Asthma and COVID-19 risk: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
The risk of being infected with SARS-CoV-2 was reduced in patients with asthma compared to the non-asthma group. No significant differences in hospitalisation, ICU admission, ventilator use and mortality were found between groups. https://bit.ly/3izKB9h

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Abstract

Background Individual case series and cohort studies have reported conflicting results in people with asthma on the vulnerability to and risk of mortality from coronavirus disease 2019 (COVID-19).

Research question Are people with asthma at a higher risk of being infected or hospitalised or poorer clinical outcomes from COVID-19?

Methods A systematic review and meta-analysis based on five main databases including the World Health Organization COVID-19 database between 1 December 2019 and 11 July 2021 on studies with a control (non-asthma) group was conducted. Prevalence and risk ratios were pooled using Sidik–Jonkman random-effects meta-analyses.

Findings 51 studies with an 8.08% (95% CI 6.87–9.30%) pooled prevalence of people with asthma among COVID-19 positive cases. The risk ratios were 0.83 (95% CI 0.73–0.95, p=0.01) for acquiring COVID-19; 1.18 (95% CI 0.98–1.42, p=0.08) for hospitalisation; 1.21 (95% CI 0.97–1.51, p=0.09) for intensive care unit (ICU) admission; 1.06 (95% CI 0.82–1.36, p=0.65) for ventilator use; and 0.94 (95% CI 0.76–1.17, p=0.58) for mortality for people with asthma. Subgroup analyses by continent revealed a significant difference in risk of acquiring COVID-19, ICU admission, ventilator use and death between the continents.

Interpretation The risk of being infected with severe acute respiratory syndrome coronavirus 2 was reduced compared to the non-asthma group. No statistically significant differences in hospitalisation, ICU admission and ventilator use were found between groups. Subgroup analyses showed significant differences in outcomes from COVID-19 between America, Europe and Asia. Additional studies are required to confirm this risk profile, particularly in Africa and South America, where few studies originate.

Introduction

Asthma is one of the most common chronic conditions with an estimated prevalence of >300 million people globally [1]. As coronavirus disease 2019 (COVID-19) continues to spread across the world with >4.05 million deaths as of 15 July 2021 [2], there are concerns that people with asthma are at a higher risk of acquiring the disease, or of poorer outcomes.

There are differing reports on the vulnerability of asthmatics to COVID-19 based on various local or national level case series and analyses [3]. Several meta-analyses have been conducted, but their conclusions suffer limitations from the inclusion of COVID-19 non-PCR-confirmed cases and inclusion of case series in their analyses which confer significant selection bias [4–6] (supplementary table S1). Most focus only on mortality, but not on other important considerations such as risk of being infected, hospitalised, admission to an intensive care unit (ICU) and importantly ventilator use when admitted [7–9].

A comprehensive understanding of COVID-19 risk among asthmatics globally is crucial as countries lift lockdown, and for prioritisation of vaccine allocation considering the limited supply of vaccines globally.

Hence, we aimed to conduct a comprehensive systematic review and meta-analysis based only on controlled studies with reverse transcriptase (RT)-PCR-confirmed COVID-19 cases to ascertain the pooled prevalence and overall risk of infection, hospitalisation, ICU admission, ventilator use and mortality from COVID-19 among patients with asthma.

Methods

Search strategy and selection criteria

This systematic review and meta-analysis form part of a living systematic review on the risk of COVID-19 for people with asthma. Our first meta-analysis, which included studies up to 26 May 2020, has been published previously [5] and included pre-prints due to the early stage of the pandemic at that point. The protocol was prospectively registered and published in PROSPERO (www.crd.york.ac.uk/PROSPERO CRD42020222303) (appendix 1). The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (www.prisma-statement.org) was used in reporting this study.

A comprehensive search of electronic databases including Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, PubMed, MEDLINE and the World Health Organization COVID-19 database were conducted between 1 December 2019 and 11 July 2021. In addition, a hand search of references of relevant systematic reviews was conducted. In the case of missing information, we contacted the authors whenever possible. If the study identified patients with chronic respiratory conditions, we asked them to specify if this included asthma and requested these data.

We included all primary controlled studies reporting on adults with confirmed COVID-19 based on positive RT-PCR, with a pre-existing diagnosis of asthma, published in the English language. Asthma was defined according to definitions in the individual studies and included those sourced from medical records, physician-diagnosed and self-reported asthma. We excluded studies with $\leqslant$15 participants, pre-prints and those not published in English. The search strategy is available in appendix 2.

Data collection

Two reviewers (AS and SA) screened titles and abstracts and excluded irrelevant studies using Rayyan QCRI [10]. Full-text articles were subsequently reviewed independently, and disagreement resolved *via* consensus and referral to a third reviewer (CJ). Potential overlaps between studies were identified at full-text review to prevent double counting individual patients. A decision on inclusion was made by comparing the study country, location, setting (hospital/community), participant (adults/children), study period and sample size. Data extraction was conducted using a standard electronic form while quality assessment of included studies was performed using the Newcastle–Ottawa Scale [11]. Disagreements were resolved by discussion within the wider team (AS, SA, GL and CJ). No institutional review board approval was required as this study did not independently or prospectively collect patient data.

Outcomes

The outcomes were 1) the risk of acquiring COVID-19, expressed as the proportion of confirmed COVID-19 patients with a pre-existing diagnosis of asthma; 2) risk of hospitalisation from COVID-19 (proportion of confirmed COVID-19 patients hospitalised with asthma); 3) risk of being admitted to ICU (proportion of confirmed COVID-19 patients with asthma admitted to ICU); 4) risk of being ventilated (proportion of confirmed COVID-19 patients with asthma treated with mechanical ventilation once admitted to ICU); and 5) risk of death (proportion of confirmed COVID-19 patients with asthma who are dead or alive).

Data analysis

Descriptive statistics were utilised to summarise the details of the included studies in table 1. The Newcastle–Ottawa Scale [11] was used to assess the methodological quality of included studies based on the relevant study designs cohort or case–control. One star is allocated in the domains of selection and outcome or exposure and up to two stars are allocated to the comparability domain. A total of nine stars are allocated across all three domains. An overall score of 1–3 stars is categorised as low quality, 4–6 as medium quality and 7–9 as high quality.

Two main sets of meta analyses were performed. To pool the prevalence of asthmatics among those with COVID-19, we used the binomial distribution to model the within-study variability and calculated Wilson score 95% confidence intervals.

For all the binary outcomes, we performed Sidik–Jonkman random-effects meta-analysis (assuming that there is not only one true effect size, but a distribution of true effect sizes). We assessed the quantitative

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TABLE 1 Characteristics of included studies

First author [reference]	Country	Setting	Design	Study period	COVID-19 positive		Age (years)		Male (n)	Current smokers (n)	COPD (n)	Diabetes (n)	Hypertension (n)	NOS score (out of 9)
					Asthma (n)	Overall (n)	Mean	Median						
Ahlström [17]	Sweden	Mixed	Case–control study	6 March to 27 May 2020	133	1981		61	1465		75	522	982	9
Almazeedi [41]	Kuwait	Hospital	Retrospective cohort study	24 February to 20 April 2020	43	1096		41	888	44	5	155	177	9
Arslan [46]	Turkey	Hospital	Retrospective cohort study	18 March to 15 May 2020	58	767	51.99		374	80	43	137	220	8
Ashinyo [47]	Ghana	Hospital	Retrospective cohort study	23 March to 29 June 2020	24	307	37.9		174			20	219	7
Aveyard [13]	Mexico	Hospital	Retrospective cohort study	27 February to 21 June 2020	4942	178 306		44.1	88 083					8
Baumer [12]	UK	Hospital	Prospective cohort study	9 March to 7 May 2020	12	52	54.82		29					8
Bergman [18]	Sweden	Mixed	Case–control study	To mid-September 2020	4493	68 575	46		26 808		2168	4897	16 416	9
Beurnier [48]	France	Hospital	Prospective cohort study	15 March to 15 April 2020	37	112		60	49			17	32	9
Calmes [49]	Belgium	Hospital	Retrospective cohort study	18 March to 17 April 2020	57	596	58.75[#]		294					9
Castilla [19]	Spain	Mixed	Retrospective cohort study	July to December 2020	2330	35 387		38.8	17 172	6119	1404	1893	4543	9
Chhiba [50]	USA	Hospital	Retrospective cohort study	1 March to 15 April 2020	220	1526		53.3[#]	654	43				9
Choi [20]	South Korea	Mixed	Retrospective cohort study	To 15 May 2020	218	7372		44.5[#]	3000					9
Dennis [30]	UK	Hospital	Retrospective cohort study	1 March to 27 July 2020	1557	17 606	67		10 560		231	421		9
Eggert [51]	USA	Hospital	Retrospective cohort study	1 March to 30 September 2020	598	5596		38.4	2635	123	88	609	1021	9
Emami [52]	Iran	Hospital	Retrospective cohort study	20 February to 1 March 2020	25	1239	51.48		692	27		176		7
Ferastraoaru [53]	USA	Hospital	Retrospective cohort study	14 March to 27 April 2020	951	4558		60.5						9
Fong [54]	UK	Hospital	Retrospective cohort study	1 March to 31 May 2020	102	617		65						9
Garcia-Pachon [14]	Spain	Community	Retrospective cohort study	3 March to 12 April 2020	10	376		54	192					8
Green [21]	Israel	Mixed	Retrospective cohort study	February to June 2020	153	2266	33.31		1200	102		200	276	9

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TABLE 1 Continued

First author [reference]	Country	Setting	Design	Study period	COVID-19 positive		Age (years)		Male (n)	Current smokers (n)	COPD (n)	Diabetes (n)	Hypertension (n)	NOS score (out of 9)
					Asthma (n)	Overall (n)	Mean	Median						
Guan [55]	China	Hospital	Retrospective cohort study	December 2019 to 6 May 2020	244	39420		55.7	19 655					9
Gude-Sampedro [22]	Spain	Mixed	Retrospective cohort study	6 March to 7 May 2020	288	10454	58		4172	258	180	619	1457	9
Gupta [29]	USA	Hospital	Retrospective cohort study	To 4 March 2020	30	529		70	286	39	36	289	416	6
Hansen [23]	Denmark	Mixed	Retrospective cohort study	1 February to 10 July 2020	354	5104		54.6	2399		432	598		9
Ho [38]	USA	Hospital	Retrospective cohort study	7 March to 7 June 2020	468	10523	58.35		5707		286	1679	2662	9
Je [56]	Australia	Hospital	Retrospective cohort study	March to April 2020	22	197	45		94		4	8	28	7
Kim [57]	South Korea	Hospital	Case–control study	February to May 2020	66	2200	56.71		785	92	30	378	645	9
Kipourou [58]	Kuwait	Hospital	Prospective cohort study	24 February to 27 May 2020	235	3995		40.4	2814	140	17	730	778	9
Lee [15]	South Korea	Community	Retrospective cohort study	January to 27 May 2020	686	7272		45.3	2927			1041	1401	9
Lemus Calderon [59]	Spain	Hospital	Retrospective cohort study	To July 2020	577	6310	59		2983	873		1641	3239	9
Liao [60]	USA	Hospital	Retrospective cohort study	11 March to 23 June 2020	41	113	50		53	2	57	11	18	9
Lieberman-Cribbin [61]	USA	Hospital	Retrospective cohort study	29 February to 24 April 2020	272	6245		57	3060					8
Lombardi [62]	Italy	Hospital	Retrospective cohort study	20 February to 20 April 2020	20	1043		52.5[#]	704					9
Louie [24]	Australia	Mixed	Case series	19 March to 15 May 2020	10	99		54	51		2	8	14	8
Lovinsky-Desir [63]	USA	Mixed	Prospective cohort study	11 February to 7 May 2020	163	1298		52	762	55				9
Martos-Benítez [25]	Mexico	Mixed	Retrospective cohort study	1 January to 12 May 2020	1188	38324	46.9		22 362	3277	889	7168	8340	9
Mash [64]	South Africa	Hospital	Retrospective cohort study	March to June 2020	67	1376	46.3		571	95	50	364	564	8
Mather [65]	USA	Hospital	Case–control study	February to November 2020	88	1045		64.6	352		18	221	307	8
Murillo-Zamora [66]	Mexico	Hospital	Retrospective cohort study	4 March to 15 August 2020	1448	66123		52.4	40 124		2619	21840	26728	9

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TABLE 1 Continued

First author [reference]	Country	Setting	Design	Study period	COVID-19 positive		Age (years)		Male (n)	Current smokers (n)	COPD (n)	Diabetes (n)	Hypertension (n)	NOS score (out of 9)
					Asthma (n)	Overall (n)	Mean	Median						
Nystad [26]	Norway	Mixed	Retrospective cohort study	1 March to 13 May 2020	515	7632		33.22[#]			161	468	977	7
Patone [27]	UK	Mixed	Retrospective cohort study	1 November to 26 January 2021	29 792	198 420	37.7		93 765	22 134	1873	10 347	19 636	9
Robinson [67]	USA	Hospital	Case–control study	4 March to 2 July 2020	562	3248		51	911	131		321	107	8
Rosenthal [68]	USA	Hospital	Retrospective cohort study	March to May 2020	105	727	49.46					165	278	8
Salacup [69]	USA	Hospital	Retrospective cohort study	1 March to 24 April 2020	18	242		66	123		30	118	180	8
Schönfeld [28]	Argentina	Mixed	Retrospective cohort study	3 March to 2 October 2020	12 580	207 079		41	103 487	4074	4405	20 058	39 833	9
Shah [70]	USA	Hospital	Retrospective cohort study	3 February to 31 March 2020	4	33		63	22	0	1	9	16	8
Tutiya [71]	Brazil	Hospital	Retrospective cohort study	13 March to 7 June 2020	7	114		32.4	0			12	13	7
Valverde-Monge [72]	Spain	Hospital	Retrospective cohort study	31 January to 17 April 2020	113	2539		62.66	1275	154	89	403	1054	9
Wang [40]	China	Hospital	Retrospective cohort study	28 January to 25 February 2020	68	562		47	265					8
Yang [37]	South Korea	Community	Retrospective cohort study	1 January to 15 May 2020	725	7340	47.1		2970		350	951	1638	9
Yordanov [16]	France	Mixed	Prospective cohort study	March to August 2020	814	7320	43		2301	790	87	402	978	6
Zhang [31]	China	Hospital	Retrospective cohort study	29 December 2019 to 16 February 2020	1	290		57	155	10	6	27	81	8

COVID-19: coronavirus disease 2019; NOS: Newcastle–Ottawa Scale. [#]: imputed values based on weighted average.

heterogeneity by conducting a formal test of homogeneity and evaluating the proportion of variability due to heterogeneity (I^2). Pre-specified subgroup analyses were conducted by continent and by the quality of the studies (low, medium, high) and univariable meta-regressions using age and proportions of current and former smokers as covariates.

The assessment of small-study effects has been done by regression-based Egger test and eyeball evaluation of the contour-enhanced funnel plots.

Along with the pooled effect sizes and 95% confidence intervals, we also reported the prediction intervals. All pooled results are presented in the form of forest plots. All statistical analyses were performed using Stata 16 (StataCorp LLC, College Station, TX, USA).

Results

The searches resulted in 32 379 citations. After duplicates were removed, 20 559 titles and abstracts were screened, 19 559 articles were excluded. Of the remaining 1000 articles, 949 were excluded after full-text review. A total of 51 studies were included in the review. Studies with overlapping patient populations were excluded if they reported the same outcome (figure 1).

Descriptive characteristics

This review is based on a pooled sample of 1 471 643 COVID-19-tested patients, of whom 965 551 were COVID-19 positive with reported information related to asthma. The sample sizes ranged from 52 [12] to 417 366 [13]. Most of the studies were hospital-based (34 studies) while three were studies [14–16] in the community and 14 had a mixed setting [16–28]. Studies originate from 21 countries spread on all five continents: Europe (n=17), North America (n=13), Asia (n=12), South America (n=5), Africa (n=2) and Australia (n=2). The summary of included studies is presented in table 1.

Among COVID-19 positive patients, based on RT-PCR assay results, the mean±SD age of participants was 52.0±12.9 years, 42.64% were male (n=459 640 from 47 out of 51 studies), 5.4% were current smokers (n=38 672 from 23 out of 51 studies) and 9.8% were former smokers (n=43 622 from 10 out of 51 studies). The prevalence of asthma among those infected with COVID-19 was 8.08% (95% CI 6.87–9.30%; test of homogeneity p<0.001). ∼25% had hypertension (n=135 274 from 35 out of 51 studies), 14.3% had diabetes (n=78 923 from 38 out of 51 studies) and 3% had COPD (n=15 636 from 29 out of 51 studies).

Risk-of-bias results

Scores on the Newcastle–Ottawa Scale ranged between 6 and 9 (maximum 9) [16, 29], with a higher score indicating a higher quality. All studies scored ⩾7 and were of high quality. A full assessment is presented in supplementary table S3.

Meta-analysis of the risk of acquiring COVID-19

The pooled analysis of 10 studies (n=785 151) showed a risk ratio reduction in acquiring COVID-19 of 17% for people with asthma compared to those without asthma (risk ratio 0.83, 95% CI 0.73–0.95; p=0.01; figure 2). There was considerable heterogeneity (I^2=98.46%) across the studies. Meta-regression by age revealed that older age was associated with increased risk of acquiring COVID-19 in individuals with asthma (meta-regression coefficient 0.014, 95% CI 0.004–0.025; p=0.006). Furthermore, R^2 showed that 45.51% of the variance between studies can be explained by age. Heterogeneity remains high when age is included as a moderator in the meta-regression (I^2=92.03%) meaning that it is not a main factor in the difference between studies. No statistically significant association for current smoker (five out of 10 studies; p=0.09) and former smoker were found (two out of 10 studies; p=0.94).

Meta-analysis of the risk of hospitalisation

We observed a non-statistically significant different risk for hospitalisation from COVID-19 for people with asthma compared to no asthma (risk ratio 1.18, 95% CI 0.98–1.42; p=0.08), in the 18 studies (n=411 093) included in this analysis. There was considerable heterogeneity observed (I^2=98.86%) across the studies (figure 3). Meta-regression by age, current smoker (only from nine out of 18 studies) and former smoker (only from six out of 18 studies) revealed no relevant association in risk of being hospitalised with COVID-19 in individuals with asthma.

Meta-analysis of the risk of ICU admission

There was a non-statistically significant different risk of ICU admission (risk ratio 1.21, 95% CI 0.97–1.51; p=0.09) for people with asthma compared to those without asthma in a pooled analysis of 21 studies (n=192 694). Substantial heterogeneity was observed (I^2=94.21%) across the studies (figure 4).

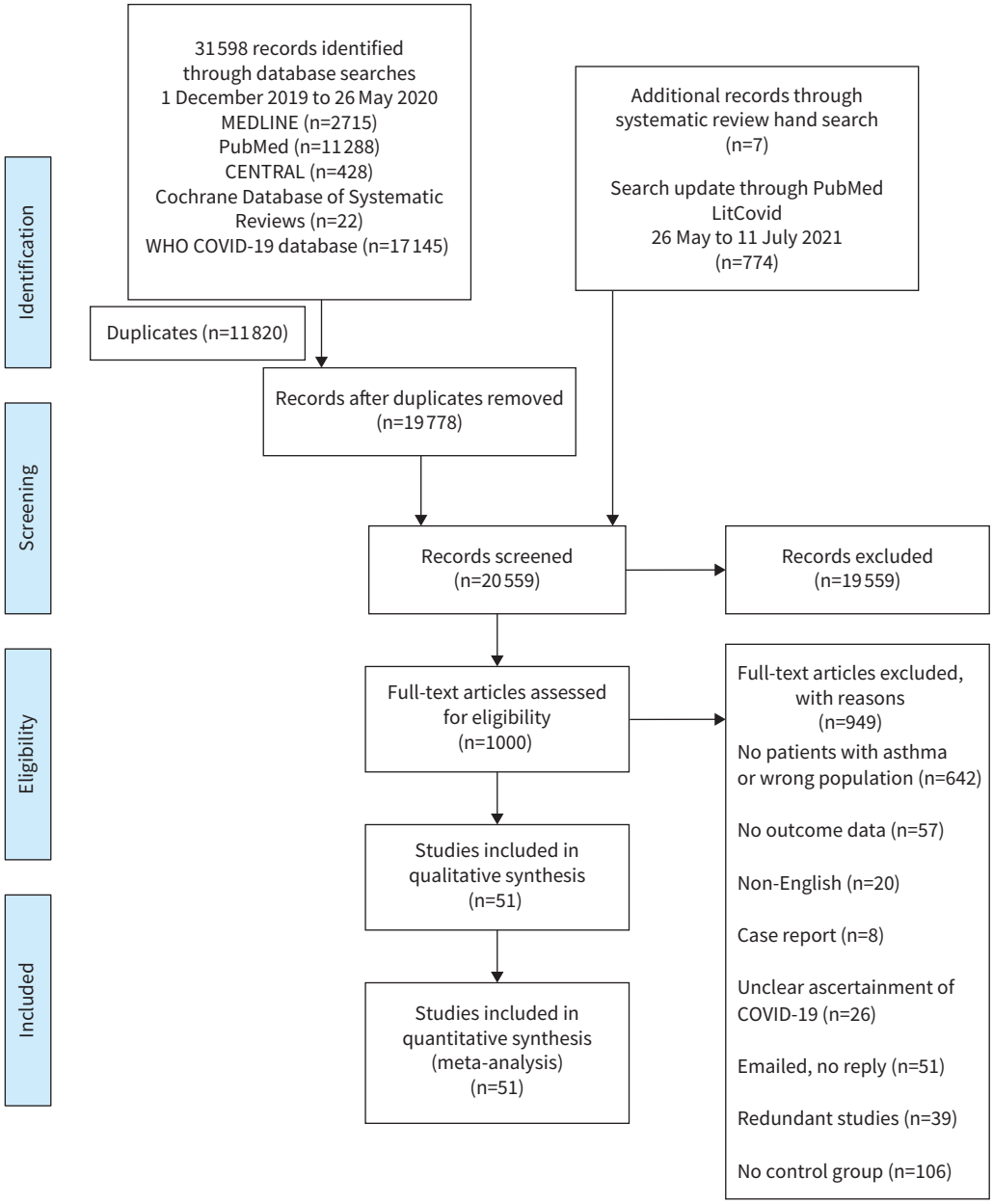

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram [73]. CENTRAL: Cochrane Central Register of Controlled Trials; WHO: World Health Organization; COVID-19: coronavirus disease 2019.

Meta-regression with former smoker (four out of 21 studies) as moderator found a statistically significant decrease in risk of ICU admission (meta-regression coefficient −0.00009, 95% CI −0.0002– -2.65×10^{6}; p=0.043). Meta-regression with age and current smoker (nine out of 21 studies) as moderator did not reveal statistically significant results (p=0.15 and p=0.37, respectively).

Meta-analysis of the risk of ventilator use when admitted into the ICU

In relation to probability of mechanical ventilation, of the 11 studies (n=101694) pooled for this analysis, there was no statistically significant difference in risk of being treated with ventilator once admitted to ICU for people with asthma compared to those without asthma (risk ratio 1.06, 95% 0.82–1.36; p=0.65). Considerable heterogeneity was observed (I^2=87.91%) across the studies (figure 5). Meta-regression with age and current smoker (four out of 11 studies) did not reveal statistically significant results (p=0.276 and p=0.260, respectively). Whereas meta-regression with former smoker as a moderator (two out of 11

Study	Asthma COVID-19$^+$	Asthma COVID-19$^-$	No asthma COVID-19$^+$	No asthma COVID-19$^-$	Risk ratio (95% CI)	Weight (%)
Avayard *et al.*	4942	8841	173 364	230 219	0.83 (0.82–0.85)	13.7
Dennis *et al.*	1557	71	16 049	1579	1.05 (1.04–1.06)	13.7
Fong *et al.*	102	812	515	5209	1.24 (1.01–1.52)	10.5
Green *et al.*	153	3 388	2113	31 815	0.69 (0.59–0.81)	11.5
Liao *et al.*	41	381	72	434	0.68 (0.48–0.98)	6.9
Lieberman-Cribbin *et al.*	272	346	5973	4814	0.79 (0.73–0.87)	12.9
Shah *et al.*	4	38	29	245	0.90 (0.33–2.43)	1.6
Yang *et al.*	725	32 120	6615	180 499	0.62 (0.58–0.67)	13.2
Yordanov *et al.*	814	824	6506	4457	0.84 (0.80–0.88)	13.5
Zhang *et al.*	1	0	248	41	0.88 (0.39–1.95)	2.4
Overall					0.83 (0.73–0.95)	

Heterogeneity: τ^2=0.03, I^2=98.46%, H^2=64.78

Test of $\theta_i=\theta_j$: Q(9)=556.13, p=0.00

Test of θ=0: z=–2.68, p=0.01

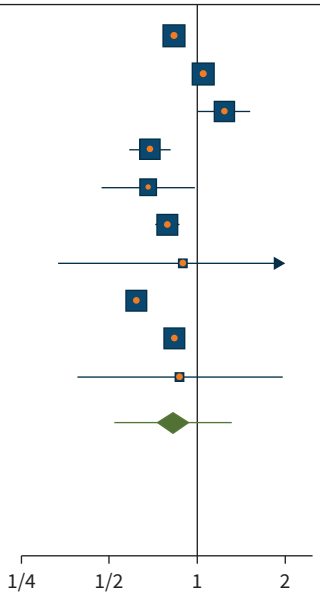

FIGURE 2 Risk of acquiring coronavirus disease 2019 (COVID-19) in individuals with asthma compared with no asthma.

Study	Asthma Hospitalised	Asthma Non-hospitalised	No Asthma Hospitalised	No Asthma Non-hospitalised	Risk ratio (95% CI)	Weight (%)
Bergman *et al.*	1208	3285	12 381	51 701	1.39 (1.32–1.46)	6.4
Castilla *et al.*	147	2183	1933	31 124	1.08 (0.92–1.27)	6.1
Chhiba *et al.*	115	105	738	568	0.93 (0.81–1.06)	6.2
Eggert *et al.*	100	498	505	4493	1.66 (1.36–2.02)	6.0
Ferastraoaru *et al.*	581	370	1915	1692	1.15 (1.08–1.22)	6.4
Garcia-Pachon *et al.*	4	6	154	212	0.95 (0.44–2.05)	3.0
Green *et al.*	17	136	173	1940	1.36 (0.85–2.17)	4.5
Gude-Sampedro *et al.*	103	185	2389	7777	1.52 (1.30–1.78)	6.1
Ho *et al.*	233	235	4669	5386	1.07 (0.98–1.18)	6.3
Lee *et al.*	642	44	6169	417	1.00 (0.98–1.02)	6.4
Lemus Calderon *et al.*	131	466	2033	3680	0.62 (0.53–0.72)	6.1
Louie *et al.*	5	5	14	77	3.25 (1.48–7.13)	3.0
Martos-Benitez *et al.*	367	821	14 938	22 198	0.77 (0.70–0.84)	6.3
Nystad *et al.*	127	515	898	7117	1.77 (1.49–2.09)	6.1
Robinson *et al.*	119	443	487	2199	1.17 (0.98–1.40)	6.0
Rosenthal *et al.*	39	66	235	387	0.98 (0.75–1.29)	5.6
Schonfeld *et al.*	2359	10 221	39 344	155 155	0.93 (0.89–0.96)	6.4
Tutiya *et al.*	4	3	18	89	3.40 (1.58–7.32)	3.0
Overall					1.18 (0.98–1.42)	

Heterogeneity: τ^2=0.14, I^2=98.86%, H^2=88.06

Test of $\theta_i=\theta_j$: Q(17) =383.66, p=0.00

Test of θ=0: z=1.77, p=0.08

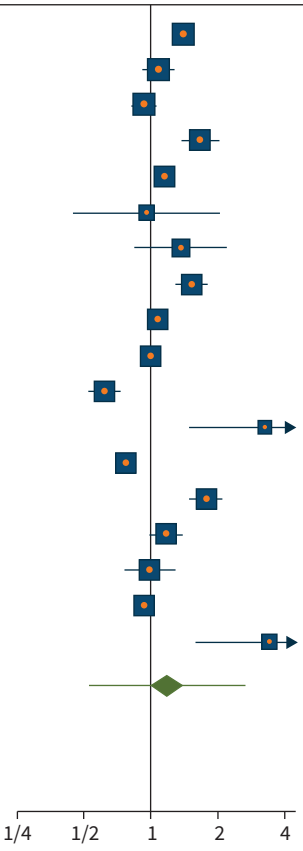

FIGURE 3 Risk of hospitalisation when infected with coronavirus disease 2019 in individuals with asthma compared with no asthma.

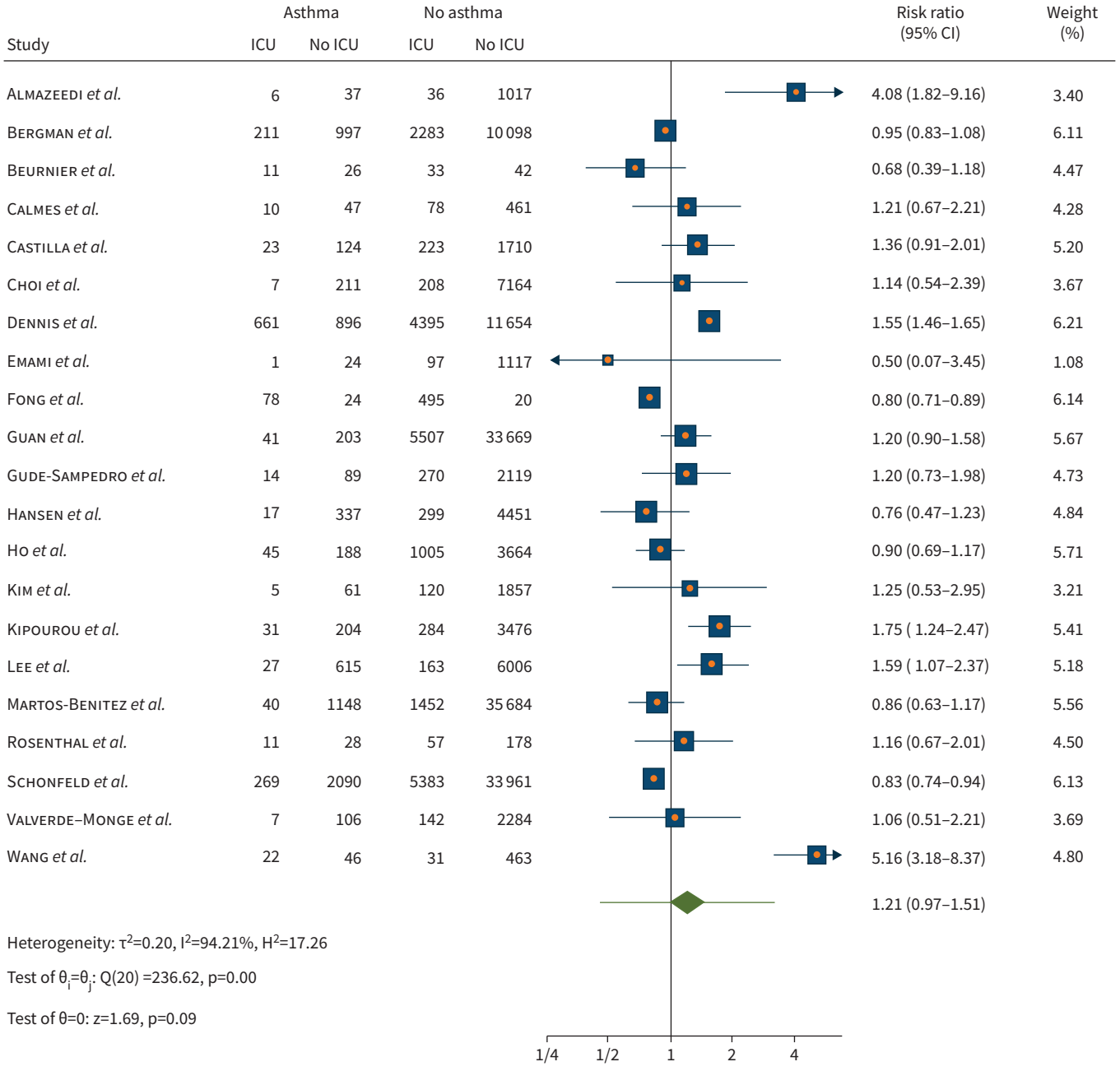

FIGURE 4 Risk of intensive care unit (ICU) admission when infected with coronavirus disease 2019 in individuals with asthma compared with no asthma.

studies) found a reduction in risk of ventilator use (meta-regression coefficient −0.0022, 95% CI −0.0037– −0.0007; p=0.004).

Meta-analysis of the risk of death

There was a non-statistically significant different risk of death from COVID-19 for people with asthma compared to those without asthma in the 32 studies (n=379 381) pooled for this analysis (risk ratio 0.94, 95% CI 0.76–1.17; p= 0.58). Considerable heterogeneity was observed (I^2=94.85%) across the studies (figure 6). When age was included as moderator for meta-regression, there was no statistically significant reduction in risk of death by age (p=0.219). No statistically significant association was also found for current smoker (14 out of 21 studies) and former smoker (seven out of 21 studies) as a moderator (p=0.458 and p=0.288, respectively).

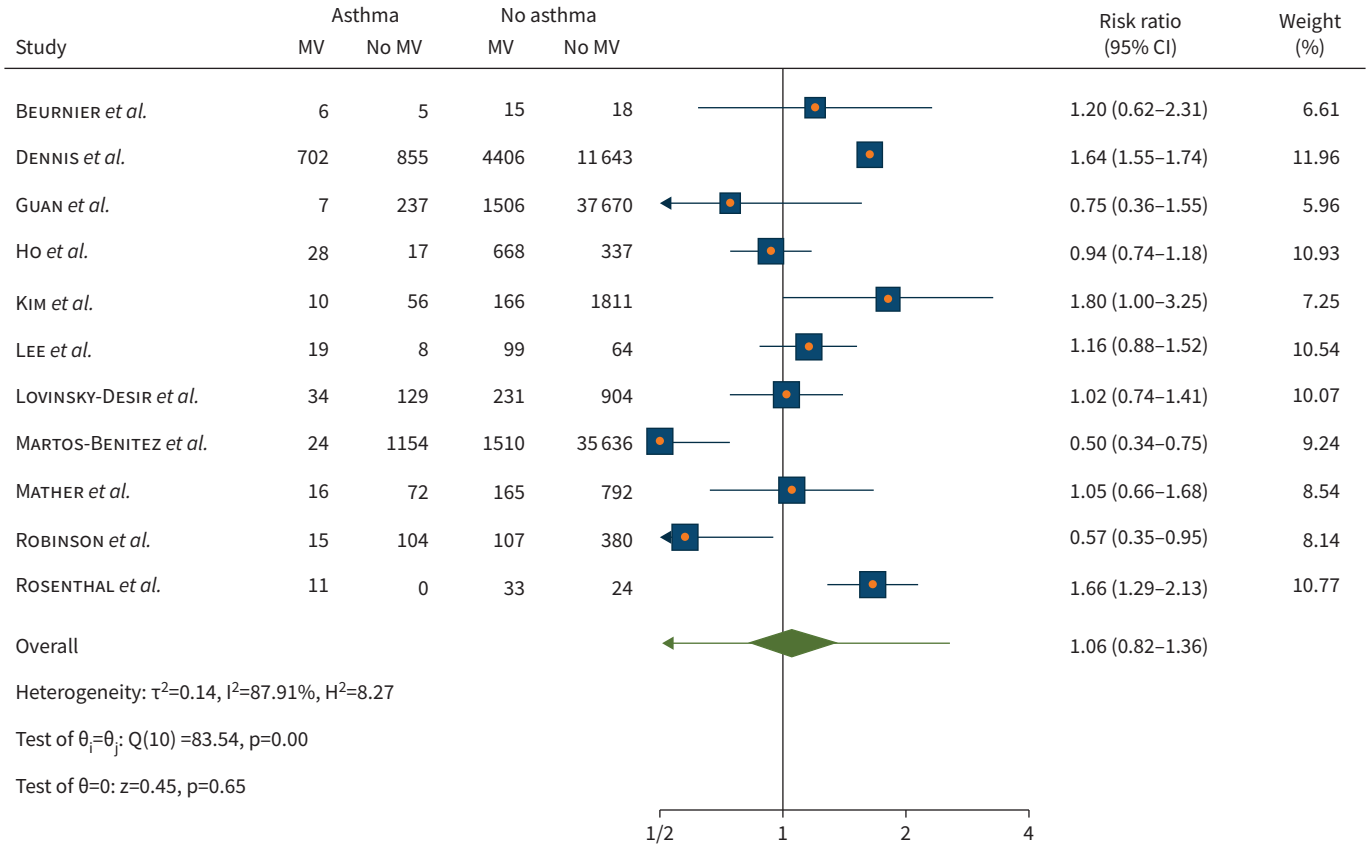

FIGURE 5 Risk of mechanical ventilator (MV) use upon admission to intensive care unit with coronavirus disease 2019 in individuals with asthma compared with no asthma.

Subgroup analyses

Subgroup analyses by continent revealed substantial differences in risk of acquiring COVID-19 between the continents (statistically significant at p=0.001) during the period up to 11 July 2021. It showed the lowest risk in Asia (risk ratio 0.66, 95% CI 0.57–0.75) followed by North America (risk ratio 0.78, 95% CI 0.69–0.89), South America (risk ratio 0.84, 95% CI 0.82–0.85) and Europe (risk ratio 1.01, 95% CI 0.82–1.26). No major differences were found between continents in hospitalisation (p=0.128). However, relevant differences in ICU admission were found between continents (statistically significant at p=0.007). The highest risk was found to be in Asia (risk ratio 1.81, 95% CI 1.12–2.91) followed by Europe (risk ratio 1.04, 95% CI 0.86–1.27), North America (risk ratio 0.96, 95% CI 0.72–1.27) and lowest in South America (risk ratio 0.84, 95% CI 0.75–0.93).

In addition, risk of ventilator use was statistically significant different across the continents (p<0.001). The highest risk was found to be in Europe (risk ratio 1.59, 95% CI 1.26–2.00), followed by Asia (risk ratio 1.19, 95% CI 0.74–1.91), North America (risk ratio 1.02, 95% CI 0.74–1.42) and South America (risk ratio 0.50, 95% CI 0.82–1.36). Similarly, risk of death was quite different across the continents (p=0.011). The highest risk was found to be in Asia (risk ratio 2.01, 95% CI 1.19–3.39), followed by Europe (risk ratio 0.85, 95% CI 0.68–1.05), North America (risk ratio 0.79, 95% CI 0.58–1.06) and South America (risk ratio 0.72, 95% CI 0.47–1.12).

Subgroup analyses by study quality for risk for death showed significantly higher risk in the one study of medium quality compared to the 30 higher-quality ones (risk ratio 1.45, 95% CI 1.14–1.87 *versus* risk ratio 0.92, 95% CI 0.74–1.15; p=0.007).

Publication bias

Egger's test showed evidence of small-study effects for the pooled proportion of COVID-19-positive (RT-PCR) individuals (p<0.0001) and risk of hospitalisation (p=0.0199), but not for all other outcomes

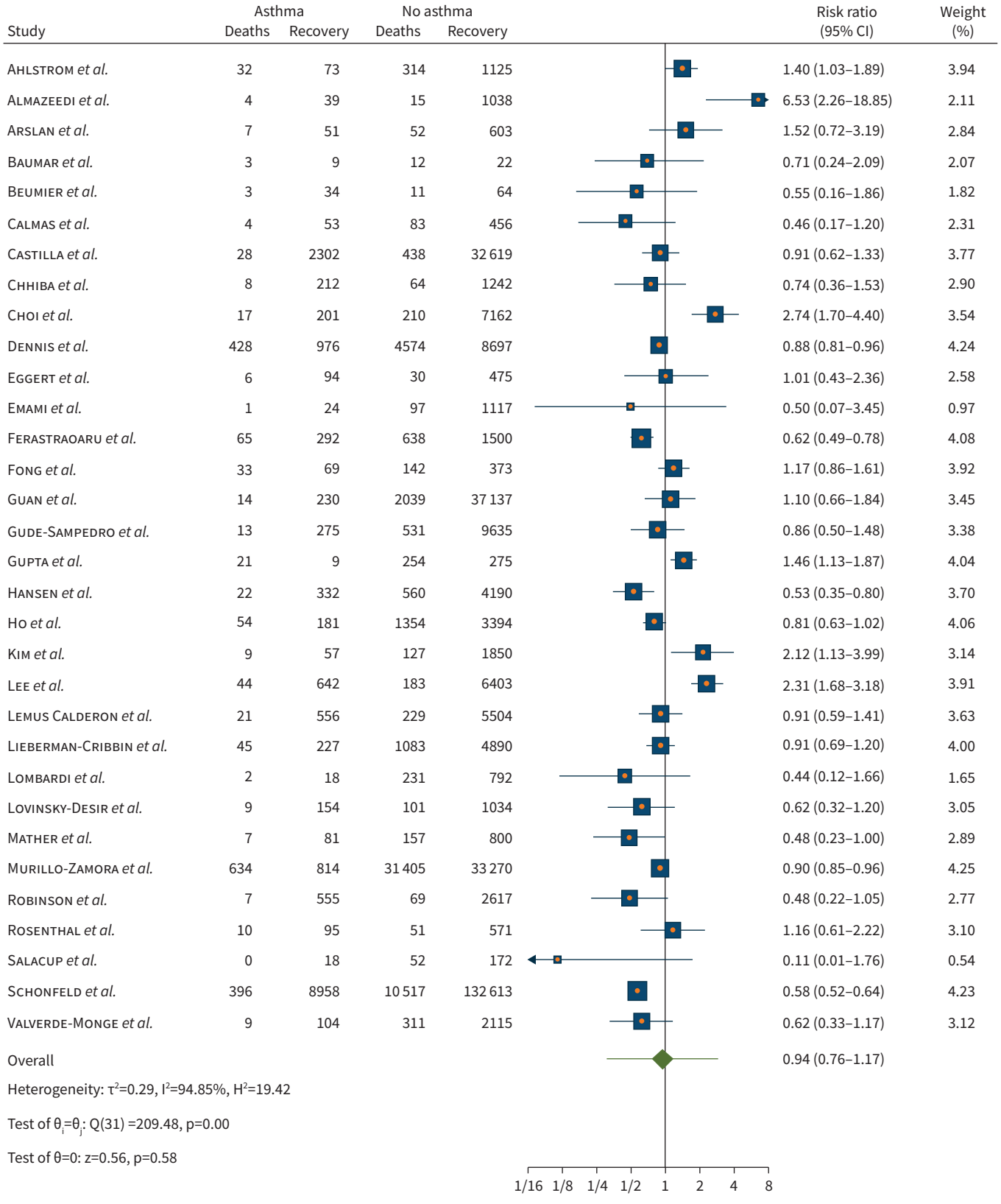

FIGURE 6 Risk of death when infected with coronavirus disease 2019 in individuals with asthma compared with no asthma.

(supplementary table S3). Eyeball assessment of the contour enhanced funnel plots revealed asymmetry only for the risk of hospitalisation, but not other outcomes (supplementary figures S1–S6).

Discussion

This meta-analysis aimed to rigorously assess the vulnerability of patients with asthma to COVID-19 based on controlled studies. It revealed an 8.08% prevalence of asthma among those who tested COVID-19 positive based on RT-PCR. This pooled prevalence is higher than the 7.46% prevalence in our previous meta-analysis [30] which analysed studies including pre-prints until May 2020. Only one study [31] from the previous meta-analysis was included in this meta-analysis. This is due to the tighter inclusion criteria of including only published studies with a non-asthma control group, and excluding case series and single-arm cohort studies. Furthermore, both these prevalence rates were lower than the global prevalence of self-reported asthma symptoms of 8.6% [32].

While the proportion estimated in this meta-analysis is lower than in two recent studies in the UK [27] which reported a prevalence of ∼15% in those infected with the B.1.1.7 variant; lower prevalence rates have been reported in other studies in Italy [33] and in Turkey [34] (2.1% among 2000 patients and 3.7% among 565 patients, respectively).

In the studies that report them, we found a high pooled proportion of hypertension (25.7%) and diabetes (14.3%) as comorbidities. These were mostly contributed by hospital studies (22 of the 35 studies reporting hypertension and 24 of the 38 studies reporting diabetes).

This study found a statistically significant risk reduction of 17% (95% CI 5–27%) for acquiring COVID-19, similar to the 14% reduction reported in our previous study [5]. This result is similar to a study from Missouri, USA which reported lower COVID-19 test positivity rates in asthmatics *versus* non-asthmatics (69.2% *versus* 81.9%) [35]. Furthermore, a community study in Mexico showed a lower proportion of asthmatics in a COVID-19 positive group compared to a negative group (2.8% *versus* 3.7%; OR 0.74, 95% CI 0.71–0.77) [21, 36].

Subgroup analyses by continent revealed significant differences in risk of acquiring COVID-19 between the continents, the lowest risk being in Asia (risk ratio 0.66, 95% CI 0.57–0.75) followed by North America (risk ratio 0.78, 95% CI 0.69–0.89), South America (risk ratio 0.84, 95% CI 0.82–0.85) and Europe (risk ratio 1.01, 95% CI 0.82–1.26). Additionally, we noted the consistent nature of the risk reduction in three out of the four regions where data are available. The risk reduction in Asia was found to be consistent in the three studies pooled from China [31], Israel [21] and South Korea [37]; all countries with a high testing regime which might account for this variance between regions. However, analysis of community studies such as this could better reflect the true nature of the risk compared to analysis of hospital-based studies. In addition, it is important to note that this result may not reflect other countries in Asia such as India and Southeast Asia where testing regimes have not been as extensive.

Several possible mechanisms might contribute to a lower risk of acquiring COVID-19 in people with asthma compared to a non-asthmatic population. A retrospective study by Ho *et al.* [38] showed that not only is asthma associated with lower risk of poor outcomes, but the presence of eosinophilia ($\geqslant$200 cells·μL^{-1}) both in those with and without asthma was also reported to be associated with reduced mortality risk. While not statistically significant, a higher proportion of those with asthma in this study had eosinophilia compared to non-asthmatics (38.2% *versus* 32.3%) [38].

Furthermore, a lower risk of acquiring COVID-19 may be attributed to the expression of the angiotensin-converting enzyme (ACE)2 receptor, which is significantly lower in asthma patients compared to those with COPD and healthy controls, as reported in another study [6] which showed that ACE2 expression is increased with older age (at p=0.03). This supports the result of our analysis, which showed strong evidence of increasing age being associated with increased risk of acquiring COVID-19. Finally, people with asthma have been advised by health authorities to practise social distancing and be particularly careful to avoid contracting COVID-19. This was especially the case early in the pandemic when the added risks of having an underlying lung condition were assumed to be substantial. To the extent that these messages [39] were taken seriously by people with asthma, their risk of acquiring infection could have been commensurately reduced.

We also found similar risks for hospitalisation, ICU admission when hospitalised and ventilator use in this study. Even so, we note that for hospitalisation, while not statistically significant, the pooled point estimate

suggests a possible 18% increased risk of hospitalisation from COVID-19 for people with asthma, with a wide confidence interval (95% CI −2–42%).

Similarly, for ICU admission, while not statistically significant, the pooled point estimate suggests a possible 21% increased risk of ICU admission from COVID-19 for people with asthma (95% CI −3–51%). One study from China [40] and another from Kuwait [41] reported risk ratios of 5.16 and 4.08, respectively, far greater than in other studies. These differences in risk may be linked to resource allocation and availability or difference in vulnerability due to ethnicity or other environmental factors.

An important finding of this current study and our previous meta-analysis is the similar risk of death between asthmatics and non-asthmatics from COVID-19. While this may be due to a variety of factors, two recent randomised controlled trials of budesonide (an inhaled corticosteroid frequently prescribed to patients with asthma) [42, 43] have raised the possibility that this is an effect of the inhaled corticosteroid. They reported that early administration of inhaled budesonide reduced the likelihood of urgent medical care and reduced time to recovery from COVID-19. One of these studies, the STOIC open-label trial in 146 participants showed a number needed to treat of eight with budesonide to reduce COVID-19 deterioration, and that clinical recovery occurred a day faster in the budesonide group compared to usual care (7 days, 95% CI 6–9 days *versus* 8 days, 7–11 days; log-rank test p=0.007) [42]. The other study is an interim analysis of the PRINCIPLE trial published as a pre-print, which randomised 751 participants to budesonide compared with 1028 usual care and 643 on other interventions showed a faster recovery in the budesonide group compared to usual care (hazard ratio 1.208, 95% Bayesian credible interval (BCI) 1.076–1.356; probability of superiority 0.999, estimated benefit of 3.011 days, 95% BCI 1.134–5.41 days) [43].

A limitation of this study is the inclusion of very few studies originating from Africa and South America. Additionally, most of the studies were hospital-based, which is likely to be a consequence of including only COVID-19 cases confirmed by RT-PCR. We chose RT-PCR positivity to give more certainty to our estimation of the association between asthma and several important COVID-19 outcomes. As PCR testing regimens show substantial variation between countries, our results might not be generalisable to regions which are poorer and marginalised or to groups that might be less likely to seek testing. In these regions, it is likely that due to under-testing the true proportion of asthmatics as well as the general public with COVID-19 is substantially higher than official reports, by a magnitude of multiple folds [44, 45].

Potential selection bias to those more unwell may also be present due to the large number of hospital-based studies included in this review. Even so, 10 of the studies found to calculate the risk of getting the infection were community based (n=726 269), which we hope provides a better representation of risk for the general community.

There was minimal information provided on smoking (only 23 out of 51 studies indicated the proportion of current smokers, and 10 out of 51 indicated the proportion of former smokers). Hence, based on the 10 studies, we found that being a former smoker was associated with a lower risk of ICU admission; however, this minimal information limits the generalisability of our assessment of the impact of smoking. Despite these limitations, the majority of studies we included were of high quality with minimal selection bias due to their large sample sizes, data sourcing through electronic health records or data linkages which resulted in minimal loss to follow-up. Additionally, we used hard outcome measures such as COVID-19 infection (PCR positivity), hospitalisation, ICU admission and death, which are generally well-defined globally, limiting the risk of classification bias. Funnel plots and Egger's test for small-study effects were also conducted to explore the presence of publication bias and we found that most outcomes do not show signs of publication bias.

Furthermore, our conclusions are based on studies which report details of both asthma and non-asthma patients where COVID-19 infection status was confirmed by RT-PCR results and not only by symptoms or suspected cases in the context of the pandemic. We did not have access to information that would enable us to determine if people with asthma were over-represented among mild or asymptomatic cases that did not receive testing.

In conclusion, the findings from this analysis indicate the prevalence of asthma was 8.08% among people who were RT-PCR-positive for COVID-19 in these controlled studies. The overall findings suggest that people with asthma are at lower risk of being infected with COVID-19 compared to those without asthma, but have a similar risk of hospitalisation, ICU admission, ventilator use and mortality when RT-PCR-positive. With the fast evolution of the severe acute respiratory syndrome coronavirus 2 virus and the emergence of variants globally, caution must be maintained for people with asthma. There remains a

need for higher-quality community studies as well as regular risk assessments and review of new data throughout the pandemic. Furthermore, additional studies are required to confirm this risk profile, particularly in Africa and South America, where none of the eligible studies originated.

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Conflict of interest: None declared.

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