KCE REPORT 344

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

LONG COVID: PATHOPHYSIOLOGY – EPIDEMIOLOGY AND PATIENT NEEDS

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HEALTH SERVICES RESEARCH

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DIEGO CASTANARES-ZAPATERO, LAURENCE KOHN, MARIE DAUVRIN, JENS DETOLLENAERE, CHARLINE MAERTENS DE NOORDHOUT, CELIA PRIMUS-DE JONG, IRINA CLEEMPUT, KOEN VAN DEN HEEDE

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COLOPHON

Title:	Long COVID: Pathophysiology – epidemiology and patient needs
Authors:	Diego Castanares-Zapatero (KCE), Laurence Kohn (KCE), Marie Dauvrin (KCE), Jens Detollenaere (KCE), Charline Maertens de Noordhout (KCE), Celia Primus-de Jong (KCE), Irina Cleemput (KCE), Koen Van den Heede (KCE)
Information specialist	Patrice Chalon (KCE)
Project facilitator:	Nathalie Swartenbroeckx (KCE)
Reviewers:	Nancy Thiry (KCE), Pascale Jonckheer (KCE), Marijke Eyssen (KCE), Karin Rondia (KCE)
External experts and stakeholders:	Dirk Avonts (Domus Medica), Tatiana Besse-Hammer (CHU Brugmann, Bruxelles), Brigitte Bouton (AVIQ – Agence pour une Vie de Qualité), Eric Brassine (AXXON – Beroepsvereniging voor kinesitherapeuten – Association de défense professionnelle de la kinésithérapie), Peter Bruynooghe (AXXON), Gilles Caty (CHWAPI – Centre Hospitalier de Wallonie Picarde), Caroline Cools (CHU UCL Mont-Godinne Namur), Sabine Corachan (LUSS – Ligue des usagers des services de santé), Tom De Boeck (Agentschap Zorg en Agentschap), Brecht Devleesschauwer (Sciensano), Philippe Devos (BVAS – Belgische vereniging van artsensydicaten), Luk Dieleman (AXXON), Frédérique Donnay (UKB – Union des Kinésithérapeutes de Belgique), Marc Geboers (Zorgnet ICURO), Marijke Gielen (Landsbond van Onafhankelijke Ziekenfondsen), Rik Gosselink (Katholieke Universiteit Leuven), Julia Hepp (Ministerium der Deutschsprachigen Gemeinschaft), Bernard Landtmeters (Christelijke Mutualiteiten), Patricia Lanssiers (GIBBIS), Alizée Lassaux (CHU UCL Mont-Godinne Namur), Chantal Lefebvre (UCLouvain), Ann Li (Post-Covid gemeenschap), Patrick Linden (AZ Delta), Natalie Lorent (UZ Leuven), Marleen Louagie (RIZIV – INAMI), Henri Monbailliu (Koningin Elisabeth Instituut Oostduinkerke), Leen Muysewinkel (RIZIV – INAMI), Jo Nijs (Vrije Universiteit Brussel – VUB), Thomas Orban (GBO-Cartel – Syndicat Médecins généralistes francophones), Joke Platteeuw (AZ Delta), Maxime Résibois (CRéSaM – Centre de Référence en Santé Mentale), Gregory Reychler (GIBBIS), Sandrine Scaux (FEDRIS), Olivier Schmitz (UCLouvain), Pierre Seeuws (Ergotherapie Vlaanderen), Anne-Sophie Spiette (‘Covid long, nous existons Belgique’), Stefan Teughels (Domus Medica), Isabelle Van Der Brempt (FOD Volksgezondheid – SPF Santé Publique), Viviane Van Elshocht (CM – Christelijke Mutualiteit), Anne Van Meerbeeck (VPP – Vlaams Patiëntenplatform), Sigrid Vancorenland (CM), Ann Vandenbruel (KU Leuven), Paul Verbanck (Laboratory of Neurophysiology & Movement Biomechanics, Université Libre de Bruxelles – ULB), Emilie Verreckt (CHU UCL Mont-Godinne Namur), Dirk Vissers (Universiteit Antwerpen), Bénédicte Vos (Solidaris), Bert Winnen (RIZIV – INAMI), Sarah Wolf (AIHTA – Austrian Institute for Health Technology Assessment), Joke Wuyts (FOD Volksgezondheid – SPF Santé Publique), Jean Yombi (UCLouvain), Ingrid Zechmeister-Koss (AIHTA – Austrian Institstute for Health Technology Assessment)

External validators: Sibyl Anthierens (Universiteit Antwerpen, Department of Family Medicine and Population health), Jan Peter William Himmels (FHI – Norwegian Institute of Public Health; abstained from voting), Elaine Maxwell (NIHR – National Institute for Health Research)

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LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
[18]FDG PET/CT	Positron emission tomography with 2-deoxy-2-[fluorine-18] fluoro- D-glucose integrated with computed tomography
ACE2	Angiotensin converting enzyme 2
aOR	Adjusted odds ratio
aRR	Adjusted risk ratio
ATP	Adenosine triphosphate
AUC	Area under the curve
AVD - AOT	Assistance Ventilatoire à Domicile / AdemhalingsOndersteuning Thuis
BPI	Brief Pain Inventory
CEC	Circulating endothelial cells
CI	Confidence Interval
CFS	Chronic Fatigue Syndrome
CNS	Central nervous system
CoQ10	Coenzyme Q10
COVID-19	Coronavirus Disease-19
CPS1	Carbamoyl phosphate synthase
CRA-CAR	Centres de Revalidation Ambulatoire - Centra voor Ambulante Revalidatie
DASS 21	Depression Anxiety and Stress Scale 21
DLCO	Diffusing capacity for carbon dioxide
DMG/GMD	Dossier Médical Global / Globaal Medisch Dossier
ECMO	Extracorporeal membrane oxygenation
ED	Emergency department
ENT	Ear, Nose and Throat specialist

EQ-5D-5L	EuroQol 5 dimensions 5 levels questionnaire
FAS	Fatigue assessment score
GABA	Gamma amino butyric acid
GAD7	General Anxiety Disorder 7 Questionnaire
GFAP	Glial fibrillary acidic protein
GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HGF	Hepatocyte Growth Factor
HLA	Histocompatibility Leucocyte Antigen
ICAM 1	Intracellular adhesion molecule 1
ICU	Intensive care unit
IDO-1	Indolamine 2,3- dioxygenase
IL17	Interleukin 17
IL1β	Interleukin1β
IL6	Interleukin 6
IQR	Interquartile range
ITU	Intensive therapy unit
LCN2	Lipocalin 2
LUSS	Ligue des Usagers des Services de Santé
ME/CFS	Myalgic encephalopathy/Chronic fatigue syndrome
MIS-C	Multisystem inflammatory syndrome in children
MMP7	Matrix metalloproteinase-7
mMRC	Modified medical research council
MoCA	Montreal Cognitive Assessment

MRI	Magnetic Resonance Imaging
NDRG1	N-Myc downstream regulated gene 1
NETs	Neutrophil Extracellular Traps
NfL	Neurofilament light chain fibrillary acidic protein
NIHDI	National Institute for Health and Disability Insurance
OR	Odds ratio
p38 MAP kinase	p38 mitogen-activated kinase
PCR	Polymerase chain reaction
PHQ2	Patient Health Questionnaire 2-item scale
PHQ9	Patient Health Questionnaire-9
PICS	Post-Intensive Care Syndrome
PRDX3	Peroxiredoxin 3
PRT	Patienten Rat und Tref
PSQI	Pittsburgh Sleep Quality Index
PTSD	Post-traumatic stress syndrome
RANTES	Regulated on Activation Normal T Expressed and Secreted
RR	Risk ratio
SARS-CoV-2	Severe acute respiratory syndrome coronavirus-2
SE	Standard Error
SD	Standard Deviation
TGFβ1	Tumour Growth Factor beta 1
TMPRSS2	Transmembrane protease, serine 2
TNFα	Tumour Necrosis Factor α
TSQ	Trauma Screening Questionnaire

VAS	Visual Analogue Scale
VPP	Vlaamse PatientenPlatform

SCIENTIFIC REPORT

CHAPTER 1. INTRODUCTORY CHAPTER

1 WHY THIS REPORT?

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 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.[1] While the majority of patients recovered in the weeks after the infection, it became clear, as time progressed, that some people 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 - severe acute respiratory syndrome) 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 utilization, 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 October 2021[a]) and national and international agencies (e.g. a dynamic review published by the British National Institute for Health research in October 2020[4]; a guideline published by the British National Institute for Health and Care Excellence – NICE in December 2020[5]; guidance on symptom management for general practitioners published in February 2021 by the French agency 'Haute Autorité de Santé[6] – HAS'; a policy brief published in February 2021 by the European Observatory on Health Systems and Policies[7]).

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 and the 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 2). The webpage[8] was launched in January 2021 with a pragmatic review on the epidemiology of Long COVID[9] and an analysis of publicly available patients' stories[10]. Since then, we published an intermediate report on the pathophysiology of long COVID[11] in May 2021 and an update of the literature review about Long COVID in June 2021.[12] Since the current start of the KCE-project 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.[13]

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.[14]

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.[15]

[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)

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:**Literature review on the epidemiology and pathophysiology of long COVID:** How can long COVID be defined? How frequent is it? What are the most common symptoms? Which are the risk factors? What are the underlying pathophysiological mechanisms?
- **Patient survey and interviews:** What are the needs and experiences of patients with long COVID complaints?
- **Analysis of current Belgian legislation and reimbursement rules:** Which (reimbursed) services exist in Belgium to care for patients with long-COVID complaints?

In Table 1 we give an overview of the research questions and main methods. The detailed information about the research methods is described in each of the separate chapters.

Table 1 – Overview of the scientific report: main research questions and methodology

Research Question	Methodology	Chapter
What is the epidemiology of long COVID?	• Literature review	Chapter 2
Wat are the underlying pathophysiological mechanisms of long COVID symptoms?	• Literature review	Chapter 3
What are the lived experiences and unmet needs among long COVID patients?	• Online survey among persons with self-reported long COVID	Chapter 4
	• In-depth interviews with persons with self-reported long COVID • Online forum with persons with self-reported long COVID	Chapter 5
Which services are currently reimbursed for long COVID patients?	• Document analysis and expert consultation	Chapter 6

CHAPTER 2. EPIDEMIOLOGY

1 DISCLAIMER

The current work is based on the available evidence at the moment of writing the report (09/08/2021). There are still major evidence gaps, as studies are ongoing and science requires time to build up. A part of the available literature is not peer-reviewed and hence not necessarily conforms to the high-quality standards for scientific research.

2 KEY POINTS

- **Available evidence on the prevalence of long COVID remains limited and insufficient to formulate sound conclusions. Synthesising the information is challenging since studies are highly heterogeneous and the reported prevalences vary substantially.**
- **There is still no clear widely accepted definition of long COVID. Long COVID encompasses distinct phenotypes (or clusters of symptoms) that can broadly vary and evolve over time. As such, people may experience different patterns of symptoms that could have multiple causes. It seems essential to distinguish those related with permanent organ impairment from those not related with organ damage.**
- **Reported prevalences differ according to the targeted population and follow-up time:**
  - **In studies in which (almost) all included patients were not hospitalised during the acute phase, the median reported percentage of persistent symptoms whithin the first 3 months after the onset of the COVID-19 was 32% (ranging from 5 to 36%). However, in studies in which almost all patients have been hospitalised, the median was higher (51%, ranging from 32 to 78%).**
  - **Between 3 and 6 months, studies that predominantly included patients who have not been hospitalised, a median prevalence of 26% (ranging from 2 to 62%) with persistent symptoms is reported. For those studies including mostly patients that were hospitalised during the acute phase, the reported prevalence is higher (median 57%) and ranges between 13 and 92%.**
  - **Although symptoms seem to improve over time, at 6 months of follow-up, the median reported prevalence is still 25% (ranging from 13 to 53%) in studies including patients who**

were not hospitalised. Higher rates reaching the median value of 62% (ranging from 50 to 93%) have nonetheless been reported in patients who have been hospitalised.

  - Current evidence does not precisely allow to distinguish between the prevalence of symptoms following organ damage and symptoms unrelated to organ damage. Since the appearance of symptoms can besides COVID-19 have other non-mutual exclusive underlying causes (hospital stay, post-intensive care syndrome), the prevalence of long COVID might be overestimated.

- In the first three months, the most commonly reported persistent symptoms in the group of long COVID patients are fatigue (up to 98%), dyspnoea (up to 88%), headache (up to 91%) and taste/smell disorders (up to 58%). Between 3 and 6 months, the most frequent symptoms were fatigue (up to 78%), cognitive disorders (up to 55%) and respiratory symptoms such as dyspnoea or dysfunctional breathing (up to 58%). Beyond 6 months, fatigue (median 51%) and dyspnoea (median 30%) are 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. In addition to the symptoms, an impact on activities of daily life and (social) functioning is reported.
- The risk for being hospitalised and the risk for developing new clinical issues involving multiple organ systems requiring medical care is increased in the aftermath of COVID-19, in both groups of patients who were hospitalised or not during the acute phase of infection. Long COVID is reported regardless of the initial severity of COVID-19 and even in patients who remained initially asymptomatic.
- 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 and sufficiently long follow-up; it is unclear if the risk factors that have been identified can be generalised to all categories of patients. 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 developping long COVID. Although long COVID seems to be prevalent across all age categories, people aged 35 to 69 years appear to be more likely to be affected. Females seem to be more likely to develop long COVID than males.
- The current findings are based on studies presenting substantial limitations: (1)The absence of a homogeneous definition of long COVID with clear clinical criteria does not allow to make an accurate diagnosis. It is not always straithforward to distinguish long COVID from other overlapping conditions, especially when permanent organ damage is lacking. (2) Included populations vary widely according to demography, level of care received during the acute infection, sample sizes. (3) Study designs are heterogeneous (time of inclusion, follow-up duration). Many of them did not include a control group and present loss to follow-up. They are prone to recruitment and recall bias. (4) There is a lack of standardised and validated measures for symptom reporting. (5) Data on long COVID patients who had an asymptomatic infection are scarce.
- Long COVID has to be differentiated from Post-Intensive-Care-Syndrome (PICS), comprising long-term physical, psychological and cognitive disabilities that can occur in patients who have previously been hospitalised in Intensive care unit (ICU).

3 BACKGROUND

3.1 Awareness and reporting

After more than one year into the COVID-19 pandemic, evidence has surged that many symptoms can persist or appear after recovery from the acute period of illness. Those symptoms are reported after both mild or severe COVID-19. They adversely impact daily life and induce a societal burden, as the number of affected patients is increasingly growing.

Whilst many epidemiological data report that a proportion of people endure lingering symptoms after recovery from the acute disease, there is no globally accepted definition of this issue, yet. 'Long COVID' is now the most commonly used term but several terms such as 'post-COVID condition', long-haul COVID', 'post-COVID syndrome', 'post-acute COVID symptoms', 'post-acute sequelae' or 'chronic COVID' are found in the literature and encompass a wide range and variety of symptoms.

For the purpose of this review, we considered studies describing long-term symptoms following the acute phase of COVID-19 if they were observed at least 4 weeks after disease onset. We stratified by length of follow-up: early in the time-course of the disease (up to 12 weeks), between 3 and 6 months and after 6 months follow-up.

3.2 How to define long COVID?

Due to its wide heterogeneity of presentation, there is, currently, a lack of international consensus regarding the definition of long COVID. The World Health Organisation (WHO) is currently running a project aiming to result in an international consensus about a definition an clinical criteria for long COVID (a report is expected to be published in October 2021).[b]

In December 2020, the National Institute for Health and Care Excellence (NICE) proposed a definition of long COVID, based on the time beyond disease onset, when signs and symptoms, not explained by an alternative diagnosis are being reported: 'ongoing symptomatic COVID-19' is used for patients who have symptoms from 4 to 12 weeks beyond acute COVID-19, whereas 'post-COVID-19 syndrome' is the term used for those still experiencing symptoms after 12 weeks.[5]

Long COVID is increasingly being seen as an active and evolving medical condition bringing into play all organs. A broad spectrum of symptoms is commonly reported. People can continue to undergo single or multiple symptoms beyond the acute phase or develop new ones, or even undergo a relapsing trend.

There is substantial uncertainty about what causes long COVID and its management could vary according to related causal mechanisms. To this end, it is of utmost importance to distinguish people who have symptoms following organ damage that occurred during the hospitalisation (for example lung sequelae after prolonged mechanical ventilation) from people who undergo a mild-to-moderate disease and who were not hospitalised. For instance, the Centers for Disease Control and Prevention (CDC) proposed to make the distinction between several types of post COVID conditions and to consider the longer effects of COVID-19 hospitalisation or treatments consequences as a particular entity.[16] In this vein, some of these effects can include Post-Intensive-care-Syndrome that refers to a subset of patients who have been hospitalised in the intensive care unit[17] and must be differentiated from long COVID.

Interestingly, Amenta et al. (2020) proposed that symptoms could be classified into several groups: (1) residual symptoms that persist after recovery from acute illness, (2) organ dysfunction persisting after initial recovery, and (3) new symptoms coming up after asymptomatic or mild

[b] 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)

infection. This classification emphasises the fact that long COVID is a multi-organ condition and that further research is required to better classify the causes and types of symptoms.[18]

Definition and symptoms classification are subject to modification in the light of a new understanding of the disease. Some studies have indeed suggested a certain level of organ impairment, even in people who undergo a mild form of the disease.[19]

Of importance, long COVID has to be differentiated 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. Literature specifically relating to PICS is not considered in the present work.[17, 20]

Post Intensive Care Syndrome (PICS)[17, 20]

The Post-Intensive Care Syndrome (PICS) refers as 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 years (ICU-acquired weakness)
- Mental health problems including anxiety, depression and post-traumatic stress disorders.
- Cognitive disorders including memory or concentration disorders or executive functions.

4 RESEARCH QUESTIONS

The following research questions are formulated for this systematic review:

- What is the prevalence of long COVID following a confirmed or suspected COVID-19?
- What are the symptoms of long COVID and their frequency?
- What are the risk factors for developing long COVID

5 METHODS

We followed the KCE Process Book for conducting the search. A pragmatic review was performed in January 2021[9] and two preliminary systematic reviews were performed in May 2021 (pathophysiology of long COVID)[11] and June 2021 (epidemiology of long COVID).[12] The literature sources have been searched in February and May 2021; additional manual searches have been performed until 09 August 2021. Details of the search strategy are presented in Appendix 1 and Appendix 2 (See Supplement to Chapter 2)

5.1 Structured questions and search concepts

The research question was transformed into a PEOD (Population-Exposure-Outcome-Design) structured search question and was set up prior to conduct the review (See Supplement to Chapter 2). Keywords and search concepts were collected through experts' opinion, existing recent publications retrieved after preliminary literature searches, and consultation of controlled vocabularies (Medical Subject headings = MeSH; Excerpta Medica = Emtree). Considering the topic specificities, only keywords related to the problem were sought.

	Inclusion criteria	Exclusion criteria
Population	People experiencing symptoms beyond 4 weeks onward (≥ 4 weeks and > 12 weeks) with appropriate denominator reported*	
Exposure	COVID-19 confirmed (PCR, antibodies) or not (but clinically and/or radiologically)	
Outcome	• Prevalence of reported symptoms (any symptoms including biological disturbances) and daily life consequences • Risk factors for long COVID	
Design	N ≥ 250 patients included Studies conducted in Europe and the USA Cohort study, Cross-sectional study	Case report, Case series, Mixed method (qualitative)
Language	English, French, Dutch, Spanish	Other languages

** For prevalence assessment: denominator corresponding to the percentage of acute COVID-19 cases. For risk factors assessment, percentage of long COVID.*

5.2 Identification of studies

A set of bibliographical databases and registers to search was identified based on the search questions. Considering the topic specificities (recent topic), full text databases and preprint registries were also sought (See Supplement to Chapter 2). A search query was developed with the assistance of a medical information specialist and adapted to each database. Considering the topic specificities (recent topic, no clear concept, several synonyms), a pure keyword strategy was chosen. Search in those databases was supplemented by collecting additional references from different sources (external experts, exploratory searches in the bibliographical databases, identification of cited references and looking into the bibliography of key references). It was completed by a regular scan of more recent literature through PubMed, MedRXIV and international websites on COVID-19 (WHO, NICE, CDC, HAS).

All identified references were imported in Endnote X.8. The duplicate search results were detected based on title match using the build-in tool from EndNote, and supplemented by manual identification after sorting on title.

5.3 Selection of studies

The selection of studies followed a three-stepped process conducted by the information specialist (PC) and one researcher (DC). In case of doubt the researcher performing the data extraction asked to cross-check the extraction by a second researcher (KV).

The first step of studies identification was based on title and abstract screening using the research question and human context by the information specialist: irrelevant studies that were out of scope were excluded during this screening phase and potentially relevant studies were kept.

The second step was based on title and abstract screening using the PEOD and exclusion criteria by the researcher: irrelevant studies were discarded. The full text of the retained studies was then sought.

In the third phase assessing eligibility of inclusion, the researchers selected studies according to the PEOD criteria: we selected studies that measured the prevalence of long COVID in a population of COVID patients, the distribution of symptoms in long COVID patients and/or identified risk factors for long COVID. We limited our selection to studies reporting symptoms ≥ 4 weeks after the onset of the initial disease and conducted in Europe or the

US, for better inference to the Belgian population in terms of epidemiology, risk factors such as comorbidity and health-seeking behaviour. We decided to select only studies that have included at least 250 COVID-19 cases. Data on risk factors were based on studies adjusting for potential confounding factors such as age, sex and comorbidities. Languages were restricted to English, French, Dutch, and Spanish.

5.4 Quality Assessment

Risk of bias and quality of included studies was assessed using quality criteria based on the National Institute of Health Quality Assessment Tool for Observational and Cohort Studies, as proposed by Nasserine et al.[21] The criteria included the following items: (1) prospective cohort, (2) representativeness, (3) reported severity of the initial illness (and level of care), (4) retention (number in final sample/number of eligible patients), (5) repeated outcome measurements, (6) use of tools and/or scales to measure the presence of symptoms. Quality appraisal was performed by one researcher (DC) and validated by a second one (KV).

6 RESULTS

6.1 Included studies

The search through bibliographical databases (See sources of databases) yielded 29 587 hits, which was reduced to 12 762 after duplicates removal. 12 716 records were discarded based on title and abstract screening.

From the 46 full texts articles that were retrieved and assessed for eligibility, 18 were excluded. Additionally, 33 articles detected in the references of included studies, or by conducting a quick update search in PubMed, were also retrieved and assessed; 13 were excluded.

As a result, 48 articles met our inclusion criteria and were included in the analysis. [22-65] The selection of studies is summarised in the flow diagram (See Supplement to Chapter 2)

Among the retrieved articles, 28 had already been identified in our preliminary pragmatic review published in June 2021.[12]

Sources of databases

Source (Interface)	Set	Date of the search (*)	Limits
CINHAL (EBSCOhost)		2021-05-03	none
Cochrane Database of Systematic Reviews		2021-05-03	none
coronacentral.ai/	longhaul	2021-05-03	none
Econlit (OVID)	1886 to April 22, 2021	2021-05-03	none
Embase (Embase.com)		2021-05-03	none
europepmc.org/		2021-05-03	preprint
JBI EBP Database	Current to April 28, 2021Current to January 13, 2021*	2021-05-03	none

Journals@Ovid Full Text	April 30, 2021	2021-05-03	none
MEDLINE (OVID)	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 30, 2021>	2021-05-03	none
Ovid Nursing	1946 to April Week 5 20211946 to January Week 4 2021	2021-05-07	none
PsycInfo (OVID)	1806 to April Week 4 2021	2021-05-03	none
scilit.net/		2021-05-03	preprint

* *A first search was performed in February 2021, all database have been searched again in May 2021 (with no time limitation)*

Thirty-six studies were observational cohort studies[22-54, 65, 66] and 11 were cross-sectional studies.[45, 55-63, 65, 67] One study was a case-control study.[64]

Eight studies included data from several countries. Eight studies were from the UK, 2 studies from France, 6 from Spain, 4 from Italy, 9 from the US, 3 from Switzerland, 3 from Norway, 2 from Germany and the remaining three studies were from Denmark, Sweden, The Netherlands. Seven studies were preprints, still under review.[43, 45, 46, 54, 55, 65, 68]

Twelve studies included several points of follow-up.[23, 28, 30, 34, 39, 40, 51, 54, 55, 61, 68] By stratifying by the follow-up duration, we identified 23 studies with 1 to 3 months follow-up, 22 in the 3 to 6 months period and 13 with a follow-up longer than 6 months (several studies were used several times) (See Table 2 and Table 3). Two studies assessed the symptoms at one year follow-up.[63, 69] Samples sizes widely varied and ranged from 256 to 448 176 included patients.

Regarding the characteristics of the infection and level of care at the initial period, 11 studies included exclusively hospitalised patients[22, 29, 38, 39, 42, 43, 51, 52, 58, 64, 66] while 9 studies solely reported on ambulatory patients. [23, 24, 30, 34, 45, 49, 59, 65, 69] Other studies included a mixed population of ambulatory and hospitalised patients: 3 studies had a majority of hospitalised people[27, 28, 32], whereas 21 others comprised both patients who were hospitalised or not.[25, 26, 35-37, 40, 41, 44, 47, 48, 50, 53, 55-57, 60-63] Four studies did not clearly relate the proportion of hospitalised patients at the acute phase of illness.[31, 33, 46, 68]

The majority of studies included patients who experienced symptoms at the time of acute infection. Eight studies reported a limited proportion of patients who remained asymptomatic during acute COVID-19.[23, 40, 50, 53-55, 61, 65] Symptoms were mostly self-reported and collected through phone calls[24, 29, 35, 37, 38, 42, 45, 50-52, 58, 64-66, 69] or by electronic questionaires[23, 25-27, 30, 33, 34, 44, 48, 49, 55-57, 59-61, 68] Eleven studies assessed symptoms through a medical visit follow-up. [28, 32, 34, 38-40, 43, 51, 53, 54, 63] One study evaluated the symptoms with a medical visit at 45 days and a phone call at 7 months.[51] Retrospective cohort studies retrieved the data through medical records.[22, 41, 46, 47, 67]

Among the retrieved studies, we made a distinction between studies for which COVID-19 patients were used as denominator from those in which only long COVID patients have been selected. The latter exclusively pick out patients with persisting symptoms and cannot be used to determine the prevalence of long COVID among COVID-19 cases. These studies that only assessed persisting symptoms in long COVID patients were only used to describe the frequency and duration of symptoms and are presented in Table 4. Moreover, in each article, when data that are required to assess the frequency of symptoms in long COVID patients were available (number of long COVID patients and the number of symptomatic patients), we calculated the symptom frequency in the long COVID group. (See 6.4).

6.2 Prevalence estimate

6.2.1 *Studies with 1 to 3 months of follow-up*

We found 14 studies allowing us to assess the prevalence of long COVID between 1 to 3 months: 9 observational cohort studies[23, 24, 28-30, 34, 35, 51, 52] and 5 cross-sectional studies[55, 58, 61, 62, 68] (See Table 2). Among those, 2 were preprint articles currently under review.[55, 68] One study also assessed the effect of corticosteroids on lung function.[29]

All studies were based on self-reported symptoms by means of telemedicine through COVID app monitoring, phone or online surveys and medical visits. COVID-19 was confirmed in each study except one study that comprised 71% of patients with confirmed infection. However, the prevalence of symptoms was estimated, in this study, on patients with positive PCR, as a denominator.[68] Four studies included patients who were asymptomatic at the acute phase.[23, 40, 55, 61]

The number of patients ranged from 277 to 4 438 in epidemiological studies, whereas the survey from ONS included 21 622 participants. The majority of patients were middle-aged. Four studies included non-hospitalised patients,[23, 24, 30, 34] while 4 other studies included patients who have been hospitalised.[29, 51, 52, 58] Five studies involved a mixed group with ambulatory and hospitalised patients.[28, 35, 55, 61, 62] Among them, four studies comprised a majority of ambulatory patients along with a limited proportion of hospitalised ones[35, 55, 61, 62] and in another one, the majority of patients were hospitalised.[28] One study did not clearly mention the proportion of hospitalised patients.[68]

Globally, studies showed that among patients who were affected by COVID-19, the proportion of those who had persistent symptoms ranged from 5.2 to 78% (See Table 2 and Figure 1):

- Studies that included a minor proportion of patients hospitalised at the acute phase or patients who were not hospitalised reported lower prevalences ranging from 5.2 to 36% with a median value 32%.[23, 24, 30, 34, 35, 55, 61] If a distinction was made between both types of studies, those that included exclusively patients who were not hospitalised reported prevalences ranging between 5.2 and 26% (median value 17%).[23, 24, 30, 34]

- Studies that included patients predominantly hospitalised (including ICU) reported higher prevalences that ranged between 32 and 78% (median value 50.9%).[28, 29, 51, 52, 58] The study from Myall et al.[29] and Chopra et al.[52] reported prevalences of 32 and 39%, respectively while the study from Mandal et al.[58] and Meije et al.[51] reported that up to 71.8% to 78% of patients had at least one symptom at similar follow-up timepoints. Those studies included patients who were hospitalised on ICU and for whom mechanical ventilation was sometimes initiated. The study of Moreno-Perez et al., reported a prevalence of 50.9% and included 66% of hospitalised patients.[28] However, the reported prevalence was at a rather similar level of 36.6%, when the subgroup of patients with severe pneumonia was excluded.

- Interestingly, one study showed an increase of the prevalences ratio according to the initial severity of COVID-19. ICU patients had a greater prevalence than patients-hospitalised on general wards or ambulatory patients.[62]

- The study of Perlis et al.-preprint did not clearly mentioned the hospitalisation status and reported a prevalence of 7.5% at 2 months after initial illness.[68]

An illustration of long COVID epidemiological data: the British Office of National statistics.

The Office of National Statistics (ONS) estimated the prevalence of self-reported ongoing symptoms following COVID-19 by using the UK Coronavirus Infection survey (CIS) data. Updates of the results are regularly published on the website:

- CIS is a survey sample of respondents randomly selected from households in the UK, who are monthly followed-up (weekly for the first month from enrolment). It aims to find out how many people are getting COVID-19 and how many are still experiencing symptoms, as well as the response to vaccination. This study runs over the course of one year and is carried out by ONS, in partnership with other organisations (University of Oxford, University of Manchester, Public Health England, Welcome Trust, IQVIA, Glasgow Lighthouse Laboratory and UK Biocentre Milton Keynes). At each visit, respondents are swab-tested and report whether they are still experiencing symptoms (from a list of common COVID-19 symptoms) along with their impact on their daily-life activities. Blood samples are taken in some participants.
- In the update of April 2021, an estimated 1.1 million people in the UK reported experiencing long COVID symptoms persisting more than 4 weeks after the first suspected initial infection. Among them 697 000 (63%) developed COVID-19 at least 12 weeks previously, and 70 000 (6%) first had COVID-19 at least one year previously. Prevalence rates were higher in people aged 35 to 69 years, females, those living in a deprivated area and those with pre-existing day-to-day activities limitations. Among people who had developed COVID-19 at least 12 weeks previously, those symptoms were negatively impacting the daily-living activities of 422 000 (60.6%), with 127 000 of them (18.1%) reporting substantial limitations.
- Particularly, among a sample of 21 662 COVID-19 positively tested participants from 26 April 2020 to 6 March 2021, the prevalence of infected people with ongoing symptoms after 12 weeks was 13.7% (14.7% in females and 12.7% in males). A matched control group was used to assess the 'excess' prevalence due to COVID-19 and revealed a prevalence eight times lower (2.8% at 5 weeks; 1.7% at 12 weeks) than the prevalence of COVID-19 patients. The most prevalent symptoms persisting for at least 12 weeks after infection were fatigue, cough, headache and muscle pain.
- In the update of June 2021, an estimated 1.0 million people living in private households in the UK (1.6% of the UK population) were experiencing self-reported long COVID. This number moderately decreased further by 962 000 (1.5% of the UK population) in the update of July 2021 and 945 000 (1.46% of the UK population) in the update of August 2021. The proportion of symptoms durations remained rather stable with 86% to 89% of people who experienced symptoms for at least 12 weeks and around 40% of people who first had COVID-19 one year before. The most prevalent symptoms were fatigue, shortness of breath, difficulty concentrating and muscle pain. Loss of smell has been recognised as the fourth most prevalent symptom in the update of August 2021. Activity limitation showed little change and is somewhat stable around 60-65%. Daily-life limitations are most commonly reported in people aged 50 to 69 rather than among younger people. In adjusted statistical models (logistic regression), and after restricting the analysis to confirmed COVID-19 cases, the likelihood to report long COVID was higher in middle aged adults, females (1.3 times more likely than males) and people with pre-existing health conditions. [61, 70, 71]

6.2.2 *Studies with 3 to 6 months of follow-up*

Seventeen studies allow to assess the prevalence of long COVID between 3 to 6 months: 12 observational cohort studies[23, 28, 30, 32, 34, 38-40, 42, 43, 53, 54], and 5 cross-sectional studies[55, 59, 61, 65, 68] (See Table 2). Among these, several studies included different time-points of follow-up: 7 studies were already used to determine the prevalence between 1 to 3 months[23, 28, 30, 34, 55, 61, 68] and three beyond 6 months.[39, 40, 54] Three studies were under review.[43, 54, 55]

All studies were based on self-reported symptoms by means of phone calls, online questionnaires, app monitoring. Nine studies included patients in a multidisciplinary outpatient clinic[28, 32, 34, 38-40, 43, 53, 54] and 6 of them included biological, respiratory and psychological assessments by means of various tests.[32, 38, 40, 43, 53, 54] Mean ages fluctuated from 38 to 63 years. Four studies included only hospitalised patients[38, 39, 42, 43], while 5 studies focused on ambulatory patients[23, 30, 34, 59, 65] while one study did not mention the hospitalisation status.[68] Seven studies included a mixed population (ambulatory and hospitalised patients).[28, 32, 40, 53-55, 61] Among those, two studies involved a majority of hospitalised patients[28, 32], while the five others had a minority of hospitalised patients.[40, 53-55, 61] One preprint- study did not mentioned the level of care at the acute phase.[68]

Based on those included studies, the prevalence of long COVID between 3 and 6 months was highly heterogeneous and ranged from 2.3 to 92.5% (See Table 2 and Figure 1):

- Six studies were conducted predominantly on patients who required an hospitalisation. The prevalence of persisting symptoms extended between 13.3 and 92.5% (median 57%):
    - The four studies that exclusively included patients who were initially hospitalised reported higher prevalences that exceeded 50%.[38, 39, 42, 43] Morin et al., and Ghosn et al. reported on persistent symptoms in 51 and 68%, respectively.[38, 39] They included only patients with severe or critical COVID-19 at the initial phase. In both studies, the proportions of patients who required ICU admission was 29.7 and 29%, respectively. Romero-Duarte et al. included 10.8% ICU patients and reported a prevalence of 63.9% within 6 months after hospital discharge [42] whereas the PHOSPH COVID study decribed a higher prevalence of 92.5% at 5 months.[43] It included a substantial proportion of severe patients with 26.7% of them who required mechanical ventilation, or extracorporeal membrane oxygention (ECMO).[43]
    - Two studies were conducted on a mixed group of ambulatory and hospitalised patients with a majority of them hospitalised.[28, 32] Venturelli et al. have estimated the presence of ongoing symptoms at 51%, after hospital or emergency department discharge.[32] A high proportion of patients were hospitalised (88%) and followed-up at multidisciplinary outpatient clinic. Conversely, in a quite similar group with, Moreno-Perez et al. reported a marked decrease of prevalence from 50.9% before 3 months to 13.3% of respiratory symptoms after 3 months.[28]
- Prevalences were overall lower in studies that predominantly included non-hospitalised patients and ranged between 2.3 and 62% with median value 26%.[23, 30, 34, 40, 55, 59, 61, 65] Perlis et al reported a prevalence of 3.3% at 4 months but without mentioning the hospitalisation status.[68] Nevertheless, in a limited cohort of 312 patients (with 21% hospitalised), Blomberg et al. revealed that still 61% of patients had symptoms at 6 months.[53]

  In a study conducted in the Netherlands, Wynberg et al. detailed the prevalence according the severity level: patients who suffered from mild COVID-19 reported less frequently ongoing symptoms than the patients who undewent a more serious level of COVID-19 (See Table 2). They described a slower time to recovery of symptoms within the more severe subgroups.[54]
- Seven studies reported prevalences at different time points. We noticed a decreasing trend (Figure 1): higher prevalences were reported in the first 11 weeks after disease onset compared to measurements performed 12 or more weeks after symptom onset (ranging from 2.3 to 29%).[23, 28, 30, 34, 55, 61, 68]

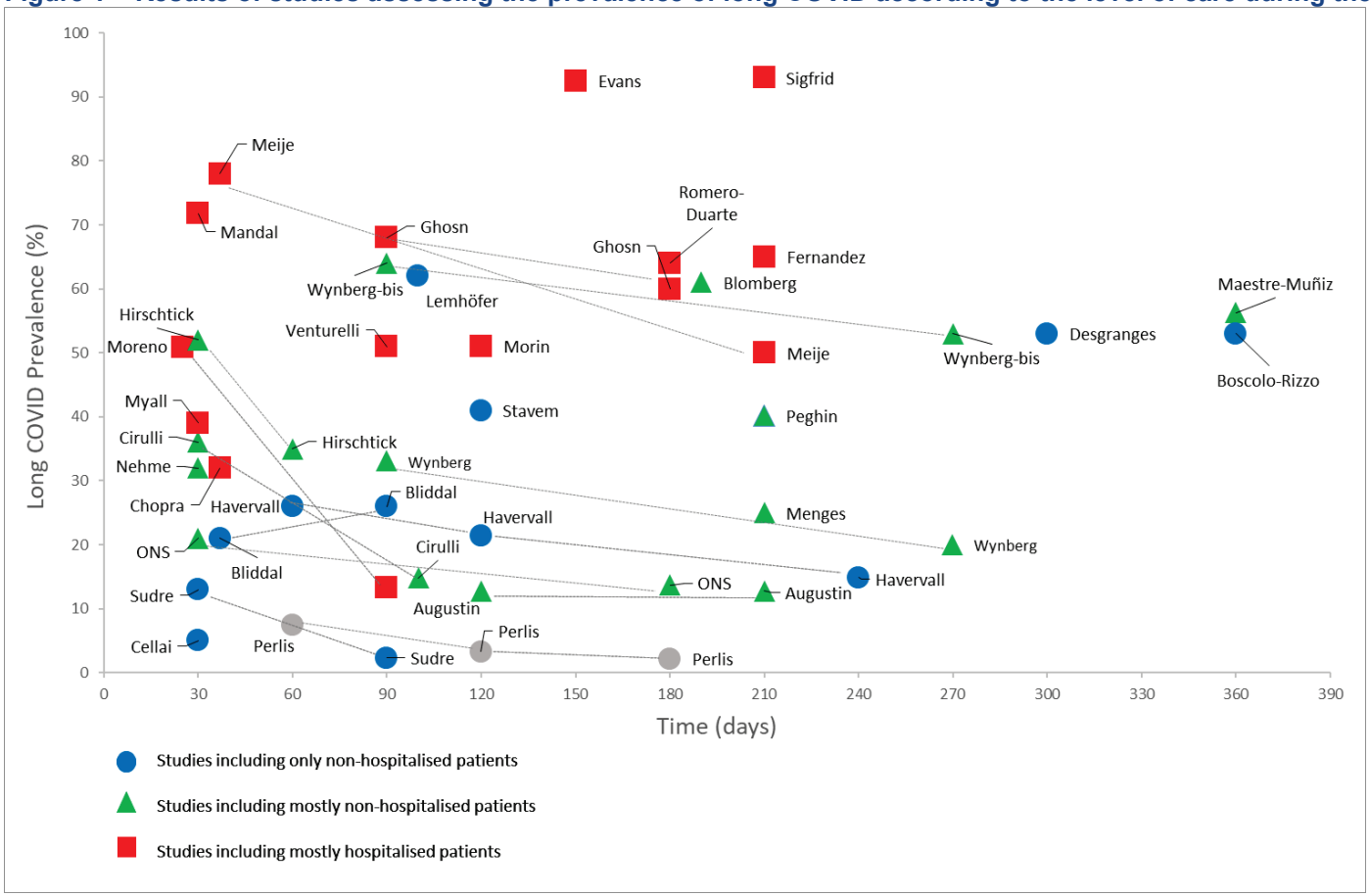
6.2.3 Studies with follow-up ≥ 6 months

Nine observational cohort studies[34, 39, 40, 44, 45, 50, 51, 54, 66], one cross sectional study[68] and one case control study[64] allowed to assess the prevalence of long COVID at more than 6 months of follow-up. Four studies involved only hospitalised participants[39, 51, 64, 66] whereas two studies comprised ambulatory patients.[34, 45] One preprint- study did not mentioned the level of care at the acute phase [68] and the remaining studies included both types of patients.[40, 44, 50] Two studies were still under review.[54, 68]

Based on those, the global prevalence was again heterogeneous and extended from 2.2 to 93.3%.

- In the four studies that focused only on patients who were hospitalised at the beginning of the illness, the reported prevalences were higher and ranged between 50 and 93% (median value 62%).[39, 51, 64, 66] All studies included ICU patients.
- In studies that comprised a majority of non-hospitalised patients (or exclusively ambulatory patients)[34, 40, 44, 45, 50, 54] the prevalence ranged between 12.8 and 53% (median value 25%):
    - In the study from Haverval et al., long-term immunological response after COVID-19 in young low-risk ambulatory patients was assessed. Healthcare workers from a hospital in Sweden were followed. Blood samples were performed every 4 months to assess the presence of antibodies against SARS-CoV-2 and symptoms were obtained through an app using standardised questionnaires. A decreasing trend in prevalence was observed over time in 323 seropositive participants. At 2 and 4 months, symptoms were present in 26 and 21.4%, respectively (See Figure 1). Almost 15% reported a minimum of one symptom for at least 8 months, while only 3.4% of seronegative patients did.[34] The second study focusing exclusively on ambulatory patients reported a higher prevalence of 53% but authors considered the occurrence of symptoms within a wide period ranging from 3 to 10 months. This does not represent the observed prevalence after 6 months and, in this vein, it could have been overestimated.[45]
    - Another study prospectively followed patients whith predominantly mild COVID-19 in the acute phase. At 7 months, the prevalence was 12.8%. A high rate of dropouts was mentioned (only 37% of the initial number of patients were followed). Missing patients were called and 24.2% of reached dropouts reported over the phone the presence of symptoms (without medical assessment).[40]
    - At 6 to 8 months after diagnosis, a prospective cohort study assessed patients with 19 % of whom hospitalisation was required (with 2.3% at ICU). Symptoms were reported by 25% of patients and 26% reported that they had not fully recovered.[44] Another study, conducted in Italy, included a limited proportion of hospitalised patients and identified 40.2% of patients with various persisting symptoms after 6 months.[50]
    - In a similar way as the numbers reported at 3 months, the study from Wynberg et al. showed that the proportion of symptomatic patients at 9 months was 53% in the more severe groups (moderate, severe, critical), that was twice the value of people who had experienced a mild COVID-19.[54] The global prevalence at 9 months still reached 42%.
- A study reported a prevalence of 2.2% but did not mention the hospitalisation status.[68]
- One study, conducted in Spain, with one year follow-up was included. In a cohort of patients discharged from hospital or emergency department, it was shown that 56.1% had still symptoms at one-year follow-up. The level of severity was somewhat high with a prevalence of pneumonia of 74.4%.[63] Another study assessed the prevalence of symptoms one year after acute infection in mild to moderate patients and reported a rate of 53% of participants with at least one symptom.[69]

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.[4]

Table 2 – Results on long COVID prevalence

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
Cellai M[24], US	Telemedicine clinic program (regular phone calls) Confirmed infection (PCR)	Prospective cohort study n = 496	Persistent self-reported symptoms 6 weeks after onset of COVID-19	Ambulatory	1-3 m	5.2% (26/496)	Not reported	Published
Cirulli E[55], US	Participants to online survey in 2 projects Confirmed infection (PCR)	Cross-sectional survey n = 357	Self-reported symptom lasting longer than 30 days after COVID-19 onset (from a list of 32 symptoms)	Hospitalised 2.5%	1-3 m ≥ 3 m	at 30 days: 36.1% (129/357) ≥ 3 months: 14.8%	Not reported	Under review
Sudre C[30], UK, US and Sweden	Self-reporting in Covid Symptom Study App (start logging when still asymptomatic) Confirmed infection (PCR)	Prospective cohort study n = 4 182	Any self-reported symptom > 28 days after onset of COVID-19	Ambulatory	1-3 m ≥ 3 m	> 28 days: 13.3% (558/4182) ≥ 3 months: 2.3%	Not reported	Published
Moreno-Perez O[28], Spain	Outpatient structured evaluation after hospital or emergency discharge Confirmed infection (PCR) or seroconverted	Prospective cohort study n = 277	Persistence of ≥ 1 symptom or abnormal spirometry or chest X-Ray at 10-14 weeks after onset of COVID-19	Hospitalised 66 % ICU 8.7%	1-3 m > 3 m	1-3 months: 50.9% (141/277) > 3 months: 13.3% (37/277) with respiratory symptoms 7.5% (21/277) with neurological symptoms	Not reported	Published
Mandal S[58], UK	Phone or in-person interview of every patient after hospital discharge who had	Cross sectional study n = 384	Self-reported symptoms 4-6 weeks after discharge and	Hospitalised	1-3 m	71.8% (276/384)	• Dyspnoea 53% • Cough 34% • Fatigue 69%	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
	tested COVID-19 positive		biological, respiratory and mental assessment					
Myall K[29], UK	Phone interview 4 weeks after hospital discharge Confirmed infection (PCR or clinically/radiologically)	Prospective cohort study n = 837	Self-reported ongoing symptom 4-6 weeks after discharge	Hospitalised ICU 54%	1-3 m	39% (325/837)	Not reported	Published
Nehme M[35], Switzerland	Phone call 30-45 days after diagnosis (remote follow-up care system) Confirmed infection (PCR)	Prospective cohort study n = 669	Self-reported ongoing symptom 30-45 days from diagnosis	Hospitalised 6%	1-3 m	32% (214/669)	Not reported	Published
Chopra V[52], US	Phone contact 60 days after hospital discharge	Prospective cohort study n = 488	Self-reported cardio-pulmonary symptoms, return to normal activity, financial impact, emotional, and mental health	Hospitalised	1-3 m	Persistent cardiopulmonary symptoms: 32% (159/488)	Not reported	Published
Hirschtick J[62], US	A sample from participants to the Michigan COVID-19 Recovery Surveillance Study (study project on public health surveillance) was invited to complete a survey online or via a phone call (PCR-confirmed infection)	Cross sectional survey n = 593	Evaluation of the recovery from acute COVID-19. Those who had not yet recovered were asked to report the symptoms they were still experiencing at	Hospitalised 32,4% ICU 10.1%	1-3 m	Weighted percentages: at 30 days: 52.5% at 60 days: 35% At 60 days: • non-hospitalised: 26.9%	Not reported	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
			the time of the survey.			• hospitalised 51.8% • ICU: 65%		
Office for National Statistics (ONS)[61], UK	Positive COVID-19 patients who responded to the National Coronavirus (COVID-19) Infection Survey (CIS)	Cross sectional survey n = 21 622	Self-reported persistent symptoms at 5 weeks or ≥ 12 weeks after COVID-19 onset	Hospitalised 7.9% to 8.6%* * among those who first had infection at least 12 weeks previously	1-3 m 3-6 m	≥ 5 weeks: 21% ≥ 12 weeks: 13.7%	≥ 5 weeks: • Fatigue 11.8% • Cough 10.9% • Headache 10.1% • Myalgia 7.7% ≥ 12 weeks: • Fatigue 8.3% • Cough 7% • Headache 7.2% Myalgia 5.6%	*Not applicable*
Venturelli S[32], Italy	Inclusion in an outpatient post-discharge multidisciplinary program after hospital or ED discharge Confirmed infection (PCR or seroconversion) 99%	Prospective observational study n = 767	Ongoing symptoms (psychological, biological, respiratory evaluations) at 12 weeks	Hospitalised 88% ICU 9.7%	3-6 m	51% (394/767)	• Fatigue 44% (334/758) • Dyspnoea 29.7% (228/767) • Post traumatic psychological disorders 30.5% (222/727) • Anxiety 11.2% (82/727) • Depression 4.5% (33/727) • Functional finding: impaired lung function (DLCO) 19% (136/716)	Published
Morin L[38], France	Telephone assessment 3-4 months after hospital discharge Ambulatory visit for a subset of patients with relevant symptoms	Prospective cohort study n = 478	Symptoms at 4 months after hospital discharge	Hospitalised	3-6 m	51% (244/478)	• Fatigue 31.1% (131/431) • Memory difficulties 17.5% (73/416)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
							• Concentration difficulties 10% (41/416) • New-onset dyspnoea in 16.3% (78/478) • Cough 5% (21/420) • Chest pain 8.1% (34/418) • Headache 5.5% (23/420) • Anosmia 6% (25/419) • Persistent paresthesia 12.1% (51/421) • Anorexia 7.8% (34/436)	
Bliddal S[23], Denmark	Identification through Danish Civil Registration System on basis of positive PCR for COVID-19. Patients were invited (via the national digital postbox) to complete a questionnaire	Prospective cohort study n = 445	Persistent symptoms > 4 weeks and > 12 weeks	Ambulatory	1-3 m 3-6 m	> 4 weeks: 21% (36% of 198/334) > 12 weeks: 26% (40% of 129/202)	Not reported	Published
Stavem K[59], Norway	Identification of patients through PCR positivity and invitation to a postal survey or electronically	Cross-sectional cohort survey n = 451	Persistent symptoms from 1.5 to 6 months after symptom onset (median 117 days)	Ambulatory	3-6 m	41% (185/451)	• Dyspnoea 16% • Smell disorders 12% • Taste disorders 10% • Sore throat, cough, wheezing, runny nose <10% • Arthralgia <10% • Digestive symptoms (diarrhoea, nausea, abdominal pain) <10% • Blurred vision, conjunctivitis <10% • Cramps <10%	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
							• Enlarged lymph nodes <10%	
Lemhöfer C[65], Germany	Based on public health department data, positively tested patients were selected and a questionnaire were sent by post.	Cross sectional study n = 365	Patients were asked to specify their persisting health problems (with use of a grading scale)	Ambulatory	3-6 m	62% (226/365)	• Fatigue 37.5% (137/365) • Pain 28.2% (95/365) • Respiratory problems 26% (95/365) • Sleep disorders 24.9% (110/365) • Anxiety 18.4% (91/365) • Restriction of movements 17.3% (67/365) • Smell disorders 16.2% (63/365) • Taste disorders 15.1 % (59/365) • Circulatory problems 15.1% (55/365) • Bowel disorders 14% (51/365) • Muscular problems 12.9% (47/365) Bladder dysfunction 7,.9% (29/365)	Under review
Romero-Duarte S[42], Spain	Data retrieved from follow-up consultation (primary care and hospital specialities) and periodic telephonic reports. PCR confirmed infection	Retrospective observational study n = 767	Self-reported symptoms at any time after hospital discharge during 6 months follow-up, hospital readmission, return to the emergency services and death	Hospitalised patients ICU 10.8%	3-6 m	≤ 6 months: Symptoms: 63.9%* (509/797) Return to emergency department 20% (160/797) Hospitalisation 4.4% (35/767)	• Dyspnoea 28% (223/797) • Fatigue 22.1% (176/797) • Diarrhoea 10.3% (82/797) • Mental health disorders 12.2% (97/797) • Dermatological issues 9.3% (74/797) • Superinfection 7.9% (63/797)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
						Death 1% (8/797)	• Neurological issues 20.8% (166/797) Less frequent symptoms: ○ Smell/taste 7.2% (57/797) ○ Headache 5.3% (42/797) ○ Cardiovascular 5.8% (46/797) ○ Ophtalmological 4.6% (37/797) ○ Nephrological 4.5% (36/797) ○ Haematological 4.4% (35/797) ○ Urological 4.3% (34/797) ○ Otorhinological 3.1% (25/797) ○ Endocrine 1.5% (12/797)	
Blomberg B[53], Norway	All patients diagnosed at the only centralised testing facility in the city of Bergen were invited to participate, and also admitted to the city's two hospitals (PCR confirmed infection)	Prospective cohort study n = 312	Patients attended a follow-up clinic and were interviewed by medical staff at baseline, 2 and 6 months (assessment of fatigue through Chalder fatigue scale). A biological sample is performed at 2 months.	Hospitalised 21%	3-6 m	At 6 months: 61% (189/312)	Whole cohort: • Fatigue 37% (116/312) • Concentration problems 26% (82/312) • Smell and/or taste disorders 25% (78/312) • Memory problems 24% (75/312) • Dyspnoea 21% (66/312) Non-hospitalised patients: • Fever 2% (4/247) • Cough 6%(15/247) • Dyspnoea 15% (38/247)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
							• Palpitations 6% (15/247) • Stomach upset 6% (15/247) • Taste/smell disorders 27% (67/247) • Fatigue 30% (69/247) • Concentration problems 19% (44/247) • Memory problems 18% (42/247) • Sleep disturbances 9% (13/247) • Headache 11% (28/247) • Dizziness 10% (24/247) • Tingling in fingers 4% (9/247)	
Evans R[43], UK	Hospital-discharged patients were invited to attend a research visit between 2 and 7months after discharge. Median follow-up 5 months (IQR4-6) Confirmed infection in 89.5%	Prospective cohort study n = 1 077	Outcomes were collected using the following validated questionnaires. Blood tests were undertaken and respiratory tests performed	Hospitalised	3-6 m	At least one symptom at follow-up (5 months): 92.5% (797/861*) * Available data for 861 participants. The most conservative calculation would be 74% (797/1 077)	• Anxiety (GAD7 >8): 24% (253/1031) • Depression (PHQ9 ≥10): 27% (282/1029) • PTSD (PCL5 ≥28): 12% (126/1030) • Dyspnoea (dyspnoea12) 6% (63/1017) • Fatigue (FACIT): 16% (168/1036) • Pain (BPI): 15% (127/801) • Cognitive symptoms (MoCA) <23: 17% (150/888)	Under review

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
Havervall S[34], Sweden	Healthcare workers participating in an online survey and regular clinical/ biological assessment	Prospective cohort study n = 1 395	Ongoing symptoms (at least one moderate to severe symptoms) at 8 months	Ambulatory	2-6 m	≥ 2 months: 26% (84/326) ≥ 4 months: 21.4% (69/323) ≥ 8 months: 14.9% (48/323)	• Anosmia 9% (29/323) • Fatigue 4% (13/323) • Agueusia 3.7% (12/323) • Dyspnoea 1.9% (6/323) • Sleeping disorders 2.2% (7/323) • Headache 1.5% (5/323) • Palpitations < 1% (2/323) • Concentration impairment < 1% (2/323) • Muscle/joint pain < 1% (2/323) • Memory impairment < 1% (1/323)	Published
Ghosn J[39] ,France	Patients who were hospitalised were assessed through physician visits 3 and 6 months after hospital admission	Prospective cohort study n = 1 137	Systematic assessment of ten persisting symptoms at 3 and 6 months	Hospitalised ICU 29%	3-6 m > 6 m	≥ 3 month: 68% (655/957) ≥ 6 months*: 60% (639/1068) *at 6 months, 24% with ≥ 3 symptoms	• Fatigue nearly 40% • Dyspnoea > 20% • Joint pain nearly 20% • Myalgia nearly 20% • Headache > 10% • Rhinorrhea 10% • Cough 10% • Sore throat <10% • Agueusia 7% • Anosmia 7%	Published
Augustin M[40], Germany	Invitation of each patient with confirmed infection (PCR) for follow-up medical visits at month 4 and 7, regardless of symptoms	Prospective cohort study n = 958	Assessment of long-lasting symptoms with systematic questionnaires at 4 and 7 months after symptom onset	Hospitalised 2.9% ICU 0.7%	3-6 m > 6 m	At 4 months: 12.8% (123/958) At 7 months: 12.8% (123/958)	At 4 months*: • Anosmia 12.4% (55/442) • Agueusia 11.1% (49/442) • Fatigue 9.7% (43/442) • Shortness of breath 8.6% (38/442)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
			(or positive testing) Median follow-up 6.8 months				At 7 months*: • Anosmia 14.7% (52/353) • Agueusia 14.2% (50/353) • Fatigue 13.6% (48/353) • Shortness of breath 11% (39/353) *Due to the a high rate of dropout, we calculated the most conservative estimate at 7 months: ○ Anosmia 5.4% (52/958) ○ Agueusia 5.2% (50/958) ○ Fatigue 5.0% (48/958) ○ Shortness of breath 4.1 % (39/958)	
Menges G[44], Switzerland	Inclusion through contact tracing of the Department of Health, based on mandatory laboratory reporting of all individuals diagnosed with SARS-CoV-2 (PCR)	Prospective cohort study n = 431	Assessment of recovery and long-lasting symptoms through electronic questionnaire at 6 to 8 months after diagnosis and assessment of fatigue, dyspnoea, depression by using appropriate scales (FAS	Hospitalised 19% ICU 2.3%	> 6 m	Not fully recovered 26% (111/431) Symptoms 25% (106/431)	<u>Objectively measured symptoms</u>: • Fatigue 55% (233/431) • Dyspnoea (mMRC ≥ 1) 22% (96/431) • Symptoms of depression 26% (111/431) <u>Self-reported symptoms</u>: • Fatigue 12% (52/431) • Cough 10% (41/431) • Sore throat 9% (38/431) • Headache 9% (37/431) • Smell/taste disorder 5% (21/431)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
			mMRC,DASS-21)				• Rash 0.7% (3/431)	
Peghin M[50], Italy	Consecutive patients attending the Infectious Disease Department with a diagnosis of COVID-19 (PCR confirmed)	Prospective cohort study n = 599	Assessment of symptoms that developed during or after COVID-19 and continued for ≥12 weeks. Phone interview six months after disease onset (median 191 days), by trained nurses/physicians with a questionnaire investigating specific persistent symptoms potentially associated with COVID-19.	Hospitalised 26% ICU 3.8%	> 6 m	Symptoms after 6 months: 40.2% (241/599) 22.9% (137/599): ≥ 1 symptom 10.8% (65/599): 2 symptoms 6.5% (39/599): ≥ 3 symptoms	• Fatigue 13% (78/596) • Anosmia/dysgueusia 10.4% (62/596) • Neurological disorders 9.6% (57/596) • Dyspnoea 6% (36/596) • Psychiatric disorders 4.9% (29/596) • Hair loss 3.7% (22/596) • Cutaneous lesions 3.4% (20/596) • Upper respiratory tract infection 3.4% (20/596) • Headache 2.7% (16/596) • Cough 2% (12/596) • Gastro-intestinal disorders 1.5% (9/596) • Chest pain 0.8% (5/596) • Ocular disorders 0.3% (2/596)	Published
Meije Y[51], Spain	Patients discharged from hospital were identified in the electronic hospital database (79% confirmed COVID-19). Medical appointment at 45 days and phone contact 7 months after hospital discharge.	Prospective cohort study n = 294	Presence of symptoms through a standard follow-up protocol checklist of symptoms and adverse events, including psychological manifestations. Laboratory testing and chest-X ray	Hospitalised	> 6 m	At 45 days: 78% (228/294) At 7 months: 50% (147/294)	At 45 days: • Asthenia 53% • Respiratory symptoms 56% At 7 months: • Psychological disorders 49% (145/294) • Asthenia 26.5% (78/294) • Dyspnoea 9.5% (28/294)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
			were performed during the 45 days visit.				• Cough 5.8% (17/294) • Chest pain 2.7% (8/294) • Diarrhoea 2.7% (8/294) • Migraine 4.1% (12/294) • Anosmia 9.2% (27/294) • Dysgueusia 8.9% (26/294) • Myalgia 13.3% (39/294) • Neurological symptoms 17.7% (52/294) • Alopecia 10.2% (30/294)	
Fernandez-De-las Peñas C[64], Spain	Structured phone call to all included patients with myalgia during the acute phase of COVID-19	Case control study* n = 738 *age and sex-matched COVID-19 patients without myalgia at the acute phase	Ongoing symptoms appeared after hospital discharge (list of predefined symptoms), mood disorders and new-onset musculoskeletal pain	Hospitalised ICU < 10%	> 6 m	Symptoms at 7 months: 65% (480/738) 1-2 symptom(s) 48% (357/738) ≥ 3 symptoms* 16.5% (123/738) * A significantly greater proportion of patients with myalgia during the acute phase reported ≥ 3 symptoms (20% vs 13%)	Most prevalent symptoms*: • Fatigue 64% (475/738) • Memory loss 18% (136/738) • Hair loss 21% (157/738) • Dyspnoea 59% (436/738) • Musculoskeletal pain 38% (284/738) • Depressive symptoms 22% (164/738) • Anxiety symptoms 17% (127/738) • Poor sleep quality 37% (274/738) * Due to the high number of symptoms, all were not reported (list available on demand)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
Desgranges F[45], Switzerland	Structured and standardized phone survey (14 predefined symptoms) 3 months after diagnosis (majority of health care workers). Patients were called at different moments: 3-5 months: n = 190 5-7 months: n = 102 7-10 months: n = 126	Prospective cohort study n = 507 (418 patients with PCR+ and 89 controls with symptoms but negative PCR)	Persisting symptoms, need for hospitalisation, seek for medical care and anthropometric data	Ambulatory	3-10 m	Symptoms > 3 and ≤ 10 months: 53% (223/418)* versus 37% (33/89) in the control group (p<0.05) * Prevalence was similar between the three surveyed periods	Most reported symptoms*: • Fatigue 32% (132/418) • Smell/taste disorders 22% (93/418) • Dyspnoea 16%(66/418) • Headache 12% (50/418) • Memory problems 11% (48/418) • Hair loss 10% (43/418) • Sleep disorders 10% (41/418) • Chest pain 5% (21/418) • Nausea 2.6% (11/418) • Blurred vision 4.8% (20/418) • Numbness 3.8% (14/418) • Loss of balance 2.9% (12/418) * Due to the high number of symptoms, all were not reported (list available on demand)	Under review
Perlis R[68], US	Ten waves of a online survey were conducted within 7 months, applying nonprobability sampling using representative quotas in order to balance age, gender, and race/ethnicity. Confirmed infection in 71% (n = 4 448)	Cross sectional survey n = 6 211	Persisting symptoms	Not clearly mentioned	> 6 m	Presence if symptoms in the group of patients with positive PCR at 2 months: 7.5% (332/4 438) at 4 months: 3.3% ≥ 6 months: 2.2%	Not reported	Under review

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
Wynberg E[54], The Netherlands	Identification from notification data at the Public Health Service of Amsterdam (phone contact) for non-hospitalised patients and direct contact on the ward for hospitalised ones (PCR confirmed infection)	Partly* prospective study n = 301 * 210/301 prospectively selected	Presence of symptoms through questionnaires plus biological samples (blood, saliva, stools, nose and throat swabs) and respiratory tests	Hospitalised 44% ICU 11%	> 6 m	At 3 months: • Mild 33% • Moderate 63.9% • Severe/critical 81.7% At 9 months: 42% of the whole cohort with ≥ 1 symptom: • Mild 20% • Moderate 53% • Severe/critical 52.9%	Not reported for the whole cohort	Under review
Sigfrid L[66], UK	Hospital discharged patients with confirmed or highly suspected COVID-19 consented to be contacted by phone and/or by post (or in outpatient clinic)	Prospective cohort study n = 327	Presence of self-reported symptoms and self-reported recovery after initial COVID-19 (median follow-up 7 months). Use of several scales to assess symptoms (Washington Disability Group Short Form, Visual analog scale for fatigue, MRC, Quality of life EQ5D5L)	Hospitalised (mechanical ventilation 28,1%, high flow nasal canula or non-invasive ventilation 15%)	> 6 m	At 7 months: Reported symptoms 93,3% (305/325) Not fully recovered 54,7% (179/327)	Symptoms*: • Fatigue 82,8% (255/308) • Dyspnoea 53,5% (175/327) • Sleep disorders 46.2%(151/327) • Headache 39,4% (129/327) • Join or muscle pain 37% (121/327) • Chest pain 15,3% (50/327) • Palpitations 23,2% (76/327) • Diarrhoea 17.7% (58/327) • Loss of smell 12.8% (42/327)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
							* Due to the high number of symptoms, all were not reported (list available on demand)	
Maestre-Muñiz M[63] Spain	Follow-up medical visit at one year after hospital or emergency department discharge for confirmed COVID-19	Cross sectional study n = 543	Ongoing symptoms: structured interview with appropriate scales and evaluation of physical or cognitive impairment and worsening of pre-existing disease	Hospitalised 43%	12 m	At one year: 56.9% (309/543) • Hospital discharged : 66.8% (155/232) • Emergency department discharged : 49.5% (154/311)	Symptom still present at one year*: Breathelessness 19% (105/543) Fatigue 19% (105/543) Agueusia 7% (39/543) Anosmia 7% (39/543) Hair loss 1.6% (9/543) Memory problems 17% (94/543) Sleep disorders 11% (60/543) Muscle weakness 7% (40/543) Headache 9% (49/543) Myalgia 11% (62/543) Mood change (49/543) Gastro-intestinal symptoms 1% (6/543) Chest pain (23/543) 4% Skin rash 2.6% (14/543) Palpitations 4.6% (25/543) Concentration problem 5% (29/543) Sore throat 2% (12/543) * authors presented the differences between hospitalised and non-hospitalised patients, prevalence of symptom within 1 year, and recovery	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up (months)	Prevalence	Symptom-specific prevalence	Publication status
							time (results available on demand)	
Boscolo-Rizzo O[69], Italy	Patients with PCR confirmed COVID-19 completed a baseline phone questionnaire within 3 weeks after infection. Patients were re-contacted by phone 12 months after onset of symptoms.	Prospective cohort study n = 304	Self-reported persisting symptoms at 12 months	Ambulatory	12 m	53% (161/304)	• Fatigue 27% (83/304) • Smell-taste disorders 22% (67/304) • Dyspnoea 12,8% (39/304) • Muscle pain 9.2% (28/304)	Published

Legend:BPI: Brief Pain Inventory; DASS-21: Depression Anxiety and Stress Scale 21; DLCO: Diffusing capacity for carbon dioxide; Dyspnoea12: Dyspnoea-12 Questionnaire; FACIT: FACIT Fatigue Scale; FAS: Fatigue Assessment Score; GAD7: General Anxiety Disorder 7 Questionnaire; HADS: Hospital Anxiety and Depression Scale; ICU: Intensive care unit; mMRC modified medical research council;MoCA: Montreal Cognitive Assessment; PCR: Polymerase chain reaction;PCL5: Post Traumatic Stress Disorder Checklist ; PHQ9: Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Quality Index

6.3 Prevalence of long COVID for specific organ systems or symptoms

In this section, we only describe studies reporting prevalence on specific symptoms affecting one or several particular organ systems. Results are presented in Table 2 (symptom-specific prevalence column) and Table 3. We retrieved 26 observational cohort studies[22, 25-27, 31-34, 36-39, 41-51, 53, 64, 67] and one cross-sectional study.[61] Among these, 8 had a follow-up of 3 months[26, 27, 31, 33, 37, 47, 48, 61], while 11 evaluated symptoms between 3 and 6 months.[22, 25, 32, 36, 38, 41-43, 46, 53, 67] Eight studies had a follow-up beyond 6 months.[34, 39, 44, 45, 49-51, 64] Three studies were under review.[43, 45, 46]

Four studies appraised mental health[27, 31, 36, 48] and 4 evaluated the olfactory or taste disorders.[25, 26, 33, 37] One study focused on cognitive disorders.[49] Seventeen other studies reported on general symptoms[32, 34, 38, 39, 41-47, 50, 51, 53, 61, 64, 67] and 3 were focused on mortality and/or hospital readmission.[22, 42, 67]

6.3.1 Mental health and neurocognitive symptoms

In a large retrospective observational study, Taquet et al. reported a frequency of 5.8% of new onset psychiatric illness in the aftermath of COVID-19. Anxiety or mood disorders (mainly depression) were reported up to 3 months after the onset of COVID-19 in respectively 4.7 and 2% of patients.[31] At 6 months, in a larger cohort with a hospitalisation rate of 19.6%, the same authors reported a rate of 12.84% of new-onset psychiatric or neurological illness. This rate was higher and reached 25.79% in more severe patients who had been admitted to an intensive therapy unit (ITU). Anxiety was reported in 7.11% of the total cohort and almost 10% in the more severe subgroup who needed intensive therapy. Insomnia in both groups was 2.53 and 4.24%, respectively. Psychotic disorders or brain vascular disorders, such as stroke or haemorrhage, were less frequent (below 1%).[36]

Mental health problems were more often identified in two cohort studies that included COVID-19 patients that had visited the emergency department (with a proportion of them hospitalised), at a prevalence rate of 47 and 55%.[27, 48]

Six months after acute COVID-19, the study of Søraas et al. reported on memory and concentration disorders at prevalences rates of 11 and 12%, respectively. The cohort comprised exclusively patients who were not admitted to the hospital.[49]

6.3.2 Olfactory and smell symptoms

In three prospective cohort studies that mainly included ambulatory patients, self-reported olfactory disorders within 1 to 3 months after onset of disease varied between 26 and 42%, in those having developed anosmia or hyposmia at the acute phase of the disease.[26, 33, 37] One of these studies reported also 33.8% of taste disorder.[26] One prospective cohort study investigated the olfactory abnormalities through objective and validated tests. The prevalence of self-reported olfactory disorders was 24,2% at 2 months. In a subgroup of patients, objective olfactory testing revealed prevalence of 15.3% at 2 months and 4.7% at 6 months, in those who were anosmic/hyposmic during acute COVID-19.[25] A cross sectional study reported the prevalences of smell and taste problem within the first six months by 12 and 10%, respectively.[59]

6.3.3 General symptoms

One cross-sectional study [61] and one cohort study[34] reported on general symptoms at different time points following acute infection during the first three months, while 7 cohort studies assessed the prevalence of general symptoms between 3 and 6 months[32, 38, 41-43, 46, 53] Seven cohort studies[34, 39, 44, 45, 50, 51, 66] and one case-control studies [64] estimated the prevalence of general symptoms beyond 6 months whereas 2 cohort studies were conducted at one year.[63, 69]

6.3.3.1 *Up to 3 months*

- In the update of the Coronavirus Infection Survey (CIS) from April 2021, the UK Office for National Statistics (ONS) reported that the most prevalent self-reported symptoms that persist at least 5 weeks after acute infection were fatigue (11.8%), cough (10.9%), headache (10.1%) and muscle pain (7.7%). The most prevalent symptoms that persisted at least 3 months were the same as those reported at 5 weeks, but prevalences were lower for all symptoms. However, ONS mentioned that those estimates must be interpreted with caution because of a low amount of participants still reporting symptoms at 12 weeks.[61] In the updates of July and June 2021, the most prevalent symptoms were fatigue, shortness of breath followed by muscle ache and concentration difficulties. The number of total patients with patients was reported in these updates rather than the prevalence among patients who had been infected.[70, 71]
- One retrospective cohort study reported the occurrence of new-onset symptoms 1 to 4 months after diagnosis: respiratory issues was the most prevalent symptom in patients who were hospitalised or not, at levels of was 3.7% and 2.1%, respectively.[47] (See Table 3)

6.3.3.2 *Between 3 and 6 months*

- Between 3 and 6 months, 9 studies assessed the prevalence of general symptoms.[32, 38, 41-43, 53, 59, 65, 67] Among them, four reported on a majority of patients discharged from hospital.[32, 38, 42, 43], 3 on mixed groups[41, 53, 67] and 2 on ambulatory patients.[59, 65]
- Among studies with mainly hospitalised patients, fatigue was the most prevalent symptom (16-44%, median: 26%). The prevalence of dyspnoea ranged between 6 and 29% (median 22%).Other prevalent symptoms were mental health and cognitive problems. Two studies focused on PTSD and reported prevalence from 12 to 30%.[32, 43] It should be noted that both studies included critically-ill subjects.

  The study from Blomberg et al. included ambulatory and hospitalised patients and showed that the prevalence of fatigue, dyspnoea and

cognitive disoders was higher in patients who required hospitalisation.[53] Other reported symptoms and their prevalence are presented in Table 2. Daugherty et al. retrospectively showed, in a cohort of patients who were predominantly not hospitalised, that 14% of patients had at least one new type of clinical sequelae that required medical care 4 months after COVID-19. New symptoms were identified across a wide range of organ systems including cardiovascular, respiratory, renal, haematological and mental issues.[41]

The studies conducted on ambulatory patients reported fatigue, taste disorders and respiratory problems as the most prevalent symptoms.[59, 65]

- A large retrospective cohort study assessed the medical issues during the first 6 months after infection. When compared to a control historical group of patients who had Influenza, cardiac, respiratory and renal disorders were more frequently reported. Alopecia and taste/smell disorders were also more frequently reported in patients who had COVID-19.[46]
- Another large retrospective study using the national healthcare databases of the US Department of Veterans Affairs, observed a higher occurrence of medical issues and use of health resources along with a higher risk of death, both in hospitalised and non-hospitalised COVID-19 patients, in comparison with control groups.[67]

6.3.3.3 Beyond 6 months

- Beyond 6 months, 8 studies reported on the prevalence of specific symptoms.[34, 39, 44, 45, 50, 51, 64, 66] Among them, 4 involved post-hospitalised patients[39, 51, 64, 66] while 3 others included only ambulatory patients.[34, 45, 50] Two other studies comprised heterogeneous groups with both types of participants.[44]
    - Among studies on post-hospital discharged patients, fatigue, dyspnoea and mental health problems were the most common prevalent symptoms: fatigue extended between 26 and 82% (median value 52%) while dyspnoea ranged between 10 and 59% (median value 36%). Mental health symptoms were reported in two studies by a rate of 22 and 49%, respectively.[51, 64]
    - Fatigue and dyspnoea were also the most prevalent symptoms in studies that included ambulatory and hospitalised symptoms.[44, 50] In a cohort comprising 19% of hospitalised patients, Menges et al. used appropriate scales (FAS, mMRC and DASS-21) to assess fatigue, dyspnoea and depression that were reported in 55, 25 and 26%, respectively. However, self-reported fatigue was lower (12%) that the prevalence estimated with the FAS (See Table 2).[44] Peghin et al. reported a quite similar prevalence of fatigue by 13%.[50]
    - One observational cohort study estimated the prevalence of long COVID beyond 6 months in patients who were not hospitalised. The prevalence of symptoms over time was reported among a cohort of seropositive or seronegative for SARS-CoV-2 (See Table 2).[34] The most prevalent symptoms at 8 months were anosmia (9%), fatigue (4%) and ageusia (3.7%). Other less frequent symptoms included dyspnoea, sleeping disorders, headache, palpitations, concentration/memory impairment or muscle/joint pain. The prevalence of those symptoms decreased all over time. The other study on ambulatory patient describes fatigue and dyspnoea as the most prevalent symptoms.[45]

6.3.3.4 One year follow-up

At one year follow-up, one study reported fatigue and dyspnoea as the most prevalent symptoms by a rate of 19%. Taste or smell disorders were still present in 7% of patients and neurocognitive problems in 17%.[63] A study conducted in patients who suffered from mild to moderate forms reported fatigue as most prevalent symptoms (27%). The other symptoms were smell-taste disorders and dyspnoea at rates of 22 and 12.8%, respectively.[69]

6.3.4 *Hospital readmission and mortality*

Two studies focused on hospital readmission and mortality[22, 42]

- Ayoubkhani et al. conducted a large retrospective observational and matched cohort study in the UK that included 47 780 participants who were discharged from the hospital.[22] They reported on the rates of hospital readmission, mortality and new-onset diseases over a mean follow-up of 140 days and compared them to control cases matched on clinical and demographic characteristics. Twenty-nine percent of COVID-19 patients were re-admitted to the hospital whereas 9.2% of matched-control patients did. Mortality rate was 12.3% in the COVID-19 group versus 1.7% in the matched- control group. Likewise, rates of new-onset multi-organ dysfunctions (respiratory or cardiometabolic) were significantly raised in COVID-19 subjects when compared to controls (See Table 3).[22]
- Romero-Duarte et al. reported 20.3% of patients who returned to the emergency department and 12.1% were hospitalised within 6 months after COVID-19.[42]

Table 3 – Results on prevalences of long COVID for specific organ systems or symptoms

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up	Prevalence	Prevalence of specific symptom	Publication status
Taquet M, UK[31], US	Data extraction from electronic database in positive COVID-19 patients (confirmed infection PCR or antigen testings 92.2%)	Retrospective observational cohort study n = 62 354	New-onset psychiatric disorders within 14 to 90 days after COVID-19 onset	Percentage of hospitalisation not mentioned	1-3 m	5.8%	• Anxiety disorder 4.7% (adjustment disorder, generalised anxiety disorder, PTSD, panic disorder) • Mood disorder 2% (depression 1.7%) • Psychotic disorder 0.1% • Insomnia 1.9% • Dementia 0.44%	Published
Taquet M[36], UK, US	Data extraction from electronic database in positive COVID-19 patients Confirmed infection (ICD-10 codes U07.1)	Retrospective observational cohort study n = 236 379	New-onset psychiatric or neurological disorders in the 6 months after COVID-19	Hospitalised 19.6% ITU 3.8%	3-6 m	Whole COVID-19 cohort: 12.84% Patients admitted in ITU: 25.79%	• Anxiety disorders 7.11 % • Psychotic disorders 0.42% • New insomnia 2.53% • Intracranial haemorrhage 0.28% • Ischaemic stroke 0.76% • Parkinsonism 0.11% • Dementia 0.67%	Published
Mazza M[27], Italy	Clinical interview and self-reported questionnaires in COVID-19 patients assessed at ED and hospitalised or not. (no information on testing)	Prospective observational cohort study n = 402	Mental health assessment at one month after COVID-19 onset	Hospitalised 75%	1-3 m	56%	• PTSD 28% • Depression 31% • Insomnia 40% • Anxiety 42% • Obsessive-compulsive symptoms 20%	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up	Prevalence	Prevalence of specific symptom	Publication status
Naidu S[48], UK	Virtual follow-up service for all adults discharged from hospital with a clinical diagnosis of COVID-19 (with or without positive swabs). Patients with positive scores for mental health issues were provided a referral link to local psychology services	Prospective observational cohort n = 760	Mental health assessment (PHQ-2 for depression and TSQ) for PTSD. Median follow up 65 days (IQR: 37.5-92.5)	Patients treated in the emergency department, inpatient wards and intensive care	1-3 m	47.0% (357/760) with persisting psychiatric (and physical) symptoms	• 13.8% (105/760) screened positive for depression • 10.5% (80/760) - screened positive for PTSD	Published
Soraas A[49], Norway	Participants invited after being tested for SARS-CoV-2 (or randomly selected non-tested participants) and completed online baseline- and follow-up questionnaires	Prospective observational cohort n = 651 (13 001 patients completed the questionnaire)	Memory problems assessment at 8 months ater infection	Ambulatory	> 6 m	11% with persisting memory problems (72/651) versus 4% in the SARS-CoV-2 negative group and 2% in the untested randomly selected group	Concentration problems 12% (81/651)	Published
Makaronidis J[26] , UK	Invitation of people with acute loss of smell/taste through primary care centers (recruitment via online platform). Follow-up by a questionnaire that was sent. Serology positive in 81.5%	Prospective cohort study n = 467	Smell/taste disorders at 4-6 weeks after COVID-19 onset	Ambulatory Hospitalised 2.3%	1-3 m	Smell* 42.2% (151/357) Taste* 33.8% (116/343) * of those who developed olfactory and taste disorders during the acute phase	Not reported	Published
Chiesa-Estomba C[33],	Identification of patients with total or partial loss of smell	Prospective cohort study	Self-reported persistent	Ambulatory	1-3 m	Persistent loss of smell* 37% (277/751)	Not reported	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up	Prevalence	Prevalence of specific symptom	Publication status
France and European	through database from 3 hospitals. Contact after 30 days for olfactory assessment via online questionnaire Confirmed infection (PCR)	n = 751	olfactory dysfunction	Hospitalised (no clear % mentioned, no critically-ill patients)		Partial smell recovery* 14% (107/751) *of those who developed olfactory and taste disorders during the acute phase		
Villarreal I[37], Spain	Phone interview in healthcare workers with PCR positive for COVID-19	Prospective cohort study n = 256	Olfactory and taste disorders at 1 month after acute infection	Hospitalised 3.5%	1-3 m	26% (43/161)* * of those who developed olfactory and taste disorders during the acute phase	Not reported	Published
Lechien J[25], **Belgium and Europe**	Online questionnaire was completed at the end of the disease or at the hospital discharge and within the 2-month post-infection (identification through hospital databases)	Prospective cohort study n = 1 363	Self-reported olfactory dysfunction at 2 and 6 months (objective testing in a subset)	Hospitalised 2%	3-6 m	At 2 months: 24.1%*# (328/1363) At 6 months: 4,7% * of those who developed olfactory and taste disorders during the acute phase # In a subgroup of patients performing objective olfactory testing, 15,3% had olfactory dysfunction	Not reported	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up	Prevalence	Prevalence of specific symptom	Publication status
Ayoubkhani D[22], UK	Identification through electronic health and mortality records (ICD10 codes: U07.1 and U07.2)	Retrospective matched cohort study n = 47 780	Over a mean follow-up of 140 days, assessment of: - Hospital readmission - Cause of death - Organ dysfunctions	Hospitalised	3-6 m	Not reported	• Hospital re-admission 29.4% in COVID-19 patients vs 9.2% in the control group • Death after discharge 12.3% in COVID-19 patients vs 1.7% in the control group • New-onset organ dysfunctions in COVID-19 patients versus control group: ○ Respiratory disease 21.5% vs 0.8% ○ Diabetes 1.1% vs 0.3% ○ Cardiovascular 2.6% vs 0.5%	Published
Daugherty S[41], US	Identification through electronic health from 3 data sources within the United Health Group Clinical Discovery Database (ICD10 codes: U07.1, U07.2, B34.2, B97.29) Confirmed infection (PCR)	Retrospective cohort study n = 193 113* Three comparative groups matched by propensity score * Total cohort: 266 586 and 193 113 with follow-up	Assessment of risk and relative hazards for developing clinical sequelae requiring medical care after COVID-19 in 18-65 years patients, over a follow-up of 4 months after acute infection (median 95 IQR 42-135)	Hospitalised* 8.2% ICU* 1.1% * calculated on a total of 266 586	3-6 m	14.02% with at least 1 new type of clinical sequelae that required medical care (27 074/193 113): • 10.01%: one sequela • 4.01%: > 1 new sequelae	In comparison with control groups, higher risk difference and higher hazard ratio* for several new clinical outcomes*: • Neurological disorders • Cardiovascular disorders • Hypercoagulability • Kidney disorders • Respiratory disorders • Mental health and neurocognitive issues * clinical outcomes were grouped per organ system given the high number. Results are available upon request.	Published
Spotnitz M[46], US	Data extraction from 3 electronic databases of COVID-19 patients (confirmed infection PCR). A control group consisted of patients	Retrospective cohort study n = 448 176	Ongoing symptoms and medical conditions within 1 to 6 months	Not reported	1- 6 m	≤ 6 months (in 3 databases): • 36% (42 991/119 510) • 24%	Five diagnoses * had higher relative risk in COVID-19 compared to Influenza patients: • smell/taste disorders • myocarditis • acute kidney injury • dyspnoea	Under review

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up	Prevalence	Prevalence of specific symptom	Publication status
	with a diagnosis of Influenza between October 1, 2018 and May 1, 2019					(74 320/ 306 142) • 27% (6 198/ 22 524)	• alopecia Respiratory illness, musculoskeletal disease, and psychiatric disorders were more frequent in in the COVID-19 cohort than in the control group *prevalences of each symptom were not reported because numerous. They are available on demand	
Chevinsky J[47], US	Data extraction from electronic databases of COVID-19 patients (Premier Healthcare Database Special COVID-19 Release). A propensity score-matched group of control uninfected patients was used.	Retrospective cohort study n = 74 446	Ongoing symptoms within 1 to 4 months after COVID-19 diagnosis	Hospitalised 37% (n= 27 589; children= 305) ICU 39% of adults Ambulatory 63% (n= 46 857; children= 2 368)	1-3 (4) m	≤ 4 months: • Hospitalised adult patients: 7% (1 900/ 27 284) • Ambulatory adult patients: 7.7% (3 418/ 44 489)	New-onset symptoms*: Symptoms in hospitalised adult patients*: -Respiratory 3.7% (535/14 602) -Central nervous system 2.8% (543/19 503) -Urinary tract infection 2% (410/20 426) -Circulatory 1.7% (381/22 810) -Non-specific chest pain 1.6% (359/ 22 932) Symptoms in non-hospitalised patients*: -Respiratory 2.1% (499/23 571) -Digestive 2.1% (667/32 123) -Non-specific chest pain 1.6% (573/35 940) -Central nervous system 1.7% (577/ 34 903) -Headache 1.2% (427/36 882) -Circulatory 1.2% (440/39 102) -Malaise/Fatigue 1.1% (417/39 157) -Urinary tract infection 1.0% (408/39 476)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up	Prevalence	Prevalence of specific symptom	Publication status
							*denominator, is the number of adult case-patients of the total who were not previously diagnosed with the given condition	
Al Ali Z[67], US	Data selected from selected from US Department of Veterans Affairs (VA) electronic healthcare databases: • a cohort of indivuals with positive test for COVID-19 and without hospitalisation was compared to a matched cohort of individuals without COVID-19. • a second cohort of hospitalised patients with COVID-19 was comparted to a matched cohort of individuals hospitalised for seasonal Influenza	Retrospective cohort study n = 73 435 (non-hospitalised) n = 13 654 (hospitalised)	Death, medical diagnoses, laboratory abnormalities, medication use from 30 days after COVID-19 diagnosis until the end of follow-up (median 126 days; IQR 81-203 for non-hospitalised group and median 150 days; IQR 150-217)	Ambulatory and hospitalised	1-6 m	/	Risk of incident occurrence of diagnoses expressed in **number per 1000 patients, at 6 months** (95CI) in non-hospitalised patients*: • Respiratory signs/symptoms 28.51 (26.40-30.50) • Respiratory insufficiency 3.37 (2.71-3.92) • Lower respiratory disease 4.67 (3.96-5.28) • Nervous system signs/symptoms 14.32 (12.16-16.36) • Neurocognitive disorders 3.17 (2.24-3.98) • Nervous system disorders 4.85 (3.65-5.93) • Headache 4.10 (2.49-5.58) • Malaise-fatigue 12.64 (11.24-13.93) • Muscle disorders 5.75 (4.60-6.74) • Muscle pain 13.89 (9.89-17.71) • Anaemia 4.79 (3.53-5.93) • Acute pulmonary embolism 2.63 (2.25-2.92) • Hypertension 15.18 (11.53-18.62) • Arrythmia 8.41 (7.18-9.53) • Circulatory signs 6.65 (5.18-8.01) • Chest pain 10.08 (8.63-11.42) • Heart failure 3.94 (2.97-4.80) • Oesophagal disorders 6.90(4.58-9.07) • Gastro-intestinal disorders 3.58 (2.15-4.88) • Dysphagia 2.83 (1.79-3.76)	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Duration of follow-up	Prevalence	Prevalence of specific symptom	Publication status
							• Abdominal pain 5.73 (3.70-7.62) ** risk of death HR 1.59 (95CI: 1.46-1.73)* Risk of incident occurrence of diagnoses expressed in **number per 1000 patients, at 6 months** (95CI) in hospitalised patients*: • Neurological disorders 19.78 (12.58-26.19) • Nervous system and cognitive issues 16.16 (10.40-21.19) • Mental health issues 7.75 (4.72-10.10) • Cardiovascular disorders 17.92 (10.73-24.35) • Gastro-intestinal issues 19.28 (12.72-25.13) • Pulmonary embolism 18.31 (15.83-20.25) • Malaise/fatigue 36.45 (28.13-44.15) ** risk of death HR 1.51 (95CI 1.30-1.76)* Due to the high number of symptoms, all were not reported (list available on demand)	

Legend: HR: Hazard ratio; ITU: Intensive therapy unit; PCR: Polymerase chain reaction; PHQ-2: Patient Health Questionnaire 2-item scale ;PTSD: Post-traumatic stress disorder; TSQ: Trauma Screening Questionnaire

6.4 Most common symptoms and their frequency among patients with long COVID

We report the frequency of symptoms among long COVID patients through studies assessing symptoms in this subgroup. In this case, the number of long COVID patients is used as a denominator. As mentioned above, when original data were available in the article (number of long COVID patients and the number of symptomatic patients), we calculated the symptom frequency among long COVID subjects such that only long COVID patients were included in the denominator.

We obtained data on symptom frequency in long COVID patients based on 27 articles:16 observational cohort studies,[23, 24, 28, 30, 32, 34, 35, 40, 42, 44, 45, 50, 51, 53, 66, 69] 10 cross-sectional surveys.[55-60, 62, 63, 65, 68] and 1 case-control study.[64](See Table 4) Among these studies, 23 were already been used to determine long COVID prevalence.[23, 24, 28, 30, 32, 34, 35, 40, 42, 44, 45, 50, 51, 53, 55, 58, 62-66, 68, 69] Two articles reported on the same study.[57, 60] Eleven studies were conducted between 1 and 3 months[23, 24, 28, 30, 35, 55-58, 60, 62], 6 in the 3-6 months period[32, 40, 42, 53, 59, 65] and 8 beyond 6 months.[34, 44, 45, 50, 51, 64, 66, 68] Two studies were conducted at one year.[63, 69] Four articles were preprints.[45, 55, 65, 68]

Five studies included patients who were hospitalised at the acute phase of infection[42, 51, 58, 64, 66] and two others with patients who were predominantly hospitalised.[28, 32] Eight studies included patients who were not hospitalised at the acute phase[23, 24, 30, 34, 45, 59, 65, 69] and 12 articles included both hospitalised and non-hospitalised patients.[28, 35, 40, 44, 50, 53, 55-57, 60, 62, 63] One study did not clearly mention the hospitalisation status.[68] Not all articles reported on the exact estimation of the frequency of the symptoms and only mentioned whether they were frequently reported or not.

We noticed that reported frequencies highly varied across studies. Furthermore, while some symptoms were reported continuously, relapsing-remitting presentation of symptoms was also described. Other frequent symptoms are systematically described below:

- The most commonly identified long-term symptoms up to 3 months of follow-up in long COVID patients were fatigue (16%-98%; median 76%; 11 studies)[23, 24, 28, 30, 34, 35, 55-58, 60, 62], dyspnoea (10-88%; median 43%; 12 studies)[23, 24, 28, 30, 34, 35, 55-58, 62, 68], headache (9-91%; median 22.5%; 11 studies) [23, 24, 28, 30, 34, 35, 55-57, 62, 68], taste or smell disorders (10-57.6%; median 22%; 10 studies)[23, 28, 30, 34, 35, 55, 56, 59, 62, 68]
- The most commonly identified symptoms at 3 to 6 months follow up were fatigue (16-78%; median 60%; 7 studies) [23, 32, 34, 42, 53, 56, 65], cognitive disorders (6-55%; median 38%; 5 studies) [23, 34, 38, 53, 56], dyspnoea or dysfunctional breathing (16-58%; median 38%; 8 studies).[32, 34, 38, 42, 53, 56, 59] Post-exertional malaise was reported in one study at a rate of 89% in the first months and still 72% at 6 months[56].
- Beyond 6 months, fatigue was reported in 8 studies and ranged between 32 and 84% (median 51%).[34, 40, 44, 45, 50, 51, 64, 66] One study still described a frequency of 99% in a cohort of patients who were initially hospitalised.[64] Dyspnoea was also identified in 7 studies and ranged between 15 and 57% (median 30%).[34, 40, 45, 50, 51, 64, 66] One study that included hospitalised patients reported a higher frequency of 91%. [64]

We globally did not notice substantial differences between the types of symptoms among studies with ambulatory patients and studies with hospitalised patients. However, it should be noted that a clear distinction between both groups is not easy since many studies mixed hospitalised and non-hospitalised patients.

General health

General symptoms regularly reported include fatigue, muscle weakness, headache, pain (muscular, joint or bone pain), sleep disorders and less frequently low-grade fever or skin disorders (See Table 4). Fatigue was the most reported symptom over time, in the three time periods (see above) Studies with one year follow up still reported frequency of 34 and 51%, respectively.[63, 69] Headache was frequently described over time (11 studies from 1-3 months)[23, 24, 28, 30, 34, 35, 55-57, 62, 68], 4 studies between 3-6 months[23, 34, 42, 56], 8 studies beyond 6 months[34, 44, 45, 50, 51] and one study at one year.[40, 63, 64, 66] Exercise tolerance (post-exertional malaise) is also part of the reported complaints, reported by the international survey of Davis et al. This symptom was frequently reported up to 6 months after the acute phase.[56] Pain (bone, joint, muscles pain) was reported in 9 studies in the first 3

months after acute infection.[23, 28, 34, 55-57, 60, 62, 68] Sleep disorders are reported during all follow-up periods and at one year, a study reported a frequency of 19%.[63]

Respiratory

- Respiratory symptoms like dyspnoea are frequent but highly variable in the aftermath of COVID-19 (from 10 to 88% in the first three months).[23, 24, 28, 30, 34, 35, 55-58, 62, 68] Frequencies were high in both cohort studies and surveys. Between 3 and 6 months after infection, 8 studies reported frequency ranging from 16 to 58% of patients. [32, 34, 38, 42, 56, 59] and one study reported general respiratory problems at a rate of 42%.[65] Beyond 6 months, 7 studies reported lower frequencies between 15 and 57%[34, 40, 45, 50, 51, 64, 66], except one that reported a frequency of 91% in a cohort of hospitalised patients.[64]
- Importantly, the frequency of dyspnoea in patients with long COVID has to be distinguished from its prevalence as an organ-specific symptom following acute COVID-19, frequently associated with lung damages. Functional measurements of lung damage were also performed in several included studies. Alteration of lung diffusion capacity was described in two studies[32, 38] including patients who were initially hospitalised and one study reported functional alterations, mainly marked by obstructive patterns at spirometry assessment[28] (See Table 3 and Table 4).
- Chest pain (or chest tightness) ranged from less than 10 to 88.5% in 6 studies conducted in the first 3 months.[23, 24, 55, 57, 62, 68] Three studies reported frequencies from 2 to 16% after 6 months.[45, 50, 51, 66] while one study reported a low prevalence of chest pain beyond 12 weeks. [63]
- Cough is also frequently reported in long COVID patients within the first three months after acute infection. Frequencies ranged from 10.9 to 66% in 9 studies.[23, 28, 35, 55-58, 62, 68] Three studies reported frequencies from 5 to 39% beyond 6 months.[44, 50, 51]

Cardiovascular

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% in 5 studies.[24, 30, 55-57] Two studies described palpitations at a frequency of about 10% between 3 and 6 months[34, 42] and one study reported a frequency of 4% at 8 months.[34] while another revealed 25% among patients who were previously hospitalised.[66]

Neurological

- Cognitive disorders are some of the most common neurological symptoms (often referred to as 'brain fog'). Symptoms are disabling and vary widely (memory disorders, concentration, executive functioning difficulties). In the first 3 months, reported frequencies were particularly heterogeneous ranging from 4 to 85% (median 9%). The highest value came from the international survey of Davis et al.[56] and they were reported in 7 studies during this period.[23, 28, 30, 34, 55, 56, 62] and in 5 studies between 3 and 6 months, with a higher median frequency at 38% (range 6-55%) [23, 34, 38, 53, 56] After 6 months, 4 studies reported on several cognitive problems. [34, 45, 50, 64] Frequencies ranged between 2 and 28% but were was not reported in all studies.
- Olfactory and/or taste dysfunction are also very often identified among long COVID patients. Ten studies (5 cohort studies[23, 28, 30, 34, 35], 5 cross-sectional studies[55, 56, 59, 62, 68]) reported these symptoms in 10.8% to 57.6% of patients in the first three months, whereas three studies described frequencies ranging from 11 to 51% from 3 to 6 months.[34, 42, 53] Not all studies provide the crude values. After 6 months, 7 studies reported frequencies from 18 to 60% (median 26%).[34, 40, 44, 45, 50, 51, 66]
- Other neurological symptoms include dizziness, tinnitus, visual disorders or peripheral neuropathy (See Table 4).

Mental health

Anxiety and mood disorders (mainly depression) are the most commonly reported mental health symptoms over time (7 studies).[32, 38, 42, 50, 56, 64, 65] As mentioned previously, they were longitudinally studied in two retrospective cohorts (See 1.1). Post-traumatic stress disorder (PTSD) is also part of the reported problems and was reported in three studies, in which patients required intensive care or emergency services.[28, 32, 38]

Gastroenterological

Gastroenterological conditions were reported mainly in the first three months, in 8 studies.[23, 24, 28, 30, 35, 55, 56, 62] The reported symptomatology largely varied: diarrhoea, acid reflux, loss of appetite or nausea. Some studies did not elaborate on the type of symptoms[30, 35] or did not mention the frequency.[30] Gastrointestinal symptoms varied between 5 and 85%. Moreno et al. reported diarrhoea in 5.3% of cases.[28] Nehme et al. reported a low frequency beyond one month and did not go into detail of symptoms.[35] In the survey of Davis et al. that included 50% of people < 60 years, a frequency of 85% was reported with diarrhoea as the most prevalent symptom in the first three months after acute infection.[56]

During the 3-6 months period, 3 studies reported frequencies ranging from 10 to 24%.[23, 42, 65] Beyond 6 months, 3 studies reported a rather similar frequency (4-5%)[45, 50, 51] while one study that included exclusively hospitalised patients reported a higher frequency of 19%.[66] The study with one year follow-up outlined a frequency of 2%.[63]

Skin disorders

Various skin disorders are reported in the survey from Davis et al (rash, petechiae, chilblain-like lesions) at a frequency of 59.1%.[56] One study reported a frequency of 10% hair loss in the first three months. [62] Beyond 6 months, 4 studies reported on hair loss with frequencies fluctuating between 9 and 33%.[45, 50, 51, 64] Another one reported on skin rash or toe lesions.[66]

Table 4 – Frequency of symptoms among long COVID patients

Authors	*Inclusion criteria*	*Design and Sample Size*	*Outcome and timing since acute COVID-19*	*Study population*	*Symptoms frequency*	Duration of follow-up (months)	Publication status
Cellai M[24], US	Telemedicine clinic program (regular phone calls) Confirmed infection (PCR)	Prospective cohort study n = 496	Persistent self-reported symptoms 6 weeks after onset of COVID-19	Ambulatory	• Respiratory symptoms (dyspnoea, chest tightness) 88.5% (23/26) • Fatigue 65% (17/26) • Headache 50% (13/26) • Gastrointestinal symptoms 34% (9/26) • Palpitations 23% (6/26) • Low grade fever 11% (3/26) • 69.2% (18/26) reported at least 4 concurrent symptoms	1-3 m	Published
Cirulli E[55], US	Participants to online survey in 2 projects Confirmed infection (PCR)	Cross-sectional survey n = 357	Self-reported symptom lasting longer than 30 days after COVID-19 onset (from a list of 32 symptoms)	Hospitalised 2.5%	Most frequent: • Anosmia, ageusia, • Dyspnoea, chest pain • Memory loss, confusion, difficulty concentrating Others: • Decreased alertness, dizziness • Headache, insomnia • Muscle weakness • Dry cough • Tachycardia • Bone or joint pain • Fatigue • Tingling, sensitive skin, back pain • Acid reflux, diarrhoea	1-3 m	Under review
Sudre C[30], UK, US and Sweden	Self-reporting in Covid Symptom Study App (start logging when still asymptomatic) Confirmed infection (PCR)	Prospective cohort study n = 4 182	Any self-reported symptom > 28 days after onset of COVID-19	Ambulatory	• Fatigue 97.7% • Headache 91.2% • Dyspnoea (?) • Anosmia (?) • Cardiac symptoms 6.1% • Lower respiratory symptoms (?) • Concentration or memory issues 4.1% • Tinnitus/earache 3.6% • Neuropathy 2% • Fever (?) • Gastroenterological symptoms (?)	1-3 m	Published

Authors	*Inclusion criteria*	*Design and Sample Size*	*Outcome and timing since acute COVID-19*	*Study population*	*Symptoms frequency*	Duration of follow-up (months)	Publication status
Moreno-Perez O[28], Spain	Outpatient structured evaluation after hospital or emergency discharge Confirmed infection (PCR) or seroconverted	Prospective cohort study n = 277	Persistence of ≥ 1 symptom or abnormal spirometry or chest X-Ray at 10-14 weeks after onset of COVID-19	Hospitalised 66 % ICU 8.7%	• Dyspnoea 17.2% • Cough 10.6% • Fatigue 17.6% • Anosmia-Dysgeusia 10.8% • Cognitive disorders 7.6% • Headache 8.9% • Myalgia, arthralgia 9.8% • Diarrhoea 5.3% • Functinal finding: spirometry alterations 4.7%	1-3 m	Published
Goertz Y[57] and **Vaes A[60], The Netherlands and Belgium**	Persistent symptoms reported in social media in patients who experienced COVID-19 Confirmed: 16%[1] - 17%[2] [1] Goertz Y et al. [2] Vaes A et al.	Cross-sectional survey n = 2 113[1] n = 1 837[2]	Any symptoms > 3 weeks to 3 months after infection onset	Hospitalised 5%	Goertz et al.: • Fatigue 87% • Dyspnoea 71% • Chest tightness 44% • Headache 38% • Muscle pain 36% • Heart palpitation 32% • Cough 29% Vaes et al.: • Fatigue: 98% • Sleeping disorders 88% • Pain 87% • Increased need for care: - Care-dependent: 31% - Limitation in daily activities: 41.1% in the independent group	1-3 m	Published
Davis H[56], Europe and US	Persistent symptoms in people who experienced symptoms consistent with COVID-19, reported on a survey through social media and support groups Confirmed infection: 27%	Cross-sectional survey n = 3 762	Persistent symptoms >28 days	Hospitalised 8.4%	**1-3 months (most frequent)*:** • Fatigue 98% • Post extertional malaise 89% • Cognitive dysfunction 85.1% • Headache 77% • Cardiovascular symptoms 86 % • Musculoskeletal symptoms 93.6% (muscle 69%, joint 52%) • Sore throat 59% • Respiratory symptoms 93% (dyspnoea 77%, cough 66%	1-3 m 3-6 m	Published

Authors	*Inclusion criteria*	*Design and Sample Size*	*Outcome and timing since acute COVID-19*	*Study population*	*Symptoms frequency*	Duration of follow-up (months)	Publication status
					• Gastrointestinal symptoms (diarrhoea, loss of appetite, abdominal pain) 85% • Anxiety 57.9% • Depression 47.3% • Taste and smell disorders 57.6% • Sleep disorders 78.6% • Skin disorders 59.1% **At 6 months (most frequent)*:** • Fatigue 77.7% • Post extertional malaise 72.2% • Cognitive dysfunction 55.4% • Sensorimotor symptoms 55.7% • Headache 53.6% • Relapses of symptoms 85.9% • Dyspnoea 38% • Muscle pain 43.7% * Due to the high number of symptoms, all were not reported (list available on demand)		
Nehme M[35], Switzerland	Phone call 30-45 days after diagnosis (remote follow-up care system) Confirmed infection (PCR)	Prospective cohort study n = 669	Self-reported ongoing symptom 30-45 days from diagnosis	Hospitalised 6%	• Fatigue • Dyspnoea • Taste/smell disorders • Cough • Headache • Digestive symptoms	1-3 m	Published
Bliddal S[23], Denmark	Identification through Danish Civil Registration System on basis of positive PCR for COVID-19. Patients were invited (via the national digital postbox) to complete a questionnaire	Prospective cohort study n = 445	Persistent symptoms > 4 weeks and > 12 weeks	Ambulatory	<u>> 4 weeks</u>: • Fatigue 16% • Concentration or memory difficulties 13% • Reduced sense of smell 10% • Shortness of breath 10% • Headache < 10% • Muscle/joint pain <10% • Cough/chest pain <10% • Digestive symptoms <10% <u>> 12 weeks</u>:	1-3 m 3-6 m	Published

Authors	*Inclusion criteria*	*Design and Sample Size*	*Outcome and timing since acute COVID-19*	*Study population*	*Symptoms frequency*	Duration of follow-up (months)	Publication status
					• Fatigue 16% • Concentration difficulties 13% • Headache < 10% • Reduced sense of smell < 10% • Muscle/joint pain <10% • Cough/chest pain <10% Digestive symptoms <10%		
Mandal S[58], UK	Phone or in-person interview of every patient after hospital discharge who had tested COVID-19 positive	Cross sectional study n = 384	Self-reported symptoms 4-6 weeks after discharge and biological, respiratory and mental assessment	Hospitalised	• Breathlessness: 74% (204/276) • Cough: 47.5% (131/276) • Fatigue: 96% (265/276)	1-3 m	Published
Hirschtick J[62], US	A sample from participants to the Michigan COVID-19 Recovery Surveillance Study (study project on public health surveillance) was invited to complete a survey online or via a phone call (PCR-confirmed infection)	Cross sectional survey n = 593	Evaluation of the recovery from acute COVID-19. Those who had not yet recovered were asked to report the symptoms they were still experiencing at the time of the survey.	Hospitalised 32,4% ICU 10.1%	• Fatigue 52.9% • Dyspnoea 43.9% • Taste/smell disordres 19.4% • Muscle/joint pain: 18.4% • Weakness 16.4% • Cough 15.9% • Headache 9.9% • Chest pain/tightness 9.9% • Hair loss 9.8% • Cognitive dysfunction 9.1% • Nasal congestion 7.9% • Sleep disorders 6% • Dizziness 5.6% • Gastro-intestinal symptoms 5.4% • Heart rate issues 5.1%	1-3 m	Published
Perlis R[68], US	Ten waves of a online survey were conducted within 7 months, applying nonprobability sampling using representative quotas in order to balance	Cross sectional survey n = 6 211	Persisting symptoms	Not clearly mentioned	<u>Symptoms at 2 months</u>: • Fever 49% • Chills 42% • Shaking 40% • Congestion 53% • Muscle pain 45% • Cough 40%	1-3 m	Under review

Authors	*Inclusion criteria*	*Design and Sample Size*	*Outcome and timing since acute COVID-19*	*Study population*	*Symptoms frequency*	Duration of follow-up (months)	Publication status
	age, gender, and race/ethnicity				• Sore throat 46% • Headache 34% • Dyspnoea 41 % • Anosmia/agueusia 55%		
Havervall S[34], Sweden	Healthcare workers participating in an online survey and regular clinical/ biological assessment	Prospective cohort study n = 1 395	Ongoing symptoms (at least one moderate to severe symptoms) at 8 months	Ambulatory	<u>Frequencies at 2, 4 and 8 months</u>: • Anosmia 56, 51, 60% • Fatigue 32, 32 27% • Agueusia 30, 25, 25% • Dyspnoea 17, 16, 13% • Sleeping disorders 12, 13, 15% • Headache 11, 12, 10% • Palpitations 10, 10, 4% • Concentration impairment 8, 9, 4% • Muscle/joint pain 7, 7, 4% • Memory impairment 6, 6, 2%	2-6 m	Published
Stavem K[59], Norway	Identification of patients through PCR positivity and invitation to a postal survey or electronically	Cross-sectional cohort survey n = 451	Persistent symptoms from 1.5 to 6 months after symptom onset	Ambulatory	• Dyspnoea 39% • Smell disorders 29% • Taste disorders 24%	3-6 m	Published
Lemhöfer C[65], Germany	Based on public health department data, positively tested patients were selected and a questionnaire were sent by post.	Cross sectional study n = 365	Patients were asked to specify their persisting health problems (with use of a grading scale)	Ambulatory	• Fatigue 60% • Pain 42% • Respiratory problems 42% • Sleep disorders 48% • Anxiety 40% • Restriction of movements 29% • Smell disorders 28% • Taste disorders 26% • Circulatory problems 24% • Bowel disorders 22% • Muscular problems 20% • Bladder dysfunction 12%	3-6 m	Under review
Venturelli S[32], Italy	Inclusion in an outpatient post-discharge multidisciplinary	Prospective observational study	Ongoing symptoms (psychological, biological, respiratory	Hospitalised 88%	• Fatigue 85% • Dyspnoea 58% • PTSD 56% • Anxiety 21%	3-6 m	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Symptoms frequency	Duration of follow-up (months)	Publication status
	program after hospital or ED discharge Confirmed infection (PCR or seroconversion) 99%	n = 767	evaluations) at 12 weeks		• Depression 8%		
Romero-Duarte S[42], Spain	Data retrieved from follow-up consultation (primary care and hospital specialities) and periodic telephonic reports PCR confirmed infection	Retrospective observational study n = 767	Self-reported symptoms at any time after hospital discharge during 6 months follow-up, hospital readmission, return to the emergency services and death	Hospitalised patients	• Dyspnoea 44% • Fatigue 35% • Diarrhoea 16% • Mental health disorders 19% • Dermatological issues 15% • Superinfection 12% • Neurological issues 33% • Smell/taste 11% • Headache 8% • Cardiovascular 9% • Ophtalmological 7% • Nephrological 7% • Haematological %7 • Urological 7% • Otorhinological 5% • Endocrine 2%	3-6 m	Published
Blomberg B[53], Norway	All patients diagnosed at the only centralised testing facility in the city of Bergen were invited to participate, and also admitted to the city's two hospitals (PCR confirmed infection)	Prospective cohort study n = 312	Patients attended a follow-up clinic and were interviewed by medical staff at baseline, 2 and 6 months (assessment of fatigue through Chalder fatigue scale). A biological sample is performed at 2 months.	Hospitalised 21%	• Fatigue 61% • Concentration 43% • Smell/taste disorders 41% • Memory problems 40% • Dyspnoea 35%	3-6 m	Published
Menges G[44], Switzerland	Inclusion through contact tracing of the Department of Health,	Prospective cohort study	Assessment of recovery and long-lasting	Hospitalised 19%	• Fatigue 49% (52/106) • Cough 39% (41/106) • Sore throat 36% (38/106)	> 6 m	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Symptoms frequency	Duration of follow-up (months)	Publication status
	based on mandatory laboratory reporting of all individuals diagnosed with SARS-CoV-2 (PCR)	n = 431	symptoms through electronic questionnaire at 6 to 8 months after diagnosis and assessment of fatigue, dyspnoea, depression by using appropriate scales (FAS mMRC,DASS-21)	ICU 2.3%	• Headache 35% (37/106) • Taste/smell disorders 20% (21/106)		
Meije Y[51], Spain	Patients discharged from hospital were identified in the electronic hospitaldatabase (79% confirmed COVID-19). Medical appointment at 45 days and phone contact 7 months after hospital discharge.	Prospective cohort study n = 294	Presence of symptoms through a standard follow-up protocol checklist of symptoms and adverse events, including psychological manifestation. Laboratory testing and chest-X ray were performed during the 45 days visit.	Hospitalised	Symptoms at 7 months: • Psychological disorders 98% (145/147) • Asthenia 53% (78/147) • Dyspnoea 19% (28/147 • Cough 11% (17/147) • Chest pain 5.5% (8/147) • Diarrhoea 5.5% (8/147) • Migraine 8% (12/147) • Anosmia 18% (27/147) • Dysgueusia 8.7% (26/147) • Myalgia 26% (39/147) • Neurological symptoms 35% (52/147) Alopecia 20% (30/147)	> 6 m	Published
Peghin M[50], Italy	Consecutive patients attending the Infectious Disease Department with a diagnosis of COVID-19 (PCR confirmed)	Prospective cohort study n = 599	Assessment of symptoms that developed during or after COVID-19 and continued for ≥12 weeks. Phone interview six months after disease onset (median 191	Hospitalised 26%	• Fatigue 32% • Anosmia/dysgueusia 26% • Neurological disorders 24% • Dyspnoea 15% • Psychiatric disorders 12% • Hair loss 9%% • Cutaneous lesions 8 • Upper respiratory tract infection 8% • Headache 7%	> 6 m	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Symptoms frequency	Duration of follow-up (months)	Publication status
			days), by trained nurses/physicians with a questionnaire investigating specific persistent symptoms potentially associated with COVID-19.		• Cough 5% • Gastro-intestinal disorders 4% • Chest pain 2% • Ocular disorders 1%		
Fernandez-De-las Peñas C[64], Spain	Structured phone call to all included patients with myalgia during the acute phase of COVID-19	Case control study* n = 738 *age and sex-matched COVID-19 patients without myalgia at the acute phase	Ongoing symptoms appeared after hospital discharge (list of predefined symptoms) mood disorders use of HADS and PSQI scales) and new-onset musculoskeletal pain at 7.2 months after hospital discharge	Hospitalised	• Fatigue 99% • Memory loss 28% • Hair loss 33% • Dyspnoea 91% • Musculoskeletal pain 59% • Depressive symptoms 34% • Anxiety symptoms 26% • Poor sleep quality 57%	> 6 m	Published
Augustin M[40], Germany	Invitation of each patient with confirmed infection (PCR) for follow-up medical visits at month 4 and 7, regardless of symptoms	Prospective cohort study n = 958	Assessment of long-lasting symptoms with systematic questionnaires at 4 and 7 months after symptom onset (or positive testing)	Hospitalised 2.9%	• Anosmia 42% • Agueusia 41% • Fatigue 39% • Dyspnoea 32%	3-6 m > 6 m	Published

Authors	*Inclusion criteria*	*Design and Sample Size*	*Outcome and timing since acute COVID-19*	*Study population*	*Symptoms frequency*	Duration of follow-up (months)	Publication status
			Median follow-up 6.8 months				
Desgranges F[45], Switzerland	Structured and standardized phone survey (14 predefined symptoms) 3 months after diagnosis (majority of health care workers). Patients were called at different moments: 3-5 months:n=190 5-7 months: n= 102 7-10 months: n =126	Prospective cohort study n = 507 (418 infected patients with PCR+ and 89 controls with symptoms but negative PCR)	Persisting symptoms, need for hospitalisation, seek for medical care and anthropometric data	Ambulatory	• Fatigue 59% • Smell/taste disorders 42% • Dyspnoea 30% • Headache 22% • Memory problems 22% • Hair loss 19% • Sleep disorders 18% • Chest pain 9% • Nausea 5% • Blurred vision 9% • Numbness 6% • Loss of balance 5%	3-10 m	Under review
Sigfrid L[66], UK	Hospital discharged patients with confirmed or highly suspected COVID-19 consented to be contacted by phone and/or by post (or in outpatient clinic)	Prospective cohort study n = 327	Presence of self-reported symptoms and self-reported recovery after initial COVID-19 (median follow-up 7 months).		• Fatigue 84% • Dyspnoea 57% • Sleep disorders 50% • Headache 42% • Join or muscle pain 40% • Chest pain 16% • Palpitations 25% • Diarrhoea 19% • Loss of smell 14%	> 6 m	Published
Maestre-Muñiz M[63], Spain	Follow-up medical visit at one year after hospital or emergency department discharge for confirmed COVID-19	Cross sectional study n = 543	Ongoing symptoms: structured interview with appropriate scales and evaluation of physical or cognitive impairment and	Hospitalised 43%	• Breathelessness 34% • Fatigue 34% • Agueusia/ anosmia 13 • Hair loss 3% • Memory problems 30% • Sleep disorders 19% • Musck weakness 13% • Headache 16% • Myalgia 20% • Mood change 16%	> 12 m	Published

Authors	Inclusion criteria	Design and Sample Size	Outcome and timing since acute COVID-19	Study population	Symptoms frequency	Duration of follow-up (months)	Publication status
			worsening of pre-existing disease		• Gastro-intestinal symptoms 2% • Chest pain 7% • Skin rash 5% • Palpitations 8% • Concentration problem 9% • Sore throat 4%		
Boscolo-Rizzo O[69], Italy	Patients with PCR confirmed COVID-19 completed a baseline phone questionnaire within 3 weeks after infection. Patients were re-contacted by phone 12 months after onset of symptoms.	Prospective cohort study n = 304	Self-reported persisting symptoms at 12 months		• Fatigue 51% • Smell-taste disorders 41% • Dyspnoea 24% • Muscle pain 17%	> 12 m	Published

Legend: DLCO: Diffusing capacity for carbon dioxide; ICU: Intensive care unit; PCR: Polymerase chain reaction; PTSD: Post-traumatic stress disorder

6.5 Consequences on daily-life

Among the studies included in the review, 10 studies showed that the burden of persisting symptoms has an impact on the quality of life, daily life activities or the return to work.[28, 38, 39, 44, 52, 56, 60, 61, 65, 66] Five studies involved mainly hospitalised patients[28, 38, 39, 52, 66] whereas the other studies included predominantly non-hospitalised or ambulatory patients during initial illness.[44, 56, 60, 61, 65]

The more robust evaluation of the impact of long COVID on daily-life activities has been conducted by the ONS-national survey, conducted in the UK. In the update of April 2021, it was estimated that 61% of patients with long COVID experienced at least some limitation to their daily-life activities and 17.9% reported important limitations.[61] In the more recent updates of June and July 2021, it was estimated that 63.7% of people self-reporting long COVID experienced at least some limitation to their daily-living activities.[70, 71] Among them, 18.8% underwent substantial limitations. This impairment of daily-life limitation was greatest in subjects aged 50 to 69 years and 35 to 49 years in comparison with younger people who reported more frequently not having limitations.

- Other studies conducted principally on ambulatory patients reported substantial limitations on the day-to-day activities and consequences on the working life:
  - In a survey conducted in Belgium and The Netherlands, authors reported limitations in daily activities or care-dependency in the ambulatory setting. 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 after infection reported to be at least to a limited extent dependent on others in the performance of daily activities.[60]

- Davis et al. 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 due to a bad health state (being on sickness or disability leave, being fired, quitting or being unable to find a job). They showed that cognitive problems including memory disorders negatively impacted their daily life (making decisions, following conversations, remembering medications, driving, cooking, watching children,…).[56] Similarly, another cross sectional study conducted in people who underwent mild to moderate COVID-19, described a limitation in daily-life activities in 49% of them.[65] Various dimensions were altered: daily routine, care support for others, relationships, using hands/fingers, private and public transportations.
- Menges et al. reported that 44% of patients had temporal or permanent changes in the scope of their job. The proportion of participants reporting financial difficulties was 11% and those with reduced income reached 12%.[44]

- Studies conducted predominantly on patients who were hospitalised reported also meaningful consequences:
  - Using the the 36-Item Short-Form Health Survey questionnaire, Morin et al found an alteration of the quality of life, 4 months after hospital discharge.[38]
  - Moreno-Perez et al. observed that the impact of COVID-19 on quality of life was significantly more frequent in patients with chronic symptoms compared to those without chronic symptoms (66.9% versus 43.2%).[28]
  - In another large prospective cohort study conducted in France, about one-third of those who had a professional occupation had not resumed work after 6 months.[39]
  - In the UK, Sigfrid et al. reported in hospital discharged patients that 24,1% of them underwent a new or worsened disability 7 months after acute infection. The most affected domains were mobility followed by memory and concentration.[66]

6.6 Risk factors for long COVID

6.6.1 *Included studies*

Among the studies included in the review, 17 cohort studies[22, 23, 26-28, 30 , 39-42, 44, 45, 50, 51, 53, 54, 69] and two cross sectional studies aimed at measuring the association between potential risk factor and long COVID (or specific symptoms of long COVID) [55, 62] Results are are presented inTable 5.

Thirteen studies assessed the risk factors for long COVID per se[23, 28, 30, 39, 40, 44, 45, 50, 51, 53, 55, 62, 69] while one cohort study was limited to the psychiatric symptoms of long COVID[27] and another cohort study focused on olfactory disorders.[26] Three cohort studies reported on the mortality, hospital/emergency admission or organ dysfunction following COVID-19.[22, 41, 42] One study described factors associated with the time to complete recovery of persisting symptoms.[54]

Fourteen studies reported adjusted odds ratio[23, 26-28, 30, 39, 40, 42, 44, 45, 50, 51, 55, 69] while 3 studies provided risk ratio or risk difference.[22, 41, 53] and two provided a prevalence ratio or a hazard ratio.[54, 62] Symptoms were self-reported and collected either through a COVID app to monitor patients [30], an online-phone survey [23, 26, 44, 45, 50, 51, 55, 62, 69] or through a search in electronic medical records.[22, 41, 42] Six studies were based on medical visit follow-up.[27, 28, 39, 40, 53, 54] Two studies were still under review.[45, 55]

6.6.2 *Risk factors*

Evidence regarding risk factors for long COVID is still very sparse and studies that aimed at determining them are limited and considerably heterogeneous. Moreover, there is no study with large follow-up, yet. Characteristic such as gender, obesity, severity and the level of care at the initial illness were analysed in several studies but it remains still unclear if

they can be generalised to all categories of patients. Results are presented in Table 5.

6.6.2.1 Gender

- In the update of April 2021, the survey from UK ONS found that a higher percentage of female (23.0%) than male (18.7%) participants reported symptoms that persisted for at least 5 weeks.[61] However, there was a degree of uncertainty over this finding (wide confidence intervals). In the more recent updates of June and July 2021, the reported prevalence was greater in female patients. In adjusted analysis and when restricting the analysis to confirmed COVID-19 cases, they were 1.3 times more likely to report long COVID than males.[70, 71]
- Two studies showed that males were less likely to experience long-term symptoms[40, 44] and, similarly, 6 others found that the female gender was associated with long COVID.[23, 39, 45, 50, 53, 69]
- The female gender is also associated with the likelihood of mental health issues and persistent smell/taste disorders (See below).[26, 27]
- Finally, regarding the risk for new clinical conditions 4 months after acute infection, a large retrospective study in the US showed that excess of risk rarely differed according to gender (anosmia, fatigue were commonly diagnosed in women whereas myocarditis, hypercoagulability, deep vein thrombosis, kidney injury, sleep apnea were more commonly diagnosed in men).[41]

6.6.2.2 Number of symptoms during initial illness

Long COVID patients are also more likely to have experienced a higher number of symptoms in the acute phase of the COVID, according to 5 studies.[30, 40, 50, 55, 69] The presence of symptoms such as fatigue, headache, dyspnoea, pain with a deep breath, sensitive skin, hoarse voice and myalgia (viral symptoms) in the acute phase of the disease were recognised as risk factors for developing long COVID, in two studies.[30, 55] One of those found that three variables - number of symptoms in the first week, age and sex - allowed to distinguish individuals with long COVID from those with short duration in a sample of patients from three countries (AUC 77%).[30] One study showed an association between the self-reported severity of symptoms during the acute illness and the presence of persisting symptoms.[62]

Another study showed that patients who presented symptoms such as thoracic pain, persistent fever or pneumonia were more likely to undergo hospital or emergency service admission.[42]

6.6.2.3 Level of care during acute during initial illness

Several studies reported on the association between the level of care during the initial illness and persisting symptoms.[28, 39, 44, 50, 53, 62]

- Moreno-Perez et al. found, in the adjusted analysis, that clinical signs of severity (based on chest X-ray and heart rate) at the initial visit to the emergency department were predictive of long COVID, in those presenting with severe pneumonia.[28]
- Four studies identified an association between persisting symptoms and the initial level of care (hospitalisation, ICU admission)[39, 50, 53, 62]

6.6.2.4 Age

The association of age and long-term symptoms remains somewhat controversial.

- One study showed that patients who developed long COVID tended to be older.[30]
- Ayoubkhani et al. compared a large cohort of individuals discharged from hospital after COVID-19 with matched control subjects from the general population. The rate ratio for mortality, hospital readmission and organ dysfunctions were greater in patients less than 70 compared to those 70 or older.[22]
- Daugherty et al. showed that the risk for new-onset clinical issues increased with age and pre-existing comorbidities but younger patients

and those without comorbidities had also an increased risk of developing new clinical sequelae, in comparison to control groups.[41]

- The April Update from UK ONS showed that people aged 35 to 49 years have the greatest prevalence of symptoms at 5 weeks followed by those aged 50 to 69 years and 25 to 34 years.[61] In the more recent updates from June and July 2021, prevalence of self-reported long COVID was greatest in people aged 35 to 69 years. After adjusting for other characteristics and restricting the analysis to confirmed COVID-19 cases, adults aged 35 to 49 years and 50 to 69 years were 1.7 times more likely to report long COVID than subjects older than 70 years. The likelihood of long COVID was lower in children aged 2 to 16 years than in all adult age groups. [70, 71]
- A study with 9 months follow-up reported that increased age was associated with a slower recovery from several symptoms such as cough, dyspnoea and myalgia.[54] while a study with one year follow-up showed that 40-54 years-old subjects were more likely to develop symptoms that those aged less than 40 years.[69]

6.6.2.5 Other risk factors

- A lower baseline level of SARS-CoV-2 immunoglobulins (several months after acute infection) was associated with persistent symptoms in one study.[40]
- A preprint article identified that patients with long COVID were more likely to have blood type A.[55]
- Obesity may be associated with the likelihood of long COVID according to 4 studies.[23, 44, 45, 69] Another one showed that obese patients recovered from persisting symptoms more slowly than non-obese patients.[54]
- One cohort study on the psychiatric symptoms of long COVID found that female patients or those with a previous psychiatric history were more likely to present psychiatric symptoms one month after hospitalisation or an emergency department visit for COVID-19.[27]

  The cohort study on the olfactory dysfunction evidenced, after adjustment for confounding factors, that female sex and presence of parosmia were associated with unresolved smell loss at 4 weeks of follow-up.[26]

Table 5 – Results on risk factors for long COVID in the selected studies

First author, country	Inclusion criteria	Outcome and timing	Risk factors (association measurement and 95%CI)	Other results
Sudre C[30], UK, US, Sweden	Inclusion by prospective self-reporting of symptoms in the COVID Symptom Study App (start logging when still asymptomatic)	Any symptom > 28 days after onset, self-reported	Adjusted analysis (age and sex), compared to "short" (<10 days) COVID, symptoms during first week of COVID (aOR ratio; 95CI): • Fatigue 2.83 (2.09-3.83) • Headache 2.62 (2.04-3.37) • Dyspnoea 2.36 (1.91-2.91) • Hoarse voice 2.33 (1.88-2.90) • Myalgia 2.22 (1.8-2.73)	Main predictors: age, sex, symptoms in 1st week (AUC 76.8%). In 70+ years (aOR ratio; 95CI): Fever 5.51 (1.75-17.36) Loss of smell 7.35 (1.58-34.22) Hoarse voice 4.03 (1.21-13.42) and comorbidities
Cirulli E[55], US	Participants to online survey in 2 projects, with positive COVID test	Any self-reported short and long-term symptom at 30, 60, 90 days from onset (list of 32 symptoms)	Adjusted analysis at day 30 (aOR ratio; 95CI): • Number of initial symptoms • Dyspnoea • Pain with deep breath • Sensitive skin • Blood type A No risk factor at 60 and 90 days (in multivariate)	Comorbidities and sex were risk factors in the unadjusted analysis, not in the multivariate analysis, probably due to low sample size

Moreno-Perez O[28], Spain	Outpatients structured evaluation after hospital or ED discharge in patients with confirmed infection	Persistence of ≥ 1 symptom or abnormal spirometry or chest X-ray at 10-14 weeks after onset	Adjusted analysis, (aOR ratio; 95CI):
			• For long COVID (overall): no significant risk factor
			• For those with initial severe pneumonia:
			  ○ opacities of lung surface on X-rays >50% 2.87 (1.13-7.32)
			  ○ higher heart rate at admission 1.03 (1.01-1.06)
				Predictors of spirometry abnormalities in overall cohort: estimated glomerular filtrate, male sex, comorbidities (high Charlson index associated with lower incidence)
				
				Higher imaging score at acute disease was associated with persistence of X-ray signs in overall cohort aOR (95CI): 1.66 (1.30-2.11) and severe

First author, country	Inclusion criteria	Outcome and timing	Risk factors (association measurement and 95%CI)	Other results
				pneumonia patients 1.68 (1.28,2.19)
Mazza M[27], Italy	COVID-19 patients assessed at ED and hospitalised or not; no information on testing	Mental health assessment at one month after hospital or ED discharge	Adjusted analysis (sex, previous status and hospitalisation): • Female sex • Previous psychiatric history	Older age and long duration of hospitalisation were risk factors in the unadjusted analysis Hospitalisation was not a risk factor
Bliddal S[23], Denmark	Identification through Danish Civil Registration System on basis of positive PCR for COVID-19. Patients were invited (via the national digital postbox) to complete a questionnaire	Persistent symptoms > 4 weeks and > 12 weeks	Adjusted analysis (sex, age, smoking, BMI, comorbidity and time from symptom start to follow-up) for the risk of symptoms after 4 weeks (aOR ratio; 95CI): • Female sex 2.91 (1.32-6.39) • BMI 1.13 (1.05-1.22)	In a subgroup of 117 women with follow-up > 4 weeks, BMI is a risk factor aOR 1.10 (1.0-1.20) Being healthcare worker was not a risk factor 1.50 (0.60-3.8)
Hirschtick J[62], US	A sample from participants to the Michigan COVID-19 Recovery Surveillance Study (study project on public health surveillance) was invited to complete a survey online or via a phone call (PCR-confirmed infection)	Evaluation of the recovery from acute COVID-19. Those who had not yet recovered were asked to report the symptoms they were still experiencing at the time of the survey.	Adjusted analysis (demographic and clinical correlates) for the risk of symptoms at 60 days (prevalence ratio; 95CI): • Hospitalisation 1.4 (1.02-1.93) • Self- reported initial severity of illness: 1.71 (1.02-2.88) • Previous psychological conditions 1.42 (1.00-2.00)	Age was not a risk factor of long-lasting symptoms in multivariate analysis
Ayoubkhani D[22], UK	Identification through electronic health and mortality records (ICD10 codes: U07.1 and U07.2)	Assessment of mortality, hospital readmission, organ dysfunctions > 3 months after hospital discharge	• In COVID-19 patients, rates of all outcomes were greater in 70+ patients than in those aged less than 70. • In COVID-19 patients, rates of all outcomes other than diabetes were greater in the white ethnic group than in the non-white group. • After matching for baseline personal characteristics (age, sex, ethnicity, region, index of multiple deprivation category, and	Greater rates of death and hospital readmission in patients admitted to ICU

First author, country	Inclusion criteria	Outcome and timing	Risk factors (association measurement and 95%CI)	Other results
			smoking status) and comorbidities, rate ratio were greater in patients less than 70 than those 70+ and in non-white ethnicity, for all outcomes.	
Daugherty S[41], US	Identification through electronic health from three data sources within the UnitedHealth Group Clinical Discovery Database (ICD10 codes: U07.1, U07.2, B34.2, B97.29)	Assessment of risk and relative hazards for developing clinical sequelae requiring medical care after COVID-19 in 18-65 years patients, at 4 months after acute infection	• Risk differences were increased in older individuals, had pre-existing conditions, and were admitted to hospital because of Covid-19. • Younger patients (aged ≤50), those with no pre-existing conditions, or not admitted to hospital for covid-19 also had an increased risk of developing new clinical sequelae, in comparison to control groups	Risk for new clinical sequelae after acute covid-19 rarely differed between men and women, apart from fatigue and anosmia (more commonly diagnosed in women)
Makaronidis J[26], UK	Invitation of people with acute loss of smell/taste through primary care centers (recruitment via online platform). Serology assessment.	Smell/taste disorders at 4-6 weeks after onset	Adjusted analysis (age, ethnicity, patterns of smell loss and smoking) for the risk of persistent smell loss (aOR; 95CI): • Female sex 2.46 (1.47-4.13) • Presence of parosmia 2.47 (1.54-4.00)	Age was not recognised as a risk factor 0.99 (1.01-1.03)
Ghosn J[39], France	Patients who were hospitalised were assessed through physician visits 3 and 6 months after hospital admission.	Ongoing self-reported symptoms within a list of 10 symptoms at 3 and 6 months after hospital admission	Adjusted analysis for the risk of having 3 or more symptoms at 6 months follow-up (aOR; 95CI): • Female sex 2.40 (1.75-3.30) • ≥ 3 symptoms at admission 2.04 (1.45-2.89) • ICU admission at the acute phase 1.55 (1.09-2.18)	Comorbidities and age were not associated with the presence of symptoms at 6 months in univariate analysis
Romero-Duarte A[42], Spain	Data retrieved from follow-up consultation (primary care and hospital specialities) and periodic telephonic reports	Self-reported symptoms at any time after hospital discharge at any time during 6 months follow-up, hospital readmission, return to the emergency services and death	Adjusted analysis for return to emergency services (aOR, 95CI): • Persistent fever 2.23 (1.18-4.19) • Thoracic pain 2.55 (1.33-4.90) • Anosmia/dysgueusia 0.28 (0.10-0.74) • Arrhythmia or palpitations 3.08 (1.21-7.79) • Superinfection 1.90 (1.05-3.42) • Pneumonia 7.65 (1.27-45.97)	

First author, country	Inclusion criteria	Outcome and timing	Risk factors (association measurement and 95%CI)	Other results
			• Dermatological symptoms 1.75 (1.01-3.03) Adjusted analysis for hospital readmission: • Persistent fever 8.31 (2.31-29.89) • Nephrological disorders 6.49 (1.50-21.14) • Superinfection 3.14 (1.05-9.40) • Pneumonia 11.81 (1.40-99.39)	
Augustin M[40], Germany	Follow-up medical visits at month 4 and 7 months after acute infection (PCR confirmed), regardless of symptoms	Assessment of long-lasting symptoms with systematic questionnaires	Adjusted analysis for the risk to develop long-term symptoms (aOR, 95CI)*: • Lower baseline level of SARS-CoV-2 IgG 1.90 (1.13-3.18) • Number of symptoms 1.29 (1.08-1.55) • Male gender 0.59 (0.36-0.98) *We observed a difference between odds ratio mentioned in the text and the tables. We asked authors for more details but we did not received a response.	
Menges G[44], Switzerland	Inclusion through contact tracing of the Department of Health, based on mandatory laboratory reporting of all individuals diagnosed with SARS-CoV-2 (PCR)	Assessment of recovery and long-lasting symptoms through electronic questionnaire at 6 to 8 months after diagnosis and assessment of fatigue, dyspnoea, depression by using appropriate scales (FAS mMRC,DASS-21)	<u>Adjusted analysis for not having recovered at 6 to 8 months (aOR, 95CI)</u>: • Severe symptoms during acute illness 2.05 (1.27-3.34) • Comorbidities 2.08 (1.24-3.50) • Male gender 0.53 (0.33-0.85) <u>Adjusted analysis for fatigue at 6 to 8 months (aOR, 95CI)</u>: • Age group: 18-35 ref; 40-64 0.59 (0.39-0.91); ≥ 65 0.41 (0.21-0.78) <u>Adjusted analysis for dyspnoea at 6 to 8 months (aOR, 95CI)</u>: • Male gender 0.45 (0.26-0.76) • Hospitalisation 4.17 (2.23-7.91) • BMI 1.14 (1.08-1.20)	No evidence for an association of depression with age, sex, initial hospitalisation, severity of symptoms at diagnosis, or the presence of comorbidities

First author, country	Inclusion criteria	Outcome and timing	Risk factors (association measurement and 95%CI)	Other results
			• Comorbidities 2.71 (1.38-5.36)	
Peghin M[50], Italy	Consecutive patients attending the Infectious Disease Department with a diagnosis of COVID-19. Phone interview	Assessment of symptoms that developed during or after COVID-19 and continued for ≥12 weeks	Adjusted analysis for symptoms ≥ 6 months (aOR, 95CI): • Female gender: 1.55 (1.05-2.27) • Number of symptoms during acute COVID-19: 1.81 (1.59-2.05) • Level of care: ○ Ward versus outpatient: 1.87 (1.19-2.94) ○ ICU versus outpatient : 3.10 (1.18-8.11)	In a subgroup of patients (n=281) the presence of antibodies (IgG against SARS-CoV-2) at 6 months was associated with the presence of symptoms (OR 2.56; 95CI: 1.48-4.38)
Blomberg B[53], Norway	All patients diagnosed at the only centralised testing facility in the city of Bergen were invited to participate, and also admitted to the city's two hospitals (PCR confirmed infection). Assessment at follow-up clinic.	Patients attended a follow-up clinic and were interviewed by medical staff at baseline, 2 and 6 months	Adjusted analysis for a high fatigue score at 6 months (aRR, 95CI): • Female gender: 1.09 (1.02-1.16) • Asthma/COPD: 1.14 (1.03-1.25) • Severity of initial illness 1.06 (1.02-1.10) • IgG titers at 2 months: 1.07 (1.02-1.12)	
Meije Y[51], Spain	Patients discharged from hospital were identified in the electronic hospitaldatabase (79% confirmed COVID-19). Medical appointment at 45 days and phone contact 7 months after hospital discharge.	Presence of symptoms through a standard follow-up protocol checklist of symptoms and adverse events, including psychological manifestations	Adjusted analysis for dyspoea at 45 days (aOR, 95CI): • Severe hypoxaemia 1.87(1.38-2.56)	
Desgranges F[45], Switzerland	Structured and standardized phone survey (14 predefined symptoms) 3 months after diagnosis (majority of health care workers).	Persisting symptoms, need for hospitalisation, seek for medical care	Adjusted analysis for long-term symptoms and fatigue (aOR, 95CI): • Female gender 1.67 (1.09-2.56) • Overweight or obesity 1.67 (1.10-2.56)	Female gender was associated with taste/smell symptoms: aOR (95CI): 1.88 (1.09-3.22)
Wynberg E[54], The Netherlands	Identification from notification data at the Public Health Service of Amsterdam (phone contact) for non-hospitalised patients and	Presence of symptoms through questionnaires plus biological samples (blood, saliva, stools, nose and throat swabs) and respiratory tests	Adjusted analysis for the time to complete recovery (aHR, 95CI): • Obesity was associated with a slower recovery (0.54; 0.32-0.90) and with a slower recovery of cough (0.56; 0.35-0.89) and taste/smell disorders (0.44; 0.25-0.76)	

First author, country	Inclusion criteria	Outcome and timing	Risk factors (association measurement and 95%CI)	Other results
	direct contact on the ward for hospitalised ones.		• Increased age was associated with a slower recovery from cough (0.81; 0.72-0.92), dyspnoea (0.82; 0.70-0.96), myalgia (0.74; 0.65-0.85) • Having one comorbidity associated with a slower recovery from fatigue (0.45; 0.28-0.72)	
Boscolo-Rizzo O[69], Italy	Patients with PCR confirmed COVID-19 completed a baseline phone questionnaire within 3 weeks after infection. Patients were re-contacted by phone 12 months after onset of symptoms	Self-reported persisting symptoms at 12 months	Adjusted analysis for the risk of persisting symptoms at 12 months (aOR; 95CI): • Female gender: 1.64 (1.00-2,70) • Age 40-54 years (reference <40): 1,92 (1.03-3.44) • BMI > 25: 1.67 • ≥ 8 symptoms during acute COVID-19 (reference < 2 symptoms): 8.71 (2.73-27.76)	

Legend: aOR: adjusted odds ratio;aRR: adjusted risk ratio; AUC: area under the curve; BMI: Body mass index; COPD: chronic obstructive pulmonary disease; 95CI: 95% confidence interval; DASS-21: Depression Anxiety and Stress Scale 21;ED: emergency department; FAS: Fatigue Assessment Score; ICU: Intensive care unit; mMRC modified medical research Council; OR: odds ratio

6.7 Quality Assessment

The evaluation of the quality of evidence is presented in Table 6. Studies were overall of moderate or low quality due to low retention, low standardisation rates and a moderate rate of longitudinal design.

Most studies had a prospective approach and reported the baseline severity of COVID-19 along with the initial level of care (hospitalisation, ICU admission). A total of 36 studies randomly selected eligible patients.[22-24, 28-32, 35, 36, 38-47, 49-55, 58, 61-66]

Studies who did not, were cross sectional survey that recruited patients with long COVID symptoms.[56, 57 , 59, 60]. The other type of studies who did not randomly selected eligible patients were involved in specific complaints such as mental health[27, 48] or taste/smell symptoms.[25, 26, 33, 37] A study included healthcare workers.[34]

A low rate (< 80%) of retention of eligible participants in the final sample (or not reported) was identified in 32 on the total of 44 studies [22-25, 27, 31-33, 36, 38-42, 44-47, 49-52, 55-60, 62, 66, 68, 69]

A total of 12 studies assessed the outcome at different time-points [23, 30, 34, 39, 40, 51, 54-56, 61, 62, 68] and 18 studies used standardised scales or tools but partly limited to some outcomes[26-29, 32, 34, 38, 39, 43, 44, 48, 49, 51, 53, 58, 63, 64, 66] (only 6 studies assessed almost all outcomes with standardised scales [27, 32, 38, 43, 44, 48]).

Table 6 – Quality assessment of included studies

Study (n=48)	Prospective cohort	Representativeness	Baseline severity	Retention	Repeated outcome(s) measurement(s)	Use of scales
Al-Aly Z et al[67]	0	1	1	0	0	0
Augustin M et al[40]	1	1	1	0	1	0
Ayoubkhani D et al[22]	0	1	1	0	0	0
Bliddal S et al[23]	1	1	1	0	1	0
Blomberg B et al[53]	1	1	1	3	0	1
Boscolo-Rizzo et al[69]	1	1	1	2	0	0
Cellai et al[24]	1	1	1	0	0	0
Chevinsky J et al[47]	0	1	1	0	0	0
Chiesa-Estomba C et al[33]	1	0	0	0	0	0
Chopra V et al[52]	1	1	1	0	0	0
Cirulli E et al[55]	0	1	1	0	1	0
Daugherty S et al[41]	0	1	1	0	0	0
Davis H et al[56]	0	0	1	0	1	0
Desgranges F et al[45]	1	1	1	0	0	0
Evans R et al[43]	1	1	1	3	0	2
Fernandez-De-las Peñas C et al[64]	1	1	1	3	0	1
Ghosn et al[39]	1	1	1	0	1	1
Goertz Y et al[57]	0	0	1	0	0	0
Havervall S et al[34]	1	0	1	3	1	1
Hirschtick J et al[62]	0	1	1	0	1	0
Lechien J et al[25]	1	0	1	0	0	0
Lemhöfer C et al[65]	0	1	1	0	0	0
Maestre-Muñiz M et al [63]	1	1	1	1	0	1
Makaronidis K et al[26]	1	0	1	2	0	1
Mandal S et al[58]	1	1	1	1	0	1
Mazza M et al[27]	1	0	0	0	0	2

Study (n=48)	Prospective cohort	Representativeness	Baseline severity	Retention	Repeated outcome(s) measurement(s)	Use of scales
Meije Y et al[51]	1	1	1	0	1	1
Menges G et al[44]	1	1	1	0	0	2
Moreno-Perez et al[28]	1	1	1	1	0	1
Morin L et al[38]	1	1	1	0	0	2
Myall K et al [29]	1	1	1	2	0	1
Naidu S et al[48]	1	0	1	2	0	2
Nehme M et al[35]	1	1	1	3	0	0
Office for National Statistics (UK)[61]	1	1	1	3	1	0
Peghin M et al[50]	1	1	1	0	0	0
Perlis R et al[68]	0	1	0	0	1	0
Romero-Duarte et al[42]	0	1	1	0	0	0
Sigfrid et al[66]	1	1	1	0	0	1
Soraas A et al[49]	1	1	1	0	0	1
Sponitz M et al[46]	0	1	0	0	0	0
Stavem et al[59]	0	0	1	0	0	0
Sudre C et al[30]	1	1	1	3	1	0
Taquet M et al [31]	0	1	0	0	0	0
Taquet M et al[36]	0	1	1	0	0	0
Vaes A et al[60]	0	0	1	0	0	0
Venturelli S et al[32]	1	1	1	0	0	2
Villarreal I et al[37]	1	0	1	3	0	0
Wynberg E et al[54]	1*	1	1	2	1	0

*Legend: (1) prospective cohort (0=NO; 1=YES); (2) representativeness (0=NO: strategy unclear or non consecutive enrolees ; 1=YES: patients randomly selected or all elegible patients were included); (3) baseline severity of illness reported (0=NO; 1=YES); (4) initial retention: number in final sample/number of eligible patients (0 = not reported or low retention <70%, 1 =retention of 70-80%, 2 = retention of 81-90% and 3 = retention> 90%); (5) repeated outcome measurements during study period (0 = outcomes were measured once; 1= outcomes were measured more than once); (6) established outcome scales/tools to measure symptom prevalence 0 = no use; 1 = some use; 2 =use for most outcomes) *patients partially included in a prospectively.*

7 DISCUSSION

7.1 Main findings

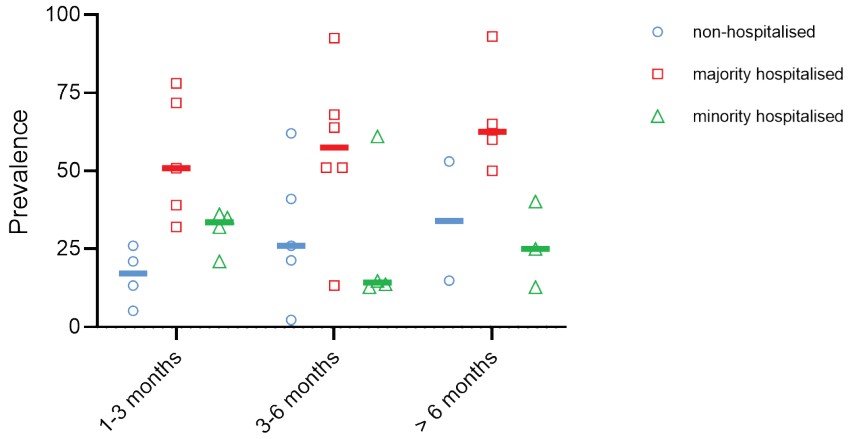
The current body of evidence about the epidemiology of long COVID is still limited. There is a huge variation of the reported prevalence and no sufficient evidence is available to determine patients at risk for developing long COVID. Our results are in line with a recent review from the UK National Institute for Health Research (NIHR) that outlined the high variability in reported prevalence and the absence of reliable evidence for risk factors.[4]

The largest and more robust study, up to now, is the national survey from ONS.[61] Based on the update of April 2021, results allowed to conclude that at least 13.7% of patients positively tested for COVID-19 continued to report symptoms after 12 weeks. A matched control group was used to assess the 'excess' prevalence due to COVID-19 and revealed that it was eight times lower than the prevalence of COVID-19 patients. The updates of June and July 2021 estimated that 1.5% of the population (962 000 people) were experiencing self-reported long COVID. The prevalence was greater among females and among people aged 35-69 years. The most frequently reported symptoms were fatigue, dyspnoea, muscle ache and cognitive complaints.[70, 71]

Since our previous preliminary report published in January and June 2021[12], results have changed in the light of newly published evidence. We noticed that the definition of long COVID or post-COVID conditions vary widely and that prevalences are consequently extremely heterogeneous (See Figure 2). In our research process, we reported the prevalence according to the initial level of care. We noticed that prevalences are indeed higher in patients who were initially hospitalised. Prevalences tend to decrease over time but we did not notice a substantial difference between '3-6 months' and 'beyond 6 months' periods.

- Based on the studies in which almost all patients were not hospitalised at the early illness, we report a median prevalence of 32% in the first 3 months. For those in which patients were predominantly hospitalised, our reported median prevalence was 51%.
- In the 3-6 months period, we report a median prevalence of 26% by considering the studies that mostly included non-hospitalised patients. Regarding the studies that involved mainly hospitalised patients, we report a median prevalence of 57%.
- For patients who were mainly not hospitalised during acute COVID-19, we describe a prevalence still reaching 25% beyond 6 months (range from 13 to 53%). The median prevalence for studies comprising a majority of hospitalised people, the median prevalence was at the level of 62%.

Figure 2 – Reported prevalences over time and according to the level of care during the acute phase



Legend: Squares, triangles and circles represent each reported prevalence at several times. Bars represent the median prevalences.

Given these wide range in reported prevalence it is hard to give precise estimates about prevalence of long COVID. Nevertheless when we take the lower bound (13%) of published prevalenecs beyond 6 months in the group with non-hospitalised persons about 1 in 7.7 persons have still symptoms after 6 months of the onset of acute COVID-19. Moreover, most studies report higher prevalence rates and in patients that were hospitalised most studies report that about 50% have still symptoms after 60 months. Therefore, based on the current evidence the KCE estimates that at least 1 in 7 persons still has symptoms (with large variation in impact on tehir daily life) after 6 months. These estimates will have to be adjusted when more robust studies are published.

The most frequently reported symptoms in long COVID patients were:

- Fatigue, dyspnoea, headache, agueusia/dysgueusia during the first three months after infection
- Fatigue, cognitive issues, dyspnoea between 3 and 6 months
- Fatigue and dyspnoea beyond 6 months

We did not retrieve sufficient evidence to clearly establish risk factors for long COVID. Although long COVID seems to be prevalent across all age categories, people aged 35 to 69 years appear to be more likely to be affected. Female gender, number and intensity of symptoms along with the level of care at the early phase may be risk factors to develop long COVID.

7.2 Limitations of available evidence

The included studies suffer from several shortcomings:

- First, the definition of long COVID is still heterogeneous and this can give rise to difficulties when trying to synthesise information:
    - There is currently emerging evidence that long COVID encompasses distinct phenotypes (or clusters of symptoms) that can overlap and evolve over time.[30, 61] For instance, people can experience exclusively cognitive disorders, while others will present only respiratory symptoms. However, it should be noted that studies widely report on symptoms that are considered regardless of their phenotype or whether they are related to distinct causes and permanent organ damage.
    - People may indeed experience symptoms possibly related to organ damage (see chapter 3). For instance, pulmonary sequelae can arise after prolonged mechanical ventilation in critically-ill patients. This gives rise to many difficulties in accurate diagnosis. Current evidence does not clearly allow to distinguish between the symptoms following organ damage from those unrelated to organ damage. Both types of symptoms are included in studies regardless if this distinction.

      Moreover, determining the extent to which symptoms are specifically related to COVID-19 remains challenging. According to the available evidence, the distinction between patients who suffered from organ damage because of interventions at the hospital (or a worsening of prexisting comorbidities) and another cause cannot be made. This overlap contributes to the observed heterogeneity and illustrates that long COVID relates to several conditions.

      Hence, the higher prevalence of symptoms observed in patients who were hospitalised could potentially be related to higher likelihood to develop organ impairment when the disease is severe. This emphasises the fact that this particular subset of patients with long-lasting symptoms may represent a different phenotype of the long COVID entity. In this way, the entity of long COVID can partially overlap with other issues such as post-intensive care syndrome, for instance.

      Other studies that were not selected in our systematic review observed a similar trend. For instance, a short survey conducted in the UK by the NIHR reported this difference according to the hospitalisation status (it was not included in the review because results were not described in detail).[4] Nearly a third of those who were not hospitalised experienced at least one enduring symptoms at one month and still 10% after three months. For those who were admitted to the hospital, between 50 and 89% had at least one remaining symptom after two months.[4] Similarly, a study conducted

in China, that was excluded from our analysis for country exclusion, showed that 76% of discharged patients reported at least one symptom at 6-month follow-up.[72] Another study, also excluded from our analysis for limited sample size, identified a high proportion (51.6%) of respiratory damages (diffusion capacity) after hospital discharge.[73]

- The severity of persistent symptoms following COVID-19 may also differ. The study from Ayoukhani et al., for example, emphasised that hospital discharged patients had an increased risk of multi-organ dysfunctions.[22] Daugherty et al. retrospectively showed in a cohort of patients who were predominantly not hospitalised that the risk for new clinical problems requiring medical care was also high in this group.[41]

  Conversely, another recent nationwide cohort study in Denmark estimated that the risk of severe complications was low in COVID-19 who did not require hospital admission. By comparing with non-COVID-19 matched subjects, the authors showed that the risk of receiving one of 25 selected new hospital diagnoses within 6 months after infection, or the risk of initiating a new drug therapy was low. Only the risk of venous thromboembolism, receiving a hospital diagnosis of dyspnoea, initiating new drugs (bronchodilator therapy or triptans) were slightly increased. It may be noted that this study mainly focused on patients who did not experience severe COVID-19 and that the prevalence could be underestimated since they reported on symptoms that led to hospital encounter.[74]

- The question of knowing whether and to what extent all reported symptoms are excess symptoms in comparison with other infectious diseases, could also be addressed. Similar multi-organ long-term consequences have been reported after other types of coronaviruses or other viral or bacterial infections.[75, 76] Nevertheless, those symptoms were not so precisely and longitudinally assessed as for long COVID, and no clear conclusion can be drawn, up to now.

- In the same line, it is very difficult to ascertain that symptoms are typical for long COVID or if they would have occurred anyway. Similarly, for health conditions already existing before COVID-19 (e.g.mental health disorders), there is no possibility to distinguish a relapse that would have occurred independently of the infection or really a specific long COVID symptom. In the same vein, symptoms pre-existing before COVID-19 are not mentioned in studies. The UK-ONS survey included a control group of people with the same age and sex profile as those tested positive for SARS-CoV-2, but who were unlikely to have been infected. Reported symptoms were significantly height fold lower in the control group (prevalence of symptoms at 5 weeks at 2.8% and 1.7% at 12 weeks).

- Second, there are also variations across the studies regarding the targeted patient populations:

  - Study populations were markedly different in terms of severity of the level of care at the acute phase and hospitalisation. Our analyse retrieved studies with a high proportion of hospitalisation (including ICU admission) along with studies with less than 10% hospitalisation or exclusively ambulatory patients. It is important to note that the threshold for hospitalisation can vary across countries together with practices within hospitals (use of non-invasive ventilation, admission to ICU, mechanical ventilation or ECMO initiation) and that it probably varied throughout the pandemic. Moreover study populations included COVID-19 confirmed (PCR, antibodies) cases as well as non-confirmed cases (but suspected). Reporting a general prevalence is not reliable enough with such a high heterogeneity.

  - Moreover, demographic variables, health conditions and risk factors for long COVID also vary among studies. The ONS-update of April 2021 identified that prevalence was greatest among people aged 35 to 69 years, females, and those with a pre-existing activity-limiting health condition.[61] We noticed, in this review, that people who were hospitalised were likely to be older probably because older patients were more severely ill. Evidence on the female gender as a risk factor seems still limited and the impact of chronic comorbidities is poorly considered across studies.

- Sample sizes, time of inclusion and follow-up duration of studies vary widely. Although we only selected studies with a sample size of at least 250 COVID-19 cases, the studies included for risk factors report a lack of power for multivariate analysis and state that the lack of significance should not be taken for a lack of association. It should also be noted that follow-up is more precise for hospital discharged patients since some studies proposed multidisciplinary follow-up clinics.

- Variability of time of inclusion (after infection confirmation, after onset of symptoms, after hospital discharge), follow-up duration, number of follow-ups, the omission of reporting frequencies of symptoms, and important loss to follow-up are hurdles to correctly estimate long COVID prevalence.

- Studies are prone to several bias. Most studies are based on self-reported symptoms and this may lead to recall biases and cause misclassification. The use of a COVID app and an online survey to recruit patients may also result in a selection bias. One study, for instance, reported an under-representation of male and elderly patients.[30] Besides, those with more severe illness might have been less likely to enter data in the app, and this may result in an underestimation of the prevalence.[30] However, it is also likely that those experiencing persistent symptoms will be more likely to participate in studies. Conversely, some studies organised a structured assessement through medical visits and through the use of appropriate and objective measurements tools. Overall, those studies mainly included emergency or hospital-discharged patients.[28, 32, 38]

  Recruitment bias was observed in studies that assessed the olfactory disorders in which only those who reported smell or taste disorders were followed-up. It is likely that prevalence was overrated.

  Furthermore, the lack of control group in many studies can lead to an overestimation of prevalence.

- Due to the nascent nature of COVID-19, physicians might have underestimated and overlooked the long COVID symptoms early in the pandemic. Moreover, testing was not available at the beginning of the pandemic making difficult to associate the complaint of non-tested patients with COVID-19. Besides, since testing is often required in studies and was initially limited to hospitalised people, this can account for a selection bias for the patients infected during the first wave of the pandemic.

Few studies report on patients who remained without symptom at the acute phase. This is a limitation and may also bias the estimation of prevalence. Based on data from 1 959 982 COVID-19 patients, FAIR Health in the US estimated that 19% of patients who remained asymptomatic during acute illness, had still persisting symptoms, one month or more after initial diagnosis.[77]

7.3 Limitations of this review

This review has several limitations:

- First, due to our strict selection criteria and our distinction between prevalence of long COVID (or symptom) and symptom frequency, our conclusions may differ from other reviews that include studies from any setting, with a lower sample size, and which report risk factors identified in non-adjusted analyses as well, or studies not comparing long COVID to short COVID.

- Second, the interpretation of results is limited by our inclusion criteria, since we include only studies from Europe and US. Risk factors and comorbidities can considerably vary also within the countries that we selected.

- Third, the paediatric population is underrepresented in our review. Studies including children are sparse and have frequently limited size (case reports, case series). Reported prevalences are heterogeneous but lower than prevalences reported in adults. In the update of June 2021, the ONS survey described that self-reported long COVID was lower in children aged 2 to 16 years than in the adult age group. The prevalence of long-lasting symptoms beyond 12 weeks was 7.4% (update of April 2021). One of the largest study, at the present time,

(preprint) was conducted in Russia and reported a prevalence of 24.3%, several months after hospital discharge (median follow-up 256 days).[79] The most frequently reported symptoms were fatigue, sleep disturbances and sensory problems. Another large study conducted on 1734 positive-tested children aimed at determinig the illness duration. Only 2.2% of them presented to the emergency department or were admitted to hospital. For 4.4% of children, the disease lasted at least 4 weeks, with fatigue, headache and anosmia as commonest symptoms, while 1.8% of experienced a prolonged illness, for at least 8 weeks. Negative-tested symptomatic children were matched to positive-tested children. Few children (0.9%) who tested negative reported an illness durartion of 28 days or more.[80] A study conducted in Switzerland reported lower prevalences in a group of children who were not hospitalised.[81] A comparison was made between 109 children seropositive for SARS-CoV-2 and seronegative ones (various testings phases performed on a randomly selected sample among schools). Four percents of seropositive children reported persisting symptoms, versus 2% in the seronegative group. The symptoms lasting more that 3 months were fatigue, difficulty of concentrating and increased need for sleep. A cohort study conducted on children in England aimed to describe the phenotype and prevalence of post-COVID physical symptoms (and mental health issues) among 3 065 children with confirmed COVID-19 and 3 739 negative controls. The cohort of SARS-CoV-2 PCR-positive children aged 11-17 years was matched on timing of testing, age, sex and geographical area to PCR negative-controls. Participants were invited to fill a questionnaire. The study emphasised the importance of having a control test-negative group to objectively interpret the prevalence estimates of symptoms: three months after testing, both groups presented symptoms but the prevalence was higher in the positive tested group (66.5% in positive-tested children versus 53.4% in negative-tested ones). In addition, the prevalence of multiple symptoms (more than 3 symptoms) was higher in the children who got sick with COVID-19 that in control group (30.3% versus 16.2%). The most frequent symptoms were tiredness, headache, loss of smell and shortness of breath.[82]

- Data aiming at quantifying the burden of long COVID on unemployment, sick-leave or disability leave (See 6.5 Consequences on daily-life) may considerably be influenced by the laws of each country and will have to be interpreted with great caution.
- We did not report the list of excluded studies and we did not analyse whether our conclusion varied from the conclusions of studies with smaller sample sizes.
- The data extraction was not done in duplicate. However a sample of studies was checked by a second researcher (in case of doubt the researcher performing the data extraction asked to cross-check the extraction by a second researcher).

Limitations for the assessment of long COVID prevalence and risk factors

- **Variability in the definition of long COVID across studies:**
  - **Symptom pattern variability**
  - **Permanent organ damage as sequelae of the acute phase, or not**
  - **Severity of persistent symptoms and requirement for hospital admission**
  - **Difficulty in knowing to what extent long COVID symptoms are excess symptoms**
  - **Difficulty in accurate diagnosis (overlap with different disease, prexisting symptoms or comorbidities)**
- **Heterogeneity of targeted populations:**
  - **Severity and level of care of acute infection (ambulatory, hospitalisation, need for ICU admission)**
  - **Characteristics and risk factors of studied populations**

- **Sample sizes variability**

- **Variability of study design: time of inclusion, follow-up duration, number of follow-ups, omission of reporting frequencies of symptoms and large loss to follow-up**
- **High risk of recall bias (self-reporting; no objective measurement) and lack of control group in most studies**
- **Underestimation in people who were infected during the first wave of pandemic and were not tested**
- **Few data on long COVID is available in patients who had asymptomatic infection**

7.4 Perspectives

- A proper and appropriate definition of long COVID would guide more efficiently the future research on its diagnosis and the management. More research on the characterisation and classification of long COVID symptoms is indeed needed. To this end, a distinction should have to be made between long COVID symptoms and post-COVID conditions that refers for the most part to symptoms related to residual organ damage (and post-intensive care syndrome) and, sometimes, not necessarily specific to COVID-19. Picking out what is related to PICS or other overlapping issues would allow a better definition and characterization of subgroups.
- Since there is now evidence that long COVID symptoms fluctuate over time, further studies should always promote assessments at different time points and seek for markers of evolution.
- In order to minimise recall bias, newly conducted studies should assess symptoms during medical visits and by using appropriate and validated tools such as spirometry, cardiac echography or validated measurement scales. This approach could probably reduce the hetereogeneity of reported prevalences. Since long COVID symptoms might overlap with other issues and seeing that it is not uncommon to present long-lasting symptoms after some infections, a control population should be included in the experimental design.
- Better quality data are needed. Accordingly, determining long COVID prevalences within each level of severity would harmonise the results.
- Addressing the question of the underlying causes of long COVID is a priority to better classify complaints and provide new insights on how to prevent and manage it.
- Even if children seem to be protected from critical form of COVID-19, capturing more data into paediatric long COVID is urgently needed to built appropriate guidelines for management.
- Looking ahead, attention should be paid to the effect of vaccination on long COVID evolution will probably shed light on its pathophysiology. Also the development of long COVID among vaccinated with breakthough infections has to be further evaluated.[83]

CHAPTER 3. PATHOPHYSIOLOGY

1 DISCLAIMER

The current work is based on the available evidence at the moment of writing the report (09/08/2021). There are still major evidence gaps, as studies are ongoing and science requires time to build up. A part of the available literature is not peer-reviewed and hence not necessarily conforms with the high quality standards for scientific research.

2 KEY POINTS

- **The pathophysiology contributing to long COVID symptoms is so far unkown. Since the spectrum of symptoms is very wide, responsible mechanisms are probably numerous and intertwined.**
- **While many articles elaborate on the putative mechanims involved in the symptomatology, there is little empirical data on the pathophysiology based on measurements among long COVID patients. In addition, the quality of data is limited due to heterogenous timings of inclusion, different initial disease severity and a lack of a comparator group. As such, the reported results need to be interpreted with caution. The current literature is highly hypothetical, cannot be generalised and is subject to change.**
- **A distinction has to be made between two categories of mechanisms by which persisting symptoms come about:**
  - **Organ injury at the early phase of infection;**
  - **Persisting and/or residual symptoms without evidence of readily measurable markers of organ injury.**
- **Current literature suggests the following general pathophysiological mechanisms:**
  - **Virus-driven tissue damage**
  - **Dysregulated immune and inflammatory reactions in response to the infection or to an occult viral persistence, giving rise to multiple disorders (microcirculation disorders associated with coagulation and fibrosis pathway activation, autoimmune manifestations and metabolic disturbances)**

3 BACKGROUND

3.1 Understanding the pathophysiology

The underlying mechanisms responsible for persisting or new symptoms following the acute phase of COVID-19 remain unknown and their pathophysiology is yet to be deciphered.

Hitherto, current research has mainly focused on the pathophysiological mechanisms involved in the acute phase and subsequent organ dysfunctions. Work on those mechanisms has mainly focused on the description of single organ involvement. However, a challenge with regard to understanding of the pathophysiology of long COVID is that the clinical spectrum is highly variable and can affect many organ systems.[84-86] In this respect, the clinical picture of long COVID can presumably not be ascribed to a single pathophysiological mechanism. More research on this topic will shed light on how SARS-CoV-2 may chronically affect some people.

Likewise, many articles indicate that organ injuries developed during the acute phase can account for the long COVID symptomatology. On the other hand, there is now compelling evidence that patients who experienced mild or moderate forms can present symptoms unassociated with residual organ dysfunctions from the early phase.[19, 30, 87] 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.[18]

Only a minority seems to be susceptible to develop long COVID. Exploring risk factors could help to elucidate the pathophysiology. When seeking to understand the processes by which long COVID comes about, another pitfall may arise from the fact that long COVID patients who remained asymptomatic at the acute phase could be overlooked and are not included in studies. This lack of awareness and monitoring of evolution can lead to omit crucial pathophysiological pathways. Indeed, it has been shown that asymptomatic patients displayed a weaker immune reaction.[19] Since a weaker immune response could play a role in long COVID[88], a longer duration of viral shedding could persistently activate the immune system and hypothetically take part in long-term immunity disorders.[19, 84]

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. In this regard, some studies have raised awareness about the role of viruses on the onset of neurodegenerative diseases and cancer.[89, 90] For the purpose of this review, we did not consider studies that hypothesised on such very long-term putative consequences.

3.2 Classifying mechanisms associated with symptoms

Classifying symptoms can help to understand pathophysiology. In this review we proposed to classify the symptoms as (1) those with evidenced organ dysfunction (such as pulmonary fibrosis, altered cardiac contractility, renal failure) and (2) symptoms not clearly associated with an organ dysfunction (such as headache, persistent fatigue, post-exertional malaise, dyspnoea without visible lung damages, psychiatric and neurocognitive disorders). In this view, the related pathophysiological mechanisms could be classified as follows:

- Persistent tissue/organ injury following the acute phase;
- Other unresolved, ongoing or recurrent reactions without evidence of classically recognized tissue/organ injury.[c]

[c] Evidenced structural (or microstructural) alterations of tissue leading to organ dysfunction.

4 RESEARCH QUESTION

The research questions are formulated as: What is the pathophysiology of long COVID and which pathophysiological mechanisms have been demonstrated in patients?

5 METHODS: IDENTIFICATION OF THE RELEVANT LITERATURE

We followed the KCE Process Book for conducting the search[d]. The search was conducted from 03 February to 09 August 2021.

This systematic review has regularly been updated: a preliminary systematic review were published before the current final version.[11]

5.1 Structured question and search concepts

The research question was transformed into an adapted PICO (PEOD: Population-Exposure-Outcome-Design), structured search question (See Supplement to Chapter 3). The review questions were thus based on the framework population, exposure, outcome, design (PEOD). Keywords and search concepts were collected through experts' opinion, existing recent publications retrieved after preliminary literature searches, and consultation of controlled vocabularies (Medical Subject headings = MeSH; Excerpta Medica = Emtree). Considering the topic specificities, only keywords related to the problem were sought.

	Inclusion criteria	Exclusion criteria
Population	People experiencing symptoms beyond 4 weeks, onward	Non-human experimental studies
Exposure	COVID-19 confirmed (PCR, antibodies), or suspected (clinically, radiologically)	
Outcome	Pathophysiological mechanisms likely to explain long COVID symptoms	• Studies that focus only on acute mechanisms • Studies that hypothesised on very long-term putative consequences such as neurodegenerative diseases or cancer
Design	Case series, systematic review, cohort study, experimental study (no limitation on number of patients)	Case reports
Language	English, French, Dutch, Spanish	Other languages

[d] http://processbook.kce.fgov.be/

5.2 Identification of studies

A set of bibliographical databases and registers were identified based on the search questions. A search query was developed with the assistance of a medical information specialist and adapted to each database. Considering the topic specificities (recent topic, no clear concept, several synonyms), full text databases and pre-print registries were sought and a pure keyword strategy was chosen. (See Supplement to Chapter 3). Searches in those databases were supplemented by collecting additional references from different sources (external experts, exploratory searches in the bibliographical databases, identification of cited references and looking into the bibliography of key references).

All identified references were imported in Endnote X.8, the duplicate search results were detected based on title match using the build-in tool from EndNote, and supplemented by manual identification after sorting on title.

5.3 Selection of studies

The selection of studies followed a three step process conducted by the information specialist (PC) and one researcher (DC).

The first step of studies identification was based on title and abstract screening using the research question and human context by the information specialist: irrelevant studies that were out of scope were excluded during this screening phase and potentially relevant studies were kept.

The second step was based on title and abstract screening using the PEOD and exclusion criteria by the researcher: irrelevant studies were discarded. Subsequently, full text papers of the retained studies were sought.

In the third phase assessing the eligibility of inclusion, we selected studies according to the PEOD criteria: the researchers selected studies that hypothesised on the pathophysiology likely to explain long-term disorders following COVID-19 or articles assessing the pathophysiology in patients with long COVID. Articles were excluded if the content was essentially focused on the acute pathophysiological mechanisms, involved in the initial phase of the infection and not likely to account for lingering symptoms However, we included those that suggested or discussed the possibility that early pathophysiological disturbances could account for chronic symptoms. We excluded studies that hypothesised on very long-term putative consequences such as neurodegenerative diseases or cancer. Languages were restricted to English, French, Dutch, and Spanish). Seeing that majority of articles are exploratory studies based on a translational approach, with limited sample sizes, critical appraisal was not undertaken. The selection of studies is summarised in the flow diagram (See Supplement to Chapter 3)

5.4 Reporting: distinction between merely theoretical articles and articles based on COVID-19 patients

To report the retrieved findings, we made a distinction between studies merely elaborating on the putative hypothesis of the pathophysiology of long COVID, and those in which patients were involved in the research process. The latter can, more precisely, give insight into the specific pathophysiology of long COVID manifestations and consequently give a much more accurate picture of what is really known. Both types of articles were analysed separately and presented in Table 6 and Table 7 (each article is individually summarised in Appendix 3- See Supplement to Chapter 3).

6 RESULTS

6.1 Included studies

The search through bibliographical databases (See Table Sources of databases) yielded 29 587 hits, which was reduced to 12 762 after duplicates removal. 12 645 records were discarded based on title and abstract screening.

From the 117 full texts articles that were retrieved and assessed for eligibility, 43 were excluded because they did not provide data or hypothesis on the aetiology of persistent symptoms or they hypothesised on long-term neurodegenerative diseases.

Additionally, 36 articles detected in the references of included studies or by conducting a quick update search in PubMed, were also retrieved and assessed: 26 were included (including 10 articles reporting autopsy results).

As a result, 100 studies met our inclusion criteria and were included in the analysis. The selection of studies is summarised in the flow diagram (See Supplement to Chapter 3).

Sources of databases

Source (Interface)	Set	Date of the search (*)	Limits
CINHAL (EBSCOhost)		2021-05-03	none
Cochrane Database of Systematic Reviews		2021-05-03	none
coronacentral.ai/	longhaul	2021-05-03	none
Econlit (OVID)	1886 to April 22, 2021	2021-05-03	none
Embase (Embase.com)		2021-05-03	none
europepmc.org/		2021-05-03	preprint
JBI EBP Database	Current to April 28, 2021Current to January 13, 2021*	2021-05-03	none
Journals@Ovid Full Text	April 30, 2021	2021-05-03	none
MEDLINE (OVID)	Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 30, 2021>	2021-05-03	none
Ovid Nursing	1946 to April Week 5 20211946 to January Week 4 2021	2021-05-07	none
PsycInfo (OVID)	1806 to April Week 4 2021	2021-05-03	none
scilit.net/		2021-05-03	preprint

** A first search was performed in February 2021, all database have been searched again in May 2021 (with no time limitation)*

6.1.1 Literature on hypothetical mechanisms

We found 54 articles only addressing hypothesis on potential mechanisms that could be involved in the long COVID symptoms. Among them, 34 speculated on mechanisms that could specifically explain long COVID symptoms[91-124] whereas 18 articles focused on acute disorders that could, to some extent, result in persisting symptoms.[125-142] In the latter, the suggested mechanism was organ injury as a complication of acute disease and from which persistent symptoms can emerge. Particularly, the reported organ injuries were the following: stroke[127, 133, 136], myocardial infarction and fibrosis[122, 124, 130, 132, 136, 138, 140] acute encephalitis[124, 131] neuromuscular disorders[121, 122, 124, 127, 129, 137] renal failure[122, 124, 141, 142] and hepatobiliary damages.[124, 125] Seven articles reported lung fibrosis as a mechanism occurring in the specific setting of severe pneumonia at the early phase.[122, 124, 128, 134, 135, 138, 140] Other articles reported on endocrine disorders unrelated

to organ damage and included hypothesis onnew-onset diabetes[143] and thyroid disorders.[144] Pathophysiology and associated symptoms are presented in Table 6.

6.1.2 *Literature involving patients in the research process.*

We retrieved 46 articles which related to patients data. Among those, ten articles reporting on post mortem analysis gave an insight into pathophysiological mechanisms, even though their relevance for long COVID remains questionable since they include patients who died from critical illness.[145-154] Studies appraised a wide range of symptoms and mechanisms: neurological[148, 152, 155-167] ,respiratory[145-147, 151, 168-171] cardiovascular/coagulation[149, 150, 153, 154, 172-176] gastro-intestinal[177], dermatological[178-180], and immune system.[158, 168, 175, 181-189] One article included patients with Multiple inflammatory syndrome in children (MIS-C).[190]

They were highly heterogeneous in time elapsed from infection to chronic symptoms ranging from one to 6 months. In addition, sample size was limited and control groups were lacking in 11 studies.[159, 161, 162, 169, 170, 175, 178-181, 184] Mostly, studies included patients who were hospitalised during the acute phase of infection: 14 studies considered only hospitalised patients[157-159, 164, 165, 168, 171-174, 177, 183, 185, 190] whereas 13 studies included both hospitalised and non-hospitalised patients.[156, 160, 163, 166, 169, 170, 176, 178, 179, 181, 184, 187, 188] Two study included exclusively non-hospitalised patients[155, 182] and another study included non-hospitalised symptomatic and asymptomatic patients.[182] Five studies did not mention the hospitalisation status.[161, 162, 167, 175, 180] The hospitalisation status at the time of initial illness is summerised in Appendix 4 (See Supplement to Chapter 3) Experimental tools included magnetic resonance imaging, nuclear medicine ([18F]FDG PET/CT), blood sample analysis and cytology/histology (mucosa brush cytological sampling, skin and bowel biopsy). Results are presented in Table 7.

Table 7 – Articles describing the hypothetical mechanisms that may be involved in the long COVID symptoms

System	Involved symptom(s)	Mechanisms	N	Studies
Neurologic	Neurocognitive symptoms Psychiatric disorders (anxiety, depression, trauma-related disorders)	**1) Neuro-inflammation hypothesis** Brain dysfunction or neuronal injury through a persistent inflammatory process secondary to the viral invasion or dysregulated immunity processes (indirect consequences of infection). Symptoms can vary according to the involved brain region (i.e cortical regions, limbic system, brainstem): (a) Central nervous system (CNS) can undergo inflammation secondary to viral invasion that occurs via trans-neuronal retrograde pathway through olfactory sensory neurons or via hematogenous invasion through the blood-brain barrier (endothelial cells and epithelial cells of choroid plexus). Leucocytes can serve as vector for dissemination towards CNS. (b) Pro-inflammatory cytokines can disrupt blood-brain barrier (BBB) and increase its permeability to cytokines and leucocytes transmigration. Inflammation processes may induce: • A release of cytokines leading to an activation of the coagulation and the formation of microthrombosis impairing tissue vascularization and neurotransmission.	22	Scoppettuolo P[107] *et al* Stefano G[109] *et al* Gasmi A[131] *et al* Ogier M[103] *et al* Baig A[93] *et al* Iadecola C[97] *et al* Yong S[117] *et al* Azizi S[127] *et al* Najjar S[102] *et al* de Erausquin G[96] *et al* Bouças A[94] *et al et al* Steardo L [108] *et al* Troyer E[110] *et al*

System	Involved symptom(s)	Mechanisms	N	Studies
		• Exacerbated microglia activation could also be a key-component for neuro-inflammation and could lead to cerebral homeostasis disruption. Activated microglial cells release pro-inflammatory cytokines, chemokines and generate oxidative stress (reactive oxygen species) that may lead to a long-lasting and self-perpetuating neuro-inflammation contributing to brain dysfunction (neurotransmission disorders, excitotoxicity and tissue damages) involving various pathways (p38MAP-kinase, ATP-P2X7 receptors) Systemic inflammatory reaction can lead to hypothalamic-pituitary-adrenocortical axis dysfunction that can participate in de dysregulation of systemic immune activity and subsequent neuro-inflammation. **2) Autoimmunity hypothesis** Inflammatory state during SARS-CoV-2 infection can favour an aberrant immune response against nervous system: autoimmunity phenomena through cell-mediated and humoral immune responses (role of molecular mimicry) **3) Metabolic brain disorder hypothesis (associated with neuro-inflammation)** • Mitochondrial dysfunction due to the integration of virus in mitochondrial genome that may lead to reduced energy metabolism and hypoxic conditions that favour neuro- inflammation. • Cytokine-induced activation of IDO-1 (indoleamine 2,3-dioxygenase) disrupting the kynurenine pathway involved in depression. Increased local levels of angiotensin 2 could also take part in this mechanism. **4) Residual viral (or virus antigen) infection hypothesis** Due to insufficient immune response, residual virus, and/or antigen load remains and contribute to a low grade smoldering inflammatory response. **5) Potential involvement of gut-brain axis** **6) Secondary brain damage** Indirect nervous system damage via the systemic complications of acute illness (haemodynamic and coagulation disorders, arrythmia, severe systemic inflammation, delirium)		Ribeiro D[105] *et al* Mukaetova-Ladinska E[101] *et al* Low RN[100] *et al* Ostergard L[104] *et al* Ren A[139] *et al* Song W[119] *et al* Andrade B[122] *et al* Korompoki *E*[124] *et al* Kumar S[118] *et al*

System	Involved symptom(s)	Mechanisms	N	Studies
Neurologic	Headache and pain	**1) Activation of nerves (peripheral trigeminal nerve, nerve roots) by several proposed mechanisms:** • Nerve viral invasion • Local increase of Angiotensin 2 and decrease of Angiotensin 1-7 (involved in nociception) • Vasculopathy (unbalanced vasoconstriction, oxidative stress) • Pro-inflammatory cytokines and hypoxia **2) Pain in the setting of neurological complications** (stroke, Guillain Barré syndrome, myelitis) **3) Inflammation** may induce or aggravate damage in various tissues such as joints and muscle, triggering pain-related symptoms **4) Glymphatic-lymphatic system congestion hypothesis.** Damages to olfactory sensory neurons, may lead to a reduced outflow of cerebrospinal fluid through the cribriform plate, causing a congestion of the glymphatic system with secondary cranial hypertension and subsequent toxic build-up within the central nervous system.	6	Su S[137] *et al* Bolay H[115] *et al* Attal N[126] *et al* Wostyn P[112] *et al* Low RN[100] *et al* Yong S[113] *et al*
Neurologic	Persistent fatigue	**Several potential mechanisms are proposed:** • Neuro-inflammation and subsequent neurotransmission disorders (neurotransmitters concentration, intrinsic excitability, inflammation, changes in axonal conduction due to demyelination) • Psychological factors (neurotransmitters levels can vary after COVID-19 and give rise to psychological disorder accounting for fatigue worsening) • Peripheral factors (musculoskeletal impairment) in chronic fatigue • Environmental factors (social isolation temperature, humidity) • Associated comorbidities • Glymphatic-lymphatic system congestion hypothesis: reduced outflow of cerebrospinal fluid following olfactory sensory neurons damages leading to a certain level of intracranial pressure and accumulation of toxins accumulation within the brain • Bioenergetic disorders (muscle) due to mitochondria dysfunction	6	Wostyn P[112] *et al* Islam M[98] *et al* Rudroff T[106] *et al* Low RN[100] *et al* Wood E[111] *et al* Korompoki *E et al*[124]

System	Involved symptom(s)	Mechanisms	N	Studies
Neurologic	Olfactory dysfunction	Olfactory dysfunction due to viral invasion and subsequent inflammation and cells injury: ACE2 present in epithelial cell of olfactory mucosa (sustentacular cells). Mechanism still unclear: no clear evidence of ACE2 on olfactory sensory neurons.	2	Gasmi A[131] et al Iadecola C[97] et al
Cardiorespiratory	Cardiorespiratory dysautonomic symptoms (palpitations, post-exertional malaise, exercise intolerance, breathlessness, chest pain)	**Dysautonomy hypothesis** Virus- or immune-mediated disruption of the autonomic nervous system (autoimmunity, microcirculation disorders): intrathoracic chemo and mechanoreceptors involved in the cardiovascular and respiratory reflexes or brainstem and cortical regions involved in the cardiorespiratory control, that may lead to various symptoms such as dizziness and other cardiovascular symptoms. • Consecutive ionic changes and neuro-hyperexcitability ensues • Increased smooth muscle cells tone (vasoconstriction) could lead to hypoperfusion of different organs	5	Dani M[95] *et al* Low RN[100] *et al* Yong S[113] *et al* Motiejunaite J[91] *et al* Korompoki *E*[124] *et al*
Cardiovascular	Thromboembolic complications (stroke, pulmonary embolism)	**Endothelial dysfunction (endotheliitis) and subsequent activation of coagulation are the mechanisms for cardiovascular complications.** These cardiovascular issues can lead to chronic symptoms, associated with organ damages. Thrombo-inflammation can affect large blood vessels. Microcirculation impairment can also lead to tissue ischaemia. • Endothelial invasion (ACE2 receptor) and consecutive dysfunction with coagulation activation and platelets/leucocytes attraction and activation • Coagulation activation through the systemic cytokines release • Direct viral-induced activations of platelets (ACE2 receptor) leading to inflammation and coagulation activation • Inflammatory reaction-platelets and leucocytes attraction and thrombogenicity • Neutrophil extracellular traps (NETs): inflammation-coagulation (factor XII) • Direct complement activation (inflammation) • Pericytes invasion and endothelial cells injury (loss of endothelial homeostasis and integrity) • Antiphospholipids antibodies (endothelial/coagulation activation)	6	Ostergaard L[104] *et al* Moschonas I[133] *et al* Roberts K[136] *et al* Evans P[130] *et al* Andrade B[122] *et al* Korompoki *E*[124] *et al*
Cardiovascular	Heart disorders (impaired contractility,	**Cardiomyocyte impairments and endothelial cells within the heart are the mechanisms proposed for cardiac complications.** These mechanisms can predispose for cardiac problems and/or symptoms after recovery and predispose them to late complications (arrythmia, cardiac insufficiency):	8	Ostergaard L[104] *et al* Evans PC[130] *et al* Mitrani R[132] *et al*

System	Involved symptom(s)	Mechanisms	N	Studies
	dyspnoea, arrythmia)	• Direct cardiomyocyte viral invasion (through ACE2 receptor) that may contribute as a trigger for heart tissue inflammation and account for contractility impairment: acute or subacute myocarditis • Coronary endothelial cells dysfunction hypothesis: inflammatory role of endothelium (viral invasion through ACE2 receptor) with subsequent leucocytes recruitment and coagulation activation (micro-thrombi) • Residual inflammation could lead to subsequent cardiac remodeling (fibrosis) • Interaction with adipose tissue of epicardium (positive for ACE2) could be a mechanism of long-term arrythmia and coronary disease (adipokines release)		Moschonas I[133] *et al* Roberts K[136] *et al* Evans P[130] *et al* Orinsky B[138] *et al* Korompoki *E*[124] *et al*
Respiratory system	Dyspnoea Cough Chest pain Exercise limitation	• Lung fibrotic remodeling after severe pneumonia can manifest in respiratory symptoms. Unlike functional respiratory disorders potentially associated with autonomic nervous system dysfunction, the mechanisms leading to fibrosis are associated with long-term lung injuries and occur mainly in severely-ill patients at the initial phase of infection: ○ Pulmonary alveolar inflammation after viral invasion ○ Degeneration of alveolar epithelial lining with emergence of hyaline membranes ○ Excessive cytokines production (host inflammatory response) and enhanced influx of inflammatory cells ○ Severe lung tissue scarring and fibrosis due to collagen deposition following aberrant fibroblast proliferation and differentiation (myofibroblasts; TGF-β1, transforming growth factor beta 1 pathway) ○ Decreased expression of ACE2 receptor and angiotensin 1,7 peptides ○ Exposure to high supplemental oxygen concentration may result in a greater oxidative and contribute to inflammation and fibrosis stress • Unresolved (micro-) vasculature damages that can account for persistent respiratory symptoms which may be a potential precursor to chronic thromboembolic disease and pulmonary hypertension. • Dysautonomy hypothesis (See above Cardiorespiratory system)	8	Murthy K[135] *et al* Ojo A[134] *et al* Dhawan R[128] *et al* Yong S[113] *et al* Oronsky B[138] *et al* Andrade B[122] *et al* Korompoki *E*[124] *et al* Tanni S[140] *et al*
Immune system	Wide range of symptoms	• **Chronic dysregulated immune system activation with subsequent cytokine release and chronic low grade inflammation leading to multiple organ dysfunction.** This hypothesis suggests that inflammation could be responsible for persistent symptoms (no specificity on the type of symptoms):	6	Galeotti C[116] *et al* Low RN[100] *et al* Afrin B[92] *et al* Kazama I[99] *et al*

System	Involved symptom(s)	Mechanisms	N	Studies
		○ Autoimmunity phenomena would result from inflammation and dysregulated immune responses. It could also result of a molecular mimicry with viral and self- antigens. ○ Genetic polymorphism in the cytokine genes' regulatory regions could explain a predisposition to present symptoms and account for inter-individual differences in the severity and occurrence of symptoms • **Mast cell activation syndrome hypothesis** suggested as aetiology of persistent symptoms (multisystem disorder with inflammatory and allergic issues). The mast cell would be activated via the cytokines release. This could lead to lung fibrosis via a stimulation of fibroblast activity. • **Persistent smoldering infection**: the natural down-regulation of the strong initial inflammatory response could allow the virus to persist and replicate in the body with ongoing inflammation and autoimmunity phenomena as a consequence		Yong S[113] *et al* Jacobs J [120] *et al*
Gastro-intestinal and hepato-biliary system	Gastro-intestinal symptoms: anorexia, dyspepsia, nausea/vomiting diarrhoea abdominal pain	Several potential mechanisms are suggested to persistent digestive symptoms. • **Post-infection gastro-intestinal dysfunction:** ○ Viral invasion-local inflammation followed by leucocytes infiltration in the digestive mucosa generating a local inflammation ○ Role of persistent gut microbiome for maintaining a status of chronic low grade intestinal inflammation (motility disorders, mucosal hyperpermeability, bile acid malabsorption) ○ Hypothesis of gut as undetected virus reservoir ○ Contributions of genetic predisposition and interaction between gut and environmental and psychological factors • **Autonomic nerve system disorder hypothesis:** virus- or immune-mediated disruption of the autonomic nervous system (vague nerve) leading to gut motility disorders	5	Schmulson M[114] *et al* Abdel-Moneim A[125] *et al* Yong S[113] *et al* Andrade B [122] *et al* Korompoki *E* [124] *et al*
Musculoskeletal system	Muscular weakness Bone and joint disorders (pain, mobility)	• **Muscle:** ○ Pro-inflammatory cytokines-induced disruption of myocytes ○ Cytokines-induced muscle fibroblast activation leading to fibrosis ○ Neuronal demyelination • **Bone:**	4	Disser N[129] *et al* Andrade B [122] *et al* Ahmed S [121] *et al* Korompoki *E* [124] *et al*

System	Involved symptom(s)	Mechanisms	N	Studies
		○ Microvascular blood flow impairment secondary to hypercoagulability, leukocyte aggregation, and vessel inflammation that contribute to the development of osteonecrosis • **Joints:** ○ Autoimmunity (virus persistence, dysregulated immune response, triggering of connective tissue diseases) and NETs activation		
Endocrine system	Thyroid disorders Diabetes	**Thyroid** • Direct damage on the thyroid gland • Low-T3 syndrome in hospitalised subjects (inflammation due to severe COVID-19) • Subacute thyroïdis **Diabetes** • Possible viral invasion of the pancreatic β cell that precipitates new-onset diabetes	3	Gentile S[143] *et al* Trimboli P[144] *et al* Korompoki *E*[124] *et al*
Renal system	Alteration of renal function	Several mechanisms potentially involved in renal dysfunction: • Consequence of the severity of acute infection: critical illness and mechanical ventilation and toxic effects (rhabdomyolysis, medications) • Viral invasion (podocytes and proximal tubular cells express ACE2) • Microangiopathy and intra-renal activation of the coagulation • Alterations of the renin-angiotensin-aldosterone pathway • Glomerulopathy as rare complication (as observed with other viral infections) • Possible genetic susceptibility	4	Andrade B [122] *et al* Almaguer-Lopez[141] *et al* Korompoki *E*[124] *et al* Le Stang MB[142] *et al*
Multisystem Inflammatory Syndrome in Children (MIS-C)	• Fever • Multiple organ dysfunction • Mucocutaneous disorders • Abdominal symptoms • Cardiovascular disorders • Neurological disorders	Several mechanisms proposed to explain MIS-C: • Genetical predisposition host factors • Uncontrolled T-cell immune response (triggered by SARS-CoV-2) • Complement activation • Molecular mimicry between antigens and host tissues (autoimmunity)	4	Buonsenso D[123] *et al* Korompoki E[124] *et al* Andrade B[122] *et al* Ahmed S[121] *et al*

Table 8 – Articles approaching the hypothetical pathophysiology of symptoms in patients

System	Involved symptom(s)	Mechanisms	N	Studies
Neurology	Smell disorders Cognitive disorders Pain Insomnia	**Functional brain disturbances** • In comparison with matched subjects, identification of hypometabolic activity in various cerebral zones by using [18F]FDG PET/CT: olfactory bulb, limbic/paralimbic structures, thalamus, orbito-frontal cortex, cerebellum, and brainstem. • Significant associations are observed between hypometabolism and long-term functional complaints: hyposmia/anosmia, memory/cognitive impairment, pain and insomnia. • Absence of significant brain hypermetabolism, suggesting the absence of brain inflammation (in both studies). • Reduced activity of the GABA inhibition by transmagnetic stimulation	4	Sollini M[158] *et al* Guedj E[160] *et al* Blazhenets G[164] *et al* Versace V[165] *et al*
Neurology	Headache Vision disorders Mood change Fatigue Myalgia Taste/smell disorders Numbness Tremor	**Neuro-inflammation and brain microstructural modifications** • In comparison to healthy subjects, micro-structural and volumetric and vascularisation disorders are evidenced through magnetic resonance imaging (MRI) patients who recovered from COVID-19. • Neurochemical signs of neurons injury and microglia activation: several proteins markers of neuronal dysfunction, higher levels of cytokines (IL-4, IL-6), higher levels of IgG • Indirect signs suggesting the role of neuro-inflammation on mood disorders symptoms: patients treated by interleukin inhibitors (IL-1β and IL-6) at the initial phase of COVID-19 had less signs of depression (but not PTSD) • In patients who died from COVID-19, an association was found between MRI abnormalities and brain vascular lesions (congestion, clotting, vessel wall abnormalities, signs of activated microglia) • In patients who died from COVID-19, identification of neuroinvasion (cortical neurons and endothelial cells) and neuronal damages with ischaemic zones.	8	Lu H[157]*et al* Benedetti F[159] *et al* Lee MW[148] *et al* Song E[152] *et al* Ameres M[155] *et al* Kanberg N[156] *et al* Sun B[166] *et al* Qin Y[163] *et al*
Neurology	Persistent olfactory dysfunction	**Structural lesions in the olfactory and taste system at imaging and histology** • Olfactory nerve morphological abnormalities at imaging (tomodensitometry, magnetic resonance imaging) suggesting direct/indirect injury to olfactory neuronal pathways • Brush cytological sampling: neuroepithelium remains inflamed (high levels of cytokines including IL-6, myeloids cells) with persistent SARS-CoV-2 RNA. • In biopsy of taste buds in the tongue: invasion and replication of SARS-CoV-2 in taste buds type II cells.	3	Kandemirli S[161] *et al* De Melo G[162] *et al* Doyle M[167] *et al*

System	Involved symptom(s)	Mechanisms	N	Studies

Cardiovascular system	Fatigue
	Dyspnoea
	Chest pain
	Headache
	Joint pain
	Ocular disorders
		Persistent vascular inflammation
		• Signs of macrovascular vascular inflammation (vasculitis):
		  ○ Using [18F]FDG PET/CT, in comparison with age/sex-matched controls, evidence of increased [18F]FDG uptake in several vascular regions (thoracic aorta, right iliac artery, and femoral arteries).
		• Signs of microvascular inflammation (endothelial dysfunction) in comparison with control subjects, using blood sample analysis:
		  ○ Identification of microvascular retinal impairment assessed by optical coherence tomography (compared to control group).
		  ○ Persistent cytokine-driven endothelial cells dysfunction (compared to control group):
		  ▪ Increased number of circulating endothelial cells
		  ▪ Pro-coagulant and pro-inflammatory phenotype in patients with cardiovascular risks
		  ▪ Increased level of cytokines
		  ▪ Signs that endothelial cells could be targeted by cytotoxic leucocytes)
		  ○ At autopsy, evidence of endothelial cells and cardiomyocytes viral invasion with signs of structural alterations
		Auto-antibodies able to modulate the cardiac frequency and vascular tone
		• G protein-coupled receptor antibodies acting as receptor agonists on the β2-adrenoceptor, the α1- adrenoceptor, angiotensin II AT1-receptor, angiotensin 1,7 and endothelin receptors.
		Persistent alteration of coagulation (sustained increased of D-dimer levels)
			9	Sollini M[174] *et al*
				Savastano A[173] *et al*
				Chioh F[172] *et al*
				Varga Z[153] *et al*
				Bulfamante G[154] *et al*
				Lindner D[149] *et al*
				Roshdy A[150] *et al*
				Wallukat G *et al*[175]
				Towsend L[176] *et al*

Respiratory	Dyspnoea Chest pain Cough Fatigue Breathlessness	**Persistent inflammation and dysregulated host response of lung repair** • Increased plasma biomarkers of lung inflammation and fibrosis (Lipocalin 2, Matrix metalloproteinase-7, Hepatocyte growth factor). Biomarkers were significantly higher in patients who needed intensive care. • Compared with healthy subjects, [18F] FDG PET/CT abnormalities suggesting persisting inflammation in lungs, mediastinal lymph nodes, spleen, and liver. • Correlation of iron metabolism disorders with persisting respiratory symptoms suggesting an involvement of iron homeostasis disturbances in end-organ damage:	8	Chun H[169] *et al* Sonnweber T[170] *et al* Bai Y[168] *et al* De Michele S[147] *et al* Schaller T[151] *et al* Ackermann M[145] *et al* Carsana L[146] *et al* Xu J[171] *et al*

System	Involved symptom(s)	Mechanisms	N	Studies
		○ Persisting hyperferritinemia was significantly associated with severe lung pathologies in computed tomography scans and a decreased performance status (6 minutes walking test) • Relationship between metabolic abnormalities and lung sequelae (DLCO) • At autopsy, signs of fibrosis, endothelial injury, microangiopathy, coagulation activation (microthrombi) and angiogenesis		
Gastro-intestinal system		**Gut microbiota modifications after recovery** • Decreases gut commensals with known immunomodulatory potential • Perturbed composition of microbiota correlated with plasma inflammatory cytokines and chemokines concentrations and blood markers (C- reactive protein, lactate dehydrogenase, aspartate aminotransferase, gamma-glutamyl transferase)	1	Yeoh Y[177]et al
Immune system	Multi-system symptoms	**Persistent immune inflammatory response impairing organ functioning** • In comparison with healthy subjects, signs of remaining inflammation in blood samples analysis (increased levels of proteins involved in mitochondrial function, leucocytes function, urea cycle, protease inhibitors). • In comparison with healthy subjects, identification of long-lasting phenotypic and functional disorders of lymphocytes: persistence of a cytotoxic program in $CD8^+$ T cells and elevated production of cytokines that could impact tissue integrity and cytokines responsiveness. Decreased amount of dendritic cells and persisting alterations of markers of activation. • Magnetic resonance imaging suggests signs of mild organ impairment (even in low risk patients): heart, lungs, kidneys, liver, pancreas, spleen. Correlation between the extent of extra-pulmonary MRI abnormalities and exercise intolerance (cardiopulmonary exercise test, six-minute walk test) and markers of inflammation • Abnormalities at [18F] FDG PET/CT suggesting persisting inflammation in several organs (lungs, mediastinal lymph nodes, spleen, liver, adrenal glands) • No association between vitamine D levels with persistent symptoms nor CT-abnormalities, or impaired pulmonary function testing. **Autoimmunity** • Auto-antibodies against the nociception-like opioid receptor • Auto-antibodies against immunomodulatory proteins (including cytokines, chemokines, complement components and cell-surface proteins) and against tissues (vascular cells, coagulation factors and platelets, connective tissue,	12	Doykov I[182] *et al* Dennis A[181] *et al* Shuwa H[183] *et al* Bai Y[168] *et al* Sollini M[158] *et al* Pizzini A[184] *et al* Raman B[185] *et al* Wallukat G[175] *et al* Wang E[187] *et al* Gaebler[188] *et al* Richter A[186] *et al* Perez-Gomez A[189] *et al*

System	Involved symptom(s)	Mechanisms	N	Studies
		extracellular matrix components and various organ systems, including lung, the central nervous system compartment, skin, gastrointestinal tract) **Persistence of the SARS-CoV-2 in tissues** • Persistence of SARS-CoV-2 nucleic acids and immunoreactivity in the small bowel several months after initial infection		
Dermatological system	Various skin disorders	**Potential immune or inflammatory mechanisms in skin lesions.** On skin biopsy, description of: • Lymphocytic or neutrophilic infiltrates • Endotheliitis • Microangiopathy • Microthrombosis • Leucocytoclatsic vasculitis	3	Genovese G[178] *et al* Sharma S[179] *et al* McMahon D[180] *et al*
Multisystem Inflammatory Syndrome in Children (MIS-C)		Comparisons of inflammatory characteristics in children with Kawasaki disease, children infected with COVID-19 and children presenting with MIS-C: • More pronounced lymphopenia was more pronounced in MIS-C than in children with mild SARS-CoV-2 infection, Kawasaki disease • Higher CRP and ferritin levels and lower platelet counts in MIS-C compared to Kawasaki disease and children with COVID-19 • Difference in cytokines profiles (Interleukins 7 and 8) • Specific differences between immune cell responses in MIS-C and patients with Kawasaki disease • IL-17 significantly lower in MIS-C than in Kawasaki patients • Identification of plasma proteins distinguishing MIS-C from Kawasaki • Presence of auto-antibodies could be involved in the pathogenesis of MIS-C	1	Consiglio C et al[190]

Central nervous system

The long-term symptoms related to central and peripheral nervous systems can arise from early neurological complications such as stroke, encephalitis, Guillain Barré syndrome or from factors related to the hospitalisation (delirium in ICU, immobilization, exposure to sedative agents, sepsis, sequelae of the initial disease severity).[124, 139]

The other long-term neurological symptoms include neurocognitive problems, mental health diseases, smell and taste disorders and dysautonomia. Those symptoms entails several overlapping mechanisms.

Reported hypothetical mechanisms:

- Twenty-two publications elaborated on the putative mechanisms that could contribute to neurocognitive disorders (difficulty of concentration, memory and executive functions disorders, 'brain fog') and psychiatric impairment (mood disorders, post-traumatic stress syndrome, anxiety, insomnia).[93, 94, 96, 97, 100-105, 107-110, 117-119, 122, 124, 127, 131, 139] Mechanisms are numerous and mainly encompass neuroinflammatory disorders (See Table 7).

  According to this hypothesis, brain dysfunction is secondary to inflammatory phenomena following viral invasion of the brain, or to proinflammatory cytokines that reach the central nervous system. Microglia, which is a network of cells scavenging neurons and involved in homeostasis and brain immune defense, can 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.[191]

  As a consequence of inflammation, hypercoagulation could lead to the formation of microthrombosis impairing correct vascularization, neurotransmission and potentially inducing neuron injury (through ischaemia or excitotoxicity). On the other hand, a bioenergetics failure due to mitochondrial dysfunction has also been proposed as a consequence of inflammatory reaction or viral invasion.

  In that way, 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. Besides, brain damages can also be secondary to the severity and complications of the acute infection.[107]

- Six articles proposed that autoimmune manifestations against the central nervous system could be triggered, via a molecular mimicry with viral proteins or via a dysregulation of inflammatory processes as a consequence of the acute phase of the infection. This relationship between COVID-19 and autoimmunity has been suggested because autoimmune complications have been reported in the early course of infection.[107, 110, 116, 122, 124, 127]

- Three articles speculated that the gut-brain axis could be modified and involved in central nervous system dysfunction[100, 110, 122] and 3 other articles elaborated on the indirect nervous system damage via the complications of acute illness.[101, 122, 139]

- Regarding the persistent smell and taste disorders, 2 studies reported on the role of neuroepithelial viral invasion and subsequent inflammation as mechanisms contributing to olfactory dysfunction.[97, 131]

- Six articles suggested mechanisms contributing to pain and headache[100, 112, 115, 117, 126, 137] and six articles proposed mechanisms involved in chronic fatigue.[98, 100, 106, 111, 112, 122] 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 pluridimensional factors (psychological, environmental, comorbidities) could also be involved. Interestingly, one article proposed for both symptoms, a dysfunctional brain glymphatic drainage leading to cerebrospinal fluid congestion (intracranial hypertension) and toxins accumulation within the brain.[112]

Findings reported in clinical studies:

Clinically, studies gave contrasting results:

- Three studies evaluated brain metabolism using the uptake of [18F]FDG PET/CT in symptomatic patients 3 to 4 months after infection.[158, 160, 164] In comparison with matched subjects, hypometabolic activity was underscored in various cerebral areas involved in the symptoms (cognitive symptoms, headache, pain, sleep and smell disorders). Interestingly, zones with hypermetabolism were not identified in both studies. Such hypermetabolic zones would have suggested brain inflammation.
- Conversely, by using magnetic resonance imaging (MRI), 3 months after infection, one study evidenced brain micro-structural, volumetric disorders in symptomatic patients, supporting a possible neuro-inflammation.[157] Another one provided evidence of brain structural changes in grey and white matters along with their vascularisation, in patients who recovered from severe or mild COVID-19.[163] In this line, two autopsy studies reported signs of microvascular impairment and inflammation.[148, 152]
- Three studies reported increased plasmatic biomarkers of neuronal injury and microglia activation or higher levels of inflammatory cytokines and antibodies, early after onset of infection.[155, 156, 166] Finally, one study indirectly suggested elements in favour of neuro-inflammation by showing that patients treated with anti-cytokines drugs displayed less depressive symptoms in the long run.[159]
- By using neurophysiology testing, one study identified an impairment of GABA-ergic intracortical circuits in patients with fatigue and dysexecutive disorders after COVID-19.[165]
- Two studies depicted abnormalities in the neuroepithelium (persistent inflammation and presence of viral RNA) and olfactory nerve in patients presenting long-term smell disorders.[161, 162] One study showed a viral invasion and replication within the cells of taste buds of the tongue.[167]

Cardiovascular and coagulation

Cardiovascular complications may arise during the acute infection and result from coagulation disorders, Those complications include myocardial injury. Type 1 myocardial infarction can occur through a destabilisation and rupture of atherosclerotic plaque, while type 2 myocardial infarction may be consecutive to limited coronary perfusion, endothelial dysfunction or as a consequence of severe hypoxia.[122]

Stroke or pulmonary embolism are other complications that may give rise to long-lasting sequelae.[127, 133, 136]

Reported hypothetical mechanisms:

Five articles hypothesised on the mechanisms contributing to thromboembolic complications[104, 122, 130, 133, 136] while 6 articles elaborated on hypothesis involved in heart complications.[104, 122, 130, 132, 133, 136] Mechanisms involved in heart and vessels disorders are overlapping.[122]

- Endothelial dysfunction with subsequent activation of coagulation (thromboinflammation) and cardiomyocytes invasion are the key mechanisms for vessels and heart complications along with platelets and leucocytes disorders or angiotensin 2 dysregulation. Acute and subacute myocarditis have been reported.[124, 130]

  The heart could subsequently undergo structural alterations (remodeling) due to fibrosis pathway activation. Such evolution can be responsible for of heart failure or arrythmia.[124]

  The development of anti-phospholipids antibodies could be another factor contributing to the hypercoagulation and thrombotic complications. Such antibodies have been identified in COVID-19 patients and associated with increased NETosis.[130, 133]
- Five articles suggested that cardiovascular symptoms could result from another mechanisms unrelated to organ injury.[91, 95, 100, 117, 124] They hypothesised on the possibility of an autonomic nervous system disruption. This would result from virus- or immune-mediated damages of the intrathoracic chemo and mecano-receptors or in the zones of the brainstem controlling ventilation (via microcirculation damages in the

receptors or autoimmunity disorders). Cardiovascular and respiratory reflexes disruption could account for numerous cardio-respiratory symptoms (exercise intolerance, post-extertional malaise, palpitation, orthostatic syndrome, inappropriate respiration during exercise, breathlessness). As a consequence of dysregulated respiration (at rest or during exercise), decrease of blood carbon dioxyde could lead to several disabling symptoms (syncope, palpitations, chest pain, muscular hyperexcitability, breathlessness).

Findings reported in clinical studies:

- Three studies assessed the cardiovascular impairment: one in macro vessels and two in microcirculation.[172-174] A study suggested signs of vascular inflammation in large vessels by using [18F]FDG PET/CT in patients who were hospitalised and who complained about persisting symptoms, 30 days after recovery.[174]
- Manifestations of microcirculation abnormalities were suggested in two studies. One article observed microvascular retinal impairments, 2 months after recovery from COVID-19.[173] Another study detected interesting biological hallmarks of endothelial dysfunction (cytokines, cell phenotypes and circulating endothelial cells).[172]
- A persistent alteration of the coagulation was evidenced in convalescent patients, regardless of the severity of the initial COVID-19.[176]
- In patients complaining of dysautonomic symptoms (postural orthostatic tachycardia syndrome), antibodies against catecholamines receptors and able to modulate heart frequency were identified. Other auto-antibodies against Angiotensin 2 receptor and endothelin were also found.[175]
- Finally, four autopsy studies showed evidence of viral invasion of endothelial cells and cardiomyocytes with signs of inflammation and dysfunction.[149, 150, 153, 154]

Respiratory system

Reported hypothetical mechanisms:

Distinct potential mechanisms can account for respiratory symptoms:

- Functional respiratory symptoms without evidence of lung injury and related to dysautonomic disorders have been discussed in the paragraph on cardiovascular alterations.[91, 95, 100, 117]
- Because fibroproliferative diffuse alveolar damage has been shown at the autopsy of patients who died from COVID-19 [146, 147, 151] and because ground glass opacities have been evidenced in survivors on imaging [19, 192-194] lung fibrosis is a potential long-term complication. Eight articles evoked the mechanisms leading to lung fibrosis which generally occur after severe respiratory inflammation and injury.[113, 122, 124, 128, 134, 135, 138, 140] One of them emphasised that prolonged exposure to supplemental oxygen in most severe cases, can lead to an increased oxydative stress in the lungs and contribute to maintain the inflammatory status and favour the activation of fibrotic pathways.[140] One article emphasised the potential role of lung vascular damages (including in microvessels) that may result in pulmonary hypertension and participate on long-term respiratory symptoms.[128]

Findings reported in clinical studies:

Clinically, three studies focused on the mechanisms of persisting lung inflammation and included exclusively patients who were hospitalised at the early phase.[168-170]

- One study found elevated biomarkers of inflammation and fibrosis in a group of patients with chronic respiratory complaints, regardless of hospital admission.[169] Another evidenced signs of persisting lung inflammation using [18F]FDG PET/CT in patients who needed mechanical ventilation.[168]
- One study suggested a relationship between respiratory impairments and iron metabolism.[170]

- In patients with lung sequelae, a study showed metabolic abnormalities (involved with lung repair/fibrosis) correlating with lung diffusion capacity (DLCO).[171]
- Four autopsy studies demonstrated fibrosis, endothelial injury, microangiopathy, coagulation activation (microthrombi) and angiogenesis.[145-147, 151]

Immune system

Reported hypothetical mechanisms:

As already described in the previous paragraphs, inflammatory and dysregulated immune response are the foremost hypothesis involved in the onset of long COVID symptoms. Five articles evoked the potential underlying immune system disorders through which chronic symptoms could come about.[92, 99, 100, 113, 116] Such a hypothesis encompasses the potential emergence of immune disorders and could also account for inter-individual susceptibility to develop long COVID. Among those articles, two articles considered that mast cell activation syndrome could contribute to long COVID symptomatology. This syndrome bears similarities with long COVID.[92, 99] One article suggested that SARS-CoV-2 is not completely suppressed after acute illness and could persist and replicate. This occult presence would drive a smoldering inflammation and trigger autoimmunity processes. In this view, the virus would not have been completely suppressed because of the natural down-regulation of the initial inflammatory response.[120]

Findings reported in clinical studies:

Clinically, several articles, identified signs that support the involvement of immune abnormalities in patients:

- A study revealed long-lasting T-cells functional and phenotypic abnormalities that could contribute to cytokines dysregulation. In this line, another study showed signals of remaining inflammation even in patients who presented an asymptomatic form of COVID-19.[183] Another study identified a decrease of the amount of dendritic cells combined with alterations of markers of activation 7 months after infection.[189]
- Two studies using [18F]FDG PET/CT found signs of hypermetabolism in various organs [158, 168] while two studies showed signs or mild multi-organ impairment, using MRI.[181, 185] Among those, one study demonstrated a correlation between the extent of extra-pulmonary MRI abnormalities and exercise intolerance along with biomarkers of inflammation.[185]
- Since vitamin D has been suggested to play a role in COVID-19 susceptibility and evolution, a preliminary publication from an ongoing trial assessed the impact of vitamin D on long term respiratory symptoms but did not find out any relationship with persistent symptoms or pulmonary disorders.[184]
- Auto-antibodies against several organs and also againts the nociception receptors were described in two studies that included convalescent patients who were hospitalised or not. The prevalence of auto-antibodies was higher in patients who were more severely ill and needed to be hospitalised.[175, 186] Similarly, auto-antibodies against immunomodulatory proteins (including cytokines, chemokines, complement components and cell-surface proteins) and against several tissues were found at the acute phase of infection, in hospitalised patients. Although the timing does not correspond to long COVID timeframe, this finding provides information on the fact that autoimmunity could be play a role in the symptomatology because those autoantibodies could alter immune function.[187]
- A study rose the question of the persistence of SARS-CoV-2 in tissues. Biopsies from lower gastrointestinal tract showed the persistence of SARS-CoV-2 nucleic acids and immunoreactivity in the small bowel in asympomatic subjects several months after COVID-19.This study suggests that residual proteins of the virus in tissue could favour a persisting immune reaction giving rise to long COVID symptoms.[188]

Gastro-intestinal system

Reported hypothetical mechanisms:

Proposed hypothesis include the persistence of low-grade gastro-intestinal tract inflammation.[113, 114, 125] or autonomous nerve system dysfunction.[113] In one article, it is suggested that hepato-biliary damages in the acute infection could take part in chronic symptoms.[125]

Findings reported in clinical studies:

One study evidenced persistent alterations of microbiota after recovery, characterised by a underrepresentation of commensals known for immunomodulatory potential. A correlation between those disorders and inflammatory markers was shown.[177]

Musculoskeletal system

Four articles proposed that bone, joints and muscle pain could be attributed to thromboinflammatory-related tissue injuries and autoimmune processes.[121, 122, 124, 129]

Dermatological system

Many skin disorders have been reported. Underlying pathophysiology is still not well explored and various abnormalities have been described on skin biopsies. They include leucocytes infiltration, microthombi and vasculitis.[178] Temporary hair loss could be ascribed to telogen effluvium phenomenon, triggered by the initial infection.[86]

Skin lesions highly vary. Their duration were investigated through an international register that included 234 patients and reported that pernio lesions and livedo reticularis lasted longer than the other lesions (morbilliform, urticarial, papulosquamous lesions).[179, 180]

Renal system

Four articles reported on the kidney damages.[122, 124, 141, 142] Acute kidney injury has been described in critically-ill patients who required renal replacement therapy. [86] However, alterations of the renal function have also been described in patients who did not have renal dysfunction during acute infection.[72, 86] The underlying pathophysiology is still not well described. Several mechanisms have been suggested as causes to the progression to chronic kidney disease. SARS-CoV-2 is able to invade several kidney cell types such as podocytes or cells from the proximal tubule due to the expression of ACE2 on their surface.[141] It has been identified from kidney biopsy or autopsy. [86] Besides, endothelial dysfunction and microangiopathy have been proposed along with alterations of the renin-angiotensin-aldosterone system.[122, 141] One article described the possibility of a glomerulopathy as observed for others viral infections.[142]

Endocrine system

Three articles reported on endocrine disorders.[124, 143, 144] 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 diabetes.[143] Since ACE2 is expressed on the pancreatic β cell, SARS-CoV-2 could damage the cell and precipitate diabetes. [143]

Thyroid can be affected by COVID-19 through different potential mechanisms. Direct damage to the thyroid could occur through direct invasion (ACE2 is expressed by the gland) or indirectly by the release of cytokines at the early phase of illness that could induce inflammation within the thyroid gland. [144] On the other hand, other conditions have been described such as low T3 syndrome in severely-ill hospitalised patients, or late-onset autoimmune subacute thyroïdis.[144]

Multisystem inflammatory syndrome in children

Five articles reported on the Multi inflammatory syndrome in children (MIS-C).[121-123] It represents a rare complication that shares many similarities with Kawasaki disease and toxic shock syndrome (See Box 2). Its pathophysiology is currently incompletely known and might result from autoimmune processes in response to a dysregulated inflammation induced by the acute infection. A study compared inflammatory markers of MIS-C patients with patients with Kawasaki disease or acute COVID-19.[121-123] Specific features of MIS-C were identified (more severe lymphopenia, low platelets, different immune cells response and higher levels of inflammatory markers).[190]

Box 2 – Multisystem inflammatory syndrome in children (MIS-C):

- Early in the pandemic, several cases of hyperinflammatory syndrome with multi-organ dysfunction were reported in children. This rare condition was called 'Pediatric Inflammatory Multisystem Syndrome temporally related with COVID-19' (PIMS-TS) or 'Multisystem inflammatory syndrome in children' (MIS-C).
- Common symptoms are fever, mucocutaneous rash, conjunctivitis, adenopathy, digestive symptoms and cardiovascular signs such as shock or coronary arteries aneurysms. Neurological manifestations are also reported. Children older than 5 years and adolescents are predominantly involved.
- This syndrome shares similarities with Kawasaki disease, and toxic shock syndrome:
  - Toxic shock syndrome develops in a setting of an acute infection with Staphylococcus aureus or Steptococcus pyogenes and associates shock and multi-organ failure. An uncontrolled cytokines release occur in response to microbial proteins that acts as superantigens. A genetic predisposition may be involved in the pathophysiology.
  - Kawasaki disease is a rare vasculitis of medium-sized arteries that can cause coronary arteries aneurysms. It mainly affects children younger than 5 years old. Pathophysiology involves autoimmunity phenomena possibly triggered by viral infections. In the most severe cases, activated neutrophils induce a destruction of wall vessels with subsequent development of aneurysms.

Table 9 – Summary on evidence in studies involving COVID-19 patients

- Central nervous system:
  - Brain hypometabolic activity at [18F]FDG PET/CT in symptomatic patients, several months after infection
  - Signs of brain microstructural disorders at MRI, 3 months after COVID-19 (and increased biomarkers of neuroglia activation or neuron injury, early after the acute infection)
  - Alterations of the GABAergic intracortical circuits
  - Signs of viral invasion and inflammation of neuroepithelial cells of the olfactoty mucosa and taste bud cells of the tongue, in patients with anosmia or agueusia
- Cardiovascular and coagulation:
  - Vascular inflammation at [18F]FDG PET/CT, in symptomatic patients
  - Microvascular retinal impairments, several months after recovery from COVID-19.
  - Biomarkers of endothelial dysfunction (cytokines, cell phenotypes and circulating endothelial cells), after acute infection

- Autoimmunity: antibodies against catecholamines, angiotensine or endothelin receptors

- Immune system:
  - Signs of multi-organ inflammation at [18F]FDG PET/CT in symptomatic patients
  - Persisting T-cells functional /phenotypic abnormalities. Persisting deficit and alterations of markers of activation of dendritic cells.
  - Autoimmunity: antibodies against immunomodulatory proteins, tissues and nociceptive receptors
  - Persistence of SARS-CoV-2 fragments within tissues (small bowel)
- Gastro-intestinal system: alterations of microbiota one month after recovery
- Respiratory system:
  - Biomarkers of inflammation and fibrosis in a group of patients with chronic respiratory complaints, several weeks after infection
  - Persisting pulmonary inflammation at [18F]FDG PET/CT
  - Metabolic disorders (metabolomic assessment)
- Dermatological system: signs of vasculitis, leucocytes infiltration and coagulation activation at biopsy.

7 DISCUSSION

7.1 Main Findings

Up to now, there is no explicit evidence about what causes long COVID. Many hypothesis have been proposed. Knowledge on the mechanisms by which long-lasting symptoms come about remains limited. Whilst some mechanisms from the acute phase such as coagulopathy or hyperinflammation are now better described, we do not yet have enough insight into their contribution to long-term complaints. Studies involving patients have provided arguments that put forward the possibility of organ dysfunctions through inflammatory and autoimmune mechanisms. Importantly, two studies provided arguments consistent with the hypothesis of persistent and occult virus presence by identifying viral particles in biopsies, several months beyond the acute infection.[162, 188]

7.2 Limitations of available evidence

The literature aiming at describing the specific pathophysiology involved in long COVID is still nascent. Articles reporting patient data are highly heterogeneous and have many limitations.

- First, the characteristics of the patients included in studies considerably vary. Long COVID symptoms refer to a unspecific group of issues and symptoms that can have different combinations. Although current literature aims at better describing subtypes of long COVID, the patients included in the retrieved studies presented a wide variety of symptoms. Research on the underlying mechanisms are frequently conducted regardless of the type of symptoms.

  In addition, the initial severity and level of care of targeted patients varies considerably. Conversely, some studies included asymptomatic patients.

  Included studies do not always represent the group of long COVID patients because many of them have included patients who were hospitalised during the acute infection. (see Supplement to Chapter 3).

- Second, the study designs are heterogeneous. Sample sizes of studies is very frequently limited and the time-points of inclusions particularly differ across studies. There is no study describing the natural evolution on the underlying studied mechanism. Due to the exploratory design of studies on pathophysiology, the selection of patients is not necessarily mentioned. This represents a significant bias.
- Third, many studies use healthy volunteers as control group rather than patients who had COVID-19 but did not develop long COVID.
- It is important to emphasise that some results may be difficult to interpret. For instance, the studies in which MRI suggests signs of organ impairment, associate those abnormalities with symptoms or biomarkers, but do not much enlighten the underlying mechanisms. Furthermore, the relationship between detected abnormalities and symptoms or clinical conditions is not frequently examined.
- It should be noted that symptoms such as fatigue are difficult to appraise since the causes are complex and multifactorial. Several mechanisms may also be in play simultaneously. In this setting, long COVID could share some similar elements of post- infectious fatigue (observed after viruses such as Influenza or other coronaviruses) or with Chronic Fatigue Syndrome.

7.3 Perspectives

There is an urgent need to unravel the mechanisms leading to long COVID in order to better define the trials assessing therapeutic interventions.

- Further research should perform a better categorisation of clusters of symptoms that would allow to assess the pathophysiology associated with long COVID subtypes. In this line, the exploration of pathophysiology should be performed at different time-points in order to better identify the timeline of mechanisms and the natural history of long COVID.
- The consequences from acute infection on organs should be distinguished from late-onset mechanisms.
- In addition, well-designed studies should also include COVID-19 patients who were not hospitalised at the acute phase of illness and consider subjects who had COVID-19 without having developed long COVID as control groups.

Limitations for the assessment of underlying mechanism in experimental studies on the pathophysiology of long COVID

- Patients characteristics: variability of symptoms, severity of symptoms, severity of the initial illness and level of care
- Heterogeneous study designs: limited sample sizes, different timing of patients inclusion; no longitudinal investigation of the underlying mechanisms, high risk of selection bias
- Use of healthy volunteers as control group rather than COVID-19 patients who did not develop long COVID
- Difficulty of results interpretation (indirect or no clear relationship between detected abnormalities and clinical conditions)
- Difficulty to apparaise the underlying mechanims of symptoms such as fatigue (probable intertwined, simultaneous and multifactorial mechanisms) and possible overlap with other issues

CHAPTER 4. PATIENT SURVEY: ONLINE QUESTIONNAIRE TO IDENTIFY THE UNMET NEEDS OF LONG COVID PATIENTS

1 KEY POINTS

KCE analysed 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). Most of the respondents tested positive for COVID-19 (86%) or were clinically 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 COVID-19 (87%) and people with a high education level (56%). The majority of respondents had symptoms for > 3months: 37% (3-6 months); 45% (> 6 months).

Based on the results of this chapter, we make several observations, such as:

- **Long COVID patients report a wide range of symptoms (nearly half of respondents reported ≥ 11 symptoms). The five most common symptoms reported 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, symptoms were more commonly reported among patients who were hospitalised during acute COVID-19 (average number of symptoms 12.9 for hospitalised 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).**
- **Acute COVID-19 had a negative impact on subjective health. A significant decrease in EQ-5D-5L score (mean beta: -0.20; 95%CI: -0.22;-0.18; p<0.001) was observed after acute COVID-19. Long COVID increased the proportion of health problems in all EQ-5D-5L dimensions with, in general, a shift from no health problems towards slight and moderate health problems. Hospitalised patients reported health problems more frequently compared to non-hospitalised patients 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. These findings were confirmed by subjective health scored via a Visual Analogue Scale.**
- **Sixty percent of the respondents who had a paid employment before COVID-19 reported an incapacity to work. Among them more than one third (38% due to health status) 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%) compared to the mid- (34%) and long duration group (37%). No significant differences between hospitalised and non-hospitalised patients were observed.**
- **The most consulted healthcare professionals are GPs (91%) followed by medical specialists (51% of wich pulmonologist or cardiologist) and physiotherapists (30%). Respondents who were hospitalised reported to have 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 respondents were satisfied or very satisfied with their contacts with the healthcare system (ranging from 75% for GP's to 85% for psychologists). Only for emergency departments this percentage was lower (66%). Also, the satisfaction seems to be lower in the group with symptoms > 6months after onset COVID-19 (e.g. satisfaction with GP: 67.6% versus 78.6% in the mid- and 86.7% in the short duration groups).
- About one in three respondents reported having experienced unmet needs. Among them, the most frequently reported were information needs (52%), need for competent staff (24%), and accessibility to care (23%).
- Less than half of the patients (41%) reported to receive a 'treatment' of which most (71%) report to have received prescribed drugs. Patients that were hospitalised received more frequently a treatment (64% versus 38% in non-hospitalised patients). Noteworthy is that 55% of those with a treatment have received a treatment entailing 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 these results should be interpreted with caution because it is sometimes difficult for patients to distinguish between disease symptoms and treatment side effects.
- Respondents 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%). Moreover, 39% of the respondents would like to be more involved in the choices about their treatment(s) for long COVID.
- More than one in three respondents (37%) reported experiencing a financial impact of long COVID due to loss of income, medical expenses or a combination of both.
- More than one in two (52%) respondents reported to need support with daily life activities due to long COVID, mainly for cleaning (86%), preparation of meals (70%) and transportation/journeys (51%). Informal caregivers play an important role when additional support is given. Categories for which almost exclusively support is given by informal caregivers are meals and transportation. When professional support is provided this is mostly for hygiene (22%), dressing (19%) and housekeeping (11%).

2 AIM

This chapter is based on an online questionnaire including patients with self-reported long COVID. All statements and quotes used to illustrate answers are the points of view and opinions of the respondents.

This chapter encompasses two main objectives:

- **Identify unmet needs of patients with long COVID**. This chapter describes the methods and results of an online survey, performed to examine the characteristics and (unmet) needs of people who developed long-term health problems after COVID-19 to improve their care and the information they receive.
- **Pilot a generic methodology to identify unmet needs developed in a parallel KCE study among long COVID patients**. The starting point for the online questionnaire in the current study is a generic instrument to measure unmet patient needs. This instrument is the result of an ongoing research in the context of KCE study (2017-14-HSR-unmet needs[e]). Therefore, the secondary aim of this chapter was to evaluate if the survey (including the type of questions), in combination with interviews and/or a forum, is appropriate to identify patient (unmet) needs.

[e] https://kce.fgov.be/en/study-program/study-2017-14-hsr-method-for-the-identification-of-the-real-needs-of-patients (last access: 25 August 2021)

3 METHODS

3.1 Data collection tool

3.1.1 Development of the online questionnaire

Generic questionnaire unmet needs

The questionnaire used in the current study is based on the generic questionnaire developed in the context of KCE project 2017-14-HSR-unmet needs[e]. The full methodological details of the development of this generic questionnaire will be published in this report (publication expected early 2022). In summary, the questionnaire was developed starting from a literature review that identified the most common methods to measure unmet medical needs. All these methods were listed and broad dimensions were identified. For each dimension, the KCE research team listed the appropriate questions from the initial methods. In some cases, questions were reformulated to meet the generic nature of the questionnaire. The draft questions were submitted to a Delphi panel consisting of patient representatives (from umbrella organisations of patient associations and sickness funds) to find a consensus on the relevance and clarity of each question and the completeness of the questionnaire.

Adaptations made for long COVID

For the purpose of the current study, the generic questionnaire was adapted to the long COVID condition, by reformulating some questions (e.g. using “long COVID” instead of the generic term “your disease”) and by adding questions that are specific for long COVID (See Supplement to Chapter 4). The adaptations were based on a quick scan of the literature[5, 60, 87, 195-197] and a pragmatic review about the epidemiology of long COVID (definition, prevalence, range and frequency of symptoms and risk factors).[9]

Translation and face-validity

The questionnaire was first developed in French and afterwards translated to Dutch by KCE researchers. A comparison of the two versions was carried out to ensure that both versions were identical in terms of structure and content. Subsequently, both versions were proofread by team members, two representatives of patient umbrella organisations (one French-speaking (i.e. LUSS) and one Dutch-speaking (i.e. VPP)) and one researcher of Sciensano.

Online version: Patient Survey

Once the versions were proofread by the KCE research team, they were imported into an online platform (LimeSurvey hosted on the KCE server) in both languages. To pre-test the survey on the understandability of the questions and the user-friendliness of the online version, KCE researchers recruited five non-scientific citizens with different ages and backgrounds. The online questionnaire was adapted based on their feedback. Finally, KCE team members pre-tested the online version in French and Dutch. Unfortunately, despite all quality checks, the response categories for the variable 'age' were programmed differently in the Dutch and French questionnaire.

- Dutch: < 18y; 18-24y; 25-44y; 45-64y; 65-74y; 75y+
- French: < 18y; 18-30y; 31-40y; 41-50y; 51-60y; 60y+

As a consequence, we reported the age of respondents seperatly for the French and Dutch respondents.

Ethical committee approval

Before launching the questionnaire, the research protocol, including the questionnaire, was submitted to and approved by the ethical committee of the 'Cliniques Universitaires de Bruxelles' (P2020/704 / B40620200000319). The approval was valid from 15/01/2021 till 30/11/2021.

3.1.2 Final questionnaire

Study introduction and patient approval

The questionnaire begins with a box explaining to the participants the purpose of the survey, the steps that follow the survey, and the requirements for completing the online questionnaire (inclusion criteria – see further). Then, respondents were asked to give informed consent before participating.

The online questionnaire includes 33 questions structured around 5 main topics

The questionnaire consisted of 33 questions (long COVID specific questions are identified by an *) organised around the following themes:

- *General information*: a distinction was made between people who were answering for themselves, for another adult (unable to answer the questionnaire him/herself) or for a minor. The other questions in this section related to demographic characteristics of the respondents: gender, age, place of residence (province), level of education and employment status (paid employment, disability, health sector employment);
- *Acute episode of COVID-19**: this section was designed to provide information on the respondents' experience during the acute phase of COVID-19: how and by whom they were diagnosed; whether they were hospitalised (general COVID or on intensive care unit; with or without ventilation) and the duration of their hospitalisation; presence and duration of COVID-19 symptoms;

- *General health status*: this section aimed at comparing respondents' health status before and after COVID-19*[f], using the EQ-5D-5L[g] as quality of life instrument. The EQ-5D-5L asks respondents to describe their health status on five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item had five response categories, reflecting the level of problems experienced in each dimension (no problems, slight problems, moderate problems, severe problems, extreme problems). In addition, respondents are asked to score their health state before and after COVID-19 on a visual analogue scale, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state);
- *Other illnesses*: the aim of this section was to find out whether respondents had comorbidities and if so, which one(s). For this purpose, a non-exhaustive list was proposed, as well as an open field, where respondents could mention other comorbidities that were not included in the list;
- *Long COVID**: the questions in this section aimed at describing the physical, psychological and care consequences of long COVID. The questions addressed the symptoms (physical and psychological) experienced by the respondents; the use of and access to care; the financial consequences of long COVID; the level of information sought and received by the respondents; and the treatments together with their medium and long-term effects.

Combination of pre-defined response categories and open field

For most of the questions, respondents were given a choice of answers (often based on the literature) but they were also given the opportunity to add elements in an open field. Open field responses were analysed using thematic coding and afterwards recoded into existing categories (if possible). To create these categories, we retained the main idea(s) contained in each participant's response; if the response could be interpreted in different ways, we classified it in the 'Other' category to avoid misinterpretation.

For several questions, respondents were asked to indicate their level of satisfaction. In many instances, responses to specific questions led to new sub-questions (e.g. when the respondent indicated 'Yes', he/she had to specify his/her answer). In addition, all comments that did not answer the question posed were classified as 'Not applicable'.

Last question: recruitment candidates for online forum or in-depth interviews

At the end of the questionnaire, participants were asked whether they were willing to participate in either the online discussion forum, or an individual interview or none of these two (cfr infra).

3.2 Participants

Recruitment of the participants

Several communication channels (KCE website, e-mailing, social networks, general media and long COVID patient support groups) were used to reach the target population. The call for participation included a link to a page on the KCE website where the same communication was available and the link to the survey and informed consent was accessible. Patients who recognised themselves in the description of the call for participation could directly access the online survey via the link on the KCE webpage. In addition, we asked the sickness funds, the umbrella patient organisations (LUSS and VPP) and the general media (press conference, COVID-19 crisis centre) to share the information.

[f] The generic questionnaire did only foresee to question the health status once. Since long COVID is preceded by an acute phase the health status might have changed rapidly. Therefore it was decided to ask the current perceived health status as well as the health status before COVID-19.

[g] https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/ (last access: 18 June 2021)

In- and exclusion criteria

Respondents had to meet the following criteria to participate in the survey:

- been infected with COVID-19 (self-declared or based on a test) ;
- not or no longer hospitalised at the time of the survey;
- having, at the time of the survey, long COVID symptoms or having had COVID symptoms for more than 4 weeks after the onset of the COVID-19 disease;
- living in Belgium.

When the respondent represented another adult (who met the inclusion criterion but was unable to respond his- or herself because of his/her health condition) or a minor who met the inclusion criteria, he/she had to respond as if the patient he/she represented would answer the questionnaire.

3.3 Data collection process

The survey was launched on the 27th of January 2021 and ran until the 14th of February 2021. The call was relaunched approximately one week after the start of the survey to reach as many people as possible. We also asked the patient organisations LUSS and VPP to re-launch their invitation to their networks. The call was also mentioned by the Sciensano representative during the daily press briefing of the national COVID crisis center (date: 09/02/2021) and was picked up by general media (online newspapers).

3.4 Analysis

Subgroup analyses were performed to more accurately assess the needs of patients with long COVID. Subgroup variables were: hospitalisation status (hospitalised versus non-hospitalised), duration of COVID-19 symptoms groups (short: 4 weeks to 3 months; mid: 3 to 6 months; long: more than 6 months) and age of respondents (children (<18 years) versus others).

Individual subjective health states described with the EQ-5D-5L tool (e.g. 11111 for perfect health and 55555 for the worst health conditions) were valued using the most recent Belgian valuation set (2021).[198]

Statistical analysis performed and software used

ANOVA one-way and Tukey post-hoc pairwise comparisons were used to compare average Delta (VAS before-VAS after COVID), Beta (EQ-5D-5L before-EQ-5D-5L after) and the number of symptoms by duration of symptoms groups (short: 4 weeks to 3 months, mid: 3 to 6 months, long: > 6months). Univariate and multivariate linear regression analysis were used to estimate the factors significantly associated with Beta. The factors introduced in the regression analysis were: gender (male/female), language (French/Dutch), region (Brussels, Flanders and Wallonia), age group (French <18,18-30,31-40,41-50,51-60, >60; Dutch <18,18-24,25-44,45-64,65-74, >74), education level (no diploma/primary, lower secondary, upper secondary, short type, long type), paid job (Yes/No), health job (Yes/No), number of comorbidities, duration of COVID symptoms groups (short, mid, long), Delta, hospitalisation (Yes/No), emergency care (Yes/No), number of long COVID symptoms, type of long COVID symptoms (breathing difficulties (Yes/No), fatigue (Yes/No), lack of energy (Yes/No), concentration problem (Yes/No), headache (Yes/No), difficulty or loss of memory (Yes/No), muscle pain and weakness (Yes/No), joint pain (Yes/No), insomnia (Yes/No)), long COVID treatment (Yes/No), inability to work (Yes/No), financial impact of long COVID (Yes/No), help for daily activities (Yes/no), needs (to talk to other people (Yes/No), to health professional (Yes/No), to other patients (Yes/No), need for additional help (Yes/No), for administrative support (Yes/No), for religious support (Yes/No)) and type of long COVID information received (none received, not clear at all, not very clear, fairly clear and very clear). Paired t-tests were applied to compare average Delta and Beta by hospitalisation status. T-tests (unequal variance) were used to compare the number of reported symptoms by hospitalisation status. Chi-squared tests were applied to compare proportions of comorbidities groups, most commonly reported symptoms, incapacity to work, social support needs, financial impact of COVID-19, back to work status, duration of symptoms (short, mid, long) by hospitalisation status, healthcare utilisation and treatment for long COVID by hospitalisation status and by duration of symptoms groups. The statistical analyses were performed with SAS Entreprise Guide (7.1) and the figures plotted with R Studio (1.4.1106). A p-value below 0.05 was considered as significant.

Open-ended questions analysis

Responses to the open-ended questions were re-coded by theme and grouped to be analysed in a quantitative way. The recoding of the healthcare professions was done based on the medical specialties defined for the question on the use of healthcare professionals. We focused on professionals providing care and/or seeing patients in consultation; other professions such as administrative professions were categorised as 'other'.

For reported comorbidities, open-ended responses were merged with existing categories (i.e. categories proposed in the online questionnaire) and if not possible, new categories were created based on the literature and/or after consultation among researchers. This was the same process for open-ended questions related to symptoms, treatments, side effects and type of health professionals consulted.

Responses to open-ended questions related to tedious treatment, long-term side effects, financial aspects, support needs, network and unmet medical needs were illustrated through quotes (one in each national language if possible).

4 RESULTS

4.1 Description of the participants

4.1.1 Demographic data

At the end of the online survey, 1 395 participants had fully completed the questionnaire and after applying the exclusion criteria (section 3.2), 1 320 participants were retained for the analysis (33 participants did not live in Belgium, 15 had COVID symptoms for less than four weeks and 31 reported no symptoms of long COVID (4 participants met two exclusion criteria)). The majority of respondents were women (74.8%) and from Flanders (59.0%). The most represented provinces among the participants were Antwerpen (16.5%), Oost-Vlaanderen (13.0%) and Vlaams-Brabant (13.2%). There was a relatively large proportion of people with a high level of education (non-university higher education (30.5%); university education (25.4%)) and who had paid work before acute COVID-19 (82.0%) (Table 10). Most of the respondents (97.1%) answered the online questionnaire for themselves and only a minority for another adult (1.8%) or a child (1.1%) (Table 10).

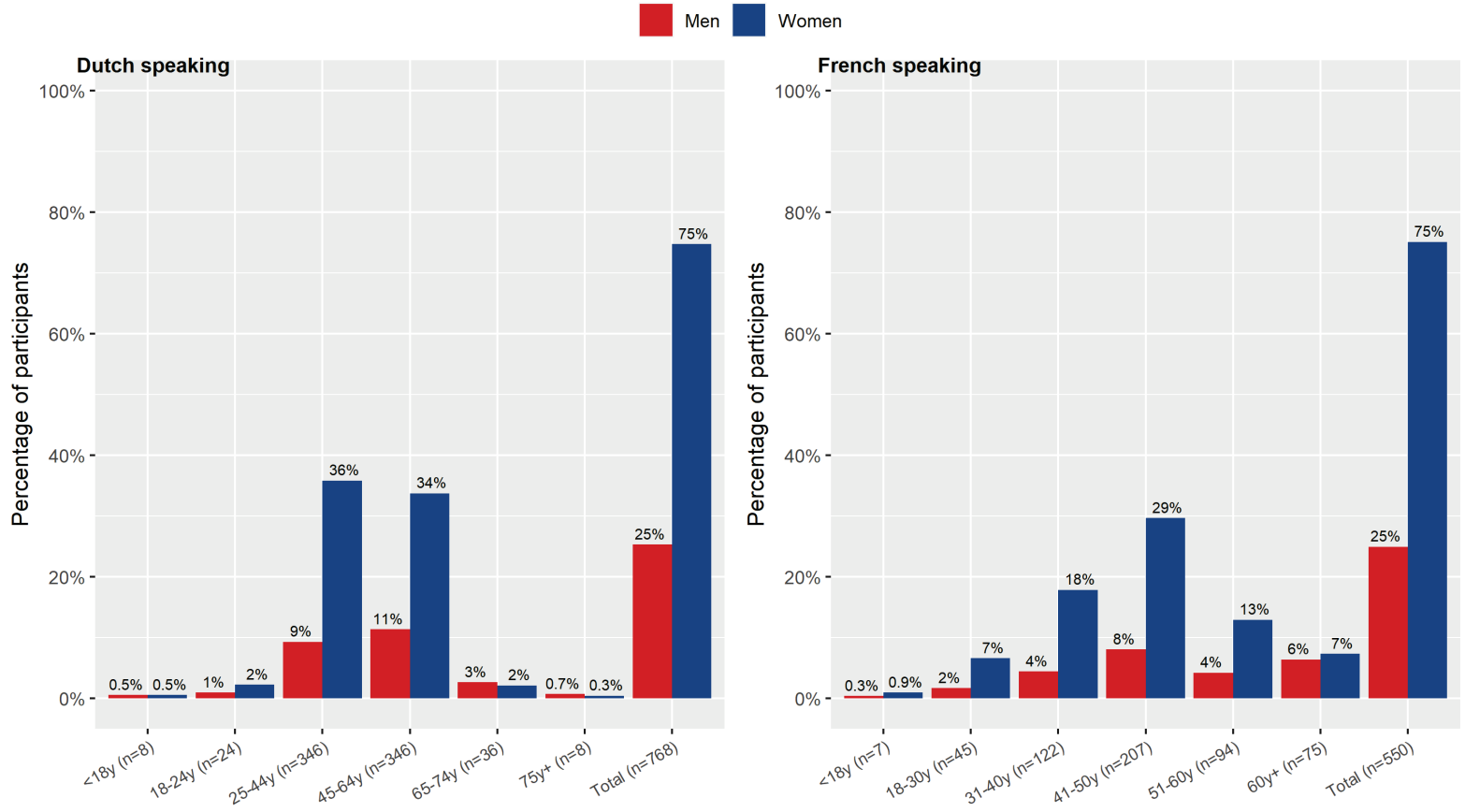
Table 10 – Description of the participants in the online survey (n=1 320)

Variable		N (%)
Status of the respondent: completing the survey for		
	Yourself	1 282 (97.1)
	Another adult	24 (1.8)
	A minor	14 (1.1)
Gender		
	Women	987 (74.8)
	Men	331 (25.1)
	Other	2 (0.1)
Language		
	Dutch	769 (58.3)
	French	551 (41.7)

Region	
Flanders	779 (59.0)
Wallonia	398 (30.0)
Brussels	143 (11.0)
Province	
Antwerpen	218 (16.5)
Vlaams-Brabant	174 (13.2)
Oost-Vlaanderen	172 (13.0)
Bruxelles	143 (10.8)
West-Vlaanderen	115 (8.7)
Liège	113 (8.6)
Hainaut	109 (8.3)
Limburg	100 (7.6)
Brabant Wallon	83 (6.3)
Namur	68 (5.2)
Luxembourg	25 (1.9)
Paid job	
Yes	1 076 (82.0)
Education level	
No diploma	10 (0.8)
Primary education	18 (1.4)
Lower secondary education or 1st or 2nd level secondary education	58 (4.4)
Upper secondary education or general secondary education at the 3rd level	204 (15.5)
Post-secondary non-tertiary	71 (5.4)
Non-university higher education of the short type	403 (30.5)
Academic baccalaureate	95 (7.2)
Non-university higher education of the long type, master's degree at a university	72 (5.5)
University education, bachelor's, engineer or master's degree	335 (25.4)
Doctorate with thesis	36 (2.7)
Other diploma	13 (1.0)
I don't know	5 (0.4)

The Dutch-speaking population (n=769) was predominantly female and aged between 25 and 64. Women were also more numerous in all age groups. There were relatively few respondents under 18 (1%) and over 75 (1%) years of age (Figure 3).

Figure 3 – Gender and age distribution of the participants, by language (Dutch (n=769), French (n=551))



NB: One participant (0.1%) aged 25-44y reported another type of gender

NB: One participant (0.2%) aged <18y reported another type of gender

4.1.2 Employment status

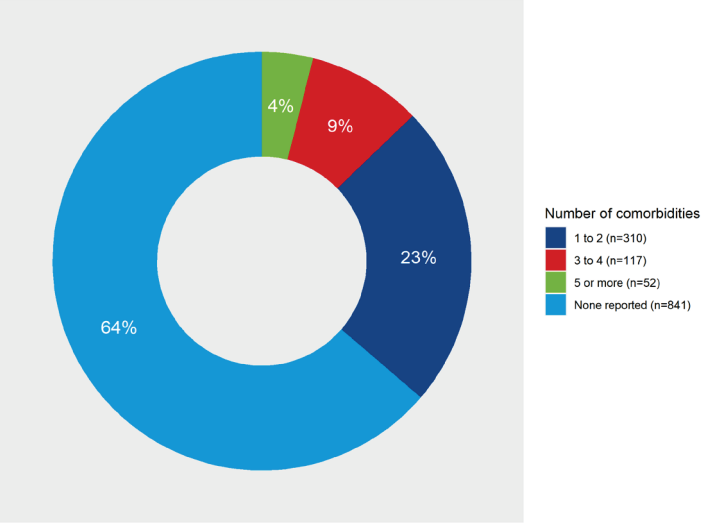
More than 80% of the respondents were in paid employment before being infected with SARS-COV-2 and 30% were working in the health sector (38% were nurses). Information on the impact of COVID-19 on employment status is available in subsection 4.2.2.1.

4.1.3 Existing comorbidities

64% reported no comorbidities prior to COVID-19

Slightly more than 36% of respondents reported having at least one comorbidity before COVID-19. Yet the vast majority of respondents had no (63.7%) comorbidities and 23.9% of the patients reported only one to two comorbidities (Figure 4).

Figure 4 – Number of comorbidities among participants (n=1 320)



Most frequent reported pre-existing co-morbidities

The four most frequently reported comorbidities among patients who reported suffering from comorbidities (n=489) were disease of the locomotor system (bones, joints, muscles) (12.1%), respiratory diseases (10.0%), heart and blood vessel disease (7.6%) and digestive disease (7.2%).

Patients who were hospitalised reported more pre-existing comorbidities

Patients who were hospitalised reported significantly more comorbidities than patients who were not hospitalised (p<0.001). One quarter of the patients who were hospitalised for COVID-19 (26.4%) reported at least three comorbidities while among the non-hospitalised patients, only 10.7% reported at least three comorbidities (Table 11).

Table 11 – Number of comorbidities, by hospitalisation status (n=1 320)

Number of comorbidities	Hospitalised (n=174) N (%)	Not hospitalised (n=1 146) N (%)	p-value	Total N (%)
			***	
None	87 (50.0)	754 (65.8)		841 (63.7)
1 to 2	41 (23.6)	269 (23.5)		310 (23.5)
3 to 4	26 (14.9)	91 (7.9)		117 (8.9)
5 or more	20 (11.5)	32 (2.8)		52 (3.9)

*** Chi-squared, p<0.001*

In the subgroup of patients with the longest duration of COVID-19 symptoms, the number of comorbidities is higher

The number of comorbidities is also significantly related to the duration of the acute COVID-19. The higher the number of comorbidities, the longer the duration of COVID-19. Six percent of the patients who have (had) symptoms of COVID-19 for more than 6 months reported five comorbidities or more vs.. 1.1% and 3.1% in the short and mid duration categories (Table 12).

Table 12 – Number of comorbidities, by COVID-19 duration (n=1 318*)

	Short (N=267)	Mid (N=484)	Long (N=567)	p-value	Total (N=1 318)
				**	
None	177 (66.3%)	312 (64.5%)	351 (61.9%)		840 (63.7)
1 to 2	71 (26.6%)	115 (23.8%)	123 (21.7%)		309 (23.4)
3 to 4	16 (6.0%)	42 (8.7%)	59 (10.4%)		117 (8.9)
5 or more	3 (1.1%)	15 (3.1%)	34 (6.0%)		52 (3.9)

***Chi-squared, p=0.01; *Missing duration for two respondents; Short = 4 weeks to 3 months; Mid=3 to 6 months; Long=More than 6 months*

Pre-existing co-morbidities in minors with long COVID

In the less than 18 years population (n=16), 13 (81.2%) reported no comorbidities, two (12.5%) reported one to two comorbidities and one (6.3%) reported three to four comorbidities.

4.1.4 Acute COVID-19 episode

4.1.4.1 Test/diagnosis

Small minority without a test or clinical diagnosis of COVID-19

Three percent of the participants (40/1 320) responded that they were not diagnosed or tested positive for COVID-19 at all. For 27.5% of them (n=11), it was because there was no test available at the time of infection.

Eleven percent with a clinical diagnosis but no test

10.7% of the respondents (141/1 320) were diagnosed as positive by a physician based on symptoms, without being tested positive by a PCR-test, blood sample or diagnostic imaging techniques.

Vast majority tested positive for COVID-19

Of those who tested positive (n=1 139), most were tested by a nose swap PCR test only (51.4%) and 22.3% were tested by multiple techniques. Some participants (n=121) responded being tested positive for COVID-19 but did not select any diagnostic technique (Table 13).

Table 13 – Diagnosis techniques among tested positive respondents (n= 1 139)

	N (%)
Blood	152 (13.3)
Nose swap PCR	586 (51.4)
Imaging	25 (2.2)
Blood, nose swap PCR and imaging	56 (4.9)
Blood and nose swap PCR	136 (11.9)
Blood and imaging	22 (1.9)
Nose swap PCR and imaging	41 (3.6)
None of the proposed diagnosis techniques	121 (10.6)

Finally, 78.3% (1 034/ 1 320) responded "Yes" to the question **"***Has a doctor or other health care professional confirmed that the symptoms you are currently experiencing (or have experienced) are the result of COVID-19*?"

4.1.4.2 COVID-19-related hospitalisation

Table 14 shows the main information reported by the respondents with regard to their hospitalisation in the context of COVID-19. Thirteen percent (174/1 320) of respondents were hospitalised for a duration of less than one week (33.9%), one to two weeks (37.4%) or more than two weeks (28.7%). Just over thirty percent of those hospitalised were admitted to an intensive care unit and the majority of them (73.6%) had been on respiratory assistance (Table 14).

Table 14 – Description of hospitalised respondents (n= 174)

	N (%)
Length of stay	
1 to 2 weeks	65 (37.4)
< 1 week	59 (33.9)
> 2 weeks	50 (28.7)
Intensive care (n=174)	
No	121 (69.5)
Yes	53 (30.5)
Respiratory assistance (n= 53)	
Yes	39 (73.6)
No	14 (26.4)

4.1.5 Duration COVID-19-related symptoms

Most patients still had symptoms at the time of completion of the questionnaire

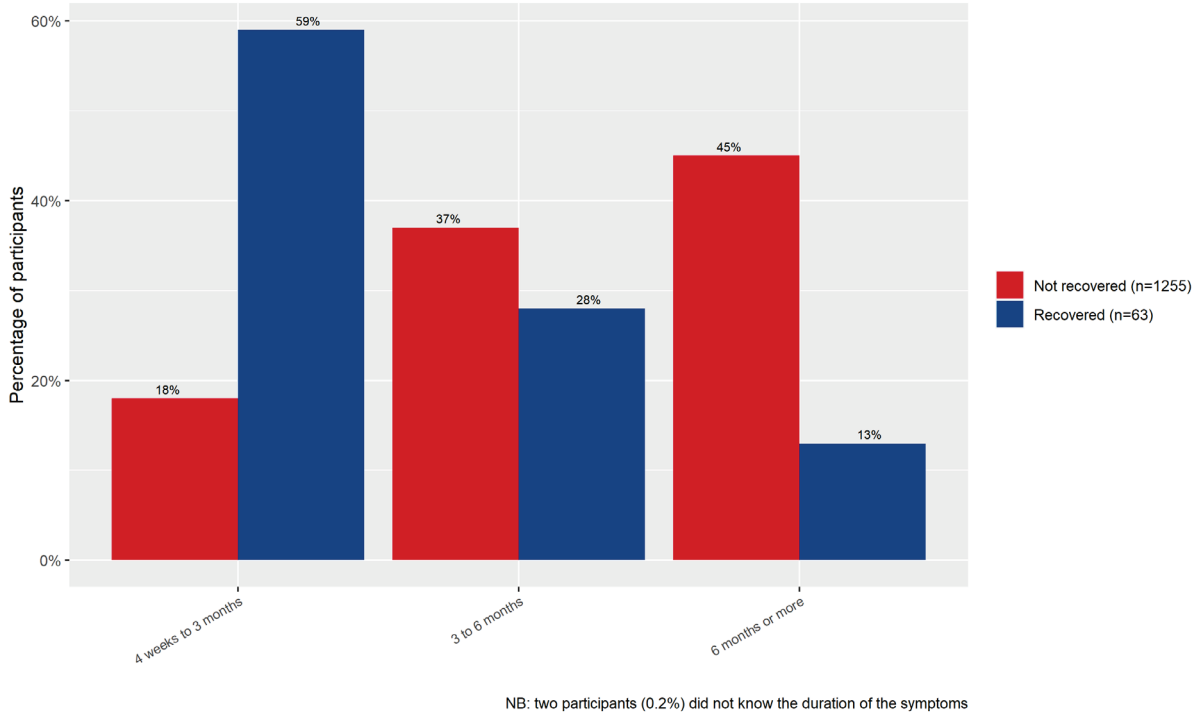
1 255 out of 1 320 respondents (95%) still had COVID-19-related symptoms at the time of the online survey. In Figure 5, patients still having symptoms at the time of the survey are shown in red, while those without symptoms are shown in blue.

For those who no longer had symptoms at the time of survey completion, more than 59% (n= 38) reported that their symptoms lasted between 4 weeks and 3 months.

Most patients with ongoing symptoms has symptoms for more than 3 months

For those who still had symptoms, this had been going on for more than 3 months at the time of the survey (37% between 3 and 6 months and 45% 6 months and more).

Figure 5 – Duration of COVID-19-related symptoms, by recovering status



NB: two participants (0.2%) did not know the duration of the symptoms

Half of the participants who had been hospitalised in the acute phase of COVID-19 have (had) symptoms for more than 6 months (52.3%). The proportion of hospitalised participants is significantly higher in the mid (3-6 months) and long (>6 months) duration of symptoms groups than in the proportion of non-hospitalised participants (Table 14). However, the duration of symptoms was not significantly related to hospitalisation in the intensive care unit (Table 16).

Table 15 – Duration of symptoms, by hospitalisation status

	Hospitalised N=174 N (%)	Not Hospitalised N=1 144 N (%)	p-value	Total N=1 318 N (%)
			**	
Short (4 weeks-3months)	39 (22.4)	228 (19.9)	NS	267 (20.3)
Mid (3 to 6 months)	44 (25.3)	440 (38.5)	**	484 (36.7)
Long (>6 months)	91 (52.3)	476 (41.6)	*	567 (42.0)

**Chi-squared p-value<0.05, ** Chi-squared p-value<0.01, NS=Not significant, Duration is missing for n=2*

Table 16 - Duration of symptoms, by hospitalisation in ICU status

	Hospitalised ICU N=53 N (%)	Hospitalised not ICU N=121 N (%)	p-value	Total N=174 N (%)
			NS	
Short (4 weeks-3months)	7 (13.2)	32 (26.5)		39 (22.4)
Mid (3 to 6 months)	16 (30.2)	28 (23.1)		44 (25.3)
Long (>6 months)	30 (56.6)	61 (50.4)		91 (52.3)

NS=Not significant (Chi-squared), ICU=Intensive Care Unit

4.2 About their long COVID

4.2.1 Symptom description

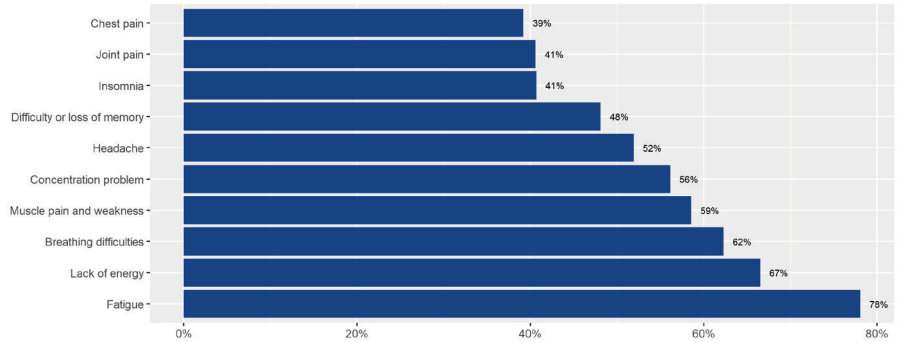
The three most frequent reported symptoms were fatigue, lack of energy and breathing difficulties

Ninety-seven percent of the respondents (1 281/1 320) reported symptoms related to long COVID (3% did not answer the question). Participants who answered “no” to the question were excluded from the analysis (see section 8.3.4).

The most common reported symptoms were fatigue (78.1%), lack of energy (66.5%), breathing difficulties (62.3%), muscle pain and weakness (58.5%), concentration problem (56.1%), headache (51.9%), difficulty/loss of memory (48.1%), insomnia (40.7%), joint pain (40.6%), and chest pain (39.2) (Figure 6 and Table 17). The complete list of symptoms (and their frequency) is available in the Appendix (See Appendix Chapter 4).

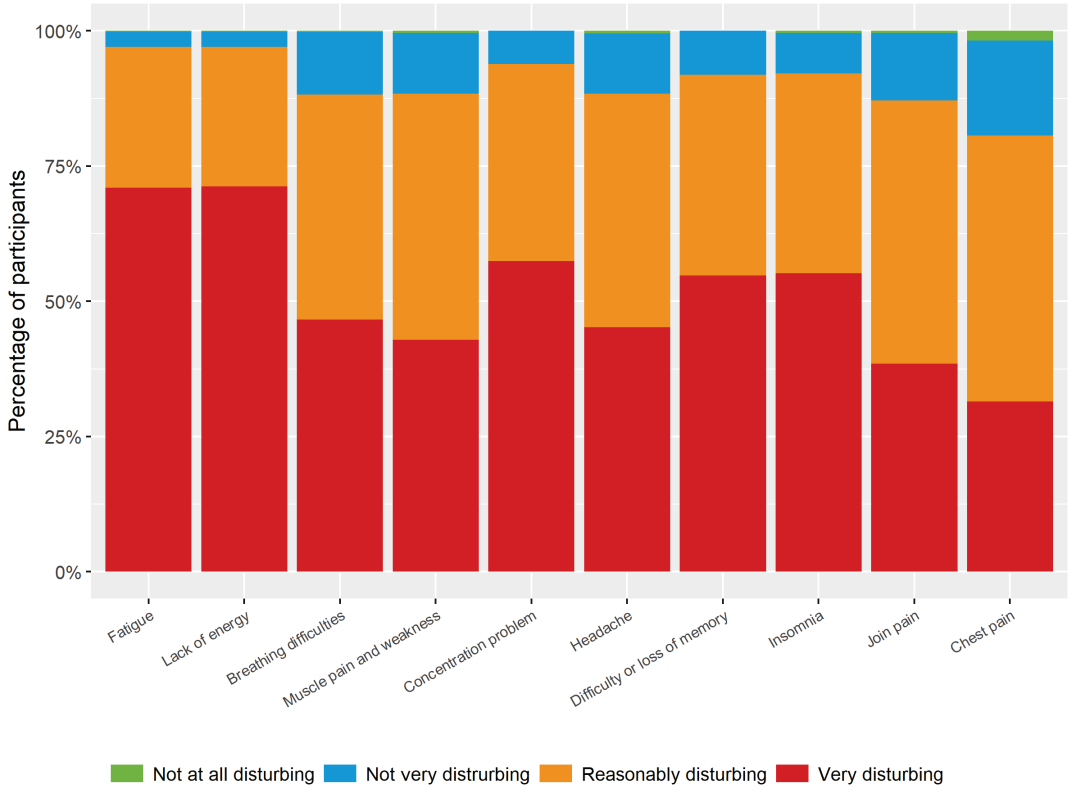
Among the children (n=16), the most frequently reported symptom was fatigue as well (93.8%), followed by loss of energy (56.3%) and concentration problems (43.8%) (Figure 6).

Figure 6 – Top 10 most commonly reported symptoms (n=1 281)



For each symptom reported, respondents also indicated how disturbing they felt it was. The level of burden of the whole list of reported symptoms is available in the Appendix (See Supplement to Chapter 4). Among the 10 most commonly reported symptoms, lack of energy and fatigue were those which were qualified as the most disturbing by the respondents, respectively 71.2% and 71.0% reported that it was very disturbing (Figure 7).

Figure 7 – Level of burden of the 10 most common reported symptoms



Differences in symptom frequency between patients who were hospitalised and those who were not

When symptom frequency is compared between hospitalised and non-hospitalised patients some similarities and differences can be observed. From Table 17 it can be observed that the top 5 of most common symptoms is the same. Furthermore, the most common symptom (fatigue) is very similar for patients who were hospitalised and non-hospitalised 79.0% and 77.9%, respectively. Yet the reported frequencies were for most symptoms, in general, lower in the patient group of non-hospitalised patients. Participants who were hospitalised more frequently reported lack of energy (hospitalised 69.5% vs. not hospitalised 66.1%, p<0.05), breathing difficulties (76.6% vs. 60.1%, p<0.05) muscle pain and weakness (71.3% vs. 56.6%, p<0.05), concentration problems (64.1% vs. 54.9%, p<0.05), difficulty or loss of memory (59.9% vs. 46.3%, p<0.05), and joint pain (48.5% vs. 39.4%, p<0.05) with regards to the participants who were not hospitalised (Table 17).

Table 17 – Top 10 most commonly reported symptoms, by hospitalisation group (n=1 281)

Symptoms	Hospitalised N=167 N (%)	Not hospitalised N=1 114 N (%)	p-value	Total N (%)
Fatigue	132 (79.0)	868 (77.9)	NS	1 000 (78.1)
Lack of energy	116 (69.5)	736 (66.1)	*	852 (66.5)
Breathing difficulties	128 (76.6)	670 (60.1)	*	798 (62.3)
Muscle pain and weakness	119 (71.3)	631 (56.6)	*	750 (58.5)
Concentration problem	107 (64.1)	612 (54.9)	*	719 (56.1)
Headache	83 (49.7)	582 (52.2)	NS	665 (51.9)
Difficulty or loss of memory	100 (59.9)	516 (46.3)	*	616 (48.1)
Insomnia	69 (41.3)	452 (40.6)	NS	521 (40.7)
Joint pain	81 (48.5)	439 (39.4)	*	520 (40.6)
Chest pain	60 (35.9)	442 (39.7)	NS	502 (39.2)

**Chi-squared, p-value <0.05; NS=Not significantly different*

Among the patients who had been hospitalised, those admitted in the intensive care unit (ICU) more frequently reported fatigue (ICU 88.7% vs. not ICU 70.2%, p<0.01) and memory problems (ICU 71.7% vs. not ICU 64.5%, p<0.05) than those who had been hospitalised but not admitted to intensive care (Table 17).

Table 18 – Top 10 most commonly reported symptoms, by hospitalisation in ICU status (n=174)

Symptoms	Hospitalised ICU n=53 N (%)	Hospitalised not in ICU n=121 N (%)	p-value	Total N=174 N (%)
Fatigue	47 (88.7)	85 (70.2)	**	132 (79.0)
Breathing difficulties	43 (81.1)	85 (70.2)	NS	128 (76.6)
Muscle pain and weakness	39 (73.6)	80 (66.1)	NS	119 (71.3)
Lack of energy	38 (71.7)	78 (64.5)	NS	116 (69.5)
Concentration problem	34 (64.2)	73 (60.3)	NS	107 (64.1)
Difficulty or loss of memory	38 (71.7)	78 (64.5)	*	100 (59.9)
Headache	19 (35.8)	64 (52.9)	*	83 (49.7)
Joint pain	26 (49.1)	55 (45.5)	NS	81 (48.5)
Insomnia	22 (41.5)	47 (38.8)	NS	69 (41.3)
Chest pain	14 (26.4)	46 (38.0)	NS	60 (35.9)

**Chi-squared p-value<0.05, **Chi-squared p-value <0.01; NS=Not significantly different; ICU=Intensive Care Unit*

Almost half of respondents (48.5%) reported more than 11 symptoms related to long COVID. The average number of symptoms was significantly different between hospitalised and non-hospitalised patients (hospitalised average reported symptoms (DS): 12.89 (7.97); not hospitalised: 11.54 (7.67); p=0.04). Overall patients who had been hospitalised reported more symptoms than the non-hospitalised patients (Table 19).

Table 19 – Number of reported symptoms, by hospitalisation status

Number of symptoms	Hospitalised N (%)	Not hospitalised N (%)	Total N (%)
0 to 6	36 (20.7)	305 (26.6)	341(25.8)
7 to 11	38 (21.8)	301 (26.3)	339 (25.7)
More than 11	100 (57.5)	540 (47.1)	640 (48.5)
Mean[DS]	12.86 [7.98]	11.54 [7.67]**	11.71 [7.72]

***T-test (unequal variance) hospitalised vs. not hospitalised; p-value=0.04*

Differences in symptom frequency depending on duration after onset acute COVID-19

When looking at the frequency of symptoms with regard to the duration of symptoms after acute COVID-19 onset, several observations can be made. The most reported symptoms are similar (i.e. top three: fatigue, lack of energy and breathing difficulties) between duration groups but the proportion of participants who reported lack of energy, concentration problems, difficulty or loss of memory, muscle pain and weakness, joint pain, insomnia and chest pain is significantly different across duration of symptoms groups (p<0.001). Overall, these symptoms are higher among patients who experienced COVID symptoms for a longer period of time. There is an exception for fatigue and headache, which are more frequently reported in mid duration group than in the other groups (short-long) but the differences are not significantly different (Table 20).

Table 20 – Top 10 most commonly reported symptoms, by symptom duration group (n=1 281)

Symptoms	Short N=267 N (%)	Mid N=484 N (%)	Long N=567 N (%)	p-value	Total N (%)
Fatigue	189 (70.8)	375 (77.5)	436 (76.9)	NS	1 000 (78.1)
Lack of energy	162 (60.7)	299 (61.8)	390 (68.8)	*	852 (66.5)
Breathing difficulties	149 (55.8)	287 (59.3)	362 (63.8)	NS	798 (62.3)
Concentration problem	123 (46.1)	252 (52.1)	344 (60.7)	*	750 (58.5)
Headache	124 (46.4)	250 (51.7)	291 (51.3)	NS	719 (56.1)
Difficulty or loss of memory	89 (33.3)	210 (43.4)	317 (55.9)	*	665 (51.9)
Muscle pain and weakness	140 (52.4)	256 (52.9)	354 (62.4)	*	616 (48.1)
Joint pain	94 (35.2)	164 (33.9)	261 (46.0)	*	521 (40.7)
Insomnia	89 (33.3)	168 (34.7)	263 (46.4)	*	520 (40.6)
Chest pain	80 (30.0)	178 (36.8)	244 (43.0)	*	502 (39.2)

Chi-squared, p-value <0.05; Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months; missing duration for n=2; NS=Not significantly different

The participants with longer duration of symptoms reported significantly more symptoms that the participants with shorter duration of symptoms (Table 21 and Table 22).

Table 21 – Number of reported symptoms, by duration of symptoms

Number of symptoms	Short N (%)	Mid N (%)	Long N (%)
0 to 6	79 (29.6)	150 (31.0)	111 (19.6)
7 to 11	72 (27.0)	132 (27.3)	134 (23.6)
More than 11	116 (43.4)	202 (41.7)	322 (56.8)
Mean [DS]	9.80 [6.69]	10.82 [7.40]	13.40 [8.10]***

*Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months; missing duration for n=2; ***Anova one-way p-value <0.001, see Table 22 for Tukey tests*

Table 22 – Comparison of average symptoms, by symptom duration group

Duration group*	Difference between means of symptoms	95% CI		p-value
Long – Mid	2.58	1.48	3.68	***
Long – Short	3.60	2.28	4.92	***
Short – Mid	1.02	-0.33	2.38	NS

**Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months, **Tukey's test; p<0.05; NS=Not significantly different; CI=Confidence Interval*

4.2.2 Impact of COVID-19 on subjective health

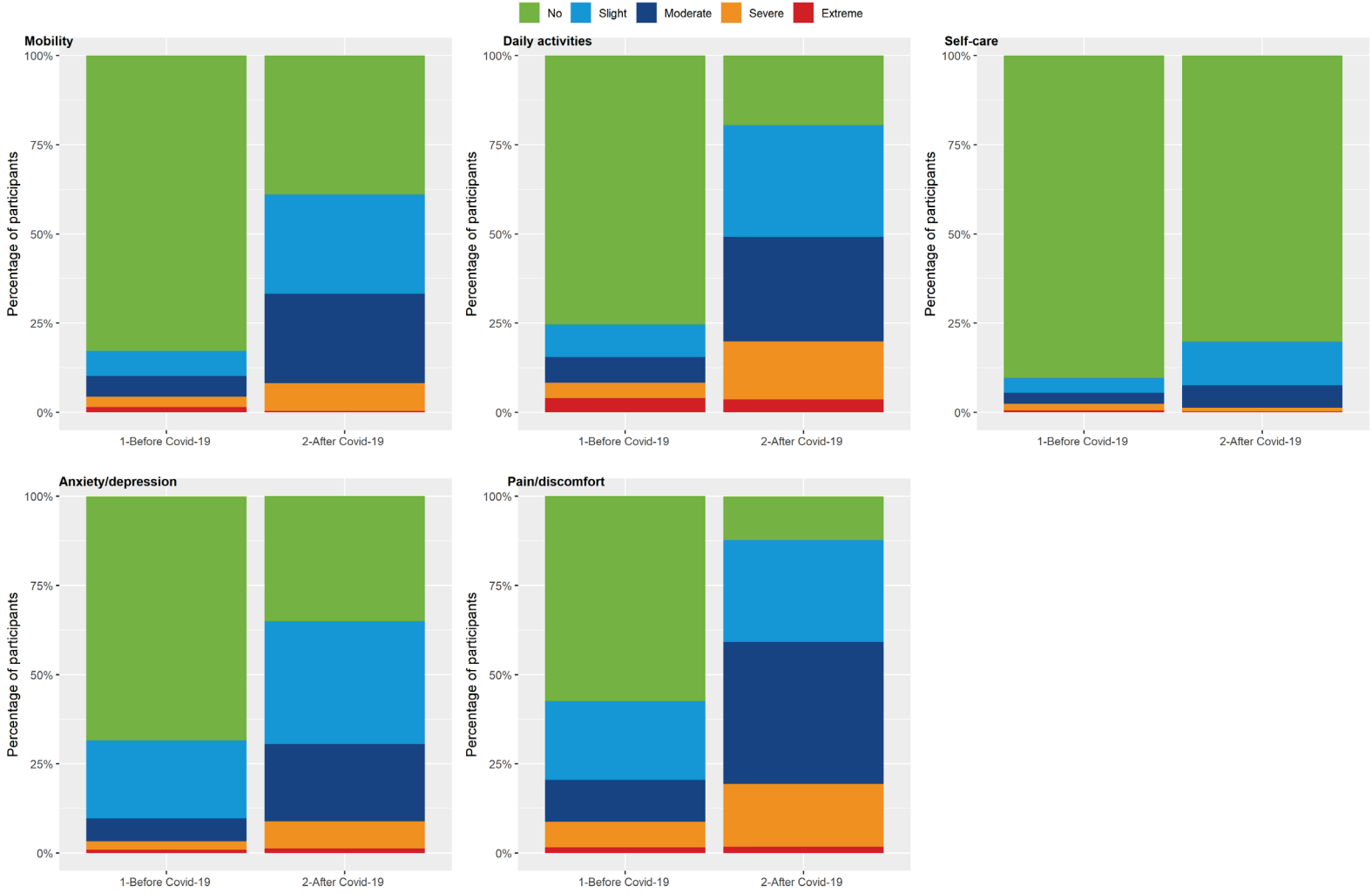
Long COVID increased the proportion of slight and moderate health problems in all EQ-5D-5L dimensions

We assessed the impact of COVID-19 on patients' health status by means of the EQ-5D-5L instrument. The EQ-5D-5L encompasses five dimensions of health: mobility, self-care, usual activities, pain/discomfort, anxiety/depression. In all dimensions, the proportion of respondents with health problems increased after acute COVID-19. This increase is important for four out of five dimensions: usual activities (+55.8%), pain/discomfort (+45.2%), mobility (+43.9%), anxiety/depression (+33.4%), and more restricted for the self-care dimension (+10.2%). The lower impact on the self-care dimension could be partly explained by the underrepresentation of the elderly among the respondents (see section 8.4). Overall, we observed a shift from patients with no problems before COVID-19 to mild to moderate problems after infection. For usual activities and pain/discomfort, there was an increase of respectively 12.0% and 10.4% in the "severe problems" category. Overall, few patients have extreme problems after COVID-19 (Table 23, Figure 8).

Table 23 – Self-reported level of problems on each EQ-5D-5L dimension of quality of life before and after COVID-19

	After-Before (%) Mobility	After-Before (%) Self-care	After-Before (%) Usual Activities	After-Before (%) Pain/discomfort	After-Before (%) Anxiety/depression
No problems	-43.9	-10.2	-55.8	-45.2	-33.4
Slight problems	+20.9	+8.0	+22.1	+6.5	+12.6
Moderate problems	+19.3	+3.2	+22.2	+28.1	+15.2
Severe problems	+4.8	-0.7	+12.0	+10.4	+5.2
Extreme problems	-1.0	-0.3	-0.5	+0.2	+0.5

Figure 8 – Self-reported level of problems on each EQ-5D-5L dimension of quality of life before and after COVID-19



COVID-19 had a greater impact on subjective health among hospitalised patients. Hospitalised patients reported more frequently health problems after COVID-19 than non-hospitalised patients

In almost all the EQ-5D-5L dimensions (except for the pain/discomfort dimension) the hospitalised patient reported more frequently health problems after COVID-19 than the non-hospitalised participants (hospitalised vs. not hospitalised: mobility + 16.9%, self-care +11.5%, usual activities +6.5%, +11.2%). The most impacted dimensions by COVID-19 and hospitalisation were mobility and self-care. Impact of COVID-19 on pain/discomfort health problems is the same regardless of the hospitalisation status (hospitalised +44.3% vs. not hospitalised + 45.3%) (Table 24).

Table 24 – Self-reported level of problems on each EQ-5D-5L dimension of quality of life before and after COVID-19, by hospitalisation status

	Not hospitalised (n=1 146)					Hospitalised (n=174)				
	After-Before (%) Mobility	After-Before (%) Self-care	After-Before (%) Usual Activities	After-Before (%) Pain/ discomfort	After-Before (%) Anxiety/ depression	After-Before (%) Mobility	After-Before (%) Self-care	After-Before (%) Usual Activities	After-Before (%) Pain/ discomfort	After-Before (%) Anxiety/ depression
No problems	-41.7	-8.6	-55.0	-45.3	-31.9	-58.6	-20.1	-61.5	-44.3	-43.1
Slight problems	+22.3	+7.2	+22.6	+8.1	+11.1	+12.1	+12.6	+19.0	-3.5	+22.42
Moderate problems	+16.8	+2.2	+21.3	+27.0	+15.3	+35.1	+9.8	+28.2	+35.6	+14.95
Severe problems	+3.3	-0.7	+11.7	+10.1	+5.2	+14.4	-0.6	+13.8	+12.6	+5.18
Extreme problems	-0.7	-0.09	-0.6	+0.3	+0.4	-2.9	-1.7	+0.6	-0.6	+0.57

Acute COVID-19 has a larger impact on subjective health in participants with long duration symptoms than in participants with lower duration of symptoms, whatever the EQ-5D-5L dimension.

Patients suffering from long duration symptoms reported more frequently health problems after COVID-19 than the participants with a lower duration of symptoms, whatever the EQ-5D-5L dimension. Overall, the impact of acute COVID-19 on subjective health increased with the duration of the symptoms. In other words, the longer the duration of symptoms, the higher is the impact of COVID-19 on subjective health (Table 25).

Table 25 – Self-reported level of problems on each EQ-5D-5L dimension of quality of life before and after COVID-19, by symptom duration

	Short (n=267)					Mid (n=484)					Long (n=567)				
	After-Before (%) Mobility	After-Before (%) Self-care	After-Before (%) Usual Activities	After-Before (%) Pain/ discomfort	After-Before (%) Anxiety/ depression	After-Before (%) Mobility	After-Before (%) Self-care	After-Before (%) Usual Activities	After-Before (%) Pain/ discomfort	After-Before (%) Anxiety/ depression	After-Before (%) Mobility	After-Before (%) Self-care	After-Before (%) Usual Activities	After-Before (%) Pain/ discomfort	After-Before (%) Anxiety/ depression
No problems	-33.3	-7.1	-43.8	-34.8	-26.2	-44.6	-8.7	-55.2	-47.3	-30.8	-48.5	-12.9	-62.3	-48.5	-39.0
Slight problems	+16.9	+6.0	+22.5	+8.6	+12.4	+21.7	+7.2	+21.5	+8.9	+6.8	+22.2	+9.5	+22.6	+3.7	+17.5
Moderate problems	+12.7	+1.1	+14.6	+21.4	+9.7	+20.2	+2.3	+22.7	+29.8	+17.8	+21.5	+4.9	+25.4	+30.0	+15.7
Severe problems	+4.1	0.0	+7.9	+5.6	+3.0	+3.5	-0.4	+11.0	+7.4	+5.6	+6.2	-1.2	+14.8	+15.2	+5.8
Extreme problems	-0.4	0.0	-1.1	-0.8	+1.1	-0.8	-0.4	0.0	+1.2	+0.6	-1.4	-0.4	-0.52	-0.4	+0.0

Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months; missing duration for n=2

The analysis of the EQ-5D-5L scores (valued using the Belgian value set) confirmed the results presented above. COVID-19 had a negative impact on subjective health. A significant decrease in EQ-5D-5L score (mean beta: -0.20; 95%CI: -0.22;-0.18; p<0.001) was observed after acute COVID-19 and the decrease was even more pronounced among the respondents who were hospitalised (mean beta hospitalised: -0.24 (95% CI:-0.30;-0.18); not hospitalised: -0.19 (95% CI: -0.21;-0.17); p=0.15) (Table 25). The duration of symptoms also had a significant impact on the EQ-5D-5L score after acute COVID-19. The longer the symptoms last, the greater the negative impact on subjective health. The difference in EQ-5D-5L score before and after infection is significant between participants with short and long symptoms duration (Mean beta short duration:-0.14 (95% CI:-0.18;-0.10); long duration: -0.23 (95% CI:-0.26;-0.20); p<0.001) (Table 26;Table 27).

Table 26 – EQ-5D-5L before and after COVID-19, by hospitalisation status

Hospitalisation	N	Variable	Mean	SD	95% CI	p-value
						NS
No	1146	EQ-5D-5L before	0.85	0.24	0.83;0.86	
		EQ-5D-5L after	0.66	0.24	0.64;0.67	
		Beta°	-0.19	0.33	-0.21;-0.17	
Yes	174	EQ-5D-5L before	0.82	0.29	0.77;0.86	
		EQ-5D-5L after	0.58	0.28	0.53;0.62	
		Beta°	-0.24	0.41	-0.30;-0.18	
Total	1 320	EQ-5D-5L before	0.84	0.25	0.83;0.86	**
		EQ-5D-5L after	0.65	0.25	0.63;0.66	
		Beta°	-0.20	0.34	-0.22;-0.18	

*°Beta= EQ-5D-5L after- EQ-5D-5L before; new Belgian tariffs (2021 [198]) have been used to valuate the individual scores obtained with EQ-5D-5L tool; **Paired t-test total before-after: p<0.001; T-student NS=Not significantly different; CI=Confidence Interval*

Table 27 – EQ-5D-5L value before and after COVID-19, by duration of the symptoms

Duration of symptoms	N Obs	Variable	Mean	SD	95% CI	p-value
						***
Short	267	EQ-5D-5L before	0.83	0.23	0.81;0.86	
		EQ-5D-5L after	0.70	0.24	0.67;0.72	
		Beta°	-0.14	0.32	-0.18;-0.10	
Mid	484	EQ-5D-5L before	0.86	0.23	0.84;0.88	
		EQ-5D-5L after	0.66	0.23	0.64;0.68	
		Beta°	-0.19	0.32	-0.22;-0.17	
Long	567	EQ-5D-5L before	0.83	0.28	0.81;0.86	
		EQ-5D-5L after	0.61	0.26	0.58;0.63	
		Beta°	-0.23	0.37	-0.26;-0.20	

*Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months, missing duration for n=2; *** One-way Anova; p<0.001 (for Tukey comparison tests see Table 28).*

Table 28 – Comparison of beta (EQ-5D-5L after - EQ-5D-5L before), by COVID-19 symptom duration group

Duration group*	Difference between means Beta	95% CI		p-value
Long – Mid	-0.03	-0.08	0.01	NS
Long – Short	-0.09	-0.15	-0.03	***
Short – Mid	0.06	-0.01	0.12	NS

**Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months, **Tukey's test; p<0.05; NS=Not significantly different*

Univariate linear regression analyses were also conducted to further analyse the factors associated with Beta (i.e. EQ-5D-5L after - EQ-5D-5L before COVID infection), the impact of COVID-19 on subjective health. In terms of characteristics of the participants, gender, region and the average number of comorbidities prior to COVID-19 were significantly associated with Beta. More specifically, the female participants valuated their health status significantly lower (EQ-5D-5L average score decrease of 0.108 (Standard Error (SE) 0.0020)) after the infection than male, the participants who lived in the Walloon region valuated their health status significantly worse after infection than the participants from Brussels and with each increase of one comorbidity, Beta decreased on average by 0.013 (SE 0.006) (Table 29). All factors studied in relation to (long) COVID-19 (with the exception of hospitalisation) and to needs related to long COVID had a significantly negative impact on the EQ-5D-5L score (Table 29). The association of lack of energy (-0.163 (SE 0.020)), financial impact of long COVID (-0.162 (0.019), fatigue (-0.154 (0.023)), inability to work (-0.145 (0.021)) and concentration problems (-0.145 (0.019)) with Beta is 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 is observed that Beta is significantly associated with patients with symptoms of more than 6 months (long) (compared to patients with short duration of COVID-19 symptoms). This is the same finding as reported in Table 28 (Table 30).

Table 29 – Factors associated to Beta (EQ-5D-5L after - EQ-5D-5L before), univariate linear regression analysis

		Coef	SE Coef	p-value
CARACTERISTICS				
Gender (ref=Female)$		0.108	0.020	**<0.001**
Language (ref=Dutch)		-0.025	0.020	0.187
Region	Brussels (ref)	0.000		
	Flanders	-0.035	0.031	0.256
	Wallonia	-0.072	0.033	**0.029**
Age (Dutch)	<18 (ref)	0.000		
	18-24	-0.021	0.146	0.886
	25-44	0.065	0.128	0.610
	45-64	0.066	0.128	0.604
	65-74	0.078	0.140	0.577
	>74	-0.264	0.179	0.140
Age (French)	<18 (ref)	0.000		
	18-30	0.114	0.119	0.338
	31-40	0.087	0.113	0.444
	41-50	0.023	0.112	0.834
	51-60	0.014	0.114	0.904
	>60	0.081	0.115	0.482
Education level	No diploma/primary (ref)	0.000		

	Lower secondary	-0.004	0.078	0.960
	Upper secondary	-0.050	0.067	0.455
	Short type	-0.067	0.066	0.309
	Long type	-0.063	0.066	0.341
Paid job (ref=No)		-0.009	0.024	0.700
Health job (ref=No)		-0.043	0.023	0.056
Number of comorbidity		-0.013	0.006	**0.020**
LONG COVID				
Duration of COVID symptoms	Short (ref)	0.000		
	Mid	-0.055	0.026	**0.032**
	Long	-0.090	0.025	**<0.001**
Delta (VAS after-VAS before)		-0.009	0.000	**<0.001**
Hospitalisation (ref=No)		-0.048	0.028	0.085
Emergency care use (ref=No)		-0.069	0.023	**0.002**
Number of long COVID symptoms		-0.014	0.001	**<0.001**
Long COVID symptom: breathing difficulties (ref=No)		-0.121	0.019	**<0.001**
Long COVID symptom: fatigue (ref=No)		**-0.154**	0.023	**<0.001**
Long COVID symptom: lack of energy (ref=No)		**-0.163**	0.020	**<0.001**
Long COVID symptom: concentration problem (ref=No)		**-0.145**	0.019	**<0.001**
Long COVID symptom: headache (ref=No)		-0.116	0.019	**<0.001**
Long COVID symptom: difficulty or loss of memory (ref=No)		-0.119	0.019	**<0.001**
Long COVID symptom: muscle pain and weakness (ref=No)		-0.142	0.019	**<0.001**
Long COVID symptom: Join pain (ref=No)		-0.081	0.019	**<0.001**
Long COVID symptom: insomnia (ref=No)		-0.119	0.019	**<0.001**
Long COVID treatment (ref=No)		-0.115	0.019	**<0.001**
Inability to work (ref=No)		**-0.145**	0.021	**<0.001**
Financial impact (ref=No)		**-0.162**	0.019	**<0.001**
NEEDS				
Help for daily activities (ref=No)		-0.136	0.019	**<0.001**
Need: to talk to people (ref=No)		-0.108	0.018	**<0.001**
Need: to talk to profess (ref=No)		-0.114	0.019	**<0.001**
Need to talk to other (ref=No)		-0.084	0.021	**<0.001**
Need for additional help (Ref=No)		-0.142	0.0202	**<0.001**
Need for administrative help (ref=No)		-0.100	0.0297	**<0.001**
Need for religious support (ref=No)		-0.135	0.0544	**<0.001**
Type of long COVID information received	Very clear (ref)	0.000		

	Fairly clear	-0.046	0.032	0.153
	Not very clear	-0.068	0.035	0.054
	Not clear at all	-0.111	0.043	**0.009**
	None received	-0.059	0.034	0.085

SE=Standard Error, coef=coefficient, $Other gender (n=2) have been excluded in the analysis, Beta= EQ-5D-5L after- EQ-5D-5L before; new Belgian tariffs (2021 [198]) have been used to valuate the individual scores obtained with EQ-5D-5L tool.

Table 30 – Factor associated to Beta (EQ5D-5L* before-EQ5D-5L after), multivariate linear regression analysis

		Coef	SE coef	p-value
LONG COVID**				
Duration of COVID-19 symptoms	Short (ref)	0.000		
	Mid	-0.049	0.026	0.056
	Long	-0.088	0.025	**0.001**
Delta (VAS after-VAS before COVID-19)		-0.009	0.000	**<0.001**
Emergency care use (ref=No)		-0.073	0.022	**<0.001**
Number of long COVID symptoms		-0.014	0.001	**<0.001**
Long COVID symptom: breathing difficulties (ref=No)		-0.112	0.019	**<0.001**
Long COVID symptom: fatigue (ref=No)		-0.135	0.023	**<0.001**
Long COVID symptom: lack of energy (ref=No)		-0.152	0.020	**<0.001**
Long COVID symptom: concentration problem (ref=No)		-0.133	0.019	**<0.001**
Long COVID symptom: headache (ref=No)		-0.104	0.019	**<0.001**
Long COVID symptom: difficulty or loss of memory (ref=No)		-0.109	0.019	**<0.001**
Long COVID symptom: muscle pain and weakness (ref=No)		-0.129	0.019	**<0.001**
Long COVID symptom: join pain (ref=No)		-0.064	0.020	**0.001**
Long COVID symptom: insomnia (ref=No)		-0.109	0.019	**<0.001**
Long COVID treatment (ref=No)		-0.103	0.019	**<0.001**
Inability to work (ref=No)		-0.135	0.021	**<0.001**
Financial impact (ref=No)		-0.151	0.019	**<0.001**
NEEDS **				
Help for daily activities (ref=No)		-0.118	0.019	**<0.001**
Need to talk to people (ref=No)		-0.098	0.019	**<0.001**
Need to talk to professional (ref=No)		-0.104	0.019	**<0.001**
Need to talk to others with disease (ref=No)		-0.077	0.021	**<0.001**
Need for additional help (ref=No)		-0.137	0.020	**<0.001**
Need for administrative help (ref=No)		-0.100	0.030	**0.001**

Need for religious support (ref=No)		-0.128	0.054	**0.018**
Type of long COVID information received	Very clear (ref)	0.000		
	Fairly clear	-0.050	0.032	0.119
	Not very clear	-0.069	0.035	**0.047**
	Not clear at all	-0.109	0.042	**0.010**
	None received	-0.058	0.034	0.088

*SE=Standard Error, coef=coefficient, Beta= EQ-5D-5L after- EQ-5D-5L before; *new Belgian tariffs (2021 [198]) have been used to valuate the individual scores obtained with EQ-5D-5L tool, ** corrected for gender, region and number of comorbidities*

The VAS score is significantly different before and after acute COVID-19.

Patients scored their health status as worse after the infection. Patients who have been hospitalised for COVID-19 or who experience symptoms post-COVID-19 for more than 6 months report the highest impact on the visual analogue scale.

The results of the VAS score confirm what was found with the descriptive part of the EQ-5D-5L instrument, i.e. long COVID has a significant impact on health status valuation. There is a significant difference in VAS score before and after COVID (VAS before – VAS after (Delta): 25.70; p<0.001). Participants attributed a lower (0 being the worst health status – 100 being the best health status) VAS score after COVID-19 (average before: 84.83 (SD 12.71) – average after: 59.52 (SD 18.43)). This difference is significantly higher in hospitalised respondents (Delta not hospitalised 25.19; Delta hospitalised 29.05; p<0.001) (Table 31, Figure 9). VAS scores are also significantly different between groups of people who experienced symptoms for a short versus a long period of time (p<0.05) (Table 33, Table 32, Figure 9).

Table 31 – Visual analogue scale (VAS) scores before and after COVID-19, by hospitalisation status

Hospitalisation	N	Variable	Mean	SD	95% CI	p-value
						***
No	1 146	VAS before	84.97	12.75	84.23;85.71	
		VAS after	60.22	18.49	59.15;61.30	
		Delta°	**25.19**	16.96	24.21;26.18	
Yes	174	VAS before	83.94	12.45	82.08;85.81	
		VAS after	54.89	17.60	52.36;57.52	
		Delta°	**29.05**	17.51	26.43;31.67	
Total	1 320					
						**
		VAS before	84.83	12.71	84.15;85.52	
		VAS after	59.52	18.46	58.52;60.52	
		Delta°	**25.70**	17.07	24.78;26.63	

*°Delta = VAS after-VAS before; SD= Standard Deviation; CI= Confidence Interval; **Paired t-test total before-after: p<0.001; ***T-test (equal variance) Delta hospitalised – not hospitalised: p<0.001*

Figure 9 – Average Visual Analogue Scale (VAS) score before and after COVID-19, by hospitalisation status (right) and by duration of the symptoms (left) (n=1 320)

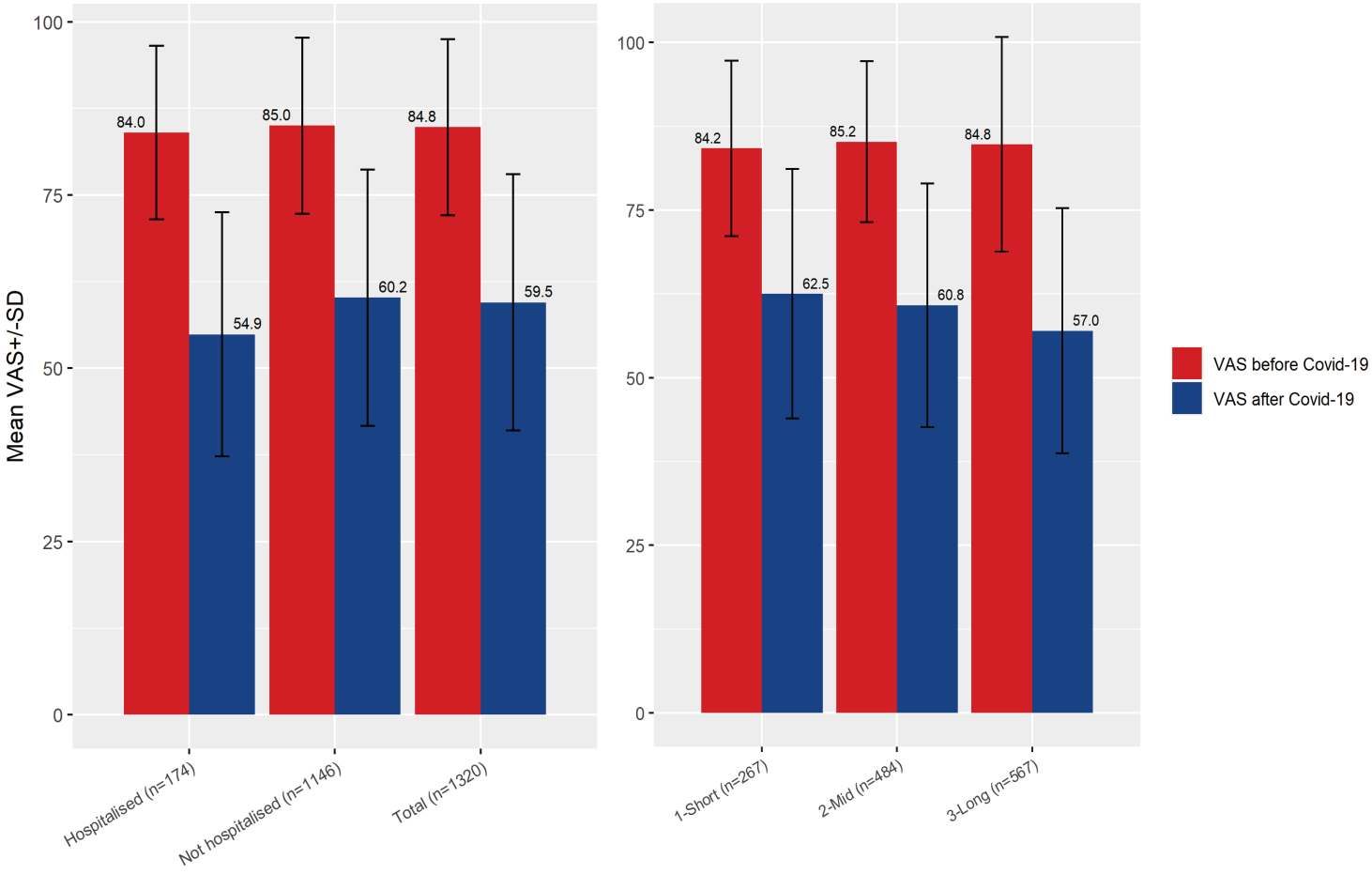


Table 32 – Visual Analogue Scale (VAS) score before and after COVID-19, by duration of the symptoms (n=1 320)

Duration of symptoms	N Obs	Variable	Mean	SD	95% CI	p-value
						***
Short	267	VAS before	84.19	13.10	82.61;85.77	
		VAS after	62.48	18.60	60.24;64.72	
		Delta	21.97	15.96	20.04;23.89	
Mid	484	VAS before	85.23	12.00	84.16;86.31	
		VAS after	60.83	18.17	59.21;62.46	
		Delta	24.82	17.49	23.26;26.39	
Long	567	VAS before	84.84	13.04	83.76;85.92	
		VAS after	56.98	18.29	55.47;58.49	
		Delta	28.29	16.82	26.90;29.67	

*Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months, missing duration for n=2; SD= Standard Deviation; CI=Confidence Interval; ***One-way Anova; p<0.001 (for Tukey comparison tests see Table 33).*

Table 33 - Comparison of delta (VAS score after-VAS score before), by COVID symptom duration group

Duration group	Difference Between Means Delta	95% CI		p-value
Long – Mid	3.461	1.007	5.916	*
Long – Short	6.319	3.376	9.263	*
Short – Mid	-2.858	-5.882	0.166	NS

*Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months; CI=Confidence Interval; *Tukey's test; p<0.05, NS=Not significantly different*

4.2.2.1 *Impact on employment*

More than half of the respondents with long COVID had an incapacity to work; among them more than a third were still not back to work.

Of the 1 076 people who had a job before acute COVID-19, more than half had an incapacity to work (642/1 076). For patients with an hospitalisation during acute COVID-19, 89.7% (113/126) reported job incapacity while this was 55.7% (529/950) in long COVID patients who were not hospitalised (p<0.001) (Table 33). Patients with long symptom duration were more frequently on job incapacity (68.5%) than the patients with short (52.8%) or mid (53.3%) symptom duration (p<0.001) (Table 35).

Table 34 – Incapacity to work, by hospitalisation status for COVID-19 (n=1 076)

	Hospitalised N (%)	Not hospitalised N (%)	p-value	Total N (%)
			***	
Incapacity	113 (89.7)	529 (55.7)		642 (59.7)
No incapacity	13 (10.3)	421 (44.3)		434 (40.3)
Total	126	950		1 076

****Chi-squared test, p<0.001*

Table 35 – Incapacity to work, by symptoms duration (n=1 076)

	Short N (%)	Mid N (%)	Long N (%)	p-value	Total N (%)
				***	
Incapacity	114 (52.8)	211(53.3)	317 (68.5)		642 (59.7)
No incapacity	102 (47.2)	185 (46.7)	146 (31.5)		434 (40.3)
Total	216	396	463		1 076

****Chi-squared test, p<0.001, long vs. short (p<0.001), long vs. mid (p<0.001), short vs. mid (p=0.9). Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months; missing duration for n=2.*

Overall, 33.5% of the respondents returned to work as before while 26.2% restarted part-time and 38% did not yet return to the job because of their health status. Also, 2.3% of the respondents indicated that they could not yet resume their job because of general COVID-19 measures. The percentage of respondents that could not resume work because of their health status was higher among patients that were hospitalised (43%) compared to those who were not hospitalised (39.9%) (p=0.13) (Table 36). It was also higher among patients with short symptoms duration (50.9%) with regards to those who had long (36.8%) or mid symptoms duration (33.9%) (p<0.001) (Table 37).

Table 36 – Back to work status, by hospitalisation status (n=642)

	Hospitalised N (%)	Not hospitalised N (%)	p-value	Total N (%)
			NS	
Back to work, as before	29 (25.7)	186 (35.2)		215 (33.4)
Back to work, less than before	3 (30.1)	134 (25.3)		168 (26.2)
Not back to work, because health state	49 (43.4)	195 (36.9)		244 (38.0)
Not back to work, because COVID measures	1 (0.9)	14 (2.6)		15 (2.3)
Total	113	529		642

NS=Not significantly different; Chi-squared test

Table 37 – Back to work status, by symptom duration (n=642)

	Short N (%)	Mid N (%)	Long N (%)	p-value	Total N (%)
				***	
Back to work, as before	40 (35.1)	118 (41.3)	57 (23.6)		215 (33.4)
Back to work, less than before	15 (13.2)	61 (21.3)	92 (38.0)		168 (26.2)
Not back to work, because health state	58 (50.9)	97 (33.9)	89 (36.8)		244 (38.0)
Not back to work, due to COVID measures	1 (0.9)	10 (3.5)	4 (1.7)		15 (2.3)
Total	114	286	242		642

****Chi-squared, p<0.00; long vs. short (p<0.001), long vs. mid (p=0.02), short vs. mid (p=0.01); Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months; missing duration n=2*

4.3 Reported healthcare utilization long COVID patients

General practitioner: most consulted professional – vast majority of long COVID patients is satisfied with the care received

Within the context of long COVID, the general practitioner (GP) was the most frequently consulted healthcare professional (90.8% of the respondents reported that they consulted a GP). This was followed by medical specialists (50.8% of the respondents), physiotherapists (30.3%), staff of emergency departments (21.4%) and psychologists (16.3%) (Table 38). Most of the participants were very satisfied or satisfied with the contact with their GP (75.3% very satisfied or satisfied), medical specialists (pulmonologist (80.4%), cardiologist (79.2%), ENT specialist (76.3%)), physiotherapists (86.9%), or psychologist (84.8%). The satisfaction with emergency department professionals was somewhat lower: 66.1% of respondents reported being satisfied or very satisfied (Table 39).

Table 38 – Healthcare utilisation (n=1 320)

	Total (%)
GP	1 199 (90.8)
Medical specialist*	670 (50.8)
Physiotherapist	399 (30.2)
Emergency department Team	283 (21.4)
Psychologist	212 (16.3)
Rehabilitation department team	100 (7.6)
COVID-Unit team	91 (6.9)
Osteopath**	58 (4.4)
Home nursing	39 (3.0)
Speech & Language therapist	32 (2.4)
Alternative medicine**	31 (2.3)
Social worker	23 (1.7)

** See Table 42 for information on medical specialists; **these are not formal healthcare workers but were included in the questionnaire to get an estimate on the use of alternative and complementary medicine in the group of long COVID patients*

It is interesting to observe that the satisfaction of participants with COVID-19 symptoms for > 6 months is (significantly) lower than the other participants (short-mid duration) whatever the type of healthcare used. This difference in satisfaction is particularly observed for GP contacts. Differences in satisfaction may reflect an improvement in the knowledge of COVID and therefore in the care management of patients suffering from COVID over time. But it can also reflect patients' exasperation with the duration of their symptoms which are not relieved by health professionals (Table 39).

Table 39 – Proportion of satisfied or very satisfied respondents, by healthcare provider and by duration of symptoms

		Short N (%)	Mid N (%)	Long N (%)	p-value	Total N (%)
GP		202 (86.7)	342 (78.6)	353 (67.6)	***	898 (75.3)
Specialist	***Pulmonologist***	54 (100)	98 (89.9)	172 (71.7)	***	324 (80.4)
	Cardiologist	40 (93.0)	76 (84.4)	153 (73.9)	**	270 (79.2)
	Neurologist	13 (86.7)	28 (73.7)	77 (60.6)	NS	118 (65.6)
	ENT specialist	18 (94.7)	25 (80.6)	62 (70.5)	NS	106 (76.3)
Physiotherapist		53 (100)	101 (87.1)	191 (83.8)	**	345 (86.9)
Emergency department team		38 (80.9)	55 (69.6)	94 (59.9)	*	187 (66.1)
Psychologist		22 (95.7)	43 (87.8)	113 (81.9)	NS	178 (84.8)
Revalidation department team		7 (100)	20 (87.0)	55 (78.6)	NS	81 (81.0)
Covid-Unit team		25 (92.6)	24 (96.0)	26 (74.3)	*	75 (86.2)

**** Chi-squared p-value <0.001; ** Chi-squared p-value <0.01; * Chi-squared <0.05; Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months; duration is missing for n=2*

Self-reported healthcare utilisation: similarities and differences between patients who had been hospitalised for COVID-19 and those who had not

Almost all patients, whether they had been hospitalised for COVID-19 or not, consulted a general practitioner (89.7% and 90.4% respectively). For the other healthcare professionals, the reported healthcare utilisation differed between the two groups. Patients who had been hospitalised were significantly more likely to consult a medical specialist (78.2%) than the patients who had not been hospitalised (46.6%) (p<0.001). The same observation can be made for the other healthcare services presented in Table 40 i.e. for the physiotherapist, emergency department team, psychologist, rehabilitation department team and COVID-Unit team.

Table 40 – Healthcare utilization, by hospitalisation status (n=1 320)

	Not hospitalised (%) N=1 146	Hospitalised (%) N=174	p-value
GP	1 036 (90.4)	156 (89.7)	NS
Medical specialist*	534 (46.6)	136 (78.2)	***
Physiotherapist	303 (26.4)	96 (55.2)	***
Emergency department Team	178 (15.5)	105 (60.3)	***
Psychologist	161 (14.0)	51 (29.3)	***
Rehabilitation department team	53 (4.6)	47 (27.0)	***
Covid-Unit team	29 (2.5)	62 (35.6)	***

** See Table 42 for information on specialist, ***Chi-squared, p-value<0.001; NS=Not significantly different*

Self-reported healthcare utilization: highest in long COVID patients >6 months post infection

Patients with more than 6 months of duration of COVID-19-related symptoms reported significantly more use of health services than patients with more recent duration of COVID-19-related symptoms (4-12 weeks or 3 months-6 months), regardless of the type of health service. For all three groups of COVID-19 symptom duration, general practitioners, medical specialists and physiotherapists were the health professionals consulted by most patients (Table 41).

Table 41 – Healthcare utilization, by duration status (n=1 318)

	Short N=267	Mid N=484	Long N=567	p-value
GP	233 (87.3)	435 (89.9)	522 (92.1)	*
Specialist^	89 (33.3)	196 (40.5)	384 (67.7)	*
Physiotherapist	53 (19.9)	118 (24.4)	228 (40.2)	*
Emergency department Team	47 (17.6)	79 (16.3)	157 (27.7)	*
Psychologist	23 (8.6)	50 (10.3)	139 (24.5)	*
Revalidation department team	7 (2.6)	23 (4.8)	70 (12.3)	*
COVID-Unit team	28 (10.5)	79 (16.3)	36 (6.3)	*

*^See Table 42 for information on specialist, *Chi-squared, p-value<0.05, Missing duration for two respondents; Short = 4 weeks to 3 months; Mid=3 to 6 months; Long=More than 6 months*

Pulmonologists and cardiologists reported as most consulted medical specialists

The variety of consulted medical specialists illustrates that COVID-19 (and by extension long COVID) is a multi-system disorder not limited to the respiratory system. Among the participants who reported having consulted a medical specialist (n=670), the most consulted were the pulmonologist (63.4%), the cardiologist (55.1%), the neurologist (29.2%) and the ENT specialist (22.0%) (Table 42).

Table 42 – Most consulted specialists amongst patients suffering from long COVID (n=670)

Specialist	N (%)
Pulmonologist	412 (63.4)
Cardiologist	358 (55.1)
Neurologist	190 (29.2)
Nose, Throat and Ear (ENT) Specialist	143 (22.0)
Specialist in Physical Medicine and Rehabilitation	103 (15.8)
Gastroenterologist	98 (15.1)
Ophthalmologist	65 (10.0)
Psychiatrist	59 (9.1)
Infectious Disease Specialist	54 (8.3)
Dermatologist	50 (7.7)
Rheumatologist	43 (6.6)
Paediatrician	8 (1.2)
Geriatrician	2 (0.3)
General Internist (General Internal Medicine)	1 (0.2)

Care perceived as needed but not received

To the question *'Is there care for long COVID that you did not get when you needed it?'* 33.0% of the respondents (n= 1 320) answered 'Yes'. Patients who had been hospitalised for COVID-19 reported more (38%), though not statistically significant, unmet care needs compared to patients who had not been hospitalised for COVID-19 (32%) (Table 43).

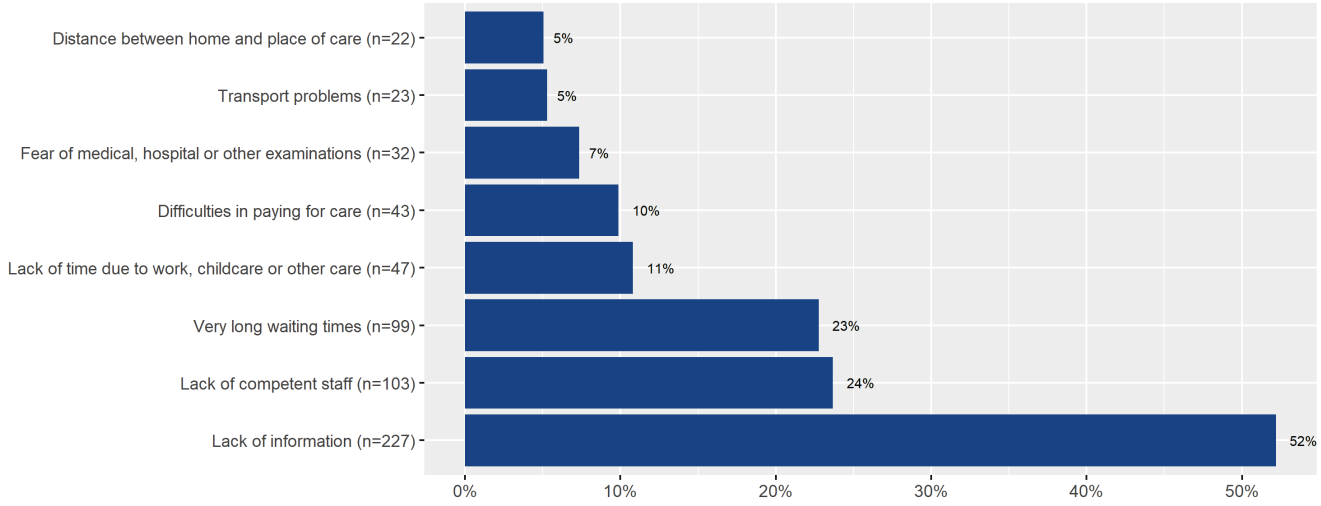
Table 43 – Unmet care needs, by hospitalisation status (n=1 320)

	Not-hospitalised N (%)	Hospitalised N (%)	Total N (%)
Yes	367 (32.0)	68 (38.1)	435 (33.0)
No	494 (43.1)	72 (41.4)	566 (42.9)
Do not know	285 (24.8)	34 (19.5)	319 (24.2)
Total	1 146 (86.8)	174 (13.2)	1 320

Lack of information is the most frequently reported cause of unmet care needs

The most common reported reasons for unmet care needs (reported by 435 respondents) were the lack of information (52%), the lack of competent staff to give care needed (24%), and the very long waiting times to get access to care (23%) (Figure 10).

Figure 10 – Causes of unmet care needs (n=435)



Some respondents added unmet needs in the free-text boxes (n=148). Each free-text boxes contained one or several answers. Some respondents referred to the acute episode of COVID: this does not fit into our analysis (quotes), although we acknowledge that for the patients this might be an important first step in their care. In addition, there were also a number of people who considered a screening test as care.

The main reasons for unmet care needs are illustrated inBox 3.

Box 3 – Illustrations of unmet needs given in the open-ended question on healthcare utilization

- **Physicians' knowledge (or lack of knowledge) about the condition and general attitude: either physicians were unaware of this new condition for which little or no scientific data were available, or physicians did not take into account the patients' symptoms and attributed them to persistent symptoms of COVID (without talking about long COVID) or to psychological factors.**

  'Heb indruk dat huisarts niet goed wist wat of hoe met COVID'

  'La non connaissance complète des séquelles du COVID'

  'on pensait que j'exagerais'

- **Patient profile: some participants explained that they had not received care because their profile was not considered to be 'at risk' or their state of health was not considered to be 'serious' enough to justify a contact with the healthcare system.**

  'Wegens niet op IC gelegen te hebben heb ik geen recht om revalidatie te volgen in erkend centrum.'

  'Ma médecin m'a dit de ne pas aller à l'hôpital car ils ne me prendraient pas vu mon âge.'

- **Lack of physical consultations: while most respondents who mentioned this reason were excluded because they were talking about the acute episode, also patients with long COVID had to deal with the situation that in a certain period of time consultations were only done at a distance when patients had symptoms. Some clearly expressed that the remote consultations did not result in an appropriate response for their health condition and care needs.**

  'Pas de possibilité de voir le généraliste, consultations tous les quatre– -cinq jours par téléphone.'

  'enkel telefonisch consult mogelijk of zelfs onderzoek niet mogelijk wegens COVID restricties'

- **Refusal of access to care or lack of offer of care by healthcare professionals with or without justification.**

  'Refus des médecins de faire des analyse plus poussées... refus d'essayer des traitements'

  'eigen huisarts en kinesist wilden geen COVID patiënten behandelen; zijn bang om het zelf te krijgen'

- **Other various reasons such as: fear of the medical profession, feelings of shame, cost or limited reimbursement of healthcare services, lack of information on where to turn, etc.**

  'Ik schaamde me omdat ik dacht dat mijn omgeving me niet geloofde/me zou uitlachen'

  'Je ne sais pas à qui m'adresser'

  'Pas assez de concentration pour trouver les infos, faire les démarches'

4.4 Treatments and satisfaction

Just under half of respondents are following (or have followed) 'treatment' for long COVID. Hospitalised participants reported following a treatment for long COVID more frequently than the participants who had not been hospitalised. The most common treatments were prescribed drugs, complementary treatments and over-the-counter drugs.

To the question, « *Are you taking (or have you taken) any treatment for your long COVID*? », 41% of respondents (545/1 320) answer 'Yes'. Patients who had been hospitalised reported significantly following a treatment for long COVID more frequently than the participants who had not been hospitalised (hospitalised: 64.4%; not hospitalised: 37.8%; p-value<0.001). The patients with short duration of symptoms (4 weeks-3 months) reported following a treatment for long COVID significantly less frequently than the patients with mid or long duration of symptoms (short vs. mid: 35.2% vs. 40.5%, p-value=0.04 ; short vs. long: 35.2% vs. 45.0%, p-value=0.02). The majority of participants was taking a prescribed drug (71.0%) and/or a complementary treatment (54.1%), like vitamins, homeopathy, naturopathy, food supplements, etc. (Table 44). Among the participants who received prescribed, complementary or over-the-counter drugs, only a little more than a half were very satisfied or satisfied with the treatment received (satisfied or very satisfied: prescribed drugs 57.3%, complementary drugs 57.5% and over-the-counter drugs 55.8%).

The proportion of participants who followed prescribed drugs, complementary treatment, over-the-counter drugs and oxygen at home for long COVID was significantly higher amongst participants who had been hospitalised than amongst the non-hospitalised respondents (Table 44).

Table 44 – Self-reported treatment for long COVID, by hospitalisation status

Treatments	Hospitalised (n=112) N (%)	Not hospitalised (n=433) N (%)	p-value	Total (n=545) N (%)
Prescribed drugs	89 (79.5)	298 (68.8)	*	387 (71.0)
Complementary treatment	46 (41.1)	249 (57.5)	**	295 (54.1)
Over-the-counter drugs	16 (14.3)	100 (23.1)	*	116 (21.3)
Physiotherapy	14 (12.5)	47 (10.9)	NS	61 (11.2)
Multidisciplinary rehabilitation	7 (6.3)	15 (3.5)	NS	22 (4.0)
Oxygen at home	14 (12.5)	3 (0.7)	***	17 (3.1)
Other	4 (3.6)	13 (3.0)	NS	17 (3.1)
Olfactive therapy	0 (0.0)	7 (1.6)	NS	7 (1.3)
Respiratory assistance	1 (0.9)	1 (0.2)	NS	2 (0.4)
Osteopathy	0 (0.0)	2 (0.5)	NS	2 (0.4)
Nervous vagus stimulation	0 (0.0)	2 (0.5)	NS	2 (0.4)
Speech therapy	0 (0.0)	2 (0.5)	NS	2 (0.4)

**Chi-squared p-value<0.05, **Chi-squared p-value<0.01; ***Chi-squared p-value<0.001; NS=Not significantly different*

The duration of symptoms was not significantly associated with the reported treatment (Table 45).

Table 45 – Self-reported treatment for long COVID, by duration of symptoms

Treatments	Short N (%)	Mid N (%)	Long N (%)	p-value
Prescribed drugs	65 (69.1)	149 (76.0)	173 (67.8)	NS
Complementary treatment	44 (46.8)	110 (56.1)	141 (55.3)	NS
Over-the-counter drugs	27 (28.7)	38 (19.4)	51 (20.0)	NS
Physiotherapy	11 (11.7)	17 (8.7)	33 (12.9)	NS
Multidisciplinary rehabilitation	2 (2.1)	6 (3.1)	14 (5.5)	NS
Oxygen at home	4 (4.3)	9 (4.6)	4 (1.6)	NS
Other	2 (2.1)	5 (2.6)	10 (3.9)	NS
Olfactory therapy	0 (0.0)	3 (1.5)	4 (1.6)	NS
Respiratory assistance	1 (1.1)	0 (0.0)	1 (0.4)	NS
Osteopathy	0 (0.0)	1 (0.5)	1 (0.4)	NS
Nervous vagus stimulation	0 (0.0)	0 (0.0)	2 (0.8)	NS
Speech therapy	0 (0.0)	0 (0.0)	2 (0.8)	NS

Short: 4 weeks-3months; Mid: 3 months-6 months; Long: ≥6 months; missing duration n=2; Chi-squared, NS=Not significantly different

More than half of the respondents with treatment does not consider it as burdensome

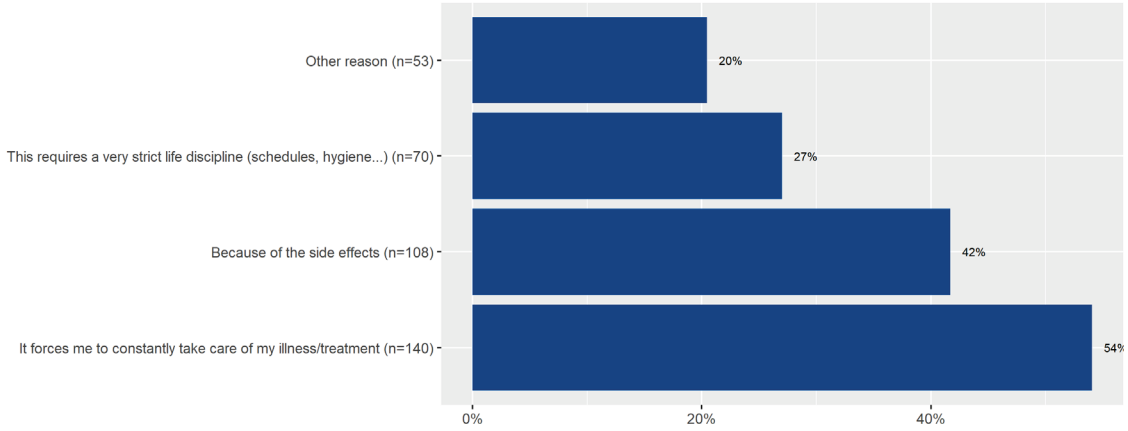
The majority of respondents (52.5%; 286/545) did not find their treatment burdensome (Table 45). Yet 259 out of 545 respondents indicated that there was a burden: 142 (26%) found it rather burdensome, 73 (13.4%) very burdensome and 44 (8.1%) extremely burdensome.

Table 46 – Burden of treatment (n=545)

	N (%)
Not at all burdensome	286 (52.5)
Rather burdensome	142 (26.1)
Very burdensome	73 (13.4)
Extremely burdensome	44 (8.1)

The most frequent reason why respondents experienced some kind of burden was because it reminds them constantly to take care of their medical condition/treatment (n=140 or 54%). Burden due to side-effects was also frequently mentioned (42% or 108/259) (Figure 11).

Figure 11 – Reported reasons why treatments were experienced as rather, very or extremely burdensome (n=259)



Box 4 presents other reasons reported by those who did find their treatment burdensome.

Box 4 – Other reasons reported to by those who did find their treatment burdensome

The treatment was tiring (n=11). Fatigue could, according to the participants, take several forms: fatigue related to multiple journeys, multiple consultations but some participants expressed the fact that it was the rehabilitation session itself that was tiring and required a lot of energy.

'Te vermoeiend' 'prend beaucoup (…) d'énergie'

The treatment was painful (n=14): for instance the rehabilitation sessions could be painful but patients also complained about pain after the rehabilitation sessions.

'Pijn tijdens de behandeling (osteopathie)' 'Na de kinesitherapie (0,5h) (…) had ik achteraf ook extra spierpijn'

The treatment was discouraging (n=9): progress was very slow and/or not very visible. Patients are confronted with their limits, feel alone/isolated or not listened to by medical professionals, experience a lack of follow-up or consideration for their situation.

'Sous puff de cortisone depuis des mois, plusieurs fois par jour, pas vraiment d'évolution, j'en ai marre!'

'Dagelijks inspanningen leveren en heel weinig vooruitgang.'

Other reasons mentioned (n=18): time consumption, cost, impact on professional and/or family life.

Reported side effects: difficult to distinguish from long COVID symptoms

Among the respondents who are following (or have followed) treatment for long COVID, 27.2% reported suffering from side-effects (n=148/545).

The most reported side-effects of the long COVID treatment were fatigue or exhaustion (19.6%), heart palpitations (13.5%), constipation and/or diarrhea (9.5%), headaches (7.4%), shortness of breath and breathing difficulties (6.8%), abdominal pain (6.8%), nausea/vomiting (6.8%), high blood pressure (6.1%) and dry mouth (6.1%) (Table 46). Several headings are found in both categories (treatment side-effects or long COVID symptoms). Fatigue, for instance, is the most frequently reported side-effect of treatment and the most frequently reported symptom of long COVID (see subsection 4.2.1). These results should be interpreted with caution.

Table 47 – Top 10 most reported side effects of long COVID treatment (n=148)

Side effects	N (%)
Fatigue and/or exhaustion	29 (19.6)
Heart palpitations	20 (13.5)
Weight gain	20 (13.5)
Constipation and/or diarrhoea	14 (9.5)
Headaches	11 (7.4)
Shortness of breath, breathing difficulties or respiratory problems	10 (6.8)
Abdominal pain	10 (6.8)
Nausea/vomiting	10 (6.8)
High blood pressure	9 (6.1)
Dry mouth	9 (6.1)

Only 24% of the respondents (132/545) were concerned about possible long-term adverse effects from one or more of the treatments they received to treat their long COVID. Participants had two types of concerns (see Box 5).

Box 5 – Main concerns about possible long term adverse effects from long COVID treatments

Concerns about the consequences of COVID-19 and/or long COVID (n=72): these consequences did not answer the question asked about treatments and were therefore excluded from the analysis.

Concerns about taking medication for long COVID (n=42):

- concerns about possible dependency that could develop when medicines are taken over a long period of time (n=4).

'Dosage difficile, dépendance'

'Dank zij de puffers is de pijn op de borst dragelijker. Maar ik ben bang dat dit misschien permanent zal zijn …….. en niet na maanden zal verdwijnen en ik afhankelijk zal blijven van deze medicatie'

Concerns about side-effects that sometimes lead to other serious health problems or about the lack of effectiveness of medicines or even deterioration of health due to the use of specific drugs (n=38)

'Langdurig gebruik corticosteroïden verzwakt het immuunsysteem'

'Beaucoup de médicaments et peut-être un risque de problème hépatique'

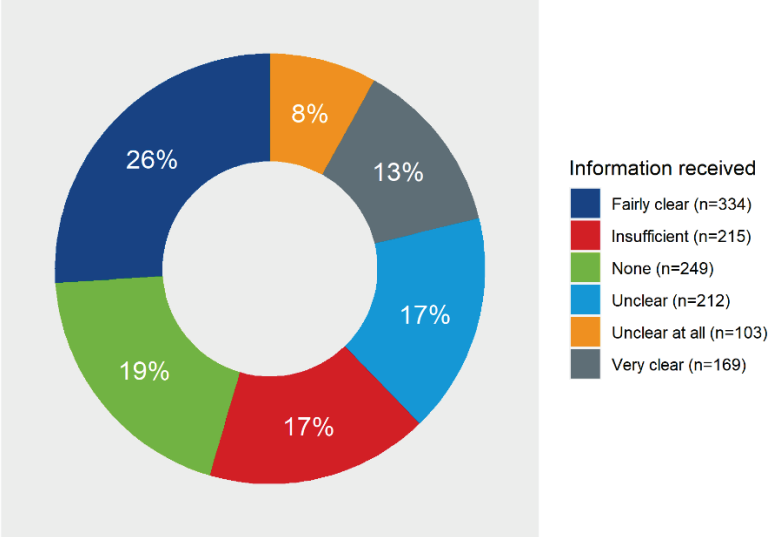
'J'ai l'impression que je ne guéri pas et que mon état se dégrade avec des traitements'

4.5 Information needs

A clear need for better and more information on long COVID and its treatment

There is a need for (clear) explanation regarding long COVID and its treatment. Issues with the provision of information were reported by 60.1% (779/1 295[h]) of the respondents. It is remarkable that 19.2% of the respondents (249/1 295,) indicated that they did not receive information at all from healthcare staff. Even when information was received, it was insufficient or unclear for 16.6% (215/1 295) and 24.3% (315/1 295) of the participants respectively. Only 38.8% (503/1 295) of the respondents received fairly good or very clear explanations regarding long COVID and its treatment (Figure 12).

Figure 12 – Distribution of the quality of information regarding long COVID and its treatment (n=1 295)



NB: 25 participants did not know the quality of information received

Healthcare workers ask for more additional information compared to people not professionally active in the healthcare sector

To the question "*Did you request additional information to long COVID and its treatment?",* 76.8% of the respondents (1 014/1 320, 'did not know if they asked for additional information' for n=15) responded 'No'.

We observed that the healthcare workers requested significantly more frequently additional information than non-health workers (82.6% of health

h 25 participants did not know the quality of information received

workers vs. 76.3% of non-health workers requested additional information, p=0.02).

Additional information requested and quality of the information received

In Table 48, a link is made between the requested additional information and the perceived quality of information. We aimed to show if the proportion of respondents who reported requested for additional information is higher among the participants who received no, insufficient or poor quality (unclear, completely unclear) information.

There was a greater proportion of patients who requested additional information among those who did not receive information at all (i.e. those who answered "none" to the question concerning the quality of the information received). Of those who initially reported receiving no information, 30.5% did not ask for additional information. Participants who received insufficient, completely unclear and unclear information more frequently requested for additional information than the respondents who did not initially receive information (Table 48).

Table 48 – Information needs, by quality of the initial information received (n=1 292)

Additional info requested	None N (%)		Insufficient N (%)		Completely unclear N (%)		Unclear N (%)		Fairly clear N (%)		Very clear N (%)		Do not know N (%)	Total N (%)
Yes	173	(69.5)	173	(80.5)	95	(92.2)	190	(89.6)	245	(73.4)	128	(75.7)	10 (43.5)	1 014 (78.5)
No	76	(30.5)	42	(19.5)	8	(7.8)	22	(10.4)	89	(26.6)	41	(24.3)	13 (56.5)	291 (22.5)
Total	249	(100)	215	(100)	103	(100)	212	(100)	334	(100)	169	(100)	23 (100)	1 292

15 patients responded "I don't know" on the question whether they requested additional information

Type of additional information requested

Of the respondents who requested additional information (n=1 014), the most commonly requested additional information related to changes in the health state (73.8%), the illness (67.5%) and the treatment possibilities (61.7%) (Table 49). In Box 6 a summary of the answers to the open-ended question is given.

Table 49 – Type of additional information requested (n= 1 014)

Kind of information	N (%)
Changes in health state	748 (73.8)
Their illness	684 (67.5)
Treatment possibilities	626 (61.7)
Clinical trials related to treatment	287 (28.3)
How the diagnosis was made	269 (26.5)
Patient associations	175 (17.3)
Available support services	163 (16.1)
Place where treatment is possible	125 (12.3)
Accompaniment, psychological support, coaching	116 (11.4)
Access to personal health data	109 (10.7)
Cost of the treatment and the expenses in charge of patient	70 (6.9)
Therapeutic education	56 (5.5)
Other type of information*	29 (2.9)
Patients' rights	42 (4.1)
Return to home and possible accommodation	16 (1.6)

**See Box 6 for details*

Box 6 – Other types of additional information requested (n=29)

Professional accommodations (n=1)

Long-term complications of the acute disease (n=3)

'cardiovascular risk, neurological risk'

'reduced vision, chest pain after Covid-19'

Recognition/status of the disease as professional disease (n=3)

Sharing experiences of other patients who have (had) long COVID (n=8)

Medical and scientific publications either on long COVID or other similar illnesses like SARS-Cov-2 (n=8)

Loss of income (n=1)

Other different personal request (n=5)

- e.g. confinement of family

Perceived need to be more involved in decision making

Finally, 39.4% of the participants (520/1 320) would like or have liked to be more involved in the choices about their treatment(s) for long COVID. This proportion is significantly different between the health workers and the non-health workers (37.7% vs. 40.8%, p<0.01); but not significantly different between the hospitalised and non-hospitalised respondents (39.4% vs. 39.1%, p=0.06).

4.6 Financial impact

More than one in three respondents reported experiencing a financial impact of Long COVID

To the question: "*Has your health condition related to long COVID (had) a financial impact on your household?*" almost 58% (n=764/1 320) of respondents answered 'No', 37% (n=491/1320) answered 'Yes'; and 5% (n=65/1320) 'Don't know'. The proportion of respondents with financial impact of COVID-19 was significantly higher among those who were hospitalised (hospitalised: 52.3% vs. not hospitalised: 34.9%, p<0.001) and among those who reported post-acute COVID-19 > 6 months (long: 47.1%, mid: 32.6%, short: 24.7%, p<0.001).

Those who experienced a financial impact of their disease were asked for which reason(s) but not all of them gave a reason. We received answers from 479 out of 491 respondents to experience a financial impact. Each of these 479 respondents gave one or several reasons. The main responses had been classified into the following broad categories: loss or lowering of income due to illness; increased medical expenses; a combination of both and direct costs related to long COVID. Loss or absence of income/employment (n=214), medical expenses (n=68) or a combination of

both (n=56) are the main reasons reported for financial impact. More details on the financial impact of COVID-19 are presented in Box 7.

Box 7 – Main reported financial impacts of long COVID

- **Loss or absence of income/employment**

The main reported reason for loss of income was the fact that respondents had been ill and received a health insurance benefit (n=71) which is lower than their full salary and also implies a loss of additional benefits (e.g. loss of meal vouchers).

'Ik leef nu op een uitkering van het ziekenfonds. Dat is ongeveer 1/3 van mijn normaal netto loon'

'Pas de chèque repas, impact sur mon plan cafétéria'

When returning back to work several respondents reported that they were not able to start full-time straight away. Respondents reported that they had returned to work part-time, which also reduced their income.

'J'ai travaillé à mi-temps pendant 8 mois parce qu'il était impossible physiquement et mentalement de travailler à temps plein à cause des symptômes invalidants du COVID long'

'Loss income included people without rights to social security benefits, those who lost their job due to illness or those who was already unemployed which have a higher financial impact of their condition.'

'Contrat CDD non renouvelé car beaucoup d'absence sur plusieurs mois... Pas de compréhension de la part de l'employeur.'

'Job verloren wegens tijdelijk contract niet te verlengen.'

'Heb moeten leven van een minimale OCMW uitkering (had geen jaar gewerkt dus geen recht op)'

- **Work Incapacity**

A distinction was made between respondents who mentioned an incapacity for work and the payment of compensation (these patients were categorised in the loss of income category) and the respondents who mentioned an incapacity for work without financial compensation.

'Je ne sais plus travailler beaucoup, trop vite épuisé'

'Ik heb door deze COVID-infectie al maanden (> 6 maanden) mijn werk niet kunnen hervatten.'

For some respondents, the loss income was not limited to themselves. Several respondents reported that their absence of work coincided with income loss of their partners who were ill at the same time. Other stated that after being absent of work due to illness they also had to take additional time off to care for their relatives who were off sick.

'Ik krijg sinds begin juni een ziekte uitkering. Dit is minder dan mijn loon, (…). Mijn man heeft dit ook, dus het gaat om veel geld elke maand'

'Mon mari a dû prendre congé sans soldes pour s'occuper des 4 enfants pendant 4 semaines.'

There are contradictory statements from respondents with self-employed status. Some of them (n=12), specifically mentioned a loss of income due to the payment of indemnities.

'Étant indépendante, j'ai touché le minimum.'

'Als zelfstandige krijg je per maand iets meer dan 1000,00€.'

Other respondents with self-employed status indicated that they had no income.

'Pas de revenus car indépendante'

'Als zelfstandige heeft de zaak moeten sluiten, dus geen inkomen'

- **Medical expenses**

The reported financial impact related to medical expenses mainly concerned (n=48/68) reimbursed services related to medical examinations, consultations with the general practitioner and/or specialist(s) and hospitalisation. In this case, the financial difficulty related to the fact that having to make an advance payment before being reimbursed and to the multiplicity of health professionals consulted to get a diagnosis. Yet the reported financial impact also concerns expenses for services that are not or only partly reimbursed (e.g. consultations with psychologist), alternative therapies (n=20) and non-reimbursed products (e.g. vitamin supplements).

'Tous ces rendez-vous médicaux chez divers spécialistes, les prises de sang et autres analyses, les séances kinés et psy... ont quand même constitué un sacré budget sur les 8 derniers mois.'

'Kosten hospitaal €14 7000. Vrouw opgenomen gedurende een maand op neurologie. Door weerbots feit van mijn ziekte €40 000 kosten kine, psychiater, acupunctuur personal coach €6 000 tot nu toe.'

'Traitement via vitamines très coûteux (de l'ordre de 200€ Tous les mois et demi)'

- **Combination of loss of income and increased medical expenses**

Some respondents clearly indicated that a combination of the above two factors was the cause of their financial difficulties.

'Coûts d'un traitement et perte financière des revenus'

'Kostprijs van de zorgverleners, en/of onderzoeken tijdens verlies van inkomen'

- **Direct costs related to long COVID**

This category concerns purchases and adaptations directly related to long COVID which are not directly medical expenses or alternative therapies. It concerns for instance the purchasing of an electric bicycle to deal with their limited physical capacity, the purchasing of protective equipment (e.g. masks), additional household costs, and increased costs for transport (e.g. frequent medical visits.)

'Véél hogere uitgaven aan medicatie, kine therapie, (…) mondmaskers, handschoenen, ontsmettingsproducten voor handen, kuisen'

'Aankoop medische hulpmiddelen (krukken, wandelstok, elektrische fiets omdat gewoon fietsen niet meer lukt)'

'Dépenses additionnelles pour aide-ménagère'

'Tous les frais engendrés par (…) les nombreux trajets vers les hôpitaux.

4.7 Social support needs for activities of daily living due to long COVID

More than one in two Long COVID patients require support with activities of daily living

Almost 52% (n=686/1 320) 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 more frequently reported help needs for daily activities than the participants who were not hospitalised (hospitalised 69.5% vs. not hospitalised 49.3%, p<0.001). Hospitalised respondents also required significantly more help for hygiene (hospitalised 33.9% vs. not hospitalised 10.3%, p<0.001), dressing (28.9% vs. 9.4%, p<0.001) and transportation/journeys (66.1% vs. 47.3%, p<0.001).

Duration of the symptoms also played a significant role in the help needed. Patients with post-acute COVID-19 >6 months had more frequently help needs than patients with mid or short duration of symptoms (long 57.8%, mid 47.1%, short 48.1%, p<0.01). Duration of symptoms was also significantly related to help 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).

Informal caregivers play an important role when additional support is needed

The extent to which respondents reported to have received care and by whom differs per topic. Globally, in more than 80% of cases, participants reported receiving social support, which could be from an informal caregiver or a professional caregiver. The activities of daily living for which participants received the most support were hygiene (90%), dressing (89%) and transport (86%). For support with housecleaning, meals, these percentages were lower with respectively 81%, and 83%.

From Figure 13 it can be observed that informal caregivers play an important role in the provision of social support. In more than 65% of cases that reported exeperiencing a need for social support, this help was provided by an informal caregiver. The percentage varied from 68% for hygiene care to 82% for transportation/journeys.

The role of professional caregivers was very limited in the support with meals (4%) and transportation (3%). The percentage of respondents that reported to have received professional care was the highest for hygiene care (22%) and dressing (19%) followed by house cleaning (11%).

The proportion of informal and professional carers who brought help for hygiene and dressing was significantly different between hospitalised and not hospitalised respondents (p<0.001). Indeed the informal carers were more frequently solicited for dressing and hygiene in non-hospitalised patients than the professional carers. Also, the non hospitalised participants almost received no help for these two daily life activities whereas hospitalised participants received it more frequently (Table 50).

There was no difference in the type of social support received between the different symptom duration groups (short, mid and long).

Figure 13 – Social support needs of patient with long COVID

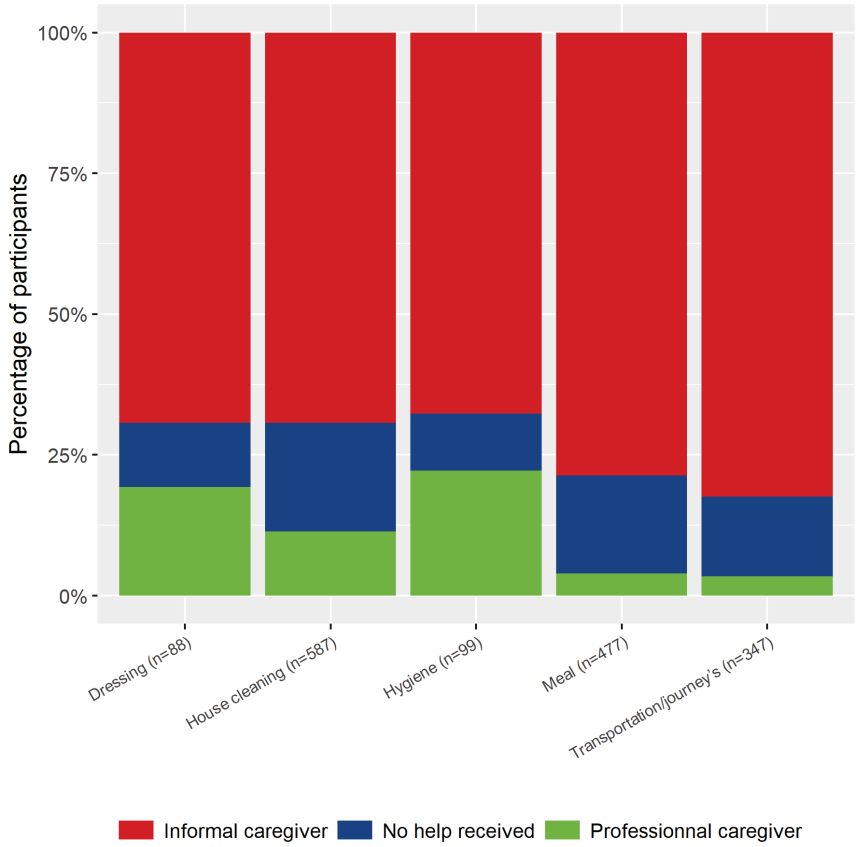


Table 50 – Social support needs of patient with long COVID, by hospitalisation status

		Hospitalisation N (%)	No hospitalisation N (%)	p-value
Hygiene				***
	Informal caregiver	21 (51.2)	46 (79.3)	
	Professional caregiver	20 (48.8)	2 (3.4)	
	No help	0 (0.0)	10 (17.2)	
Dressing				***
	Informal caregiver	18 (51.4)	43 (81.1)	
	Professional caregiver	16 (45.7)	1 (1.9)	
	No help	1 (2.9)	9 (17.0)	
Transportation/ journey's				NS
	Informal caregiver	64 (80.0)	222 (83.1)	
	Professional caregiver	6 (7.5)	6 (2.2)	
	No help	10 (12.5)	39 (14.6)	
Cleaning				NS
	Informal caregiver	65 (65.0)	342 (70.2)	
	Professional caregiver	18 (18.0)	49 (10.1)	
	No help	17 (17.0)	96 (19.7)	
Meal preparation				NS
	Informal caregiver	66 (77.6)	309 (78.8)	
	Professional caregiver	6 (7.1)	13 (3.3)	
	No help	13 (15.3)	70 (17.9)	

****Chi-squared, p-value<0.001, NS=Not significant*

Respondents reported a need for several other activities

Additional to the predefined needs in the questionnaire, other needs were expressed in the open field by 94 respondents (Box 8).

Box 8 – Need for several other activities

- **Shopping and/or carrying heavy things (n=46),**
- **Caring for children and pets (n=33)**
- **Administrative tasks (including making medical appointments or asking questions to healthcare professionals; n=15)**
- **Need for companionship, listening and moral/psychological support was mentioned by 11 participants.**
- **Needs resulting specifically from the symptoms of long COVID (n=21) i.e. needs to 'compensate' for long COVID problems such as problems with concentration or memory:**

  'Administratie, door concentratie en geheugen problematiek'

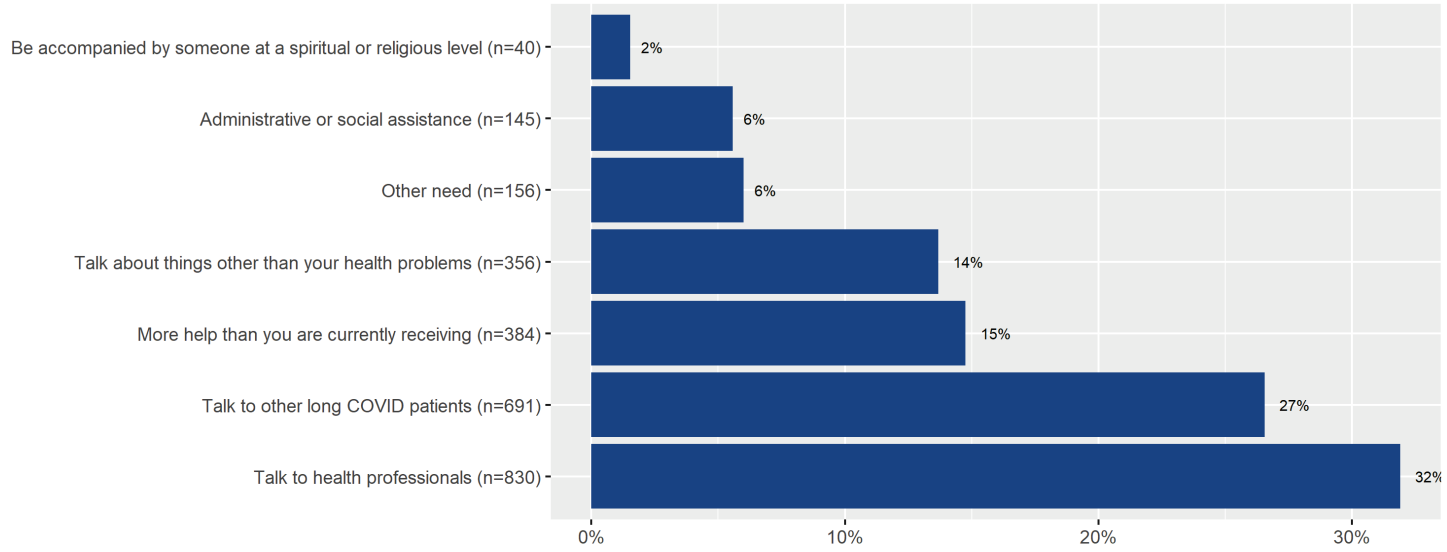
  'Vérifier après moi'

  'Psychomotricité fine car bouts des doigts sensibles et douloureux (ouvrir une canette, ouvrir une pression, etc...)

4.8 Specific needs related to long COVID

Patients were asked whether they experienced specific needs due to their health condition that were unrelated to their normal activities of daily living or normal functioning. The pre-specified response categories referred for instance to the need to talk to someone about long COVID or spiritual support. Figure 14 shows the frequency of the different pre-specified response options (patients could indicate more than one response category).

Figure 14 – Needs of patients related long COVID (n=1 320)



On the question of which additional needs they experienced related to long COVID, the two most frequently reported were: the need to talk to a health professional (32%) and the need to talk to other patients with long COVID (27%). Only 2% of the participants felt the need to be accompanied by a spiritual or religious person.

Respondents could add additional needs in an open field (covered under 'other needs' in Figure 14). Among these other needs, there was a need for more understanding of their health condition (mentioned 24 times) by family and friends but also in the professional environment (colleagues, boss). The need for treatment or physiotherapy to relieve symptoms was mentioned 15 times.

Talking about their health condition with someone they trust

More than half of the participants (n=673/1 320) had no difficulty finding someone they trusted to talk to about their condition. On the other hand, 18% (n=235/1 320) said that they had no need for it.

About one in four respondents (347/1 320) reported difficulties to find someone they trust to talk about their health condition.

5 CONCLUSION

The online survey allowed us to have a good overview of the experiences and perceived (unmet) needs of people who developed long-term health problems after COVID-19 in Belgium.

We analysed the answers of 1 320 participants of whom the majority were women. However, as we are not able to know whether our sample is representative of the population with long COVID, we cannot conclude that long COVID is more frequent in women compared to men. In addition, as discussed below, a large proportion of the respondents were people working in the care sector, and positions in this sector are more frequently held by women. There was also a large proportion of people with a high level of education and who had paid work before acute COVID-19 and around a third were working in the health sector. There were relatively few respondents under 18 and over 75 years of age. This may be partly explained by the type of survey (online) and the fact that people working in healthcare are generally more sensitive to responding to a survey that affects them personally and professionally.

Participants predominantly reported no comorbidities before COVID-19 but hospitalised participants with COVID-19 symptoms for > 6 months reported more frequently comorbidities than the participants with COVID-19 symptoms between 4 weeks and 6 months who had not been hospitalised. Among the respondents who reported comorbidities, the most frequent were disease of the locomotor system (bones, joints, and muscles), respiratory disease, heart and blood vessel disease and digestive disease. However, these results should be taken with caution. For example, some participants may have reported comorbidity (illness for more than 6 months) when it could actually be a symptom of long COVID. Respiratory diseases in patients with symptoms for more than 6 months are particularly targeted. In addition, our sample is a relatively young population and may not represent the reality with regard to comorbidities as these are more frequently present in the elderly. The majority of respondents reported that their symptoms were confirmed by a health professional as being the result of COVID-19 (by a test or clinical diagnosis of COVID-19). The three most frequently reported symptoms were fatigue, lack of energy and breathing difficulties and most of the respondents still had symptoms when completing the questionnaire (more than 3 months). General practitioners were the most consulted professionals and the vast majority of long COVID patients is satisfied with the care received (with an exception for emergency care where satisfaction was lower). In addition, satisfaction was also lower in the longer symptom duration group (> 6months after onset COVID-19).

Several impacts of long COVID have been reported by respondents. First, more than half of the respondents with long COVID had an incapacity to work; among them, more than a third were still not back to work. Second, in all five dimensions of EQ-5D-5L, the proportion of respondents with health problems increased after acute COVID-19. The VAS score is also significantly different before and after acute COVID-19. Patients scored their health status as worse after the infection and this was even more pronounced among the participants who had been hospitalised and with long symptom duration (> 6months after the onset of COVID-19). Finally, a financial impact had been reported by more than one in three respondents. The main explanations given were: the loss or lowering of income due to illness; the increased medical expenses; and direct costs related to long COVID.

Regarding the treatment of long COVID, forty percent of respondents are following or have been following at least one. The most common treatments were prescribed drugs, complementary treatments and over-the-counter drugs. The participants who had been hospitalised and who reported mid or long duration of symptoms more frequently reported following a treatment for long COVID than the participants with short duration of symptoms and who had not been hospitalised. Although the majority of respondents did not find their treatment burdensome, some of them reported the fact that their treatment was tiring, painful and discouraging (i.e. progress was very slow and/or not very visible for example). The burden due to side effects was also mentioned: 27% reported suffering from side effects; the most reported were fatigue or exhaustion and heart palpitations. We observed that the boundary between long COVID symptoms and long COVID treatment side effects is blurred. The condition (as well as the way to treat it) being still poorly known

seems to complicate the distinction between treatment side-effects (reported in this section) and symptoms of long COVID.

Possible long-term adverse effects from one or more of the treatments were concerns too for some respondents, in particular concerns about side-effects that sometimes lead to other serious health problems or about the lack of effectiveness of medicines or even deterioration of health due to the use of specific drugs.

A secondary aim of our survey was to test whether this methodological approach was appropriate to identify patient needs. More than a third of the respondents reported unmet care needs mainly due to a lack of information, a lack of competent staff, and the very long waiting times to get access to care. Answers to open-ended questions revealed other reasons such as physicians' (lack of) knowledge about long COVID, general attitude of the physicians towards patients complaining, symptoms and patients' profile not considered to be 'at risk' or health states 'seriousness' to justify a contact with the healthcare system.

There is a need for a (clear) explanation regarding long COVID and its management. Issues with the provision of information were reported by 60% of the respondents.

Nearly 40% of the participants would like or would have liked to be more involved in the choices about their treatment(s) for long COVID.

Needs for support with activities of daily living were explored as well: more than one in two patients suffering from long COVID required support with activities of daily living. The participants with symptom duration of > 6 months post-acute COVID-19 and who were hospitalised reported more frequently to need help with activities of daily living than participants with 4 weeks-6 months symptom duration who were not hospitalised. Participants needed the most help with cleaning, preparation of meals and transportation/journeys with an important role played by informal caregivers. Other expressed needs were shopping and/or carrying heavy things, caring for children and pets, administrative tasks (including making medical appointments or asking questions to healthcare professionals and the need for companionship, listening and moral/psychological support was mentioned too. There were also needs resulting specifically from the symptoms of long COVID i.e. needs to 'compensate' for long COVID problems such as problems with concentration or memory.

On the question of which additional needs they experienced related to long COVID, the two most frequently reported were: the need to talk to a health professional and the need to talk to other patients with long COVID. Other reported needs were a need for more understanding of their health condition by family and friends but also in the professional environment (colleagues, boss) when about one in four respondents reported difficulties to find someone they trust to talk about their health condition.

Our study is suffering from limitations, some of these have already been mentioned above.

First, as noted above, it is not clear whether the sample studied is representative of the Belgian population with long COVID. Indeed, women and health workers were overrepresented in the sample. On the other hand, some groups were underrepresented, especially children (<18 years) and elderly (>75 years; who have been particularly affected by the COVID-19 pandemic). The choice of an online survey played a role in the fact that the sample is not representative of the Belgian population suffering from long COVID.

An online survey also does not prevent some people from answering the survey more than once. For example, some people might have experienced a change in their condition during the survey and therefore decided to respond more than once. Unfortunately, it is not possible to control for this type of potential bias because it was not possible to send a personal invitation to participate in the survey.

The duration of symptoms after acute COVID-19 and other significantly related factors may have been impacted by the cohort effect. This means that not all individuals experienced COVID-19 at the same time and that their responses may be influenced by this factor. Since we did not know the date of infection, we did not correct for this factor. However, most analyses were performed by symptom duration subgroup, which partially circumvents this limitation.

There was also a problem with the understanding of some questions asked in the survey, which appeared in several ways: a discrepancy in the answers given (respondents did not answer the question asked, they went off-subject or they tended to anticipate the next questions or the open box was an opportunity for them to express their dissatisfaction on one or more points). It was not uncommon for participants to answer the next question.

In addition, some respondents seemed to confuse the (unmet) needs they had during the acute phase of COVID-19 with the needs they (had) during their long COVID.

Finally, the answers to the open-ended questions were sometimes difficult to interpret, often because the respondents were not explicit enough in their answers. Furthermore, for the same question, respondents with the same profile could give different answers (e.g. when some self-employed people said that they did not receive any income during their long COVID while others said that they received allowances (bridging rights or minimum income).

CHAPTER 5. QUALITATIVE APPROACH

1 KEY POINTS

KCE recruited among the participants on the online survey (see Chapter 4) 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 were included: with – and without hospitalisation, with different duration of persisting symptoms (4 weeks – 3 months; 3-6 months; > 6 months.

Based on the results of this chapter, we make several observations, such as:

- **Patients reported a wide variety of symptoms (not always clear to them if related to long COVID) and described the impact of symptoms on their daily life varying from limited to life-changing. They are often forced to adapt their activity level. Common symptoms such as fatigue and concentration problems are experienced as overwhelming and hamper patients to perform simple tasks (e.g. walking, cleaning, driving a car) which they did before without any problem. Moreover, the accumulation of different symptom as well as the fluctuating and unpredictable nature (periods of improvement followed by relapse, symptoms improve while new symptoms appear) are experienced as a never-ending story. This is difficult to cope with and creates feelings of anxiety and uncertainty (e.g. will they ever get better?).**
- **Patients report that that the diagnostic work up is not proactive but rather organized on a on a symptom-by-symptom basis: a comprehensive diagnostic assessment is lacking.**

- 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. Yet, when COVID-19 was not formally diagnosed (e.g. no PCR test during first wave of pandemic because of limited test capacity) it becomes even more difficult. 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 minimization of their symptom severity, …
- Patients report that the treatment approach is not coordinated nor standardized 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 standardized and/or coordinated treatment approach patients tend to search solutions themselves including complementary and unconventional therapies (e.g. vitamin & food supplements, osteopathy, accupuncture…). Limited access to conventional services with specific expertise in long COVID (ranging from mono-disciplinary physiotherapy to multidisciplinary rehabilitation) was also described.
- The impact of long COVID on the professional activity can be large. Patients report that they are still incapable to work or restarted but with reduced labor time, a different job-content or with less energy and productivity as 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-esteeem 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).
- Long COVID can also have a financial impact mainly due to health related expenses (co-payment reimbursed services, non-reimbursed services as well as not conventional treatments and therapies) and/or loss of income.
- 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 negative reactions of others (e.g. disbelieve, stigmatization) on symptoms in their social or professional environment (e.g. feeling down or guilty, self-isolation, tensions in relationships). From patients' stories it can be deduced that the level of distress might increase when symptoms last longer. Respondents indicated that it is important to better inform the general population as well as the medical professionals about long COVID.
- 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)
- Patient reports about their relationship with healthcare professionals are mixed: positive (e.g. GP and/or medical specialists who listen to complaints and looks for solutions in partnership with the patient) to negative. The latter group of reactions is dominated by feelings of not being taken seriously by healthcare professionals. In addition other negative experiences such as lack of holistic approach, lack of empathy, etc. are reported. Due to a lack of coordination of care and out of necessity patients have to coordinate their own care and look for solutions themselves. 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 .

- **Patients experience a need to be recognized as 'long COVID patients'**
- **The need to be 'recognized' is partly related to their need of clear information needs about long COVID both for the medical community (to enable them to inform patients correctly but also to increase their awareness about long COVID) as for the general population. Patients want correct information (knowns and unknowns) and want to be kept informed about the evolving medical and scientific insights in long COVID.**
- **In addition patients identified the following needs:**
  - **a multidisciplinary, 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;**
  - **specific treatments for cognitive and concentration problems (also called brain fog) or voice troubles;**
  - **sharing experiences with peers (but some feel also overwhelmed by or do not trust the reactions of others on not professionally moderated social networks;**
  - **support:**
    - **early reimbursed psychological support;**
    - **practical (e.g. with household activities) to take off the pressure from their relatives;**
    - **spiritual;**
    - **administrative.**

2 AIM

In this chapter we describe a qualitative study that aimed to deepen the understanding (based on the online survey – see Chapter 4) of the patients' perspectives on the management of long COVID and their needs.

3 METHODS

The approach to identify patient needs is part of another KCE research project (2017-14-HSR_unmet needs) which aimed to develop a generic tool to identify unmet patient needs. The interview guide used in the current chapter is based on the generic one developed in the context of the other project.[i] In the current study it is the first time that this generic methodology to evaluate unmet needs via a triangulation of methods (online survey, in-depth interviews, and online forum) was tested in a specific patient population.

3.1 Participants

We have opted for online approaches to recruit participants. This choice was made because long COVID is an umbrella terminology including a heterogeneous patient population without clear clinical criteria and covering all age groups. In addition, at the time of the study recruitment the healthcare services covering the care for these patients were (if available at all) unclear not allowing to recruit patients via contacts with healthcare professionals.

Respondents participating to the online survey (see Chapter 4) were offered the opportunity to participate in either an online forum or individual interviews.

By using several formats of qualitative data collection it was aimed to: increase participation, cover a wide range of - patient profiles and to limit the selection bias due to the digital divide and/or the passage through the written word.

3.1.1 Selection of the participants

Interviews

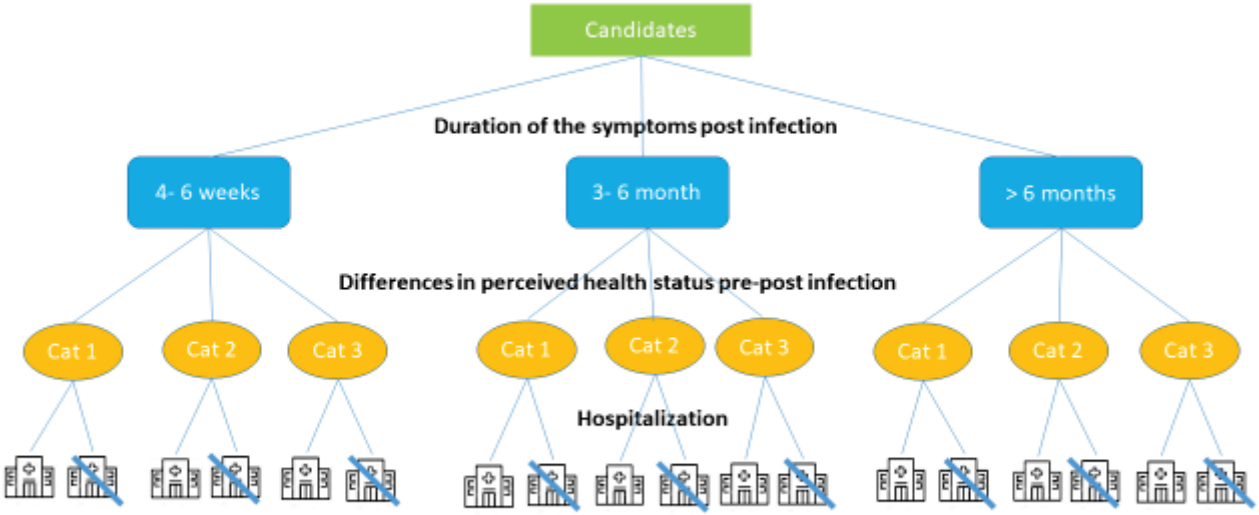
We planned to conduct a maximum of 36 individual interviews, 18 in French and 18 in Dutch. In order to achieve a maximum of variation in respondent profiles, the researchers prioritised the recruitment of participants who agreed to participate to the interview from each language group according to the following segmentation criteria.

- Duration of symptoms since onset acute COVID-19: short: 4-12 weeks / mid: 3- 6 months / long: > 6 months;
- Delta (VAS before – VAS after COVID) shared in tertiles: Difference in perceived health score (VAS) before and after COVID-19
- Hospitalization during acute COVID-19 phase versus no hospitalization.

We excluded patients who have been in intensive care unit to avoid any confusion with PICS.

[i] The methodological evaluation of the use of this generic tool to identify patient needs will be described in KCE-study HSR-2017-14.

Figure 15 – Segmentation of the candidates for interviews



In each segment of the long COVID population candidating for the interview through the online survey, maximum 3 participants were randomly selected: one effective and 2 substitutes (if there are)

Forum

We decided to limit the number of participants in the forum to 200 (100 in French and 100 in Dutch) in order to allow for a realistic management of the forum posts (e.g. interaction, surveillance on respecting the pre-defined rules, etc.) with regard to the means allocated to the research.

It was foreseen that in case too many people wanted to participate in the forum, the researchers could select the patients such that a balanced sample was obtained. The following criteria were used to make the selection (if required): the duration of the symptoms (4-12 weeks / >12 weeks), whether or not they were hospitalised, and whether they were active in the labour market before the illness/not active. In addition, it was foreseen to further balance the sample for gender, age and place of residence (province).

3.1.2 Contact procedure

Interviews

Participants selected to participate in the interviews firstly received a phone call to confirm they were still willing to participate and to plan the interview. Once they agreed they received the confirmation and informed consent form by e-mail. In this email they also had access to an explanation of how to log in via Zoom® and a video explaining how to sign the informed consent with Adobe® sign.

If they changed their mind or if they did not respond to three phone call attempts, the substitute with the same profile (if any) was contacted.

Not selected candidates were contacted by e-mail to explain the reason for the exclusion or to place potential participants on a back-up list in case of withdrawal or need to contact specific additional profile (according to the first analysis of the material, in order to insure data sufficiency).

Forum

The participants selected to participate in the forum received an email confirming their selection one week prior to the launching of the forum and the explanations how to connect to the forum.

3.2 Data collection

3.2.1 Data collection tools

The topics covered during the interviews and the forum were derived from a literature review on unmet needs (will be reported in the scientific report of the ongoing KCE-study). Some parts were adapted to the long COVID context , based on the main concerns reported by the participants in the online survey, from a specific literature review on long COVID[5, 57, 87, 196, 197, 199] and social networks discussions.

Interview guide

Development

The interview guide was first developed in French on paper and afterwards translated to Dutch by KCE researchers. A comparison of the two paper versions was carried out to ensure that both versions were identical in terms of structure and content. Subsequently, both versions were proofread by team members and two representatives of patient umbrella organisations (one French-speaking (i.e. LUSS) and one Dutch-speaking (i.e. VPP)).

Final interview guide

The final interview guides are presented in appendix. They cover the following topics:

- Perceived health status before COVID-19 infection
- Symptoms of long COVID
- Diagnosis and treatment of long COVID
- Information and support network
- Relationships with the medical profession
- Long COVID and work
- Social and family relations

Forum

Preparation of the platform

The forum was conducted via the Moodle© platform.

Several actions have been undertaken to ensure the effective functioning of the forum:

- The establishment of a charter of good behavior to be signed by participants before accessing the discussion forum (like the inform consent).
- The possibility of communicating with another forum participant on a one-by-one basis was removed from the Moodle™ platform as part of this project. The reason for this was twofold. We wanted to: focus on discussions between participants that were regulated by two moderators; and avoid important information that would not be captured by the KCE researchers and moderators.
- The use of the generic email address dedicated to the KCE forums (forum@kce.be) to centralize communication between KCE researchers and forum participants.
- Via the generic email address, a weekly mail was sent to stimulate respondents' participation and to inform them when a new theme was available.
- The possibility for moderators to delete or anonymize information such as telephone numbers, names and addresses of health care providers or facilities.

Preparation of the moderation

The moderators and research team received training in forum facilitation and moderation with an external company (Tree Company).

Topic guide for the forum

The topic guide was developed according to the interview guide.

The following six themes were proposed to participants:

- Theme 1: Symptoms of long COVID
- Theme 2: Diagnosis and Treatment of long COVID
- Theme 3: Information and support network
- Theme 4: Relationships with the medical profession
- Theme 5: Long COVID and work
- Theme 6: Social and family relations

The 7th and final theme concerned the offering of an opportunity for participants to highlight their essential needs.

1. Development

For each theme, one or more open-ended questions were foreseen. These were written in French and then translated into Dutch by a Dutch-speaking researcher from the team. Questions were discussed within the team to judge their relevance and clarity in both languages. The two moderators had than a chance to become familiar with the different themes they would have to moderate and to appropriate them. In addition, in order to facilitate moderation, the research team proposed stimulus questions to the moderators.

2. Pretest

In a first step, the themes and associated questions were discussed.

In a second step, the themes were implemented in the online version via the Moodle platform. KCE researchers, the moderators and the trainer (Tree Company) tested it using every forum's user profile (participants, moderators, administrators) by several team members.

The online forum was then adapted according to the comments to get a final version.

3. Final discussions topics

Table 50 summarizes the different retained themes and their related sub-topics. The full questionnaire is presented in appendix.

Table 51 – Final themes and associated sub-topics

Theme	Sub-topic
Theme 1: Symptoms of long COVID	Most disturbing symptoms
Theme 2: Diagnosis and Treatment of long COVID	Difficulties with diagnosis Difficulties with treatment Unresolved symptoms Use of alternative treatments
Theme 3: Information and support network	Difficulties in finding information Missing information Impact of missing information Searching for missing information
Theme 4: Relationships with the medical profession	Relationships with caregivers
Theme 5: Long COVID and work	Difficulties at the professional level
Theme 6: Social and family relations	Impact of long COVID on social and family relationships
Essential needs	None

3.2.2 Data collection process

Interviews

Due to the sanitary context of the COVID-19 pandemic, data collection had to be organised remotely to avoid direct contact between participants. Therefore interviews were organised unsing a web conferencing tool.

Interviews were conducted via Zoom© in French by 2 French-speaking researchers and in Dutch by 2 Dutch-speaking researchers, all researchers had a background in Health Service Research at KCE.

The interviews lasted approximately 1 h-1h30.

Each interview has been recorded and transcribed verbatim by an external company. All names of participants, institutions or care providers have been removed during transcription.

Forum

The forum has taken place via the Moodle™ platform.

The participants received, the day when the forum was launched, an email informing them that the online forum was open.

In order to access the forum questions, potential participants had to confirm their informed consent after registering on the platform.

The different themes of the forum were opened one after the other according to a predefined schedule (Table 51).

Table 52 – Calendar of the online forum

Date	Action
1st of March 2021	LAUNCH OF THE PLATFORM Theme 1: Treatment enduring COVID-19 Theme 2: symptoms enduring COVID-19
8th of March 2021	Theme 3: Information and support network Theme 4: Relationships with the medical profession
15th of March 2021	Theme 5: Long COVID and work Theme 6: Social and family relations
19th of March	Essential needs
26th of March	Closure of the online forum and sending of a ‘satisfaction’ survey for participants and non-participants

The discussions on the forum have been moderated by a collaborator from platforms of patients associations, i.e. the “Ligue de Usagers de Soins de Santé” (LUSS) Suggesiotn

for the French-speaking group, the “Vlaamse Patienten Platform” (VPP) for the Dutch-speaking group.

In addition, the KCE researchers and moderators communicated about the forum throughout its duration via a Teams group set up for this purpose. In addition ad hoc meetings were also organized.

3.3 Analysis

We performed a qualitative thematic inductive analysis on the transcripts of the interviews and the export of the discussions of forum using NVIVO® software, which allows structuring the collected information and facilitates the analysis by the researchers.

All the French-speaking material (transcripts of interviews and export of the discussion of the forum) was coded by one native speaking researcher and all the Dutch-speaking material by two native speaking researchers. They met several times to build a final common nodes tree. It served as structure for the reporting of the results.

Each interview was considered as a unit as was each forum.

4 RESULTS

4.1 Description of the participants

4.1.1 Interviews

We carried 33 interviews, 52% Dutch-speaking; 48% French-speaking. Most participants were female. Two participants responded in the name of a relative.

Table 53 – Description of the participants to the interview

ID	Language	Gender	Age	Province	Paid job	Health care profesional	Highest educational level	Duration of the symptoms[#]	Difference VAS[$]	Hospitalized
1	D	M	41-50	West-Vlaanderen	No	No	Superior	Short	Cat 2	Yes
2	D	W	41-50	Antwerpen	Yes	Nurse	Superior	Short	Cat 3	Yes
3	D	W	31-40	Oost-Vlaanderen	Yes	Nurse	Superior	Long	Cat 3	Yes
4	D	M	31-40	Limburg	Yes	No	Secondary school –High level	Mid	Cat 1	Yes
5	D	W	41-50	Antwerpen	Yes	No	Superior	Long	Cat 3	No
6	Fr	W	41-50	Brabant Wallon	No	Pharmacist	Master Degree	Mid	Cat 1	Yes
7	D	W	31-40	Oost-Vlaanderen	Yes	Nurse	Superior	Mid	Cat 2	No
8	D	W	31-40	Antwerpen	Yes	No	Superior	Long	Cat 2	Yes
9	D	W	41-50	West-Vlaanderen	Yes	Spiritual councellor	Master Degree	Short	Cat 3	No
10	Fr	M	51-60	Brabant Wallon	No	No	Master Degree	Short	Cat 1	Yes
11	D	M	51-60	Antwerpen	No	Missing	Master Degree	Short	Cat 1	Yes
12	D	W	41-50	Bruxelles	No	No	Superior	Short	Cat 1	No
13	Fr	M	18-30	Hainaut	No	Missing	Bachelor	Long	Cat 3	No
14	Fr	W	31-40	Brabant Wallon	Yes	Nurse	Superior	Long	Cat 2	No
15	D	M	31-40	Oost-Vlaanderen	Non	No	Secondary school - High level	Mid	Cat 1	No
16	Fr	M	> 60	Namur	No	Missing	Master degree	Mid	Cat 3	No

ID	Language	Gender	Age	Province	Paid job	Health care profesional	Highest educational level	Duration of the symptoms[#]	Difference VAS[$]	Hospitalized
17	Fr	W	41-50	Bruxelles	Yes	Dietist	Superior	Long	Cat 1	No
18	D	W	31-40	Antwerpen	Yes	Nurse	Master Degree	Mid	Cat 3	No
19	D	W	31-40	Antwerpen	Yes	Educator	Superior	Long	Cat 2	No
20	D	M	51-60	Vlaams-Brabant	No	Missing	Secondary school - High level	Long	Cat 3	Yes
21	D	M	41-50	West-Vlaanderen	No	No	Secondary school - High level	Short	Cat 1	No
22	D	W	31-40	Antwerpen	Yes	No	Superior	Short	Cat 2	No
23	Fr	W	18-30	Namur	No	Nurse	Superior	Short	Cat 2	No
24	D	W	41-50	Antwerpen	No	No	Master Degree	Long	Cat 1	No
25	Fr	W	41-50	Namur	Yes	No	Master Degree	Short	Cat 1	No
26	Fr	M	> 60	Liège	Yes	No	No diploma	Long	Cat 2	Yes
27	Fr	W	<18	Vlaams-Brabant	No	Missing	No diploma	Mid	Cat 3	No
28	Fr	W	51-60	Bruxelles	Yes	No	Master Degree	Mid	Cat 1	No
29	Fr	W	51-60	Vlaams-Brabant	Yes	Physician	Master Degree	Mid	Cat 2	No
30	Fr	M	>60	Hainaut	No	Missing	Secondary school –low level	Short	Cat 2	Yes
31	Fr	M	> 60	Brabant-Wallon	No	Missing	Primary school	Short	Cat 2	No
32	Fr	W	51-60	Brabant Wallon	Yes	No	Doctorate	Short	Cat 3	No
33	D	W	31-40	Oost-Vlaanderen	Yes	Physician	Master Degree	Mid	Cat 3	Yes

** Response by a relative* *Fr: French-speaking; D: Dutch-speaking* *W: Women; M: Men* *[#]Short: 4-12 weeks; Mid: 3 month – 6 month; Long: > 6 month*
[$]Cat 1 : <=20 ; Cat 2 : < 20 – 39.99; Cat 3: >= 40

4.1.2 Forum

In total, 167 participants to the online survey wanted to participate to the forum: 68 French-speaking and 99 Dutch-speaking. They were all invited. Nevertheless, finally 101 effectively participated, i.e. 45 French-speaking and 56 Dutch-speaking.

Table 54 – Description of the participants to the forum (N= 97)*

	N (%)
Socio demographic information	
Status of respondent	
Hi/herself	96 (99.0)
Another adult	1 (1.0)
A minor	0 (0.0)
Gender	
Women	75 (77.3)
Men	22 (22.7)
Other	0 (0.0)
Language	
Dutch	54 (55.7)
French	43 (44.3)
Age (Fr, n=43)	
< 18y	0 (0.0)
18-30 y	3 (7.0)
31-40 y	7 (16.3)
41-50 y	20 (46.5)
51-60	8 (18.6)
>60 y	5 (11.6)

Age (NI, n=54)		
	< 18y	0 (0.0)
	18-24 y	0 (0.0)
	25-44 y	25 (46.3)
	45-64 y	26 (48.1)
	65-74 y	1 (1.9)
	> 75 y	2 (3.7)
Region		
	Flanders	54 (55.7)
	Wallonia	33 (34.0)
	Brussels	10 (10.3)
Paid job (Yes)		78 (80.4)
Education level		
	Doctorate with thesis	2 (2.1)
	University education, bachelor's, engineer or master's degree	32 (33)
	Non-university higher education of the long type, master's degree at a university	5 (5.2)
	Non-university higher education of the short type	25 (25.8)
	Academic baccalaureate	7 (7.2)
	Post-secondary non-tertiary	9 (9.3)
	Upper secondary education or general secondary education at the 3rd level	12 (12.4)
	Lower secondary education or 1st or 2nd level secondary education	5 (5.2)
	Primary education	0 (0.0)
	No diploma	0 (0.0)
	Other diploma	0 (0.0)
	I don't know	0 (0.0)
Number of comorbidities		

	None	56 (57.7)
	1 to 2	26 (26.8)
	3 to 4	13 (13.4)
	5 or more	2 (2.1)
VAS after-Vas before (mean; DS)		27.0 (16.2)
COVID Issues		
Hospitalized (Yes)		22 (22.7)
Duration		
	1 to 2 weeks	4 (18.2)
	< 1 week	9 (40.9)
	> 2 weeks	9 (40.9)
Intensive care (Yes)		9 (40.9)
Respiratory assistance (Yes)		7 (77.8)
Duration of the symptoms		
	4-12 weeks	14 (14.4)
	12 weeks – 6 months	30 (30.9)
	> 6 months	53 (54.6)
VAS difference before and after COVID		
	Cat 1	45 (46.39)
	Cat 2	31 (31.96)
	Cat 3	21 (21.65)

** For 4 participants no match (FR n=2, NL n=2) possible between Lime survey and Forum database*

4.2 Long COVID symptoms

Participants described a long list of symptoms that impact them, some of them having a higher impact than others. The qualitative approach does not allow any statements on the frequency of the symptoms, but rather gives an insight into how they occur and their impact on patients' daily and professional live (see next sections).

Respondents stated that they were not always sure about the origin of the symptoms they experience, i.e. whether their symptoms are be related to COVID-19 or not.

> *« Moi les nodules je pense que c'est, je pense que c'est ça mais on ne sait pas. Après, donc, ma fille, elle a eu un kyste qui est apparu au niveau du cou, franchement enfin aussi 2 semaines après le COVID, donc je suis convaincue que c'est ça. Mais on ne sait pas et donc les médecins sont quand même en général très prudents et disent "non, c'est un hasard" mais ça fait quand même beaucoup de hasards quoi. » (Patient 25, not hospitalised)*

COVID-19 is described as an alien, a monster, a piece of waste or a medusa.

> *« Mon explication c'est que le virus est sous contrôle quand on est calme. Quand on commence à se bouger, ça augmente le rythme cardiaque et ça propage le virus de plus belle dans tous le corps, comme une méduse se laisse flotter au fils des vagues…Alors voilà mes conclusions qui n'appartiennent qu'à moi:- C'est une crasse, notre corps n'a jamais croisé une saleté comme celle-là. Et je pense que pour mon cas, il est toujours en moi. » (Forum)*

A wide variety of symptoms reported during patients' stories

The (most of the) following symptoms were also reported via the online survey but were explained in more detail during the qualitative data collection:

- Fatigue: The fatigue experienced by long COVID patients is described as an irresistible need to rest or sleep or as a lack of energy.

> *« La fatigue m'empêche d'avoir l'énergie nécessaire pour mener à bien mon travail et mes tâches quotidiennes de la vie courante. Souvent, c'est dégressif : Le matin est le moment où je me sens le mieux. Entre 15 et 16h, une fatigue fulgurante s'installe - Quand je fais une sieste si je peux me l'accorder, je dors automatiquement +- 3h. Cette fatigue ne me quitte plus jusqu'au lendemain matin. J'ai un sommeil profond, et mes nuits se sont allongées entre 10 à 12h (là où j'étais à +-7h de sommeil avant COVID). » (Forum)*

This fatigue is overwhelming, it could come up after an activity, even a light one such as wash dishing, at the end of the day or suddenly without any clear explanation.

> *« Après peut-être avoir fait la vaisselle il fallait me coucher, c'était toujours à chaque fois une activité et du repos. Je savais, ma journée devait être recoupée en plusieurs, plusieurs, allez, plusieurs, des étapes. » (Patient 14, not hospitalised)*

> *« C'est vraiment les fins de journée où je suis fatiguée et ça, mais vraiment un effet d'interrupteur, donc je suis vraiment obligée de, de m'arrêter parce que je ne sais plus rien faire, mais vraiment plus rien faire. » (Patient 25, not hospitalised)*

It is also be described as increased length of recuperation after an effort.

> *« Suite à des test à l'effort demandé par un Dr en médecine physique dans le cadre d'une étude COVID long : il est flagrant que je ne récupère pas normalement... En effet, aucun problème pour faire le maximum lors de ces tests (vélos, marche rapide, exercices statique) par contre il m'a fallu 6h pour retrouver un rythme cardiaque normal, je suis resté plus de 3h au-dessus de 100 (mon rythme cardiaque au repos est entre 50 et 60)... Ceci peut en partie expliquer les fatigues après efforts, même léger... » (Forum)*

The fatigue could also have a negative impact on the sexual activity (erection problems and decreased libido).

- Cognitive problems: Patients described manifestations of brain fog, i.e. memory difficulties, concentration problems and problems to find the right words, also among children. Respondents experience this as very delibiating as it hampers their everyday's functioning (e.g. social activities, concentrating at work, household activities, etc.).

  "Moeilijk op woorden kunnen komen, zinnen niet kunnen afmaken, heel veel moeite met concentratie (bijvoorbeeld tijdens het werk om de 5 minuten jezelf afvragen wat je nu weer aan het doen was... 'welke map wou ik nu terug openklikken' of 'wat ging ik nu weer doen eigenlijk'),verward in de zin dat je heel vaak dingen vergeet of soms het gevoel hebt dat je even in een mist zit waarbij alles even wazig is in je hoofd--> dit zijn allemaal symptomen waar ikzelf voor de ziekte nooit of nooit last van gehad heb; je zou kunnen zeggen ja iedereen is wel eens moe en dan laat je brein het wel eens afweten, maar dit is vele malen erger dan dat en ook abnormaal dat het zo frequent aanwezig blijft." (Forum)

  « Je suis incapable de gérer 2 choses en même temps alors que j'étais une véritable pieuvre à 10 bras. Si on me parle, je me perds dans mon activité. Je dois souvent mettre sur papier les procédures pour ne pas me perdre avant d'entreprendre une tâche. Je ne sais plus lire que des choses très simples. Les romans ne doivent pas multiplier les informations...» (Forum)

  "Als ik bijvoorbeeld de afwas doe en ik zeg iets tegen mijn dochter. "Oh, wilt gij de vuilzak buitenzetten?". In gedachte zeg ik dat dan.(…)Maar dan zeg ik van: "Zet gij efkes de vuilzak in de slaapkamer?". (…) En dan aan haar reactie weet ik dat ik iets… Maar ik vind dat niet onoverkomelijk." (Patient 2, hospitalised)

  "Voor mij persoonlijk zijn de cognitieve problemen het meest storende. De simpelste dingen onthouden, focus, begrijpend lezen, een gesprekspartner volgen etc. Het zijn allemaal zaken die ik in het dagelijks leven constant tegen kom en mij tegenwoordig erg veel moeite kosten. Zo opende ik vanmorgen nog de koelkast om mijn telefoon oplader te pakken en liep ik vervolgens zo'n 5 keer mijn slaapkamer in om daar te vergeten wat ik wilde doen." (Forum)

  « Alors que [ma fille] c'est une enfant qui sait vous dire- qui a une très très bonne mémoire, elle me disait: "Je sais plus quel jour on est... Je ne sais plus : ma tête est chamboulée, ma tête est chamboulée maman. (…) Et, parfois elle cherchait l- les mots. Elle me dit : "Je l'ai sur le bout de la langue." C'est une expression que je n'ai jamais entendue chez [elle]…"Maman, je l'ai là, je l'ai là, mais je n'arrive pas, je ne sais pas ce que c'est." Elle me disait que quand on lui demande de faire ses exercices, elle me dit : "Je n'arrive pas, c'est trop dur, ma tête est chamboulée! Tu comprends pas ma douleur !" Tout le temps. "Tu ne ressens pas ma douleur, tu ne ressens pas ma douleur, je n'arrive pas à faire l'exercice ! » (Patient 27, hospitalised)

  Concentration problems have a huge impact and make simple activities such as driving a car difficult and/or dangerous.

- Respiratory difficulties
  - Pulmonary capacity

    « Je suis tout le temps essoufflé, je ne sais plus me permettre de, de marcher enfin de vivre correcte, comme normalement j'ai envie de vivre. Par exemple si je vais faire une balade dans un bois, avant je sentais vraiment l'air qui passait pendant, dans les poumons, je sentais vraiment que je vivais entre guillemets. Maintenant ben quand je respire, je respire, ben j'ai vraiment l'impression que, que je ne profite même pas de, c'est comme si je ne savais pas respirer entièrement en fait, c'est, c'est, c'est désagréable. » (Forum)

    « Des difficultés respiratoires, heureusement seulement présentes à l'effort mais il arrive tout de même que je ressente une oppression respiratoire à certains moments : j'ai remarqué cela dans un jacuzzi privé (alors que jamais auparavant) mais également dans certaines positions couchées, comme si mes poumons étaient 'écrasés'. » (Forum)

  - Persistent cough and mucus

    « Toux liée à l'irritation de ma gorge: en parlant ou la nuit, ou encore en fin de journée (toux incoercible: je m'étrangle en parlant et c'est

handicapant pour les visioconférences et les cours que je donne). Cela m'éveille et me tient éveillée la nuit. » (Forum)

- Sleep apneaInsomnia (on top of fatigue)

  "Slapeloosheid. Dat heb ik ook. Ik ben dus enorm moe, maar 's nachts kan ik niet slapen. Ja ja. Dat je eigenlijk 's nachts wakker ligt. Ik ben beneden. Ik ben moe, ik kruip in bed. Uh ik slaap twee uur, drie uur, en dan is het op een keer gedaan." (Patient 21, not hospitalised)

- Pain:
  - Headaches
  - Muscle and joint pain (also experienced by persons being fit and sporty before acute COVID-19)

    « Les douleurs musculaires: dès que je fais un effort, j'ai mal partout. Autant je faisais du sport avant régulièrement... autant ici j'ai perdu tous mes muscles. Je repars à 0. Quand je soulève mes poids et que j'essaye péniblement de terminer ma série, après je ne sais même plus tenir mon téléphone en main car je n'ai plus de force. » (Forum)

    « J'ai commencé à être essoufflé, fatigué, pas bien, j'avais des douleurs au niveau du cœur et tout. J'ai voulu rentrer chez moi et en fait j'étais tout blanc, coup de fatigue énorme. Et en marchant j'ai constaté que ma jambe gauche ne communiquait plus correctement, et ça, et je me dis "mais c'est bizarre ça " parce que je ne savais presque plus marcher de la jambe gauche, je boitais, j'ai manqué de tomber sur, sur le trajet en fait. » (Patient 13, not hospitalised)

  - Chest pain - pericarditis

- Postural orthostatic tachycardia syndrome

  « Pour moi les symptômes les plus dérangeants sont: le stop (syndrome tachycardie orthostatique posturale), il m'empêche de me tenir debout sans bouger plus de 10 min généralement. Il entraîne de la tachycardie, une oppression thoracique (ou j'ai l'impression de manquer d'air et d'hyper ventiler). » (Forum)

- Dizziness and balance problems
- Digestive system: nausea, stomach pain, disturbed intestines, loss of appetite
- Temperature of the body disturbed: fever or sensation of cold

  « Pour moi le symptôme le plus difficile à vivre est une légère fièvre. Avant, j'étais toujours à 36,4. Maintenant, j'oscille entre minimum 37,5 à 38,4. » (Forum)

  « J'ai aussi des frissons à partir de 15-16 heures tous les jours et ma température corporelle baisse. » (Forum)

- Circulation system troubles: pain or bad circulation in the extremities of the body

  « Dans la première partie de l'infection (6 mois) les symptômes étaient reliés aux organes sanguins: piqure aiguë au cœur dans les poumons, dans les reins, veines qui gonflent et douloureuses. Ces DOULEURS ne sont plus présentes actuellement Par contre le FONCTIONEMENT de certains de ceux-ci peuvent dans certains cas ne pas fonctionner de manière optimale. » (Forum)

  « Le froid s'installe au niveau des membres (pieds bas de jambes, main avant-bras). On a l'impression que la circulation est coupée. » (Forum)

  « Les fourmillements, bon il fait plus froid, et puis les doigts c'était, il suffisait que je prenne quelque chose dans, dans un congélateur pour que boum, pendant 3 secondes j'avais les doigts blancs. » (Patient 16, not hospitalised)

- Persistent troubles of taste and smell: loss or amplification

  « L'hyperosmie est très présente et me donne des malaises directement. Il faut que je m'éloigne de l'odeur qui dérange et que je prenne l'air frais longtemps pour que ça passe. » (Forum)

  « Troubles du goût et de l'odorat, et plus précisément confronté à la parosmie. De nombreux goûts et odeurs ne correspondent pas à ce que je connaissais avant la COVID. Une odeur et un goût unique (que je ne connais pas) remplace l'ensemble de ceux-ci. Je suis à un stade où je ne supporte plus de rester à la cuisine quand nos pains cuisent au four. » (Forum)

- Hearing loss and tinnitus

  « Mi-décembre, là ça a commencé à, à devenir un peu catastrophique quoi, j'ai commencé à avoir des acouphènes.(…) et me réveiller, directement j'ai un, un, un, un, petit, un petit bruit dans l'oreille, qui équivaut, je ne connais pas votre âge, on ne demande pas mais quand on était jeunes où on mettait la radio le soir et il y avait plus de programme après minuit, 1 heure du matin et donc notre radio elle faisait bzzzz, c'est exactement ça que j'ai dans l'oreille. » (Patient 16, not hospitalised)

- Failing eyesight
- Voice instability

  "Maar dan heeft dat toch eh ja, dat mijn stem wegvalt, als ik nu echt voel van, ik ga over mijn grens hè, eigenlijk, vanmorgen heb ik gespeeld, pak dat ik nu echt tot vanavond praktijk zou hebben, dan zou ik vanavond terug, terug problemen krijgen met mijn stem." (Patient 24, not hospitalised)

  « Un symptôme qui m'handicape beaucoup : La dysphonie, je n'arrive plus à tenir une conversation sans que ma voix déraille, ou qu'elle s'éteint et devient inaudible... Ce qui est une gêne, surtout au téléphone. En plus, cela revient tout le temps en cycle, et j'ai remarqué que cela accentue l'essoufflement, l'oppression thoracique. » (Forum)

- Integumentary system disorders: Hair loss, eczema, itching, tingling, hyper-sedation, burning
- Zona
- Nodules on the lungs or thyroïd

  « J'ai deux nodules, un au niveau du poumon gauche, (…) Mais ça, ça vient du COVID aussi. C'est une cochonnerie qui vient du COVID, parce que je n'avais pas ça avant. Avant, j'avais fait des scanners, j'avais rien eu du tout, j'avais déjà fait des scanners avant, et avant les scanners, donc j'avais rien. » (Patient 30, hospitalised)

- Hormonal disorder by women

They also mentionned other effects :

- Fasciculation and tingeling

  « J'ai des fasciculations dans tous le corps. Vous savez comme quand vous avez la paupière qui bouge toute seule. » (Forum)

  « Les picotements commencent dès le réveil jusqu'à l'endormissement. Rien pendant la nuit. Des fois ça pique très fort, et puis ça passe. » (Forum)

- Acute sensitivity to substances like medicines or alcohol

  « Et j'ai constaté quelque chose de, de dingue c'est que les médocs, le peu de médicaments que je prenais, je ne les supportais plus. Ça, j'avais tout le temps des, des dyspnées à chaque médicament que je prenais, j'attrapais des plaques, j'attrapais des, des effets seconds, indésirables qui étaient assez forts, ce que je n'avais pas, enfin j'avais une sensibilité aux médicaments avant mais là c'était vraiment amplifié. Je me dis "ce n'est pas possible, j'arrive même plus à me soigner d'une simple pierre aux reins ou un truc comme ça". » (Patient 13, not hospitalised)

  « J'avais envie d'une BIEEERE. Erreur. Bourré après 1/3 de la bouteille, je ressens tous les symptômes amplifiés par 10 ! Ne vous inquiétez pas, je re-bois un petit verre sans problème maintenant. Mais oubliez pendant les premier 6 mois. Aujourd'hui je bois un petit verre par semaine, sans trop de problème. » (Forum)

- Effect of anesthesia
- Evolution of other diseases

  « Il y a 15 jours j'ai quand même été travailler deux trois jours avec des jeunes, une équipe de jeunes, j'ai eu froid, boom, j'ai eu une, une pointe de bronchite quoi, chose que je n'ai pour ainsi dire, jamais quoi, il faut vraiment.
  Interviewer: Donc vous vous sentez très fragilisé… .
  Interviewee: Ah oui, oui, oui, ça, c'est sidérant quoi. Et tout met beaucoup plus longtemps à guérir quoi. (…) Il a, il a fallu plus d'une semaine et demi pour guérir cette petite pointe de bronchite, j'ai dû

passer par des aérosols et tout et tout quoi, ça ne partait pas quoi, ce que je n'avais jamais avant quoi. » (Patient 16, not hospitalised)

Symptoms are fluctuating: some days are better than others

Patients experience the accumulation of symptoms as cumbersome. In addition, they state that it is also difficult to cope with the fluctuating nature: after a period of apparent improvement they relapse.

"Het ergste vind ik de optelsom van de symptomen, die ook dagelijks kunnen wijzigen, sommige verdwijnen, andere komen in de plaats. Sommige komen ook nog steeds terug. Momenteel, bijna een jaar later, nog steeds vlagen van erge vermoeidheid/malaise, inspanningsintolerantie, pijn in bovenbenen, brainfog, cognitief nier meer goed functioneren, oorsuizen en rauw gevoel in keel en luchtpijp." (Forum)

« Ce n'est pas régulier : Je peux un jour, marcher 10km sans problème particulier et le lendemain, avoir une difficulté réelle à me rendre jusqu'au toilette.» (Forum)

« Pour ma part les symptômes s'accentuent en rapport avec ce que j'ai fait le matin. Aujourd'hui par exemple, j'ai essayé d'aider ma sœur dans sa compta... donc assise sur une chaise de bureau, en position statique... à 14h00 les douleurs étaient intenables, j'ai dû m'allonger, vers 15h, je n'arrivais plus à dire quelque chose de cohérent.» (Forum)

Symptoms are cyclic

In the early period after the infection all symptoms coincide while after some time some symptoms tend to improve. Nevertheless, some patients describe that it sometimes feel as a never-ending story: they had the feeling that once a symptom improved a new one was popping up.

« Je dirais que ce sont des choses un peu cycliques, c'est-à-dire que quand un symptôme va mieux, le suivant pointe le bout du nez et donc je suis tout le temps avec des, des cycles, donc soit. Bon au début, c'était un peu tout en même temps évidemment hein mais, mais après quand le respiratoire allait un peu mieux, oh ça revenait sur le mal de tête ou sur la fatigue. Et donc c'est, oui, c'est, ce sont vraiment des, des cycles qui reviennent. » (Patient 32, not hospitalised)

Symptoms are sudden and unpredictable

Patients also described that symptoms are very unpredictable. They experienced new symptoms or a deterioration in existing symptoms without feeling a warning sign whatsoever. As a consequence they feel a set-back when it is too late and already have crossed their (physical) limits. Fatigue in particular is described as very unpredictable. As a consequence on some days they can handle an activity which they cannot on other days.

"En je gaat van groen naar rood, zonder oranje knipperlicht, zonder voorafgaande waarschuwing. Je weet pas dat je over je grenzen bent gegaan als het te laat is." (Forum)

"Het rare is dat het moeilijk te voorspellen is wanneer die vermoeidheid komt opzetten. Soms kan ik zonder terugval gaan wandelen, soms is diezelfde wandeling net teveel en gaat het licht uit. Het is vooral afhankelijk van hoeveel ik op een dag doe." (Forum)

4.3 Diagnosis of COVID and long COVID

Acute COVID-19 is not always diagnosed

For some people who were infected during the first wave of the pandemic, the access to PCR tests was limited (e.g. mild symptoms, younger age groups, no comorbidities, no hospitalisation). As a consequence, several patients reported that acute COVID-19 was not formally diagnosed, complicating the diagnosis of long COVID afterwards.

> *"Er waren in maart 2020 geen testen voorhanden voor jonge, gezonde mensen met milde symptomen, zoals ik. Contact via de huisarts verliep enkel telefonisch; bovendien was de arts die ik normaal consulteer niet beschikbaar. Ik moest het dus stellen met een telefonisch consult met iemand die mij helemaal niet kende als patiënt." (Forum)*

Lack of objective criteria to diagnose Long COVID

Even in cases where acute COVID-19 was diagnosed, the diagnosis of long COVID remains a huge challenge according to the respondents. Reported reasons are: the absence of clear clinical criteria, absence of knowledge among healthcare professionals about this new medical condition, difficulties to express the symptoms, difficulties to match symptoms with results of examinations (laboratory tests, medical imaging, etc.).

Several patients self-diagnosed their long COVID

As a consequence, patients self-diagnosed long COVID by recognising themselves in stories on Facebook or reports on the internet, or through the social media without any certainty or formal diagnosis.

> *« Comme son nom l'indique, pour diagnostiquer un COVID long, il faut un certain temps de recul. Personne ne m'a diagnostiqué comme tel mais je suis personnel soignant donc j'ai vite compris que je faisais partie des personnes qui gardaient des symptômes après quelques semaines. » (Forum)*

> *"De diagnose heb ik min of meer zelf gesteld. Je leest er over, zoekt actief informatie op en trekt je conclusie." (Forum)*

Patients are looking themselves for explanations for their symptoms and the evolution of the disease.

> *« Ce que j'observe c'est que les symptômes (et donc celui qui en est la cause aussi) passe à travers mon corps d'organe entre organe. Quand il a fait le tour, par je ne sais quel miracle les symptômes s'estompent. Jamais tout à fait mais ça va vraiment mieux avec le temps. J'ai l'impression qu'il s'installe. Et les symptômes alors le confirment. J'ai le pouce qui bouge tout seul au mois de décembre, plus en janvier. Tient c'est le tour de son voisin, l'index à s'y mettre. Aussi, quand je fais un exercice sportif, je le paie cash 2-3 jours. Et mon explication c'est que le virus est sous contrôle quand on est calme. … mon explication c'est que le virus est sous contrôle quand on est calme. Quand on commence à se bouger, ça augmente le rythme cardiaque et ça propage le virus de plus belle dans tous le corps. » (Forum)*

> *"Mijn aanvoelen is ook dat COVID zich vanaf dag 1 op mijn meest gevoelige plaatsen heeft gemanifesteerd. Daardoor lijkt het alsof je neigt naar burnout, want het zijn ook tekenen van oververmoeidheid." (Forum)*

> *« Impression que le COVID révèle un problème hormonal qui existait déjà avant mais qui est apparu de manière manifeste avec l'infection virale. » (Forum)*

The experienced impact by patients because of lack of awareness among healthcare professionals

Patients who were confronted with physicians that were unfamiliar with and not well informed about long COVID, described that this had an impact in several ways:

- The symptoms tend to be minimized

> *« Tout ce qu'elle m'a dit "enfin madame, vous avez 60 ans, vous devez être encore bien content d'être comme vous êtes comparé à, aux patients qu'on a vus en réa". » (Patient 29, not hospitalised)*

> *« Ma généraliste que j'adore pourtant, aujourd'hui m'a dit "oh bah, c'est le stress, vous avez trop de choses en tête, etc." alors que ces*

problèmes de mémoire sont vraiment inhabituels (par rapport à avant COVID) et très bizarres (je cherche mes mots, je ne sais pas finir mes phrases, j'ai beaucoup de mal à me concentrer sur des taches mentales etc.). » (Forum)

- Some physicians tend to attribute the symptoms quite rapidly to a psychological cause.

  *"Die vermoeidheid, niet vooruit slepen bij het trachten sporten, piepende longen.... wijst op burnout en depressie en verminderde conditie omwille van lockdown.... terwijl ik voorheen super gezond en sportief was (8000km gefietst in 2019, 2 * week tennis, e.a.). De oorzaak leek dus voornamelijk mentaal te zijn volgens de huisarts. Wou me zelfs antidepressiva voorschrijven, wat ik weigerde. In totaal dan 9 maanden ziekteverlof (omwille van "burnout, asthenie, depressie etc.". Dankzij het zelf opzoeken van lotgenoten (FB), lezen van artikels e.d. begon ik te beseffen dat ik eerder last had van postvirale vermoeidheid." (Forum)*

  « Mijn neuroloog zei al snel dat het tussen mijn oren moest zitten dat ik nog steeds niet genezen was ... ik ben zelfs bijna opgenomen geweest in een psychiatrisch ziekenhuis om tot mezelf te komen ☺. » (Forum)

  « Et la plupart du temps les symptômes passent pour de l'angoisse, de l'anxiété et une grosse fatigue car nos examens sont tout à fait normaux généralement. Car les examens vont être effectué à un certain moment où peut être les symptômes ne sont pas au plus forts et passent inaperçues (style la crise de tachycardie, la chute de tension, la dyspnée etc...) et dès lors cela confortent le diagnostic que c'est de l'angoisse due à la situation actuelle ! »(Forum)

- Patients are being blamed of not trying hard enough to take up an active lifestyle.

  « On disait toujours "oui, c'est parce que vous avez un manque d'activité physique" mais c'est, pour moi ce n'est pas cohérent parce que justement je, j'ai tout, je refaisais quand même des efforts, je remarchais, j'essayais de revivre une vie normale et à chaque fois c'était une rechute sur rechute sur rechute, mon corps ne, ne supportait plus rien en fait. » (Patient 13, not hospitalised)

This feeling of patients of not being understood is reinforced by the fact that their complaints are not objectified by medical imaging or other tests.

« Je me bats avec le corps médical pour les problèmes de picotement au cœur et poumons qui ne m'ont jamais quittés. Echo du cœur, IRM: RAS. Le test d'effort m'indique que je suis à 130% d'effort pour les gens de mon âge. » (Forum)

"Ik ben dan vorige maand de laatste keer bij de huisarts geweest en ik heb eens hem gevraagd, eh neem alstublieft wat bloed af. En eh daar had ik geen rood meer in, in m'n uitslag. '…) Had ik geen waarde die, die wat hoger of lager waren dan gepland. Maar, maar zo voelt het niet. Ik bedoel, ze kunnen me, m'n longen en ja, hebben geen schade blijkbaar, of, of weet ik wat ook, maar, maar het klopt niet met wat ik voel eigenlijk." (Patient 20, hospitalised)

Patients are also asking physicians to perform medical examinations in their search to objectify their complaints.

« Je peux vous assurer que plusieurs médecins que j'ai croisés ne voulaient rien entendre car le point a - détection du virus était négatif. Tous les symptômes étaient balayés de la table et les causes des symptômes réels n'ont jamais été investigués ! C'est le patient en tant que novice en médecine a dû provoquer les différents examens pour m'assurer que je n'avais pas de problèmes grave. Un comble…» (Forum)

In some cases, doubts concerning the cause of the symptoms remain: is it a 2nd episode of COVID-19 or persistent COVID-19

"En terug eigenlijk opgenomen in de eh COVID-afdeling omdat men niet zeker was… Enfin, uiteraard de wisser eh die is terug uhm positief eh weergegeven. Uhm wat eigenlijk, ja, denk ik normaal is binnen drie weken na of binnen drie à vier weken na een COVID-besmetting." (Patient 1, hospitalised)

Lack of a formal diagnosis creates uncertainty and hampers an adequate management of Long COVID

This lack of a formal diagnosis leads to doubts among patients as well as difficulties to find solutions.

> *« Cela a été un peu troublant car on ressent toute une série de symptômes et... on ne peut rien faire qu'attendre que cela ne passe... et comme dans certains cas cela est très long, on se pose des questions, on se demande si cela n'est pas imaginaire... bref on doute de sa propre santé mentale... » (Forum)*

> *« Je me rends compte aussi que dans mon mal-être par rapport à ça, je me dis "quelle est la part jouée par le fait qu'on est en confinement depuis un an, qu'on est, qu'on peut pas voir la famille comme on veut et qu'on peut pas voir ses amis, qu'on va plus au resto ?". Donc est-ce que je fais, je fais partie des gens qui commencent probablement à en avoir gros sur la patate parce que ça devient très long ? Quelle est la part de ça sur ma fatigue, est-ce que ce n'est pas purement mental et que c'est aussi une conséquence de plein de gens qui souffrent simplement du confinement et que moi je mets ça sur le fait que j'ai eu un épisode COVID ? Mais bon, chaque fois je retombe dans ma même pensée, je me dis "ben non, parce que ce n'est pas pour ça quand même que je vais avoir des douleurs musculaires, que je vais être crevée comme je le suis, que je vais continuer à avoir des problèmes de, d'odorat et de goût qui sont pas. » (Patient 12, not hospitalised)*

> *"Ik wilde ook niet per se een diagnose, ik wilde vooral graag geholpen worden. Maar achteraf gezien zou een 'officiële' diagnose toch voor iets meer bevestiging zorgen, want nu twijfel ik soms nog aan mezelf - ook al waren / zijn de symptomen (grieperig, serieuze ademnood, niks meer kunnen) overduidelijk..." (Forum)*

Lack of comprehensive diagnostic approach: diagnosis often on a symptom-by-symptom basis

Patients are referred to a specialist according to an isolated symptom and have visited several disciplines depending on the type of symptoms. However, some of them are not referred to specialists at all.

> *"Mijn arts zei me zelfs: maar mevrouw, waarom zou ik u doorsturen naar specialisten om allerhande onderzoeken te doen als die toch niets gaan vinden? Zo ben je snel einde verhaal... Alles wordt toch zo graag onder de mat van het psychosomatische geschoven..." (Forum)*

Patients reported it as positive when physicians attribute their symptoms to COVID-19

Nevertheless, we also collected positive experiences in cases where physicians clearly named the medical condition 'long COVID' or related the symptoms to COVID-19.

> *"Ik denk niet dat dat ooit zo benoemd is. Uh, maar wel, die hebben altijd verwezen dat dat door COVID was," (Patient 22, not hospitalised)*

> *« Elle m'a dit que c'était un des symptômes qu'elle avait constaté chez d'autres patients et que c'était peut-être un COVID à long terme. » (Patient 17, not hospitalised)*

And this is also the case when the patient has the opportunity to meet someone with an expertise in COVID-19.

4.4 Treatments used

Variety of symptoms and the many uncertainties about long COVID results in unstandardized treatment approach

Because of the large range of symptoms, and the absence of clear diagnostic criteria, patients received or used a huge diversity of treatments. A list of the treatments are presented in the results section of the online survey.

- Prescribed drugs : The most current symptomatic treatment used is paracetamol and corticoids. But other are also prescribed depending on the symptoms. Anxiolytics and antidepressiant drugs are also mentioned for mental health problems.
- Food- and vitamin supplements

> *"Ik neem supplementen. De reden waarom, is vooral omdat je alles zou proberen om beter te worden...Magnesium voor de spieren, Vitamine*

C, Zink, Vitamine D, multi-vitamine supplementen met aminozuren, Q10, etc." (Forum)

- Physiotherapy, including vestibular physiotherapy .Physiotherapy was used to aleviate symptoms (e.g. vertigo, repiratory complaints) but also to help in the physical reconditioning. It is prescribed or not. While several particpants experience it as useful, several also indicated that it is very tiring, pushing them beyond their limits what some experience as not tailed enough to the context of long COVID patients.

  "In juli-augustus was ik op aanraden van de huisarts al met kinesitherapie gestart maar die oefeningen bleken te zwaar en zorgden voor een erge terugval. » (Forum)

  "De kine daar heb ik echt wel heel veel uh dinge van gehad ook. Ja. Uhm. Dat heeft mij ook wel goed gedaan. Maar dan, mijn beurten zijn nu om hè, die 18 beurten. Ik heb uh morgen mijn laatste. Ja. (Patient 5, not hospitalised)"

- Management in a post COVID units (not always possible without diagnose)

  "Ik heb ook geprobeerd om in een post-COVID revalidatieprogramma terecht te kunnen maar dat werd geweigerd, wellicht omdat ik geen officiële diagnose kon voorleggen?" (Forum)

- Nervous vagus stimulation
- Speech therapy
- Participation in research such as stimulation of the vagus nerf or taste and smell rehabilitation
- Oxygen at home
- Naturopathie

Patients also reported to have made their own treatment scheme (with medicines, or not) trying cocktails of food supplements, or techniques to get better, such has overcome their limits to improve their state.

« J'ai globalement fabriqué mon auto-protocole - en fonction de ce que je lisais. (…) J'ai bricolé par moi-même mais difficile d'expliquer dans un forum. J'ai lu énormément, de manière compulsive. Tout ce que j'ai développé est rationnel. » (Forum)

The efficacy of all of the reported treatments are variable from a patient to another, and not necessary durable in time. Some of them have side-effects.

"Die medicatie [tegen migraine] heeft dan weer heel veel bijwerkingen eh waar dat je dan, ja, suf van wordt. Dus ik moet dat dan, ja, nu zoeken op welk tijdstip dat ik die kan innemen. Ik kan niet met de auto rijden daardoor." (Patient 18, not hospitalised)

Unconventional therapies: patients search for solutions when traditional medicine does not help them

Several patients reported that they tried unconventional therapies. These are often described as a way to search and find responses to symptoms that are not treated by the GP or medical specialists

"Het enige wat ik krijg van de huisarts is briefjes voor (gedeeltelijke) arbeidsongeschiktheid. Er is geen andere begeleiding of zoektocht naar een oplossing. Zelfs bij de neuroloog ondervond ik weinig kennis over en interesse in long COVID, 'het zal wel een psychologisch probleem zijn'. De osteopaat (waar ik op eigen initiatief naartoe ga) is bij mij de enige die mij ook echt behandelt en een oorzaak zoekt van mijn klachten." (Forum)

« La médecine "traditionnelle" ne proposant rien qu'attendre, j'ai envie de me reconnaitre au plus vite et je me suis tournée vers l'homéopathe, l'ostéopathe. Une médecine en douceur, en respect mais soutenante et encourageante. Les médecins traditionnels m'envoient chez le psy... » (Forum)

- Acupucture or chinese medicine

"En ik bezoek al sinds augustus op geregelde basis een acupuncturist (met opleiding als arts in Wuhan) en ook dat brengt beterschap. Let wel, de eerste maanden had ik een erg hevige reactie en terugval van enkele dagen na een behandeling, maar dan ging het daarna wel een stukje beter dan voor de behandeling." (Forum)

- Osteopathy

"Op aanraden van mijn zus en andere coronapatiënten ben ik naar een osteopaat gegaan. Ik had dit nog nooit eerder gedaan, maar ik ben aangenaam verrast. Mijn osteopaat luisterde heel goed naar mijn klachten. De plaatsen (soms ook onverwachte plaatsen) waar hij spanning voelde, waren ook de plaatsen waar het pijn deed als hij duwde. Hij gaf mij duidelijke uitleg over mijn klachten en de mogelijk oorzaken. Ik kreeg echt het gevoel dat hij wist waarmee hij bezig was en hoe hij mij kon helpen. Dat gevoel kreeg ik helemaal niet bij mijn huisarts en neuroloog. Na de 3e/4e sessie bij de osteopaat merkte ik duidelijke vooruitgang. Hopelijk blijft het zo verdergaan" (Forum)

- Homeopathy

« Si je m'en sors bien d'après l'étonnement des médecins "traditionnels : pneumologue, médecin de médecine physique, médecin traitant, ORL, dermatologue, ... qui observent ce qui se passe en attendant que cela s'arrange tout seul...c'est grâce à mon homéopathe, naturopathe (médecin généraliste) qui m'a fait une prise de sang super complète après 6 semaines de retour à la maison et qui a tout de suite mis le doigt sur des choses qui n'allaient pas. Il me soutient par des compléments alimentaires, vitamines, oligo-éléments... j'ai l'impression qu'il vise juste et fait vraiment progresser et qu'il me soutient au mieux. Gros inconvénient : aucun remboursement... Si c'est placebo, cela en vaut quand même la peine... » (Forum)

- Other alternative and well-being practices: Yoga, Reiki, energy therapy, relaxtaion, mindfulness

"Yoga is heel traag en zacht, zonder te veel pushen. De nadruk ligt op het activeren van het parasympatisch zenuwstelsel om zo de vecht of vlucht reactie van het zenuwstelsel te stoppen. Het autonoom zenuwstelsel lijkt immers aangetast door COVID. Bij de mindfulness probeer ik te focussen op positieve zaken en te aanvaarden dat de situatie is zoals ze is." (Forum)

"Ik heb relaxatietechnieken geleerd via een relaxatietherapeut om terug in slaap te vallen als ik s' nachts wakker wordt met spierspanningen." (Forum)

« Je me fais suivre aussi par un ostéopathe et une logopède qui travaille sur les réflexes moteurs primordiaux, sur les réflexes toniques asymétriques du cou... » (Forum)

- Olfactory therapy

« On m'a conseillé de l'aromathérapie pour rééduquer mon odorat. J'ai essayé de reconnaitre des huiles essentielles au moins une fois par jour pendant un mois (lavande, palmarosa, giroflier, gaulthérie, menthe poivrée, eucalyptus, ravitsara, ...) Petit à petit, je pouvais les différencier sans vraiment en reconnaître le parfum de mes souvenirs. L'odorat n'est toujours pas au top (4 mois plus tard), j'ai l'impression d'avoir atteint un plateau duquel je ne progresse plus. » (Forum)

- Other

  - Rest
  - Life hygiene: physical exercises and healthy diet

« Avoir une alimentation la plus saine possible, oui, j'ai essayé (…) de mieux manger, sainement, des fruits, des légumes, des jus d'orange, voilà, j'essaie d'adapter quand même un peu. Moi je mangeais déjà sainement mais je veux dire, encore plus je vais faire attention (…) Et de l'activité physique … » (Patient 6, hospitalised)

"Ik was op dat moment (klachten sinds maart, diagnose infectioloog oktober) al bezig met oefeningen (online post-COVID yoga en krachtoefeningen via een Engelse yogadocente die zelf longCOVID heeft) en opbouwen wandelen/fietsen met E-bike." (Forum)

4.5 Impact of long COVID on the patient

In the section below we describe how patients experienced the impact of long COVID on their daily life, their educational/professional activities as well as the financial impact and the administrative burden with which patients are confronted.

4.5.1 Impact on daily life

Symptoms with a life-changing impact

Long COVID does not have impact to the same extent on all individuals and could have a different impact on daily life. Several patients experience the symptoms – mainly fatigue, brain fog and pain – and the irregular and unpredictable nature of their symptoms as life-changing. Patients report that they are unable to perform 'normal activities as before'. This can, for example, be driving, cooking, shopping or playing with grand-children.

> *"Nu (maand 5) (…) sommige dagen voel ik mij nog heel moe. Na te lange fysieke inspanningen (wandelen, fietsen of huishoudelijke taken) ben ik extreem moe, totaal uitgeput." (Forum)*

> *"Energieniveau is na 4 maanden nog steeds maar 10% (te weinig energie om te kunnen werken, maximaal half uur kunnen wandelen, zelfs telefoongesprekken en een ziekenbezoek van vrienden zijn te vermoeiend): reden waarom dit storend is: gooit mijn leven compleet overhoop. Ik kan niet werken, niet sporten, geen activiteiten doen met vrienden en familie, huishouden." (Forum)*

> *« Quand je vais jouer au football avec mon petit-fils, que je ne sais même pas jouer 10 minutes avec lui, pour moi ça m'atteint. » (Patient 30, hospitalised)*

Patients adapt their activity level

Some patients adapt their activities to stay quiet, such as reading or writing. Avoiding stress is also a major strategy of patients to avoid bad consequences.

> *« En tout cas moi mon idée, c'est d'enlever ce qui me cause du stress parce que je sens que c'est ce qui enclenche beaucoup de douleur au niveau de la tête de la fatigue. » (Patient 32, not hospitalised)*

4.5.2 Impact on professional activities or education

Incapacity to work or difficulties to restart

Long COVID heavily impacts patients' professional life. The long duration of the disease might lead to "work incapacity" (health insurance status).

However, some patients mention that they have to continue working or have to restart quickly because they are self-employed. For them, not working means a substantial loss of income. And those who are not able to work are very concerned by their professional future because they are losing clients.

> *"Ik hoop na bijna een jaar nog altijd op een volledig herstel en een volwaardige terugkeer naar mijn job - maar ben niet zeker of dat ooit lukt, en ik maak me zorgen over mijn professionele (en daaraan gelinkt financiële) toekomst." (Forum)*

Going back to work is important for patients' self-image and to feel useful

Some people report that returning to work is important for their mental health or to keep their brain active, sometimes even if physicians have discouraged them to do so because of their health status.

> *« Quand j'avais émis le souhait de recommencer à travailler, parce que en fait, oui, parce que je dis comme plainte la fatigue mais y a aussi les problèmes cognitifs hein. Et mais alors, je m'étais dit [rires] que si je ne retravaillais pas, mon cerveau, je n'allais pas entraîner mon cerveau et en fait c'était ça qui m'avait un petit peu motivée aussi à retravailler. Je me dis "si je ne retravaille pas, surtout à mon âge, je ne vais jamais entraîner mon cerveau". Donc c'est moi qui ai voulu recommencer à travailler et c'est elle qui m'a freiné, qui dit "mais alors tu recommences avec un mi-temps médical, surtout pas recommencer tout à fait ». (Patient 29, not hospitalised)*

> *"Ik ben heel verdrietig geweest omdat ik niet kon werken, want ik heb in het begin geprobeerd om deeltijds te werken. Maar ik weet niet of dat dat eigen aan de zorgsector is, maar in de voorziening waar ik werkte was dat toen niet mogelijk. Dat was eind juni. Want ik had heel graag blijven werken en ja dat was dus niet mogelijk. En ik heb mij daar heel*

lang schuldig over gevoeld omdat ik zoiets had van ja, ik wou helemaal niet stoppen en zie mij hier nu zitten, ik loop de muren op en ik werd maar ook niet direct beter natuurlijk. En van de controle arts helemaal, thuis." (Patient 19, not hospitalised)

Living alone could also be a reason to restart working quickly, in order to reduce isolation.

« Et être isolé et en arrêt maladie pendant une longue période, je ne le sentais pas bien au niveau moral quoi. » (Patient 10, hospitalised)

Keeping contact with work (e.g. reading emails, regular contact with colleagues) is perceived as a facilitator for the reintegration process, although in some cases it is also felt as an additional stressor.

The reintegration process: reduced labour time or other modifications

Restarting work is not always possible, even after a year of work incapacity. When reintegration started, many patients included in our study started to work or go to school progressively, reintegrating their professional or educational activities part time.

This working time arrangement has been proposed by the employer or a physician.

The progressive return to work was organised either through the use of part-time medical care, or by the patient himself, who chose to alternate medical absences and periods of work.

« Moi j'y avais pensé et mon (…) responsable (…), m'avait téléphoné pendant ma maladie pour me dire "voilà, si tu veux quand même reprendre un mi-temps médical, tu peux parce qu'il y a du télétravail à proposer". Donc elle m'avait déjà ouvert une brèche, je me suis dit "ok, je vais en discuter avec mon médecin si je peux". Donc c'est comme ça que j'en ai parlé alors au cardiologue qui m'a dit, il ne voit pas d'inconvénient, il a fait le rapport pour la mutuelle. Et j'ai déposé, la mutuelle a donné son accord. » (Patient 14, not hospitalised)

Some people restart their work full time and request medical leave for medical rehabilitation appointments only when they have to go to their medical rehabilitation appointments.

Other patients use their remaining annual leaves to recover so that they would not relapse, because they fear the administrative workload and/or the loss of income.

« Comme il y avait les jours de congés, que ça permet de faire à la demande, je trouvais que c'était la meilleure solution. Mon employeur à titre principal n'était pas contre. » (Patient 32, not hospitalised)

« Le médecin a considéré que comme j'avais pas de température je pouvais reprendre. Oui, en même temps je n'arrive pas à parler tellement je toussais [rires] donc c'était quand même un souci. Et voilà, après la question ne s'est pas vraiment posée puisque de toute façon j'avais, il me restait des jours de congés et si je les prenais pas c'était perdu. Donc je me suis arrangée comme ça ». (Patient 25, not hospitalised)

The reintegration process could consist of an adaptation of the type of work but this has to be decided in concertation with the occupational physician, which did not always happen.

« Non, et je dirais une remise de travail adaptée. Alors pour, pourquoi ne pas voir avec la médecine du travail qui, je trouve, nous a un petit peu abandonnés pendant cette période-là. Parce que tout ce qui était vaccin contre la grippe, ils ne les ont pas faits cette année parce que, pour le contact COVID et cetera. Donc je trouve qu'on a été un petit peu abandonnés. Et je pense que quelqu'un qui a eu le COVID aurait dû passer à la visite médicale pour peut-être expliquer ses symptômes et pouvoir adapter sa reprise de travail. » (Patient 28 not hospitalised)

Another possibility is to adapt the rhythm of work, even in cases of part time work: for example, working in the morning, allowing more breaks or allowing naps.

« Le matin ça va toujours (…). Dès qu'il est midi, c'est déjà beaucoup moins bien (…). Si je sais que j'ai une réunion l'après-midi, ben je vais essayer de me reposer avant midi parce que sinon je sais que j'aurai trop mal à la tête le soir, ou que je n'arriverai pas à terminer ma réunion donc je serai un peu gênée... » (Patient 32, not hospitalised)

« Je devais faire un travail de groupe, bon y a eu un moment, parce que j'avais beaucoup de symptômes qui revenaient, des essoufflements et tout, je devais arrêter de travailler, je devais couper complètement mon PC, attendre une heure ou 2, essayer de prendre un Dafalgan mais voilà quoi. Et puis je reprenais quand je savais et je devais alterner comme ça. » (Patient 13, not hospitalised)

Teleworking is felt to be helpful for the reintegration process because the adaptation is easier.

« J'ai la chance de pouvoir travailler à mon rythme et de pratiquer du télétravail la plupart du temps ce qui laisse la possibilité de se reposer lorsque c'est nécessaire. Je pense que ce serait une bonne chose pour les personnes subissant un COVID long...hélas ce n'est pas possible dans tous les secteurs. » (Forum)

"ik kan gelukkig telewerken en ben er van overtuigd dat ik anders veel langer in ziekteverlof had geweest" (Forum)

"Ik combineer telewerken met mijn ziekenhuiswerk en ben daar wel dankbaar voor. Maar het is niet evident." (Forum)

Even with additional measures patients feel exhausted, relapse or are less productive than before and are, on top of that, confronted with the psychological burden related to these consequences

Even after going through part-time medical treatment before a full return to work, some patients had to stop working again or are not sure if they will be able to continue working full-time in the long term. It seems very difficult to restart work and find the right balance: restarting, overdoing, stopping, recovering, restarting, overdoing, work less…are common and recurrent patterns.

« Ce qu'il y a, c'est que si je dois de nouveau ré-arrêter parce que je me rends compte que y a, y a des moments où c'est limite quoi ! Là, vous me voyez le matin. Les gens, quand ils me voient arriver le matin, ils disent "ah ça va" et puis quand ils me voient, hier soir j'avais une réunion qui s'est prolongée fin d'après-midi, bon ils voyaient bien que j'avais, que j'étais juste bonne à me mettre au lit. (…) parfois y a des jours où je me pose, je me pose des questions, oui. Heureusement, c'était dimanche, dimanche je suis restée engluée, couchée dans le divan, je n'ai pas du bouger, j'étais de nouveau, ça n'allait pas. Heureusement que c'était dimanche, c'est, mais je n'ai pas su bouger, dimanche j'ai fait le strict minimum du minimum qu'il y avait à faire dans la maison. » (Patient 29, not hospitalised)

When patients returned to work, they say they are not able to work as usual.

« Je veux dire, j'ai repris le travail oui, mais on est en plus du tout aussi, autant à la hauteur du, de la capacité de travail que je pouvais avoir avant. » (Patient 10, hospitalised)

Not being efficient during work leads to feelings of guilt…

"Het is enorm storend om als een naïeve beginneling vragen te beginnen stellen aan de collega's over projecten waarin ik een maand of wat eerder blijkbaar wél al betrokken ben geweest, maar totaal vergeten ben..."

« Je pense que du 1er janvier jusqu'au 15 janvier j'étais en congé maladie. Et puis je me suis rendu compte que ça me stressait terriblement, parce que je, je devais corriger, je me disais "mais je suis en congé maladie et je me suis dit mais je ne sais pas si c'est une bonne décision", que le stress que je me causais parce que j'étais en congé de maladie n'était pas bon. Donc pour me calmer j'ai dit 'ben c'est jour de congé'. Vous me direz, ça ne change rien, on est d'accord mais psychologiquement ce n'est pas la même chose de prendre ses jours de congé de retard pour du pro mérité, on va dire comme ça, par rapport à passer sur la mutuelle, je le sentais pas de trop, donc. » (Patient 32, not hospitalised)

"Dat blijft, ik denk dat het eerder voor mij moeilijker is, omdat, ik ben er altijd van uitgegaan ben van oh, we gaan dat stap voor stap terug uh opstarten. Maar ik heb nooit gedacht dat dat weer zo lang ging duren en, het duurt dan eigenlijk nog langer, als eigenlijk in maart dan. En dat vind ik dan, ja. Ik voel mij daar enorm schuldig over zelf. Uhm. Ja. Omdat ik dacht van, wow, allez als je dat nu in oktober had gevraagd van, dan had ik nu al wel lang terug uh die 80% gewoon aan de slag geweest. Daar was ik echt wel van uitgegaan. Dus dat, dus voor mezelf vind ik dat moeilijk." (Patient 5, not hospitalised).

…as well as being absent, because the work has to be taken over by colleagues…

> *« Dès que je retravaille, ça fait mal. Donc à la fin, on se pose des questions. Vous me direz qu'alors je ferais peut-être mieux d'être sur la mutuelle. Mais je ne sais pas donc j'admets que ça me, ça me turlupine, vous l'avez compris, je suis quand même assez active professionnellement et ça m'embête de ne pas pouvoir l'être, ça m'embête par rapport à ma collègue qui ben forcément alors se retrouve avec plus de travail» (Patient 32, not hospitalised)*

…even more if patients work in the healthcare sector.

> *"Wat dat zeer frustrerend is als, als [zorgverlener] hè want je wilt in een gezondheidscrisis wilt je niet uitvallen. Daar heb ik het in het begin heel moeilijk mee gehad." (Patient 18, not hospitalised)*

All these difficulties are not always understood by the professional environment, which is sometimes suspicious about the 'real' fatigue or the colleague.

> *« Les remarques des collègues ou chef sont : si j'avais été chef tu aurais eu droit à une inspection de la médecine du travail ; fatigué, normal en passant la nuit devant la tv et l'ordinateur,... Jalousie, incompréhension je m'attends au pire à mon retour ...*
> *Réponse : comme je vous comprends... moi mon patron me fait des appels vidéos pour voir ma tête, et être certain que je suis vraiment malade...Il est clair que, d'après certains collègues avec qui j'ai encore des contacts, ça va être chaud quand je vais recommencer. » (Forum)*

Going back to work is difficult even more so when adaptations to the job or work regimen are not possible

When adaptations in work regimen or type of work are not possible and patients are going back to work as before they often feel exhausted.

> *« Mon employeur ne croit pas au COVID long et la reprise a été sans aménagement. Je suis épuisée en fin de journée. » (Forum)*

Impact on the career: changing jobs - stop working or limited career perspective

Because of the symptoms some patients feel they are not able to stay in the same function

> *« Demain il est possible qu'il soit décidé à la médecine du travail que je doive reprendre mon travail. J'ai postulé un autre poste car j'en suis incapable. Physiquement et psychologiquement. Physiquement je ne suis pas des plus à plaindre, mais je reste essoufflé au repos régulièrement et fatigué. Difficile de me concentrer... On verra demain, je n'ai pas envie de quitter mon emploi actuel mais je n'aurai peut-être pas le choix. Et si je ne réussis pas les tests de ce nouvel emploi ? Le poste que je postule me semble très intéressant mais est-ce vraiment opportun de changer d'emploi maintenant dans ma situation »(Forum)*

…or even consider to stop working.

> *« Je me demande vraiment si je ne vais pas arrêter de travailler parce que ça m'embête de tout le temps avoir ses douleurs à la tête. Donc comme je vous l'ai dit, je suis mariée, je n'ai pas d'enfant donc je peux me permettre si je veux d'arrêter de travailler. Ce n'était pas vraiment prévu hein, soyons clairs. (…) Ben si, si c'est pour avoir tout le temps mal à la tête, ce n'est pas très agréable. Je veux dire tout le temps essayer de travailler, à chaque fois avoir mal à la tête, je pense que si je ne travaillais pas du tout, j'aurais peut-être pas mal à la tête. Parce que ben je n'aurais pas le même travail intellectuel mais…Bon maintenant, vous me direz peut-être que j'aurais mal à la tête quand même [rires]. Mais, mais, j'a, j'admets que j'y réfléchis. (…) mais c'est pas si simple que ça d'arrêter, je suis d'accord avec vous mais, si vraiment ça va pas, je ne vais pas non plus , nuire à ma santé si je me rends compte que ça ne va pas vraiment pas. Mais donc ça fait partie de mes, de mes réflexions. » (Patient 32, not hospitalised)*

The long absences or repeated absences could have an impact on the career perspectives of patients. One of the patients said that her employer has taken advantage of her absence to implement cut-backs. She assumes that her employer will continue to do so, anticipating that his employee will

not return to full-time work. The patient therefore does not know whether she will be able to return to her previous contract.

> *"En nu was het al zo dat men eh dus de collega's eh… Men wil geen vervanging geven voor mij. Eh dus zij moeten maar roeien met de riemen die ze hebben en uhm… Ja, toen zeiden ze: "Ja, eh en eigenlijk zou er moeten bespaard worden dus we gaan er eigenlijk van uit dat zij nooit meer zo veel eh zal kunnen werken dus dan moet ze maar eh in plaats van de fulltime dat ze nu heeft…(…) Dan maar aan 70 of 80 procent komen werken.". Ja maar, allee, zij beslissen dat maar…voor mij. Dat ik dan… Allee, wie zegt er dat ik als ik dan hersteld ben … ja, niet weer ga kunnen werken als voordien?" (Patient 9, not hospitalised)*

For employees in the public sector, to be in sick leave will delay their appointment. In some case the employee could even be put on compulsory early retirement.

> *« Je suis enseignante dans le secondaire inférieur. Je ne suis pas nommée et, je suis amenée à changer d'école chaque année pour l'instant. J'ai "droit" à 15 jours de maladie par année scolaire (ce qui d'habitude est tout à fait suffisant) et si je les dépasse, je reçois alors une indemnité de ma mutuelle. Ce qui me pose vraiment problème avec les deux absences prolongées que je vis, c'est que mes jours d'ancienneté ne sont plus comptabilisé quand je suis indemnisée par la mutuelle, ma nomination est donc retardée ! (…) Pour le moment il me reste des jours maladie à prendre mais après ??? » (Forum)*

> *« J'ai été en arrêt de travail mais j'ai aussi pris sur moi pour ne plus l'être parce que par rapport à ma situation personnelle, au niveau emploi, enfin j'ai eu 2 gros, enfin ma dépression majeure que j'ai eue et puis un autre problème que j'ai eu, un autre problème de santé au niveau de la colonne, j'ai épuisé mes, mes jours de congés de maladie dans l'administration. Et donc je pouvais être mis en disponibilité si j'avais de nouveau une longue période de congés de maladie. » (Patient 10, hospitalised)*

In the private sector early retirement is also possible. This happened to the spouse of one the respondents, aged 62 years.

> *« Il avait dit "ben je vais continuer un mi-temps médical jusqu'à mes 64 ans". Et là ils ont dit "non, puisque vous pouvez prendre votre pension anticipée à 62 ans, ben voilà, il faudra terminer l'année prochaine". Ce n'était pas possible pour eux de terminer jusque 64, jusqu'à mi-temps quoi. (…) Son seul regret, c'est de ne pas continuer à travailler jusque 64 ans parce que c'est quelqu'un d'hyper actif et que du jour au lendemain il a dû tout arrêter et (…) Ça c'est la conséquence du COVID qui pour lui est la plus lourde finalement. » (Patient 26, hospitalised)*

One patient who decided not to stop working after the acute phase was advised by her employer to change jobs.

> *« A mon retour, il m'a clairement dit que je devais me poser la question de plutôt faire un métier de bureau dans le secteur public histoire que ça "puisse mieux arranger mon état de santé et mon temps familial, que c'est pour mon bien à titre préventif". Je suis vendeuse depuis 7 ans dans la même boîte et j'ai continué à travailler malgré la difficulté, sans prendre le temps de me soigner convenablement. Je n'ose même pas imaginer la pression pour ceux qui n'arrivent même plus à se rendre sur leur lieu de travail. » (Forum)*

Some people with long COVID decided to quit their job.

> *"Mijn geheugen, concentratie en focus is sinds de COVID een stuk slechter geworden. Daardoor heb ik afscheid moeten nemen van mijn job" (Forum)*

Impact on studies

A student explained that he was obliged to spread his education through two years instead of the 1 year initially foreseen.

Respondents also reported that it is difficult for them to make projections for the future

> *« Je ne sais pas comment je ferai en septembre de l'année prochaine pour l'université parce que bon, là, les cours vont recommencer donc il faudra bien que j'y sois. Ici je viens de recevoir le, la demande du président, "est-ce que l'année prochaine tu donnes toujours tes cours ?". Pour le moment je n'ai pas répondu mais je crois que je vais devoir*

lui répondre, mais qu'est-ce que je réponds? » (Patient 32, not hospitalised)

« Donc, d'un côté je me disais si jamais, si je connaissais cette maladie et que je savais qu'elle prenait qu'un an, je forcerais pas ma fille à faire ses devoirs. Je n'en ai vraiment rien à faire. (…) Je lui dirais : repose-toi, ce n'est pas grave, fais ce qu'il te plaît, mais ne te casse surtout pas la tête avec les devoirs. Bah, maintenant, comme c'est compliqué, personne ne sait combien de temps ça va durer, alors on se demande : est-ce qu'elles vont rater une année ? 2 ? 3 ? Je n'en sais rien du tout. » (Patient 27, not hospitalised)

4.5.3 Financial impact

Long COVID has a financial impact on patients, because of loss of income, increased healthcare expenses or because they had engaged expenses for activities they are not able to do anymore.

Loss of income

Firstly, as mentioned before, patients who had to stop working have generally a loss of income, except for civil servants who continue to get their salary even when they are on sick leave.

The longer the work incapacity, the higher the financial impact. Indeed the replacement income paid by the sickness fund is 60% of the basic salary. Patients may, therefore, find it difficult to pay their rent or daily expenses and may need to seek (financial) support from their relatives.

« C'est toujours des gros stress parce qu'on ne sait pas comment on va payer son loyer, on ne sait pas comment on va faire ci ou on va faire ça. (…) Ma famille m'a prêté de l'argent pour pouvoir un peu avancer dans les charges. (…) Je suis en arrêt depuis octobre de manière continue donc voilà. Et c'est toujours un pourcentage que la mutuelle nous paie, je pense 60%, ce n'est pas grand-chose. » (Patient 14, not hospitalised)

Some patients, despite feeling not capable to work, hesitated between continuing to work (to avoid loss of income due to sick leave) or staying at home.

« Pour mon boulot principal, si je vais, si je suis sur la mutuelle, ben je pense que je gagne un tiers de ce que je gagne actuellement. Donc j'admets que ça rentre dans le calcul. Un tiers pour mon boulot principal et je perds tout pour [mon travail complémentaire] donc (…) En tout cas je sais par expérience que si je commence à retravailler à mi-temps, ben franchement c'est, c'est une aumône, donc je suis un peu méchante mais par rapport à ce que je gagne, j'y perds énormément. » (Patient 32, not hospitalised)

Self-employed people who did not want to stop their business activities completely, had to find solutions to be replaced or to hire an extra employee generating extra and unforeseen expenditures.

« Il y a quelques mois, j'en étais à une semaine complète pour faire ce que je fais normalement dans une journée de 8h-10h. Maintenant, je dirais la moitié mais au niveau financier ce n'est pas tenable. Egalement, j'ai dû prendre des students pour faire les choses qui nécessitaient un déplacement car pas la force de me déplacer partout sur Bruxelles ou dans le pays en ce moment. J'ai aussi dû annuler les cours que je donne à des personnes âgées. J'ai essayé en ligne mais bien trop fatiguant. Les seniors étaient plus en forme que moi. » (Forum)

Increased healthcare expenses

- In the ambulatory sector
  The multiplication of ambulatory consultations and medical examinations accumulate expenses and have a finacial impact on the household budget of patients.

  « La stimulation du nerf vague, je l'ai fait pendant 2 semaines, ça a été mieux après. Puis j'ai eu une légère petite rechute et j'ai voulu atténuer un peu ça donc j'ai redemandé un peu l'appareil à louer, c'était quand même 125 €. Je n'ai pas réussi à demander un remboursement de la mutuelle sur ça. (…) j'ai peut-être un statut, un statut BIM pour les médecins traitants, en attendant c'est '1 €, 2 €, 3 € pour les consultations. À force, voilà, on fait la facture, ça remonte quand même. Et puis il y a eu l'ambulance aussi enfin, j'ai eu beaucoup de

choses, on n'a pas eu, on n'a pas de remboursement sur tout non plus. » (Patient 13, not hospitalised)

Patients reported that physicians prescribed several not (fully) reimbursed treatments before finding the appropriate treatment (trial-and-error). The costs of this approach accumulates to considerable amounts for some patients.

« C'est lourd. Parce que l'infection au CHU 100 €, à chaque fois il faut, c'est, c'est le fait de sortir l'argent. (…). Parce que si je compte, il a été quasi un an chez la neurologue, je lui ai donné quasi plus, plus de, de 1 000 € moi à la neurologue hein. Ben j'ai été remboursée de 6, presque 600 € mais il faut les sortir tous les mois les 80 €. Et alors elle vous fout des médicaments qui coûtent 70 €, "on va essayer ça", c'est 70 €. Ça ne va, "essayez toute la boîte, si ça ne va pas on va essayer un autre". Voilà, c'est faire des essais de traitements qui sont toujours, qui sont pas bon marché quoi. Elle avait mis par exemple du Tanakan à mon mari pour oxygéner, c'est du ginkgo pour oxygéner son cerveau, c'est 70 € la boîte, c'est remboursé à telle et telle et telle condition, mon mari n'était pas dans les conditions, voilà. » (Patient 26, hospitalised)

- In the hospital sector
  For some patients, substantial out-of-pocket expenses were included in the hospital bill. For example, non-reimbursed blood tests were carried out.

  "Er waren bloedtesten gedaan die totaal niet werden terugbetaald door de mutualiteit. En die kwamen per test op 40 euro…En dat hebben ze tijdens mijn ziekenhuisopname vier keer gedaan….Dus … dat zijn zo dingen waar dat de mensen ook niet bij s-… Want die artsen schrijven dat maar gewoon voor hè." (Patient 2, hospitalised)

  "(…) Want dat remgeld, want die rekenen… Elke dag komen die op consultatie…Hè dan nog eens een fotooke. De radioloog rekent ook nog eens een consultatie. De klinisch bioloog voor dat labo ook nog eens consultatie…Eh er wordt eens een filmke van mijn hart gemaakt, de cardioloog rekent ook nog eens al dat remgeld. … Dat telt wel op. (…) Zelfs al rekenen die er maar een paar euro's bij boven op dat remgeld, dat is wel maal zoveel hè." (Patient 2, hospitalised)

Having a complementary private hospitalisation insurance is important in these cases.

- Reimbursed physiotherapy is experienced as limited
  Patients who need a lot of physiotherapy regret that only a limited number of sessions are reimbursed. Indeed, physiotherapy sessions seem to have a considerable financial impact for several patients.

- Nutritional supplements and vitamins are not reimbursed
  As mentioned earlier, some patients with long COVID take nutritional supplements and vitamins. These are not reimbursed by the health insurance and the total bill can reach a few hundred euros per month.

  "Als ik kijk naar wat ik voor die eh supplementen allemaal uitgeef dat, dat zijn gigantische eh bedragen hè dus uhm…Het ligt gauw aan, aan 100 … 100, 200 euro per maand eigenlijk". (Patient 9, not hospitalised)

  « Il y a juste mon pharmacien qui est très content de me voir très souvent. [rires] Oui mais non, c'est vrai, c'est quand même … quand je vois la somme, c'est effarant quoi ! Allez, quand vous prenez des vitamines D homéopathiques, la petite boîte là, tu dois avoir consommé 5 boîtes de Dafalgan en 5 mois, plus des compléments trucs, des compléments machin, … ». (Patient 16, not hospitalised)

- Non conventional therapies are not reimbursed
  This also applies to non-conventional therapies (such as osteopathy or acupuncture), which are also not reimbursed.

- Psychotherapy is not always reimbursed
  Psychotherapy is not always reimbursed by the health insurance, although some sickness funds provide small financial compensation via the complementary insurance.

  "Niet iedereen kan 60 euro per uur betalen voor een psycholoog, zeker niet als je door arbeidsongeschiktheid al op een lager inkomen valt en veel medische kosten hebt."(Forum)

Consequently, some patients experience financial difficulties and prefer to limit their healthcare consumption.

> *"Respondent: Maar dat is ook zo omdat dat mijn klachten zijn vooral.. intensiever. Het is nu, ik ga nu één keer per week omdat het financieel kost dat ook gewoon veel geld, en om cru te zeggen ik ben al een jaar elke maand in min aan het gaan, ja je kunt dat ook niet blijven trekken, en dat bepaalt ook wel de, het feit dat je daar toch wel ja, ja je moet daar rekening mee houden hé om dus cru te zeggen.*
> *Interviewer: Dus dat limiteert ook wel een beetje de hulp die je verder zoekt?*
> *Respondent: Ja, zeker. Ja dat is ook de reden dat ik psycholoog en al die zaken gewoon direct heb, heb afgezegd vanaf dat ik op zoek ging naar die revalidatie enzo." (Patient 19, not hospitalized)*

Financial losses due to inability to engage in prepaid activities

Being long COVID patient impaired some patients to engage in activities that were already paid in advance, such as sport activities for children.

> *« J'ai perdu 1000 euros parce que j'ai inscrit mes filles en sport, mais là, je ne vais pas pouvoir les récupérer peut-être ces 1000 euros. C'est une année de perdue. Elles ont même pas, même pu faire 1 mois. » (Patient 27, hospitalised)*

4.5.4 Psychological impact

Patients are confronted with a variety of feelings due to their condition and because they do not feel the same as they did before their infection. Some feelings are related to symptoms, others to the evolution of these symptoms through time and others by the way other people (relatives, colleagues, etc.) consider them.

Feeling anxious because of long COVID symptoms

The perceived symptoms could induce a feeling of anxiousness for some people who feared to die or lose control of their body.

> *"Het belemmert mij heel hard, die, die druk op mijn borst dat dat soms geeft is zo beangstigend en is zo, daar kan mijn lichaam volledig overheersen." (Patient 7, not hospitalised)*

> *"Het was, ja het was verschrikkelijk. [lacht] Het was echt een, een, een helse periode. Ik dacht dat ik doodging. Eh ja, op den duur krijg je ook angst, angst, en, en, en ja, die hartkloppingen en, en ja, ze wist-, op den duur zei, zei mijn man ook: Zal ik u niet laten opnemen, want zo gaat het niet verder? Maar ik heb dat wel niet gedaan, omdat ik wist van, ja, dat haalt niet uit. Het is echt, allee, het is niet vastgesteld, want de, de test was negatief, maar ik had dit nog nooit van m'n leven niet meegemaakt. Nog nooit." (Patient 8, hospitalised)*

Uncertainty regarding diagnosis or origin of the symptoms could also create anxiety.

> *« Je suis passée par un état dépressif parce que ' personne ' ne peut nous dire vraiment : 'oui c'est les suites de l'infection...' et que forcément on peut s'imaginer le pire... » (Forum)*

> *« Ca a un impact sur le stress, très clairement, car quand on ne sait pas, on s'imagine le pire. "Il n'y a pas pire psychologiquement que de ne pas savoir" » (Forum)*

Fear for the future and evolution of the condition

The current absence of knowledge on the long COVID condition and its evolution provokes feelings of fear about the future among long COVID patients. This includes fears about their future health status, their future way of life, their future professional life and their future private life (e.g. the possibility to have children).

> *"Gevoel van onrust en angst, ongerustheid over de toekomst. Kan ik op deze manier bvb nog kinderen krijgen, kan mijn lichaam een zwangerschap aan? Wat gaat de impact zijn op mijn verdere leven?*

Wat als het niet meer lukt om voltijds te werken? Dus ook financiële zorgen. Het gevoel van zorgeloosheid is weg" (Forum)

« il y a un moment où je me suis retrouvée, où je me suis dit "mais si ça continue comme ça, ben qu'est-ce que je vais faire, enfin j'aurai plus de perspectives". » (Patient 28, not hospitalised)

« Allons-nous garder des séquelles? Je me demande certains jours si je vais retrouver une vie "normale", retrouver mon énergie, mes mots, mon bien-être... ma vie... » (Forum)

Loss of confidence in the medical field

When the symptoms are not objectified by medical examinations, the patient may lose confidence.

"Geen enkel vertrouwen meer, zelfs langs de straat lopen heb ik intussen schrik voor gekregen: Vandaag gewoon rustig aan het wandelen (2 à 3 km per uur of zo) voelde ik het ineens opkomen, extreem moe, hartslag 135, koud zweet, misselijk en zwarte vlekken voor de ogen...Gaan zitten, na 10 minuten nog steeds hartslag 130 en nog steeds extreem moe...zuurstof gehalte in bloed gemeten: 99%, en lichaamstemperatuur 36 graden. Na een half uur zitten is de hartslag uiteindelijk toch gedaald...Ik heb het gevoel dat als ik niet op tijd was gaan zitten ik zou zijn bewusteloos gevallen (maar kan dat natuurlijk niet bewijzen). Aangezien op het cardiogram dat gemaakt is niets te zien is en ik 2 dagen in observatie geweest ben in ziekenhuis, niets gevonden werd, en een longscan leverde ook niets op, neemt niemand dit bijgevolg serieus." (Forum)

« Ce que je trouve le plus dur psychologiquement parlant ce sont les doutes de part cette absence de PCR et de par la sérologie négative. C'est comme si on n'existait pas et c'est très douloureux à vivre surtout quand on est malade depuis près d'un an. » (Forum)

Difficulties to accept the situation

Patients sometimes have a hard time

- To accept the fact that they do not function in the same way as before or have reduced abilities to perform activities as before. -

  "Ik ben iemand dat haar werk, zeker in de COVID-crisis, heel graag deed. Uhm en, en mentaal was dat voor mij heel moeilijk dat ik er nu nog nota bene juist langdurig ging uitvallen. Daar heb ik heel lang mee geworsteld en dat zal mijn herstel zeker geen goed gedaan hebben uhm omdat je probeert, ja, rapper terug te kunnen keren dan dat gaat en dan uw lichaam toelaat. En daar heb ik het heel moeilijk mee gehad met het te aanvaarden." (Patient 18, not hospitalised)

  « Mon mari a vécu un gros contrecoup en janvier, car il ne me reconnaissait pas: au quotidien, j'étais une pieuvre à 10 bras, réagissant sur tout au quart de tour, hyper-disponible... Progressivement, il chemine et accepte la situation (comme moi, j'ai dû entrer dans une démarche de ce type pour moi-même et m'apprivoiser différente...) » (Forum)

- To accept living with their symptoms.

  « Je vais voir un Psy, qui elle, me comprendra. Ça a été la meilleur aide - non sans douleur: elle pose les bonnes questions qui font mal ! Qui me fait prendre conscience qu'un jour on meurt (naïf que je suis), que ça a l'air d'une maladie chronique et qu'il va falloir vivre avec un bon moment. Nondidju, qu'est-ce qu'elle m'a retourné ma psy ! Il m'a fallu certainement 5-10 mois pour accepter mes symptômes et encore aujourd'hui j'aspire à ma vie d'avant. » (Forum)

- To accept that they may cause a burden on their relatives' life

  « Il y a des choses que je ne sais plus faire comme je voudrais. Mais, ma femme, je sais que à côté de ça, des fois elle voudrait peut-être bouger, aller promener ou autre chose quand il fait bon, et si elle voit que je traîne la patte, elle se dit "non, non, on ira demain, on ira un autre jour". Et je sens bien qu'elle le fait exprès pour moi. Et ça, ça ne me va pas du tout … ça c'est psychologique. » (Patient 30, hospitalised)

- To feel like an old person

  "Je post COVID" ik" is in niets vergelijkbaar met de pré COVID "ik", op 1 jaar is er precies 15 jaar ouderdom bijgekomen." (Forum)

  « En 6 mois de temps, t'es pas passé de normal à pré-sénile! » (Patient 16, not hospitalised))

Feelings of guilt

Feelings of guilt were reported in different forms and levels of severity. Examples include patients feeling guilty to be alive since they survived COVID while others died ….

« Je suis rentrée bosser coupable dans mon corps et dans ma tête ! J'ai reçu un dossier a remplir de la médecine du travail pour une reconnaissance comme maladie du travail (je travaille dans un hôpital), je ne l'ai pas rempli car là aussi par rapport à d'autres je m'en sors bien, certains collègues sont morts ... » (Forum)

- … or feeling guilty because they are not able to take up their role in society (e.g. at work) as before.

  "ik ben heel verdrietig geweest omdat ik niet kon werken, want ik heb in het begin geprobeerd van deeltijds te werken, maar ik weet niet of dat dat de zorgsector is, maar in de voorziening was dat toen niet mogelijk, dat was eind juni, want ik had heel graag blijven werken en m ja dat was dus niet mogelijk. En ik heb mij daar heel lang schuldig over gevoeld omdat ik zoiets had van ja, ik wou helemaal niet helemaal stoppen en zie mij hier nu zitten, ik loop de muren op en ik werd maar ook niet direct beter natuurlijk." (Patient 19, not hospitalised)

No recognition and feelings of abandonment

Because of the lack of awareness, patients with long COVID have the feeling that they are not taken seriously and this causes psychological distress.

« Le COVID long, on commence seulement à vouloir en parler publiquement, ceux qui osaient été traités de malades imaginaires. Ceux de la première vague, dont je fais partie, ont gravement souffert psychiquement et physiquement de ce manque d'information. » (Forum)

« L'impact : c'est surtout que l'on s'est sentis abandonné, j'ai cru que je devenais folle, que je somatisais, et pourtant toute cette douleur était bien réelle. L'impact fut aussi bien psychique que physique. » (Forum)

Increased psychological distress as time passes

The fact that it is unknown how long their complaints will last causes additional psychological distress as time evolves. Not really seeing the end of their problems and the lack of a clear perspective is difficult.

« Voilà, j'ai peut-être plein de niaque pour retrouver ma vie d'avant et que , au bout des mois qui passent, ben c'est la lassitude, on voit plus le bout du tunnel … » (Patient 6, hospitalised)

« J'étais tellement contente d'être en vie, de pouvoir marcher, le fait de pouvoir respirer, de pouvoir aller dehors, enfin chaque petit pas était une joie pour moi en me disant "waouh c'est trop bien, je peux marcher 2 mètres dehors". Et puis finalement c'est vrai que c'est dans la deuxième phase, quand on est plus contaminant et quand on n'arrive plus à faire des, des progrès comme on voudrait, retrouver la vie d'avant, peut-être que c'est plutôt maintenant que je me dis, maintenant que vous parlez d'aide psychologique, que ce serait peut-être plus nécessaire. Parce qu'à un moment, il y a une lassitude qui se crée, qui fait qu' on a, on n'a pas les rendez-vous que je voudrais avancer plus vite tous mes rendez-vous médicaux, je voudrais avancer plus vite dans ma récupération. Et ça n'avance pas. » (Patient 6, hospitalised)

…But there are always people looking at the bright side of life

People who are, due to the long COVID, confronted with limitations of their body and functioning also report that this opened new perspectives and they now have a better understanding of their body and learned to appreciate new activities.

« Grâce" à ce COVID long j'aurais appris la patience, adaptation, positive attitude, écoute du corps,... » (Forum)

4.5.5 Impact on relationships with others

Being a long COVID patient impacts the relationship with the social entourage, such as colleagues, friends or family.

Lack of understanding

Patients report to experience a lack of understanding from their entourage

- Because of a lack of information in the general population on long COVID they people are afraid to be contamined

  « Quand on est passé dans un épisode COVID, enfin, on devient vraiment un pestiféré, voilà, oui c'est ça, c'est le mot que, qu'on, qu'on prend, un pestiféré ou quelqu'un qui, ce que je comprends tout à fait. Mais en fait je ne pensais pas que ça allait durer si longtemps. » (Patient 6, hospitalised)

  " (…) dat een aantal je behandelen of je lepra hebt (ook al is de besmetting een jaar oud, die volgen dus het coronanieuws duidelijk niet zoals wij en zijn nauwelijks geïnformeerd)." (Forum)

- Because of the difficulties to explain what they experience, mainly because patients themselves do not know what it precisely is

  "En dat vind ik heel moeilijk om aan de mensen uit te leggen: maar ik ben niet … de persoon van vier maanden geleden. Totaal niet. " (Patient 18, not hospitalised)

  « J'ai des contacts virtuels/ téléphoniques avec mes amis les plus proches. Mais en général, ils ne comprennent pas exactement ce que j'ai, il est difficile d'expliquer quelque chose à quelqu'un quand nous même on ne sait pas ce qui se passe ! Ils ne sont pas dans le jugement, j'ai déjà beaucoup de chances :) » (Forum)

- Because symptoms are often invisible and people look at the outside while they experience delibiating symptoms

  "Eh sociaal gezien is het ook heel lastig dat er zoveel onbegrip is. Heel veel mensen begrijpen gewoon niet dat ik er van buiten zeer goed uitzie, maar binnen, ja, ja, dus echt gewoon niet goed ben. Eh dus dat is ook heel lastig." (Patient 9, not hospitalised)

  « Comprendre que ça a laissé des séquelles importantes à mon mari parce que ça ne se voit pas, ça ne se voit pas hein, c'est des séquelles qui ne se voient pas sauf quand il perd la voix. Mais sinon ça ne se voit pas du tout quoi hein. Vous voyez mon mari, vous diriez "ben il a des séquelles lui ?". Non, ça ne se voit pas du tout. » (Patient 26, hospitalised)

Reactions of the working or social environment and the family towards long COVID patients vary. It depends, amongst others, on the type of relationship before the condition.

At work, colleagues can be an appreciated support, motivating to restart working

«J'ai gardé le contact avec les gens avec qui je travaille et on a une petite équipe très chouette. Et en fait c'est ça qui m'a motivée à retravailler, c'est au moins, en fait la seule chose qu'on ait le droit de faire en période COVID c'est quoi ? [rires] C'est de travailler. Heureusement que j'ai une petite, que je travaille une partie de mon travail, c'est avec une petite équipe avec qui je m'entends très très bien et bon le fait de retravailler ça m'a quand même moralement et intellectuellement aidée » (Patient 29, not hospitalised)

…or suspicious about an absence of motivation to go back to work

« En ce qui concerne mon employeur, j'ai l'impression qu'il ne s'en fait pas plus que ça ! Rien de méchant de dit mais à chaque fois au téléphone j'ai plutôt l'impression qu'ils ne me croient pas trop ou du moins au COVID long. Pour les collègues, certains prennent de mes nouvelles et d'autres pas .... Pour certains ils pensent que je ne veux pas revenir travailler vue la situation difficile actuellement ... » (Forum)

Interviewees also mentioned that some people in their environment (friends, colleagues, relatives) try to minimize symptoms or to find alternative explanations for long COVID symptoms.

"In mijn relatie zorgt dat soms wel voor wat spanningen. Het komt vaak over alsof ik iets niet wíl doen, terwijl ik het gewoon fysiek niet aankan. Ik merk ook dat ze soms zoeken naar andere verklaringen voor mijn vermoeidheid en daarmee de impact van long COVID onderschatten.

Bijvoorbeeld toen ik fysiek kapot was na een fietstochtje en wandeling met vriendinnen, kreeg ik te horen dat ik "misschien gewoon door de eerste zon wat vermoeid was". Of ze vergelijken mijn situatie met zichzelf: "ik ben ook moe". Maar ik voel wel degelijk een groot verschil tussen normale vermoeidheid of een winterdipje en wat ik nu meemaak." (Forum)

« Comme ce n'est pas encore très connu du grand public, pas médiatisé, les gens pensent parfois que l'on exagère. Je parle ici du brain fog. Quand je dis à mon entourage que c'est un symptôme post-COVID, il me répond que j'ai toujours été distraite. Oui, je le sais, mais PAS A CE POINT LA !Oublier mon sac à main avec tous mes papiers 3x en 1 semaine, ne pas me souvenir d'une discussion à laquelle j'ai participé il y a quelques heures (J'ai dis ça moi ?), aucun souvenir de ce que j'ai mangé la veille si je l'ai accompagné d'un verre de vin,...Trous de mémoires affolants, perte des mots,...Mais comment objectiver cela ? Comment le mesurer? Le prouver? » (Forum)

… or do not want to know or talk about it (ignorance is bliss)

"Dat wringt natuurlijk. Bijkomend merk ik ook dat een aantal het liever niet weet (wat niet weet wat niet deert, dat is hun manier om met de angst om te gaan, kop in't zand)" (Forum)

"Je merkt ook dat het enkelen op de zenuwen werkt dat je er best wel meer van weet dan zij, ze willen het echt liever allemaal niet horen, niet weten." (Forum)

One participant made the analogy with other chronic illnesses which are not taken seriously.

« Pour ce qui est de la reconnaissance d'être malade par les autres, je pense que c'est comme toutes les maladies chroniques, il y a beaucoup de moqueries, beaucoup de gens ne nous prennent pas au sérieux... » (Forum)

The burden of long-lasting symptoms for the people close to a long COVID patient

The persistent nature of the symptoms is sometimes difficult to live with for the people in the social environment of long COVID patients …

« Parce que évidemment en phase aiguë pas du tout, tout le monde était aux petits soins pour moi et tout le monde comprenait bien, et dans la première phase de ma récupération aussi. Comme j'ai commencé à pouvoir sortir, marcher, tout le monde et même dans la famille, tout le monde, et les médecins, même le cardiologue qui me suit. Mais au bout d'un certain temps, quand ça dure trop longtemps, maintenant, pendant cette phase-ci , ils commencent à en avoir marre [rires]. » (Patient 6, hospitalised)

« Les touts proches (la bulle) eux sont parfois agacés ou lassés de ce que représente l'incertitude au jour le jour. On ne sait jamais si je vais être bien ou pas, comment vont être les journées... » (Forum)

"Eh hier in eh met de huisgenoten was dat ook een periode heel lastig, maar dat is nu wel een stukje beter. Dat ja, dat ik niet meer zo normaal kan ja, het huishouden doen alsof dat ik het vroeger deed." (Patient 9, not hospitalised)

…and friends can even chose to distance themselves from the patient when the situation of the long COVID patient does not improve.

« Certains ne prennent même plus de mes nouvelles car ils en ont marre d'entendre que ça ne va pas. » (Forum)

Negative reactions from the entourage have negative effects on the patient

Reactions from the entourage could hurt the patients, provoking feelings of

- guilt

"ik heb mij heel lang heel schuldig gevoeld .. dat ik thuis zat. En … en ja het het gevoel van ogen die rond mij zijn en die daar geen idee van hebben en die dat het in mijn ogen, maar dat is natuurlijk interpretatie, die dat het afkeuren. En ..omdat er zo weinig over geweten is, kunnen mensen ook moeilijk naar iets teruggrijpen van zo is het, of… (…) En .. ja, en dat is soms moeilijk te verklaren want ik ga nog wel bijvoorbeeld met de hond wandelen, dat is dan opgesplitst en afhankelijk wat mij die dag afgaat, op die moment afgaat, … maar ja daar ben ik, ja daar heb

ik het heel lastig mee gehad. Ja het veroordelend gevoel van anderen. Ja." (Patient 19, not hospitalised)

- sadness

  « La gamme de réactions va de "solidaire mais étonné" à dubitatif voire dans le déni. J'ai une amie chère qui s'est éloignée parce qu'elle a déjà perdu des amies de maladie et je pense qu'inconsciemment elle veut se protéger de la souffrance que cela représente. Mais moi je souffre de son éloignement. » (Forum)

- tensions

  « L'énorme différence entre le discours officiel (guéri en 10 jours) et le sentiment d'être toujours malade des mois après ont fait passer la réaction " je ne viens pas te voir de peur de te transmettre cette maladie" en une version "tu n'as pas envie de me voir et tu as trouver une excuse toute faite. » (Forum)

  « (…) mes angoisses ne favorisent pas une bonne ambiance à la maison. Comme dans beaucoup de ménage je crois, c'est un peu plus tendu. » (Forum)

- avoidance of others or talking about the condition

  "Ik vermijd contact op te nemen met collega's en vrienden, ik wil niet voortdurend moeten antwoorden op de vraag hoe het gaat. Ik ben erg beschaamd over het feit dat dit zo lang aansleept, zou het onbegrip ook liever niet ervaren dus ga ik contact uit de weg. Dit met uitzondering van een goeie vriendin en mijn dichtste familie." (Forum)

  « J'essaye d'en parler un minimum à mon entourage mais vu la durée ça commence à se savoir. Malheureusement ça "trie" nos contacts... » (Forum)

- Self-isolation

  "Ik ga niet gaan wandelen, want als mensen zien dat ik ga wandelen, gaan die denken dat ik weer goed ben, dus dat ik eigenlijk kan gaan werken. Terwijl dat dat, ja, wandelen was in het begin echt wel heel goed nadenken, bij elke stap dat ik zette, hoe snel dat ik hem zette, hoe groot, hoe eh, dus dat was, ja, niet zomaar wandelen voor mij. Maar voor mensen lijkt dat: Ah, ze is gaan wandelen, dus ze is beter, dus ze kan terug komen werken." (Patient 7, not hospitalised)

Long COVID patients feel that their situation is recognized by some people in their entourage

Nevertheless, respondents reported that they experience that people understand their situation. This is particularly so when they have had long COVID themselves or know someone who has (had) it …

« Il y a deux ou trois personnes qui comprennent, celles qui sont touchées par des symptômes/séquelles persistantes » (Forum)

« (…) le cardiologue lui-même bien, (…) il avait fait à la première vague et il n'avait pas été bien pendant 3 mois. Donc il savait ce que c'était être moche par un COVID pendant 3 mois. Donc lui il m'a pris tout à fait au sérieux. » (Patient 29, not hospitalised)

« X a dit que c'était pas possible d'avoir des séquelles comme ça et surtout des séquelles neurologiques avec une paralysie de la jambe, c'est un peu bizarre, il comprenait pas très bien. en plus de temps en temps il perd sa voix aussi . Il ne comprenait pas comment le matin il parlait normalement et que 1 heure après il n'avait presque plus de voix, … jusqu'au jour où le mari de la directrice a été malade, il a eu des séquelles au niveau respiratoire lui et une grande fatigue aussi, elle a compris qu'il y avait quelque chose après le COVID. » (Patient 26, hospitalised)

…as well as some family members, friends or colleagues who worried about the patient.

« De mon côté j'ai une famille formidable, nous avons reçus mon mari et moi beaucoup de soutien .Notre état les a plutôt tracassé. Nous pouvons en parler sans contrainte en famille et avec nos amis (par téléphone ☺) » (Forum)

"Ik heb heel veel steun gehad, dat mag niet, dat moet ik ook wel zeggen, aan mijn, aan mijn gezin, mijn man die dat elke dag kookt, uhm, ik heb een poetshulp, dus daar moest ik me geen uh zorgen over maken. En ik heb een geweldige werkgever. Uh. Dat moet ik ook wel eventjes

zeggen want uh ik denk dat dat anders niet evident is." (Patient 5, not hospitalised)

« Sur le plan professionnel, je suis encouragée et soutenue très chaleureusement par tout le monde (ils ont eu si peur...) » (Forum)

Talking about it increases general understanding of long COVID

« Maintenant qu'on parle des COVID longs, il comprend que depuis que j'ai retravaillé, je suis au lit à 9 heures, 8 h 30, 9 heures, dès qu'on a mangé je suis au lit. Il ne faut pas me demander de rester plus longtemps. Je suis crevée le soir. » (Patient 29, not hospitalised)

4.5.6 Administrative burden

A burden for the patient

Once a patient has to stop working, he is confronted with an administrative burden 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.

"En hoe dikwijls dat ik al heb moeten bellen voor verduidelijking…. Allee, en ik beschouw mijzelf nu toch als [lacht] normaal intelligent. Allee, hoeveel keer…Dat ik heb al heb moeten bellen van: "Zeg eh wat, wat moet ik hier juist doen?". [lacht] Want dat staat dan echt wel, allee, heel moeilijk omschreven. Hoeveel papieren dat er verdwijnen want dat moet dan via de post want er staat dan geen e-mailadres op…Ooh. Maar nu, ça va. Nu denk ik al redelijk goed maar twee maand geleden als je alles moet regelen dat, dat is er echt te veel bij." (Patient 2, hospitalised)

« Ah. Toute la paperasse, de la paperasserie, que ce soit de la mutuelle, que ce soit Fedris que ce soit le travail pf, c'est des papiers tout le temps, tout le temps, tout le temps. Ça n'arrête pas. » (Patient 26, hospitalised)

A burden for the healthcare system

This administrative burden also impacted the relationship with the GP because, for each type of insurance, the patient has to ask a physician to fill out forms. This is often inconvenient.

"Krijgt je daar ook nog brieven van eh dat je toestemming moet geven aan uw arts dat, dat, dat ze in uw dossier kunnen. Dan komen daar ook weer ooh… Ik durf gewoon niet meer bellen naar de dokter. Ik voelde mij op een gegeven moment gewoon een stalker…Hoeveel mailtjes en telefoontjes dat ik heb gedaan." (Patient 2, hospitalised)

Contacts with the sickness fund

Patients in medical incapacity have to deal with many administrative formalities.

« C'est moi qui ai demandé à recommencer avec mon horaire normal, pas parce que je me sentais mieux, c'est parce que point de vue paperasserie par rapport à la mutuelle, c'est tellement compliqué les mi-temps médicaux que je n'arrêtais pas de remplir des papiers pour la mutuelle, que ça me pompait déjà pas mal d'énergie. (…) Ils envoient tout le temps des papiers, savoir ce que vous avez travaillé, machin truc, ils envoient toutes les semaines, enfin il faut remplir tout le temps, tout le temps, tout le temps des papiers. Et on s'est, c'est, et alors chez nous, enfin où je travaille, le service RH n'est pas très compétent, on n'est pas du tout aidés, …, c'est d'un compliqué point de vue administratif que je me suis dit "mais zut, alors je reprends ". Mon mari dit "mais encore un papier de la mutuelle, encore un papier de la mutuelle", il dit "mais tu n'arrêtes pas de remplir les papiers". Et pour être sûre que ça arrive, je devais tout scanner et renvoyer par mail parce que je me méfie de la poste » (Patient 29, not hospitalised)

Sickness funds are sometimes helpful in the process…

« Il y a beaucoup, beaucoup de démarches administratives à faire... hum… mais après bon, je ne connaissais pas du tout ce genre de démarches, de paperasses à faire mais ça va, ça s'est bien passé dans l'ensemble. … Les conseillères de la mutuelle sont très à l'écoute et ,

je trouve que c'est quand même bien pris en charge on va dire. » (Patient 17, not hospitalised)

But not always…

« il y avait une enquête de satisfaction de la mutuelle, je leur ai dit que point de vue administratif c'était d'un compliqué complet et qu'il fallait faire une simplification administrative. J'ai rempli leur enquête parce que je trouve ça, mais je suis universitaire. D'accord, je n'ai pas l'esprit très clair comme d'habitude mais pour les gens c'est le même questionnaire pour tout le monde. Pour les gens peu instruits, c'est impossible de remplir ces documents. Ce sont des documents impossibles à remplir quoi (…). » (Patient 29, not hospitalised)

This administrative burden can push people to restart work earlier than they should.

« (…) alors je me suis dit "zut, je reprends mon horaire normal comme ça j'ai l'entièreté de mon salaire et pf". Mais ça c'est vraiment, la partie administrative, sinon je serais bien restée avec mon mi-temps médical, c'était plus, plus confortable parce que j'ai besoin de faire encore en fait une sieste. » (Patient 29, not hospitalised) »

Also the meetings with the medical advisor of sickness funds are experienced as cumbersome by some patients. Some patients report that it is a reason why they restart working while in fact they have the feeling that it is too early to go back to work.

« Oui, par rapport à l'employeur, par rapport au médecin-conseil, à la mutuelle, donc je n'ai pas envie d'aller tout le temps voir ce bonhomme…qu'est-ce qu'il peut savoir de la douleur que j'ai à la tête, enfin ? Je sais pas, je n'ai pas vraiment envie de me…, je ne sais pas comment, il pourrait mesurer …, ça pourrait être vrai comme faux ce que je lui raconte (…). Moi je sens que je suis fatiguée, je me sens un peu mal à l'aise parce que (…) si vous avez le bras cassé ou si vous savez plus marcher ça se voit, ici ça se voit pas de trop! (…) vous savez, je ne sais pas si vous avez déjà été chez le médecin-conseil, Ils sont rarement très sympathiques, franchement. Moi ce sont des gens que je n'aime pas trop voir. (…) des personnes que je n'aime pas trop rencontrer parce que, (…) on a une pathologie, il faut aller se défendre, moi je n'aime pas ça enfin. » (Patient 32, not hospitalised)

The delay to receive a financial compensation due to the job inactivity is problematic for some people.

« J'ai eu beaucoup de difficultés à ce niveau avec la mutuelle. Je n'ai pas eu les indemnités à temps parce que mon dossier n'était pas traité. (…) c'est toujours des gros stress parce qu'on ne sait pas comment on va payer son loyer, on ne sait pas comment on va faire ci ou on va faire ça. » (Patient 14, not hospitalised)

These aspects are not specific to long COVID, but features of the condition (e.g. new diagnoses such as persistent COVID, COVID-pneumonia) and the epidemic aspect created an additional workload to the sickness funds.

"Hoe? Niet goedgekeurd? Ik heb het verdorie op mijn werk opgelopen. Waarom zou dat niet goedgekeurd worden… Allee, ik kan bewijzen dat ik nog doodziek ben…Waarom wordt dat niet goedgekeurd… Dus dan belt je. "Ah ja, maar mevrouw, u moet dat begrijpen. Op uw tweede ziektebriefje stond niet dat dat nog hoorde bij die COVID-pneumonie."…Ondertussen geen geld op uw rekening, geen… Ja, als alleenstaande moeder…Ge belt naar de mutualiteit… "Ja mevrouw, het is hier enorm druk. U moet dat begrijpen."…JE belt een week later nog eens terug: "Ja mevrouw, u moet dat begrijpen. En daarbij, wij hebben nog een brief voor bijkomende informatie opgestuurd. Daar hebben we niks van gehoord." "Eh jawel, ik heb daar toen op die datum op geantwoord.". "Ah, we gaan het is een nakijken. Ah ja, hier is hij."."(Patient 2, hospitalised)

Executing the right to income assurance

Because of the lack of knowledge about long COVID, insurers do not intervene in the post-acute COVID sickness leave.

"[Mijn verzekering] is tussengekomen voor november en december. Ze vinden, tegen de diagnose van 6(!) dokters in, dat ik niet arbeidsongeschikt ben sedert 01/01/2021 omdat een post viraal syndroom niet bestaat volgens hen... Er is thans een minnelijke medische expertise opgestart" (Forum)

Recognition of long COVID as an occupational illness

Next to the administrative burden, tree main problems related to the recognition of (long) COVID as an occupational illness were raised during the qualitative data collection: a lack of information on the recognition process, the time necessary for the recognition and the uncertainty on the duration of the coverage.

For healthcare workers, COVID can be recognized as an occupational illness when the COVID infection occurred at work. The employer is not always aware of this.

> *« J'attends des nouvelles... J'ai envoyé tout le dossier mais j'ai dû tout, tout, tout faire toute seule quoi parce que, là, je n'ai vraiment pas été aidée du tout, pas du tout. (…) Pour moi c'était une maladie professionnelle .,. à mon travail ils savaient pas du tout me dire … à qui je devais m'adresser, comme maladie professionnelle. J'ai dû tout chercher moi-même. » (Patient 29, not hospitalised)*

Patients are not sure whether long COVID will be recognized as an occupational disease, which has implications for the amount of income replacement. The coverage is higher for occupational diseases than the regular incapacity fees.

It may take a long time before the recognition is accorded to the patient, delaying the financial compensation and bringing patients in financial difficulties.

> *« Je suis maman solo et financièrement ce n'est pas facile ...je suis étonnée de la lenteur de la reconnaissance de la maladie en maladie professionnelle... » (Forum)*

> *« Oui j'ai entendu parler que voilà, quand on était infirmier, on pouvait rentrer sa demande. J'ai rentré mon dossier chez eux et à chaque fois que je faisais des rechutes, je leur envoyais un certificat parce qu'ils m'avaient déjà envoyé un numéro de suivi. Et donc à chaque fois, je les ai contactés pour demander où en était mon dossier, ils m'ont dit "écoutez madame, ce n'est pas parce qu'il y a eu le COVID qu'on n'a plus de médecins, c'est toujours un seul pour tous les dossiers donc on ne sait pas quelle année vous allez avoir une réponse. » (Patient 14, not hospitalised)*

The duration of the insurance coverage is unknown.

> *"Eh ik hoor van mensen die zeggen: "Ja, zelfs als het er-erkend wordt erkennen ze het maar voor vier maanden.". … dus ja, ik bedoel ja, ik ben ik al langer dan vier maanden ziek…Dus dan krijg je, allee, 90 procent van je loon uitbetaald. Uhm terwijl nu, ja, met de ziekenkas…" (Patient 9, not hospitalised)*

4.6 The place of the patient in the healthcare system

4.6.1 The relationships with health care professionals

General statements about patients' experiences with healthcare professionals

The stories from long COVID patients participating in the in-depth interviews and the forum revealed some findings on how long COVID patients experience their relationship with healthcare professionals. Some general statements about these experiences include:

- Many patients feel that carers do not take their complaints seriously

> *« Le soucis principal que j'ai observé c'est que d'habitude avec un virus, tout le monde sait que après 1 bonne semaine, on est sur pied. He bien ici ça ne fonctionne pas pour tout le monde. Et donc quand tu tentes d'expliquer que ce n'est pas ce que tu vis, on te prend pour un dingue et on te regarde de travers...Et ce n'est pas que chez monsieur tout le monde qui réagit comme cela. Les médecins aussi! » (Forum)*

> *« Le praticien et les infirmières qui m'ont fait l'examen étaient étonnés qu'il soit écrit "COVID long" sur ma prescription. J'ai vraiment eu l'impression qu'ils ne me prenaient pas au sérieux, pourtant c'est dans ce même hôpital que je suis suivie...Est ce que "TOUT" le corps médical est tenu au courant des symptômes longue durée du COVID? Ça serait déjà une bonne première étape qu'il le soit afin que nous malades, nous puissions plus facilement parler de nos douleurs aux médecins sans*

avoir l'impression qu'on nous prend pour des fous... et du coup, plus de cohésions et d'interactions entre les différents spécialistes qui nous suivent. » (Forum)

- Some patients have the feeling that healthcare is a business which limits the time taken by healthcare professionals to really listen to them. Patients state that it is important that healthcare professionals take the time to listen to them, for instance, to make the correct diagnosis.

  « A ' heure actuelle on est plus dans un service commerciale ou le côté humain n'existe quasi plus ! Heureusement certains médecins restent polis, courtois et écoute mais la plupart du temps la consultation est vite fait et expédie .... Rendement ! Alors que pour établir un diagnostic correct cela se base sur au moins 70% d'écoute des plaintes du patient. » (Forum)

  « (…) Pourtant vous inquiétez pas, les factures suivent sans problèmes, jamais de retard, toujours très pro-actif dans les rappels ;-) » (Forum)

  « Ne soyons pas naïf, même (et surtout) en médecine moderne, il faut de la rentabilité et être productif. Une rentabilité (3-4 consultations par heure) ne match pas avec l'encadrement requis pour les patients qui souffrent du COVID (long). Il faut du temps. » (Forum)

- Patients experienced a lack of empathy

  « L'attitude de certains médecins est tout simplement odieuse:- Patient non écouté, aucune preuve d'empathie. Une petite piqure de rappel comment gérer une relation patient-médecin ? Ou une petite relecture rapide du serment d'Hippocrate ne leur ferait pas de tort ;-) » (Forum)

  "ik merk ook wel bij de psycholoog dat het soms wel wat lastig zit. Eh ook bij de kine, ja, bij de revalidatie nu, merk ik dat, dat soms, die zeggen gewoon: Ja, ga terug gaan werken. Eh maar dan denk ik ja, onze job is echt wel fysiek super intensief. We moeten minstens twintig uur starten, dus dat is vijf halve dagen plus nog twee uur revalidatie. Dat is gewoon echt niet haalbaar voor mij." (Patient 7, not hospitalised)

  « Plutôt que de me dire "voilà, ça va prendre longtemps, ne vous plaignez pas, ça va prendre des mois ou même des années". Elle m'avait dit , je sais bien, j'entends encore sa parole, "ne venez pas dans 15 jours ou 3 semaines, de nouveau vous plaindre, ça va être long" ». (Patient 6, hospitalised)

  « La généraliste, elle est très humaine, ça oui mais la pneumologue non. Tout ce qu'elle m'a dit "enfin madame, vous avez 60 ans, vous devez être encore bien content d'être comme vous êtes comparé aux patients qu'on a vus en réa". » (Patient 29, not hospitalised)

  « J 'essaye de me dire que les soignants ont eu une année atrocement difficile et compliquée mais au bout de la chaine parfois, ce manque d'attention est douloureux. Parfois je ris en me disant que je regarde une série médicale pour voir des médecins tout gentils avec les patients ;) (non pas docteur house ;)) Un sourire, un petit mot ou juste "on est là, on ne vous laisse pas tomber", ça pourrait vraiment faire la différence. » (Forum)

- Some patients expressed the concern that long COVID will become a condition that will be part of a long list of chronic diseases that are medically not well understood, according to some patients, due to a failing medical science

  « Le filet contre l'errance médicale vaut pour un grand nombre de maladies : maladies chroniques à origine infectieuse, arthrite rhumatoïde, hypothyroïdie, la longue liste des syndromes inexpliqués comme l'intestin irritable (même si c'est expliqué quand on suit la science mais c'est inexpliqué chez nos médecins), fatigue chronique, fibromyalgie, ... avec une capacité pour le patient d'être l'auteur de propositions pour sortir des impasses imposées, avec une forme d'autorégulation par le retour "malades" des innovations (et pas seulement la méthode en triple aveugle qui dicte ce qui est bien et pas bien), ... » (Forum)

Patients' perception about the attitude of GPs

As already mentioned and illustrated before the GP is often the first healthcare professional which is contacted when patients experience persisting symptoms after an acute COVID-19. Patients reported both positive and negative experiences. In the next section we will first describe some negative experience and then some positive experiences.

A difficult relationship with the GP is explained by long COVID patients by the fact that the diagnosis of long COVID is not easy or because their complaints are not taken seriously by the GP.

Some patients also reported that they experience that GPs do not follow them up for a sufficiently long period of time after the acute phase of the disease.

> *« Le généraliste je l'aime bien parce que il nous a toujours suivis mais je trouve que ça prise en charge post-COVID, c'est zéro quoi. Pendant le COVID, pendant qu'on a été malades, ça c'est 10 / 10 parce que il nous a téléphoné le matin, il nous téléphonait le soir pour voir comment on allait. Et si j'avais besoin, je retéléphonais sur le coup de midi. Et ça chapeau, chapeau, chapeau, chapeau. Mais après, le poste COVID, ça non, zéro ». (Patient 26, hospitalised)*

When patients experience the relationship with their GP as negative or difficult this can have many different consequences, such as:

- Patients will not consult their GP when they feel that their complaints are not taken serious.

  "En eenmaal je dan wel mag komen: maar mevrouw toch, het is psychosomatisch, je loopt tegen een burnout aan. Ik kon hem tegen de muur kwakken. Nee, ik heb geen burnout! Maar jullie zorgverlening zou daartoe bijdragen. Sindsdien durf ik eigenlijk niet meer te gaan, uit angst om weer dat label te krijgen. Ik heb nu al 1 maand een stijve nek, maar jah... een zoveelste symptoom van mijn zogenaamde burnout zeker? Ik had voorheen echt een goede band met mijn huisarts. Zo jammer hoe dit geëvolueerd is..." (Forum)

  « Et aussi je pense qu'il y a la peur de ne pas être écouté. Enfin, qu'on me dise… bon voilà… c'est des petites séquelles qui n'ont pas de conséquences sur la qualité de vie et que du coup, ça prend de l'énergie de consulter et de devoir cherche un autre médecin spécialiste qui pourrait... … » (Patient 17, not hospitalised)

- Patients feel unconfortable and ashamed because they have to explain their symptoms over and over again and it is like they only do this to get their medical certificates …

  "Ambetant gevoeld bij de huisarts, omdat ik heel moeilijk kon uitleggen hoe dat ik, hoe dat ik, hoe dat ik het ervaarde of zelf voelde en .. dat ik op den duur mijn eigen schuldig voelde omdat ik zo het gevoel had dat is precies zo elke keer dat ik hier kom dat ik voor een verlenging van de ziekte moet, of dat ik, vorige week zei ik dat het goed ging, nu gaat het weer slecht, zo die contradicties waar dat ik mij heel vervelend bij voelde. Ook nu gaat het lichamelijk slecht, volgende week is het dan misschien juist een dag dat het goed gaat, zo van ja." (Patient 19, not hospitalised)

- Even when the communication with the physician is good some patients experienced that once the 'objective results (e.g. oxygen saturation)' of the medical examinations or tests became better, they had the feeling that physicians took their complaints less seriously.

  "Tot nu toe is er eigenlijk geen enkel van de symptomen opgelost, die komen per cyclus van een week of twee allemaal wel eens terug.....soms heb je 1 goede dag, je denkt het is over,maar de dag erna is het dan 2x erger...Het enige dat momenteel opgelost is, is de lage zuurstofsaturatie in het bloed, deze is van 85 naar 99%wat maak niet dat je minder moe/uitgeput/miserabel bent, maar enkel dat de dokters het (nog) minder ernstig nemen...wat zo'n beetje het enige meetbare symptoom, en dat is weg dus alles is opgelost, en verder zoeken we niet blijkbaar :-(" (Forum)

  «Mes généralistes pourtant super à l'écoute me conseillent de "reprendre le cours de ma vie et ne plus faire attention aux symptômes", mais comment reprendre le cours de sa vie quand on n'est pas bien et qu'on n'a pas de réponses? C'est très dur... » (Forum)

Due to the general sanitary measures many medical consultations were organised remotely (e.g. by telephone). Yet these remote consultations were not always appreciated and patients stated that this was not the appropriate setting to discuss all the problems that they experienced.

> *"Alle problemen die je ervaart in die periode moeten via telefoon besproken worden of je wordt gestuurd naar triagepost/spoedgevallen. De toegang tot een normale gezondheidszorg wordt afgesnoerd, waardoor de arts ook niet mee is in het verhaal van zijn patiënt. Dat artsen elkaar ook openlijk tegenspreken en zij zich baseren op tegenstrijdige bronnen en adviesorganen, maakt dat je als patiënt tussen twee vuren zit. Het belang van maatschappij staat voor uw persoonlijk belang, is een zin die ik helaas enkele keren heb gehoord..." (Forum)*

Patients also reported several positive experiences such as:

- The GP takes the patient seriously

  « Le médecin m'a dit "mais vous avez toujours le virus en vous, c'est pour ça que vous êtes malade, c'est pour ça que vous êtes fatigué, parce que votre corps lutte toujours contre le virus et produit des anticorps". Je dois dire que la réponse me, m'a, m'a tout à fait satisfait parce que ça correspondait à ma réalité quoi hein. » (Patient 16, not hospitalised)

- The GP follow his/her patient

  "Waardoor ik me eigenlijk bij mijn huisartsen wel genoeg opgevolgd voelde. Ook al vond ik het zelfs soms vreemd dat ik niet verder naar het ziekenhuis moest voor onderzoek. Mijn huisartsen hebben denk ik wel alles gedaan wat ze konden doen op die moment om mij verder te helpen en mij gerust te stellen" (Patient 22, not hospitalised)

- The GP is searching for solutions

  « Le médecin de terrain et généraliste est beaucoup plus à l'écoute, il est à l'écoute totale et reste proche du problème. On sent qu'il veut trouver la solution et fait lui-même des recherches. C'est formidable. » (Forum)

- The GP takes up the coordination of care

  "Als ik bij mijn huisarts ga, die luistert altijd heel goed, die zorgt altijd dat ik bij de juiste mensen terecht geraak."(Patient 3, hospitalised)

- The GP takes the time to listen to the patient

  « J'ai mon médecin, (…) j'ai eu l'assistante du médecin aussi qui m'a pris en charge aussi en même temps que mon médecin. Elle était hyper gentille, elle est venue parfois, elle est parfois restée 10 minutes, un quart d'heure avec moi pour parler avec moi et tout. Donc c'est, à ce niveau-là, je veux dire, je suis bien suivi, (…). » (Patient 30, hospitalised)

  « J'ai même trouvé, enfin c'était pas du tout dans mes habitudes d'avoir des consultations téléphoniques, on va le dire comme ça. Et non, ça je trouve que ça s'est vraiment bien passé, et, c'est important d'avoir un médecin traitant en qui on a confiance et qui prend le temps. Donc ça, je n'ai jamais eu l'impression, je me doute qu'il n'avait pas beaucoup de temps mais je n'ai jamais eu l'impression que je l'embêtais quand je l'appelais quoi enfin. » (Patient 32, not hospitalised)

- The GP treats the patient as a partner in the care process

  « L'avantage, c'est que enfin ah, tout ce, je me, tout ce que j'ai fait, je l'ai toujours fait en, en concertation avec mon médecin traitant. Mais qui était tout à fait conscient que j'avais des séquelles du, du COVID donc y a jamais eu de mise en doute, en tout cas de mon généraliste. » (Patient 10, hospitalised)

Patients' perception about the attitude of medical specialists

Also the relationship with medical specialists varied. Patients stated that some medical specialists gave them the feeling that they were a burden to them while for others they were clearly an intellectual challenge (i.e. unexplained problems for which they want to find a solution).

> *« Chaque spécialiste qui me suit depuis ma sortie de clinique (pneumologue, médecin de médecine physique, neurologue, ORL, dermato, virologue,...) a ses hauts et ses bas. Pour certains je reste une pestiférée...pour d'autres, je suis une curiosité intellectuelle qui pourra illustrer leurs lectures ou nourrir leur réflexion. » (Forum)*

> *« On s'est fait engueulés de l'infectiologue comme quoi on n'avait rien à faire là. Et alors mon mari qui dit "bah écoutez, si je n'ai rien à faire là, dites-moi où je dois aller"… "si vous avez pas envie de me recevoir, ben tant pis !" ». (Patient 26, hospitalised)*

Some patients reported that they think this different attitude of medical specialists is linked to the level of experience they have with long COVID patients.

> *« Les spécialistes dans les hôpitaux. - ca dépend de leurs expériences et du nombre de cas qu'ils ont vu qui se plaignent de persistance de symptômes après PCR+. » (Forum)*

4.6.2 The role of the patient

While many patients experienced problems during their contacts with the healthcare system, they are generally acknowledging that the situation is not easy for the healthcare professionals either (e.g. lack of scientific evidence about the long COVID condition, overburdened due to the COVID-19 pandemic).

> *« La petite difficulté que je peux dire, c'est quand j'étais aux urgences. Mais je peux comprendre aussi parce que c'était dans la crise, c'était aux urgences, parce que j'ai été 2 fois aux urgences depuis le début, j'ai été au mois de mai de l'année passée, pour dire toujours que j'avais toujours cette oppression et dire que je voulais qu'on me garde en observation au moins par rapport à mon anémie qui me fatiguait. Mais je pense qu'ils faisaient de leur mieux c'est juste ce moment où je pense que j'ai eu des, des difficultés à l'écoute, ils étaient débordés. » (Patient 14, not hospitalised)*

> *« Dans la pléthore d'études qui arrivent chez les médecins tous les jours, s'ils doivent encore trouver du repos pour être un peu disponibles à leurs patients, tout ne saurait pas être lu tous les jours. Il faut en plus qu'ils continuent à se tenir au courant pour toutes les autres pathologies.... Les médecins, doivent suivre des formations continuées (GLEM) régulièrement. Tout tourne autour du COVID depuis maintenant 1 an. Pour une maladie, 1 an de recul est excessivement court et la recherche va dans tous les sens... Nous avons la malchance d'être dans les cobayes et Il est très difficile d'accepter pour nous que la médecine a ses limites et malheureusement nous n'aurons jamais pour le moment de vraies réponses. » (Forum)*

Nevertheless their experiences with the healthcare system during long COVID changed their view on their role as a patient. It became clear that they have to be pro-active and take the lead in the coordination of their own care.

> *« J'ai bien compris que le médecin familiale qui venait chez vous à 3 heures du mat et qui faisait des recherches de son côté est une époque révolue. Et ça a comme conséquence que c'est au malade de se battre avec le corps médical pour: être écouté, être compris, émettre des doutes, s'auto prescrire des examens, se renseigner ... être simplement pris en charge... » (Forum)*

Patients have the feeling that they have to do activities (e.g. looking up evidence and information about long COVID) because it is not done by the physicians, while it is their job.

> *« (…) en fait j'ai l'impression qu'on fait un peu le boulot que les médecins devraient faire. C'est-à-dire qu'on (…) on se renseigne sur pas mal de trucs pour essayer de comprendre d'où provient notre problématique (…), des fois, on regarde quand même des études scientifiques. Le problème c'est qu'on n'a pas les connaissances pour, on n'est pas non plus médecins, il faut quand même qu'un spécialiste puisse nous suivre, ce n'est pas à nous à faire le travail que les*

médecins devraient faire. Et en plus de ça on n'a pas les compétences pour. pour un traitement on peut pas s'automédiquer, on ne peut pas prendre des médicaments comme ça et ça, c'est le danger » (Patient 13, not hospitalised)

« Bref, je suis comme vous, un Harry Potter qui essaie de comprendre ce qui se passe dans nos corps alors que c'est le job de la médecine... » (Forum)

An active role in the diagnosis

As we already explained above, some patients searched actively to get a diagnosis, auto-prescribing scanner or blood tests. Some insisted to go further in the examinations.

« Mais c'est vraiment parce que moi par moi-même je fouille et que je vois certaines choses. Par exemple au CHU ils ont fait une ponction lombaire et dans la ponction lombaire il y avait des choses qui me tracassaient énormément. Et on, et personne n'a réagi, que je me suis dirigée vers la neurologue et elle a dit "écoutez , c'est vrai que c'est tracassant, on va refaire une ponction lombaire". » (Patient 26, hospitalised)

An active role in the monitoring of the symptoms

Many patients monitor vital observations themselves: temperature, blood pressure and oxygenation. Monitoring their vital observations might give them a feeling of reassurance.

« Oui, je l'ai toujours avec moi, quand je vais courir, parce que on se sent mal mais on n'arrive pas à mettre un mot sur qu'est-ce qui ne va pas, est-ce que c'est ma saturation, est-ce que c'est la tachycardie, je le sens mais oui, non j'ai toujours besoin d'avoir ça avec moi non-stop pour moi. » (Patient 6, hospitalised)

Some write down all symptoms and their evolution in a notebook. Others test their effort resistance to follow the evolution of their physical condition.

An active role in the treatment, rehabilitation and follow up

Some patients decide to take the initiative to consult a medical specialist because their contacts with their GP did not result in a solution.

“En dan eh tot eh, ik ging maandelijks naar de huisarts, maar ja, veel meerwaarde had dat niet eigenlijk. Die nam mijn bloeddruk, die, die luisterde naar m'n longen. Nu, in het ziekenhuis zeiden ze ook, uw, ik ben dan op eigen initiatief naar de cardioloog geweest, omdat ik dacht van, ik ga dat zelf uitsluiten.” (Patient 20, hospitalised)

« Au niveau de mon médecin généraliste, je trouvais qu'il était limité parce qu'à chaque fois il me disait "ça va passer" mais ça passait pas mes douleurs. Donc je me suis dit à moi-même " si je pense que j'ai un problème au thorax et à la poitrine, ou au cœur" parce que j'avais des palpitations, en fait c'est ça qui m'a fait des tachycardies, je me suis dit "allez", je me suis dit toute seule que voilà, je vais prendre rendez-vous chez un cardiologue. » (Patient 14, not hospitalised)

“De eerste weken heb ik veel verschillende pijnstillers gekregen voor de hoofdpijn, maar niets werkte. Sindsdien heb ik het gevoel dat hij niet echt weet wat te doen om mij te helpen. Ik heb zelf het initiatief genomen om naar een osteopaat te gaan. Sinds de 3e/4e sessie gaat het heel wat beter met mijn klachten (hoofdpijn en vermoeidheid). Dit is de enige behandeling die ik nu krijg.” (Forum)

“Ondertussen ook al bij een cardioloog en neuroloog langs geweest, allemaal op eigen initiatief, maar daar proberen ze bepaalde gevaarlijke zaken uit te sluiten door onderzoeken (ECG, EEG, echo's, fietsproef, CT scans, MRI, etc...)” (Forum)

« Et puis on vous dit même pas "je vais vous donner un rendez-vous chez un neurologue", c'est, c'est, c'est, c'est par moi-même que je dois insister pour aller voir tel ou tel médecin. » (Patient 26, hospitalised)

“We hebben alles zelf gedaan. We ondervonden heel weinig hulp van de huisarts.” (Forum)

…or to start rehabilitation with a physiotherapist.

> *"Eh en dan zagen, zag ik toevallig ook door nog eens een reportage te zien of nog eens te kijken naar het nieuws, zag ik inderdaad mensen in de ziekenhuizen die revalidatie kregen. En plots dacht ik van, ik ga dat ook doen. Ik ga naar de kinesist. [lachend] Ja, dat, dat kan en dan inderdaad dan eh ben ik naar de kinesist hier gegaan en die ja, ondertussen was die dan wel al op de hoogte en, en zei die dat dat heel goed was en dan heb ik echt revalidatieoefeningen gekregen. En die doe ik tot op de dag van vandaag nog ongeveer elke dag. Daar ben ik dan eigenlijk stap voor stap zo, met die dingen ben ik dan zo terug beter geworden." (Patient 24, not hospitalised)*

An active role in the communication between the healthcare professionals

It happens that information does not smoothly go from a practitioner to another. One of the reasons is, according to the patients, that there are access difficulties since different electronic platforms are used.

In some cases, patients made the transfer of information themselves, using these e-health platforms.

> *« Heureusement qu'on a accès au Réseau Santé wallon, que je peux sortir les rapports, que je peux les téléchargerpour les envoyer à tel et tel organisme. » (Patient 26, hospitalised)*

An active role in the search for information or explanation

Some patients reported that they have the feeling that they became healthcare professional or researcher themselves.

> *« Sur le côté médical, nous n'avions que la réponse "Je ne sais pas". Alors j'ai continué à me renseigner sur les différentes recherches, les dons de sang de personnes qui ont été contaminées, ce qui se disaient en Chine, en Amérique. Je me suis questionnée sur le SRAS où la fatigue semblait similaire. Ça a été mon premier espoir. Ensuite la révélation de certaines lésions découvertes aux USA pour expliquer le manque de respiration Post-COVID et de là, j'en ai conclus que j'étais dans le bon. J'ai eu l'envie de partager tout ça, avec ceux qui le vivent aussi. Et on continue encore, ensemble, à trouver des informations pertinentes grâce maintenant, aux médecins qui s'y intéressent. » (Forum)*

> *« J'ai rencontré des chercheurs, des professeurs: les langues tombent. On parle franchement, aucune hypothèse n'est écartée, On accepte de dire "je ne sais pas", "votre hypothèse est pertinente", J'ai même un chercheur avec lequel j'ai gardé contact car je cherche des infos d'études cliniques sur internet. Il est très intéressé. Il m'envoie du coup des études aussi...et même les résultats de ses recherches en cours... » (Forum)*

> *« Nous sommes contraint de chercher car - s'il y a une chose qui est certaine c'est que le virus de la curiosité a épargné une bonne partie du corps médical - nous compensons un déficit ... avant je culpabilisais avec ce type de démarche, je m'en excusais, le COVID aura eu pour effet de m'ôter tout sentiment de culpabilité à ce sujet, je suis devenu beaucoup plus unilatéral que je ne l'étais. Il y aura pour moi un avant, un après. » (Forum)*

> *« Je fais beaucoup de recherches par moi-même, vive l'open science ! Je suis en veille permanente, à un point tel que j'informe les médecins de ce que j'apprends via ma veille. » (Forum)*

Some physicians appreciated the insights of the patients and decided to collaborate with them …

> *« Mon médecin traitant est généralement content de me voir pour avoir de nouvelles informations :-) Ces informations viennent de la recherche à laquelle je participe actuellement ou d'échange sur les différents forums COVID longs, de longues heures de tris, de recherches, traductions et malheureusement jamais de sites officiel » (Forum)*

> *« J'ai fait plusieurs examens à ma demande et à sa demande aussi, j'ai fait des examens pour exclure d'autres complications comme une thrombose ou quoi que ce soit. À chaque fois, il était à l'écoute si je demandais quelque chose, il faisait électrocardiogrammes, échographies pour montrer vraiment s'il y avait vraiment un problème au cœur. À chaque fois on éliminait toutes les possibilités. Et il, il était*

ouvert à tout, il n'était pas contraire à quoi que ce soit que, avec quoi je venais. » (Patient 14, not hospitalized)

…but it is not always like that. Patients also stated also that their input was not always welcomed by physicians. They had the feeling that physicians did not took them as a credible partner in the decision-making process.

« Les médecins me prenaient pour un extra-terrestre quand je leur parlais d'étude, lien, preuve à l'appuis et étaient perdus. - Cela parait incroyable (mais vrai, comme dans l'émission) que j'ai dû rencontrer des sommités du monde médical et de la recherche qui passent régulièrement à la TV pour être pris enfin sérieusement en compte » (Forum)

« Plus récemment, un hématologue a tout mis sur un "burn out" ... l'interne que j'ai vu ensuite - sur conseil de mon ORL, a repris les considérations de l'hématologue à son compte. J'avançais l'explication des mastocytes, notamment au niveau des problèmes intestinaux. Je me vois encore en fin de consultation "mais enfin, toutes les études récentes démontrent que les dérangements intestinaux type intestin irritable sont dus à une présence excessive des mastocytes" ... elle conteste. La semaine qui suit l'étude la KUL sort : https://www.rtbf.be/info/societe/detail_syndrome-du-colon-irritable-des-chercheurs-en-ont-trouve-la-cause-ouvrant-la-voie-a-un-traitement?id=10672723 . On présente cela comme une découverte mondiale mais cela fait bien 10 ans que c'est su aux USA ... Ceci pour expliquer l'exaspération - avec le caractère presque vexatoire et désespérant de la sortie de l'étude qui confirme le fait que je puisse avoir raison face aux médecins. » (Forum)

Because of their experiences in the way the GP took care of their long COVID complaints, some patients decided to change GPs

« Il y a eu un médecin, je n'ai pas eu trop l'impression. Après je suis passé par un autre médecin généraliste qui lui est quand même beaucoup plus ouvert et qui cherche justement à comprendre. Il est un peu désemparé en fait parce que il suit mon évolution, il voit que j'essaie de faire de trucs pour aller mieux et puis il voit que j'ai des rechutes. » (Patient 13, not hopitalised)

4.7 Role of social networks

Because long COVID is a new condition, social networks are prominent in the communication or exchange of information among patients. Furthermore, social networks are often a starting point to a more formal organisation with the aim to support patients, under the format of a self-help group.

Patients subscribed to it in order to find answer to their questions and to get to know if they are alone to suffer during weeks, have unexplained symptoms, etc. They need to be reassured and find also tips and tricks to get better.

"Wat mij wel vooruithielp was dat ik op een dag een vreemd nieuw symptoom had (verschillende bloeduitstortingen zonder reden) en dat ik meteen 30 reacties kreeg van anderen toen ik een oproep lanceerde of dit er ook "bij hoorde". Dat gaf wel wat geruststelling, ook al was er geen oplossing. En sommige linken naar studies zijn ook wel nuttig." (Forum)

« Si je poste un message (j'invente) : "je suis inquiète car j'ai tel et tel symptôme, est ce que quelqu'un a déjà eu ça?" les réponses me rassurent car souvent il y a une autre personne souffrant de COVID long qui a en effet eu ça. J'essaye aussi du coup à mon tour de rassurer quand je peux ou de partager ma propre expérience. Les soignants n'ont pas toujours vécu le COVID de près, donc on ressent bien quad on est "entre nous", qu'on a très souvent les mêmes expériences avec la maladie. Il y a aussi par exemple beaucoup d'empathie envers les personnes qui participent et qui ont par exemple été hospitalisées etc. et ces personnes-là ont aussi beaucoup d'empathie pour les personnes comme moi qui ont été/sont malades à la maison... » (Forum)

" Dus ik heb mij voorgenomen maar toch om omdat het rare was, je ziet in het nieuws en in de berichtgeving zie ja van mensen die dat die COVID hebben die dan direct geur- en smaakverlies hebben zoals bijvoorbeeld mijn schoonzus, mijn zus hebben ook COVID gehad. En die hadden toen, tijdens de infectie hadden die geen geur, geen smaak, en bij mij is het oké, ik had niets tijdens de infectie. En twee maanden en een half nadien, dan pas. Dus ja dat voelt wel raar, en dan zoek je

eigenlijk wel ergens bevestiging, heeft iemand dat ook gehad? En dat was de reden waarom dat ik in feite de Facebook groep ben gegaan, en ik heb ook de vraag gesteld, ik heb een post gezet met in verband met heeft iemand dezelfde symptomen? En er zijn heel veel mensen die twee maand, drie maand na de infectie juist hetzelfde hebben gehad." (Patient 15, not hospitalised)

It easier to find people through Internet than in person.

Stories of other patients provide comfort and could give hope.

« Voir dans les longs COVID l'expérience des gens, dans, sur les groupes de soutien, qui de mois en mois vont mieux , qui donnent des pistes de ce qu'ils font, de ce qu'ils ne font pas, de ce qui marche, de ce qui ne marche pas dans leur essai de, de, ben ça, ça apporte quand même, oui. D'abord on voit qu'il y en a beaucoup de personnes, qui même au bout d'un an commencent à aller mieux. Alors est-ce que c'est le vaccin ou pas ? On n'en sait rien mais ils vont mieux. Donc ça, ça apporte quand même du soutien, plutôt que le corps médical, (…)» (Forum)

And it offers patients a platform where they find support and recognition as 'someone affected by long COVID'.

"Ik ben heel dankbaar voor de Facebook groep long COVID waar ik veel steun, erkenning en begrip kreeg." (Forum)

Nevertheless, not everybody appreciate to go on Facebook groups:

It could make people sick, because it is discouraging to read all what could occur.

"Als ik op de Facebook groep kijkt, daar word je gewoon depressief van. Want als daar iemand nieuw is en die zegt van ik heb daar last van, of ik heb milde klachten gehad, dan boren die die direct de grond in van oh, maar dat is nog maar het begin, je gaat nog keilang klachten hebben, ja en uiteraard hebben die mensen dan daarna keilang klachten. En dan, staat daar zo nu de nieuwe bewering op dat je niet moet revalideren en dat je enkel naar je lichaam moet luisteren. En dat ze dan ja 15 kg verdikt zijn na een jaar en nog geen kwartier kunnen wandelen, ja…Als je als nieuw iemand die verhalen allemaal leest, dat is al, oh en zeker niet terug beginnen werken, ja dan word je gewoon ziek hé." (Patient 3, hospitalised)

People are not interested in reading the constant grumbling or complaining of other people without acting to search for help by health professionals. Patients think that some people just want to talk about themselves. Moreover, the value and validity of the information is also questionable.

4.8 Patients' unmet needs

4.8.1 Information needs

Long COVID patients report to experience a lack of information on several aspects: about the condition itself or how to communicate about it, about the costs related to the examinations and the interpretation of their results, and about the evolution of the scientific research.

Lack of information on long COVID

The lack of information and knowledge on long COVID creates stress and uncertainty among patients. They want to understand why they feel what they feel. Patients report a lack information (and/or scientific knowledge) on several aspects of long COVID, such as:

- The underlying causes of the experienced symptoms, including why some people have long COVID and others not, and clinical criteria to diagnose and assess their symptoms

  « J'ai encore à ce jour encore des symptômes neuros: des picotements, fasciculations, mal de tête. Bon si on n'a pas d'anticorps, qu'on a toujours des symptômes, c'est quoi la CAUSE de tout ça ?!? » (Forum)

  « Il y a des gens qui ont des améliorations, suivie de rechutes. De nouveau, POUQRUOI ? Quelles sont les causes des rechutes ? » (Forum)

  "Ik mis een duidelijke wetenschappelijk-medische uitleg. Wat gebeurt er in mijn lichaam? Waarom heb ik hier als gezonde, jonge persoon zoveel / zo lang last van? Is er iets mis met mijn immuunsysteem? Wat heeft mijn lichaam nodig om te herstellen? ..." (Forum)

But they recognize that such information is also missing for health care professionals

- The duration of contagiousness of people who are symptomatic (for a long period)

  « Je me dis "ben normalement", enfin on ne sait plus, on ne sait plus si on est contaminants par moments. Si après 4 mois, je me dis "bon maintenant je peux plus [rires] transmettre ça je pense". Mais il n'y a pas de limite, y a pas de délai, on ne sait pas dire après "ben voilà, à partir d'aujourd'hui maintenant tu n'es plus contaminante", ça, ça reste aussi un petit peu difficile à vivre je trouve. » (Patient 6, hospitalised)

- The expected duration of their symptoms , the evolution (will symptoms continue to fluctuate, improve, disasppear or detteriorate) and potential sequelae,as well as ways to deal with their symptoms (self-care) and which treatments, rehabilitation to follow.

  "Wat gebeurt er met je lichaam? Hoe lang zouden de meeste symptomen kunnen aanhouden? Vergelijking met andere virusinfecties? Hoe kan ik mezelf behandelen? Self-care? Wat is een goede opbouw op lange termijn? Wat kan ik beter wel of niet doen om sneller te genezen? (…)Heb ik mentaal problemen of zijn mijn symptomen echt?" (Forum)

  « Dans la société, on informe sur des chiffres, sur l'état des hôpitaux, sur quelques personnes particulières, mais il n'y a aucune informations sur la longueur du temps nécessaire pour se reconstruire, pour surmonter tous les séquelles après passage aux soins intensifs. » (Forum)

  « Le médecin généraliste, je ne dis pas qu'il est mauvais mais qui connaisse bien cette maladie et qu'il puisse me dire "voilà, attention Monsieur, ne faites pas ceci, ne faites pas cela", comment ça va se passer, » (Patient 30, hospitalised)

  « Si je vais chez la pneumologue, dans l'idéal je voudrais qu'elle me dise " voilà tout ce qu'on sait sur les patients, comme vous et ce qu'on peut mettre comme pistes, tout un protocole de, de, kiné, de ci, de là, enfin de, de choses à faire". Et quelque chose qui soit, entre guillemets le mieux possible cadré, » (Patient 6, hospitalised)

  « Oui ou bien , je veux dire à partir du moment où on peut expliquer " en règle générale on trouve ce type d'amélioration", je sais bien qu'on ne sait pas, on n'a pas assez de recul pour reconnaitre la durée. Mais bon, si on pouvait déjà mesurer le fait que ça va mieux ou pas moins, ou moins mal » (Patient 32, not hospitalised)

…But in the meantime, patients are well aware that this information need can, with the current scientific knowledge about this very recent condition, not properly be met by physicians or public authorities. The medical community as well as policy makers are only at the early stage of discovering the condition and its complexity.

« Comme le COVID est une nouvelle maladie, il y a déjà un manque de connaissances scientifiques à son sujet (beaucoup d'articles scientifiques mais peu concernant les COVID long...) , j'ai envie de dire qu'il est difficile de savoir quelles informations manquent dans le sens ou on aimerait déjà connaitre ce à quoi sont du nos symptômes (COVID ok mais pourquoi si long chez les uns et pas chez les autres?) , comment se soigner, est ce que ça partira un jour ou est-ce que c'est une maladie à vie? » (Forum)

« Mon médecin traitant attendait des informations officielles et semblait aussi désemparée que moi. Elle avait la sincérité de le dire. » (Forum)

In conclusion, patients express a clear need for more insight in this condition. They would like physicians to have information at their disposal they can use to properly inform patients such that the patient's condition can be better managed (by the healthcare professionals as well as by the patients themselves).

"In de eerste plaats moeten alle artsen en zorgverleners beter geïnformeerd worden over langdurige COVID. Nu is de situatie vaak zo dat je als patiënt een arts moet overtuigen dat de symptomen die je ervaart niet tussen je oren zitten. Moeten overgaan naar zelfstudie, zelfdiagnose en zelf een zoektocht doen naar een gepaste oplossing is volgens mij een grote stap achteruit. Als er dan gewerkt wordt aan een

uniforme en officiële informatiebron - geen dokter Google a.u.b. - laat die dan toegankelijk zijn voor zowel leken als zorgverleners." (Forum)

"Huisartsen zouden in die zin op de hoogte moeten zijn dat ze post-COVID kunnen herkennen en kunnen doorverwijzen naar een multidisciplinair team/aanspreekpunt waar je serieus genomen wordt en ook geholpen." (Forum)

The time spent on waiting for this information delays the start of the identification of long COVID as well as the rehabilitation.

Information on the cost of the examinations

In their search (induced by patients and/or physicians) for an explanation for their symptoms, several patients reported having had a battery of medical examinations and tests that are not always well reimbursed. Patients stated that this kind of information is also needed in advance.

« Après remboursements. Donc on a dû sortir 400 € de notre poche et ça on n'était pas prévenus. Ça, j'étais un peu… pas fâchée mais bon elle aurait pu prévenir et dire que elle avait fait des tests qui ne sont pas bon marché. Et au CHU, par exemple ils ont dit " on va vous faire" je ne sais plus quoi, une prise de sang ou quoi, mais ce sera une centaine d'euros, est-ce que vous êtes pour ou contre ? Mon mari avait dit "ben je suis pour", mais on avait prévenu. Mais la neurologue, elle n'avait pas prévenu… quand on a reçu la note, 400 €, pfou !. » (Patient 26, hospitalised)

Explanations on the results of the tests

When patients have had tests and medical examinations they stated that the test results were not always well-explained to them. Even when a test does not provide an explanation for their experienced symptoms, patients prefer to be informed about this finding. Patients indicated that they had to take the initiative to get this information from their physician.

« Quand je dit au médecin généraliste "docteur, ce n'est pas normal…, qu'est-ce que vous lisez dans le, le protocole de la ponction lombaire ?" "Ah bah oui ben c'est ça c'est ça, ben oui mais on ne sait pas très bien expliquer pourquoi". Mais moi je veux une explication, je veux savoir pourquoi c'est comme ça, pourquoi est-ce que c'est positif alors que normalement ça ne doit pas être positif. » (Patient 26, hospitalised)

« Et donc mi-novembre je n'étais toujours pas bien, vraiment pas bien, donc j'ai reconsulté ma médecin qui m'a dit " on va refaire une prise de sang". J'ai eu les résultats 2 jours ou 3 jours après et là j'étais à 100 d'immunité. Donc je lui ai surtout posé la question "que veut dire le 100 ?", "100, c'est 100 % ou 100 de quoi ?". Ben c'est presque impossible à, à savoir à quoi correspond ces 100. (…) Voilà, ça c'est une des grandes questions où j'ai toujours pas de réponse. » (Patient 16, not hospitalised)

On how to react on and interact with their environment

Patient also experienced a need to get information on how they can communicate about their condition with their entourage (e.g. family, friends, and employer).

"Hoe communiceer ik naar mijn partner of werkgever over mijn toestand?" (Forum)

On the evolution of the research and scientific knowledge

Some patients would like to be kept informed on the new scientific findings about long COVID. Such information is often not available or accessible to the general population.

« J'aimerais bien avoir un suivi parce que, pas spécifiquement de votre part, quoi, hein, mais avoir le suivi de l'étude, ça me paraît être logique…Voyez ? Et on aurait un, entre guillemets, un canal info qui puisse me dire que dans 3 semaines, "ah bien voilà, nous on vient de recevoir une étude sur le COVID long, où on a commencé à vacciner des personnes sur le COVID long et visiblement ça ne donne aucun effet", ou "visiblement on constate des effets positifs". Donc est-ce que vous ne pouvez pas envisager de vous faire vacciner ? Voilà. Parce que je ne pense pas que je vais trouver facilement dans les semaines ou les 2 mois qui viennent ce type d'info qui n'est pas ouverte au grand

public parce que ça ne concerne qu'une portion COVID de la population quand même ... » (Patient 16, not hospitalised)

They identified that either health care practitioners need to access easily up-to-date information.

« Parfois aussi, et c'est mon cas, ma généralistes est super à l'écoute et convaincue de ma contamination et de la persistance de mes symptômes, mais elle-même a du mal à trouver l'info. » (Forum)

This information as to base on scientific knowledge that has to be developed. In that way, patients claimed for more research.

« Il est temps de passer la seconde vitesse et de comprendre les causes. Chacune et chacun a un historique clinique, une génétique, une immunité différente). Donc chaque patient atteint par le COVID devra avoir un diagnostic personnel » (Forum)

Information need to be correct

Patients searched for information everywhere: on the internet, general media (TV, radio newspapers), Facebook, and also in their personal or professional networks.

« J'aijustement une copine qui est neuropsychiatre et je voulais parler, (…) des problèmes cognitifs parce que j'étais vraiment embêtée par rapport à ça. » (Patient 29, not hospitalised)

« Le bouche à oreille… j'ai quand même la chance et l'opportunité de travailler dans différentes maisons médicales. Que je vois beaucoup de collègues médecins avec qui je peux en parler et d'avoir leur échos et essayer de voir ce qu'ils ont entendu d'un ORL qui serait un peu plus, on va dire, plus à l'écoute des besoins, d'aider des patients qui ont un COVID de longue durée… . J'avais pensé plutôt à ça ». (Patient 17, not hospitalised)

« Il est difficile de trouver des informations sur le COVID long, du moins en Belgique. On peut en trouver au fur à mesure sur le net, des articles provenant d'autres pays mais en Belgique rien ..... Comme si cela n'existait pas. Heureusement que dans d'autres pays cela a été pris plus au sérieux que chez nous. Et heureusement que chez nous il existe quelques groupes pour trouver des informations, échanger et avoir du soutien durant cette épreuve. » (Forum)

Patients reported that they find it important that the information gives hope.

« La recherche sur internet me plombe le moral, cela va dans tous les sens... et je suis certaine qu'il y a un certain nombre de fausses informations qui sont parfois bien négatives et porteuses d'informations destructrices pour notre rétablissement. » (Forum)

4.8.2 Therapeutic needs

Specific needs were raised by participants related to their long COVID pathway.

A need for healthcare professionals that listen to the needs and experiences of long COVID patients

Even 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.

"Artsen moeten durven toegeven dat ze het niet weten. Nu heb ik de indruk dat ze vanuit hun ivoren toren er toch maar een etiket opplakken (vaak psychosomatisch) omdat de aandoening niet binnen hun opgedane kennis past. Dat getuigt van een zekere arrogantie die ik vooral bij specialisten heb ervaren. Ze moeten ook eens écht naar hun patiënt luisteren, er voor openstaan dat de patiënt misschien wel eens beter op de hoogte kan zijn van deze aandoening. De kennis komt

vanuit de patiënten en niet vanuit de medische wereld. Luister daar naar. En leer er van." (Forum)

Need of a multidisciplinary approach

Patients expressed the need of a multidisciplinary approach. This should cover the entire care pathway: from the diagnosis to rehabilitation. , through a rapid referral to specialists in order to rule out alternative diagnoses.

"Door het niet bestaan van nazorg trajecten is het aan mij als individu om de juiste artsen te vinden. Een multidisciplinair team gericht op COVID zou het diagnose proces een stuk makkelijker maken. " (Forum)

"Afhankelijk inderdaad van, het is inderdaad zo hè, van de ernst van de symptomen dat je eigenlijk ja goed onderzocht wordt, dat je rapper wordt doorverwezen naar ne specialist denk ik, naar ne neuroloog of ne longspecialist. Ne hartspecialist. Heel belangrijk denk ik. Uh om toch bepaalde dingen uit te sluiten of hè". (Patient 5, not hospitalised)

They experience the need for a pathway:

- With referral to the appropriate specialist. During the diagnostic phase it is, for instance, important that a GP refers patients fast enough to the appropriate medical

  « Une prise en charge un peu plus pluridisciplinaire et un peu plus d'écoute. (…) Je pense que les personnes comme moi qui l'ont fait de façon modérée mais pas légère avec des séquelles quand même… … par la suite, je me suis sentie, comment je vais dire, laissée et que je n'étais pas aiguillée… mon médecin a essayé de m'aiguiller. Elle fait ce qu'elle peut. Elle n'a pas un répertoire de prestataires de soins qui sont impliqués au niveau des séquelles. » (Patient 17, not hospitalised)

  « Où se soigner, quelles sont les équipes ouvertes et/ou capable de nous suivre (pour le futur 🤰)? » (Forum)

- With communication between the physicians

  "Multidisciplinaire aanpak. Alles is nu versnipperd. Je gaat naar de huisarts, van daar naar de longarts, dan naar de cardioloog, dan de neuroloog, etc. De huisarts is de enige link, maar de meeste huisartsen hebben nog te weinig inzicht in wat de lange termijn gevolgen zijn van COVID. Er is geen onderlinge communicatie tussen de specialisten." (Forum)

  "Je gaat naar de huisarts, van daar naar de longarts, dan naar de cardioloog, dan de neuroloog, etc. De huisarts is de enige link, maar de meeste huisartsen hebben nog te weinig inzicht in wat de lange termijn gevolgen zijn van COVID. Er is geen onderlinge communicatie tussen de specialisten. Nood aan multidisciplinaire teams die de patiënten opvolgen. Met opvolging ook bij de revalidatie (maximale inspanningstesten, tussentijdse evaluatie en longfunctietesten, onderzoeken, etc.)" (Forum)

- With a comprehensive follow up (not restricted to a medical assessment)

  "Ambulante zorg/ opvolging voor mensen die thuis moeten uitzieken. Een zorgmedewerker die eens opbelt om te vragen hoe het gaat. Eventueel hulp bij boodschappen / voorzien van warme maaltijden (zeker bij alleenstaanden). Het heeft 6 weken geduurd tot een huisarts mij wilde zien, er waren geen consultaties, enkel telefonisch "blijf thuis en neem dafalgan"." (Forum)

- With a rehabilitation plan…

  "Nood aan multidisciplinaire teams die de patiënten opvolgen. Met opvolging ook bij de revalidatie (maximale inspanningstesten, tussentijdse evaluatie en longfunctietesten, onderzoeken, etc.)" (Forum)

- …for patients discharged from the hospital…

  "Hè want, want gelijk als ze afscheid namen in het ziekenhuis van, goeie revalidatie, trek uwen plan, dat is, dat is geen hulp hè. (…) Allee, ik bedoel. Die had evengoed kunnen zeggen van, wij raden aan van dat en dat en dat en dat. Dat hebben ze niet gedaan eigenlijk". (Patient 20, hospitalised)

  « Personne n'a une route, on n'a personne qui quand on lui dit attention, vous allez avoir ceci, l'essoufflement ça va venir un petit peu à la fois, les choses qui peuvent arriver. (…) Et ça, ça manque (…) parce

qu'évidemment c'est nouveau. C'est nouveau pour tout le monde. Le cancer on commence à le connaître (…) Mais, mais là (…) on pourrait quand même donner une route à suivre , guider la personne en fait à ce qu'il peut faire et ne pas faire. Je pense que ça aiderait beaucoup, beaucoup. Et pour ça, il faut voir la personne, il faut venir voir la personne ou bien il faut inviter la personne à aller à l'hôpital (…) et on leur dit "voilà, maintenant on va venir voir, venez une heure de 7 à 8 et voilà", vers un psychologue, un médecin, on l'ausculte un petit peu, voir ce qu'on peut faire et lui dire les marches à suivre et la psychologue voit comment la personne perçoit cette maladie, perçoit sa vie. » (Patient 30, hospitalised)

- …But even so for patients that were not hospitalized during the acute COVID-19.

  " Als je niet in het ziekenhuis beland bent, heb je geen enkele opvolging/erkenning van de ziekte of van de gevolgen" (Forum)

  "Ik denk… Sowieso je hebt altijd opvolging hè. [zucht] Eens dat je in een ziekenhuis geweest zijt eh uhm gaan ze zeggen van: "Binnen zoveel weken op consultatie wil ik u terugzien.". Of dit of dat.. En dan, bam, is, is dat ergens wel gestart en gaan ze dan ook wel u multidisciplinair kunnen doorverwijzen naar een kinesist of bij mij bijvoorbeeld in verband met die duizeligheid of zo. Dat had, had dan ook misschien wel kunnen gebeuren. Want dat denk ik dan nu ook. Ik heb oefeningen gehad voor die extreme draaiduizeligheid. Maar er bestaan ook oefeningen voor mensen met Ménière en dergelijke. Misschien had ik van in het begin oefeningen gedaan heb dat ik geen als of, of maar kortdurend last gehad van duizeligheid. Ik heb dat nu maanden gehad. Dat had ook een wereld van verschil geweest in, in, in uw welbevinden en in dingen die ik kon thuis. Dus ja." (Patient 18, not hospitalised)

Patients experience the need that not everything should be left to the initiative of the individual care provider but that some kind of support or coordination should be concentrated at a more central level (e.g. a hospital or other meso-level structures).

"Oplossingen bieden. Luisteren en, en, en die verhalen centraliseren en, en trachten een oplossing te bieden die, die werkt. (…) Misschien via, ja, moet dat via een ziekenhuis? Ik weet dat niet. Maar dat mag desnoods provinciaal zijn, maar ergens iemand dat dus echt de knowhow heeft of, of toch wel alles, heel veel weet van, van, van alles. En die al die dingen verzamelt. En die dan zo, en die hoort van tja, die is, dat, die is daar goed mee geweest of die is daar goed mee geweest, en die dan misschien die middelen die kan overvragen of, of presenteren aan andere mensen. Zoiets." (Patient 20, hospitalised)

Need of a guidance

Patients often receive very general instructions (e.g. referral to physiotherapist or medical specialists such as neurology). They expect more guidance (e.g. which medical specialist to contact? What is their expertise in long COVID?) from healthcare professionals .

« Parce que quand on me dit "allez voir le neurologue", ben je vais prendre qui moi comme neurologue ? Je ne connais pas de neurologue. » (Patient 26, hospitalised)

Need for specialists with specific (long-) COVID expertise

Because of the lack of knowledge among the healthcare professionals, patients would like to be oriented to the ones with specific expertise in (long-) COVID, someone who knows more than the patient him/herself.

"België loopt hopeloos achter en er is nood aan onderzoek en multidisciplinaire teams want COVID richt schade aan op celniveau en dat ga je met alleen revalidatieartsen niet oplossen. Ik zou zo graag eens een dokter ontmoeten die iets weet en die mij iets kan vertellen dat ik zelf nog niet uitgevist heb!" (Forum)

"Een juiste behandeling vereist dat je moet worden behandeld door de juiste persoon. Ik denk dat we een groot tekort hebben aan mensen die voldoende vertrouwd zijn met COVID-19." (Forum)

« [J'ai besoin d]'un médecin, d'un médecin spécialiste qui s'y connaît vraiment en COVID-19, qui aurait pu me guider, me dire "attention, les douleurs musculaires, l'essoufflement, c'est dû à ça, dû à ça, ça va se

passer comme ça. Dans votre cas ça va se passer comme ça". Qu'il me guide, qu'il me donne un couloir où je, que je puisse me baser et me dire "voilà, ça c'est normal, ça ce n'est pas normal, je dois faire attention". » (Patient 30, hospitalised)

« J'ai commencé à faire des recherches et puis je me suis dit "mais il faudrait trouver quelqu'un qui est vraiment spécialisé parce qu'un médecin, bon mon médecin je l'aime beaucoup mais je sens aussi que lui n'a pas l'expertise, il est dans le bain, il soigne ses patients mais il ne sait absolument pas me conseiller. » (Patient 12, not hospitalised)

Need for treatments

Patients want to get rid of their symptoms and some are ready to do everything what is possible (e.g. trial and error, non-conventional treatments)

"Ik wil alles uitproberen want ik wil hier .. uit geraken. Ik zeg eh alles behalve als het effe kan een hersenbiopsie bij leven." (Forum)

Some specific treatments seems, according to patient, to be unavailable: voice-improvement therapies and an approach to deal with brain fog

« Besoin de retrouver ma voix, alors que l'examen ORL ne trouve rien d'anormal. Cette dysphonie m'handicape, encore aujourd'hui, » (Forum)

4.8.3 Need of support

Psychological support

Some patients have experienced COVID-19 as a trauma and felt the need for a post traumatic approach but it has never been proposed to them. A psychological support could already have been a useful start.

« Dès le début, je pense pour la phase post-traumatique, entre autre parce que, il faut savoir que quand j'ai repris le travail, et en plus que je suis dans le milieu du soin, ça a été difficile. (…) un moment, je me suis même dit que je commençais à développer des troubles du comportement que ça soit au niveau désinfection … parce que je ne veux pas revivre ce que j'ai vécu il y a un an. La peur de le ravoir… de le refaire comme je l'ai eu. Il y cette peur-là qui reprend le dessus par moment, en me disant si je suis contaminée à nouveau… Effectivement, un moment, il y avait trop de lavage de main, désinfection tout le temps. Je me suis rendue compte que ça devenait même par moment obsessionnel. C'est que je me suis dit que ce n'était pas une mauvaise idée de consulter …en tout cas une thérapeute, un psychiatre ou un psychologue, peu importe. Mais voilà, je n'ai pas fait la démarche. » (Patient 17, not hospitalised)

After the acute episode, psychological support is not always proposed to long COVID patients. Nevertheless, patients think it could be useful in order to accept the situation, think about the perspectives to live with the condition and manage the feelings of guilt (because of their state or inability to return to work) and anxiety.

"Psychologische ondersteuning, ook de mentale impact is niet te onderschatten. Je eigen lichaam voelt plots zo anders, schrik voor de toekomst en hoe het verder gaat evolueren." (Forum)

« Mon médecin m'a bien suivie vraiment pendant la période critique. Alors une fois que j'ai été mieux, ben lui son boulot était fini. Et, et c'est que là que, peut-être, psychologiquement, pour parler de cette fatigue et se demander si c'est normal et de pouvoir la gérer [avec un psychologue] (...) Oui, pour, pour pouvoir répondre à certaines interrogations qui étaient plus dues, après le COVID, plus morales que physiques, parce que le physique, la fatigue induit un moral plus bas évidemment donc. (..) Parce que il y a un moment où je me suis retrouvée, où je me suis dit "mais si ça continue comme ça, ben qu'est-ce que je vais faire, enfin j'aurai plus de perspectives". Donc c'est plutôt moral, pour pouvoir, je veux dire, relancer un peu la machine, quelques pistes, de réflexion qui relancent un petit peu, ... » (Patient 28, not hospitalised)

« Si je n'étais pas une personne un peu plus consciente de moi-même, là je serais en état de dépression complet hein, de pas être capable de bouger de faire des trucs et tout, ça me mettrait la tête en l'air ! Je comprends, c'est vrai. Et je comprends qu'ils ont besoin spécifiquement d'une aide de quelqu'un, ne fût-ce que pour leur expliquer que ce n'est

pas de notre faute. Il y a toujours une responsabilité quand c'est comme ça. » (FR232 352) (Patient 16, not hospitalised)

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 at one moment in time, but this feeling might change when symptoms last. Lack of energy to engage in psychological care might also be a reason for not accepting psychological support in the early stages.

« Je tiens à le signaler quand même que le dernier jour [de mon hospitalisation] on m'a demandé si je voulais une aide psychologique. À ce moment-là, je me suis dit "mais enfin pourquoi elle me demande si je veux une aide psychologique ?". Je ne voyais pas franchement le, je m'en suis rendu compte après, quand je suis rentré chez moi, que j'aurais dû dire oui. Que, quand je suis, quand on est dans la chambre, on fait 2 mètres, on est à la table. On fait 2 mètres, on est dans la salle de bains. Chez moi, quand j'étais dans le divan, il me fallait faire au minimum (…) 12 à 13 pas pour aller aux toilettes. Je le faisais en 2 fois, je devais m'asseoir en 2 fois. Pour quelqu'un qui a l'habitude de faire 2 heures de marche sans avoir aucune douleur, sans avoir rien du tout, c'est là que ça devient drôle. Ça, ça devient extrêmement difficile psychologiquement, physiquement aussi certes, mais surtout psychologiquement. Et là j'aurais dû, j'aurais dû accepter l'aide psychologique. Et je pense que tous les gens qui sortent de l'hôpital, d'office passer devant un psychologue parce que c'est extrêmement délicat. On se demande qu'est-ce qui se passe. Je suis quelqu'un qui veut aller de l'avant, mais parfois qui veut aller trop de l'avant, je m'écoute un petit peu trop parfois. (…) et on se dit "mais ça va aller, ça va aller". Mais on essaie de forcer alors qu'on ne doit pas forcer, on ne doit surtout pas forcer, on doit écouter son corps comme on dit et quand on est fatigué dormir. Mais ce n'est pas toujours facile. Alors je n'ai pas accepté cette aide psychologique, et quand je suis rentré chez moi, j'en ai pleuré. » (Patient 30, hospitalised)

"Maar die heeft mij dan wel eh telefonisch zo wat (...) Maar ik was daar niet klaar voor toen. Ik was zo slecht nog. (…) ja dat ging eigenlijk niet op dat moment. Dat was echt zo wat. (…) Maar toen was ik echt nog zo slecht dat dat eigenlijk, ja, dat ging gewoon niet. Ik kon niet praten zolang, ik was uitgeput, dat ging totaal niet. Het was de moment ook niet voor het op een rijtje te zetten nog niet." (Patient 8, hospitalised)

According to the respondents, psychological support has to be reimbursed because it is expensive. Some respondents mentioned that it has a financial impact especially because they already have a reduced income due to the condition.

"Niet iedereen kan 60 euro per uur betalen voor een psycholoog, zeker niet als je door arbeidsongeschiktheid al op een lager inkomen valt en veel medische kosten hebt."(Forum)

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.

« Et donc moi, c'est toujours ça qui me fait peur quand on dit qu' il faudrait un suivi psychologique important, enfin plus, plus conséquent et mieux organisé pour le long COVID. Mais il ne faudrait pas que, parce qu'on demande un suivi psychologique plus important, qu'on considère que les patients qui continuent à avoir des problèmes liés au COVID, c'est psychologique et donc psychiatrique et donc santé mentale. » (Patient 10, hospitalised)

A place to convene with peers

Besides (possible) psychological support, patients mentioned the need to have a place to convene and talk to other people suffering of the same condition.

"Ik probeer nog alles zelf te doen heb ook veel steun aan mijn man spijtig genoeg woont mijn familie ver van mij ik moet met de auto en dat gaat niet altijd want ik kan mij moeilijk concentreren ik weet niet of dat al bestaat maar een praatgroep kan misschien wel veel helpen" (Forum)

Spiritual support

Respondents mentioned also a need for spiritual support to help them to reflect on their identity, not only as a patient but also in general.

> *"Ik denk dat het goed is dat er eh psychologische ondersteuning is maar ook bijvoorbeeld die eh spirituele noden. Mensen denken soms dat, niet dat ze dat nodig hebben maar uiteindelijk gaat dat over wie dat ze zijn…dat gaat niet over eh één of andere god of zo of, of… buitenaardse wezens. Maar het gaat gewoon over wie ben ik en eh ik ben wel meer dan, dan nu een patiënt. En eh dat, dat ook dat eh dat ook daar mensen eh kunnen in ondersteund worden." (Patient 9, not hospitalised)*

Practical support

Patients expressed the need to receive help in their daily life, to cook, to take care for their children, do the housekeeping, etc. Many mentioned the possibility to receive help from close family member but stated that also for these persons it is not easy, especially when they are also ill.

This kind of support is not foreseen and there are long waiting lists up to several months.

> *"Aangezien mijn man het professioneel heel druk heeft, heb ik nu hulp van een poetsvrouw en soms een tuinman. Want ik geraak op mijn eentje niet rond met het huishoudelijk werk en de tuin daar zie ik mij helemaal geen beginnen aan..." (Forum)*

> *"Ik kan mijn huishouden nog altijd niet doen. Dus ik had geprobeerd om te regelen dat ik hulp kreeg voor… Te koken, wat te poetsen, eens naar de winkel te gaan. Wachttijd, drie maanden." (Patient 2, hospitalised)*

> *« J'aurais bien aimé avoir quelqu'un pour faire par exemple le ménage chez moi parce que jusqu'à aujourd'hui c'était trop difficile. Mon mari fait ce qu'il peut mais on a 3 enfants, il faut déjà s'en occuper, il faut faire la cuisine et tout. Mais je m'étais dit "où est-ce que je peux même demander de l'aide pour avoir une femme de ménage de temps en temps ? ». (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 but it should be also available for young or single people.

> *"Ik denk dat je vooral moet gaan kijken naar die mensen die onvoldoende ondersteuning hebben algemeen. Maar zo doen we dat eigenlijk altijd ook in het ziekenhuis hè. Dus mensen die terug naar huis moeten eh in een systeem dat onvoldoende ondersteund is. Dan ga je, ja, met de sociale dienst, sociaal assistent ga je daar zaken op poten zetten. Ik denk eh post-COVID dat men daar op bedacht moet zijn dat dat ook het geval is voor jonge mensen….Waar dat je normaal gezien geen ondersteuning gaat voorzien. Dus normaal gezien doen we dat alleen voor oudere mensen…Of alleenstaande oudere mensen. Ik denk dat dat absoluut noodzakelijk is dat dat afgetoetst wordt. Eh ook bij, bij iedereen post-COVID." (Patient 33, hospitalised)*

As already explained, administrative simplification is also required to remove barriers towards an adequate recovery. In addition an increased efficacy of the sickness funds is expected.

4.8.4 Need for recognition as 'someone affected by long COVID' or 'long COVID patient'

Patients have a need to be recognized as 'someone affected by long COVID' by the general population or as 'long COVID patient' by the institutions in general and by policy and politics.

It is felt that such a recognition would help people in the patients' entourage to understand what it means to live with long COVID….

> *« Être reconnu au niveau des politiques et de la population, non pas pour se faire plaindre mais pour avoir un minimum de respect et qu'on arrête de nous prendre pour des anxieux ou fainéant et profiteurs de la société ..... On ne parle jamais du COVID long, alors pour les gens ça n'existe pas ! » (Forum)*

> *« Pour moi seule la reconnaissance officielle de notre statut va peut-être améliorer cette perception de ce que nous vivons... C'est comme*

dans beaucoup d'autres situations, tant que l'on n'y est pas confronté, on ne mesure pas vraiment... » (Forum)

At the policy and political level, patients ask to get access to the same rights and benefits as 'classical patients' or 'chronic patients'.

« Le DIAGNOSTIQUE est une élément de la plus haute importance pour les COVID long: Pas de diagnostic confirmé, cela signifie- pas de frais de soins remboursés par les caisses d'assurance.- Pas pris au sérieux ceux qui sont en incapacité de travail- Incompréhension des autres… » (Forum)

« Il y a également un grand manque de reconnaissance institutionnel. Quid de nos boulots? Des aides auquel nous pourrions prétendre pour nous aider au quotidien peut-être (…) Il y a vraiment un manque général d'informations, d'encadrement global et de soutien. » (Forum)

The recognition of long COVID as a disease would increase the visibility and awareness of the condition amongst the broader public and subsequently the level of understanding amongst key persons in the patients' entourage' Information about long COVID should also clarify that consequences can occur in hospitalised patients but also in non-hospitalized patients, even after a mild and asymptomatic acute phase.

"Meer informatie openbaar maken over langdurige gevolgen van COVID, zodat iedereen op de hoogte is. Er is teveel onbegrip. (Werkgevers, mutualiteiten, verzekeringen, collega's, etc.). Nog vaak leeft het idee dat jonge/gezonde mensen op 2 weken genezen zijn. Velen gaan dan te vlug terug aan het werk, met een terugval als gevolg." (Forum)

"Om te starten meer bekendheid geven aan de langdurige symptomen van post COVID, en dit niet alleen bij gehospitaliseerden of patiënten die in coma lagen. Nu lijkt het in de media precies of (bijna) enkel zij langdurige klachten hebben." (Forum)

4.9 Suggestions from patients to improve the management of long COVID patients

To conclude the interviews we asked participants to formulate proposals to improve the management of long COVID patients. The suggested proposals are **a response to the needs they expressed.** We list below the suggestions that were voiced by patients.

General suggestions

- Creation of a long COVID task force: a multidisciplinary group of experts that objectively follows the scientific evolutions around long COVID

  "Ik vind dat er een soort taskforce, allee, een werkgroep moet samengesteld worden met mensen uit verschillende disciplines, artsen uit verschillende disciplines. Die op een zo objectief mogelijke manier gaan kijken hiernaar en die gaan proberen al dan niet een logische verklaring te vinden voor wat men vindt en die eh op die manier ook een eh educated guess kunnen maken over eh behandeling die zou kunnen helpen. "(Patient 33, hospitalised)

- Recognition of long COVID as a long term or chronic disease (similar to other chronic diseases), also for children and young people

  "Ik denk dat in de eerste plaats de erkenning van langdurige COVID belangrijk is. Alle belangrijke actoren (zorgverleners, werkgevers, ziekenfondsen, overheid, ...) moeten zich bewust zijn dat dit een reëel en langdurig of chronisch probleem is. Wat oplossingen betreft, zou ik dan verwachten dat dit op dezelfde manier gebeurt als bij andere langdurige/chronische aandoeningen." (Forum)

- Recognition of the sequelae of long COVID

  « J'aimerai qu'en plus de la maladie longue durée, il soit pris en compte, les dommages irréversibles causés par ce virus, je prends mon cas particulier, une occlusion veineuse de l'œil gauche en plein COVID m'ont fait perdre 8 dixième. Je ne suis pas le seul. » (Forum)

Information related suggestions

- Clarify the name of the condition: avoid to use the « post COVID » terminology since it gives the impression that 'the COVID diseases is finished', while patients still experience symptoms. Patients prefer the use of long COVID as terminology.

« Eviter que les médecins parlent de "POST" constitue une condition essentielle ... le virus est toujours actif, c'est démontré scientifiquement. » (Forum)

« COVID de longue durée est:- Un patient qui après un test confirmé (ou pas?) positif l'infection du virus sars-cov-2 (a)- continue de souffrir de un ou plusieurs symptôme(s) qui sont persistent ou récurent (vague) (b)- X jours après l'infection initiale(c) » (Forum)

- A central internet website managed by the authorities dedicated to long COVID, where the (evolutive) scientific knowledge is reported.

"In feite zou alle bestaande informatie, zowel uit binnen- als buitenland (want in veel landen staan ze al een heel stuk verder dan in België), best gegroepeerd worden op een betrouwbare pagina. En niet enkel voltooide studies, want dat duurt jaren, maar ook tussentijdse verslagen, nieuwe inzichten etc.. Alle onderzoeken over de verschillende symptomen, alle mogelijke behandelmethodes, etc... groeperen zodat zowel artsen als patiënten gemakkelijk de nodige en juiste info vinden." (Forum)

« La création d'un site (je pense que ça serait plus facile pour certaines personnes de trouver) ou une rubrique sur un site déjà existant (AVIQ, ou SPF santé publique, ...) qui permettrait de reprendre les informations actuellement déjà connues et fiables ... et les éventuelles études en cours. Ainsi que les divers spécialistes (la discipline je veux dire) que l'on pourrait consulter dans le cadre d'un COVID long. Et aussi les hôpitaux qui ont déjà ouvert des consultations pour le COVID long Bien sûr les informations proviendraient de plusieurs structures reconnues médicalement et du monde entier. Cela serait utile pour les patients mais aussi les professionnels de la santé, le fait de tout centraliser ferait gagner du temps et permettrait de faciliter l'accès à l'information. Malheureusement il y aura une partie de la population qui ne sera peut-être pas au courant si ils ne sont pas connectés ... donc informer un maximum les médecins traitants me semblent un point primordial » (Forum)

- Media communication that is less frighthening

Long COVID management

- Define clinic criteria for long COVID diagnosis (symptoms and examinations), even in absence of positive PCR results. An instrument for physicians that allows to classify and follow-up the evolution of symptoms should be developed.

« Les médecins doivent avoir un outil de suivit et d'évolution de symptômes. Une grille avec persistance/évolution par symptômes permettait de confirmer ce qu'on appelle "un COVID long", d'identifier quels sont les examens qui sont requis, trouver les causes, et quel traitement peuvent aider, etc. » (Forum)

- Develop a personalized patient trajectory

« Sur base de ma propre expérience, ce qui manque le plus pour augmenter l'efficacité des traitements, c'est que le traitement soit bien ajusté aux besoins du patient. Je me sens un peu stupide d'écrire cela, tellement cela semble évident, mais la plupart du temps, le patient n'est pas considéré comme un partenaire de sa santé, son expérience unique par rapport à comment il perçoit ses symptômes n'est que très peu prise en compte. Du coup, les traitements proposés - surtout dans un cadre aussi flou que celui du COVID-19 long - ne sont pas toujours bien adaptés et, sauf exception, la réaction du patient au traitement n'est pas suivie de manière très systématique, ni rigoureuse. » (Forum)

- With an (automatic) invitation for follow-up consultations

"il faut inviter la personne à aller à l'hôpital (…) on devrait commencer à rappeler les personnes qui ont été à l'hôpital ou ceux qu'on connait qu'ils ont eu une maladie que, cette maladie a été un petit peu plus proche et on leur dit "voilà, maintenant on va venir voir, venez une heure de 7 à 8 et voilà", vers un psychologue, un médecin, on l'ausculte un petit peu, on voit ce qu'on peut faire et lui dire les marches à suivre et

la psychologue voit comment la personne perçoit cette maladie, perçoit sa vie ». (Patient 30, hospitalised)

« Dès que peut-être après, je ne sais pas moi, 2 semaines, 1 mois, 3 mois, on est diagnostiqués COVID long, et on enclenche la démarche et le suivi qui va avec. Je veux dire, c'est comme si on diagnostique un cancer à quelqu'un, on va suivre tout ce qu'il faut pour le, l'aider. Si quelqu'un a déjà des symptômes peut-être après 2 mois, en fonction de ce qu'ils auront décidé, le COVID long, ça peut être défini après 2 mois, et puis on, on fait un suivi. » (Patient 14, not hospitalised)

- With visits at home after hospitalisation not only by healthcare practitioners but also by a pyschologist (in tandem with the healthcare practitioner)

« [Ou on pourrait organiser une visite à domicile par] un couple de personnes qui fasse la partie médicale et en même temps psychologique qui passe chez, chez les personnes. Ça ferait je pense beaucoup de bien, faire un petit rapport. Et encore une fois, …, si jamais tout va bien, ça va. » (Patient 30, hospitalised)

- Multidisciplinary management, following the WHO recommendations
- Coordination by the GP or by another physician

« Je pense que un- quand une personne va chez le généraliste, le généraliste doit être outillé pour orienter ses patients. Pour au moment où on suspecte par exemple : tiens, y a un COVID long, OK. Y a tel et tel service ; pour les enfants, y a tel et tel service ; voilà la prise en charge, voilà les facilités, la gratuité,… » (Patient 27, hospitalised)

« Il serait intéressant qu'un médecin collecte les différents rapports d'une équipe pluridisciplinaire. Centraliser les rapports et faire le lien » (Forum)

- The GP should give an information folder on long COVID and how to manage the symptoms
- A convention with additional services (e.g. social worker) on top of the regular reimbursed services should be developed analogues as is done for other chronic conditions (e.g. diabetes)

« une convention comme les diabétiques (…) il y aura une assistante sociale qui pourrait guider dans les démarches si vous avez besoin d'aide pour le ménage, (…).(Patient 26, hospitalised)

- The establishment of local Post COVID clinics where multidisciplinary expertise (healthcare professionals with specific expertise on long COVID) is available in one place allowing an accurate diagnoses as well as management of the long COVID symptoms. These clinics should also abe ccessible for children

“Idealiter zouden er gespecialiseerde post-COVID afdelingen in ziekenhuizen zijn waar patiënten de onderzoeken voor alle verschillende symptomen kunnen krijgen (cardiologie, pneumologie, neurologie, gastro-enterologie, reumatologie, immunologie, revalidatie, ...) en waar artsen up-to-date zijn en blijven met de internationale kennis over long COVID. Dit alles ook voor kinderen In het VK heeft men deze post-COVID clinics al (hoewel ze nog niet allemaal even optimaal werken). Men focust er op de meest belastende symptomen en probeert daarin hulp te bieden. Zo worden bvb. patiënten met aanhoudende vermoeidheidsklachten doorverwezen naar klinieken voor patiënten met ME/CVS of Physios for ME of long COVID Physios (geen van deze lijken beschikbaar in België).” (Forum)

« Il y a un suivi, c'est-à-dire qu'il y a surtout une, une disponibilité plus grande par rapport à, par rapport à la prise en compte. En clair ben, voilà, avec le neurologue à [lieu] moi j'étais plus en confiance, je leur ai expliqué, et j'ai eu un rendez-vous le lendemain avec un neurologue. Et le docteur X, c'est elle qui a, qui a jugé la nécessité de faire un, une scintigraphie du cerveau. Et, suite à ça, le neurologue a examiné, il y a quand même une prise en charge de toute la problématique et ça c'est vrai, c'est quand même important, genre, on va d'abord déjà examiner tout ce qu'on a et on vous recontacte en fonction. Et c'est [lieu] qui m'a proposé un rendez-vous avec un neurologue, un rendez-vous avec l'ORL parce que les problèmes que je leur ai expliqués, par téléphone se maintenaient et que ils ont programmé ça. Donc moi ce qui

m'apporte beaucoup par rapport à ma situation, c'est les échanges qu'on peut avoir et la disponibilité de l'équipe de [lieu], par rapport à à des patients comme moi et d'autres parce qu'on est quand même quelques-uns à être pris en charge. Et ça je trouve que c'est quand même un élément qui est important. » (Patient 10, hospitalised)

« On doit se battre pour avoir les rapports et les transmettre nous-mêmes aux autres spécialités (on se demande à quoi sert la plateforme réseau santé Wallonie-Bruxelles, soit ils le disent qu'ils n'ont pas accès de l'ordinateur ou ne se posent même pas la question .... question de temps ??) Les prises de rendez-vous sont difficiles, alors que si tout est fait globalement dans une même institution et programmée sur plusieurs jours, cela serait plus rapide et accessible. » (Forum)

« Etablir euh une prise en charge globale et mieux coordonnée et plus proche des lieux de vie des gens, un part, un centre dédié aux patients COVID par province, je pense que ça serait bien utile » (Patient 10, hospitalised)

Administrative aspects

- Administrative simplification;
- Possibility to send documents online (cf tax);
- Centralisation of documentation for all the insurances (health, income guarantee, occupational disease);
- Recognition of long COVID as an occupational disease for a larger group of professions, i.e. police, firemen, houskeeper;
- The possibility to get administrative support, not only for hospitalized patients.

Reimbursement

- Expanding the reimbursement of psychotherapy;
- Reimbursement of complementary treatment;

« Les compléments phyto ou autre sont utiles, ils aident ... si la recherche publique que j'ai évoqué avant démontre une efficacité, il serait logique de proposer une prise en charge par le système de sécurité sociale. Il n'y a pas de raison qu'un complément en phytothérapie soit discriminé par rapport à une molécule artificielle. Juste qu'aujourd'hui cela ne fait pas l'objet de recherches ad hoc parce que ce n'est pas brevetable ... je raisonne en termes sociaux ... les compléments me coutent cher chaque mois, je ne regrette pas pour autant de le faire car ça m'aide pas mal, je peux me le permettre (jusqu'à maintenant en tout cas) mais je me mets à la place de ceux qui cumulent les problèmes avec des revenus moindres, des difficultés sociales ... ils peuvent être dans l'impasse encore plus grande d'avoir des difficultés de se soigner. » (Forum)

- Increase the number of physiotherapy sessions that are reimbursed.

Change mind-sets

- Create awareness among the general public about long COVID;

« Etre reconnu au niveau des politiques et de la population, non pas pour se faire plaindre mais pour avoir un minimum de respect et qu'on arrête de nous prendre pour des anxieux ou fainéant et profiteurs de la société ..... On ne parle jamais du COVID long, alors pour les gens ça n'existe pas ! » (Forum)

« Pour ce qui est de la reconnaissance d'être malade par les autres, je pense que c'est comme toutes les maladies chroniques, il y a beaucoup de moqueries, beaucoup de gens ne nous prennent pas au sérieux... A part travailler sur la sensibilisation, je ne vois pas comment. » (Forum)

- Create awareness among the healthcare professionals (and physicians in particular) about long COVID;

« Je pense donc que l'utilisation actuelle des tests produit des résultats incomplets, ceux-ci ne doivent pas être le SEUL et UNIQUE outil pour établir un diagnostic COVID LONG. Il existe trop de témoignages avec des personnes qui sont PCR & sérologie négative mais souffrent de syndromes persistant.==> Informer le corps médical y compris les médecins généralistes que ce scénario existe pour qu'ils arrêtent de

prendre les patients pour des fous et qu'ils nous prescrivent de l'aspirine et des anxiolytiques par défaut » (Forum)

« Informer le corps médical pour les informer à quel point le COVID long existe et est handicapant que ce soit au niveau des activités journalières ou professionnelles. » (Forum)

« Je pense que ce genre de problème se passe de moins en moins car les cas COVID long commence à être réellement reconnu ce qui n'était pas le cas en juillet car cette maladie "n'existait pas ". Revoir le passé pourra sans doute aider certains soignant à "changer leur fusil d'épaule" 😉" (Forum)

- Train physicians to be open-minded and open to collaborate with 'patient-researchers';

« Et moi je crois que les médecins devraient être un peu formés à tout ça, les conséquences que ça peut avoir pour pas exclure tout le temps. Parce que si on se base que sur des problèmes psychosomatiques mais qu'on ne va pas au-delà et qu'on ne cherche pas non plus les maladies qui peuvent être plus rares qui sont un peu plus difficiles avec diagnostic,… » (Patient 13, not hospitalised)

- Communication towards the patients;
- Adapt the language so that communication between healthcare professionals, scientists and patients is possible. It is important that the medical worls listens to patients which often requires that communcation is adapted;

« La principale action que j'espère pour un future proche, est une réelle communication du monde scientifique vers des patients qui ne le sont pas du tout. Un langage ad hoc afin de mieux comprendre afin de se faire comprendre » (Forum)

- Give direct access to the patient to his/her health examination/tests results.

« Il serait utile que les patients puissent enfin avoir un accès direct aux résultats de leurs propres tests (sanguins, imagerie, etc.). Je trouve dégradant de devoir demander l'autorisation à mon médecin pour avoir accès aux résultats concernant mon corps. Je perds à chaque fois du temps et de l'argent à courir derrière les résultats de mes tests et ne me sens pas du tout, mais alors pas du tout considérée comme partenaire de ma santé! » (Forum)

Support

- "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 (e.g. because of a potential the reaction of their treating physician) to answer.

« Ces groupes Facebook sont déjà pas mal, à part que il n'y a pas d'encadrement, il n'y a pas une réponse possible par un professionnel de soins de santé. Ou alors faire ce genre de groupes Facebook mais avec un encadrement qui pourrait avoir une réponse de quelqu'un parce que sinon, parfois, dansf ce genre de groupes Facebook, y a des personnes, (…) qui arrivent avec leurs croyances (…) s'il n'y a pas un modérateur…, parfois un encadrement est aussi important dans ce genre de groupe. » (Patient 6, hospitalised)

« Anonyme, je pense que ce serait mieux parce que ça aussi sur Facebook, moi parfois je n'ose pas répondre parce que justement en tant que femme de médecin, je me dis "et si on me connaît » (Patient 6, hospitalised)

Research

- Centralise data (e.g. on symptoms): patients could decalre voluntarly their symptoms and evolution;

« Une base de données où toute personne qui a le corona au début puisse mettre ses symptômes. (…) si vous aviez dès le départ, donc sur base volontaire, on ne peut pas forcer les gens à le faire, sur base volontaire on mentionne tout ce qu'on a au fur et à mesure, je crois qu'on aurait une super belle base de données. (…) je trouve ça dommage qu'on n'ait pas connecté cette information. (…) l'idéal ce serait de commencer au début, au moment où on a les symptômes. Si

on nous proposait d'aller sur cette base, ceux qui ne veulent pas n'y vont pas, mais si on nous proposait, moi je pense que la plupart des gens seraient favorables ! Et bon quelque part, ça permet d'avoir un historique des choses, je sais bien que c'est sur base volontaire mais enfin quand on voit le nombre de personnes qui ont eu le corona, ça nous permettrait plus facilement de, ben de voir des profils, peut-être que c'est... Je ne sais pas moi, la succession de mes symptômes qui est la même chez un certain nombre de personnes quoi, des choses comme ça (…) Maintenant, c'est un peu tard à moins qu'on prévoit une troisième vague [rires] » (Patient 32, not hospitalised)

- Research on the causes, the diagnosis and the treatment of long COVID;

« Il est réellement temps de mettre les bouchés double sur un traitement ANTI VIRAL en utilisant des molécules existantes ou en regardant ce qui se fait déjà dans d'autres pays qui ont des résultats dans les soins ! » (Forum)

- Research on classification of the symptoms according to the evolution of the disease;
- Research on specific cases (children, family, serious cases).

« Il est GRAND TEMPS de faire une ETUDE sur les enfants ! Désolé, mais je suis plus inquiet des effets à long terme sur les enfants porteurs de ce virus que des parents COVID long !!==> VACCIN ENFANT - A revoir totalement ! (ou à commencer à étudier...) » (Forum)

« Peut-être qu'il y a un facteur que les scientifiques pourraient relever, pour essayer de comprendre pourquoi est-ce que mes filles et moi, on a eu ça, et pas mon mari. Est-ce qu'il n'y a pas quelque chose dans les gênes. » (Patient 27, hospitalised)

Work

- Authorise teleworking;

« Je pense que certains métiers ou il est possible de travailler de la maison, et en fonction de la catégorie de la gravité, il faudrait instaurer et laisser la possibilité au malade de travailler de la maison de manière flexible. » (Forum)

- Adapted tasks to enable a return to work.

Quality of care

- Assess satisfaction regarding the physicians.

« Instaurez un systèmes de quality of services comme dans le privé. Une société indépendante fait des samples de satisfaction de la prise en charge des patients (client dans le privé) et vous aurez un bulletin par médecin. Les gens répondent honnêtement, s'il y a des feedback négatifs, ça ne doit pas être pris comme un blâme. Mais une source d'information qui permettrait aux médecins de se remettre en question. Dans le privé, on appelle ça le continuous service improvement (amélioration du service continu) Ça existe en médecine ? Alors pourquoi pas?" (Forum)

5 LIMITS OF THE QUALITATIVE APPROACH

As usual, this chapter is based on the experiences and opinions of the consulted long COVID patients.

We noticed that a large proportion of the participants to the interview are working in the healthcare sector. This is partly due to our channels of recruitment (cf limitation of the survey) and the fact that healthcare workers were also highly exposed (and affected) by COVID-19. Nevertheless, it might also be due to the way we selected patients. We developed a programme to select people at random from each segment of the list of participants which volunteered to participate. This selection process already started before the survey was closed. Since caregivers were the first to be participate on the survey they had a greater chance of being drawn than participants that participated at a later stage. We therefore tried to balance this by replacing drop-outs primarily with caregivers, with a preference for parents who had responded in their child's place or respondents with a lower socio-economic profile. Because we did not had ti select participants to the forum, this aspect was not an issue for this part of the qualitative data collection.

The final sample is nevertheless biased a little with more experiences of respondents with middle and high socio-economic status.

Another limitation is that we excluded patients who had a stay in intensive care in order to deepen the experience of long COVID without confusion with a PICS. In order to allow to a maximum of people to participate in the forum, we did not made this exclusion. In consequence it was difficult to exactly know if patients were talking about specific long COVID problems or PICS problems.

In the forum, it was also difficult to make a distinction between experiences related to acute COVID and those to long COVID. This was complicated by the fact that people reacted slowly or not at all to clarification questions launched by the moderator.

Finally we noticed that the interaction we expected from the forum format at the start was not sufficiently reached. A hypothesis is that topics were consensual and in consequence do not invite to react.

CHAPTER 6. OVERVIEW OF EXISTING INTERVENTIONS IN THE BELGIAN HEALTH CARE SYSTEM

1 KEY POINTS

GENERIC MEASURES OF HEALTH INSURANCE

- **All long COVID patients (will) benefit from the 4 types of Maximum Billing when criteria are met. Patients can directly ask their sickness funds for a reassment of their situation in case of change in the household income in order to benefit from an increased maximum billing.**
- **Among the long COVID patients, some of them could be granted the statute "chronic disease patient" *(statut affections chroniques / statuut chronische aandoening)* if they:**
  - ***have a minimum of health expenditures during the 2 last civil years OR**
  - ***benefit from the fix-payment for chronic diseases and have reached a threshold of personal contributions to health care**
- **Several measures allow the general practicioners and medical specialists to care for complex patients in the current nomenclature.**
- **Despite their potential to cover complex needs through a multidisciplinary approach, conventions are not accessible to all patients since there are specific criteria the patient should meet to be eligible for the convention. In practice, only a minority of long COVID patients could enter a convention.**

RESPIRATORY DIMENSION

- **Short-term oxygen therapy is offered to patients with acute hypoxaemia for a period of 3 months. Oxygen is delivered by the community pharmacist. Due to special COVID measures, patients can receive oxygen therapy for 9 months through the short-term scheme (normally 3 months).**
- **Long-term oxygen therapy will only concern long COVID patients with severe respiratory sequels.**

- **Home assistance for ventilation conventions will only concern long COVID patients with severe respiratory sequels.**
- **The convention Rehabilitation for severe chronic respiratory problems has a therapeutic offer corresponding to the needs of long COVID patients whose main symptoms concern the respiratory system. The multidisciplinary character of the convention allows for a proper identification of the needs and a comprehensive support of the patients, including for psychological and social dimensions. The inclusion criteria are therefore restrictive and only a very small minority of long COVID patients might be eligible.**

MUSCULOSKELETAL DIMENSION

- **All long COVID patients could benefit from at least 18 physiotherapy sessions per year (*courante pathologie*/ *pathologie courante*). However, the complex nature of long COVID may require a higher number of sessions per year in congruence with 'severe disorders' (pathologies on the List E) or 'acute / chronic disorders (pathologies on Lists Fa/Fb).Currently, long COVID patients are only eligible for a higher number of physiotherapy sessions as defined for the List E, List Fa, List Fb, if they comply with specific inclusion criteria.**
- **Long COVID patients could benefit from the K nomenclature (physical medicine and rehabilitation), especially for those who have been hospitalised, during their hospital stay or after being hospitalised if their treating physician attests the need for specific rehabilitation. K nomenclature is available in a large number of hospitals, making it accessible to a large number of patients during a hospital stay or as part of an ambulatory treatment.**
- **No limitative list exists for K20/K15 (maximum 48 sessions: K20: 18 sessions followed by K15: 30 sessions) making it accessible for long COVID patients.**
- **Access to the multidisciplinary rehabilitation under the K nomenclature is restricted to some pathologies listed in the Article 23§11 of the nomenclature. Long COVID patients could be eligible if they have the following health conditions:**
  - **code 301 myopathy with clear change in functional capacity (K60 – 120 sessions),**
  - **code 202 polyneuropathy with modification of the functional autonomy (K60- 120 sessions)**
  - **or code 504 pulmonary rehabilitation for obstructive or restrictive respiratory deficiency with a FEV below 60% and/or attested desaturation (K30-60 sessions).**
- **Sp services are specialised in the treatment and rehabilitation of patients with cardiopulmonary (Sp1), locomotor (Sp2), neurological (Sp3), psycho-geriatric (Sp6) and chronic (Sp5) conditions and are accessible after a hospitalisation.**
- **In principle, the convention 950, 951 and 771 could be open to long COVID patients under the conditions they fit the inclusion criteria: these criteria are restrictive and the number of centres is limited.**
- **Support from an occupational therapist is possible after a stay in a rehabilitation centre 950, 951 or 771 or via the sickness funds of the patients: in practice, this is likely to concern a limited number of long COVID patients.**

NEUROLOGICAL DIMENSION

- **The nomenclature only plans the reimbursement of a neuropsychological assessment as part of a diagnosis of dementia: long COVID patients are thus not eligible for this assessment, except in the context of an exclusion diagnosis (e.g. a patient for whom a differential diagnosis may be needed).**
- **Assessment of cognitive fonctions may occur in the framework of a rehabilitation program (K nomenclature; conventions 950 and 771; CAR/CRA: however not all centres offer such an**

assessment. To be eligible, patients should fulfill specific criteria.

- In principle, long COVID patients could access 950 conventions or 771 conventions if their sequels correspond to the inclusion criteria. These criteria are therefore restrictive and the final decision will remain the responsibility of the advisory physician of the sickness funds.
- The current offer for Chronic Fatigue Syndrome includes a multidisciplinary diagnostic assessment, organised in only one centre. After a diagnosis of CFS made by the reference centre, patients have access to the cognitive behavioural therapy with therapists having concluded a specific agreement with the NHIDI (limited offer). No specific offer of physiothapy exists for patients with a Chronic Fatigue Syndrom.
- Long COVID patients with persistent pain could benefit from the List Fa, if the pattern of their COVID related chronic pain is similar to a complex regional pain syndrome and motor deficit due to polyneuropathies; from the K nomenclature, if the chronic pain requires multidisciplinary rehabilitation therapy; or from the regular physiotherapy sessions. Those with the most severe form might benefit from the services organised in reference centres for chronic pain under the authority of the FPS Public Health. There is however no information about the inclusion criteria for these conventions.

CARDIAC DIMENSION

- The convention for cardiac rehabilitation is focused on specific cardiac pathologies: only long COVID patients with severe cardiac complications may benefit from this convention.

MENTAL HEALTH DIMENSION

- Long COVID patients aged of 15 years and more can benefit from the 8 individual reimbursed sessions with a clinical psychologist per year. For those in need for specialised psychological care, a maximum of 20 sessions is reimbursed per year. Specific measures are also reimbursed for children and adolescents until 23 years old.
- Long COVID patients can consult a psychiatrist on their own initiative and will be reimbursed according the nomenclature.
- Long COVID patients have right to a physiotherapy prescription for relaxation therapy (part of 18 reimbursed sessions a year).
- Post-traumatic stress disorder is only covered and managed within the framework of the national health insurance in a very limited way. For long COVID, it implies that patients can only be assisted through consultations with a psychiatrist, the consultation being reimbursed as part of the national health insurance.
- Support groups and patient platforms play a role in the social support of patients and their relatives: besides the role played by the Ligue des Usagers des Services de Santé (LUSS), the Patienten Rad und Tref (PRT) and the Vlaamse PatientenPlatform (VPP) at policy level, numerous support groups have been launched at the initiative of patients or health care professionals.

SOCIAL DIMENSION

- Social services of the hospitals, the sickness funds and the CPAS-OCMW could provide social support to long COVID patients.
- Three actors play a major role in supporting the return to work of patients: the advisory physician, the occupational physician and the controlling physician 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, the reinsertion trajectory and the reintegration trajectory constitute a formal mechanism to support the return to work.

- **The general measures for employees and self-employees apply also for long COVID patients.**
- **COVID is acknowledged as a professional disease for the professionals of the health care sector. Other professional categories could also benefit from this acknowledgement under specific conditions.**
- **So far, there is no specific guidance for long COVID patients returning to work in Belgium**

2 INTRODUCTION AND OBJECTIVES

Patients experiencing long COVID have to cope with a wide range of symptoms and complaints, whose magnitude and severity vary from one patient to another (see Chapter 2).

Although the combination of these symptoms and complaints is quite specific to long COVID, these are, in general, not unique and could potentially already be managed by the current Belgian health care system, within the current framework of the national health insurance.

This chapter has two main objectives:

- To provide an overview of the existing benefits for patients with persisting health problems
- To describe the existing interventions and health care programs likely to cover (part of) the needs of (part of) long COVID patients as identified by the literature review on the pathophysiology of long COVID. We hypothesise that some interventions could already include these patients, with or without adaptations of the current nomenclature or could serve as a model to develop new interventions to deal specifically with long COVID.

Patients who stayed for more than 7 days under respiratory assistance in intensive care units are at-risk of developing a Post-Intensive Care Syndrome (PICS): PICS is not specific to COVID-19 and is the topic of another KCE study [200, 201].

In this chapter, we aim to identify both health care interventions but also interdisciplinary / multidisciplinary assessments that could support the evaluation about the most appropriate health care delivery for long COVID patients.

3 METHODS

We conducted a systematic search of the health care nomenclature and the documents produced by the National Institute of Health and Disability Insurance (NIHDI) to get an overview of the reimbursed health care services corresponding to the different dimensions of long COVID. These dimensions were previously identified via a scoping review (see Chapter 2). As long COVID is complex and concerns a wide range of symptoms, this report focuses on the most frequently reported complaints in the literature: respiratory complaints, musculoskeletal complaints, general fatigue, neurological and cognitive complaints (including taste and smell disorders) and mental health distress. A specific section was also elaborated about the existing measures supporting the return to work as this problem was highlighted by the patient associations. When deemed necessary, clarification questions were sent to the NIHDI.

In addition, experts and/or practitioners who could provide concrete insights into one or more aspects of long COVID were contacted. These people were identified either through their participation in a previous KCE project, or through the team's network of personal contacts, or through a recommendation from a previously contacted person. Although the number of patients that report to suffer from long COVID increases, specific interventions and initiatives are still scattered and not well known, which limits the identification of experts. Besides, due to the recent nature of this medical condition, there is a lack of data about the effectiveness of the interventions for long COVID patients. A common guide, adapted to the field of expertise of the person contacted, was used for each interview by video-conference. Thirteen interviews were conducted between February and July 2021. When deemed necessary, clarification questions were sent to the NIHDI and several meetings were organised with NIHDI experts. The full list of participants is mentioned in the colophon of this report.

4 GENERIC MEASURES FOR (CHRONIC) PATIENTS

4.1 Basic principles[j]

The compulsory health insurance is managed by the NIHDI, which allocates a prospective budget to the sickness funds. Sickness funds are non-profit, private players that operate the reimbursement system of health care services covered by the compulsory health insurance for their members and the payment of a replacement income in case of long-term illness. All Belgian residents[k] must be affiliated to a sickness fund of their choice or to the public auxiliary fund[202]. In addition, Belgian residents can also take out voluntary health insurance for services that are only partially covered, or are not covered, by the compulsory health insurance (for example, for extra-billings when patients opt for a single room in hospitals). Voluntary health insurance is provided by both non-profit-making mutual insurance companies and sickness funds, and by private for-profit insurers[202]. Compulsory health insurance covers 99% of Belgian residents for a large range of services and with no selection based on health risks[202].

Almost all reimbursed services are described in the nationally established fee schedule (called the nomenclature), which specifies the official fees and cost-sharing mechanisms determined through conventions and agreements negotiated yearly or every 2 years between representatives of sickness funds and health care providers[l]. Reimbursement decisions are based on criteria such as the therapeutic added value of the intervention and the budget impact. Evidence-based practices with a high therapeutic value are preferably reimbursed, whereas comfort or aesthetic services, such as plastic surgery and orthodontics, are only reimbursable under certain conditions (for example, breast reconstruction after cancer). When looking

j This section is retrieved and adapted from the Health in Transition Report of 2020 with the authorisation of Sophie Gerkens.

k Exceptions exist for both Belgian and non-Belgian residents but are out-of-the-scope of this report.

l Some reimbursed services such as the conventions are outside the nomenclature (see 4.2.5 for details).

at patients' out-of-pocket payments, reimbursement is more limited for mental health care and for dental care compared with other care services. To avoid overconsumption and promote the responsible use of public money, the large majority of patients have to pay in advance the fees for services and then request reimbursement from their sickness fund. Initially, a third-party payment system (where sickness funds directly pay their share) was only applied for the purchase of prescribed medicines and hospital/residential care, but this is being gradually extended to primary care (currently for vulnerable social groups and chronic patients)[202].

The provision of care is based on the principles of independent medical practice, direct access (no gatekeeping), free choice of physicians and of health care facilities (including hospitals), and predominantly fee-for-service payment (although in recent years, the use of fixed payments has increased). Reimbursed health care services are provided by both public and private institutions and individual health care providers who mainly comply with the same set of rules, enjoy the same therapeutic freedoms and offer the same services. Patients are free to choose their health care providers and can access most of the specialised and inpatient care without prior assessment by a general practitioner (GP)[202].

4.2 Universal and supplementary measures

Table 55 provides an overview of the protection measures included in the national health insurance. Universal measures are accessible to all persons benefiting from the national health insurance, independently of their level of income or social situations. This means that all these measures are accessible to long COVID patients. Additional measures aim to prevent the financial risks related to the disease and disability. These are conditioned by the financial situation of the patients.

Table 55 – Overview of financial facilities to cover health care expenditures[m]

Overview of financial facilities to cover health care expenditures
Universal basic measures - *Maximum Billing*: guarantee that he household will not pay more than a maximum amount per year for its health care use (see 4.2.1 for details) - *Global medical record* (DMG/GMD): increased reimbursement for a consultation with a GP when a DMG/GMD is open by the GP - *Gatekeeping*: reduction of fees in specialty medicine if the referral to a specialist is made by a GP - *Third payer*: payment only of the medical expenses remaining to be paid by the patient, in particular during hospitalisation or at the pharmacy. - *Consultation with a health care provider who agrees with the NIHDI on tariffs* "professionnel conventionné / geconventioneerde zorgverlener": guaranteed payment of the official rate when consulting with a physician, dentist, physiotherapist, etc. - *Care for type 2 diabetes or chronic renal failure*: full reimbursement of consultations with the GP and the specialist in the pathology concerned. This applies solely to patients who have concluded a *care pathway contract* with their general practitioner and specialist doctor and who, at the time they concluded that contract, fulfilled specific conditions (e.g. being treated with 1 or 2 injections of insulin or incretin mimetics per day or considering such treatment for patients who are still being treated with oral antidiabetics). - *Chronic disease status* " (*statut affections chroniques / statuut chronische aandoening*): granting of third-payer payment or a reduction in the maximum annual amount within the maximum billing for patients with a chronic condition (see 4.2.3 for details) **Additional measures, depending on the patient's financial situation** - *Increased intervention* (*intervention majorée / verhoogde tegemoetkoming*): reduction in the amount of medical costs to be paid by the patient - *Social maximum billing*: guarantee that the household will not pay more than a maximum amount per year for its health care (see 4.2.1 for details). - *Social third-party payment*: the patient pays the GP only the part of the costs he/she has to pay. The sickness funds pays the health insurance contribution directly to the GP. This mechanism is reserved for certain categories of beneficiaries. **Exceptional measure via the** Special Solidarity Fund In the case of medical services not reimbursed by the health care insurance, under specific conditions, reimbursement for: - Rare indication for the prescription of the service - Rare disease - Rare disease requiring continuous and complex medical care - Medical device and/or a service which is an innovative medical technique (excluding medications) - Child with a chronic disease requiring treatment - Care provided abroad - Unmet medical need (only for reimbursement of medications)

[m] Table adapted from the NIHDI website.

4.2.1 System of Maximum Billing

Since 2002, a system called 'Maximum Billing' (*maximum à facturer MAF / maximumfactuur MAF)* was installed in addition to the system of the preferential reimbursement levels. The Maximum Billing is set according to the family's net income, such that each household has a maximum annual out-of-pocket maximum for all "necessary health care expenses". As soon as expenses reach the set ceiling, any further health care costs are fully covered by the sickness funds for the remaining part of the year. The Maximum Billing cover the following health care costs:

- Personal contributions for the health care expenses, up to the officially agreed fees, relating to physician consultations and visits, and those relating to all technical treatments by GP and/or specialists, physiotherapists, nursing staff and paramedics;
- Personal contributions for the health care expenses relating to necessary pharmaceuticals (i.e. categories A, B and C) and personal contributions towards costs for pharmaceuticals in hospitals;
- Personal contributions towards the per diem rate paid for inpatient care, limited to the first year in a psychiatric hospital;
- Personal contributions related to certain types of expensive medical devices.

There are four types of Maximum Billing:

- *Social Maximum Billing (MAF social / sociale MAF)*: a threshold is applied at the household level for specific vulnerable groups; it is applicable to most of households with preferential reimbursement; as soon as the limit is exceeded, the co-payments are reimbursed. The total ceiling of the household that benefits from the increased intervention is 450 EUR (fixed threshold).
- *Maximum Billing for children*: the lower threshold is applied at the level of the child; all children under 19 years with total co-payments exceeding the threshold become individually entitled without taking into account family income (650 EUR);
- *Income Maximum Billing (MAF revenus -inkomens-MAF)*: the principle of Maximum Billing is applied in a gradual way according to net family income (calculation based on 2 years ago). Due to the COVID-19 pandemic and COVID-related work incapacity, the net family income of numerous households has been negatively impacted and has consequences for determining the income Maximum Billing. If, the household income falls below one of the two lowest ceilings (for example due to a long period of unemployment or incapacity for work), the patient can ask his/her sickness funds to re-examine the application on the basis of the current income and possibly adjust the threshold.
- *Maximum Billing for Chronically Ill Patients (MAF pour les malades chroniques- MAF chronische zieken)* the total threshold is reduced by EUR 100 (indexed amount) for a year x if either the total of the shares of the costs (co-payments) of one of the members of the household amounted to at least EUR 450 (indexed amount) per year during the 2 previous calendar years or a member of the household has been granted 'chronic status' during that year x. This reduction applies to the three Maximum Billing above.

All Long COVID patients (will) benefit from the 4 types of Maximum Billing when criteria are met.

Patients can directly ask their sickness funds for a reassessment of their situation in case of change in the household income in order to benefit from an increase maximum billing payment.

4.2.2 Increased reimbursement

Increased reimbursement (*intervention majorée / verhoogde tegemoetkoming*), also called preferential regimen (*régime préférentiel / voorkeurregeling)* allows patients to pay less for some specific services (consultations, medications, hospitalizations…).

Benefiting from majored intervention is automatically granted to persons who benefit from a social integration income via the CPAS-OCMW (for at least 3 months), or a guaranteed income to elders, or an allowance for disabled persons via the Federal Public Service Social Security. The majored intervention is automatically to children with a recognized handicap of at least 66%, unaccompanied minors and for orphans of mother and father.

Other categories of persons could also benefit from the majored intervention but have to apply for it to their sickness funds. Two situations exist.

The first situation concerns the following social situations : the patient is widow(er), or invalid, or retired, or recognised as a disabled person, or completely unemployed or unable to work for at least one year or in a single-parent family. In this case, the current household income must be below an annual ceiling set according to the number of people in the household.

The second situation concerns patients who are not in one of the precited social situations. They may still apply for the majored intervention on the sole basis of their financial situation. Again, the total household income must be below an annual ceiling set according to the number of people in the household.

Details about the majored interventions could be found on the NIHDI website and on the websites of the different sickness funds.

4.2.3 A specific statute for persons with a chronic disease

According to the Royal Decree of December 15, 2013 enforcing the Article 37vicies/1 of the Law of July 1994 on the national health insurance, patients with a chronic disease could benefit from the statute **"**chronic disease patients". This statute aims to facilitate access to care through a third-party payer system and a specific system of Maximum Billing (described above). Three categories of patients could benefit from this statute "chronic diseases patients" (*statut affections chroniques / statuut chronische aandoening*).

The first category is patients reaching a defined threshold of health expenditures (including the interventions of the sickness funds and the patient personal contributions but not the extra-billings) per quarter for eight consecutive quarters (= corresponding to two civil years).

The second category is patients who already benefit of fixed payments for chronically ill patients *(intervention forfaitaire pour malades chroniques/ forfait voor chronisch zieken)*. These patients are eligible for the statute "chronic diseases patients" if their personal contributions exceed a defined amount (=similar mechanism than the Maximum Billing). The fixed payment for chronically ill patients is automatically granted by the sickness funds to patients who meet the following criteria related to a dependence situation and not to a specific disease (the amount of the financial intervention depending on the condition):

- Patients with agreement of the advisory physician of the sickness funds for a 6-month physiotherapy treatment because of a chronic and severe pathology (= the so-called List E – see section 6.1 for details) OR
- Patients who benefit from majored family allowances, integration allowances, allowances for elders or for handicapped persons (whose degree of autonomy has been fixed at least 12 points under the terms of the Law of February 27, 1987), allowance for a third party as defined by the Law of June 27, 1969, or allowance granted to the holder with family responsibilities because of the need for the assistance of a third person or a flat-rate allowance for the assistance of a third person OR

- Patients being hospitalised for a least 120 days during the last 12 months or being admitted at least 6 times during the same period[n] OR
- Patients benefiting from a fix-payment for nursing care type B or C for at least a 3-month period. A fix-payment type B corresponds to patients with a dependence score of 3 or 4 in the dimensions “Hygiene” and “Getting dressed”, a dependence score of 3 or 4 in the dimensions “Mobility” or “Going to the bathroom”, and a dependence score of 3 or 4 in the dimensions “Incontinence” or “Alimentation” on the Katz Scale[o]. A fix-payment for nursing care type C is granted to patients with a dependence score of 4 in the dimensions « Hygiene”, “Getting dressed”, “Mobility” or “Going to the bathroom”, and a dependence score of 3 or 4 in the dimensions “Incontinence” or “Alimentation” (at least one of the dimension should have a value of 4 and the other at least a score of 3). For the patient, it implies a nurse visit twice or three times a day and, at least, a daily grooming.

The third category is for patients with a rare disease (one patient out of 2000) whose personal health care expenditures reach a defined threshold (including the interventions of the sickness funds and the patient personal contributions but not the extra-billings) per quarter for 8 consecutive quarters (= corresponding to 2 civil years).

Among the long COVID patients, some could be granted the statute “chronic disease patient” if they:

- **had to cover a defined amount of health care expenses during the last 2 civil years OR**
- **had to cover a defined amount of personal contributions to health care AND are in the conditions to benefit from the fix-payment for chronic diseases:**
  - **benefit from a 6-month physiotherapy treatment for a pathology of the List E (severe and chronic diseases) OR**
  - **benefit from specific social allowances OR**
  - **hospitalisation for a least 120 days or had at least 6 hospitalisations in 12 months’ time OR**
  - **benefit from a fix-payment for nursing care type B & C for at least a 3-month period: this is likely to concern (older) patients who were severely impacted by the COVID and/or had pre-existing health conditions leading to increased dependance for their daily activities.**

4.2.4 *Specific benefits for physicians facing complex patients*

For the GP, the nomenclature plans a supplementary fee for an “unusual” consultation, i.e. the first consultation or visit by the GP coordinating the global patient record when the patient aged of 75 and older is returning home after a hospital stay of at least 14 days (codes 101032, 101076 for consultations; codes 103132, 103412, 103434 for a visit). This consultation or visit should aim at explaining and planning the follow-up of the patients.

GP could also attest for a supplementary fee when visiting a patient at the hospital, once a week, with the obligation of reporting the results of the concertation with hospital specialist in the patient medical record (code 109273).

In situations where the patient is staying at home and is expected staying at home for at least one month with a diminution of physical autonomy, a multidisciplinary concertation could be organised between heath care professionals and caregivers in the framework of an integrated health care service at home (Royal Decree of May 14, 2003 on the conditions for the

[n] See the website of the NHIDI for more details.

[o] The Katz Scale is an assessment scale of the degree of dependency of a patient in 6 dimensions of the daily activities. https://www.inami.fgov.be/fr/professionnels/sante/infirmiers/soins/Pages/echelle-evaluation-katz.aspx

delivery of benefits as defined in the article 34, 13° of the law on compulsory health insurance of July 14, 1994). This could be organised maximum 4 times a year and should involve at least 3 health care providers among which the GP and the home nurse when the patient benefits from such services. The patient (or his/her representant) should also attend the concertation. This concertation aims at establishing a health care plan for the patient and, to this aim, should use a validated assessment tool.

The code 102223 involves the multidisciplinary geriatric assessment of the patient by the geriatrician, with report to the GP. This assessment should include a functional, physical, mental and social assessment, through validated tools. This is therefore limited to patients aged of 75 years and older.

For all patients, specialists in internal medicine could attest a code 102955/102970 for a first consultation with examination on the basis of the existing elements in the medical file of a patient presenting a complex pathology without a precise diagnosis and for which treatment has not given sufficient results.

The nomenclature also includes specific fees in some specialities for the coordination and/or the multidisciplinary concertation such as the code 350276 for the multidisciplinary concertation in oncology (follow-up concertation) as attested by the coordinating physician or the code 477724 corresponding to the coordination of the diagnosis and treatment plan by a multidisciplinary team caring for a hospitalised patient with a stroke.

Among the general special services, the nomenclature includes the possibility for a specialist in medical oncology of having a consultation of at least 30 minutes (see Royal Decree October, 5 2018 (in force December 1st, 2018) with erratum December 6, 2018– codes 350070 & 350092). However, only patients who had benefited of an intervention of a limitative list (see the Supplement to Chapter 6 for the content of the limitative list).

Several measures allow the general practicioners and medical specialists to care for complex patients in the current nomenclature.

4.2.5 *Conventions[p] with the NIHDI*

A convention is a financing method used in the Belgian health care system that allows certain care to be financed by means of a single lump sum related to a specific condition/problem. Conventions are concluded between the NIHDI and health care institutions, which must comply with certain conditions. They are drawn up, concluded and managed by the NIHDI Board of Directors, which includes the medical directors of all the sickness funds. The content of the conventions may vary, but they all include conditions relating to their duration, management, multidisciplinary team, patients, financial means, and more and more also clear evaluation criteria. The KCE report 299 distinguished 5 types of conventions [203, 204].

- Conventions focused on providing classic rehabilitation services;
- Conventions focused on providing multidisciplinary care ('case management'), e.g. convention for diabetes;
- Conventions focused on providing multidisciplinary diagnosis and support, e.g. convention for memory clinics;
- Conventions focused on providing multidisciplinary counselling, e.g. convention for female genital mutilations;
- Outliers that do not fit in either of the previous groups, e.g. abortion clinics.

The full list of conventions could be found in the Supplement to Chapter 6.

p "Convention" should be understood as "contract".

Cumulative restrictions are included in each convention. However, the advisory physician is free to authorise cumulating when the conventions do not cover the same pathological areas: for example, it would be possible to cumulate a locomotor/neurological rehabilitation programme with an oxygen therapy or respiratory assistance programme. Besides, some conventions are compatible with the K nomenclature that is the nomenclature on rehabilitation care under the supervision of a specialist in physical medicine and rehabilitation. Some of the possibly relevant conventions for long COVID patients are detailed in the following sections.

Despite their potential to cover complex needs through a multidisciplinary approach, conventions are not accessible to all patients since there are specific criteria the patient should meet to be eligible for the convention: in practice, only a minority of long COVID patients could enter a convention.

5 RESPIRATORY DIMENSION

Regarding respiratory diseases, in addition to the interventions included in the nomenclature (e.g. consultations with a specialist in pneumology or sessions with a physiotherapist – see also section 6.1), the NIHDI covers the following specific programs for the general population: short term oxygen therapy, long-term oxygen therapy, support for sleep apnoea, mechanical ventilator assistance at home, functional rehabilitation and personalised care for those suffering of chronic asthma. Patients suffering from a rare or a severe chronic disease, as cystic fibrosis, are covered by other programs such as a specific convention or the “List E” (see section 6.1 for details).

5.1 Short term oxygen therapy

Patients needing oxygen for less than 3 months per year could benefit of the short term oxygen therapy, prescribed by any physician. The 3 months of treatment could be either consecutive, either three distinct periods of 1 month.

Target groups

Short-term treatment with oxygen can be prescribed in 3 situations: acute hypoxaemia, hypoxaemia in palliative patients and cluster headache.

In case of acute hypoxaemia, the prescribing doctor must apply to the advisory physician of the sickness funds for authorisation of reimbursement for both gaseous oxygen and an oxygen concentrator. There is no standard form for the application for reimbursement. In the application, hypoxaemia must be clinically documented. For this reason, the application should include the following:

- the type of oxygen therapy desired (gaseous oxygen or oxygen concentrator)
- AND the diagnosis of the condition causing the acute hypoxaemia (e.g. COPD, chronic heart failure, etc.)

- AND a description of the complaints that are indicative of such a condition (e.g. cyanosis, tachypnoea, etc.)
- AND/OR the results of recent saturation tests

In addition, the patient must have a monthly prescription for a maximum of 1 month each, with the following elements: oxygen gas according to the international non-proprietary name, the dosage (in litres per minute and number of hours per day) and, if applicable, the oxygen humidifier or the use of an oxygen concentrator.

Other rules for the prescription apply for palliative care patients and patients with a cluster headache.

Provision of oxygen

Oxygen (and oxygen concentrator) is delivered by the community pharmacist, the hospital pharmacist only for patients living in "community" (nursing homes, psychiatric home) or directly by the oxygen supplier after concertation with the community pharmacist or the hospital pharmacist.

Reimbursement rules

Medical oxygen and the oxygen concentrator are reimbursed under category A according to rules of prescription. There is therefore no cost to the patient for the oxygen as such. The sickness funds pays the pharmacist, the hospital pharmacist or the supplier via the pharmacist:

- the flat rate for the installation and the intervention of the sickness funds for the rental of the gas cylinder and the oxygen concentrator
- accessories and possible oxygen humidifier

The (hospital) pharmacist also receives a lump sum for coordinating the pricing and accompanying the treatment with gaseous oxygen or the oxygen concentrator.

If the delivery is made by a supplier who charges more than the maximum amount of the sickness funds contribution for the rental of the gas cylinder, accessories and any oxygen humidifier, the pharmacist or hospital pharmacist may charge the patient a supplement for these items; this supplement may not exceed 20% of the maximum amount of the contribution.

Specific measures during the Covid pandemic

For gaseous oxygen and oxygen concentrators, if the current authorisation expires, it is automatically extended by 2 months and allows reimbursement for up to 9 one-month periods, to defer the switch to long-term oxygen therapy if necessary.

Interchangeability of authorisations/approvals issued by advisory physicians for oxygen therapy: an authorisation/approval given for one type of oxygen therapy is also valid for another type of oxygen therapy. These provisions take effect on 1st April 2020 and apply until the end of the crisis.

From February, 12.2021 a number of new oxygenators are reimbursed (see the Royal Decree of 26 January 2021 - updated to 1st June 2021). They complete the series of oxygen concentrators that were already reimbursed.

- **Short term oxygen therapy is offered to patients with acute hypoxaemia during a period of 3 months. Oxygen is delivered by the community pharmacist.**
- **Due to Covid special measures, patients can receive oxygen therapy for 9 months through the short-term scheme (normally 3 months).**

5.2 Long-term oxygen therapy (convention 781)

Patients suffering from **severe chronic respiratory insufficiency** could benefit from the convention for long-term oxygen therapy at home. In the case of patients with a long COVID, this convention will be more beneficial to those having been under mechanical ventilation or intubation during their hospitalisation and/or suffering from a PICS [200]

Target groups

Three target groups are identified in the convention with strict inclusion criteria. The full list could be found in the Supplement to Chapter 6. Besides, depending on the target group, extra support could be provided as portable oxygen concentrator.

Requirements for the hospital team

This convention is concluded with hospital pneumology departments. It covers the supply and monitoring of oxygen concentrators and their accessories for a period of more than three months to patients living in their own home, of relatives or of a person close to them. It also covers the provision and monitoring of oxygen therapy in the following places: nursing homes, rest and care homes, psychiatric care homes, day care centres, residences for children, young people or disabled people approved by the federated entities (semi-boarding schools, medico-pedagogical institutes), protected housing initiatives, convalescent homes, psychiatric hospitals and functional rehabilitation centres.

Content of the convention

The hospital undertakes to provide 24-hour medical and technical care, with a response within 3 hours in the event of a technical incident. The convention also includes the training of the patient and his/her relatives in the management of oxygen therapy. The GP and the pharmacist are informed and involved in part of the monitoring and follow-up of the patient under oxygen therapy. The convention also includes a fix-payment for the electricity.

Centres included in the convention

A large number of hospitals offer support for long term oxygen therapy. The full list could be found on the NIHDI website[q].

Long-term oxygen therapy will only concern long COVID patients with severe respiratory sequels.

5.3 Convention for ventilator assistance at home (convention 7852)

The convention for home-based ventilator assistance (*assistance ventilatoire à domicile AVD / ademhalingsondersteuning thuis AOT*) - long term – covers several forms of respiratory impairments such as patients with or without a tracheostomy, patients whose alveolar hypoventilation is related to a restrictive respiratory condition of pleural, pulmonary, neuromuscular or skeletal origin, or an obstructive respiratory condition and who are tracheotomised or patients suffering from obesity-hypoventilation syndrome. Supplement to Chapter 6includes the full list of inclusion criteria for long term ventilator assistance at home by type of assistance. Access to the AVD/AOT convention is subject to a prescription from a specialist doctor (pulmonologist or paediatrician) and the agreement of the advisory physician of the sickness funds. The detailed conditions and patient profiles could be found on the NIHDI website

Any reimbursable AVD/AOT includes long-term, comprehensive and coordinated care under the shared medical responsibility of the centre's prescribing doctor, the GP and the referring specialist (Article 5 of the convention). The interdisciplinary team is composed of 2 specialist doctors with experience in ventilation and AVD/AOT, nurses and staff specifically trained to manage the technical aspects of the equipment. The team is responsible for the rental and monitoring of the respiratory assistance equipment, including therapeutic education of the patient and the training of his/her relatives (family members or health care professionals). Within the framework of the convention, the partner centre undertakes to provide a 24-hour on-call service. The institution collaborates with the referring medical specialist for the follow-up of the patients: follow-up includes consultations and measures of the gazometry (Article 14 of the convention).

[q] Last update of the webpage: 2 July 2018

The current AVD/AOT convention is concluded with 16 hospitals. A maximum of 21 AVD/AOT agreements can be concluded for the whole of Belgium (Article 34 of the convention).The list of the hospitals could be found on the NIHDI website.

Home assistance for ventilation conventions will only concern long COVID patients with severe respiratory sequels.

5.4 Convention rehabilitation for severe chronic respiratory problems (convention 7815)[r]

Eligibility criteria

This convention is aimed for patients suffering from severe respiratory diseases that would benefit from health care provided in functional rehabilitation facilities. The overall aim of the treatment is the reduction of the symptoms and the improvement of quality of life, including adherence to treatment and the adoption of health-promoting behaviours. This convention includes adults or adolescents over the age of 14, with chronic obstructive pulmonary disease (COPD), severe chronic bronchial asthma, other severe respiratory diseases (bronchiectasis, cystic fibrosis, etc.), who have undergone lung surgery, or who have been diagnosed with a lung disease, who have undergone lung volume reduction surgery for obstructive lung disease or thoracotomy; candidate for lung transplantation; with restrictive disease caused by interstitial disease / secondary to infections / secondary to neuromuscular disease or chest wall disease; or who have undergone lung transplantation. The underlying condition must be in a stable state, i.e. without periods of exacerbation that required intensive medical therapy.

In addition to these conditions, the patients (at the exception of patients with a long transplantation) have to be in a stable state, i.e. without periods of exacerbation requiring intensive medical therapy, and have:

- either a forced expiratory volume in one second FEV_1 of < 50% of the predicted value, measured in a stable state and, if part of the medical treatment, after bronchodilation;
- OR a diffusion capacity of < 50% of the predicted value

They have also to comply with 2 out of the 5 following criteria:

- have inspiratory and/or expiratory respiratory muscle strength of less than 70% of the normative mean value (see the annex of the convention for details)
- have a quadriceps strength of less than 70% of the predicted value determined by the formula: FQpred = 124 - [2.21*age] + [1.78*body weight] + 55.9 (= _ only), where FQpred = n. Newton-meters (Nm), age = n. years, body weight = n. kilograms
- in the cyclo-ergometry, achieve, due to his/her chronic respiratory condition, a maximum performance of less than 90 watts
- for beneficiaries over 50 years of age, result on the 6-minute walk test a distance (6MWD) of less than 70% of the value predicted by applying the formula: 6MWDpred = 484 + [3.5*height] - [4.9*BMI] - [5.3*age] + 52(= _ only) where 6MWDpred = m, height = cm, and BMI = weight/height2 = Kg/m2
- have a total Chronic Respiratory Disease Questionnaire (CRDQ) score of less than 100 for all dimensions: "dyspnoea", "fatigue", "emotions" and "control", or a score of less than 20 for the "dyspnoea" dimension

[r] Inrichtingen voor revalidatie van patiënten lijdend aan ernstige chronische ademhalingsstoornissen / Etablissements de rééducation Troubles respiratoires

Team prerequisites

Inside the centre, the multidisciplinary team consists of a coordinating physician specialized in pulmonology with additional certification in rehabilitation, a physician assistant in pulmonology; physiotherapists; and other professionals including occupational therapist, psychologist, dietician and social worker. The services can be provided on an outpatient basis or during a stay in the institution.

Accessibility to the programme

Access to the programme is conditional on a medical examination with the necessary technical examinations: some examinations may have been requested by a professional not belonging to the rehabilitation team (such as the GP). The agreement is given by the advisory physician of the sickness funds.

Content of the programme

Considering the patient's needs and preferences, the rehabilitation programme includes medical follow-up, therapeutic patient education and at least three interventions of the following disciplines: physiotherapy (muscle and exercise training, breathing rehabilitation, relaxation techniques), occupational therapy, psychology, social support and dietetics. The programme includes 60 sessions of at least 2 hours each over 6 months. Some of the sessions could be delivered at the patient's home. The centre could also organise group sessions for a maximum of 5 patients together. In case the group session targets patients and their relatives (e.g. for educational purposes) there is no maximum number of participants.

Collaboration with the rehabilitation team and the treating physician

The collaboration between the rehabilitation team and the treating physician (GP or a medical specialist) providing the follow-up treatment could consist either in the participation of the treating physician to a team meeting of the rehabilitation team where the functional rehabilitation programme and/or the preparation of the discharge are discussed; either in collecting the data necessary for an evaluation of the cost of the patient's consumption of health care services within the meaning of the Article 34 of the Law on national health insurance of 14 July 1994, before and after the end of the first functional rehabilitation programme, with a view to comparing them, and their transmission via a written report to the rehabilitation team (Article 12 §4). These services may be financed within two years of the first functional rehabilitation programme, according to nomenclature code 104355 (Article 13 §4).

Centres included in the convention

To date[s], only 4 hospitals are concerned by this convention (institutions with a 7815 code): U.Z. Gasthuisberg KUL (Leuven), U.Z. Gent, the Centre Hospitalier de l'Ardenne (Libramont) and the CHU de Liège. Despite a positive evaluation of the benefits of this convention on patients health and wellbeing, so far, no extra budget has been planned to expand the number of centres. At this stage, these conventions are still considered as “pilot projects”. The limited number of centres and the absence of a centre in the Brussels region limit the accessibility to these services.

The convention Rehabilitation for severe chronic respiratory problems has a therapeutic offer corresponding to the needs of long COVID patients whose main symptoms concern the respiratory system. The multidisciplinary character of the convention allows for a proper identification of the needs and a comprehensive support of the patients, including for psychological and social dimensions. The inclusion criteria are however restrictive and only a very small minority of long COVID patients might be eligible.

[s] Last update of the NIHDI webpage : July 2016

6 MUSCULOSKELETAL DIMENSION

The rehabilitation care covered by the national health insurance scheme can, in general, be divided in three main categories: care provided by physiotherapists (M nomenclature) prescribed by any GP or specialist; care provided under the supervision of a doctor specialising in physical medicine and rehabilitation (K nomenclature); and care provided under rehabilitation conventions with the NIHDI or with the federated entities.

Inpatient rehabilitation care is provided by both categorical (=hospitals with a single specialization in rehabilitation and/or geriatric care) and general hospitals. Since the 6th State Reform the categorical hospitals are under the authority of the federated entities. Yet some of the categorical hospitals merged with an acute hospital before the 6th State Reform and are thus considered as 'acute hospitals'[t,u]. The categorical hospitals, in general, focus on the rehabilitation of complex impairments or when specialised knowledge is required (rehabilitation and specialised centres, including reference centres).

In some hospitals (without a rehabilitation convention with the NIHDI), the physical medicine and rehabilitation is financed by the "nomenclature of medical acts". In other hospitals, the physical medicine and rehabilitation is financed in part by the "nomenclature of medical acts" and in part by the insurance allowance fixed by an rehabilitation convention with the NIHDI.

Sectors – partially or totally - transferred to the federated entities as part of the 6th State Reform are: 1) (neuro)locomotor diseases and disabilities[v], 2) mobility aids, 3) mental and neurological disorders (including mental disorders in children (day and residential centres), mental and neurological disorders treated by outpatient rehabilitation centres, autism, early mother-child relationship disorders, mental disorders in adults (schizophrenia, anxiety disorders, etc.), drug addiction, 4) sensory impairments including visual impairment, hearing impairment treated in outpatient rehabilitation centre or in a specialised centre, 5) respite units for young patients.

KCE reports 57, 87 and 140 have previously investigated physiotherapy and physical and rehabilitation medicine, locomotor and neurological rehabilitation as well as cardiac rehabilitation in Belgium[205-207].

Services aiming at improving the functional dimension are also likely to impact the cognitive, the neurological and the cardiopulmonary dimensions (see also sections 7 & 8). As stated in a previous KCE report, *"the differentiation between "musculoskeletal" and "neurological" is not always very clear. Many neurological patients also present musculoskeletal problems. For example, stroke patients can also be admitted in musculoskeletal beds"* [205]. Similarly the differentiation with other pathologies such as cardiology and pneumology could be confusing. For example, the stroke patient will have in nearly all cases a cardiovascular problem. In order to rehabilitate a stroke patient, the treatment for the first 6 months-1 year focuses on the recovery if the functions (musculoskeletal). After that period the stroke patients mobility needs to be retained by mobilisation but there is a need to train his/her muscles and endurance and physical activity, to further prevent deterioration and regain general function which is in the field of cardiac rehabilitation.

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t Only 8 Flemish rehabilitation hospitals have been transferred. Before their transfer, these institutions only had Sp (inpatient rehabilitation)- and G-beds (geriatric rehabilitation) at their disposal.

u This chapter does not describe the hospital budget (at the Federal level provided via the Budget of Financial Means which covers the non-medical activities, such as the services for accommodation and nursing activities).

v For this sector, only a few 771 conventions have been transferred. The other 771 conventions, all the 950 conventions and the 951 conventions have remained under NIHDI authority. The nomenclature K and M and the speech therapy have also remained NIHDI competencies.

6.1 Rehabilitation care provided by physiotherapists under the M nomenclature

Eighteen sessions of physiotherapy per year

In the absence of a pathology from lists E, Fa or Fb[w], or other specific categories of services for which a specific reimbursement is provided, a patient may receive a maximum of 18 outpatient sessions per calendar year and per pathology at the best reimbursement rate, whether these sessions are provided in the physiotherapist's private practice, in a physical medicine and rehabilitation department of a hospital or at the patient's home (codes 560011, 560114, 560210, 560313, 560416, 564395, 560534, 560571).

The nomenclature for the regular care also includes specific benefits for consultative sessions by a physiotherapist (codes 560092 private practice – 560195 at hospital - 560291 in an outpatient medical service– 560394 at patient's home). This consultative session requires a prescription by the treating physician, eventually before prescribing a treatment. This session includes a written report, including a treatment plan, at the attention of the treating physician. This could be invoiced once a year per pathological situation (Royal Decree 18 December 2002 – in force 1st of January 2003) + Royal Decree 3rd February 2019 – in force 1st September 2010). This therefore mainly concerns patients with chronic respiratory or neuromuscular diseases or oncologic patients.

Similarly, specific benefits are also planned for a written report of the physiotherapist.

Additional sessions only with limited access

A waiver may be submitted to the advisory physician of the sickness funds, resulting in a new prescription for 2 x 9 sessions (maximum 3 x 18 sessions for 3 different pathologies). The same limitation applies to services provided in approved functional rehabilitation centres (codes 560534 (outpatient)-560545 (inpatient)), i.e. individual physiotherapy sessions in which the physiotherapist's personal contribution per beneficiary reaches an overall average duration of 30 minutes (M 24 value).

Interventions excluded from reimbursement

The nomenclature also imposes certain limitations, meaning that some treatments are not reimbursed. The list includes certain treatments/techniques that cannot be considered as mobilisation techniques or physical mobilisation techniques or physical therapies such as ocular or orthopaedic gymnastics, magnotherapy, sonotherapy (to be distinguished from ultrasound therapy which is not covered here), foot reflexology, auriculotherapy, hippotherapy, applications of heat and/or cold performed alone, acupuncture services, spinal traction by mechanical table, electric motor or suspension, and endermology. Services of a purely aesthetic nature, personal hygiene services (in particular gymnastics, fitness, sauna and tanning) and services to accompany or prepare for any sporting activity (e.g. stretching exercises) are also excluded from reimbursement.

A higher number of physiotherapy sessions for a limited number of conditions

For patients whose state of health requires more intensive physiotherapy treatment, NIHDI has established lists of health conditions and pathologies that may give rise to a higher number of physiotherapy sessions and/or a higher reimbursement, whether the sessions are carried out at home, in a private practice or in a health care institution[x] (while remaining outside the K nomenclature). The lists can be found in the Supplement to Chapter 6. The pathologies are categorised as follows, under the generic appellation of "lists" although no list exists *per se*:

- **List E** (Royal Decree 23 March 1982. Article 7 §3.2°): severe and chronic pathologies (see the Supplement to Chapter 6 for the content of the list) and health conditions that may give rise to an increased

[w] The lists refer to the Article 7 §14 5° of the M nomenclature.

[x] In this situation, physiotherapy could be delivered on an inpatient or outpatient basis.

reimbursement of outpatient physiotherapy sessions, without limitation per year. Consequently, patients are exempted of the co-payment. The so-called List E includes, e.g., chronic pulmonary obstructive or restrictive affections or functional loss of limbs. The first request for approval for a List E condition is made via a specialist doctor: the GP can introduce the request for extension. The approval is valid during 3 years. The request for approval must include an assessment by a specialist doctor, including a physiotherapy assessment. Reimbursement under the List E is not degressive. A maximum of 2 sessions could be provided per day. The List E covers physiotherapy sessions for ambulatory or hospitalised patients.

- **List Fa** (acute F – nomenclature M - Article 7, §14, 5°, A – see the Supplement to Chapter 6 for the content of the list): The patients can receive a maximum of 60 physiotherapy sessions reimbursed at the best rate of reimbursement, for a period of one year (365 days from the date of the first session performed). The GP may prescribe these sessions if a report has been drawn up beforehand by the specialist doctor: this report will be attached to the request made by the GP to the patient' sickness funds. This list includes patients who have stayed in intensive care (code 490). For patients who have been in intensive care, the physiotherapist must send a notification to the patient's sickness funds. In this case, a specialist's report is not required. The List Fa also includes, among others, motor deficits and incapacities following a mononeuropathy, a polyneuropathy or a myopathy; algoneurodystrophia; causalgia or Südeck disease (former appelations of the complex regional pain syndrome). At clinical level, the aim of this intensive physiotherapy treatment the first year after diagnosis is to preserve or restore the capacities of the patients. The List Fa covers physiotherapy sessions only for ambulatory patients, independently of the place of delivery.
- **List Fb** (chronic F - Article 7, §14, 5°, B- see the Supplement to Chapter 6 for the content of the list): this list includes pathologies that require regular physiotherapy treatment that may last several years. Examples are chronic polyneuropathy or fibromyalgia. Also patients with a Chronic Fatigue Syndrome (CFS) can benefit if prescribed by a reference centre for CFS (see section 7.3). In this case, a maximum of 60 sessions is reimbursed at the best reimbursement rate per calendar year for a period from the 1st session performed to 31 December of the 2nd calendar year following the year of this 1st session (renewal possible depending on the patient's state of health). The reimbursement of sessions is degressive from the 61st session onwards, although the reimbursement remains preferential compared to physiotherapy sessions for pathologies not included in the list. For pathologies on the Fb list, the co-payment remains the same for the sessions 1- 80 in a calendar year. The Royal Decree of 22 July 2010 – in force since 1st September 2010 –acknowledges the respiratory failure for patients with a functional rehabilitation convention for long-term at home oxygenotherapy or mechanical respiratory support at home in the List Fb. The List Fb covers physiotherapy sessions only for ambulatory patients, independently of the place of delivery.

- **All long COVID patients could benefit from at least 18 physiotherapy sessions per year (*courante pathologie / pathologie courante*). However, the complex nature of long COVID may require a higher number of sessions per year in congruence with 'severe disorders' (pathologies on the List E) or 'acute / chronic disorders (pathologies on Lists Fa/Fb).**
- **Currently, long COVID patients are only eligible for a higher number of physiotherapy sessions as defined for the List E, List Fa, List Fb, if they comply with specific inclusion criteria.**

6.2 Physical medicine and rehabilitation services under the K nomenclature

Patients may also receive rehabilitation sessions under the supervision of a specialist in physical medicine and rehabilitation whose physical presence is required in the institution: these services are included in the K nomenclature, applying to both outpatient and inpatient services. The main advantage of the K nomenclature is that it is available in almost all hospitals. Patients who stayed in intensive care units or were hospitalised because of the COVID are then likely to benefit from K nomenclature as part of their rehabilitation program while staying at the hospital or after discharge. Having been hospitalised is however not a prerequisite as some patients may have needs in rehabilitation and physical medicine.

Types of fees

The different fees vary from K15 (the least reimbursed) to K60 (the most reimbursed). K20/K15 reimbursement is provided for treatments combining one or more monodisciplinary techniques (maximum 48 sessions: K20: 18 sessions followed by K15: 30 sessions). There is no limitative list for the K20/K15, contrary to K30, K45 or K60.

Certain specific pathologies may benefit from multidisciplinary functional rehabilitation sessions (K30, K45 and K60), the number of sessions (60 or 120) depending on the pathology (e.g. cerebral lesions with neurological deficits such as stroke, myopathy or polyneuropathy with clear change in functional capacity, algodystrophy etc). The Article 23§11 reports the list of pathologies eligible for the multidisciplinary rehabilitation, by precising under which fees are applicable. For long COVID patients, the following health conditions could be of interest: code 301 myopathy with clear change in functional capacity (K60 – 120 sessions), code 202 polyneuropathy with modification of the functional autonomy (K60- 120 sessions) or code 504 pulmonary rehabilitation for obstructive or restrictive respiratory deficiency with a FEV below 60% and/or attested desaturation (K30-60 sessions). This latter could be prescribed by a pneumologist. The pathologies under the codes 202 and 301 are objectifiable via electromyogram. The full list of conditions eligible for multidisciplinary rehabilitation is presented in the Supplement to Chapter 6.

After a first series of K20 (18 sessions), K30 (60 sessions) or K60 sessions (60 or 120), subsequent sessions can only be billed as K15, or the patient can switch to physiotherapy treatment under the M nomenclature (Section 10 Physical Medicine and Rehabilitation - Article 22).

The K nomenclature is in force in units Sp, rehabilitation centres 771 and rehabilitation centres 950, with some rules to prevent cumulation (see sections 6.4 & 6.5 for details).

Multidisciplinary benefits under the K nomenclature

Besides diagnostic and therapeutic acts (K15 or K20) under the sole responsibility of the specialist in physical medicine and rehabilitation, the Article 22 of the Section 10 Physical Medicine and Rehabilitation also describes multidisciplinary therapeutic benefits under the codes 558810–558821, 558014–558025, 558832–558843, 558994. These multidisciplinary benefits require the participation of two allied health professionals, including at least a physiotherapist or an occupational therapist. For the codes 558810; 558821; 558832; 558843, besides physiotherapists and occupational therapists, the following disciplines are accepted: speech and language therapist, clinical psychologist, dietician, and orthopaedic prosthetist (interpretative rule 15).

Access to the multidisciplinary rehabilitation under the K nomenclature is restricted to some pathologies listed in the Article 23§11 of the nomenclature. Long COVID patients could be eligible if they satisfy the following health conditions:

- **code 301** myopathy with clear change in functional capacity (K60 – 120 sessions),
- **code 202** polyneuropathy with modification of the functional autonomy (K60- 120 sessions)

- **or code 504** pulmonary rehabilitation for obstructive or restrictive respiratory deficiency with a FEV below 60% and/or attested desaturation (K30-60 sessions).

The reimbursement of codes 558434 – 558445 (rehabilitation associated to occupational therapy), 558095 – 558106 (treatment of lymphedema), 558132 – 558143 (pelvic rehabilitation), 558810 – 558821 (multidisciplinary rehabilitation 60 minutes), 558014 – 558025 (multidisciplinary rehabilitation – 90 minutes), 558832 – 558843 (multidisciplinary rehabilitation 120 minutes) and 558994 (outpatient multidisciplinary rehabilitation for back problems-) - is only authorised for rehabilitation treatments carried out under the coordination of a doctor specialising in physical medicine and rehabilitation in a physical medicine department integrated into an approved hospital establishment in which, in addition to the doctor specialising in physical medicine and rehabilitation, the disciplines of physiotherapy and occupational therapy are present on a full-time basis. Full-time should be understood here as "full-time equivalent". Both disciplines are present at all times during the rehabilitation treatment. Patients must always be accompanied in the execution of their individual rehabilitation programmes although the sessions could be delivered to a group of patients. In addition, the department can call upon the functions of speech therapy and clinical psychology within the institution (Article 23 §6).

When a patient benefits from a K30, K45 or a K60, a weekly interdisciplinary meeting with the medical specialist on rehabilitation and physical medicine is compulsory.

Specific application of the K nomenclature in the context of COVID-19 during the hospital stay

Specifically for COVID-19 patients during the hospital stay (in intensive care or not), since 14 March 2020, with retroactive effect, hospital specialists can bill certain multidisciplinary services of the K nomenclature, supplemented by additional services for patients who are or have been hospitalised in an intensive care unit. Also, in the hospital setting, a 2nd daily physiotherapy session is available for COVID-19 patients hospitalised after an intensive care stay, for the remainder of their hospital stay (see the Royal Decree of 31 July 2020 – published 14 August 2020 related to measures for post-COVID-19 rehabilitation and for additional supervision of the COVID-19 wards of isolated geriatric departments and isolated specialised treatment and rehabilitation departments).

K nomenclature is available in a large number of hospitals, making it accessible to a large number of patients during a hospital stay or as part of an ambulatory treatment.

Long COVID patients could benefit from the K nomenclature (physical medicine and rehabilitation), especially for those who have been hospitalised, during their hospital stay or after being hospitalised if their treating physician attests the need for specific rehabilitation.

No limitative list exists for K20/K15 making it accessible for long COVID patients.

Access to the multidisciplinary rehabilitation under the K nomenclature is restricted to some pathologies listed in the Article 23§11 of the nomenclature. Long COVID patients could be eligible if they satisfy the following health conditions:

- **code 301 myopathy with clear change in functional capacity (K60 – 120 sessions),**
- **code 202 polyneuropathy with modification of the functional autonomy (K60- 120 sessions)**
- **or code 504 pulmonary rehabilitation for obstructive or restrictive respiratory deficiency with a FEV below 60% and/or attested desaturation (K30-60 sessions).**

6.3 Inpatient rehabilitation care in units Sp1 - Sp2 - Sp3 or G

Funded via the hospital budget (*BMF-BFM*), the Sp unit is primarily intended for patients for whom an outpatient rehabilitation programme is not possible in the first instance, either because of their state of health or because of their social and family situation. The Sp services carry out an active and multidisciplinary rehabilitation activity. They may specialise in the treatment and rehabilitation of patients with cardiopulmonary (Sp1), locomotor (Sp2), neurological (Sp3), psycho-geriatric (Sp6) and chronic (Sp5) conditions. Patients should be medically stabilised but require either further medical development, medical follow-up or ongoing management. However, these rehabilitations units are not aimed at long-term stay.

Access to the services

The stay in the Sp unit may be directly organised after a hospitalisation in an acute service (i.e. after a cardiac surgery or a stay in intensive care), at the request of the attending hospital physician. It is also possible for the patient to return home but then finds that his or her situation requires a stay in a rehabilitation centre: in this case, the GP can make the request for this stay. However, the rehabilitation specialist will have to give his/her final approval for the patient's admission.

Content of the care program

Rehabilitation services are organised around a multidisciplinary team of doctors, nurses, physiotherapists, occupational therapists, sports therapists, psychologists, speech therapists and social workers. Depending on the service, it is possible to propose a trial return home to ensure that the patient can adapt to his/her capacities.

Rehabilitation in a G unit is intended for patients aged 75 and over, with an increased focus on age-related functional decline. In addition to the rehabilitation itself, rehabilitation in a G unit can also be supported by the presence of a geriatric liaison team to facilitate the transition from hospital to home.

Sp services are specialised in the treatment and rehabilitation of patients with cardiopulmonary (Sp1), locomotor (Sp2), neurological (Sp3), psycho-geriatric (Sp6) and chronic (Sp5) conditions and are accessible after a hospitalisation.

6.4 General functional rehabilitation centres for locomotor and neurological disorders (convention 950)

Content

General functional rehabilitation centres for locomotor and neurological disorders provide intensive multidisciplinary therapy, on an outpatient or inpatient basis, for a limited period, the duration of treatment being determined by the patient's pathology. They are then covered by convention 950. Certain specific diseases give access to this type of centre, after their acute phase or immediately after an attack. Pathologies covered by the convention 950 are: acquired para- or tetraplegia; brain injury causing severe neuromotor disorders or speech and language disorders or other severe neuropsychological disorders; chronic progressive diseases of the brain and/or spinal cord, with motor or intellectual sequelae, during the intensive rehabilitation phase after an attack; amputation of an upper or lower limb; Cerebral palsy; congenital conditions of the spine and/or spinal cord; dysmelia and phocomelia; myopathies: progressive hereditary muscular dystrophies, Thomsen's congenital myopathy and autoimmune polymyositis; cystic fibrosis; severe locomotor and psychological disorders due to a rheumatoid arthritis at Steinbrocker stage III and IV[y] or to a

[y] The Steinbrocker functional classification is used by for the physical function assessment, to rate the extent of physical disability on a four-level scale, ranging from Class I, "complete functional capacity to carry out all usual duties without handicaps", to Class IV, "largely or wholly incapacitated with (the person) bedridden or confined to wheelchair [208].

spondylitis with peripheral involvement at Steinbrocker stage III or IV, possibly with neurological complications.

Access to the convention

Access to a 950 centre requires a prescription by a specialist in physical medicine and rehabilitation. The specialist doctor draws up an individual functional rehabilitation programme and communicates it to the patient's advisory physician at the sickness funds, who must give his or her agreement for the programme to be implemented and included in the convention. The team includes doctors, physiotherapists, psychologists, occupational therapists and social workers. The convention covers for interdisciplinary team meetings as well as concertation with the family and the GP. Rehabilitation centres for locomotor and neurological disorders (951) offer similar programmes of care to the centres covered by conventions 950 and 771 (see also 7.2.1), but with a shorter duration. They are only accessible to patients who started a rehabilitation in a 950 or 771 centre.

Exclusion criteria

The 950 convention is not compatible with certain other services. If the patient has already undergone functional rehabilitation for a disease or disorder in a functional rehabilitation establishment linked by a convention with the Insurance Committee of the NIHDI, or has received K30-K60 functional rehabilitation services for the same disease or disorder (see also 6.2), the total duration of rehabilitation under the 950 convention may not exceed the maximum duration stipulated for the condition (Article 5§5). A 950 centre that has already provided K30 or K60 sessions must subtract these from the number of sessions that the patient may take.

Current offer

A total of 44 centres is currently available across Belgium[z]. The list of the centres could be found on the website of the NIHDI.

In principle, long COVID patients may be benefit from the services covered by the convention 950 if they fit within the (restrictive) inclusion criteria.

6.5 Specific functional rehabilitation centres (convention 771[aa])

Content

The NIHDI has conventions with specific functional rehabilitation institutions (convention 771), offering inpatient and outpatient locomotor and neurological rehabilitation to patients with specific problems. The 771 centres differ from one to another, among other things regarding the pathologies that qualify for rehabilitation. Examples of eligible troubles and pathologies concerned are: paraparesis; tetraparesis; paraplegia; tetraplegia; severe locomotor and/or neuropsychological disorders following traumatic brain injury / neurosurgical intervention on the brain; Guillain-Barré syndrome; severe locomotor and/or neuropsychological disorders following one of the following degenerative or demyelinating diseases of the central nervous system: amyotrophic lateral sclerosis, Wilson's disease, Friedreich's ataxia, atrophy of the brain, and Friedreich's ataxia, olivopontocerebelar atrophy, multiple sclerosis, leukodystrophia, Arnold-Chiari malformation, syringomyelia; hemiplegia/hemiparesis with severe neuro-psychological disorders; complete monoplegia of an upper limb; amputation of the upper limb above the hand; amputation of the lower limb at the proximal third of the femur or with disarticulation of the hip; amputation of both lower limbs at the level of the tibia or femur; severe locomotor and psychological disorders due to Steinbrocker stage III or IV rheumatoid arthritis OR spondylitis with peripheral involvement at Steinbrocker stage III

[z] Last update of the webpage: April, 15 2019.

[aa] See the here the list of the centres under a 771 convention.

or IV, possibly with neurological complications; polytrauma: bone, joint or neuromuscular injuries to several limbs, or complex injuries to the head, trunk or pelvis with deep organ damage.

Multidisciplinary team

A 771 centre has a multidisciplinary team, under the responsibility of a medical director, including: psychologists / neuropsychologists / orthopedagogues, speech therapist / specialist in neurolinguistics, physiotherapists (full time), occupational therapists (full time), nurses, and social workers. Dieticians and technicians in rehabilitation (e.g. bandaging specialist) should be available when needed.

The convention plans a weekly interdisciplinary team meeting and an individualised interdisciplinary rehabilitation patient record.

Access to the convention

Admission to these establishments is based on a medical file and, depending on the establishment, on an assessment carried out by the interdisciplinary team. The stay or outpatient care is also subject to the approval of the advisory physician of the sickness funds. However, as mentioned above, there is lots of diversity among the 771 centres, each centre being able to specialise for certain pathologies or health conditions.

Current offer of services

So far, 5 centres with a convention 771 remains under the authority of the NIHDI, the remaining centres being transferred to the federated entities. The 771 centres under the NIHDI authority are: Centre Neurologique William Lennox (Ottignies), Centre de réadaptation fonctionnelle Neurologique de l'Hôpital ERASME (Anderlecht), Service de Médecine Physique et de Réadaptation des Cliniques universitaires Saint- Luc (Woluwé-Saint-Lambert), Dienst motorische revalidatie van het Centrum voor Locomotorische en Neurologische Revalidatie UZ Gent (Gent), and UZ Leuven.

Additional information over the specific rehabilitation centres managed by the federated entities could be found on the websites of the Zorg en Gezondheid Agentschap for the Flemish Region, the Commission Communautaire Commune for the Brussels Region, the Agence pour une Vie de Qualité for the Walloon Region, and on the website of the Deutschsprachige Gemeinschaft for the German-speaking Community.

In principle, the convention 771 could be open to long COVID patients if they fit within the inclusion criteria: these criteria are restrictive, the number of centres is very limited.

6.6 Occupational therapy services

In addition to the multidisciplinary treatments provided in conventions 950, 951 and 771 described above, an occupational therapist may also provide services (in whole or in part) in the patient's usual place of residence. It must be prescribed by a doctor attached to the rehabilitation establishment (950, 951 or 771) where the patient has previously received treatment and is subject to the agreement of the sickness funds' advisory physician.

Content of the assessment

The observational assessment by the occupational therapist is a comprehensive assessment of the functional capacities and incapacities of the patient in activities of daily living (such as personal care, eating, interpersonal relations, locomotion); in personal, school, work, socio-cultural and leisure activities, in physical, sensory-motor, intellectual, relational, behavioural terms, in his/her physical, social and cultural environment; and which results in a written report of the examinations carried out, addressed to the prescribing doctor. In addition, the occupational therapist also sends the observation report to the patient's GP. The observational assessment takes at least 180 minutes, including the occupational therapists travel time. However, the time taken to draw up the written report may not be included in the minimum 180 minutes.

Offer

The patient can benefit from the following services (lasting 180 minutes, including travel):

- 1 observation session - the patient may still be hospitalised for revalidation;
- 7 situational sessions: reserved for outpatients who have already had an assessment;
- 2 information, advice and learning sessions: reserved for outpatients who have already had an assessment;
- 1 final functional assessment service: reserved for outpatients who have already had an assessment.

As part of their special benefits, some sickness funds offer home visits by occupational therapists with a view to adapting the home. These services are most often intended for elderly and/or disabled people. The occupational therapist could also play a role in helping patients returning to work (see 9.15).

Support from an occupational therapist is most likely to occur in the course of a stay in a rehabilitation centre 950, 951 or 771 or via the sickness funds of the patients. In practice, this is likely to concern a limited number of long COVID patients.

7 NEUROLOGICAL DIMENSION

7.1 Assessment of cognitive troubles

Neurologists, psychiatrists or geriatricians are entitled to prescribe a neuropsychological assessment. This assessment is partially covered by the NIHDI in case of suspicion of an early dementia (code 477573). This assessment includes a validated and detailed neuropsychological examination (minimum duration of 45 minutes) of the important cognitive functions affected in the dementia syndrome (according to DSM IV): memory, language skills, visual-spatial skills, attention and executive functions. Other examinations, such as an MRI, a CT scan or even a PET scan, may be prescribed by the specialist in order to objectify brain damage.

For patients benefiting from a R60 or a K60 lump sum or for patients in a 771 convention (see also sections 7.2.1 & 6.5), the specialist in physical medicine may ask for a neuropsychological assessment as part of the comprehensive evaluation when establishing the rehabilitation program for the patients. Patients could then benefit from a rehabilitation program with a neuropsychologist. However, not all centres offer such an assessment and treatment.

Patients may also consult a neuropsychologist on their own initiative or on the advice of their treating physician (GP, neurologist, specialist in physical medicine and rehabilitation, pneumologist, specialist in infectious diseases), for an assessment of their cognitive functions. This (less thorough) assessment is not reimbursed by the NIHDI, but some sickness funds contribute to the cost as part of their supplementary coverage.

So far, no specific care programs for patients with olfactory loss have been identified.

The nomenclature only plans the reimbursement of a neuropsychological assessment as part of a diagnosis of dementia: long COVID patients are thus not eligible for this assessment, except in the context of an exclusion diagnosis (e.g. a patient for whom a differential diagnosis may be needed).

Assessment of cognitive fonctions may occur in the framework of a rehabilitation program (K nomenclature; conventions 950 and 771; CAR/CRA (see sections 6.2, 6.4, 6.5, 7.2.1 & 7.2.2): however not all centres offer such an assessment. To be eligible, patients should fulfill specific criteria.

7.2 Rehabilitation services for cognitive troubles

Depending on the results of the assessment and the patient's original problems, an individualised cognitive rehabilitation programme is drawn up. This programme may involve speech therapists, occupational therapists, psychologists or neuropsychologists. It can be provided in different types of centres.

7.2.1 General functional rehabilitation centres for locomotor and neurological disorders (convention 950) and specific functional rehabilitation centres (convention 771)

The section 6.4 already describes the centres under the convention 950 and the section 6.5 describes the centres under the convention 771.

As previously mentioned, these centres offer comprehensive care, including care for cognitive disorders: these interdisciplinary treatments are covered by the convention 950 concluded with locomotor and neurological rehabilitation establishments. All the centres under the convention 950 use the same terms, which does not exclude the specialisation of certain centres in neuropsychological disorders. Including a multidisciplinary team, including neuropsychologists, under the supervision of a specialist in physical medicine and rehabilitation, these centres offer residential or outpatient care, with 2-hour sessions. The daily duration of cognitive rehabilitation services is not clearly defined in the text of the 950 conventions: it is a daily package, without specifying the duration, which allows the care teams to adapt the care to the needs of the patients. The patient's admission to this convention is conditional on the submission of a file, including proof of the presence of cognitive lesions (medical imaging), and subject to the agreement of the advisory physician.

The pseudo-nomenclature in application in 950 centres includes the lump sum R30-R60[bb], with outpatient and inpatient codes. The R30-R60 include multidisciplinary rehabilitation with a treatment time of 60 and 120 minutes per session respectively. The conditions for reimbursement of these benefits are like those for the K30-K60 nomenclature. In addition to these R30-R60 services, rehabilitation centres in sector 9.50 may also include packages that differ from one pathology to another[209].

In specific functional rehabilitation centres (convention 771), cognitive rehabilitation can be offered as well, if the patient complies with the inclusion criteria.

In principle, long COVID patients could access 950 conventions or 771 conventions if their sequelae correspond to the inclusion criteria. These criteria are however restrictive and the final decision will remain the responsibility of the advisory physician of the sickness funds.

7.2.2 Outpatient rehabilitation centres (Centres de revalidation ambulatoire CRA - Centra voor ambulante revalidatie CAR)

Depending on the federated entities since the 6th State Reform, the outpatient rehabilitation centres of type 953 and 965 are indicated for the care of people with mental health, hearing, speech or neurological disorders. They mainly (but not exclusively) care for children (up to their 19th birthday). Some of these centres care for children or adults with a brain injury of vascular, toxic, tumour, infectious or traumatic origin, without symptoms of dementia. At the time of admission to the institution, patients must present disorders in neuro-psychological functions (cognitive functions, functions

[bb] To be distinguished from R-nomenclature: nomenclature for mono-disciplinary speech therapy. There is no relation between the 2 R-codes.

related to communication, functions related to the control of emotions, functions related to social behaviour, functions related to the experience of feelings and to personality), possibly in conjunction with physical disorders (motor lesions, loss of the senses) which lead to disruptions in the person's daily life, whether at the affective, family, social, professional or recreational level...

Additional information over the specific rehabilitation centres managed by the federated entities could be found on the websites of the Zorg en Gezondheid Agentschap for the Flemish Region, the Commission Communautaire Commune for the Brussels Region, the Agence pour une Vie de Qualité for the Walloon Region, and on the website of the Deutschsprachige Gemeinschaft for the German-speaking Community.

Similarly to the centres under the 771 convention, there is no unique model of health care program inside the CRA/CAR centres, and the offer is unequally organised, leading to disparities in access and health care coverage.

Conditions for access and eligilibily criteria are under the authority of the federated entities.

7.2.3 Memory Clinics

Description

Memory clinics are covered by a convention with the NHIDI: they are accessible to patients suffering from early-stage dementia, on prescription from a specialist or GP, subject to a prior assessment by a neurologist, geriatrician or psychiatrist. The physician who carries out the assessment must have made or confirmed a diagnosis of early dementia, in accordance with the specific provisions of the health care nomenclature, prescribed a rehabilitation programme, provided by a memory clinic approved by the NHIDI, and establishes a comprehensive treatment plan demonstrating that the beneficiary meets the conditions for continuing to live at home or in the home of a relative, outside any institutional care or accommodation for the elderly, for a period of at least 12 months from the date of the start of the rehabilitation programme (Article 3 §1 of the convention). Entry into the convention is subject to the prior approval of the sickness funds' advisory physician (the request for reimbursement should be sent within the 30 days of the start of the rehabilitation program).

Assessment

Within the framework of the agreement, the care team must summarise the medical examinations and cognitive tests previously carried out and complete them in order to accurately assess the preserved and lost abilities, to define and provide a cognitive rehabilitation programme on this basis, in order to teach the patients alternative strategies which will enable them to carry out certain daily acts using their preserved abilities, training the relative(s) who will assist the patients in their daily life, advising and supervising the adaptations of the daily environment that will help to alleviate the cognitive difficulties, providing information to the beneficiaries, their relatives and care providers on the disease, its evolution and consequences, and providing psychological support to the patients and their carers (Article 4 of the convention).

Health care offer

These activities are carried out by an interdisciplinary team consisting of specialist doctors (geriatrician, neurologist, neuropsychiatrist or psychiatrist), psychologists, occupational therapists, social workers and administrative staff. The treatment includes at least two sessions at home. A total of 25 sessions (for those aged 65 and over) or 35 sessions (for those aged of 64 and below) are planned for a period of 24 months: two sessions can take place on the same day. The rehabilitation is divided into 3 phases: an assessment phase, a rehabilitation phase and a maintenance phase. The assessment phase and the rehabilitation phase take place during the first 12 months, the maintenance phase during the following 12 months (Article 4 § 2 of the 2019 amendment).

This programme cannot be combined with services provided in a geriatric day centre. The services provided for in the nomenclature are not included in the agreement. At least two consultations must take place with the GP (at the beginning and end of the treatment).

Existing centres

Twelve centres are currently under convention: Geheugenkliniek ZNA Hoboken, Geheugenkliniek geriatrie-neurologie UZ Brussel (Jette), Clinique de la mémoire des Cliniques universitaires Saint-Luc (Woluwé), Clinique de la mémoire du Grand hôpital de Charleroi, Clinique de la mémoire "Memory Team" (Saint Vith), Clinique de la mémoire de la Polyclinique Universitaire Centre-Ville (Liège), Geheugenkliniek van de Autonome verzorgingsinstelling Ziekenhuis Oost-Limburg (Genk), Clinique de la mémoire du centre Hospitalier de l'Ardenne (Libramont), Clinique de la mémoire des Cliniques universitaires UCL Mont-Godinne (Yvoir), AZ Sint-Blasius Campus Dendermonde (SBD), Geheugenkliniek UZ Leuven, Geheugenrevalidatie Noord West-Vlaanderen (Bruges).The list could be found on the website of the NIHDI[cc].

Long COVID patients with cognitive impairement are not eligible for this convention as access requires a 'suspicion of dementia'. Nevertheless, several aspects of the content of this convention might also be relevant to (part of) the long COVID patients and could serve as a source of inspiration for future actions.

7.3 Measures for chronic fatigue syndrome

In 2020, the Superior Health Council published a report on the Chronic Fatigue Syndrome (CFS), also called myalgic encephalomyelitis[210]. Acknowledging the need for a better care of the patients, this report concludes with 3 major recommendations: 1) stimulating the knowledge about the CFS and the clinical approach, 2), creating a health care network, 3) stimulating the clinical research.

Since July 2019, the NIHIDI no longer reimburses the 18 specific 45-minutes physiotherapy sessions for patients suffering from chronic fatigue and/or fibromyalgia. Patients with fibromyalgia benefit from a maximum of 60 physiotherapy sessions reimbursed at the best rate of reimbursement under the conditions of the List Fb (see section 9.11.1). For patients with a CFS, physiotherapists cannot attest anymore 60 sessions as there is no more reference centre as described in the nomenclature : there are currently no specific physiotherapy sessions reimbursed for the CFS patients.

Two other measures exist for the management of the CFS: the first concerns the centres for the multidisciplinary diagnosis of the CFS while the second involves the cognitive-behavioural treatment of the CFS.

Convention Chronic Fatigue Syndrome

The Article 16§1 of the amended version of the convention published in 2020 defines Chronic Fatigue Syndrome as follows. "*The following three symptoms must be present at least half the time:*

- *A substantial reduction or impairment of the ability to participate as before in occupational, educational, social or personal activities, which lasts for more than six months and is accompanied by fatigue that is frequently intense, is new or has a definite beginning (has not been present all life), that is not the result of constant excessive exertion, which is not substantially diminished by rest*.
- *Deterioration of the symptoms after physical or mental exertion (exertion intolerance or post-exertional malaise, PEM).*
- *Unrefreshed and disturbed sleep*

In addition, at least one of the two following symptoms must be present:

- *Memory and thinking problems*
- *Deterioration of the symptoms when standing or sitting upright (orthostatic intolerance)".*

The Chronic Fatigue Convention aims to cover the reimbursement of services for which there is no reimbursement: multidisciplinary operation of CFS diagnostic centres, participation of the GP and outpatient treatment by

[cc] Last update of the webpage: April, 16, 2019

"cognitive behavioural therapists". The "Multidisciplinary Diagnostic Centre for CFS" is a hospital unit, consisting of a multidisciplinary team including internal medicine specialist, physical medicine and revalidation specialist, psychiatric specialist, cognitive behavioural therapist for CFS and administrative staff.

Referral is made by the GP: the diagnosis is confirmed by an internal medicine specialist. Once the diagnosis has been confirmed, an assessment is carried out by the interdisciplinary team, i.e. a clinical and technical examination by the internal medicine specialist and the psychiatry specialist.

Based on the assessment, a therapeutic programme is proposed and discussed with the GP: the latter may receive remuneration for this participation, whether face-to-face or at a distance (minimum 15 minutes). The GP is informed of the treatment plan. The therapeutic program mainly relies on cognitive behavioural therapy, although other measures could be envisioned outside the framework of the convention.

The CFS diagnostic centre organises, together with the patient, his/her treatment with cognitive behavioural therapy: an initial prescription for 3 sessions is provided to the patient. After evaluation by the diagnostic centre, the prescription can be renewed 2 times for 7 sessions. A total of 17 sessions could be performed. A session is always individual and should last 50 minutes. This can be supplemented by extra sessions of physiotherapy according to the reimbursement rules in force.

The current offer for Chronic Fatigue Syndrome is limited to a multidisciplinary diagnostic assessment, organised in one centre only.

After a diagnosis of CFS made by the reference centre, patients have access to cognitive behavioural therapy with therapists having concluded a specific agreement with the NHIDI.

No specific offer of physiothapy currently exists for patients with a Chronic Fatigue Syndrome

7.4 Measures for chronic pain

Patients diagnosed with a fibromyalgia can benefit of a maximum of 60 physiotherapy sessions per year. For other forms of chronic pain, patients could benefit from the List Fa, if they have a diagnosis of complex regional pain syndrome and mono or polyneuropathies with objectified motor deficit; from the K nomenclature, if the chronic pain requires rehabilitation therapy; or from the regular physiotherapy sessions

7.4.1 Fix-payment "chronic pain"

The Article 4§1st of the National Convention HOP/2020 describes the fix-payment for the management in chronic pain as reported in the nomenclature N87 as organised in day hospital, with 3 different categories depending on the techniques covered. The appendix of the National Convention HOP/2020 includes the nominative list of the interventions covered by this Article 4§8. These interventions rely on the use of invasive and non-invasive techniques to control the pain (i.e. infiltrations, sympathectomy or cordotomy).

7.4.2 Reimbursement of analgesics

In addition, the Royal Decree of 9 April 2017 allows a financial intervention of the NIHDI for 20% of the costs of analgesics containing paracetamol or a combination of paracetamol and codeine for patients diagnosed with chronic pain[211]. The treating physician should attest of the need for this treatment and the advisory physician of the sickness funds provides the authorisation. The patient could then directly benefit from the reimbursement when showing up at the pharmacy. The authorisation is granted for maximum one year by application.

7.4.3 Multidisciplinary centres for treatment of chronic pain

Since 2013, 35 hospitals have a specific contract with the FPS Public Health. This contract includes a fixed payment for the development of a multidisciplinary centre for the treatment of the chronic pain based on the bio-psychosocial model. According to the feedback of 2014, the teams are

mainly composed of anaesthetists and specialists in physical medicine, nurses, psychologists, physiotherapists, social workers and occupational therapists[212]. Activities offered to the patients also include group sessions. There is, however, no information about the inclusion criteria and the length of the waiting list. The list of the hospitals could be found on the website of the FPS Public Health.

Long COVID patients with persistent pain could benefit from the List Fa, if the pattern of their COVID-related chronic pain is similar to a complex regional pain syndrome and motor deficit due to polyneuropathies; from the K nomenclature, if the chronic pain requires multidisciplinary rehabilitation therapy; or from the regular physiotherapy sessions. Those with the most severe form might benefit from the FPS contracts for chronic pain. There is, however, no information about the inclusion criteria for these conventions.

8 CARDIAC DIMENSION

Regarding cardiac sequels, in addition to the interventions included in the nomenclature (e.g. consultations with a specialist in cardiology or sessions with a physiotherapist – see also sections 6.1, 6.2 & 6.3), the NIHDI covers cardiac rehabilitation services under the convention 7821. The KCE report 140 already investigated the cardiac rehabilitation[207].

8.1 Cardiac rehabilitation services (convention 7821)

The Royal Decree of 10 January 1991 establishes the nomenclature of the rehabilitation services as defined by the Article 23§2 of the 1994 Law on the national health insurance[213].

Target group

The Chapter IV describes the services offered for patients in need of a cardiac rehabilitation program (codes 771201, 771212 & 771223) during or immediately after a hospitalisation because of 1) acute myocardial infarction, 2) coronary surgery, 3) therapeutic percutaneous endovascular intervention on the heart and/or on the coronary arteries, under medical imaging control, 4) surgical intervention for congenital or acquired malformation of the heart or for valvular lesion, 5) heart and/or lung transplantation, and 6) cardiomyopathy with left ventricular dysfunction.

Intervention of the sickness funds

The access to the convention requires the approval of the advisory physician of the sickness funds after examination of the application submitted by the cardiac rehabilitation centre. The sickness fund contributes to the costs of the rehabilitation programme (third-party payment system). In particular, it contributes to the cost of one rehabilitation session per day. The patient's personal share (*ticket modérateur-remgeld*) for each rehabilitation session is carried out as part of the rehabilitation programme. The patient is hospitalised during the first assessment and for at least part of the rehabilitation programme, and pays the usual costs associated with a hospital stay. When following the rehabilitation programme, the patient can

no longer obtain an intervention on the same day for a consultation with an internist, paediatrician or cardiologist, physiotherapy sessions or other rehabilitation services.

Content of the program

The nomenclature includes the multidisciplinary rehabilitation assessment, including prognosis and opinions about the rehabilitation program, under the responsibility of a doctor certified both as a specialist in cardiological rehabilitation and as a specialist in cardiology, internal medicine, paediatrics or physical medicine. The assessment should also include the evaluation by at least two of the following professionals: physiotherapist, psychologist, social worker, dietician, or an occupational therapist with a specialisation in social and professional insertion of disabled persons. The interdisciplinary treatment is provided under the supervision of the medical doctor, and includes at least two disciplines (physiotherapist, psychologist, social worker, dietician etc).

Current offer

A total of 59 centres are accredited by the NIHDI. The list could be found on the website of the NIHDI. Centres outside the list of the NIHDI have no specialist in cardiac rehabilitation: patients then benefit of a less intensive treatment. In practice, these needs are covered by the M nomenclature.

The convention for cardiac rehabilitation is focused on specific cardiac pathologies: only long COVID patients with severe cardiac complications may benefit from this convention.

9 MENTAL HEALTH DIMENSION

The mental health aspects related to the long COVID include anxiety, depression and, to a lesser extent, post-traumatic stress disorder. These three dimensions were also mentioned in relation to the Post-Intensive Care Syndrome (PICS)[200]. For a more complete description of the organisation of mental health care in Belgium, we refer to the KCE 318 report[214].

The Mental Health @ Work network, a partnership between various federal institutions (FPS Public Health, FPS Employment, FEDRIS, NHIDI, Superior Health Council, FPP Social Security), has launched a "COVID-19" section on their website, with relevant information and measures on the subject. Some of the topics that will be covered are: reimbursement of first line psychological care for all; prevention of burn-out: free support path for hospital and care workers; impact on mental health and psychosocial care (opinion of the HSC); exceptional measures for medical care and services, work organisation (information for employers and teleworking) and the periodic reports of the Social Impact Working Group COVID-19. The regions and the communities have also reinforced the offer for mental health services, but this offer is not specific for long COVID patients[ddeeffgghhii].

dd https://glatigny.cfwb.be/home/presse--actualites/publications/publication-presse--actualites.publicationfull.html

ee http://luttepauvrete.wallonie.be/actualites/COVID-19-get-wallonia-des-psychologues-suppl%C3%A9mentaires-en-wallonie-pour-un-montant-de-86

ff https://ccf.brussels/des-aides-psychosociales-pour-faire-face-a-limpact-du-COVID-19/

gg https://www.zorg-en-gezondheid.be/psychosociale-ondersteuning-tijdens-corona-epidemie

hh https://www.zorg-en-gezondheid.be/innovatief-project-verleent-psychologische-ondersteuning-via-dezorgsamenbe

ii https://www.zorg-en-gezondheid.be/vlaanderen-investeert-25-miljoen-in-actieplan-mentaal-welzijn-zorgen-voor-morgen

9.1 Psychological care

On 2 December 2020, a Memorandum of Understanding was concluded between the Federal Government and the federated entities on a coordinated approach to strengthening the provision of mental health care, in particular for the vulnerable target groups most affected by the COVID19 pandemic. The 32 mental health care networks will have a coordinating role in which they will take initiatives to organise primary mental health care provision. This convention is in force since September 2021. The major adaptations consists of the suppression of the gatekeeping by a prescribing physician and the organisation of health care according to two categories of age. Since septembre 2021, patients can use either the "children and adolescents" network (up to and including 23 years of age) or the "adults" network (from 15 years of age). These age categories overlap to ensure a suitable offer for people aged 15 to 23 inclusive, who can thus choose their mental health care network (youth or adult) according to the nature of their needs.

First-line psychological care

First line psychological care encompasses the following missions:

1. Support for beneficiaries with mental health problems through group interventions aiming at strengthening mental health and preventing mental health problems, strengthening self-care competencies and/or supporting informal care. This mission is carried out by clinical psychologists/clinical orthopedagogues, preferably in collaboration with health care professionals and experts by experience (*experts du vécu - ervaringdeskundige)*. Experts by experience could only intervene under the supervision of mental health professionals and within the framework of their expertise (e.g. assessment of the problems present and clarification of the complaint). The group support could be delivered in a service, institution or a community facility (*outreaching*).
2. Individual support to beneficiaries who can be helped by a limited number of first-line psychological interventions. These interventions aim at maintaining or, if necessary, regaining a healthy lifestyle and a satisfactory quality of life. These interventions are provided in individual sessions (including distance care - telemedicine). These short-term and/or low-intensity psychological interventions focus on the following activities: assessment of the current problems and clarification of the request; guided self-help, psycho-education; promotion of the autonomy and resilience of the beneficiary or his/her family environment; support of the first-line actors around the beneficiary; referral to specialised care and/or referral to other care organisations and/or patient and family associations... (Article 3 of the convention).

First-line psychological care is available to all patients, without prescription. The sessions should therefore be dispensed by a psychologist or an orthopedagogist who has previously contracted an agreement with a mental health network under the terms of the NIHDI.

The first session is free, allowing the psychologist to assess the demand and the patient personal situation before proposing a tailored treatment. The patient personal contribution is then of 11 euros for an individual session (4 euros for those benefiting from the majored intervention) and 2.5 euros for a group session.

For the general first line psychological care, per period of 12 months, children and adolescents (below 23 years) have right to 10 individual sessions (face-to-face or teleconsultation) or 8 group sessions while adults (above 15 years) have right to 8 individual sessions (face-to-face or teleconsultation) or 5 group sessions (Article 6).

Specialised psychological care

Specialised psychological care is aimed at patients in need for specialised psychological care because of an underlying psychological problem. These psychological interventions are aimed at psychodiagnosis and treatment. This specialised function can be carried out in different ways: individual intervention, distance care (telemedicine) or specific group intervention. Interventions are adapted to the problem and specific techniques are used (e.g. group intervention for people with ADHD or intervention for parents of anxious children). This treatment is carried out by clinical psychologists/clinical orthopedagogists with specific skills, demonstrable

through the portfolio of the health care professional (Article 5 of the convention).

Per period of 12 months, children and adolescents (below 23 years) have a right to an average number of 10 individual sessions (maximum 20 sessions) or maximum 15 group sessions, while adults (above 15 years) have a right to an average number of 8 individual sessions (maximum 20) or maximum 12 group sessions (Article 6).

More details and the text of the convention between the NIHDI and the mental health networks could be found on the NIHDI website.

Specific measures for self-employed workers

Because of their vulnerability, self-employed workers could benefit of 8 free sessions of psychological care since May 2021[215]. This initiative takes place in the context of the post-Covid-crisis. Self-employed workers in psychological distress can receive 8 sessions of psychological care, entirely free of charge, from a registered psychologist or clinical orthopedagogue who has concluded an agreement with the ASBL “Un pass dans l'impasse”. This non-profit organisation has specialised for several years in an approach geared towards the self-employed and their needs. It coordinates this action at national level, in collaboration with Flemish, Walloon and Brussels partners. The patient could directly contact the association or be contacted by it: in this case, the patient may have been signalled by a “sentinel”, that is a person who is professionally in contact with self-employed workers and may trigger an “alert” via an online platform (upon agreement of the patient). The entire honorarium of the psychologist is directly paid by the NIHDI (61,79 € per session in 2021, with annual indexation)[jj].

Long COVID patients aged 15 years and more can benefit from 8 individual reimbursed sessions with a clinical psychologist per year. For patients from 15 years and more in need for specialised psychological care, a maximum of 20 sessions is reimbursed per year.

Specific measures also exist for children and adolescents until 23 years and for self-employees.

9.2 Consultations with a psychiatrist

Patients have the possibility to consult with a psychiatrist without being referred by their GP. The service will be reimbursed in accordance with the rules in force at the NIHDI, upon submission of the certificate of care to the sickness funds.

The same conditions apply to the relatives of COVID-19 patients who require psychological and/or psychiatric care.

When a family session is deemed necessary by the psychiatrist, the consultation should last at least 60 minutes, for members of a same household, including an eventual written report (codes 109535 for 2 persons, 109550 from the third person, code 109653 with a registered psychiatrist, independently of the number of persons) as reported in the Chapter II of the nomenclature on consultations, visits and advices; psychotherapies and other benefits.

The psychiatrist could also attest of a code 109572 for a session of at least 90 minutes with a group of 8 patients, including an eventual written report. In this case,

[jj] See the agreement model on the website of the NIHDI in French and Dutch for more details.

- Fees for psychotherapeutic treatments cannot be cumulated with fees for technical services performed on the same day by the same or another psychiatrist.
- The fees for psychotherapeutic treatments cannot be added together, nor can they be added to the fees for the consultation carried out on the same day by the same or another psychiatrist.
- The consultations under the codes 109535, 109550 and 109572 imply that each person in the group is treated with their consent for the diagnosis or treatment of their own psychiatric problems. Hetero anamnesis with family members or other persons in the patient's entourage is covered by the fees for consultations or visits provided for elsewhere.
- For the codes 109535, 109550 and 109572 only, a second specialist in psychiatry (excluding trainee doctors in psychiatry) who is actively present during the treatment sessions for the entire duration required may also certify them.

Long COVID patients can consult a psychiatrist on their own initiative and will be reimbursed according the nomenclature.

9.3 Physiotherapy sessions for relaxation

Prescriptions could be issued for relaxation therapy with a physiotherapist under the nomenclature for regular care as part of the 18 annual sessions [216]. This could be prescribed for patients experiencing symptoms “anxiety-panic attacks”.

Long COVID patients have right to a physiotherapy prescription for relaxation therapy (under the terms of the 2x9 sessions reimbursed per year).

9.4 Measures for the post-traumatic stress disorder

Post-Traumatic Stress Disorder (PTSD) can occur 3 to 6 months after the traumatic event, or even longer: it may concern both patients and health care professionals but also relatives as reported in the KCE report on the PICS [200]. Proper management of PTSD requires specialised and long-term care by trained psychiatrists and psychologists. In 2017, the Superior Health Council published recommendations for the prevention and management of psycho-social after-effects in the context of individual or collective emergencies[217], including PTSD, but initiatives remain sparse and are mainly developed by the Belgian Defence, the fire brigades or the police as part of the well-being and prevention at work for soldiers, police officers and fire workers.

At the level of the Defence, the crisis psychology centre of the Military Hospital has developed specific expertise for the support of soldiers returning from operations but offers, on an ad hoc basis, support to civilians as well.

Outside the armed forces and the fire brigade, some psychiatrists and psychologists have specialised, in a personal capacity, in therapies to deal with PTSD, but there is no database to identify them at present.

Other initiatives and interventions also exist as the Tension & Trauma Releasing Exercises® offered to the volunteers of the Belgian Red Cross, the Trauma Clinic of the CHU Brugmann or the reference centre for the psychic trauma of the Cliniques universitaires Saint-Luc. These initiatives are however not systematically organised for those exposed to high risk of PTSD although the COVID-19 has stressed the need for such support for both health care professionals, patients and their relatives.

Post-traumatic stress disorder is only covered and managed within the framework of the national health insurance in a very limited way. For long COVID, it implies that patients can only be assisted through consultations with a psychiatrist, the consultation being reimbursed as part of the national health insurance.

9.5 Support groups for patients

Numerous self-help groups have been launched at the initiative of the patients such as "*Post-Covid gemeenschap*" et "les *Oubliés du Covid long Belgique*". These groups are used as a resource by patients to be informed about available health care professionals, tips and tricks to tame the effects of long COVID, etc. These groups also serve as a place for social support between their members as they share a same experience.

Offering group sessions as part of a physiotherapy treatment could also help patients to connect with patients suffering from the same health experiences.

Support groups and patient platforms play a role in the social support of patients and their relatives: besides the role played by the Ligue des Usagers des Services de Santé (LUSS), the Patienten Rad und Tref (PRT) and the Vlaamse PatientenPlatform (VPP) at policy level, numerous support groups have been launched at the initiative of patients or health care professionals.

10 SOCIAL DIMENSION

10.1 Social support accessible to all

All patients registered to a sickness funds could benefit from social support: depending on the sickness funds, the services will vary but, at minimum, the social service of the sickness funds could inform the patients about the rights and benefits. At the local level, the municipalities oversee providing social support for all the residents of their territory, independently of their administrative and legal status, via the CPAS-OCMW.

Similarly, the social services of the hospitals could help patients in numerous administrative procedures but also to organise support at home. Some conventions have social workers as members of the teams. In primary care, social nurses or social workers are also available for supporting patients.

Social services of the hospitals, the sickness funds and the CPAS-OCWM could provide social support to long COVID patients.

10.2 Returning to work after a sickness absence

Similarly to other patients with persisting symptoms and complaints, also long COVID patients may be absent from work[kk] for one to several months, or even (longer than) a year. The degree of recovery of the patients will also influence their capacity to return to their previous occupation, for example those suffering from persistent fatigue may be not able anymore to work 7h a day, those with cognitive impairments may not be able to perform the same tasks.

Primary incapacity for work corresponds to the first year of incapacity for work. During this period, any return to work of less than 14 days is considered a relapse (which does not end the current period of primary

[kk] Attention should also be paid to children, adolescents and youths at risk of long term absence from school or to students who are not able to cope with their studies (e.g. university). Collaboration with school health services could help the children and students to get back to school. Social services, teachers and professors have also a role to play to limit the impact of the absence from school on the future of these children and youths.

incapacity). Invalidity begins at the start of the 2nd year of incapacity for work. During this period, any return to work of less than 3 months is considered a relapse (which does not end the period of invalidity).

10.2.1 Basic principles

Every employee has right to a guaranteed salary by its employer for a defined period (15 days for worker, 30 days for a salaried). After this period, the patient falls under the responsibility of the sickness funds which intervene for a defined proportion of the salary. The difference could be endorsed by a private insurance.

Unemployed are also covered by the NIHDI in case of primary incapacity: during the first 6 months of incapacity for work, the allowance is equal to the unemployment allowance benefit, limited to 60% of the gross amount lost (capped or limited to an amount per day). More details could be found on the website of the NIHDI.

Self-employees have right to indemnities from the NIHIDI under specific conditions. Once being in incapacity for work, the self-employee has 7 calendar days to report it (not including the first day of incapacity for work). He/she has right to allocations if he/she has paid their social allowances for at least 2 trimesters and is acknowledged as unable to work, meaning he/she cannot have any professional activity. If the self-employee is entitled to indemnities, and the period of the work incapacity (recognised by the advisory physician) exceeds 7 days, the self-employee may be entitled to compensation from the first day of this period. However, if the self-employee is recognised as being unable to work for less than 8 days, the 7-day waiting period will apply and no indemnities will be allowed. More information could be found on the website of the NIHDI.

10.2.2 Key actors

The **occupational physician** (*médecin du travail-arbeidsarts*) is employed by the preventive and protective service at work: this service is either internal at the enterprise, i.e. for large companies or with elevated safety risks as chemical industries, or external. The occupational physician examines the health and well-being of employee as a preventive measure. Decisions are taken independently of the employer and the employee. The occupational physician (both internal and external) therefore works independently (in accordance with the ethical code for occupational physicians recognised by the International Commission on Occupational Health). The occupational physician plays a role in the incapacity to work but can never control whether an employee is legitimately absent or not. He will never make a home visit: consultations are organised either in the enterprise, either in the offices of the services of the prevention and protection at work (SPPW). The occupational physicians assess the abilities of the employees to perform their habitual tasks when returning to work. He/she may suggest adaptations to support the return of the patients, but the advices are not compulsory. In case of disaccord with the decisions taken by the SPPW, the employees may introduce a complaint to the regional direction of the well-being at work. The regional directions are in charge of the monitoring of the law on welfare in companies and institutions (except SEVESO); the supervision of other laws such as the law on medical control; and the assistance to the Chemical Hazards Control Division for specialised medical surveillance.

The **controlling physician** (*médecin-contrôle / controlearts*) is employed by the employer. The controlling physician is given the task by the employer to check whether an employee is unable to work due to illness or accident. He/she can check the employee throughout the period of incapacity for work, not only during the period of guaranteed pay. However, the employer will mainly have a short-term absence checked because he must pay the employee's wages himself during this period. The controlling physician consults at patient's home or may request that the patients come to its practice.

The **advisory physician** (*médecin-conseil / adviserend arts)* of the sickness funds carries out his/her function on behalf of the NIHDI (National Institute for Health and Disability Insurance). One of his tasks is to assess and examine whether a person is entitled to sickness benefit from the NIHDI, once the period of the guaranteed salary is reached (after 2 or 4 weeks depending on the employee status). The patients should at least have a loss of 2/3 of their gain capacity to be considered eligible for sickness benefits.

The advisory physician also has an advisory function. He/she can, for example, recommend that the employee returns to work gradually or undergoes retraining to enable him/her to do another job. If a return to part-time work is recommended, the advisory physician's authorisation is required, but this is deemed to have been granted if the patient sends his request to his/her sickness funds no later than 24 hours before the effective date of the partial return. The advisory physician has a maximum of 30 working days from the date of resumption of work to give his/her written authorisation or refuse it.

If the advisory physician refuses the declaration of illness, an appeal can be made against this decision. This is possible via the labour court of the employee's place of residence. It is possible to appeal up to 3 months after the decision. Among other resources for patients, the LUSS published a folder to help patients to prepare their visit with the advisory physician[ll].

10.2.3 Existing measures to support return to work

Reinsertion trajectory of the NIHDI

The reinsertion trajectory aims at promoting the return to the labour market through adapted work, another professional occupation or a training for salaried employees or unemployed under a medical incapacity. This trajectory is developed in collaboration between the employee, the advisory physician of the sickness funds, the treating physician[mm] and the occupational physician[218].

To enter a reinsertion trajectory, the patient should have sufficient remaining capacities to be able to start the program. The NIHDI defines the remaining capacities "as the physical and mental abilities and aptitudes that allow a return to the labour market". These will be assessed by the advisory-physician.

The initiative for a reinsertion trajectory is taken either by the patient himself/herself, either by the advisory physician. Within 2 months after the declaration of the work incapacity, the advisory physician may initiate a reinsertion trajectory by first checking whether the patient has an employment contract or not.

In case the patient is employed or has a statutory position, the reinsertion trajectory will be coordinated by the occupational physician under the jurisdiction of the FPS Labour (see below the reintegration trajectory of the FPS Labour).

In case the patient is unemployed or has no work contract (at the exception of the statutory personnel), the reinsertion trajectory will be coordinated by the advisory physician of the sickness funds. The advisory-physician will first perform a medical and social examination and discuss reinsertion possibilities with the patient. One month later, the advisory physician will propose a concrete reinsertion proposal to the patient. The proposal is

ll The folder could be found on the website of the LUSS.

mm The treating physician could any physician involved in the care of the patient (e.g. for Long COVID patients, it could be a neurologist or a specialist in physical medicine).

discussed and signed by both parties: the advisory physician will then monitor the implementation of the plan.

Reintegration trajectory of the FPS Employment, Labour and Social Dialogue[nn]

Since 2016, a new section 6/1 has been added to the Royal Decree of 28 May 2003 on health surveillance of workers regarding the reintegration of workers who are unable to work. It provides for a tailor-made reintegration trajectory, which aims to accompany workers with long-term incapacity for work towards adapted work or other work temporarily or permanently. For those interested in rapid information, the FPS Employment published a folder on Returning to work after a sickness absence[219].

For employees who are unable to work, it is preferable to focus first on the possibilities of reintegration with their own employer, because they will generally be able to return to the agreed job in the long term, if necessary after a gradual return. Another advantage is that the employee can be reintegrated in a familiar work context, with colleagues and an employer with whom he or she is familiar and with whom he or she has a connection, which increases the chances of a successful reintegration.

During this reintegration process, an important role is played by the prevention consultant/occupational physician, who is not only familiar with the working environment and the work in a particular company, but who can also act as a known contact point for the employer and the employee. The prevention consultant/occupational physician is also part of a multidisciplinary team within the internal or external prevention service. If necessary, this makes it possible, for example, to call on ergonomists or prevention consultants specialising in psychosocial aspects.

The aim of this reintegration scheme is to promote the reintegration or return to work of a worker who is unable to perform his or her agreed work temporarily or permanently (Article I.4-72, paragraph 1).

In the case of an employee who can no longer perform his or her agreed work temporarily, suitable work or other work may be sought until the agreed work can be resumed. For example, after an infection due to COVID, the worker may need time to recover or may be tired a lot and therefore not yet able to return to work full time or to make long journeys. In this case, gradual return to work can be a useful tool to allow the worker to return to work at the pace of his or her recovery, and the job can be temporarily adapted, or alternative work sought. This adaptation can be completed gradually until the worker is again doing the agreed work. A gradual return to work is usually possible with the continuation of (part of) the sickness insurance benefit, provided that the advisory physician of the sickness funds agrees to this.

For workers who are definitively unfit for the agreed job, either on the basis of a certificate from the treating physician or on the basis of a decision by the prevention consultant/occupational physician, a permanent solution must be sought, through adapted work or another job. The return to work after an occupational accident or disease is excluded: both the Industrial Accidents Act of 10 April 1971 and the Coordinated Acts on Occupational Diseases of 3 June 1970 contain a procedure for returning to work which is independent of this reintegration route (Article I.4-72, paragraph 2).

Three actors play a major role in supporting the return to work of patients: the advisory-physician, the occupational physician and the controlling physician 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, the reinsertion trajectory and the reintegration trajectory constitute a formal mechanism to support the return to work.

The general measures for employees and self-employees apply also for long COVID patients.

[nn] This section is translated and adapted from the webpage of the PFS Employment, Labour and Social Dialogue https://emploi.belgique.be/fr/actualites/trajet-de-reintegration-pour-les-travailleurs-en-incapacite-de-travail

10.3 COVID and long COVID as professional diseases

The Federal Agency for Professional Risks (Fedris) has recognised COVID-19 as an occupational disease for workers in certain sectors. This means that they can claim compensation if they have been affected by the disease and diagnosed by a laboratory test (except in exceptional severe cases).

Target groups

This measure concerns 1) employees in the health care sector who are at significantly increased risk of being infected with the virus (occupational disease code 1.404.03), 2) salaried employees in the critical sectors and essential services who worked during the period from 18 March to 17 May 2020 inclusive (occupational disease code 1.404.04), provided that: a) the working conditions or the nature of the work activities carried out regularly make it impossible to maintain a distance of 1.5 metres in contact with other people; b) no more than 14 days have elapsed between the onset of the illness and the date of the employee's last actual work performance outside the home, and c) the company where the employee was working is on the list of companies in critical sectors and essential services (+ a maximum of 14 days may elapse between the occurrence of the illness and the removal of the company from the list)[220].

Other employees can file a claim with Fedris but, in this case, the burden of proof will be on the victim: it means that the employee should prove that he/she contracted the disease in the course of their professional activities and not in other circumstances. It should be noted that Fedris is only competent for those in the private sector and in provincial and local administrations.

In addition, COVID-19 can be recognised as an accident at work under certain conditions. In order to do so, employees who believe they are victim of such an accident must report it to their employer as soon as possible. In May 2021, there was an ongoing discussion about the possibility of acknowledgement when several cases occur in a same enterprise[221]. In July 2021, discussions were also ongoing about acknowledging COVID-19 as a professional disease for police and firemen[oo].

Data

In 2020, Fedris received twice as many applications for recognition for COVID than for other occupational diseases. Around 73 to 74% of the applications concern patients with a sickness leave of 4 to 6 weeks, with around 5% of the patients with more than 9 weeks of incapacity[221].

On July, 6, 2021, 20 230 cases concerning employees in the health care sector were reported by occupational physicians (since March 2020) while 17 484 applications for indemnities were submitted (since March 2020). Thirteen applications concerned a deceased and 9 concerned an aggravation of the health problem. Applications concern 85% of women and 15% of men. An age gradient is observed: the number of applications is the most elevated between 40 and 60 years. Reimbursement of health care was granted for 2325 applications. For 4019 applications, a decision was made granting a period of temporary incapacity. In 73% of these decisions, the period of incapacity is between 2 and 4 weeks. In 15% of these decisions, the temporary incapacity lasts between 4 and 6 weeks. In 6% of these decisions, the temporary incapacity lasts between 6 and 9 weeks, and, in 6% of cases, more than 9 weeks. One decision was taken about a permanent incapacity where a permanent rate of 100% was awarded after a period of more than 7 months of temporary incapacity[221].

For salaried workers with COVID-19 working in critical sectors and essential services during the period from 18 March to 17 May 2020, 313 cases were reported by occupational physicians (since March 2020) while 381 applications for indemnities were submitted (since March 2020). Two applications concerned a deceased and one concerned an aggravation of the health problem. Victims were aged of 44 years and older in 71% of the situations; 37% of the application concerned women. Reimbursement of

[oo] https://www.nieuwsblad.be/cnt/dmf20210705_97066376

health care was granted for 18 applications. For 55 applications, a decision was made granting a period of temporary incapacity[222].

Applications could also be made via the "open system", that is persons working outside the health care sector who are professionally exposed to the COVID-19 and must prove they were infected because of their professional occupation. A total of 78 cases were reported since March 2020 and 273 applications for indemnities were submitted: 174 applications were dismissed[222].

Data are regularly updated and published on the website of Fedris.

Process of acknowledgement

The application could be submitted:

- By the occupational physician: in this case, Fedris will contact the employee and provides her/him with the documents to be completed
- By the employee herself/himself: the website of Fedris includes the list of the documents that need to be completed by the patient and his/her treating physician. Acknowledgement for COVID infections are mostly introduced by pneumologists.

To attest of the infection, the patients should provide a laboratory test (antigen, PCR, or serologic test). Acknowledgement could be granted based on clinical symptoms and results of medical imagery (e.g. thoracic CT scan). The decision is taken by the advisory physician of Fedris. When the patient displays objective lesions, the decisions are quite straightforward. When the symptoms are more difficult to objective, such as persisting fatigue, pain, headaches, the acknowledgement is more complex.

Information and documents could be found on the website of Fedris.

Consequences of acknowledgement

When Fedris recognises COVID-19 as an occupational disease, the patients could receive:

- Compensation for temporary incapacity to work, provided that this incapacity to work lasts at least 15 calendar days. For the period of temporary incapacity for work, the person concerned is entitled to a daily allowance equal to 90 per cent of the average daily pay (calculated based on the person's maximum salary). The amount of the allowance paid to the worker concerned is reduced by the guaranteed wage (which is reimbursed to the employer) and the payments made by the sickness funds.
- Reimbursement of the personal share of the health care costs related to the recognised occupational disease (the co-payment), regardless of the duration of the (temporary) incapacity for work. Fedris can reimburse the costs incurred during the 120 days preceding the submission of the claim for compensation[pp].
- In the event of permanent damage, compensation for permanent disability may also be granted, i.e. if the patient can attest of permanent consequences of COVID.

In case of death as a result of COVID-19 contamination, some relatives may also be entitled to compensation.

In case of a negative decision, patients may reintroduce a demand if their health deteriorates, i.e. new symptoms, objectively detectable lesions …

[pp] Category D medicines, for which there is no intervention by the compulsory health insurance (e.g. basic painkillers), cannot be reimbursed by Fedris either.

COVID-19 is acknowledged as a professional disease for the professionals of the health care sector.

Other professional categories could also benefit from this acknowledgement under specific conditions.

10.4 Disability management & coaches

Since 2014, the NIHDI has developed the concept of Disability Management, that is a method aiming at supporting the preservation or the return to work of an employee in work incapacity. This method includes a systematic approach at the work place level and coordinated actions around the patient, in collaboration with the employer, the occupational physicians, the advisory physicians and the treating physicians, together with their multidisciplinary team [216].

Another initiative supported by the NIHDI are the ReumaCoach. Funded since 2017, as a partnership with ReumaNet, ReumaCoachs proposes a personalized accompaniment of workers with a rheumatological disorder at their request. The coach prepares the return to work, at part or full time, in considering rights and preferences of workers. The coach assesses, with the patient, their physical health, their talents and interests and identifies the possibilities of adaptation of the workplace. The coach could also help to prepare the meetings with the employer and with the occupational physician.

So far, there is no specific guidance for long COVID patients returning to work in Belgium.

11 CONCLUSION

As described in the chapter on the epidemiology, patients living with long COVID constitute a heterogeneous group of population and suffer 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.

However over the last years several research projects have been attempting at improving the management of the needs of complex (and chronic) patients (see, i.e., the KCE report 190 on the health care organisation for chronic patients in Belgium[223], the KCE report 199 on the evaluation of the rehabilitation conventions, the KCE reports 57 (physiotherapy and physical and rehabilitation medicine), 87 (locomotor and neurological rehabilitation) and 140 (cardiac rehabilitation), the recommendations of the Observatory of Chronic Diseases and the reports of the High Superior Council). Besides, guidelines have been issued for some of the precited health problems, especially to support the GP, such as the management of depression or chronic pain.

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 billing and the "statute 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 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. All long COVID patients (will) benefit from the four types of maximum billing when criteria are met. Patients can directly ask their sickness funds for an update of their

situation in case of change in the household income in order to benefit from an increased maximum billing.

Besides, some long COVID patients can also benefit from the **statute "chronic disease patient"** (*statut affections chroniques / statuut chronische aandoening*) if they have a minimum of health expenditures during the 2 last civil years **OR** if they benefit from the fix-payment for chronic diseases and have reached a threshold of personal contributions to health care. The **fix-payment for chronic diseases** *(intervention forfaitaire pour malades chroniques/ forfait voor chronisch zieken)*is delivered to patients who have been hospitalised for a least 120 days or had at least 6 hospitalisations; OR received a 6-month physiotherapy treatment on the grounds of the List E; OR benefit from certain lump sum payments for home nursing reserved for (old) dependent patients; OR benefit from specific social allowances.

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 monodisciplinary[qq] 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. poly-neuropathy and myopathy; respiratory dysfunction with ESW<50%) for which multidisciplinary rehabilitation is considered as an evidence-based approach (K30, K45 and K60-nomenclature);
- Eight reimbursed sessions for persons from 15 years of age or older with a psychologist per year based on a medical prescription, with a possibility of 20 extra sessions when the patient needs specialised psychological care;
- Expanding reimbursed services via specific criteria might also be applicable to 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 session) when certain criteria are met. These specific measures need to be studied in the context of long COVID.

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) or 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 but long COVID patients might benefit if they fit the regulations in force. An example is an increased

[qq] While the reimbursement rules refer to 'monodisciplinary' , in practice many hospitals organise it in a multidisciplinary way

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 cover services for disciplines which are not or only to a very limited extent covered under standard reimbursement (e.g. services provided by psychologists, dieticians, social worker) or with a higher frequency or intensity (e.g. physiotherapy). Several conventions exist that are related to problems which are also encountered by long COVID patients. 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:

- Long term Oxygen therapy will only concern long COVID patients with severe respiratory sequelae. Nevertheless, outside the system of conventions, 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;
- Home assistance for ventilation will only concern long COVID patients with severe respiratory sequelae;
- Rehabilitation for severe chronic respiratory problems which is restricted to (a.o. criteria) patients with a forced expiratory volume in one second (FEV1) below 50% of the predicted value;
- General functional rehabilitation centres for locomotor and neurological disorders (convention 950) is in principle open for long COVID patients (after a decision of advisory physician sickness fund) 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 remarks holds for convention 771 (which is since the 6th State Reform 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 rehablitation conventions;
- Chronic Fatigue Syndrome : a multidisciplinary diagnostic assessment and cognitive behavioural therapy is part of the convention organised by only one centre (no other hospitals submitted an application for this convention).

Neurocognitive assessment and rehabilitation: limited options

As described in the chapter on pathophysiology, neurocognitive problems are an important and invalidating symptom for many long COVID patients. The possibilities to have a neurocognitive assessment under the current regulation are limited. A neuropsychological asssessment 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 functions 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 GP, for an assessment of their cognitive functions. This (less thorough) assessment is not reimbursed by the NIHDI, but some sickness funds contribute to the cost as part of their supplementary coverage package. 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 as follow-up after a hopitalisation; memory clinics for patients wih early stage of dementia).

Work re-integration

Three actors play a major role in supporting the return to work of patients: the advisory physician, the occupational physician and the controlling physician, 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, the reintegration trajectory of the NIHDI and the reintegration trajectory of the FPS Labour constitute a formal mechanism to support the return to work. The general measures for employees and self-employees also apply to long COVID patients.

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