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Usher Network for COVID-19 Evidence Reviews

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

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Summary

Objective: There have been a number of investigations into whether pre-existing respiratory diseases increase the risk of serious COVID-19 outcomes. Asthma has been a particular focus with considerable interest in whether asthma severity is a risk factor for serious COVID-19 outcomes. This rapid review aimed to summarise evidence on the risk of being hospitalised, being admitted to intensive care, or dying from COVID-19 in people with severe asthma.

Methods: We searched Ovid MEDLINE(R), WHO COVID-19 literature database, and medRxiv by a wide-ranging search strategy using two search strings relating to COVID-19 and asthma on 19 July 2021. We sought to include studies among children and adults examining severe COVID-19-related outcomes such as hospitalisation, admission to intensive care unit, ventilation or intubation, and/or mortality. Severe asthma was defined as asthma: i) requiring high-dose inhaled corticosteroids (ICS) and a second controller; ii) use of systemic corticosteroids to prevent asthma from becoming "uncontrolled"; iii) asthma that remained "uncontrolled" despite therapy; or iv) any other guideline definition of asthma severity on the basis of medication use. Eligible studies had definitions of severe asthma, confirmed COVID-19 cases based on RT-PCR and relevant comparators (e.g., people with mild or no asthma). We utilised the Joanna Briggs Institute critical appraisal tools to assess the quality of included studies. We summarised evidence by types of severe COVID-19 outcome and by asthma medications regimens. To assess external validity, we examined severe COVID-19 outcomes by study settings such as population-based studies and hospital-based studies.

For time-to-event outcomes, we performed a general inverse variance method using random-effects meta-analyses (employing the DerSimonian-Laird estimator) and explored the reasons for heterogeneity through subgroup analyses and the assessment of the I^2 statistic. All analyses were done using RevMan 5.4.1.

Results: Of the 1843 records initially identified, nine cohort studies, including only adults, met our eligibility criteria. No studies in children were identified. Most of the included studies (7/9) were assessed as having high quality (assessment score > 80%). Of these nine cohort studies, five were population-based, three were hospital-based, and one was a community-based. Overall, severe asthma was defined by two main asthma medication regimens: high-dose ICS use in six studies; and oral corticosteroid (OCS) use in 4 studies. One study defined severe asthma using both criteria. Three studies were excluded from the analysis for one of two reasons: i) no cases reported, ii) different outcome evaluation methods. Subsequently, six studies were included in the analysis, three of which were population-based. For the risk of mortality from COVID-19, we examined associations with severe asthma according to study settings or medication regimens, but not for COVID-19 hospital admission due to a lack of data. For the COVID-19 hospital admission, two studies, including a population-based cohort and a community-based cohort, showed adults with severe asthma had a hazard ratio (HR) of 1.29 with a 95% confidence interval (CI) of 1.22 to 1.37. Three population-based cohort studies showed that adults with severe asthma had a higher HR for COVID-19 related death of 1.15 (95% CI: 1.01 to 1.31) than those with mild asthma or no asthma. Two hospital-based

cohort studies also showed a higher HR of 1.96 for death from COVID-19 (95% CI: 1.26 to 3.04). When we differentiated adults with severe asthma by asthma medications regimens, two population-based cohort studies showed that high-dose ICS had an HR of 1.27 (95% CI: 0.87 to 1.85) for death from COVID-19 compared to those with mild asthma or no asthma. In contrast, two hospital-based cohort studies showed a higher HR for death from COVID-19 of 1.96 (95% CI: 1.26 to 3.04) compared to those with no severe asthma or no asthma. Lastly, two studies, including a population-based and a hospital-based cohort, showed that in adults with severe asthma, OCS use had an HR of 1.13 (95% CI: 1.01 to 1.26) compared with non-severe or no asthma.

Conclusion: The findings from this review suggest that adults with severe asthma have a higher risk of hospitalisation and death from COVID-19 than those with mild asthma or without asthma. In adults with severe asthma, OCS use during one year might be associated with an increased risk of COVID-19-related death; however, more data are needed to confirm this association. According to the population-based studies, the use of high-dose ICS was not associated with an increased risk of death from COVID-19. In contrast, high-dose ICS use in adults with severe asthma admitted to hospital might be associated with the high risk of death from COVID-19. However, the potential impact of other risk factors should be examined to confirm this association. Given the high heterogeneity across studies, our findings should be taken cautiously in application to other settings or populations. Lastly, there is an urgent need for data on whether asthma severity is a risk factor for serious COVID-19 outcomes in children and young people.

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Lead reviewers: Bohee Lee, Evropi Theodoratou, Ruth McQuillan

Reviewers (in alphabetical order): Eldad Agyei-Manu, Nadege Atkins, Urmila Bhattacharyya, Marshall Dozier, Grace Lewis

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Introduction

The coronavirus disease 2019 (COVID-19) is a serious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has resulted in a global health emergency (Tabari et al., 2020), affecting both adults and children (Viner et al., 2021). Older people and people with comorbidities such as diabetes mellitus, hypertension, cancer

and respiratory disease are known to have an increased likelihood of developing serious illness (Booth et al., 2021, Zheng et al., 2020).

Severe (uncontrolled) asthma is a chronic pulmonary disease that requires the frequent use of daily oral steroids or inhaled medications by affected patients to reduce asthma symptoms (Chung et al., 2014). Pulmonary function tests, especially spirometry, show that patients with severe asthma have a significant reduction in their lung function (Gallucci et al., 2019). Asthma has been a particular focus with considerable interest in whether asthma severity is a risk factor for serious COVID-19 outcomes. For instance, the US Centers for Disease Control and Prevention (CDC) has suggested that people with uncontrolled or moderate-to-severe asthma may have a higher risk of COVID-19 infection (CDC, 2021).

In a recent systematic review and meta-analysis with 57 studies, Sunjaya and colleagues (2021) demonstrated that people with asthma were at lower risks of acquiring COVID-19 and hospitalisation with COVID-19. Also, their findings showed that asthma was not associated with severe COVID-19 outcomes such as intensive care unit (ICU) admission, mechanical ventilation and death(Sunjaya et al., 2021). Given that non-severe asthma was more prevalent in their study (9.61% for non-severe asthma vs 4.13% for severe asthma), there is a need to clarify the associations between severe asthma and serious COVID-19 outcomes. Identifying severe asthma as a risk factor for COVID-19 would be essential in prioritising people with severe asthma for COVID-19 vaccination, designing relevant prevention strategies for COVID-19 infection, and help the immediate development of new severe asthma treatments/therapies for optimal management.

Objectives and research questions

The primary aim of this review is to explore associations between severe asthma and severe COVID-19 outcomes. This aim was achieved through two research questions: (1) what severe outcomes of COVID-19 were examined in relation to severe asthma?; (2) are people with severe asthma at a higher risk of being hospitalised, being admitted in intensive care or of poor clinical outcomes due to the SARS-CoV-2 infection?

Methods

This rapid review was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-2020) protocols statement (Page et al., 2021). A study protocol was first developed and registered on PROSPERO (CRD42021270284).

Search strategy

We developed a search strategy by combining two search strings, including terms related to COVID-19 and asthma. The search strategy was designed to identify studies that reported characteristics of severe asthma patients who required hospitalisation, ICU admission, mechanical ventilation or intubation, and death due to SARS-COV-2 infection. We also added search terms “systematic review” and/or “meta-analysis” in the search strategy.

We searched the Ovid MEDLINE(R), WHO Covid literature database, and medRxiv. Draft searches were piloted in each database and then finalised. Searches were conducted on 19 July 2021 by MD. Only papers in English were included in this review. Finalised search strategies are presented in Table S1 in Appendix.

Screening and selection of studies

Following the searches, all identified citations were collated and imported into Covidence, where the first deduplication of records was conducted. Additional duplicates were identified manually during the title and abstract screening.

Severe asthma was defined as asthma: i) requiring high-dose inhaled corticosteroids (ICS) and a second controller; ii) use of systemic corticosteroids to prevent asthma from becoming "uncontrolled"; iii) asthma that remained "uncontrolled" despite therapy; or iv) any other guideline definition of asthma severity based on medication use (Chung et al., 2014, National Institute for Health and Care Excellence, 2020).

Eligible studies had definitions of severe asthma, confirmed COVID-19 cases based on Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) and relevant comparators (e.g., people with mild or no asthma). The definition of serious COVID-19 was severe clinical outcomes related to COVID-19, such as mortality, ICU admission, mechanical ventilation, and hospitalisation with pre-existing severe asthma.

After excluding duplicates, title and abstract screening and full-text review were conducted for each study by two independent reviewers from a group of five reviewers (BL, EAM, NA, UB, GL), utilising the inclusion and exclusion criteria outlined in Table 1. During the selection of studies, any disagreements were resolved by a third independent reviewer or by the other two lead reviewers (ET, RM).

Table 1: Inclusion and exclusion criteria

	Inclusion	**Exclusion**
Population	Patients (adults or children) with confirmed COVID-19 based on RT-PCR	Studies which only referenced the "COVID-19" broadly
Exposure	Severe asthma diagnosed by clinicians or by validated or non-validated guidelines	Self-reported asthma patients
Comparator	Patients (adults or children) with confirmed COVID-19 based on RT-PCR that developed severe disease with no 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 in any design besides those specified in the exclusion criteria	Modelling studies, opinion, editorials, reviews, and laboratory studies
Geographical location	Studies conducted in any country or countries	No restrictions based on geographical location
Language	Studies published in English language	Studies published in a language other than English

Data extraction and data analysis

To facilitate data extraction by reviewers, we used a well-adapted Excel spreadsheet. The data extraction form was piloted before formal data extraction. Data for each study were extracted by a single reviewer and cross-checked by a second reviewer from a group of five reviewers (BL, EAM, NA, UB, GL). Any disagreements were resolved through discussions among the five reviewers under the supervision and guidance of ET and RM.

Initially, we aimed to identify studies investigating paediatric populations, but there was no data examining COVID-19 paediatric patients with pre-existing severe asthma. Therefore, we only extracted and analysed adult patient data in this review.

We extracted data on study characteristics and study findings as follows: First author, year published, study design, country, study methods (data collection and recruitment), overall population (total number), demographic characteristics (age, gender, ethnicity), severe asthma patients (numbers and proportion), dates for data collection, the definition of severe asthma, eligibility criteria, study settings, statistical analysis methods, and relevant results.

Study findings were presented as risk ratio (RR) / odds ratio (OR) / hazard ratio (HR) and 95% confidence intervals.

Risk of bias assessment

We used the Joanna Briggs Institute (JBI) critical appraisal tools to assess the quality of evidence of eligible studies (The Joanna Briggs Institute, 2021). Depending on the study design, an appropriate questionnaire consisting of eight to eleven questions was completed by two independent reviewers from a group of five reviewers (BL, EAM, NA, UB, GL). Any form of disagreement was jointly discussed among the five reviewers under the supervision of ET and RM.

The appraisal tools were composed of questions related to the selection of study participants, measurement of exposures and outcomes, adjustment for potential confounders, and follow-up periods. Each question was answered with either “Yes”, “No”, “Unclear” or “Not applicable”. The reviewers calculated the percentage of “Yes” responses among all questions to attain comparable quality scores amongst the selected studies. The overall quality score for each study, therefore, ranged from 0 to 100%. Studies with a score between 80% and 100% were considered high quality, those with a score less than 80% but greater than 50%

were considered moderate quality, and those with a score less than 50% were considered low quality.

Data synthesis

We summarised evidence by types of severe COVID-19 outcome and by asthma medications regimens. To assess external validity, we examined severe COVID-19 outcomes by study settings such as population-based studies and hospital-based studies. For time-to-event outcomes, we performed a general inverse variance method using random-effects meta-analyses, employing the DerSimonian-Laird estimator. To explored the reasons for heterogeneity, we conducted subgroup analyses and calculated I^2, tau^2, and Cochrane's Q. In general, if the I^2 test was moderate to high (> 50%), we investigated the possible causes of heterogeneity. All results were presented in the form of forest plots using RevMan 5.4.1, a program developed by Cochrane. The results were presented in narrative synthesis if a meta-analysis was not feasible due to high heterogeneity across studies.

Results

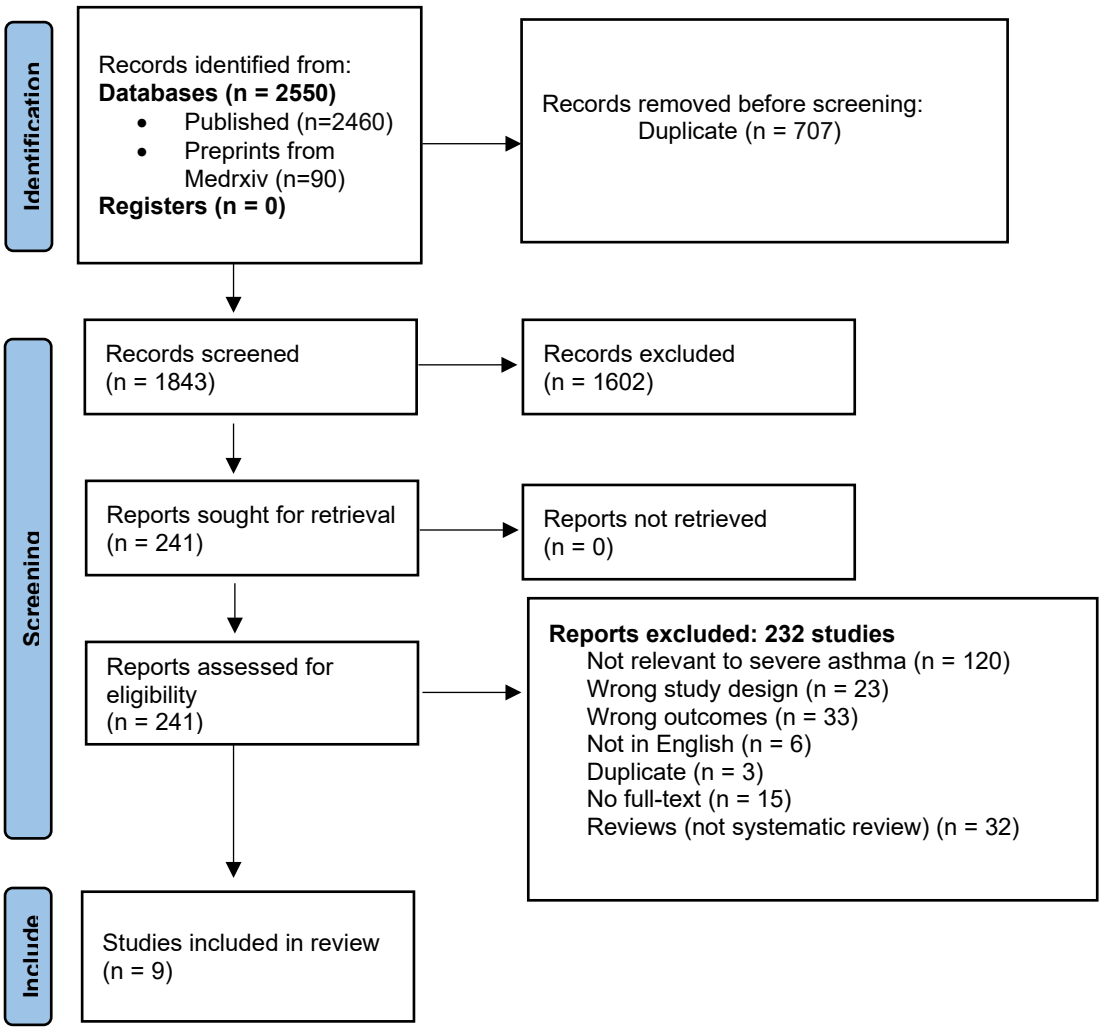

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) screening process

Characteristics of included studies

Initially, we identified 1843 records after deduplication. After title and abstract screening, we included 241 records in the full-text screening. Of these, nine articles were retained for data analysis after data extraction and risk of bias assessment (Aveyard et al., 2021, Bloom et al., 2021, Choi et al., 2021, Eger et al., 2020, Fong et al., 2021, Garcia-Pachon et al., 2021, Robinson et al., 2021, Schultze et al., 2020, Williamson et al., 2020). The screening process is summarised in a PRISMA flow chart (**Figure 1**).

Table 2 summarises the characteristics of the nine included studies. All studies were published in academic journals. Five studies used data from the United Kingdom(Aveyard et al., 2021, Bloom et al., 2021, Fong et al., 2021, Schultze et al., 2020, Williamson et al., 2020), and one each from South Korea (Choi et al., 2021), the USA (Robinson et al., 2021), Spain (Garcia-Pachon et al., 2021) and the Netherlands (Eger et al., 2020). The minimum duration for data collection was 1.5 months (Eger et al., 2020), whereas the maximum period was 17 months (Choi et al., 2021).

Study designs

All the included studies were cohort studies: four retrospective and five prospective studies. Of these nine studies, five were population-based cohort studies (Aveyard et al., 2021, Choi

et al., 2021, Eger et al., 2020, Schultze et al., 2020, Williamson et al., 2020). Two studies utilised the primary care electronic health record (EHR) managed by The Phoenix Partnership (TPP, UK), which were linked with death data from the Office for National Statistics (ONS) in England through the OpenSAFELY platform (Schultze et al., 2020, Williamson et al., 2020). This platform covered 17 million people, which is 40% of the population in England. Another UK study analysed data from 1205 GP practices in England, covering approximate 8 million patients through QResearch Database (Aveyard et al., 2021). This database was linked to ONS, Hospital Episode Statistics and the Intensive Care National Audit and Research Centre (ICNARC) Case Mix Programme database from all ICUs in England. A Korean study used national medical claims data, The Health Insurance Review & Assessment Service (HIRA), covering all Korean, including inpatients and outpatients (Choi et al., 2021). A Dutch study used severe asthma data from the Dutch Severe Asthma Registry (RAPSODI) and the general population data from the Dutch National Institute for Public Health and the Environment and the Statistics Netherlands' database. Therefore, this study was also considered population-based (Eger et al., 2020). Overall, seven large cohort studies were included: one QReseach cohort (Aveyard et al., 2021), two OpenSAFELY cohorts (Schultze et al., 2020, Williamson et al., 2020), one ISARIC cohort (Bloom et al., 2021) from the UK, the RASPSODI cohort (Eger et al., 2020) from the Netherlands, the HIRA cohort (Choi et al., 2021) from South Korea, and the MGB cohort (Robinson et al., 2021) from the USA.

Three studies were hospital-based (Fong et al., 2021, Garcia-Pachon et al., 2021, Bloom et al., 2021). One UK study used data from the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) WHO Clinical Characterisation Protocol UK (CCP-UK) study. The ISARIC WHO CCP-UK is a prospective cohort study actively recruiting inpatients across England, Scotland and Wales (Bloom et al., 2021). Also, two studies were based on data from each tertiary hospital in the UK (Fong et al., 2021) and Spain(Garcia-Pachon et al., 2021).

In one study in the USA, data were from Mass General Bringham (MGB), an extensive health care system including primary, secondary and tertiary health system in Boston, USA. This research identified adults (≥ 18 years old) with confirmed COVID-19 by PCR and non-allergic or allergic asthma at MGB. Given that this MGB system included a wide range of medical service users and its coverage was limited in the greater Boston area, we did not consider this study as a population-based study. To distinguish from studies that range broader regions or countries, this study was considered a community-based cohort study (Robinson et al., 2021).

In assessing poor COVID-19 outcomes, hospitalisation was reported in four studies (Aveyard et al., 2021, Eger et al., 2020, Robinson et al., 2021, Garcia-Pachon et al., 2021), admission to intensive care unit (ICU) in three studies (Aveyard et al., 2021, Choi et al., 2021, Eger et al., 2020), ventilation/ intubation in two studies (Eger et al., 2020, Robinson et al., 2021), and mortality in eight studies (Aveyard et al., 2021, Bloom et al., 2021, Choi et al., 2021, Eger et al., 2020, Fong et al., 2021, Schultze et al., 2020, Williamson et al., 2020, Robinson et al., 2021). However, in the study of Choi et al. (2020), there were no severe COVID-19 related cases in the severe asthma group (Choi et al., 2021). Eger et al. (2020) counted admissions to ICU for intubation, so we took this case as both admissions and ventilation/intubation cases (Eger et al., 2020). Robinson et al. (2020), there were no deaths out of 44 severe asthma patients (Robinson et al., 2021).

Sample characteristics

A total of 395,018 severe asthma patients were included (see Table S2 in Appendix). Severe COVID-19 outcomes in adults with severe asthma were available in eight studies (Aveyard et al., 2021, Bloom et al., 2021, Eger et al., 2020, Fong et al., 2021, Garcia-Pachon et al., 2021, Robinson et al., 2021, Schultze et al., 2020, Williamson et al., 2020). Only one study included patients under 16 years old, but data related to severe asthma was unavailable in this age group (Bloom et al., 2021). Initially, we aimed to investigate severe asthma in children, but none of the eligible studies looked at the paediatric population.

Table 2. Characteristics of studies included in the review (n=9)

Author (year)	Country	Cohort	Population	Definitions of COVID-19 outcomes	Data collection time	Design	Severe COVID-19 risk				Included in a meta-analysis
							Hospitalisation	ICU	Ventilation/ Intubation	Mortality	
Aveyard et al. (2021)	England, UK	QResearch database ver. 44	1205 General practices linked to all ICUs in England	RT-PCR test confirmed and suspected cases	3 months; 24 January to 30 April, 2020	Retrospective cohort study	**Yes**	**Yes**	No	**Yes**	**Yes**
Bloom et al. (2021)	UK	ISARIC CCP-UK study – national, multicentre	Hospitals in England, Scotland, and Wales - inpatients	RT-PCR test confirmed and suspected cases	7 months; 17 January to 17 August, 2020	Prospective cohort study	No	No	No	**Yes**	**Yes**
Choi et al. (2020)	South Korea	HIRA - COVID-19 nationwide patient medical claims data	Hospitals in South Korea: inpatients	RNA-PCR tests	17 months; Mar 2019 to 15 May 2020	Retrospective cohort study	No	**Yes**[a]	No	**Yes**[a]	No
Eger et al. (2020)	Nether-land	Dutch Severe Asthma Registry RAPSODI – national, multicentre; DNIPESN database – Dutch general population	15 Hospitals for the RAPSODI registry General population	PCR confirmed and suspected cases or typical symptoms with positive SARS-CoV-2 serology results	1.5 months; 17 March to 30 April, 2020	Prospective cohort study	**Yes**	**Yes**[b]	**Yes**	**Yes**	No[c]
Fong et al. (2020)	England, UK	EHR – single centre	A large tertiary hospital - inpatients	RT-PCR test	3 months; 1 March to 31 May, 2020	Retrospective cohort study	No	No	No	**Yes**	**Yes**
Garcia-Pachon et al. (2021)	Spain	EHR – single centre	A large tertiary hospital – inpatients	RT-PCR test	9 months; 3 March to 11 December, 2020	Retrospective cohort study	**Yes**	No	No	No	No
Robinson et al. (2021)	USA	MGB Enterprise Data Warehouse, MGB Research Patient Data Registry, and the COVID-19 Datamart – multicentre	Hospitals (two tertiary hospitals, community hospitals, primary and specialty outpatient centres) in the greater Boston – inpatients, outpatients	PCR test	4 months; 4 March to 2 July, 2020	Retrospective cohort study	**Yes**	No	**Yes**	**Yes**[d]	**Yes**

Author (year)	Country	Cohort	Population	Definitions of COVID-19 outcomes	Data collection time	Design	Severe COVID-19 risk				Included in a meta-analysis
							Hospitalisation	ICU	Ventilation/ Intubation	Mortality	
Schultze et al. (2020)	UK	OpenSAFELY - Primary care EHR data linked with death data from the Office for National Statistics in England	EHR data for 40% of the population in England, UK	ICD-10. U07.1 ("COVID-19, virus identified") and U07.2 ("COVID-19, virus not identified")	2 months; 1 March to 6 May, 2020	Prospective cohort study	No	No	No	**Yes**	**Yes**
Williamson et al. (2020)	England, UK	OpenSAFELY- Primary care EHR data linked with death data from the Office for National Statistics in England	EHR data for 40% of the population in England, UK	ICD-10. U07.1 ("COVID-19, virus identified") and U07.2 ("COVID-19, virus not identified")	3 months; 1 February to 6 May, 2020	Prospective cohort study	No	No	No	**Yes**	**Yes**

ICU, intensive care unit; ISARIC, the International Severe Acute Respiratory and emerging Infection Consortium; CCP-UK, WHO 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 record; MGS, Mass General Brigham; a, zero case (out of 4 patients); b, admission to ICU for intubation; c, excluded in meta-analysis due to different comparator – general population; d, zero case (out of 44 patients)

Severe asthma definitions

All studies defined severe asthma according to the asthma medications regimens, with two studies considering control of asthma (Eger et al., 2020, Garcia-Pachon et al., 2021) (**Table 3**). Overall, severe asthma was defined by two main asthma medication regimens: high-dose inhaled corticosteroids (ICS) use in six studies (Aveyard et al., 2021, Bloom et al., 2021, Eger et al., 2020, Garcia-Pachon et al., 2021, Schultze et al., 2020, Fong et al., 2021); and oral corticosteroids (OCS) use in 4 studies (Choi et al., 2021, Fong et al., 2021, Robinson et al., 2021, Williamson et al., 2020). Given that one study defined severe asthma using both regimens and did not examine outcomes by each regimen, we included this study in both groups (Fong et al., 2021).

In the QResearch cohort study, Aveyard and colleagues did not mention the medication regimens for severe asthma in the published paper. After contacting study authors, we decided to include this paper in the high-dose ICS group (Aveyard et al., 2021). In the ISARIC cohort study, Bloom and colleagues did not analyse results according to ICS dose; however, they assumed that patients with severe disease were more likely to use high-dose ICS (Bloom et al., 2021). Therefore, this study was also included in the high-dose ICS group.

In the OpenSAFELY cohort study, Schultze and colleagues did not describe severe asthma. However, 92.5% of participants in the high-dose ICS group in the study used a second controller, which was matched with our severe asthma definition. In this respect, people with asthma using high-dose ICS in the study were deemed those with severe asthma (Schultze et al., 2020).

Table 3. Definition of patients with severe asthma amongst included studies (n=9)

Author (year)	Definition of severe asthma used
Aveyard et al. (2021)	Patients who were prescribed at least three different classes of asthma medication, including ICS, the year prior to cohort entry
Bloom et al. (2020)	Patients taking ICS plus LABA plus another maintenance medication
Choi et al. (2020)	Patients taking OCS for a duration of over 90 days
Eger et al. (2020)	Patients with asthma that requires treatment with high-dose ICS, plus a second controller (and/or systemic corticosteroids) to prevent it from becoming 'uncontrolled' or which remains 'uncontrolled' despite this therapy according to ERS/ATS guidelines.
Fong et al. (2020)	Patients managed with high-dose treatment or continuous/frequent OCS use according to BTS guidelines
Garcia-Pachon et al. (2021)	Patients with asthma that is uncontrolled despite high ICS plus LABA, or that requires high-dose ICS plus LABA to remain controlled according to GINA guidelines
Robinson et al. (2021)	Patients who used (1) asthma biologics (anti-IgE, anti-interleukin-5/interleukin-5 receptor, or anti-interleukin-4 receptor) in the last 1 year or (2) OCS ≥ 3 times in the last 1 year, or (3) theophylline in the last 1 year
Schultze et al. (2020)	Patients prescribed high-dose ICS within 4 months before entering the study cohort
Williamson et al. (2020)	Patients who used OCS within 1 year

ICS, Inhaled corticosteroids; LABA, Long-acting beta-agonist; OCS, Oral corticosteroids; ERS/ATS, European Respiratory Society (ERS) and American Thoracic Society (ATS); BTS, British Thoracic Society; SIGN, Scottish intercollegiate Guidelines Network; GINA, Global Initiative for Asthma

Quality assessment of included studies

Based on the JBI critical appraisal tool for cohort studies standards and the calculation of the quality score for each included study, seven out of nine studies in the review were of high

quality (Aveyard et al., 2021, Bloom et al., 2021, Choi et al., 2021, Fong et al., 2021, Robinson et al., 2021, Schultze et al., 2020, Williamson et al., 2020). These high-quality studies had an average quality score of 93%. The authors of these studies presented sufficient information on study participants, potential confounders, and the follow-up period of studies. A study by Garcia-Pachon et al. (2021) was of low quality, having a quality score of 36%. Given that this study was a short communication type, full information was not available. Table 4 shows the summary of results from the quality assessment of the nine included studies.

Table 4. JBI Quality assessment of included studies (n=9)

Study	Were the two groups similar and recruited from the same population ?	Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Was the exposure measured in a valid and reliable way?	Were conf ounding factors identified?	Were strategies to deal with confounding factors stated?	Were the groups/part icipants free of the outcome at the start of the study (or at the moment of exposure)?	Were the outcomes measured in a valid and reliable way?	Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Were strategies to address incomplete follow up utilised?	Was appropriate statistical analysis used?	Scoring[§] (%)	Overall Study Quality
Aveyard et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100	High
Bloom et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100	High
Choi et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	81	High
Eger et al. (2020	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes	63	Moderate
Fong et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100	High
Garcia-Pachon et al. (2021)	Yes	Yes	Yes	No	No	Yes	Unclear	No	Unclear	Unclear	No	36	Low
Robinson et al. (2021)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	81	High
Shultze et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	100	High
Williamson et al. (2020)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	91	High

[§]Scoring scale: high 80 – 100%, moderate 50 – 79%, low <50%

Severe asthma and severe COVID-19 outcomes risks

Overall, four severe COVID-19 outcomes were identified: hospitalisation, ICU admission, ventilation or intubation, and mortality. Table 5 summarises the detailed findings for severe COVID-19 outcomes. Six studies were included in the analysis, and three of which were population-based. For the risk of mortality from COVID-19, we examined associations with severe asthma according to study settings or medication regimens, but not for COVID-19 hospital admission due to lack of data.

Table 5. Severe COVID-19 outcomes in adults[§] (n=9)

Author (year)	Control group		Severe asthma group	
	OR/RR/HR	**95%CI**	**OR/RR/HR**	**95%CI**
	Hospitalisation			
Aveyard et al. (2021)	No respiratory disease: reference		HR 2.14	**2.02 – 2.26**
			HR[a] 1.65	**1.56 – 1.75**
			HR[b] 1.47	**1.39 – 1.55**
			HR[c] 1.29	**1.22 – 1.37**
Eger et al. (2020)	Dutch general population: reference		OR[d] 14.0	**6.6 – 29.5**
Robinson et al. (2021)	No asthma: reference			
	No severe asthma			
	HR 1.12	0.92 – 1.36	HR 1.53	0.89 – 2.64
	HR[e] 1.03	0.84 – 1.26	HR[e] 1.73	0.98 – 3.04
	HR[f] 0.94	0.75 – 1.17	HR[f] 1.99	0.82 – 4.79
	ICU admission			
Aveyard et al. (2021)	No respiratory disease: reference		HR 1.79	**1.49 – 2.15**
			HR[a] 1.64	**1.37 – 1.98**
			HR[b] 1.33	**1.10 – 1.60**
			HR[c] 1.30	**1.08 – 1.58**
Choi et al. (2020)	Step 1 (mild asthma): reference		Step 5	
	Step 2 OR 0.36	0.04 – 3.63	OR 0.00	0.00 – 999.999
	Step 3 OR 0.00	0.00 – 999.99	OR[g] 0.00	0.00 – 999.999
	Step 4 OR 0.53	0.10 – 2.71		
	Step 2 OR[g] 0.06	0.00 – 1.85		
	Step 3 OR[g] 0.00	0.00 – 999.99		
	Step 4 OR[g] 0.08	0.00 – 1.58		
	Ventilation/ intubation			
Eger et al. (2020)	Dutch general population: reference		OR[d] 40.8	**16.9 – 98.5**
Robinson et al. (2021)	No asthma: reference			
	No severe asthma			
	HR 0.49	**0.26 – 0.95**	HR 1.95	0.75 – 5.11
	HR[e] 0.47	**0.24 – 0.92**	HR[e] 2.10	0.77 – 5.76
	HR[f] 0.47	0.22 – 1.01	HR[f] 85.2	**5.55 – 1310**
	Mortality[‡]			
Aveyard et al. (2021)	No respiratory disease: reference		**HR 1.78**	**1.62 – 1.95**
			HR[a] 1.35	**1.23 – 1.48**
			HR[b] 1.21	**1.11 – 1.34**
			HR[c] 1.08	0.98 – 1.19
Bloom et al. (2021)	No asthma: reference		**HR[h] 2.08**	**1·32–3.26**
	No asthma therapy HR 1.21	0.75-1.95		
	SABA HR 1.01	0.62-1.65		
	ICS only HR 0.99	0.65-1.49		
	LABA plus ICS HR 1.03	0.68-1.55		
Choi et al. (2020)[†]	Step 1 (mild asthma): reference		Step 5	
	Step 2 OR 0.43	0.08 – 2.32	OR 0.00	000 – 999.999
	Step 3 OR 0.40	0.04 – 3.63	OR[g] 0.00	000 – 999.999

	Step 4 OR 0.97	0.31 – 3.08		
	Step 2 OR[g] 0.07	0.01 – 1.00		
	Step 3 OR[g] 0.06	0.00 – 2.06		
	Step 4 OR[g] 0.41	0.04 – 3.96		
Eger et al. (2020)	Dutch general population: reference		OR[d] 5.0	0.7 – 35.8
Fong et al. (2020)	No severe asthma: reference		Sub-distribution HR[i] 0.87	0.16 – 4.67
Schultze et al. (2020)	SABA only: reference			
	Low or medium ICS		High ICS	
	HR 1.36	**1.01 – 1.84**	**HR 2.30**	**1.64 – 3.23**
	HR[a] 1.02	0.76 – 1.37	**HR[a] 1.61**	**1.15 – 2.27**
	HR[j] 1.14	0.84 – 1.54	**HR[j] 1.55**	**1.10 – 2.18**
	HR[k] 1.16	0.86 – 1.56	**HR[k] 1.6**	**1.13 – 2.25**
Williamson et al. (2021)	No asthma: reference			
	No recent OCS use		Recent OCS use	
	HR[a] 1.13	**1.07 – 1.20**	HR[a] 1.55	**1.39 – 1.73**
	HR[k] 0.99	0.93 – 1.05	HR[k] 1.13	**1.01 – 1.26**

§ Garcia-Pachon et al. (2021) was not included because the only number and percentage were available; †: step 1,SABA or SAMA; step 2, ICS, LTRA, or xanthine; step 3, ICS/LABA alone, ICS + LTRA, or ICS + xanthine; step 4, ICS/LABA + LAMA, ICS/LABA + LTRA, or ICS/LABA + xanthine; step 5 (severe asthma), oral corticosteroid with a duration over 90 days; ‡Robinson et al. (2021) was not included in a meta-analysis due to statistical estimates were not available. Abbreviations: NA, Not applicable; HR, hazard ratio; OR, odds ratio; aHR adjusted for age/sex; bHR adjusted for demographic ethnicity, socioeconomic status, region of England, body-mass index (categorical variable), and smoking status (with current intensity of smoking as categorical variables); cHR adjusted for non-smoking-related illness (hypertension, type 1 diabetes, chronic liver disease, chronic neurological disease) and smoking-related illness (coronary heart disease, stroke, atrial fibrillation, type 2 diabetes, chronic kidney disease). Data for people with cystic fibrosis, sarcoidosis, extrinsic allergic alveolitis, idiopathic pulmonary fibrosis, other interstitial lung disease, and lung cancer not presented because fewer than five people had the outcome; dHR adjusted for obesity, diabetes or cardiovascular disease; eHR adjusted for age, sex, date of SARS-CoV-2 Test; fHR adjusted for age, sex, and date of SARS-CoV-2 test date, race, ethnicity, payor, smoking status, body mass index, and Charlson comorbidity index; gHR adjusted for age, sex, underlying disease, and asthma medications/severity; hHR only RT-PCR confirmed cases, adjusted for age, sex, ethnicity, IMD quintile, smoking, obesity, chronic cardiac disease, malignant neoplasm; iHR adjusted for other comorbidities; jHR adjusted for age, sex, BMI, Indices of multiple deprivations, diagnosed hypertension, heart disease, diabetes, cancer, immunosuppressive conditions, chronic kidney disease, influenza vaccination status, pneumococcal vaccianation status, statin sue, exacerbation history; kHR adjusted for age, sex, BMI, Indices of multiple deprivations, diagnosed hypertension, heart disease, diabetes, cancer, immunosuppressive conditions, chronic kidney disease, influenza vaccination status, pneumococcal vaccianation status, statin sue, exacerbation history, oral steroids use; lHR adjusted for age (using a four-knot cubic spline for age), sex, BMI, smoking, IMD quintile, hypertension or high blood pressure, asthma, chronic heart disease, diabetes, non-haematological cancer, haematological malignancy, reduced kidney function, liver disease, stroke or dementia, other neurological disease, organ transplant, asplenia, rheumatoid arthritis, lupus or psoriasis, and other immunosuppressive condition

Hospital admission for COVID-19

Three studies reported the risk of hospitalisation in the severe asthma patient group (Aveyard et al., 2021, Eger et al., 2020, Robinson et al., 2021) (**Figure 2**). Of these, two studies, including a national population-based cohort and a community-based cohort, were included in the meta-analysis (Aveyard et al., 2021, Robinson et al., 2021). The result showed that adults with severe asthma had a hazard ratio (HR) of 1.29 with a 95% confidence interval (CI) of 1.22 to 1.37.

The population-based study by Eger and colleagues was not included in the analysis (Eger et al., 2020). Given that severe asthma with their comparators, the general population, were not from the same cohort, we did exclude this study from the meta-analysis to mitigate heterogeneity between studies.

According to this study, the prevalence of COVID-19 hospital admission in adults with severe asthma was higher than the general Dutch population (1.10% for the RAPSODI vs 0.08% for the Dutch population). Also, adults with severe asthma on biologic therapy had a higher odds ratio (OR) of 14.0 for hospital admission than the general Dutch population (95% CI: 6.6 to 29.5).

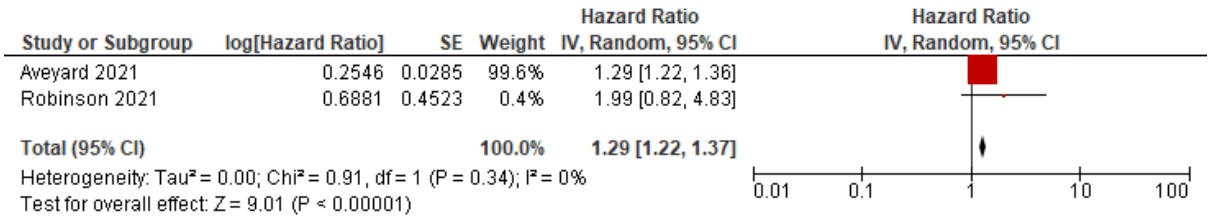

Figure 2. Forest plot of the meta-analysis for the association between severe asthma and hospitalisation due to COVID-19.

Mortality for COVID-19

Eight studies examined the association between severe asthma and COVID-19 mortality (**Table 2**). Of these studies, we did not include three studies in the meta-analysis due to a very small sample size (severe asthma, n = 4)(Choi et al., 2021),different comparators (Eger et al., 2020), and no COVID-19 related death (Choi et al., 2021, Robinson et al., 2021). Eger and colleagues reported a higher prevalence of COVID-19 related death in adults with severe asthma on biologic therapy in the RAPSODI registry compared with the general Dutch population (0.16% for the RAPSODI vs 0.03% for the Dutch population)(Eger et al., 2020). They also observed an OR of 5.0 for death in adults with severe asthma on biologic therapy compared with the general Dutch population (95% CI: 0.7 to 35.8) (**Table 5**).

Hence, five studies were included in the analysis (**Figure 3**). When ignoring settings and medication regimens, the result showed that adults with severe asthma had a higher HR of 1.25 for death from COVID-19 compared to those with mild asthma (requiring only SABA) or no asthma (95% CI: 1.05 to 1.48) (Aveyard et al., 2021, Bloom et al., 2021, Fong et al., 2021, Schultze et al., 2020, Williamson et al., 2020). However, there was significant heterogeneity between studies (I^2 = 66%, p = 0.02).

When only including population-based cohorts, which included three studies (Aveyard et al., 2021, Schultze et al., 2020, Williamson et al., 2020), adults with severe asthma had a higher HR for COVID-19 related death of 1.15 (95% CI: 1.01 to 1.31) than those with mild asthma or no asthma. Also, the level of heterogeneity was moderately high (I^2 = 57%, p= 0.10).

Two hospital-based cohort studies also showed a higher HR of 1.96 for death from COVID-19 (95% CI: 1.26 to 3.04).

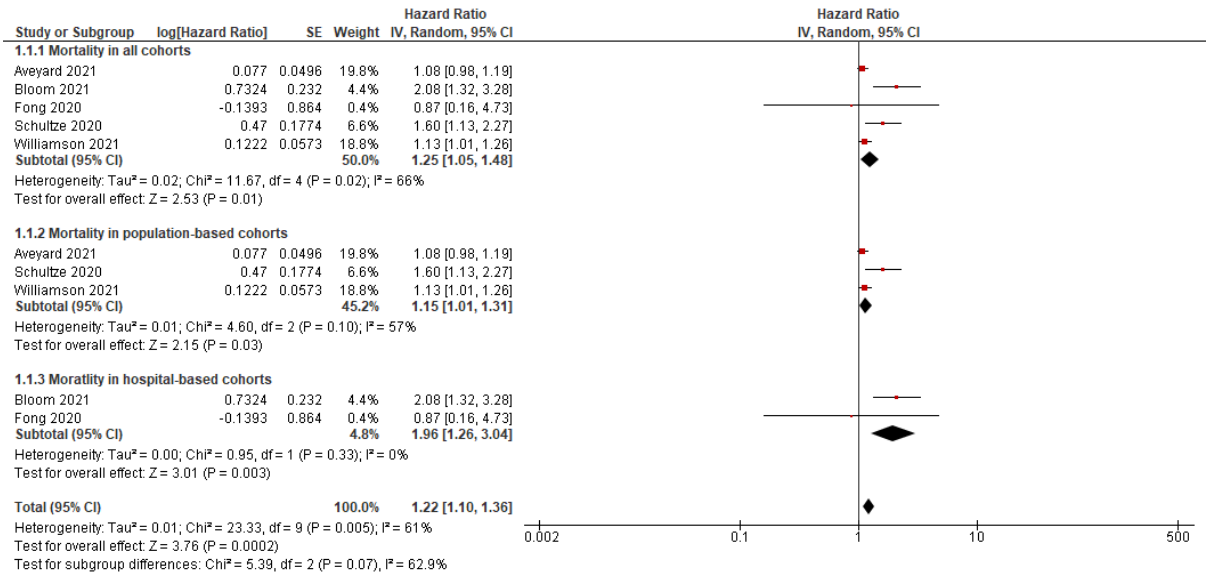

Figure 3. Risk of in all cohorts and mortality in population-based cohorts

Mortality in severe asthma by asthma medications regimens

We examined the risk of mortality for COVID-19 in subgroups of severe asthma by asthma medications regimens (**Figure 4**).

Two studies, including a population-based and a hospital-based cohort, showed that in adults with severe asthma, OCS use had an HR of 1.13 (95% CI: 1.01 to 1.26) compared with non-severe or no asthma (Fong et al., 2021, Williamson et al., 2020).

When ignoring settings, four studies showed that adults using high-dose ICS use were not associated with an increased HR for mortality compared to those with mild asthma or no asthma (HR: 1.43; 95% CI: 0.98 to 2.08) (Aveyard et al., 2021, Bloom et al., 2021, Schultze et al., 2020, Fong et al., 2021).

Two population-based cohort studies showed that high-dose ICS had an HR of 1.27 (95% CI: 0.87 to 1.85) for death from COVID-19 compared to those with mild asthma or no asthma. In contrast, two hospital-based cohort studies showed a higher HR for death from COVID-19 of 1.96 (95% CI: 1.26 to 3.04) compared to those with no severe asthma or no asthma.

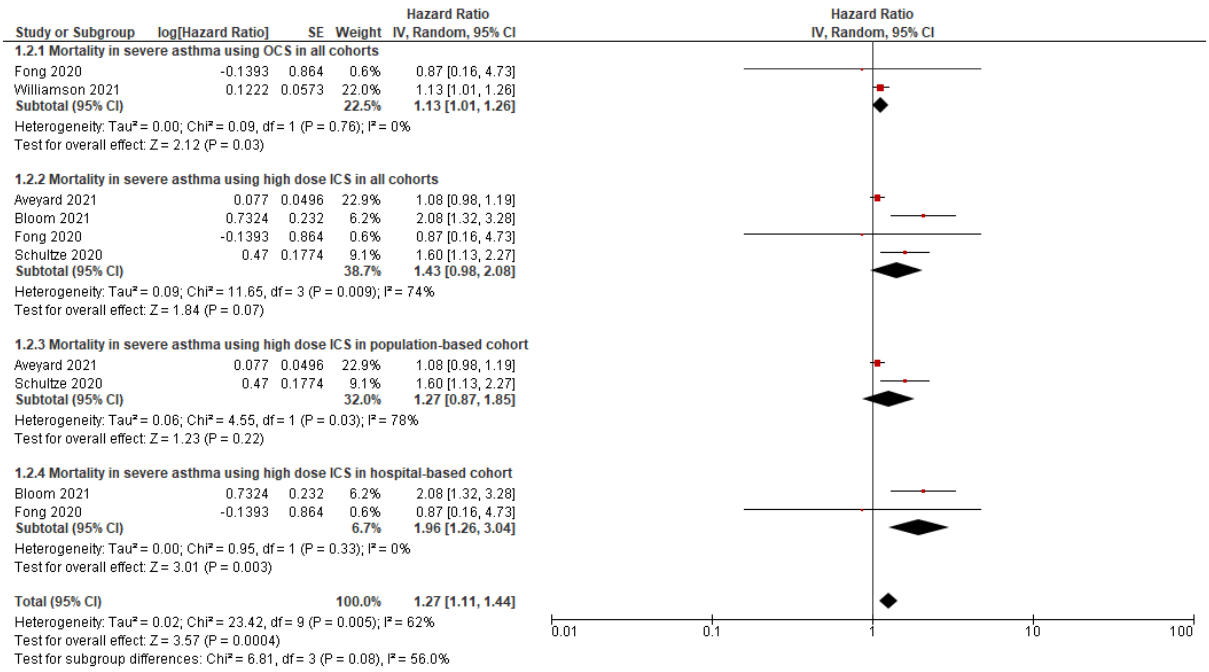

Figure 4. Mortality in severe asthma by asthma medications regimens

ICU admission

Two population-based studies examined the association between severe asthma and ICU admission related to COVID-19 (Aveyard et al., 2021, Choi et al., 2021). One UK study showed a higher risk for ICU admission in adults with severe asthma even after adjusting for confounding factors such as age and sex, other demographic factors, and comorbidities than those without any respiratory disease (Aveyard et al., 2021). In this study, severe asthma requiring the use of high dose ICS had a higher HR of 1.30 (95% CI: 1.08 to 1.58) for ICU admission after adjustment for all respiratory disease and comorbidities compared to those without any respiratory disease. However, no ICU admission case was observed in severe asthma requiring OCS within 1 year in Korea (Choi et al., 2021).

Ventilation / intubation

Two studies compared mechanical ventilation risk in relation to severe asthma (Eger et al., 2020, Robinson et al., 2021). In a Dutch study, severe asthma requiring high dose ICS showed a higher intubation prevalence than the general Dutch population (0.79% for the RAPSODI vs 0.02% for the general Dutch population). Also, severe asthma had an OR of 40.8 for intubation (95% CI: 16.9 to 98.5) compared with the general Dutch population (Eger et al., 2020). According to a community-based study, the rate of event per 1000 person-days of the mechanical ventilation was 1.6 (95% CI: 0.2 to 3.0) in the severe asthma group using OCS within 1 year (Robinson et al., 2021). There was no significant difference between severe and non-severe asthma after matching age, sex, and date of SARS-CoV-2 test (HR: 2.10; 95% CI: 0.77 to 5.76) (Robinson et al., 2021).

Discussion

Summary of our findings

To date, this is the first systematic review to examine the relationship between severe asthma and severe COVID-19 outcomes. Principally, the current review found that adult patients with severe asthma had an increased risk of severe COVID-19 outcomes in terms of COVID-19-related hospitalisation and mortality. Due to the unavailability of relevant data, we could not examine the relationship between severe asthma and severe COVID-19 outcomes in the paediatric population.

Of nine included studies, seven high-quality studies examined hospitalisation, ICU admission, mechanical ventilation or intubation and mortality related to COVID-19 in people with severe asthma. Findings from two studies demonstrated that severe asthma was associated with a significantly higher risk of hospitalisation for COVID-19 with low heterogeneity. Of these two studies, the population-based study showed different risks for hospitalisation by age. In people with severe asthma, people younger than 40 years had the highest HR of 2.99 (95% CI: 2.39 to 3.75) compared to those aged 40 to 59 years (HR: 1.86; 95% CI: 1.64 to 2.10), those aged 60 to 79 years (HR: 1.34; 95% CI: 1.23 to 1.47) and those aged 80 years and above (HR: 0.89; 95% CI: 0.80 to 0.98). Also, women with severe asthma had a higher HR of 1.40 (95% CI: 1.29 to 1.51) for hospital admission than men (HR: 1.18; 95% CI: 1.08 to 1.28) (Aveyard et al., 2021). In the community-based study, in 44 severe asthma patients, 23 (52%) people aged 36 to 55 and 33 (75%) women were hospitalised; however, HRs were not available (Robinson et al., 2021). Although our meta-analysis showed low heterogeneity, there is a potential impact of suspected COVID-19 cases on outcomes in the population-based cohort study (Aveyard et al., 2021).

For mortality, three population-based cohort studies demonstrated that adults with severe asthma were associated with an increased risk of COVID-19 related death compared to those with mild asthma using only SABA or no respiratory diseases with moderately high heterogeneity. Such high heterogeneity could be due to different sample sizes and asthma medication use, different comparators, the inclusion of suspected COVID-19 cases and different covariates, including data collection time. The same trend was evident in the hospital-based cohort studies with low heterogeneity, but the sample sizes and included ages between the two studies were quite different. For example, in the ISARIC study, we used HRs for mortality from people aged 16-49 years (n = 201), with 24 deaths (Bloom et al., 2021). A single centre study in the UK had relatively older patients than those in the ISARIC study, with one death out of 39 adults with severe asthma (Fong et al., 2021).

To address the heterogeneity, we conducted subgroup analysis according to asthma medications regimens. Findings showed that severe asthma defined by OCS use was associated with a 13% increased mortality risk compared to those with no asthma or no severe asthma. However, this association might not be generalisable to other populations. As we assumed that there would be OCS users according to severe asthma definitions in the study by Fong and colleagues, the exact number of OCS users would be very low considering

the sample size of severe asthma (Fong et al., 2021). Therefore, the HR from the analysis was the same as that from the OpenSafely cohort by Williamson and colleagues (Williamson et al., 2020).

In contrast, we found that high-dose ICS users were not at increased risk of mortality from COVID-19 when including all settings and all types of populations. When we differentiated studies by settings, two population-based cohort studies - the QResearch cohort and another OpenSafely cohort - showed similar results with high heterogeneity (Aveyard et al., 2021, Schultze et al., 2020). However, this result can be changed if we included the regular ICS users who received at least two prescriptions in the 150 days before the study entry from the QResearch cohort. In this cohort, 76.1% of regular ICS users were using at least three airway medications, as such they can be classified as having severe asthma. The overall HR was 1.15 (95% CI: 1.01 to 1.31) in the regular ICS users adjusted for other comorbidities and potential confounding factors, which would be similar to the ones in the OpenSAFELY cohort. But the researchers were concerned about potential misclassification(Aveyard et al., 2021).

Given that most of the included studies collected data in the early stage of the pandemic, governmental COVID-19 mitigations might affect behavioural changes in people with severe asthma. In this regard, Aveyard et al. (2021) examined the impact of shielding or national lockdown in England introduced in England at the end of March 2020 on severe COVID-19 risks. Their findings showed that there were significantly higher risks of hospitalisation and ICU admission regardless of shielding, but not in mortality (Aveyard et al., 2021). Likewise, Williamson et al. (2020) also commented that there was no significant difference between people less compliant with social distancing policies and those more compliant in their sensitivity analysis [21]. However, it is still possible that social distancing and shielding policies would affect patients differently in these studies. Another possible explanation for the high heterogeneity stands in different statistical approaches. Our analyses only included full-adjusted HRs, which were derived from different adjustments across included studies. In addition, misclassification due to including non-laboratory-confirmed COVID-19 cases can result to high heterogeneity. Four studies only included confirmed COVID-19 cases, and five studies included both laboratory-confirmed and non-laboratory-confirmed COVID-19 subjects. For example, the HR from Bloom et al. (2020) was derived from adjustments for severity on admission, age, asthma medications and comorbidities. Also, if we include highly suspected COVID-19 subjects, the HR was 1.96 (95% CI: 1.25 to 3.08) compared to people with no asthma, which was slightly lower than the HR only including RT-PCR confirmed COVID-19 cases.

Our findings are contrary to some previous studies. A large cohort study of COVID-19 in the Severe Asthma Network in Italy (SANI) suggested that severe asthma is not associated with an elevated risk of COVID-19 related mortality (Heffler et al., 2021). Also, Antonicelli and colleagues surveyed clinicians of the Italian Registry of Severe Asthma (IRSA) network, which showed that there was no ICU admissions and hospitalisation in people with severe asthma (Antonicelli et al., 2021). Also, they observed no difference in the hospitalisation rate of

severe asthma patients in pre-pandemic compared with that in the pandemic in a region where both hospitalisations were observed (Antonicelli et al., 2021). These findings can be explained by self-awareness (Heffler et al., 2021) or the use of high-doses of ICS or OCS (Chung et al., 2014). Some studies described the low risk of severe COVID-19 outcome in severe asthmatics based on a protective effect of Th2-inflammation. Type 2 inflammation, common with severe asthmatic symptoms, triggers reducing cellular receptors such as angiotensin-converting enzyme 2 (ACE2), which is a receptor for SARS-CoV-2 (Chung et al., 2020, Jackson et al., 2020). Respiratory allergies or interleukin (IL)-13 are associated with a significant reduction in ACE 2 expression, resulting in decreasing susceptibility of SARS-CoV-2 (Yao et al., 2020).

Our findings did not support harmful associations between high-dose ICS use and COVID-19 related death in adults, which is in line with some population studies. A case-control study in Korea revealed no significant increase in COVID-19 related mortality in ICS adult users whose cumulative ICS dose was $\geq$ 15 000 μg in the last 12 months, compared to non-ICS users amongst the asthma patients after adjusting for baseline demographic characteristics and comorbidities (Choi et al., 2020). Also, 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 (Sen et al., 2021). Some in-vitro models showing inhibitory effects of ICS alone or in combination with beta-agonists on coronavirus HcoV-229E replication and cytokine production could support protective effects of ICS treatment (Yamaya et al., 2020, Matsuyama et al., 2020).

Nevertheless, there is a need to reduce the large degree of heterogeneity across studies by adjusting for confounding factors, including unmeasured ones or standardising diagnostic criteria.

Limitations

There were some limitations in this review. Firstly, we might have missed some literature despite our wide-ranging search strategies and robust screening. We did not include other databases due to time constraints. Since we only included studies published in English, there is a possibility of excluding papers due to language bias. In addition, some studies included suspected COVID-19 cases without performing RT-PCR tests, and this may likely influence some of the COVID-19 outcomes which were assessed.

Also, there is a risk of double counting using two OpenSAFELY cohort studies. Although they used different statistical approaches, high dose ICS users in Schultze et al. (2020) can be double-counted in Williamson et al. (2020), considering the same cohort and overlapping data collection time. To address the risk of double counting, we used HRs adjusted for oral steroids for Schultze et al. (2020) only.

Lastly, although our findings showed positive associations between severe asthma and an increased risk of COVID-19 mortality, there were high heterogeneities in the comparator

groups, participants characteristics, sample size and statistical approach. Given that four studies included less than 100 severe asthma cases and covariates adjusted in regression models (Choi et al., 2021, Fong et al., 2021, Garcia-Pachon et al., 2021, Robinson et al., 2021), it might affect the generalisability of our findings or results from meta-analysis) to different populations.

Implications for future studies/public health practices

The current meta-analysis relied upon available data, meeting our inclusion criteria. However, there is an urgent need for further high-quality data/studies, particularly for children with severe asthma who contract SARS-COV-2. In addition, although we observed some different impacts of asthma medication regimens on mortality from COVID-19, further research to investigate associations between specific asthma medications and COVID-19 outcomes are also needed.

Given high heterogeneities across studies, our findings should be taken cautiously in application to other settings or other populations. Ideally, individual patient data meta-analysis could be considered to mitigate heterogeneity in study design and statistical approach.

Conclusion

This is the first review examining population-based cohorts and the associations between severe asthma defined by medication use and severe COVID-19-related outcomes. The findings from this review suggest that adults with severe asthma have a higher risk of death and hospitalisation from COVID-19 than those with mild asthma or no asthma. However, adults with severe asthma taking OCS were associated with a higher risk of COVID-19-related death, but not in adults using high-dose ICS. There is an urgent need for robust research for the paediatric population with severe asthma and associated COVID-19 outcomes.

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Appendices

Table S1. Search strategy

Database	**Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to 16 July, 2021>**
Data of search	20210719
Search history	1 Coronavirus/ or Betacoronavirus/ or Coronavirus Infections/ or COVID-19/ or SARS-CoV-2/ (99842) 2 coronavirus*.ti,ab,kw,kf. (71669) 3 ("COVID-19*" or COVID19* or "COVID-2019*" or covid).ti,ab,kw,kf. (139891) 4 1 or 2 or 3 (168754) 5 exp Asthma/ (132635) 6 asthma*.ti,ab,kw. (166747) 7 5 or 6 (186452) 8 4 and 7 (1056) 9 (201912* or 2020* or 2021*).ed. (1863193) 10 8 and 9 (624) 11 Meta-Analysis as Topic/ (20060) 12 meta analy$.tw. (205579) 13 metaanaly$.tw. (2293) 14 Meta-Analysis/ (137650) 15 (systematic adj (review$1 or overview$1)).tw. (210729) 16 exp Review Literature as Topic/ (17201) 17 or/11-16 (353888) 18 cochrane.ab. (100332) 19 embase.ab. (112217) 20 (psychlit or psyclit).ab. (915) 21 (psychinfo or psycinfo).ab. (43064) 22 (cinahl or cinhal).ab. (33973) 23 science citation index.ab. (3319) 24 bids.ab. (571) 25 cancerlit.ab. (635) 26 or/18-25 (181397) 27 reference list$.ab. (19536) 28 bibliograph$.ab. (19689) 29 hand-search$.ab. (7510) 30 relevant journals.ab. (1245) 31 manual search$.ab. (4958) 32 or/27-31 (47481) 33 selection criteria.ab. (32317) 34 data extraction.ab. (24842) 35 33 or 34 (54726) 36 Review/ (2830831) 37 35 and 36 (30308) 38 Comment/ (918455) 39 Letter/ (1143778) 40 Editorial/ (573745) 41 animal/ (6876398) 42 human/ (19503831) 43 41 not (41 and 42) (4828537) 44 or/38-40,43 (6735758) 45 17 or 26 or 32 or 37 (423705) 46 45 not 44 (402661) 47 10 and 46 (21) 48 10 not 47 (603)
Number of results	624
Systematic reviews	21
Others	603
Database	**WHO Covid literature database**
Data of search	Date of search 20210719
Search history	(tw:(asthma)) Sub set to identify SRs: (tw:("systematic review" or "meta analy*" or metaanaly* or meta-analys* or "rapid review" or "evidence summary" or "evidence synthesis"))
Number of results	1836

Systematic reviews	47
Others	1789
Database	**Medrxivr (https://mcguinlu.shinyapps.io/medrxivr/)**
Data of search	Date of search 20210719
Search history	2019nCoV Betacoronavirus Corona Virus Coronavirus Coronovirus \\bCoV\\b \\bCoV2\\b COVID HCoV-19 \\bnCoV\\b SARS CoV 2 SARS2 SARSCoV SARS-CoV (Aa)sthma Sub set to identify SRs: (Ss)ystematic review (Mm)eta analy (Mm)etaanaly (Mm)eta-analys (Rr)apid review (Ee)vidence summary (Ee)vidence synthesis
Number of results	90
Systematic reviews	4
Others	86

Table S2. Demographic characteristics of included studies (n=9)

	Total population	Total COVID-19 confirmed cases	Control group (N, %)	Control group with severe COVID-19 outcome cases[a]	Age, Median (IQR)	SA (N, %)	SA with severe COVID-19 outcome cases	SA, Age
Aveyard et al. 2021	8,256,161	8,256,161	No respiratory disease 4,693,447	5274 (0.11%) Hospitalisation: 3127 ICU: 672 Death: 1475	Overall population Mean (SD) 48.2 (18.6)	385,702	1,969 (0.02%) Hospitalisation: 1369 ICU: 124 Death: 476	+20 yrs
Bloom et al. 2021	8,950	8,950	No asthma 7,083	382 (5.39%) Death: 382	Mean (SD) 16-49 yrs 38.9 (8.6)	201	24 (11.9%) Death: 24	NA
Choi et al. 2020	NA	7,590	Step 1 (mild asthma) 51	8 (15.69%) ICU: 3 Death: 5	40-49 yrs (n= 1), 70+ yrs (n= 3)	4	0 ICU: 0 Death: 0	Range 40-49 yrs Range 70+ yrs
Eger et al. 2020	Dutch population 13,363,687	Dutch population 37,418 (0.28%)	Dutch population 13,363,687	17,373 (0.13%) Hospitalisation: 10,691 ICU for intubation: 2,673 Death 4,009	Range 20-90 yrs	634	9 (1.42%) Hospitalisation: 7 ICU for intubation: 5 Death: 1	Range 18-89 yrs
Fong et al. 2021	6638	617 (9.3%)	Non-SA[b] 63	32 (50.79%) Death: 32	Overall population: 65 (42, 79) Asthma patients: 64 (47, 78)	39	1 (0.02%) Death 1	NA
Garcia-Pachon et al. 2021	NA	2,995	Non-SA 72	15 (20.83%) Hospitalisation: 15	Asthma patients 49 (34, 61)	5	2 (40%) Hospitalisation: 2	NA
Robinson et al. 2021	NA	3,248	No asthma 210	66 (31.43%) Hospitalisation: 45 Ventilation: 12 Death: 9	No asthma (n = 2686)c Mean (SD) 51(17)	44	19 (43.2%) Hospitalisation: 14 Ventilation: 5 Death: 0	NA
Shultz et al. 2020	NA	33,356,521	SABA only: 108,411 Low/medium ICS: 608,972	424 (0.06%) SABA only Death: 49 (0.05%) Low/medium ICS Death: 375 (0.06%)	SABA only: 48 yrs (35, 60) Low/medium dose ICS: 53 yrs (40, 66)	101,077	105 (0.10%) Death: 105	Median (IQR) 55 yrs (44,67)
Williamson et al. 2020	NA	17,278,392	With no recent OCS use 2,454,403	1,211 (0.05%) Death: 1,211	Range 18 - 80+ yrs	291,670 (1.7%)	335 (0.11%)/291,670	NA

NA, Not applicable; SD, Standard deviation; IQR, Interquartile range; SA, Severe asthma; [a]matched with cases in severe asthma group; [b]calculated from COVID0-19 tested SA and total number of patients with asthma ;[c]Age, sex, and date of SARS-CoV-2 diagnosis matched comparators