Asthma and risk of infection, hospitalization, ICU admission and mortality from COVID-19: Systematic review and meta-analysis

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ABSTRACT

Objective: As COVID-19 spreads across the world, there are concerns that people with asthma are at a higher risk of acquiring the disease, or of poorer outcomes. This systematic review aimed to summarize evidence on the risk of infection, severe illness and death from COVID-19 in people with asthma.

Data sources and study selection: A comprehensive search of electronic databases including preprint repositories and WHO COVID-19 database was conducted (until 26 May 2020). Studies reporting COVID-19 in people with asthma were included. For binary outcomes, we performed Sidik-Jonkman random effects meta-analysis. We explored quantitative heterogeneity by subgroup analyses, meta regression and evaluating the $I^2$ statistic.

Results: Fifty-seven studies with an overall sample size of 587,280 were included. The prevalence of asthma among those infected with COVID-19 was 7.46\% (95\% CI = 6.25–8.67). Non-severe asthma was more common than severe asthma (9.61\% vs. 4.13\%). Pooled analysis showed a 14\% risk ratio reduction in acquiring COVID-19 (95\% CI = 0.80–0.94; $p<0.0001$) and 13\% reduction in hospitalization with COVID-19 (95\% CI = 0.77–0.99; $p=0.03$) for people with asthma compared with those without. There was no significant difference in the combined risk of requiring admission to ICU and/or receiving mechanical ventilation for people with asthma (RR = 0.87 95\% CI = 0.94–1.37; $p=0.19$) and risk of death from COVID-19 (RR = 0.87; 95\% CI = 0.68–1.10; $p=0.25$).

Conclusion: The findings from this study suggest that the prevalence of people with asthma among COVID-19 patients is similar to the global prevalence of asthma. The overall findings suggest that people with asthma have a lower risk than those without asthma for acquiring COVID-19 and have similar clinical outcomes.

Abbreviations: ACE-2: angiotensin-converting-enzyme-2; CDC: United States Center for Disease Control and Prevention; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; ICU: intensive care unit; ICS: inhaled corticosteroids; MERS: Middle East Respiratory Syndrome; RRR: relative risk reduction; SARS-CoV-1: severe acute respiratory syndrome coronavirus 1; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Introduction

As COVID-19 continues to spread across the world with devastating impact, there are concerns that people with asthma are at a higher risk of acquiring the disease, or of poorer outcomes. This is based on three main factors. Firstly, people with chronic respiratory conditions such as asthma were historically reported to be at higher risk compared to their counterparts during the Middle East Respiratory Syndrome (MERS), caused by a virus with close sequence homology to SARS-CoV-2 (1). Thus, it appeared likely that this is also the case with COVID-19. Secondly, viral respiratory infections such as coronaviruses are potent triggers of asthma exacerbations (2). Lastly, inhaled and oral corticosteroids, a mainstay treatment for persistent...
asthma, and for acute exacerbations respectively, may increase susceptibility to COVID-19 infection and its severity (2). While these theories seem plausible, there is limited evidence to support them.

Current evidence shows that asthma is not in the top 10 comorbidities associated with COVID-19 fatalities, with obesity, diabetes and chronic heart disease being most commonly reported (3). This is consistent with trends observed during the SARS-CoV-1 epidemic. Early reports from Wuhan in China suggest that asthma is underrepresented compared to the population prevalence (4). However, the United States Center for Disease Control (CDC) has reported that among younger patients hospitalized for COVID-19, obesity, asthma and diabetes were the most common comorbidities (3).

There have been recommendations from various government agencies (5,6) across the world advising people with asthma to be more cautious and self-isolate longer which affects their livelihood, mental health and quality of life. People with asthma were reported have a higher prevalence of anxiety and stress than non-asthma controls (7). A qualitative study in the United Kingdom among patients with respiratory disease including asthma reported that they were fearful of death if infected with COVID-19 and confused with the mixed messages on shielding they received (8). Additionally despite this advice, evidence for the longer duration of self-isolation for people with asthma is scant. The overall objective of this systematic review is to provide the best available evidence on the risk of infection, severe illness (requiring admission to ICU and/or mechanical ventilation) and death from COVID-19 in people with asthma.

Methods

Search strategy and selection criteria

The protocol of this systematic review was pre-registered and published in PROSPERO (CRD42020185673). All studies on COVID-19 until the 26th of May 2020 were screened for inclusion. The details of the full search strategy and study selection procedures are outlined in Supplementary appendix 1.

Data analysis

Two main sets of meta analyses were performed. To pool the proportions of people with asthma among those with COVID-19, we used the binomial distribution to model the within-study variability and calculated Wilson score test-based confidence intervals.

For all the binary outcomes, we performed Sidik-Jonkman random effects meta-analysis. We assessed the quantitative heterogeneity by conducting a formal test of homogeneity and evaluating the proportion of variability due to heterogeneity ($I^2$). We performed univariable random effects meta regressions including age and the proportion of current and former smokers as covariates, and conducted subgroup analyses by continent (America, Asia, Europe) and by the quality of the studies (low, medium, high).

We performed several sensitivity analyses. For hospitalization, we calculated the number of non-hospitalized patients from the total number of COVID-19 patients in each group subtracted from those hospitalized. As such, we were able to pool a larger number of studies for this outcome. For death, we performed a best-case (all patients not dead were taken as “alive”) and a worst-case analysis (all patients reported as not having yet recovered were taken as “dead”). Lastly, we removed one outlier study (9) from the base-case sensitivity analysis. The assessment of small-study effects were done by regression-based Egger test and eyeball evaluation of the contour-enhanced funnel plots.

In the forest plots along with the pooled effect sizes and 95% confidence intervals, we also reported the prediction intervals (to show the range of true associations that can be expected in future studies) (10). All statistical analyses were performed using Stata 16 (StataCorp LLC, College Station, TX, USA).

Results

We identified 34856 records, of which 34845 were retrieved through database searching. The selection process is presented in a PRISMA flow diagram (Figure 1). Overall, 57 studies (54 references (3,9,11–62)) were included in the report. Of the 57 studies included totaling 587280 people who were tested for COVID-19, there were 41 cohort studies (25 conducted retrospectively, 15 prospectively and 1 ambispective), 12 case series, 1 case control, 1 RCT, 1 quasi-experimental and 1 diagnostic study. Sample sizes ranged from 8 (34) to 119528 (21) people. Most of the studies were hospital-based (45 studies) while 6 were studies in the community and 6 with mixed setting. Studies were from Asia ($n=19$), Europe ($n=14$), North America ($n=22$) and South America ($n=2$). The summary table of included studies are presented in Table 1.

A total of 349592 tested positive for COVID-19. Four studies (3,14,33,59) only included children ($n=211$). The remaining studies consisted of adults or a mixed population (21). Mean age of the
The prevalence of asthma among those infected with COVID-19 was 7.46% (49 studies, 95% CI 6.25–8.67; test of homogeneity \(p < 0.001\)) as shown in Figure S1. In the six studies where asthma was described by severity \((n = 3313)\), non-severe asthma among people with COVID-19 was more common than severe asthma \((9.61\%, 95\% \text{ CI} = 6.09–13.13 \text{ vs. } 4.13\%, 95\% \text{ CI} = 1.35–6.91)\), see Figure S2.

The pooled analysis of 6 studies \((n = 369405)\) showed a Risk Ratio Reduction (RRR) in acquiring COVID-19 of 14% for people with asthma compared to those without asthma \((RR = 0.86, 95\% \text{ CI} = 0.80–0.94; p < 0.0001; \text{ Figure 3})\). There was moderate heterogeneity \(I^2 = 62.19\%\) across the studies.
Table 1. Summary of included studies.

| Study                        | Country                  | City                     | Setting            | Design                        | Total Sample Size | Asthma (n) | Overall (n) | Mean (SD) | Median (IQR) | Male (n, from overall sample) | Current smokers (n) |
|------------------------------|--------------------------|--------------------------|--------------------|------------------------------|-------------------|------------|-------------|-----------|--------------|-------------------------------|---------------------|---------------------|
| Arentz et al. (11)           | USA                      | Washington              | Hospital           | Prospective Cohort Study     | 21                | 2          | 21          | 70b       |                           | 11                             | 0                   |
| Argenziano et al. (12)        | USA                      | New York                | Hospital           | Case Series                  | 1000              | 113        | 1000        | 63 (50–75) |                           | 596                            | 49                  |
| Auld et al. (13)             | USA                      | Georgia                 | Hospital           | Retrospective Cohort Study   | 217               | 19         | 217         | 64 (54–73) |                           | 119                             | 0                   |
| Belladjer et al. (14)         | France, Switzerland      |                          |                    | Prospective Cohort Study     | 35                | 3          | 35          | 10 (2–16) |                           | 18                              | 0                   |
| Bhatraju et al. (15)         | USA                      | Seattle                 | Hospital           | Case Series                  | 24                | 3          | 24          | 64 (18)   |                           | 15                              | 0                   |
| Borba et al. (16)            | Brazil                   |                          | Hospital           | Randomized Controlled Trial  | 81                | 4          | 81          | 51.1 (13.9) |                           | 61                              | 4                   |
| Borobia et al. (17)          | Spain                    | Madrid                  | Hospital           | Prospective Cohort Study     | 2226              | 115        | 2226        | 61 (46–78) |                           | 1074                            | 157                 |
| Docherty et al. (22)         | UK                       |                          | Hospital           | Prospective Cohort Study     | 20133             | 2540       | 20133       | 73 (58–82) |                           | 12068                           | 852                 |
| Fadel et al. (23)            | USA                      | Michigan                | Hospital           | Quasi Experimental Study     | 213               | 33         | 213         | 62 (51–62) |                           | 109                             | 88                  |
| Goyal et al. (24)             | USA                      | New York                | Hospital           | Case Series                  | 393               | 49         | 393         | 62.2 (48.6–73.7) |                           | 238                             | 20                  |
| Grasselli et al. (25)         | Italy                    | Lombardy                | Hospital           | Case Series                  | 1043              | 29         | 1043        | 63 (11)   |                           | 838                             | 0                   |
| Jacobs et al. (26)           | USA                      | Hospital                | Prospective Cohort Study | 32                | 3          | 32          | 52.41 (12.49) |                           | 22                              | 0                   |
| Ji et al. (28)               | South Korea              |                          | Hospital           | Retrospective Cohort Study   | 28                | 1          | 28          | 42 (21–73) |                           | 15                              | 0                   |
| Kim et al. (29)              | South Korea              |                          | Hospital           | Case Series                  | 13                | 1          | 13          | 31 (17.8–55.8) |                           | 6                                | 0                   |
| Lechien et al. (30)          | France, Italy, Spain, Belgium, Switzerland | Hospital | Retrospective Cohort Study | 1420              | 93         | 1420        | 39.17 (12.09) |                           | 458                             | 203                 |
| Li et al. (31)               | China                    | Wuhan                   | Hospital           | Ambispective cohort study    | 548               | 5          | 548         | 60 (48–69) |                           | 279                             | 41                  |
| Lian et al. (32)             | China                    | Zhejiang province       | Hospital           | Retrospective Cohort Study   | 788               | 6          | 788         | 48.5b     |                           | 407                             | 54                  |
| Licari et al. (33)           | Italy                    | South Lombardy and Liguria | Hospital | Case Series                  | 40                | 1          | 40          | 5 (1–12.5) |                           | 19                              | 0                   |
| Ling et al. (34)             | Hong Kong                |                          | Hospital           | Retrospective Cohort Study   | 8                 | 0          | 8           | 64.5 (42–70) |                           | 4                               | 1                   |
| Lokken et al. (35)           | USA                      | Washington              | Hospital           | Retrospective Cohort Study   | 46                | 4          | 46          | 29 (26–34) |                           | 0                               | 0                   |
| Mahdavinia et al. (36)       | USA                      | Community               | Hospital           | Retrospective Cohort Study   | 935               | 241        | 935         | 45.71b    |                           | 337                            | 0                   |
| Merza et al. (38)            | Iraq                     |                          | Hospital           | Prospective Cohort Study     | 15                | 2          | 15          | 28.06 (16.42) |                           | 9                                | 0                   |
| National Committee on Covid-19 Epidemiology (9) | Iran        |                          | Hospital           | Mixed                       | 14991             | 307        | 14991       | 54.7b     |                           | 8544                            | 0                   |
| OPEN Safely Collaborative(20) | UK                       |                          | Hospital           | Prospective Cohort Study     | 5683              | 911        | 5683        | 49.65b    |                           | 3585                            | 393                 |
| Peng et al. (40)             | China                    | Wuhan                   | Hospital           | Case Series                  | 11                | 1          | 11          | 61 (51–69) |                           | 8                               | 6                   |
| Pongpirul et al. (41)        | Thailand                 | Bangkok                 | Hospital           | Retrospective Cohort Study   | 11                | 0          | 11          | 61 (28–74) |                           | 6                              | 0                   |
| Richardson et al. (45)       | USA                      | New York                | Hospital           | Case Series                  | 5700              | 479        | 5700        | 63 (52–75) |                           | 3437                            | 2691               |
| Sun et al. (50)              | China                    | Beijing                 | Hospital           | Retrospective Cohort Study   | 63                | 2          | 63          | 47 (3–85) |                           | 37                              | 0                   |
| Tomlins et al. (51)          | UK                      | North Bristol           | Hospital           | Retrospective Cohort Study   | 95                | 21         | 95          | 75 (59–82) |                           | 60                              | 0                   |
| Wang et al. (52)             | China                    | Shenzhen                | Hospital           | Retrospective Cohort Study   | 55                | 1          | 55          | 49 (2–69) |                           | 22                              | 0                   |
| Wei et al. (54)              | China                    | Wuhan                   | Hospital           | Retrospective Cohort Study   | 14                | 1          | 14          | 36 (±6)   |                           | 4                               | 0                   |
| Wichmann et al. (56)         | Germany                  | Hamburg                 | Hospital           | Prospective Cohort Study     | 12                | 2          | 12          | 73 (52–87) |                           | 9                               | 0                   |
| Wu et al. (57)               | China                    | Jiangsu province        | Hospital           | Retrospective Cohort Study   | 80                | 0          | 80          | 46.1 (15.42) |                           | 39                              | 0                   |
| Yasukawa et al. (58)         | USA                      | Washington              | Hospital           | Case Series                  | 10                | 2          | 10          | 53.2b     |                           | 7                               | 0                   |
| Zhang et al. (61)            | China                    | Wuhan                   | Hospital           | Retrospective Cohort Study   | 290               | 1          | 290         | 57b       |                           | 155                             | 10                  |
| Zhu et al. (62)              | China                    | Ningbo                  | Hospital           | Case Series                  | 127               | 0          | 127         | 50.90 (15.26) |                           | 0                               | 0                   |
| Pre-prints                   |                          |                          |                    |                              |                   |            |             |           |                           |                                |                    |
| Burn et al. (CUI/MCI) (18)   | USA                      | Hospital                | Prospective Cohort Study | 916                | 65         | 916         | 61.4b     |                           | 476                             | 0                   |
| Burn et al. (STARR =) (18)   | USA                      | California              | Hospital           | Prospective Cohort Study     | 141               | 19         | 141         | 60b       |                           | 80                              | 0                   |
| Burn et al. (VA) (18)        | USA                      | Veterans Affair         | Hospital           | Prospective Cohort Study     | 577               | 57         | 577         | 65.6b     |                           | 542                             | 0                   |
| Carr et al. (19)             | UK                       | Southeast London        | Hospital           | Retrospective Cohort Study   | 452               | 65         | 452         | 67 (28)   |                           | 248                             | 0                   |

(Continued)
We observed a significant RRR in hospitalization from COVID-19 of 13% for people with asthma compared to no asthma (RR = 0.87, 95% CI = 0.77–0.99, p = 0.03), in the 4 studies (n = 121127) included in this analysis. There was moderate heterogeneity observed (I^2 = 62.76%) across the studies. See Figure 4(A).

There was a non-significantly different risk of developing severe illness from COVID-19 requiring admission to ICU for people with asthma compared to those without asthma (RR = 1.19, 95% CI = 0.93–1.53, p = 0.16), in a pooled analysis of 6 studies (n = 4325). Low heterogeneity is observed (I^2 = 0.10%) across the studies. See Figure 4(B).

In relation to probability of mechanical ventilation, of the 6 studies (n = 47245) pooled for this analysis, there was a non-significantly different risk of developing severe illness from COVID-19 requiring mechanical ventilation for people with asthma compared to those without asthma (RR = 1.16, 95% CI = 0.83 to 1.63, p = 0.39). Substantial heterogeneity is observed (I^2 = 88%) across the studies. See Figure 4(C).

We also observed a non-significantly different risk of developing severe illness requiring admission to ICU and/or mechanical ventilation once hospitalized for people with asthma compared to those without asthma (RR = 1.13, 95% CI = 0.94–1.37, p = 0.19). Heterogeneity was substantial (I^2 = 59.53%) across the included studies. See Figure 4(D).

There was a non-significantly different risk of death from COVID-19 for people with asthma compared to those without asthma (RR = 0.87, 95% CI = 0.68–1.10; p = 0.25) in the 9 studies (n = 7820) pooled for this analysis. Moderate heterogeneity is observed (I^2 = 45%) across the studies. See Figure 5.

The meta-regression by age demonstrates that older age is associated with an increased risk of acquiring COVID-19 in people with asthma (Meta-regression coefficient 0.0064, 95% CI = 0.0003 to 0.012; p = 0.038). The R-squared test showed that about 70% of the variance between studies in risk of acquiring COVID-19 can be explained by age. Hence, low heterogeneity (I^2 = 35.1%) was observed after including age as a moderator. The meta-regression by age of the other outcomes did not show statistically significant associations.

The subgroup analysis by continent revealed a higher risk of requiring admission to ICU once hospitalized in Asia (RR = 1.21, 95% CI =
and America (RR = 1.21, 95% CI = 0.92–1.59) compared to Europe (RR = 1.03, 95% CI = 0.38–2.78), however the difference between the groups was not statistically significant (p = 0.96). In contrast, a borderline statistically significant test group difference (p = 0.052) was observed between risk of being ventilated in Europe (RR = 1.66, 95% CI = 0.52–5.25) compared to Asia (RR = 1.41, 95% CI = 1.12–1.78) and America (RR = 0.95, 95% CI = 0.75–1.20).

The sensitivity analysis including more studies (n = 37) showed a borderline statistically significant lower risk of hospitalization from COVID-19 of 5% for people with asthma compared to no asthma (RR = 0.96, 95% CI = 0.93–0.99, p = 0.02). See Figure S4.

Sensitivity analysis (all patients not dead taken as alive) did not demonstrate a significant increase risk of death from COVID-19 in people with asthma compared to no asthma (RR = 1.01, 95% CI = 0.59–1.72), (p = 0.97). The National Committee on COVID-19 Epidemiology Iran study (9) contributed a weight of 10.0% to this result with a very high RR = of 12.70 compared to the rest of the studies. When this study was removed from the analysis, the 3% increase in death changed to a 13% reduction in death in people with asthma compared to no asthma (RR = 0.87, 95% CI = 0.72–1.04, p = 0.13; Figure S4). In comparison, the worst-case sensitivity (all patients who have not yet recovered were taken as ‘dead’) analysis also showed 3% increase in the odds of recovery in people with asthma compared to no asthma (RR = 0.97, 95% CI = 0.84–1.13, p = 0.72; Figure S4).

**Discussion**

This systematic review aims to assess the vulnerability of people with asthma during the COVID-19
Figure 4. Risk of severe illness from COVID-19 among those with asthma compared to no asthma.
pandemic. The results revealed a 7.46% prevalence of asthma among those who tested positive for COVID-19. Although these studies come from countries with differing asthma prevalence, overall this pooled prevalence is similar to the prevalence of self-reported asthma symptoms of 8.6% (64). In the studies that reported on the severity of asthma, we found that non-severe asthma among people with COVID-19 was more common than severe asthma (9.6% vs 4.13%) as in most populations (65,66).

We found a 14% (95% CI = 0.80–0.94) lower risk of acquiring COVID-19 in people with asthma, which is an absolute reduction of 50 cases per 1,000 people. This is consistent with the trend observed during the SARS pandemic (67). There are several possible explanations for this risk reduction which include the observation that people with T2-high asthma have downregulated angiotensin-converting-enzyme-2 (ACE-2) receptors that may reduce their risk of infection with SARS-CoV-2 (68). Early evidence from the Severe Asthma Research Program-3 has shown that inhaled corticosteroid (ICS) therapy, the main treatment modality in asthmatics is associated with lower ACE-2 (one of the binding sites for SARS-CoV-2) expression (69). This may confer a reduction in vulnerability to COVID-19 and development of less severe disease.

Subsequent to our analysis, two studies were published which we would have included if they had been available prior to our cutoff date. In a study of electronic medical records of patients aged 65 years or younger with severe COVID-19, admitted to hospital in New York City, asthma diagnosis was not associated with worse outcomes, regardless of age, obesity, or other high-risk comorbidities (70). Mahdavinia (36) showed that duration of hospitalization showed a trend to be longer among patients with a history of asthma compared to those without in the 50–64 years age group but this was not associated with a higher rate of death nor with ARDS. These findings are in keeping with the results of our review. Finally, in a review of papers in English published prior to 7 May 2020, compared to population prevalence, asthma prevalence among patients hospitalized for COVID-19 infection was similar and significantly lower than asthma prevalence among patients hospitalized for influenza (71).

Although it was initially considered likely that SARS-CoV-2 infection would increase exacerbation risk for people with asthma, there are several reasons why this may not be the case. Lower interferon levels in people with asthma are also hypothesized to be protective against cytokine storm which occurs in severe COVID-19 patients (72). Behavioral aspects may have also played a role in reducing the vulnerability of asthmatics to COVID-19 and previous experience of viral infections triggering asthma exacerbations caused anxiety among patients and caregivers (74,75). This followed government advice...
during the peak of the pandemic in countries like the United Kingdom, which classified severe asthmatics as a vulnerable group and advised them to shield for 12 weeks at home (5). A study in USA showed that during the pandemic, there was a 14.5% relative increase in daily controller adherence in asthmatics and COPD patients which supports this posit (76). All these factors may have worked together in reducing the risk of acquiring COVID-19 in people with asthma.

Increasing age is strongly associated with an increased risk of acquiring COVID-19 among asthmatics and explained 70% of the in-between study variance in our analysis. This is an expected finding and in line with other COVID-19 studies showing age as one of the most important predictors for vulnerability to COVID-19 and prognosis (22,77,78).

A statistically significant risk reduction in hospitalization from COVID-19 of 13% (95% CI = 0.77–0.99, \( p = 0.03 \)) in people with asthma was observed, validated by the results of the sensitivity analysis. This is consistent with the findings of several more recent studies which showed that having asthma is not associated with an increased risk of hospitalization 0.96 (95% CI = 0.77–1.19) (79) and that people with asthma are underrepresented among hospitalized patients with severe pneumonia from COVID-19 (80). In the majority of studies included in our review treatment was not recorded. However, some in vitro studies suggest that inhaled corticosteroids may have a protective effect in which case the use of ICS may be a contributing factor in reducing the risk of acquiring COVID-19 as well as the risk of severe illness warranting hospitalization. Further, the RECOVERY trial showed that dexamethasone lowered the incidence of death in severe COVID-19 patients receiving respiratory support compared to their counterparts (81). As systemic corticosteroids are also given to treat acute exacerbations of asthma, it is possible that this is one mechanism by which people with asthma who are hospitalized with COVID-19 do not have worse outcomes.

Our aggregated-data meta-regression and previous studies have shown that older age and presence of other comorbidities such as hypertension and diabetes in people with asthma are strongly associated with the severity of COVID-19 (82) and that asthma is not a major risk factor (83). However, many of the included studies did not report comorbidities, individual patient data and more studies are needed before firm conclusions can be drawn.

In contrast, our pooled analysis showed a 19% (95% CI = 0.93–1.53; \( p = 0.16 \)) increase in the risk of developing severe illness from COVID-19 requiring admission to ICU once people with asthma are hospitalized. Although not statistically significant in our review, this finding is similar to a recent UK Biobank study which reported a 39% increase risk for severe COVID-19 among those with asthma (adjOR 1.39; 95%CI 1.13–1.71; \( p = 0.002 \)) (84). Airflow limitation due to bronchospasm and mucus plugging would be expected to compound the hypoxemia characteristic of diffuse alveolar damage in COVID-19 patients with underlying asthma, requiring more intensive respiratory support (85).

Similarly, people with asthma have a 16% (95% CI = 0.83–1.63; \( p = 0.39 \)) increased risk of requiring mechanical ventilation, albeit not statistically significant with quite a wide confidence interval. Those in Europe have a higher risk of being ventilated compared to Asia and America, which was statistically significant and possibly due to differences in criteria for mechanical ventilation between continents especially early in the pandemic.

Increasing age is not statistically associated with a increased risk of mechanical ventilation in people with asthma. One study reported that asthma prolonged the intubation time in patients <65 years (36) which suggests that asthma has a greater impact on COVID-19 course in younger people. On the other hand, a recent study in Spain (86) among asthmatics reported that those who acquire COVID-19 were older with a greater prevalence of comorbidities compared to those who were COVID-19 negative. Those older and with comorbidities were also reported to be more likely hospitalized. Of note, there was a low rate of hospitalization reported in this study among those with COVID-19 of 0.23%.

There is a no evidence of a difference in the risk of death from COVID-19 for people with asthma (RR = 0.87, 95% CI = 0.68–1.10; \( p = 0.19 \)). A study in New York also reported that asthma was not associated with mortality (87). We note that the mean age of the pooled studies was 52 years. As, previous studies have shown that case fatality rate increases substantially above 50 years of age, our findings might present a conservative estimate of the potential reduction in risk of death (22,77,78).

This review has rigorously adhered to the guidelines of performing systematic reviews. We undertook extensive searches of the databases and additional resources including preprint repositories, agency reports and open datasets. We acknowledge that the findings were partly based on unpublished preprints at the time of analysis, however, we also utilized open routinely collected datasets from national government databases when available and find this to be a strength of this study. While we note that reporting quality
does not always relate to study quality, a recent study has reported small absolute differences in quality of reporting of reporting between peer-reviewed and pre-print articles (88). Hence, we expect their inclusion to not substantially impact the pooled findings.

Based on the result of the regression-based Egger's test (Table S2), there was no evidence of small-study effects. From the eyeball assessment of the contour-enhanced funnel plots we considered that the risk of severe illness requiring mechanical ventilation and the risk of death as showing potential publication bias as they look quite asymmetric (see Figure S3).

A limitation of this review is the synthesis of primarily observational studies, short duration of follow-up, mainly self-reported asthma and variable reporting of outcomes which may introduce bias in the pooled effect. To mitigate this risk, we performed sensitivity analyses to explore the robustness of the findings under different assumptions and meta-regression to examine the impact of age on the study effect size. Another limitation is the varying case definition and quality of the studies. However, in the context of a pandemic situation, achieving uniformity and high-quality diagnostic data is challenging. This has resulted in some comparisons being based on only four to five studies and informed by one to two large studies which may limit generalizability.

Asthma and COPD are also often misdiagnosed in practice (89,90), we have mitigated this risk through including studies which only explicitly mention asthma, corresponding with authors for clarification when ambiguous and a comprehensive search of literature including studies from various centers. Even so, error may have occurred in the original diagnosis or in the “label” the patient chose to convey. Noting that patients with COPD would likely have more severe preexisting lung damage and be at greater risk of poor outcomes from COVID-19, this misclassification may confound the results to show greater severity when infected with COVID-19 among asthmatics (91).

Although we had hoped to include treatment with inhaled corticosteroid or systemic corticosteroid, and subgroups of pediatrics and the elderly, as well as the different asthma phenotypes in the analysis, this was precluded by the limited data available on these clinical variables.

Finally, a proportion of patients with COVID-19 experience prolonged effects following the acute illness, now termed “Long COVID” (92). The most common symptoms of fatigue, breathlessness and cough may be more likely or prominent in people with background airways disease. Although beyond the scope of this analysis it will be crucial to examine these risks in further studies of people with asthma and COVID-19.

In summary, the findings from this study suggest that the prevalence of people with asthma among COVID-19 patients is similar to the global prevalence of asthma. The overall findings based on available evidence suggest that people with asthma are not at increased risk for acquiring COVID-19 compared to those without asthma and have similar clinical outcomes. Further high-quality primary studies and data sharing on asthma and COVID-19 globally is needed to improve our understanding of how SARS-CoV-2 impacts those with asthma.

Declaration of interest
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