Literature screening report – Update 7

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

Report submission date:	17.03.2022

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Note:	The references listed at the end of this report are uploaded and can be retrieved from the FOPH's COVID-19 Literature database in Citavi. Please contact Marc Wittwer (FOPH) - marc.wittwer@bag.admin.ch

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 of Long COVID, and healthcare responses to Long COVID in Europe have been developed together with FOPH to serve their needs best.

The final analysis for the review's 7th update included 40 reviews and 141 primary studies. Prevalence estimates were heterogeneous and included a wide range of study populations. Overall, the prevalence estimate for adults in the general adult population based on high-quality studies is estimated at 20%. We identified seven population-based and/or control group studies reporting Long COVID prevalence estimates (⩾4week follow-up) in children and teenagers. All seven included either exclusively non-hospitalized or primarily non-hospitalized children, with a median prevalence estimate of 2.9% (range 0.8% - 13.2%).

Reviews reported more than 50 symptoms, with fatigue, headache, dyspnea, smell and taste disturbances, and cognitive impairment being most common. Preliminary evidence suggests that in adults, female sex, age (35-60), comorbidities, the severity and symptom burden of acute disease,

obesity and the presence of IgM and IgG antibodies are associated with Long COVID. In children, Long COVID may be associated 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.

Most studies (n=31) reported socio-economic implications beyond 12 weeks. Among those, most reported high rates of reduced quality of life (14/31), followed by limitations in daily functioning (12/31), disrupted work-life (10/31), disrupted social life (3/31), and disrupted family life (1/31). Fewer studies (n=12) reported socio-economic implications below 12 weeks. Most of these reported disrupted work-life (6/12), reduced quality of life (3/12), functioning limitations (2/12), disrupted social life (1/12), and stigma (1/12).

The evidence on the treatment and rehabilitation of Long COVID has not been established yet, however, is underway (54 registered trials on the treatment and 47 registered trials rehabilitations 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.

Our review critically synthesizes available evidence on the prevalence of Long COVID among 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

KEY MESSAGES

The WHO defines 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."*

Burden of disease

- The median of six reported prevalence estimates for non-hospitalized adults is 14% (7.5% - 41%)
- The median of six reported prevalence estimates in mixed (hospitalized & non) adult samples is 27% (2.3% - 53.1%)
- Two study reports Long COVID in previously hospitalized adults, reporting a prevalence of 7% and 37.6%
- The median of seven estimates among mostly non-hospitalized children and teenagers is 2.9% (0.8% - 13.2%)

Symptoms, risk, and protective factors

- Reviews reported more than 50 symptoms
- Fatigue, headache, dyspnea, smell and taste disturbances, and cognitive impairment are the most common
- Symptoms can be very debilitating, as well as remit and relapse
- In adults, female sex, age (35-60), comorbidities, the severity of acute disease, obesity, and the presence of IgM and IgG antibodies may be increasing the risk for Long COVID
- In children, female sex, age (5-17 years), female sex, history of allergic conditions, other pre-existing chronic conditions, and hospitalization during acute infection may be increasing the risk for Long COVID

Socio-economic implications

- Many of those living with Long COVID report functional restrictions, as well as impaired family and social life
- Many of those living with Long COVID remain out of work for longer periods adjust their workloads
- Overall, Long COVID seems to have a negative impact on quality of life

Background

Long-term health consequences of SARS-CoV-2 are increasingly being reported worldwide, gradually receiving the attention of researchers, healthcare providers, and policymakers. 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 [1]. 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 [2]. Long COVID is a novel syndrome that is broadly defined by the persistence of physical and/or mental symptoms following a SARS-CoV-2 infection for a longer than usual period. The definitions and terminology around that novel syndrome are emerging and incoherent. Equally emerging is our understanding of how to diagnose, treat and manage Long COVID, with evidence rapidly evolving, however, many questions remain unanswered. Funding bodies around the world launched funding opportunities on the long-term consequences of COVID-19. Congress of the United States (US) approved funding of more than one billion US $ and the United Kingdom Research and Innovation (UKRI) issued a call for research into the longer-term effects of Covid19 in non-hospitalized individuals with funding of 18.5 English £ [3][4]. In the meantime, those affected describe an impairing, debilitating, and complex disease, sometimes keeping them out of work and social life [5]. 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 of the novel syndrome. 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 risk and protective factors?
- What is the current social and economic impact 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 five 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.

The review was updated on March 2022 to include new evidence from reviews and primary studies. Primary studies were identified in two 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 (b) the socio-economic impact of Long COVID, as these two 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 four different sections, each corresponding to one of the research sections. Information was synthesized narratively and guided by the five 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 NICE guidelines [6], 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. 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).

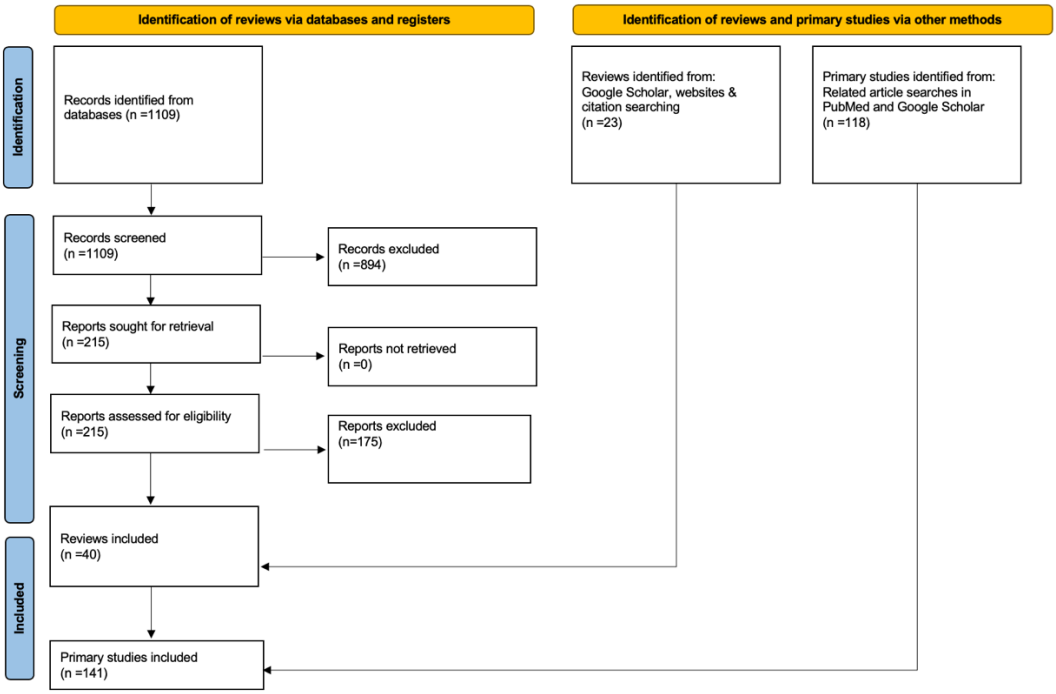
Risk of bias (quality) assessment

The quality of reviews was assessed using the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) checklist [7]. The quality of primary studies that report prevalence estimates (≥ 12-week follow-up for adults, ≥ 4-week follow-up for children) was evaluated with three items, adapted from the Hoy et al.[8] 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

For the March 2022 update, our database searches yielded 99 additional references (a total of 1109 since the review's first version). 72 of those were excluded at the title and abstract screening and 27 manuscripts were screened full text. That led to the exclusion of 22 further studies, leading to the inclusion of 5 new reviews (40 in total). For the March 2022 update, we included new evidence from 20 primary studies, 13 of them included in at least one of the 7 reviews and 7 identified through related article searches in PubMed and Google Scholar (141 primary studies in total since the reviews first version). 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 [9]



Characteristics of included reviews

Of all included reviews, one was published in 2020, 35 in ,2021 and four in 2022. Most studies were traditional systematic reviews (n=24), followed by systematic reviews with a meta-analysis (n=8), pragmatic reviews (n=3), rapid reviews (n=2), rapid living systematic reviews (n=2), and a scoping review (n=1). Three addressed pediatric patients and adolescents, one middle-aged and young adults, and the remaining (n=26) 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 14 scoring critically low, 12 scoring low, 13 scoring moderate, and one scoring high-quality points. The full quality assessment table is provided in appendix 1.2.

Characteristics of included primary studies

Most primary studies (n=86) were published in 2021, followed by 43 publications in 2020 and 12 in 2022. The majority were conducted in Europe (n=90), followed by North America (n=27), Asia (n=22), Africa (n=1), South America (n=1), and one multinational study. Methodologically, most primary research is based on prospective cohorts (n=99), followed by cross-sectional and survey designs (n=24), retrospective cohorts (n=16), case series, and case-control studies (n=2). Most studies included hospital-based samples and previously hospitalized participants (n=61). Exclusively non-hospitalized participants were included in 27 studies while the remaining 53 had mixed samples of previously hospitalized, as well as non-hospitalized participants.

Evolving definitions of Long COVID

Terminology

This review has adopted the term Long COVID, being the currently most widespread and broad description of long-term SARS-CoV-2-related complications [10] and the term most accepted by persons living with Long Covid, the literature provides a very diverse set of terminology. 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” [10]–[16]. 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 [17]–[20].

Definitions

The WHO has recently 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" [21]. The literature provides alternative definitions. Michelen et al. [17] 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 [16] [17]. Beyond symptoms, others also include abnormal, but potentially asymptomatic clinical parameters persisting as part of Long COVID [11]. Several reviews referred to the recently published National Institute for Health and Care Excellence (NICE) guidelines, which classify Long COVID in two 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 [10][15][17][6][22]. Others disagree with that "by exclusion" approach, as it might fail to capture the very broad spectrum of post-acute complications [16], including SARS-CoV-2-triggered new health conditions and worsening of pre-existing health conditions [10]. Others set the cut-offs at 60 days after diagnosis or at least 30 days after recovery/hospital discharge [23]. The dynamic review of the 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 [10]. 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 [10][24]. Others broadly defined it as lasting or persisting outcomes after recovery from acute disease [25]. Terminology also varies between studies conducted in Switzerland, with the population-based Zurich Coronavirus Cohort study using the term "Post-COVID-19 Syndrome" [2] and the Geneva-based cohort study "Long COVID" [1].

SUMMARY – Evolving definitions of Long COVID

- the literature provides a diverse set of terminology, with "Long COVID" being the most widespread and accepted
- The WHO defines Long COVID as symptoms occurring within 3 months of a SARS-CoV-2 infection and lasting for more than 2 months, with no alternative diagnosis

Burden of Disease (evidence from primary studies)

Studies reporting Long COVID prevalence estimates vary methodologically, including 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) [10]. It is therefore essential to view all current estimates with their methodologies and respective definitions in mind.

In total, 70 of the 141 included studies provided overall Long COVID prevalence estimates at ≥ 12 weeks after acute infection. Twenty-one studies included population-based samples and/or control groups and are reported in detail. Prevalence estimates reported in the 49 primary studies without control groups or population-based samples are provided in appendix 2. We report 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 estimate for controls). There is currently no robust evidence on how the omicron variant influences Long COVID.

Adults

We identified 14 population-based and/or control group studies reporting Long COVID prevalence estimates (≥ 12week follow-up) in adults, summarized in Table 1. Three population-based and three studies with control groups reported prevalence estimates for non-hospitalized adults with a median estimate of 14% (7.5% - 41%). Three population-based and three studies with control groups included samples with non-hospitalized as well as previously hospitalized participants, with a median estimate of 27% (2.3% - 53.1%). Finally, two studies (with a control group) report the prevalence among previously hospitalized participants, estimating the prevalence at 7% and 37.6% respectively.

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.[26] [p]	451	NA	NA	6-24 [positive test]	41	-	-
Graham et al.[27] [c]	100	NA	50	18 – 23 [symptom onset]	67.8	60.3	7.5
Havervall et al.[28] [c]	323	NA	1027	≥ 32 [January 2020]	15	3	12
#Desgranges et al.[29] [c]	418	NA	89	12-40 [acute disease]	53	37	16
Chevinsky et al.[30] [p ;c]	46857	NA	46857	4-17 [acute disease]	7.7	-	-
Bliddal et al. [31] [p]	445	NA	NA	4-12 [July 2020]	40	-	-
hospitalized & non-hospitalized adults							
Menges et al.[32] [p]	431	19	NA	29 [acute disease]	26	-	-
Petersen et al.[33] [p]	180	4	NA	18 [acute disease]	53.1	-	-
Sudre et al.[34] [c]	4182	14	4182	≥ 12 [symptom onset]	2.3	-	-
#Cirulli et al.[35] [c]	357	3	5497	12 [January 2020]	14.8	7	7.8
Logue et al.[36] [c]	177	9	21	12-36 [symptom onset]	32.8	4.8	28
#Whittaker et al. [37] [p]	46687	3	NA	⩾ 12 [August 2020]	3.5	-	-
hospitalized adults							
Xiong et al.[38] [c]	538	100	184	>12 [hospital discharge]	49.6**	12	37.6
Chevinsky et al.[30] [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 provide the most robust prevalence estimates currently reported, all are subject to certain limitations. Stavem et al.[26] included a predominantly female and older sample (>50 years of age), with the study's findings being subject to recall bias. Graham et al. [27] are 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. [28] are 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.[32] (conducted in Switzerland) as well Petersen et al. [32] did not

assess pre-COVID physical or mental health, while the very low estimate by Sudre et al. [34] 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. [35] 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 seven population-based and/or control group studies reporting Long COVID prevalence estimates (⩾4week follow-up) in children and teenagers, summarized in Table 2. Six studies included exclusively non-hospitalized or primarily non-hospitalized children, with a median prevalence estimate of 2.9% (0.8% - 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.[39] [p ; c]	109	NA	1246	>12 [October 2020]	4	2	2
#Miller et al.[40] [c]	175	NA	4503	⩾4 [February 2020]	4.6	1.7	2.9
Stephenson et al.[41] [p ; c]	3065	NA	3739	12 [September 2020)	66.5	53.3	13.2
Zavala et al.[42] [p ;c]	472	0.01%	387	4 [February 2021]	6.7	4.2	2.5
Borch et al. [43] [p ; c]	15041	NA	15080	>4 [January 2021]	28	27.2	0.8
Berg et al. [p ; c]	6630	NA	21640	4-48 [acute illness)	61.9	57	4.9
Hospitalized and non-hospitalized children							
Molteni et al.[44] [c]	1734	2	1734	⩾4 [symptom onset]	4.4	0.9	3.5

#=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 seven estimates need to be viewed in consideration of the following methodological characteristics. The Swiss Ciao Corona study by Radtke et al. [39] had the primary aim of investigating seroprevalence rates in Swiss schools. 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 [40]. As with Ciao Corona, the study encompassed tested, as well as non-tested children [40]. The findings by Miller et al. [40] are limited by the study's small sample size. Molteni et al.[44] 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 one to three months after acute infection, with the source population including PCR-confirmed children and young people [45]. 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 [46], [47].

Risk of bias assessment for studies reporting prevalence estimates

Risk of bias was assessed for all 21 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, ten studies (48%) scored "low risk" for the first item ("is the target population representative of the national population"), nine studies (43%) scored "low risk" for the second item ("is some sort of random selection used to select the sample"), and seven (33%) scored "low risk" for the third item ("is the likelihood of non-response bias minimized")[8]. 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

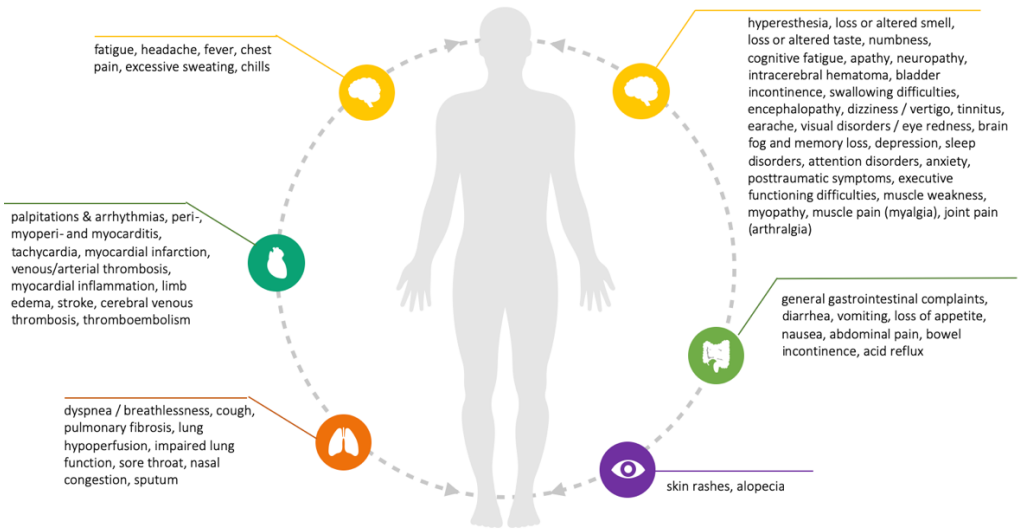
- Long COVID affects both, adults and children
- the median prevalence estimates of Long COVID in adults lie between 14% and 27%
- the median prevalence estimate of Long COVID children is much lower, at 2.9%

What are the reported Long COVID symptoms, as well risk and protective factors?

Symptoms

Symptoms are the primary focus of most identified reviews. The most commonly mentioned symptoms include fatigue, which also seems to be the most prevalent one (also amongst those with mild initial disease) [10], 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 [1], [2].

A group of patients exclusively experiences fatigue or upper respiratory complaints, while others multiple and multi-system symptoms [10]. While many continuously experience one or multiple symptoms, reviews report and flare-ups, also described as the "corona coaster" [10][15]. Symptoms are often reported as debilitating, having a strong negative impact on mental health and quality of life [16]. 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 [48]–[50]. Most existing reviews 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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Risk and protective factors

Table 3: Risk factors adults

Outcome	Reported risk factors	References
Long COVID occurrence	(1) female sex (2) age (35-60) (3) comorbidities (mental and physical, three or more, especially asthma, other lung diseases, hypertension, hypoxia, hypothyroidism, psychological conditions (4) severity of acute disease (e.g., hospitalization, duration of hospitalization, higher imaging scores, ICU need, duration of oxygen supplementation, pneumonia, presence of dyspnea) (5) more than five 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	[10] [12] [15] [16] [17][19] [20] [22] [25] [31] [48] [51] [52] [53] [54] [55] [56] [57] [58] [59] [60] [61]
Long COVID severity • cardiovascular	(1) number of symptoms during acute disease	[53] [58] [62] [63] [64] [65] [46]

• increased disability • prolonged fatigue • prolonged dyspnea	(2) severity of acute disease (ICU need, longer hospital stay, presence of dyspnea and confusion) (3) not being vaccinated (4) age (35-60) (5) comorbidities (cancer, respiratory function abnormalities, depression) (6) female sex (7) BMI 25 or above	

For some of these factors, the evidence seems to be mixed or symptom-dependent. For example, smell and taste disturbances do not seem to be associated with most of these risk factors, and if so, are more common in younger age groups [16][17]. Similarly, the NIHR review, as well as Sarfraz and colleagues emphasize that Long COVID seems to be more common in young adults (and children) than expected, with about 20% of young individuals not returning to baseline health at 16 days after infection [10] [20]. Crook et al., as well as Nasserie et al. report that the 35-49 age groups might be the most heavily affected, followed by the 50-69 age group [23][51]. The remaining ambiguity around Long COVID risk factors may be due to differences in reporting, study designs, variations in participant characteristics (clinical, demographic, socio-economic), as well as Long COVID's complex and multifaceted pathophysiology [54].

Only one study provided a detailed symptom progression over time, following up 3762 Long COVID patients to 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 three months, the number of symptoms was highest at month 2, with an overall slower decline [66].

Socio-cultural factors

Mental symptoms, especially posttraumatic ones seem to be affecting younger people, women, and those with responsibilities for others [16]. Preliminary evidence additionally suggests that ethnic minorities and those living further away from urban regions might be affected the strongest, likely due to social and infrastructural inequities [67]. 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 inability to work remotely, lack of adequate personal protective equipment, and overcrowded living conditions [56].

Risk factors in children

Preliminary evidence on risk factors for children suggests that age (5-17 years), sex (female), history of allergic conditions, other pre-existing chronic conditions, and overall poorer physical and mental health, as well as hospitalization during acute infection, may be associated with Long COVID and Long COVID duration (>2 months) [43], [47], [49], [50], [55]. In particular, Long COVID-19 may be linked with the mast cell activation syndrome and the immunological response of T-helper type 2 (Th2) in children with allergic diseases [68].

Sex gap

Female sex is an often-mentioned risk factor for the occurrence of Long COVID as well as certain debilitating Long COVID symptoms [31], [68]. 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 [68]. 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 [68]. There is currently no robust evidence on the role of sex to the severity of Long COVID

Protective factors

Beyond physical fitness levels, being treated with interferon β-1b based triple antiviral therapy during hospital stay and potentially immunosuppression (still under debate), no further protective factors are reported in any of the identified reviews [12], [51], [55].

SUMMARY – Symptoms, Risk- and protective factors

- Long COVID is associated with over 50 different symptoms, most commonly fatigue,
- Risk factors are not well understood yet, but female sex, age, certain comorbidities, the severity of acute SARS-CoV-2 infection, obesity, and the presence of IgM and IgG antibodies seem to increase the risk for Long COVID
- In addition to all the above, not being vaccinated may increase the risk of more severe Long COVID, yet evidence remains limited
- physical fitness levels, being treated with interferon β-1b based triple antiviral therapy during hospital stay and potentially immunosuppression (still under debate) are the only currently reported protective factors

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, (c) and 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. Most studies (n=31) reported socio-economic implications beyond 12 weeks. Among those, most reported high rates of reduced quality of life (14/31), followed by limitations in daily functioning (12/31), disrupted work-life (10/31), disrupted social life (3/31), and disrupted family life (1/31). Fewer studies (n=12) reported socio-economic implications below 12 weeks. Most of these reported disrupted work-life (6/12), reduced quality of life (3/12), functioning limitations (2/12), disrupted social life (1/12), and stigma (1/12).

Family and social functioning

About 17% (24/141) of all included primary studies reported some degree of daily life, family, and social functioning impairment related to Long COVID. Many report functional restrictions that often require lifestyle changes, changes in physical activity levels, restricted social life, and role limitations [69][70][71][72]. They also report that symptoms affect their family life and often limit their ability to care for others [10]. Neurological, cognitive, and mental symptoms, such as anxiety or memory loss strongly impact daily living and quality of life, while routine activities, such as driving and cooking can become very difficult or even impossible [12][15][16][73]. Two cohort studies report 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 [74][75]. 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 [76][77], with about 15% still reporting social and home disruptions 8 months after disease onset [28]. One population-based cross-sectional study from Denmark reports that children and teenagers with Long COVID are 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 [47].

For some, even those who were completely independent before, these limitations are often severe enough that require daily assistance, or at least some form of dependency [10][15][78]. 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 [28]. Two cohort studies, both following-up previously hospitalized patients for about 2 months report that 16% of participants faced reduced self-care capacity due to Long COVID [75][79]. 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 [80]. 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 [81]. An important proportion of previously independent patients experience Long COVID impairments that deem them full care-dependent [10]. Finally, about 16% (n=16) of all included primary studies report that the majority of those living with Long COVID perceive their quality of life as significantly reduced [27], [82]–[88].

Often, those living with Long COVID report 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 [89].

Work-related implications

Inevitably, Long COVID is also expected to have a considerable impact on the workforce [10]. About 12% (17/141) of all included primary studies report employment-related consequences of Long COVID. In studies on previously hospitalized patients, absence from work due to Long COVID is reported from 9% to 40% of those previously employed at 2 to 3 months after discharge [74] [75][90][91]. For those heavily affected with neurological sequelae, absence from work is also reported as high as 59% at 6 months after hospital discharge [73].

Research on primarily mild to moderate and non-hospitalized SARS-CoV-2 cases report that about 11% to 23% remain absent from work (or had long absence periods) at 3 to 7 months after acute disease [77][66][92]. 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 work at 6 weeks after acute illness [76][93]. Beyond full absence, studies report 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 report that 15%, 29%, and 40% of their employed participants reported work impairments and adjusted their employment to their current circumstances [46]. Another large prospective cohort study with previously hospitalized participants from France reports that 29% of those initially employed had not returned at 6 months [94]. These numbers range from 8% to 45% for previously mild to moderate cases at follow-up of 3 to 8 months [28][77][66]. Finally, two studies report permanent employment loss related to deteriorating health, with one reporting that 11% and the other 13.8% of their previously employed participants were unemployed at 2 months after acute disease [74][95]. A US-based survey reports that unemployment and financial insecurity were more common among Long COVID respondents, which were associated with younger age [96].

The NIHR review reports UK-based survey results with about 80% of all young patients (25 to 55 years) reporting that Long COVID has negatively affected their work life, with about half of them additionally reporting related financial difficulties [10]. Other surveys report that about 45% of Long COVID patients were forced to reduce their workload at three months and beyond, while about 20% of them were not able to work half a year later [10][15]. 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 [10][69].

SUMMARY – Social and economic impact

- Long COVID can have an impact daily life, family life and social functioning
- Long COVID often leads to disrupted work life and long absences
- Long COVID often reduces quality of life

Treatment and Rehabilitation

The evidence on the treatment and rehabilitation of Long COVID has not been established yet, however is underway. A search on clinicaltrials.gov and ISRCTN revealed 101 registered trials on the treatment (n=54) and rehabilitations of Long COVID (n=47). 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 101 registered trials, 54 are still recruiting, 27 are not recruiting yet and 17 are completed but with no published results yet. For more details see appendix 5.

SUMMARY – Treatment and rehabilitation

- Multiple trials on Long COBVID treatment and rehabilitation are underway
- None of these trials have published results yet
- 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 [5]
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 • £18.5m funding for long covid research
Germany	• Large hospitals offering Long COVID consultations and post-COVID outpatient services (focus on interdisciplinary care) • 70+ ambulant covid 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

Italy	• Launch of post-COVID wards in some hospitals • Launch on multidisciplinary Post-COVID-19 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 post-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 post-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 Post-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 chronic covid-19 patients (Jan. 2022) • Certified Post-Covid Rehabilitation Centers (e.g., 18 centers in the Occitaine Region), Outpatient Clinics and Hospital Units • €2.2m funding for long covid research
Austria	• Patient organization "Long Covid Austria" • 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
Switzerland	• 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

	• Long COVID Citizen Science Board (University of Zurich)

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Appendix 1

List of newly included studies (update 7)

Ali Akbar Asadi-Pooya, et al. 2021. Risk factors associated with long covid syndrome: A retrospective study. *Iranian Journal of Medical Sciences* 46, 6: 428–436. https://doi.org/10.30476/ijms.2021.92080.2326

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Hannah R Whittaker, Claudia Gulea, Ardita Koteci, Constantinos Kallis, Ann D Morgan, Mark Weeks, Rikisha Gupta, and Jennifer K Quint. 2022. Post-acute COVID-19 sequelae in cases managed in the community or hospital in the UK: a population based study. *preprint*.

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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 [48]	Critically low
More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis [11]	Moderate
COVID-19 sequelae in adults aged less than 50 years: A systematic review [69]	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 [12]	Moderate
Proposed delay for safe surgery after COVID-19 [13]	Moderate
Late Complications of COVID-19; a Systematic Review of Current Evidence [14]	Low
Characterising long-term covid-19: a rapid living systematic review [17]	Moderate
Occurrence of long COVID: a rapid review [97]	Critically low
Long COVID, a comprehensive systematic scoping review [16]	Critically low
Living with COVID19. Second Review [10]	Critically low
Epidemiology of Long Covid. A Pragmatic Review of the Literature [15]	Critically low
Post-COVID-19 Syndrome: The Persistent Symptoms at the Post-viral Stage of the Disease. A Systematic Review of the Current Data [19]	Moderate
Post-acute COVID-19 syndrome [22]	Critically low

Long-COVID and Post-COVID Health Complications: An Up-to-Date Review on Clinical Conditions and Their Possible Molecular Mechanisms [18]	Critically low
Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis [53]	Moderate
Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology [98]	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 [23]	Moderate
Cardio-Pulmonary Sequelae in Recovered COVID-19 Patients: Considerations for Primary Care [20]	Low
Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review [99]	Moderate
Global prevalence of prolonged gastrointestinal symptoms in COVID-19 survivors and potential pathogenesis: A systematic review and meta-analysis [100]	Low
Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis [52]	High
Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review [101]	Low
Long covid—mechanisms, risk factors, and management [51]	Low
Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review [102]	Low
Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis [103]	Low
Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19 [23]	Low

"Long COVID": an insight [104]	Critically low
How common is Long COVID in children and adolescents? [50]	Critically low
Symptoms, complications and management of long COVID: a review [89]	Critically low
Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection [67]	Critically low
Follow-Ups on Persistent Symptoms and Pulmonary Function Among Post-Acute COVID-19 Patients: A Systematic Review and Meta-Analysis [105]	Moderate
Short-term and Long-term Rates of Postacute Sequelae of SARS-CoV-2 Infection . A Systematic Review [106]	Moderate
Persistent symptoms following SARS-CoV-2 infection among children and young people: a meta-analysis of controlled and uncontrolled studies. [49]	Moderate
Long-term effects of COVID-19 on mental health: A systematic review	Low
Global Prevalence of Post-Acute Sequelae of COVID-19 (PASC) or Long COVID: A Meta-Analysis and Systematic Review	Low
Prevalence of long-term effects in individuals diagnosed with COVID-19: an updated living systematic review	Low
Post-COVID-19 Syndrome	Critically low
Clinical patterns of somatic symptoms in patients suffering from post-acute long COVID: a systematic review	Critically low

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. [107]#	Cohort	48	100	≥12	71	a. high risk
						b. high risk
						c. high risk
Venturelli et al. [79]	Cohort	767	87	12 (median)	51.4	a. high risk
						b. high risk
						c. high risk
Moreno-Perez et al. [83]	Cohort	277	66	10-14	50.9	a. high risk
						b. high risk
						c. low risk
Sonnweber et al. [108]	Cohort	145	75	> 14	41	a. high risk
						b. high risk
						c. low risk
Buonsenso et al. [109]#	Survey	129	7	>17	52.7	a. high risk
						b. high risk
						c. low risk
Arnold et al. [84]	Cohort	110	100	8-12	74	a. high risk
						b. high risk
						c. low risk
Munblit et al. [110]#	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. [111]	Cohort	55	100	12	64	a. High risk
						b. high risk
						c. low risk
Lerum et al. [71]	Cohort	103	100	12	54	a. high risk
						b. high risk
						c. low risk
Tabatabaei et al. [112]	Cohort	52	76.7	13 (mean)	42.3	a. high risk
						b. high risk
						c. low risk
Huang et al. [113]	Cohort	1733	100	26 (median)	76	a. high risk
						b. high risk
						c. low risk
Jacobson et al. [77]	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. [114]#	Survey	6211	-	≥ 24	2.2	a. low risk
						b. high risk
						c. high risk
Han et al. [115]	Cohort	114	100	24	35	a. high risk
						b. high risk
						c. low risk
Blanco et al. [116]	Cohort	100	100	15 (median)	52	a. high risk
						b. high risk
						c. high risk
Sykes et al. [117]	Cohort	134	100	16 (median)	86	a. high risk
						b. high risk
						c. high risk
Morin et al. [118]	Cohort	478	100	12- 16	51	a. high risk
						b. high risk
						c. high risk
	Cohort	102	0	12 (mean)		a. high risk

Horvath et al. [119]					36 (smell alterations) 28 (taste alterations)	b. high risk c. high risk
Bellan et al. [120]	Cohort	238	100	12-16	53.8 (functional impairment) 17.2 (PTSD symptoms)	a. high risk b. high risk c. high risk
Suárez-Robles et al. [121]	Cohort	134	100	13	>40	a. high risk b. high risk c. high risk
Simani et al. [122]	Cohort	120	100	24	17.5 (fatigue) 5.8 (PTSD)	a. high risk b. high risk c. low risk
Shah et al. [123]	Cohort	60	100	12	58	a. high risk b. high risk c. high risk
Khalaf et al. [124] #	Cohort	538	51.3	12	84.6	a. low risk b. low risk c. high risk
Townsend et al. [125]	Cohort	153	48	11 (median)	62	a. high risk a. high risk c. high risk
Darley et al. [126]	Cohort	78	12	up to 16	39.7	a. unclear b. high risk c. high risk
Wong et al. [86]	Cohort	78	100	12	76	a. high risk b. high risk c. low risk
De Santis et al. [127]	Cohort	113	0	12	75.9	a. high risk b. high risk c. low risk

Frontera et al. [73]	Cohort	382	100	24	>90	a. high risk
						b. high risk
						c. high risk
Mazza et al. [128]	Cohort	226	100	12	35.8	a. high risk
						b. high risk
						c. low risk
Ghosn et al. [94]	Cohort	1137	100	24	60	a. high risk
						b. high risk
						c. high risk
Horwitz et al. [129]	Cohort	152	100	24	74	a. high risk
						b. high risk
						c. high risk
Frontera et al. [96]	Survey	999	0	18 (mean)	25	a. low risk
						b. high risk
						c. high risk
Augustin et al. [130]	Cohort	353	2.9	28	34.8	a. high risk
						b. high risk
						c. high risk
Darcis et al. [131]	Cohort	199	100	24	>47	a. high risk
						b. high risk
						c. high risk
Romero-Duarte et al. [92]	Cohort	797	100	24	63.9	a. high risk
						b. high risk
						c. low risk
Ashkenazi-Hoffnung et al. [132]	Cohort	99	88	16	58.9	a. high risk
						b. high risk
						c. high risk
Blomberg et al. [133]	Cohort	312	21	24	61	a. high risk
						b. low risk
						c. low risk
Osmanov et al. # [134]	Cohort	518	100	20	24.3	a. high risk
						b. high risk

						c. high risk
Smane et al. [135]	Cohort	30	17	15	30	a. high risk
						b. high risk
						c. high risk
Rauch et al. [136]	Cohort	147	8.7	24	67	a. high risk
						b. high risk
						c. high risk
Budhiraja et al. [62]	Cohort	990	100	12-48	32%	a. High risk
						b. low risk
						c. high risk
Peghin et al. [59]	Cohort	559	26.2	27	40.2	a. high risk
						b. high risk
						c. high risk
Wong-Chew et al. [137]	Cohort	4670	100	12	68	a. high risk
						b. high risk
						c. high risk
Shoucri et al. [138]	Case series	1190	100	42	26.4	a. high risk
						b. high risk
						c. high risk
Asadi-Pooya et al. [61]	cohort	4681	100	12-42	57	a. low risk
						b. low risk
						c. high risk
Tleyjeh et al. [55]	cohort	222	100	28	29.7	a. high risk
						b. high risk
						c. high risk
Naik et al. [57]	cohort	1234	100	13	9.9	a. hjgh risk
						b. high risk
						c. high risk
Boscolo-Rizzo et al. [65]	cohort	357	09	42	53	a. High risk
						b. high risk
						c. hjgh risk

*risk of bias assessment based on three 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. [35]	a. high risk
	b. high risk
	c. high risk
Desgranges et al. [29]	a. high risk
	b. high risk
	c. low risk
Graham et al. [27]	a. high risk
	b. high risk
	c. low risk
Havervall et al. [28]	a. high risk
	b. high risk
	c. high risk
Logue et al. [36]	a. high risk
	b. high risk
	c. low risk
Menges et al. [32]	a. low risk
	b. low risk
	c. high risk
Miller et al. [40]	a. high risk

	b. high risk
	c. high risk
Molteni et al. [44]	a. high risk
	b. high risk
	c. high risk
Petersen et al. [33]	a. low risk
	b. low risk
	c. low risk
Radtke et al. [39]	a. low risk
	b. low risk
	c. high risk
Stavem et al. [26]	a. high risk
	b. high risk
	c. high risk
Sudre et al.[34]	a. high risk
	b. high risk
	c. high risk
Xiong et al. [38]	a. high risk
	b. high risk
	c. low risk
Chevinsky et al. [30]	a. low risk
	b. low risk
	c. low risk
Zavala et al. [42]	a. low risk
	b. low risk
	c. high risk
Stephenson et al. [45]	a. high risk
	b. low risk
	c. high risk
Bliddal et al. [31]	a. low risk
	b. low risk
	c. high risk
Whittaker et al. [37]	a. low risk
	b. high risk
	c. low risk
Borch et al. [43]	a. low risk
	b. low risk

	c. high risk
Berg et al. [47]	a. low risk
	b. low risk
	c. high risk

*risk of bias assessment based on three 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

Registered trials on Long COVID treatment and rehabilitation

- 101 registered trials on Long Covid or Post Covid Syndrome
  - 54 investigating treatment options
    - 36 medical interventions (4x prednisone, 4x oxygen therapy)
    - 5 dietary interventions
    - 4 behavioral interventions
    - 3 health technology interventions
    - 6 "other" interventions (aromatherapy, acupuncture, osteopathic)
  - 47 investigating rehabilitation
    - 24 behavioral or physical exercise interventions (11 in combination with digital interventions)
    - 6 health technology interventions
    - 2 medical interventions
    - 1 dietary intervention
    - 14 "other" rehabilitation interventions
- Status of the Trials:
  - 25 not yet recruiting
  - 54 recruiting
  - 2 active, but not recruiting
  - 17 completed