Risk of serious COVID-19 outcomes among adults and children with moderate-to-severe asthma: a systematic review and meta-analysis

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Shareable abstract (@ERSpublications)
This systematic review demonstrated that adults with severe asthma requiring high-dose inhaled corticosteroids or oral corticosteroids have a higher risk of hospitalisation from COVID-19 than those with mild asthma or no asthma. https://bit.ly/3zYiWaO

Abstract

Background The Joint Committee on Vaccination and Immunisation in the United Kingdom requested an evidence synthesis to investigate the relationship between asthma and coronavirus disease 2019 (COVID-19) outcomes.

Objective We conducted a systematic review and meta-analysis to summarise evidence on the risk of severe COVID-19 outcomes in people with uncontrolled asthma or markers of asthma severity.

Methods High-dose inhaled corticosteroids (ICS) or oral corticosteroids (OCS) were used as markers of asthma severity, following international or national asthma guidelines. Risk of bias was assessed using Joanna Briggs Institute tools. Adjusted point estimates were extracted for random-effects meta-analyses and subgroup analyses.

Results After screening, 12 studies (11 in adults and one in children) met the eligibility criteria. Adults using high-dose ICS or OCS had a pooled adjusted hazard ratio (aHR) of 1.33 (95% CI 1.06–1.67, I^2=0%) for hospitalisation and an aHR of 1.22 (95% CI 0.90–1.65, I^2=70%) for mortality for COVID-19. We found insufficient evidence for associations between markers on COVID-19 mortality in the subgroup analyses.

Conclusions Adults with severe asthma are at increased risk of COVID-19 hospitalisation compared to nonusers. Our analysis highlighted the dearth of studies in children with asthma investigating serious COVID-19 outcomes.

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory condition caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has resulted in a pandemic [1], affecting both adults and children [2]. Older people and people with comorbidities such as type 2 diabetes mellitus, hypertension, cancer and some other respiratory diseases are known to have an increased likelihood of developing severe COVID-19 outcomes such as hospitalisation, admission to intensive care unit (ICU), having to go on a ventilator, or death [3, 4].

According to the International Severe Acute Respiratory and Emerging Infection Consortium, 14% of COVID-19 patients in the United Kingdom (UK) had an underlying diagnosis of asthma, although asthma

was not linked to a higher fatality rate [5]. To the contrary, current evidence shows that asthma may have potential protective effects due to the use of inhaled corticosteroids (ICS). In a recent systematic review and meta-analysis of 57 studies, people with asthma were at lower risk of acquiring COVID-19 or hospitalisation with COVID-19 than those without asthma [6]. In a recent randomised controlled trial in the UK, an ICS, inhaled budesonide (800 µg twice daily for 14 days) was protective in reducing the risk of hospital admissions or COVID-19 related deaths [7].

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) requested an evidence synthesis to inform national policy deliberations on COVID-19 vaccines and boosters in children and adults with asthma. One of the deliberations they had to advise on was whether people with severe asthma should receive vaccines or boosters for COVID-19 and how to identify those people using routinely collected health data. After further discussions with British Thoracic Society and JCVI, we considered reframing this using markers of severity/uncontrolled asthma. Hence, this review aimed to provide the best evidence of severe outcomes of COVID-19 in relation to markers of asthma severity.

Methods

This systematic review was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-2020) protocols statement [8]. A study protocol was developed and registered on the International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/PROSPERO/ identifier number CRD42021270284).

Search strategy

We developed a search strategy by combining terms for two concepts: COVID-19 and asthma. The search strategy was designed to identify studies that reported the characteristics of severe asthma patients who required hospitalisation, ICU admission, mechanical ventilation or intubation, and death from SARS-CoV-2 infection. All results were screened, but to facilitate the identification of existing reviews, we also used the Scottish Intercollegiate Guidelines Network MEDLINE filter for systematic reviews (adapted for other databases) [9].

We searched Ovid MEDLINE, the World Health Organization COVID-19 literature database and medRxiv. Draft searches were piloted in each database, refined, run for this review on 19 July 2021 and updated 23 September 2021 and 18 January 2022 by M. Dozier. Detailed search strategies are provided in supplementary table E1.

Screening and selection of studies

Two independent reviewers from a group of six reviewers (B. Lee, E. Agyei-Manu, N. Atkins, U. Bhattacharyya, G. Lewis, J. Rostron) conducted title and abstract screening and full-text screening on www.Covidence.org. Additional duplicates were identified and removed manually during title and abstract screening. Eligible studies presented severe asthma definitions, included confirmed COVID-19 cases using reverse transcriptase (RT)-PCR and compared outcomes with relevant comparators (e.g. people with mild or no asthma). We selected studies that included both confirmed and clinically highly suspected COVID-19 cases due to limited access to RT-PCR in the early months of the COVID-19 pandemic.

The following criteria were used to screen records. We used European Respiratory Society and American Thoracic Society guidelines and Global Initiative for Asthma (GINA) to define severe asthma, either as 1) requiring high-dose ICS (e.g. inhaled budesonide: for adults and adolescents (aged ⩾12 years) >800 µg·day^{-1}; for children 6–11 years >400 µg·day^{-1}) and a second controller; 2) use of oral corticosteroids (OCS); or 3) asthma that remained "uncontrolled" despite therapy [10, 11]. We also included studies using any other guideline definitions of asthma severity based on medication use [11, 12]. Severe outcomes for COVID-19 were defined as COVID-19 related hospitalisation, mortality, ICU admission or mechanical ventilation. Table 1 outlines the eligibility criteria. Disagreements were resolved by a third reviewer (E. Theodoratou or R. McQuillan).

Risk-of-bias assessment

We used Joanna Briggs Institute (JBI) critical appraisal tools to assess the quality of evidence of eligible studies [13]. Studies were assessed independently by two reviewers and the percentage of "yes" responses among all questions was calculated (ranging from 0% to 100%) to attain comparable quality scores among the selected studies. Studies with a score ⩾80% were considered high quality, those with a score ⩾50% but <80% were considered moderate quality, and those with a score <50% were considered low quality.

TABLE 1 Inclusion and exclusion criteria		
	Inclusion	**Exclusion**
Population	Patients (adults or children) with confirmed COVID-19 based on RT-PCR or clinically highly suspect cases	Studies which only referenced "COVID-19" broadly
Exposure	Severe asthma diagnosed by clinicians or by validated or nonvalidated guidelines	Self-reported asthma patients
Comparator	Patients (adults or children) with confirmed COVID-19 based on RT-PCR and without pre-existing severe asthma diagnosis	Studies without any comparator
Outcome	1) Risk of hospitalisation for people with severe asthma 2) Risk of ICU admission/mechanical ventilation for people with severe asthma 3) Risk of death for people with severe asthma	1) Asymptomatic or mild to moderate COVID-19 symptoms 2) Studies focusing only on the pathophysiology of COVID-19 in asthma or severe asthma
Study design	Studies of any design besides those specified in the exclusion criteria	Modelling studies, opinion pieces, editorials, reviews and laboratory studies
Geographical location	Studies conducted in any country or countries	No restrictions based on geographical location
COVID-19: coronavirus disease 2019; RT-PCR: reverse transcriptase PCR; ICU: intensive care unit.		

Data extraction and data analysis

Evidence was summarised by types of severe COVID-19 outcomes. Information on study settings such as population-based or hospital-based and asthma medication regimens were extracted. We did not extract data on vaccination status. For the associations, we extracted adjusted risk ratios, odds ratios (aOR) or hazard ratios (aHR) and 95% confidence intervals. We performed a general inverse variance method using random-effects meta-analysis, employing the restricted maximum-likelihood estimation and Hartung–Knapp–Sidik–Jonkman adjustment [14]. To explore the reasons for heterogeneity, we calculated τ^2, I^2 and Cochrane's Q. Subgroup analyses were conducted by study settings and asthma medication regimens. As all of the analyses included <10 studies, we did not assess publication bias using funnel plots, Begg correlation or Egger test. We presented all results in the form of forest plots using R software (version 4.1.2). The results were presented narratively when meta-analysis was not possible due to excessive heterogeneity between studies or a lack of research.

Results

Characteristics of included studies

Out of 2649 records identified after deduplication, 317 underwent full-text screening. Of these, 12 studies were retained for data extraction [15–26]. The screening process is summarised in a PRISMA flow chart (figure 1).

Table 2 summarises the characteristics of the included studies. Seven studies were from the UK [15–19, 24, 25], two each were from South Korea [21, 23] and the United States (USA) [22, 26] and one study was from the Netherlands [20]. Nine studies were population-based [15, 18–21, 23–26] and three studies were hospital-based [16, 17, 22].

Markers of asthma severity

Supplementary table E3 summarises markers of asthma severity used in the included studies. Five studies classified asthma severity by high-dose ICS use [15, 16, 18, 20, 26] and four studies used OCS use [17, 19, 21, 22, 24, 25]. Three studies adopted broader markers, but did not provide outcomes of subgroups of either high-dose ICS or OCS use [17, 22, 23]. Studies where medication regimens were not clearly defined were categorised after contacting the authors [15] or after discussion with reviewers [16, 18]. For patients who were treated with three medications from different classes, ICS plus long-acting β-agonist plus another medication, we classified them as the high-dose ICS group, since such patients were more likely to use high-dose ICS [16]. Two studies by Sнι and co-workers [24, 25] categorised asthma severity by the number of OCS used (from none to two courses) and hospitalisation within 1 or 2 years before March 2020. To reduce heterogeneity among the included studies, we utilised estimates of one course of OCS within 1 year as a minimum estimate for hospitalisation and mortality. Since an estimate of OCS use within 1 year for ICU admission includes COVID-19-related mortality, we used the estimate for OCS use within 2 years to obtain each estimate.
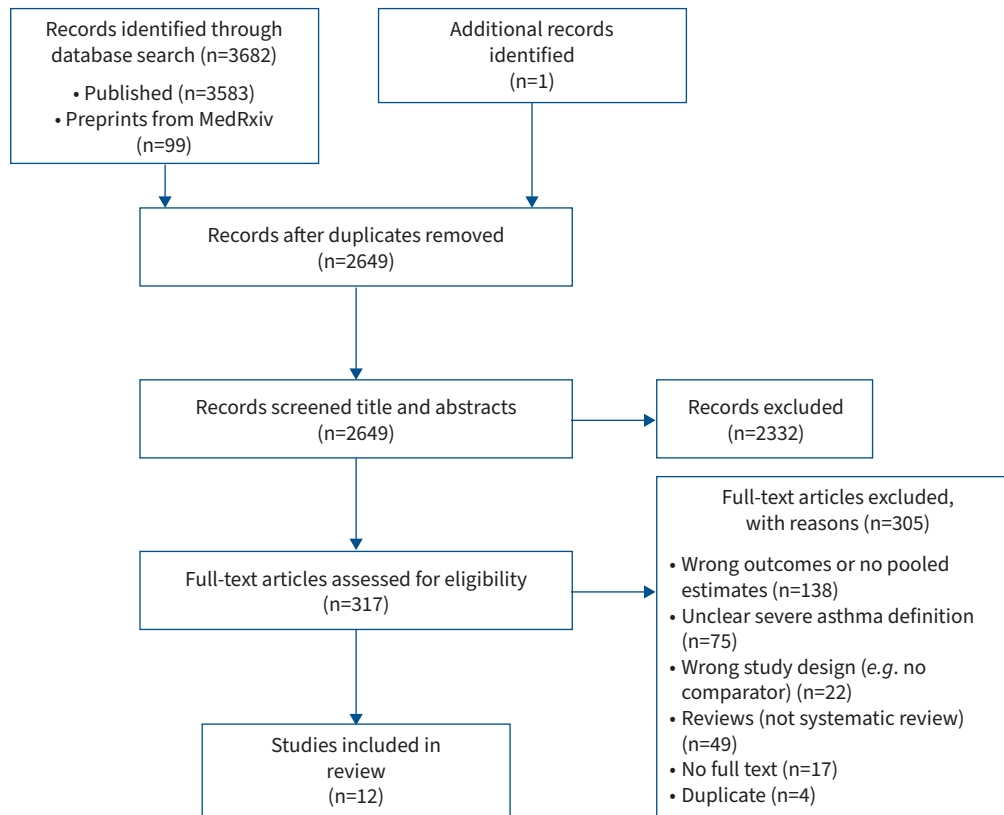
FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses screening process.

Risk of bias of included studies

Based on the JBI critical appraisal tool standards for cohort studies and the calculation of the quality score, 11 out of 12 studies in the review were assessed as high quality. One study was assessed to be of moderate quality, scoring 63% [20]. Details are available in supplementary table E4.

Severe COVID-19 outcomes in children

Out of 12 studies, three included children (aged <18 years) [16, 21, 24], but only one study provided point estimates of outcomes of interest [24]. In a Korean study, 22 children were categorised as GINA steps 4 (n=22) and 5 (n=0), but no estimates in children were available [21]. In a UK study of children (aged <16 years) with asthma (n=74), five used OCS and 11 used ICS and other controllers, and only a small number of children with asthma were admitted to ICU (n=10), none of whom died [16]. Another UK study of children aged 5–17 years demonstrated that two or more courses of OCS were associated with an increased risk of COVID-19 hospital admission compared with those without asthma (aHR 3.53, 95% CI 1.87–6.67), but not one course of OCS (aHR 1.52, 95% CI 0.90–2.57) [24]. However, the number of COVID-19 related deaths was very few (n<5) in this group [24].

Severe COVID-19 outcomes in adults

We conducted a meta-analysis with the aHRs which were adjusted for covariates, resulting in excluding three articles [20, 23, 26] presenting aORs, which are not interchangeable with aHRs. A separate meta-analysis was conducted with these three studies (supplementary figures E1–E3).

Figure 2 summarises the risks of severe COVID-19 outcomes for adults with severe asthma requiring high-dose ICS or OCS. The result of the meta-analysis showed that adults with severe asthma had a higher aHR of 1.33 (95% CI 1.06–1.67, I^2=0%) for hospital admission than those without asthma or any respiratory diseases (figure 2a).

Two population-based studies examined the association between severe asthma and ICU admission related to COVID-19 and the pooled aHR was 1.26 (95% CI 0.89–1.79, I^2=0%) [15, 25] (figure 2b). Although

TABLE 2 Characteristics of studies included in the review (n=12)

First author (year) [reference]	Country	Data source	Population	COVID-19 confirmation	Data collection time	Design
Aveyard (2021) [15]	England	QResearch database version 44	Adults (≥20 years) from 1205 general practices linked to all ICUs in England	RT-PCR test confirmed and suspected cases	24 January to 30 April 2020	Retrospective cohort study
Bloom (2021) [16]	UK	ISARIC CCP-UK study (national, multicentre)	Child (<16 years) and adult (≥16 years) inpatients from hospitals in England, Scotland and Wales	RT-PCR test confirmed and suspected cases	17 January to 17 August 2020	Prospective cohort study
Choi (2021) [21]	South Korea	HIRA COVID-19 nationwide patient medical claims data	Child (<19 years) and adult (≥20 years) inpatients and outpatients from hospitals in South Korea	RT-PCR tests	March 2019 to 15 May 2020	Retrospective cohort study
Eger (2020) [20]	The Netherlands	Dutch Severe Asthma Registry RAPSODI (national, multicentre) DNIPESN database (Dutch general population)	1) Adults (≥18 years) from 15 hospitals for the RAPSODI registry 2) Adults (≥18 years) from the general population	RT-PCR test confirmed and suspected cases	17 March to 30 April 2020	Prospective cohort study
Fong (2021) [17]	England	EHR (single centre)	Adult (≥18 years) inpatients from a large tertiary hospital	RT-PCR test	1 March to 31 May 2020	Retrospective cohort study
Robinson (2022) [22]	USA	MGB Enterprise Data Warehouse, MGB Research Patient Data Registry and the COVID-19 Datamart (multicentre)	Adult (≥18 years) inpatients and outpatients from hospitals in the greater Boston area	RT-PCR test	4 March to 2 July 2020	Retrospective cohort study
Schultze (2020) [18]	UK	OpenSAFELY primary care EHR data linked with death data from the Office for National Statistics in England	Adults (≥18 years) in England	RT-PCR test confirmed and suspected cases	1 March to 6 May 2020	Prospective cohort study
Williamson (2020) [19]	England	OpenSAFELY primary care EHR data linked with death data from the Office for National Statistics in England	Adults (≥18 years) in England	RT-PCR test confirmed and suspected cases	1 February to 6 May 2020	Prospective cohort study
Jung (2021)[#] [23]	South Korea	Korea National Health Insurance Database COVID-19 medical claims data	Adult (≥20 years) inpatients and outpatients from hospitals in South Korea	RT-PCR test	1 January 2020 to 4 June 2020	Retrospective cohort study
Shi (2022)[¶] [24]	Scotland	EAVE II (national, multicentre)	Children aged 5–17 years in Scotland	RT-PCR test	1 March 2020 to 27 July 2021	Retrospective cohort study
Shi (2022) [25]	Scotland	EAVE II (national, multicentre)	Adults (≥18 years) in Scotland	RT-PCR test	1 March 2020 to 27 July 2021	Retrospective cohort study
Zein (2022) [26]	Ohio and Florida, USA	Cleveland Clinic's COVID-19 research registry	Adults (≥18 years) in Ohio and Florida, USA	RT-PCR test	1 April 2020 to 31 March 2021	Retrospective cohort study

COVID-19: coronavirus disease 2019; ICU: intensive care unit; RT-PCR: reverse transcriptase PCR; ISARIC: International Severe Acute Respiratory and Emerging Infection Consortium; CCP-UK: World Health Organization Clinical Characterisation Protocol UK; HIRA: Health Insurance Review and Assessment Service; RAPSODI: Registry of Adult Patients with Severe Asthma for Optimal Disease Management; DNIPESN: Dutch National Institute for Public Health and the Environment and the Statistics Netherlands Database; EHR: electronic healthcare records; MGB: Mass General Brigham; EAVE II: Early Pandemic Evaluation and Enhanced Surveillance of COVID-19. [#]: separate estimates of hospitalisation, ICU admission and ventilation were not available; [¶]: the number of COVID-19 related deaths was small (n<5) in children with asthma.
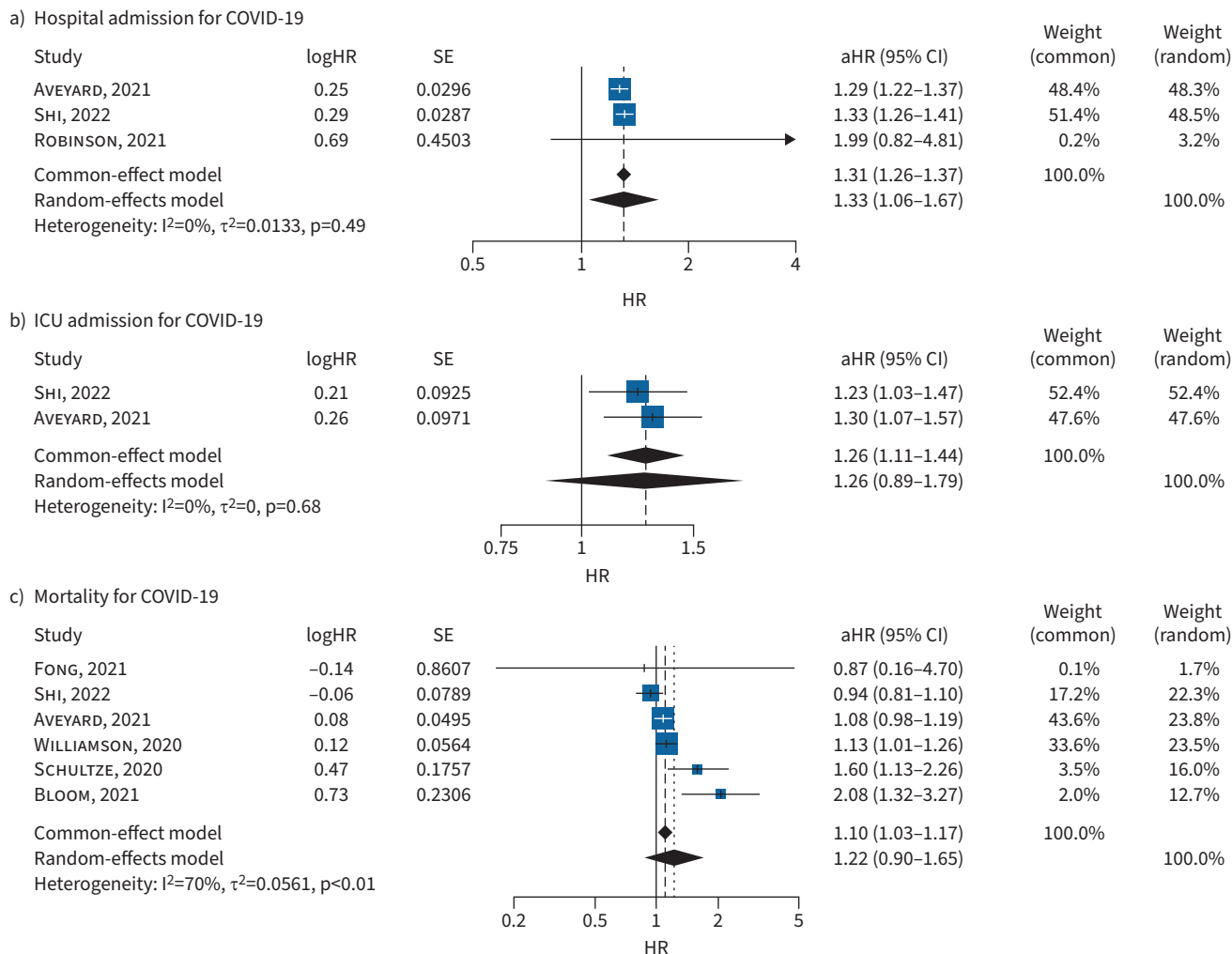
FIGURE 2 Adjusted hazard ratios (aHRs) for severe coronavirus disease 2019 (COVID-19) outcomes. a) Hospital admission; b) intensive care unit (ICU) admission; c) mortality for COVID-19.

both studies showed a higher risk for ICU admission in adults with severe asthma, they used different markers for severe asthma (three different asthma medications [15], *versus* one course of OCS within 2 years [25]).

For mechanical ventilation/intubation, only two studies investigated mechanical ventilation risk in relation to severe asthma [20, 22]. In a cohort study by EGER *et al.* [20], people in the Registry of Adult Patients with Severe Asthma for Optimal Disease Management (RAPSODI) requiring high-dose ICS showed a higher intubation prevalence than the general Dutch population (0.79% for RAPSODI *versus* 0.02% for the general Dutch population). In addition, in this group, severe asthma had an OR 40.8 for intubation (95% CI 16.9–98.5) compared with the general Dutch population. According to ROBINSON *et al.* [22], the rate of event per 1000 person-days of mechanical ventilation was 1.6 (95% CI 0.2–3.0) in the severe asthma group using OCS within 1 year. There was no significant difference between severe and nonsevere asthma after matching for age, sex and date of SARS-CoV-2 test (aHR 2.10, 95% CI 0.77–5.76) [22].

Lastly, 11 studies examined the association between severe asthma and COVID-19 mortality [15–23, 25, 26]. Of these studies, there were no COVID-19 deaths in two studies [21, 22]. Three studies presenting odds ratios were included in a separate meta-analysis, which showed OR 1.07 (95% CI 0.15–7.82, I^2=30%) (supplementary figure E3) [20, 23, 26]. When six aHRs were included in the meta-analysis [15–19, 25], severe asthma in adults was not associated with a higher aHR (1.22, 95% CI 0.90–1.65; I^2=70%) (figure 2c).

a) Study setting

Study	logHR	SE	aHR (95% CI)	Weight (common)	Weight (random)
Subgroup: Population-based setting					
SHI, 2022	−0.06	0.0789	0.94 (0.81–1.10)	17.2%	22.3%
AVEYARD, 2021	0.08	0.0495	1.08 (0.98–1.19)	43.6%	23.8%
WILLIAMSON, 2020	0.12	0.0564	1.13 (1.01–1.26)	33.6%	23.5%
SCHULTZE, 2020	0.47	0.1757	1.60 (1.13–2.26)	3.5%	16.0%
Common-effect model			1.09 (1.02–1.16)	97.8%	
Random-effects model			1.10 (0.84–1.46)		85.5%
Heterogeneity: I^2=66%, τ^2=0.0131, p=0.03					
Subgroup: Hospital-based setting					
FONG, 2021	−0.14	0.8607	0.87 (0.16–4.70)	0.1%	1.7%
BLOOM, 2021	0.73	0.2306	2.08 (1.32–3.27)	2.0%	12.7%
Common-effect model			1.96 (1.27–3.04)	2.2%	
Random-effects model			1.96 (0.12–31.28)		14.5%
Heterogeneity: I^2=0%, τ^2=0, p=0.33					
Common-effect model			1.10 (1.03–1.17)	100.0%	
Random-effects model			1.22 (0.90–1.65)		100.0%

Heterogeneity: I^2=70%, τ^2=0.0561, p<0.01
Test for subgroup differences (fixed effect): χ^2_1=6.91, df=1 (p<0.01)
Test for subgroup differences (random effects): χ^2_1=5.99, df=1 (p=0.01)

b) Asthma medication regimens

Study	logHR	SE	aHR (95% CI)	Weight (common)	Weight (random)
Subgroup: OCS					
SHI, 2022	−0.06	0.0789	0.94 (0.81–1.10)	17.2%	22.3%
WILLIAMSON, 2020	0.12	0.0564	1.13 (1.01–1.26)	33.6%	23.5%
Common-effect model			1.06 (0.97–1.16)	50.8%	
Random-effects model			1.04 (0.32–3.33)		45.8%
Heterogeneity: I^2=72%, τ^2=0.0122, p=0.06					
Subgroup: High-dose ICS					
FONG, 2021	−0.14	0.8607	0.87 (0.16–4.70)	0.1%	1.7%
AVEYARD, 2021	0.08	0.0495	1.08 (0.98–1.19)	43.6%	23.8%
SCHULTZE, 2020	0.47	0.1757	1.60 (1.13–2.26)	3.5%	16.0%
BLOOM, 2021	0.73	0.2306	2.08 (1.32–3.27)	2.0%	12.7%
Common-effect model			1.14 (1.04–1.25)	49.2%	
Random-effects model			1.42 (0.84–2.40)		54.2%
Heterogeneity: I^2=75%, τ^2=0.822, p<0.01					
Common-effect model			1.10 (1.03–1.17)	100.0%	
Random-effects model			1.22 (0.90–1.65)		100.0%

Heterogeneity: I^2=70%, τ^2=0.0561, p<0.01
Test for subgroup differences (fixed effect): χ^2_1=1.17, df=1 (p=0.28)
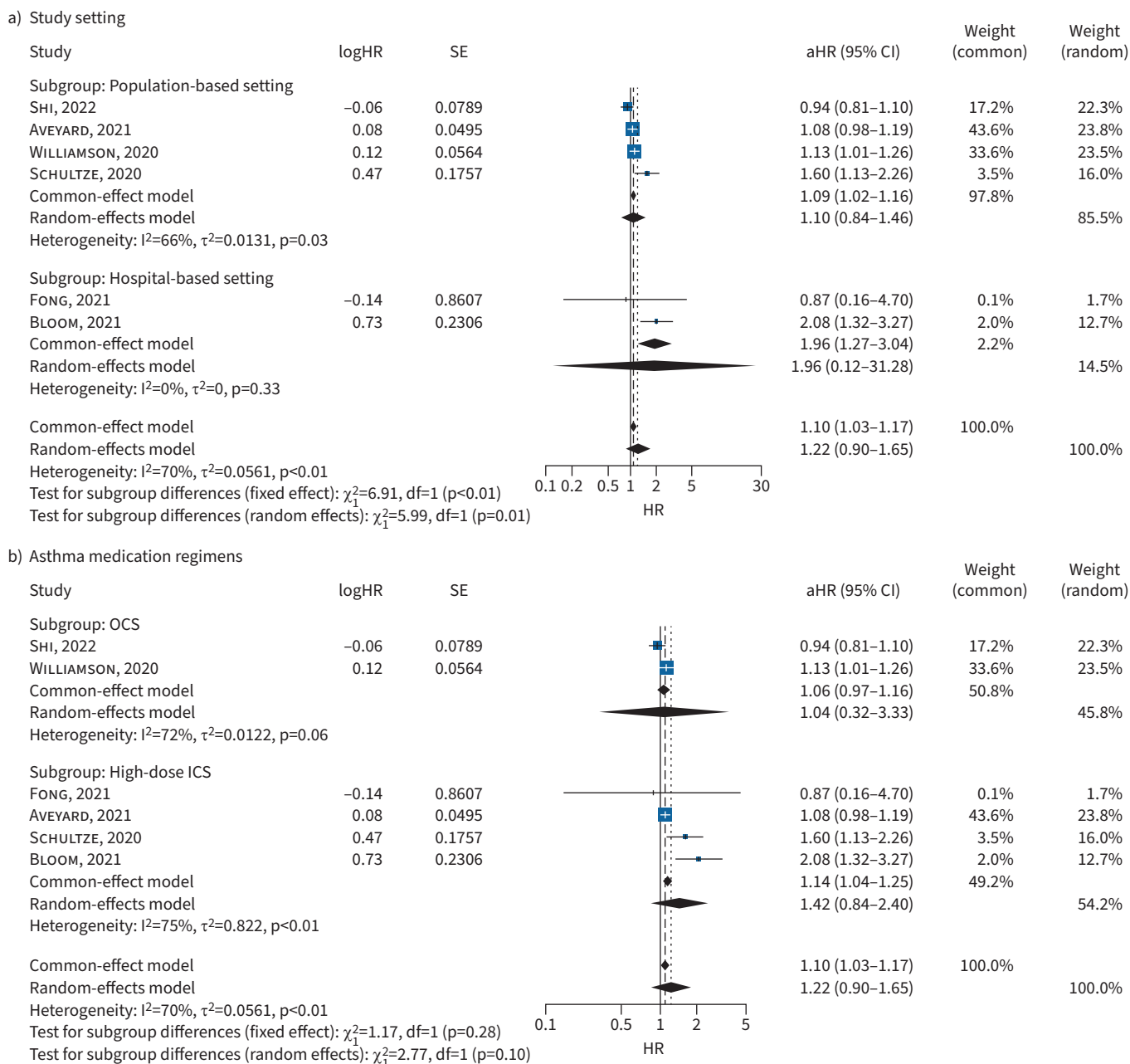Test for subgroup differences (random effects): χ^2_1=2.77, df=1 (p=0.10)

FIGURE 3 Adjusted hazard ratios (aHRs) for coronavirus disease 2019 (COVID-19) mortality in subgroup analyses. a) Study setting; b) asthma medication regimens. df: degrees of freedom; OCS: oral corticosteroids; ICS: inhaled corticosteroids.

Figure 3a and b shows the risks of mortality for COVID-19 in subgroups by study setting and by asthma medication regimens.

The pooled aHR derived from four population-based cohorts [15, 18, 19, 25] was 1.10 (95% CI 0.84–1.46), with moderately high heterogeneity (I^2=66%) (figure 3a). Two hospital-based cohort studies also showed a higher aHR of 1.96 for death from COVID-19 (95% CI 0.12–31.28) compared to those with no asthma or no severe asthma, with low heterogeneity (I^2=0%).

For OCS, two population-based studies showed that severe asthma patients on OCS had an aHR of 1.04 (95% CI 0.32–3.33; I^2=72%) compared to patients with nonsevere or no asthma [19, 25] (figure 3b).

For high-dose ICS, four studies were included in the analysis (figure 3b). Use of high-dose ICS had an aHR of 1.42 in adults, compared to those with mild or no asthma (aHR 1.42, 95% CI 0.84–2.40; I^2=75%) [15–18]. When dividing the studies by settings again, two population-based cohort studies [15] showed an aHR of 1.27 (95% CI 0.11–14.76, I^2=78%) and two hospital-based studies [16, 17] showed an aHR for death from COVID-19 of 1.96 (95% CI 0.12–31.28, I^2=0%) compared to those with nonsevere or no asthma.

Discussion

Our findings show that high-dose ICS or OCS use in adults with severe asthma was associated with a higher risk of hospitalisation for COVID-19, but not ICU admission and mortality. Our subgroup analyses demonstrated there was insufficient evidence supporting the association between high-dose ICS or OCS use in adults with severe asthma and an increased risk of COVID-19 mortality, compared to those with mild/moderate asthma or no asthma. However, we observed high heterogeneity between studies, and it may be due to different sample sizes, different comparators, the inclusion of suspected COVID-19 cases or different covariates used in their statistical analyses (supplementary tables E2 and E5).

It is noteworthy that severe asthma definitions used in some studies were too broad or unclear to classify asthma regimens binarily. Therefore, it may cause the potential misclassification of people with nonsevere asthma as severe asthma. Five studies [15, 16, 18, 21, 22] commented that some patients with severe asthma might have been misclassified as those with nonsevere or non-high-dose ICS users due to limited access to full medication information. For instance, in AVEYARD et al. [15], participants had to use one of three asthma medications in a 1-year period. This would mean someone prescribed a single prescription of salbutamol and other medicines in different classes once a year would be classified as "severe asthma". In BLOOM et al. [16], participants reported their medication within 2 weeks of hospital admission. Participants in the OpenSAFELY research could be prescribed an ICS at any point in the 4 months leading up to their enrolment. Similarly, four studies using data in the early pandemic [15, 16, 18, 19] might have some clinically suspected patients being incorrectly identified as having COVID-19 due to inaccessibility of testing. Therefore, these definitions could have led to misclassification and may have limited findings.

The behavioural change due to governmental COVID-19 mitigations could have affected outcomes. AVEYARD et al. [15] examined the impact of shielding or national lockdown in England on severe COVID-19 risks in people with severe asthma by comparing the pre-shielding period (31 March 2020) to the post-shielding period (1–30 April 2020). However, they did not find any effects of shielding. Regardless of shielding, severe asthma increased hospitalisation and ICU admission risks except for mortality. WILLIAMSON et al. [19] did not find any differences in the aHRs for mortality between early censoring in early April 2020 and patients who were more likely to comply with the shielding and physical distancing in England.

Our findings are in line with other studies. A case–control study in South Korea revealed no significant increase in COVID-19 related mortality in ICS adult users whose cumulative ICS dose was ⩾15 000 µg in the past 12 months, compared to non-ICS users in asthma patients, after adjusting for baseline demographic characteristics and comorbidities [27]. In addition, a large cohort study using the Cleveland Clinic COVID-19 registry showed that ICS therapy did not increase the risk of COVID-19 related mortality in adults with COPD compared with those with COPD not taking ICS; however, the dose of ICS was not detailed in their report [28]. Some in vitro models showing inhibitory effects of ICS alone or in combination with β-agonists on coronavirus HCoV-229E replication and cytokine production could support protective effects of ICS treatment [29, 30]. Some studies hypothesised that a protective effect of type 2 T-helper (Th2) cell inflammation might explain the low risk of severe COVID-19 outcome in severe asthmatics. Type 2 inflammation, common with severe asthmatic symptoms, triggers reducing cellular receptors such as angiotensin-converting enzyme (ACE)2, a receptor for SARS-CoV-2 [31, 32]. Respiratory allergies or interleukin-13 are associated with a significant reduction in ACE2 expression, resulting in decreasing susceptibility to SARS-CoV-2 [33]. Therefore, future studies should consider asthma types concerning severe outcomes of COVID-19 [34].

We acknowledge some limitations to this review. Firstly, we might have missed some literature, as we excluded studies not having clear severe asthma definitions. In addition, there was a risk of overlapping cases using two OpenSAFELY cohort studies [18, 19]. Although they used different statistical approaches, high-dose ICS users in SCHULTZE et al. [18] may have also been included in WILLIAMSON et al. [19], considering that both studies used the same cohort and overlapping data collection times. To address the risk of double counting, we only used hazard ratios adjusted for oral steroids for SCHULTZE et al. [18]. Although our findings did not show positive associations between severe asthma and COVID-19 mortality,

there was high heterogeneity in the comparator groups (nonsevere asthma, no asthma or mild asthma), participants' characteristics (*e.g.* age, sex), sample size and statistical approach. To address other comorbidities that are known to be associated with poor COVID-19 outcomes, we used aHRs for all underlying diseases from the studies. However, types of other comorbidities were not consistently applied across the included studies.

We did not examine publication bias that can be caused by small studies, because evaluating publication bias is not reliable with <10 studies [35]. Thus, our meta-analyses could be limited not only by high heterogeneity but also by the small number of studies. We noticed that most of the studies included in the main meta-analyses were from the UK. Studies from the Netherlands [20], South Korea [23] and the USA [26] were analysed separately because of different types of estimates (odds ratios) (supplementary figures E1–E3), showing no associations between severe asthma and serious outcomes. We did not intend to conduct subgroup analyses by country, but this result could be considered as one of the limitations of this study.

Lastly, we did not consider biological drug treatment as a marker of asthma severity. However, a study using the Italian Registry of Severe Asthma network showed that biological drug users did not have higher risk of hospitalisation, ICU admission and mortality [36]. Another large cohort study of COVID-19 in the Severe Asthma Network in Italy (including 65% biologicals users) did not show a higher mortality (7.7%) than the general population (14.5% in Italy) [37].

As we did not further investigate risks by sex, sex-related differences in the severity of COVID-19 were not considered in this review. However, two included studies showed different risks for hospitalisation by sex. In the study by AVEYARD *et al.* [15], women with severe asthma showed higher risks not only for hospitalisation (aHR 1.40, 95% CI 1.29–1.51), but also for ICU admission (aHR 1.80, 95% CI 1.37–2.37) than men. ROBINSON *et al.* [22] also observed higher hospitalisation rates in women with severe asthma (n=33, 75%) than in men. Such difference could be explained by hormonal changes that can modify the prevalence of the immunological asthma endotype, resulting in more frequent nonatopic asthma in women than in men. Therefore, it could cause different responses to SARS-CoV-2 infection, driven by greater Th1 activity in nonatopic asthma than in atopic asthma [38]. Further investigations are needed to clarify whether female sex with severe asthma could be a risk factor for COVID-19 hospitalisation.

This is the first systematic review to examine whether severe asthma is associated with severe COVID-19 outcomes. Despite our extensive searches, very few studies were identified for the paediatric population with asthma. One large population-based study demonstrated that previous recent hospital admission and two or more OCS use could be risk factors of COVID-19 related hospitalisation [24]. Still, as the authors noted, the small numbers of COVID-19 outcome cases were included in this study due to a lack of records for emergency room attendance. Thus, further research would be needed on the paediatric population with severe asthma. Furthermore, although positive effects of COVID-19 specific therapies reducing progression to serious COVID-19 outcomes are well evident and this could confound the associations, most studies were done before treatments became available. Future studies should consider this covariate in the analysis and confirm the associations of severe asthma with serious outcomes. Contrary to the findings from SUNJAYA *et al.* [6] and YU *et al.* [7] which suggest that people with mild or well-controlled asthma may have protective effects due to ICS use, the evidence from our review shows that adults with moderate-to-severe or poorly controlled asthma requiring high-dose ICS or OCS have a higher risk of hospitalisation than those with mild or no asthma. It is noteworthy that some of the primary studies included in this review used proxies to grade asthma severity (*i.e.* either number of high-dose ICS use or OCS use) rather than using actual ICS or OCS dosage levels to classify people according to disease severity. Due to the complexities in differentiating asthma control from asthma severity, the evidence from this review may suggest an association with asthma control. Thus, adults with poorly controlled asthma (*i.e.* severe asthma) may be at a higher risk of hospitalisation or death from COVID-19, hence the need for adequate control in severe asthma treatment and management.

In conclusion, there is limited evidence demonstrating that those with severe asthma are at increased risk of COVID-19 mortality compared to those with mild asthma or no asthma. However, high-quality evidence demonstrated that severe asthma requiring high-dose ICS or OCS was associated with a higher risk of COVID-19 hospitalisation compared to mild asthmatics and/or nonasthmatic controls. Therefore, it may be beneficial to reduce hospitalisation rates by accelerating COVID-19 boosters for people with severe asthma. Further research is urgently needed for the paediatric population with severe asthma and associated COVID-19 outcomes.

Points for clinical practice

High-quality evidence demonstrated that severe asthma in adults had a 33% higher hospitalisation risk (95% CI 1.06–1.67%) with COVID-19 than those with mild or no asthma. Therefore, it may be beneficial to reduce hospitalisation rates by accelerating COVID-19 boosters for people with severe asthma. Further research is urgently needed for the paediatric population with severe asthma and associated COVID-19 outcomes.

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