Literature screening report

Post COVID-19 Condition: Definition, prevalence, therapy, pathogenesis, socio-economic implications, and relation to post-acute sequelae of other viral infections (final report)

Report submission date: 01.12.2023
Responsible author(s): Vasileios Nittas, Milo A. Puhan
Affiliation: Epidemiology, Biostatistics and Prevention Institute, University of Zurich
Co-authors: Alessia Raineri, Julia Kopp
Coordination contact: Jorgen Bauwens (SSPH+) – jbauwens@ssphplus.ch

Preamble

A large number of scientific publications become available daily, reflecting the rapid development of knowledge and progress of science on COVID-19 related issues. Leading authorities should base decisions or policies on this knowledge; hence they need to master the actual state of this knowledge. Due to the large number of publications shared daily, decision-makers heavily depend on accurate summaries of these publications, in the different public health domains. Therefore, the authors of this report were mandated by the Swiss School of Public Health Plus (SSPH+), on request of the Federal Office of Public Health (FOPH), to inform the FOPH on recent findings from the literature.

Table of Contents

Background and aims

Our knowledge of the long-term health consequences of SARS-CoV-2 is continuously evolving. Post COVID-19, or otherwise widely known as Long COVID, is a multifaceted condition with primary healthcare and broader public health implications.[1] Fully understanding why and how post COVID-19 condition (PCC) develops, how it can be prevented, and how it is best treated is therefore an essential step towards mitigating its burden. Generated knowledge should be holistic, including the broader public health and socio-economic dimensions of PCC. While many European countries have launched initiatives to establish care and support pathways for PCC patients, the need for stronger and more targeted action remains. The Swiss Federal Office of Public Health (FOPH) has commissioned a report that will analyze the current healthcare situation and PCC patient needs.[2]

This living literature screening report aims to provide a concise and regularly updated state of the knowledge, focusing on the following five areas: (1) definitions, (2) prevalence, (3) symptoms, risk factors, and potential causes, (4) therapy and rehabilitation, (5) socio-economic implications, (6) relation to post-acute sequelae of other viral infections, and (7) healthcare and policy responses. The formulated questions are provided in textbox 1. These have been co-defined with the FOPH to provide findings that best serve their policy needs.

Textbox 1: Focus areas and corresponding questions

Definitions
Q1: Are there any new and relevant definitions?

Prevalence
Q2: What are the reported prevalence estimates?

Symptoms, risk factors, and pathogenesis
Q3: What are the clinical manifestations, symptom clusters, influencing factors, and potential causes?

Therapy and rehabilitation
Q4: What are the available and potential measures for therapy and rehabilitation?

Socio-economic implications
Q5: What are the socio-economic implications?

Relation to post-acute sequelae of other viral infections
Q6: How does PCC relate to post-acute sequelae of other viral infections?

Healthcare and policy responses
Q7: What are the healthcare and policy responses in other European nations and North America?

Methods

We conducted (a) weekly automatic PubMed searches and (b) regular manual searches in Google Scholar and relevant websites (e.g., governmental). Findings are published by the FOPH every three to four months. This current covers the period from August to November 2023 and additionally draws from our literature screening report "Long COVID: Evolving Definitions, Burden of Disease and Socio-Economic Consequences" published by the FOPH in December 2022.[3] We included all types of research studies, including systematic reviews and meta-analyses. For Q2 (prevalence), we predominantly reported studies with population-based samples and/or control groups and a mean follow-up of 12 weeks. Studies were classified as population-based if they used sampling procedures that are generally accepted to yield representative samples (e.g., probability sampling or census data). For Q2, we also reported estimates provided by health organizations, such as the United States (US) Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). For Q4 (therapy and rehabilitation) we also reported upcoming studies, registered in clinicaltrials.gov. For Q7 (healthcare and policy responses), we primarily considered policy and news reports. For all remaining questions, we prioritized studies that we considered to be the most reliable, with representative samples and well-designed methodologies. We did not conduct a formal quality assessment of included studies, however, reported new findings in relation to study limitations and overall data reliability. Narrative reviews, editorials, opinion papers, and case reports were excluded.

Structure

The findings are presented in three parts. First, a constantly updated, cumulative state of the knowledge summary, covering Q1 to Q7. Second, a research update, covering Q1 to Q6 and presenting the latest evidence. Third, a response update (Q7) that provides an overview of public health responses in Europe, the US, and Canada.

Part 1: Executive summary

In total, 23 new studies were identified and included (a total of 84 studies). The studies included in the report's previous versions are listed in Appendix 1. The new studies are listed in Appendix 2. The next paragraphs (1.1 to 1.7) provide a cumulative state of the knowledge summary, drawing from recent studies (as reported in part 2), as well as from our previously published literature screening report "Long COVID: Evolving Definitions, Burden of Disease and Socio-Economic Consequences".[3]

1.1: Definitions

Long COVID and post COVID-19 condition are the currently most used terms in the literature. The WHO defines PCC as "(…) a *condition that occurs in individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis".*[4] Recently, it added a definition of PCC in children and adolescents. The definition strongly overlaps with that for adults, primarily differing in the highlighted symptoms. It states that PCC can be assumed in "*individuals with a history of confirmed or probable SARS-CoV-2 infection, when experiencing symptoms lasting at least 2 months which initially occurred within 3 months of acute COVID-19*".[5] The definition highlights fatigue, anosmia, and anxiety as the most common symptoms in children and adolescents.[5] The debate for a clearer distinction between the terms Long COVID and post-COVID has been intensifying.[6] A recent review identified substantial heterogeneity of PCC definitions in the scientific literature, suggesting that although certain definitions have been commonly accepted (e.g., WHO, NICE), most studies fail to adhere to these.[7]

1.2: Prevalence

The prevalence of PCC among adults with confirmed SARS-CoV-2 infections in Switzerland is estimated at about 23% at six months post-infection and 17% at 12 months post-infection.[8] Germany's Robert Koch Institute reported analyses conducted by Germany's central health insurance institute , indicating a PCC prevalence (ICD-10 code U09.9) between 7% and 13%.[9] Prevalence estimates based on the ICD-10 code tend to be lower, primarily due to the current underutilization of the code. Austria's Vienna Center for Electoral Research and Corona Panel Project reported prevalence estimates of about 19% and 18% respectively, similar to the US Household Pulse Survey, which reported a prevalence between 11% and

17%.[10,11,12] A recent study from the UK reported a PCC prevalence of 10.2%, 7.5%, and 5.2% at 4 weeks, 12 weeks, and 52 weeks respectively.[13] The WHO reported that *"studies show that around 10–20% of people infected by SARS-CoV-2 may go on to develop symptoms that can be diagnosed as long COVID"*.[14] When considering that, over the entire duration of the pandemic, around 1 out of 4 infections were diagnosed by a SARS-CoV-2 test,[15] the prevalence of PCC among all infected adults might range between 5-10%. All reported prevalence estimates apply to the definition provided by the WHO unless otherwise stated.[4] Recent studies from the US report similar prevalence estimates.[16]

Among all infected children and adolescents, we estimate the overall PCC prevalence to be about 3%. This estimate is based on two population-based studies.[17,18] The first, the Swiss Ciao Corona study was based on a random sample and encompassed both tested and untested children.[17] The second, a household cohort study conducted in England and Wales also included tested and untested children.[18] In both studies, selection bias (based on actively seeking care and testing) was considered to be low.[3] Two recent studies, both from the UK, reported higher prevalence estimates. The first, a cross-sectional population-based survey reported a prevalence of 4.4% for children aged 5–11 years and 13.3% for children aged 12-17 years.[19] The second, a national cohort study, included children between the ages of 11 to 17 years and reported a PCC prevalence of 14.2% (12-16% amongst those infected with Omicron).[20,21] Both studies had limitations that might overestimate PCC prevalence. The first did not include a control group and the second had a low response rate.

1.3: Symptoms, clusters, influencing factors, and pathogenesis

The literature reports over 50 different PCC symptoms. In adults, the most frequently reported symptom is fatigue, followed by post-exertional malaise, dyspnoea, cough muscle pain/weakness, concentration and sleep problems, chest tightness, loss of smell and taste, memory impairments, anxiety, and depression.[3,22,23] A recent review identified three PCC phenotypes: (1) Cardiorespiratory, (2) systemic inflammatory, and (3) neurological.[23] In children, altered or lost smell, anxiety, fatigue, headache, loss of appetite, earache/ringing in ears, sore throat, sore eyes, fever, sleep disturbances, and muscle fatigue are some of the most commonly reported symptoms (in addition to 35 less common symptoms, outlined in table 1).[5,24,25]. A recent systematic review highlighted the long-term respiratory PCC symptoms in children, with dyspnoea, chest pain, cough, and chronic obstructive sleep apnea being among the most common .[26] Children with PCC may also at higher risk for mental health problems.[27] In most cases (among children and

adults), symptoms tend to improve over time.[28] Mean duration is estimated at nine months among hospitalized and four months among non-hospitalized individuals, with about 15% of PCC patients still experiencing symptoms 12 months post-infection.[22] In terms of prognosis, an ongoing population-based cohort study (Zurich SARS-CoV-2 Cohort) reported recovery and symptom trajectories in Switzerland.[8] At 12, 18, and 24 months, 18.5%, 19.2%, and 17.2% of persons with a previously confirmed SARS-CoV-2 infection reported persistent symptoms respectively. At 24 months, 10.4% reported mild, 3.9% moderate, and 1.9% severe PCC.[8]

For adults, the literature on risk factors is emerging and provides new evidence on the role of vaccines and reinfections.[29-32] In adults, female sex, age (40+ years), comorbidities, previous diagnosis of a psychological condition, the severity of acute disease (hospitalization or intensive care unit (ICU) treatment), obesity, non-vaccination, the presence of IgM and IgG antibodies, and active smoking may be increasing the risk for PCC.[3,29,33,34]. Many of these factors, such as the number of symptoms during acute disease, the severity of acute disease, missing vaccination, increasing age, and comorbidities, have been previously linked to the severity of PCC (e.g., cardiovascular involvement, increased disability, prolonged fatigue).[35-38] In children and adolescents, female sex, age (12-17 years), history of allergic conditions, other pre-existing chronic conditions, overall poorer physical and mental health, and severity of acute disease (hospitalization, number of symptoms) may be increasing the risk for PCC.[3,19,39]. Whether and how these factors impact PCC severity for children and adolescents remains an evidence gap.

Regarding protective factors, early reports highlighted good physical fitness levels, being treated with certain antiviral therapies (see section 1.4) during acute infection, and a nutrition rich in vitamins B, C, D, E, magnesium, selenium, zinc, flavonoids, and polyphenols, curcumin, and sulforaphane during acute disease might be associated with lower PCC risk.[3,40] Recent evidence suggested that (1) an Omicron infection (as compared to wild-type, Alpha, and Delta), (2) previous vaccination (one or two doses), and (3) reinfection (with no Long COVID after the first infection) may all be associated with lower chances of new-onset PCC in adults.[29-32,34,41-45] Previous evidence suggested that for some, post-infection vaccination may be associated with reduced PCC severity (therapeutic effects), yet, the evidence remains mixed and unclear.[46-49] Whether and how the remaining protective factors are associated with PCC severity remains an evidence gap. In children, the evidence on PCC protective factors is not established yet. Previous evidence suggested that vaccination decreases the chances of severe acute disease in children.[50] Considering that the severity of acute disease is a PCC risk factor, it could be assumed that vaccination may

act as a protective factor for children and adolescents, yet recent evidence does not confirm that assumption yet.[51] Whether and how protective factors impact PCC severity remains an evidence gap. A recent study reported that for children between 12 and 17 years, (1) male sex, (2) being of Asian ethnic background, and (3) living in more affluent neighborhoods were associated with lower odds for PCC development.[19] Asymptomatic acute disease and an Omicron infection were also both associated with lower PCC risk in children.[52]

PCC pathogenesis remains unclear. However, plausible theories are emerging. Previous and recent publications highlight the most prominent theories, being (1) immune dysregulation, (2) microbiota dysbiosis, (3) autoimmunity and immune priming, (4) blood clotting and endothelial abnormalities, (5) dysfunctional neurological signaling, (6) prolonged various persistence and/or reactivation of other viruses, and (7) unrepaired tissue damage.[40,53,54] A review has proposed the theory that tachykinins, primarily substance P, could be one causal factor for PCC.[55] Table 3 provides a list of potential PCC mechanisms according to symptom clusters.[56]

1.4: Therapy and rehabilitation

There is currently no established PCC cure. Most treatments aim to reduce symptoms. Currently, there are six ongoing Swiss studies registered in clinicaltrials.gov (see table 4). The first is a phase two randomized controlled trial (RCT) aiming to evaluate the efficacy and safety of temelimab for treating PCC-related neuropsychiatric symptoms.[57] The second RCT aims to evaluate the effects of 10 mg fampridine (4-Aminopyridine) on working memory performance in individuals with PCC and subjective cognitive impairment.[58] The third trial aims to evaluate the effects of Pycnogenol®.[59] A fourth trial aims to evaluate the efficacy of BC 007.[60] The fifth aims to assess the effects of respiratory training on dyspnoea and exercise breathing, and the sixth to describe the kinetics of cardio-pulmonary exercise training.[61,62] Beyond Switzerland, a search in clinicaltrials.gov revealed 4 recently completed trials (total of 31) on PCC treatment and rehabilitation (see Appendix 3). Results were identified for eight of those (see Appendix 3). Li et al recently published a review in Nature Signal Transduction and Targeted Therapy and provided an updated list of candidate treatments (see updated table 5).[63] Three trials on preventive treatments reported that early administration of metformin, nirmatrelvir, or molnupiravir (during acute SARS-CoV-2 infection) may reduce the risk for PCC.[64-66] Al-Aly recently published a viewpoint in the Lancet Infectious Diseases providing an overview of current PCC prevention options, adding following antiviral drugs: irmatrelvir (in combination

with ritonavir) and ensitrelvir.[67] Al-Aly outlined that the evidence is still preliminary, and many uncertainties remain.[67]

The WHO's living guidance for COVID-19 management provided recommendations on the rehabilitation of adults with PCC.[14] It outlined the importance of (1) standardized symptoms assessment and outcome measurements, (2) adequate follow-up systems, and (3) appropriate referral systems. The guidance also provides rehabilitation recommendations for specific PCC symptoms (see Appendix 4).[14] The patient-led association Long COVID Physio recently published a list of principles and recommendations for safe PCC rehabilitation (see table 6).[68] One systematic review and one RCT reported first evidence of the effectiveness of respiratory rehabilitation and exercise training rehabilitation on improving respiratory symptoms and the quality of life of PCC patients.[69,70] A recently published systematic review and meta-analysis provided a list of PCC rehabilitation approaches for physical capacity and quality of life (see textbox 2).[71]

1.5: Socio-economic implications

In a subset of patients, PCC has a negative impact on quality of life and can lead to functional restrictions, as well as impaired family and social life.[72-75] PCC also negatively impacts work life, primarily in those with moderate to severe symptoms. A study from Switzerland reported 5.8% of patients with PCC had direct work-life disruptions or even complete inability to work (1.6%).[76] Reports from the United Kingdom (UK) and the US highlighted that about 16-25% of PCC patients had at some point adjusted their working hours or remained out of work.[77,78] A recently published qualitative study (n=510) emphasized the complexity of PCC's impact on work life. Participants outlined that the diversity and episodic nature of PCC symptoms interferes with the organization of work-related activities while being attached to remaining PCC stigma and disbelief, both at work and in medical settings.[79]

Robust and reliable data on the socio-economic implications of PCC remain scarce, yet first reports have started to emerge. A UK-based retrospective matched cohort study reported that the incremental costs per patient were significantly higher for those diagnosed with PCC, primarily linked to telephone consultations, and adding up to about £23 million in national costs.[80] The US-based COVID-19 Longhauler Advocacy Project estimated the average medical cost per PCC patient at about $36,000.[81] A recent study from Germany estimated the PCC-related costs due to production loss between €3.4 and €5.9 billion (in 2021).[82] In the same year, pension costs related to rehabilitation were estimated at around €2.1 billion,

and the economic burden on the healthcare system at around €332 million.[82] The US Household Pulse survey found that respondents reporting PCC symptoms were about twice as likely to experience significant housing insecurity.[83] A not yet peer-reviewed study from the UK analyzed data from four longitudinal surveys (n=20,112) and found that among those reporting long-term symptoms, PCC was associated with lower self-perceived financial well-being and a higher number of new benefit claims, independent of sex and educational level.[84]

1.6: Relation to post-acute sequelae of other viral infections

The long-term symptoms of SARS-Cov-2 are not a surprising or unexpected phenomenon.[85] At least since the Russian and Spanish flu (1898 and 1918) post-viral syndromes have been described with symptoms very similar to those reported for PCC.[86,87] Other well-known viral pathogens, such as polio, Ebola, dengue, SARS-CoV-1, chikungunya, West Nile virus, and MERS-CoV are linked to the development of largely unexplained post-viral syndromes (see table 7).[88,89] The clinical presentation of post-viral syndromes, including PCC, is heterogeneous but exhibits a set of common systemic symptoms, such as exertion intolerance, fatigue, unrefreshing sleep, flu-like symptoms, neurocognitive and sensory symptoms, as well as muscle and joint pain.[88] Dyspnoea, fatigue, reduced exercise capacity, and psychological impairment are common long-term symptoms shared between SARS-CoV-1, SARS-CoV-2, and MERS-CoV.[89]

A key similarity between many post-viral syndromes, including PCC, is the diagnosis of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).[85,88] A considerable subset of PCC patients meet the criteria for ME/CFS.[40,85] Common symptoms for both PCC and ME/CFS patients are fatigue, post-exertional malaise, headaches, dysautonomia, postural tachycardia syndrome, exercise intolerance, sleep problems, impaired memory, impaired attention, depression, anxiety, reduced activity, myalgia, arthralgia, muscle weakness, hot and cold spells, loss of appetite, palpitations, nausea, diarrhea, and chills. Chronic fatigue has also been reported after SARS-CoV-1 infections and MERS-CoV and is observed in adults and children.[63,90] Current theories suggest that autoimmunity, viral mimicry, Epstein-Barr virus reactivation, and autonomous dysfunction could all lead to PCC with ME/CFS.[91] Furthermore, endothelial dysfunction and autoantibodies to G protein-coupled receptors may also play a role in the development of ME/CFS in PCC patients.[91] Potential mechanisms were summarized in a recent review published in Nature Signal Transduction and Targeted Therapy and are: immune and inflammatory responses, vascular dysregulation, and autonomic or metabolic adaptation.[63] A German study reported that PCC patients with ME/CFS had

more severe symptoms, with stronger fatigue, post-exertional malaise, and slower improvement over time.[91] Currently there are no recognized pharmacological or non-pharmacological treatments of post-viral syndromes.[92-95] For ME/CFS, there are currently two drugs being researched. The first is rintatolimod, a TLR-3 agonist, and the second is N-acetylcysteine.[96] Graded exercise therapy should not be considered a recommended ME/CFS treatment anymore.[95] A recent meta-analysis pooling individual patient data from eight trials found that cognitive behavioral therapy had positive effects on fatigue severity and functional impairment.[97]

At this point, it is difficult to compare the prevalence of post-viral syndromes across pathogens. The main reason is that such population-wide testing for a virus was done for the first time during the COVID-19 pandemic. Thus, population-based studies have a stronger basis for valid estimates of the prevalence of PCC since testing ranged from asymptomatic individuals to patients with severe COVID-19. Such studies could not be conducted before the COVID-19 pandemic. Yet, that has sparked new research that aims to assess long-term symptoms following different pathogens. For example, an ongoing study from Australia (currently only available as a research poster) aims to compare post-viral syndromes following SARS-CoV-2 and influenza infections. Preliminary results are available for the first three months after infections, notably before one can establish a diagnosis of PCC according to the WHO definition.[98] The study found similar prevalence estimates of prolonged symptoms (up to 12 weeks) after SARS-CoV-2 and influenza infections and concluded that there was no evidence of a difference in the risk of developing moderate to severe long-term symptoms.[98]

1.7: Healthcare responses

Some noteworthy new healthcare and policy responses are Germany's new commitment to PCC research (announcement of €150 million in funding) and easier access to medicine for PCC patients, the US National Institutes of Health RECOVER initiative, and newly established secretary's advisory committee on Long COVID, as well as Canada's Post-COVID-19 Interdisciplinary Clinical Care Network.[99-102] The health ministers of the G7 countries agreed that there is an urgent need for stronger research on PCC and promised a joint research initiative to be initiated in 2024.[103] Table 8 provides an overview of healthcare responses and policies in Europe, the US, and Canada.

Part 2: Research and therapy update

2.1: Are there any new and relevant definitions?

No new terms or definitions were identified for PCC in adults. The WHO definitions for adults and children remain the most widely acknowledged definitions to date.[4] Yet, a recent review of clinical trials, identified through PubMed and clinicaltrials.gov, identified substantial heterogeneity in PCC definitions.[7] Of 92 identified studies, about 54% defined PCC in relation to laboratory-confirmed SARS-CoV-2 infections. The review also found that studies used eight different time durations, ranging from four to 52 weeks. About 36% did not mention any specific durations.[7] These findings suggest, that although certain definitions have been commonly accepted (e.g., NICE, WHO), most studies fail to adhere to these.[7] Another recently published study emphasizes that PCC prevalence varies drastically when using different PCC definitions.[16] The study used survey data, including 8.927 test-positive and 3.526 test-negative participants in the Netherlands, and assessed PCC prevalence across six definitions: (1) presence of one or more PCC-related symptoms; (2) presence of one or more PCC-related symptoms with a significantly higher prevalence in test-positive than test-negatives; (3) presence of one or more PCC-related symptoms with a high severity score; (4) Who definition; (5) currently feeling unrecovered; (6)) presence of one or more PCC-related symptoms at 3 months. The prevalence of PCC ranged from 26.9% to 64.1%, highlighting the impact of the chosen definition on reported prevalence estimates.[16]

2.2: What are the reported prevalence estimates?

2.2.1 PCC prevalence in adults

A recently published study from the US used data from US Census Bureau's Household Pulse Survey (= 461,550).[104] The study found that about 30% of those with a previous infection had reported PCC symptoms for three months or longer, corresponding to 14.4% of all respondents.[104] A US-based multicenter study of adults with COVID-like symptoms (1,288 test-positive and 453 test-negative) reported that about 16% had PCC symptoms at 12 months after the test result, with no significant difference between those who tested positive and negative.[105] A large study (n=242,712) from the UK repeatedly sampled random cross-sections of the population in England to assess the prevalence of SARS-CoV-2 and PCC. Among participants with a confirmed and symptomatic infections (n=130,251), 10.2%, 7.5%, and 5.2% reported symptoms at 4 weeks,

12 weeks, and 52 weeks respectively.[13] Limitations: The studies might be limited by reporting, recall, and selection bias.[13,104,105]

2.2.2 PCC prevalence in children and adolescents

A recently published sub-study of the Children and young people with Long COVID (CLoCk) study, a national, matched prospective cohort study with participants aged 11-17 years in England, described the prevalence of PCC among those infected or reinfected with Omicron.[21] The study included children and teenagers that had a test in January 2022, with a final sample of 332 test-positive first infections, 243 test-positive reinfections, and 311 test-negatives. The study found that amongst those infected with Omicron, 12%-16% reported PCC symptoms at three and six months after acute disease (infection or reinfection). Limitations: High likelihood of nonresponse bias.[21]

2.2.3 Reported by national and international organizations

In early 2022, Santé Publique France conducted a study of the prevalence and impact of PCC, which showed that 30% of respondents infected with SARS-CoV-2 had PCC (according to the WHO definition). This corresponds to a prevalence of 4% in the general population. A new, more robust study was carried out between September and November 2022. The results remain to be officially presented.[106] The Vienna Center for Electoral Research reports an estimate of 19% among those with confirmed infections.[12]

2.3: What are the clinical manifestations, symptom clusters, influencing factors, and potential causes?

2.3.1 Clinical manifestations & trajectories

For adults, all symptoms have been described extensively in our previous literature screening report.[40] Recent studies did not add any new symptoms but confirmed that the most common symptoms include fatigue, post-exertional malaise, dyspnoea, cough muscle pain/weakness, concentration and sleep problems, chest tightness, loss of smell and taste, memory impairments, anxiety, and depression.[23,107] A recent systematic review and meta-analysis reported that the most common symptoms between one and three months were fatigue, post-exertional malaise, dyspnoea, and anxiety. The most reported symptoms between four to six months were fatigue, post-exertional malaise, dyspnoea, and depression. Beyond six

months, the most common symptoms were fatigue, post-exertional malaise, muscle pain/weakness, anxiety, and depression.[23] Limitations: The review is limited by high heterogeneity among primary studies.[23]

For children and adolescents, the evidence is emerging and summarized in table 1. A recent systematic review highlights the long-term respiratory PCC symptoms in children, with dyspnoea, chest pain, cough, and chronic obstructive sleep apnea being among the most common.[26]

Table 1. PCC symptoms in children and adolescents (updated) [5,24-26]

Fatigue	Altered smell or anosmia	Anxiety
Chest pain	Cognitive difficulties	Cough
Diarrhoea	Dizziness	Dyspnoea
Earache	Fever	Headache
Insomnia	Joint pain or swelling	Light sensitivity
Loss of appetite	Mood swings	Myalgia
Nausea	Palpitations	Postural symptoms
Rash	Stomach pain	Sore eyes or throat
Exercise intolerance	Heart rate variations	Dysphagia
Nasal congestion	Constipation	Rhinorrhoea
Sleep disturbances	Paraesthesia	Muscle weakness
Tremors	Sleep apnoea	

*this table was extracted from the original publication without any major language adjustments[5]

2.3.2 PCC clusters/subtypes

A recent systematic review and meta-analysis reported some of the common and consistently reported PCC clusters in the literature.[23] These were three and are listed in table 2.

Table 2. PCC clusters[23]

Phenotype	Description
Cardiorespiratory	Fatigue, dyspnoea, chest pain, muscle pain, headache, and palpitations
Systematic inflammatory	Dizziness, gastrointestinal symptoms, muscle pain, muscle weakness, hair loss, and sleep disorders
Neurological	Anosmia, paraesthesia, headache, neuropathies, dizziness, vision and balance problems, memory problems, and poor concentration

*this table was extracted from the original publication with minor language adjustments[23]

2.3.3 Influencing factors (incl. variants, vaccination, reinfections)

The evidence on risk and protective factors for adults is evolving but mostly confirmed previous findings.[40] A recent Norwegian study, using data from 214,667 previously infected individuals, explored potential demographic, socio-economic, and healthcare-related PCC risk factors.[108] The study found that individuals who had a previous diagnosis of a psychological condition (OR 2.12, 95% CI 1.84–2.44), respiratory illness (OR 2.03, 95% CI 1.78–2.32), or general health problems (OR 1.78, 95% CI 1.52–2.09) had higher odds of developing PCC. Limitation: The study's outcomes were based on healthcare utilization excluding those who might have not had access to healthcare.[108]

A prospective cohort from Belgium followed up 8,238 adults from the time of confirmed SARS-CoV-2 infection and until three months later, aiming to explore the association between SARS-CoV-2 variants and PCC.[44] The study's outcome and exposure variables were PCC symptoms at follow-up and SARS-CoV-2 variants respectively. Findings suggested that those infected during the Alpha- (OR 1.61 95% CI 1.33-1.96) and Delta (OR 1.73, 95% CI 1.54-1.93) waves had significantly higher odds of PCC than those infected during the Omicron period. Participants infected during the Alpha and Delta periods were most likely to report neurocognitive, and respiratory symptoms, as well as loss of taste and smell.[44] Similar findings were reported by a recent digital population-based cohort study from Germany.[45] Data were collected from "DigiHero", an online health research platform, active across seven German federal states. Based on a sample of 17,008 individuals with at least one SARS-CoV-2 infection, the study found that those infected with the wildtype variant (OR 6.44, 95% CI 5.49-7.56) had the highest odds of developing PCC, followed by those infected with the Alpha and Delta variants, compared to those infected with the Omicron variant (lowest PCC risk).[45] Limitations: The studies might be subject to some selection and recall bias.[44,45]

A study recently published study used machine learning and electronic health record data from the National COVID Cohort Collaborative to identify PCC predictors.[109] The sample included 2,190,579 patients, of which 17,063 were diagnosed with PCC. Two machine learning models were applied, a logistic regression and a random forest. The features extracted from the electronic health records to train the algorithms included: symptoms, drugs during acute infection, treatments, prior illnesses, and demographic data. The study found that age (increasing), gender (female), cough, fatigue, albuterol, obesity, diabetes, and chronic lung disease were strong PCC predictors. Limitations: Data lacked information on variants and vaccinations.[109]

The evidence on influencing factors in children is emerging, yet less clear. A cohort study from England assessed the physical and mental health and children and teenagers six months after SARS-CoV-2 infection, exploring potential variations by vaccination status.[51] The study included 6,407 test-positive and 6,542 test-negative participants. At six months, PCC was present in 24.5% of test-positive and 17.8% of test-negative children and teenagers. Mental health, overall well-being, fatigue, and quality of life were similar between the two groups, as well as between those vaccinated and unvaccinated. Limitations: The study might be subject to non-response, selection, and recall bias.[51]

2.3.4 Pathogenesis

A review article recently published in microorganisms provides a comprehensive overview of potential PCC mechanisms according to symptom clusters.[51] A summary of these is provided in table 3.

Table 3. Potential PCC mechanisms according to symptom clusters

Symptoms/ sequelae	Potential mechanisms
Concentration problems; brain fog; sleep disturbances; headaches; anosmia; encephalopathy; strokes; seizures	BBB vulnerability Neuroinflammation Astrocytes and microglia activation Hypometabolism Immune dysregulation Hypercoagulopathy
Chest pain; fatigue; dyspnoea; myocarditis; pericarditis; arrythmias; thromboembolic events	Endothelitis Chronic immune dysregulation Dysautonomia Dysregulation of RAAS
Cough; pneumothorax infections; pulmonary hypertension; pulmonary fibrosis	Hyperinflammation Prolonged fibrolast activity Dysautonomia Oxidative stress Microcirculation damage Persistent viral toxicity

	Activation of matrix Metalloproteinases
Nausea; dysphagia; abdominal pain; irritable bowel syndrome; abnormal liver function; cholangiopathy	Viral persistence Chronic inflammation Microbiome changes

*this table was extracted from the original publication with no major language adjustments[51]

2.4: What are the available and potential measures for therapy and rehabilitation?

2.4.1 Treatment and rehabilitation research (Switzerland)

There is no established PCC cure. Most treatments that are currently explored aim to reduce diverse PCC symptoms. A search in clinicaltrials.gov and Google did not reveal any new ongoing treatment trials in Switzerland. The six currently ongoing trials are listed in table 4.

Table 4. Ongoing PCC trials in Switzerland

Trial	Description
Temelimab as a Disease Modifying Therapy in Patients with Neuropsychiatric Symptoms in Post-COVID-19 or PASC Syndrome[57]	▪ Phase: Phase two RCT (24 weeks), recruiting ▪ Aims: To evaluate the efficacy and safety of temelimab (54mg/kg) for treating PCC-related neuropsychiatric symptoms in patients who had SARS-CoV-2 but did not receive ICU treatment
Influence of Fampridine on Working Memory in Individuals with Post COVID-19 Condition with Subjective Cognitive Impairment[58]	▪ Phase: recruiting ▪ Aims: To evaluate the effects of 10 mg fampridine (4-Aminopyridine), a potassium channel-blocking agent, on working memory performance in individuals with PCC with subjective cognitive impairment

PYCNOVID Study[59]	▪ Phase: Recruiting ▪ Aims: To evaluate whether Pycnogenol® improves overall health in individuals with post-COVID-19 syndrome
Disease-related Fatigue Monitoring Based on Body Signals Measured on the Skin (Fatignals)[61]	▪ Phase: Recruiting ▪ Aims: To assess the use of physiological parameters as predictors of disease-related fatigue. Wearable devices are used to monitor cancer and PCC patients during their stay in a rehabilitation clinic. The study will also assess the effects of respiratory training in reducing dyspnoea and improving exercise breathing patterns in PCC patients
A Prospective, Double-blind, Randomized, Parallel Group, Placebo Controlled, Multicentre, Phase II Study to Investigate the Efficacy, GPCR Autoantibody Neutralizing Effect, Safety, and Tolerability of BC 007 in Participants With Long COVID[60]	▪ Phase: Recruiting ▪ Aims: To investigate the efficacy, GPCR autoantibody neutralizing effect, safety, and tolerability of BC 007 in PCC patients
Kinetics of Physiological and Symptomatic Responses to CardioPulmonary Exercise Testing (CPET) in Subjects With Persistent Exercise Intolerance After COVID-19: an Open-Source Exercise Network[62]	▪ Phase: Ongoing ▪ Aims: To describe the kinetics of cardio-pulmonary exercise training conducted by pulmonologists and cardiologists across French-speaking regions of the world (including Canada, France, and Switzerland)

2.4.2 Treatment and rehabilitation research (globally)

A search on clinicaltrials.gov revealed 4 new completed trials (a total of 31) on PCC treatment and rehabilitation (see Appendix 3). We identified associated publications (results) for only eight of those (references to full manuscripts added in Appendix 3). A list of ongoing drug trials is provided in the publication of Scheibenbogen et al. and summarized in table 5.[96] Li et al recently published a review in Nature Signal Transduction and Targeted Therapy and provided an updated list of candidate treatments (see updated table 5).[63]

Table 5. Potential PCC treatments, including ongoing trials (updated)[40,63,96,110,111]

Symptoms and/or biological mechanism	Potential treatment(s)
Post-exertional malaise	Pacing
Postural tachycardia syndrome	β-blockers, pyridostigmine, fludrocortisone, midodrine, ivabradine, increase salt and fluid intake, intravenously administered salt, compression stockings, exercise training
Immune dysfunction	Intravenous immunoglobulin
Cognitive dysfunction, depression, anxiety	Famotidine, cognitive pacing and post-concussion syndrome protocols
Fatigue; ME/CFS	Coenzyme Q10, d-ribose, pacing, personal sleep and dietary management, anhydrous enol-oxaloacetate, hyperbaric oxygen therapy, oxygen-ozone autohemotherapy, Nicotinamide adenine dinucleotide plus naltrexone, Prospekta, acupuncture
Pain, fatigue, neurological symptoms	Low-dose naltrexone, lithium
Fatigue, unrefreshing sleep, brain fog	Low-dose aripiprazole

Autoimmunity / autoantibodies	BC007, CD20 monoclonal antibodies, C19 monoclonal antibodies, BTK inhibitor
Abnormal clotting	Anticoagulants
Abnormal clotting	Apheresis
Viral persistence	Paxlovid, Nirmatrelvir
Endothelial dysfunction	Sulodexide, Mitoquinone
Gastrointestinal symptoms	Probiotics, L-Arginine plus Vitamin C
Dysautonomia	Stellate ganglion block
Endothelial function, microcirculation, inflammatory markers, and oxidative stress	Pycnogenol®
Inflammation (overall	Kinase inhibitors, antihistamines, minocycline, metformin
Vascular damage	Pyridostigmine, β2/3 reception antagonists, PDE5 inhibitor
Neuromodulation	Low dose aripiprazole, methylphenidate, Guanfacine
Myocardial dysfunction, tachycardia, dyspnoea	Hyperbaric oxygen therapy, Metopropol Succinate
Respiratory symptoms	UC-MSC treatment, inspiratory muscle training
Olfactory dysfunctions	Nasal Irrigation (ambroxol, betamethanose, rinazine)
Pain	TNX-102 SL
Chronic cough	UC-MSC-derived exosomes

Pulmonary fibrosis	Sirolimus
Neuropsychiatric symptoms	Temelimab
Cognitive impairment	Vortioxetine
Multiple/ generalized symptoms	Nirmatrelvir-Ritonavir, Imatinib-Infliximab

A recently published systematic review and meta-analysis provided a list of PCC rehabilitation approaches for physical capacity and quality of life.[71] These are summarized in textbox 2. The review concluded that these rehabilitation approaches were associated with improved outcomes compared with the current standard of care. Yet, the certainty of evidence was concluded as still being moderate to low.[71]

Textbox 2: PCC rehabilitation approaches for physical activity and quality of live[71]

- Clinician-supported home-based aerobic, resistance, and endurance exercise training
- Posture, breathing and clearance techniques, and thoracic expansion
- Aerobic and cardiovascular exercise
- Balance exercises and stretching
- Coaching and motivational interviewing
- Inspiratory and respiratory muscle training
- Low-intensity pulmonary rehabilitation
- Cough exercises and diaphragmatic training

2.4.3 Preventive treatment research (globally)

We did not identify any new primary research on preventive PCC treatment. Al-Aly recently published a viewpoint in the Lancet Infectious Diseases providing an overview of current prevention options.[67] Beyond vaccines, the paper outlines that the following antiviral drugs, administered during the acute phase of a SARS-CoV-2 infection, might reduce the risk for PCC: irmatrelvir (in combination with ritonavir), molnupiravir, and ensitrelvir. Al-Aly outlined that the evidence is still preliminary, and many uncertainties remain. For example, it is still unclear whether higher doses or longer administration improve the protective effect. In addition, many countries only administer antivirals to high-risk patients. It is therefore not clear whether these drugs are also protective for low-risk populations. Furthermore, there is an urgent need to better understand how antivirals reduce the consequences of reinfections in those who already live with PCC.[67]

2.5: What are the socio-economic implications?

Robust and reliable data on the socio-economic implications of PCC remain scarce. Particularly, targeted research that explores the long-term effects of the pandemic on working-age populations is still lacking and urgently needed.[112] A large (n=510) recently published qualitative study revealed the complexity of PCC's impact on the lives of working-age individuals who aim to return to work.[79] Participants outlined that the diversity and episodic nature of PCC symptoms interfere with the organization of work-related activities while being attached to remaining stigma and disbelief, both at work and in medical settings. The study also outlined the central role of medical providers in supporting transitions to work life.[79]

A not yet peer-reviewed study from the UK analyzed data from four longitudinal surveys (n=20,112) and estimated the associations between PCC and financial measures (e.g., self-perceived financial well-being, income, benefit claims).[84] The study found that among those reporting long-term symptoms, PCC was associated with lower self-perceived financial well-being and a higher number of new benefit claims, independent of sex and educational level.[84] Limitations: The study's findings have not been peer-reviewed yet and should thus be interpreted with caution.

2.6: How does PCC relate to post-acute sequelae of other viral infections?

The long-term symptoms of SARS-CoV-2 are not a surprising or unexpected phenomenon.[88] Many other well-known viral pathogens are linked to the development of long-term symptoms (see table 7).[88]

Table 7. Viral pathogens with known post-viral conditions[88,89,113]

Viral pathogen	Name(s) of post-viral condition
Ebola	Post-Ebola syndrome, post-Ebola virus disease syndrome
Dengue	Post-dengue fatigue syndrome
Polio	Post-polio syndrome
SARS-CoV-1	Post-SARS-syndrome
Chikungunya	Post- chikungunya chronic inflammatory rheumatism, post-chikungunya disease
Epstein-Barr virus	N/A
West Nile virus	N/A
Ross River virus	N/A
Coxsackie B virus	N/A
H1N1/09 influenza	N/A
Varicella-zoster virus	N/A
MERS-CoV	N/A
Respiratory syncytial virus	N/A
Rhinovirus	N/A
Human Herpes Virus (HHV6)	N/A
Powassen virus	N/A

*this table's content was extracted from the original publications with minor language adjustments[88,89]

We did not identify any new studies comparing the symptoms of PCC to other post-viral conditions. All previous findings are summarized in the report's first part (section 1.6)

2.6.1 Prevalence estimates of post-viral syndromes

The poor understanding of post-viral syndromes leads to a lack of clinical recognition, underdiagnosis, and inadequate care.[88] Thus, data on their prevalence are limited.[88] Pre-COVID-19, the prevalence of ME/CFS was estimated between 0.2-0.8% (e.g., estimated at 0.3% in Germany).[91,114] All previous findings are summarized in the report's first part (section 1.6).

2.6.2 Myalgic encephalomyelitis/chronic fatigue syndrome

It is by now well established that a subset of PCC patients fulfils all diagnostic criteria of ME/CFS. Chronic fatigue has also been reported after SARS-CoV-1 infections and MERS-CoV.[90] The underlying mechanisms remain unclear.[91] Potential mechanisms, as summarized in a recent review published in Nature Signal Transduction and Targeted Therapy, are: immune and inflammatory responses, vascular dysregulation, and autonomic or metabolic adaptation.[63] ME/CFS is observed in adults and children.[63] A recent review compared the shared symptoms and biological abnormalities between PCC and ME/CFS.[115] Some of the commonly shared symptoms include fatigue, post-exertional malaise, headaches, sleep problems, impaired memory, impaired attention, depression, anxiety, reduced activity, myalgia, arthralgia, muscle weakness, hot and cold spells, loss of appetite, palpitations, dyspnoea, nausea, diarrhea, chills, and orthostatic intolerance. The review emphasized that underlying biological abnormalities of both illnesses likely change over time, with evidence suggesting the involvement of the autonomic nervous system, immune system, previous infections, metabolism, and the cardiopulmonary system.[115]

2.6.3 Treatment of post-viral syndromes

As in the report's previous version, we did not identify any broadly recognized pharmacological or non-pharmacological treatments for post-viral syndromes.[92-94] Most approaches mainly aim to alleviate individual symptoms. For many post-viral syndromes, and especially ME/CFS, there has been little interest in treatment research by the pharmaceutical industry.[96] The complexity and unknown underlying factors of many post-viral syndromes were major barriers.[96] For ME/CFS, there are currently no approved drugs or widely accepted treatments. Currently, two drugs being researched for ME/CFS. The first is rintatolimod, a TLR-3 agonist, and the second is N-acetylcysteine.[96] A recent meta-analysis pooling individual patient data from eight trials found that cognitive behavioral therapy had positive effects on fatigue severity and functional impairment.[97]

Part 3: Response update

Below (table 8), we provide all identified ongoing and new healthcare and policy responses in Europe, the US and Canada.

Table 8: Recent healthcare and policy responses in Europe, the US and Canada (updated)

Country/Region	Healthcare and policy responses
Switzerland	▪ Long Covid Schweiz, Sulser & Partner, and Altea have published a guide for employers who want to support workers affected by PCC to return to work[116] ▪ Medix recently updated its factsheet and guidelines for PCC for primary care[1] ▪ Inselspital Bern developed the Long-COVID App "INSELhealth cofit" with the aim to support patients with PCC as well as medical professionals[117] ▪ FOPH funding for research between 2021 and 2022[2] ▪ Recommendations on Post-Covid-19 Condition for primary care, organized and paid by the FOPH[118] ▪ Switzerland offers at least 49 specialized PCC consultations and 47 rehabilitations across the country[119]
United Kingdom	▪ NHS England will invest a further £90 million in PCC services in 2022/2023[120] ▪ Introduction of "Your COVID Recovery" as part of the NHS support for PCC patients[121] ▪ Expansion of the number of facilities that provide specialized post-covid services[120] ▪ The National Institute for Health and Care Excellence (NICE) provided official guidance for recognizing, investigating, and rehabilitating patients with PCC[122]
Germany	▪ Baden-Wurttemberg supports PCC research with €2 million to four university hospitals (Freiburg, Heidelberg, Tübingen, Ulm). The goal is to have a care concept at the end of the 18-month project[123] ▪ BMG-Initiative Long COVID: The federal ministry started the initiative to educate the population about PCC[99] ▪ The Hanover University of Medicine plans to set up a virtual rehabilitation clinic that will bundle scientific findings and practical treatment knowledge on

	PCC. The aim is to support physicians in treating patients affected by PCC in Lower Saxony[124] ▪ Researcher at UKSH (University Hospital of Schleswig-Holstein) developed a "Post-Covid-Score" to help physicians refer patients to the right specialists[125] ▪ PCC patients are to be given easier access to medicines. A commission at the Federal Institute for Drugs and Medical Devices is to draw up a list of medicines that can also be prescribed and paid for outside of the marketing authorization for PCC[126] ▪ The government of Schleswig-Holstein strengthens PCC care with €3.55 million in funding [127] ▪ A pilot project of the four state-owned university paediatric hospitals in Freiburg, Heidelberg, Tübingen and Ulm aims to improve the care of children and adolescents with PCC. The Ministry of Health is supporting the project with €1 million[128] ▪ Health minister Karl Lauterbach announced €150 million for PCC research
France	▪ The government has committed €14 million in funding for PCC research[129] ▪ PCC support and coordination units that can be contacted by professionals, patients, and carers. The support units provide information, identify medical and social care providers, and help to set up and coordinate them
Belgium	▪ Researchers at Ku (Katholieke Universiteit) Leuven have been working to develop evidence-based guidelines to help healthcare professionals provide PCC care. Launched in November 2022 for general practitioners, physiotherapists, occupational therapists, psychologists, and dieticians[130]
Netherlands	▪ The Ministry of Health, Welfare, and Sport is collaborating with various organizations to better comprehend PCC and offer aid to those affected[131]
United States	▪ Expansion of post-COVID care clinics[132] ▪ Department of Health and Human Services published the National Research Action Plan on Long COVID as a response to the Presidential Memorandum on addressing the long-term effects of COVID-19[133]

	▪ Department of Health and Human Services published the "Services and Supports for Longer-Term Impacts of COVID-19 Report" as a response to the Presidential Memorandum on addressing the long-term effects of COVID-19[134] ▪ A budget of $10 million has been allocated to Agency's for Healthcare Research and Quality Fiscal Year 2023 budget to tackle PCC[135] ▪ The National Institutes of Health created the RECOVER Initiative to generate more knowledge on PCC[100] ▪ A new Office of Long COVID Research and Practice is formed to study the condition and help those who have been diagnosed with it[136] ▪ The US Department of Health and Human Services establishes secretary's advisory committee on PCC[102] ▪ The US government is awarding $45 million in grants to help clinics treating PCC, develop new models of care, and expand access[137]
Canada	▪ New investment of 9 million to create and evaluate evidence-based guidelines and tools to support patients, caregivers, and health professionals[138] ▪ Budget 2022 also provides 20 million over 5 years to the Canadian Institutes of Health Research. Supports research related to the long-term effects of COVID-19 infections[138] ▪ Task Force on Post COVID-19 Condition Report published recently[139] ▪ Post-COVID-19 Interdisciplinary Clinical Care Network that offers research, education and care[101] ▪ Canadian Conference dedicated to PCC, devoted to bringing together top Canadian researchers, policy-makers, and people living with PCC to share knowledge[140]
WHO	▪ Addition of "Rehabilitation of adults with Post COVID-19 condition" in the Living Guidance for Clinical Management of COVID-19[14] ▪ In September 2022, WHO/Europe partnered with Long COVID Europe to develop 3 goals (the 3 Rs), calling upon governments and health authorities to focus attention on PCC and those affected by it through greater: (1)

	recognition and knowledge sharing, (2) research and reporting, and (3) rehabilitation that is based on evidence and effectiveness[141]
G7	▪ Health ministers of the G7 countries agreed that there is a need for stronger research on PCC. A joint research initiative will be created for this purpose, which is to be initiated in the year 2024 under the Italian Presidency[103]

References

1. mediX. Long Covid (Factsheet). 2023; https://www.medix.ch/wissen/guidelines/long-covid-factsheet/.
2. BAG. Coronavirus: Laufende Arbeiten. 2023; https://www.bag.admin.ch/bag/de/home/krankheiten/ausbrueche-epidemien-pandemien/aktuelle-ausbrueche-epidemien/novel-cov/post-covid-19-erkrankung/laufende-arbeiten.html#58987217.
3. Nittas V, Puhan M. *Long COVID: Evolving Definitions, Burden of Disease and Socio-Economic Consequences.* https://www.bag.admin.ch/bag/en/home/das-bag/publikationen/forschungsberichte/forschungsberichte-uebertragbare-krankheiten/forschung-wissenschaft-covid-19.html2022.
4. WHO. *A clinical case definition of post COVID-19 condition by a Delphi consensus.* https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1#2021.
5. WHO. *A Clinical Case Definition for Post-COVID-19 Condition in Children and Adolescents by Expert Consensus* https://www.who.int/publications/i/item/WHO-2019-nCoV-Post-COVID-19-condition-CA-Clinical-case-definition-2023-12023.
6. Chirumbolo S, Tirelli U. Post-COVID or long-COVID? That is the question. *Pol Arch Intern Med.* May 23 2023;133(5).
7. Haslam A, Olivier T, Prasad V. The definition of long COVID used in interventional studies. *Eur J Clin Invest.* Aug 2023;53(8):e13989.
8. Ballouz T, Menges D, Anagnostopoulos A, et al. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study. *BMJ.* May 31 2023;381:e074425.
9. Robert Koch Institut. Coronavirus SARS-CoV-2 - Long COVID (Stand: 22.8.2023). 2023; https://www.rki.de/SharedDocs/FAQ/NCOV2019/FAQ_Liste_Gesundheitliche_Langzeitfolgen.html.
10. Universiteat Wien. Austrian Corona Panel Project (ACPP). 2023; https://viecer.univie.ac.at/coronapanel/.
11. Burns A. Long COVID: What Do the Latest Data Show? 2023; https://www.kff.org/policy-watch/long-covid-what-do-latest-data-show/#:~:text=Among%20those%20who%20have%20ever,are%20no%20longer%20reporting%20symptoms.
12. University of Vienna. Long Covid in Österreich: Häufigkeit und Symptome. 2023; https://viecer.univie.ac.at/corona-blog/corona-blog-beitraege/blog-154-long-covid-in-oesterreich-haeufigkeit-und-symptome/.
13. Atchison CJ, Davies B, Cooper E, et al. Long-term health impacts of COVID-19 among 242,712 adults in England. *Nat Commun.* Oct 24 2023;14(1):6588.
14. WHO. Living Guidance for Clinical Management of COVID-19: Rehabilitation of adults with post COVID-19 condition. 2023; https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.2.

15. CDC. Estimated COVID-19 Burden. 2021; https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/burden.html.
16. Pagen DME, van Bilsen CJA, Brinkhues S, et al. Prevalence of Long-term Symptoms Varies When Using Different Post-COVID-19 Definitions in Positively and Negatively Tested Adults: The PRIME Post-COVID Study. *Open Forum Infect Dis.* Oct 2023;10(10):ofad471.
17. Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents. *JAMA.* Jul 21 2021;326(9):868-869.
18. Miller F, Nguyen DV, Navaratnam AM, et al. Prevalence and Characteristics of Persistent Symptoms in Children During the COVID-19 Pandemic: Evidence From a Household Cohort Study in England and Wales. *Pediatr Infect Dis J.* Dec 1 2022;41(12):979-984.
19. Atchison CJ, Whitaker M, Donnelly CA, et al. Characteristics and predictors of persistent symptoms post-COVID-19 in children and young people: a large community cross-sectional study in England. *Arch Dis Child.* Jul 2023;108(7):e12.
20. Stephenson T, Pinto Pereira SM, Nugawela MD, et al. Long COVID-six months of prospective follow-up of changes in symptom profiles of non-hospitalised children and young people after SARS-CoV-2 testing: A national matched cohort study (The CLoCk) study. *PLoS One.* 2023;18(3):e0277704.
21. Pinto Pereira SM, Mensah A, Nugawela MD, et al. Long COVID in Children and Young after Infection or Reinfection with the Omicron Variant: A Prospective Observational Study. *J Pediatr.* Aug 2023;259:113463.
22. Wulf Hanson S, Abbafati C, Aerts JG, et al. Estimated Global Proportions of Individuals With Persistent Fatigue, Cognitive, and Respiratory Symptom Clusters Following Symptomatic COVID-19 in 2020 and 2021. *JAMA.* Oct 25 2022;328(16):1604-1615.
23. Kuodi P, Gorelik Y, Gausi B, Bernstine T, Edelstein M. Characterization of post-COVID syndromes by symptom cluster and time period up to 12 months post-infection: A systematic review and meta-analysis. *Int J Infect Dis.* Sep 2023;134:1-7.
24. Sansone F, Pellegrino GM, Caronni A, et al. Long COVID in Children: A Multidisciplinary Review. *Diagnostics (Basel).* Jun 7 2023;13(12).
25. Jiang L, et al. A Systematic Review of Persistent Clinical Features After SARS-CoV-2 in the Pediatric Population. *Pediatrics.* 2023.
26. Martino L, Morello R, De Rose C, Buonsenso D. Persistent respiratory symptoms associated with post-Covid condition (Long Covid) in children: a systematic review and analysis of current gaps and future perspectives. *Expert Rev Respir Med.* Jul-Dec 2023;17(10):837-852.
27. Mat Hassan N, Salim HS, Amaran S, et al. Prevalence of mental health problems among children with long COVID: A systematic review and meta-analysis. *PLoS One.* 2023;18(5):e0282538.
28. Fernandez-de-Las-Penas C, Cancela-Cilleruelo I, Rodriguez-Jimenez J, et al. Trajectory of Post-COVID Self-Reported Fatigue and Dyspnoea in Individuals Who Had Been Hospitalized by COVID-19: The LONG-COVID-EXP Multicenter Study. *Biomedicines.* Jun 29 2023;11(7).
29. Tsampasian V, Elghazaly H, Chattopadhyay R, et al. Risk Factors Associated With Post-COVID-19 Condition: A Systematic Review and Meta-analysis. *JAMA Intern Med.* Mar 23 2023.

30. Nehme M, Vetter P, Chappuis F, Kaiser L, Guessous I, CoviCare Study T. Prevalence of Post-Coronavirus Disease Condition 12 Weeks After Omicron Infection Compared With Negative Controls and Association With Vaccination Status. *Clin Infect Dis.* May 3 2023;76(9):1567-1575.
31. Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of covid-19 vaccination on long covid: systematic review. *BMJ Med.* 2023;2(1):e000385.
32. Bosworth ML, Shenhuy B, Walker AS, et al. Risk of new-onset Long Covid following reinfection with SARS-CoV-2: community-based cohort study. *MedRxiv.* 2023.
33. Bernas SN, Baldauf H, Real R, et al. Post-COVID-19 condition in the German working population: A cross-sectional study of 200,000 registered stem cell donors. *J Intern Med.* Mar 2023;293(3):354-370.
34. Kessler R, Philipp J, Wilfer J, Kostev K. Predictive Attributes for Developing Long COVID-A Study Using Machine Learning and Real-World Data from Primary Care Physicians in Germany. *J Clin Med.* May 17 2023;12(10).
35. Ballouz T, Menges D, Anagnostopoulos A, et al. Natural course of post COVID-19 condition and implications for trial design and outcome selection: A population-based longitudinal cohort study. *MedRxiv.* 2022.
36. Iqbal FM, Lam K, Sounderajah V, Clarke JM, Ashrafian H, Darzi A. Characteristics and predictors of acute and chronic post-COVID syndrome: A systematic review and meta-analysis. *EClinicalMedicine.* Jun 2021;36:100899.
37. Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med.* Mar 2022;28(3):583-590.
38. Stavem K, Ghanima W, Olsen MK, Gilboe HM, Einvik G. Prevalence and Determinants of Fatigue after COVID-19 in Non-Hospitalized Subjects: A Population-Based Study. *Int J Environ Res Public Health.* Feb 19 2021;18(4).
39. Zheng YB, Zeng N, Yuan K, et al. Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review. *J Infect Public Health.* May 2023;16(5):660-672.
40. Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol.* Mar 2023;21(3):133-146.
41. Ballouz T, Menges D, Kaufmann M, et al. Post COVID-19 condition after Wildtype, Delta, and Omicron SARS-CoV-2 infection and prior vaccination: Pooled analysis of two population-based cohorts. *PLoS One.* 2023;18(2):e0281429.
42. Ceban F, Kulzhabayeva D, Rodrigues NB, et al. COVID-19 vaccination for the prevention and treatment of long COVID: A systematic review and meta-analysis. *Brain Behav Immun.* Jul 2023;111:211-229.
43. Brannock MD, Chew RF, Preiss AJ, et al. Long COVID risk and pre-COVID vaccination in an EHR-based cohort study from the RECOVER program. *Nat Commun.* May 22 2023;14(1):2914.
44. Thi Khanh HN, Cornelissen L, Castanares-Zapatero D, et al. Association between SARS-CoV-2 variants and post COVID-19 condition: findings from a longitudinal cohort study in the Belgian adult population. *BMC Infect Dis.* Nov 8 2023;23(1):774.
45. Diexer S, Klee B, Gottschick C, et al. Association between virus variants, vaccination, previous infections, and post-COVID-19 risk. *Int J Infect Dis.* Nov 2023;136:14-21.

46. Arnold DT, Milne A, Samms E, Stadon L, Maskell NA, Hamilton FW. Are vaccines safe in patients with Long COVID? A prospective observational study. *MedRxiv.* 2021.
47. Gaber T, Ashish A, Unsworth A, Martindale J. Are mRNA Covid 19 vaccines safe in Long Covid patients? A Health Care Workers perspective. *BJMP.* 2020;14(1).
48. Strain WD, Sherwood O, Banerjee A, Van der Togt V, Hishmeh L, Rossman J. The Impact of COVID Vaccination on Symptoms of Long COVID: An International Survey of People with Lived Experience of Long COVID. *Vaccines (Basel).* Apr 21 2022;10(5).
49. Nehme M, Braillard O, Salamun J, et al. Symptoms After COVID-19 Vaccination in Patients with Post-Acute Sequelae of SARS-CoV-2. *J Gen Intern Med.* May 2022;37(6):1585-1588.
50. Klein N, et al. Effectiveness of COVID-19 Pfizer-BioNTech BNT162b2 mRNA Vaccination in Preventing COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Nonimmunocompromised Children and Adolescents Aged 5–17 Years — VISION Network, 10 States, April 2021–January 2022. *Morbidity and Mortality Weekly Report.* 2022;71(9).
51. Pinto Pereira SM, Nugawela MD, Rojas NK, et al. Post-COVID-19 condition at 6 months and COVID-19 vaccination in non-hospitalised children and young people. *Arch Dis Child.* Apr 2023;108(4):289-295.
52. Morello R, Mariani F, Mastrantoni L, et al. Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study. *EClinicalMedicine.* May 2023;59:101961.
53. Su S, Zhao Y, Zeng N, et al. Epidemiology, clinical presentation, pathophysiology, and management of long COVID: an update. *Mol Psychiatry.* Jul 25 2023.
54. Altmann DM, Whettlock EM, Liu S, Arachchillage DJ, Boyton RJ. The immunology of long COVID. *Nat Rev Immunol.* Jul 11 2023.
55. Janket SJ, Fraser DD, Baird AE, et al. Tachykinins and the potential causal factors for post-COVID-19 condition. *Lancet Microbe.* Aug 2023;4(8):e642-e650.
56. Tziolos NR, Ioannou P, Baliou S, Kofteridis DP. Long COVID-19 Pathophysiology: What Do We Know So Far? *Microorganisms.* Sep 30 2023;11(10).
57. Keddad K, Berthuy N. Temelimab as a Disease Modifying Therapy in Patients With Neuropsychiatric Symptoms in Post-COVID 19 or PASC Syndrome. 2022; https://clinicaltrials.gov/study/NCT05497089.
58. Gerhards C, Faludi T. Influence of Fampridine on Working Memory in Individuals With Post COVID-19 Condition With Subjective Cognitive Impairment (FamC). 2022; https://clinicaltrials.gov/study/NCT05274477.
59. Radtke T. *Pycnogenol® in People With Post-COVID-19 Condition: a Quadruple-blind, Randomized, Placebo-controlled Trial.* https://clinicaltrials.gov/study/NCT05890534?locStr=Switzerland&country=Switzerland&distance=50&cond=Long%20COVID,%20Post-COVID,%20Post%20COVID&rank=22023.
60. Müller J. A Prospective, Double-blind, Randomized, Parallel Group, Placebo Controlled, Multicentre, Phase II Study to Investigate the Efficacy, GPCR Autoantibody Neutralizing Effect, Safety, and Tolerability of BC 007 in Participants With Long COVID. 2023; https://clinicaltrials.gov/study/NCT05911009.
61. Martins N. *Disease-related Fatigue Monitoring Based on Body Signals Measured on the Skin.* https://classic.clinicaltrials.gov/ct2/show/NCT05853055#contacts2023.

62. Andres-Rieth L. *Kinetics of Physiological and Symptomatic Responses to CardioPulmonary Exercise Testing (CPET) in Subjects With Persistent Exercise Intolerance After COVID-19: an Open-Source Exercise Network.* https://clinicaltrials.gov/study/NCT05532995?locStr=Switzerland&country=Switzerland&distance=50&cond=Long%20COVID&rank=82023.
63. Li J, Zhou Y, Ma J, et al. The long-term health outcomes, pathophysiological mechanisms and multidisciplinary management of long COVID. *Signal Transduct Target Ther.* Nov 1 2023;8(1):416.
64. Bramante CT, et al. Outpatient treatment of COVID-19 and the development of Long COVID over 10 months: a multi-center, quadrupe-blind, parallel group randomized phase 3 trial. *SSRN preprints* 2023.
65. Xie Y, Choi T, Al-Aly Z. Association of Treatment With Nirmatrelvir and the Risk of Post-COVID-19 Condition. *JAMA Intern Med.* Mar 23 2023.
66. Xie Y, Choi T, Al-Aly Z. Molnupiravir and risk of post-acute sequelae of covid-19: cohort study. *BMJ.* Apr 25 2023;381:e074572.
67. Al-Aly Z. Prevention of long COVID: progress and challenges. *Lancet Infect Dis.* Jul 2023;23(7):776-777.
68. DeMars J, Brown DA, Angelidis I, et al. What is Safe Long COVID Rehabilitation? *J Occup Rehabil.* Jun 2023;33(2):227-230.
69. Ashra F, Jen HJ, Liu D, et al. Effectiveness of respiratory rehabilitation in patients with COVID-19: A meta-analysis. *J Clin Nurs.* Aug 2023;32(15-16):4972-4987.
70. Romanet C, Wormser J, Fels A, et al. Effectiveness of exercise training on the dyspnoea of individuals with long COVID: A randomised controlled multicentre trial. *Ann Phys Rehabil Med.* Jun 2023;66(5):101765.
71. Pouliopoulou DV, Macdermid JC, Saunders E, et al. Rehabilitation Interventions for Physical Capacity and Quality of Life in Adults With Post-COVID-19 Condition: A Systematic Review and Meta-Analysis. *JAMA Netw Open.* Sep 5 2023;6(9):e2333838.
72. Raman B, Cassar MP, Tunnicliffe EM, et al. Medium-term effects of SARS-CoV-2 infection on multiple vital organs, exercise capacity, cognition, quality of life and mental health, post-hospital discharge. *EClinicalMedicine.* Jan 2021;31:100683.
73. Lerum TV, Aalokken TM, Bronstad E, et al. Dyspnoea, lung function and CT findings 3 months after hospital admission for COVID-19. *Eur Respir J.* Apr 2021;57(4).
74. van den Borst B, Peters JB, Brink M, et al. Comprehensive Health Assessment 3 Months After Recovery From Acute Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis.* Sep 7 2021;73(5):e1089-e1098.
75. Willi S, Luthold R, Hunt A, et al. COVID-19 sequelae in adults aged less than 50 years: A systematic review. *Travel Med Infect Dis.* Mar-Apr 2021;40:101995.
76. Kerksieck P, Ballouz T, Haile SR, et al. Post COVID-19 Condition, Work Ability and Occupational Changes: Results from a Population-based Cohort. *MedRxiv.* 2023.
77. Trades Union Congress. Workers' experiences of long Covid. 2023; https://www.tuc.org.uk/research-analysis/reports/workers-experience-long-covid.
78. Bach K. New data shows long Covid is keeping as many as 4 million people out of work. 2022; https://www.brookings.edu/articles/new-data-shows-long-covid-is-keeping-as-many-as-4-million-people-out-of-work/.

79. Stelson EA, Dash D, McCorkell L, et al. Return-to-work with long COVID: An Episodic Disability and Total Worker Health analysis. *Soc Sci Med.* Dec 2023;338:116336.
80. Tufts J, Zemedikun DT, Subramanian A, et al. The cost of primary care consultations associated with long COVID in non-hospitalised adults: a retrospective cohort study using UK primary care data. *MedRxiv.* 2023.
81. C-19LAP. COVID-19 Longhauler Advocacy Project (C19LAP). 2020; https://www.longhauler-advocacy.org.
82. Gandjour A. Long COVID: Costs for the German economy and health care and pension system. *BMC Health Serv Res.* Jun 14 2023;23(1):641.
83. Packard SE, Susser E. Association of Long COVID with housing insecurity in the United States, 2022-2023. *medRxiv.* Jun 19 2023.
84. Rhead R, Wels J, Moltrecht B, et al. Long COVID and financial outcomes: Evidence from four longitudinal population surveys. *medRxiv.* 2023.
85. Proal AD, VanElzakker MB. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An Overview of Biological Factors That May Contribute to Persistent Symptoms. *Front Microbiol.* 2021;12:698169.
86. Honigsbaum M. "An inexpressible dread": psychoses of influenza at fin-de-siecle. *Lancet.* Mar 23 2013;381(9871):988-989.
87. Stefano GB. Historical Insight into Infections and Disorders Associated with Neurological and Psychiatric Sequelae Similar to Long COVID. *Med Sci Monit.* Feb 26 2021;27:e931447.
88. Choutka J, Jansari V, Hornig M, Iwasaki A. Unexplained post-acute infection syndromes. *Nat Med.* May 2022;28(5):911-923.
89. Narasimhan H, Wu Y, Goplen NP, Sun J. Immune determinants of chronic sequelae after respiratory viral infection. *Science Immunology.* 2022;7.
90. Krishna B, Wills M, Sithole N. Long COVID: what is known and what gaps need to be addressed. *Br Med Bull.* Sep 12 2023;147(1):6-19.
91. Legler F, Meyer-Arndt L, Mödl L, et al. Long-term symptom severity and clinical biomarkers in post-COVID-19/chronic fatigue syndrome: results from a prospective observational cohort. *eClinicalMedicine.* 2023;63.
92. Chandan JS, Brown KR, Simms-Williams N, et al. Non-Pharmacological Therapies for Post-Viral Syndromes, Including Long COVID: A Systematic Review. *Int J Environ Res Public Health.* Feb 16 2023;20(4).
93. Li Hi Shing S, Chipika RH, Finegan E, Murray D, Hardiman O, Bede P. Post-polio Syndrome: More Than Just a Lower Motor Neuron Disease. *Front Neurol.* 2019;10:773.
94. Bandara S, et al. Management of Dengue and Post Dengue Complication Syndrome: A Review. *Acta Scientific Microbiology.* 2019;2(4).
95. Toogood PL, Clauw DJ, Phadke S, Hoffman D. Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): Where will the drugs come from? *Pharmacol Res.* Mar 2021;165:105465.
96. Scheibenbogen C, Bellmann-Strobl JT, Heindrich C, et al. Fighting Post-COVID and ME/CFS - development of curative therapies. *Front Med (Lausanne).* 2023;10:1194754.
97. Kuut TA, Buffart LM, Braamse AMJ, et al. Does the effect of cognitive behavior therapy for chronic fatigue syndrome (ME/CFS) vary by patient characteristics? A systematic review and individual patient data meta-analysis. *Psychol Med.* Nov 6 2023:1-10.

98. Brown M, al. e. Long COVID: the next public health crisis? A comparison with influenza in Australia. In: Health QDo, ed. *3rd ECCMID, Denmark* 2023.
99. German Federal Ministry of Health. BMG Initiative Long COVID. 2023; https://www.bmg-longcovid.de/en.
100. RECOVER. RECOVER: Researching COVID to Enhance Recovery. 2023; https://recovercovid.org.
101. Provincial Health Services Authority. Post-COVID-19 Interdisciplinary Clinical Care Network. 2023; http://www.phsa.ca/our-services/programs-services/post-covid-19-care-network.
102. U.S Department of Health and Human Services. HHS Establishes Secretary's Advisory Committee on Long COVID. 2023; https://www.hhs.gov/about/news/2023/11/16/hhs-establishes-secretarys-advisory-committee-long-covid.html.
103. Bundesministerium fuer Gesundheit. G7-Initiative gibt Long-COVID-Betroffenen weltweit Hoffnung. 2023; https://www.bundesgesundheitsministerium.de/ministerium/meldungen/gesundheitsminister-treffen-in-japan.html.
104. Blanchflower DG, Bryson A. Long COVID in the United States. *PLoS One.* 2023;18(11):e0292672.
105. Juan CC, et al. Prevalence of Symptoms ≤12 Months After Acute Illness, by COVID-19 Testing Status Among Adults — United States, December 2020–March 2023. *Morbidity and Mortality Weekly Report.* 2023;72(32).
106. Santé Publique France. COVID long : 2 millions de personnes présentaient une affection post- COVID-19 fin 2022. 2023; https://www.santepubliquefrance.fr/les-actualites/2023/covid-long-2-millions-de-personnes-presentaient-une-affection-post-covid-19-fin-2022.
107. Bowyer RCE, Huggins C, Toms R, et al. Characterising patterns of COVID-19 and long COVID symptoms: evidence from nine UK longitudinal studies. *Eur J Epidemiol.* Feb 2023;38(2):199-210.
108. Reme BA, Gjesvik J, Magnusson K. Predictors of the post-COVID condition following mild SARS-CoV-2 infection. *Nat Commun.* Sep 20 2023;14(1):5839.
109. Antony B, Blau H, Casiraghi E, et al. Predictive models of long COVID. *EBioMedicine.* Oct 2023;96:104777.
110. Leitman M, Fuchs S, Tyomkin V, Hadanny A, Zilberman-Itskovich S, Efrati S. The effect of hyperbaric oxygen therapy on myocardial function in post-COVID-19 syndrome patients: a randomized controlled trial. *Sci Rep.* Jun 10 2023;13(1):9473.
111. Momtazmanesh S, Ansari S, Izadi Z, et al. Effect of famotidine on cognitive and behavioral dysfunctions induced in post-COVID-19 infection: A randomized, double-blind, and placebo-controlled study. *J Psychosom Res.* Sep 2023;172:111389.
112. Gallegos M, Morgan ML, Burgos-Videla C, Caycho-Rodriguez T, Martino P, Cervigni M. The impact of long Covid on people's capacity to work. *Ann Work Expo Health.* Aug 9 2023;67(7):801-804.
113. Weldon EJt, Hong B, Hayashi J, et al. Mechanisms and Severity of Exercise Intolerance Following COVID-19 and Similar Viral Infections: A Comparative Review. *Cureus.* May 2023;15(5):e39722.

114. Froehlich L, Hattesohl DBR, Jason LA, Scheibenbogen C, Behrends U, Thoma M. Medical Care Situation of People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in Germany. *Medicina (Kaunas).* Jun 23 2021;57(7).
115. Komaroff AL, Lipkin WI. ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature. *Front Med (Lausanne).* 2023;10:1187163.
116. Bieri M, Rangelov N, Rudolf P, Scherrer F, Simonet A, Utiger A. *Ratgeber Zurück zur Arbeit*2023.
117. Altea Network. Long COVID Apps – praktische Hilfe auf dem Handy. 2023; https://altea-network.com/blog/76-apps-for-lc-symptoms.
118. BAG. Behandlungsempfehlungen zur Post-Covid-19-Erkrankung. 2023; https://www.bag.admin.ch/bag/de/home/das-bag/aktuell/news/news-31-08-2023.html.
119. BAG. Coronavirus: Sprechstunden und Rehabilitationsangebote. 2023; https://www.bag.admin.ch/bag/de/home/strategie-und-politik/nationale-gesundheitsstrategien/post-covid-19-erkrankung/sprechstunden-rehaangebote.html.
120. NHS. NHS sets out long COVID action plan for thousands of people with persistent symptom. 2022; https://www.england.nhs.uk/2022/07/nhs-sets-out-long-covid-action-plan-for-thousands-of-people-with-persistent-symptom/.
121. NHS. Your COVID Recovery. 2023; https://www.yourcovidrecovery.nhs.uk.
122. NHS England. Post-COVID syndrome (long COVID). 2023; https://www.england.nhs.uk/coronavirus/post-covid-syndrome-long-covid/.
123. Part of the Laend. Land unterstützt Long-COVID-Forschung mit zwei Millionen Euro. 2023; https://www.baden-wuerttemberg.de/de/service/presse/pressemitteilung/pid/land-unterstuetzt-long-covid-forschung-mit-zwei-millionen-euro.
124. Medizinische Hochschule Hannover. Post-COVID: Virtuelle Rehabilitationsklinik unterstützt Hausarztpraxen. 2023; https://longcovid.mhh.de/fuer-patientinnen/virtuelle-covid-rehaklinik.
125. UKSH. Erste Ergebnisse der COVIDOM-Studie zu Langzeitfolgen von Covid-19. 2023; https://www.uksh.de/220718_pi_covidom_erste_ergebnisse-path-13576,9874,13830,191994.html.
126. BMG Germany. Runder Tisch berät zur Versorgung von Long-COVID-Erkrankten. 2023; https://www.bundesgesundheitsministerium.de/presse/pressemitteilungen/runder-tisch-beraet-zur-versorgung-von-long-covid-erkrankten-pm-12-09-23.
127. Schlweswig-Holstein. Landesregierung stärkt Long-COVID-Versorgung in Schleswig-Holstein – 3,55 Millionen Euro Förderung für drei Projekte am UKSH. 2023.
128. Baden-Württemberg.de. Modellprojekt zu Long COVID bei Kindern und Jugendlichen. 2023; https://www.baden-wuerttemberg.de/de/service/presse/pressemitteilung/pid/modellprojekt-zu-long-covid-bei-kindern-und-jugendlichen.
129. La Galaxie Senat. Réponse du Ministère de la santé et de la prévention publiée le 19/01/2023. 2022; https://www.senat.fr/questions/base/2022/qSEQ221103743.html.
130. KU Leuven. Nieuwe richtlijn schept duidelijkheid over behandeling van aanhoudende COVID-klachten. 2022; https://nieuws.kuleuven.be/nl/2022/nieuwe-richtlijn-schept-duidelijkheid-over-behandeling-van-aanhoudende-covid-klachten.

131. Government of the Netherlands. Post COVID Condition (Long COVID). 2023; https://www.government.nl/topics/coronavirus-covid-19/post-covid-condition-long-covid.
132. NYC Health+ Hospitals. COVID-19 Services. 2022; https://www.nychealthandhospitals.org/services/covid-19/.
133. US Department of Health and Human Services. *National Research Action Plan on Long COVID.* https://www.covid.gov/assets/files/National-Research-Action-Plan-on-Long-COVID-08012022.pdf2022.
134. US Department of Health and Human Services. *Services and Supports for Longer-Term Impacts of COVID-19.* https://www.covid.gov/assets/files/Services-and-Supports-for-Longer-Term-Impacts-of-COVID-19-08012022.pdf2022.
135. Agency for Healthcare Research and Quality. AHRQ Efforts To Address Long COVID. 2023; https://www.ahrq.gov/coronavirus/long-covid.html.
136. US Department of Health and Human Services. HHS Announces the Formation of the Office of Long COVID Research and Practice and Launch of Long COVID Clinical Trials Through the RECOVER Initiative. 2023; https://www.hhs.gov/about/news/2023/07/31/hhs-announces-formation-office-long-covid-research-practice-launch-long-covid-clinical-trials-through-recover-initiative.html.
137. Aboulenein A. U.S. government awards $45 million for long COVID clinics. 2023; https://www.reuters.com/business/healthcare-pharmaceuticals/us-government-awards-45-million-long-covid-clinics-2023-09-20/.
138. Government of Canada. Government of Canada invests new funding for post COVID-19 condition, in line with recommendations from the Chief Science Advisor's report. 2023; https://www.canada.ca/en/public-health/news/.
139. Government of Canada. Post-COVID-19 Condition in Canada: What we know, what we don't know, and a framework for action (Pre-Report). 2023; https://science.gc.ca/site/science/en/office-chief-science-advisor/initiatives-covid-19/post-covid-19-condition-canada-what-we-know-what-we-dont-know-and-framework-action-pre-report.
140. Québec Fdrd. 1st Canadian Symposium on Long COVID. Research excellence as a vehicle for solutions. 2023; https://frq.gouv.qc.ca/en/event/1st-canadian-symposium-on-long-covid-research-excellence-as-a-vehicle-for-solutions/.
141. WHO Europe. Increasing Recognition, Research and Rehabilitation for Post COVID-19 Condition (long COVID). 2023; https://www.who.int/europe/activities/increasing-recognition-research-and-rehabilitation-for-post-covid-19-condition-long-covid.
142. Burki T. Clinical case definition of post-COVID-19 condition in children: a good start, but improvements are needed. *Lancet Respir Med.* Apr 2023;11(4):314.
143. Wang F. Machine learning identifies long COVID patterns from electronic health records. *Nat Med.* Jan 2023;29(1):47-48.
144. Zhang H, Zang C, Xu Z, et al. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes. *Nat Med.* Jan 2023;29(1):226-235.
145. Hedberg P, Granath F, Bruchfeld J, et al. Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection. *J Intern Med.* Feb 2023;293(2):246-258.

146. Brunvoll SH, Nygaard AB, Fagerland MW, et al. Post-acute symptoms 3-15 months after COVID-19 among unvaccinated and vaccinated individuals with a breakthrough infection. *Int J Infect Dis.* Jan 2023;126:10-13.
147. Tene L, Bergroth T, Eisenberg A, David SSB, Chodick G. Risk factors, health outcomes, healthcare services utilization, and direct medical costs of patients with long COVID. *Int J Infect Dis.* Mar 2023;128:3-10.
148. Fawzy NA, Abou Shaar B, Taha RM, et al. A systematic review of trials currently investigating therapeutic modalities for post-acute COVID-19 syndrome and registered on WHO International Clinical Trials Platform. *Clin Microbiol Infect.* May 2023;29(5):570-577.
149. Reese JT, Blau H, Casiraghi E, et al. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes. *EBioMedicine.* Jan 2023;87:104413.
150. O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: A systematic review and meta-analysis. *EClinicalMedicine.* Jan 2023;55:101762.
151. Ballering AV, van Zon SKR, Olde Hartman TC, Rosmalen JGM, Lifelines Corona Research I. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet.* Aug 6 2022;400(10350):452-461.
152. Magnusson K, Kristoffersen DT, Dell'Isola A, et al. Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants. *Nat Commun.* Nov 30 2022;13(1):7363.
153. Funk AL, Kuppermann N, Florin TA, et al. Post-COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection. *JAMA Netw Open.* Jul 1 2022;5(7):e2223253.
154. Lippi G, Henry BM, Favresse J, Plebani M. Addressing standardized definitions of post-COVID and long-COVID. *Clin Chem Lab Med.* Jul 26 2023;61(8):1361-1362.
155. Ha E, Kim H, Han M. Long COVID in children and adolescents: Prevalence, Clinical Manifestations, and Management Strategies. *e-cep.* 2023.
156. Wolff Sagy Y, Feldhamer I, Brammli-Greenberg S, Lavie G. Estimating the economic burden of long-Covid: the additive cost of healthcare utilisation among COVID-19 recoverees in Israel. *BMJ Glob Health.* Jul 2023;8(7).
157. Gottlieb M, Spatz ES, Yu H, et al. Long COVID Clinical Phenotypes up to 6 Months After Infection Identified by Latent Class Analysis of Self-Reported Symptoms. *Open Forum Infect Dis.* Jul 2023;10(7):ofad277.
158. Howe S, Szanyi J, Blakely T. The health impact of long COVID during the 2021-2022 Omicron wave in Australia: a quantitative burden of disease study. *Int J Epidemiol.* Jun 6 2023;52(3):677-689.
159. Hastie CE, Lowe DJ, McAuley A, et al. Natural history of long-COVID in a nationwide, population cohort study. *Nat Commun.* Jun 13 2023;14(1):3504.
160. Scholkmann F, May CA. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences. *Pathol Res Pract.* Jun 2023;246:154497.
161. Qasmieh SA, Robertson MM, Teasdale CA, et al. The prevalence of SARS-CoV-2 infection and long COVID in U.S. adults during the BA.4/BA.5 surge, June-July 2022. *Prev Med.* Apr 2023;169:107461.

162. O'Kelly B, Vidal L, McHugh T, Woo J, Avramovic G, Lambert JS. Safety and efficacy of low dose naltrexone in a long covid cohort; an interventional pre-post study. *Brain Behav Immun Health.* Oct 2022;24:100485.
163. Dunabeitia JA, Mera F, Baro O, Jadad-Garcia T, Jadad AR. Personalized Computerized Training for Cognitive Dysfunction after COVID-19: A Before-and-After Feasibility Pilot Study. *Int J Environ Res Public Health.* Feb 10 2023;20(4).
164. Versace V, Ortelli P, Dezi S, et al. Co-ultramicronized palmitoylethanolamide/luteolin normalizes GABA(B)-ergic activity and cortical plasticity in long COVID-19 syndrome. *Clin Neurophysiol.* Jan 2023;145:81-88.
165. Hasenoehrl T, Palma S, Huber DF, et al. Post-COVID: effects of physical exercise on functional status and work ability in health care personnel. *Disabil Rehabil.* Sep 2023;45(18):2872-2878.
166. Oliver-Mas S, Delgado-Alonso C, Delgado-Alvarez A, et al. Transcranial direct current stimulation for post-COVID fatigue: a randomized, double-blind, controlled pilot study. *Brain Commun.* 2023;5(2):fcad117.
167. Martin A, Lupfer C, Amen R. Sodium Pyruvate Nasal Spray Reduces the Severity of Nasal Inflammation and Congestion in Patients with Allergic Rhinitis. *J Aerosol Med Pulm Drug Deliv.* Dec 2022;35(6):291-295.
168. McIntyre R, et al. Vortioxetine for the treatment of post-COVID-19 condition: a randomized controlled trial. *Brain.* 2023.
169. Ibrahim A, et al. A randomized controlled trial examining the impact of low vs. moderate-intensity aerobic training in post-discharge COVID-19 older subjects. *European Review for Medical and Pharmacological Sciences.* 2023.

Appendices

Appendix 1: Studies included in previous reports

1. Clinical case definition of post-COVID-19 condition in children: a good start, but improvements are needed[142]
2. Long COVID: major findings, mechanisms and recommendations[40]
3. Machine learning identifies long COVID patterns from electronic health records[143]
4. Data-driven identification of post-acute SARS-CoV-2 infection subphenotypes[144]
5. Post COVID-19 condition diagnosis: A population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection[145]
6. Post-acute symptoms 3-15 months after COVID-19 among unvaccinated and vaccinated individuals with a breakthrough infection[146]
7. Post-COVID-19 condition in the German working population: A cross-sectional study of 200,000 registered stem cell donors[33]
8. Risk Factors Associated With Post–COVID-19 Condition: A systematic Review and Meta-analysis[29]
9. Prevalence and risk factor for long COVID in children and adolescents: A meta-analysis and systematic review[39]
10. Prevalence of Post-COVID Condition 12 Weeks After Omicron Infection Compared With Negative Controls and Association With Vaccination Status[30]
11. Risk factors, health outcomes, healthcare services utilization, and direct medical costs of patients with long COVID[147]
12. A systematic review of trials currently investigating therapeutic modalities for post-acute COVID-19 syndrome and registered on WHO International Clinical Trials Platform[148]
13. Characterising patterns of COVID-19 and long COVID symptoms: evidence from nine UK longitudinal studies[107]
14. Generalisable long COVID subtypes: findings from the NIH N3C and RECOVER programmes[149]
15. A systematic review and meta-analysis conducted by UCL Great Ormond Street Institute of Child in collaboration with the World Health Organization[5]
16. The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: a systematic review and meta-analysis[150]

17. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study[151]

18. Effect of covid-19 vaccination on long covid: systematic review[31]

19. Risk of new-onset Long Covid following reinfection with SARS-CoV-2: community-based cohort study[32]

20. Outpatient Treatment of COVID-19 and the Development of Long COVID Over 10 Months: A Multi-Center, Quadruple-Blind, Parallel Group Randomized Phase 3 Trial[64]

21. Association of Treatment With Nirmatrelvir and the Risk of Post–COVID-19 Condition[65]

22. Post-covid medical complaints following infection with SARS-CoV-2 Omicron vs Delta variants[152]

23. Post–COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection[153]

24. Unexplained post-acute infection syndromes[88]

25. Long COVID or Post-acute Sequelae of COVID-19 (PASC): An overview of biological factors that may contribute to persistent symptoms[85]

26. Immune determinants of chronic sequelae after respiratory viral infection[89]

27. Post-COVID or long-COVID? That is the question[6]

28. COVID-19 vaccination for the prevention and treatment of long COVID: A systematic review and meta-analysis[42]

29. Addressing standardized definitions of post- COVID and long-COVID[154]

30. Recovery and symptom trajectories up to two years after SARS-CoV-2 infection: population based, longitudinal cohort study[8]

31. Long COVID in Children: A Multidisciplinary Review[24]

32. Epidemiology, clinical presentation, pathophysiology, and management of long COVID: an update[53]

33. Tachykinins and the potential causal factors for post- COVID-19 condition[55]

34. Long COVID risk and pre-COVID vaccination in an EHR-based cohort study from the RECOVER program[43]

35. Trajectory of Post-COVID Self-Reported Fatigue and Dyspnoea in Individuals Who Had Been Hospitalized by COVID-19: The LONG-COVID-EXP Multicenter Study[28]

36. Long COVID in children and adolescents: Prevalence, Clinical Manifestations, and Management Strategies[155]

37. Mechanisms and Severity of Exercise Intolerance Following COVID-19 and Similar Viral Infections: A Comparative Review[113]

38. Fighting Post-COVID and ME/CFS – development of curative therapies[96]

39. Effectiveness of respiratory rehabilitation in patients with COVID-19: A meta-analysis[69]

40. A Systematic Review of Persistent Clinical Features After SARS-CoV-2 in the Pediatric Population[25]

41. Long COVID: Costs for the German economy and health care and pension system[82]

42. Estimating the economic burden of long-Covid: the additive cost of healthcare utilisation among COVID-19 recoverees in Israel[156]

43. Characteristics and predictors of persistent symptoms post-COVID-19 in children and young people: a large community cross-sectional study in England[19]

44. The effect of hyperbaric oxygen therapy on myocardial function in post-COVID-19 syndrome patients: a randomized controlled trial[110]

45. Effect of famotidine on cognitive and behavioral dysfunctions induced in post-COVID-19 infection: A randomized, double-blind, and placebo-controlled study[111]

46. Prevalence of mental health problems among children with long COVID: A systematic review and meta-analysis[27]

47. Long COVID Clinical Phenotypes up to 6 Months After Infection Identified by Latent Class Analysis of Self-Reported Symptoms[157]

48. Predictive Attributes for Developing Long COVID—A Study Using Machine Learning and Real-World Data from Primary Care Physicians in Germany[34]

49. The health impact of long COVID during the 2021–2022 Omicron wave in Australia: a quantitative burden of disease study[158]

50. The immunology of long COVID[54]

51. What is Safe Long COVID Rehabilitation?[68]

52. Association of Long COVID with housing insecurity in the United States, 2022-2023[83]

53. Natural history of long-COVID in a nationwide, population cohort study[159]

54. Effectiveness of exercise training on the dyspnoea of individuals with long COVID: A randomised controlled multicentre trial[70]

55. COVID-19, post-acute COVID-19 syndrome (PACS, "long COVID") and post-COVID-19 vaccination syndrome (PCVS, "post-COVIDvac-syndrome"): Similarities and differences[160]

56. The prevalence of SARS-CoV-2 infection and long COVID in U.S. adults during the BA.4/BA.5 surge, June–July 2022[161]

57. Long COVID—six months of prospective follow-up of changes in symptom profiles of non-hospitalised children and young people after SARS-CoV-2 testing: A national matched cohort study (The CLoCk) study[20]

58. Long COVID—six months of prospective follow-up of changes in symptom profiles of non-hospitalised children and young people after SARS-CoV-2 testing: A national matched cohort study (The CLoCk) study[20]

59. Risk factors for post-COVID-19 condition (Long Covid) in children: a prospective cohort study[52]

60. Molnupiravir and risk of post-acute sequelae of covid-19: cohort study[66]

61. Long-term symptom severity and clinical biomarkers in post-COVID-19/chronic fatigue syndrome: results from a prospective observational cohort[91]

Appendix 2: New included studies

1. The definition of long COVID used in interventional studies[7]

2. Prevalence of Long-term Symptoms Varies When Using Different Post-COVID-19 Definitions in Positively and Negatively Tested Adults: The PRIME Post-COVID Study[16]

3. Long COVID in Children and Young after Infection or Reinfection with the Omicron Variant: A Prospective Observational Study[21]

4. Characterization of post-COVID syndromes by symptom cluster and time period up to 12 months post-infection: A systematic review and meta-analysis[23]

5. Persistent respiratory symptoms associated with post-Covid condition (Long Covid) in children: a systematic review and analysis of current gaps and future perspectives[26]

6. Association between SARS-CoV-2 variants and post COVID-19 condition: findings from a longitudinal cohort study in the Belgian adult population[44]

7. Association between virus variants, vaccination, previous infections, and post-COVID-19 risk[45]

8. Post-COVID-19 condition at 6 months and COVID-19 vaccination in non-hospitalised children and young people[51]

9. The long-term health outcomes, pathophysiological mechanisms and multidisciplinary management of long COVID[63]

10. Prevention of long COVID: progress and challenges[67]

11. Rehabilitation Interventions for Physical Capacity and Quality of Life in Adults With Post-COVID-19 Condition: A Systematic Review and Meta-Analysis[71]

12. Return-to-work with long COVID: An Episodic Disability and Total Worker Health analysis[79]

13. Long COVID and financial outcomes: Evidence from four longitudinal population surveys[84]

14. Long COVID: what is known and what gaps need to be addressed[90]

15. Does the effect of cognitive behavior therapy for chronic fatigue syndrome (ME/CFS) vary by patient characteristics? A systematic review and individual patient data meta-analysis[97]

16. Long COVID in the United States[104]

17. Prevalence of Symptoms ≤12 Months After Acute Illness, by COVID-19 Testing Status Among Adults — United States, December 2020–March 2023[105]

18. Predictors of the post-COVID condition following mild SARS-CoV-2 infection[108]

19. Predictive models of long COVID[109]

20. The impact of long Covid on people's capacity to work[112]

21. Medical Care Situation of People with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome in Germany[114]

22. ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature[115]

23. Long-term health impacts of COVID-19 among 242,712 adults in England[13]

Appendix 3: Completed PCC treatment and rehabilitation trials globally (clinicaltrials.gov)

Study title (as indexed in clinicaltrials.gov) *trials with published results (see reference)	Intervention (type)
Pilot Study into LDN and NAD+ for Treatment of Patients with Post-COVID-19 Syndrome[162]	Naltrexone (drug)
*Personalized Computerized Training Program for Cognitive Dysfunction after COVID-19[163]	Personalized computerized cognitive training (device)
Clinical Trial of Efficacy and Safety of Prospekta in the Treatment of Post-COVID-19 Asthenia	Prospekta (drug)
Vagus Nerve Stimulation for Post-COVID-19 Syndrome	Auricular transcutaneous vagus nerve stimulation (device)
*Effects of PEA-LUT on Frontal Lobe Functions and GABAergic Transmission in Long COVID Patients[164]	Palmitoylethanolamide co-ultramicronized with antioxidant flavonoid luteolin (dietary supplement)
Feasibility of Cannabidiol for the Treatment of Long COVID	MediCabilis Cannabis sativa 50 (drug)
*The Effects of a Multi-factorial Rehabilitation Program for Healthcare Workers Suffering from Post-COVID-19 Fatigue Syndrome[165]	Exercise (procedure)
Stellate Ganglion Block to Treat Long COVID-19 Case Series	Stellate Ganglion Block (procedure)
*Transcranial Direct Stimulation for Persistent Fatigue Treatment Post-COVID-19[166]	Active tDCS (device)

Effects of Cranial Electrotherapy Stimulation (CES) on Anxiety of Patients after COVID-19	Application of CES via ear clips (device)
Feasibility Pilot Clinical Trial of Omega-3 Supplement vs. Placebo for Post-COVID-19 Recovery Among Health Care Workers	Omega-3 (dietary supplement)
Telerehabilitation Program in Persistent COVID-19	Exercise and tele-coaching (procedure)
Inspiratory Muscle Trainer and SARS-CoV-2 (COVID-19) Persistent Symptoms	Inspiratory muscle trainer (device)
Biosound Therapy as a Treatment for Long COVID Patients	Biosound Therapy System (procedure)
*Effects of Sodium Pyruvate Nasal Spray in COVID-19 Long Haulers[167]	Sodium pyruvate nasal spray (drug)
COVID-19 Sequelae: Treatment and Monitoring. A Dietary Supplement Based on Sea Urchin Eggs With Echinochroma A	Echinochrome A (dietary supplement)
Homeopathic Treatment of Post-acute COVID-19 Syndrome	Homeopathic Medication (drug)
*Vortioxetine for Post-COVID-19 Condition[168]	Vortioxetine (drug)
Effects of Cardiopulmonary Rehabilitation in Participants With Post-COVID 19 Syndrome.	Pulmonary rehabilitation exercises at the Rehabilitation Center or Home Intervention (procedure)

Effectiveness of Supportive Psychotherapy Through Internet-Based Teleconsultation on Psychological and Somatic Symptoms, Neutrophil-Lymphocyte Ratio, and Heart Rate Variability in Post Covid-19 Syndrome Patients	Supportive Psychotherapy (procedure)
Circuit Training Program in Post COVID-19 Patients	Circuit Training Exercise Program or Aerobic Training Exercise Program (procedure)
Aerobic Exercise in People With Post-COVID-19	Aerobic exercise or Conventional rehabilitation
Effectiveness of Modified Diaphragmatic Training for Gastroesophageal Reflux Disease Post Covid-19	Modified diaphragmatic training (procedure)
Quality of Life and Lung Function on Post Covid-19 Patient (Covid-19)	Breathing exercise, Aerobic exercises (procedure)
Exercise Training Six-Months After Discharge in Post-COVID-19 Syndrome	Aerobic exercise and strength training (procedure)
Community-based Individualized Homeopathic Rehabilitation in Post COVID-19 Patients	Homeopathy (drug)
*Low Versus Moderate-intensity Aerobic Training in Post-discharge COVID-19 Subjects[169]	Aerobic exercise (procedure)
Exercise and Post-COVID/Long COVID19: Effects of Different Training Modalities on Physical Performance, Heart Rate Variability, Inflammation, Health-Related Quality of Life, Cognitive Function and Post-COVID/Long COVID19 Symptoms	Endurance training Concurrent training

Efficacy and Security of the Magnesium and Vitamin D Combination as Adjuvant Treatment of Post-COVID Syndrome. A Randomised Double-blind Clinical Trial	Dietary supplements
Effects of Respiratory Muscle Training Combined With an Exercise Training Program in Individuals With Long-term Post-COVID -19 Symptoms	Inspiratory and expiratory muscle training
Development and Clinical Trials of a Rehabilitation Platform to Accelerate the Recovery of Patients With COVID Neuromotor Sequelae	Training with a robotic hand exosceleton

Appendix 4: WHO living guidance PCC rehabilitation recommendations[14]

Symptom/ Condition	Recommendations
Post-exertional malaise	▪ Education and skills training on energy conservation techniques (pacing)
Arthralgia	▪ Pain education, skills training on self-management strategies, prescription of short-term anti-inflammatory drugs, and physical exercise training
Dyspnoea	▪ Education and skills training on self-management strategies such as breathing control techniques, pacing approaches, and physical exercise training
Cognitive impairments	▪ Education, skills training on self-management strategies, and cognitive exercises
Fatigue	▪ Education, skills training on energy conservation techniques (pacing), and a cautious physical exercise training

Depression	▪ Psychological support, mindfulness-based approaches, peer support, and physical exercise training
Olfactory dysfunction	▪ Education and skills training for olfactory training
Orthostatic intolerance	▪ Education and skills training on self-management strategies and physical exercise training
Dysphagia	▪ Education and skills training on positioning, manoeuvres and dietary modifications, and swallowing exercises

*this table's content was extracted from the original publication with minor language adjustments[14]