



## Early View

Original research article

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Asthma and Coronavirus Disease 2019 Risk: A systematic review and meta-analysis

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**Conflict of Interests:**

All authors have no conflicts of interest to declare.

## Abstract

**Background** Individual case series and cohort studies have reported conflicting results on the vulnerability to and risk of mortality of people with asthma from COVID-19.

**Research Question** Are people with asthma at a higher risk of being infected, hospitalized or of poorer clinical outcomes from COVID-19?

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

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

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

**Keywords:** asthma, COVID-19, critical care, mortality

## Introduction

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

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

A comprehensive understanding of COVID-19 risk among asthmatics globally is crucial as countries lift lockdown, and for prioritisation of vaccine allocation considering the limited supply of vaccines globally. Hence, we aimed to conduct a comprehensive systematic review and meta-analysis based only on controlled studies with rt-PCR confirmed COVID-19 cases to ascertain the pooled prevalence and overall risk of infection, hospitalisation, ICU admission, ventilator use and mortality from COVID-19 among asthmatics.

## Methods

### Search strategy and selection criteria

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

### Search strategy and selection criteria

A comprehensive search of electronic databases including Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, PubMed, Medline, and WHO COVID-19 database were conducted between 1 December 2019 until 11 July 2021. A hand search

of references of relevant systematic reviews was also conducted. In the case of missing information, we contacted the authors whenever possible. If the study identified patients with chronic respiratory conditions, we asked them to specify if this included asthma and requested these data.

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

### **Data collection**

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

### **Outcomes**

The outcomes were (i) the risk of acquiring COVID-19, expressed as the proportion of confirmed COVID-19 patients with a pre-existing diagnosis of asthma; (ii) risk of hospitalization from COVID-19 (proportion of confirmed COVID-19 patients hospitalized with asthma); (iii) risk of being admitted to ICU (proportion of confirmed COVID-19 patients with asthma admitted to ICU); (iv) risk of being ventilated (proportion of confirmed COVID-19 patients with asthma treated with mechanical ventilation once admitted to ICU) and (v) risk of death (proportion of confirmed COVID-19 patients with asthma that are dead or alive).

## Data analysis

Descriptive statistics were utilised to summarise the details of the included studies in Table 1. The Newcastle-Ottawa Scale (NOS)[11] was used to assess the methodological quality of included studies based on the relevant study designs cohort or case-control. One star is allocated in the domains of selection and outcome or exposure and up to 2 stars are allocated to the comparability domain. A total of 9 stars are allocated across all three domains. An overall score of 1-3 stars is categorized as low quality, 4-6 as medium quality and 7-9 as high quality.

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

For all the binary outcomes, we performed Sidik-Jonkman random effects meta-analysis (assuming that there is not only one true effect size but a distribution of true effect sizes). We assessed the quantitative heterogeneity by conducting a formal test of homogeneity and evaluating the proportion of variability due to heterogeneity ( $I^2$ ). Prespecified subgroup analyses were conducted by continent and by the quality of the studies (low, medium, high) and univariable meta-regressions using age and proportions of current and former smokers as covariates.

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

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

## Results

The searches resulted in 30,682 citations. After duplicates were removed, 18,553 titles and abstracts were screened, 17,553 articles were excluded. Of the remaining 1,000 articles, 949 were excluded after full-text review. A total of 51 studies were included in the review. Studies with overlapping patient populations were excluded if they reported the same outcome (Figure 1).

### *Descriptive Characteristics*

This review is based on a pooled sample of 1,471,643 COVID-19 tested patients of which 965,551 were COVID-19 positive with reported information related to asthma. The sample sizes ranged

from 52[12] to 417,366 people[13]. Most of the studies were hospital-based (34 studies) while three were studies[14-16] in the community and fourteen had a mixed setting[16-28]. Studies originate from 21 countries spread on all 5 continents – Europe (n=17), North America (n=13), Asia (n=12), South America (n=5), Africa (n=2) and Australia (n=2). The summary of included studies is presented in Table 1.

Among COVID-19 positive patients, based on rt-PCR assay results, the mean age of participants was  $52.0 \pm 12.9$  years, 42.64% were males (n=459,640 from 47/51 studies), 5.4% were current smokers (n=38,672 from 23/51 studies) and 9.8% were former smokers (n=43,622 from 10/51 studies). The prevalence of asthma among those infected with COVID-19 was 8.08% (95% CI 6.87-9.30; test of homogeneity  $P < 0.001$ ). About 25% had hypertension (n=135,274 from 35/51 studies), 14.3% had diabetes (n=78,923 from 38/51 studies) and 3% had chronic obstructive pulmonary disease (COPD) (n=15,636 from 29/51 studies).

#### *Risk of Bias Results*

Scores on the NOS ranged between 6[16, 29] to 9 (maximum 9), with a higher score indicating a high quality. All studies scored 7 or above and were of high quality. A full assessment is presented in Table S3.

#### *Meta-Analysis of the Risk of acquiring COVID-19*

The pooled analysis of 10 studies (n=785,151) showed a Risk Ratio Reduction (RRR) in acquiring COVID-19 of 17% for people with asthma compared to those without asthma (RR 0.83, 95% CI 0.73-0.95;  $p=0.01$ ; Figure 2). There was considerable heterogeneity ( $I^2=98.46\%$ ) across the studies. Meta-regression by age revealed that older age was associated with increased risk of acquiring COVID-19 in individuals with asthma (Meta-regression coefficient 0.014, 95% CI = 0.004 to 0.025,  $p=0.006$ ). Furthermore, the R-squared showed that 45.51% of the variance between studies can be explained by age. Heterogeneity remains high when age is included as a moderator in the meta-regression ( $I^2=92.03\%$ ) meaning that it is not a main factor in the difference between studies. No statistically significant association for current smoker (5/10 studies;  $p=0.09$ ) and former smoker were found (2/10 studies;  $p=0.94$ ).

#### *Meta-Analysis of the Risk of hospitalization*

We observed a non-statistically significant different risk for hospitalization from COVID-19 for people with asthma compared to no asthma (RR 1.18, 95% CI 0.98-1.42,  $p=0.08$ ), in the 18 studies

(n=411,093) included in this analysis. There was considerable heterogeneity observed ( $I^2=98.86\%$ ) across the studies. See Figure 3. Meta-regression by age, current smoker (only from 9/18 studies) and former smoker (only from 6/18 studies) revealed no relevant association in risk of being hospitalized with COVID-19 in individuals with asthma.

#### *Meta-Analysis of the Risk of ICU admission*

There was a non-statistically significant different risk of ICU admission (RR 1.21, 95% CI 0.97-1.51,  $p=0.09$ ) for people with asthma compared to those without asthma in a pooled analysis of 21 studies (n=192,694). Substantial heterogeneity was observed ( $I^2=94.21\%$ ) across the studies. See Figure 4. Meta-regression with former smoker (4/21 studies) as moderator found a statistically significant decrease in risk of ICU admission (Meta-regression coefficient  $-0.00009$ , 95% CI =  $-0.0002$  to  $-2.65 \times 10^{-6}$ ,  $p=0.043$ ). Meta-regression with age and current smoker (9/21 studies) as moderator did not reveal statistically significant results ( $p=0.15$  and  $p=0.37$  respectively).

#### *Meta-Analysis of the Risk of ventilator use when admitted into the ICU*

In relation to probability of mechanical ventilation, of the 11 studies (n=101,694) pooled for this analysis, there was no statistically significant difference in risk of being treated with ventilator once admitted to ICU for people with asthma compared to those without asthma (RR 1.06, 95% CI 0.82 to 1.36,  $p=0.65$ ). Considerable heterogeneity was observed ( $I^2=87.91\%$ ) across the studies. See Figure 5. Meta-regression with age and current smoker (4/11 studies) did not reveal statistically significant results ( $p=0.276$  and  $p=0.260$  respectively). Whereas meta-regression with former smoker as a moderator (2/11 studies) found a reduction in risk of ventilator use (Meta-regression coefficient  $-0.0022$ , 95% CI =  $-0.0037$  to  $-0.0007$ ,  $p=0.004$ ).

#### *Meta-Analysis of the Risk of death*

There was a non-statistically significant different risk of death from COVID-19 for people with asthma compared to those without asthma in the 32 studies (n=379,381) pooled for this analysis (RR 0.94, 95% CI 0.76-1.17,  $p=0.58$ ). Considerable heterogeneity was observed ( $I^2=94.85\%$ ) across the studies. See Figure 6. When age was included as moderator for meta-regression, there was no statistically significant reduction in risk of death by age ( $p=0.219$ ). No statistically significant association was also found for current smoker (14/21 study) and former smoker (7/21 study) as a moderator ( $p=0.458$  and  $p=0.288$  respectively).



### *Subgroup Analyses*

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

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

Subgroup analyses by study quality for risk for death showed significantly higher risk in the one study that is medium quality compared to the thirty higher quality ones (RR 1.45, 95% CI 1.14-1.87 vs RR 0.92, 95% CI 0.74-1.15;  $p$ -value 0.007).

### *Publication Bias*

The Egger's test for small study effects showed evidence of small study effects for the pooled proportion of COVID-19 (rt-PCR) positive individuals ( $p<0.0001$ ) and risk of hospitalization ( $p=0.0199$ ), but not for all other outcomes (Table S3). Eyeball assessment of the contour enhanced funnel plots revealed asymmetry only for the risk of hospitalisation but not other outcomes (Figure S1-S6).

## Discussion

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

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

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

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

Subgroup analyses by continent revealed significant differences in risk of acquiring COVID-19 between the continents, the lowest risk being in Asia (RR 0.66, 95% CI 0.57-0.75) followed by North America RR 0.78, 95% CI 0.69-0.89), South America (RR 0.84, 95% CI 0.82-0.85) and Europe (RR 1.01, 95% CI 0.82-1.26). Additionally, we noted the consistent nature of the risk reduction in three of the four regions where data is available. The risk reduction in Asia was found to be consistent in the three studies pooled from China[31], Israel[21] and South Korea[37], all countries with a high testing regime which might account for this variance between regions.

However, analysis of community studies such as this could better reflect the true nature of the risk compared to analysis of hospital-based studies. It is also important to note that this result may not reflect other countries in Asia such as India and Southeast Asia where testing regimes have not been as extensive.

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

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

We also found similar risks for hospitalisation, ICU admission when hospitalised and ventilator use were found in this study. Even so, we note for hospitalisation while not statistically significant the pooled point estimate suggests a possible 18% increased risk of hospitalization from COVID-19 for people with asthma with a wide confidence interval (95% CI -2% to 42%).

Similarly, for ICU admission, while not statistically significant the pooled point estimate suggests a possible 21% increased risk of ICU admission from COVID-19 for people with asthma (95% CI -3% to 51%). One study from China (Wang[40]) and another from Kuwait (Almazeedi[41]) reported a risk ratio of 5.16 and 4.08 respectively, far greater than in other studies. These

differences in risk may be linked to resource allocation and availability or difference in vulnerability due to ethnicity or other environmental factors.

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

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

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

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

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

In conclusion, the findings from this analysis indicate the prevalence of asthma was 8.08% amongst people who were rt-PCR positive for COVID-19 in these controlled studies. The overall findings suggest people with asthma are at lower risk of being infected with COVID-19 compared to those without asthma but when rt-PCR positive, have a similar risk of hospitalisation, ICU admission, ventilator use and mortality. With the fast evolution of the SARS-CoV-2 virus and the emergence of variants globally, caution must be maintained for people with asthma. There remains a need for higher quality community studies as well as regular risk assessments and review of new data throughout the pandemic. Furthermore, additional studies are required to confirm this risk profile, particularly in Africa and South America where none of the eligible studies originated.

## **Contributions**

AS and SA completed search of the literature, title/abstract screening and inclusion/exclusion review, data extraction and quality assessment and contributed to writing the review. GL performed the statistical analysis and contributed to writing the review. CJ initiated this review,

engaged co-authors, was third independent reviewer, and oversaw the study from inception to completion. She contributed to writing and reviewing all draft manuscripts.

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### **Declaration of Interests**

All authors have nothing to disclose.

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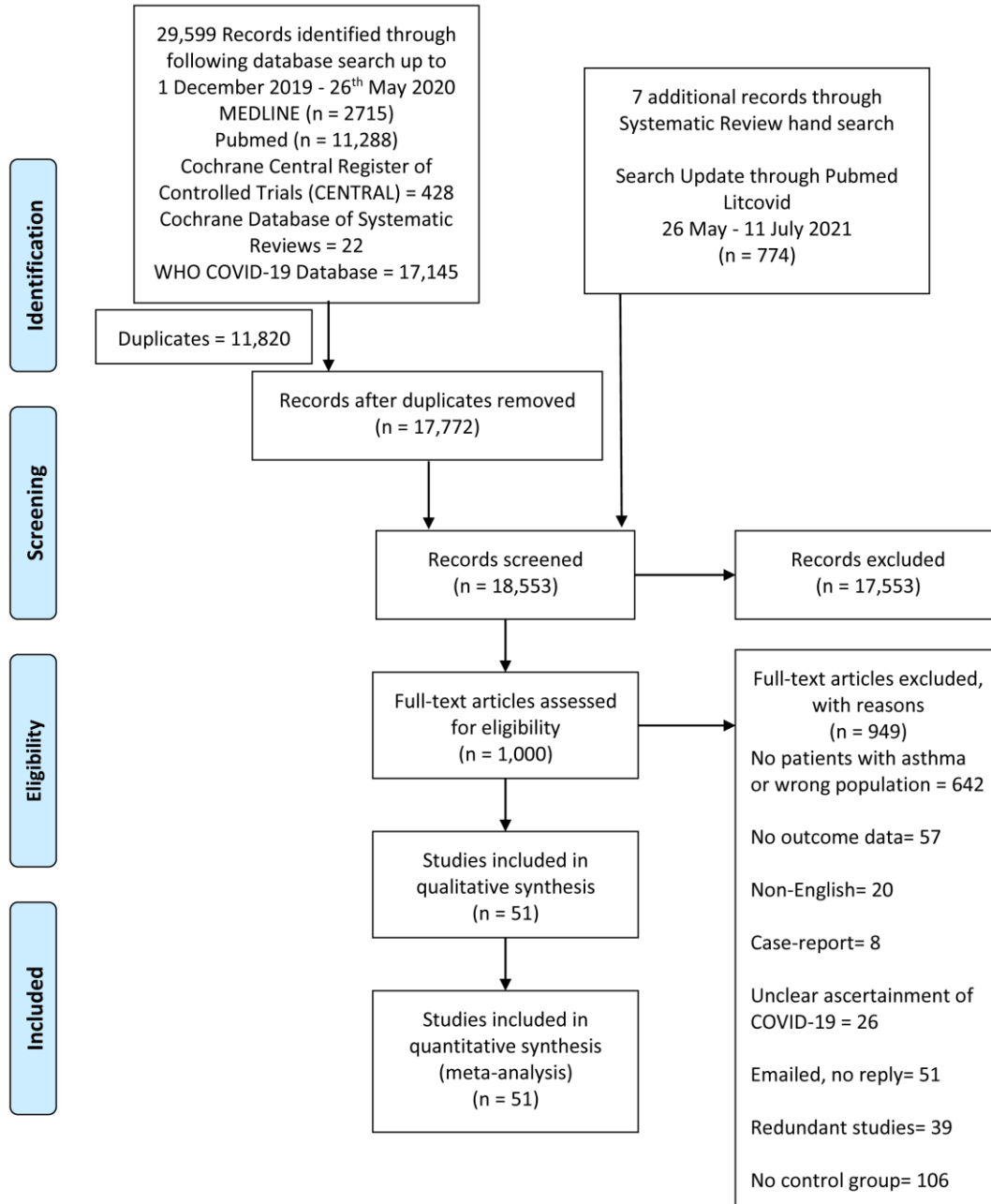
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## Figure Legends



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Figure 1. PRISMA Flow Diagram

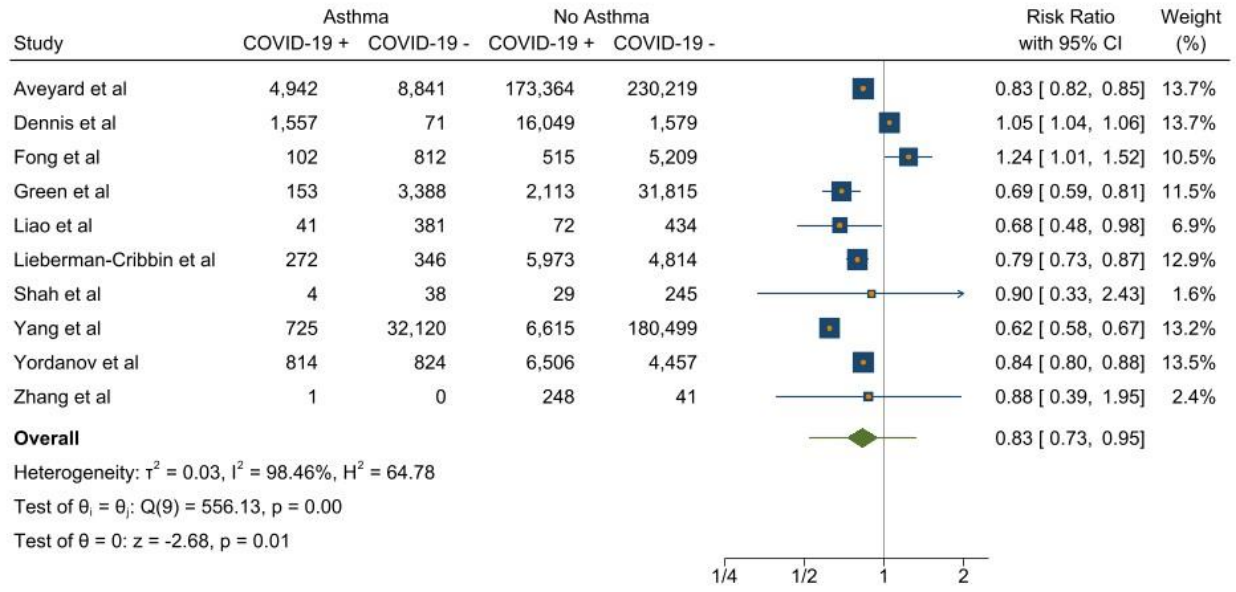


Figure 2. Risk of acquiring COVID-19 in individuals with asthma compared with no asthma

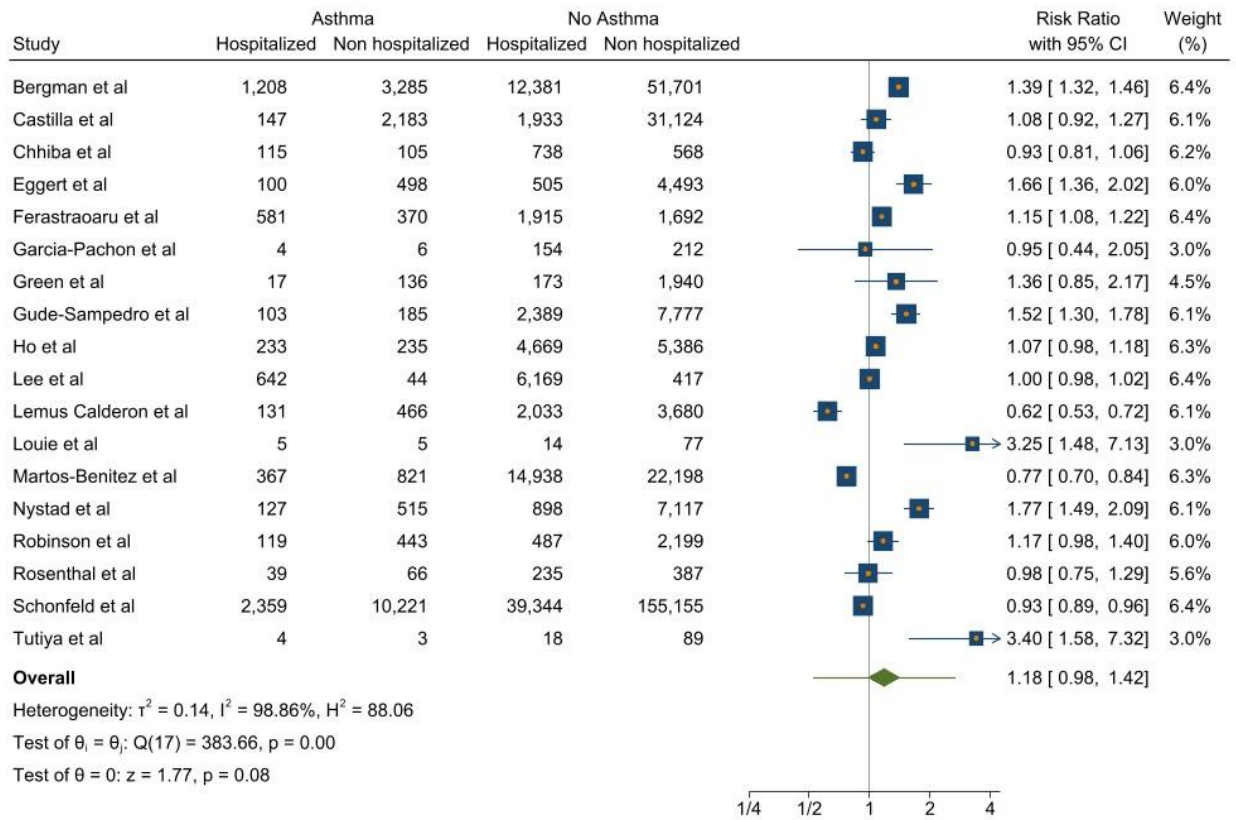


Figure 3. Risk of hospitalization when infected with COVID-19 in individuals with asthma compared with no asthma

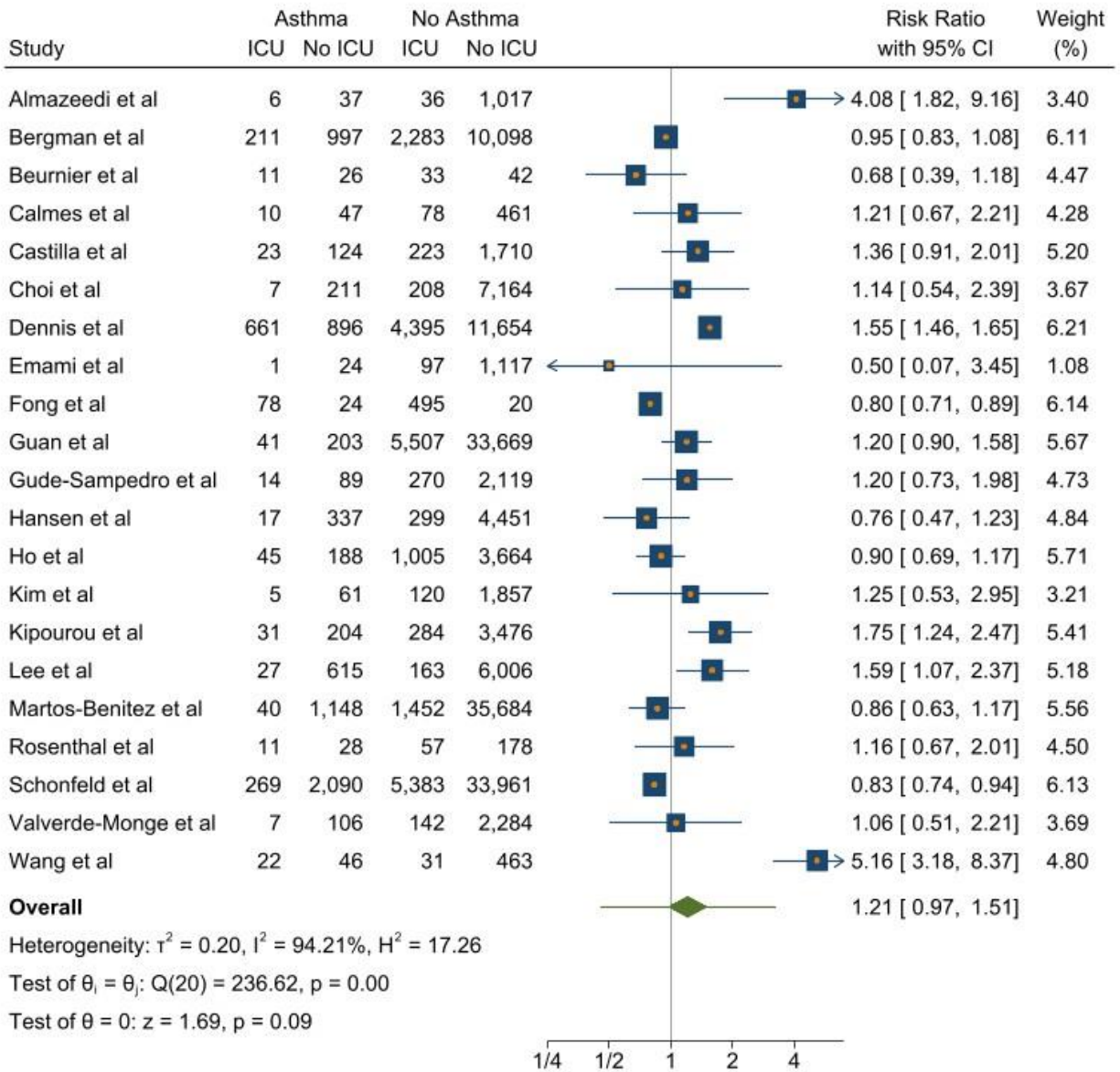


Figure 4. Risk of ICU admission when infected with COVID-19 in individuals with asthma compared with no asthma

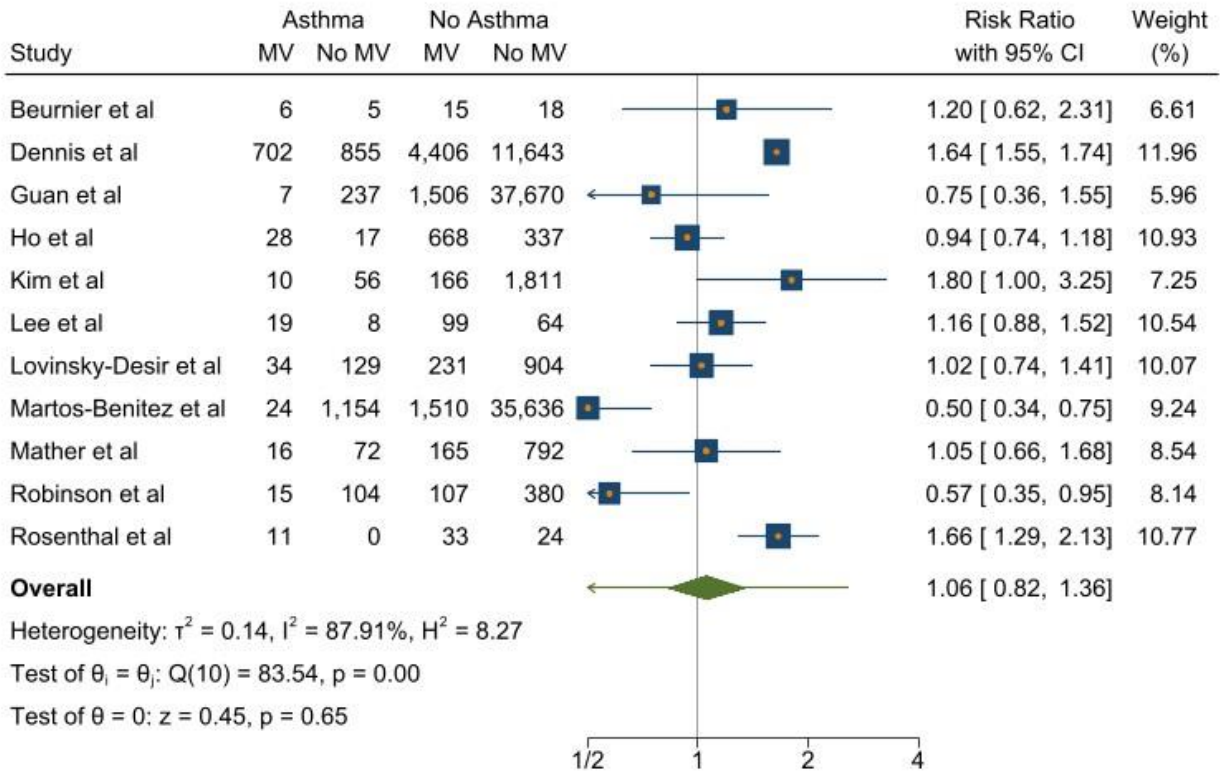


Figure 5. Risk of mechanical ventilator use upon admission to ICU with COVID-19 in individuals with asthma compared with no asthma



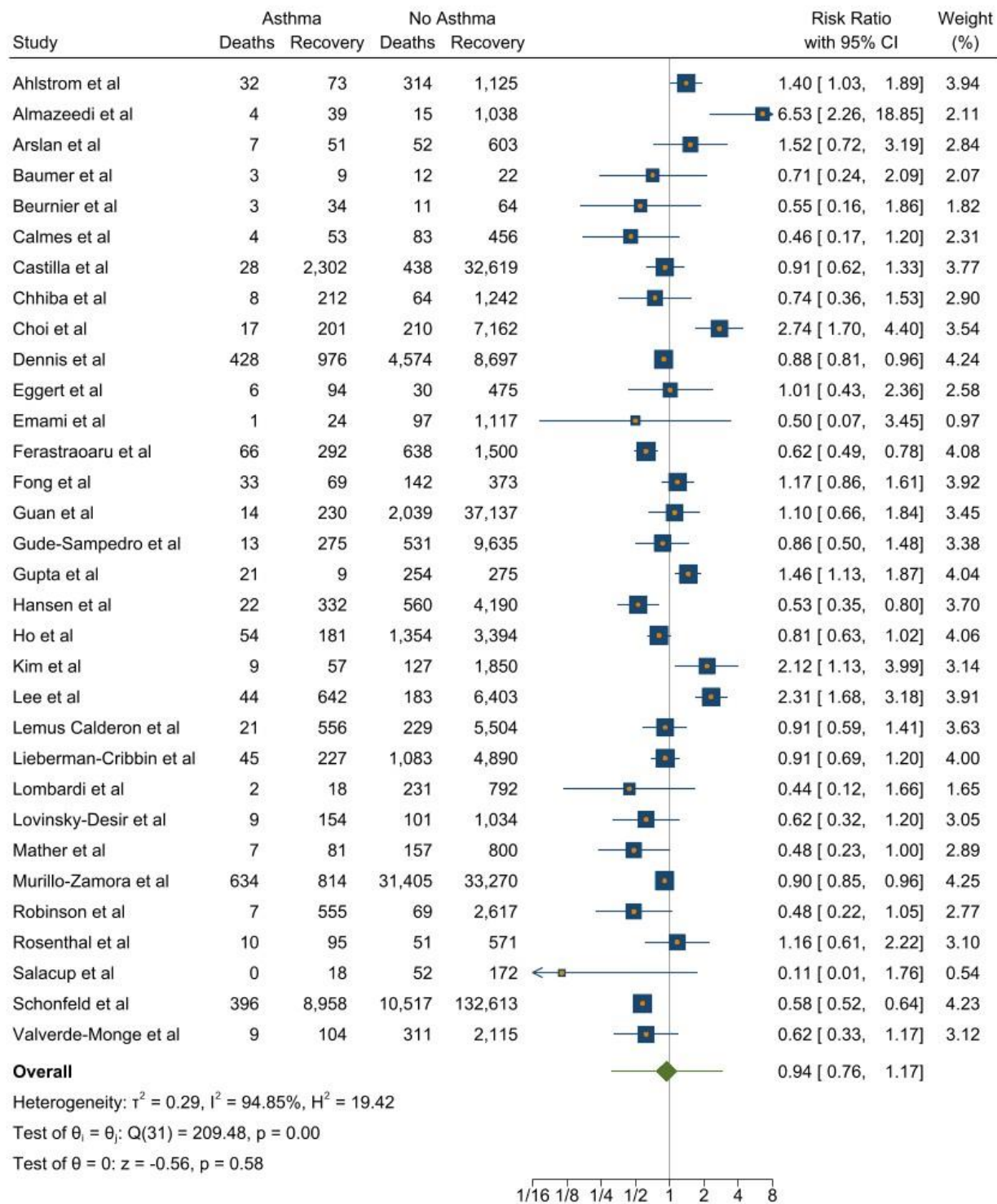


Figure 6. Risk of death when infected with COVID-19 in individuals with asthma compared with no asthma



Table 1 – Characteristics of Included Studies

Study	Country	Setting	Design	Study Period	COVID-19 Positive		Age (years)		Male (n)	Current smokers (n)	CO PD (n)	Diabetes (n)	Hypertension (n)	NOS Score (Out of 9)
					Asthma (n)	Overall (n)	Mean	Median						
Ahlstrom et al[17]	Sweden	Mixed	Case Control Study	6 Mar-27 May 2020	133	1981		61	1465		75	522	982	9
Almazeedi et al[41]	Kuwait	Hospital	Retrospective Cohort Study	24 Feb-20 Apr 2020	43	1096		41	888	44	5	155	177	9
Arslan et al[46]	Turkey	Hospital	Retrospective Cohort Study	18 Mar-15 May 2020	58	767	51.99		374	80	43	137	220	8
Ashinyo et al[47]	Ghana	Hospital	Retrospective Cohort Study	23 Mar-29 Jun 2020	24	307	37.9		174			20	219	7
Aveyard et al[13]	Mexico	Hospital	Retrospective Cohort Study	27 Feb to 21 Jun 2020	4942	178306		44.1	88083					8
Baumer et al[12]	United Kingdom	Hospital	Prospective Cohort Study	9 Mar-7 May 2020	12	52	54.82		29					8
Bergman et al[18]	Sweden	Mixed	Case Control Study	To mid-Sept 2020	4493	68575	46		26808		2168	4897	16416	9
Beurnier et al[48]	France	Hospital	Prospective Cohort Study	15 Mar-15 Apr 20	37	112		60	49			17	32	9
Calmes et al[49]	Belgium	Hospital	Retrospective Cohort Study	18 Mar-17 Apr 2020	57	596	58.75*		294					9
Castilla et al[19]	Spain	Mixed	Retrospective Cohort Study	Jul-Dec 2020	2330	35387		38.8	17,172	6119	1404	1893	4543	9
Chhiba et al[50]	USA	Hospital	Retrospective Cohort Study	1 Mar-15 Apr 2020	220	1526		53.3*	654	43				9
Choi et al[20]	South Korea	Mixed	Retrospective Cohort Study	up to 15 May 2020	218	7372		44.5*	3000					9
Dennis et al[30]	United Kingdom	Hospital	Retrospective Cohort Study	1 Mar-27 July 2020	1557	17606	67		10560		231	421		9
Eggert et al[51]	USA	Hospital	Retrospective Cohort Study	1 Mar-30 Sept 2020	598	5596		38.4	2635	123	88	609	1021	9
Emami et al[52]	Iran	Hospital	Retrospective Cohort Study	20 Feb-1 Mar 2020	25	1239	51.48		692	27		176		7

Ferastraoaru et al[53]	USA	Hospital	Retrospective Cohort Study	14 Mar-27 Apr 2020	951	4558		60.5						9
Fong et al[54]	UK	Hospital	Retrospective Cohort Study	1 Mar-31 May 2020.	102	617		65						9
Garcia-Pachon et al[14]	Spain	Community	Retrospective Cohort Study	3 Mar-12 Apr 2020	10	376		54	192					8
Green et al[21]	Israel	Mixed	Retrospective Cohort Study	Feb-June 2020	153	2266	33.31		1200	102		200	276	9
Guan et al[55]	China	Hospital	Retrospective Cohort Study	Dec 2019-6 May 2020	244	3942 0		55.7	1965 5					9
Gude-Sampedro et al[22]	Spain	Mixed	Retrospective Cohort Study	6 Mar-7 May 2020	288	1045 4	58		4172	258	180	619	1457	9
Gupta et al[29]	USA	Hospital	Retrospective Cohort Study	To 4 Mar 2020	30	529		70	286	39	36	289	416	6
Hansen et al[23]	Denmark	Mixed	Retrospective Cohort Study	1 Feb-10 Jul 2020	354	5104		54.6	2399		432	598		9
Ho et al[56]	USA	Hospital	Retrospective Cohort Study	7 Mar-7 Jun 2020	468	1052 3	58.35		5707		286	1679	2662	9
Je et al[57]	Australia	Hospital	Retrospective Cohort Study	Mar-Apr 2020	22	197	45		94		4	8	28	7
Kim et al[58]	South Korea	Hospital	Case Control Study	Feb-May 2020	66	2200	56.71		785	92	30	378	645	9
Kipourou et al[59]	Kuwait	Hospital	Prospective Cohort Study	24 Feb-27 May 2020	235	3995		40.4	2814	140	17	730	778	9
Lee et al[15]	South Korea	Community	Retrospective Cohort Study	Jan-27 May 2020	686	7272		45.3	2927			1041	1401	9
Lemus Calderon et al[60]	Spain	Hospital	Retrospective Cohort Study	up to July 2020	577	6310	59		2983	873		1641	3239	9
Liao et al[61]	USA	Hospital	Retrospective Cohort Study	11 Mar-23 Jun 2020	41	113	50		53	2	57	11	18	9
Lieberman-Cribbin et al[62]	USA	Hospital	Retrospective Cohort Study	29 Feb-24 Apr 2020	272	6245		57	3060					8
Lombardi et al[63]	Italy	Hospital	Retrospective Cohort Study	20 Feb-20 Apr 2020	20	1043		52.5*	704					9
Louie et al[24]	Australia	Mixed	Case Series	19 Mar-15 May 2020	10	99		54	51		2	8	14	8
Lovinsky-Desir et al[64]	USA	Mixed	Prospective Cohort Study	11 Feb-7 May 2020	163	1298		52	762	55				9

Martos-Benitez et al[25]	Mexico	Mixed	Retrospective Cohort Study	1 Jan-12 May 2020	1188	3832 4	46.9		2236 2	3277	889	7168	8340	9
Mash et al[65]	South Africa	Hospital	Retrospective Cohort Study	Mar-June 2020	67	1376	46.3		571	95	50	364	564	8
Mather et al[66]	USA	Hospital	Case Control Study	Feb- Nov 2020	88	1045		64.6	352		18	221	307	8
Murillo-Zamora et al[67]	Mexico	Hospital	Retrospective Cohort Study	4 Mar-15 Aug 2020	1448	6612 3		52.4	4012 4		261 9	2184 0	26728	9
Nystad et al[26]	Norway	Mixed	Retrospective Cohort Study	1 Mar-13 May 2020	515	7632		33.22*			161	468	977	7
Patone et al[27]	UK	Mixed	Retrospective Cohort Study	1 Nov-26 Jan 2021	2979 2	1984 20	37.7		9376 5	22134	187 3	1034 7	19636	9
Robinson et al[68]	USA	Hospital	Case Control Study	4 Mar-2 Jul 2020	562	3248		51	911	131		321	107	8
Rosenthal et al[69]	USA	Hospital	Retrospective Cohort Study	Mar-May 2020	105	727	49.46					165	278	8
Salacup et al[70]	USA	Hospital	Retrospective Cohort Study	1 Mar-24 Apr 2020	18	242		66	123		30	118	180	8
Schonfeld et al[28]	Argentina	Mixed	Retrospective Cohort Study	3 Mar-2 Oct 2020	1258 0	2070 79		41	1034 87	4074	440 5	2005 8	39833	9
Shah et al[71]	USA	Hospital	Retrospective Cohort Study	3 Feb-31 Mar	4	33		63	22	0	1	9	16	8
Tutiya et al[72]	Brazil	Hospital	Retrospective Cohort Study	13 Mar-7 Jun 2020	7	114		32.4	0			12	13	7
Valverde-Monge et al[73]	Spain	Hospital	Retrospective Cohort Study	31 Jan-17 April 2020	113	2539		62.66	1275	154	89	403	1054	9
Wang et al[40]	China	Hospital	Retrospective Cohort Study	28 Jan-25 Feb 2020	68	562		47	265					8
Yang et al[37]	South Korea	Community	Retrospective Cohort Study	1 Jan-15 May 2020	725	7340	47.1		2970		350	951	1638	9
Yordanov et al[16]	France	Mixed	Prospective Cohort Study	Mar-Aug 2020	814	7320	43		2301	790	87	402	978	6
Zhang et al[31]	China	Hospital	Retrospective Cohort Study	29 Dec-16 Feb 2020	1	290		57	155	10	6	27	81	8

\*Imputed values based on weighted average

## SUPPLEMENTARY INFORMATION

### Asthma and Coronavirus Disease 2019 Risk: A systematic review and meta-analysis

Table S1. Summary of Prevalence and Risk for COVID-19 among asthmatics in previous systematic reviews and meta-analyses

Study	Period	Sample Size	Prevalence <sup>#</sup> % (95% CI)	Risk Ratio except where stated (95% CI)					
				Acquiring	Hospital	ICU	MV	ICU + MV	Death
Broadhurst et al[1]	To 7 May 2020	30,496	6.8 (3.7–10.7)						
Sunjaya et al[2]	To 26 May 2020	587,280	7.46% (6.25-8.67)	0.86 (0.80- 0.94; p < 0.0001)	0.87 (0.77- 0.99, p = 0.03)	1.19 (0.93- 1.53, p=0.16)	1.16 (0.83- 1.63, p= 0.39)	0.87 (0.94- 1.37, p = 0.19)	0.87 (0.68- 1.10, p = 0.25)
Mendes et al[3]	To June 2020	161,271	1.6%						
Hussein et al[4]	To 15 July 2020	107,983	11.2% (9.1%– 13.3%) (Only hospital studies)		0.94 (0.84- 1.04, p=0.074)	1.64 (0.67- 3.97, p=0.27)	1.27 (95% CI = 1.02–1.58, p=0.030)		0.80 (0.65- 0.97, p=0.026)
Liu et al[5]	To 18 August 2020	410,382	1.1% to 16.9%		1.15; 95% CI, 0.92- 1.43, P = 0.19	1.19; 95% CI, 0.92- 1.54, 0.17	0.91; 95% CI, 0.71- 1.17; P = 0.42		0.90; 95% CI, 0.73- 1.11; p = 0.31
Wang et al[6]	To 1 Sept 2020	32,187						Severe COVID- 19 OR = 1.09, 95% CI: 0.79- 1.51, P = .61	OR = 0.84, 95% CI: 0.58-1.23, P = .37
Shi et al[7]	To 20 Sept 2020	403,392	8.3% (95% CI 7.6-9.0%)					Combined with death 0.91 (0.78-	0.80 (0.74- 0.86, p=0.13)

								1.06, P < 0.001)	
Terry et al[8]	To Dec 2020	878,239 (hospitalized, severe and mortality groups combined)	10.0% (95% CI, 8.0–12.2%) (Hospitalised) 9.5% (95% CI, 8.0–11.0%) (In community)		1.06 (0.94–1.19); P= 0.37			1.18 (0.98–1.42); P= 0.07	0.89 (0.77–1.02); P= 0.09

\*ICU – Intensive Care Unit; MV – Mechanical Ventilation

#Prevalence among COVID-19 positive cases

Table S2. Study Quality Assessment

Study	Selection Bias	Comparability	Exposure	Total Score	Quality
Ahlstrom et al[9]	4	2	3	9	High
Almazeedi et al[10]	4	2	3	9	High
Arslan et al[11]	3	2	3	8	High
Ashinyo et al[12]	3	1	3	7	High
Aveyard et al[13]	3	2	3	8	High
Baumer et al[14]	3	2	3	8	High
Bergman et al[15]	4	2	3	9	High
Beurnier et al[16]	4	2	3	9	High
Calmes et al[17]	4	2	3	9	High
Castilla et al[18]	4	2	3	9	High
Chhiba et al[19]	4	2	3	9	High
Choi et al[20]	4	2	3	9	High
Dennis et al[21]	4	2	3	9	High
Eggert et al[22]	4	2	3	9	High
Emami et al[23]	3	2	3	7	High
Ferastraoaru et al[24]	4	2	3	9	High
Fong et al[25]	4	2	3	9	High
Garcia-Pachon et al[26]	3	2	3	8	High
Green et al[27]	4	2	3	9	High
Guan et al[28]	4	2	3	9	High
Gude-Sampedro et al[29]	4	2	3	9	High
Gupta et al[30]	3	1	2	6	Medium

Hansen et al[31]	4	2	3	9	High
Ho et al[32]	4	2	3	9	High
Je et al[33]	3	1	3	7	High
Kim et al[34]	4	2	3	9	High
Kipourou et al[35]	4	2	3	9	High
Lee et al[36]	4	2	3	9	High
Lemus Calderon et al[37]	4	2	3	9	High
Liao et al[38]	4	2	3	9	High
Lieberman-Cribbin et al[39]	4	1	3	8	High
Lombardi et al[40]	4	2	3	9	High
Louie et al[41]	3	2	3	8	High
Lovinsky-Desir et al[42]	4	2	3	9	High
Martos-Benitez et al[43]	4	2	3	9	High
Mash et al[44]	4	1	3	8	High
Mather et al[45]	3	1	3	7	High
Murillo-Zamora et al[46]	4	2	3	9	High
Nystad et al[47]	4	0	3	7	High
Patone et al[48]	4	2	3	9	High
Robinson et al[49]	4	2	3	8	High
Rosenthal et al[50]	4	2	3	8	High
Salacup et al[51]	3	2	3	8	High
Schonfeld et al[52]	4	2	3	9	High
Shah et al[53]	3	2	3	8	High
Tutiya et al[54]	3	1	3	7	High
Valverde-Monge et al[55]	4	2	3	9	High
Wang et al[56]	3	2	3	8	High
Yang et al[57]	4	2	3	9	High
Yordanov et al[58]	2	1	3	6	Medium
Zhang et al[59]	3	2	3	8	High

**Table S3- Assessment of Publication Bias**

Outcomes	Egger Test (P-value)
Proportion of COVID-19 among asthmatics	<0.0001
Risk of acquiring COVID-19	0.9730
Risk of hospitalisation from COVID-19	0.0199
Risk of requiring admission to ICU	0.6228
Risk of requiring admission to ICU then mechanical ventilation	0.2702
Risk of mortality	0.2835

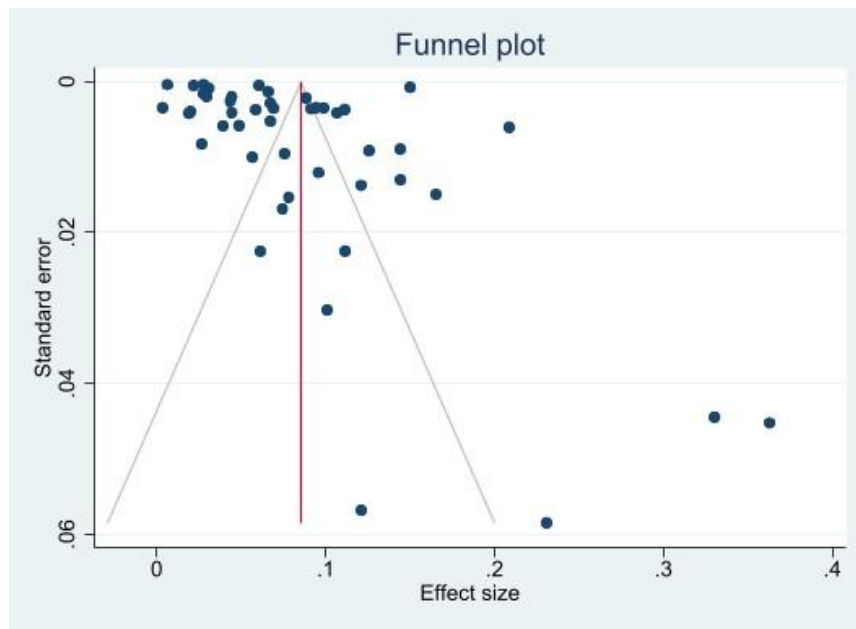


Figure S1. Proportion of COVID-19 among asthmatics

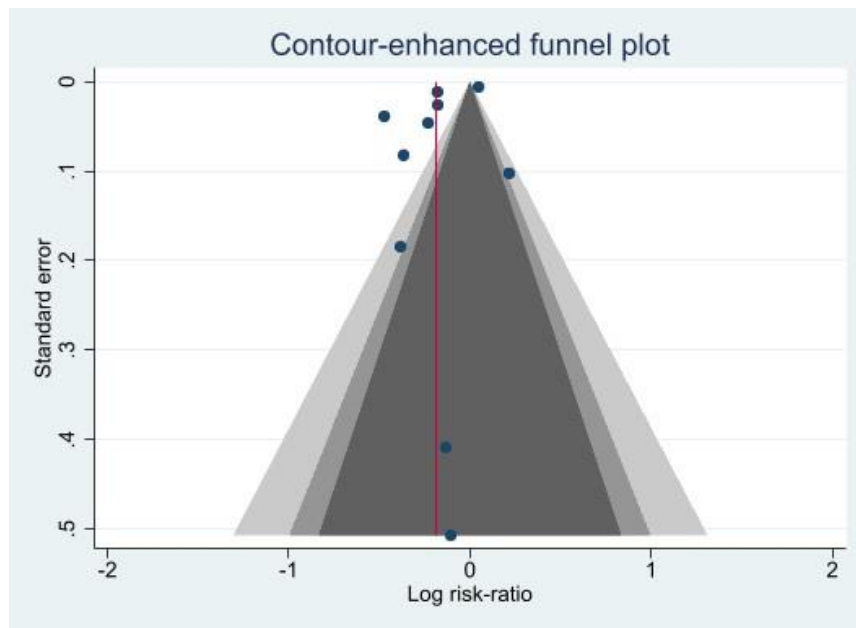


Figure S2. Risk of acquiring COVID-19

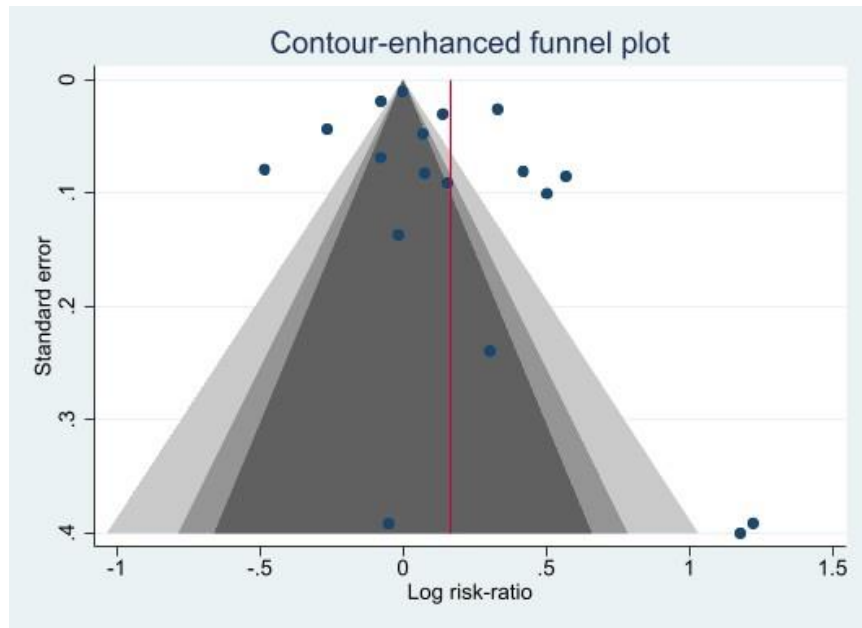


Figure S3. Risk of hospitalisation from COVID-19

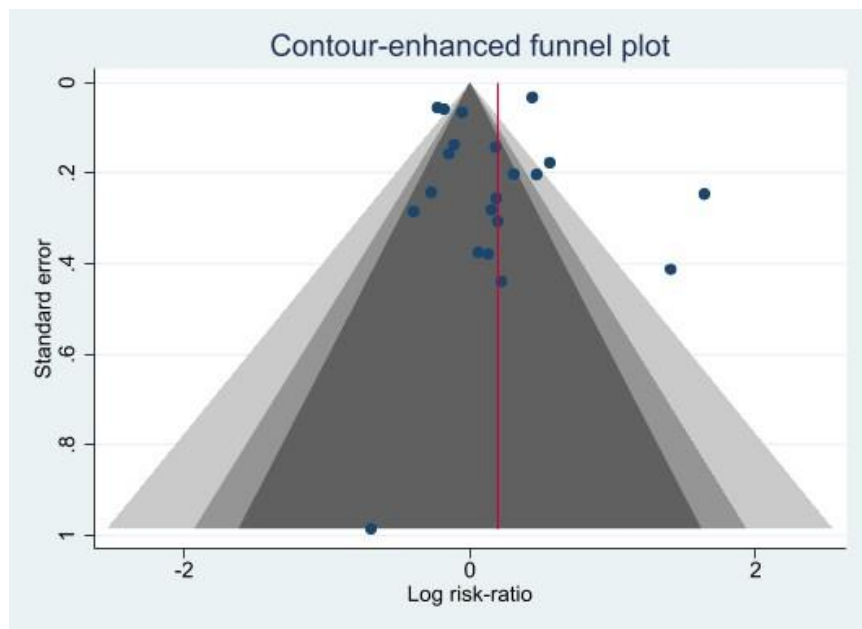


Figure S4. Risk of requiring admission to ICU



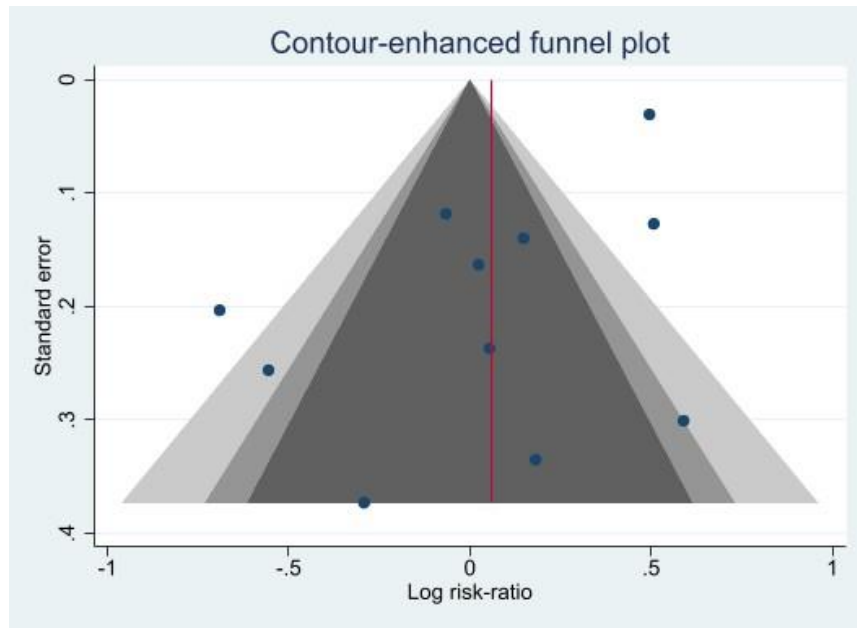


Figure S5. Risk of requiring admission to ICU then mechanical ventilation

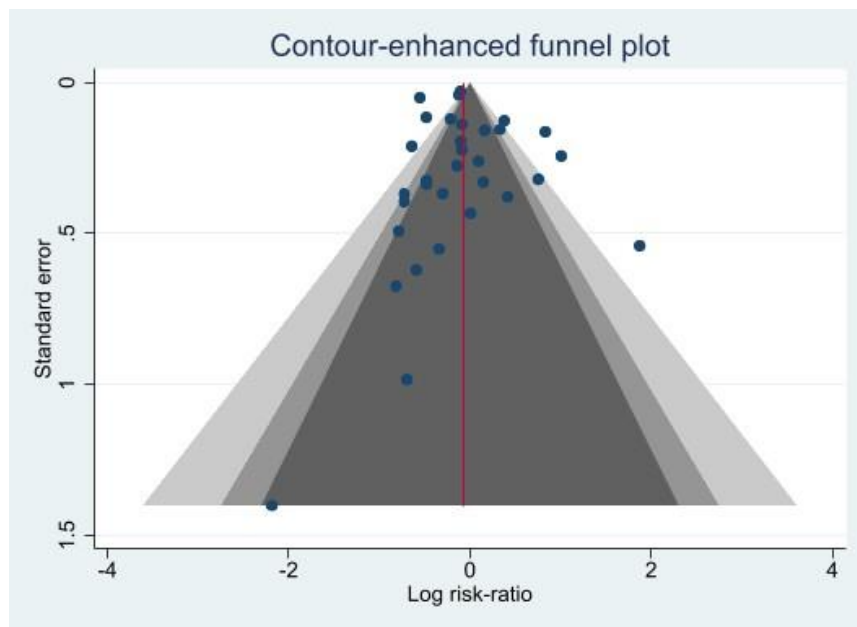


Figure S6. Risk of mortality

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