias of prevalence estimates. For studies using the Medical Research Council (MRC) or modified MRC (mMRC) dyspnoea scale, we excluded those using cut-off points different from mMRC score ⩾1 (or equivalently, MRC score ⩾2) to make sure the prevalence estimates were comparable across included studies.

For the synthesis of evidence on risk factors and mechanisms for post-COVID breathlessness, we included relevant cohort, case–control, cross-sectional or case series studies. Cohort/case–control studies and randomised/nonrandomised trials investigating the effectiveness of interventions for post-COVID breathlessness were also included.

Data extraction

We extracted the following information from eligible studies for meta-analysis: 1) sample size and prevalence of post-COVID breathlessness; 2) definition of post-COVID breathlessness and relevant scales and cut-off points; 3) methodological characteristics (*i.e.* follow-up period, source of study population, follow-up method); 4) population characteristics (*i.e.* country, age, sex, ethnicity/race, severity of COVID-19 infection); and 5) subgroup prevalence estimates (*e.g.* by sex). Graphical prevalence data [10–14] were extracted using PlotDigitizer (www.plotdigitizer.sourceforge.net/).

The following data from studies on risk factors, mechanisms, or interventions were also extracted: 1) sample size, population characteristics, and follow-up time and method; 2) assessed risk factors, clinical parameters, or interventions; 3) definition of post-COVID breathlessness; and 4) statistical methods and results.

Study quality assessment

The study quality of included papers for meta-analyses was evaluated using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Studies Reporting Prevalence Data [15]. We assigned an overall quality rating of high, moderate or low to each study after a qualitative evaluation based on the nine items in the checklist.

Data analysis and synthesis

Random-effects meta-analyses were conducted to estimate the pooled prevalence of post-COVID breathlessness and its confidence interval [16] in COVID-19 survivors. In consideration of the heterogeneity in the definition and measurement of breathlessness, we separated the overall analysis by three definition categories: studies that did not use a breathlessness scale (*i.e.* directly measuring the presence or absence of the symptom); studies that used the MRC or the mMRC dyspnoea scale; and studies using other scales to measure breathlessness. Study-specific 95% CIs were estimated using the Wilson's score CI method [16]. The heterogeneity of prevalence estimates across studies was assessed by the I^2 statistic and Q test. A funnel plot for the prevalence estimate after logit transformation was created to identify publication bias, followed by an Egger's test.

For studies directly measuring the presence or absence of the symptom, we also stratified the meta-analysis by follow-up periods, *i.e.* 1–6 months and ⩾7 months, and by hospitalised and nonhospitalised patients. Further subgroup meta-analyses were conducted to investigate potential risk factors for post-COVID breathlessness and potential sources of heterogeneity, such as mean/median age, sex, continent of study population, definition of post-COVID breathlessness (whether defined as new/worse breathlessness than pre-COVID baseline level or not), severity of COVID-19 infection (intubation/intensive care unit (ICU)/World Health Organization (WHO) clinical progression scale [17] ⩾6 *versus* nonsevere) and follow-up method. Between-group heterogeneity was tested based on Q statistics and DerSimonian-Laird subgroup weights [16]. In the subgroup analyses by sex and severity of infection, since several studies contributed to multiple estimates of breathlessness prevalence (*e.g.* a single study reported the prevalence estimates for men and women separately), multilevel meta-analysis models with study ID as random effects were used to address the intra-study correlation [18]. No subgroup meta-analyses were conducted for studies using MRC/mMRC dyspnoea scale or other scales due to insufficient number of eligible studies.

Several sensitivity analyses were performed by: 1) excluding studies with any children/adolescents (<18 years old); 2) excluding studies in which at least one patient was followed for ⩽28 days (*e.g.* a study reported follow-up data between 14–176 days post-infection [19]); 3) excluding studies rated as low quality; 4) excluding studies based on electronic health record data to reduce methodological heterogeneity; and 5) repeating the meta-analyses using prevalence estimates after logit transformation or Freeman-Tukey double arcsine transformation [16]. We also assessed the influence of each study by recalculating the pooled prevalence after removing that study.

Finally, data from studies on risk factors, mechanisms or interventions of post-COVID breathlessness were qualitatively synthesised due to substantial methodological heterogeneity or limited number of studies.

Statistical analyses were performed using Stata (version 14, StataCorp, College Station, TX) and the metafor package [18] in R (version 4.1.2, R Core Team). All statistical tests were two-sided and the significance level was defined as $p<0.05$.

Results

Search results and study characteristics

The literature search yielded 1 893 records. After screening, 119 eligible papers remained, of which 104 were included in the meta-analyses (two papers were only included in the subgroup analyses) [10–14, 19–27, 29–44, 47–50, 52–66, 77, 85–138]; 56 were included in the qualitative synthesis (41 contributed to both) (figure 1).

Characteristics of the 104 papers included in meta-analyses are presented in table 1. Two pairs of papers [20–23] reported follow-up data from identical/overlapping populations, but at different time points, thus two papers [21, 23] were only included in subgroup meta-analyses but not the overall meta-analysis (*i.e.* leaving 102 papers). Most studies were conducted in the UK (n=16), Italy (n=12), China (n=11), the USA (n=11), Spain (n=7), France (n=8) and Turkey (n=5). The sample size of the included papers varied from 55 to 9 816 (median 154). The mean/median follow-up length ranged from 1–12 months. Most papers reported follow-up data of hospitalised patients with COVID-19 (n=61) or mixed samples of hospitalised/nonhospitalised patients (n=34). Most studies recruited adult patients only, while only two studies [24, 25]

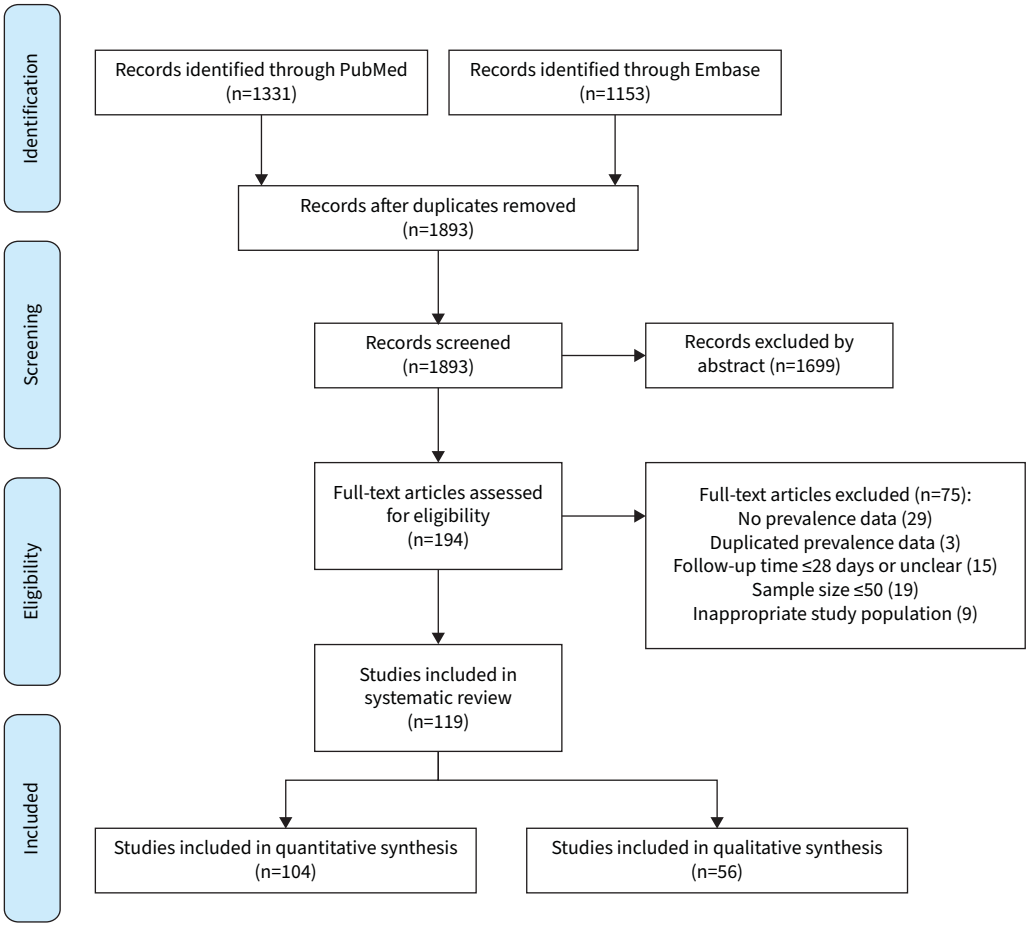

FIGURE 1 PRISMA flowchart.

focused on children/adolescents with COVID-19 and seven studies included a small proportion of children/adolescents. Thirty-seven papers used clinical scales to measure post-COVID breathlessness, such as the MRC/mMRC dyspnoea scale (n=22) and the New York Heart Association Functional Classification (n=3) which are functional measures of breathlessness rather than direct measures of presence of the symptom. Twenty-nine papers used self-reported breathlessness level before COVID-19 as a baseline when assessing post-COVID breathlessness. Only seven papers included a control group without COVID-19. The most common follow-up method was in-person research/clinic visit (n=54), followed by phone interview (n=27) and online survey (n=7); three studies were based on electronic health records.

Quality assessment

The study quality of most papers for meta-analysis was rated as moderate (n=49) or low (n=32), while 23 studies had high overall quality [15]. The commonest sources of potential bias were lack of representativeness of the target population, small sample size, low response rate, lack of validated measures for breathlessness, and lack of reliable follow-up methods (supplementary table 1).

Prevalence of post-COVID breathlessness among COVID-19 survivors

After excluding two papers reporting data from duplicated populations [21, 23], data from the remaining 102 papers with a total of 42 872 COVID-19 survivors were synthesised in the meta-analysis. The meta-analysis was conducted separately by different definitions of breathlessness: no scale (71 papers), MRC or mMRC dyspnoea scale (22 papers) and other scales (14 papers); 5 of the 102 papers measured post-COVID breathlessness using more than one definition. The pooled prevalence of post-COVID breathlessness was 26% (95% CI 23–29) in studies directly measuring presence or absence of the symptom, 41% (95% CI 34–48) in studies using MRC/mMRC dyspnoea scale and 51% (95% CI 42–60) in studies using other scales (figure 2). Substantial heterogeneity across studies was observed in each of the three meta-analyses (I^2=98.8%, 97.4% and 95.9%, respectively; p<0.001).

TABLE 1 Study characteristics of 104 papers included in the meta-analyses

First author	Sample size	Country	Mean/ median age, years	Only adults	Male proportion	Scale for breathlessness	Compared with pre-COVID level	Breathlessness prevalence	Hospitalisation	Follow-up method	Follow-up period, months
Abdelrahman [86]	172	Egypt	42	Yes	0.34		Yes	0.22	Mixed	Phone	–
Anaya [49]	100	Colombia	49	Yes	0.47		No	0.24	Mixed	Visit	7–12
Aparisi [26]	70	Spain	55	Yes	0.36	NYHA functional class ⩾2	No	0.586	Mixed	Visit	1–6
Ares-Blanco [87]	155	Spain	59	Yes	0.48		No	0.31	Mixed	Phone	1–6
Armange [88]	214	France	39	Yes	0.40		No	0.402	Nonhosp	Online	1–6
Arnold [89]	110	UK	55	Yes	0.62		No	0.39	Hosp	Visit	1–6
Asadi-Pooya [24]	58	Iran	12	No	0.48		Yes	0.12	Hosp	Phone	–
Augustin [90]	442 (4 months), 353 (7 months)	Germany	43	Yes	0.48		No	0.086 (4 months), 0.136 (7 months)	Nonhosp	Visit	1–6, 7–12
Aul [91]	387 (370)	UK	63	Yes	0.57		No	0.365	Hosp	Phone	1–6
Aydin [63]	116	Turkey	49	No	0.48		No	0.19	Hosp	Phone	1–6
Baldini [62]	55	Argentina	55	–	0.73		No	0.55	Hosp	Visit	1–6
Bell [92]	303	USA	44	No	0.30		No	0.257	Nonhosp	Online	1–6
Blomberg [93]	312	Norway	46	No	0.49		No	0.21	Mixed	Visit	1–6
Boari [94]	94	Italy	71	–	0.67		Yes	0.36	Hosp	Visit	1–6
Çalik Kütükcü [95]	100	Turkey	37	Yes	0.41		No	0.58	Mixed	Visit	1–6
Carfì [96]	143	Italy	57	Yes	0.63		No	0.434	Hosp	Visit	1–6
Carvalho-Schneider [97]	150	France	49	Yes	0.44		Yes	0.367	Mixed	Phone	1–6
Cheng [98]	113	UK	58	Yes	0.68	MRC increase	Yes	0.363	Hosp	Visit	1–6
Cortés-Telles [59]	186	Mexico	47	–	0.61		No	0.376	Mixed	Visit	1–6
Damanti [99]	67	Italy	63	–	0.85	mMRC ⩾1	No	0.478	Hosp	Visit	1–6
Dankowski [100]	102	Poland	52	Yes	0.44		No	0.422	Mixed	Visit	1–6
Darcis [101]	199	Belgium	61	Yes	0.63		No	0.47	Hosp	Visit	1–6
Daynes [10]	131	UK	60	–	0.59	COPD assessment test	No	0.731	Hosp	Phone	1–6
D'Cruz [35]	119 (115)	UK	59	Yes	0.62	mMRC increase, numerical rating scale ⩾4	Yes	0.443, 0.322	Hosp	Visit	1–6
de Graaf [61]	81	Netherlands	61	Yes	0.63	NYHA functional class ⩾2	No	0.617	Hosp	Visit	1–6
Diaz-Fuentes [102]	111	USA	60	Yes	0.47		No	0.559	Mixed	Visit	1–6
Dreyer [103]	1518 (977)	USA	42	Yes	0.12		No	0.119	Mixed	Online	1–6
Erol [25]	121	Turkey	9	No	0.54		No	0.0826	Mixed	Visit	1–6
Evans [104]	1077 (767)	UK	58	Yes	0.64	Numerical rating scale increase	Yes	0.481	Hosp	Visit	1–6
Faverio [50]	312 (283)	Italy	62	Yes	0.73	mMRC ⩾1	No	0.31	Hosp	Visit	1–6
Fernández-de-Las-Peñas [105]	1950	Spain	61	–	0.53		Yes	0.233	Hosp	Phone	7–12
Fortini [36]	59	Italy	68	–	0.53		Yes	0.373	Hosp	Visit	1–6
Froidure [37]	126	Belgium	60	–	0.59	mMRC ⩾1	No	0.357	Hosp	Visit	1–6
Gaber [106]	138	UK	–	Yes	0.08		No	0.399	Nonhosp	Online	1–6
Galván-Tejada [19]	141	Mexico	39	–	0.49		No	0.099	–	–	1–6
Gamberini [55]	178	Italy	64	–	0.73	mMRC ⩾1	No	0.584	Hosp	Visit	7–12
Garrigues [53]	120	France	63	–	0.63	mMRC ⩾1, no	No	0.533, 0.417	Hosp	Phone	1–6
Gautam [42]	200 (144)	UK	57	–	0.63	mMRC ⩾1	No	0.632	Hosp	Visit	–
Ghosn [11]	948 (3 months), 1065 (6 months)	France	61	–	0.63		No	0.304 (3 months), 0.263 (6 months)	Hosp	Visit	1–6

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https://doi.org/10.1183/16000617.0071-2022

TABLE 1 Continued

First author	Sample size	Country	Mean/ median age, years	Only adults	Male proportion	Scale for breathlessness	Compared with pre-COVID level	Breathlessness prevalence	Hospitalisation	Follow-up method	Follow-up period, months
González [107]	60	Spain	60	Yes	0.74	mMRC ⩾1	No	0.467	Hosp	Visit	1–6
Halpin [108]	100	UK	67	Yes	0.54	Likert scale increase	Yes	0.5	Hosp	Phone	1–6
Horwitz [21]	126	USA	62	Yes	0.60	PROMIS® dyspnea characteristics instrument ⩾1	No	0.63	Hosp	Online/ phone	7–12
Huang [22]	1615	China	57	Yes	0.52	mMRC ⩾1	No	0.259	Hosp	Visit	1–6
Huang [23]	1276 (1271)	China	59	Yes	0.53	mMRC ⩾1	No	0.3	Hosp	Visit	7–12
Huang [12]	382	USA	55	No	0.41		Yes	0.17	Nonhosp	EHR	–
Italia [43]	123	Italy	62	–	0.68	NYHA functional class ⩾2	No	0.341	Hosp	Visit	1–6
Jacobs [109]	128	USA	57	Yes	0.62		No	0.453	Hosp	Online/ phone	1–6
Karaarslan [110]	300	Turkey	53	Yes	0.60	Likert scale	No	0.263	Hosp	Phone	1–6
Klein [111]	103	Israel	35	Yes	0.62		Yes	0.078	–	Phone	1–6
Landi [112]	131	Italy	56	Yes	0.61		Yes	0.44	Hosp	Visit	1–6
Lerum [29]	103	Norway	59	Yes	0.52	mMRC ⩾1	No	0.54	Hosp	Visit	1–6
Liang [60]	76	China	41	Yes	0.28	0–4 grade ⩾1	No	0.605	Hosp	Visit	1–6
Lindahl [30]	101 (93)	Finland	60	Yes	0.53	mMRC ⩾1	No	0.645	Hosp	Online/ printed	1–6
Lund [77]	9816	Denmark	50	No	0.42		Yes	0.014	Mixed	EHR	–
Maestre-Muñiz [113]	543	Spain	65	Yes	0.51		Yes	0.193	Mixed	Phone	7–12
Mahmud [114]	355	Bangladesh	40	Yes	0.58		Yes	0.07	Hosp	Phone	1–6
Mallia [115]	401	UK	59	Yes	0.60	MRC increase, no	Yes	0.408, 0.464	Mixed	Visit	1–6
Mandal [116]	384	UK	60	–	0.62	0–10 scale ⩾1	No	0.53	Hosp	Phone/visit	1–6
Mechi [44]	112	Iraq	51	–	0.66		No	0.3036	Mixed	Visit	7–12
Meije [56]	294	Spain	69	Yes	0.57		No	0.299	Hosp	Visit	1–6
Menges [31]	431 (395)	Switzerland	47	Yes	0.50	mMRC ⩾1	No	0.24	Mixed	Online	7–12
Moradian [117]	200	Iran	56	–	0.80		No	0.185	Hosp	Phone	1–6
COMEBAC Study Group [85]	478	France	61	Yes	0.42		Yes	0.163	Hosp	Phone	1–6
Motiejunaite [64]	114	France	57	Yes	0.67		No	0.4	Mixed	Visit	1–6
Mumoli [118]	88	Italy	63	Yes	0.74		No	0.494	Hosp	Visit	1–6
Munblit [119]	2649 (2620)	Russia	56	Yes	0.49		No	0.174	Hosp	Phone	7–12

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TABLE 1 Continued

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Naik [54]	1234	India	41	Yes	0.69		No	0.061	Mixed	Visit/phone	1–6
Nehme [120]	479 (30–45 days), 410 (7–9 months)	Switzerland	43	Yes	0.38		Yes	0.111 (30–45 days), 0.117 (7–9 months)	Nonhosp	Online/ phone	1–6, 7–12
O'Keefe [121]	290	USA	44	Yes	0.25		No	0.141	Mixed	Online	1–6
O'Sullivan [122]	155	UK	39	–	0.82		No	0.767	Mixed	Phone	1–6
Peluso [13]	143 (4 months), 68 (8 months)	USA	48	Yes	0.56		Yes	0.224 (4 months), 0.206 (8 months)	Mixed	Visit	1–6, 7–12
Qin [47]	647	China	58	–	0.44		Yes	0.087	Hosp	Visit	1–6
Raman [48]	58	UK	55	–	0.59	MRC ⩾2	No	0.643	Hosp	Visit	1–6
Righi [123]	448	Italy	56	Yes	0.55		Yes	0.11	Mixed	Phone/visit	1–6
Riou [52]	81	France	61	–	0.73		No	0.2	Hosp	Visit	1–6
Sathyamurthy [124]	279	India	71	Yes	0.64		No	0.018	Hosp	Phone	1–6
Seeßle [41]	146 (5 months), 96 (12 months)	Germany	57	Yes	0.49		Yes	0.271 (5 months), 0.375 (12 months)	Mixed	Visit	1–6, 7–12
Shah [32]	73	Canada	65	Yes	0.60	UCSD-SOBQ >10	No	0.425	Hosp	Visit	1–6
Shang [27]	796	China	62	Yes	0.51		No	0.204	Hosp	Phone	1–6
Shendy [125]	81	Egypt	34	Yes	0.32	Numerical rating scale (0–10) ⩾1	No	0.741	Mixed	Phone	1–6
Shoucri [126]	364	USA	61	Yes	0.52		No	0.159	Hosp	EHR	1–6
Sigfrid [33]	327	UK	60	Yes	0.59	MRC increase	Yes	0.468	Hosp	Post/phone/ visit	7–12
Skjorten [38]	156 (126)	Norway	56	Yes	0.62	mMRC ⩾1	No	0.47	Hosp	Visit	1–6
Sonnweber [58]	145 (133)	Austria	57	Yes	0.55		No	0.36	Mixed	Visit	1–6
Stavem [127]	451	Norway	50	Yes	0.44		No	0.16	Nonhosp	Post/online	1–6
Suárez-Robles [128]	134	Spain	59	–	0.46		No	0.403	Hosp	Phone	1–6
Sultana [129]	186	Bangladesh	35	Yes	0.66		No	0.102	Mixed	Phone	1–6
Sun [130]	932	China	58	No	0.40		No	0.072	Hosp	Phone	1–6
Szekely [66]	71	Israel	53	Yes	0.66		No	0.225	Mixed	Visit	1–6
Tawfik [14]	120	Egypt	34	Yes	0.42		No	0.647	Mixed	–	1–6
Taylor [131]	675	UK	56	–	0.58	MRC increase, no	Yes	0.578, 0.344	Mixed	Online/ phone	1–6
Todt [132]	251	Brazil	53	Yes	0.60	mMRC increase	Yes	0.279	Hosp	Phone	1–6
Tosato [133]	165	Italy	73	Yes	0.62		No	0.515	Hosp	Visit	1–6
Varghese [134]	116	Germany	41	Yes	0.85		No	0.06	Mixed	Visit	1–6
Venturelli [135]	767	Italy	63	Yes	0.67	mMRC ⩾1, no	No	0.298, 0.218	Mixed	Visit	1–6
Vijayakumar [65]	80	UK	59	Yes	0.66		No	0.46	Hosp	Visit	1–6

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TABLE 1 Continued

First author	Sample size	Country	Mean/ median age, years	Only adults	Male proportion	Scale for breathlessness	Compared with pre-COVID level	Breathlessness prevalence	Hospitalisation	Follow-up method	Follow-up period, months
Weerahandi [20]	152	USA	62	Yes	0.63	PROMIS® dyspnea characteristics instrument ⩾1	No	0.743	Hosp	Online/ phone	1–6
Wu [136]	132	China	45	No	0.55	mMRC ⩾1	No	0.068	Hosp	Visit	1–6
Wu [57]	83	China	60	Yes	0.57	mMRC ⩾1	No	0.81 (3 months), 0.05 (12 months)	Hosp	Visit	1–6, 7–12
Yin [40]	337	China	54	–	0.51	0–4 grade ⩾1	Yes	0.27	Hosp	Visit	7–12
Yomogida [34]	366	USA	39	Yes	0.43		No	0.128 (2 months), 0.104 (7 months)	Mixed	Phone	1–6, 7–12
Zayet [137]	354	France	50	Yes	0.37		Yes	0.11	Mixed	Online	7–12
Zhang [39]	2433	China	60	Yes	0.50		Yes	0.041	Hosp	Phone	7–12
Zhao [138]	55	China	48	Yes	0.58		No	0.1455	Hosp	Visit	1–6

Sample sizes in brackets refer to valid cases in the prevalence calculation. Studies that did not use a scale to measure breathlessness defined it as the presence/absence of the symptom. NYHA: New York Heart Association; Nonhosp: nonhospitalised patients; Hosp: hospitalised patients; MRC: Medical Research Council Dyspnoea Scale; mMRC: modified Medical Research Council Dyspnoea Scale; UCSD-SOBQ: University of California San Diego–Shortness of Breath Questionnaire; EHR: electronic health record.

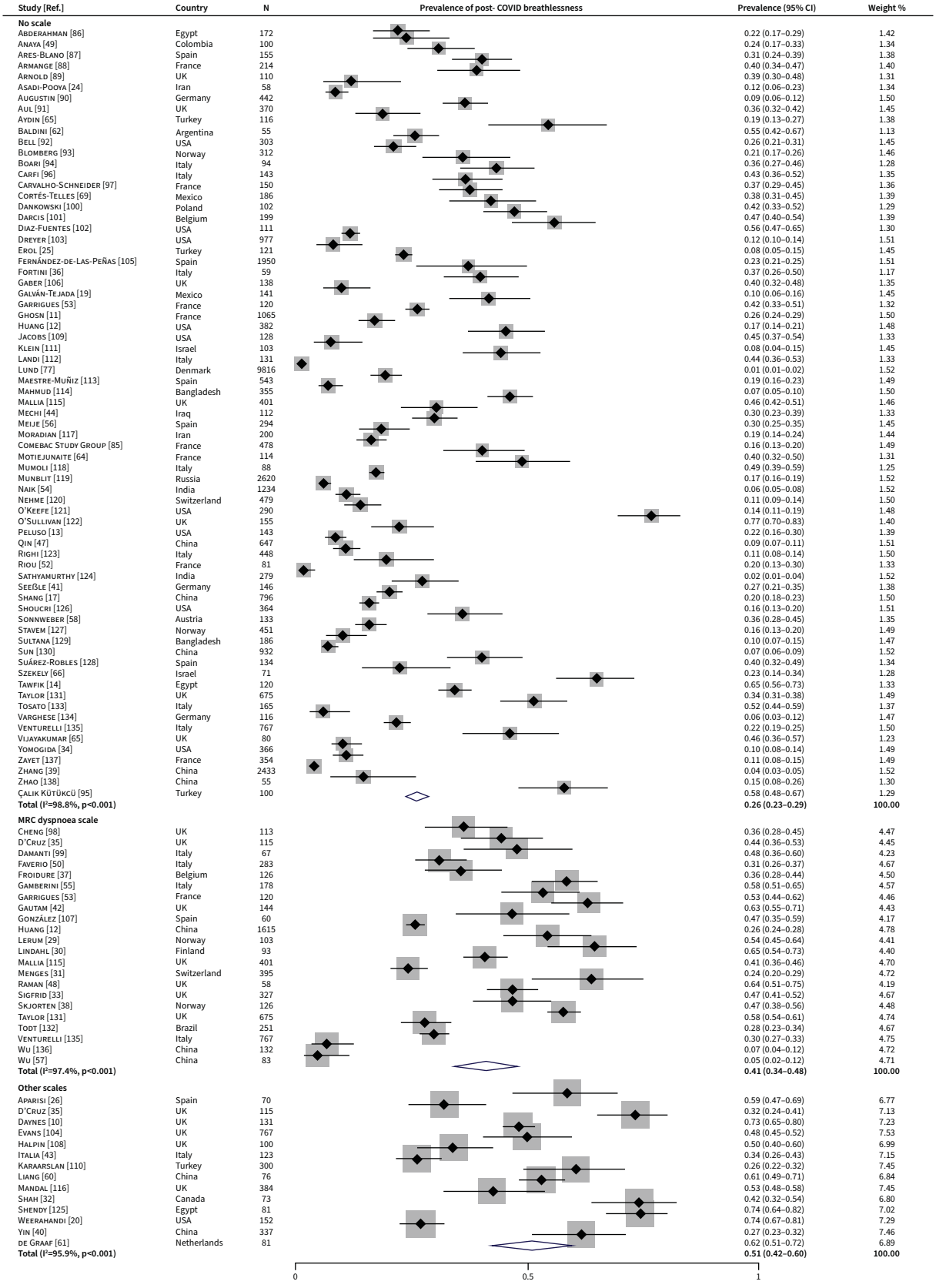

FIGURE 2 Forest plot for the overall prevalence of post-COVID breathlessness by definition of breathlessness. MRC: Medical Research Council Dyspnoea Scale.

We further differentiated between hospitalised and nonhospitalised COVID-19 survivors for studies directly measuring presence or absence of the symptom. There were 35 papers reporting data from hospitalised patients and 10 from nonhospitalised patients, of which four papers with mixed samples reported subgroup prevalence estimates by hospitalisation or not. The subgroup meta-analysis demonstrated a higher prevalence of post-COVID breathlessness in hospitalised patients (27%, 95% CI 23–30) compared with nonhospitalised patients (17%, 95% CI 10–24) (figure 3). The between-subgroup heterogeneity was statistically significant (p=0.020).

We also compared papers reporting follow-up data at 1–6 months (n=60) and 7–12 months post-COVID (n=14), of which six papers reported data from multiple time points. This subgroup meta-analysis showed a decreased prevalence of post-COVID breathlessness over time, with estimates of 28% (95% CI 25–32) and 20% (95% CI 15–26), respectively (figure 4). Significant between-subgroup heterogeneity was detected (p=0.014).

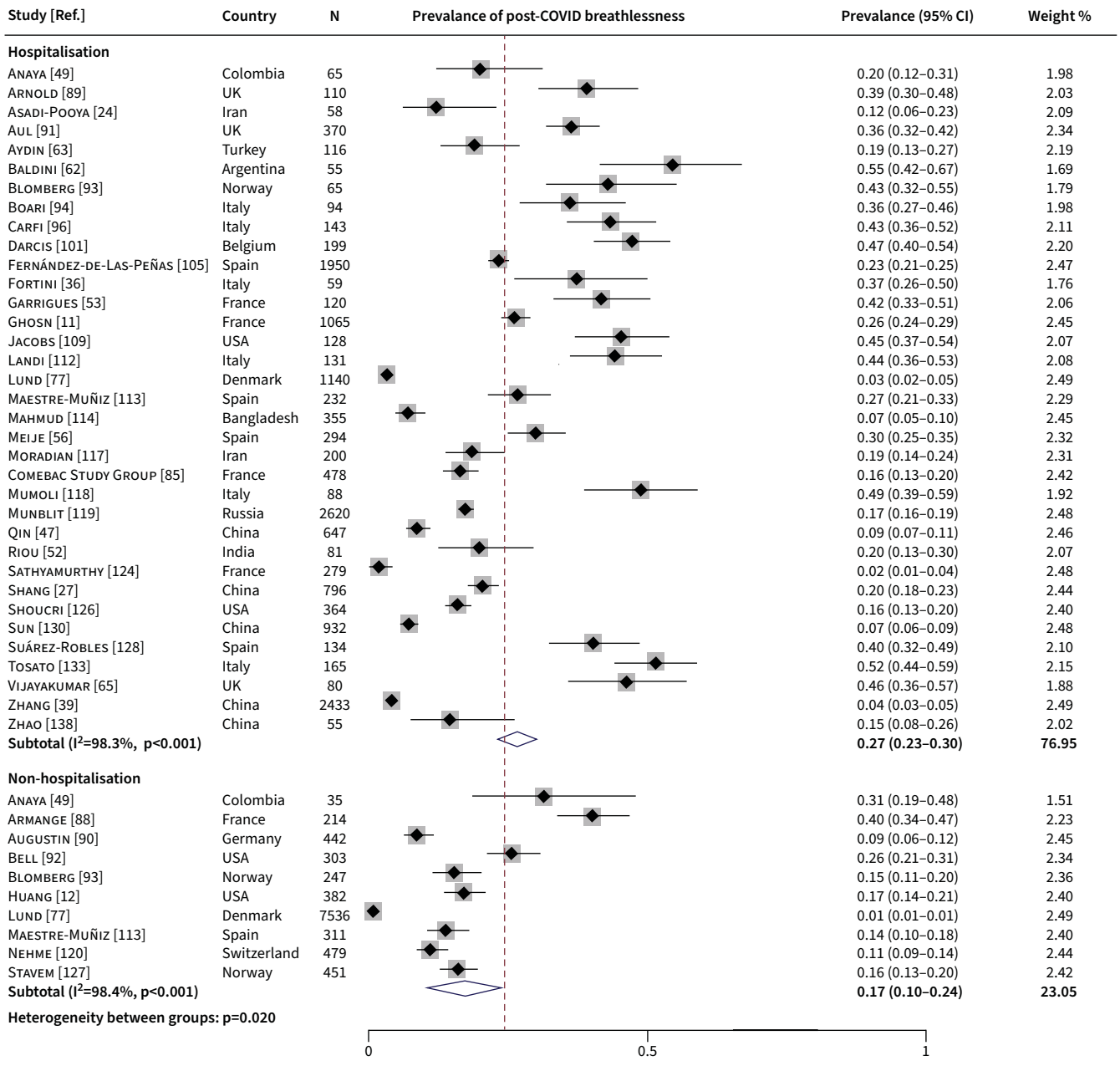

FIGURE 3 Forest plot for the prevalence of post-COVID breathlessness in hospitalised *versus* nonhospitalised patients.

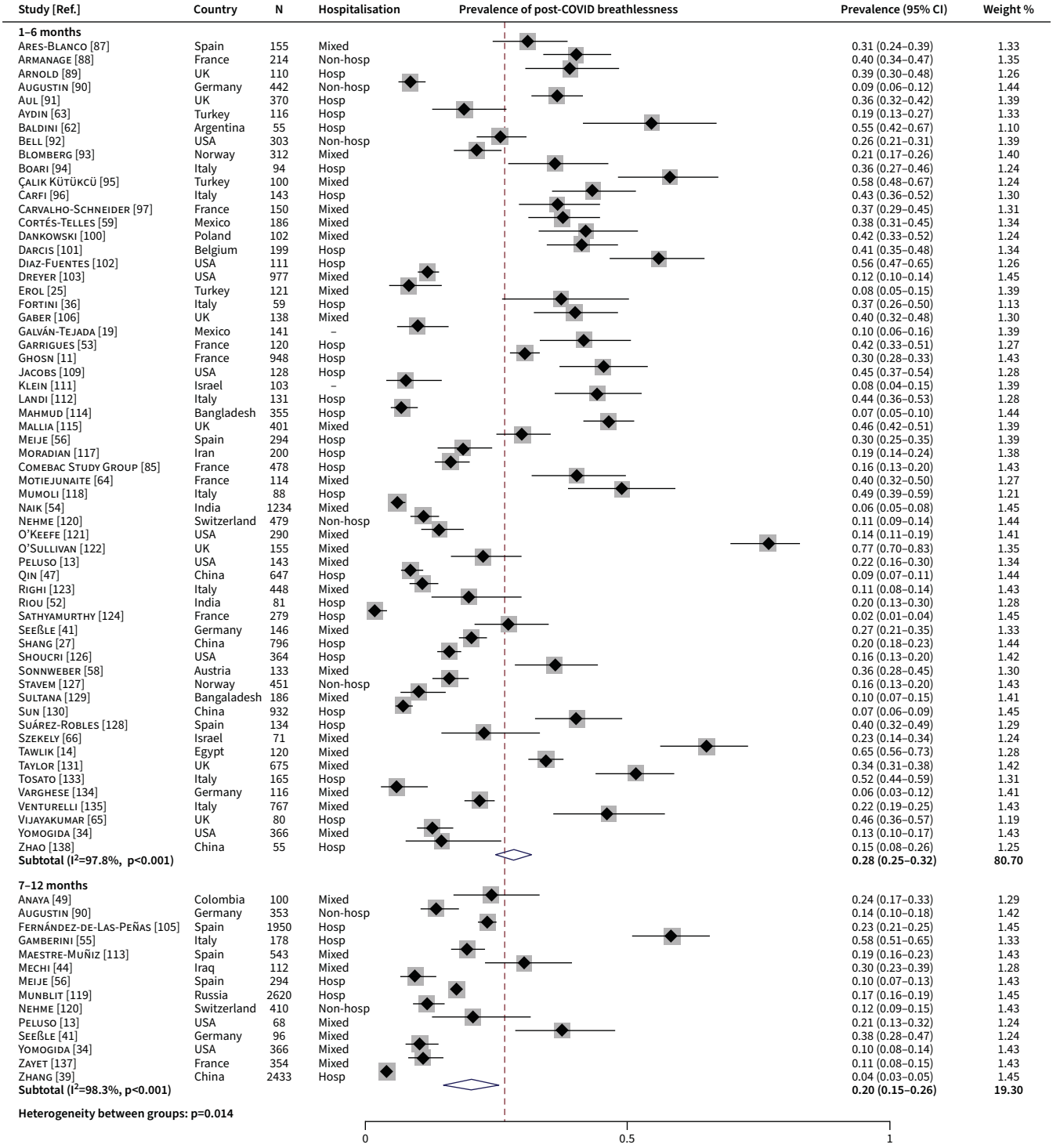

FIGURE 4 Forest plot for the prevalence of post-COVID breathlessness at different follow-up time points. Hosp: hospitalised patients; Nonhosp: nonhospitalised patients.

Both the funnel plots (supplementary figure 1) and Egger's tests (p>0.10) suggested no evidence of publication bias. The results of the sensitivity analyses showed prevalence estimates consistent with the main analyses (supplementary table 2). The influential analysis indicated no single study had a major impact on the pooled prevalence estimate (supplementary table 3).

Subgroup analyses for risk factors of post-COVID breathlessness

Further subgroup meta-analyses were conducted in studies directly measuring presence or absence of the symptom (*i.e.* without scales). Based on the sex-specific data reported from five papers, female survivors were more likely to report post-COVID breathlessness than males (22% *versus* 14%; p<0.001) (figure 5). Studies with mean/median patient age below 50 years reported lower prevalence of post-COVID breathlessness than studies with the mean/median patient age between 50–60 years or above 60 years (21% *versus* 29% or 29%, respectively; p=0.024). Patients in studies conducted in Asia had lower prevalence of post-COVID breathlessness than patients in Europe or North America (13% *versus* 31% or 23%; p<0.001). Patients with severe/critical COVID-19 infection (intubation/ICU/WHO scale [17] ⩾6) had higher prevalence of post-COVID breathlessness than nonsevere patients (26% *versus* 16%; p<0.001).

As for methodological heterogeneity, the prevalence of post-COVID breathlessness varied by different follow-up methods (figure 5). The pooled prevalence estimates were 33%, 21% and 23% for in-person visit, phone interview and online survey, whereas the estimate based on electronic health record data was much lower (11%) despite reflecting period prevalence instead of point prevalence. In addition, studies that defined post-COVID breathlessness in comparison to recalled pre-COVID breathlessness level reported a lower prevalence than the other studies that defined post-COVID breathlessness based solely on the post-COVID level (18% *versus* 30%; p<0.001).

Qualitative synthesis of studies on risk factors, mechanisms and treatments of post-COVID breathlessness

Of the 56 papers included in the qualitative synthesis (supplementary tables 4–5), 46 reported data on risk factors or mechanisms of post-COVID breathlessness and 10 evaluated rehabilitation interventions or potential therapies.

Inconsistent results for multiple risk factors were reported. Nine studies [26–34] showed a higher prevalence of post-COVID breathlessness in female patients than males (four with statistical significance and five with borderline statistical significance), but another five studies [35–39] did not detect an association and one

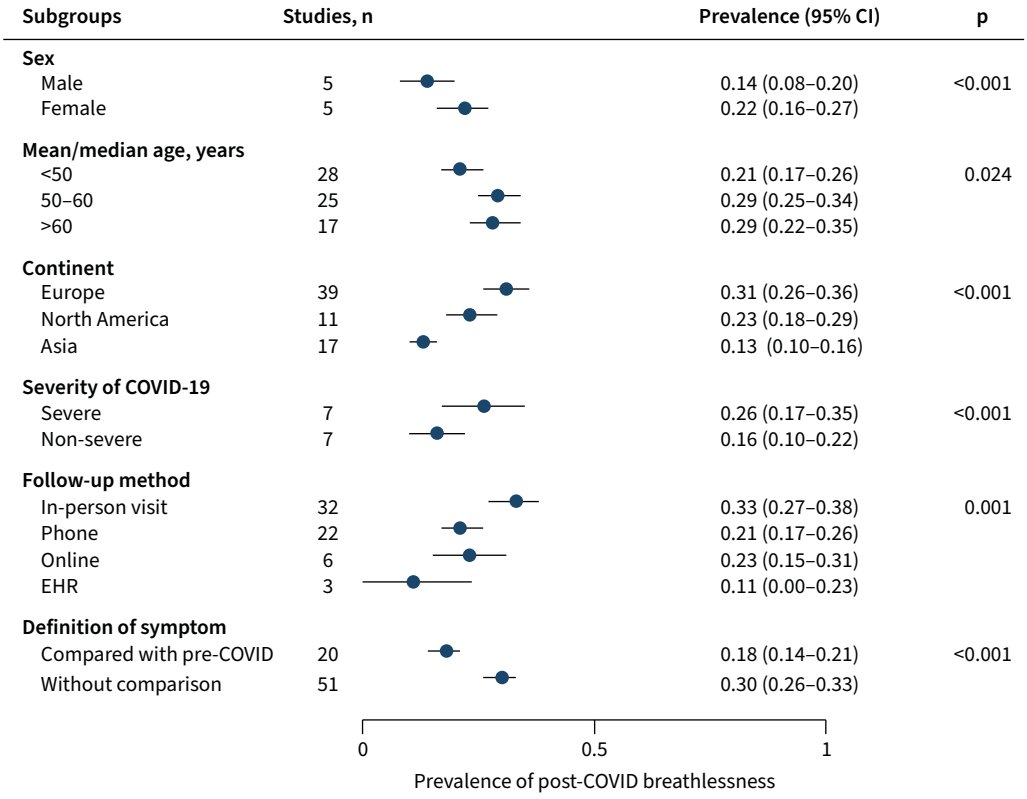

FIGURE 5 Subgroup meta-analyses for the prevalence of post-COVID breathlessness. Between-group heterogeneity was tested based on Q statistics and DerSimonian-Laird subgroup weights (except for a multilevel meta-analysis for heterogeneity by sex or severity of COVID-19). EHR: electronic health record.

study [40] showed the opposite association. Two studies [39, 40] showed a positive association between age and post-COVID breathlessness; one study [41] reported that patients aged between 50–59 years were more likely to report post-COVID breathlessness than those aged 60 years and over; and 11 studies [26, 27, 29, 31–38] did not detect a significant association with age. Four papers [31, 32, 39, 40] found no association between smoking and post-COVID breathlessness. Several studies identified that obesity (n=3) [31, 38, 42], hypertension (n=2) [39, 42], cardiovascular diseases (n=2) [42, 43] or diabetes (n=2) [42, 44] was significantly associated with higher risk of post-COVID breathlessness; however, two [35, 45], four [26, 28, 32, 35], four [26, 28, 32, 39] and six studies [26, 32, 35, 38, 39, 46], respectively, did not detect the associations. Regarding pre-morbid obstructive lung diseases, three studies [35, 39, 42] identified an association with a higher risk of post-COVID breathlessness but another five studies [26, 28, 31, 32, 36] did not. Three studies [28, 31, 40] found a significant association with overall comorbidity while two studies [33, 36] found no association. Clinical severity of acute COVID-19 infection was positively associated with post-COVID breathlessness in five studies [22, 39, 40, 47, 48], but nine studies [27, 31, 36, 37, 42, 49–52] did not identify this association. Only one study [40] (out of eight studies [28, 29, 31, 35, 39, 40, 42, 53]) showed a higher prevalence of post-COVID breathlessness in patients managed in ICU. In contrast, two studies [31, 54] showed a higher prevalence estimate in hospitalised *versus* nonhospitalised patients, and three [28, 39, 40] and one [55] studies found positive associations with lengths of hospital stay and days of invasive mechanical ventilation. One paper [56] reported that individuals with a ratio of arterial oxygen partial pressure to fractional inspired oxygen (P_{AO_2}/F_{IO_2}) <200 during hospitalisation were at higher risk of post-COVID breathlessness. Mixed results were shown for the trajectory of post-COVID breathlessness. Four papers [21, 39, 57, 58] reported a decreased prevalence over time, while two papers [23, 41] found an increased trend and three papers [31, 32, 40] detected no change.

Regarding underlying mechanisms, several papers reported that post-COVID breathlessness was correlated with reduced spirometry parameters (n=5) [32, 42, 58–60], lower diffusion capacity for carbon monoxide (D_{LCO}) (n=7) [32, 36, 55, 58, 59, 61, 62] and lung imaging abnormalities (computed tomography (CT) (n=3) [40, 58, 63], lung ultrasound (n=1) [36], chest radiograph (n=1) [42]), but four [26, 37, 55, 61], four [26, 37, 60, 64] and three papers [35, 37, 65] found no significant associations with these three measurements, respectively. One paper [26] reported that patients with post-COVID breathlessness had reduced exercise capacity based on the 6-minute walk test, lower predicted peak oxygen consumption and worse performance in cardiopulmonary exercise testing; another paper [59] also found a reduced 6-minute walk distance and lower end-exercise oxygen saturation, and two additional papers [38, 66] supported the findings in cardiopulmonary exercise testing. Four papers [26, 32, 61, 66] assessed echocardiogram results during follow-up but only one [66] detected an association with post-COVID breathlessness. One paper [63] identified a correlation with higher C-reactive protein (CRP) level at the follow-up visit, but another paper [42] did not. Three papers [32, 35, 48] reported significant associations between post-COVID breathlessness and symptoms of depression and anxiety, one of which also reported an association with post-traumatic stress disorder [35].

Two randomised controlled trials (RCT) [67, 68] assessed interventions for the prevention or treatment of post-COVID breathlessness. One RCT in Iran [67] showed that among 55 outpatients with mild COVID-19 infection, those receiving sofosbuvir/daclatasvir plus hydroxychloroquine had a lower risk of persistent dyspnoea at 1-month follow-up compared with a control arm receiving hydroxychloroquine alone (15% *versus* 42%, p=0.035).

The other RCT in China [68] evaluated a home-based telerehabilitation programme for COVID-19 (breathing control and thoracic expansion, aerobic and lower limb muscle strength exercise) and showed that, among 120 formerly hospitalised COVID-19 survivors with residual dyspnoea, the intervention group had a lower mMRC dyspnoea level than controls immediately after the 6-week intervention period (p=0.001), but not at the 28-week follow-up.

Seven observational studies [69–75] also suggested that rehabilitation exercises were associated with reduced persistent breathlessness in hospitalised or mild cases of COVID-19. Another small-scale observational study [76] showed that the use of Pycnogenol-Centellicum supplementation was associated with improved breathlessness after COVID-19.

Discussion

Our meta-analyses showed that 26% of COVID-19 survivors reported the presence of breathlessness symptom >4 weeks post-infection, and 41% of survivors reported reduced physical capacity due to post-COVID breathlessness based on the MRC/mMRC dyspnoea scale. The pooled prevalence of self-reported breathlessness symptom decreased significantly over time from 28% at 1–6 months

post-COVID to 20% at 7–12 months. Significant variations in the prevalence estimate were observed across different clinical and population characteristics and methodological approaches.

The overall prevalence estimate was consistent with previous meta-analyses on post-COVID symptoms [2–7]. Post-COVID breathlessness has been associated with reduced quality of life [26], posing limitations to survivors' everyday life and challenges in returning to normal [35]. The pooled prevalence of post-COVID breathlessness obtained from previous meta-analyses ranged from 24% to 37% among COVID-19 survivors [2–7]. However, these studies had a relatively limited time frame (<7 months post-COVID) and did not capture the large number of more recent data with longer-term follow-up of COVID-19 survivors. Although the time course of persisting breathlessness has aroused a controversy due to inconsistent findings from previous studies with multiple follow-up visits [41, 57, 58], our meta-analysis by follow-up duration supports the trend of decreasing prevalence over time. Nevertheless, one in five survivors still suffered from breathlessness 7–12 months after their acute illness, implying that this is not a symptom that simply requires more time to recover and highlighting the unmet need in those affected survivors for timely medical intervention or treatment. We should also bear in mind that the medical needs are likely to vary among patients due to the underlying pathophysiological aetiology of this symptom, especially given the protean effects of this coronavirus (*e.g.* in respiratory and cardiovascular systems), which are complicated by potential consequences of treatment during acute infection (*e.g.* prolonged immobilisation and ventilator-induced lung injury).

When interpreting the prevalence of post-COVID breathlessness among COVID-19 survivors, it is important to distinguish from their pre-existing breathlessness symptom before infection or the population's baseline level. Our subgroup meta-analysis restricted to 20 studies that used recalled pre-COVID breathlessness level as baseline reference when defining self-reported post-COVID breathlessness showed 18% (95% CI 14–21) of patients with COVID-19 reported new or worse breathlessness at the follow-up visit compared with their pre-COVID level. In addition, five of the included studies compared the prevalence of breathlessness between COVID-19 survivors and non-COVID-19 controls. Four of these [19, 23, 48, 77] demonstrated significantly higher prevalence in COVID-19 survivors than controls; the other study [66] observed higher prevalence of breathlessness in controls due to the specific selection criteria (*i.e.* historical nonpatients with COVID-19 who performed combined cardiopulmonary exercise testing and stress echocardiography in their institution). Similar to patients with COVID-19, a large proportion of survivors of severe acute respiratory syndrome (SARS) also experienced persistent breathlessness. A study on 1-year outcomes of 117 SARS survivors showed that 44%, 49% and 45% of the survivors reported breathlessness at the 3-, 6- and 12-month follow-up visits, respectively [78]. Another follow-up study of 50 long-term survivors of acute respiratory distress syndrome (ARDS) showed that 32% of them complained of breathlessness on moderate exercise [79].

We observed a significant difference in pooled prevalence of self-reported post-COVID breathlessness between hospitalised and nonhospitalised patients (27% *versus* 17%). In addition, the pooled prevalence was significantly higher in patients treated for severe or critical acute COVID-19 compared with nonsevere patients (26% *versus* 16%). Female sex was also shown to be a risk factor for post-COVID breathlessness; it is worth further investigation whether the observed sex difference could be explained by differences in absolute spirometric volumes or ventilatory capacity, as suggested by previous data in the general population [80, 81] and in patients with COPD [82]. Despite the limited data on ethnicity/race reported by included papers, we found that studies in Asia had lower pooled prevalence than studies in Europe or North America, which highlights the ongoing need to investigate the ethnic heterogeneity in post-COVID symptoms and also raises the possibility of cultural differences in post-COVID symptom assessment/reporting. Other potential risk factors reported by previous studies included age, obesity and comorbidities (*e.g.* obstructive lung diseases), but the existing evidence for these risk factors was inconsistent and inconclusive. Future confirmatory research of these risk factors could pave the way for personalised risk prediction of post-COVID breathlessness and the stratification of high-risk individuals for targeted intervention or preventive therapies. Moreover, studies with multiple regression models mutually adjusting for these variables are needed to ascertain their relative contributions to post-COVID breathlessness and to account for potential confounding bias.

Our meta-analysis also revealed substantial methodological heterogeneity in the estimation of prevalence of post-COVID breathlessness, including different definitions of post-COVID breathlessness and different follow-up methods. This emphasises the need to account for specific methodological approaches used when interpreting results from individual studies on post-COVID symptoms [83].

The available evidence is insufficient to draw firm conclusions about the underlying mechanisms of post-COVID breathlessness. Previous studies reported inconsistent results for the role of impaired lung

function or lung pathologies (based on pulmonary function tests and imaging data), oxygen desaturation related to exertion, and systemic inflammation, though correlations between mental health disorders (depression and anxiety) and post-COVID breathlessness appear to be more robust [32, 35, 48]. In addition, two clinical investigations [84, 85] of COVID-19 survivors who reported persistent breathlessness identified a range of potential causes, such as a cardiorespiratory cause (parenchymal abnormality, pulmonary embolism, cardiac complications), fibrotic changes, dysfunctional breathing, underlying chronic lung diseases or physical deconditioning. Together, these results suggest that the experience of post-COVID breathlessness may be shaped by multiple factors. Consistent evidence suggests that pulmonary rehabilitation can prevent or reduce post-COVID breathlessness [68–75], although confirmatory evidence from large-scale multicentre RCTs is needed. Corrective measures for specific underlying physiological sequelae should also be considered on a case-by-case basis.

Several limitations in this systematic review should be noted. Substantial between-study heterogeneity was detected in our meta-analyses despite our efforts to identify sources of heterogeneity, which is commonly observed in meta-analyses of prevalence data. Future studies with similar methodological approaches and population characteristics could allow a set of more precise subgroup meta-analyses. Since different starting points for the follow-up period were used by different studies, we applied an operational definition of post-COVID breathlessness as >28 days after either acute COVID-19 infection, symptom onset, initial COVID-19 diagnosis/positive test or hospital discharge. This is a conservative definition because the symptom onset, initial COVID-19 diagnosis/positive test, or hospital discharge occurred after acute COVID-19 infection. In addition, little information on COVID-19 strains or variants was reported in the included papers and the patient recruitment period was either missing or had a wide range in many papers which could not be used to infer underlying variants reliably. Whether different COVID-19 variants (especially the Omicron variant) differ in their long-term respiratory consequences warrants further research. Finally, the heterogeneous or limited evidence on risk factors, mechanisms and treatments of post-COVID breathlessness precluded our ability to perform quantitative syntheses.

In conclusion, this systematic review and meta-analysis demonstrated that over one-quarter of COVID-19 survivors reported post-COVID breathlessness. The prevalence of post-COVID breathlessness decreased over longer-term follow-up and is likely to be influenced by population characteristics (initial disease severity, sex, and continent) and methodological approaches. Given inconsistencies in the available data, no firm conclusion can yet be drawn regarding the pathophysiological mechanisms of post-COVID breathlessness. The limited body of available evidence supports the implementation of rehabilitation exercises in COVID-19 survivors, while confirmatory trials are awaited. Future mechanistic research into the pathophysiology and targeted preventive interventions or treatments for post-COVID breathlessness are needed to meet the growing need for health services of at-risk or affected COVID-19 survivors.

Provenance: Submitted article, peer reviewed.

Author contributions: A. Sheikh and B. Zheng contributed to the conception and design of the work. B. Zheng wrote the first draft of the manuscript with input from L. Daines and A. Sheikh. B. Zheng and Q. Han contributed to the acquisition and analysis of data. All authors critically reviewed the manuscript and approved the final version before submission.

Conflict of interest: A. Sheikh is a member of the Scottish Government Chief Medical Officer's COVID-19 Advisory Group and its Standing Committee on Pandemics, and a member of the UK Government's Risk Stratification Subgroup and AstraZeneca's Thrombotic Thrombocytopenic Taskforce; all roles are unremunerated. P. Pfeffer reports grants from NIHR, outside the submitted work. M. Shankar-Hari reports grants from National Institute for Health Research, outside the submitted work. C.E. Brightling reports grants from UKRI-MRC/DHSC-NIHR. R.A. Evans reports a grant from NIHR Clinician Scientist Fellowship, outside the submitted work. L.V. Wain reports grants from GSK, grants from Orion, outside the submitted work. L.G. Heaney reports personal fees from Novartis, Hoffman la Roche/Genentech Inc, Sanofi, Evelo Biosciences, GlaxoSmithKline, AstraZeneca, Teva, Theravance and Circassia; grants from Medimmune, Novartis UK, Roche/Genentech Inc, GlaxoSmithKline, Amgen, Genentech/Hoffman la Roche, AstraZeneca, Medimmune, Aerocrine and Vitalograph; and other support from Boehringer Ingelheim, Chiesi and Napp Pharmaceuticals, outside the submitted work. All other authors declare no competing interests.

Support statement: This study was supported by a grant to the University of Leicester from the MRC–UK Research and Innovation (UKRI) and the Department of Health and Social Care (DHSC) through the National Institute for Health Research (NIHR) rapid response panel to tackle COVID-19 (grants: MR/V027859/1 and COV0319). The study was also supported by the UK Health Data Research BREATHE Hub and the Chief Scientist Office of the Scottish Government (COV/LTE/20/15). Funding information for this article has been deposited with the Crossref Funder Registry.

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