Literature screening report – Update 9

Long COVID: Evolving Definitions, Burden of Disease and Socio-Economic Consequences

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Abstract

The long-term health consequences of SARS-CoV-2 are an emerging public health problem. Yet, Long COVID's burden remains to be fully explored and understood. This review summarizes existing and emerging evidence on the prevalence of Long COVID, its symptoms, risk and protective factors, as well as potential socio-economic implications. The specific research questions on definitions of Long COVID, the burden of disease, symptoms, risk factors, the social and economic impact, as well as treatment and rehabilitation of Long COVID, and the European healthcare responses to Long COVID have been developed together with FOPH to serve their needs best.

The literature screening report's 9th update included 233 studies (57 reviews and 176 primary studies). The median of 7 prevalence estimates for non-hospitalized adults is 12% (4.5% - 41%) for persons with confirmed SARS-CoV-2 infection [1]–[7]. The median of 8 prevalence estimates in mixed (hospitalized & non) adult samples is 20% (2.3% - 53.1%) [8]–[15]. Two studies report Long COVID in previously hospitalized adults, with prevalence estimates of 7% and 37.6% [5], [16]. The US Department of Health and Human Services and the US Centers for Disease Control and Prevention (CDC) report a prevalence of about 20% [17]. Based on the triangulation of all these numbers, we estimate the Long COVID prevalence for adults in the general adult population with confirmed SARS-CoV-2 infection at about 20%. When considering that, over the entire duration of the pandemic, around 1 out of 4 infections are diagnosed by a SARS-CoV-2 test, the prevalence of Long COVID among all infected is around 5%. The majority of persons with Long COVID had mild impairment. A longitudinal cohort study from Switzerland including 1543 infected participants and 628 non-infected control participants provide first evidence of disease severity among those living with Long COVID. The study reports that at 6 months,

25% experience Long COVID symptoms, with 17% reporting mild, 4% moderate, and 3% severe health impairment (1% missing) [8].

We identified 8 population-based and/or control group studies reporting Long COVID prevalence estimates (≥ 4-week follow-up) in children and teenagers [18]–[25]. All 8 included either exclusively non-hospitalized or primarily non-hospitalized children, with a median prevalence estimate of 2.7% (range 0.31 % - 13.2%) [18]–[25].

Reviews reported more than 50 symptoms, often following a remitting-relapsing pattern. The Long COVID Global Burden of Disease Report (GBD) suggested 3 main symptom clusters: fatigue; cognitive problems; and respiratory problems. The study estimates that about 51% of all Long COVID patients experience fatigue-related symptoms, 35% cognitive-related symptoms, and 60% respiratory symptoms [26]. Preliminary evidence suggests that in adults, female sex, age (20+ years), comorbidities, the severity and symptom burden of acute disease, obesity, non-vaccination, the presence of IgM and IgG antibodies, and active smoking are Long COVID risk factors [27]–[31]. Preliminary evidence additionally suggested that ethnic minorities, under-resourced, socio-economically deprived, disparate communities, and those living further away from urban regions might be affected the strongest, likely due to social and infrastructural inequities [32]–[34]. In children, Long COVID risk may increase with age (5-17 years), female sex, history of allergic conditions, other pre-existing chronic conditions, and overall poorer physical and mental health, as well as hospitalization during acute infection [35]–[37]. A review on pediatric Long COVID reports that persistently high levels of inflammatory response mediating cytokines (interleukin (IL)-6 and IL-1β) could lead to prolonged symptoms, such as fatigue and headaches. Similarly, the presence of autoantibodies against G-protein coupled receptors (GPCRs) could explain some of the neurological and cardiovascular Long COVID symptoms [37].

Preliminary evidence from 8 studies suggests that vaccination (prior to infection) may decrease the risk of developing Long COVID. Evidence around the therapeutic effects of vaccination (post-infection) remains mixed [38]–[45]. Current evidence on how new variants impact the risk of developing Long COVID is uncertain. Two studies report reduced Long COVID risk after an Omicron infection, compared to previous variants [7], [46]. Another study found reduced risk after an Alpha variant infection, however, increased risk after a Delta or Omicron infection, compared to Wildtype SARS-CoV-2 [45]. A study pooling data from 1350 SARS-CoV-2-infected individuals from 2 population-based cohorts in Switzerland reports evidence that the combination of vaccination and an Omicron infection has a lower Long COVID risk, reporting 58% lower odds compared to non-vaccinated Wildtype infections [47].

We identified 36 studies that provided information on the socio-economic implications of Long COVID beyond 12 weeks, reporting limitations in daily functioning and social life, reduced quality of life, as well as disrupted work and family life. The US-based COVID-19 Longhauler Advocacy Project estimates that 95% of Long COVID patients (most of which are of working age) had their employment impacted, with about half of those working part-time and half being out of work for longer periods of time [48]. The project estimates the average medical cost per patient at about 36000 US Dollar [48]. About 41% of surveyed long-haulers have filled or are about to file for disability support [48]. About 20% had to sell personal belongings to cover medical expenses and another 20% have exhausted all financial resources [48].

Solid evidence on the treatment and rehabilitation of Long COVID has not been established yet, however, is underway. We searched clinicaltrials.gov and ISRCTN and identified 164 registered trials, globally. Of these, 89 registered trials on the treatment and 75 on the rehabilitation of Long COVID. Most of the treatment trials focus on medical treatments (prednisone, oxygen therapy), followed by dietary and behavioral interventions, health technology interventions, and alternative therapies such as aromatherapy, acupuncture, and osteopathic treatments. Most of the rehabilitation trials focus on behavioral or physical exercise interventions, often combined with digital devices, followed by health technology interventions and medical treatments. None of these trials have published results yet. Two reviews provide early evidence on the effectiveness of pulmonary rehabilitation and tele-rehabilitation [49], [50].

Our review critically synthesizes available evidence on the prevalence of Long COVID and outlines the multifaceted nature of its symptoms, as well as the remaining uncertainty around their progression, underlying risk factors, and the broader socio-economic implications. To fully understand the complexity of living with Long COVID, well-designed prospective studies, with reported Long COVID definitions, accompanied by qualitative, person-centered research and representative, inclusive samples will be key.

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Preamble

A large number of scientific publications become available daily, reflecting the rapid development of knowledge and progress of science on COVID-19 related issues. Leading authorities should base decisions or policies on this knowledge; hence they need to master the actual state of this knowledge. Due to the large number of publications shared daily, decision-makers heavily depend on accurate summaries of these publications, in the different public health domains. Therefore, the authors of this report were mandated by the Swiss School of Public Health plus (SSPH+), on request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature

*All newly added information (since last update) is marked in green

KEY MESSAGES

The World Health Organization (WHO) defines post COVID-19 condition (Long Covid) as "(…) a *condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis."* [51]

Burden of disease

- The median of 7 prevalence estimates for non-hospitalized adults is 12% among persons with confirmed SARS-CoV-2 infection (4.5% - 41%) [1]–[7]
- The median of 8 prevalence estimates in mixed (hospitalized & non) adult samples is 20% (2.3% - 53.1%) among persons with confirmed SARS-CoV-2 infection [8]–[15]
- Two studies report Long COVID in previously hospitalized adults, with prevalence estimates of 7% and 37.6% among persons with confirmed SARS-CoV-2 infection [5], [16]
- Based on the current evidence, we estimate the overall Long COVID prevalence for adults with a confirmed infection at about 20% and about 5% in all persons with SARS-CoV-2 infection
- A study from Switzerland (n=1543) reports that at 6 months, 25% (348/1418, 125 with missing data) reported persisting symptoms, with 17%, 4%, and 3% reporting mild, moderate and severe impairment, respectively [8]
- Another Swiss study reports vaccination and an omicron infection has a lower risk of leading to Long COVID (58% lower odds compared to non-vaccinated Wildtype infections) [47]
- The median of 7 estimates among children and teenagers is 2.7% (range 0.31 % - 13.2%) [18]–[25]

Symptoms, risk, and protective factors

- Reviews reported more than 50 symptoms
- About 60% experience respiratory symptoms; 51% fatigue-related and 35% cognitive symptoms [26]
- In most cases, symptoms tend to improve over time. Mean duration is estimated at about 9 months among hospitalized and 4 months among non-hospitalized individuals, with about 15% of Long COVID patients still experiencing symptoms 12 months after infection [26]
- In adults, female sex, age (20+ years), comorbidities, the severity of acute disease, obesity, non-vaccination, the presence of IgM and IgG antibodies and active smoking may be increasing the risk for Long COVID [27]–[31]
- In children, female sex, age (5-17 years), history of allergic conditions, other pre-existing chronic conditions, overall poorer physical and mental health, and hospitalization during acute infection may be increasing the risk for Long COVID [35]–[37]

- Preliminary evidence suggests that vaccination (prior to infection) may decrease risk of developing Long COVID [38]–[45]. Evidence around the therapeutic effects of vaccination (post-infection) remains mixed [14], [52]–[59].

Socio-economic implications

- Long COVID can lead to functional restrictions, as well as impaired family and social life [60]–[63]
- Long COVID symptoms can lead to longer work absences and the need to adjust workloads [64]–[67]
- In a Swiss study (n=1543), those experiencing severe symptoms reported that their work ability was on average half as good as their pre-infection work ability (at 18 months) [yet unpublished data, number of participants followed up until 18 months n=1184, number and percentage of participants with severe symptoms = 27 (2.3%)]
- Overall, Long COVID has a negative impact on quality of life [68]–[71]

Treatment and rehabilitation

- Two reviews provide early evidence on the effectiveness of pulmonary rehabilitation and tele-rehabilitation [49], [50]
- Multiple trials on Long COVID treatment and rehabilitation are underway (registered on clinicaltrials.gov and ISRCTN)
- None of these registered trials have published results yet

Background

Long-term health consequences of SARS-CoV-2 are increasingly being reported worldwide. A cohort study from the University Hospital of Geneva found that 32% of 669 in- and outpatients reported at least one symptom after, on average 6 weeks, with fatigue, dyspnea and loss of taste or smell being the most common persistent symptoms [72]. The population-based Zurich Coronavirus Cohort study found that 26% of the first 431 patients enrolled from March to August 2020 have not recovered fully after 6 – 8 months, with around 10% still severely impaired [73]. Long COVID is broadly defined by the persistence of physical and/or mental symptoms following a SARS-CoV-2 infection for a longer than usual period. Funding bodies around the world launched funding opportunities on the long-term consequences of COVID-19. The Congress of the United States (US) approved funding of more than 1 billion US Dollar and the United Kingdom Research and Innovation (UKRI) issued a call for research into the longer-term effects of COVID-19 in non-hospitalized individuals with funding of 18.5 million British Pounds [3], [4]. In the meantime, those affected describe an impairing, debilitating, and complex disease, sometimes keeping them out of work and social life [74]. Generated knowledge should ideally be holistic, including the broader public health and socio-economic dimensions of Long COVID, enabling and informing crucial healthcare and policy responses. While many European countries have launched

initiatives to establish care and support pathways for Long COVID patients, the need for stronger and more targeted action remains.

Aim

To provide a summary of existing evidence on the public health implications of Long COVID. This is to be achieved through a holistic focus, combining the medical/clinical, social, economic, and broader healthcare system aspects. The specific research questions have been developed together with FOPH to serve their needs best.

Questions addressed

- What are the evolving definitions of Long COVID?
- What is the current Long COVID burden of disease?
- What are the reported Long COVID symptoms, as well as risk and protective factors?
- What is the current social and economic impact of Long COVID?
- What do we know about the treatment and rehabilitation of Long COVID?
- What healthcare and social system responses to Long COVID in Europe?

Methodology

We conducted a systematic review of reviews (umbrella review) following PRISMA guidelines. We searched the following electronic databases: Medline (EBSCOhost), CINAHL (EBSCOhost), WHO COVID-19 (including Elsevier, MedRxiv), and Embase (excluding Medline). We developed a sensitive search strategy consisting of the following keywords: “COVID-19”, “Covid”, “SARS-CoV-2”, “chronic-COVID”, “long-COVID”, “long COVID”, “long-term COVID”, “post-COVID”, “long-term symptom”. “long-term clinical features”, “long-term sequela”, “long-term complication”, “long-term impact”, “long-term implication”, “long-term consequence”, “long-term effect”, “post-acute”, “long-tail”, “recurrent”, “lingering”, “persist”, “post-discharge”, “prolonged symptom”, “post-chronic”, “long-haul”. Keywords were combined and refined using Boolean operators and truncations, adjusted to each of the databases. We additionally searched google scholar, screening the first 5 result pages. Finally, we manually screened the reference lists of all included reviews. All references were screened in duplicate, at title and abstract, as well as full-text level. The fifth research question (healthcare and social system responses) was addressed through the manual screening of key governmental and other relevant web pages.

This literature screening report was updated in October 2022 to include new evidence from reviews and primary studies. Primary studies were identified in 2 stages. First, we identified all primary studies included in at least one of the eligible systematic reviews. Second, using those primary studies, we conducted related article searches in PubMed and Google Scholar, capturing newer primary studies that might not have been included yet in one of our reviews. We then included and synthesized primary studies from both stages that fulfilled all eligibility criteria. Data synthesis for primary studies was focused on (a) the burden, and (b) the socio-economic impact of Long COVID, as these 2 elements were not adequately addressed in systematic reviews.

Textbox 1: Eligibility criteria

Eligibility criteria for reviews

- Reported a review methodology (systematic or scoping reviews, rapid reviews, pragmatic reviews)
- Thematically focused (entirely or partially) on Long COVID

Eligibility criteria for primary studies

- Included in one of the reviews or identified through a related article search
- Must be surveys, cross-sectional or cohort studies including laboratory or clinically confirmed SARS-CoV-2 cases for at least 6 weeks (from acute disease, test, hospital discharge, enrollment, or study start)

Data extraction, analysis, and synthesis

Review data was extracted with a pre-defined data extraction sheet including methodological characteristics (type of review, number of included studies, socio-demographic focus, geographic distribution of primary studies) and 4 different sections, each corresponding to one of the research sections. Information was synthesized narratively and guided by the 5 research questions. Primary study data was extracted with a separate, predefined extraction sheet including information on study design, sample size, recruitment period, the severity of acute SARS-CoV-2 infection, sample socio-demographics, follow-up lengths, socio-economic implications, and prevalence estimates.

Reporting of prevalence estimates

In accordance with the WHO definition [51], prevalence estimates for adults were only reported for studies with a mean follow-up at 12 weeks or above. For children, we report prevalence estimates at 4

weeks and beyond, as estimates at 12 weeks and beyond are currently scarce. We only provided a detailed report of prevalence estimates derived from studies with population-based samples and/or control participants, as these studies are more likely to yield more robust and less biased estimates. We calculated and reported the median values of all eligible studies, grouped according to study population (non-hospitalized, hospitalized, and mixed). Studies were classified as population-based if they used sampling procedures that are generally accepted to yield representative samples (e.g., probability sampling or census data). Therefore, we consider that no further weighting of results is required. Given the diversity of studies and heterogeneity of results, we do not deem it appropriate to conduct an additional meta-analysis (yet, we have included and synthesized all currently available and eligible systematic reviews with or without meta-analyses). We also considered available estimates provided by health organizations (e.g., the US Centers for Disease Control and Prevention, WHO). We triangulated all that evidence to provide an estimated prevalence among adults with confirmed SARS-CoV-2 infection.

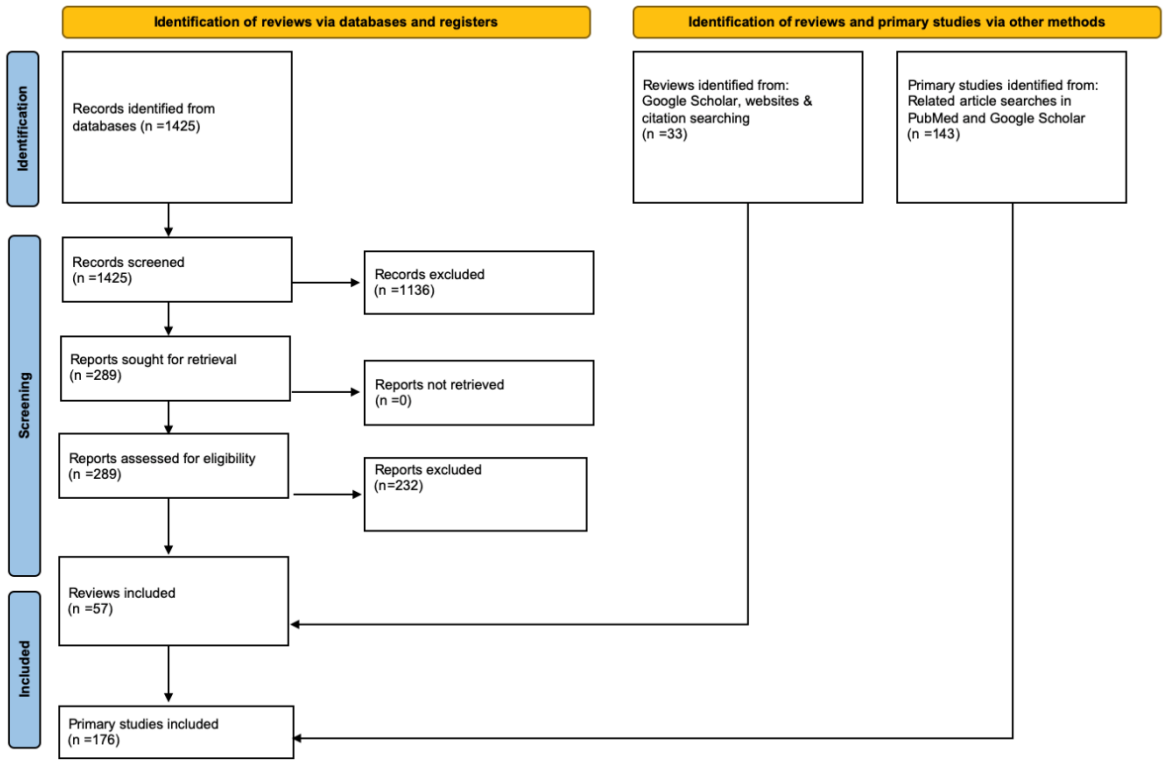
Risk of bias (quality) assessment

The quality of reviews was assessed using the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) checklist [75]. The quality of primary studies that report prevalence estimates (≥ 12-week follow-up for adults, ≥ 4-week follow-up for children) was evaluated with 3 items, adapted from the Hoy et al. [76] checklist for prevalence studies. The first item assessed whether the target population is a good representation of the national population. The second determined whether the sample was selected with some form of random and/or consecutive procedure. The third item assessed whether the likelihood of non-response bias was minimized.

Results and findings

This literature screening report is based on 233 included studies (57 reviews and 176 primary studies). The latest update added 8 new reviews and 24 new primary studies. Figure 1 provides the cumulative PRISMA flowchart of our searches. Please find the list of all newly added reviews and primary studies in appendix 1.

Figure 1: PRISMA Flowchart for included reviews and primary studies [77]



Characteristics of included reviews

Of all included reviews, 1 was published in 2020, 35 in 2021, and 21 in 2022. Most studies were traditional systematic reviews (n=30), followed by systematic reviews with a meta-analysis (n=15), pragmatic reviews (n=4), rapid reviews (n=5), rapid living systematic reviews (n=2), and scoping reviews (n=1). Six addressed pediatric patients and adolescents, 1 addressed middle-aged and young adults, and the remaining (n=51) did not report a specific socio-demographic focus. Those that specifically addressed the geographic distribution of their primary studies, emphasized that most of them are from Europe and the USA, with almost none conducted in low-income settings. The overall quality of included reviews was assessed as low to moderate, with 20 scoring critically low, 14 scoring low, 18 scoring moderate, and 5 scoring high-quality points. The full quality assessment table is provided in appendix 1.2.

Characteristics of included primary studies

43 primary studies were published in 2020, 87 in 2021, and 46 in 2022. The majority were conducted in Europe, followed by North America, Asia, Africa, and South America. Methodologically, most primary

research is based on prospective cohorts (n=122), followed by cross-sectional and survey designs (n=27), retrospective cohorts (n=23), case series, and case-control studies (n=4).

Evolving definitions of Long COVID

Terminology

This literature screening report has adopted the term Long COVID, being the currently most widespread and broad description of long-term SARS-CoV-2-related complications [78] and the term most accepted by persons living with Long COVID. Some of the commonly used terms include "long haulers," "post-acute COVID-19", "persistent COVID-19 symptoms", "post COVID-19 manifestations", "post COVID-19 syndrome", "chronic COVID-19 syndrome", "post-infectious COVID-19", "post-recovery", "post-acute sequelae of SARS-CoV-2 infection" (PASC) and "post COVID-19 recovery syndrome" [78]–[84]. Inevitably, the reason for the abundant terminology is the emerging nature of Long COVID itself, as well as of the evidence around it, which still lacks consensus on the range, prevalence, and duration of symptoms [27], [30], [85], [86].

Definitions

In October 2021, the WHO published a clinical case definition of Long COVID, using the term post COVID-19 condition, developed by a Delphi consensus approach. The WHO defines Long COVID as "(…) *condition that occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis. Common symptoms include fatigue, shortness of breath, cognitive dysfunction but also others and generally have an impact on everyday functioning. Symptoms may be new-onset following initial recovery from an acute COVID-19 episode or persist from the initial illness. Symptoms may also fluctuate or relapse over time"* [51]. The literature provides alternative definitions. Michelen et al. [30] attempted to broadly and pragmatically define long COVID as not recovering for several weeks or months following the start of symptoms that were suggestive of COVID-19, irrespective of previous COVID-19 testing. That definition includes clinically confirmed and suspected cases and considers that many patients do not have the access to adequate testing [84] [30]. Beyond symptoms, others also included abnormal, but potentially asymptomatic clinical parameters persisting as part of Long COVID [79]. Several reviews referred to the UK's National Institute for Health and Care Excellence (NICE) guidelines (published in 2020), which classified Long COVID into 2 categories: (1) "ongoing symptomatic COVID-19" for symptoms lasting from 4 to 12 weeks and (2) "Post-COVID-19 syndrome" or "chronic COVID-19 syndrome" for persisting symptoms beyond 12 weeks after disease

onset; both categories only hold if symptoms cannot be explained by alternative diagnoses [30], [78], [83], [87], [88]. Others disagreed with that "by exclusion" approach, as it might fail to capture the very broad spectrum of post-acute complications [84], including SARS-CoV-2-triggered new health conditions and worsening of pre-existing health conditions [78]. Others set the cut-offs at 60 days after diagnosis or at least 30 days after recovery/hospital discharge [89]. The dynamic review of the US National Institute for Health Research (NIHR) expanded that notion by emphasizing that Long COVID might not be a single condition, but multiple syndromes, such as the post-intensive care syndrome, post-viral fatigue syndrome, and long-term COVID syndrome [78]. More specific approaches proposed specific Long COVID subtypes, depending on whether disease manifestation is due to (1) left-over symptoms from acute infection, (2) infection-triggered organ dysfunctions, or (3) infection-triggered new syndromes [78], [90]. Others broadly defined it as lasting or persisting outcomes after recovery from acute disease [91]. Terminology also varies between studies conducted in Switzerland, with the population-based Zurich Coronavirus Cohort study using the term "Post-COVID-19 Syndrome" [73] and the Geneva-based cohort study "Long COVID" [72].

SUMMARY – Evolving definitions of Long COVID

- The literature provides a diverse set of terminology, with "Long COVID" being the most widespread and accepted
- In October 2021, the WHO defined the post COVID-19 condition as symptoms occurring within 3 months of a SARS-CoV-2 infection and lasting for more than 2 months, with no alternative diagnosis [51]

Burden of Disease (evidence from primary studies)

Studies reporting Long COVID prevalence estimates varied methodologically, such as in their sample recruitment methods (e.g. hospital, non-hospital, self-selection), follow-up periods, definitions of Long COVID, and their ability to distinguish between symptoms directly related to SARS-CoV-2, specifically those that have developed (or exacerbated) after infection, and unrelated symptoms (e.g. from pre-existing conditions) [78]. It is therefore essential to view all current estimates with their methodologies and respective definitions in mind.

In total, 80 of the 176 included studies provided overall Long COVID prevalence estimates at ≥ 12 weeks after acute infection. In total, 25 studies included population-based samples and/or control groups and are reported in detail. Prevalence estimates reported in the primary studies without control groups or

population-based samples are provided in appendix 2. We reported prevalence estimates according to the study's source population (hospitalized, non-hospitalized, or both) and age groups (adults, children). For studies with control groups, we report adjusted prevalence estimates (difference between the estimate for cases and the estimate for controls). We presented prevalence estimates as percentages of confirmed SARS-CoV-2 infections but not absolute numbers of Long COVID patients. The reason for that is that new variants, reinfections, and the introduction of vaccines influence the risk of developing Long COVID, making it close to impossible to estimate and provide absolute numbers. Advanced modeling would be needed to take all these factors into account and provide valid estimates of the absolute number of persons affected by Long COVID. Please note that the Global Burden of Disease (GBD) analysis does provide absolute numbers but the underlying evidence base largely covers infections with wildtype and alpha and not periods with infections with delta or omicron hardly any period that already reflects the effect of vaccines [26].

Adults

We identified 17 population-based and/or control group studies reporting Long COVID prevalence estimates (≥ 12-week follow-up) in adults, summarized in Table 1. Three population-based and 4 studies with control groups reported prevalence estimates for non-hospitalized adults with a median estimate of 12% (4.5% - 41%). Five population-based and 3 studies with control groups included samples with non-hospitalized as well as previously hospitalized participants, with a median estimate of 20% (2.3% - 53.1%). Finally, 2 studies with control groups reported prevalence estimates among previously hospitalized participants, estimated at 7% and 37.6%, respectively. The US Department of Health and Human Services and the US Centers for Disease Control and Prevention (CDC) reported a prevalence of about 20% [17]. The WHO estimated the prevalence of Long COVID between 10-20% [92]. The recently published Long COVID GBD Report reported that 6.2% of 1.2 million symptomatic SARS-CoV-2 infected individuals (across 22 countries) experienced persistent symptoms 3 months after acute infection in 2020 and 2021 [26]. Please note that this estimate of 6.2% refers to any SARS-CoV-2 infections, thus, also those without PCR or rapid antigen test confirmation [26]. Therefore, the denominator is 3-4 times higher than in primary studies that included persons with confirmed infection. Considering all the above (median 12% for non-hospitalized adults, median 20% for mixed-samples, 7%-37.6% for hospitalized adults) and the estimates provided by large governmental agencies (CDC, 20%), we estimate the overall Long COVID prevalence to be about 20%. When considering that over the entire duration of the pandemic, around 1 out of 4 infections are diagnosed by a SARS-CoV-2 test, the prevalence of Long Covid among all infected is around 5%. These are merely estimates and derived through triangulation.

Table 1: Prevalence estimates for adults

Authors (Reference)	Cases (n=)	% hospitalized]	Controls (n=)	Follow-up period in weeks [follow-up start]	Symptom prevalence cases (%)	Symptom prevalence controls (%)	Adjusted prevalence (% cases – % controls)
non-hospitalized adults							
Stavem et al. [1] [p]	451	NA	NA	6-24 [positive test]	41	-	-
Graham et al. [2] [c]	100	NA	50	18 – 23 [symptom onset]	67.8	60.3	7.5
Havervall et al. [3] [c]	323	NA	1027	≥32 [January 2020]	15	3	12
#Desgranges et al. [4] [c]	418	NA	89	12-40 [acute disease]	53	37	16
Chevinsky et al. [5] [p ;c]	46857	NA	46857	4-17 [acute disease]	7.7	-	-
Bliddal et al. [6] [p]	445	NA	NA	4-12 [July 2020]	40	-	-
Antonelli et al. [7] [c]	56003	NA	41362	>4 [December 2021]	4.5	-	-
hospitalized & non-hospitalized adults							
Menges et al. [9] [p]	431	19	NA	29 [acute disease]	26	-	-
Petersen et al. [10] [p]	180	4	NA	18 [acute disease]	53.1	-	-
Sudre et al. [11] [c]	4182	14	4182	≥12 [symptom onset]	2.3	-	-
#Cirulli et al. [12] [c]	357	3	5497	12 [January 2020]	14.8	7	7.8
Logue et al. [13] [c]	177	9	21	12-36 [symptom onset]	32.8	4.8	28
Ayoubkhani et al. [14]	28356	3.5	NA	20 [acute disease]	23.7	-	-
#Whittaker et al. [15] [p]	46687	3	NA	≥12 [August 2020]	3.5	-	-
#Ballouz et al. [8] [c ; p]	1543	8	628	48 [acute disease]	16	-	-
hospitalized adults							
Xiong et al. [16] [c]	538	100	184	>12 [hospital discharge]	49.6**	12	37.6
Chevinsky et al. [5] [p; c]	27589	100	27589	4-17 [acute disease]	7	-	-

#=still at preprint stage at time of data extraction; P=population-based sample; C=includes control participants; NA= not applicable

**study provides multiple prevalence estimates, according to symptom groups. 49.6% is the highest reported prevalence (generally symptoms). Studies conducted in Switzerland are marked with the Swiss flag.

Although by research design, the above studies provided the most robust prevalence estimates currently reported, all are subject to certain limitations. Stavem et al. [1] included a predominantly female and older sample (>50 years of age), with the study's findings being subject to recall bias. The study by Graham et al. [2] was limited by its small sample size and the fact that many cases only underwent serology testing, not allowing for accurate identification of infection start. The findings reported by Havervall et al. [3] were limited by the risk of recall bias, as well as the use of serology testing, neither allowing for a clear identification of infection times nor a clear differentiation between SARS-CoV-2-related symptoms and pre-existing ones. Biddal et al. suffered from low response rates,

with respondents being older and more often female. Menges et al. [9] (conducted in Switzerland) as well Petersen et al. [9] did not assess pre-COVID physical or mental health, while the very low estimate by Sudre et al. [11] might be due to lacking representation of elderly subgroups (>70) and the interference of Long COVID symptoms with study reporting, which occurred via an app (more severe cases not willing/capable of reporting symptoms). Finally, Cirulli et al. [12] measured any symptoms persisting longer than 90 days since the beginning of the pandemic (January 2020) without differentiating before and after the test result.

Children and Teenagers

We identified 8 population-based and/or control group studies reporting Long COVID prevalence estimates (≥ 4-week follow-up) in children and teenagers, summarized in Table 2. 6 studies included exclusively non-hospitalized children, with a median prevalence estimate of 2.7% (0.8% - 13.2%). Including all 8 studies, also those with mixed samples (hospitalized and non-hospitalized, the median prevalence remains at 2.7% (0.31% - 13.2%).

Table 2: Prevalence estimates for children and teenagers

Authors [Reference]	Cases (n=)	% hospitalized]	Controls (n=)	Follow-up period (weeks) [follow-up start]	Symptom prevalence cases (%)	Symptom prevalence controls (%)	Adjusted prevalence (% cases – % controls)
Non-hospitalized children							
Radtke et al. [18] [p ; c]	109	NA	1246	>12 [October 2020]	4	2	2
#Miller et al. [19] [c]	175	NA	4503	≥4 [February 2020]	4.6	1.7	2.9
Stephenson et al. [20] [p ; c]	3065	NA	3739	12 [September 2020]	66.5	53.3	13.2
Zavala et al. [21] [p ;c]	472	0.01%	387	4 [February 2021]	6.7	4.2	2.5
Borch et al. [22] [p ; c]	15041	NA	15080	>4 [January 2021]	28	27.2	0.8
Berg et al. [23] [p ; c]	6630	NA	21640	4-48 [acute illness]	61.9	57	4.9
Hospitalized and non-hospitalized children							
Molteni et al. [24] [c]	1734	2	1734	≥4 [symptom onset]	4.4	0.9	3.5
Merzon et al. [25][p]	20601	<1	NA	≥12 [February 2020]	0.31	NA	NA

#=still at preprint stage at time of data extraction; P=population-based sample; C=includes control participants; NA= not applicable. Studies conducted in Switzerland are marked with the Swiss flag.

Again, all 8 estimates need to be viewed in consideration of the following methodological characteristics. The Swiss Ciao Corona study by Radtke et al. [18] had the primary aim of investigating seroprevalence rates in Swiss school children. The sample size was small and based on seroprevalence, not distinguishing between symptoms before and after SARS-CoV-2 infection, as the actual time points of infection were not assessed. Thus, the study's source population included tested, non-tested, symptomatic, as well as asymptomatic children. Miller et al. used data from a large household cohort survey (with a broader focus on COVID-19) in England and Wales [19]. As with Ciao Corona, the study encompassed tested, as well as non-tested children [19]. The findings by Miller et al. [19] are limited by the study's small sample size. Molteni et al. [24] focused on illness duration and symptom profile of symptomatic and tested children. The study's mobile self-reporting nature might have introduced self-report bias and other errors. Stephenson et al., which report the highest prevalence estimate, as well as Zavala et al., focused on long-term symptoms 1 to 3 months after acute infection, with the source population including PCR-confirmed children and young people [93]. Both studies are limited by low response rates and potential selection bias. The main limitations of Sugiyama et al. and Berg et al. are the risk of recall bias, non-response bias, and the likelihood of many unknown previously SARS-CoV-2 positive controls that have never been tested [23], [94].

Prevalence estimates across emerging variants

Current evidence on how new variants impact the risk of developing Long COVID is uncertain. Two studies reported reduced Long COVID risk after an Omicron infection, compared to previous variants [7], [46]. Another study found reduced risk after an Alpha variant infection, however, increased risk after a Delta or Omicron infection, compared to Wildtype SARS-CoV-2 [45]. A study pooling data from 1350 SARS-CoV-2-infected individuals from 2 population-based cohorts in Switzerland reported strong evidence that the combination of vaccination and an Omicron infection indicates lower Long COVID risk, reporting 58% lower odds compared to non-vaccinated Wildtype infections [47].

Disease severity

A longitudinal cohort study from Switzerland, including 1543 infected participants and 628 non-infected controls, provided first evidence of disease severity among those living with Long COVID. Severity was assessed using the EuroQol-visual analogue scale (EQ-VAS). Mild health impairment was defined as non-recovery and EQ-VAS scores above 70; moderate health impairment was defined as non-recovery and EQ-VAS scores between 51 and 70, and severe health impairment was defined as non-recovery and EQ-VAS scores equal or below 50. The cut-offs were chosen based on Swiss population normative values

and COPD studies (some COPD studies used similar cut-off values to quantify the impact of COPD/dyspnea on patients' quality of life).

At 6 months, 25% (348/1418, 125 with missing data) reported persisting symptoms, with 17%, 4%, and 3% reporting mild, moderate and severe impairment, respectively [8]. Data from the same study reported that 67% of Long COVID patients had at least one additional healthcare contact [8]. Another study, pooling data from 10 population-based cohorts (n=48901) reported that 15% - 28% of Long COVID patients experienced severe and disabling symptoms [95].

Risk of bias assessment for studies reporting prevalence estimates

The risk of bias was assessed for all 25 studies reporting prevalence estimates at 12 weeks and beyond for adults and 4 weeks and beyond for children (all studies listed in Tables 1 and 2). Overall, 14 studies (56%) scored "low risk" for the first item ("is the target population representative of the national population"), 11 studies (44%) scored "low risk" for the second item ("is some sort of random selection used to select the sample"), and 9 (36%) scored "low risk" for the third item ("is the likelihood of non-response bias minimized")[76]. Appendix 3 provides a summary of all risk of bias scores for studies with control groups and/or population-based samples (for all studies listed in Tables 1 and 2).

SUMMARY – Burden of Disease

- Long COVID affects both, adults and children
- The median Long COVID prevalence estimate for non-hospitalized adults with confirmed infection is 12% (4.5% - 41%)
- The median Long COVID prevalence of studies with mixed samples of persons with confirmed infection is 20% (2.3% - 53.1%)
- Two studies report Long COVID prevalence in hospitalized adults with confirmed infection, 7% and 37.6% respectively
- Considering all the above and the estimates provided by the CDC (20%) and WHO (10-20%), we estimate the Long COVID prevalence at 20% among adults with confirmed SARS-CoV-2 infection and 5% among all infected persons [17], [92]
- The median prevalence estimate of Long COVID children is much lower, at 2.7% (0.31% - 13.2%)
- A Swiss study reports that at 6 months, 17%, 4%, and 3% of SARS-CoV-2 patients experience mild, moderate, and severe Long COVID symptoms, respectively [8]

- Prevalence across emerging variants remains uncertain. Evidence from a Swiss study suggests lower prevalence of Long COVID after an omicron infection among vaccinated individuals [47]

*All newly added information (since last update) is marked in green

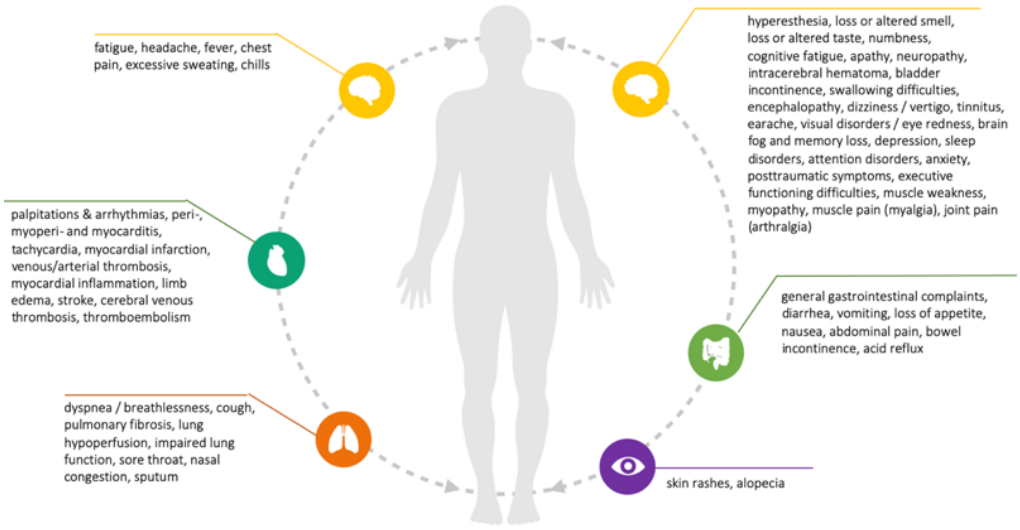
Symptoms

Symptoms are the primary focus of most identified reviews. The most commonly mentioned symptom is fatigue [78], [96], followed by headaches, chest pain, breathing difficulties, smell and taste disturbances, muscle and joint pain, cognitive impairments, sleep and anxiety disorders. These were also the most commonly reported symptoms among patients in Switzerland [72], [73].

A group of patients exclusively experiences fatigue or upper respiratory complaints, while others experience multiple and multi-system symptoms [78]. While many continuously experience symptoms, reviews reported periods of improvement and flare-ups, also described as the “corona coaster” [78], [83]. The Long COVID GBD Report suggested 3 main symptoms clusters: fatigue; cognitive problems; and respiratory problems [26]. The study estimated that about 51% of all Long COVID patients experience fatigue-related symptoms, 35% cognitive-related, and 60% respiratory-related symptoms [26].

The evidence for pediatric Long COVID patients remains limited, however, there are indications of multisystem inflammatory syndrome development, as well as a range of symptoms that are also common among adults, including fatigue, cough, breathing difficulties, heart palpitations, headaches, attention difficulties and cognitive deficits, muscle weakness, and pain, joint pain, dizziness, sore throat, abdominal pain, diarrhea, sleep disturbances, depression, smell and taste alterations, loss of appetite and weight, and skin rashes [97]–[99]. Additional 2 reviews focusing on children reported that symptoms did not differ significantly compared to adults, while 1 in 10 children with Long COVID is reported to have a reduced quality of life [36], [37].

Most existing studies did not classify disease and symptom severity based on indicators such as the number of medical visits or inability to work. These are important indicators, which, if combined with lived experience of symptoms, their duration, as well as their interference with social life can provide a holistic picture of disease burden. Appendix 4 provides a list of all reported potential Long COVID symptoms and the reviews they were reported in.



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Symptom progression over time

4 primary studies and 3 reviews provided a detailed symptom progression over time. The first study followed up 3762 Long COVID patients up to 7 months. Of these, 6.9% recovered 28 days after acute disease, with the remaining 93.2% still having symptoms during survey completion. The probability of symptoms lasting beyond 7 months was estimated at 92%. In those who recovered in less than 3 months, the number of symptoms was highest at week 2, and in those with Long COVID for over 3 months, the number of symptoms was highest at month 2, with an overall slower decline [66]. The second study followed up 968 patients online for a median of 25 weeks [100]. Over the follow-up period, 16% of patients went into remission, and 33% of those relapsed. Overall, the chance of persisting symptoms after 1 year was estimated at 85%. About half of all symptoms decreased gradually over time, with the strongest decline in loss of appetite, loss of taste, and cough. About 34% of symptoms showed no strong change in prevalence over time and a few, such as neck and back pain, even increased. Overall, symptom burden decreased during the first 3 months and started increasing again after 6 months [100]. The third study, conducted in Switzerland, reported that 49% of participants indicated return to normal health status in less than a month from acute infection, 18% reported full recovery until month 3 and 25% had not recovered 6 months after infection. At 12 and 18 months, 16% and 15% still reported Long COVID symptoms [8]. Finally, the Long COVID GBD Report estimated that the mean Long COVID symptom duration is about 9 months among hospitalized and 4 months among non-hospitalized individuals. About 15% of those with symptoms 3 months after infection will continue experiencing symptoms at 12 months [26].

The first systematic review looked at the prevalence of Long COVID symptoms at different follow-up periods and reports the following. Fatigue, dyspnea, sleep disorders, and concentration difficulties were the most common symptoms between 3 and 6 months. Effort intolerance, sleep disorders, and dyspnea were most common between 6 and 9 months, while fatigue and dyspnea were most common between 9 and 12 months [101]. The second systematic review explored symptom prevalence at 12 months and reports fatigue, dyspnea, arthromyalgia, depression, anxiety, memory loss, concentration difficulties, and insomnia as the most prevalent symptoms [102]. The third systematic review was conducted with data from previously hospitalized patients and a 1-year follow-up. It reported that the prevalence of all symptoms was highest between 5-8 months after acute infection, with most symptoms decreasing after 9 months, except fatigue, dyspnea, depression, arthralgia, anosmia, ageusia, and dizziness [103].

Risk and protective factors

Table 3: Risk factors adults

Outcome	Reported risk factors	References *Reference lines in this column do not correspond to any particular risk factor but include all references that mention at least one of the eight risk factors (in no particular order).*
Long COVID occurrence	(1) female sex (2) age (20+) (3) comorbidities (mental and physical, 3 or more, especially asthma, other lung diseases, hypertension, hypoxia, hypothyroidism, psychological conditions (4) severity of acute disease (e.g., hospitalization, duration of hospitalization, higher	[26][27][28][29][30][31][6][78][83][84][86][88][91][97][101] [28][104][105][106][107][108][109][110][111][112][113][114] [115][116][117]

	imaging scores, ICU need, duration of oxygen supplementation, pneumonia, presence of dyspnea) (5) more than 5 symptoms during acute disease, including fatigue, headache, dyspnea, chest pain, sensitive skin, hoarse voice and myalgia (5) obesity (higher BMI) (6) presence of lgM and IgG antibodies (7) active smoking (8) diet poor in anti-inflammatory/antioxidant sub- stances	
Long COVID severity • cardiovascular • increased disability • prolonged fatigue • prolonged dyspnea • Increased duration (12 months)	(1) number of symptoms during acute disease (2) severity of acute disease (ICU need, longer hospitalization, presence of dyspnea and confusion) (3) not being vaccinated (4) age (35-60) (5) comorbidities (cancer, respiratory function abnormalities, cholesterol levels, depression)	[8][94][105][110][118][119][120][121]

	(6) pre- existing fatigue and pain or discomfort (7) female sex (8) BMI 25 or above (9) post- exertional malaise, chest pain, palpitations, arthralgia, cough, reduced concentration or memory, or visual disturbances at 6 months	

Socio-cultural factors

Mental symptoms, especially posttraumatic symptoms seem to be affecting younger people, women, and those with responsibilities for others [84]. Preliminary evidence additionally suggested that ethnic minorities, under-resourced, socio-economically deprived and disparate communities and those living further away from urban regions might be affected the strongest, likely due to social and infrastructural inequities [32]–[34]. This could be associated with the link between illness severity and income, given that low-income individuals are more likely to be exposed to greater viral dose due to the inability to work remotely, lack of adequate personal protective equipment, and overcrowded living conditions [108].

Risk factors in children

Preliminary evidence on risk factors for children suggested that age (5-17 years), sex (female), obesity, history of allergic conditions (e.g. chronic allergic rhinitis), other pre-existing chronic conditions (e.g. ADHA, chronic urticaria), overall poorer physical and mental health, recurrent acute infections, as well as hospitalization (or ICU admission) during acute infection, may increase Long COVID risk and Long COVID duration (>2 months) [22], [23], [25], [98], [99], [107]. As it occurs in adults, severe acute infection has been associated with an exacerbated immune response that can lead to long-lasting damage [36]. In particular, Long COVID may be linked to the mast cell activation syndrome and the immunological response of T-helper type 2 (Th2) in children with allergic diseases [36], [122]. A review on pediatric Long COVID reported that persistently high levels of inflammatory response mediating

cytokines (interleukin (IL)-6 and IL-1β) could lead to prolonged symptoms, such as fatigue and headaches. Similarly, the presence of autoantibodies against G-protein coupled receptors (GPCRs) could explain some of the neurological and cardiovascular Long COVID symptoms [37].

Sex gap

Female sex is an often-mentioned risk factor for the occurrence of Long COVID, delayed full recovery, as well as certain debilitating Long COVID symptoms, such as fatigue, dyspnea, anxiety, and depression [6], [33], [115], [122]–[124]. A recent systematic review and meta-analysis reported a statistically significant link between female sex and Long COVID for symptoms such as fatigue, headaches, and gastrointestinal problems [125]. Furthermore, females appeared to be more likely to experience psychological Long COVID symptoms, such as anxiety and depression [125].

This is likely due to sex-based differences of innate and acquired immunological responses that make females more susceptible to certain conditions. The fact that sex-based differences are not as prominent in children reinforces the hypothesis of strong sex hormone involvement [122]. Another potential theory draws parallels to Lyme disease, in which the pathogen remains hidden and causes higher inflammatory responses in women than men. Similarly, SARS-CoV-2 could remain hidden in various organs causing Long COVID [122]. There is currently no robust evidence on the role of sex to the severity of Long COVID. Further theories suggest that females are more attentive to their bodies, overall reporting more somatic symptoms, which could explain part of the differences in Long COVID incidence [31]. Besides gender-related social factors and stereotypes, this also has physiological explanations, as sex hormone and immune system differences are closely linked to the experience of pain [114].

Protective factors

Some of the early reported potentially protective factors were physical fitness levels, being treated with interferon β-1b based triple antiviral therapy during hospital stay, and potentially immunosuppression (still under debate) [28], [107]. An increasing number of reports have highlighted the role of nutrition during acute disease in preventing Long COVID. Vitamins B, C, D, E, magnesium, selenium, zinc, flavonoids and polyphenols, curcumin, and sulforaphane are all expected to reduce the risk [116].

The role of vaccination

It is currently being investigated whether vaccines reduce the risk of developing Long COVID or even have a therapeutic effect. We have identified 17 observational studies examining the association between COVID-19 vaccines and Long COVID symptoms. Eight explored the associations between pre-infection vaccination and Long COVID (preventive) [38]–[45], and 9 explored the associations between post-infection vaccination and long COVID (therapeutic) [14], [52]–[59]. Overall, all but 1 study that explored pre-infection vaccination reported that vaccination was associated with lower Long COVID incidence, or at least lower symptom burden (median OR=0.38; 0.16-0.75).

Evidence around post-infection vaccination remains blurry, with studies reporting both, improving and worsening of symptoms. Four out of 9 studies provided statistically significant associations between post-infection vaccination and Long COVID improvement. Three studies with no comparison group reported more participants with improved than with worsened symptoms (yet worsening symptoms were reported). One study with no comparison group reported more participants with worsening than with improved symptoms. All 17 studies were observational and overall evidence strength is reported to be low to medium. Many studies relied on self-reported, cross-sectional data. No causality can be inferred. Most studies reported data from earlier pandemic phases. A more detailed description of all studies can be found in Appendix 5.

SUMMARY – Symptoms, Risk- and protective factors

- Long COVID is associated with over 50 different symptoms
- The Long COVID GBD Report estimates that 60% of Long COVID patients experience respiratory symptoms; 51% experience fatigue-related and 35% cognitive symptoms [26]
- In most cases, symptoms tend to improve over time. Mean duration is estimated at about 9 months among hospitalized and 4 months among non-hospitalized individuals, with about 15% of Long COVID patients still experiencing symptoms 12 months after infection [26]
- Risk factors are not well understood yet, but female sex, age, certain comorbidities, the severity of acute SARS-CoV-2 infection, obesity, smoking, and the presence of IgM and IgG antibodies seem to increase the risk for Long COVID [27]–[31]
- Physical fitness levels, being treated with interferon β-1b based triple antiviral therapy during hospital stay, a healthy nutrition and potentially immunosuppression (still under debate) are the only currently reported protective factors [28], [107], [116]

- Early evidence suggests that vaccination (prior to infection) may decrease risk of developing Long COVID. Evidence around the therapeutic effects of vaccination (post-infection) remains mixed [38]–[45]

*All newly added information (since last update) is marked in green

Social and economic impact

Understanding the full impact of Long COVID requires the careful consideration of its socio-economic implications. We focused on (a) family and social functioning, (b) work-related implications, and (c) broader economic consequences. The most common limitations of studies reporting socio-economic implications were (1) short follow-up periods, (2) small sample sizes, and (3) single-centered cross-sectional, as well as high risk for (4) selection and recall bias. In total, 36 studies reported socio-economic implications beyond 12 weeks. Among those, most reported limitations in daily functioning and social life (n=19) [3], [13], [129]–[135], [61]–[63], [66], [67], [126]–[128], followed by reduced quality of life (n=17) [2], [9], [126], [131], [132], [136]–[138], [13], [61]–[63], [66], [69], [70], [121], and disrupted work and family life (n=17) [3], [66], [141], [142], [67], [128], [132]–[135], [139], [140]. More details are provided in the paragraphs below.

The COVID-19 Longhauler Advocacy Project is a US-based project that aims to raise awareness around the socio-economic consequences of Long-COVID, calling for immediate action to support all those affected [48]. The project's advocacy is based on several poll-derived estimations (US population) which report that 95% of Long COVID patients (most of which are of working age) had their employment impacted, with about half of those working part-time and half being out of work for longer periods of time [48]. The average medical cost per patient is estimated at about 36000 US Dollar. About 41% of surveyed long-haulers have filled or are about to file for disability support. About 20% had to sell personal belongings to cover medical expenses and another 20% have exhausted all financial resources [48].

Family and social functioning

Studies reported functional restrictions that often require lifestyle changes, changes in physical activity levels, restricted social life, and role limitations, affecting family life and often limiting the ability to care for others [60]–[63], [78]. Five studies reported that severe neurological, cognitive, and mental symptoms, such as anxiety, memory loss, and sleep disturbances can strongly impact daily living and quality of life, turning routine activities, such as driving and cooking into difficult or even impossible

tasks [80], [83], [84], [133]. Two cohort studies reported that 12% and 44% of their participants had difficulties or were unable to perform usual daily activities at about 2 months after being hospitalized with a SARS-CoV-2 infection [64], [65]. This is also the case for those living with Long COVID after mild to moderate acute infections, with studies reporting that about 50% of their participants were facing daily activity impairments after 2 months and 5 months [67], [128], with about 15% still reporting social and home disruptions 8 months after disease onset [3]. One population-based cross-sectional study from Denmark reported that children and teenagers with Long COVID were more likely to miss school days for prolonged periods (16 or more days), which has a direct impact on family life and the employment of parents [23]. A review confirmed that Long COVID school attendance and participation in extracurricular activities, both of which are key to a child's development and well-being [37].

For some, even those who were completely independent before, these limitations were often severe enough to require daily assistance, or at least lead to some form of dependency [78], [83], [143]. At 8 months after mild acute infection, 11% of 323 Swedish cohort participants reported some degree of disruption in at least one disability scale category [3]. Two cohort studies, both following up previously hospitalized patients for about 2 months reported that 16% of participants faced reduced self-care capacity due to Long COVID [65], [127]. Another cohort study reported that 8% of their sample was dependent on others for completing daily life activities 3 to 6 months after SARS-CoV-2-related hospitalization [129]. A cross-sectional observational study of 183 previously hospitalized patients (6-month follow-up) in Spain reported significant everyday life functioning limitations among 56% of intensive care unit patients and 17.9% among those who did not require intensive [130]. An important proportion of previously independent patients experienced Long COVID impairments that deemed them fully care-dependent [78]. Finally, 17 primary studies reported that the majority of those living with Long COVID perceived their quality of life as significantly reduced [2], [68]–[71], [131], [137], [138].

Often, those living with Long COVID reported inadequate social support, feeling 'abandoned' and 'dismissed' by healthcare providers and very often relatives and friends. The advice they receive remains limited and conflicting. All these factors combined and stigma impact the mental health of people with Long COVID, who often report anxiety, depression, and PTSD [144].

Work-related implications

Inevitably, Long COVID is also expected to have a considerable impact on the workforce [78]. In studies on previously hospitalized patients, absence from work due to Long COVID was reported from 9% to 40% of those previously employed at 2 to 3 months after discharge [64], [65], [139], [145]. For those

heavily affected with neurological sequelae, absence from work was also reported as high as 59% at 6 months after hospital discharge [133].

Research on primarily mild to moderate and non-hospitalized SARS-CoV-2 cases reported that about 11% to 23% remained absent from work (or had long absence periods) at 3 to 7 months after acute disease [66], [67], [146]. A cohort study with a mixed sample (hospitalized and non-hospitalized) reported that 70% of participants were absent from work for a period of 13 weeks or more, while another one reported that 31% were still out of work at 6 weeks after acute illness [128], [147]. Beyond full absence, studies reported that many of those living with Long COVID are forced to adjust or reduce their workload levels. Two cohort studies following up previously hospitalized patients for about 2 months in Japan and the UK reported that 29%, and 40% of their employed participants reported work impairments and adjusted their employment to their current circumstances [65], [94]. Another large prospective cohort study with previously hospitalized participants from France reported that 29% of those initially employed had not returned to work after 6 months [142]. These numbers ranged from 8% to 45% for previously mild to moderate cases at follow-up of 3 to 8 months [3], [66], [67]. Two studies reported permanent employment loss related to deteriorating health, with 1 reporting that 11% and the other 13.8% of their previously employed participants were unemployed at 2 months after acute disease [64], [140]. A US-based survey reported that unemployment and financial insecurity were more common among Long COVID respondents, which were associated with younger age [134]. Finally, the population-based Zurich Coronavirus cohort study (n=1543) reported unpublished data on the self-assessed work ability of Long COVID participants at 18 months (n=1184) using the CHRODIS+ Work Ability Index. From a scale of 0 (currently not able to work at all) to 10 (work ability at its best), on average, participants with mild Long COVID (15.3%) reported a work ability of 8. The average self-reported work ability of those with moderate (3.7%) Long COVID symptoms was 7, and that of severe Long COVID (2.3%) patients at about 4.5. In other words, those with more severe symptoms felt on average that their work ability was only half as good as before. Reduced work ability and resulting financial difficulties were reported to impact health and overall well-being, adding to stress and anxiety [16].

The NIHR review reported UK-based survey results with about 80% of all young patients (25 to 55 years) indicating that Long COVID had negatively affected their work life, and about half of them additionally mentioning financial difficulties [78]. Other surveys reported that about 45% of Long COVID patients were forced to reduce their workload at 3 months and beyond, while about 20% of them were not able to work half a year later [78], [83]. While there is no evidence on the broader economic implications of Long COVID yet, there is enough evidence that it affects a significant proportion of the formerly healthy

working population, which will likely lead to long-term economic as well as healthcare system strains [60], [78].

SUMMARY – Social and economic impact

- Long COVID can have an impact on daily life, family life, and social functioning [60]–[63], [78]
- Long COVID often leads to disrupted work (or school) life and long absences [23], [64], [65].
- In a Swiss study (n=1543), those experiencing severe symptoms reported that their work ability was on average half as good as their pre-infection work ability (at 18 months) [yet unpublished data, number of participants followed up until 18 months n=1184, number and percentage of participants with severe symptoms = 27 (2.3%)]
- Long COVID often reduces quality of life

*All newly added information (since last update) is marked in green

Treatment and Rehabilitation

The evidence on the treatment and rehabilitation of Long COVID has not been established yet, however it is underway. A search on clinicaltrials.gov and ISRCTN revealed 164 registered trials on the treatment (n=89) and rehabilitation (n=75) of Long COVID. Most of the treatment trials focus on medical treatments (prednisone, oxygen therapy), followed by dietary and behavioral interventions, health technology interventions, and alternative therapies such as aromatherapy, acupuncture, and osteopathic treatments. Most of the rehabilitation trials focus on behavioral or physical exercise interventions, often combined with digital devices, followed by health technology interventions and medical treatments. Of these 164 registered trials, 78 are still recruiting, 63 are not recruiting yet and 23 are completed but with no published results yet. For more details see appendix 6.

A systematic review reported preliminary evidence on the positive effects of pulmonary rehabilitation on exercise capacity and pulmonary functioning, as well as dyspnea, fatigue, and anxiety among previously hospitalized Long COVID. Yet, it remains unknown how pulmonary rehabilitation compares to other forms of rehabilitation [49]. Another review explored the role of tele-rehabilitation in Long COVID, reporting that it has the potential to improve functional capacity, dyspnea, performance, and physical components without posing any significant adverse event risk [50].

SUMMARY – Treatment and rehabilitation

- Reviews provide early evidence on the effectiveness of pulmonary rehabilitation and tele-rehabilitation [49], [50]
- Multiple trials on Long COVID treatment and rehabilitation are underway
- None of these trials have published results yet
- The research focus currently lies on drug therapies and behavioral interventions

European responses

Table 4 provides a list of current European health and social care responses.

Country	Responses [74]
United Kingdom	• NHS established care pathways for patients with symptoms 6 weeks after disease onset • NICE published Long COVID guidelines • Establishment of 80 NHS post-COVID clinics • Launch of NHS "Your COVID Recovery" digital initiative, providing self-care and self-management support • Hospitalized COVID-19 patients followed up at week 6 remotely • £50m funding for Long COVID-19 research
Germany	• Large hospitals offering Long COVID consultations and Long COVID outpatient services (focus on interdisciplinary care) • 70+ ambulant COVID-19 centers (only 2 with focus on post viral fatigue, 2/3 not adequately interdisciplinary)

	• Patient organization “Long Covid Deutschland” • Developed clinical guidelines, factsheets for healthcare personnel • Lay clinical guidelines for patients • Research and treatment of long-term effects of COVID-19 infections part of the government’s coalition agreement • Action Plan against Long COVID published by the German Society for ME/CFS and “Long Covid Deutschland” • €6.5m funding for Long COVID research • €5m funding for Long COVID treatment research (May 2022)
Italy	• Launch of Long COVID wards in some hospitals • Launch on multidisciplinary Long COVID Day-Hospital in several metropolitan areas (Rome, Monza, Modena, Milan, Genoa) • Specialized pediatric outpatient clinics at San Marco Hospital of Catania (Sicily) and Bambino Gesù Children’s Hospital (Rome) • Provision of Long COVID rehabilitation services by AbilityAmo (non-profit), including telemonitoring, home care, interdisciplinary and psychological support • Clinical guidelines for physicians and patients
Czech Republic	• Launch of Long COVID Care Centre for patients with symptoms 3 months after infection • Increase collaboration of GPs with pulmonary specialists for long-term care of patients

Spain	• Guidelines for treating Long COVID patients, by Spanish Society of GPs • Rehabilitation guidance services provided by hospitals and primary care facilities, targeting Long COVID patients • €1.8m governmental grant to open first Long COVID Clinic (expected to open in March 2022) • €1m funding for Long COVID research
Belgium	• Hospitals providing multidisciplinary services for post-ICU patients, at home or in specialized centers • Development of post-discharge care pathways • Initiative from Belgium's National Institute for Health and Disability Insurance to cover the cost for specialized Long COVID treatment
France	• National Authority for Health (HAS) published official guidelines for Long COVID follow-up • Patient organization "Association Covid Long France" • Law for the creation of a referral and management platform for Long COVID patients (Jan. 2022) • Certified Long COVID Rehabilitation Centers (e.g. 18 centers in the Occitaine Region), Outpatient Clinics and Hospital Units • 2.2 million Euro funding for Long COVID research
Austria	• Patient organization "Long COVID Austria" • Ministry for Social Affaires launches a Long Covid Information Website • Ministry for Social Affaires tasks "Gesundheit Österreich GmbH" to produce a report on the

Switzerland	status quo and possible challenges concerning Long COVID (January – April 2022) • Ministry for Social Affaires supports initiative "Aufatmen" that combines singing, breathing and physical exercises for patients suffering from Long COVID • Austrian Society for General and Family Medicine (ÖGAM) published official guidelines for Long COVID follow-up • Treatment primarily through GPs and existing specialized departments at hospitals • Long COVID Schweiz – Association and support for those affected • "Verband Long COVID" – Association dealing with legal issues concerning Long COVID • RAFAEL website – information platform for Long COVID patients in French language • Long COVID consultation hours in various large cities (in hospitals) • Long COVID citizen science board. Citizen science project by the Epidemiology, Biostatistics and Prevention Institute of the University of Zurich to develop priority research questions around Long COVID • Altea network for people living with Long COVID

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Appendix 1

List of newly included studies (update 9)

Antonelli, Michela, et al. "Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study." *The Lancet Infectious Diseases* 22.1 (2022): 43-55.

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Appendix 1.2

AMSTAR Scores for Reviews

Title and reference	AMSTER Score (quality)
Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19 [97]	Critically low
More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis [79]	Moderate
COVID-19 sequelae in adults aged less than 50 years: A systematic review [60]	Moderate
Rehabilitation and COVID-19: a rapid living systematic review by Cochrane Rehabilitation Field updated as of December 31st, 2020 and synthesis of the scientific literature of 2020 [80]	Moderate
Proposed delay for safe surgery after COVID-19 [81]	Moderate
Late Complications of COVID-19; a Systematic Review of Current Evidence [82]	Low
Characterizing long-term covid-19: a rapid living systematic review [30]	Moderate
Occurrence of long COVID: a rapid review [148]	Critically low
Long COVID, a comprehensive systematic scoping review [84]	Critically low
Living with COVID19. Second Review [78]	Critically low
Epidemiology of Long Covid. A Pragmatic Review of the Literature [83]	Critically low

Post-COVID-19 Syndrome: The Persistent Symptoms at the Post-viral Stage of the Disease. A Systematic Review of the Current Data [27]	Moderate
Post-acute COVID-19 syndrome [88]	Critically low
Long-COVID and Post-COVID Health Complications: An Up-to-Date Review on Clinical Conditions and Their Possible Molecular Mechanisms [85]	Critically low
Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis [105]	Moderate
Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology [149]	Critically low
Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments [43]	Low
Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19 [89]	Moderate
Cardio-Pulmonary Sequelae in Recovered COVID-19 Patients: Considerations for Primary Care [86]	Low
Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review [150]	Moderate
Global prevalence of prolonged gastrointestinal symptoms in COVID-19 survivors and potential pathogenesis: A systematic review and meta-analysis [151]	Low

Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis [104]	High
Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review [152]	Low
Long covid—mechanisms, risk factors, and management [28]	Low
Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review [153]	Low
Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis [154]	Low
Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19 [89]	Low
“Long COVID”: an insight [155]	Critically low
How common is Long COVID in children and adolescents? [99]	Critically low
Symptoms, complications and management of long COVID: a review [144]	Critically low
Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection [32]	Critically low
Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis [156]	Moderate
Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection. A Systematic Review [157]	Moderate

Persistent symptoms following SARS-CoV-2 infection among children and young people: a meta-analysis of controlled and uncontrolled studies. [98]	Moderate
Long-term effects of COVID-19 on mental health: A systematic review [158]	Low
Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review [159]	Low
Prevalence of long-term effects in individuals diagnosed with COVID-19: an updated living systematic review [160]	Low
Post-COVID-19 Syndrome [161]	Critically low
Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review [162]	Critically low
Post-acute sequelae of COVID-19 (PASC): a meta-narrative review of pathophysiology, prevalence, and management [33]	Critically low
Long COVID-19 in Children: From the Pathogenesis to the Biologically Plausible Roots of the Syndrome [116]	Critically low
Evidence mapping and review of long-COVID and its underlying pathophysiological mechanism [117]	Critically low
Post-acute Sequelae in COVID-19 Survivors: an Overview[163]	Critically low
Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis [101]	High

Prognostic Factors for Post-COVID-19 Syndrome: A Systematic Review and Meta-Analysis [124]	High
The effectiveness of pulmonary rehabilitation for Post-COVID symptoms: A rapid review of the literature [49]	Critically low
Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms [102]	Moderate
Telerehabilitation improves physical function and reduces dyspnea in people with COVID-19 and post-COVID-19 conditions: a systematic review [50]	Moderate
Persistent neurological manifestations in long COVID-19 syndrome: A systematic review and meta-analysis [96]	Low
Post-COVID-19 syndrome in children [36]	Critically low
Post COVID-19 Condition in Children and Adolescents: An Emerging Problem [37]	Critically low
Long-Term Consequences of COVID-19 at 6 Months and Above: A Systematic Review and Meta-Analysis [125]	Moderate
Sequelae of COVID-19 among previously hospitalized patients up to 1 year after discharge: a systematic review and meta-analysis [103]	High
A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic: call for research priority and action [164]	Moderate
Impact of COVID-19 vaccination on the risk of developing long-COVID and on existing long-COVID symptoms: A systematic review [165]	High

Sex differences in sequelae from COVID-19 infection and in long COVID syndrome: a review [166]	Moderate

Appendix 2

Prevalence estimates reported in studies (follow-up ≥ 12 weeks) without control groups or population-based samples & their risk of bias assessment

Authors [Reference] (# = preprint at time of data extraction)	Study Design	Cases (n=)	Hospitalized (%)	Follow-up (weeks)	Prevalence (%)	Risk of Bias*
Savarraj et al. [167]#	Cohort	48	100	≥12	71	a. high risk
						b. high risk
						c. high risk
Venturelli et al. [127]	Cohort	767	87	12 (median)	51.4	a. high risk
						b. high risk
						c. high risk
Moreno-Perez et al. [69]	Cohort	277	66	10-14	50.9	a. high risk
						b. high risk
						c. low risk
Sonnweber et al. [168]	Cohort	145	75	> 14	41	a. high risk
						b. high risk
						c. low risk
Buonsenso et al. [169]#	Survey	129	7	>17	52.7	a. high risk
						b. high risk
						c. low risk
Arnold et al. [70]	Cohort	110	100	8-12	74	a. high risk
						b. high risk
						c. low risk
Munblit et al. [136]#	Cohort	2649	100	31 (median)	47.1	a. low risk
						b. high risk
						c. high risk
Davis et al. [66]#	Survey	3762	8.4	Up to 24	66.7	a. high risk
						b. high risk
						c. high risk
Zhao et al. [170]	Cohort	55	100	12	64	a. High risk
						b. high risk
						c. low risk
Lerum et al. [62]	Cohort	103	100	12	54	a. high risk

						b. high risk
						c. low risk
Tabatabaei et al. [171]	Cohort	52	76.7	13 (mean)	42.3	a. high risk
						b. high risk
						c. low risk
Huang et al. [172]	Cohort	1733	100	26 (median)	76	a. high risk
						b. high risk
						c. low risk
Jacobson et al. [67]	Cohort	118	18.6	12-16	64.2 (non-hospitalized) 81.5 (hospitalized)	a. high risk
						b. high risk
						c. high risk
Perlis et al. [173]#	Survey	6211	-	≥ 24	2.2	a. low risk
						b. high risk
						c. high risk
Han et al. [174]	Cohort	114	100	24	35	a. high risk
						b. high risk
						c. low risk
Blanco et al. [175]	Cohort	100	100	15 (median)	52	a. high risk
						b. high risk
						c. high risk
Sykes et al. [176]	Cohort	134	100	16 (median)	86	a. high risk
						b. high risk
						c. high risk
Morin et al. [177]	Cohort	478	100	12- 16	51	a. high risk
						b. high risk
						c. high risk
Horvath et al. [178]	Cohort	102	0	12 (mean)	36 (smell alterations) 28 (taste alterations)	a. high risk
						b. high risk
						c. high risk
Bellan et al. [179]	Cohort	238	100	12-16	53.8 (functional impairment)	a. high risk
						b. high risk
						c. high risk

					17.2 (PTSD symptoms)	
Suárez-Robles et al. [180]	Cohort	134	100	13	>40	a. high risk
						b. high risk
						c. high risk
Simani et al. [181]	Cohort	120	100	24	17.5 (fatigue) 5.8 (PTSD)	a. high risk
						b. high risk
						c. low risk
Shah et al. [182]	Cohort	60	100	12	58	a. high risk
						b. high risk
						c. high risk
Khalaf et al. [183] #	Cohort	538	51.3	12	84.6	a. low risk
						b. low risk
						c. high risk
Townsend et al. [141]	Cohort	153	48	11 (median)	62	a. high risk
						a. high risk
						c. high risk
Darley et al. [184]	Cohort	78	12	up to 16	39.7	a. unclear
						b. high risk
						c. high risk
Wong et al. [131]	Cohort	78	100	12	76	a. high risk
						b. high risk
						c. low risk
De Santis et al. [185]	Cohort	113	0	12	75.9	a. high risk
						b. high risk
						c. low risk
Frontera et al. [133]	Cohort	382	100	24	>90	a. high risk
						b. high risk
						c. high risk
Mazza et al. [186]	Cohort	226	100	12	35.8	a. high risk
						b. high risk
						c. low risk
Ghosn et al. [142]	Cohort	1137	100	24	60	a. high risk
						b. high risk
						c. high risk

Horwitz et al. [187]	Cohort	152	100	24	74	a. high risk
						b. high risk
						c. high risk
Frontera et al. [134]	Survey	999	0	18 (mean)	25	a. low risk
						b. high risk
						c. high risk
Augustin et al. [135]	Cohort	353	2.9	28	34.8	a. high risk
						b. high risk
						c. high risk
Darcis et al. [188]	Cohort	199	100	24	>47	a. high risk
						b. high risk
						c. high risk
Romero-Duarte et al. [146]	Cohort	797	100	24	63.9	a. high risk
						b. high risk
						c. low risk
Ashkenazi-Hoffnung et al. [189]	Cohort	99	88	16	58.9	a. high risk
						b. high risk
						c. high risk
Blomberg et al. [190]	Cohort	312	21	24	61	a. high risk
						b. low risk
						c. low risk
Osmanov et al. # [191]	Cohort	518	100	20	24.3	a. high risk
						b. high risk
						c. high risk
Smane et al. [192]	Cohort	30	17	15	30	a. high risk
						b. high risk
						c. high risk
Rauch et al. [193]	Cohort	147	8.7	24	67	a. high risk
						b. high risk
						c. high risk
Budhiraja et al. [118]	Cohort	990	100	12-48	32%	a. High risk
						b. low risk
						c. high risk
Peghin et al. [29]	Cohort	559	26.2	27	40.2	a. high risk
						b. high risk

						c. high risk
Wong-Chew et al. [194]	Cohort	4670	100	12	68	a. high risk
						b. high risk
						c. high risk
Shoucri et al. [195]	Case series	1190	100	42	26.4	a. high risk
						b. high risk
						c. high risk
Asadi-Pooya et al. [112]	cohort	4681	100	12-42	57	a. low risk
						b. low risk
						c. high risk
Tleyjeh et al. [107]	cohort	222	100	28	29.7	a. high risk
						b. high risk
						c. high risk
Naik et al. [109]	cohort	1234	100	13	9.9	a. hjgh risk
						b. high risk
						c. high risk
Boscolo-Rizzo et al. [121]	cohort	357	09	42	53	a. high risk
						b. high risk
						c. hjgh risk
Kostev et al. [196]	cohort	6568	0	>12	1.7	a. high risk
						b. high risk
						c. low risk
Yoo et al. [113]	cohort	800	85	12	30.8	a. high risk
						b. high risk
						c. high risk
Righi et al. [197]	cohort	465	51	36	20	a. high risk
						b. high risk
						c. high risk
Miyazato et al. [123]	cross-sectional	457	-	84	8.8	a. high risk
						b. high risk
						c. high risk
The PHOSP-COVID Collaborative Group [115]	cohort	807	100	84	71.1	a. high risk
						b. high risk
						c. high risk

*risk of bias assessment based on 3 items, adapted from Hoy et al (reference 15, manuscript).: a) is the target population representative of the national population; b) was some sort of random selection used to select the sample, OR was a census undertaken? C) was the likelihood on non-response bias minimal? # = still at preprint stage

Appendix 3

Risk of bias assessment of studies (follow-up ≥ 12 weeks) reporting prevalence estimates and including control groups and/or population-based samples

Authors [Reference, as in manuscript]*	Risk of Bias
Cirulli et al. [12]	a. high risk
	b. high risk
	c. high risk
Desgranges et al. [4]	a. high risk
	b. high risk
	c. low risk
Graham et al. [2]	a. high risk
	b. high risk
	c. low risk
Havervall et al. [3]	a. high risk
	b. high risk
	c. high risk
Logue et al. [13]	a. high risk
	b. high risk
	c. low risk
Menges et al. [9]	a. low risk
	b. low risk
	c. high risk
Miller et al. [19]	a. high risk
	b. high risk
	c. high risk
Molteni et al. [24]	a. high risk
	b. high risk
	c. high risk
Petersen et al. [10]	a. low risk
	b. low risk
	c. low risk
Radtke et al. [18]	a. low risk
	b. low risk

	c. high risk
Stavem et al. [1]	a. high risk
	b. high risk
	c. high risk
Sudre et al. [11]	a. high risk
	b. high risk
	c. high risk
Xiong et al. [16]	a. high risk
	b. high risk
	c. low risk
Chevinsky et al. [5]	a. low risk
	b. low risk
	c. low risk
Zavala et al. [21]	a. low risk
	b. low risk
	c. high risk
Stephenson et al. [93]	a. high risk
	b. low risk
	c. high risk
Bliddal et al. [6]	a. low risk
	b. low risk
	c. high risk
Whittaker et al. [15]	a. low risk
	b. high risk
	c. low risk
Borch et al. [22]	a. low risk
	b. low risk
	c. high risk
Berg et al. [23]	a. low risk
	b. low risk
	c. high risk
Merzon et al. [25]	a. low risk
	b. low risk
	c. low risk
Antonelli et al. [7]	a. low risk

	b. high risk
	c. high risk
Ballouz et al. [8]	a. low risk
	b. low risk
	c. low risk

*risk of bias assessment based on 3 items, adapted from Hoy et al (reference 15, manuscript).: a) is the target population representative of the national population; b) was some sort of random selection used to select the sample, OR was a census undertaken? c) was the likelihood on non-response bias minimal?

Appendix 4

Reported Long COVID Symptoms

Symptoms (number of reviews reporting symptom)
SYSTEMIC fatigue (n=33), headache (n=19), fever (n=8), chest pain (n=19), excessive sweating (n=1), chills (n=1)
RESPIRATORY dyspnea / breathlessness (n=31), cough (n=19), pulmonary fibrosis (n=4), lung hypoperfusion (n=1), impaired lung function (n=4), thromboembolism (n=5), sore throat (n=7), nasal congestion (n=3), sputum (n=3)
CARDIOVASCULAR & HEMATOLOGICAL palpitations & arrhythmias (n=11), peri-, myoperi- and myocarditis (n=2), tachycardia (n=3), cardiac stroke (n=1), venous/arterial thrombosis (n=1), myocardial inflammation (n=2), limb edema (n=2)
NEUROLOGICAL & NEUROCOGNITIVE hyperesthesia (n=1), loss or altered smell (n=24), loss or altered taste (n=21), numbness (n=1), muscle weakness (n=6), cognitive fatigue (n=1), apathy (n=1), stroke (n=2), neuropathy (n=2), myopathy (n=1), muscle pain (myalgia) (n=16), joint pain (arthralgia) (n=15), intracerebral hematoma (n=1), cerebral venous thrombosis (n=1), bladder incontinence (n=2), swallowing difficulties (n=1), encephalopathy (n=1), dizziness / vertigo (n=5), tinnitus (n=4), earache (n=1), visual disorders / eye redness (n=3), hearing loss (n=2), spasms (n=1), muscle atrophy (n=1), brain fog and memory loss (n=16), depression (n=11), sleep disorders (n=17), attention disorders (n=12), anxiety (n=13), posttraumatic symptoms (n=5), executive functioning difficulties (n=4), ataxia (n=2), change of voice (n=1), dysphagia (n=1), tingling (n=1)
GASTROINESTINAL general gastrointestinal complaints (n=5), diarrhea (n=11), vomiting (n=6), loss of appetite (n=8), nausea (n=6), abdominal pain (n=7), bowel incontinence (n=1), acid reflux (n=2), gastrointestinal bleeding (n=1), constipation (n=1), sudden loss of body weight (n=2)
CUTANEOUS skin rashes (n=9), alopecia (n=7)

Appendix 5

Studies on the role of vaccination in Long COVID

Studies on pre-infection vaccination (preventive)

Study	Brief summary
Antonelli, Michela, et al. "Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study." *The Lancet Infectious Diseases* 22.1 (2022): 43-55.	Antonelli M et al. conducted a large, nested case-control study using self-reported data from UK-based of a COVID symptom mobile phone app. Cases had to have either one or two vaccinations and subsequent infection (breakthrough infection). Fully vaccinated cases were half as likely to report long-term symptoms (≥28 days) than unvaccinated controls. Partially vaccinated cases showed no difference from unvaccinated cases.
Al-Aly, Ziyad, Benjamin Bowe, and Yan Xie. "Long COVID after breakthrough SARS-CoV-2 infection." *Nature Medicine* (2022): 1-7.	Al-Aly et al. conducted a prospective cohort study 33.940 breakthrough infection participants. Vaccinated cases were less likely to die, as well as have at least 1 long-term symptom (≥30 days) at 6 months compared with unvaccinated cases.
Arjun, M. C., et al. "Prevalence, characteristics, and predictors of Long COVID among diagnosed cases of COVID-19." *medRxiv*(2022).	Arjun et al. surveyed 487 COVID-19 cases in a single hospital and concluded that fully vaccinated participants were more likely to have long COVID symptoms 4 weeks from the date of diagnosis than unvaccinated participants. These results are conflicting with all other studies.
Kuodi, Paul, et al. "Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients infected	Kuodi et al. conducted a cross-sectional nested study 951 COVID-19 cases, 294 of which were fully and 340 partially vaccinated. Their findings suggest that vaccinated participants (2 or 3

between March 2020 and November 2021." *MedRxiv* (2022).	doses) were at least half as likely to report 7 out of 10 common long COVID symptoms. These findings were stronger in the older age group (>60).
Senjam, Suraj Singh, et al. "Assessment of Post COVID-19 Health Problems and its Determinants in North India: A descriptive cross section study." *medRxiv* (2021).	Senjam et al. conducted a cross-sectional study, examining whether pre-infection vaccination was associated with Long COVID symptoms 4 to 12 weeks after acute illness in 773 participants. Fully vaccinated participants were less likely to have Long COVID symptoms.
Simon, Michael A., Ryan D. Luginbuhl, and Richard Parker. "Reduced Incidence of Long-COVID Symptoms Related to Administration of COVID-19 Vaccines Both Before COVID-19 Diagnosis and Up to 12 Weeks After." *medRxiv* (2021).	Simon et al. conducted a retrospective cohort, examining whether vaccination before or after infection was associated with long COVID symptoms 12 to 20 weeks after acute disease, including 240,648 cases. Only about 1% of those had received their vaccine before, and about 7% within 12 weeks after infection. Those vaccinated before were much less likely to have any long COVID symptoms compared to those remaining unvaccinated. Those vaccinated up to 12 weeks after diagnosis were less likely to report multiple long COVID symptoms.
Taquet, Maxime, Quentin Dercon, and Paul J. Harrison. "Six-month sequelae of post-vaccination SARS-CoV-2 infection: a retrospective cohort study of 10,024 breakthrough infections." *Brain, behavior, and immunity* 103 (2022): 154-162.	Taquet et al. conducted a retrospective cohort study, analyzing data from the mostly US-based TriNetX electronic health records network and comparing individuals (n=9479) receiving a COVID-19 vaccine at least 2 weeks before infection and influenza vaccinated matched controls. Their findings suggest no association

	between vaccination (at least one dose) and Long COVID 6 months after infection. Those with two vaccine doses were less likely to be diagnosed with some long COVID symptoms such as anosmia, fatigue, hair loss, myalgia, and general pain.
Azzolini, Elena, et al. "Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers." *JAMA* (2022).	Azzolini et al. conducted a prospective cohort study, following up 2560 healthcare professionals from 9 Italian healthcare facilities. Their findings suggest that 2 or 3 doses of vaccine, compared with no vaccination, were associated with lower long COVID prevalence.

Studies on post-infection vaccination (therapeutic)

Study	Brief summary
Arnold, David T., et al. "Are vaccines safe in patients with Long COVID? A prospective observational study." *MedRxiv* (2021).-55.	Arnold et al. conducted a prospective cohort study, examining the association between post-infection vaccination in previously hospitalized patients and long COVID symptoms. The study included 44 vaccinated participants and 22 matched controls. At 1 month after vaccination more vaccinated participants reported their symptoms improved than unvaccinated participants, and fewer vaccinated participants reported their symptoms worsened than those unvaccinated. A similar percentage of vaccinated and unvaccinated participants had unchanged symptoms.
AYOUBKHANI, Daniel, et al. Trajectory of long covid symptoms after covid-19 vaccination: community-based cohort study. *bmj*, 2022, vol. 377.	Ayoubkhani et al. looked at Long COVID symptoms among 28356 participants who were vaccinated post-infection. A first vaccine dose was associated with about 13% decrease in the odds of Long COVID. The second dose was associated an initial decrease of about 9%. Associations were similar for mRNA and adenovirus vaccine types.
Gaber, Tarek AZ K., et al. "Are mRNA covid 19 vaccines safe in long covid patients? A health care workers perspective." *British Journal of Medical Practitioners* 14.1 (2021): NA-NA.	Gaber et al. conducted a UK-based prospective study, including 67 healthcare workers with Long COVID receiving the vaccine post-infection. About 21% reported improvement in 1 or more of their symptoms, 12% reported worsening in symptoms, and 67% reported no change in their symptoms.

Strain, William David, et al. "The Impact of COVID Vaccination on Symptoms of Long COVID: An International Survey of People with Lived Experience of Long COVID." *Vaccines* 10.5 (2022): 652.	Strain et al. asked 812 individuals with Long COVID (mainly in the UK) if and how their symptoms changed after vaccination. About 57% of participants reported an improvement in symptoms after vaccination, 25% of participants reported no change in symptoms, while 19% of participants reported a worsening of symptoms, with Moderna having the most participants report an improvement and least report a deterioration.
Scherlinger, Marc, et al. "Effect of SARS-CoV-2 vaccination on symptoms from post-acute COVID syndrome: results from the national VAXILONG survey." *medRxiv* (2021).	Scherlinger et al. asked 380 French-speaking adults with Long COVID whether their symptoms improved or worsened after vaccination. Their findings suggest that 31% experienced overall worsening of symptoms, while about 22% experienced overall improvement. About half reported no changes. There were no differences between vaccine types.
Tran, Viet-Thi, et al. "Efficacy of COVID-19 vaccination on the symptoms of patients with long COVID: a target trial emulation using data from the ComPaRe e-cohort in France." (2021).	Tran et al. conducted a prospective cohort study with 455 vaccinated Long COVID patients and 455 unvaccinated controls. Long COVID symptoms were less severe in vaccinated compared with unvaccinated participants 120 days after recruitment and more vaccinated than unvaccinated participants had remission of all long COVID symptoms. Few vaccinated people found their symptoms unacceptable, reporting an overall lower Long COVID impact.

Wanga, Valentine, et al. "Long-term symptoms among adults tested for SARS-CoV-2—United States, January 2020–April 2021." *Morbidity and Mortality Weekly Report* 70.36 (2021): 1235.	Wanga et al. conducted an online survey among 385 individuals with long-term symptoms, 100 of whom had a confirmed COVID-19 infection. The study asked about symptom changes after vaccination. Those with a confirmed infection were more likely to report overall improved symptoms, but also initial worsening.
Nehme, Mayssam, et al. "Symptoms after COVID-19 vaccination in patients with post-acute sequelae of SARS-CoV-2." *Journal of General Internal Medicine* 37.6 (2022): 1585-1588.	Nehme et al. conducted an online survey among 2084 individuals with Long COVID in Switzerland. Following vaccination, symptoms disappeared or improved in 35 % of cases, were stable in 29% of cases, and worsened in 3% of cases. Symptoms' evolution was reported as other in 29% of cases and 3% preferred not to answer.
Wisnivesky, Juan P., et al. "Association of Vaccination with the Persistence of Post-COVID Symptoms." *Journal of general internal medicine* (2022): 1-6.	Wisnivesky used data from a prospective cohort of 453 Long COVID patients, finding no association between vaccination and symptom improvement.

Appendix 6

Registered trials on Long COVID treatment and rehabilitation

164 registered trials on Long Covid or Post Covid Syndrome

- **89** investigating **treatment options**
  - 53 medical interventions (4x prednisone, 4x oxygen therapy)
  - 11 dietary interventions
  - 6 behavioral interventions
  - 9 health technology interventions
  - 10 “other” interventions (aromatherapy, acupuncture, osteopathic)
- **75** investigating **rehabilitation**
  - 45 behavioral or physical exercise interventions (16 in combination with digital interventions)
  - 10 health technology interventions
  - 2 medical interventions
  - 2 dietary interventions
  - 16 “other” rehabilitation interventions

- Status of the Trials:
  - 53 not yet recruiting
  - 78 recruiting
    10 active, but not recruiting
  - 23 completed