FINAL REPORT

Impact of COVID-19 on asthma: Rapid Review for Asthma Australia

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ASTHMA AUSTRALIA

The George Institute for Global Health

LIST OF ABBREVIATIONS

ARIA	Allergic Rhinitis and Its Impact on Asthma
ACE2	Angiotensin-Converting Enzyme 2
CDC	Center for Disease Control
COPD	Chronic Obstructive Pulmonary Disease
CENTRAL	Cochrane Central Register of Controlled Trials
CUIMC	Columbia University Irving Medical Centre
COVID-19	Coronavirus Disease 2019
FDA	Food and Drug Administration
GPP	Deutschen Gesellschaft Fur Padiatrische Pneumologie
DGP	Deutschen Gesellschaft Fur Pneumologie Und Beatmungsmedizin
EAACI	European Academy of Allergy and Clinical Immunology Section Pediatrics
GPA	Gesellschaft Fur Padiatrische Allergologie Und Umweltmedizin
GINA	Global Initiative for Asthma
HIRA	Health Insurance Review and Assessment Database
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
IL	Interleukin
MV	Mechanical Ventilation
MERS	Middle East Respiratory Syndrome
PECO	Population Exposure Control Outcome
pp	Pooled Prevalence
RCT	Randomised Controlled Trials
RR	Relative Risk
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
STARR-OMOP	Stanford Medicine Research Data Repository
VA	Veteran Affairs
WHO	World Health Organisation

EXECUTIVE SUMMARY

Review question

Are people with asthma more at risk of acquiring COVID-19 or of poorer outcomes?

Background

The prevalence of asthma among COVID-19 patients has been inconsistently reported. Little is known about their risk of acquiring the disease or their outcomes once infected. Despite this, various government agencies across the world have advised people with asthma to self-isolate. People with asthma are worried about their specific vulnerability and need this clarified.

Search date

We identified studies using searches conducted on the 26th May 2020.

Study characteristics

We included studies which reported on the outcomes of children and adults with COVID-19 with a pre-existing diagnosis of asthma. Mean age was 52.07 ± 16.81 years, 52.5% males. Studies were from Asia (n= 19), Europe (n=14), North America (n=22) and South America (n=2).

Key results

People with asthma have a slightly reduced risk of acquiring or being hospitalised from COVID-19. However, once hospitalised, they have a slightly increased risk of being admitted to ICU and are more likely to be intubated and mechanically ventilated. Despite this, people with asthma are slightly less likely to die from COVID- 19 compared to those without asthma.

Certainty of evidence

We rated the certainty of evidence as very low due to limitations in study design and variation across the included studies.

Conclusion

People with asthma are at a similar risk to those without asthma to acquire COVID-19. An extreme precautionary measure such as self-isolation for 12 weeks is unnecessary, and the current public health recommendation of practicing hand hygiene and physical distancing is appropriate. People with asthma should be supported to optimise their asthma control.

BACKGROUND

The coronavirus disease 2019 (COVID-19) is a respiratory infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has now spread in over 200 countries with 9.61 million individuals affected and over 489,312 deaths worldwide.[1]

Asthma is one of the most common chronic conditions with an estimated prevalence of 300 million people globally.[2] As COVID-19 continues to spread across the world, there are concerns that people with asthma are at a higher risk of acquiring the disease, or of poorer outcomes, which is mostly driven by three factors. Firstly, people with chronic respiratory conditions such as asthma were historically reported to be at higher risk compared to their counterparts during the middle east respiratory syndrome (MERS), caused by a virus with close sequence homology to SARS-CoV-2.[3] Thus, it appears likely that this is also the case with COVID-19. However, this trend was not observed during the severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1) epidemic.[4] Secondly, viral respiratory infections such as coronaviruses are potent triggers of asthma exacerbations.[5] The synergy between allergen sensitization, weaker anti-viral defences and lower interferon production are all contributing factors.[6] And lastly, inhaled corticosteroids, a mainstay treatment for persistent asthma, and prolonged use of oral corticosteroids frequently used during acute exacerbations, may impair the body's defence mechanisms against viral infections, including COVID-19[5], increasing susceptibility to infection and severity of disease. This hypothesis is supported by a systematic review of the use of systemic corticosteroids during the SARS-CoV-1 epidemic.[7] While these theories seem plausible, there is limited evidence to support them.

To date, there have been conflicting reports on the prevalence of asthma among COVID-19 patients. Early reports from Wuhan in China suggest that asthma is underrepresented compared to the population prevalence.[8] However, a case series from New York has reported a 9%[9] prevalence of asthma among COVID-19 patients which is higher than their national prevalence for asthma of 7.7%. [10] Current evidence shows that asthma is not in the top 10 comorbidities of COVID-19 fatalities, with obesity, diabetes and chronic heart disease being most commonly reported.[11] This is consistent with trends observed during the SARS-CoV-1 epidemic. However, the United States Center for Disease Control (CDC) has reported that among younger patients hospitalised for COVID-19, obesity, asthma and diabetes were the most common comorbidities.[12]

There have been recommendations from various government agencies across the world such as the United States CDC[13], Asthma Foundation New Zealand[14] and Center for Excellence in Severe Asthma[15] advising people with asthma to self-isolate which affects livelihood, mental health and quality of life. However, the evidence underlying this recommendation is unclear. Thus, Asthma Australia has requested a rapid summary of evidence to inform health promotion messaging, clinical practice and advocacy to support people with asthma during this COVID-19 pandemic.

1 AIM

Rapid evidence synthesis (RES) is a pragmatic form of research synthesis which is intended to inform recommendations and guide practice in a time-efficient manner. The overall objective of this RES was to provide the best available research evidence on the risk of infection, severe illness and death from COVID-19 of people with asthma.

1.1 Main Review question/s

- What is the evidence that having asthma poses high risk in (a) acquiring COVID-19 or (b) experiencing worse outcomes when infected with COVID-19?
- What should be the evidence-based public health measures recommended for people (children and adults) with asthma during the COVID-19 pandemic?

1.2 Sub Questions

- What proportion of people with known COVID-19 disease have a pre-existing diagnosis of asthma?
- What proportion of all people hospitalised and treated in ICU for COVID-19 have asthma?
    - What does the evidence tell us about the risk of infection of people with asthma, risk of serious illness and risk of death of people with asthma infected with SARS-CoV2?
    - What are the explanations for the findings?
    - What is the role of asthma treatments in vulnerability to or protection against complicated COVID-19?

2 METHODS

2.1 Inclusion criteria (PECO)

We included studies which met the following criteria.

2.1.1 Population

Children and adolescents, aged ≤ 18 years; and adults and older adults ≥ 18 years confirmed with COVID-19.

2.1.2 Exposure/s and intervention/s

Children and adolescents, aged ≤ 18 years; and adults and older adults ≥ 18 years confirmed with COVID-19 with a pre-existing diagnosis of asthma.

Inhaled or systemic corticosteroid and any other treatment given to people with COVID-19 with/without asthma if reported.

2.1.3 Comparison/s

Children and adolescents, aged ≤ 18 years; and adults and older adults ≥ 18 years confirmed with COVID-19 without asthma.

2.1.4 Outcome/s

- Risk of infection with COVID-19 of people with pre-existing diagnosis of asthma.
- Risk of infection with COVID-19 among those with non-severe compared to severe asthma. Non-severe asthma is defined as a lack of reported medical consult for asthma in the past year or an existing diagnosis of uncomplicated asthma.
- Risk of hospitalisation from COVID-19 in people with asthma.
- Risk of severe illness from COVID-19 (classified as requiring admission to ICU or mechanical ventilation) in people with asthma.
- Risk of death from COVID-19 in people with asthma.
- Evidence for public health measures recommended for people with asthma.
- Role of asthma treatments in the vulnerability to or protection against COVID-19.

2.2 Study designs

Randomised controlled trials (RCTs}, observational cohort studies, case series and case-control studies were considered for inclusion. Laboratory studies on the mechanisms of susceptibility to acquisition and severity of COVID-19 and studies focusing only on the pathophysiology of COVID-19 in asthma were excluded. We also excluded case reports with less than 5 participants.

2.3 Setting

We included hospital and/or community-based data from any country.

2.4 Study selection

Two reviewers independently screened all citations to determine whether they meet the inclusion criteria using Rayyan and discarded those that were irrelevant, based on the title of the publication and its abstract. If an article was possibly relevant, the full-length article was retrieved for further assessment against the inclusion criteria. Disagreements were resolved by discussion or with a third reviewer who adjudicated any persisting differences of opinion. Studies that are excluded on retrieval of full text were recorded, accompanied by a justification for exclusion.

Potential overlaps between studies were identified during 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/paediatrics), study period and size of the sample.

3 FINDINGS

3.1 Risk of acquiring COVID-19

We found a slightly reduced risk of acquiring COVID-19 among people with asthma compared with people without a diagnosis of asthma. This was a statistically significant finding.

There was no statistically significant difference between America (combination of North and South America), Asia and Europe in the risk of acquiring COVID-19 in people with asthma.

There was an observation that increased age corresponds with an increased risk of acquiring COVID-19 but smoking didn't appear to be a factor increasing this risk.

3.2 Risk of hospitalisation from COVID-19

There appeared to be a reduced risk of hospitalisation in people with asthma compared with people without a diagnosis of asthma.

The risk of being hospitalised with COVID-19 for people with asthma was greater in America than in Asia. There appears to be a positive association between age and risk of hospitalisation but this wasn't statistically significant. Being a current or former smoker did not appear to be a risk factor.

3.3 Risk of severe illness from COVID-19 (requiring admission to ICU and/or mechanical ventilation)

The analysis demonstrated a slightly increased risk of needing admission to ICU once hospitalised compared with people without asthma. It also demonstrated a slight increase in risk of requiring mechanical ventilation. When analysing the combined risk of either ICU admission or mechanical ventilation, there was therefore a slight increase in risk for people with asthma.

Neither of these outcomes were statistically significant.

Subgroup analyses of these outcomes suggests no statistically significant difference between continents. Age is positively associated with risk of ICU admission and mechanical ventilation but smoking doesn't appear to be a risk factor.

3.4 Risk of death from COVID-19

Of the studies analysed, the risk of death from COVID-19 is slightly reduced for people with asthma. When a worse-case sensitivity analysis was applied, it was demonstrated that people with asthma have a slightly increased likelihood to recover.

There was no statistically significant difference between continents regarding the risk of dying from COVID-19 among people with asthma compared with people without asthma. Increase in age was associated with increase in likelihood of dying but not statistically significantly.

4 DISCUSSION

This is the first rapid evidence synthesis to expand on the evidence base around the vulnerability of people with asthma during the COVID-19 pandemic. A total of 57 studies with an overall sample size of 587,280 people tested for COVID-19 were included.

The prevalence of asthma greatly varies between countries from less than 10% in most parts of Asia [16] to about 11% in Australia.[17] This was also reflected in our subgroup analysis which showed a differing pooled prevalence between continents.

Risk of acquiring COVID-19 infection

Although the proportions of people with asthma compared to the general prevalence of asthma seemed higher, we found a slightly lower risk of acquiring COVID-19 in asthmatics which equated to an absolute reduction of approximately 50 cases per 1,000 people. This risk reduction remains consistent in our subgroup analyses by continents and is consistent with the trend observed during the SARS pandemic in 2003.[4] There are several hypotheses with regards to this risk reduction which connects COVID-19's pathogenesis with that of asthma's pathophysiological changes and treatment.

Cytokine storms and abnormal immune responses have been postulated as potential pathological mechanisms in COVID-19 patients underlying poor outcomes. This is based on several case series in COVID-19 patients reporting significant elevation in inflammatory cytokines such as IL-2, IL-6, IL-7, IL-10 and TNF-α especially in severe patients.[18-20] Asthma being a chronic respiratory disease with chronic airway inflammation as one of its hallmarks may be expected to hasten the evolution of cytokine storms due to the greater baseline inflammation than in the general population.[21]

However, eosinophils play an important role in the pathophysiology of T2 high, or allergic asthma. Several case series on COVID-19 have suggested potential associations of eosinophilia with milder cases of COVID-19. Early studies from Wuhan reported eosinopenia in COVID-19 cases, more so in those with severe than mild disease.[19] Similarly, eosinopenia has also been reported during other coronaviruses outbreaks such as SARS-CoV-1[21] and MERS[22]. This was not reported in subsequent case series outside of China and would require further studies.

Furthermore, a recent study among 3 cohorts of children and adults have showed that the gene expression of angiotensin-converting enzyme 2 (ACE2), the cellular receptor for SARS-CoV-2 is lower in asthmatics and those with allergic rhinitis than the general population.[23] This lower receptor expression may confer a reduction in vulnerability to COVID-19 and development of a more severe disease in those with allergic asthma. Additionally, lower interferon levels in people with asthma are also hypothesised to be protective against cytokine storm which occurs in severe COVID-19 patients.[24]

Besides mechanistic considerations, behavioural aspects may have played a role in reducing the vulnerability of asthmatics to COVID-19. Early in the pandemic, the uncertainty on the impact of asthma on COVID-19 and previous experience of viral infections triggering asthma exacerbations has caused anxiety among patients and caregivers.[25, 26] This also followed government advice during the peak of the pandemic in countries like the United Kingdom, which classified severe asthmatics as a vulnerable group and advised them to shield for 12 weeks at home.[27] Combined with the heightened anxiety, asthmatics might as a result be more likely to practice physical distancing and hygiene measures. A study in USA has showed that during the pandemic, there is a 14.5% relative increase in daily controller adherence in asthmatics and COPD patients which supports this posit.[28] All these factors may work together in reducing their risk of acquiring COVID-19.

There was moderate heterogeneity observed between the studies reporting on the risk of acquiring COVID-19 and meta-regressions were conducted to explore its possible causes. The result of the

meta-regression by age showed that age contributed to 70% of the variance between the studies. Increasing age is strongly associated with a significant increase in risk of acquiring COVID-19 among asthmatics. This is an expected finding and in line with other COVID-19 studies showing age as one of the most important predictors for vulnerability to COVID-19 and prognosis.[29-32]

We also performed a meta-regression to examine the association between smoking and the risk of acquiring COVID-19. Mechanistic studies have postulated that increased susceptibility to infection may be due to the upregulation of the ACE2 receptor which is the main receptor used by SARS-CoV-2 to gain entry to host mucosa and cause active infection, a mechanism unique to this virus. Current smokers have increased gene expression of ACE2 than former smokers and non-smokers.[33] Thus, one may anticipate that smoking is a risk factor for infection. However, the results of this meta-regression revealed no association between being a current or former smoker and the risk of acquiring COVID-19. This is consistent with one review which reported that smoking is not a risk factor for COVID-19 infection [34] and another study which concluded that active smoking was linked with a decreased odds of a positive COVID-19 test result.[35] Nevertheless, the limited data in this current pandemic and previous MERS and SARS pandemics limits the comparison of findings.

Risk of hospitalisation with COVID-19

Similarly, a risk reduction in hospitalisation from COVID-19 in people with asthma is observed (an absolute reduction of approximately 51 cases per 1000 people). This reduced risk is validated by the results of the sensitivity analysis which yielded a pooled risk ratio of 0.95 (95% CI 0.90 to 1.00, P= 0.05). Early evidence from the Severe Asthma Research Program-3 (SARP) has shown that inhaled corticosteroid (ICS) therapy is associated with lower ACE2 (one of the binding sites for SARS-CoV-2) expression.[36] While not undertaken in SARS-CoV-2, *in-vitro* studies in human coronavirus also showed inhibitory activities of budesonide on coronavirus replication and cytokine production (IL-6, IL-8, IFN-β, IFN-λ_1, and IFN-γ).[37] Another *in-vitro* study (preprint) has interestingly shown that ciclesonide and mometasone (ICS) were able to suppress replication of human coronavirus (MERS-CoV) in cultured cells, but not influenza or respiratory syncytial virus replication.[38]

Similarly, Jeon et al.[39] screened over 3000 FDA approved drugs for potential antiviral properties against SARS-CoV-1. Selected compounds were then tested in vitro in cultured mammalian cells infected with SARS-CoV-2. The authors concluded that ciclesonide showed direct antiviral properties against SARS-CoV-2 with an inhibitory concentration lower than other potential drugs such as chloroquine, lopinavir and remdesivir.[39] This inhibitory effect seems to be independent to ACE2 expression as a previous study has shown that use of nasal corticosteroids was not associated with ACE2 expression.[23] Anecdotally a case report[40] from Japan and a case series[41] from China has also suggested a potential benefit of ciclesonide in treating COVID-19 patients.

The use of monoclonal antibody and other immunologics as treatment in asthmatics may also play a role in ameliorating the risk of acquiring and developing severe COVID-19 requiring hospitalisation. While not against SARS-CoV-2, a previous study using omalizumab reported it reduces viral shedding of human rhinovirus in children. Dupilumab, mepolizumab, reslizumab and benralizumab might also play a role in reducing airway inflammation and present antiviral properties.[25]

With about 80% of asthmatics using ICS[42, 43], if the above hypotheses are true, then the use of ICS may be a contributing factor in reducing the risk of acquiring COVID-19 as well as the risk of severe illness warranting hospitalisation. While the lack of individual patient data makes it difficult to draw conclusions, the meta-regression and previous studies have shown that older age and presence of other comorbidities such as hypertension and diabetes in people with asthma are strongly associated with the severity of COVID-19[44] and that asthma alone is not a major risk factor. This finding is also found in a case series of COVID-19 cases among those with immune mediated inflammatory diseases where those hospitalised are older and had more coexisting comorbidities such as hypertension, diabetes or COPD.[45] However, due to the lack of reporting of comorbidities, we were unable to explore this hypothesis.

Pooling of risk ratios for severe and non-severe and allergic and non-allergic type asthma were made impossible by the lack of reporting of asthma phenotypes. Those with severe asthma requiring

maintenance oral corticosteroids may be considered likely to be at higher risk of poorer prognosis associated with the use of OCS[7, 8]. Historically, severe asthmatics were reported to have a higher risk of hospitalisation and poorer prognosis during the SARS-CoV-1 and MERS outbreak.

Beyond the pathophysiologic underpinnings, clinical practice considerations and national guidelines on COVID-19 hospitalisation may also play a role in the risk of hospitalisation. Our subgroup analysis by continent revealed that the risk of hospitalisation is lower in Asia compared to America. This may be explained by the difference in hospital practice and health system capacity between the two continents, as well as the timing of the admission and the stage in the evolution of the pandemic - early or at the peak of the pandemic.

Risk of severe illness

In contrast to the reduction in risk of acquiring COVID-19 or hospitalisation, our pooled analysis demonstrated a slight increase in the risk of developing severe illness from COVID-19 requiring admission to ICU once hospitalised for people with asthma (equating to an absolute increase of approximately 31 cases per 1000 people). However, this was not statistically significant. The increase in risk may have several explanations. Firstly, people with asthma may be regarded as a high-risk group once hospitalised, at greater risk of developing sustained pulmonary failure with COVID-19 infection. They may have therefore been admitted to the ICU as a precautionary measure. Secondly, airflow limitation due to bronchospasm and mucus plugging would be expected to compound the hypoxemia characteristic of diffuse alveolar damage in COVID-19 patients with underlying asthma, requiring more intensive respiratory support. In our subgroup analysis, we found that the risk of being admitted to ICU once hospitalised is higher in Asia compared to America and Europe, although this was not statistically significant. The difference in ICU admission may be explained by the variance in the criteria for admission in ICU and in the ICU capacity of health care systems between continents.[46] However, there are conflicting reports from China and Italy that demonstrate the challenges of the subgroup analysis. In China, not all critical cases (defined as respiratory failure, shock and multiple organ dysfunction or failure) were admitted to ICU [47] while in Italy, up to 12% of all positive cases were admitted to ICU. Different criteria for ICU admission existed within and across countries and regions[48]

Increasing age is associated with increased risk of being admitted to ICU once hospitalised in people with asthma, however, this was not statistically significant. This is as expected and in line with what is currently reported in COVID-19 studies, [38, 90] Being a current or former smoker does not affect the risk of being admitted in ICU once hospitalised in people with asthma, This corresponds with the findings of a meta-analysis but contradicts the findings of another review which reported an increased risk of severe disease (RR 1.4, 95% CI 0.98-2,00) in smokers[94], However, it is important to note that the result of this subgroup analysis is only based on 2 studies.

Similarly, people with asthma have a slight increase risk of requiring mechanical ventilation (equating to approximately 18 more cases per 1000 people). It is likely that any decrease in PO_2 in hospitalised patients with a history of moderate to severe asthma is intubated earlier as a precaution. Those in Europe have a higher risk of being ventilated compared to Asia and America, which was statistically significant. As aforementioned, this is likely attributed to differences in criteria for mechanical ventilation between continents. In Italy, the criteria for mechanical ventilation is severe hypoxia (median PaO_2/FIO_2 of 160)[48] while in China, reports suggest that in between one-third and two-thirds of critically ill patients with COVID-19, non-invasive ventilation and high-flow nasal cannula were used.[18, 49-51] It is important to highlight that only two studies contributed to the overall risk in Europe and Grasselli et al's study had significant missing data regarding the use of respiratory support which may have influenced the rates reported. [48] The increase in the risk of mechanical ventilation could also be due to a combination of apprehension and initial lack of knowledge about the virus, resulting in a lower threshold for intubating people with asthma. This may change over time as a result of a period effect, that is whether the event occurred early in the pandemic or later, at its peak or following when much more was known.

Age is associated with an increased risk of mechanical ventilation in people with asthma, however, this was not statistically significant. One study reported that asthma particularly prolonged the intubation time in younger (<65 years) COVID-19 patients who otherwise have demonstrated a better disease course than older patients.[52] This trend might indicate that asthma has the highest impact on COVID-19 course in those younger than 65 years. Nonetheless, this is only based on 1 study with 1003 participants, there were not enough studies reporting on smoking status, as such, we were unable to perform a meta-regression. We found an increase in the combined risk of being admitted to ICU and/or mechanical ventilation for people with asthma. This increase risk is in line with those reported during influenza epidemics where asthma was associated with severity of disease and the need for mechanical ventilation in children.[53]

Risk of death

There is a reduction in the risk of death from COVID-19 for people with asthma. Several types of sensitivity analyses were conducted to confirm this finding. The base-case sensitivity analysis (all patients not dead taken as alive) showed an increase in risk of death from COVID-19 in people with asthma which is not statistically significant. However, the National Committee on COVID-19 Epidemiology Iran study[54] contributed a weight of 10.0% to this result with a very high RR of 12.70 compared to the rest of the studies, and we have endeavoured to confirm the accuracy of this anomaly. The data was checked multiple times to ensure it is accurate and also through author correspondences. The authors provided the proportion of people with asthma who died, and the crude numbers were calculated based on this. There are many factors which may have contributed to the huge numbers of deaths of people with asthma in Iran. It may be that these are self-reported cases of asthma as opposed to true clinical diagnoses. However, it is impossible to ascertain this. It might also be attributed to national health system variances in care which are not examined in this study. When this study was removed from the analysis, the increase in risk of death changed to a risk ratio reduction. In addition, the worst-case sensitivity analysis (all patients who have not yet recovered were taken as 'dead') showed an increase in the odds of recovery for people with asthma.

This finding is consistent with a study in New York investigating the association between history of asthma and mortality.[55] Similarly, they also found that asthma was not associated with mortality. However, these are again based on self-reported asthma. This reduced risk of death may once again be explained by the pathophysiology and treatment of asthma previously discussed. There was no difference in the risk of death between America and Europe. Increasing age was associated with increased risk of death but was not statistically significant. This finding is consistent with other COVID-19 studies. [29-32]

Summary

Overall, our analyses showed that in line with reports from China presented early in the pandemic and experiences from the past coronavirus epidemics, that people with asthma seem to have a lower absolute risk of acquiring COVID-19 compared to the general population. However, the current findings must be interpreted in light of the observational nature of most published studies and very low certainty assessment of the evidence as a result of methodological limitations. These include selection bias, as the majority are hospital-based, variation in the ascertainment or confirmation of diagnosis of asthma, short duration of follow-up and variable reporting of outcomes. Therefore, the findings of this review, although comprehensively covering all the available published studies at this time must be interpreted in light of the very low certainty assessment of the evidence.

4.1 Summary of statements from Asthma-Allergy Societies and Working Groups

We found 8 medical guidelines from various asthma, allergy and respiratory societies on the management of asthmatics during the COVID-19 pandemic. All guidelines unanimously supported maintaining current therapeutic regimens that have successfully been able to control the patient's asthma exacerbations. It is also their consensus that intranasal corticosteroids, biologics and immunotherapies currently showed no evidence of increasing risk of acquiring COVID-19.

Guideline Organisation	Recommendations
Italian society of pediatric allergy and immunology[56]	▪ Continue to administer medications prescribed to maintain asthma control regularly, in particular, inhaled corticosteroids (ICS), long-acting bronchodilators, antileukotrienic drugs, and, if necessary, oral corticosteroids (OCS) ▪ For patients with severe asthma, it is advisable to continue therapy with biological drugs and evaluate the possibility of home administration (or at a local hospital center) ▪ Develop Asthma Action Plans ▪ Avoid the use of nebulizers (nebulizers increase the risk of spreading the virus to other subjects and health professionals) and prefer the administration of bronchodilators and ICS through a metered dosed inhaler (MDI) with the help of a spacer ▪ Avoid Spirometry in confirmed/suspected COVID-19 patients ▪ Suspension of biologics during the acute phase of COVID-19 infection
NICE UK, British Thoracic Society[27]	▪ Tell patients on maintenance oral corticosteroids, or their parent or carer, to continue to take them at their prescribed dose because stopping them can be harmful ▪ Tell patients, or their parent or carer, that they should continue treatment because there is no evidence that biological therapies for asthma suppress immunity ▪ Tell patients, or their parent or carer, that if they develop symptoms and signs of an asthma exacerbation, they should follow their personalised asthma action plan and start a course of oral corticosteroids if clinically indicated ▪ Some patients with severe asthma will have received a letter telling them they are at high risk of severe illness from COVID-19. Tell them, or their parent or carer, to follow the advice on shielding
European Academy of Allergy and Clinical Immunology Section Pediatrics (EAACI)[57]	▪ There is no evidence that currently available asthma and allergy treatments, including antihistamines, corticosteroids, and bronchodilators, increase the risk of severe disease from **COVID-19** ▪ Optimal disease control of allergic, asthmatic, and immunodeficient children should be sought according to usual treatment guidelines

Allergic Rhinitis and its Impact on Asthma (ARIA) - EAACI[58]	▪ Not on asthma but discuss inhaled corticosteroids ▪ Current state of knowledge; topical nasal corticosteroid therapy for allergic rhinitis in children and adolescents with COVID-19 can be continued at the recommended posology ▪ Interruption of topical nasal corticosteroids is not recommended, which does not seem to reduce the immune system
Canadian Thoracic Society[59]	▪ Asthma maintenance and exacerbation management should continue according to national and international guidelines during the COVID-19 pandemic, however treatment decisions should be individualized based on patient characteristics. Optimal asthma control is expected to be the best protection against a SARS-CoV-2 exacerbation
Centre of Excellence in Severe Asthma Australia[15]	▪ People with asthma should continue maintenance treatment as prescribed during periods of stable asthma. This is highly important as having poorly controlled asthma puts patients at risk. People should continue prescribed treatment with inhaled corticosteroids ▪ Even though people with asthma do not appear to be at greater risk of COVID-19 infection, those with severe disease could experience more severe illness burden should they be infected by the virus. We therefore recommend that people with severe asthma self-isolate and practice physical distancing including from household occupants. This also includes the recommendation of staying at home unless it is essential, including working from home
German Respiratory Society, Deutschen Gesellschaft für Pneumologie und Beatmungsmedizin (DGP), Deutschen Gesellschaft für Pädiatrische Pneumologie (GPP) and Gesellschaft für Pädiatrische Allergologie und Umweltmedizin (GPA) [60, 61]	▪ There is no evidence to date that people with asthma have a higher risk of severe COVID-19 ▪ There is currently also no evidence that inhaled corticosteroid therapy (ICS) for the treatment of asthma might increase the risk of developing severe COVID-19. Since ICS therapy generally reduces the risk of asthma exacerbations and may additionally decrease the expression of the ACE-2 receptor in the airways, a protective effect is suspected instead ▪ During the SARS-CoV-2 pandemic, inhalation therapy, and in particular ICS therapy, should therefore be maintained unchanged for patients with well controlled asthma ▪ Allergen immunotherapy should also be continued
Global Initiative for Asthma (GINA) [62]	▪ People with asthma should continue to use their inhaled asthma controller medications during the COVID-19 epidemic

4.2 Strengths and Limitations

This review has rigorously adhered to the guidelines of performing systematic reviews. We undertook extensive searches of the databases and additional resources including preprint repositories, agency reports and open datasets. Although a language restriction was applied within the search process, we have taken the time to contact study authors to request missing information or confirm whether patients with chronic respiratory conditions within their studies included asthma. Thus, as far as could be ascertained we have identified and included all potentially relevant studies in this review based on the results of the search conducted on 26th May 2020. However, it is likely that from the time the search was performed to until now, more potentially relevant studies may have been published or released as preprint.

To avoid or minimise any bias in the review process, at least two reviewers independently extracted and managed data which was further checked by an external reviewer. Furthermore, the quality of the included studies was assessed using a widely used and standardised critical appraisal tool. There were overlaps among the included studies so additional care was taken to ensure no double counting of patients occurred and any redundant studies were excluded from the analysis, Albeit, it is impossible to completely rule out double counting, which is a limitation of this review.

Another limitation of this review is the synthesis of primarily observational studies, A major issue with observational evidence is that it is subject to within-study and across-study biases and to the presence of increased heterogeneity, Thus, its inclusion in a meta-analysis may introduce bias in the pooled effect. To mitigate this risk, we performed meta-regression to examine the impact of moderators such as age and smoking status on the study effect size and sensitivity analyses to explore the robustness of the findings under different assumptions, Additional problems encountered in the synthesis of observational studies include the increased risk of publication bias and selective outcome reporting, as preregistration and protocol preparation are not mandatory. Hence, we performed a regression-based Egger test and evaluated contour-enhanced funnel plots to assess any small-study effects which were considered in the interpretation of the findings and certainty of the evidence.

Another source of limitation is the varying definitions and ascertainment of asthma used in each study. Although we hoped that a previous clinical documentation on individual's health and medical history such as primary care notes, up-to-date medications lists, and other workup for asthma in the medical records were used to confirm the diagnosis of asthma, it is possible that in some studies asthma diagnoses were self-reported as part of an algorithm for COVID-19 assessment.

5 RECOMMENDATIONS

Interpretation of the Findings and linking risk to recommendations

People with asthma can be informed that the evidence available from the scientific literature to date does not indicate that having asthma represents an increased risk for acquiring COVID-19. They can be informed that they are not likely to have more severe disease in terms of a risk of requiring hospital admission, compared to others in the community who do not have asthma. If they do require a hospital admission, they may be more likely to require an admission to intensive care or assisted mechanical ventilation. Overall, people with asthma have a lower risk of death from COVID-19.

Public Health Measures Recommended for Adults and Children Based on Current Evidence

People with asthma should take all the precautions of hand hygiene, social and physical distancing to prevent transmission of infection as advised by public health officials and health authorities as given to the general community. They should additionally be conscientious about looking after their asthma and maintaining their preventative medications according to their doctor's advice. Inhaled and oral corticosteroids given for asthma do not carry any increased risk of acquiring COVID-19 or having a more severe outcome from it and may indeed be therapeutic against the virus.

6 CONCLUSION

In summary, the findings from this study suggest that the prevalence of people with asthma among COVID-19 patients are similar to the global prevalence of asthma, Those with asthma have a lower risk of acquiring and being hospitalised from COVID-19. However, when hospitalised they have a higher risk of being admitted to the ICU or receiving mechanical ventilation. The risk of hospitalisation or being admitted to the ICU differs between continents. The risk of death from COVID-19 in people with asthma is lower compared to those without asthma. The overall findings suggest that people with asthma are at a similar risk to those without asthma to COVID-19. Therefore, extreme precautionary measure such as self-isolation for 12 weeks is unnecessary, and the current public health recommendation of practicing hand hygiene and physical distancing is appropriate.

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