**Association of risk factors with Long COVID**

**A Systematic Review and Meta-Analysis**

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**Key points:**

**Question:** Which individuals are at risk of developing Long COVID syndrome?

**Findings:**In this systematic review and meta-analysis of 41 studies that included 860,783 patients, it is shown that female sex, older ager, increased BMI, smoking, pre-existing co-morbidities and previous hospitalisation or ICU admission are risk factors significantly associated with the development of Long COVID syndrome, while vaccination has a protective role.

**Meaning:**The study’s findings portray the profile of the individual who is at increased risk of developing Long COVID syndrome and suggest an additional value of vaccination in protecting against long COVID syndrome.

**Abstract**

**Importance:** Many individuals that have been infected with COVID-19 suffer with Long COVID syndrome. Identification of those at high risk of developing this syndrome is crucial as it could allow early and appropriate clinical support.

**Objective:** To evaluate the characteristics and co-morbidities that increase the risk of Long COVID syndrome.

**Data sources:** Medline and Embase databases were systematically searched from inception until December 5, 2022.

**Study Selection:** The meta-analysis included all studies that investigated the risk factors or predictors of Long COVID in adult patients (≥18 years).

**Data Extraction and Synthesis:** ORs for each risk factor were pooled from the selected studies. For each potential risk factor, the random-effects model was used to compare the risk of developing Long COVID between individuals with and without the risk factor.

**Main Outcomes and Measures:** The risk factors included patient age, sex, BMI, smoking, co-morbidities including diabetes, ischaemic heart disease, chronic kidney disease, asthma, chronic obstructive pulmonary disease, immunosuppression, anxiety/depression, previous hospitalisation or admission in intensive care unit (ICU) with COVID-19 and previous vaccination for COVID-19.

**Results:** The initial search yielded a total of 5,334 records, out of which 255 articles underwent full-text evaluation. Forty-one records, with a total of 860,783 patients, were included in the meta-analysis.The meta-analysis showed that female sex (OR 1.56, 95%CI 1.41-1.73), age (OR 1.21, 95%CI 1.11-1.33), increased BMI (OR 1.13, 95%CI 1.06-1.20), and smoking (OR 1.10, 95%CI 1.07-1.13) are associated with an increased risk of Long COVID. In addition, the presence of co-morbidities and previous hospitalisation or ICU admission were found to be associated with high risk of long COVID (OR 2.48, 95%CI 1.97-3.13 and OR 2.37, 95%CI 2.18-2.56 respectively). Vaccinated individuals were found to have a significantly less risk of long COVID compared to unvaccinated participants (OR 0.57, 95%CI 0.43-0.76).

**Conclusions and Relevance:** This systematic review and meta-analysis demonstrated that certain demographic characteristics (age, sex), co-morbidities and severe illness are associated with an increased risk of Long COVID while vaccination has a protective role against the post-COVID sequalae. These findings enable us to better understand who may develop long Covid and also advocate for the benefit of vaccination.

**Keywords:** Coronavirus disease 2019 (COVID-19); Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); Long COVID syndrome; Post-acute COVID-19 syndrome (PACS); Persistent post-COVID-19 syndrome (PPCS)

**Introduction**

The coronavirus disease 2019 (COVID-19) pandemic has resulted in significant morbidity and mortality across the world since the first cases were identified in December 20191.

Previous epidemics of viruses from the coronavirus family, such as the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome coronavirus (MERS-CoV) have resulted in persistent symptoms in infected individuals1. These included severe fatigue, decreased quality of life (QOL), persistent shortness of breath, as well as behavioural and psychological problems1. These persistent post-viral symptoms have resulted in significant burden to healthcare systems where the epidemics occurred1. Similarly, a constellation of various clinical symptoms has been described in a proportion of patients who recovered from SARS-CoV-2 induced COVID-191. This constellation of symptoms has been labelled with many names, including “post-acute COVID-19 syndrome (PACS)”, “persistent post-COVID-19 syndrome (PPCS)” and “long COVID”1.

According to the World Health Organisation, the presence of symptoms usually 3 months from the onset of COVID-19 with a duration of at least 2 months, constitutes the definition of post COVID-19 condition2. The terms 'long COVID’ and ‘post COVID-19 condition’ or ‘post-acute COVID-19 syndrome’ often have been used interchangeably over the last couple of years. The National Institute for Health and Care Excellence (NICE) recommendations propose the use of the term ‘long COVID’ to describe the presence of symptoms after the acute COVID-19 infection, with the duration of symptoms persisting for four weeks or more 3. Typical clinical symptoms include tiredness, dyspnoea, fatigue, autonomic dysfunction, headache, and persistent loss of smell or taste – although a wide range of symptoms has been described1,4. Individuals with Long COVID may need long-term clinical support4 which is estimated to cause significant economic impact5.

As such, it is imperative to recognise those who might be at risk of developing Long COVID and offer follow-up for those at the highest risk, but also plan population level public health measures. Several studies have been published investigating clinical and epidemiological predictors of Long COVID5–8. However, these studies often included analyses on relatively few patients5–8. Furthermore, wide discrepancy exists amongst published data5–8, resulting in a lot of uncertainty regarding the clinical utility of these findings. The aim of this study, therefore, is to search the available literature and pool the results from published studies to investigate the clinical and epidemiological risk factors associated with the development of Long COVID.

**Methods**

Search Strategy and Selection Criteria

MEDLINE and Embase databases were systematically searched for studies investigating the risk factors or clinical predictors for Long COVID syndrome in patients diagnosed with COVID-19 from inception until October 10, 2022. Search terms included “Long-COVID”, “Post-COVID” and “Chronic COVID”, as well as the corresponding Medical Subjects Heading (MeSH) terms. We only included peer-reviewed articles. Pre-prints were not included. The full search strategy can be found in eMethods in the Supplementary material. This systematic review and meta-analysis was conducted according the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA)9. It has been registered with PROSPERO (registration number CRD42022381002).

Data extraction

Search results were imported for abstract screening; duplicates and irrelevant studies were removed, based on predetermined inclusion and exclusion. All studies that investigated the risk factors or predictors of Long COVID, as defined by the presence of at least one symptom for ≥12 weeks in line with the WHO definition, in an adult (≥18 years) patient cohort were included. The risk factors examined for this meta-analysis included age, sex, body mass index (BMI), smoking status, co-morbidities (diabetes, asthma, chronic obstructive pulmonary disease, ischaemic heart disease, chronic kidney disease, history of immunosuppression, anxiety/depression) and COVID-19 vaccination status. Studies were excluded if they investigated persistent COVID symptoms of less than 12 weeks duration. Studies that did not provide data for any of the risk factors examined were also excluded. Studies where only univariate regression was used were excluded from the meta-analysis as we wanted to identify independent risk factor association. Full texts of studies were subsequently retrieved and scrutinised against the same criteria. The relevant data from the included studies were independently extracted by two authors, who were blinded to the authors and institutions of the studies undergoing review (H.E. and V.T.). Any disagreements were resolved by discussion with the senior author of the manuscript (V.V.).

Certain cohorts were published more than once, for example once relating to neurological Long COVID and once to cardiovascular Long COVID. To avoid double-counting patients in cohorts that were published more than once, we initially meta-analysed all the Long COVID symptoms and produced a single OR for the specific cohort that was used in this meta-analysis.

The Newcastle-Ottawa Scale10,a 9-point measure assessing the quality of cohort studies and case-control studies or case series, was used to evaluate the observational studies included.

Statistical Analysis

Quantitative synthesis of included studies was performed using *RStudio 2022.07.1+554 , R*  version 4.0.5; *(2021-03-31).*. Odds ratios for each risk factor were pooled with the random-effects model. This was deemed more appropriate than the fixed-effect model as the studies included in this meta-analysis represent samples from different populations. For studies reporting rate ratios, those were converted to ORs using methodology defined in the Cochrane Handbook for Systematic Reviews of Interventions11. Summary statistics were expressed as odds ratios and the associated 95% confidence intervals. Prediction intervals are also reported in the results. Statistical heterogeneity was assessed using the *I*2 statistic. Publication bias was assessed qualitatively by visual inspection of inverted funnel plot asymmetry and Egger’s test was performed to assess small study effects. The statistical significance threshold was *p*< 0.05.

**Results**

The search of MEDLINE and Embase databases yielded a total of 5,334 records. After removal of duplicates, 3,363 were screened at title/abstract level and 255 studies underwent full-text evaluation. Of those, 41 records with a total of 860,783 patients met the inclusion criteria and were included in the meta-analysis. e**Figure 1** in the Supplement outlines the PRISMA flowchart for study selection. **Table 1** summarises the population cohorts and the study design characteristics of all the included studies.

Thirty observational studies were ranked as having high quality and 11 observational studies were ranked as having moderate quality on the Newcastle-Ottawa Scale (eTable1).

All possible risk factors for Long COVID were investigated including patient age, sex, and body mass index (BMI), smoking status, presence of co-morbidities including diabetes mellitus (DM), ischaemic heart disease (IHD), chronic kidney disease (CKD) and chronic obstructive pulmonary disease (COPD), asthma, immunosuppression, anxiety/depression and whether patients were hospitalised or admitted in intensive care unit (ICU) with COVID-19. In addition, the role of vaccination as a risk factor for long COVID was also evaluated.

Funnel plots for all the meta-analyses are shown in the supplementary material (eFigure 2).

Sex

Thirty-eight studies including a total of 727,630 patients investigated sex as a risk factor for Long COVID. Overall, the pooled odds ratio (OR) showed that female sex was significantly associated with Long COVID (OR 1.56, 95%CI 1.41-1.73, *I2*94%) (Figure 1). However, the prediction interval (0.94, 2.61) suggested that this may not be demonstrated in all future studies. To investigate this further, we undertook subgroup analysis separating the studies that included only hospitalised patients from those that included only non-hospitalised and those that included a mixture of hospitalised and non-hospitalised patients (eFigure 3). This showed that heterogeneity was lower in studies that included only hospitalised or only non-hospitalised patients compared to those that included patients from both settings (58%, 24% and 97% respectively), with the correlation remaining significant and the prediction intervals showing evidence supporting this significance for future studies. In addition, subgroup analysis was also performed according to the study quality (high vs. moderate) as per the Newcastle-Ottawa Scale with no significant between-group differences demonstrated (eFigure 4). Meta-regression analysis according to study size showed no significance (p=0.26). Egger’s test for small study effects was not significant (p=0.15).

Age

Nine studies including a total of 324,950 patients investigated age as a risk factor for long COVID. For the meta-analysis, the risk of long COVID according to three age groups (40-69 years old and ≥ 70 years old compared to patients 18-40 years old) was examined. We found that patients in both older groups (40-69 years old and ≥ 70 years old) have significantly higher risk of long COVID when compared to adult patients <40 years old, with no significant between-group differences (OR 1.21, 95%CI 1.11-1.33, *I2*95%) (Figure 2). The prediction interval (0.84, 1.76) suggested that this may not be demonstrated in all future studies. Subgroup analysis according to study size demonstrated a high rate of heterogeneity in the group of large studies (eFigure 5). Meta-regression analysis according to study size was significant (p=0.02) indicating that study size may have influenced the results (eFigure 6). Egger’s test for small study effects was not significant (p=0.85). Subgroup analysis according to study population (not hospitalised versus a mixture of hospitalised and not hospitalised patients) showed no significant between-group differences (eFigure 7), while sensitivity analysis according to study quality demonstrated that high quality studies have higher heterogeneity (eFigure 8).

Body Mass Index

Sixteen studies including a total of 701,807 patients investigated obesity (BMI ≥30kg/m2) as a risk factor for long COVID. Obesity was found to be significantly associated with long COVID (OR 1.15, 95%CI 1.08-1.23, *I2*91%) (eFigure 9). However, this significant correlation may not be shown in all future studies as alluded by the prediction interval (0.94, 1.42). Subgroup analysis by study population (hospitalised versus non-hospitalised versus mixed), showed that the correlation remains significant in all 3 subgroups but the studies that were done in the not hospitalised patients had the lowest heterogeneity (eFigure 10). Subgroup analysis according to study quality showed that the significant correlation between obesity and long COVID was evident only in high quality studies (eFigure 11). Egger’s test was found to be significant (p<0.001), suggesting publication bias as shown in the funnel plot (eFigure 2c). Meta-regression analysis according to study size was not significant (p=0.86).

Smoking Status

Twenty studies including a total of 455,204 patients investigated if current smokers have higher risk of developing long COVID, compared to non-smokers. Overall, the pooled OR showed that smoking was significantly associated with long COVID (OR 1.10, 95%CI 1.07-1.13, *I2*0%) (figure 3). Subgroup analysis according to study quality showed no significant differences (eFigure 12). Egger’s test suggested no significant publication bias (p=0.07), while meta-regression analysis according to study size also showed no significance (p=0.14).

Co-Morbidities

Meta-analysis was performed for all the studies that investigated the presence of co-morbidities potentially associated with the risk of long COVID syndrome.

More particularly, meta-analysis of 13 studies and 639,397 patients showed that patients with asthma had significantly higher risk of developing long COVID (OR 1.24, 95%CI 1.15-1.35, *I2*53%) (eFigure 13). All studies included in this meta-analysis were of high quality therefore subgroup analysis for this factor was not conducted. Meta-regression analysis for study size showed significance (p<0.001), which was confirmed by subgroup analysis of studies according to their sample size (eFigure 14). In this, larger studies demonstrated a significant relationship between asthma and long COVID, while smaller studies with less than 1,000 patients failed to reach significance. Egger’s test showed no significant publication bias (p=0.51).

Furthermore, analysis of 10 studies and 257,340 patients showed that COPD is also a risk factor for persistent symptoms post COVID-19 infection (OR 1.38, 95%CI 1.08-1.78, *I2*77%) (eFigure 15). Nevertheless, this significance may not be shown in all future studies as indicated by the prediction interval (0.70,2.74). Subgroup analyses according to study quality is shown in eFigure 16. Meta-regression analysis for study size and Egger’s test were both non-significant (p= 0.66 and p=0.69 respectively).

Meta-analysis of 18 studies and 259,978 patients showed that patients with DM (OR 1.06, 95%CI 1.03-1.09, *I2*0%) have a significant risk of long COVID (eFigure 17). Subgroup analysis according to study quality is shown in eFigure 18. Meta-regression analysis showed that study size did not have a significant impact (p=0.15), while Egger’s test showed no publication bias (p=0.34).

The pooled analysis of eight studies with a total of 255,791 patients showed that CKD is not a significant risk factor for long COVID (OR 1.12, 95%CI 0.98-1.28, *I2*22%) (eFigure 19). Subgroup analysis according to study quality is shown in eFigure 20. Meta-regression analysis for study size showed no significance (p=0.20), while Egger’s test showed no publication bias (p=0.56).

Five studies that included 201,906 patients, investigated the association of pre-existing IHD. Meta-analysis of these showed that patients with IHD have 1.28 times higher risk of developing long COVID (OR 1.28, 95%CI 1.19-1.38, *I2*0%) (eFigure 21). Subgroup analysis according to study quality is shown in eFigure 22. Meta-regression analysis for study size and Egger’s test for small study effects did not show significance (p=0.49 and p=0.69 respectively).

Three studies with a total of 967 patients examined whether immunosuppressed patients exhibited higher risk of long COVID. Meta-analysis of those showed a significant association of immunosuppression with long COVID (OR 1.50, 95%CI 1.05-2.15, *I2*0%) (eFigure 23). Egger’s test did not show significant publication bias. Due to the small number of studies, subgroup analysis and meta-regression was not performed for these studies.

Four studies that included 634,734 patients investigated the risk of long COVID in patients with anxiety/depression. Pooled analysis of these studies showed a significant association with long COVID (OR 1.19, 95%CI 1.02-1.40, *I2*96%) (eFigure 24). Egger’s test for small study effects was not significant (p=0.49). Meta-regression analysis showed that study size did not have a significant impact (p=0.15). Subgroup analysis according to study quality is shown in eFigure 25.

Hospitalisations and ICU admission

Meta-analysis of eight studies with a total of 265,466 patients previously hospitalised for COVID-19 infection was performed. This showed that patients that required hospitalisation during their acute COVID-19 infection had significantly higher risk of developing long COVID (OR 2.48, 95%CI 1.97-3.13, *I2*86%) (eFigure 26). Subgroup analysis according to study quality is shown in eFigure 27. Meta-regression analysis for study size and Egger’s test did not demonstrate statistical significance (p=073 and p=0.78 respectively).

Similarly high risk was shown for patients that required ICU admission during the acute phase as shown by meta-analysis of 10 studies with a total of 213,441 patients (OR 2.37, 95%CI 2.18-2.56, *I2*0%) (eFigure 28). Subgroup analysis according to study quality is shown in eFigure 29. Meta-regression analysis for study size showed that there was an effect (p=0.01), however subgroup analysis of studies according to their sample size did not demonstrate significant between-group differences (eFigure 30). Egger’s test showed no significance (p=0.06).

Vaccination Status

Four studies with a total of 249,788 patients evaluated the impact of vaccination status on the risk of long COVID-19. Meta-analysis of these showed that individuals that have been vaccinated (with two doses in all included studies) had 40% less risk of developing long COVID (OR 0.57, 95%CI 0.43-0.76, *I2*91%) (figure4). The prediction interval (0.15, 2.22) suggested that this may not be demonstrated in all future studies. Subgroup analysis according to study quality and meta-regression for study size were not performed as all studies included were of high quality and included more than 1,000 patients each. Egger’s test showed no significant publication bias (p=0.80).

Sensitivity analyses

Two studies12,13 included patients that were self- or clinician- diagnosed with COVID-19 infection during the acute phase. For this reason, in addition to the above, we have performed sensitivity analyses for all the risk factors excluding those studies (eFigure 31). Overall, there were no differences in the outcomes of any risk factor investigated. Further sensitivity analysis was performed based on the studies that included ≥5 risk factors investigated (eFigure 32). There were no changes noted in the outcomes of each risk factor investigated. Meta-regression analyses by geographic location were also performed for the risk factors examined (eTable 2), however given the limited data (only 6 studies from America and 5 from Asia with the rest being from Europe), the interpretation of results should be guarded.

**Discussion**

Our meta-analysis of 41 studies and 860,783 patients demonstrated that there are certain epidemiological and clinical risk factors that are correlated with long COVID. In particular, female sex, older age, higher BMI and smoking are significantly associated with increased risk of persistent symptoms of ≥12 weeks duration post the acute infection, i.e., long COVID. In addition, pre-existing co-morbidities, including asthma, COPD, diabetes, IHD, immunosuppression and anxiety/depression, were also found to be significantly associated with higher risk of long COVID. Furthermore, patients that needed hospitalisation or ICU admission during the acute infection were found to have more than twice higher risk of long COVID compared to those who were not admitted in the hospital or ICU. On the other hand, vaccination (with 2 doses) for COVID-19 was noted to have a protective role against long COVID with vaccinated individuals having significantly less risk of having the persistent symptomatology of long COVID.

The aforementioned findings confirm that long COVID syndrome is a multi-factorial and complex clinical entity14. Our results strengthen the evidence available regarding the link between female sex and long COVID syndrome8,15,16. A previous meta-analysis by Maglietta et al. that included 13,340 patients also highlighted that female sex was significantly associated with persistent symptomatology of long COVID syndrome17. A recent large analysis and meta-regression of more than one million patients confirmed this finding16. Many authors have hypothesised mechanistic processes to explain the association between certain risk factors, including female sex, and long COVID1,18–21. For instance, it has been suggested that hormones may play a role in perpetuating the hyperinflammatory status of the acute phase even after recovery18,19 and a stronger IgG antibodies production in females in the early phase of disease has been reported20 which could play a role as well in perpetuating disease manifestations20,21.

Increasing age also appears to be an independent risk factor for long COVID as previous research has suggested12,17. Subgroup analysis showed that individuals aged 40-69 years old and those ≥70 years old have are at equally high risk of long COVID when compared with younger participants. However, it is important to take into account that the prevalence of long COVID consists of individuals who have survived the acute phase of COVID19 infection. Elderly individuals with potentially multiple underlying co-morbidities, may not survive this phase as they are at higher risk of severe infection22. As highlighted by Di Toro et al., long COVID reflects the population of COVID-19 survivors and not the epidemiology of COVID-1923.

Additionally, our results revealed that high BMI and smoking lead to a significantly higher risk of developing long COVID syndrome. These findings are in keeping with recent evidence depicting these characteristics as important risk factors for long COVID24–26. Obesity and long COVID have the common ground of a metabolic pro-inflammatory state which helps inflammatory processes and their associated signs and symptoms linger for a prolonged period of time27. Smoking has been shown to be a significant risk factor both for long COVID and for severe acute COVID-19 infection 28,29. However, it is unclear if smoking per se or the associated critical illness predisposes this cohort of patients to higher risk of long COVID.

Our meta-analysis revealed that patients that were hospitalised or admitted in ICU had more than double risk of developing long COVID syndrome. Critical illness has been found to be a significant risk factor for long COVID in previous studies. In a multicentre cohort study that included 246 patients, it was found that 74.3% had ongoing physical symptoms one year after ICU admission for COVID-1930. It should be noted however that several ICU survivors suffer from post-intensive care syndrome following an episode of critical care illness31,32. Post-intensive care syndrome is a well-recognised entity that entails a variety of symptoms that may persist for months or years and therefore there is a significant overlap with the long COVID sequalae. Nevertheless, the results of our meta-analysis and those of other studies highlight that patients with previous critical illness represent a high-risk population and their follow-up should reflect intensive plans for prevention, rehabilitation and treatment of the ongoing debilitating symptoms.

Our study showed that vaccination for COVID-19 has a protective role against long COVID, with vaccinated individuals having significantly lower risk compared to the unvaccinated individuals. This is in agreement with other studies and the United Kingdom Office of National Statistics (ONS) with the latest revealing a 42% less risk of long COVID after two doses of a COVID-19 vaccine33–35. Importantly, emerging evidence suggests that vaccination reduces the risk of long COVID and its sequalae even in individuals with other risk factors present, such as older age or high BMI34, expanding the benefits of vaccination beyond the morbidity/mortality benefit seen in acute COVID-19 phase.

Individuals with Long COVID may experience long-lasting effects requiring long-lasting support. It has been reported that 15% of individuals were absent from work due to illness5. Follow-up outpatient services may be needed to manage this syndrome and to better understand the possible association between symptoms and residual organ impairment. Healthcare systems worldwide have already been significantly burdened by the COVID-19 pandemic36 and routine follow-up may therefore not be possible to all those affected by the disease.

**Limitations**

Our review also has limitations. Some of the performed meta-analyses had considerable statistical heterogeneity, which might affect our results. Large meta-epidemiological studies have shown that studies at high risk of bias tend to overestimate the strength of associations. In addition, all the included studies were observational. Subsequently, the results of the performed meta-analyses are based on observational data. Whilst the observational studies were rated of moderate/high quality in the Newcastle-Ottawa scale, the scale itself is not without limitations37. Furthermore, by virtue of being observational, all the studies (even the ones with a high rating) have an unavoidable risk of bias. Despite this, however, and considering that randomised studies (with the current covid strains) addressing this question will not be undertaken, the use of studies providing risk factors following multivariable regression allows us to draw significantly important conclusions. . Furthermore, as discussed previously, long COVID is a clinically heterogenous disorder with countless manifestations and symptoms. In this analysis, we considered all different manifestations as a single entity. For this meta-analysis we relied on the diagnosis identified by the authors of the studies included, accepting that the definition of symptoms included between the different studies might not have been exactly the same. Finally, the studies spanned across various COVID variants and were all pooled together independently of variant. It is possible that the various variants, including the effect of vaccination, could alter the absolute value of long COVID sufferers, but it is unlikely that the risk factors associated with long COVID will change.

**Conclusions:**

Long COVID represents a complex heterogeneous disorder that has an immense impact in the lives of millions of people. Identification of potential risk factors enables us to better understand who might develop covid. Holistic approach and integrated care pathways will enable suitable support of the long COVID sufferers and will also allow physicians to better understand long COVID and its impact on physical and mental health. in addition to its strong benefit in preventing and diminishing the acute phase of the infection, COVID vaccination may decrease the development of long COVID.

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**Figure 1: Forest plot showing the effect of sex on Long COVID.** Female sex is associated with high risk of developing Long COVID syndrome, which is statistically significant.

**Figure 2: Forest plot showing the effect of age on Long COVID.** Age is associated with the risk of long COVID, with older individuals (40-69 years old and 70 years old) having a significantly higher risk of ongoing persistent symptoms compared to adults <40 years old.

**Figure 3: Forest plot showing the effect of smoking status on Long COVID.** Individuals who smoke have 1.10 times higher risk of developing Long COVID syndrome compared to those who do not smoke.

**Figure 4. Forest plot showing the association of vaccination with Long COVID.** Individuals that had been vaccinated for COVID-19 had significantly reduced risk of developing Long

COVID syndrome.

Table Characteristics of included studies

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study** | **Study design** | **Population** | **COVID-19 confirmation method** | **Study aims / Parameters tested** | **Follow-up** | **Main findings** | **Analysis / Adjustment methods** |
| **Abdelrahman et al**38 | Prospective cohort study | 172 hospitalised and non-hospitalised patients | Positive SARS-CoV-2 test | Telephone interview | 8-10 months | Age was considered a risk factor for persistent symptoms | Multivariate logistic regression analysis was used to detect the potential risk factors associated with the persistence of symptoms. |
| **Aranda et al.** 39 | Multicentre prospective cohort study | 150 hospitalised patients | RT-PCR-proven SARS-CoV-2 infection | Clinical assessment | 12 months | The multivariate regression analysis revealed that the female sex, chronic obstructive pulmonary disease, and smoking were independent risk factors for persistent dyspnoea | Univariate and multivariate logistic models were used to identify the factors associated with persistent dyspnoea. |
| **Asadi-Pooya et al.**40 | Observational cohort study | 2,696 hospitalised patients | RT-PCR-proven SARS-CoV-2 infection | Interview / questionnaire | ≥3 months after acute illness | Female sex, respiratory problems at the onset of infection, and ICU admission were significantly associated with chronic post‐COVID “brain fog” | Significant variables from univariate analyses were entered into the logistic regression analysis model |
| **Augustin et al.** 41 | Longitudinal prospective analysis | 958 non-hospitalised patients with mild COVID-19 | RT-PCR-proven SARS-CoV-2 infection | Persisting symptoms (most common: anosmia, ageusia,  fatigue or shortness of breath) | 4- and 7-months post infection | Sex not correlated with risk of PCS. Lower baseline level of SARS-CoV-2 was associated with higher risk of developing PCS.  Anosmia and diarrhoea during acute COVID-19 were independent predictors for a PCS after 7 months | Unadjusted and adjusted odds  ratios (OR) with 95% confidence intervals (CI) from logistic regression  were reported for various clinical data and patient characteristics at  baseline. |
| **Ayoubkhani et al.**42 | Cross-sectional study | 3,090 non-hospitalised patients | RT-PCR-proven SARS-CoV-2 infection or positive swab test in national testing programmes (self-reported by study participants) | Long covid incidence by vaccination status  UK COVID-19 Infection Survey | ≥12 weeks after infection | Unvaccinated individuals have higher risk of developing long covid syndrome | Double-vaccinated and unvaccinated participants were 1:1 propensity score matched within callipers of 0.1 points of the propensity score on sociodemographic characteristics: single-year of age, sex, ethnicity, country/region of residence, area deprivation quintile group, and pre-existing health/disability status |
| **Baruch et al.** 43 | National cross-sectional survey | 2,665 hospitalised and non-hospitalised patients | RT-PCR-proven SARS-CoV-2 infection | Online questionnaire | 3-6 months after positive test | Female sex, hospitalisation, and initial symptoms were associated with higher odds of fatigue, shortness of breath, cough, anxiety, sadness, and memory loss as long COVID symptoms. | Logistic regression was used to determine the risk factors for long COVID symptoms. Age, sex, wave number, healthcare worker status, initial  symptoms, and hospitalisation due to COVID-19 were used as covariates. |
| **Bellan et al.** 44 | Prospective cohort study | 238 hospitalised patients | 232 RT-PCR positive swab, 1 bronchoalveolar lavage positive, 5 SARS-CoV-2 antibodies and suggestive radiological findings | Pulmonary function tests, physical performance tests, psychological symptoms tests | 4 months after discharge from hospital | No significant association between sex, age, diabetes, CAD, obesity, CKD, COPD and functional impairment | Univariate analysis performed to identify associations with different end points. All associations with p<0.20 were then included in logistic regression model |
| **Blomberg et al.** 45 | Prospective cohort study | 312 hospitalised and non-hospitalised (home isolated) patients | Positive SARS-CoV-2 antigen or antibody test | Collection of demographic and clinical data and blood samples | 6 months after infection | At 6 months, 61% (189/312) of all patients had persistent symptoms, which were independently associated  with severity of initial illness, increased convalescent antibody titers and pre-existing chronic lung disease | Multivariable analysis was performed by binary logistic regression for  dichotomous outcome variables. Negative binomial regression was performed to analyse  factors associated with numeric outcome variables |
| **Chudzik et al.**46 | Retrospective observational study  (STOP COVID registry) | 2,218 hospitalised and non-hospitalised patients | Positive RT-PCR test and/or antigen test | Clinical assessment | 3 months post infection | Female sex, severe acute COVID-19 infection, dyspnoea, chest pain are risk factors for developing long COVID syndrome | Multivariate logistic regression models (the explanatory variables were statistically significant variables obtained by univariate analysis: duration and number of symptoms, severity of COVID-19 infection, blood pressure, diarrhoea, arthralgia, headache, leg pain, hearing dysfunction) |
| **Daitch et al.**47 | Multicentre prospective cohort study | 2,333 hospitalised patients | Positive RT-PCR test | Clinic review, history, physical examination, spirometry | Average 5 months after disease onset | Independent risk factors for long-COVID fatigue and dyspnoea included female gender, obesity, and closer proximity to COVID-19 diagnosis; older age was not an independent predictor | Multivariable analysis |
| **Debski et al.**48 | Cross-sectional study | 1,487 hospitalised and non-hospitalised patients | Positive RT-PCR test | Data collection / analysis from National Health Service digital databases | Persistent symptoms ≥12 weeks | Female sex and body mass index are risk factors significantly associated with post-COVID symptoms | Multivariable logistic regression analysis. A full model with all covariates was assessed. Backward variable selection was also used to identify the most important variables in the model. Risk profiles were based on the model with variable selection. |
| **Dias et al.** 49 | Prospective cohort study | 1,042 hospitalised patients | Laboratory confirmed COVID-19 | Telephone interview | ≥3 months since hospital discharge | In multivariable analyses, female sex,  higher body mass index, admission to intensive care unit and longer length of stay were independent predictors of long COVID | Multivariable logistic model containing all the characteristics as predictors and long COVID as the outcome |
| **Emecen et al.**50 | Cross sectional study | 5,610 hospitalised and non-hospitalised patients | Positive RT-PCR test | Telephone interview | 3rd, and 6th months after the first positive test date | Older age, female gender, bad economic status, current smoking, vaccination status, underlying co-morbidities and hospitalisation are associated with post-COVID-19 symptoms | Multivariate generalized estimating equation (GEE) regression model was used to further evaluate the factors associated with reporting symptoms one, three, and 6 months after diagnosis  The multivariate final model (model 2) was used for the meta-analysis, and this included all explanatory variables and time. |
| **Estrada-Codecido et al.** 51 | Retrospective cohort study | 206 hospitalised and non-hospitalised patients | Laboratory confirmed COVID-19 | Email survey, clinical assessment, electronic health records | 90 days post infection | Any persistent symptom was more common in older patients, those diagnosed in hospital and those with initial constitutional and rheumatologic symptoms. | Multivariable logistic regression, in­corporating pre-specified predictor variables (age, sex, presence of a cardiorespiratory comorbidity (asthma, cardiovascular diseases, or chronic lung disease), presence/absence of each symptom group at baseline assess­ment, location at time of test (outpatient versus in-hospital), and requirement for hospital admission at any time during the course of illness |
| **Fernández-de-las-Peñas et al.\***52 | Multicentre cohort study | 1,950 hospitalised patients | Positive RT-PCR test | Prevalence data and associated risk factors of post-COVID-19 cough | One year after hospital  discharge  (Mean 11.2 months) | No association was found between the presence of long-term post-COVID-19 cough and the remaining post-COVID-19 symptoms. Regression analysis did not reveal any clinical variable associated with the presence of post-COVID-19 cough | Multivariate Poisson regression prediction and risk models were constructed to identify variables independently associated with the presence of cough as persistent post-COVID-19 symptom. |
| **Fernández-de-las-Peñas et al. \***53 | Multicentre case-control study (2:1) | 145 patients with DM and 290 controls hospitalised with COVID-19 (age- and sex- matched individuals) | Positive RT-PCR test | A list of post-COVID  symptoms were systematically evaluated.  Hospital Anxiety and Depression Scale and the Pittsburgh Sleep  Quality Index were used to assess anxiety and depressive symptoms, and sleep quality, respectively. | Mean 7.2 months after hospital discharge | Diabetes is not a risk factor  for experiencing long-term post-COVID symptoms.  The most prevalent post-COVID  symptoms were fatigue, dyspnoea on exertion, and pain. No between-groups differences in any post-COVID symptom were  observed | Multivariable conditional logistic regression  models were constructed to identify the variables associated  with the presence of diabetes. |
| **Fernández-de-las-Peñas et al. \***54 | Multicentre case-control study (2:1) | 88 patients with obesity and 176 controls hospitalised with COVID-19 (age- and sex- matched individuals) | Positive RT-PCR test | A list of post-COVID  symptoms were systematically evaluated.  HADS and PSQI were used to assess anxiety and depressive symptoms, and sleep quality, respectively. | Mean 7.2 months after hospital discharge | Obesity was independently associated with a greater number of post-COVID symptoms and poor sleep quality | Multivariable conditional logistic regression models were applied to identify those variables independently associated with obesity. |
| **Fernández-de-las-Peñas et al. \***55 | Multicentre observational study | 1,142 hospitalised patients | Positive RT-PCR test | A list of post-COVID  symptoms were systematically evaluated. | Mean 7.0 months after hospital discharge | Female gender, number of days at hospital, previous comorbidities, and number of symptoms at hospital admission were associated with a higher number of long-term post-COVID symptoms. Fatigue, hair loss, and dyspnoea were the most prevalent symptoms. | Multivariate Poisson regression prediction and risk models were constructed to identify those clinical and hospitalization  variables associated with the number of persistent post-COVID symptoms. |
| **Fernández-de-las-Peñas et al. \***56 | Multicentre cohort study | 1,969 hospitalised patients | Positive RT-PCR test | The differences between COVID-19 related symptoms and post-COVID symptoms between male and female COVID-19  survivors were assessed. | Mean 8.4 months after hospital discharge | Female sex is a risk  factor for the development of some long-term post-COVID symptoms including mood disorders (fatigue, dyspnoea, pain, hair loss, ocular problems, depressive levels, worse sleep quality) | Multivariate logistic regression analysis for post-COVID symptoms adjusted by all variables collected at hospital admission (age, height, weight, pre-existing medical comorbidities, COVID-19 onset symptoms at hospital admission, intensive care unit (ICU) admission, days at hospital) |
| **Fernández-de-las-Peñas et al. \***57 | Multicentre cohort study | 1,969 hospitalised patients | Positive RT-PCR test | A list of post-COVID  symptoms were systematically evaluated | Mean 8.4 months after hospital discharge | Female gender, a greater number of symptoms at hospital admission, a greater number of pre-existing medical co-morbidities, and a longer stay at the hospital were risk factors for developing more long-term symptoms after COVID. | Multivariate logistic regressions were conducted to analyse associations between clinical and hospitalization variables with the number of symptoms after COVID (dependent variable) using Python library stats models 0.11.1. |
| **Fernández-de-las-Peñas et al. \***58 | Multicentre cohort study | 1,593 hospitalised patients | Positive RT-PCR test | Prevalence of musculoskeletal post-COVID pain | 8 and 13 months after discharge | Female sex, previous history of pain symptoms, pain symptoms at onset, and number of days at hospital were factors associated with musculoskeletal post-COVID pain 1 year after hospitalization | Multivariate logistic regression analysis |
| **Ioannou et al.**59 | Retrospective cohort study | 198,610 hospitalised and non-hospitalised patients | Positive RT-PCR test | Data from electronic health records | ≥3 months after acute infection | Factors significantly associated with  documented long-COVID care included older age, Black or American Indian/Alaska Native race, Hispanic ethnicity, geographical region, high Charlson Comorbidity Index score, having documented symptoms at the time of acute infection and requiring hospitalization or mechanical ventilation. Patients who were fully vaccinated at the time of infection were less likely to receive long-COVID care. | Multivariable logistic regression with adjustment for age, sex, self-reported race, self-reported ethnicity, urban vs rural residence, Charlson Comorbidity Index (CCI) score, VA Integrated Service Network, time period of infection (categorized by pandemic waves), and number of primary care, mental health, and specialty care encounters in the 2 years before infection |
| **Jones et al.**13 | Observational study | 310 hospitalised and non-hospitalised patients | Self- or clinician- diagnosed or test-confirmed COVID-19 | Patient-reported online questionnaire | Collection of data for 4 months  (Only data for 12+ weeks were used in this meta-analysis) | Risk predictors of long COVID were age ≥40 years, female sex, frailty, visit to A&E, and hospital admission for COVID-19 symptoms | Multivariable regression analyses (adjusted for all demographic variables, hospital visits for COVID-19, frailty, chronic co-morbid conditions, and COVID-19 status) were conducted comparing demographics, clinical characteristics, and presence of symptoms between patients with long COVID and patients with shorter symptom duration. |
| **Kisiel et al.**60 | Prospective longitudinal cohort studies | 366 non hospitalised patients | Positive RT-PCR test | Questionnaire / Survey | 51-54 weeks after positive test result  (1 year) | Among the predictors of persistent symptoms were being born abroad, low­er physical fitness compared with peers before COVID-19, body mass index >25 kg/m2, cooccurrence of hypertension and chronic pain, and having more than seven of the general COVID-19 symptoms at the onset. | The predictors of symptoms after 12 months were calculated with relative risk (RR) and 95% Cis. |
| **Kostev et al.**61 | Retrospective cohort study | 51,630 non hospitalised patients | Positive RT-PCR test or clinician-diagnosed (as per electronic records) | Data from electronic health records | 3-12 months after diagnosis of disease | Age > 30 years and female sex are significantly associated with post COVID-19 condition | Multivariable logistic regression model (Covariates included age, sex, and comorbidities) |
| **Menezes et al.** 62 | Prospective observational study | 108 hospitalised and non-hospitalised patients | Positive RT-PCR test ( 105 patients) or IgG antibody test (2 patients) and CT imaging (1 patient) | Clinical evaluation and self-administered questionnaire | 12 weeks | The simultaneous presence of 15 or more COVID-19 symptoms, age >45 years, and obesity were related to a higher probability of severe long COVID-19 | Binary logistic regression analysis with stepwise variable-filtering. Significant variables from the inferential analysis were included in the multivariate logistic regression model with a regressive stepwise criterion. |
| **Munblit et al.** 63 | Longitudinal cohort study | 2,649 hospitalised patients | Positive RT-PCR test or clinical diagnosis (when the laboratory testing was negative, inconclusive or unavailable) | Telephone interview / questionnaire | Median follow-up 218 days post discharge | Almost half of adults admitted to hospital due to COVID-19 reported persistent symptoms 6 to 8 months after discharge. Fatigue and respiratory symptoms were most common, and female sex was associated with persistent symptoms | Multivariable logistic regression was performed to investigate associations of demographic characteristics, comorbidities, and severity of acute phase COVID-19 with PS categories presence at the time of the follow-up interview. Robustness of findings was investigated via sensitivity analysis which included only a subset with confirmed SARS-CoV-2 infection |
| **Pazukhina et al.** 64 | Prospective cohort study | 1,013 hospitalised patients  (only the data from the adult cohort was used in the meta-analysis) | Positive RT-PCR test | Telephone interviews | 6 and 12 months after hospital discharge | Female sex and pre-existing hypertension are risk factors of post-COVID-19 condition | Multivariable logistic regression analysis  Selection of the variables was the following: “COVID-19 severity” variable as exposure, “post-COVID-19 condition” as an outcome, comorbidities as covariates, gender, and age as effect modifiers |
| **Peghin et al.**65 | Bidirectional cohort study | 599 hospitalised and non-hospitalised patients | Positive RT-PCR test and IgG antibody test | Telephone interview/questionnaire investigating specific persistent or emerging  symptoms potentially associated with COVID-19 | 6 months after disease onset | Female gender, a proportional increase in the number of symptoms at the onset of COVID-19 and ICU  admission were all independent risk factors for post-COVID-19 syndrome | Multivariable logistic regression was  Performed. All clinically or microbiologically relevant variables or those which were significant at p < 0.10 in univariable analysis were included, taking into account potential collinearities (e.g., the severity of acute COVID-19 and the ICU admission). |
| **Peters et al.**66 | Cross-sectional survey (employees in health or social facilities) | 1,930 hospitalised and non-hospitalised patients | Positive RT-PCR test and/or clinical diagnosis | Questionnaire | ≥3 months duration of symptoms | Risk factors for persistent symptoms were older age, female gender, previous illness, many and severe symptoms during the acute infection, and outpatient medical care | A binary logistic regression model was used to identify risk factors for persistent symptoms, and odds ratios (OR) with associated 95% confidence intervals (CI) were calculated. For this purpose, symptoms lasting longer than 3 months (PCS) versus no symptoms were defined as the dependent variable. The selection of variables depended on bivariate analysis |
| **Petersen et al.**67 | Prospective longitudinal study | 170 non-hospitalised patients | Positive RT-PCR test | Telephone interview, clinical examination, questionnaire | 3-month follow up | Long COVID was more common in people reporting daily medication use. Age, smoking status, BMI are not risk factors for long COVID syndrome. | Multivariable logistic regression analyses  (Adjusted for sex, groups, BMI categories, smoking status, self-reported daily medication use) |
| **Righi et al.**68 | Prospective cohort study | 465 hospitalised and non-hospitalised patients | Positive RT-PCR test and clinical symptomatology | Telephone interview | 9 months +/- 2 after disease onset | Patients with advanced age, ICU stay and multiple symptoms at onset were more likely to suffer from long-term symptoms | Multivariable Cox proportional  hazards model |
| **Silverberg et al.**69 | Observational study | 390 non-hospitalised patients | Anti-SARS-CoV-2 IgG antibody testing | Electronic survey | 11-month median follow-up | Female sex, severity of acute COVID-19 infection, and higher anti-SARS-CoV-2 IgG levels were associated with the highest risk of having chronic COVID-19 symptoms. | Multivariable models included all variables tested in bivariable models (age, sex, household size, household  sick contacts), as well as state of residence as a potential confounder based on theoretical differences in exposures and mitigation strategies |
| **Štěpánek et al.** 70 | Observational cohort study | 305 patients (healthcare workers) | Positive RT-PCR test | Clinical assessment | ≥ 12 weeks post symptom onset | The only statistically significant predictors of PCS were female sex  and increasing age | Logistic regression analysis with PCS as a dependent (response) variable was  applied to explore the relationship between PCS and other variables |
| **Subramanian et al.**71 | Retrospective matched cohort study | 486,149 non hospitalised patients | Positive COVID-19 test | UK-based primary care database | ≥ 12 weeks after infection | Among the cohort of patients infected with SARS-CoV-2, risk factors for long COVID included female sex, belonging to an ethnic minority, socioeconomic deprivation, smoking, obesity and a wide range of comorbidities. The risk of developing long COVID was also found to be increased along a gradient of decreasing age. | Cox proportional hazards model, adjusting for age, sex, ethnic group, socioeconomic status, index year, vaccination status, symptoms recorded before COVID-19, and comorbidities |
| **Thompson et al.**24 | Analyses of survey data from 10 UK established population based longitudinal studies (LS)# and records electronic healthcare records (EHR) (OpenSAFELY dataset of primary care) | 6,907 non-hospitalised patients from LS and 4189 from EHR (only data from the LS were included in the meta-analyses) | Self-reported COVID-19 infection | Wellcome Trust Covid-19 Questionnaire and analysis of data from EHR | ≥12 weeks | Increasing age, female sex, white ethnicity, poor pre-pandemic general and mental health, overweight/  obesity, and asthma were associated with prolonged symptoms in both LS and EHR data, but findings for other factors, such as cardio-metabolic parameters, were inconclusive. | For LS: Self-reported COVID-19 status was regressed on each exposure to assess whether COVID-19 was associated with each socio-demographic or pre-pandemic health risk factor. To determine what variables to include across LS, observed associations were meta-analysed to identify consistent predictors of COVID-19 self-report status. To avoid missingness on inverse probability weights (IPWs), covariates included in each model were imputed using multiple imputation by chained equations (MICE) and IPWs were derived across multiple imputed data sets.  For EHR: Logistic regression analysis was conducted to assess whether GP recorded long COVID was associated with each sociodemographic or pre-pandemic health characteristic. We adjusted for the same set of confounders as used in the LS analyses: age (as categorical variable), sex, ethnicity |
| **Tleyjeh et al.** 72 | Prospective cohort study | 222 hospitalised patients | Positive RT-PCR test | Telephone interviews | 122 days (median) post discharge (4 months post-acute infection) | Female gender, pre-existing hypertension and length of hospital stay were associated with an increased risk of new or persistent symptoms | A multivariate Cox proportional hazards model was constructed to identify factors associated with persistence of symptoms at follow-up with time-dependent days since discharge. Only statistically significant variables in the univariate analysis were incorporated into the multivariate Cox regression model |
| **Whitaker et al.**73 | Cross-sectional survey | 55,730 hospitalised and non-hospitalised patients | Self-reported symptomatic COVID-19 infection | Data from rounds three to five (main analysis) and round six (replication) of the Real-Time Assessment of Community Transmission-2 (REACT-2) study | 12 weeks after COVID diagnosis | Female sex, increasing age, obesity, smoking, vaping, hospitalisation with COVID-19, deprivation, and being a healthcare worker are associated with higher probability of persistent symptoms | Multivariate logistic regression model |
| **Wu et al.**74 | Cross-sectional survey | 308 hospitalised and non-hospitalised patients | Positive laboratory test or clinician-diagnosed | Online survey | 12 weeks after COVID diagnosis | Long COVID was more likely among obese individuals and those who experienced hair loss, headache, and sore throat during infection. There was a lack of evidence relating risk to age, gender, race/ ethnicity, education, current smoking status, or comorbid chronic conditions. | A multivariate logistic regression model was used to identify sociodemographic and health-related risk factors associated with long COVID |
| **Zhang et al.**75 | Retrospective cohort study | 2433 hospitalised patients | Laboratory confirmed COVID-19 | Telephone interviews (questionnaire and COPD assessment test) | 12 months after hospital discharge | Older age, female sex, and severe disease during hospital stay were associated with higher risks of fatigue. Older age and severe disease were associated with higher risks of having at least 3 symptoms. | Univariate logistic regression analysis was used to identify potential risk factors with *P* < 0.10. These were then used in a stepwise selection process in multivariate logistic regression model. |
| **Zisis et al.**76 | Retrospective study | 25,225 patients | Positive RT-PCR test | Data collection / analysis from electronic health records | 3 months post diagnosis | COVID-19 vaccine is protective against PASC symptoms, new onset of health conditions, and mortality. | Propensity score matching (1:1) using greedy nearest-neighbour method was used to balance the 2 cohorts on age, sex, race, and comorbidities. |

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ED, emergency department; PCS, post covid syndrome; RT-PCR, reverse transcription-polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

\*Where more than one studies from the same author are mentioned, only one of those was included in the meta-analysis (each to the relevant subgroup meta-analysis).

#Thompson et al have analysed 10 longitudinal studies that have included patients aged 18-96 years old. These are described in detail in Thompson et al. manuscript but in brief they include the following studies: MCS (Millennium Cohort Study), ALSPAC G0 (Avon Longitudinal Study of Parents and Children-Generation 0), ALSPAC G1 (Avon Longitudinal Study of Parents and Children-Generation 1), NS (Next Steps, formerly known as Longitudinal Study of Young People in England), BCS70 (British Cohort Study 1970), NCDS (National Child Development Study), USOC (Understanding Society: the UK Household Longitudinal Survey), GS (Generation Scotland: the Scottish Family Health Study), TwinsUK (the UK adult Twin Registry)