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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 second version of the review, we included and analyzed 11 reviews and 67 primary studies. A universally accepted term and definition for post-acute and long-term SARS-CoV2 sequelae does not exist. We identified 10 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. Prevalence estimates from studies with control subjects and/or

population-based samples range from 2.3% to 60% at or beyond 12 weeks after symptom onset/hospital discharge. The three Swiss cohort studies suggest estimates of 26%, 32% and 53%. Considering those studies without control subjects and non-population-based samples, prevalence estimates range from 2.3% to 89%. Most prevalence estimates need to be viewed with caution since all studies suffer from at least one of the following limitations. First, the prevalence of certain symptoms is not placed in relation to their prevalence in persons without SARS-CoV-2 infection before or during the pandemic. Second, reported estimates often rely on non-random, convenience samples and not on randomly selected, population-based samples. Third, certain population subgroups, including the elderly or children remain underrepresented. Especially the evidence on children remains very weak. We identified two primary studies focusing on underage populations, however, none of adequate robustness to provide confident prevalence estimates. Finally, most estimates are based on samples recruited during the first half of 2020.

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 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. 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 15% 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 [1]. The population-based Zurich Coronavirus Cohort study found that 26% of the first 431 patients enrolled from March to August 2020 have not recovered fully after 6 – 8 months, with around 10% still severely impaired [2]. Long COVID is 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 [5]. Generated knowledge should ideally be holistic, including the broader public health and socio-economic dimensions of Long COVID, enabling and informing crucial healthcare and policy responses. While many European countries have launched initiatives to establish care and support pathways for Long COVID patients, the need for stronger and more targeted action remains.

Aim

To provide a summary of existing evidence on the public health implications of Long COVID. This is to be achieved through a holistic focus, combining the medical/clinical, social, economic, and broader healthcare system aspects of the novel syndrome. The specific research questions have been developed together with FOPH 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 April 2021 to include evidence from primary studies. This was conducted 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 [6]. The quality of primary studies was assessed with three items, adapted from Hoy et al. checklist for prevalence studies [7]. 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

Our database searches yielded 374 references. 335 of those were excluded at title and abstract screening and 39 manuscripts were screened full-text. That led to the exclusion of 32 further studies, either for not addressing Long COVID (n=19), not being systematic reviews (n=11), or being older versions of already included living systematic reviews (n=2). Database searches led to the final inclusion of 7 reviews. Google Scholar and reference list searches yielded additional 4 studies. Thus, we included and analyzed a total of 11 reviews. Figure 1 provides the PRISMA flowchart of our searches. For the April 2021 update, we included evidence from 67 primary studies, 49 of them included in at least one of the 11 reviews and 18 identified through related article searches in PubMed and Google Scholar.

Figure 1: PRISMA Flowchart for included reviews
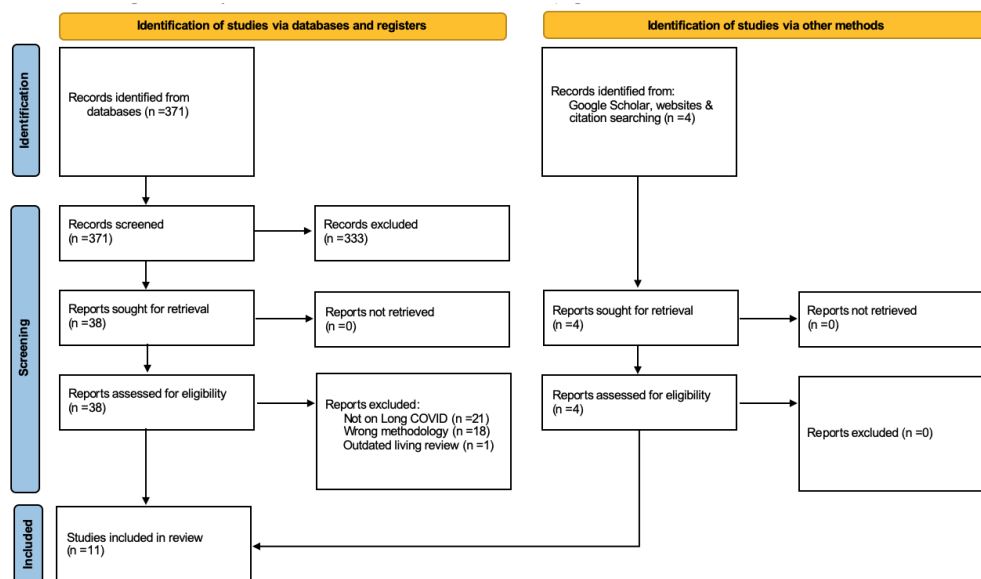
Characteristics of included reviews

One of the included studies was published in 2020, 7 were published in 2021 and 3 are currently available as preprints. Most studies were traditional systematic reviews (n=3), followed by rapid reviews (n=2), rapid living systematic reviews (n=2), pragmatic reviews (n=2) and a systematic review with a meta-analysis (n=1). Only one addressed pediatric patient, one middle-aged and young adults and the remaining (n=9) 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 4 scoring critically low, 1 scoring low and another 6 scoring moderate quality points. The full quality assessment table is provided in appendix 1.

Characteristics of included primary studies

Most primary studies (n=35) were published in 2020, followed by 32 publications in 2021. The majority were conducted in Europe (n=45), followed by North America (n=12), Asia (n=9) and one international study. Methodologically, the vast majority of primary research is based on prospective cohorts (n=44), followed by cross-sectional and survey designs (n=13), retrospective cohorts (n=8), case series and case-control studies (n=2). At the time of data extraction, a total of 7 studies were still at a preprint stage. Most studies included hospital-based samples and previously hospitalized participants (n=34). Exclusively non-hospitalized participants were

included in 10 studies while the remaining 23 had mixed samples of previously hospitalized, as well as non-hospitalized participants. Only 10 studies included controls, while 11 included samples representative of the general population. The reporting quality of most studies was assessed as low (n=40), followed by low to medium (n=19), while only 3 were assessed to be of medium and 5 of medium to high quality.

Evolving definitions of Long COVID

Terminology

A universally accepted definition for post-acute and long-term SARS-CoV2 sequelae does not exist. 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 [8] 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-acute sequelae of SARS-CoV-2 infection" (PASC) and "post COVID-19 recovery syndrome" [8]–[14]. 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 [15].

Definitions

Michelen et al. [15] 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 [14] [15]. Beyond symptoms, others also include abnormal, but potentially asymptomatic clinical parameters persisting as part of Long COVID [9]. 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" for persisting symptoms beyond 12 weeks after disease onset; both categories only hold if symptoms cannot be explained by alternative diagnoses [8][13][15][16]. Others disagree with that "by exclusion" approach, as it might fail to capture the very broad spectrum of post-acute complications [14], including SARS-CoV-2-triggered new health conditions and worsening of pre-existing health conditions [8]. 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 pos- intensive care syndrome, post-viral fatigue syndrome and long-term COVID syndrome [8]. 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 [8][17]. Terminology also varies between studies conducted in Switzerland, with the population-based Zurich Coronavirus Cohort study using the term "Post-COVID-19 Syndrome" [2] and the Geneva-based cohort study "Long COVID" [1].

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 [9] [15][18].

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) [8]. 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% [19]	(n=277)
highest reported prevalence	89% [20]	(n=119)
hospitalized, symptoms ≥12 weeks		
lowest reported prevalence	47% [21]	(n=2649)
highest reported prevalence	76% [22]	(n=1733)
non-hospitalized or mixed [2], symptoms <12 weeks		
lowest reported prevalence	13% [23]	(n=4182)
highest reported prevalence	36% [24]	(n=357)
non-hospitalized or mixed [2], symptoms ≥12 weeks		
lowest reported prevalence	2.3% [23]	(n=4182)
highest reported prevalence	53% [25]	(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 one review provided pooled prevalence estimates of 7 primary studies reporting at least one symptom at or beyond three weeks after disease onset, reporting an estimate of 80% (95% CI 65- 92) [9]. 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) [13]. 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) [13].

Akbarialiabad et al. reported a similarly heterogeneous picture with prevalence estimates ranging from 13% to 76% [14]. 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) [14]. 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) [14]. 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% [8]. 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) [8]. 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) [8][19]. 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 [8].

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

In total, 32 of the 68 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 23 studies without control participants or population-based samples. The second group includes 9 studies that were either population-based (n=2), included control groups (n=6) or both (n=1).

Prevalence estimates among the 23 of the first group ranged from 2.2% for individuals with mostly mild to moderate acute disease [26], to 86% for previously hospitalized and severely affected patients [27]. In total 2 studies reported prevalence estimates below 30%, 7 studies reported estimates between 30% and 50%, and 14 studies estimated the prevalence of Long COVID at over 50%.

Prevalence estimates form the 9 studies with controls and/or population-based samples ranged from 2.3% [23] to 60% [28]. Overall, prevalence estimates were lower than in the first group with 5 studies reporting prevalence estimates below 30% (mostly between 20 and 30%), 1 study providing estimates from 30% to 50% and 3 studies reporting a Long COVID prevalence of over 50%. Table 2 provides the prevalence estimates of these 9 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

Authors [Reference]	Study Design	Cases (n=)	Female (%)	Hospitalized (%)	Follow-up (weeks)	Prevalence (%)
Cirulli et al. [24]	Survey	233	64	3	12	24.1
Havervall et al. [29]	Cohort	323	83	0	≥ 32	15
Logue et al. [30]	Cohort	177	57	9	12-36	32.7
Sudre et al. [23]	Cohort	4182	72	14	>12	2.3
Petersen et al. [25]	Cohort	180	54	4	18	53.1
Taquet et al. [31]	Cohort	62354	56	20	24	33.6
Dennis et al. [28]	Cohort	201	71	19	20	60
Menges et al. [2]	Cohort	431	50	19	29	26
Desgranges et al. [32]	Cohort	418	71	0	12	53

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 [8]. Especially the evidence on children remains very weak. We identified two primary studies focusing on underage populations, however, none of adequate robustness to provide confident prevalence estimates. 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, one 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) of patients experience no full recovery yet or at least one persistent symptom, respectively [1][2][32]. 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 [2]. 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.

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) [8], 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 [1][2].

A group of patients exclusively experiences fatigue or upper respiratory complaints, while others multiple and multi-system symptoms [8]. 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" [8] [13]. Symptoms are often reported as debilitating, having a strong negative impact on mental health and quality of life [14]. 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 [18]. 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=10), headache (n=7), fever (n=5)
RESPIRATORY dyspnea / breathlessness (n=10), chest pain (n=3), cough (n=6), pulmonary fibrosis (n=3), lung hypoperfusion (n=1), impaired lung function (n=3), thromboembolism (n=2), sore throat (n=4), nasal congestion (n=1), sputum (n=2)
CARDIOVASCULAR palpitations & arrhythmias (n=4), peri-, myoperi- and myocarditis (n=2), tachycardia (n=1), cardiac stroke (n=1), venous/arterial thrombosis (n=1), myocardial inflammation (n=2), limb edema (n=2)
NEUROLOGICAL & MUSCOLOSCELETAL hyperesthesia (n=1), loss or altered smell (n=9), loss or altered taste (n=8), numbness (n=1), muscle weakness (n=5), cognitive fatigue (n=1), apathy (n=1), stroke (n=2), neuropathy (n=2), myopathy (n=1), muscle pain (myalgia) (n=6), joint pain (arthralgia) (n=5), intracerebral hematoma (n=1), cerebral venous thrombosis (n=1), bladder incontinence (n=2), swallowing difficulties (n=1), encephalopathy (n=1), dizziness / vertigo (n=4), tinnitus (n=1), earache (n=1), visual disorders / eye redness (n=2), excessive sweating (n=1), chills (n=1)
GASTROINESTINAL general gastrointestinal complaints (n=4), diarrhea (n=5), vomiting (n=2), loss of appetite (n=2), nausea (n=3), abdominal pain (n=2), bowel incontinence (n=1), acid reflux (n=1)
MENTAL / COGNITIVE brain fog and memory loss (n=8), depression (n=4), sleep disorders (n=6) attention disorders (n=7), anxiety (n=4), posttraumatic symptoms (n=3), executive functioning difficulties (n=2)
CUTANEOUS skin rashes (n=4), alopecia (n=3)

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 [9][15]. 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), (d) severity of acute disease (e.g. hospitalization, higher imaging scores, duration of oxygen supplementation, pneumonia), and (e) obesity [8][10][13][15] [18]. 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 [14][15]. Similarly, the NIHR review emphasizes that Long COVID seems to be more common in young adults (and children) than expected [8]. Two 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 [13] [14]. Mental symptoms, especially posttraumatic ones seem to be affecting younger people, women, and those with responsibilities for others [14]. Beyond physical activity levels [10], 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=13) 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 [33][34][35][36]. They also report that symptoms affect their family life and often limit their ability to care for others [8]. 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 [10][13][14]. 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 [37][38]. 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 [28][39], 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 [8][13][40]. 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 [38][41]. An important proportion of previously independent patients experience Long COVID impairments that deem them full care-dependent [8]. Finally, about 21% (n=14) of all included primary studies report that the majority of those living with Long COVID perceive their quality of life as significantly reduced.

Work-related implications

Inevitably, Long COVID is also expected to have a considerable impact on the workforce [8]. About 15% (n=10) 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 [37] [38][42][43] . 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 [39][44]. 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 [28][45]. 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 [29][39][44]. 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 [37][46].

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 [8]. 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 [8][13]. 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 [8][33].

European responses

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

Country	Responses [5]
United Kingdom	• NHS established care pathways for patients with symptoms 6 weeks after disease onset • NICE published Long COVID guidelines • Establishment of 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

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. Prevalence estimates from studies with control subjects and/or population-based samples range from 2.3% to 60% at or beyond 12 weeks after symptom onset/hospital discharge. Provided estimates should therefore only be considered as provisional, as the overall quality of studies and evidence strength remain weak. Equally weak is the evidence on Long COVID prevalence among children and teenagers. The currently low number and quality of studies does not allow for confident, neither preliminary prevalence estimations for underage populations.

Preliminary 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 [14]. 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	AMSTAR Score
Case report and systematic review suggest that children may experience similar long-term effects to adults after clinical COVID-19 [18]	Critically low quality
More than 50 Long-term effects of COVID-19: a systematic review and meta-analysis [9]	Moderate quality
COVID-19 sequelae in adults aged less than 50 years: A systematic review [33]	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 [10]	Moderate quality
Proposed delay for safe surgery after COVID-19 [11]	Moderate quality
Late Complications of COVID-19; a Systematic Review of Current Evidence [12]	Low quality
Characterising long-term covid-19: a rapid living systematic review [15]	Moderate quality
The occurrence of long COVID: a rapid review [47]	Critically low
Long COVID, a comprehensive systematic scoping review [14]	Critically low

Living with COVID19. Second Review [8]	Moderate quality
Epidemiology of Long Covid. A Pragmatic Review of the Literature [13]	Critically low