BMJ Open Respiratory Research

Risk of long covid in patients with pre-existing chronic respiratory diseases: a systematic review and meta-analysis

Paul Terry ,[1] R Eric Heidel ,[2] Alexandria Q Wilson ,[3] Rajiv Dhand [1]

To cite: Terry P, Heidel RE, Wilson AQ, *et al*. Risk of long covid in patients with pre-existing chronic respiratory diseases: a systematic review and meta-analysis. *BMJ Open Respir Res* 2025;**12**:e002528. doi:10.1136/bmjresp-2024-002528

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjresp-2024-002528).

Received 25 April 2024
Accepted 7 January 2025

[1]Department of Medicine, The University of Tennessee Graduate School of Medicine, Knoxville, Tennessee, USA
[2]Surgery, The University of Tennessee Graduate School of Medicine, Knoxville, Tennessee, USA
[3]Preston Medical Library, Graduate School of Medicine, University of Tennessee Medical Center, Knoxville, Tennessee, USA

Correspondence to
Professor Rajiv Dhand; rdhand@utmck.edu

ABSTRACT

Background An estimated 10–30% of people with COVID-19 experience debilitating long-term symptoms or long covid. Underlying health conditions associated with chronic inflammation may increase the risk of long covid.

Methods We conducted a systematic review and meta-analysis to examine whether long covid risk was altered by pre-existing asthma or chronic obstructive pulmonary disease (COPD) in adults. We identified studies by searching the PubMed and Embase databases from inception to 13 September 2024. We excluded studies that focused on children or defined long covid only in terms of respiratory symptoms. We used random-effects, restricted maximum likelihood models to analyse data pooled from 51 studies, which included 43 analyses of asthma and 30 analyses of COPD. The risk of bias was assessed using a ROBINS-E table.

Results We found 41% increased odds of long covid with pre-existing asthma (95% CI 1.29 to 1.54); pre-existing COPD was associated with 32% increased odds (95% CI 1.16 to 1.51). Pre-existing asthma, but not COPD, was associated with increased odds of long covid-associated fatigue. We observed heterogeneity in the results of studies of asthma related to hospitalisation status. Potential confounding and inconsistent measurement of exposure and outcome variables were among the identified limitations.

Conclusions Our findings support the hypothesis that pre-existing asthma and COPD increase the risk of long covid, including chronic fatigue outcomes in patients with asthma. Because COVID-19 targets the respiratory tract, these inflammatory conditions of the lower respiratory tract could provide mechanistic clues to a common pathway for the development of long-term sequelae in patients with long covid.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Long covid is fast becoming one of the world's major chronic diseases. Data from recent studies, along with emerging information regarding the biological underpinnings of long covid, suggest that pre-existing inflammatory lung diseases may increase the risk of long covid.

WHAT THIS STUDY ADDS

⇒ Our findings support the hypothesis that asthma and COPD increase the risk of long covid, including chronic fatigue outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Millions of adults with asthma or COPD may be at a higher risk of acquiring long covid after suffering from COVID-19. Studies to determine the pathogenesis of this new condition are urgently needed, as are measures to prevent and mitigate its effects.

INTRODUCTION

As of December 2023, there have been over 770 million confirmed cases of COVID-19 and approximately 7 million related deaths, with typically thousands of new cases reported each week.[1] Approximately 10–30% of people with COVID-19 experience debilitating long-term symptoms, a disorder that has been called long covid, post-COVID conditions (PCC) or post-acute sequelae of SARS-CoV-2 infection (PASC). This suggests that 77–231 million people worldwide have suffered from long covid, including as many as 23 million people currently in the USA.[2]

According to the US Centres for Disease Control and Prevention (CDC), long covid is a wide range of new, returning or ongoing health problems that people experience at least 3 months after being infected with SARS-CoV-2,[3] whereas the WHO defines long covid as the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection, with these symptoms lasting for at least 2 months with no other explanation.[4] Most recently, the US National Academies of Sciences, Engineering and Medicine defined long covid as an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one of more organ systems.[5 6] Symptoms of long covid may include persistent cough, malaise, fatigue, breathing difficulties, cardiovascular abnormalities, kidney disease, diabetes, neurological, cognitive

and/or mental health impairments.[7] Even mild cases of COVID-19 can lead to long covid, and the pathogenic mechanisms underlying the development of long covid remain poorly understood.[8]

According to the US National Institutes of Health, suspected and emerging risk factors for long covid include older age, female sex, the severity of COVID illness, the immune response to the initial SARS-CoV-2 infection and certain underlying health conditions associated with chronic inflammation, such as diabetes, autoimmune disease and asthma.[7] Regarding asthma, multiple pro-inflammatory pathways contribute to its development,[9] and some investigators have suggested that the association between asthma and long covid is particularly notable.[10] Therefore, we conducted a systematic review and meta-analysis to determine whether adult patients with asthma had altered risk of developing long covid. Because immune dysregulation underlies both asthma and long covid,[11 12] we separately examined whether another chronic lower respiratory tract inflammatory condition, pre-existing chronic obstructive pulmonary disease (COPD), was associated with long covid. Indeed, Tsampasian and colleagues[13] have suggested that the presence of pre-existing COPD also increases the risk of long covid. To account for different case definitions of long covid, we analysed the association according to the length of time symptoms were assessed after the initial COVID infection. Because 'fatigue' was the most addressed non-respiratory long covid outcome in published studies, we also examined the associations of pre-existing asthma and COPD with long covid-associated fatigue.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This review was completed without a protocol and was not registered. Electronic searching of the PubMed/MEDLINE and Embase (Elsevier) databases took place on 13 September 2024 and included studies published from inception to that date. The search strategy was first created in PubMed (online supplemental appendix 1) and then translated into Embase based on keywords and controlled vocabulary for long covid, asthma and COPD. Manual searches of reference lists were conducted on all eligible articles following the screening.

All articles retrieved from the database searches were imported into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia; available at www.covidence.org). Covidence identified 109 duplicates, and two additional duplicates were marked and removed manually. One author screened the titles and abstracts against the inclusion and exclusion criteria. Titles meeting the inclusion criteria had their full text retrieved for further screening by two authors. If the full text continued to meet the study inclusion criteria, data were extracted for analysis. The same two authors extracted data from the included studies. Any disagreements related to these tasks were discussed among the two authors, with a third author available to make a final decision if an agreement could not be reached.

Eligible studies provided risk estimates that directly addressed the association between pre-existing asthma or COPD and the risk of long covid. When risk ratio estimates were not published, we included studies that provided raw data from which ratio estimates could be calculated. We did not consider studies that focused primarily on children, those that examined asthma or COPD initiation or exacerbation due to long covid, those with a study population that overlapped with that of another publication, those that combined all chronic lung diseases into a single exposure, those that defined long covid only in terms of respiratory symptoms and those that did not present measures of association for asthma or COPD and did not present raw data sufficient for their secondary calculation. In this way, we identified 51 studies of pre-existing lower respiratory tract diseases and long covid[14–64] that included 43 analyses of asthma[14–21 23–31 33 34 36 38–44 48–53 55–64] and 30 analyses of COPD.[14 17 22 24–27 30 32 35 37 39–43 45–47 50–54 56 59 61–64] Four analyses examined asthma and COPD combined.[25 26 53 62] In sensitivity analyses, the latter four studies were excluded in both asthma and COPD analyses to determine whether results were meaningfully altered by their exclusion. We also ran a separate model including only those four studies as a comparison with the results of the full analyses for both asthma and COPD.

General information regarding the studies, including study location, sample size, exposure and outcome assessment, and possible sources of bias, was abstracted and summarised (online supplemental table 1). The risk of bias was more formally assessed using the ROBINS-E (ROB, risk of bias in non-randomised studies of exposure),[65] and the resulting table is shown in online supplemental appendix 2. ROB was completed by two authors. Each study was assessed for the presence of subanalyses according to specific long covid symptoms related to chronic fatigue.

Patient and public involvement

Neither patients nor members of the public were involved in the present study.

Statistical methods

The extrapolated data from the studies that met inclusion and exclusion criteria were collated in an Excel database for statistical purposes. Measures of relative risk, including risk ratios, ORs and HRs, were extrapolated when presented in studies. We calculated risk estimates when studies presented only the raw data required for their calculation. The meta suite of functions (forest plot, funnel plot and bias) in Stata (College Station, TX: StataCorp, LCC) was used to

perform a series of meta-analyses using the random-effects, restricted maximum likelihood model. ORs with 95% CIs were the primary outcomes derived from each of the studies and included in the meta-analyses. We conducted sub-analyses of the data according to the duration of symptoms after the initial diagnosis of COVID-19 that each study used to define the presence of long covid. For this analysis, categories of follow-up time were 3+ weeks, 12+ weeks and 26+ weeks. To examine the heterogeneity of study results according to hospitalisation status, study populations in which less than 25% had been hospitalised with COVID-19 in the weeks or months prior to the assessment of long covid were considered 'not hospitalised', whereas study populations in which more than 75% were hospitalised with COVID-19 were considered 'hospitalised'. Pooled effects for the OR and 95% CI were reported and interpreted for each meta-analysis. Heterogeneity across the studies examined in each meta-analysis was assessed using Cochran's Q and I^2 statistics. Publication bias was assessed using funnel plots and Begg's test. Forest plots were generated to present the results of meta-analyses, along with the respective weighting of each study expressed as a percentage. Sensitivity analyses were specified in an *a priori* fashion. Statistical significance was assumed at an alpha value of 0.05.

RESULTS

The PRISMA flow chart (figure 1) shows the number of reports at each stage of the screening process. Database searches identified 704 records, and an additional two references were found through citation searches. An automation tool removed 111 records prior to screening, and 463 were excluded at the end of the abstract screening stage. The remaining 130 records were evaluated based on their full-text content, and an additional three duplicate studies missed by automation were excluded, as well as 72 records with the wrong outcome reported (ie, not statistically reporting risk of long covid), five with inappropriate study design (ie, combining various chronic lung diseases in analysis) and one report was not in English language. A total of 51 articles were included in the evaluation. These studies varied in their sample size, the percentage of participants hospitalised due to their initial infection with SARS-CoV-2, and the methods by which information on exposure and outcome variables were obtained (online supplemental table 1).

Pre-existing asthma was associated with a statistically significant 41% increased odds of long covid in our meta-analysis of data from 43 epidemiologic studies (pooled OR=1.41, 95% CI 1.29 to 1.54, p<0.001; figure 2). Similarly, pre-existing COPD was associated with a statistically significant 32% increased odds of long covid in 30 epidemiologic studies (pooled OR=1.32, 95% CI 1.16 to 1.51, p<0.001; figure 3). Significant heterogeneity was detected for the asthma pooled effect, $Q(42)$ = 269.64, p<0.001, and the COPD pooled effect, $Q(42)$ = 269.64, p<0.001, I^2=89.87%. There was no evidence of publication bias for the asthma analysis, z=0.96, p=0.34 or the COPD analysis, z=0.54, p=0.59. The inclusion of the four studies that combined asthma and COPD into a single exposure did not meaningfully alter the results of these analyses. A separate meta-analysis of these four studies did not yield a significant effect, pooled OR=1.33, 95% CI 0.93 to 1.90;

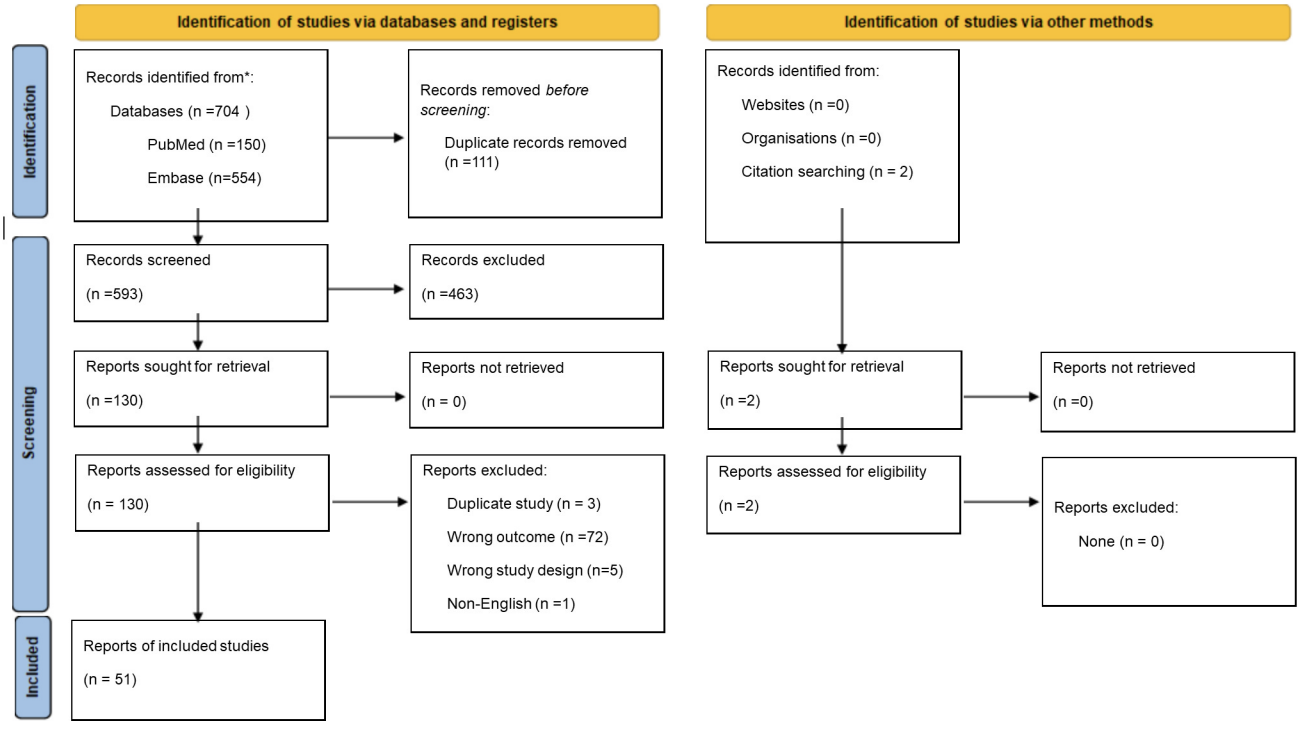

Figure 1 Data acquisition Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 flow diagram.

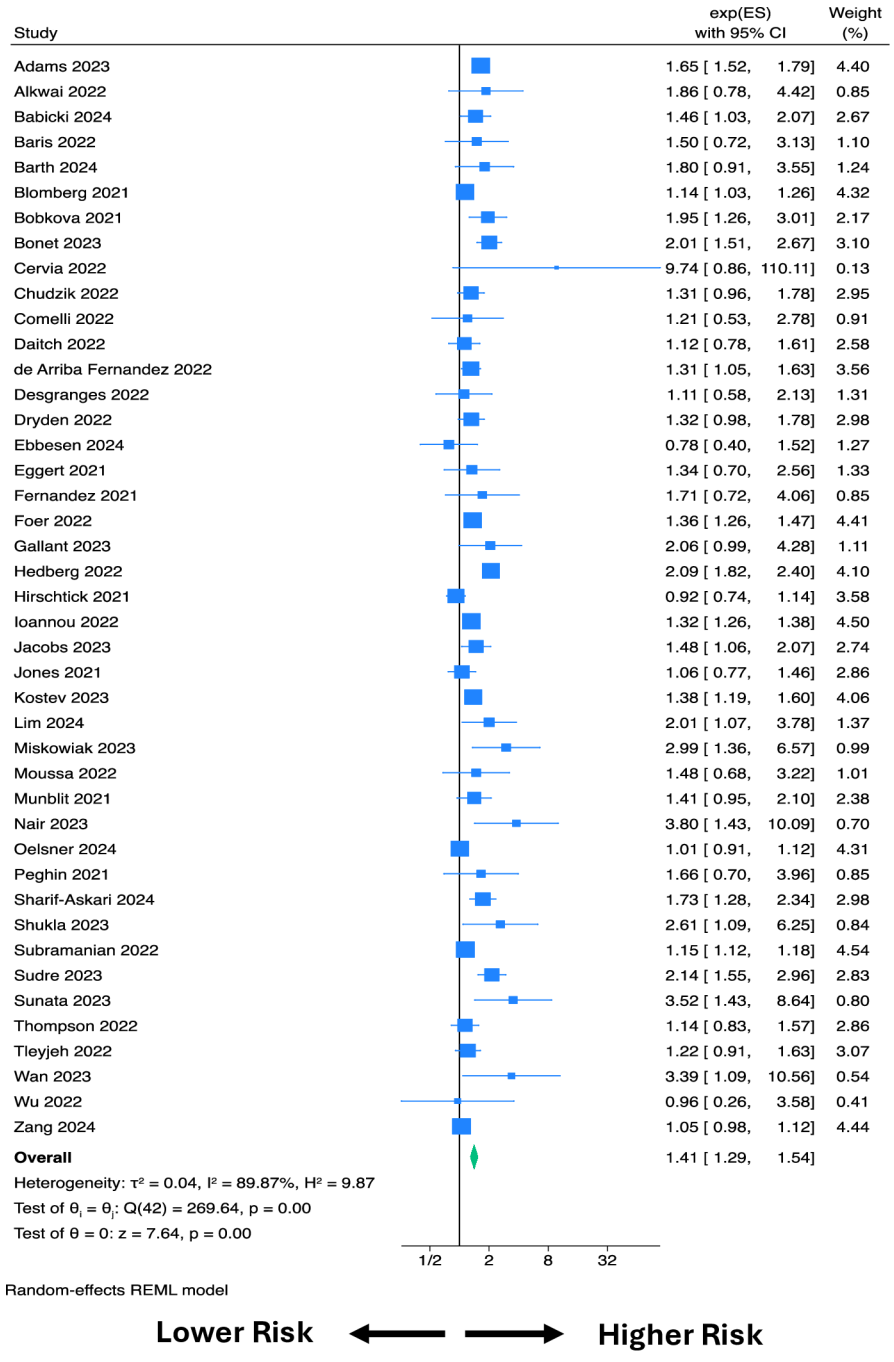

Figure 2 ORs of pre-existing asthma in adult patients with long covid.

there was no evidence of heterogeneity, Q(3) = 3.70, p=0.30, I^2=13.16%, or publication bias, z=1.70, p=0.09.

In the analysis of data from a subset of eight studies, pre-existing asthma was associated with a statistically significant 30% increased odds of chronic fatigue-related symptoms and disabilities related to COVID-19 (pooled OR=1.30, 95% CI 1.14 to 1.49, p<0.001; figure 4). There was significant heterogeneity associated with the asthma pooled effect, $Q(7)$ = 19.39, p=0.01, I^2=56.99%. No evidence of publication bias was detected for the association with asthma-related fatigue, z=0.37, p=0.71. Six studies focused on pre-existing COPD and led to a statistically non-significant 13% increased odds of long covid-related chronic fatigue (pooled OR=1.13, 95% CI 0.68 to 1.89, p=0.63; significant heterogeneity, $Q(5)$ = 19.88, p<0.001, I^2=83.29; there was no evidence of publication bias, z=−1.50, p=0.26; figure 5).

The minimum duration of long covid-defining symptoms following the initial COVID diagnosis to be considered 'long covid' also varied among studies (online

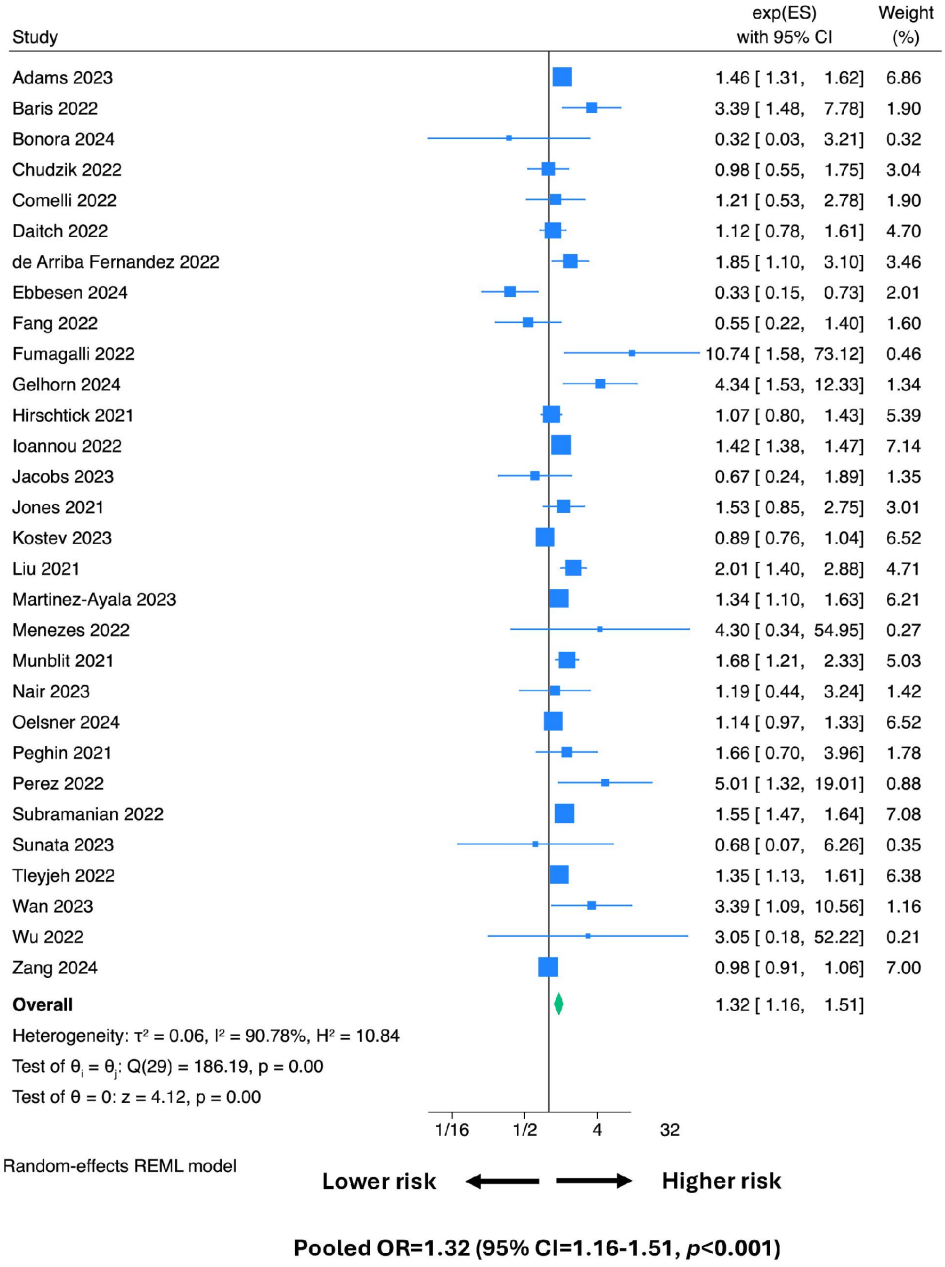

Figure 3 ORs of pre-existing chronic obstructive pulmonary disease in adult patients with long covid.

supplemental table 1). Studies of asthma that considered a minimum of 3 weeks of symptoms to be long covid showed a significant pooled effect (pooled OR=1.44, 95% CI 1.23 to 1.70, p<0.001; significant heterogeneity, $Q(15) = 77.65$, p<0.001, I^2=85.69%), as well as with a minimum of 12+ weeks (pooled OR=1.40, 95% CI 1.24 to 1.58, p<0.001; significant heterogeneity, $Q(18) = 175.32$, p<0.001, I^2=91.39%) and at a minimum of 26+ weeks (pooled OR=1.47, 95% CI 1.09 to 1.98, p<0.001; significant heterogeneity, $Q(7) = 16.00$, p=0.03, I^2=60.33%; table 1). There was no significant evidence of publication bias for the asthma results at 3+ weeks, z=0.77, p=0.44, 12+weeks, z=−0.14, p=0.94, or 26+weeks, z=1.36, p=0.17. The results according to follow-up time in studies of COPD were weaker and less consistent regarding their statistical significance (4+ weeks pooled OR=1.22, 95% CI 1.02 to 1.46, p=0.03; 12+ weeks pooled OR=1.41, 95% CI 1.16 to 1.72, p<0.001; and 26+weeks pooled OR=1.19, 95% CI 0.71 to 1.98, p=0.51) (table 1). Significant heterogeneity was detected at 4+ weeks, $Q(7) = 21.43$, p<0.001, I^2=61.35%, 12+ weeks, $Q(10) = 63.72$, p<0.001, I^2=95.19% and 26+ weeks, $Q(10) = 32.30$, p<0.001, I^2=80.30% for the COPD analyses. There was no evidence of publication bias for the COPD studies at 4+ weeks, z=0.62, p=0.054; 13+ weeks, z=0.62, p=0.53; or 26+ weeks, z=−0.16, p=1.00.

We found significant heterogeneity of results in studies of asthma according to whether patients were hospitalised due to COVID-19. Ten studies that examined asthma among patients who were mostly hospitalised with COVID-19[20 21 27 29 30 36 49 50 59] showed a pooled

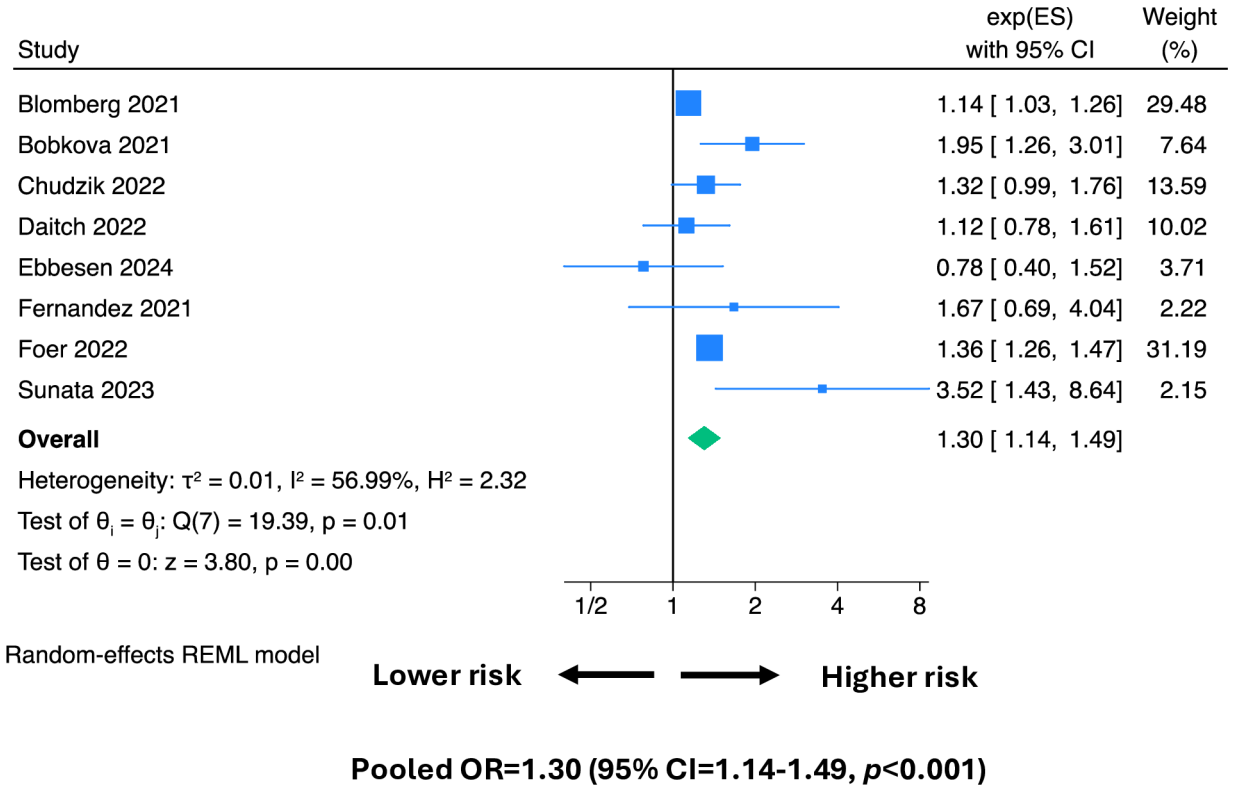

Figure 4 ORs of pre-existing asthma in adult patients with long covid defined by fatigue.

OR of 1.55 (95% CI 1.30 to 1.86), whereas 14 studies in which participants were mostly not hospitalised for their COVID-19[15 16 18 19 24 34 40 42 51 52 56 60 61] showed a pooled OR of 1.32 (95% CI 1.16 to 1.49). The meta-analysis for non-hospitalised patients showed significant heterogeneity ($Q[13] = 121.27$ $p<0.001$, I^2=94.22%, but no heterogeneity was found for hospitalised patients, $Q[9] = 15.63$, p=0.08, I^2=38.71%. There was no evidence of publication bias for either group (not hospitalised, z=0.88, p=0.38; hospitalised, z=0.89, p=0.37). With regard to non-hospitalised patients with COPD, there was a pooled OR of 1.38, 95% CI 1.24 to 1.55, p<0.001; significant heterogeneity,

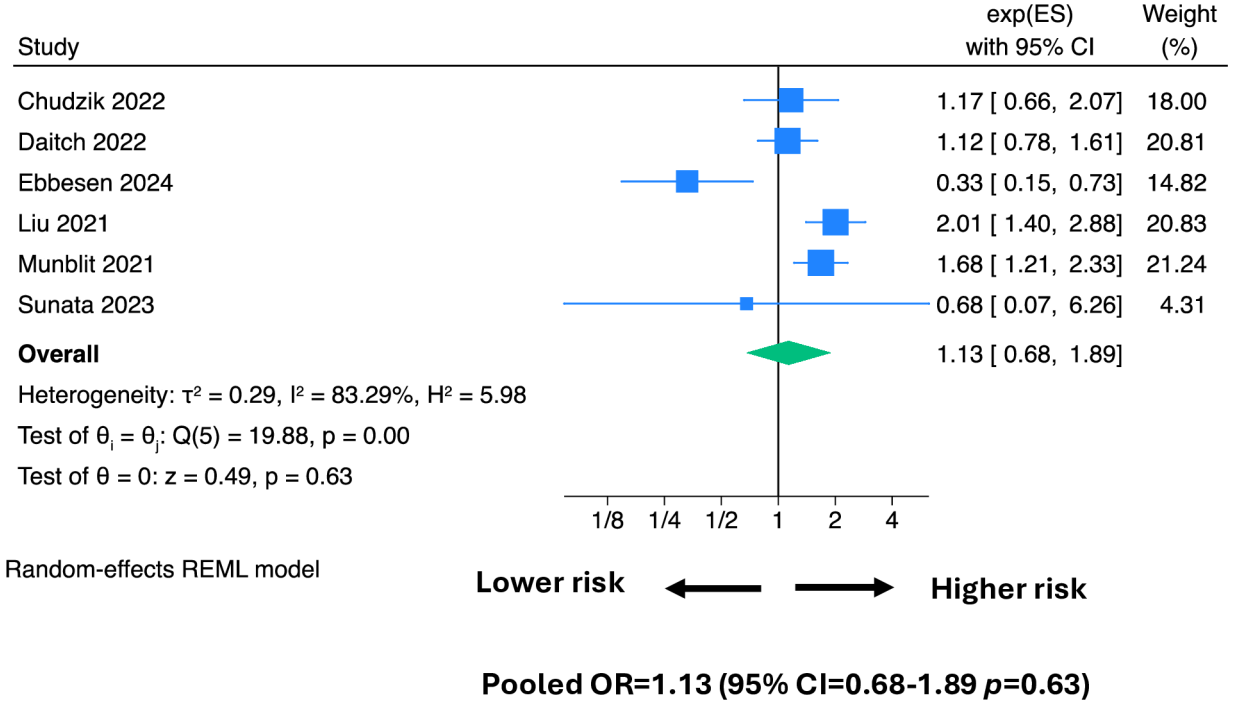

Figure 5 ORs of pre-existing chronic obstructive pulmonary disease in adult patients with long covid defined by fatigue.

Table 1 Results of epidemiologic studies in adults with asthma and chronic obstructive pulmonary disease according to the duration of follow-up for long covid

Pre-existing diagnosis	Weeks of follow-up	Pooled OR (95% CI) long covid	P value
Asthma			
	3+ weeks (16 studies)	1.44 (1.23–1.70)	< 0.001
	12+ weeks (19 studies)	1.40 (1.24–1.58	< 0.001
	26+ weeks (eight studies)	1.47 (1.09–1.98)	< 0.001
COPD			
	4+ weeks (eight studies)	1.22 (1.02–1.46)	0.03
	12+ weeks (11 studies)	1.41 (1.16–1.72)	< 0.001
	26+ weeks (11 studies)	1.19 (0.71–1.98)	0.51

COPD, chronic obstructive pulmonary disease.

$Q[7] = 22.79$, p<0.001, I^2=79.98%; there was no evidence of publication bias, z=1.11, p=0.27. In hospitalised COPD patients, a non-significant effect was detected (pooled OR=1.34, 95% CI 0.72 to 2.51, p=0.36; significant heterogeneity, $Q[8] = 31.33$, p<0.001, I^2=85.32; there was no evidence of publication bias, z=−0.31, p=0.92) (data not shown).

DISCUSSION

The results of our meta-analysis of 51 epidemiological studies support the hypothesis that pre-existing asthma and COPD confer moderate, approximately 30–40% increased risks of long covid in adults. Although most of the studies we analysed did not distinguish which of the long covid-defining symptoms were associated most directly with these exposures, eight studies that separately examined chronic fatigue showed a statistically significant 30% increased risk among COVID patients with pre-existing asthma.

Globally, there are approximately 300 million people living with asthma[66] and approximately 400 million people living with COPD.[67] We found that asthma and COPD are associated with approximately 30% to 40% increased odds of developing long covid. As such, millions of adults with asthma or COPD have acquired and/or are at higher risk of acquiring long covid after suffering from COVID-19. Although results were not statistically significant, a recently published meta-analysis found that pre-existing asthma increased odds of long covid by 42% in children and adolescents, which is similar to the 41% increased odds we observed among adults in our meta-analyses.[68] Studies to determine the pathogenesis of this new condition are urgently needed, as are measures to prevent and mitigate its effects.

Possible causes suggested for the development of long covid include persisting SARS-CoV-2 in tissues; reactivation of dormant viruses; deleterious alterations in the microbiota; microvascular blood clotting with endothelial dysfunction; dysfunctional signalling in the brainstem and/or vagus nerve; and immune dysregulation and autoimmunity and consequent long-term inflammation.[69 70] However, the mechanisms by which pre-existing lower respiratory tract diseases, such as asthma or COPD, may increase the risk of long covid remain speculative. Because inflammation and immune system abnormalities underlie asthma, COPD and long covid, investigators have speculated that shared immuno-inflammatory mechanisms may explain asthma patients' predisposition to the long-term neurological sequelae of COVID-19. For example, laboratory findings linked to an inflammatory profile have also been found to increase the risk of long covid, such as a significant decrease in total lymphocyte counts—especially CD4+T cells and CD8+T cells—and an increase in LDH, CRP and IL-6 levels, as well as IL-1, TNF-a, IP10 and mast cell activation,[69 71 72] factors that have also been shown to underlie sub-types of asthma and/or COPD.[73 74] Additionally, our analyses suggest that pre-existing asthma increases the risk of COVID-related chronic fatigue. Asthma-related type 2 cytokines (eg, IL-4, IL-5 and IL-13) can reach the anterior cingulate cortex, basolateral amygdala and other brain regions, and activate microglia and astrocytes, which has led investigators to speculate that the lung-brain axis may increase susceptibility to persistent fatigue in long covid in patients with asthma.[59]

Heterogeneity of study results was detected in several of our primary and sensitivity analyses and should be considered when making inferences based on the subsequent pooled effects. Asthma patients who were hospitalised with COVID-19 showed a higher risk of long covid than those who were not hospitalised during the acute illness phase, which is a notable source of heterogeneity observed in our analyses. Indeed, the CDC states that COVID-19 severity is associated with a risk of long covid, including related autoimmune conditions.[3] However, whether asthma or its inflammatory underpinning may interact synergistically in the development of long covid with factors that determine COVID-19 severity, as is suggested by our previous observations,[75 76] remains unclear. In a previous publication, we noted that severe

or uncontrolled asthma increased the severity and potential fatality of COVID.[76] Likewise, the use of biologicals for the treatment of asthma appeared to increase the risk. Inhaled corticosteroids, on the other hand, had a dual effect. There was an associated increased severity of COVID-19 with ICS use, but paradoxically, mortality was reduced.[76] This discrepancy could be due to differences in pharmacodynamic and pharmacokinetic properties of ICS.[77] In the present study, we found an increased odds of long covid in patients with asthma, but we were unable to categorise the odds by the severity of illness, other than hospitalisation status, and the dose and therapeutic indices of ICS used to treat the disease in the studies were not provided. However, asthma patients treated with monoclonal drugs and/or corticosteroids during the acute phase of COVID-19 were found to have decreased risk and duration of long covid in two European cohort studies,[21 78] which further suggests a link between lung inflammation and long covid. In addition, the presence of eosinophils is related to autoimmune and allergic diseases, which is consistent with the pathophysiology of long covid and may also help to explain the increased risk in patients with asthma and COPD.[21 79]

The studies we analysed had several limitations. Individual studies were susceptible to bias from several courses (online supplemental table 1; Online supplemental appendix 2). Among the potentially most influential of these, not all studies used multivariable models to adjust risk estimates for potential confounding; however, studies that did use multivariable adjustment did not tend to show meaningful differences in results from those that did not. In addition, the measurement of COVID-19, asthma, COPD and long covid varied among studies. For example, the type of asthma (atopic, non-atopic) was rarely specified, a limitation because patients with atopic asthma may be at a higher risk of long covid.[21] The severity of asthma and COPD and the use of medications to control these conditions were also rarely assessed. Studies also did not address severity of long covid symptoms, whether participants were reinfected with SARS-CoV-2 during follow-up so that treatment or symptoms of reinfections were not misclassified as long-COVID or the influence of intercurrent conditions on long covid assessment. Moreover, studies did not identify the predominant SARS-CoV-2 variants that infected their study populations. In the past 3 years, COVID-19 has evolved through several strains and sub-strains that caused illness of varying severity.[80] Because factors that influence the course or severity of COVID-19 may modify associations of lower respiratory conditions with long covid, evolving SARS-CoV-2 variants may be a source of heterogeneity in study results. Along these lines, few studies have considered study participant vaccination status or the use of anti-viral medications during the initial infection. Given these limitations, we recommend additional longitudinal studies conducted in well-defined populations with outcomes assessed prospectively and repeatedly during follow-up. Standardised measures of long covid are also recommended, including its various physical, neurological, behavioural and psychological manifestations, study participants' vaccine and treatment status, and the underlying SARS-CoV-2 variants.

In conclusion, our analyses of data pooled from studies published over the past 3 years supports the hypothesis that chronic inflammatory diseases of the lower respiratory tract, namely, asthma and COPD, increase the risk of developing long covid, including chronic fatigue outcomes. Because COVID-19 primarily targets the respiratory tract, these highly prevalent inflammatory conditions of the lower respiratory tract could provide mechanistic clues to a common pathway for the development of the long-term sequelae in patients with long covid.

Contributors RD and PT formulated study research questions. PT and AQ searched for literature. PT and REH independently read full texts, extracted data and evaluated studies for potential bias. PT, REH and RD analysed the data. PT and RD created the first manuscript draft, and all authors were involved in continued drafting the manuscript. PT is the guarantor of the work.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was determined to be 'Exempt' by the University of Tennessee Graduate School of Medicine institutional review board.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available.

ORCID iDs
Paul Terry http://orcid.org/0000-0002-0353-9197
R Eric Heidel http://orcid.org/0000-0002-1518-8072
Alexandria Q Wilson http://orcid.org/0000-0002-2649-8252
Rajiv Dhand http://orcid.org/0000-0002-3621-2422

REFERENCES

1 World Health Organization. WHO COVID-19 dashboard. Available: https://covid19.who.int/ [Accessed 11 Dec 2024].
2 U.S. Government Accountability Office. Long COVID. Science & tech spotlight: long COVID. U.S GAO. Available: https://www.gao.gov/products/gao-22-105666 [Accessed 11 Dec 2024].
3 Centers for Disease Control and Prevention. Long COVID or post-COVID conditions. Available: https://www.cdc.gov/covid/long-term-effects/?CDC_AAref_Val=https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html [Accessed 11 Dec 2024].
4 World Health Organization. Post COVID-19 condition (long COVID). Available: https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition [Accessed 11 Dec 2024].
5 National Academies of Sciences, Engineering, and Medicine (NASEM). *A long COVID definition: a chronic, systemic disease state with profound consequences*. Washington, DC: The National

Academies Press, 2024. Available: https://nap.nationalacademies.org/read/27768/chapter/2#2 [accessed 11 Dec 2024].
6 Ely EW, Brown LM, Fineberg HV, *et al*. Long Covid Defined. *N Engl J Med* 2024;391:1746–53.
7 National Institutes of Health. Long COVID. Available: https://covid19.nih.gov/covid-19-topics/long-covid#what-we-know-about-long-covid-1 [Accessed 11 Dec 2024].
8 Szabo S, Zayachkivska O, Hussain A, *et al*. What is really "Long COVID"? *Inflammopharmacology* 2023;31:551–7.
9 Peebles RS, Aronica MA. Proinflammatory Pathways in the Pathogenesis of Asthma. *Clin Chest Med* 2019;40:29–50.
10 Chen C, Haupert SR, Zimmermann L, *et al*. Global Prevalence of Post-Coronavirus Disease 2019 (COVID-19) Condition or Long COVID: A Meta-Analysis and Systematic Review. *J Infect Dis* 2022;226:jiac136:1593–607:.
11 Davitt E, Davitt C, Mazer MB, *et al*. COVID-19 disease and immune dysregulation. *Best Pract Res Clin Haematol* 2022;35:101401.
12 Chang Y-S, Turturice B, Schott C, *et al*. Immune network dysregulation precedes clinical diagnosis of asthma. *Sci Rep* 2020;10:12784.
13 Tsampasian V, Elghazaly H, Chattopadhyay R, *et al*. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med* 2023;183:566–80.
14 Adams ML, Grandpre J. Prevalence of covid-19 and long covid - results from the 2022 behavioral risk factor surveillance system, 50 states. *Infectious Diseases (except HIV/AIDS)* [Preprint].
15 Alkwai HM, Khalifa AM, Ahmed AM, *et al*. Persistence of COVID-19 symptoms beyond 3 months and the delayed return to the usual state of health in Saudi Arabia: a cross-sectional study. *Sage Open Med* 2022;8:10.
16 Babicki M, Kołat D, Kałuzińska-Kołat Ż, *et al*. The Course of COVID-19 and Long COVID: Identifying Risk Factors among Patients Suffering from the Disease before and during the Omicron-Dominant Period. *Pathogens* 2024;13:267.
17 Baris SA, Toprak OB, Cetinkaya PD, *et al*. The predictors of long–COVID in the cohort of Turkish Thoracic Society– TURCOVID multicenter registry. *Asian Pac J Trop med* 2022;15:400–9.
18 Barth S, Kulie P, Monroe A, *et al*. Prevalence and risk factors for post-COVID conditions of COVID-19 among persons with HIV in Washington, DC. *AIDS Care* 2024;1–11.
19 Blomberg B, Mohn KG-I, Brokstad KA, *et al*. Long COVID in a prospective cohort of home-isolated patients. *Nat Med* 2021;27:1607–13.
20 Bobkova P, Spiridonova E, Shihaleva A, *et al*. Asthma may influence long-term consequences of COVID-19 in hospitalised adult. *Allergy* 2021;76:476.
21 Badenes Bonet D, Caguana Vélez OA, Duran Jordà X, *et al*. Treatment of COVID-19 during the Acute Phase in Hospitalized Patients Decreases Post-Acute Sequelae of COVID-19. *J Clin Med* 2023;12:4158.
22 Bonora BM, Marassi M, Fogar P, *et al*. Circulating haematopoietic stem cells and long-term outcomes of COVID-19. *Eur J Clin Invest* 2024;54:e14150.
23 Cervia C, Zurbuchen Y, Taeschler P, *et al*. Immunoglobulin signature predicts risk of post-acute COVID-19 syndrome. *Nat Commun* 2022;13:446.
24 Chudzik M, Babicki M, Kapusta J, *et al*. Long-COVID Clinical Features and Risk Factors: A Retrospective Analysis of Patients from the STOP-COVID Registry of the PoLoCOV Study. *Viruses* 2022;14:1755.
25 Comelli A, Viero G, Bettini G, *et al*. Patient-Reported Symptoms and Sequelae 12 Months After COVID-19 in Hospitalized Adults: A Multicenter Long-Term Follow-Up Study. *Front Med (Lausanne)* 2022;9:834354.
26 Daitch V, Yelin D, Awwad M, *et al*. Characteristics of long-COVID among older adults: a cross-sectional study. *Int J Infect Dis* 2022;125:287–93.
27 de Arriba Fernández A, Alonso Bilbao JL, Espiñeira Francés A, *et al*. Assessment of SARS-CoV-2 Infection According to Previous Metabolic Status and Its Association with Mortality and Post-Acute COVID-19. *Nutrients* 2022;14:2925.
28 Desgranges F, Tadini E, Munting A, *et al*. Post-COVID-19 Syndrome in Outpatients: a Cohort Study. *J Gen Intern Med* 2022;37:1943–52.
29 Dryden M, Mudara C, Vika C, *et al*. Post-COVID-19 condition 3 months after hospitalisation with SARS-CoV-2 in South Africa: a prospective cohort study. *Lancet Glob Health* 2022;10:e1247–56.
30 Ebbesen BD, Giordano R, Hedegaard JN, *et al*. Prevalence and Risk Factors of Multitype Post-COVID Pain in a Cohort of Previously Hospitalized COVID-19 Survivors: A Danish Cross-Sectional Survey. *J Pain* 2024;25:104579.
31 Eggert LE, He Z, Collins W, *et al*. Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19. *Allergy* 2022;77:173–85.
32 Fang X, Ming C, Cen Y, *et al*. Post-sequelae one year after hospital discharge among older COVID-19 patients: A multi-center prospective cohort study. *J Infect* 2022;84:179–86.
33 Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, *et al*. Long-term post-COVID symptoms and associated risk factors in previously hospitalized patients: A multicenter study. *J Infect* 2021;83:237–79.
34 Foer D, Wang L, Karlson EW, *et al*. Post-acute covid-19 symptoms in patients with asthma: a natural language processing-based study. *Am J Respir Crit Care Med* 2022.
35 Fumagalli C, Zocchi C, Tassetti L, *et al*. Factors associated with persistence of symptoms 1 year after COVID-19: A longitudinal, prospective phone-based interview follow-up cohort study. *Eur J Intern Med* 2022;97:36–41.
36 Gallant M, Mercier K, Rioux-Perreault C, *et al*. Prevalence of persistent symptoms at least 1 month after SARS-CoV-2 Omicron infection in adults. *J Assoc Med Microbiol Infect Dis Can* 2023;8:57–63.
37 Gelhorn HL, Ghafoori P, Cutts K, *et al*. Characterizing health-related quality of life and identifying disease predictors among patients suspected of having long COVID: an analysis of COMET-ICE clinical trial data. *Front Public Health* 2024;12:1278106.
38 Hedberg P, Granath F, Bruchfeld J, *et al*. Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection. *J Intern Med* 2023;293:246–58.
39 Hirschtick JL, Titus AR, Slocum E, *et al*. Population-Based Estimates of Post-acute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Infection (PASC) Prevalence and Characteristics. *Clin Infect Dis* 2021;73:ciab408:2055–64:.
40 Ioannou GN, Baraff A, Fox A, *et al*. Rates and Factors Associated With Documentation of Diagnostic Codes for Long COVID in the National Veterans Affairs Health Care System. *JAMA Netw Open* 2022;5:e2224359.
41 Jacobs ET, Catalfamo CJ, Colombo PM, *et al*. Pre-existing conditions associated with post-acute sequelae of COVID-19. *J Autoimmun* 2023;135:102991.
42 Jones R, Davis A, Stanley B, *et al*. Risk Predictors and Symptom Features of Long COVID Within a Broad Primary Care Patient Population Including Both Tested and Untested Patients. *POR* 2021;Volume 12:93–104.
43 Kostev K, Smith L, Koyanagi A, *et al*. Prevalence of and Factors Associated With Post-Coronavirus Disease 2019 (COVID-19) Condition in the 12 Months After the Diagnosis of COVID-19 in Adults Followed in General Practices in Germany. *Open Forum Infect Dis* 2022;9:ofac333.
44 Lim SH, Lim YC, Zaki RA, *et al*. Prevalence and predictors of post-acute COVID syndrome among infected healthcare workers at University Malaya Medical Centre. *PLoS One* 2024;19:e0298376.
45 Liu Y-H, Wang Y-R, Wang Q-H, *et al*. Post-infection cognitive impairments in a cohort of elderly patients with COVID-19. *Mol Neurodegener* 2021;16:48.
46 Martinez-Ayala MC, Proanos NJ, Cala-Duran J, *et al*. Factors associated with long COVID syndrome in a Colombian cohort. *Front Med (Lausanne)* 2023;10:1325616.
47 Menezes AS Jr, Botelho SM, Santos LR, *et al*. Acute COVID-19 Syndrome Predicts Severe Long COVID-19: An Observational Study. *Cureus* 2022;14:e29826.
48 Miskowiak KW, Pedersen JK, Gunnarsson DV, *et al*. Cognitive impairments among patients in a long-COVID clinic: Prevalence, pattern and relation to illness severity, work function and quality of life. *J Affect Disord* 2023;324:162–9.
49 Moussa I, Znegui T, Sahnoun I, *et al*. 2022 Predictive factors for long COVID in adults previously hospitalized for COVID-19. *Eur Resp J*:3133.
50 Munblit D, Bobkova P, Spiridonova E, *et al*. Incidence and risk factors for persistent symptoms in adults previously hospitalized for COVID-19. *Clin Experimental Allergy* 2021;51:1107–20.
51 Nair P, Nair CV, Kulirankal KG, *et al*. Characterization and predictive risk scoring of long COVID in a south indian cohort after breakthrough COVID infection; a prospective single centre study. *BMC Infect Dis* 2023;23:670.
52 Oelsner EC, Sun Y, Balte PP, *et al*. Epidemiologic Features of Recovery From SARS-CoV-2 Infection. *JAMA Netw Open* 2024;7:e2417440.
53 Peghin M, Palese A, Venturini M, *et al*. Post-COVID-19 symptoms 6 months after acute infection among hospitalized and non-hospitalized patients. *Clin Microbiol Infect* 2021;27:1507–13.

54 Pérez-González A, Araújo-Ameijeiras A, Fernández-Villar A, *et al*. Long COVID in hospitalized and non-hospitalized patients in a large cohort in Northwest Spain, a prospective cohort study. *Sci Rep* 2022;12:3369.
55 Saheb Sharif-Askari F, Ali Hussain Alsayed H, Saheb Sharif-Askari N, *et al*. Risk factors and early preventive measures for long COVID in non-hospitalized patients: analysis of a large cohort in the United Arab Emirates. *Public Health (Fairfax)* 2024;230:198–206.
56 Subramanian A, Nirantharakumar K, Hughes S, *et al*. Symptoms and risk factors for long COVID in non-hospitalized adults. *Nat Med* 2022;28:1706–14.
57 Shukla AK, Atal S, Banerjee A, *et al*. An observational multi-centric COVID-19 sequelae study among health care workers. *Lancet Reg Health Southeast Asia* 2023;10:100129.
58 Sudre CH, Murray B, Varsavsky T, *et al*. Attributes and predictors of long COVID. *Nat Med* 2021;27:626–31.
59 Sunata K, Miyata J, Terai H, *et al*. Asthma is a risk factor for general fatigue of long COVID in Japanese nation-wide cohort study. *Allergol Int* 2024;73:206–13.
60 Thompson EJ, Williams DM, Walker AJ, *et al*. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. *Nat Commun* 2022;13:3528.
61 Tleyjeh IM, Kashour T, Riaz M, *et al*. Persistent COVID-19 symptoms at least one month after diagnosis: A national survey. *J Infect Public Health* 2022;15:578–85.
62 Wan KS, Sundram ER, Abdul Haddi AA, *et al*. Long COVID active case detection initiative among COVID-19 patients in Port Dickson, Malaysia: a retrospective study on the positive outcomes, the proportion of patients with long COVID and its associated factors. *PeerJ* 2023;11:e14742.
63 Wu Q, Ailshire JA, Crimmins EM. Long COVID and symptom trajectory in a representative sample of Americans in the first year of the pandemic. *Sci Rep* 2022;12:11647.
64 Zang C, Hou Y, Schenck EJ, *et al*. Identification of risk factors of Long COVID and predictive modeling in the RECOVER EHR cohorts. *Commun Med (Lond)* 2024;4:130.
65 Higgins JPT, Morgan RL, Rooney AA, *et al*. A tool to assess risk of bias in non-randomized follow-up studies of exposure effects (ROBINS-E). *Environ Int* 2024;186:108602.
66 Wang Z, Li Y, Gao Y, *et al*. Global, regional, and national burden of asthma and its attributable risk factors from 1990 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Respir Res* 2023;24:169.
67 Adeloye D, Song P, Zhu Y, *et al*. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. *Lancet Respir Med* 2022;10:447–58.
68 Rayner DG, Wang E, Su C, *et al*. Risk factors for long COVID in children and adolescents: a systematic review and meta-analysis. *World J Pediatr* 2024;20:133–42.
69 Davis HE, McCorkell L, Vogel JM, *et al*. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023;21:133–46.
70 Yale Medicine. What happens when you still have long COVID symptoms? Available: https://www.yalemedicine.org/news/long-covid-symptoms#:~:text=Long%20COVID%2C%20the%20condition%20where,intense%20fatigue%2C%20can%20be%20debilitating [Accessed Dec 2023].
71 Schultheiß C, Willscher E, Paschold L, *et al*. The IL-1β, IL-6, and TNF cytokine triad is associated with post-acute sequelae of COVID-19. *Cell Rep Med* 2022;3:100663.
72 Peluso MJ, Lu S, Tang AF, *et al*. Markers of Immune Activation and Inflammation in Individuals With Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection. *J Infect Dis* 2021;224:1839–48.
73 Lambrecht BN, Hammad H, Fahy JV. The Cytokines of Asthma. *Immunity* 2019;50:975–91.
74 Barnes PJ. Targeting cytokines to treat asthma and chronic obstructive pulmonary disease. *Nat Rev Immunol* 2018;18:454–66.
75 Terry PD, Heidel RE, Dhand R. Asthma in Adult Patients with COVID-19. Prevalence and Risk of Severe Disease. *Am J Respir Crit Care Med* 2021;203:893–905.
76 Terry PD, Heidel RE, Dhand R. The association of preexisting severe asthma with COVID-19 outcomes. *Curr Opin Pulm Med* 2023;29:215–22.
77 Daley-Yates PT. Inhaled corticosteroids: potency, dose equivalence and therapeutic index. *Br J Clin Pharmacol* 2015;80:372–80.
78 Cimellaro A, Addesi D, Cavallo M, *et al*. Monoclonal Antibodies and Antivirals against SARS-CoV-2 Reduce the Risk of Long COVID: A Retrospective Propensity Score-Matched Case-Control Study. *Biomedicines* 2022;10:3135.
79 Tashkin DP, Wechsler ME. Role of eosinophils in airway inflammation of chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2018;13:335–49.
80 Katella K, Yale Medicine. Omicron, Delta, Alpha, and more: what to know about the coronavirus variants. Available: https://www.yalemedicine.org/news/covid-19-variants-of-concern-omicron [Accessed Jan 2024].