Literature screening report – Update 5

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, burden of disease, symptoms, risk factors, social and economic impact of Long COVID and healthcare responses to Long COVID in Europe have been developed together with FOPH in order to serve their needs best.

Final analysis for the review's 5th update included 28 reviews and 112 primary studies. Prevalence estimates were heterogeneous. Overall, prevalence estimates for adults are estimated at about 20%. One population-based and three studies with control groups reported prevalence estimates for non-hospitalized adults with a median estimate of 14% (7.5% - 41%). Two population-based and three studies with control groups included samples with non-hospitalized as well as previously hospitalized participants, with a median prevalence estimate of 26% (2.3% - 53.1%). Finally, one study (with a control group) included only previously hospitalized participants, reporting a prevalence estimate of 37.6%. This is large methodological variation of primary studies, 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)

[1]. It is therefore essential to view all current estimates with their methodologies and respective definitions in mind.

We identified three population-based and/or control group studies reporting Long COVID prevalence estimates (≥4week follow-up) in children and teenagers. All three included either exclusively non-hospitalized or primarily non-hospitalized children, with a median prevalence estimate of 2.9% (2% - 3.5%).

Reviews reported more than 50 symptoms, with fatigue, headache, dyspnea, smell and taste disturbances and cognitive impairment being most common. Preliminary evidence suggests that female sex, older age, comorbidities, severity of acute disease and obesity are associated with Long COVID. Twenty-three studies reported some degree of Long COVID-related social and family-life impairment, with 12% to 50% of those affected facing functional restrictions and some degree of disability. Sixteen studies reported occupational and financial consequences, long absence periods in among 9% to 59% (up to 7 months after acute disease), adjusted workloads in among 8% to 45% and employment loss in among 11% to 14% of those affected.

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 clearly 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 on a daily basis, 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

- There is no single, commonly agreed definition of Long COVID. Some consensus is gradually accumulating around *"unresolved symptoms at 6 or 12 weeks (and beyond) after acute disease, if not explained by an alternative diagnosis"*

Burden of disease

- All current prevalence estimates need to be viewed with caution and considered preliminary
- The median of four reported prevalence estimates for non-hospitalized adults is 14% (7.5% - 41%)
- The median of five reported prevalence estimates in mixed (hospitalized & non) adult samples is 26% (2.3% - 53.1%)
- One study reports Long COVID in previously hospitalized adults, reporting a prevalence of 37.6%
- The median of three reported prevalence's among mostly non-hospitalized children and teenagers is 2.9% (2% - 3.5%)

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
- Female sex, older age, comorbidities, severity of acute disease and obesity 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 of time adjust their workloads

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 commonly persistent symptoms [2]. 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 [3]. Long COVID is 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 of time. 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 remaining 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 [6]. 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 in order 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 that 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 webpages.

The review was updated on September 2021 to include new evidence from review and primary studies. Primary studies were identified in two stages. First, we identified all primary studies included in at least one of 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) 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, 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 [7] , 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 reported 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).

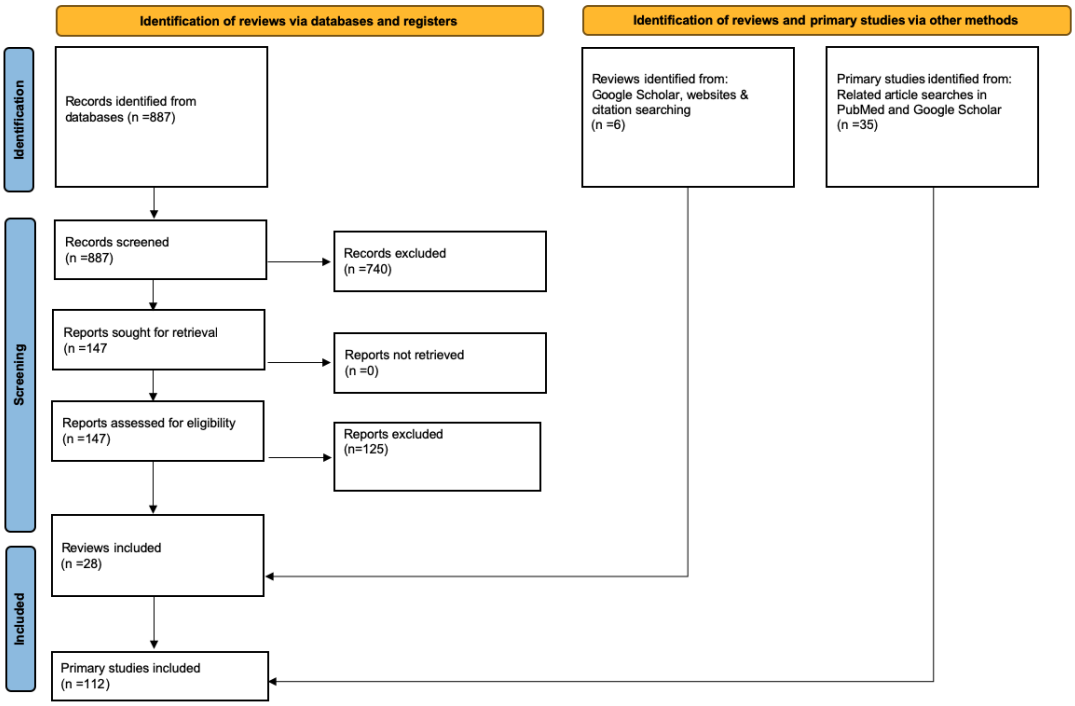
Risk of bias (quality) assessment

The quality of reviews was assessed using the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) checklist [8]. 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.[9] 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 September 2021 update, our database searches yielded 887 references. 740 of those were excluded at title and abstract screening and 147 manuscripts were screened full-text. That led to the exclusion of 125 further studies, leading to the preliminary inclusion of 22 reviews. Google Scholar and reference list searches yielded additional 6 studies. Thus, we included and analyzed a total of 28 reviews. For the September 2021 update, we included evidence from 112 primary studies, 77 of them included in at least one of the 11 reviews and 35 identified through related article searches in PubMed and Google Scholar. Figure 1 provides the PRISMA flowchart of our searches

Figure 1: PRISMA Flowchart for included reviews and primary studies [10]



Characteristics of included reviews

One of the included studies was published in 2020, 25 were published in 2021 and 2 are currently available as preprints. Most studies were traditional systematic reviews (n=16), followed by rapid reviews (n=2), rapid living systematic reviews (n=2), pragmatic reviews (n=3), systematic reviews with a meta-analysis (n=4) and a scoping review (n=1). Only one addressed pediatric patients, one middle-aged and young adults and the remaining (n=21) 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 at low to moderate, with 8 scoring critically low, 9 scoring low,10 scoring moderate and one high quality points. The full quality assessment table is provided in appendix 1.

Characteristics of included primary studies

Most primary studies (n=70) were published in 2021, followed by 42 publications in 2020. The majority were conducted in Europe (n=74), followed by North America (n=21), Asia (n=14), Africa (n=1), South America (n=1) and one multinational study. Methodologically, the vast majority of primary research is based on prospective cohorts (n=80), followed by cross-sectional and survey designs (n=20), retrospective cohorts (n=10), case series and case-control studies (n=2). At the time of data extraction, a total of 17 studies were still at a preprint stage. Most studies included hospital-based samples and previously hospitalized participants (n=54). Exclusively non-hospitalized participants were included in 19 studies while the remaining 39 had mixed samples of previously hospitalized, as well as non-hospitalized participants.

Evolving definitions of Long COVID

Terminology

A universally accepted definition for post-acute and long-term SARS-CoV2 sequelae does not exist [11]. While this review has adopted the term Long COVID, being the currently most widespread and broad description of long-term SARS-CoV-2-related complications [1] and the term most accepted by persons living with Long Covid, the literature provides a very diverse set of terminology, descriptions and definitions. 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" [1], [12]–[17]. 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 [18]–[21].

Definitions

Michelen et al. [18] 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 [17] [18]. Beyond symptoms, others also include abnormal, but potentially asymptomatic clinical parameters persisting as part of Long COVID [12]. 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 [1][16][18][7][22]. Others disagree with that "by exclusion" approach, as it might fail to capture the very broad spectrum of post-acute complications [17], including SARS-CoV-2-triggered new health conditions and worsening of pre-existing health conditions [1]. 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 [1]. 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 [1][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" [3] and the Geneva-based cohort study "Long COVID" [2]. In the absence of a commonly agreed definition, many of the included reviews simply referred to "long-term effects of COVID-19" or "late onset complications of COVID-19", setting the cut off for symptom duration or absence of full recovery at a minimum of 3 weeks after onset of symptoms, diagnosis, hospital admission or discharge [12] [18][26].

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) [1]. It is therefore essential to view all current estimates with their methodologies and respective definitions in mind.

In total, 49 of the 112 included studies provided overall Long COVID prevalence estimates at ≥ 12 weeks after acute infection. Thirteen studies included population-based samples and/or control groups and are reported in detail. Prevalence estimates reported in the 36 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 estimate for cases and estimate for controls).

Adults

We identified 10 population-based and/or control group studies reporting Long COVID prevalence estimates (≥ 12week follow-up) in adults, summarized in Table 1. One population-based and three studies with control groups reported prevalence estimates for non-hospitalized adults with a median estimate of 14% (7.5% - 41%). Two population-based and three studies with control groups included samples with non-hospitalized as well as previously hospitalized participants, with a median estimate of 26% (2.3% - 53.1%). Finally, one study (with a control group) reports the prevalence among previously hospitalized participants only, reporting an estimate of 37.6%.

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.[27] [p]	451	NA	NA	6-24 [positive test]	41	-	-
Graham et al.[28] [c]	100	NA	50	18 – 23 [symptom onset]	67.8	60.3	7.5
Havervall et al.[29] [c]	323	NA	1027	≥ 32 [January 2020]	15	3	12
#Desgranges et al.[30] [c]	418	NA	89	12-40 [acute disease]	53	37	16
hospitalized & non-hospitalized adults							
Menges et al.[31] [p]	431	19	NA	29 [acute disease]	26	-	-
Petersen et al.[32] [p]	180	4	NA	18 [acute disease]	53.1	-	-
Sudre et al.[33] [c]	4182	14	4182	≥ 12 [symptom onset]	2.3	-	-
#Cirulli et al.[34] [c]	357	3	5497	12 [January 2020]	14.8	7	7.8
Logue et al.[35] [c]	177	9	21	12-36 [symptom onset]	32.8	4.8	28
hospitalized adults							
Xiong et al.[36] [c]	538	100	184	>12 [hospital discharge]	49.6**	12	37.6

#=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.[27] included a predominantly female and older sample (>50 years of age), with the study's findings being subject to recall bias. Graham et al. [28] is limited by its small sample size and the fact that many cases only underwent serology testing, not allowing for an accurate identification of infection start. The findings reported by Havervall et al. [29] 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. Menges et al.[31] (conducted in Switzerland) as well Petersen et al. [31] did not asses pre-COVID physical or mental health, while the very low estimate by Sudre et al. [33] 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. [34] measured any symptoms persisting longer than 90 days since the beginning of the pandemic (January 2020) without differentiating before and after the test result and

Children and Teenagers

We identified three population-based and/or control group studies reporting Long COVID prevalence estimates (≥4week follow-up) in children and teenagers, summarized in Table 2. All three included either exclusively non-hospitalized or primarily non-hospitalized children, with a median prevalence estimate of 2.9% (2% - 3.5%).

Table 2: Prevalence estimates for children and teenagers

Authors [Reference]	Cases (n=)	% hospitalized]	Controls (n=)	Follow-up period [follow-up start]	Symptom prevalence cases (%)	Symptom prevalence controls (%)	Adjusted prevalence (% cases – % controls)
Non-hospitalized children							
Radtke et al.[37] [p; c]	109	NA	1246	>12 [October 2020]	4	2	2
#Miller et al.[38] [c]	175	NA	4503	≥4 [February 2020]	4.6	1.7	2.9
Hospitalized and non-hospitalized children							
#Molteni et al.[39] [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 three estimates need to be viewed in consideration of certain study limitations. The Swiss Ciao Corona study by Radtke et al. [37] had a relatively small sample size and was based on seroprevalence, not distinguishing between symptoms before and after SARS-CoV-2 infection, as the actual time points of infection were not assessed. The findings by Miller et al. [38] are limited by the study's small sample size and the study design of Molteni et al.[39] was primarily informed by research in adults, while the mobile self-reporting nature might have introduced self-report bias and other errors.

Risk of bias assessment for studies reporting prevalence estimates

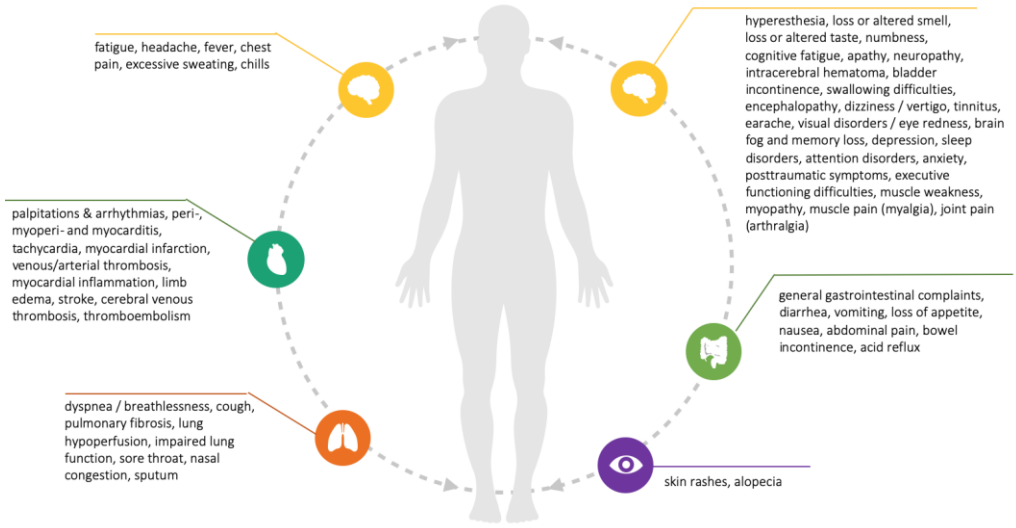
Regarding our risk of bias assessment, only three studies scored "low risk" for the first item ("is the target population representative of the national population"), three studies scored "low risk" for the second item ("is some sort of random selection used to select the sample"), and five scored "low risk" for the third item ("is the likelihood of non-response bias minimized")[9]. 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 table 1 and 2).

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) [1], followed by headaches, breathing difficulties, smell and taste disturbances, cognitive impairments, sleep and anxiety disorders. These were also the most commonly reported symptoms among patients in Switzerland [2], [3].

A group of patients exclusively experiences fatigue or upper respiratory complaints, while others multiple and multi-system symptoms [1]. While many continuously experience one or multiple symptoms, reviews report that some persons living with Long COVID experience relapsing-remitting disease, with periods of improvements and flare-ups, also described as the "corona coaster" [1][16]. Symptoms are often reported as debilitating, having a strong negative impact on mental health and quality of life [17]. 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, breathing difficulties, heart palpitations, headaches, attention difficulties and cognitive deficits, muscle weakness and pain, dizziness, sore throat, abdominal pain, depression and skin rashes [26]. Most existing reviews did not classify disease and symptom severity based on indicators such as 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

The novel and emerging nature of Long COVID, as well as the quality of current data does not provide solid grounds for confidently identifying risk factors yet [12][18]. Some of the reviews suggest that the following factors might increase the risk for Long COVID development: (a) sex (female), (b), older age (c) comorbidities (mental and physical, three or more, especially asthma [40]), (d) severity of acute disease (e.g. hospitalization, duration of hospitalization, higher imaging scores, duration of oxygen supplementation, pneumonia, presence of dyspnea, number of symptoms),(e) and obesity [1][13][16][18][20][21][22][25][26][41][42]. For some of these factors, evidence seems to be mixed or symptom-depended. 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 [17][18]. 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 [1] [21]. 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][40]. 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 [43].

Three reviews reported that experiencing more than five symptoms during acute disease, including fatigue, headache, dyspnea, chest pain, sensitive skin, hoarse voice and myalgia had a higher risk progressing to Long COVID development, which might be stronger when taking age and sex into account [16] [17] [43]. Iqbal and colleagues report the number of symptom during acute disease were highly predictive of the number of lasting symptoms at three months, especially of persisting fatigue [42]. Mental symptoms, especially posttraumatic ones seem to be affecting younger people, women, and those with responsibilities for others [17]. Beyond physical activity levels and potentially immunosuppression (still under debate) [13][40], no further protective factors are reported in any of the identified reviews.

Social and economic impact

Understanding its 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.

Family and social functioning

About 21% (23/112) 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 [44][45][46][47]. They also report that symptoms affect their family life and often limit their ability to care for others [1]. 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 [13][16][17][48]. 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 [49][50]. 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 [51][52], with about 15% still reporting social and home disruptions 8 months after disease onset [29].

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 [1][16][53]. 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 [29]. 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 [50][54]. 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 hospitalisation [55]. 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 [56]. An important proportion of previously independent patients experience Long COVID impairments that deem them full care-dependent [1]. 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 [28], [57]–[63].

Work-related implications

Inevitably, Long COVID is also expected to have a considerable impact on the workforce [1]. About 14% (16/112) 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 [49] [50][64][65]. For those heavily affected with neurological sequalae, absence from work is also reported as high as 59% at 6 months after hospital discharge [48].

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 [52][66][67]. 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 [51][68]. 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% and 40% of their employed participants adjusted their employment to their current circumstances. Another large prospective cohort study with previously hospitalized participants from France reports that 29% of those initially employed had not returned at 6 months [69]. These numbers range from 8% to 45% for previously mild to moderate cases at follow-up of 3 to 8 months [29][52][66]. Finally, two studies report permanent employment loss in relation to deteriorating health, with one reporting that 11% and other 13.8% of their previously employed participants being unemployed at 2 months after acute disease [49][70]. A US-based survey reports that unemployment and financial insecurity was more common among Long COVID respondents, which were associated with younger age [71].

The NIHR review reports UK-based survey results with about 80% of all young patients (25 to 55 years) reporting that Long COVID has negative affected their work life, with about half of them additionally reporting related financial difficulties [1]. 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 [1][16]. 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 [1][44].

European responses

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

Country	Responses [6]
United Kingdom	• NHS established care pathways for patients with symptoms 6 weeks after disease onset • NICE published Long COVID guidelines • Establishment of 40 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
Germany	• Large hospitals offering Long COVID consultations and post-COVID outpatient services (focus on interdisciplinary care)
Italy	• Launch of post-COVID wards in some hospitals • Launch on multidisciplinary Post-COVID-19 Day-Hospital in Rome • Provision of post-COVID rehabilitation services by AbilityAmo (non-profit), including telemonitoring, home care, interdisciplinary and psychological support
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
Belgium	• Hospitals providing multidisciplinary services for post-ICU patients, at home or in specialized centers • Development of post-discharge care pathways
Switzerland	• Long COVID Schweiz – Association and support for those affected • 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

Discussion / Conclusions

Long COVID is a rapidly emerging public health problem. Equally emerging is the need to fully understand its etiology, burden and broader implications. The multifaceted nature of its symptoms and the uncertainty around their progression and duration have far-reaching consequences, primarily on individual lives, but ultimately on our socio-economic infrastructures. This living systematic review aimed to assess the current status of scientific evidence around Long COVID, focusing on its definitions, burden, determining factors and socio-economic implications.

At a follow-up of 12 weeks or beyond the median estimate lies at 14% (7.5% - 41% for non-hospitalized adults and at 26% (2.3% - 53.1%) for samples with non-hospitalized as well as previously hospitalized participants. One study with a control group included only previously hospitalized participants, reporting a prevalence estimate of 37.6%. We identified three population-based and/or control group studies reporting Long COVID prevalence estimates (≥4week follow-up) in children and teenagers. All

three included either exclusively non-hospitalized or primarily non-hospitalized children, with a median prevalence estimate of 2.9% (2% - 3.5%).

Current evidence suggests that Long COVID can have debilitating consequences on mental health, quality of life, social as well as family life. The direct implications on the workforce and indirect consequences for the economy are yet to be thoroughly explored. First studies suggest that many of those living with Long COVID often face longer periods off work, reduced working hours and potentially higher risk of unemployment and financial hardship. Further knowledge gaps remain, especially on risk factors, protective factors and Long COVID's socio-economic impact. It is key to accumulate more evidence on disease determinants since the number of people living with Long COVID will likely grow [17]. To accumulate targeted evidence that will capture the needs of those affected, we are planning a citizen science project, co-created with those living with and affected by Long COVID. The project aims to identify key needs and corresponding research priorities.

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Appendix 1

AMSTAR Scores – Reviews

Title and reference	AMSTER Score
Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19 [26]	Critically low quality
More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis [12]	Moderate quality
COVID-19 sequelae in adults aged less than 50 years: A systematic review [44]	Moderate quality
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 [13]	Moderate quality
Proposed delay for safe surgery after COVID-19 [14]	Moderate quality
Late Complications of COVID-19; a Systematic Review of Current Evidence [15]	Low quality
Characterising long-term covid-19: a rapid living systematic review [18]	Moderate quality
Occurrence of long COVID: a rapid review [72]	Critically low
Long COVID, a comprehensive systematic scoping review [17]	Critically low

Living with COVID19. Second Review [1]	Critically low
Epidemiology of Long Covid. A Pragmatic Review of the Literature [16]	Critically low
Post-COVID-19 Syndrome: The Persistent Symptoms at the Post-viral Stage of the Disease. A Systematic Review of the Current Data [20]	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 [19]	Critically low
Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis [42]	Moderate
Long COVID and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)—A Systemic Review and Comparison of Clinical Presentation and Symptomatology [11]	Critically low
Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments [43]	Low quality review
Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19 [23]	Moderate quality review
Cardio-Pulmonary Sequelae in Recovered COVID-19 Patients: Considerations for Primary Care [21]	Low quality review
Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review [73]	Moderate quality review
Global prevalence of prolonged gastrointestinal symptoms in COVID-19 survivors and potential pathogenesis: A systematic review and meta-analysis [74]	Low quality review
Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: A systematic review and meta-analysis [41]	High quality review

Health-related quality of life issues, including symptoms, in patients with active COVID-19 or post COVID-19; a systematic literature review [75]	Low quality review
Long covid—mechanisms, risk factors, and management [40]	Low quality review
Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review [76]	Low quality review
Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)—A systematic review and meta-analysis [77]	Low quality review
Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19 [23]	Low quality review

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. [78]#	Cohort	48	100	≥12	71	a. high risk
						b. high risk
						c. high risk

Venturelli et al. [54]	Cohort	767	87	12 (median)	51.4	a. high risk
						b. high risk
						c. high risk
Moreno-Perez et al. [58]	Cohort	277	66	10-14	50.9	a. high risk
						b. high risk
						c. low risk
Sonnweber et al. [79]	Cohort	145	75	> 14	41	a. high risk
						b. high risk
						c. low risk
Buonsenso et al. [80]#	Survey	129	7	>17	52.7	a. high risk
						b. high risk
						c. low risk
Arnold et al. [59]	Cohort	110	100	8-12	74	a. high risk
						b. high risk
						c. low risk
Munblit et al. [81]#	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. [82]	Cohort	55	100	12	64	a. High risk
						b. high risk
						c. low risk
Lerum et al. [46]	Cohort	103	100	12	54	a. high risk
						b. high risk
						c. low risk
Tabatabaei et al. [83]	Cohort	52	76.7	13 (mean)	42.3	a. high risk
						b. high risk
						c. low risk
Huang et al. [84]	Cohort	1733	100	26 (median)	76	a. high risk
						b. high risk

						c. low risk
Jacobson et al. [52]	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. [85]#	Survey	6211	-	≥ 24	2.2	a. low risk b. high risk c. high risk
Han et al. [86]	Cohort	114	100	24	35	a. high risk b. high risk c. low risk
Blanco et al. [87]	Cohort	100	100	15 (median)	52	a. high risk b. high risk c. high risk
Sykes et al. [88]	Cohort	134	100	16 (median)	86	a. high risk b. high risk c. high risk
Morin et al. [89]	Cohort	478	100	12- 16	51	a. high risk b. high risk c. high risk
Horvath et al. [90]	Cohort	102	0	12 (mean)	36 (smell alterations) 28 (taste alterations)	a. high risk b. high risk c. high risk
Bellan et al. [91]	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. [92]	Cohort	134	100	13	>40	a. high risk b. high risk c. high risk
Simani et al. [93]	Cohort	120	100	24	17.5 (fatigue)	a. high risk

					5.8 (PTSD)	b. high risk
						c. low risk
Shah et al. [94]	Cohort	60	100	12	58	a. high risk
						b. high risk
						c. high risk
Khalaf et al. [95] #	Cohort	538	51.3	12	84.6	a. low risk
						b. low risk
						c. high risk
Townsend et al. [96]	Cohort	153	48	11 (median)	62	a. high risk
						a. high risk
						c. high risk
Darley et al. [97]	Cohort	78	12	up to 16	39.7	a. unclear
						b. high risk
						c. high risk
Wong et al. [61]	Cohort	78	100	12	76	a. high risk
						b. high risk
						c. low risk
De Santis et al. [98]	Cohort	113	0	12	75.9	a. high risk
						b. high risk
						c. low risk
Frontera et al. [48]	Cohort	382	100	24	>90	a. high risk
						b. high risk
						c. high risk
Mazza et al. [99]	Cohort	226	100	12	35.8	a. high risk
						b. high risk
						c. low risk
Ghosn et al. [69]	Cohort	1137	100	24	60	a. high risk
						b. high risk
						c. high risk
Horwitz et al. [100]	Cohort	152	100	24	74	a. high risk
						b. high risk
						c. high risk
Frontera et al. [71]	Survey	999	0	18 (mean)	25	a. low risk

						b. high risk
						c. high risk
Augustin et al. [101]	Cohort	353	2.9	28	34.8	a. high risk
						b. high risk
						c. high risk
Darcis et al. [102]	Cohort	199	100	24	>47	a. high risk
						b. high risk
						c. high risk
Romero-Duarte et al. [67]	Cohort	797	100	24	63.9	a. high risk
						b. high risk
						c. low 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 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. [34]	a. high risk
	b. high risk
	c. high risk
Desgranges et al. [30]	a. high risk

	b. high risk
	c. low risk
Graham et al. [28]	a. high risk
	b. high risk
	c. low risk
Havervall et al. [29]	a. high risk
	b. high risk
	c. high risk
Logue et al. [35]	a. high risk
	b. high risk
	c. low risk
Menges et al. [31]	a. low risk
	b. low risk
	c. high risk
Miller et al. [38]	a. high risk
	b. high risk
	c. high risk
Molteni et al. [39]	a. high risk
	b. high risk
	c. high risk
Petersen et al. [32]	a. low risk
	b. low risk
	c. low risk
Radtke et al. [37]	a. low risk
	b. low risk
	c. high risk
Stavem et al. [27]	a. high risk
	b. high risk
	c. high risk
Sudre et al.[33]	a. high risk
	b. high risk
	c. high risk
Xiong et al. [36]	a. high risk
	b. high risk
	c. low 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=26), headache (n=12), fever (n=6), chest pain (n=13), excessive sweating (n=1), chills (n=1)
RESPIRATORY dyspnea / breathlessness (n=24), cough (n=12), pulmonary fibrosis (n=3), lung hypoperfusion (n=1), impaired lung function (n=3), thromboembolism (n=5), sore throat (n=5), nasal congestion (n=3), sputum (n=3)
CARDIOVASCULAR & HEMATOLOGICAL palpitations & arrhythmias (n=9), 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=16), loss or altered taste (n=14), 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=12), joint pain (arthralgia) (n=11), 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=2), 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=12),), depression (n=7), sleep disorders (n=13), attention disorders (n=8), anxiety (n=9), posttraumatic symptoms (n=4), executive functioning difficulties (n=4), ataxia (n=2), change of voice (n=1), dysphagia (n=1)
GASTROINESTINAL

general gastrointestinal complaints (n=5), diarrhea (n=7), vomiting (n=5), loss of appetite (n=5), nausea (n=6), abdominal pain (n=4), bowel incontinence (n=1), acid reflux (n=2), gastrointestinal bleeding (n=1), constipation (n=1), sudden loss of body weight (n=1)

CUTANEOUS
skin rashes (n=7), alopecia (n=5)