Literature screening report

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

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Abstract

Long-term health consequences of SARS-CoV-2 increasingly receive the attention of researchers, healthcare providers and policymakers. The understanding of this novel syndrome is emerging and countries worldwide have launched initiatives to respond to the needs of persons living with Long Covid. This review provides a summary of existing evidence on medical/clinical, social, economic, and broader healthcare system aspects of the novel syndrome. 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. In this living review, we perform umbrella reviews or systematic reviews for each question depending on whether systematic reviews exist or not.

For this third review update, we included and analyzed 23 reviews and 102 primary studies. A universally accepted term and definition for post-acute and long-term SARS-CoV2 sequelae does not exist. We identified multiple terms with Long Covid being the most commonly used. Some defined Long Covid broadly “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”, i.e. including clinically confirmed and suspected cases. Other definitions refer to the presence of at least one symptom, a symptom complex or not having recovered at a certain time after infection.

Estimates of prevalence are very heterogeneous due to large methodological variation of primary studies, recruitment methods (e.g. hospital, non-hospital, self-selection), follow-up periods and Long COVID definitions. For adult populations and at a follow-up of 12 weeks or beyond, prevalence estimates among studies with controls ranged from 7.8% to 27.7% and among studies

with population-based samples (but without controls) from 26% to 53.1%. The three Swiss cohort studies (adult samples) suggest estimates of 26%, 32% and 53%. The prevalence estimates reported in studies without controls or non-population-based samples range from 2.3% to 89%.

Eight primary studies explored Long COVID in underage populations. Two studies included control participants and reported prevalence estimates of 2% (duration of 12 weeks or beyond) and 1.8% (at 8 weeks). The prevalence estimates reported in studies without control participants range from 4.6% (at 4 weeks or beyond) to 58.1% (at 6 months). Those studies that included only or also asymptomatic ases reported lower estimates that studies including only symptomatic children at time of infection .

More than 50 symptoms have been reported across the studies included in the reviews. The most commonly mentioned symptoms include fatigue, followed by headaches, breathing difficulties, smell and taste disturbances, cognitive impairments, sleep and anxiety disorders. Some persons living with Long COVID exclusively experience fatigue or upper respiratory complaints, while others multiple and multi-system symptoms. Some studies also report about relapsing-remitting disease, with periods of improvements and flare-ups, also described as the “corona coaster”. The evidence for pediatric Long COVID patients remains scarce, however, there are indications of multisystem inflammatory syndrome development, as well as a range of symptoms that are also common among adults. Most existing reviews did not classify disease and symptom severity based on indicators such as the number of medical visits or inability to work.

The quality of current data does not provide solid grounds for confidently identifying risk factors yet. Some of the reviews suggest that sex (female), older age, comorbidities, severity of acute disease (e.g. duration of hospitalization), number of symptoms during acute disease and obesity are associated with Long Covid. Beyond physical activity levels, none of the reviews reported on protective factors.

In terms of social and economic impact, about 19% of all included primary studies reported some degree of daily life, family and social functioning impairment related to Long COVID. Three studies report that 12% and 50% of their participants had difficulties or were unable to perform usual daily activities at about 2 months after hospitalization or disease onset, while one reported that 15% were still facing social and home life disruptions 8 months after disease onset. 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. One cohort study reported that 11% of participants faced some degree of disruption in at least one disability scale category. 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. 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 [1]. 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 Finally, about 21% of all included primary studies report that the majority of those living with Long COVID perceive their quality of life as significantly reduced.

About 12% of all included primary studies report that Long COVID negatively affects work life and increases the risk for financial hardship. 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. This ranges from 12% to 23% for mild to moderate and non-hospitalized SARS-CoV-2 cases at 3 to 7 months after acute disease. Beyond full absence, studies report that 8% to 45% of employed participants were forced to adjust or reduce their workload levels, with relatively higher percentages among previously hospitalized samples. Two studies report permanent employment loss in relation to deteriorating health, with one reporting that 11% and the other 13.8% of their previously employed participants being unemployed at 2 months after acute disease. The UK-based NIHR survey reports that about 80% of all young patients (25 to 55 years) perceived that Long COVID has negative affected their work life, with about half of them facing financial hardship. While the evidence is emerging, estimates for the proportion of persons not being able to (fully) return to work or face financial challenges vary widely and require more context-specific research, also for Switzerland. The broader economic implications of Long COVID are yet unclear.

Finally, a number of countries responded to the medical and social needs of persons with Long Covid. The UK appears to be most advanced with multidisciplinary Long Covid clinics, an online platform for information and guidance for self-management and care pathways and remote follow-up of persons who are at risk or have Long Covid.

Current literature provides a still patchy picture and the evidence should therefore only be considered as provisional. Further knowledge gaps remain, especially on prevalence, risk factors, protective factors and Long COVID's socio-economic impact. But overall, the current evidence suggests that Long Covid is of substantial public health relevance and that generated knowledge should ideally be holistic, including the broader medical, public health and socio-economic dimensions of Long COVID, enabling and informing crucial healthcare and policy responses.

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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.

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 June 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.

Eligibility criteria for reviews

- report a systematic methodology (systematic review, scoping reviews, rapid reviews)
- thematically focus (entirely or partially) on Long COVID (in abstract and main body)

Eligibility criteria for primary studies

- must be included in one of the reviews or identified through a related article search
- must be surveys, cross-sectional or cohort studies included laboratory or clinically confirmed SARS-CoV-2 phases for at least 6 weeks post the acute disease phase
- Exclude: narrative reviews, editorials, case reports, studies with a source and study population that give results that are unlikely to be applicable to the target population (general population)

Risk of bias (quality) assessment

The quality of systematic review has been assessed using the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) checklist [7]. The quality of primary studies was assessed with three items, adapted from Hoy et al. checklist for prevalence studies [8]. The first item assessed whether the sampling frame was a true or close representation of the target population. The second whether the sample was selected with some form of random and/or consecutive procedure. The third item assessed whether the likelihood of non-response was minimalized.

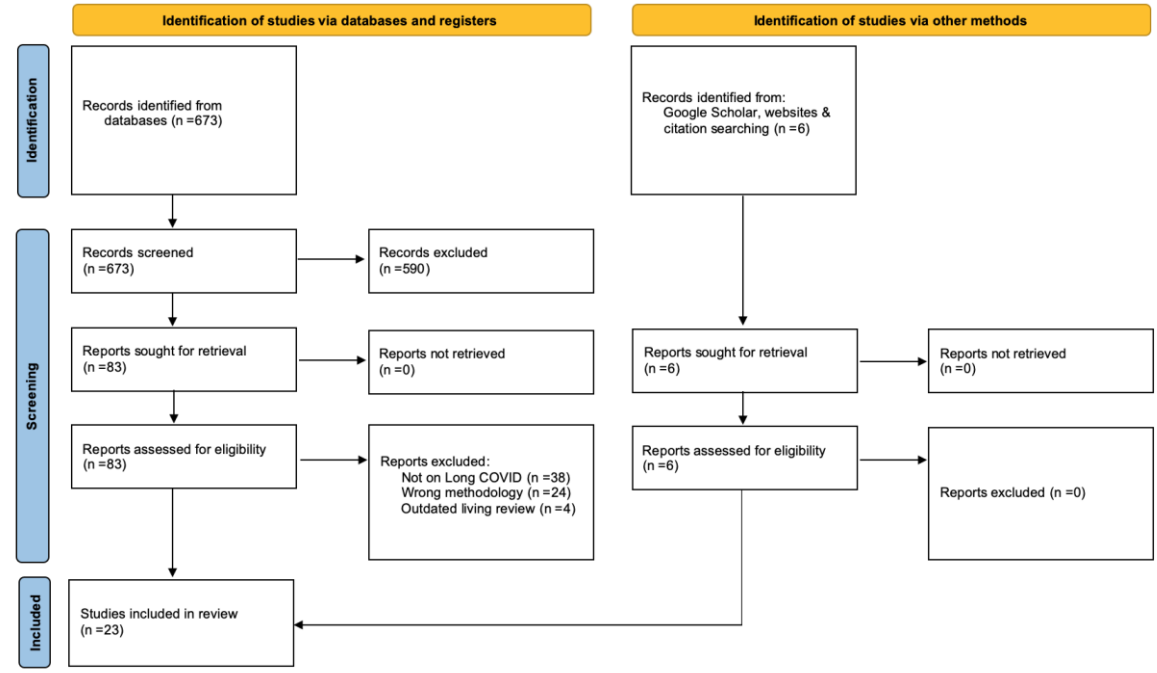
Data extraction, analysis and synthesis

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.

Results and findings

For the June 2021 update, our database searches yielded 673 references. 590 of those were excluded at title and abstract screening and 83 manuscripts were screened full-text. That led to the exclusion of 116 further studies, either for not addressing Long COVID (n=38), not being systematic reviews (n=24), or being older versions of already included living systematic reviews (n=4). Database searches led to the final inclusion of 17 reviews. Google Scholar and reference list searches yielded additional 6 studies. Thus, we included and analyzed a total of 23 reviews. Figure 1 provides the PRISMA flowchart of our searches. For the June 2021 update, we included evidence from 102 primary studies, 69 of them included in at least one of the 11 reviews and 33 identified through related article searches in PubMed and Google Scholar.

Figure 1: PRISMA Flowchart for included reviews



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Characteristics of included reviews

One of the included studies was published in 2020, 19 were published in 2021 and 3 are currently available as preprints. Most studies were traditional systematic reviews (n=12), followed by rapid reviews (n=2), rapid living systematic reviews (n=2), pragmatic reviews (n=3), systematic reviews with a meta-analysis (n=3) 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, 4 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=60) were published in 2021, followed by 42 publications in 2020. The majority were conducted in Europe (n=68), followed by North America (n=18), Asia (n=14), Africa (n=1) and one multinational study. Methodologically, the vast majority of primary research is based on prospective cohorts (n=71), followed by cross-sectional and survey designs (n=19), retrospective cohorts (n=10), case series and case-control studies (n=2). At the time of data

extraction, a total of 16 studies were still at a preprint stage. Most studies included hospital-based samples and previously hospitalized participants (n=48). Exclusively non-hospitalized participants were included in 17 studies while the remaining 37 had mixed samples of previously hospitalized, as well as non-hospitalized participants. Eighteen primary studies included controls, while 14 included samples representative of the general population. The reporting quality of most studies was assessed as low (n=62), followed by low to medium (n=27), while 5 were assessed to be of medium, 7 of medium to high quality and 1 of high quality.

Evolving definitions of Long COVID

Terminology

A universally accepted definition for post-acute and long-term SARS-CoV2 sequelae does not exist [9]. 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 [10] 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” [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

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][21][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]. 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][23]. Others broadly defined it as lasting or persisting outcomes after recovery from acute disease [24]. 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 [11] [17][25].

Burden of Disease

Evidence from Reviews

Long COVID's novel and emerging nature does not allow for confident prevalence estimates yet. Those systematic reviews that reported prevalence, did so with caution and emphasized their large heterogeneity and non-comparability of individual estimates. This is due to large methodological variation of primary studies, including their sample recruitment methods (e.g. hospital, non-hospital, self-selection), as well as follow-up periods and Long COVID definitions (e.g. symptomatic only) [10]. Therefore, whenever possible, all prevalence estimates provided below are provided with additional information on the sample sizes, follow-up periods and whether the sample includes hospitalized or non-hospitalized patients. Follow-up periods are provided in mean or median (as reported by reviews) number of weeks. Reviews reporting number of days were roughly transformed by in weeks to improve the section's readability. Table 1 provides the currently lowest and highest prevalence estimates, as reported in the 11 included reviews and divided by sample source (previously hospitalized; non-hospitalized/mixed groups) and follow-up duration (<12 weeks; ⩾12 week)

Table 1: Lowest and highest prevalence estimates, by sample source and follow-up duration

Sample and follow-up duration	Prevalence estimates [1]	Sample sizes
hospitalized, symptoms <12 weeks		
lowest reported prevalence	50.9%[26]	(n=277)
highest reported prevalence	89% [27]	(n=119)
hospitalized, symptoms ≥12 weeks		
lowest reported prevalence	47% [28]	(n=2649)
highest reported prevalence	76% [29]	(n=1733)
non-hospitalized or mixed [2], symptoms <12 weeks		
lowest reported prevalence	13% [30]	(n=4182)
highest reported prevalence	36% [31]	(n=357)
non-hospitalized or mixed [2], symptoms ≥12 weeks		
lowest reported prevalence	2.3% [30]	(n=4182)
highest reported prevalence	53% [32]	(n=180)

[1] only those reported in at least one the included reviews.

[2] mixed non-hospitalized and hospitalized may or may not be a population-based

Only two reviews provided pooled prevalence estimates of primary studies. The defined Long COVID as the persistence of at least one symptom at or beyond three weeks after disease onset, reporting an estimate of 80% (95% CI 65- 92) [11]. The second defined Long COVID as the occurrence of at least one symptom for “far longer than would be expected” and reported estimates at 30, 60, and 90 days post diagnosis or hospitalization [33]. These were estimated at 63.2%, 71.9% and 45.9%% respectively [33]. While such pooled estimates are grounded in quite heterogeneous primary studies and have to be viewed with caution, all other reviews narratively reported prevalence estimates of selected primary studies (n=7) or did not report any prevalence at all (n=3). A pragmatic review by Zapatero and colleagues from the Belgian Healthcare Knowledge Centre reported Long COVID prevalence estimates from 5.2% (n=496, >6-week follow-up) to 50.9% (n=277, 11-week follow-up) [15]. An even wide range is reported by Matribianco and colleagues, starting at 4.7% and reaching 80% [24]. Studies that included hospitalized or emergency ward admitted patients, with overall higher severity of acute infection tended to report estimates at the higher end, while those that also included non-hospitalized patients reported a maximum prevalence of about 36% (n=357, <12-week follow-up) [15].

Akbarialiabad et al. reported a similarly heterogeneous picture with prevalence estimates ranging from 13% to 76% [16]. Again, studies that exclusively focused on previously hospitalized patients reported overall higher estimates ranging from 49,6% (n=538, median 14-week follow-up) to 76% (n=1733, median 26-week follow-up) [16]. Studies that included non-hospitalized patients reported estimates from 13% (n=4182, 4 to 8-week follow-up) to 53% (n=180, mean 18-week follow-up) [16]. The comprehensive NIHR review suggests that at least 10% of all infected experience one persisting symptom at and beyond 12 weeks, with estimates ranging from as low as 2.3% to as high as 89% [10]. For those previously hospitalized, prevalence estimates range from 47% (n=2649, median 31-week follow-up) to 89% (n=119, 4 to 6-week follow-up). For those who were never hospitalized, prevalence estimates range from 2.3% (n=4182, >= 12-week follow-up), to 15% (n=21359, >= 12-week follow-up) and 36% (n=357, <12-week follow-up) [10]. NHIR also emphasized some evidence of Long COVID in children with one study reporting a 54% prevalence of at least one symptom at about 4 months after diagnosis (n=129, mean 23-week follow-up) [10][26]. Recent surveys conducted by the UK Office for National Statistics estimated that about 13% of children in the age group 2 to 11 and 14.5% in the age group 12 to 16 living in the UK had at least one persisting symptom 5 weeks after diagnosis [10].

Evidence from Primary Studies (⩾12 weeks follow-up)

In total, 44 of the 87 included studies provided overall Long COVID prevalence estimates at ⩾ 12 weeks after acute infection. We report these estimates in two groups. The first group includes 41 studies without control participants or population-based samples. The second group includes 7 studies that were either population-based (n=3), included control groups (n=3) or both (n=1). Among control studies we only included those that adequately reported prevalence estimates for both, cases and controls.

Prevalence estimates among the 41 of the first group ranged from 2.2% for individuals with mostly mild to moderate acute disease [34], to 86% for previously hospitalized and severely affected patients [35]. In total 10 studies reported prevalence estimates below 30%, 11 studies reported estimates between 30% and 50%, and 20 studies estimated the prevalence of Long COVID at over 50%.

Prevalence estimates among those studies with controls ranged from 7.8% [31] to 27.7% [36]. Prevalence estimates among studies with population-based samples (but without controls) ranged 26% [3] to 53.1% [32]. Overall, prevalence estimates were lower than in the first group with 5 studies reporting prevalence estimates below 30% and 2 studies above 30%. Table 2 provides the prevalence estimates of these 7 studies, with additional information on study design, sample characteristics, and follow-up duration.

Table 2: Prevalence estimates of studies with control participants and/or population-based samples [adult populations]

Authors [Reference] (p=population-based; c=includes controls)	Study Design	Cases (n=)	Hospitalized (%)	Follow-up (weeks)	Prevalence cases (%)	Prevalence controls (%)	Adjusted prevalence (%)
Cirulli et al. [31][P C]	Survey	233	3	12	14.8	7	7.8
Havervall et al. [37][C]	Cohort	323	0	⩾ 32	15	3	12
Logue et al. [36][C]	Cohort	177	9	12-36	32.5	4.8	27.7
Desgranges et al. [38][C]	Cohort	418	0	12	53	37	16
Petersen et al. [32][P]	Cohort	180	4	18	53.1	-	-
Menges et al. [3][P]	Cohort	431	19	29	26	-	-
Stavem et al. [39][P]	Cohort	451	0	24	41	-	-

These estimates need to be viewed with caution for several reasons. First, the prevalence of certain symptoms is rarely placed in relation to their prevalence in persons without SARS-CoV-2 infection before or during the pandemic, which potentially leads to overestimations. Second, reported estimates currently primarily rely on non-random, often self-selected samples. A very small fraction of existing studies reports prevalence estimates based on randomly selected, population-based samples. Third, certain population subgroups, including the elderly, care home residents, people with learning disabilities, as well as children remain underrepresented [10]. Finally, most the provided estimates are based on samples recruited during the early phase of the pandemic, where testing was not as widespread and captured cases were likely more severe.

Prevalence estimates in Switzerland

Three Swiss cohort studies, two conducted in Zurich, one in Geneva and one in Lausanne reported Long COVID prevalence estimates of 26% (n=385, 24 to 32-week follow-up), 32% (n=669, 4 to 6-week follow-up) and 53% (n=418, >3-month follow-up) respectively, all including adult samples [2][3][38]. The first two studies included hospitalized as well as non-hospitalized patients, while the third exclusively focused on non-hospitalized SARS-CoV-2 cases. While the Zurich ZSAC cohort sampled from all cases reported to the health directorate of Zurich between March and early August the Geneva and Lausanne cohorts were recruited from the services of the Geneva and Lausanne University Hospitals. The population-based Zurich cohort additionally reported that about 10% of initially hospitalized patients were re-hospitalized [3]. This cohort recruited another randomly selected 1100 persons with SARS-CoV-2 since August and will provide more prevalence estimates from different follow-up times after infection in due course.

Prevalence estimates among children

Eight primary studies explored Long COVID in underage populations, five of them provided prevalence estimates, and only two included control participants.

Studies with controls

First, the Swiss Ciao Corona study explored the long-term symptoms after a SARS-CoV-2 infection in school children. The sample of 109 seropositive children and 1246 seronegative controls was recruited through a randomly selected sample of 55 schools across the canton of Zurich [40]. 4% of the seropositive and 2% of the seronegative children reported an episode of at least one symptom lasting beyond 12 weeks. Ciao Corona's source population included symptomatic, as well as asymptomatic cases. Second, a large UK-based survey with 1734 symptomatic pediatric cases and 1734 controls reported a prevalence of persisting symptoms at 4.4% for cases versus 0.9% for controls 28 days after infection. At 56 days post-infection prevalence rates for cases dropped to 1.8% [40].

Studies without controls

A large (n=4768) household cohort study from England and Wales assessed the prevalence of symptoms lasting 4 weeks and beyond, reporting 4.6% for children with SARS-CoV-2 history (test or serology) [41]. The study's population also captured children with asymptomatic acute infections. A smaller Swedish cohort study with 55 previously hospitalized children looked at symptoms persisting for 60 days and beyond, estimating their prevalence at 22%, with fatigue being most commonly reported [42]. With a larger follow-up period of 3 to 6 months, a cohort study of 171 primarily non-hospitalized children in Australia reports an 8% prevalence of persisting symptoms [43]. Again, the study's sample consisted 36% of asymptomatic and 64% of symptomatic cases. The most common post-acute COVID-19 symptoms were cough and fatigue [43]. Finally, an Italian cross-sectional study with 129 participants, 26% of whom had asymptomatic and 74% symptomatic acute infections (5% requiring hospitalization), assessed symptom persistence at 6 months. The study reports a prevalence of 58.1% [44].

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, 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 [10]. 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” [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, breathing difficulties, heart palpitations, headaches, attention difficulties and cognitive deficits, muscle weakness and pain, dizziness, sore throat, abdominal pain, depression and skin rashes [25]. 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. Table 3 provides a list of all reported potential Long COVID symptoms and the reviews they were reported in.

Table 3: Reported Long COVID Symptoms

Symptoms (number of reviews reporting symptom)
SYSTEMIC fatigue (n=20), headache (n=11), fever (n=5), chest pain (n=11), excessive sweating (n=1), chills (n=1)
RESPIRATORY dyspnea / breathlessness (n=20), cough (n=11), pulmonary fibrosis (n=3), lung hypoperfusion (n=1), impaired lung function (n=3), thromboembolism (n=4), sore throat (n=4), nasal congestion (n=2), sputum (n=3)
CARDIOVASCULAR & HEMATOLOGICAL palpitations & arrhythmias (n=7), peri-, myoperi- and myocarditis (n=2), tachycardia (n=2), 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=13), loss or altered taste (n=13), 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=11), joint pain (arthralgia) (n=9), 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=11),), depression (n=6), sleep disorders (n=11), attention disorders (n=7), anxiety (n=7), posttraumatic symptoms (n=3), executive functioning difficulties (n=3), ataxia (n=1)
GASTROINESTINAL general gastrointestinal complaints (n=4), diarrhea (n=6), vomiting (n=4), loss of appetite (n=5), nausea (n=5), abdominal pain (n=4), bowel incontinence (n=1), acid reflux (n=2), gastrointestinal bleeding (n=1), constipation (n=1)
CUTANEOUS skin rashes (n=6), alopecia (n=4)

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 [11][17]. 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), (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 [10][12][15][17][19][20][22][24][25][33][45]. 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 [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]. 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 [46].

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 [15] [16] [46]. 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 [45]. Mental symptoms, especially posttraumatic ones seem to be affecting younger people, women, and those with responsibilities for others [16]. Beyond physical activity levels [12], none of the reviews reported on protective factors.

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 19% (n=19) 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 [47][48][49][50]. 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]. 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 [51][52]. 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 [53][54], with about 15% still reporting social and home disruptions 8 months after disease onset [37].

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][55]. 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 [37]. 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 [52][56]. 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 [1]. 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 [57]. 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 [26], [58]–[63].

Work-related implications

Inevitably, Long COVID is also expected to have a considerable impact on the workforce [10]. About 12% (n=12) 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 [51] [52][64][65] . Research on primarily mild to moderate and non-hospitalized SARS-CoV-2 cases report that about 12% to 23% remain absent from work (or had long absence periods) at 3 to 7 months after acute disease [54][66]. 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 [53][67]. 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. These numbers range from 8% to 45% for previously mild to moderate cases at follow-up of 3 to 8 months [37][54][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 [51][68].

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 [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][47].

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. In order to establish a first knowledge landscape, the first version of this review is limited to systematic reviews.

Current literature provides a still patchy picture. In the absence of a universally agreed definition, terminology, definitions and classifications vary. A similarly large variation is seen in reported prevalence estimates, attributable to large measurement heterogeneity and bias. Very few prevalence estimates included controlled subjects or were retrieved from population-based, representative samples. For adult populations and at a follow-up of 12 weeks or beyond, prevalence estimates among studies with controls ranged from 7.8% to 27.7% and among studies with population-based samples (but without controls) from 26% to 53.1%. New evidence on Long COVID in underage populations is currently emerging. Two large studies with control subjects from Switzerland and the UK estimate these at 2% and 1.8% respectively, while two cohorts of primarily non-hospitalized children in UK and Australia report a Long COVID prevalence between 5% to 8% [41], [43], suggesting a relatively lower disease burden than in adult populations. A smaller Swedish cohort with previously hospitalized children estimates the prevalence of persisting symptoms at 22% [42], similar to some of the large, population-based studies on adult populations. Nonetheless, current estimates should only be considered as provisional, as the overall reporting quality of studies and evidence strength remain weak.

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 [16]. 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	Critically low quality
More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis	Moderate quality
COVID-19 sequelae in adults aged less than 50 years: A systematic review	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	Moderate quality
Proposed delay for safe surgery after COVID-19	Moderate quality
Late Complications of COVID-19; a Systematic Review of Current Evidence	Low quality
Characterising long-term covid-19: a rapid living systematic review	Moderate quality
Ocurrence of long COVID: a rapid review	Critically low
Long COVID, a comprehensive systematic scoping review	Critically low
Living with COVID19. Second Review	Critically low
Epidemiology of Long Covid. A Pragmatic Review of the Literature	Critically low

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