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Risks of infection, hospital and ICU admission, and death from COVID-19 in people with asthma: systematic review and meta-analyses

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Abstract

Objectives To determine if and to what degree asthma may predispose to worse COVID-19 outcomes in order to inform treatment and prevention decisions, including shielding and vaccine prioritisation.

Design Systematic review and meta-analysis.

Setting Electronic databases were searched (October 2020) for clinical studies reporting at least one of the following stratified by asthma status: risk of infection with SARS-CoV-2; hospitalisation, intensive care unit (ICU) admission or mortality with COVID-19.

Participants Adults and children who tested positive for or were suspected to have COVID-19.

Main outcome measures Main outcome measures were the following stratified by asthma status: risk of infection with SARS-CoV-2; hospitalisation, ICU admission or mortality with COVID-19. We pooled odds ratios (ORs) and presented these with 95% confidence intervals (CI). Certainty was assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations).

Results 30 (n=112 420) studies were included (12 judged high quality, 15 medium, 3 low). Few provided indication of asthma severity. Point estimates indicated reduced risks in people with asthma for all outcomes, but in all cases the evidence was judged to be of very low certainty and 95% CIs all included no difference and the possibility of increased risk (death: OR 0.90, 95% CI 0.72 to 1.13, I^2=58%; hospitalisation: OR 0.95, 95% CI 0.71 to 1.26; ICU admission: OR 0.96, 95% CI 0.75 to 1.24). Findings on hospitalisation are also limited by substantial unexplained statistical heterogeneity. Within people with asthma, allergic asthma was associated with less COVID-19 risk and concurrent chronic obstructive pulmonary disease was associated with increased risk. In some studies, corticosteroids were associated with increased risk, but this may reflect increased risk in people with more severe asthma.

Conclusions Though absence of evidence of a clear association between asthma and worse outcomes from COVID-19 should not be interpreted as evidence of absence, the data reviewed indicate that risks from COVID-19 in people with asthma, as a whole, may be less than originally anticipated.

SUMMARY BOX

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ At the beginning of the pandemic, it was assumed that people with asthma (PWA) would be at increased risk of poor outcomes with COVID-19.
⇒ This was contradicted by early primary studies, which reported that PWA represented a lower proportion of those with COVID-19 admitted to hospital than seen in the general population.
⇒ Systematic reviews and meta-analyses on this topic have generated conflicting conclusions, with some finding an association between asthma and poor COVID-19 outcomes while others do not. Analysis of the quality of these reviews reveals significant pitfalls, ranging from incomplete risk of bias reporting to inadequate justification for exclusion of individual studies.

WHAT ARE THE NEW FINDINGS?

⇒ This systematic review is one of the largest to date on the effects of asthma on the risk of poor COVID-19 outcomes, covering a large number of studies across multiple continents.
⇒ Pooled results showed that, overall, asthma was not associated with severe COVID-19 outcomes, but evidence was judged to be of very low certainty.

Introduction

The SARS-CoV-2 pandemic has affected over 158 million people worldwide, with at least 3.28 million deaths due to COVID-19 as of 9 May 2021.[1] At the start of the pandemic, people with asthma (PWA) were assumed to be at increased risk from COVID-19, as respiratory viral infections are well

SUMMARY BOX

HOW MIGHT IT IMPACT CLINICAL PRACTICE IN THE FORESEEABLE FUTURE?

⇒ Evidence suggests that PWA are not at increased risk of acquiring SARS-CoV-2 compared with those without asthma, and have similar, if not slightly improved, clinical outcomes with COVID-19.
⇒ However, absence of evidence should not be interpreted as evidence of absence, and further high-quality primary studies are required to reinforce this conclusion.

known to cause severe adverse outcomes in patients with established asthma through stimulation of exacerbation episodes.[2]

Early, large-scale case series provided evidence to the contrary, reporting that PWA made up a lower proportion of patients with COVID-19 admitted to hospital than seen in the general population.[3–5] These findings birthed a myriad of hypothesised immunopathological mechanisms to explain this apparent reduction in susceptibility to severe COVID-19.[6 7] More recent epidemiological studies have further complicated our understanding of the association between COVID-19 and asthma, with some suggesting an association while others do not.[8–15] It is important for PWA, their carers, healthcare providers and policymakers to understand if and to what degree asthma may predispose to worse COVID-19 outcomes. Such information impacts both treatment and prevention decisions, including shielding and vaccine prioritisation.

The ambiguity of primary evidence combined with the clear importance of determining the relationship between COVID-19 and asthma has resulted in a number of systematic reviews on the subject.[16–18] Analysis of the quality of these reviews reveals significant pitfalls, ranging from incomplete risk of bias reporting to inadequate justification for exclusion of individual studies. This is reflected in the scientific brief on asthma and COVID-19 released by the WHO, in which only one of six systematic reviews on the subject were judged to be free of 'critical weakness' using the AMSTAR-2 (A MeaSurement Tool to Assess systematic Reviews-2) ratings for critical domains.[19] The single high-quality review identified through the WHO scientific brief focused on mortality and concluded that there was insufficient evidence to draw firm conclusions.[18] The review contained published literature up to 8 June 2020, and further studies have since emerged. In addition, no systematic reviews of sufficient quality have examined whether PWA are more likely to be infected with COVID-19 or be hospitalised or admitted to intensive care with COVID-19 than people without asthma.

We therefore conducted a comprehensive systematic review and meta-analysis of published literature to determine whether asthma is a risk factor for worse outcomes in both adults and children with COVID-19, focusing on the specific endpoints of infection, hospitalisation, intensive care unit (ICU) admission and mortality. We also investigated whether, within PWA, asthma medication, severity, comorbidity, age and ethnicity affected COVID-19 outcomes.

Methods

Search strategy

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and incorporates the PRISMA-Equity extension designed for systematic reviews with a focus on health equity.[20] We were commissioned by the WHO to conduct a rapid review on this topic, the protocol for which was specified and made publicly available before review conduct.[21] This review follows on from that work; our WHO review did not include statistical synthesis, and therefore following the WHO rapid review, we posted a new protocol outlining our synthesis plans, results from which are presented here (https://osf.io/c9e6d/).

We searched Medline, Embase, LitCOVID and the Cochrane study register on 8 October 2020 for COVID-19 clinical studies, published or accepted for publication but not yet published, in any language. We included any type of clinical study (randomised controlled trials, cohort studies, cross-sectional studies, case reports and series, and case–control studies) that reported the number of adults or children with asthma (as determined by the investigators) and COVID-19 (either confirmed with RT-PCR test or suspected), and specified at least one of the following outcomes stratified by asthma status: risk of infection; hospitalisation status; ICU admission status; mortality. Studies were excluded if they did not report any of our prespecified outcomes in PWA and COVID-19. The full search strategy is outlined in online supplemental appendix 1 (pp 2–4). Two reviewers independently screened titles and abstracts, and full texts of selected references, with discrepancies resolved by discussion or referral to a third reviewer. Where grey literature was identified, we contacted the authors where it was unclear if grey literature had been accepted for publication; if it had been (ie, had been subject to peer review) then we included it in our review. Non-peer-reviewed publications were excluded, as specified in advance.

Two reviewers independently assessed methodological quality using the Newcastle-Ottawa Scale (NOS) for cohort and cross-sectional studies. The NOS consists of three domains across which 9 points are available (9 for cohort studies, 6 for cross-sectional studies): selection of study groups (4 points), comparability of groups (2 points) and ascertainment of exposure and outcomes (3 points).[22] We considered a score of 1–3 stars as low quality, 4–6 as medium quality and 7–9 as high quality. We also rated the certainty of the evidence according to the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) approach,[23] which we present in a summary of findings (table 1). Two reviewers independently extracted data on patient characteristics and clinical outcomes using a bespoke extraction form which was piloted before use to facilitate efficient extraction of data. Any discrepancies were resolved by discussion. When a study presented patients with asthma as a percentage of total population, we estimated the number based on the given percentage.

Data analysis

We performed meta-analyses using the Cochrane Review Manager V.5.4 platform to determine the risk of infection with SARS-CoV-2,[24] hospitalisation with COVID-19, ICU admission with COVID-19 and risk of mortality from COVID-19 in PWA versus those without asthma, presenting results as ORs with 95% CIs. We used prevalence of asthma in patients with COVID-19 as a proxy for risk of infection, although we appreciate this is significantly limited by lack of widespread random testing. In each meta-analysis, we fitted a random effects model using the inverse-variance method, using ORs as reported within the study or calculated based on data provided in accordance with the Cochrane Handbook.[25] When producing the prevalence meta-analysis, we used prevalence ratios and calculated the 95% CIs in accordance with the Cochrane Handbook. When studies reported both adjusted and unadjusted estimates, we used the adjusted estimates and

Table 1 Summary of findings: risks of infection, hospital and ICU admission, and death from COVID-19 in people with asthma compared with people without asthma

Outcome	Number of participants (studies)	Relative effect (95% CI)	Certainty
Prevalence: as a proxy for risk of infection	83 294 (21 observational studies)	PP: 9.38% (7.38 to 11.38)	⊕◯◯◯ Very low*
Mortality	62 521 (15 observational studies)	OR: 0.9 (0.72 to 1.13)	⊕◯◯◯ Very low†
Hospitalisation	25 065 (9 observational studies)	OR: 0.95 (0.71 to 1.26)	⊕◯◯◯ Very low‡
ICU admission	13 092 (9 observational studies)	OR: 0.96 (0.75 to 1.24)	⊕◯◯◯ Very low§

*Downgraded two levels due to unexplained statistical heterogeneity, one level due to possible publication bias (skewed funnel plot).
†Downgraded one level due to unexplained statistical heterogeneity, downgraded one level due to imprecision (wide CIs).
‡Downgraded two levels due to unexplained statistical heterogeneity, downgraded one level due to imprecision (wide CIs).
§Downgraded one level due to imprecision (wide CIs).
ICU, intensive care unit; PP, pooled prevalence.

performed subgroup analysis to compare adjusted and unadjusted values. We assessed heterogeneity using the Cochrane I^2 value, and used their suggested thresholds for moderate, substantial and considerable heterogeneity.[26] We undertook sensitivity analysis removing studies at high risk of bias. The following prespecified subgroup analyses were performed: outcomes by mean/median age (up to 60 years and 60 years and above), by mean/median body mass index (BMI) (less than and greater than 30), by ethnicity (less than and greater than 50% white), by asthma severity (as defined by each study), by asthma medication and by adjustment status (studies where the effect size was adjusted for factors including age, sex, BMI and comorbidities compared with studies which did not adjust at all). We visually inspected the funnel plots for all comparisons with over 10 studies for possible publication bias. In meta-analyses with less than 10 studies, we performed Egger analysis.

We narratively report results from studies that could not be included in meta-analysis. We were also interested to know whether asthma medication, severity, comorbidity, age and ethnicity affected COVID-19 outcomes in PWA. We narratively report results from studies assessing the extent to which different characteristics within PWA predispose to our outcomes of interest, using effect direction plots.[27]

Results

A total of 824 articles were identified from the search of databases. The selection process is presented in a PRISMA flow diagram (figure 1). After initial screening based on titles and abstracts, 97 articles remained for full text evaluation. Full text analysis produced a total of 30 studies which met the inclusion criteria, 25 of which had sufficient data to be included in meta-analysis.

Of the 30 studies included[9–12 17 18 28–51] totalling 112 420 people who tested positive for or were suspected to have COVID-19, there were 24 cohort studies (22 conducted retrospectively and 2 conducted prospectively) and 6 cross-sectional analyses. All were published after peer review and no preprints were included in the analyses. Sample sizes ranged from 106 to 818 490 people, with median sample size n=1043 and IQR=7145 (445–7590). Studies were from North and South America (12), Europe (14) and Asia (4). The majority of studies used adult (18+) cohorts (19), six studies used mixed paediatric and adult cohorts and one study used a paediatric cohort. The remaining studies did not report sufficiently detailed age data to determine whether children were included. Only one study included people with suspected but unconfirmed SARS-CoV-2; this study reported only on prevalence and was not included in meta-analyses.[47] We assessed studies for possible overlap to ensure participants were not being double counted in our analyses; studies were conducted in different cohorts (eg, different hospitals) with no overlap identified.

Using the NOS, 12 studies were rated as high quality, 15 studies as medium quality and 3 studies as low quality (overall NOS scores for each study can be seen in online supplemental table 1, scores for individual domains can be seen in online supplemental appendix 1, online supplemental table 2). A summary of included studies is presented in online supplemental table 1.

Outcomes

Prevalence

Twenty-one studies reported prevalence of asthma in those suffering from COVID-19. The estimated prevalence of asthma in patients with COVID-19 ranged from 0.32% to 25.8% (median 9.14% and IQR 11.15 (3.05–14.2)). We included all of these studies in meta-analysis. Data were highly heterogeneous. The pooled prevalence of the 21 studies was 9.38% (95% CI 7.38% to 11.38%, I^2=99%, n=83 294). Among these studies, there was some asymmetry to the funnel plot, raising the possibility of publication bias (online supplemental figure 1). Overall, this evidence was judged to be of very low certainty due to unexplained statistical heterogeneity and possible publication bias.

In order to provide a more contextualised view, we compared asthma prevalence in each study population to prevalence in the general population of the country in which the study was based (figure 2).

We looked to clinical study setting (whether hospital based or community based) as a potential driving force behind the observed heterogeneity. However, high heterogeneity was maintained in subgroup analysis stratifying studies based on whether their cohorts were hospital based, community based or mixed (I^2=99% in both hospital and mixed subgroups; test for subgroup differences I^2=55%, online supplemental figure 2).

Further subgroup analysis provided evidence that BMI (test for subgroup differences I^2=60.4%, online supplemental figure 3) and ethnicity (test for subgroup differences I^2=94.9%, online supplemental figure 4) may have contributed to some of the variation. This was a contrast to subgroup analysis by age (online supplemental figure 5), where no subgroup differences were apparent (I^2=0%).

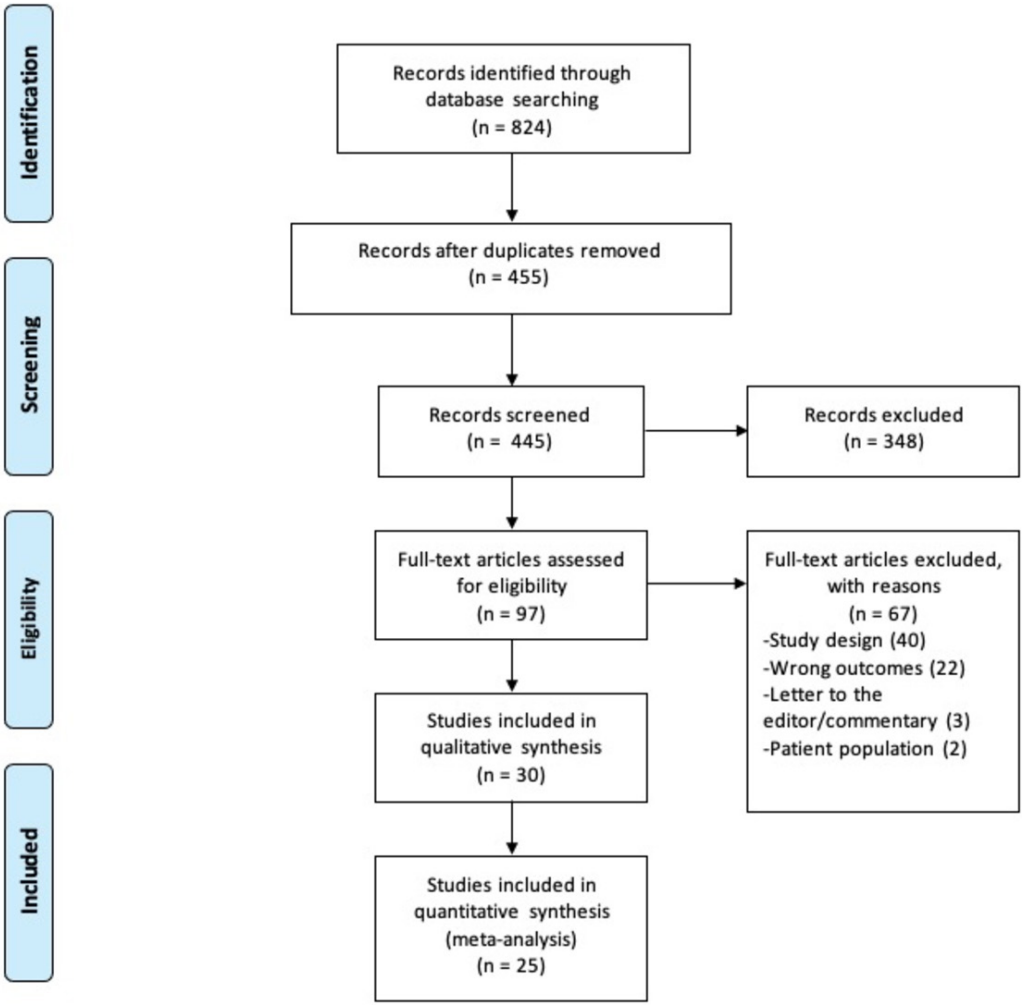

Figure 1 PRISMA diagram of study flow

We performed sensitivity analyses to assess risk of bias by removing high risk of bias studies (0–3 on the NOS). Niquini *et al* were the only high risk of bias study reporting prevalence outcomes, with removal leading to a slight increase in pooled prevalence from 9.38 (95 % CI 7.38 to 11.38, I^2=99%, n=83 294) to 9.81 (95% CI 7.92 to 11.71, I^2=99%, n=51 332), and no impact on heterogeneity.[45]

Mortality

Mortality data were reported by 15 studies. A meta-analysis of data from 13 of these studies was conducted to evaluate the association between asthma and risk of mortality in patients with COVID-19 (figure 3). The pooled effect estimate demonstrated that asthma was associated with slightly reduced odds of mortality (OR 0.90, 95% CI 0.72 to 1.13, I^2=58%, n=62 521), although CIs were wide and incorporated no difference as well as increased risk. The funnel plot analysis of these studies did not suggest publication bias (online supplemental figure 6). There was no high risk of bias studies within this outcome, therefore we did not perform a sensitivity analysis. We judged this finding to be of very low certainty due to unexplained statistical heterogeneity and imprecision (wide CIs).

Subgroup analyses by age (online supplemental figure 7) and comparing adjusted versus unadjusted estimates (online supplemental figure 8) did not explain the moderate heterogeneity observed. However, there was some evidence that both BMI (test for subgroup differences I^2=85%) and ethnicity (test for subgroup differences I^2=77%) may explain some of the variation. In the three studies where the majority of the cohort had a BMI of 30 or over, asthma was associated with an increased odds of mortality, with CIs excluding no difference (OR 1.24, 95% CI 1 to 1.53, n=2951) (figure 3), but the majority of studies did not provide BMI data. In the five studies where the majority of the cohort was of non-white ethnicity, asthma was associated with a reduced odds of mortality, with CIs excluding no difference (OR 0.75, 95% CI 0.60 to 0.93, n=41 894) (online supplemental figure 9). Again, the majority of studies did not report data on ethnicity.

The two studies not included in the meta-analysis (Abrams *et al* and Beurnier *et al*) were excluded due to the fact that neither reported mortality rates in people without asthma, and thus no OR could be extracted or calculated.[28 32] However, through utilisation of mortality rates reported in hospitalised patients without asthma in other large-scale studies over a similar time period, the data can still be interpreted narratively. Abrams *et al* reported a mortality rate (percentage of PWA who died from COVID-19) of 4.5% in New York City (NYC) hospitals, which is lower than the 32.1% mortality rate (percentage of people who died from COVID-19) in NYC hospitals reported by Thompson *et al*.[52] Beurnier *et al* reported an in-hospital mortality rate (percentage of PWA who died from COVID-19) of 8.1% in Paris, France, which was lower than that in hospital mortality rate (percentage of people who

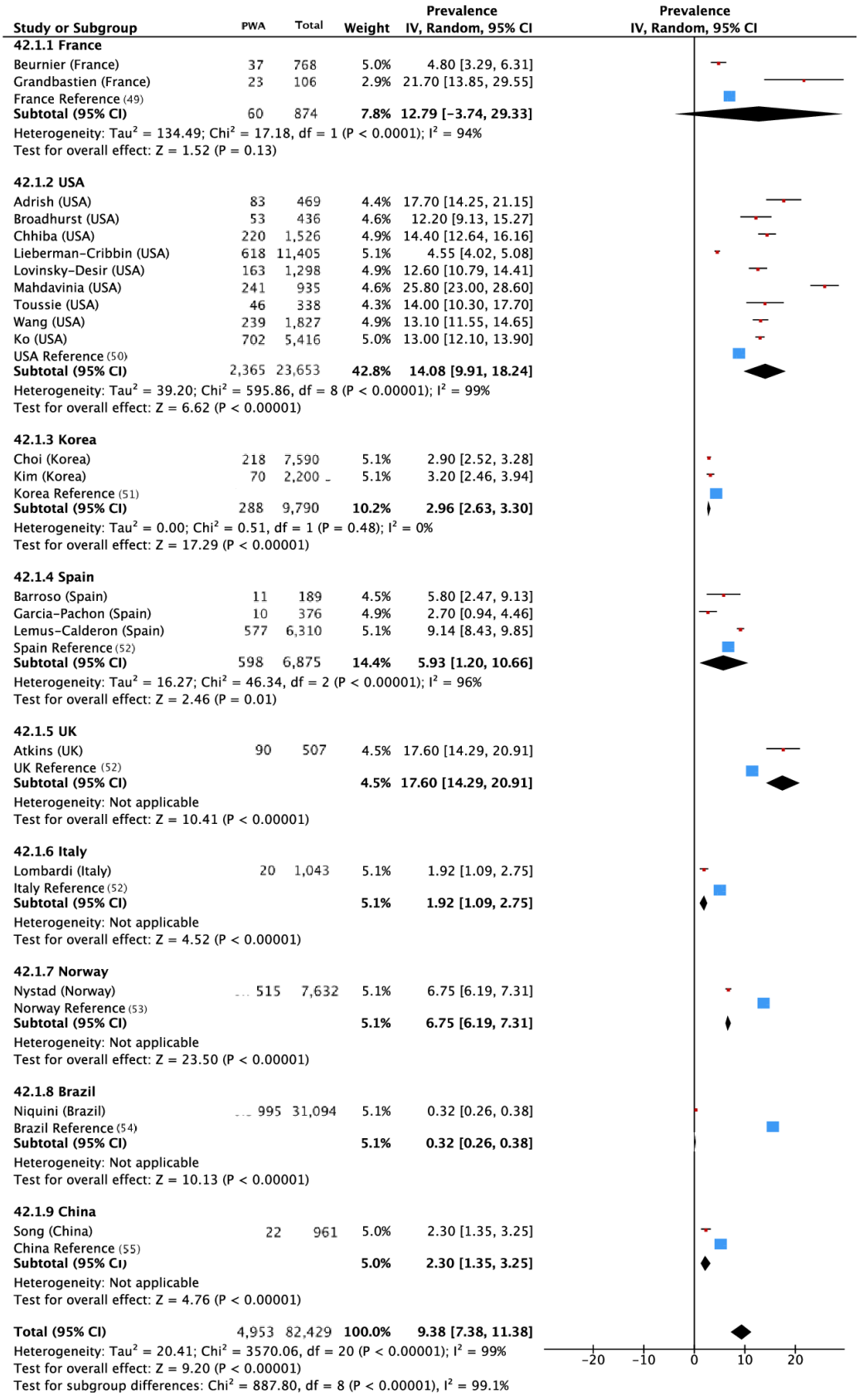

Figure 2 Prevalence of asthma in COVID-19 patients. Blue squares indicate population prevalence of asthma for comparison.[68–75]

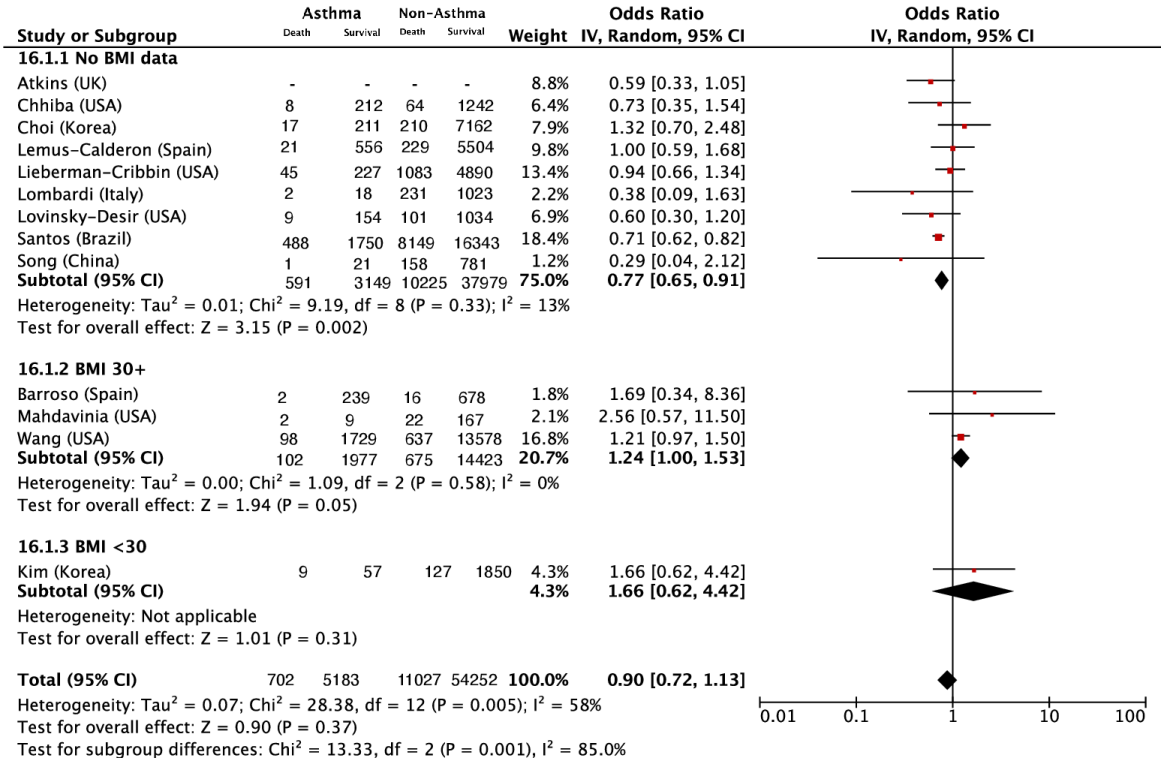

Figure 3 COVID-19 mortality in people with asthma compared to people without asthma, subgrouped by mean/median BMI. BMI, body mass index.

died from COVID-19) of 16.9% recorded by Gaudart *et al* across a similar time period.[53]

Hospitalisation

Nine studies reported hospitalisation in PWA with COVID-19. Meta-analysis revealed that asthma was associated with a slight reduction in odds of hospitalisation with COVID-19 (OR 0.95, 95% CI 0.71 to 1.26, n=25 065, I^2=94%) (figure 4), although CIs incorporated no difference as well as increased risk. Statistical heterogeneity was high, with some studies showing statistically significantly reduced risk and others showing statistically significant increases in risk. Egger analysis of these studies did not suggest publication bias (test for funnel plot asymmetry, p=0.384). There was no high risk of bias studies within this outcome, therefore we did not perform a sensitivity analysis. We judged this finding to be of very low certainty due to unexplained statistical heterogeneity and imprecision (wide CIs).

There was no evidence that ethnicity, BMI or whether studies presented adjusted or unadjusted estimates explained the heterogeneity observed (I^2=0% for all tests for subgroup differences, online supplemental figures 10–12). There was also little evidence that sample age affected heterogeneity (I^2=10.8%, figure 4).

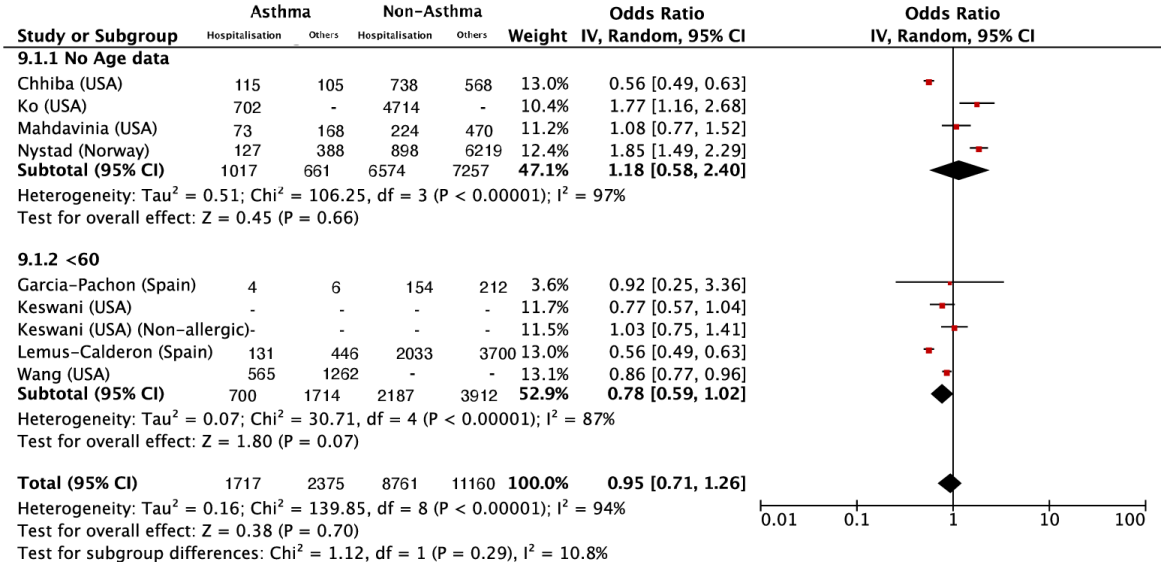

Figure 4 COVID-19 hospitalisation in PWA compared to people without asthma, subgrouped by age (mean/median age was less than 60 compared to studies which did not report age data; no studies had mean/median age >60).

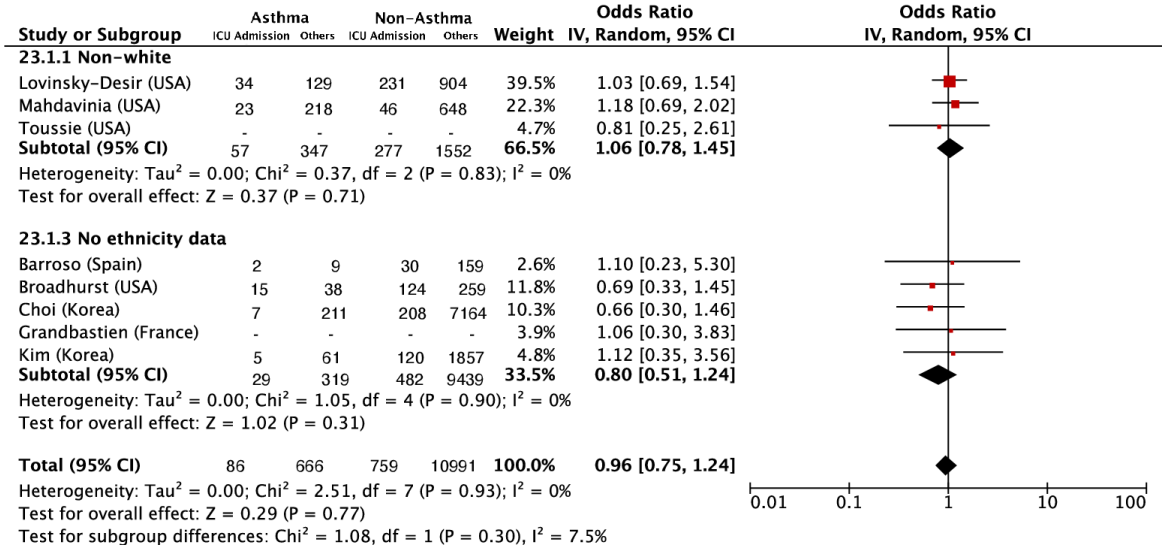

Figure 5 COVID-19 ICU admission rates in PWA compared to people without asthma, subgrouped by ethnicity (majority of the cohort (over 50%) was of white ethnicity compared to where the minority of the cohort (50% or less) was of white ethnicity). ICU, intensive care unit.

ICU admission

Data on ICU admissions were reported by nine studies. Meta-analysis of eight of these studies demonstrated that asthma was associated with a slight reduction in odds of ICU admission with COVID-19 (OR 0.96, 95% CI 0.75 to 1.24, n=13 092, I^2=0%) (figure 5), but CIs included no difference and increased risk. There was no evidence of statistical heterogeneity. Egger analysis of these studies did not suggest publication bias (test for funnel plot asymmetry, p=0.6142). There was no high risk of bias studies within this outcome, therefore we did not perform a sensitivity analysis. We also judged this finding to be of very low certainty due to unexplained statistical heterogeneity and imprecision (wide CIs).

There was no evidence of subgroup differences based on age, BMI or whether studies presented adjusted or unadjusted estimates (I^2=0% for subgroup differences in all cases, online supplemental figures 13–15). There was little evidence of subgroup difference by ethnicity (I^2=7.5%, figure 5).

The study not included in the meta-analysis (Chhiba *et al*) did not report ICU admission in people without asthma, and thus no OR could be extracted. However, through utilisation of national ICU admission data, the data can still be interpreted narratively. Chhiba *et al* reported that 8.6% of PWA hospitalised with COVID-19 were admitted to ICU in the USA. This is lower than the national average rate of ICU admission in people hospitalised with COVID-19; 32%.[54]

Do COVID-19 outcomes in PWA differ based on population characteristics?

Very few studies were sufficiently powered to detect a difference by subgroups within PWA. Data regarding our prespecified characteristics reported in more than one study can be found in table 2.

Data on inhaled corticosteroid (ICS) use were not consistent across studies, but the largest study of its type found high-dose ICS was associated with higher risk of COVID-19 mortality when compared with short-acting beta agonist (SABA).[49] A second study using the same data set found OCS (oral corticosteroid) use was also associated with greater risk in PWA[8]; no other studies evaluated OCS use. With the exception of the one study comparing ICS to SABA,[49] no significant associations were found between SABA and long-acting beta agonist and disease outcomes. Three studies reported on allergic asthma, reporting reduced prevalence[9 12] and hospitalisation[37] compared with non-allergic counterparts. Two studies investigated the importance of comorbid chronic obstructive pulmonary disease (COPD), finding it was associated with increased hospitalisation, ICU admission, mortality[18] and prevalence.[37] Only one study reported on ethnicity,[18] with univariate analyses using white ethnicity as a reference group finding that all other ethnic groups had higher risks of hospitalisation. The association was statistically significant for Black and Asian groups and remained so in an age-stratified multivariate logistic regression. Only one study looked at BMI.[38] Kim *et al* found that the association between asthma and mortality increased in those with BMI ≤25; it was unclear if this association was statistically significant.

Regarding the influence of asthma medication on COVID-19 outcomes in PWA, where associations were detected, it was unclear if these were due to mechanisms of the medications themselves, or due to the association between prescriptions for these medications and asthma severity.[49] People with allergic asthma seem to be at lower risk of severe outcomes from COVID-19 than those with non-allergic asthma,[37] but again more data are needed to confirm this. People with COPD and asthma appear at higher risk from severe COVID-19 outcomes than PWA who do not have COPD.[18] In PWA, risk from COVID-19 appears to increase with age,[18 38 43] as in the general population.

Discussion

Our systematic review contains 30 studies and to the best of our knowledge is one of the largest to date on the effects of asthma on the risk of poor COVID-19 outcomes, covering a large number of studies across multiple continents. Whether PWA are at increased risk of infection or severe outcomes from COVID-19 remains unclear, with point estimates reporting a slightly reduced risk for hospitalisation, ICU admission and death with COVID-19 in PWA compared with people without asthma, but 95% CIs encompassing no difference as well as moderately increased and moderately decreased risks. Our results revealed a 9.38% prevalence of asthma in those who tested positive for COVID-19, similar to the prevalence of

Table 2 Data from primary studies on whether COVID-19 outcomes in PWA differ based on subgroup characteristics

Study ID	Age	Medication	Asthma severity/type/comorbidities
Bozek and Winterstein[33]		Hospitalisation: ↓ Montelukast	
Chhiba *et al*[10]		ICU admission: ↑ ICS	
Choi *et al*[34]		ICU admission: ↑ ICS ↓ LABA ↓ SABA ↔ LAMA Mortality: ↑ ICS ↔ LABA ↑ SABA ↓ LAMA	Mortality: Asthma severity ↔
Kim *et al*[38]	Mortality Association between asthma and mortality ↑ with increasing age		
Keswani *et al*[37]			ICU admission: ↓ Allergic asthma (compared with non-allergic asthma)
Mahdavinia *et al*[43]	OR for association between asthma and hospitalisation ↑ with increasing age OR for association between asthma and ICU admission less clear by age (association ↑ in those aged 50–64 compared with those aged 18–49 or 65+)		
Schultze *et al*[49]		Mortality compared with SABA: ↑ Low/medium-dose ICS ↑↑ High-dose ICS	
Wang *et al*[18]	Increasing age: ↑↑ Hospitalisation ↔ ICU admission ↑↑ Mortality	Hospitalisation: ↓ ICS ↑ ICS-LABA ICU admission: ↓ ICS ↓ ICS-LABA Mortality: ↓ ICS ↓ ICS-LABA	Hospitalisation: ↑↑ COPD ICU admission: ↑ COPD Mortality: ↑ COPD
Williamson *et al*[8]		Mortality: ↑ OCS (oral corticosteroid) use	
Yang *et al*[9]			↓↓ Allergic asthma (compared with non-allergic asthma) Severe clinical outcomes (composite scores) ↓↓ Allergic asthma (compared with non-allergic asthma)
Zhu *et al*[12]			↓ Allergic asthma (compared with non-allergic asthma) ↑ COPD

Arrows indicate direction of association; double arrows indicate statistical significance.

COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; ICU, intensive care unit; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonists; PWA, people with asthma; SABA, short-acting beta agonist.

self-reported asthma symptoms globally of 8.6%. Findings were judged to be very low certainty across all outcomes using GRADE criteria, with key limitations being imprecision (with CIs incorporating both benefit and harm in all instances), possible publication bias (in one instance) and unexplained statistical heterogeneity (table 1.) The effect of ethnicity or BMI on the relationship between asthma and COVID-19 outcomes was not well reported, with only one study reporting on each variable, both of which were low powered. Further investigation into the influence these factors have on COVID-19 outcomes is required, especially when the association between BMI,[55 56] ethnicity[57] and poor COVID-19 outcomes in other chronic diseases such as diabetes is considered.

The use of ICS in COVID-19 has been subject to intense scrutiny, due to their potential to both reduce antiviral immunity juxtaposed with evidence suggesting they may reduce replication of SARS-CoV-2.[58 59] Though some high-quality studies in our review find that corticosteroids are associated with worse outcomes, these are likely confounded, with Schultz stating that the harmful association could be explained by health differences not recorded in the OpenSAFELY database from which information was obtained, most notably, asthma severity.[49] They reported an incomplete assessment of exacerbation history, a confounding variable which post hoc analysis demonstrated had one of the greatest impacts on effect size. This, combined with the fact that ICS use will be higher in people with more severe disease, suggests that ICS use does not influence the likelihood of severe COVID-19.

The PRINCIPLE (Platform Randomised trial of INterventions against COVID-19 In older people) trial has recently shown that inhaled budesonide, a common corticosteroid used in asthma management, shortens recovery times in patients with COVID-19 over the age of 50·[60] Current guidelines suggest ICS use in PWA should be continued until more evidence is available.[61]

There were limitations to this systematic review. Some analyses were limited by significant heterogeneity, even when subgrouped by geographical region, age, BMI and study quality. This may be a reflection of the fact that subgroup analyses are a relatively crude tool with which to investigate the cause of heterogeneity, as they rely on study-level aggregates as opposed to individual characteristics, and are thus prone to confounding factors. It would be more informative to look at individual data in a large, well-reported study, the likes of which are not yet available in the literature. The diagnosis of asthma in primary studies was based largely on self-report or physician diagnosis, not using more objective measures such as spirometry or peak flow. This, combined with the tendency for asthma to flip between underdiagnosis and overdiagnosis depending on where you are in the world,[62] has the potential to confound results. Furthermore, factors which influence COVID-19 outcomes, such as obesity, may contribute to asthma misdiagnosis and thus further confound the issue, particularly in those studies not reporting on BMI.[63] However, the same possible causes of confounding exist in other areas, and yet the lack of consistency observed for the relationship between asthma and COVID-19 is in contrast to other long-term conditions, notably diabetes where available research suggests clear associations of poorer outcomes.[64] When we compared unadjusted and adjusted estimates, there was no evidence of difference between the two. If data and reporting in this area improve, future reviews may wish to specify minimal sets of adjustment factors for inclusion.

Incomplete data and reporting bias are also potential issues. We cannot rule out publication bias and the small number of studies contributing to each analysis means methods for testing for publication bias are underpowered in our sample. As prespecified with WHO, we did not include preprints, which may mean some relevant evidence has been overlooked. Most of the studies reported in our review derive their data from hospitals, where multiple biases are possible; for example, studies which find higher rates of COVID-19 hospitalisation in PWA could be because PWA are more likely to contract COVID-19, or because *if having contracted COVID-19* PWA are more likely to require hospitalisation or to be referred to hospital as a precautionary measure; studies which find lower

rates of asthma in people hospitalised with COVID-19 could be because PWA have practised increased protective measures, for example, shielding, or because of incomplete recording of asthma status. In primary studies which seek to evaluate risk factors for COVID-19, authors may evaluate long lists of possible predictors, but in their results only highlight those where statistically significant differences are found. We used NOS, the most commonly used critical appraisal tool for observational studies, though its validity has been questioned.[65 66] However, there is no agreed tool for use in this sort of study, and we prespecified use of NOS in agreement with the WHO. There may also be more recent studies published beyond our search date which we have missed. None of the included studies evaluated the risk of persistence of COVID-19 symptoms (Long COVID) in PWA.[67] Finally, of the included studies exclusively in PWA, only one high-quality study looked at possible associations between asthma severity and death with COVID-19; it found none. Given the paucity of data, we cannot conclude that asthma is not a risk factor for poor COVID-19 outcomes independent of asthma severity.

In conclusion, pooled results do not suggest that PWA are at increased risk for acquiring SARS-CoV-2 compared with those without asthma, and suggest that PWA have similar clinical outcomes with COVID-19. However, results were limited by imprecision, a lack of reporting on asthma severity and, in some cases, substantial unexplained statistical heterogeneity. Though the absence of evidence of a clear association between asthma and worse outcomes from COVID-19 should not be interpreted as evidence of absence, particularly given the paucity of data on asthma severity, the data reviewed do give some indication that risks in PWA, as a whole, may be less than originally anticipated. Further high-quality primary studies are required to reinforce and broaden this conclusion in order to facilitate the development of evidence-based shielding and avoidance measures, as well as appropriate vaccination schedules.

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Contributors JH-B conceived the original review. AO, JH-B, JS, ES, JG, AM and KR screened the studies and extracted the data. AO drafted the manuscript and performed the statistical analysis with guidance from JH-B. RH, PD, KR and JH-B provided expert opinion. All authors contributed to and approved the final manuscript. All authors had full access to all the data in the study. JH-B acts as guarantor for this work.

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