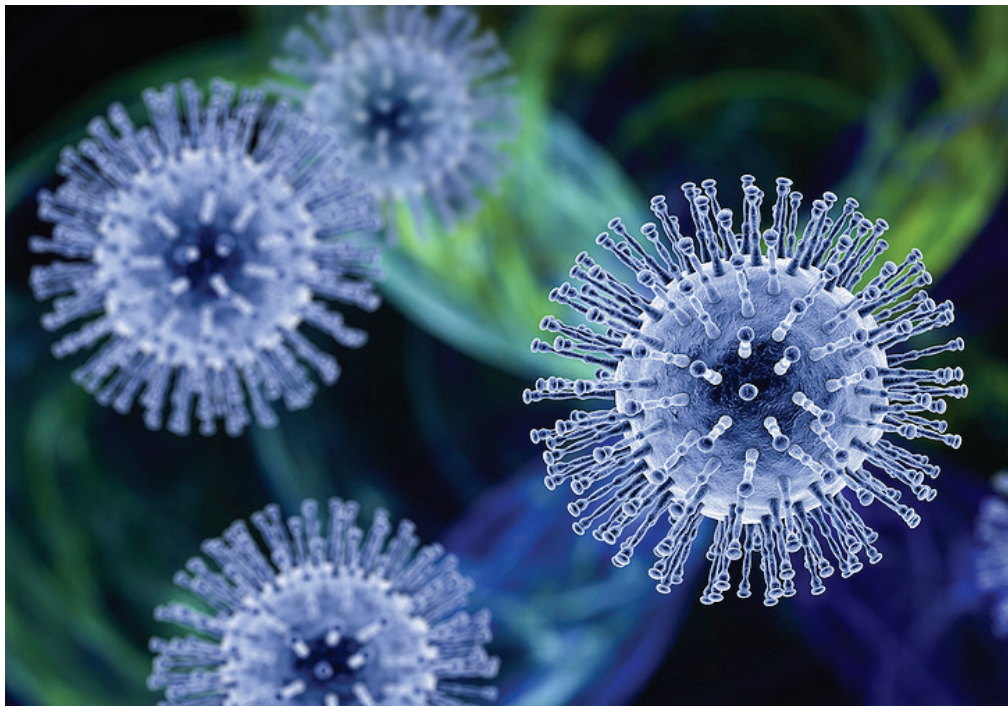


SYNTHESIS

LONG COVID: PATHOPHYSIOLOGY - EPIDEMIOLOGY AND PATIENT NEEDS



SHORT REPORT

LONG COVID: PATHOPHYSIOLOGY - EPIDEMIOLOGY AND PATIENT NEEDS

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■ SHORT REPORT

TABLE OF CONTENTS

1.	INTRODUCTION	3
1.1.	LONG COVID: NO RESTORATION TO NORMALITY FOR A PROPORTION OF PEOPLE AFTER ACUTE COVID-19	3
1.2.	SCOPE AND RESEARCH OBJECTIVES	5
1.3.	METHODS	5
2.	EPIDEMIOLOGY OF LONG COVID	6
2.1.	INTRODUCTION	6
2.2.	PREVALENCE OF COVID-19 PATIENTS THAT DEVELOP LONG COVID	8
2.3.	RISK FACTORS ASSOCIATED WITH THE DEVELOPMENT OF LONG COVID	9
2.4.	SYMPTOM FREQUENCY AMONG LONG COVID PATIENTS	9
2.4.1.	Based on the scientific literature	9
2.4.2.	Data based on the KCE online survey	10
3.	PATHOPHYSIOLOGY OF LONG COVID	11
3.1.	DIRECT AND INDIRECT LESIONS	11
3.2.	SEVERAL AND OVERLAPPING MECHANISMS ARE POSSIBLE	11
3.2.1.	Cardiovascular and coagulation systems	12
3.2.2.	Cardiorespiratory system	12
3.2.3.	Central nervous system	14
3.2.4.	Immune system	15
3.2.5.	Gastro-intestinal system	15
3.2.6.	Musculoskeletal system	16
3.2.7.	Cutaneous system	16



	3.2.8. Other systems	16
4.	LIVING WITH LONG COVID AND UNMET NEEDS	16
4.1.	THE LIFE-CHANGING IMPACT OF LONG COVID ON DAILY AND PROFESSIONAL LIFE	17
	4.1.1. Decreased quality of life and more support needs for activities of daily living.....	17
	4.1.2. Impact on professional activities	20
	4.1.3. Psychological impact.....	20
	4.1.4. Financial impact of living with long COVID	21
	4.1.5. Administrative burden	21
4.2.	HEALTHCARE UTILISATION AND SATISFACTION WITH HEALTH SERVICES	21
	4.2.1. Patient-reported contacts with the healthcare system	21
	4.2.2. Diagnostic work up for patients with self-reported long COVID	22
	4.2.3. Treatment and overall management of the disease	22
4.3.	NEEDS IDENTIFIED BY LONG COVID PATIENTS	23
5.	BELGIAN REIMBURSED SERVICES	27
6.	LONG COVID: MANY UNANSWERED QUESTIONS BUT A CLEAR NEED TO PROVIDE A HEALTH SYSTEM RESPONSE	31
6.1.	A NEW CONDITION: STRAIGHTFORWARD QUESTIONS BUT NO FINAL ANSWERS YET	31
6.2.	WHAT IS LONG COVID?	32
6.3.	PREVALENCE?	33
6.4.	CLINICAL MANIFESTATION AND MOST COMMON SYMPTOMS?	33
6.5.	WHAT DO PATIENTS EXPERIENCE?.....	33
6.6.	WHAT SERVICES AND OTHER MEASURES ARE AVAILABLE? WHAT IS LACKING?	34
6.7.	CONCLUDING REMARKS.....	36



1. INTRODUCTION

In this short scientific report we describe the main rationale, research objectives and methods, results and conclusions of the KCE study on long COVID. More details about the methods and results can be found in the full [Scientific Report](#).

1.1. Long COVID: no restoration to normality for a proportion of people after acute COVID-19

Long-term effects of COVID-19 increasingly reported by patients

In the first months of the COVID-19 pandemic, the public health response was almost exclusively focused on infection prevention & control and the management of the acute phase of COVID-19. From the early stages of the pandemic, which was declared by the World Health Organisation (WHO) in March 2020, it was recognised that the effect of SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) varies from an asymptomatic infection, through respiratory symptoms to a multi-system disease and a fatal disease.¹ While the majority of patients recovered in the weeks after the infection, it became clear, as time progressed, that some people (of all age groups, including children and adolescents) who had COVID-19, also after a mild acute phase, reported the persistence of a wide variety of symptoms. Patients started to report their stories on social media and 'long COVID', thus a terminology created by people experiencing it, was introduced already in May 2020.² Given the presence of post-infection syndromes after other viral infections (e.g. SARS-CoV-1 and MERS-CoV) the emergence of long COVID is not a surprise for the medical community but it might, due to the epidemiological magnitude of COVID-19, result in an unprecedented impact on several dimensions (e.g. post-viral burden of disease, healthcare utilisation, work incapacity).

Initiatives emerged from autumn 2020 onwards

The long COVID topic was picked up by clinical experts and policymakers and in August 2020 the WHO met with long COVID patient groups.³ In the months that followed several initiatives were started by the WHO (e.g. introduction post COVID-19 condition as ICD-10 code; a widespread consultation of experts and stakeholders with the aim to reach consensus about a definition by September 2021) and other (inter)national agencies (e.g. a dynamic review published by the British National Institute for Health research in October 2020⁴; a guideline published by the British National Institute for Health and Care Excellence – NICE in December 2020⁵; guidance on symptom management for general practitioners published in February 2021 by the French agency 'Haute Autorité de Santé⁶ – HAS'; a policy brief published in February 2021 by the European Observatory on Health Systems and Policies⁷).

Definition of long COVID: no international consensus

A clear definition of long COVID is important for the purposes of clinical diagnosis and therapeutic management, disease surveillance, and research.⁸ Yet, at the time of writing up this report (August 2021), there is not yet a globally accepted definition. 'Long COVID' is commonly used besides terms such as 'post-COVID condition', 'long-haul COVID', 'post-COVID syndrome', 'post-acute COVID symptoms', 'post-acute sequelae' or 'chronic COVID'. The WHO organised a large scale consultation among a wide range of health care professionals and patient groups with the aim to result in an international consensus about a definition and clinical criteria for long COVID (a report is expected to be published in October 2021^a).⁹ The wide range of reported symptoms and clinical manifestations indicate that long COVID can be considered as an umbrella terminology covering different groups of patients and medical conditions. Persistent symptoms might, for instance, be due to the consequence of the hospitalisation (e.g. bedridden patients) and a stay on intensive care units (ICU) in particular rather than due to the virus. As such, long COVID has to be differentiated

^a The WHO-definition on post COVID-19 condition was published on October 6th 2021 after finalization of the KCE-report

(https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1)



from Post-Intensive-care-Syndrome (PICS), a complication comprising long-term physical, psychological or cognitive disabilities that occurs in patients who have been hospitalised in ICU. This condition involves specific pathological mechanisms and may last several months to years. PICS is thus not unique for COVID-19 patients.

Categorisation based on duration of symptoms: working definition for the current report

The definition of long COVID is complicated by the fact that a clinical diagnosis of the acute COVID-19 illness might be absent. This was especially so during the early phase of the pandemic (e.g. because of limited test availability and accessibility of healthcare services). The long COVID patients without a positive test or formal clinical diagnosis of acute COVID-19 are considered within the scope of the current study.

In absence of an international agreement about a definition and clinical criteria, we used a classification based on duration of symptoms as a working definition. This was based on the NICE-guideline which makes a distinction in duration of reported signs and symptoms (not explained by an alternative diagnosis), as follows: '*ongoing symptomatic COVID-19*': 4 to 12 weeks beyond acute COVID-19; '*post-COVID-19 syndrome*' symptoms after 12 weeks.⁵ For the purpose of the current study the latter category is further divided into '3 to 6 months' and '>6 months'. In addition, we evaluated, where possible, our study findings for subgroups: acute COVID-19 with and without hospitalisation.

KCE study introduced by the patient umbrella organisation

On the request of the French umbrella organisation for patient organisations (la Ligue des Usagers des Services de Santé – LUSS) a study on the topic 'Long-COVID' was, after approval of the KCE Board, added to the research programme of 2021. The study started late December 2020. As it was anticipated that this is a rapidly evolving domain with a pressing need for information (by patients, general public and healthcare professionals), KCE decided to launch a webpage to report on intermediate study findings, as well as on important international initiatives (e.g. the NICE-guideline, the policy brief by the European Observatory) not necessarily within the scope

of our own research questions (see section 1.2). The webpage¹⁰ was launched in January 2021 with a pragmatic review on the epidemiology of long COVID¹¹ and an analysis of publicly available patients' stories¹². Since then, we published an intermediate report on the pathophysiology of long COVID¹³ in May 2021 and an update of the literature review about long COVID in June 2021.¹⁴ Since the start of the current KCE-study several other complementary research initiatives were initiated by public authorities (see Box 1).

Box 1 Other research initiatives related to long COVID initiated by Belgian public authorities

Practice guideline for primary care providers: the Belgian Evidence Based Practice Network is developing a guideline for the management and rehabilitation of long COVID patients in primary care. An academic consortium was commissioned to perform this task. They started in May 2021 and are expected to publish their guideline in May 2022.

COVIMPACT: Sciensano started in May 2021 with a cohort of people who have recently been tested positive for COVID-19 and follow them until April 2023. Every three months a follow-up questionnaire is collected to have information about physical, mental and social health.¹⁵

KCE-trials call on long COVID: KCE launched (May 2021) a call for randomized clinical studies (proof-of-concept or confirmatory trials) about interventions for management and treatment of long COVID. The selection process is in progress and it is expected that the first studies start to recruit patients in October 2021.¹⁶

HELICON: This study conducted by Sciensano in collaboration with academic partners aims to unravel the social inequalities and the long-term and indirect health effects of the COVID-19 crisis in Belgium.¹⁷



1.2. Scope and research objectives

The current KCE-study aims to provide information to policy makers to be used as one of the building blocks in the decision making process about which health care services and reimbursement rules are required for people with long COVID. In addition, we aim to inform the general public as well as healthcare professionals about the scientific insights in long COVID. More in particular we will focus on three main research parts:

- How frequent is long COVID? What are the most common symptoms? Which are the risk factors? What are the underlying pathophysiological mechanisms?
- What are the needs and experiences of patients with long COVID complaints?
- Which (reimbursed) services exist in Belgium to care for patients with long COVID complaints?

1.3. Methods

The research objective treated in this report is broad and the problem of long-COVID is complex. As is pointed out by other authors¹⁸, such study requires study designs that allow to illuminate a problem via different angles. Therefore, in this study we applied a mixed-method approach. In this section we give a short overview of the main methods used and some key figures. The methods used as well as the results are outlined in detail in the beginning of each chapter of the [scientific report](#):

- **Epidemiology of long COVID** (see Chapter 2 of the [Scientific Report](#)). A systematic review of the literature including (European and US-based) cohort and cross-sectional studies on the risk factors and prevalence of long COVID (symptoms and daily life consequences) when they included at least 250 patients. We have identified 47 studies (48 publications) and updated our search strategy until August 9th 2021.
- **Pathophysiology of long COVID** (see Chapter 3 of the [Scientific Report](#)). A systematic review of the literature about pathophysiological mechanisms likely to explain long COVID symptoms including case series, systematic reviews, cohort studies and experimental studies

without setting a minimum threshold for the number of included patients. We identified 100 studies and updated our search strategy until August 9th 2021.

- **Online survey on patients' experiences** (see Chapter 4 of the [Scientific Report](#)). The perceptions and experiences of people (n=1 320) with self-reported long COVID (persisting symptoms > 4 weeks) who participated in an online survey (January-February 2021) were analysed. Most of the respondents tested positive for COVID-19 (86%) or were clinical diagnosed as such (11%). Our sample showed a good geographical representation, included pre-dominantly women (75%), people who were not hospitalised during the acute phase of the disease (87%) and people with high education level (56% with a Master or Bachelor degree). The majority of respondents had symptoms for > 3 months: 37% (3-6 months); 45% (> 6 months).
- **Qualitative study** (see Chapter 5 of the [Scientific Report](#)). KCE recruited among the participants on the online survey, candidates for a qualitative study which aimed to complement the survey and gain more insight in the lived experiences and perceptions of patients with long COVID. In total 101 patients (56% Dutch-speaking; 44% French-speaking) participated on the online forum and 33 on the interviews (52% Dutch-speaking; 48% French-speaking). Most participants were female (77% forum; 64% interviews). For both data collection methods patients of the different subgroups of interest were included (i.e. with – and without hospitalisation during acute phase; different duration of persisting symptoms: 4 weeks – 3 months, 3-6 months, > 6 months). The quotes included in this short report were translated from French or Dutch (the original quotes can be found in the Full [Scientific report](#)).
- **Belgian reimbursement rules** (see Chapter 6 of the [Scientific Report](#)). An analysis of the current reimbursement rules in light of the main symptoms presented by long COVID symptoms (identified in the review on epidemiology). A combination of document analysis and expert consultation was used to identify the relevant issues.



2. EPIDEMIOLOGY OF LONG COVID

2.1. Introduction

Epidemiology based on a review of the scientific literature – Belgian cohort data not yet available

In this section we describe the epidemiology of long COVID based on a systematic review of the literature. At the moment of writing this report (August 2021), no cohort study with long-term follow which gives representative data for the Belgian population was available yet. Data will come available as the follow-up of people included in the COVIMPACT study progresses. The data from our survey do not allow prevalence estimates but can be used to assess symptom frequency among long COVID patients.

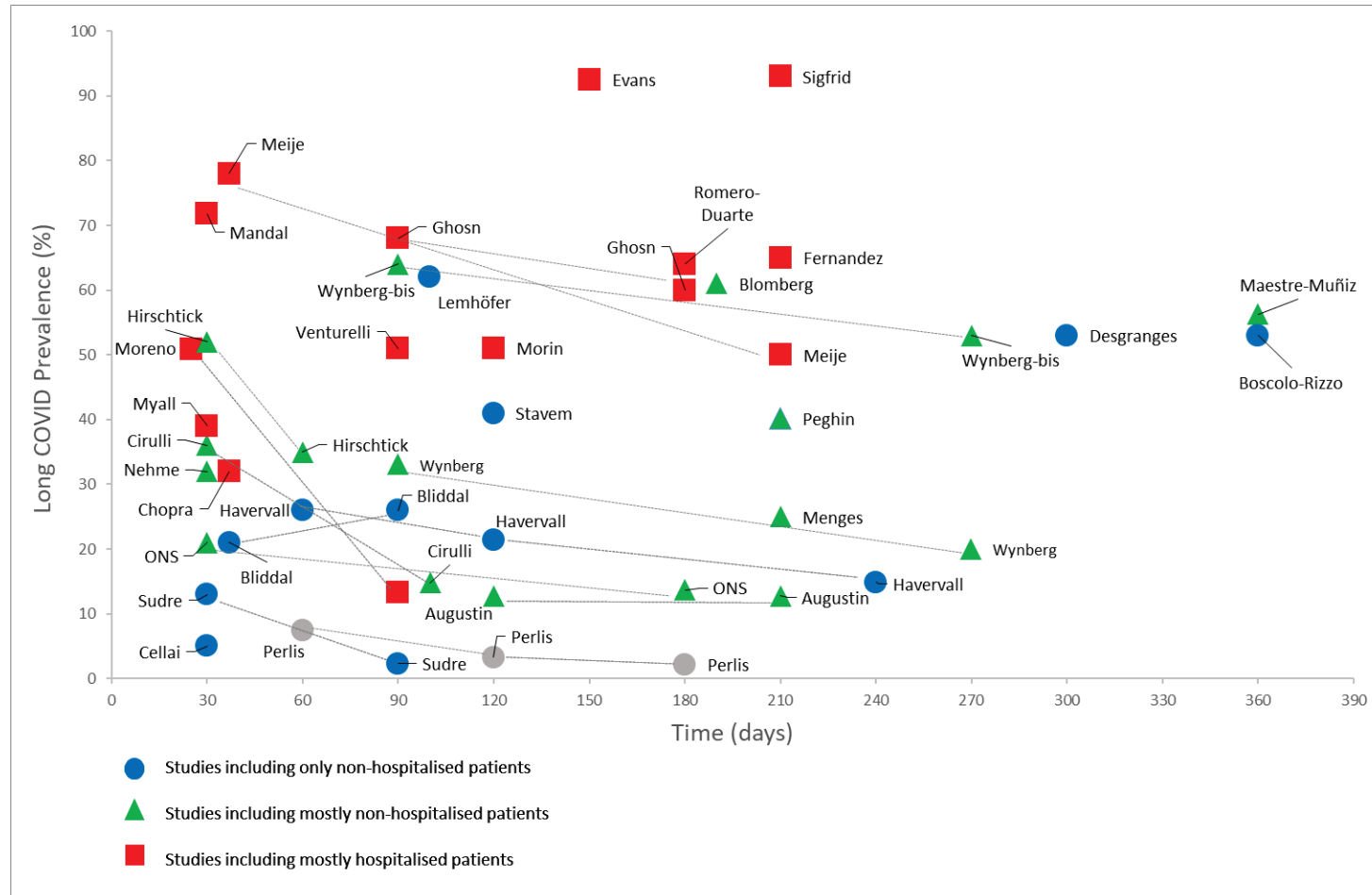
Retrieved studies: heterogeneity in definitions, study designs and data collection methods hamper precise and robust estimates

The literature review includes 48 articles (36 cohort studies¹⁹⁻⁵⁴, 1 case control study⁵⁵ and 11 cross sectional studies^{43, 53, 56-64}). Two articles referred

to the same study.^{58, 61} We have studies from 11 different countries (UK: n=8; France: n=2; Spain: n=6; Italy: n=4; Switzerland: n=3; US: n=9; Denmark: n=1; Norway: n=3; Sweden: n=1; Germany: n=2; The Netherlands=1) and eight studies included data from international studies. Nevertheless, the available evidence on the prevalence of long COVID remains limited and insufficient to formulate sound conclusions. Synthesising the information is a challenge since studies are highly heterogeneous (e.g. absence of uniform definition long COVID; study designs; time of inclusion, duration of follow-up; symptom measurement: number of symptoms, validated measurement tools, included populations: variation in demography, level of care received during the acute infection, sample sizes). Moreover the variation in reported symptoms is large and probably due to different underlying mechanisms (see section 3). Some of the symptoms can be explained by organ lesions (e.g. lung lesions such as fibrosis, especially in the group of hospitalised patients, can be linked to dyspnoea); while other symptoms might potentially be linked to an abnormal immune response and related inflammation induced by the virus. For all these reasons, the reported prevalence rates show a substantial variation (see Figure 1) and do not allow robust estimates.



Figure 1 – Results of studies assessing the prevalence of long COVID according to the level of care during the acute phase



Legend: No colour was attributed to the study of Perlis et al. since hospitalisation status is not clearly reported; 'Wynberg-bis' refers as the category of patients with higher level of severity at initial illness.

Note: this figure was inspired by a figure used in the NIHR report on long COVID.⁶⁵



2.2. Prevalence of COVID-19 patients that develop long COVID

From the review it can be observed that long COVID is prevalent both after a mild or severe acute COVID-19 and across all age groups. Prevalence rates seem to be higher among women compared to men. In general, people who have been hospitalised have higher rates of long COVID. Yet, it cannot be excluded that some of these symptoms are related to their hospital stay (e.g. bedridden patients; global deconditioning after illness) or stay on intensive care (post-intensive care syndrome) rather than due to the virus.

Prevalence^b of long COVID among hospitalised and non-hospitalised patients

The studies included in the review report the following prevalence rates for long COVID:

- Between 1 and 3 months:
 - Studies mainly including mostly non-hospitalised patients: median 32% (5-36%) of patients;^{21, 22, 28, 32, 33, 56, 62, 63}
 - Studies mainly including mostly hospitalised patients: median 51% (32-78%) of patients;^{26, 27, 49, 50, 59}
- Between 3 and 6 months:
 - Studies mainly including mostly non-hospitalised patients: median 26% (2-62%) of patients;^{21, 28, 32, 38, 51-53, 56, 60, 62}
 - Studies mainly including mostly hospitalised patients: median 57% (13-92%) of patients;^{26, 30, 36, 37, 40, 41}
- Beyond 6 months:

- Studies mainly including mostly non-hospitalised patients: median 25% (13-53%) of patients;^{32, 38, 42, 43, 48, 52}
- Studies mainly including mostly hospitalised patients: median 62% (50-93%) of patients.^{19, 37, 49, 55}

The studies with a follow-up longer than 6 months are still limited. Although it seems that for a large group of patients the symptoms tend to improve after 6 months, the reported prevalence rates remain high both for patients who were hospitalised during the acute COVID-19 as for those who were not.

Prevalence rates for specific organ systems or symptoms

Some studies focus on prevalence rates for specific organ systems or symptoms without studying a wider array of long COVID symptoms. We describe here two main groups:

- *Mental health problems*: the reported figures vary. A large study²⁹ reported a new onset of psychiatric illness (mainly anxiety and depression) among 5.8% of the study participants up to 3 months after the onset of COVID-19. Another study focusing on the new onset of psychiatric or neurological illness among a cohort of hospitalised patients at 6 months reported a prevalence of 12.8%.³⁴ The prevalence was higher in patients who were more severely ill.
- *Olfactory and smell problems*: self-reported olfactory disorders among predominantly non-hospitalised patients vary between 15% and 42%, 1 to 3 months after onset of acute COVID-19, in populations that had anosmia or hyposmia during the acute phase.^{23, 24, 31, 35} Olfactory and taste disorders are commonly self-reported. One study performed olfactory evaluations 2 months after COVID-19 and noticed that the objective prevalence was lower than the reported one (15% versus

^b Prevalence is defined as the proportion of people affected by COVID-19 found to develop long COVID symptoms (unless described otherwise)

24.1%).²³ One study with a follow up at 6 months report a decrease in prevalence to 5%.²³

For a description of prevalence rates for general symptoms (e.g. fatigue, headache, dyspnoea) see Chapter 2 [Scientific Report](#).

2.3. Risk factors associated with the development of long COVID

The risk factors to develop long COVID are still unclear. Studies that aimed to identify risk factors are limited and considerably heterogeneous. Up to now, there is no study with large follow-up. However, some studies converged towards the identification of probable risk factors. As such, there are indications in those who were not hospitalised that a higher number of symptoms at the acute phase of the disease may be a risk factor for developing long COVID. Likewise, several studies reported on the association between the level of care during the initial illness and persisting symptoms.^{26, 37, 42, 48, 51, 63} Regarding gender, we retrieved 6 studies showing an association between female gender and the likelihood to develop long-term symptoms.^{21, 37, 43, 48, 51, 66} In addition, two studies observed that men were less likely to develop long COVID.^{38, 42} The contribution of age (as a risk factor) is still controversial but long COVID seems to be prevalent across all age categories but its highest prevalence in adult population aged 35 to 69 years). Five studies identified in our search identified obesity as risk factor for persisting symptoms.^{21, 42, 43, 52, 66}

2.4. Symptom frequency among long COVID patients

2.4.1. Based on the scientific literature

Most common symptoms during the first three months after onset COVID-19: Fatigue – dyspnoea headache and taste-smell disorders

In the first three months, the most commonly reported persistent symptoms in the group of long COVID patients are fatigue (up to 98%)^{21, 22, 26, 28, 32, 33, 56-59, 61, 63}, dyspnoea (up to 88%)^{21, 22, 26, 28, 32, 33, 56-59, 63, 67}, headache (up to 91%)^{21, 22, 26, 28, 32, 33, 56-58, 63, 67} and smell or taste disorders (up to 58%).^{21, 26, 28, 32, 33, 56, 57, 60, 63, 67} Nevertheless, a wide range of symptoms (see below) are reported. In addition, a typical feature of long COVID seems to be that symptoms tend to fluctuate: periods of improvement are followed by a relapse or onset of new symptoms.

Most common symptoms beyond three months: Fatigue – cognitive disorders and respiratory problems

Beyond 3 months, the most frequent symptoms were fatigue (up to 78%)^{21, 30, 32, 40, 51, 53, 57}, cognitive disorders (up to 55%)^{21, 32, 36, 51, 57} and respiratory symptoms such as dyspnoea or dysfunctional breathing (up to 58%).^{30, 32, 36, 40, 51, 57, 60}

Beyond 6 months, fatigue (up to 84%) and dyspnoea (median value 57%) were still reported. Taste and olfactory dysfunction improve over time but may persist in the long run for a minority of patients. The type of symptoms does not seem to differ between patients who were hospitalised versus those who were not hospitalised during the acute phase. Yet, (part of the) symptoms might rather be due to their hospital stay (ICU or not) than to the virus, and when they stayed in ICU, these symptoms can be PICS (Post-intensive care syndrome).



Symptom frequency specific organ systems

Some studies report frequencies for specific symptoms. We describe the symptom frequency per organ system:

- **Respiratory system.** Dyspnoea is frequently reported (10-88% during first three months)^{21, 22, 26, 28, 32, 33, 56-59, 63, 67} alongside other respiratory symptoms such as cough (11-66%)^{21, 26, 33, 56-59, 63, 67}, chest pain or tightness (10-88.5%)^{21, 22, 56, 58, 63, 67}. Cough and chest pain are less reported beyond 6 months: 5-39%^{42, 48, 49} and 2-16%, respectively.^{19, 43, 48, 49} Studies, mainly including patients who were hospitalised during acute COVID-19, also described an alteration of lung diffusion capacity^{30, 36} and one study identified obstructive patterns at spirometry (4.7%) or abnormalities on medical imaging (9.4 %).²⁶
- **Cardiovascular symptoms** such as heart palpitations or tachycardia were mainly reported in the first 3 months after COVID-19. The reported frequency among long COVID patients varied widely from 6 to 86%.^{22, 28, 56-58} The frequency of palpitations is lower after 3 months at a level of about 10% or less.^{32, 40}
- **Neurological symptoms.** Cognitive disorders (frequently referred to as 'brain fog') are some of the most common neurological symptoms: the symptoms are variable (memory difficulties, concentration problems, executive functioning difficulties) and perceived as invalidating by patients. The range of reported frequencies is high (4 -85% during first three months^{21, 26, 28, 32, 56, 57, 63}; 6-55% after 3 months^{21, 32, 36, 51, 57}).

Olfactory and/or taste dysfunction are also very frequent symptoms (11-58% during first 3 months^{21, 26, 28, 32, 33, 56, 57, 60, 63, 67}; 11-51% between 3 and 6 months^{32, 40, 51} and with a median frequency of 26% beyond 6 months^{32, 38, 42, 43, 48, 49}). Other neurological symptoms include dizziness, tinnitus, visual disorders or peripheral neuropathy.

- **Gastrointestinal symptoms** are quite diverse (diarrhoea, acid reflux, loss of appetite or nausea) with a frequency ranging from 5 to 85% and diarrhoea the most common symptom.^{21, 22, 26, 28, 33, 56, 57, 63} Their frequencies were lower after 3 months.^{21, 40, 43, 48, 49, 53}

- **Mental health problems.** Anxiety and mood disorders (depression) are the most commonly reported mental health symptoms.^{30, 36, 40, 48, 55, 57} Post-traumatic stress disorder (PTSD) is also part of the reported problems in patients who stayed on intensive care units.^{26, 30, 36}
- **Skin disorders.** Various skin disorders are reported (rash, petechiae, chilblain-like lesions).⁵⁷ The frequency is particularly variable. Beyond 6 months, 4 studies reported on hair loss with frequencies fluctuating between 9 and 33%.^{19, 43, 48, 49, 55}

2.4.2. Data based on the KCE online survey

The most common reported symptoms highly resemble the symptoms reported in the literature. The five most common are: fatigue (78%); lack of energy (67%); breathing difficulties (62%); muscle pain & weakness (59%), and concentration problems (56%). The most frequent symptoms are following more or less the same ranking across subgroups: hospitalised versus non-hospitalised respondents and duration of symptoms (short: 4 weeks-3months; mid: 3-6 months; long: > 6 months). Yet, average number of reported symptoms was higher among patients who were hospitalised during acute COVID-19 (average number of symptoms: 12.9 versus 11.5 for non-hospitalised patients) and with a longer duration of symptoms (average number of symptoms: short: 9.8; mid: 10.8; long: 13.4).



3. PATHOPHYSIOLOGY OF LONG COVID

The underlying pathophysiology of long COVID symptoms remains at present unclear. Since long COVID symptoms vary considerably, there are probably also several responsible mechanisms which, probably to a certain extent, might also be intertwined. Many articles elaborate on the putative mechanisms involved in the symptomatology but evidence based on research among long COVID patients is sparse. Likewise, the quality of current research is limited due to variation in timings of inclusion, the initial disease severity or levels of care, and due to a lack of appropriate comparator groups. In addition, the pathophysiology of symptoms could overlap with other issues not specific to COVID-19 (e.g. pulmonary damage due to the mechanical ventilation). As such, the reported results need to be interpreted with caution. The current literature is highly hypothetical and subject to change.

3.1. Direct and indirect lesions

Current research has, so far, predominantly focused on the pathophysiological mechanisms involved in the acute phase and that lead to organ dysfunctions. However, even if organ injuries developed during the acute phase can account for some symptoms of long COVID, there is now compelling evidence that patients who experienced mild or moderate forms can present symptoms unassociated with residual organ dysfunctions.^{28, 68, 69} Even if it is conceivable that chronic manifestations can persist in the aftermath of the acute disease, specific mechanisms unrelated to organ damage need still to be unraveled.⁷⁰ This is the reason for which a distinction has to be made between two categories of mechanisms accounting for symptoms.

Organ dysfunction with lesions that can be objectified

The first type of mechanism refers to permanent organ damages that developed at the acute phase of the illness. They refer to evidenced structural (or microstructural) alterations of tissues leading to organ dysfunction. Subsequent organ dysfunctions are generally assessed by medical imaging, blood biomarkers or biopsy. Those abnormalities give rise

to symptoms associated to the involved organ such as, for instance, respiratory insufficiency secondary to pulmonary fibrosis, heart failure or renal disorders, as consequences of direct injuries developed during acute COVID-19.

Assumptions for symptoms without clear organ dysfunction: persistent viral load – autoimmune or inflammatory sequelae - metabolic disorders

The second category includes the pathophysiological mechanisms not clearly associated with organ dysfunction. In this case, unresolved, ongoing or recurrent reactions following the initial infection would be the cause of the symptoms. Those processes would be initiated in response to the acute infection or secondary to the occult persistence of SARS-CoV-2 in the body. They would give rise to multiple disorders (microcirculation disorders associated with coagulation and fibrosis pathway activation, auto-immune manifestations and metabolic disturbances). Those mechanisms induce a functional impairment of organs and bring about a wide range of symptoms, not particularly related to a specific organ. This category include symptoms such as chronic fatigue, post-exertional malaise or dyspnoea without evidenced lung damage, along with mental or neurocognitive problems. At the present time, the pathophysiological background of those conditions remained unclear and difficult to detect. Research focused on those issues is emerging and is likely to give new insights through the use of functional imaging or specific biomarkers.

In this report, we analysed separately studies merely elaborating on the putative hypothesis of the pathophysiology of long COVID, on one hand, and those in which patients were involved in the research process, on the other hand. The main data retrieved from the search are sum up below and detailed in the [scientific report](#).



3.2. Several and overlapping mechanisms are possible

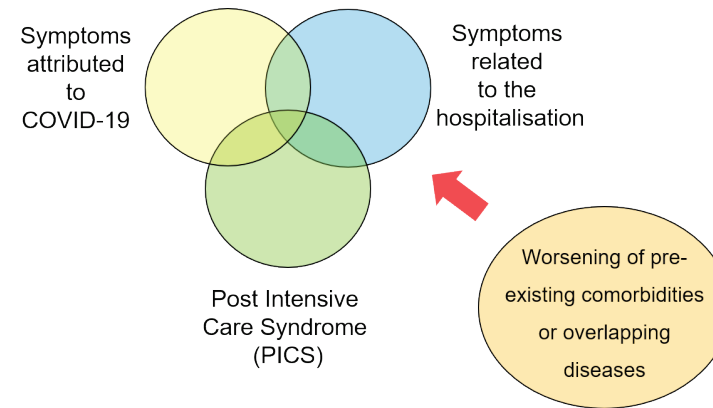
It is important to note that the reported symptomatology of long COVID could overlap with other conditions unrelated to COVID-19, such as the sequelae of prolonged hospitalisation (prolonged bed rest, deconditioning), the worsening of pre-existing comorbidities or even the Post-Intensive Care Syndrome (PICS- See Box 2 and Figure 2).^{71, 72}

Box 2 – Post Intensive Care Syndrome (PICS)

The Post-Intensive Care Syndrome (PICS) refers to long-term impairments in physical, cognitive, or mental health that arise in the survivors from critical illness. PICS is a common problem of severely-ill patients that can occur in up to 50% of them. It may decrease the quality of life and impair daily-living activities, patient autonomy or the ability to return to work. Symptoms comprises:

- An impairment of muscles and nerves that may develop during the course of the ICU stay and persist for a long time (ICU-acquired weakness)
- Mental health problems including anxiety, depression and post-traumatic stress disorders.
- Cognitive disorders including memory or concentration disorders or executive functions.^{71, 72}

Figure 2 – Difficulty to appraise pathophysiology: possible overlap between different issues



3.2.1. Cardiovascular and coagulation systems

During the acute phase of the illness, severe cardiovascular complications such as myocardial infarction, stroke or pulmonary embolism may occur. They result from coagulation disorders and can entail permanent disabling sequelae in affected organs (heart failure, neurological sequelae, etc)⁷³⁻⁷⁶

Endothelial dysfunction with subsequent activation of coagulation is thought to be the corner-stone of such phenomena. This dysfunction would be the result of the initial inflammatory reaction driven by the infection.^{73-75, 77-79} Other mechanisms such as auto-immune processes (antiphospholipid antibodies), platelets and leucocytes activations along with a dysregulation of Angiotensin 2 pathway have been suggested.^{74, 77}

3.2.2. Cardiorespiratory system

Aside from the cardiovascular disorders driven by the coagulation activation, cardiac cells could be injured directly by SARS-CoV-2, or as a consequence of the pro-inflammatory cytokines released during the initial inflammatory reaction. Structural alterations of the heart such as impairments of its contractile structure could ensue.^{73-75, 77, 78, 80} In addition, the fibrosis



pathway could be triggered and lead to a remodeling of the heart. Those processes can result in heart failure or rhythm disorders. Autopsy studies have revealed the presence of SARS-CoV-2 in the cardiac cells.⁸¹⁻⁸³

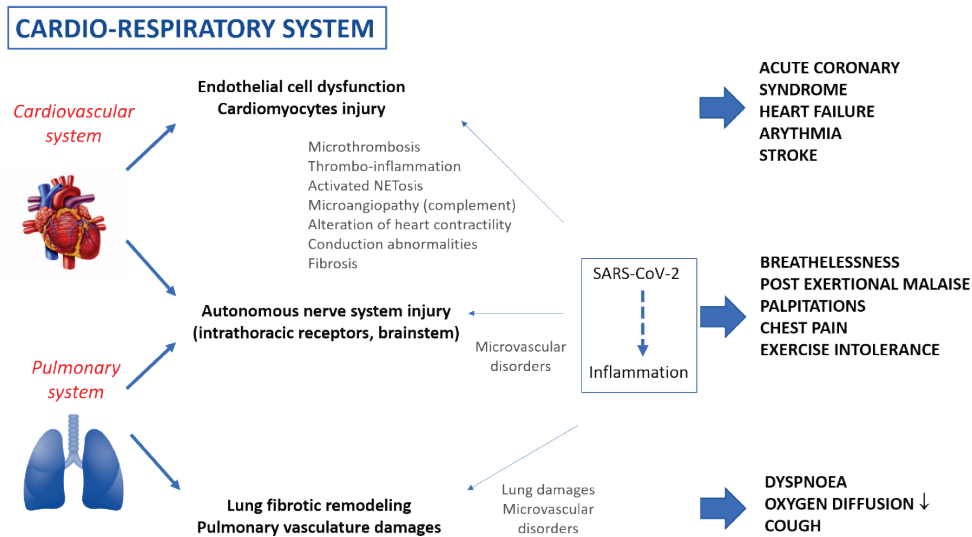
Lung fibrosis is a potential long-term complication.^{73,84-90} It has been suggested in survivors of COVID-19 and observed at autopsy.⁹¹ Lung fibrosis can occur in case of severe pneumonia regardless of the involved microbial agents. It is not a specific complication of COVID-19 but can be responsible for long-lasting dyspnoea. Damages of the pulmonary vasculature (including microcirculation) could also take a part in the long-lasting symptoms of COVID-19.⁸⁷

Cardiovascular and respiratory symptoms could also result from other mechanisms that would result from damages of the intrathoracic chemo and mecano-receptors involved in the control and regulation of respiration and

heart rate. Those damages would derive from injuries due to the SARS-CoV-2 neurotropism (cell invasion and damage), or secondary to microcirculation or autoimmune disorders. This hypothesis could explain many dysautonomic symptoms arising from a dysregulated respiration or cardiac frequency. They include breathlessness, exercise intolerance, palpitations or orthostatic malaise.⁹²⁻⁹⁵

Clinical studies have suggested micro- and macrovascular inflammation by using PET scan or biomarkers of microcirculation.⁹⁶⁻⁹⁸ Furthermore, antibodies against catecholamines receptors (and able to modulate heart frequency) have been identified, in patients complaining of dysautonomic symptoms.⁹⁹

Figure 3 – Hypothesis of the underlying pathophysiology involved in the cardio-respiratory symptoms of long COVID





3.2.3. Central nervous system

Neurocognitive and mental health problems

Several mechanisms are proposed in order to explain the long-term neurological symptoms such as neurocognitive or mental health problems. Neurocognitive disorders are called 'brain fog' and characterised by concentration or memory impairments and executive dysfunction (organisation, time management, multitasking, ...). The putative mechanisms that could be responsible for neurocognitive and mental disorders encompass brain inflammation mechanisms.

Brain dysfunction would be secondary to inflammatory phenomena following viral invasion of the brain, or to proinflammatory cytokines reaching the central nervous system. Microglia, which is a network of cells involved in homeostasis and defense, could secondarily be activated. Once activated, microglia can perpetuate neuro-inflammation through a dysregulated release of cytokines and reactive oxygen species. Microglia impairment has been associated with a large number of neuropsychiatric disorders.^{73, 76, 78, 90, 94, 95, 100-115} As a consequence of inflammation, hypercoagulation could lead to the formation of microthrombosis impairing vascularisation, neurotransmission and potentially inducing neuron injury (through ischaemia or excitotoxicity).^{104, 109} On the other hand, a bioenergetics failure due to mitochondrial dysfunction has also been proposed as a consequence of inflammatory reaction or viral invasion.^{101, 111} Autoimmune manifestations triggered, via a molecular mimicry with viral proteins, have been proposed as hypothesis.^{76, 112} This relationship between COVID-19 and auto-immunity has been suggested because auto-immune complications have been reported in the early course of infection.^{73, 76, 90, 109, 112, 116}

Whatever the mechanism, symptoms could be related to the impaired cerebral region. For example, the limbic system or cortical areas dysfunction could account for psychiatric and cognitive disorders. Clinical investigations, using magnetic resonance imaging, showed brain micro-structural several months after acute infection^{117,118} Other studies evidenced increased plasmatic biomarkers of neuronal injury and microglia activation or higher levels of inflammatory cytokines, after onset of infection.¹¹⁹⁻¹²¹ Conversely, functional studies with PET scan demonstrated brain hypometabolism rather than signs of inflammation.¹²²⁻¹²⁴

Headache and fatigue

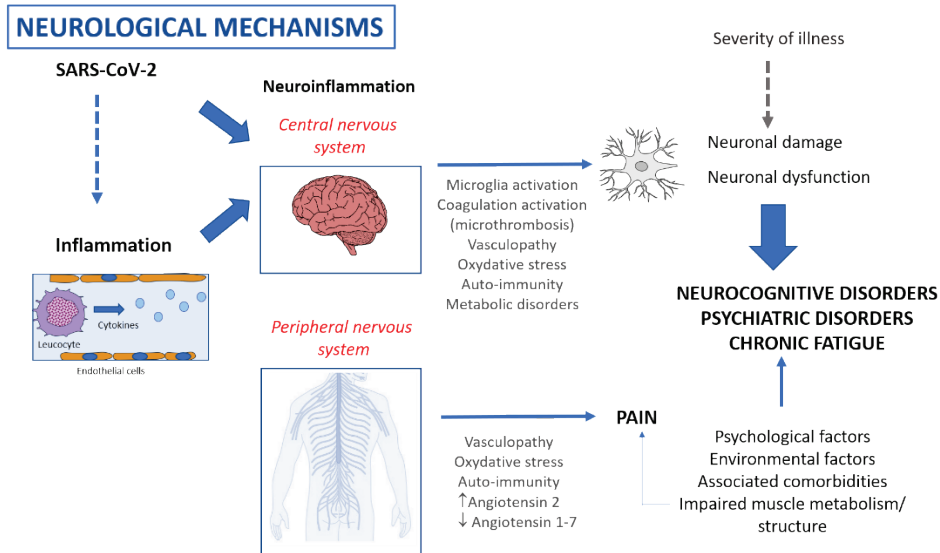
Several articles suggesting mechanisms involved in headache and pain proposed common pathways between long COVID and chronic fatigue (Myalgic Encephalomyelitis-Chronic Fatigue Syndrome; ME-CFS). Similarities concern both the many unknowns about the underlying pathophysiological mechanisms as well as the manifestation of several similar symptoms. Peripheral and central neuro-inflammation could play a role for both symptoms. Muscle mitochondrial dysfunction could take part in the physical dimension of fatigue while other pluri-dimensional factors (psychological, environmental, comorbidities) could also be involved.^{73, 94, 125-129} Yet, the trigger is more apparent in the case of long COVID compared to ME-CFS.¹³⁰

Smell and taste disorders

Regarding the persistent smell and taste disorders, neuroepithelial viral invasion and subsequent inflammation of olfactory and taste systems have been shown in patients with anosmia or dysgeusia.¹³¹⁻¹³³



Figure 4 – Hypothesis of the underlying pathophysiology involved in the neurological symptoms of long COVID



3.2.4. Immune system

As already described in the previous paragraphs, inflammatory and dysregulated immune response are the foremost hypothesis involved in the onset of long COVID symptoms. This hypothesis could also account for inter-individual susceptibility to develop long COVID (polymorphism of genes involved in the regulation of immunity). Studies using PET scan or MRI found signs of inflammation in various organs^{123,134-136}, while other studies described signs of remaining inflammation, T-cells abnormalities or autoantibodies against several organs, after recovery and even in asymptomatic patients.^{99,137-139}

Interestingly, biopsies from lower gastrointestinal tract showed the persistence of SARS-CoV-2 nucleic acids and immunoreactivity in the small bowel in asymptomatic subjects several months after COVID-19. This study

suggests that residual proteins of the virus in tissues could favor a persisting immune reaction resulting in long COVID symptoms.¹⁴⁰

Since vitamin D has been suggested to play a role in COVID-19 susceptibility and evolution, its relationship with long term respiratory symptoms has been investigated but it has not been demonstrated.¹⁴¹

3.2.5. Gastro-intestinal system

The most commonly reported symptoms are diarrhea, nausea and abdominal pain. Proposed hypothesis include the persistence of low-grade gastro-intestinal tract inflammation or an autonomous nerve system dysfunction.^{86,142,143} Hepato-biliary damages¹⁴² or alteration of the gut microbiota⁸⁶ developed during the acute infection have also been proposed to contribute to persisting symptoms.



3.2.6. *Musculoskeletal system*

Studies suggest that bone, joints and muscle pain could be attributed to thrombo-inflammatory-related tissue injuries and autoimmune processes.^{73, 90, 144, 145}

3.2.7. *Cutaneous system*

Many skin disorders have been reported. Underlying pathophysiology is still not well explored and various abnormalities have been described on skin biopsies.¹⁴⁶ Signs of inflammation, microthrombi and vascular inflammation have been observed.^{147,148}

3.2.8. *Other systems*

Some studies report on the endocrine disturbances after COVID-19. Newly diagnosed diabetes has been described in patients with COVID-19. However, the relationship between diabetes and SARS-CoV-2 has not been established yet. Viral infections (coxsackie, enterovirus) have already been proposed to play a role in triggering the onset of diabetes.^{90,149}

The thyroid can be affected by COVID-19 through different potential mechanisms (direct damage or indirectly by the release of cytokines at the early phase of illness).¹⁵⁰

Kidney injury has been described in critically-ill patients who required renal replacement therapy in the ICU.¹⁵¹ However, more specific alterations of the renal function has also been described in patients who did not have renal dysfunction during acute infection.^{151,152} Several mechanisms have been suggested such as direct cell damage or intrarenal microvascular dysfunction.^{73, 153,154}

Multi-inflammatory syndrome in children (MIS-C) is a rare complication that has been described in children and adolescents. It associates fever, skin and adenopathy disorders, conjunctivitis, digestive symptoms and cardiovascular signs (shock or coronary arteries aneurysms). Neurological manifestations are also reported. Its pathophysiology is currently not fully understood and might result from auto-immune processes.^{73,145,155} Although this syndrome shares many similarities with other pediatric diseases (Kawasaki syndrome, toxic shock syndrome), specificities have been described.¹⁵⁶



4. LIVING WITH LONG COVID AND UNMET NEEDS

In this section we describe the impact of long COVID for patients based on the literature review, the online survey and the qualitative study. The data retained from the survey and qualitative study (in-depth interviews and online forum) concern lived experiences of patients with self-reported long COVID. This section includes opinions and self-reported experiences. We refer the reader to Chapters 4 and 5 from the [scientific report](#) for more details.

4.1. The life-changing impact of long COVID on daily and professional life

4.1.1. Decreased quality of life and more support needs for activities of daily living

A wide variety of symptoms with impact on daily life: fatigue and cognitive problems have a prominent place in patients' stories

As can be expected based on the scientific literature and the KCE-survey of patients (online survey, online forum and interviews), patients report a wide variety of symptoms. Although patients indicated that it is not always clear to them if the symptoms are COVID-related, the type of reported symptoms resemble the ones reported in the scientific literature. Patients described the impact of symptoms on their daily life as varying from limited to life-changing. Symptoms are also reported by people who had a very active lifestyle before their COVID-19. Fatigue is the most frequently reported symptom by long

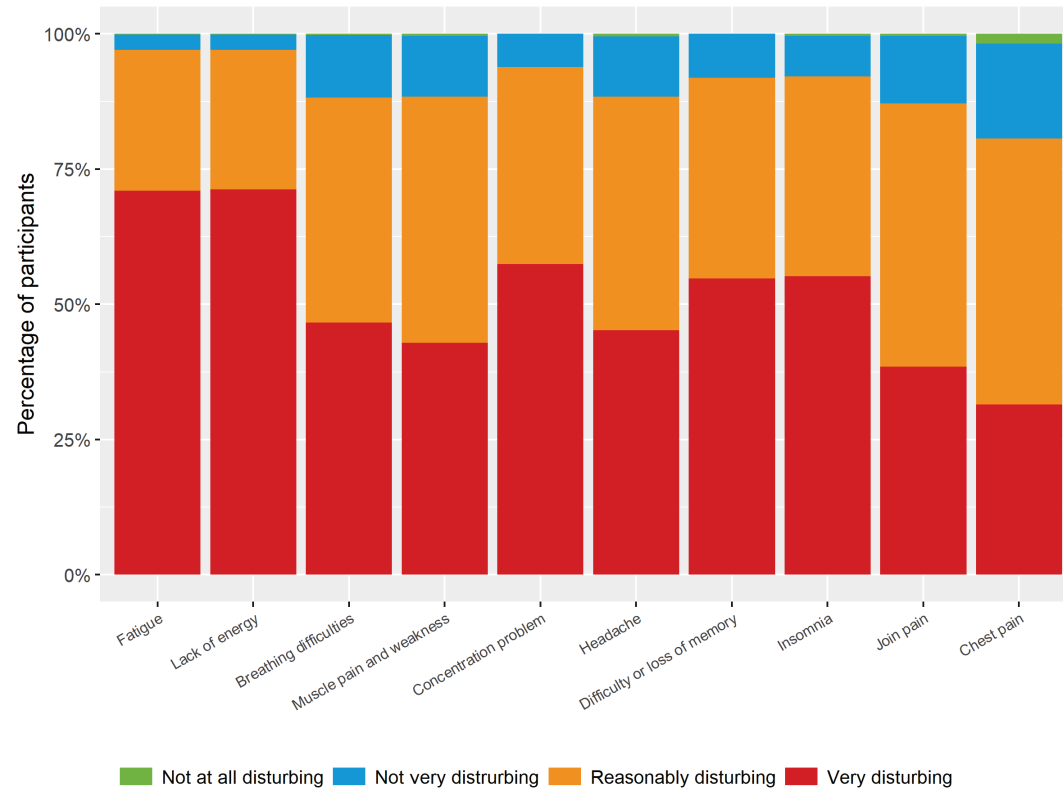
COVID patients. It is very profound tiredness and took a prominent place in the patient stories. It is experienced as very debilitating, having an impact on everyday's activities such as: decrease in physical activity, difficulties to perform household activities, incapacity to work, impact on social relations, etc.

« Fatigue takes away the energy to take up my professional activities as well as my daily activities. Often the energy level decreases throughout the day ...» (Forum)

Another symptom that was frequently reported as overwhelming and hampering patients to perform simple tasks (e.g. walking, cleaning, driving a car) which they did before without any problem is called 'brain fog' (cognitive problems).

« Difficulties to find words, not able to finish my sentences, a lot of difficulties to concentrate (ask yourself every 5 minutes what you were doing during a day at work ... 'which folder did I had to open' ... 'what exactly was I doing'), confused in the sense that you frequently forget things or have the feeling that you have a fog in your head ... everything is blurred ... these are all symptoms that are new to me .. not present before my illness ... One could say that everyone is feeling tired now and then but this is something else ... it is much worse both in intensity and frequency ... it is really not normal » (Forum)

The results from the online survey confirm the important impact of fatigue (and loss of energy) and concentration problems on patients. In Figure 5 the perceived symptom burden is shown.

**Figure 5 – Level of burden of the 10 most common reported symptoms**

Accumulation and fluctuating nature of symptoms are a source of stress and anxiety

Moreover, the accumulation of different symptoms as well as the fluctuating and unpredictable nature are experienced as very stressful, a never-ending story which also raises doubts about the future. Patients describe that periods of improvement are followed by a relapse. While some symptoms improve new symptoms can also appear. This is difficult to cope with and creates feelings of anxiety and uncertainty (e.g. “will I ever get better?”).

« I would describe the symptoms as something cyclic ... Sometimes you have the feeling that things are getting better but then new problems arise. At the beginning, all things were happening at once but afterwards, when the respiratory symptoms got better, the headaches and fatigue increased ... It really feels that it are cycles you go through and everything starts all over again ... » (Patient 32 not hospitalised)



Increased support needs with activities daily living

Data from the British Office of National Statistics (ONS) estimated that 64% of patients with long COVID experienced at least a limitation in their daily life and 19% reported significant limitations. Although impairment of daily-life was observed in all age-groups it was greatest in people aged 50 to 69 years and 35 to 49 years. In minors, the long COVID symptoms also affected daily life but to a lesser extent.^{62,157, 158} In a survey conducted in Belgium and the Netherlands, limitations in daily activities or care-dependency were reported among patients without a hospitalisation during their COVID-19 episode. The level of care dependency was assessed with the Care Dependency Scale tool. The need for assistance significantly increased after the infection (7.7% vs 52.4%) when compared with life before. Of importance, 41.1% of the patients who were not dependent on others before COVID-19, reported to have become so (at least to a limited extent) in the performance of daily activities.^{58, 61} Based on a large international survey conducted in Europe and the US it was shown that cognitive problems including memory disorders negatively impacted the daily life of long COVID patients (making decisions, following conversations, remembering medications, driving, cooking, watching children,...).⁵⁷

The results of the KCE online survey are in line with the findings of the identified studies. Indeed, almost 52% of the participants reported that they needed (or had needed) help with activities of daily living due to their long COVID. Participants needed the most help with cleaning (86%), preparation of meals (70%) and transportation/journeys (51%). The participants who were hospitalised reported significantly more support needs for daily activities than the participants who were not hospitalised (69.5% vs 49.3%). Hospitalised respondents also required significantly more help for hygiene (33.9% vs 10.3%), dressing (28.9% vs 9.4%) and transportation/journeys (66.1% vs 47.3%). Patients with long duration of symptoms had significantly more frequently support needs than patients with mid or short duration of symptoms (long 57.8%, mid 47.1%, short 48.1%). Duration of symptoms was also significantly related to support needs for transportation/journeys (long 55.5%, mid 50.9%, short 38.0%, $p < 0.01$) and for cleaning (long 88.7%, mid 86.4%, short 76.7%, $p < 0.01$).

The important role of informal caregivers was repeatedly witnessed during patient's interviews. Moreover, family and friends are an important support

at the relational and psychosocial level as well. It is important that they take the symptoms seriously and offer their support (with everyday activities but also to listen and talk to).

« I have to say .. my husband and my family were very supportive ... my husband prepared the meals everyday .. I also have a cleaning lady ... so I did not have to worry about that .. and also my employer is splendid ... very supportive and understanding ... I don't think that is always the case ... » (Patient 5, not hospitalised)

Impact on quality of life

Based on the scientific literature (see Chapter 2 [Scientific Report](#)), it can be concluded that long COVID symptoms have an impact on the quality of life.^{26, 36, 37, 50, 57, 61, 62} This was confirmed by the results of the KCE online survey. It can be observed that the quality of life decreased after a COVID-19 infection compared with before (average EQ-5D-5L: from 0.84 to 0.65). Increases in the proportion of health problems (any level of severity) was observed in all EQ-5D-5L dimensions with in general a shift from no health problems towards slight and moderate health problems, but not to the same extent. The proportion of respondents who experience health problems after COVID-19 increased by 44% for mobility; 10% for self-care; 56% for usual activities; 45% for pain and discomfort and 33% for anxiety and depression. A remarkably increase was observed in patients reported to experience severe problems for usual activities (+12%) and pain & discomfort (+10%).

Hospitalised patients reported more frequently health problems compared to non-hospitalised patients (EQ-5D-5L before and after COVID-19 for hospitalised patient: from 0.82 to 0.58; non-hospitalised: from 0.85 to 0.66) with the most impacted dimensions after hospitalisation being mobility and self-care. The negative impact of COVID-19 on subjective health (all dimensions) was larger for patients with long duration of symptoms (1-3 months: from 0.83 to 0.70; 3-6 months: from 0.86 to 0.66 points; >6 months: from 0.83 to 0.61). These findings were confirmed by subjective health scored via Visual Analogue Scale (from 0 to 100): average score of 85 before and 60 after COVID-19 (hospitalised: from 84 to 55, non-hospitalised from 85 to 60; Short duration from 84 to 63; mid duration: from 85 to 61 and long duration from 85-57).



We have conducted linear regression analyses to further analyse the factors associated with the impact of COVID-19 on subjective health (i.e. Beta: EQ-5D-5 after - EQ-5D-5L before COVID infection). Univariate analyses showed that in terms of characteristics of the participants, gender, region and average number of comorbidities prior to COVID-19 were significantly associated to Beta, with a higher impact for females, participants from Walloon region and for each additional comorbidity. All factors studied in relation to (long) COVID-19 (with the exception of hospitalisation) and to needs (e.g. need for help with daily activities) related to long COVID had a significantly negative impact on the quality of life. The association of lack of energy, financial impact of long COVID, fatigue, inability to work and concentration problems were in particularly important. After correcting the (long) COVID and needs factors for gender, region and number of comorbidities through a multivariate analysis, conclusions stayed the same, except for the variable 'duration of COVID-19 symptoms', for which it was observed that impact on quality of life is only significantly associated for patients with symptoms of more than 6 months (long) (compared to patients with short duration of COVID-19 symptoms).

4.1.2. Impact on professional activities

Difficulties to return to work: work incapacity or return to work with decreased working time

Based on our review we identified that long COVID has an impact on the return to work. A study (international survey conducted in Europe and the US) reported that 45.2% of patients who experienced long COVID reduced their work schedule compared to pre-illness and 22.3% were not working at the time of the survey because of their health status (being on sickness- or disability leave, being fired, quitting or being unable to find a job.⁵⁷ In another large study (prospective cohort) it was observed that about 1 in three patients (who have been hospitalised) did not return to work after 6 months.³⁷

Sixty percent of the respondents to the KCE-survey who had a paid employment before COVID-19 reported an incapacity to work. Among them more than one third (38%) were still not back to work or restarted work with decreased working time (26%). The percentage of people who could not

resume work was higher for the short duration group (51%, short: 4 weeks-3 months) compared to the mid- (34%, mid: 3-6 months) and long duration groups (37%, long: >6 months). No significant differences between hospitalised and non-hospitalised patients were observed.

This picture can be described more in detail via the interviews and the online forum. Patients report that they are still incapable to work or restarted with reduced labor time, a different job-content or with less energy and productivity than before. Some patients who restarted had to stop working again. The reactions of employers ranged from understanding (e.g. progressive re-integration strategy) to very suspicious about the genuineness of their health complaints. The impact of long COVID on their work can lower their self-esteem and makes them anxious and uncertain (e.g. about their job, long-term career perspective, financial situation). Some reported feelings of guilt (especially healthcare professionals unable to work in the mid of a pandemic).

« I hope, even after one year, to recover completely and to be able to return to work to work fulltime like I did before ... But I am not sure that this will be possible I am worried about my career in the future as well as about my income. » (Forum)

« Yes, I returned to work but I am not performing at the level as I did before my illness. » (Patient 10, hospitalised)

4.1.3. Psychological impact

As mentioned, long COVID can have a psychological impact related to the symptoms themselves (e.g. fear about the long-lasting nature and impact on their life) or to the impact on their professional live, both including the negative reactions (e.g. disbelieve, stigmatization) of others (e.g. colleagues, friends, family) (e.g. feeling down or guilty, self-isolation, tensions in relationships). Indeed, respondents indicated that people in their social environment do not take their symptoms serious because little is known about long COVID. Besides, patients also complain about the fact that healthcare professionals see long COVID as something that is merely psychological. They mentioned that they have the feeling that this stops them to search for other potential causes (see sections 4.2.1 and 4.2.2).



Therefore patients find it important to better inform the general population as well as the medical professionals about long COVID. From patients' stories it can also be deduced that the level of distress might increase when symptoms last longer.

« This clearly has an impact on the experienced stress ... you are thinking in worst case scenario's ... Psychologically the many uncertainties are very hard ... will there be long-lasting consequences? There are days that I doubt I will ever be able to experience a normal day in life ... to find back energy ... to be able to speak without having difficulties in finding words ... to feel good ...» (Forum)

4.1.4. Financial impact of living with long COVID

More than one in three respondents to the online survey (37%) reported to experience a financial impact because of long COVID due to loss of income, medical expenses (co-payment reimbursed services, non-reimbursed services as well as not conventional treatments and therapies) or a combination of both. The impact was significantly higher for patients who have been hospitalised and among those who have reported a long duration of symptoms. The financial impact has as consequence that some people have to cancel or postpone (not fully reimbursed) care (e.g. psychological support) for which they indicate that there is a need.

« The financial consequences of the combination of income loss and increased medical expenses are the reason why postponed consultations with the psychologists at the moment I was looking how I could rehabilitate ...» (Patient 19, not hospitalised)

4.1.5. Administrative burden

Patients report that long COVID can result in an administrative burden (e.g. related to contacts with their sickness fund, formalities to execute their right on guaranteed income assurance (if applicable), or the recognition of their condition as an occupational disease). They often feel less support to find their way in what they experience as a 'bureaucratic labyrinth'.

« The administrative burden For the sickness fund To get your recognition as an occupational disease ... administration ... administration ... administration .. it never stops ... » (Patient 26, hospitalised)

4.2. Healthcare utilisation and satisfaction with health services

4.2.1. Patient-reported contacts with the healthcare system

From the KCE-survey we can observe that the most consulted healthcare professionals by long COVID patients are GPs (91%) followed by medical specialists (of which 51% mostly a pulmonologist or cardiologist) and physiotherapists (30%).

Respondents who were hospitalised report having consulted a medical specialist more frequently compared to their non-hospitalised counterparts (78 versus 47%), physiotherapists (55% versus 26%), emergency department (60% versus 16%), psychologists (29% versus 14%) and rehabilitation department (27% versus 4.6%). Patients who went through acute COVID-19 more than 6 months ago reported significantly more use of health services than patients with a more recent onset of acute COVID-19 (4-12 weeks or 3-6 months), regardless of health service type.

Most of the respondents to the online survey were satisfied or very satisfied with their contacts with the healthcare system (ranging from 75% for GP's to 85% with psychologists). Only for emergency departments this percentage was lower (66%). Nevertheless, the satisfaction level is lower in the group of patients that experiences symptoms > 6 months (e.g. satisfaction with GP: 67.6% versus 78.6% in the mid- and 86.7% in the short duration groups).

Despite this general appreciation the qualitative study highlighted that patients experience several shortcomings during their contacts with the healthcare system. In the next sections we elaborate on some of these in more detail.

In addition other negative experiences such as lack of holistic approach, lack of empathy, etc. are reported.



4.2.2. *Diagnostic work up for patients with self-reported long COVID*

The forum and the interviews show a mixed picture about how patients experience their relationship with healthcare professionals. Several patients reported positive experiences (e.g. GP and/or medical specialists who listen to complaints and look for solutions in partnership with the patient). Nevertheless, also several rather negative experiences were described. The latter group of reactions is dominated by feelings of not being taken seriously by healthcare professionals. This is especially the case when patients underwent several medical examinations (e.g. lab tests, medical imaging) and objective abnormalities were not observed.

Patients (interviews and forum) acknowledge that a formal diagnosis of long COVID diagnosis (e.g. no consensus on clinical criteria, often no abnormalities observed on medical imaging or lab tests, lack of knowledge among physicians about this condition) is challenging. This is even more an issue when COVID-19 was not formally diagnosed (e.g. no PCR test during first wave of pandemic because of limited test capacity). Patients for whom physicians do not confirm that symptoms are a consequence of COVID-19, report negative experiences such as: being blamed as not trying hard enough to regain their physical strength and activity, being incorrectly labelled as a 'psychosomatic case', a minimisation of their symptom severity,

...

« That fatigue ... difficulties when sporting ... squeezing lungs ... indications of burnout and depression and decreased physical condition because of the lockdown ... while I was super healthy and sportive before ..The cause was mainly psychological according to my GP ... he even wanted to prescribe anti-depressant drugs ... what I refused. A total of 9 months of sickness absence because of depression, ... burnout asthenia ... » (Forum)

« This was disturbing because we experienced a list of symptoms and the only thing we could do was to wait until it got better ...and this could be a long time A period that you ask yourself the question ... is it my imagination? Are these complaints real? ... one questions its own mental state ...» (Forum)

No systematic or pro-active approach during the assessment and diagnostic work up

Patients report that the diagnostic work up is not proactive but rather organised on a symptom-by-symptom basis. They criticise the lack of a comprehensive diagnostic assessment. Some patients also point out that it took a long time before they were correctly referred.

4.2.3. *Treatment and overall management of the disease*

The overall management of long COVID symptoms is poorly coordinated and an integrated interdisciplinary approach is lacking. Patients report that the treatment approach is not coordinated nor standardised due to: absence of a clear diagnosis, symptom heterogeneity (type, number, manifestation, duration, severity), many uncertainties about long COVID, lack of awareness among healthcare professionals, etc.

Physiotherapy (but with variation in type of programs, duration and number of sessions) was a prominent therapy in patients' stories perceived as helpful by some but not by others. Due to a lack of standardised and/or coordinated treatment approach, patients tend to search solutions themselves including complementary and unconventional therapies (e.g. vitamin & food supplements, osteopathy, acupuncture...). Limited access to conventional services with professionals who are building up expertise in long COVID (ranging from mono-disciplinary physiotherapy to multidisciplinary rehabilitation) was also described. Furthermore, patients reported that some services (e.g. multidisciplinary rehabilitation) were not accessible to them because they were never hospitalised.

« multidisciplinary approach .. everything is fragmented at the moment .. you consult your GP ... from there you go to the pulmonologist ... then the cardiologist .. then the neurologist ... etc. The only link is the GP but many GPs have insufficient insight in the long-term consequences of COVID. There is no communication whatsoever between the medical specialists. » (Forum)

« If you were not hospitalised there is no formal follow-up or recognition of your illness and the consequences related to it. » (Forum)



Due to a lack of coordination of care and out of necessity patients have to coordinate their own care and look for solutions themselves.

When patients report to be in some kind of care trajectory they stated that it was initiated on their own initiative.

« The only thing what the GP does for me is to give me some sickness certificates (to justify my time off work). I do not receive any other kind of guidance or support .. no search for a solution of my problems .. even the neurologist has little knowledge about long COVID .. he also states that it is something psychological ...» (Forum)

« And it is not that they propose me to consult a neurologist ... it is up to me to ask them to refer me to one or another physician .. in fact I had to insist on it ...» (Patient 26, hospitalised)

They have the feeling that they have to explain their symptoms over-and-over again. Although patients acknowledge that there are many uncertainties and unknowns about the condition, they often have the impression that they are better informed about long COVID than the healthcare professionals. Patients described that they took up an active role in their diagnosis (e.g. by demanding tests/examinations), treatment (e.g. asking to be referred to a medical specialist or a specific rehabilitation program) and communication with healthcare professionals .

« My major concern is that usually with a viral infection you are back on your feet again after one week ... But in this case this doesn't work that way for everyone ... And thus if you try to explain it to people that you are not feeling well and are not yet recovered they look at you if you are a fool ... and that is not only the case with the guy in the street ... it also happens during contacts with physicians ...» (Forum)

There are only a limited number of prescribed treatments

Less than half of the patients participating to the KCE-survey (41%) reported to receive a 'treatment' of which most (71%) report to have received prescribed drugs. Yet, also 55% of those who reported to have received a treatment refer to complementary treatments such as vitamin supplements. About one in five people who received treatment considered this treatment as very cumbersome (13%) or extremely cumbersome (8%) with the most reported reason 'being forced to constantly take care of their medical condition/treatment'. Twenty-seven percent of people who received 'treatment' reported side-effects. However, we noticed that the reported side-effects resemble long COVID symptoms making it hard to tell if it are really side effects.

4.3. Needs identified by long COVID patients

About one in three respondents on the KCE-survey reported to have experienced unmet needs. Among them, the most frequently reported were information needs (52%), need for staff competent in the domain of COVID-19 and long COVID in particular (24%), and accessibility to care (23%).

These needs are directly linked to the experiences reported above. We clearly highlight them in this chapter.

A clear need for more information and 'recognition'

Respondents to the survey highlighted a clear need for more and better information on long COVID with 60% reporting issues with the information received. The main areas for which these respondents require more information are: changes in their health state (74%), the long COVID condition (68%), and treatment possibilities (62%). Many patients also expressed a need to talk about long COVID with healthcare professionals (32%) and other long COVID patients (27%). Patients want to be informed correctly (e.g. when lab tests or medical imaging cannot explain their symptoms, about the evolving scientific insights) by the public authorities and healthcare professionals. Patients (interviews and forum) indicated that they want correct information (knowns and unknowns) and want to be kept informed about the evolving medical and scientific insights in long COVID.



This information would not only empower them it will also take away some fears (e.g. about the future).

« What is happening with your body? How long will these symptoms last? Is it comparable with other viral infections? How can I treat myself? Self-care? What is a good approach on the long-term? What can I do or leave to get better soon? Do I have mental health problems and are my symptoms real? » (Forum)

During the interviews and the forum the terminology 'to be recognised' was frequently used. This did not only refer to the need to be 'officially or administratively recognised' to be eligible for some benefits (e.g. access to certain conventions, long COVID recognised as an occupational disease, access to same financial protection mechanisms in the national health insurance as other chronic ill patients, etc.). The need to be recognised as 'long COVID', as voiced by patients, is for a large part also to be understood as a demand to be taken seriously (e.g. by decision makers, by the medical community; research and clinicians, by the general public, by employers) and a need to create awareness about this new condition: both in the medical community as in the general public. Patients reported the need to explain that this condition can affect people of all age categories and after a mild or severe infection. Several patients stressed the importance to provide information (to the general public as well as the medical community) that long COVID is not a problem restricted to patients who have been hospitalised. This is a 'misunderstanding' which causes many problems to patients who were never hospitalised for COVID-19.

« Being recognised by politicians, policy makers and the general public... no not to complain but to experience a minimum of respect and that they stop to label us as anxious people ... free riders of the society ...Long COVID is never a subject of public debate .. no one talks about it .. it is as if it doesn't exist for people ! » (Forum)

« The DIAGNOSIS is one of the crucial elements ... of the highest importance ... No confirmed diagnosis ... means .. no reimbursement of costs related to care by the insurance not being taken serious .. not being understood by others .. especially those who are not able to get back to work ...» (Forum)

Patients expressed the need to invest in more and better information about long COVID to support the medical community and the general public (e.g. to facilitate diagnoses by standardised measurement instruments; to enable them to inform patients correctly, central website about the relevant scientific insights, etc.). This could also help to change the attitude of some healthcare professionals (e.g. those who are currently minimising the symptoms), and smoothen the care trajectory (e.g. less time lost before correct referrals are made).

«One of the first things that need to happen is that all physicians and healthcare professionals are better informed about long COVID. Patients are now often in a situation that they have to convince the physicians that their complaints are not imaginary but real. Patients have to take action ... they study about the disease ... self-diagnose ... look for the solutions themselves ...this is far from ideal ... And if action is taken to improve information about long COVID this should not look like 'Doctor Google' please ... it has to be easy and accessible for all healthcare providers and lay people as well....» (Forum)

A need for improvement in the way healthcare professionals listen to the needs and experiences of long COVID patients

Even if it is not a real therapeutic need, the first step in the care of the patient and the first unmet need in their pathway is that healthcare professionals listen to them. Patients demand to be taken seriously and state that this will require a change in the attitude of some healthcare professionals. They should be more open to listen to patient experiences. In addition it is important that, especially because this concerns a new medical condition with many unknowns, they are open-minded and curious enough to find explanations and solutions. Patients also stated that they find it important that healthcare professionals are honest and say that they do not know what is happening instead of immediately labelling it as a 'psychosomatic' condition. Patients reported that it is important to them that they get the feeling during their contacts with healthcare professionals that they listen to them in a sincere way and are open to what their patient suggests. Healthcare professionals need to work in a context that facilitates this (e.g. some patients indicated that there is currently insufficient time during



consultations; tele-consultations have benefits but also limitations to express feelings, etc).

« Physicians need to have the courage to admit that they do not know it. Now I have the impression that they label people from inside their ivory tower often as 'psychosomatic' because the condition does not fit within their current knowledge. This is a sign of arrogance that I have experienced in my contacts with several medical specialists. They really have to start with listening to the patients, with an open mind and accept that, for now, the patient is maybe better informed about the condition than the physician. The knowledge comes from the patients not from the medical world. Listen to them! And learn from it.. » (Forum)

Healthcare services adapted to the long COVID population: integrated interdisciplinary & tailored to patients' needs

Patients expressed the need for the development of an **integrated interdisciplinary**, holistic and coordinated approach of their long COVID based on a clear pathway including the diagnostic work up, the treatment, rehabilitation as re-integration at work. They need to be listened in their difficulties and guided through their pathway by staff competent in the long COVID domain. Nowadays they have the feeling to be forgotten in a landscape where care is insufficiently coordinated. It is forcing them to take the initiative a go and look around for medical care (e.g. by contacting several medical specialists).

« Because of the absence of care pathways it is left up to me as an individual to look for the most appropriate care. A multidisciplinary team with a focus on COVID would facilitate the diagnostic process...» (Forum)

The statements of patients reveal a need for organisation of care. Indeed, patients stated that post-COVID clinics with multidisciplinary teams with specific long COVID expertise will have to be developed covering both the diagnoses as the management of long COVID. A specific point of attention that was mentioned was their accessibility for children (a forgotten group of long COVID patients). Patients also suggested to develop **integrated**

interdisciplinary conventions (analogue as is done for other chronic diseases such as diabetes) to give them access to multidisciplinary expertise (e.g. social workers, psychologists, dieticians, ...) which are current not or insufficiently reimbursed.

« An ideal situation would be that the care is organised in post-COVID clinics where patients are assessed and undergo diagnostic tests depending on their symptoms (cardiology, pulmonology, neurology, gastro-enterology, rheumatology, immunology, rehabilitation, ...) ... with a team of physicians that is up-to-date about the medical and scientific evolutions within this domain ... These centres should also be accessible for children...» (Forum)

« A convention [lump sum payment allocated for care in specific centres] like the one that exists for diabetic patients (...) this should also include the payment for disciplines like the social worker who can take care of the organisation of support with care needs at home, (...).» (Patient 26, hospitalised)

Integrated interdisciplinary and tailored care also require investments in decision support and professional development

Patients reported a need to support healthcare professionals to develop expertise within this domain and to guide them in their decision making process. This will require, for instance, that clinic criteria for long COVID diagnosis (symptoms and examinations) are defined. Patients indicated that such definition should also take into account patients with long COVID symptoms without a positive PCR results (e.g. many patients, especially during the first wave, were untested but present with a clinically the same symptoms). Patients mentioned besides the need to develop a care pathway also a need to develop instruments for physicians that allow to classify and follow-up the evolution of symptoms should be developed.

«The physicians need to have tools at their disposal to monitor the evolution of symptoms ... A grid with the measurement of the persistence /evolution of symptoms would allow them to confirm what is called long COVID ... to identify the necessary tests and



examinations ... to find solutions ... identify underlying causes and which treatments could help .. etc. » (Forum)

Investment in research

Patients are aware that this is a domain under development. As such, they showed a lot of understanding for the fact that the healthcare professionals do not know the answers either. Therefore they recommended to invest in research on long COVID to allow a better understanding of the underlying mechanisms, its treatment & management, and organisational requirements (e.g. type of healthcare services). A specific need was voiced by a group of patients to invest in treatments to deal with cognitive and concentration problems (also called brain fog).

Social support needs

Patients indicated that due to their long COVID also their relatives experience a burden (e.g. taking over household activities) point to a need to provide professional support to relieve them (partly).

« Some support with household activities would have been very welcome because this is, even today, still difficult for me. My husband does what he can but we have three children and that is already a lot of work for him ... he needs to prepare meals ... do everything in fact ... And I ask myself where can I find some support to do the household? To help me now and then? ». (Forum)

Need to share experiences with peers

Patients feel a need to share experiences with peers. Several patient support and social media groups exist. While this helps some patients (e.g. to be reassured that their symptoms are real and they are not alone, to get information about available healthcare services) this is not always the case. Patients stated that information is often unfiletered (e.g. no quality assurance check) and can also overwhelm them, resulting in an insecure and anxious feeling. They expressed a need of peer groups (in person and social networks) with the support and involvement of healthcare professionals. Nevertheless, "official" self-help groups which also involve healthcare professionals, even on Facebook or by Teams, should allow to

interact in an anonymous way. Otherwise patients might be afraid to answer (e.g. because of a potential the reaction of their treating physician).

« These Facebook groups are a start but they lack a professional support there is no possibility to get a response from healthcare professionals ... creating such Facebook groups with the possibility that is moderated by professionals would increase the credibility of the support ». (Patient 6, hospitalised)

Measures to deal with the financial impact of long COVID

As stated above patients reported that they want access to financial protection mechanisms (e.g. statute of chronic disease, maximum billing) as is done for other chronic diseases. In addition some patients pointed to the need to expand the reimbursement of specific services (e.g. expand the duration and number of physiotherapy sessions, access to multidisciplinary rehabilitation for patients without a hospitalisation not meeting the current criteria, expand reimbursed sessions with a psychologist).

Indeed, the early and expanded reimbursement of psychological consultationsoften in combination with income loss) create a financial barrier to access psychological care was an important theme for several reasons (e.g. to deal with post-traumatic stress related to their acute COVID-19; to help them to accept the situation, think about the perspectives to live with the condition and manage the feelings of guilt; to deal with feelings of anxiety and depression). Respondents stressed that psychological support is in the first place required to help them to deal with the long COVID. This need should, according to patients, not be understood as a treatment for a psychological disease. Patients indicated that they prefer that psychological support is proposed to them at different time points. Early after the acute phase of COVID-19, but also regularly during follow-up. After all, patients might feel they do not need psychological support (or do not have the energy for it) at one moment in time, but this feeling might change when symptoms last. The limited reimbursement (often in combination with income loss) create a financial barrier to access psychological care.



« And I am always afraid if they say ... better psychological support is needed ... a better organised psychological care for long COVID ... the reason why this is required and requested by long COVID patients is because of the psychological consequences caused by the symptoms and not ... it should not be the reason to say that the long COVID symptoms are of a psychological nature ... have a psychiatric cause » (Patient 10, hospitalised)

« Not everyone can pay for a psychologist at a rate of 60€ per hour.... Especially not when you lose income in combination with higher medical expenses.....» (Forum)

« Psychological support ... the impact on the mental wellbeing cannot be underestimated. The own body feels suddenly very different ... fear for the future ... and how the condition will evolve over time. » (Forum)

Administrative support

Patients mentioned the need for help with administrative tasks when they are discharged from hospital. It is usually foreseen in the hospital for the elderly (e.g. via social worker) but it should be also available for young or single people. Patients see also a role for sickness funds but expect more efficiency and flexibility from them.

5. BELGIAN REIMBURSED SERVICES

The Belgian healthcare system is due to the COVID-pandemic not only confronted with an unprecedented sudden demand for critical care and acute hospital capacity to treat acute COVID-19 patients¹⁵⁹, it is also confronted with a large group of patients suffering from long COVID. As described above (see section 2), this patient population is not homogenous and suffers from a wide range of symptoms with different levels of severity and impact on everyday life. Moreover, there are still many unknowns about the underlying pathophysiological mechanisms, the diagnostic criteria, the duration of symptoms, patients' needs, effectiveness of management and treatment approach, etc. Given all these uncertainties, it is difficult to assess to what extent the Belgian healthcare system is able to absorb the needs of long COVID patients or to advise which and for whom changes are needed. In this section we summarise current reimbursement rules and to what extent they might be applicable to long COVID without being exhaustive. The recognition of long COVID as an occupational disease is considered out of scope of the current report.

General financial protective measures also apply to long COVID once the criteria are met

The Belgian compulsory health insurance, managed by the NIHDI, includes some general protective measures to support financial accessibility of healthcare services including the systems of social- and income maximum billings and the "status chronic disease patient". These protective measures have each their own finalities and criteria but have as general objective that care is not postponed due to financial reasons. The measures are, in general, not linked to specific diseases but are granted when certain criteria are met. As such, long COVID patients are eligible when these criteria are met. For instance, long COVID patients can benefit from the status "chronic disease patient": if they have been hospitalised for a least 120 days or had at least 6 hospitalisations; received a 6-month physiotherapy treatment because of severe chronic affections (in the framework of the List E related to the physiotherapy nomenclature M); when they benefit from certain lump sum payments for home nursing reserved for older patients; when they have exceeded a certain amount of health expenditure for two years (this criterion



can only be met when time progresses). A problem encountered by patients might be that they are not eligible (e.g. for the system of ‘Maximum Billing – income’) because their income is too high: calculated by default on income of two years ago (before COVID-19). Yet, a general rule exists (thus also applicable to long COVID patients) to ask to calculate the income based on another reference year when a substantial drop in income takes place. Patients have to apply for the application of this exception rule directly with their sickness fund.

Standard reimbursed services in the ‘nomenclature’ also applicable to long COVID

The reimbursement of health services by the NIHDI is not based on a recognition of diseases. Instead the Belgian health insurance system reimburses services with the objective that someone with a medical condition has access to services that allow an accurate diagnosis and treatment. Long COVID patients have, as all insured persons, access to general reimbursed services such as:

- Medical consultations with general practitioners and medical specialists;
- Standard 18 physiotherapy sessions per year (mono-disciplinary rehabilitation reimbursed via M-nomenclature);
- Physical medicine rehabilitation varying from the monodisciplinary^c physiotherapy rehabilitation based on medical prescription without a limitative pathology list (with a maximum of 48 sessions via the K15 and K20 nomenclature) to multidisciplinary rehabilitation (at least a physiotherapist and occupational therapist involved) with a maximum of 60 to 120 sessions depending on the type of pathology, when included on a limitative list of pathologies (e.g. polyneuropathy and myopathy;

^c While the reimbursement rules refer to ‘monodisciplinary’, in practice many hospitals organise it in a multidisciplinary way

^d For long COVID the most applicable (but very restrictive) possibility is pulmonary rehabilitation in case respiratory insufficiency (obstructive or

respiratory dysfunction with ESW<50%) (K30^d, K45 and K60-nomenclature);

- 8 reimbursed standard sessions per year with a psychologist (or 5 group sessions) (from the age of 15), and a maximum of 20 individual sessions for specialised psychological care (or 12 group sessions). Specific measures for children and adolescents exist (up to the age of 23). These reimbursement rules are new (since september 2021) and include a considerable increase in the accessibility of psychological care (e.g. no medical prescription required anymore for reimbursement of the 8 standard sessions) ;
- Etc....

From section 4, it is clear that these services are used by long COVID patients. Patients report to contact their general practitioner, consult medical specialists (with- or without referral from the GP), consult a psychologist and follow mono- or multidisciplinary rehabilitation (via M-/K15 & K20 and K30/K60-nomenclature respectively). Yet, patients indicated several limitations of the current reimbursement rules such as: lack of a multidisciplinary (one-stop) assessment, limitation in duration and number of reimbursed sessions with a physiotherapist and consultations with psychologist, restricted access to mono- and multidisciplinary rehabilitation (physical medicine rehabilitation) for patients that were not hospitalised. It should however be noted that also non-hospitalised patients have access to rehabilitation via the K-nomenclature (K15/K20 without restrictions and K30-K60 if they meet the medical indications) .

restrictive) with ESW<50% and/or proven desaturation after referral by a pulmonologist



Expanding reimbursed services via specific criteria also to be considered for long COVID?

The Belgian health insurance system includes several rules to expand the standard reimbursement services (e.g. prolonged consultation time internal medicine in case of complex pathology without a precise diagnosis, multidisciplinary assessment, more and longer physiotherapy sessions) when certain criteria are met.

The standard number of 18 physiotherapy sessions, for instance, can be increased when patients have pathologies belonging to the so-called lists E (severe and chronic pathologies without limitation per year), Fa (max. 60 sessions during one year – pathologies and health conditions that might benefit from physiotherapy during a fixed time period), Fb (max. 60 sessions during the first year and degressive reimbursement with increased co-payment from 61st session onwards - pathologies and conditions benefiting from regular physiotherapy during several years). Currently, long COVID as such is not part of on one of these lists. Adding long COVID to these limitative lists as such is difficult for several reasons (e.g. heterogenous group, lack of consensus about clinical criteria, absence of evidence about effectiveness). However, long COVID patients might benefit if they fit the criteria in force. An example, is an increased number of physiotherapy sessions for patients that have been hospitalised on ICU (via list Fa).

Conventions accessible for some (but few) long COVID patients

Rehabilitation conventions are a reimbursement mechanism with potential to cover complex needs through their multidisciplinary approach. Conventions have the advantage that they also cover services for disciplines which are not or only very limited covered under standard reimbursement (e.g. services provided by dieticians, social worker) or with a higher frequency or intensity (e.g. physiotherapy). as a formal mechanism to

support the return to work. Long COVID patients are eligible for these conventions when they meet the legal criteria of the convention. Yet, these criteria are very specific and were all defined before the COVID-19 pandemic. As a consequence, the number of long COVID patients that could benefit from specific conventions seems to be limited in practice. Below we list, as an illustration, some conventions which (potentially) concern (a limited proportion) of long COVID patients without the intention to be exhaustive:

- Rehabilitation for severe chronic respiratory problems which is restricted to (a.o. criteria) patients with a forced expiratory volume in one second (FEV1) below 60% of the predicted value;
- Long-term oxygen therapy will only concern long COVID patients with severe respiratory sequelae. Nevertheless, there is also a possibility for the reimbursement of short-term oxygen therapy. In light of the COVID-19 pandemic the maximum duration is temporary increased from 3 to 9 months to enable to support COVID-19 patients with respiratory needs;
- General functional rehabilitation centres for locomotor and neurological disorders (convention 950) is in principle open for long COVID patients but the criteria of the convention are very strict and in practice only applicable to very few patients (e.g. severe neurological damage after hospitalisation on ICU for COVID-19). The same remark holds for convention 771 (which is since the 6th State Reform partly transferred to the federated entities). Furthermore, patients who benefit from these conventions (limited to a few cases in practice) might also benefit from mono-disciplinary occupational therapy, a service that is not reimbursed outside the follow-up of these rehabilitation conventions;
- Chronic Fatigue Syndrome^e : a multidisciplinary diagnostic assessment and cognitive behavioural therapy is part of the convention organised

^e Defined by the NIHDI as patients meeting at least two out of three criteria: 1. a substantial decrease lasting for more than 6 months in the ability to participate in professional/educational, social or personal activities associated with fatigue characterised by its high intensity, is new or with a

clear start, is not the consequence of exaggerated efforts, not improves with sufficient rest; 2. deterioration of complaints after mental or physical efforts; 3. disturbed sleep or sleep without a positive effect on fatigue. In addition one of the two criteria need to be present: memory or thing problems; deterioration of complaints when getting up (orthostatic intolerance).



by only one centre (no other hospitals submitted an application for this convention).

Other forms of assessment and rehabilitation with can be of interest to long COVID

As described above (section 2.4) neurocognitive problems (informally referred to as ‘brain fog’) are an important and invalidating symptom for many long COVID patients. The possibilities to have a neurocognitive assessment under the current regulation is very limited. A neuropsychological assessment can be part of the diagnosis of dementia (and thus limit the eligibility of long COVID patients to those for whom a differential diagnoses of dementia is needed). Assessment of cognitive fonctions may occur in the framework of a rehabilitation program on the request of a specialist in physical medicine (in the context of K nomenclature; conventions 950 and 771) however not all centres offer such an assessment. Patients may also consult a neuropsychologist on their own initiative or on the advice of their treating physician, for an assessment of their cognitive functions. This assessment is not reimbursed by the NIHDI, but some sickness funds contribute to the cost as part of their supplementary coverage. Also the options for cognitive rehabilitation are very limited (e.g. as part of the conventions 950; 771 or as part of the conventions for ambulatory rehabilitation^f as follow-up after a hospitalisation; memory clinics for patients with early stage of dementia).

Patients with chronic pain may benefit from specific reimbursements for physiotherapy or physical medicine based on their diagnosis (e.g. complex regional pain syndrome, polyneuropathy with motor deficits). In addition, also specific medications might be reimbursed to them after approval of the advisor physician. Patients with severe chronic pain can be included in the care programs for chronic care offered by reference centres which are under the authority of the Federal Services of Public Health^g.

^f Since 6th State Reform, this a competency of the Federated entities.

^g The list of the centres could be found on the website of the FPS Public Health:

Work reintegration

Three actors play, together with the treating physician, a major role in supporting the return to work of patients: the advisory physician (sickness funds), the occupational physician (independent actor) and the controlling physician (assigned by the employer) in collaboration with the GP and/or the other health professionals involved in the follow-up of the long COVID patients. For those in total work interruption, reinsertion and reintegration programmes (organised by NIHDI & FPS Labour) exist as a formal mechanism to support the return to work. The general measures for employees and self-employees also apply to long COVID patients.

https://www.health.belgium.be/sites/default/files/uploads/fields/fpshealth_the_me_file/douleurlistehopcentremulti.pdf



6. LONG COVID: MANY UNANSWERED QUESTIONS BUT A CLEAR NEED TO PROVIDE A HEALTH SYSTEM RESPONSE

6.1. A new condition: straightforward questions but no final answers yet

Two main study parts: a literature review on epidemiology & pathophysiology and an analysis of patients experiences & needs

While the initial focus during the COVID-19 pandemic was almost exclusively on infection prevention & control and on the management of the acute phase of the illness, the attention for the long-term impact of COVID-19 steadily grew since the autumn of 2020. The number of patients who reported to experience long-term symptoms increased and patients around the world started to set up initiatives to put this new condition on the political agenda. Also KCE was asked, by the patient umbrella organisation LUSS, to conduct a study on what was called 'long COVID'. Some fairly simple questions were raised at the start of the study: What is long COVID? What is the prevalence? What are the most frequent symptoms? Why do some patients have long-term symptoms while others do not? Which are the prime experiences and needs of long COVID patients?

To answer these questions KCE conducted a study including two main parts: 1) a literature review on the epidemiology and pathophysiology of long COVID; 2) an analysis of patient needs and experiences based on an online survey, in-depth interviews and an online forum. Together with an analysis of the current reimbursement rules, this study had the ambition to be one of the elements (together with other studies and initiatives emerging in the field - see also Box 1) that could be used by policymakers as well as clinicians to support them in developing a response to deal with this new condition.

A new condition: many scientific publications often with important methodological limitations

From the outset of the study, it was clear that within the provided timeframe many uncertainties would remain. A first problem is the lack of international consensus about the clinical criteria and the definition of long COVID. This makes communication about, as well as actions to deal with the condition and its consequences difficult on several fronts: the research community (e.g. resulting in heterogeneous sampling), the general public (e.g. uninformed), clinicians (e.g. absence of or late diagnosis and referral for treatment) and policy makers (e.g. no sense of urgency).

Besides the absence of clarity about what it is, the identified studies had many shortcomings (e.g. no standardised measures, lack of control groups, selection & reporting bias, small sample sizes, insufficient follow-up duration). Moreover, no large-scale and/or representative Belgian data (e.g. no cohort representative for the Belgian population with long-term follow-up) were available when writing this report. Although the data collected (survey, interviews, forum) in the context of this study give a good view on patients' experiences and needs, we do not know if participants are (and were also not intended to be) representative of the population of long COVID patients and do not allow to make statements on prevalence, etc. Therefore, this study needs to be seen as a first step that will require further research and policy actions in the near future. Due to the limited evidence and its limitations many uncertainties remain and final answers cannot be given yet. Nevertheless, our research gives important insights to build on. Besides the many 'unknowns' there are also already 'knowns' about long COVID. In the sections below we conclude on the initial questions within this level playing field of knowns and unknowns.



6.2. What is long COVID?

Umbrella term involving multiple pathologies for patients with long-term consequences of a SARS-CoV-2 infection

Given the absence of an international accepted definition and clinical criteria for this patient-made term, when conducting this current research, we used a broad and pragmatic 'working definition'. We considered that long COVID is the state of not recovering >4 weeks following acute infection (tested or not) with SARS-CoV-2. Furthermore, we used subgroups based on duration (1-3 months; 3-6 months; >6 months) and with- or without hospitalisation. These choices seem to make sense since many variables (e.g. prevalence, impact on quality of life, required support) seem to differ between these subgroups. It is important to monitor the WHO-activities on the long COVID-definition and clinical criteria in the near future to be in line with the internal standards.

We can conclude, like several other authors^{65, 160}, that long COVID is an umbrella terminology involving multiple pathologies. A first group of patients are those with long-term consequences because of (objectifiable) organ damage (e.g. dyspnoea among patients with lung fibrosis). A second group concerns patients who suffer from symptoms as a result of their hospitalisation and stay on ICU in particular. This is not a new phenomenon and certainly not unique to COVID-19 patients. It is, for instance, well described elsewhere¹⁶¹ that a stay on intensive care might result in Post-Intensive Care Syndrome (PICS). A third group of patients concerns those who experience a deterioration of pre-existing co-morbidities (e.g. stroke, diabetes, cardiac problems). A fourth and large group of patients concerns those with symptoms for which the underlying mechanisms are still largely unknown. The raised hypotheses (e.g. inflammatory or autoimmune processes, persistent viral load, hypercoagulability, endothelial damage, dysautonomia) indicate that also this latter group might involve several different patient categories.

A recognised public-health problem

Our review of the scientific literature on the epidemiology together with the analysis of patients' reports and contacts with clinicians in the field makes us conclude that long COVID is a public health concern which impacts everyday life of many people around the world. It has an impact on quality of life, healthcare needs, and on the ability to work. Long COVID involves a wide range of symptoms. Although the symptoms are real, many uncertainties remain about, for instance the pathophysiology, the duration of symptoms and how to treat them.

Despite all these uncertainties, the initiatives taken by the WHO and countries around the world, prove that healthcare leaders recognise long COVID as a public health concern.

Continued research efforts will be needed to unravel the pathophysiological mechanisms

Today there is insufficient evidence to connect the symptoms of many long COVID patients to underlying causes.¹⁶² Therefore it is too early to say which of the hypotheses is correct. Moreover, it is possible that each of the hypotheses is true for different patients and that some patients are confronted simultaneously with different overlapping syndromes.¹⁶³ More research will be required to improve our understanding. Since only a minority of COVID-19 patients seem to be susceptible to develop long COVID, there should be more attention on the risk factors associated with long COVID development. It is worthwhile to note that patients who remained asymptomatic during the acute phase displayed a weaker immune reaction. Hence, a longer duration of viral shedding could have profoundly activated the immune system and potentially lead to long-term immunity disorders. However, overlooking this group of patients could lead to omit relevant pathophysiological pathways. Finally, it is worth noting that long-term follow-up remains, at the present time, too limited to reveal the spectrum of all potential consequences and to give a clear vision on the natural history of long COVID.



6.3. Prevalence?

Wide variety in reported prevalence rates due to study heterogeneity

The analysis of the epidemiological literature revealed an enormous variation in reported prevalence rates. Although this requires further scrutiny much of the observed variance can be explained by the heterogeneous set up of studies: observed populations (ambulatory patients, hospitalised and mixed patient populations, COVID-19 self-reported versus PCR confirmed), measurement of symptoms (number of symptoms within scope, level of standardisation symptom measurement), design (cohort versus cross-sectional), duration of follow-up, dropouts, etc. It will be important to continue to monitor prevalence of long COVID. An important initiative in that respect is the COVIMPACT study. Another option could be to include 'long COVID' in the GP surveillance system. After all, long COVID seems to be prevalent enough to include it within this surveillance system. Moreover, Belgium has, in contrast with other countries no nationwide system to monitor specific pathologies via a standardised registration of diagnostic codes within primary care practices. In England, for instance, a diagnostic code for long COVID (and the end of it) was introduced. While its introduction had registration problems (under-reporting) it has the potential to monitor the condition systematically.¹⁶⁴

High prevalence rates especially among patients who were hospitalised

Despite the wide variation, it can be concluded that prevalence of long COVID is high. Based on the included studies (see section 2) we estimate, at least one in seven patients still experience symptoms after 6 months. In the group of hospitalised patients this is even higher.

Long COVID is prevalent across all age groups and seem to be more frequent in women

It is commonly reported that the severity of acute COVID-19 increases with age and that men are more at risk. Older people and the men are more susceptible for severe illness, hospitalisation and mortality.^{4, 65} Nevertheless, long COVID seems to be highly prevalent in all age groups.

Even in minors long COVID is reported (although at lower rates and with lower impact on their daily life). The highest prevalence rates in the British ONS study, for instance, is reported in the age group from 35 to 69 years. Furthermore, long COVID appears to be more frequent in women. Finally, long COVID is reported at high rates after both a mild and a severe episode of acute COVID-19.¹⁶³

6.4. Clinical manifestation and most common symptoms?

The clinical manifestation of long COVID is quite diverse, often resulting in an impact on daily life and functioning (e.g. inability to return back to work). A wide range of symptoms are reported with the most common being fatigue, respiratory problems (breathlessness), headache, cognitive dysfunction (informally referred to as brain fog: poor memory and difficulty concentrating). But also smell- and taste dysfunction, anxiety, palpitations, dizziness and pressure on the chest are commonly reported. The nature of the symptoms is often relapsing.^{8, 160} While some patients only have a single persisting symptom (e.g. smell disorder) often patients have problems with multiple organs, suggesting that it is a multisystem disorder.¹⁶³

6.5. What do patients experience?

Long COVID symptoms are a cause for worry and anxiety

The general narrative about COVID-19 was a long time that some weeks after the infection most patients fully recover. Yet, in case of long COVID this is not the case. Patients continue to experience symptoms often with an impact on their daily functioning, their wellbeing and professional and social activities. Long COVID patients are worried about the cause of their symptoms, how long they will last and if they will ever get better. Patients who are confronted with episodes of improvement and relapses feel disappointed.



Lack of understanding

Some patients report that they feel that their complaints are not always taken seriously by their environment (e.g. their employer), the consulted healthcare professionals and the general public. They also state that a first reflection by some is to attribute these persisting symptoms to a psychological cause. To date, based on our research, we cannot identify the underlying cause. However, the current uncertainty about what causes persisting symptoms is not the same as the absence of a physical nor a psychological cause. It means that both a physical cause and a psychological cause needs to be investigated.⁶⁵

Patient involvement

Patients express a strong desire to be involved at all levels: in the diagnosis, their care, policy development, etc. Patients initially organised themselves via the social media. Yet, the information on these media are often unfiltered and can cause both reassurance (by receiving confirmation that they are not the only one experiencing these problems) as well as a cause of frustration, anxiety and stress (e.g. by getting negative messages about the prognosis). Moreover, some patients seem to become 'researchers' in the field themselves being, according to them, better informed than many healthcare professionals. Although patient empowerment is to be encouraged, this situation is far from ideal (e.g. risk of misinterpretation of findings, etc). At least it should be counterbalanced with well-informed healthcare professionals.

6.6. What services and other measures are available? What is lacking?

Services currently used in the management of long COVID complaints

In this section, we describe the services that are available and reimbursed within the Belgian healthcare system and to which long COVID patients based on patient reports and contacts with clinicians in the field, appear to be frequently referred.

A common practice in the management of long COVID patients seems to be physiotherapy. GP's often refer patients with persisting symptoms to a physiotherapist for the standard of 18 reimbursed sessions. Based on our observations (patient reports), it can be concluded that there is variability in how these sessions are used. Therefore, it seems important that, while awaiting evidence generation about clinical effectiveness, the professional and scientific organisations develop best-practice guidelines to inform physiotherapists on the field. A common critique voiced by patients was that (when they were not hospitalised) they had no access to more than the standard number of 18 sessions, while they experienced a need for it. Given the absence of evidence about the appropriate number of physiotherapy sessions, there are insufficient arguments to conclude that long COVID (or specific subgroups) has to be included in one of the lists allowing more physiotherapy sessions (e.g. E-Fa, Fb). On the other hand, if clinicians estimate that more sessions are potentially beneficial for some patients there is currently an option to prescribe 48 sessions within the context of physical medicine rehabilitation (K20/K15). Yet, this latter option seems to be insufficiently known and/or used among patients and prescribing physicians.

Also within primary care the option of consultations with a psychologist (max. 8 reimbursed sessions at time of conducting the patient survey) exists. Patients stated that these sessions are neither sufficient nor adapted to deal with the specific problems of long COVID. In addition, both physiotherapy and psychological consultations are insufficiently embedded in a 'multidisciplinary approach'. Also the use of these services does not seem to be part of a systematic care pathway. Some GP's refer patients to these services (sometimes at the request of the patient) while others do not. Some patients are referred by medical specialists but this might already be quite long after the onset of acute COVID-19 (e.g. after several separate consultations with different medical specialists).

A comprehensive integrated interdisciplinary assessment re-directing patients to a tailored pathway is currently lacking. This seems to be especially the case for patients who have not been hospitalised. Although the follow-up of hospitalised patients is more structured, especially if they stayed on ICU, also for these patients a lack of integrated interdisciplinary follow-up was pointed out as a problem. It is a misunderstanding that



possibilities for multidisciplinary rehabilitation (e.g. K-nomenclature, conventions) are restricted to hospitalised patients. Yet, in practice the criteria required for access will be more frequently met by patients who have been hospitalised. Anyway, also for the multidisciplinary treatment (e.g. K30 and K60) there are insufficient scientific elements to propose an expansion of the limitative pathology lists with long COVID.

Long COVID reveals some weak and strong points of our system

The Belgian healthcare system, like many healthcare systems, was suddenly confronted with a new large patient population. This situation reveals both the strong and weak points of our healthcare system which are not new and already experienced by many other patient groups for a long time. Moreover, every system has its budgetary constraints resulting in restrictions that will always, to a certain extent, be inherent to our healthcare system (e.g. not enough sessions with psychologists & physiotherapist, non-reimbursement of over the counter drugs, etc.). It is beyond the scope of the current report to make a case for a system change. We can only give some examples that emerged from this research.

A clear strong point is that patients with persisting complaints have access to a variety of healthcare services (see section 5) in primary care (e.g. GP consultations, physiotherapy sessions) and secondary care (e.g. consultations with medical specialists with or without referral). Long COVID patients are often (like is the case for many other long-term conditions) confronted with the combination of income loss with increased medical expenses. Yet, long COVID patients will also benefit from general financial protective measures once the general criteria are met to protect the financial accessibility of healthcare services. It is worth noting that long COVID patients can also make use of a general mechanism (e.g. as part of the system of maximum co-payment - income) to calculate the annual revenue on a different year of reference (default two years ago) if they can demonstrate a substantial decrease in income. This does not mean that the financial consequences of long COVID are not a concern, it only means that long COVID patients are protected in a similar way as other patient groups. As such, it can be concluded that patients with persisting complaints were not left alone. Also satisfaction with the healthcare services received is quite

high (bearing in mind the numerous shortcomings reported in section 5). Moreover, only one in three indicated that they have unmet needs.

Nevertheless, also some general weak points of our system can be pointed out. Our multispecialty, organ-focused healthcare system approaches the complex long COVID problematic on symptom-by-symptom basis. Patients report that they are referred to a pulmonologist for respiratory problems and to a cardiologist for palpitations, etc. This is, in se, not a problem. Yet, patients report that coordination is lacking and that they miss a multidisciplinary approach. Also the limited reimbursement of psychological care (limited number of consultations with a psychologist; consultations with psychiatrists) and limitations in the available consultation time to approach complex situations are well described elsewhere.¹⁶⁵ We noticed that patients are looking for solutions. Patients are also looking for solutions in non-conventional therapies.

Given that a majority of long COVID patients was professionally active before they got infected, and a large group of patients have difficulties to return back to work (e.g. part-time instead of full-time, need for adapted work), it becomes clear that the re-integration in the work environment is not always very pro-actively approached. The interplay (also due to shortages) between the main actors (treating physician, occupational physician, advising physician, controlling physician) is experienced as bureaucratic and insufficiently pro-active to stimulate and support an early gradual return to work. Also other problems (e.g. lack of support with administrative burden caused by their illness; lack of support or waiting lists for professional support with activities of daily living) typically reported by patients with long-term conditions were reported by long COVID patients.



6.7. Concluding remarks

Long COVID will be among us for quite some time

We can conclude that despite the recent nature of the condition and the many unanswered questions, it is time to undertake action on several domains. We do not know yet how long the persistent symptoms will last among long COVID patients. Yet, it is clear that 'long COVID' will be among us for quite some time, also when the acute consequences of the COVID-19 pandemic are under control. This will concern patients who have been hospitalised and patients who had a milder form of acute COVID-19. Specific attention will be needed for those who were not tested during the first waves of the pandemic and still have persistent symptoms.

Evidence about adequate diagnosis and treatment practices are absent

To answer the question about 'what services are needed' and 'how to organise care' we first need evidence about the (cost-)effectiveness of interventions. Given that long COVID is a new condition that is still poorly understood, the evidence about how to manage care is currently very sparse.¹⁶⁶ Therefore, public agencies around the world started initiatives that aim to generate this evidence. Also KCE launched a call for research on effectiveness of interventions. It will take some time before the evidence becomes available. In the meantime actions will be mainly expert opinion driven. Therefore, it is important that policy measures are temporary and can be reversed or fine-tuned based on scientific evaluations.

A clear need for more awareness

We see a need to create awareness about long COVID both in the general public and in health professionals. It is clear that long COVID involves several subcategories of patients requiring differential diagnosis. In the absence of evidence on the effectiveness of long COVID management and treatment strategies, the medical community will have to develop consensus-based guidelines.

Integrated interdisciplinary approach

The clinical manifestation of long COVID (e.g. wide variety of symptoms affecting several organ systems and also including an important mental health component) pleas for an integrated interdisciplinary approach for at least part of the patients. Although there are several possibilities within the currently reimbursed services, a missing link in our system for long COVID patients seems to be a one-stop interdisciplinary holistic assessment (involving e.g. medical specialists like pulmonologists, cardiologists, general internal medicine, physical medicine, psychologists, physiotherapists, social care, GPs) allowing fast diagnosis (e.g. exclusion of alternative diagnosis or deterioration of underlying comorbidities), functional assessment and fast referral to a patient tailored care pathway. This will probably be situated in the context of primary care for most (e.g. physiotherapy, consultations with psychologists, follow-up by GP) but might require more intensive follow-up (e.g. in a rehabilitation in a hospital setting) for others.

Information need

It will also be important to improve the information about the possibilities within the context of currently reimbursed services, as many healthcare professionals and patients seem to be uninformed. This creates variability in access to these services.

Monitor and adapt

Finally, given the many remaining uncertainties it will be important to monitor the scientific insights within this domain and allow that all of the measures that are taken are subject to change when new insights require adaptations.



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