Long covid—mechanisms, risk factors, and management

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ABSTRACT

Since its emergence in Wuhan, China, covid-19 has spread and had a profound effect on the lives and health of people around the globe. As of 4 July 2021, more than 183 million confirmed cases of covid-19 had been recorded worldwide, and 3.97 million deaths. Recent evidence has shown that a range of persistent symptoms can remain long after the acute SARS-CoV-2 infection, and this condition is now coined long covid by recognized research institutes. Studies have shown that long covid can affect the whole spectrum of people with covid-19, from those with very mild acute disease to the most severe forms. Like acute covid-19, long covid can involve multiple organs and can affect many systems including, but not limited to, the respiratory, cardiovascular, neurological, gastrointestinal, and musculoskeletal systems. The symptoms of long covid include fatigue, dyspnea, cardiac abnormalities, cognitive impairment, sleep disturbances, symptoms of post-traumatic stress disorder, muscle pain, concentration problems, and headache. This review summarizes studies of the long term effects of covid-19 in hospitalized and non-hospitalized patients and describes the persistent symptoms they endure. Risk factors for acute covid-19 and long covid and possible therapeutic options are also discussed.

Introduction

Coronavirus disease 2019 (covid-19) has spread across the world. As of 4 July 2021, more than 183 million confirmed cases of covid-19 have been recorded worldwide, and more than 3.97 million deaths have been reported by the World Health Organization .[1] The clinical spectrum of covid-19 ranges from asymptomatic infection to fatal disease.[2] [3] The virus responsible for causing covid-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), enters cells via the angiotensin-converting enzyme 2 (ACE2) receptor.[4] Once internalized, the virus undergoes replication and maturation, provoking an inflammatory response that involves the activation and infiltration of immune cells by various cytokines in some patients.[5] The ACE2 receptor is present in numerous cell types throughout the human body, including in the oral and nasal mucosa, lungs, heart, gastrointestinal tract, liver, kidneys, spleen, brain, and arterial and venous endothelial cells, highlighting how SARS-CoV-2 can cause damage to multiple organs.[6 7]

The impact of covid-19 thus far has been unparalleled, and long term symptoms could have a further devastating effect.[8] Recent evidence shows that a range of symptoms can remain after the clearance of the acute infection in many people who have had covid-19, and this condition is known as long covid. The National Institute for Health and Care Excellence (NICE) defines long covid as the symptoms that continue or develop after acute covid-19 infection and which cannot be explained by an alternative diagnosis. This term includes ongoing symptomatic covid-19, from four to 12 weeks post-infection, and post-covid-19 syndrome, beyond 12 weeks post-infection.[9] Conversely, The National Institutes of Health (NIH) uses the US Centers for Disease Control and Prevention (CDC) definition of long covid, which describes the condition as sequelae that extend beyond four weeks after initial infection.[10] People with long covid exhibit involvement and impairment in the structure and function of multiple organs.[11-14] Numerous symptoms of long covid have been reported and attributed to various organs, an overview of which can be seen in fig 1. Long term symptoms following covid-19 have been observed across the spectrum of disease severity. This review examines the long term impact of symptoms reported following covid-19 infection and discusses the current epidemiological understanding of long covid, the risk factors that may predispose a person to develop the condition, and the treatment and management guidelines aimed at treating it.

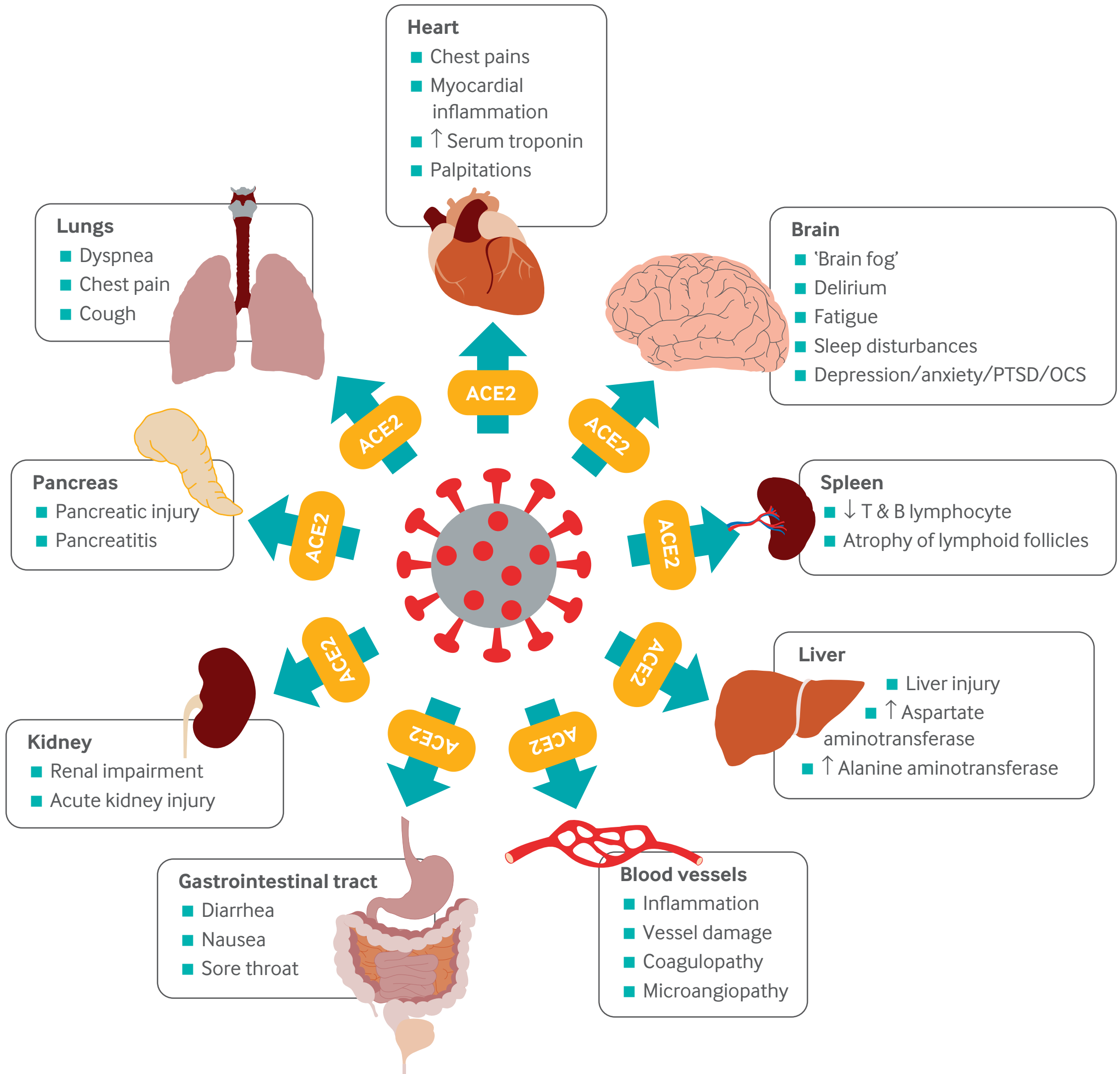

Fig 1 | Multi-organ complications of covid-19 and long covid. The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor. Once these cells have been invaded, the virus can cause a multitude of damage ultimately leading to numerous persistent symptoms, some of which are outlined here

Methods

We searched PubMed and Embase databases for articles published between January 2020 and May 2021. Our search terms were "long covid" or "post-covid-19" or "COVID long-haulers" or "SARS-CoV-2" and "epidemiology" or "fatigue" or "fatigue syndrome" or "dyspnoea" or "breathlessness" or "shortness of breath" or "cardiac" or "cardiovascular" or "heart" or "cognition" or "cognitive impairment" or "mental health" or "depression" or "anxiety" or "psychiatric" or "central nervous system" or "autonomic nervous system" or "isolation" or "loneliness" or "sleeplessness" or "sleep" or "smell" or "taste" or "olfactory" or "gustatory" or "risk factors" or "treatment". To avoid unintentionally removing articles, no filters were applied. We retrieved 61 881 articles in the first instance. To screen articles, titles were read by authors first, followed by abstracts to further narrow down the number of records considered. To avoid unnecessary exclusion of studies, limited exclusion and inclusion criteria were applied. We excluded papers that were not relevant to or did not mention long covid, while studies mentioning long covid in any capacity were initially included owing to the novelty of the field. Furthermore, we considered long covid studies regardless of their cohort sizes or study design. We discovered and read fully 227 articles on long covid, and we discussed each to determine which would be included in the finalized article. We performed further manual searching for additional articles and treatment guidelines using relevant databases, including nice.org.uk and clinicaltrials.gov. In total, 218 references were included. Studies examining long covid are limited, therefore limited exclusion criteria were applied.

Studies of long covid

Studies have assessed people who have had covid-19 to examine the symptoms associated with long covid.

These studies are summarized in table 1. The articles included throughout this review were selected in favor of quality, with large observational studies of greatest interest. Most of the studies included are cross-sectional or cohort observational studies with large cohorts; however, because of the novelty of the disease and paucity of data, studies involving smaller cohorts and case series were also included. Any patient with covid-19 may develop long covid, regardless of the severity of their infection and the intensity of the treatment they received. Patients treated on wards and intensive care units (ICUs) show little difference in incidence of long term symptoms associated with covid-19.[17] The proportion of people that develop long covid symptoms, whether they are treated with oxygen alone, with continuous positive airway pressure, or with invasive ventilation, is similar.[16] Many patients with mild acute symptoms also develop long covid symptoms,[13] in fact, studies show minimal differences between the prevalence of long covid symptoms between hospitalized and non-hospitalized covid-19 patients.[19]

Epidemiology

The reported incidence and mortality rates of covid-19 vary between countries, making it difficult to accurately predict the number of patients who will progress to long covid. Similarly, the accurate reporting of long covid is complicated. The disparity in this epidemiological data is likely the result of several factors, including differences in the base population, the accuracy of diagnosis, the reporting systems, and the capability of healthcare systems. Although determining the exact epidemiological data of long covid is difficult, this information is needed to inform healthcare systems and governments when developing support and treatment algorithms. The volume of published literature describing cases of patients with covid-19 who subsequently develop long covid symptoms is continually growing, which will allow for an improved understanding of its epidemiology.

The current disparities between long covid epidemiology reporting are owing to many reasons, including the length of follow-up period, population assessed, accuracy of self-reporting, and symptoms examined. Studies around the world have reported various incidence rates for long covid with different follow-up examination times after the acute infection, including 76% of people at 6 months,[50] 32.6% at 60 days,[51] 87% at 60 days,[15] and 96% at 90 days.[52] These finding are not fully corroborative, but they show that a substantial proportion of people who have had covid-19 may develop long covid. The UK Office for National Statistics (ONS) has released data on the prevalence of long covid symptoms.[53] They estimated that the five week prevalence of any symptom among survey respondents who tested positive for covid-19 between 22 April and 14 December 2020 was 22.1%, while the 12 week prevalence was 9.9%. These figures are worrying for patients, service providers, and governments, with many patients likely to develop long covid and require long term support and treatment. Further studies are required to consolidate our epidemiological understanding of long covid.

Covid-19 variants of concern

Since the start of the pandemic, several covid-19 variants have emerged that have an increased transmissibility and may result in more severe acute disease. In the UK, one of the first variants of concern to appear was the so called "Kent variant," from the B.1.1.7 lineage, now termed the Alpha variant. This variant has approximately 50% increased transmissibility[54] and likely increases acute disease severity.[55] As of 30 June 2021, the Alpha variant has been confirmed in more than 275 000 cases in the UK[56] and spread to at least 136 countries around the world.[57] Other variants of concern or under investigation include the Beta, Gamma, Zeta, Theta, and Kappa variants.[56] The CDC reports the emergence of variants of concern and interest in the US.[58] New covid-19 variants will continue to emerge and spread as we progress through the pandemic, for example, the Eta and Delta variants have arisen, with over 161 000 cases of the rapidly spreading Delta variant confirmed in the UK, as of 30 June 2021.[56] Recently, the Lambda variant has emerged, which will require close monitoring. The ability of these viral strains to inflict long term complications needs to be examined fully. To speculate, it may be that one variant causes more damaging long term effects than others and, therefore, patients infected with such a variant who go on to develop long covid symptoms may require additional support, as well as more rapid and intense treatment strategies to combat their long term symptoms.

Long covid definition

Long covid gained widespread attention following an account published on 5 May 2020 in *BMJOpinion* where an infectious disease professor shared his experience of seven weeks on a "rollercoaster of ill health" following covid-19.[59] The patient-made term *long covid* was then made popular following the rise in the use of #LongCovid on Twitter.[60] This, plus the growing number of peer reviewed articles published since, has highlighted a post-covid-19 syndrome that can last for many weeks after the acute infection. Long covid is now a recognized term in scientific literature. The NICE guidelines on managing the long term effects of covid-19[9] and the CDC[10] define long covid patients or covid long haulers as individuals with ongoing symptoms of covid-19 that persist beyond four weeks from initial infection.

Symptoms

Fatigue

Fatigue is more profound than being overtired; it is unrelenting exhaustion and a constant state of weariness that reduces a person's energy, motivation, and concentration. Following the SARS outbreak, up to 60% of patients reported ongoing fatigue

Table 1 | Summary of studies that have explored the persisting symptoms post-covid-19 infection, or during long covid

Study reference	Number of subjects in study	Hospitalized / non-hospitalized	Study design	Time to assessment (average)	Symptoms (% of patients)	
Carfi A, et al, 2020[15]	143	Hospitalized	Case series	60.3 days after onset	Fatigue (53.1%); dyspnea (43.4%);	joint pain (27.3%); chest pain (21.7%)
Mandal S, et al, 2020[16]	384	Hospitalized	Cross sectional (analytic)	54 days post-hospital discharge	Fatigue (46.6%); cough (28.6%);	breathlessness (56.25%); poor sleep quality (57%)
Halpin SJ, et al, 2020[17]	100	Hospitalized (32 ICU treated, 68 ward treated)	Cross sectional (analytic)	48 days after onset	Fatigue (64%); breathlessness (48%);	neuropsychological (30%); speech and swallow (8%)
Dennis A, et al, 2020[13]	201	Hospitalized: n=37; non-hospitalized: n=164	Cross sectional (analytic)	140 days after onset	Fatigue (98%); muscle ache (87.6%); shortness of breath (87.1%); headache (82.6%); joint pain (78.1%);	fever (75.1%); chest pain (73.6%); sore throat (71.1%); diarrhea (59.2%)
Tenforde MW, et al, 2020[18]	274	Non-hospitalized	Cross sectional (survey)	14-21 days after onset	Fatigue (38%); cough (46%); headache (18%); body ache (20%); loss of taste (28%); loss of smell (27%); diarrhea (14%);	congestion (32%); dyspnea (31%); nausea (13%); sore throat (18%); chest pain (20%); abdominal pain (18%); confusion (20%)
Goertz YMJ, et al, 2020[19]	2113	Hospitalized: n=112; non-hospitalized: n=2001	Cross sectional (survey)	79 days after onset	Fatigue (87%);dyspnea (71%);	chest tightness (44%);cough (29%)
Townsend L, et al, 2020[20]	128	Hospitalized: n=71; non-hospitalized: n=57	Cross sectional (analytic)	72 days after initial symptoms	Fatigue (52.3%)	
Boscolo-Rizzo P, et al, 2020[21]	187	Non-hospitalized	Cross sectional (survey)	28 days after onset	Loss of taste or smell (10.6%)	
Paderno A, et al, 2020[22]	151	Non-hospitalized	Cohort study	30 days after onset	Olfactory dysfunction (17%);	gustatory dysfunction (11%)
Puntmann VO, et al, 2020[23]	100	Hospitalized: n=33; non-hospitalized: n=67	Cohort study	71 days after onset	Cardiac involvement (78%); troponin levels (71%); ongoing myocardial	inflammation (60%); shortness of breath (36%)
Helms J, et al, 2020[24]	58	Hospitalized	Case series	At discharge from hospital	Agitation (69%); corticospinal tract syndrome (67%);	delirium development (65%); dysexecutive syndrome (36%)
Vaes AW, et al, 2020[25]	1837	Non-hospitalized	Cross sectional (survey)	79 days after onset	Requirement of personal care (52.4%)	
Arnold DT, et al, 2020[26]	110	Hospitalized	Cross sectional (analytic)	8-12 weeks after onset	Breathlessness (39%); fatigue (39%);	insomnia (24%)
Cruz RF, et al, 2020[27]	119	Hospitalized	Cohort study	4-6 weeks post-discharge	Fatigue (67.8%); breathlessness (32.2%); persistent cough (42.6%);	insomnia (56.5%); pain (49.5%)
Daher A, et al, 2020[28]	33	Hospitalized	Cohort study	6 weeks post-discharge	Fever (3%); cough (33%); dyspnea (33%); fatigue (45%); tiredness (45%); sore throat (9%);	headache (15%); loss of smell (12%); loss of taste (9%); diarrhea (9%); angina pectoris (18%)
Huang L, et al, 2020[29]	26	Hospitalized	Cross sectional (analytic)	Not reported	Abnormal cardiac findings (58%);	myocardial edema (54%)
Huang Y, et al, 2020[30]	57	Hospitalized	Cross sectional (analytic)	At least 30 days since acute infection	Slight cough (10.5%); shortness of breath (7%);	occasional wheezing (5.3%)
Raman B, et al, 2020[11]	58	Hospitalized	Cohort study	2-3 months after onset	Lung parenchymal abnormalities (32/53 60.4%); breathlessness (36/53 64%);	fatigue (30/55 55%); Liver injury (11%); renal impairment (3%)
Savarraj JPJ, et al, 2020[31]	48	Hospitalized	Cohort study	90 days after onset	Any neurological symptom (71%); fatigue (42%); post-traumatic stress (PC-PTSD-5 (29%); sleepiness (17%);	cognitive deficit (BNST) (12%); depression symptoms (PHQ-9) (11%); anxiety (GAD-7) (9%); Pain (PEG) (64%)
Sonnweber T, et al, 2020[32]	109	Hospitalized: n=87; non-hospitalized: n=22	Cohort study	60 days after onset	Iron deficiency (30%); anemia (9.2%);	hyperferritinemia (38%)
Valiente-De S, et al, 2020[33]	82	Non-hospitalized	Observational study	12 weeks after onset	Dyspnea (55.6%); asthenia (44.9%); cough (25.9%); chest pain (25.9%); palpitations (22.2%); headache (9.3%); anosmia (9.3%); dysgeusia (5.6%); fever (3.7%)	chills (3.7%); arthromyalgia (2.8%); hair loss (2.8%); diarrhea (1.9%); anxiety (6.4%); insomnia (1.9%); loss of memory (1.9%); difficulty concentrating (1.9%)
Sudre CH, et al, 2020[34]	4182	13.9% required hospital treatment, 86.1% required no hospital treatment	Cohort study	28 days after onset	Fatigue (97.7%); headache (91.2%)	
Vaira LA, et al, 2020[35]	138	Hospitalized: n=32; non-hospitalized: n=106	Cohort study	60 days after onset	Smell or taste dysfunction (7.2%)	
Tomasoni D, et al, 2020[36]	105	Hospitalized	Cross sectional (analytic)	90 days after onset	Smell or taste dysfunction (5.7%); gastrointestinal symptoms (1%); burning pain (10.5%);	dyspnea (6.7%); fatigue (31.4%); cognitive deficits (17.1%)
Mazza MG, et al, 2020[37]	402	Hospitalized: n=300; non-hospitalized: n=102	Cross sectional (analytic)	30 days post-discharge	PTSD (28%); depression (31%); anxiety (42%);	obsessive-compulsive symptoms (20%); insomnia (40%)
Klein H, et al, 2020[38]	112	Hospitalized: n=6; non-hospitalized: n=106	Cross sectional (survey)	6 months after onset	Fatigue (20.5%); smell change (13.4%); breathing difficulty (8.9%); taste change (7.1%);	memory disorders (5.4%); muscle aches (7.14%); headaches (3.57%); hair loss (2.68%)

(*Continued*)

Table 1 | Continued

Study reference	Number of subjects in study	Hospitalized / non-hospitalized	Study design	Time to assessment (average)	Symptoms (% of patients)	
Fjaeldstad AW, et al, 2020[39]	204	Non-hospitalized	Cross sectional (survey)	24 days after onset	Olfactory loss (28/100 28%);	gustatory loss (21/104 20%)
Eiros R, et al, 2020[40]	139	Hospitalized: n=23; non-hospitalized: n=116	Cross sectional (analytic)	10.4 weeks after onset	No symptoms (34%); fatigue (27%); anosmia (9%); ageusia (5%); headache (5%); sore throat (5%); abdominal pain (4%); memory loss (3%); joint pain (2%);	piloerection (1%); shortness of breath (26%); chest pain (19%); pericarditis-like chest pain (13%); palpitations (14%); dizziness (6%); at least one cardiac symptom (42%)
Xiong Q, et al 2020[41]	538	Hospitalized	Cohort study	97 days post-discharge	General symptoms (49.6%); physical decline/fatigue (28.3%); sweating (23.6%); myalgia (4.5%); arthralgia (7.6%); chills (4.6%); limb edema (2.6%); dizziness (2.6%); respiratory symptoms (39%); post-activity polypnea (21.4%); non-motor polypnea (4.7%); chest distress (14.1%); chest pain (12.3%); sputum (3%); throat pain (3.2%);	Cardiovascular related symptoms (13%); increase in resting heart rate (11.2%); discontinuous flushing (4.8%); newly diagnosed hypertension (1.3%); psychosocial symptoms (22.7%); somnipathy (17.7%); depression (4.3%); anxiety (6.5%); dysphoria (1.7%); feelings of inferiority (0.6%); alopecia (28.6%)
Weerahandi H, et al, 2020[42]	152	Hospitalized	Cohort study	37 days post-discharge	Shortness of breath (74%)	
Kamal M, et al, 2020[43]	287	Hospitalized: n=14; non-hospitalized: n=273	Cross sectional (survey)	Unclear	Fatigue (72.8%); anxiety (38%); joint pain (31.4%); continuous headache (28.9%); chest pain (28.9%); dementia (28.6%); depression (28.6%); dyspnea (28.2%) blurred vision (17.1%); tinnitus (16.7%);	intermittent fever (11.1%); obsessive-compulsive disorder (4.9%); pulmonary fibrosis (4.9%); diabetes mellitus (4.2%); migraine (2.8%); stroke (2.8%); renal failure (1.4%); myocarditis (1.4%); arrhythmia (0.3%)
Poyraz BC, et al. 2020[44]	284	Hospitalized: n=112; non-hospitalized: n=169	Cross sectional (survey)	50 days following diagnosis	Fatigue (40%); muscle aches (22%); alteration of taste (18%); headache (17%); alteration of smell (17%); difficulty in concentration (15%); daytime sleepiness (10%)	light-headedness (7%); numbness and tingling sensations on the skin (6%); dyspnea (4%); chest pain (3%); cough (2%);
Landi F, et al, 2020[45]	131	Hospitalized	Cohort study	55.8 days after onset	Cough (16.7%); fatigue (51.1%); diarrhea (3.8%); headache (10.6%); smell disorder (13.7%); dysgeusia (11.4%);	red eyes (16%); joint pain (25.1%); shortness of breath (44.2%); loss of appetite (9.9%); sore throat (6.8%); rhinitis (14.5%)
Carvalho-Schneider C, et al, 2020[46]	150	Hospitalized: n=53; non-hospitalized: n=97	Cohort study	30 days after onset	Fever (3.6%); shortness of breath (10.7%); chest pain (18%); flu-like symptoms (36%); digestive disorders (17.3%);	weight loss (15.9%); anosmia/ageusia (27.8%); heart palpitations (6.5%); arthralgia (9.8%); cutaneous signs (15.4%)
Otte MS, et al, 2020[47]	91	Non-hospitalized	Cross sectional (survey)	56.55 days after onset	Olfactory impairment (45.1%)	
Zhao YM, et al, 2020[48]	55	Hospitalized	Cohort study	3 months after onset	Gastrointestinal symptoms (30.9%); headache (18.2%); fatigue (16.4%);	exertional dyspnea (14.6%); cough and sputum (1.8%)
Frontera JA, et al, 2021[49]	382	Hospitalized	Cohort study	6 months post-discharge	Fatigue (36%); anxiety (46%); cognitive impairment (50%);	sleep problems (38%); depression (25%); limited activities of daily living (56%)

at 12 months following recovery from the acute illness.[61] In long covid, fatigue is one of the most reported manifestations, with the ONS estimating the five week prevalence of fatigue to be 11.9% among people who have had covid-19.[53] Fatigue is a common persisting symptom regardless of severity of the acute stage of covid-19. One cross-sectional study found that 92.9% and 93.5% of hospitalized and non-hospitalized covid-19 patients, respectively, reported ongoing fatigue at 79 days following onset of illness.[19] Many other cross-sectional and cohort studies report that chronic fatigue is the most frequently reported symptom following recovery from acute covid-19,[15 17 20 27 43] with one showing no association between covid-19 severity and long term fatigue.[20] These findings show that fatigue is a major manifestation of long covid.

Possible mechanisms

Chronic fatigue following viral infection may be the result of miscommunication in the inflammatory response pathways[62]; however, a cross-sectional analytical study found no association between pro-inflammatory markers and long term fatigue in covid-19 patients with persisting fatigue.[20] It is likely that a range of central, peripheral, and psychological factors play a role in the development of post-covid-19 fatigue. A narrative review explains that congestion of the glymphatic system and the subsequent toxic build-up within the central nervous system (CNS), caused by an increased resistance to cerebrospinal fluid drainage through the cribriform plate as a result of olfactory neuron damage, may contribute to post-covid-19 fatigue.[63]

Hypometabolism in the frontal lobe and cerebellum has also been implicated in covid-19 patients with fatigue and is likely caused by systemic inflammation and cell mediated immune mechanisms, rather than direct viral neuro-invasion.[64 65] It is unknown whether this finding continues into long covid.

Negative psychological and social factors associated with the covid-19 pandemic have also been linked to chronic fatigue.[66 67] Lastly, peripheral factors such as direct SARS-CoV-2 infection of skeletal muscle, resulting in damage, weakness, and inflammation to muscle fibers and neuromuscular junctions may contribute to fatigue.[68-71] Overall, it is probable that several factors and mechanisms play a role in the development of post-covid-19 fatigue. Figure 2 further outlines these possible mechanisms.

Post-COVID-19 fatigue has been compared with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), with many overlaps between the two.[72] Symptoms common to both ME/CFS and long covid include fatigue, neurological/pain, neurocognitive/psychiatric, neuroendocrine, autonomic, and immune symptoms, with both ME/CFS and long covid patients having long symptom durations, reduced daily activity, and post-exertional malaise.[72] ME/CFS remains enigmatic, therefore, research into long covid may assist in developing understanding of ME/CFS and vice versa.

Dyspnea

Breathlessness is common in people with long covid. The ONS estimates that shortness of breath has a prevalence of 4.6% at five weeks post-covid-19 infection, regardless of presence of acute respiratory symptoms or disease severity.[53] Abnormalities in diffusion capacity for carbon monoxide, total lung capacity, forced expiratory volume in the first second, forced vital capacity, and small airway function, have been seen in hospitalized covid-19 patients at time of discharge, approximately one month following onset of symptoms, showing that lung function in people who have had covid-19 may take time to recover.[73] Several studies have found that dyspnea is a common manifestation following covid-19 infection,[16 17] and one study reported that 43.4% of 143 patients assessed were still experiencing dyspnea at 60 days after covid-19 onset.[15]

Possible mechanisms

As covid-19 is principally a respiratory illness, acute illness can cause substantial damage to the lungs and respiratory tract via SARS-CoV-2 replication inside endothelial cells, resulting in endothelial damage and an intense immune and inflammatory reaction.[74 75] Those who overcome the acute infection may develop long term lung abnormalities, leading to dyspnea[76]; however, most individuals who develop long term breathing difficulties post-covid-19 have no signs of permanent or longlasting lung damage.[28 77] It is likely that only those at high risk of developing breathing difficulties, including older people, those who endure acute respiratory distress syndrome, those who have extended hospital stays, and those with pre-existing lung abnormalities, are prone to develop fibrotic-like changes to lung tissue.[78] The fibrotic state observed in some patients with ongoing dyspnea may be provoked by cytokines such as interleukin-6, which is raised in covid-19[79] and is involved in the formation of pulmonary fibrosis.[80] Pulmonary vascular thromboembolisms have been observed in patients with covid-19[81] and may have detrimental consequences in patients with long covid. An overview of the possible mechanism causing dyspnea is outlined in fig 2.

Cardiovascular abnormalities

Cardiac injury and elevated cardiac troponin levels are associated with a significantly increased risk of mortality in patients admitted to hospital with acute covid-19 infection.[82 83] Persisting cardiovascular abnormalities may be burdensome for people with long covid. A cohort study showed cardiac involvement, ongoing myocardial inflammation, and elevated serum troponin levels in many people with covid-19 at 71 days following diagnosis,[23] while a large case series showed that chest pain, possibly owing to myocarditis, was a common manifestation in patients 60.3 days following onset of covid-19 symptoms, with 21.7% of the 143 patient assessed reporting chest pain.[15] Those considered at low risk of severe covid-19, such as young, competitive athletes, have also been found to have residual myocarditis long after recovery from covid-19.[84] In addition to cardiac complaints, studies have highlighted an emerging trend in the development of new onset postural orthostatic tachycardia syndrome (POTS) in individuals post-covid-19 infection, because of autonomic dysfunction.[85-89]

Possible mechanisms

ACE2 receptors are highly expressed in the heart,[90] providing a direct route of infection for SARS-CoV-2. Studies have shown that sarcomere disruption and fragmentation, enucleation, transcriptional changes, and an intense local immune response occurs in cardiomyocytes infected by SARS-CoV-2.[91 92] Pathological responses to acute cardiac injury and viral myocarditis, such as endothelial damage and microthrombosis, can lead to the development of coagulopathy,[93] while chronic hypoxia and an increase in pulmonary arterial pressure and ventricular strain may further precipitate the incidence of cardiac injury in people who have had covid-19.[94] Furthermore, sustained immune activation can lead to fibrotic changes[95] and displacement of desmosomal proteins,[96] which could be arrhythmogenic. Viral infection has previously been shown to precede POTS[97] and, with the ACE2 receptor expressed on neurons, viral infection by SARS-CoV-2 may have direct negative

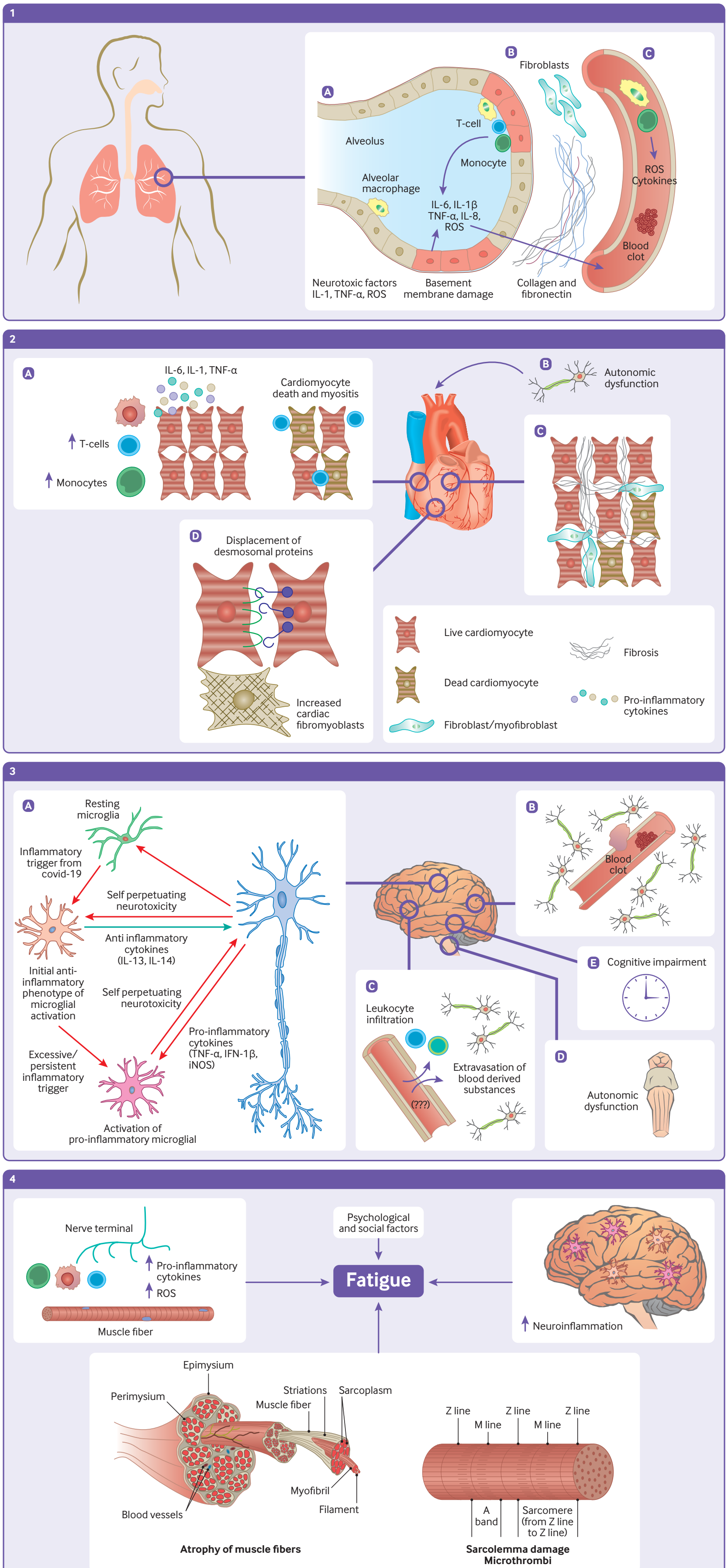

Fig 2 | Long term sequalae of covid-19 (1) In the alveoli of the lungs: (A) Chronic inflammation results in the sustained production of pro-inflammatory cytokines and reactive oxygen species (ROS) which are released into the surrounding tissue and bloodstream. (B) Endothelial damage triggers the activation of fibroblasts, which deposit collagen and fibronectin resulting in fibrotic changes. (C) Endothelial injury, complement activation, platelet activation, and platelet-leukocyte interactions, release of pro-inflammatory cytokines, disruption of normal coagulant pathways, and hypoxia may result in the development of a prolonged hyperinflammatory and hypercoagulable state, increasing the risk of thrombosis. (2) In the heart: (A) chronic inflammation of cardiomyocytes can result in myositis and cause cardiomyocytes death. (B) Dysfunction of the afferent autonomic nervous system can cause complications such as postural orthostatic tachycardia syndrome. (C) Prolonged inflammation and cellular damage prompts fibroblasts to secrete extracellular matrix molecules and collagen, resulting in fibrosis. (D) Fibrotic changes are accompanied by an increase in cardiac fibromyoblasts, while damage to desmosomal proteins results in reduced cell-to-cell adhesion. (3) In the central nervous system: (A) The long term immune response activates glial cells which chronically damage neurons. (B) Hyperinflammatory and hypercoagulable states lead to an increased risk of thrombotic events. (C) Blood-brain barrier damage and dysregulation results in pathological permeability, allowing blood derived substances and leukocytes to infiltrate the brain parenchyma. (D) Chronic inflammation in the brainstem may cause autonomic dysfunction. (E) The effects of long covid in the brain can lead to cognitive impairment.(4) Possible mechanisms causing post-covid-19 fatigue. A range of central, peripheral, and psychological factors may cause chronic fatigue in long covid. Chronic inflammation in the brain, as well as at the neuromuscular junctions, may result in long term fatigue. In skeletal muscle, sarcolemma damage and fiber atrophy and damage may play a role in fatigue, as might a number of psychological and social factors consequences on the autonomic nervous system.[98] A complex combination of infection, an autonomic nervous system induced pro-inflammatory response, and a level of autoimmunity may all contribute to the establishment of autonomic dysfunction and POTS.[89] Figure 2 depicts these mechanisms.

Cognition and mental health

Studies have explored cognitive function and deficits in patients with covid-19 and suggest that the virus can cause septic encephalopathy, non-immunological effects such as hypotension, hypoxia, and vascular thrombosis, and immunological effects such as adaptive autoimmunity, microglial activation, and a maladaptive cytokine profile.[99] Additionally, patients admitted to hospital with covid-19 have presented with a range of complaints including encephalopathy, cognitive impairment, cerebrovascular events/disease, seizures, hypoxic brain injuries, corticospinal tract signs, dysexecutive syndrome, an altered mental status, and psychiatric conditions.[24 100 101] These findings reveal that neurological symptoms associated with covid-19 are common, diverse, and could pose substantial problems for rehabilitation and ongoing care following recovery from covid-19. It is unknown who is most affected by cognitive complaints induced by covid-19 and how long they persist; however, patient experiences and published summaries of long covid have described "brain fog" to be a common and debilitating symptom.[102-104]

Critical illness, severe acute respiratory syndrome, and long term ventilator support are known to have detrimental effects on long term cognition. Before the covid-19 pandemic, a retrospective study of 1040 ICU treated patients who had respiratory failure, shock, or both during hospital stays, found that 71% had delirium which lasted around four months following discharge.[105] A similar study found that, at 3 months post-discharge, 40% of ICU treated patients had cognition scores like those of patients with moderate traumatic brain injury, while 26% had scores similar to patients with mild Alzheimer's disease. Delirium was also widely reported, with a longer duration of delirium associated with worse cognition.[106] With many covid-19 patients requiring ICU admission and mechanical ventilation, long term cognitive impairment and delirium are likely to pose considerable problems.

Stroke and headache are prevalent in those recovered from acute covid-19, with the ONS estimating the 5 week prevalence of headache at 10.1% of all covid-19 survivors.[13 18 34 43 53] Exaggerated levels of systemic inflammation, observed in some patients as a "cytokine storm," in addition to activation glial cells, poses a substantial risk to the brain and increases the likelihood of neurological manifestations including encephalitis and stroke.[74] Hypercoagulability[107] and cardio-embolisms, formed because of virus related cardiac injury,[108] are manifestations that could result in increased incidences of stroke following covid-19 infection. Covid-19 has also been associated with an increased risk of developing neurological conditions including Guillain-Barré syndrome,[109] and neurodegenerative conditions such as Alzheimer's disease.[110]

The pandemic has had a negative effect on mental health, with people who have had covid-19 exhibiting long term psychiatric symptoms including post-traumatic stress disorder (PTSD), depression, anxiety, and obsessive-compulsive symptoms following recovery from the acute infection.[36 37 111 112] Quarantine, isolation, and social distancing also have damaging effects on mental health and cognition. A rapid review article states that the longer a person is confined to quarantine, the poorer the outcomes for their mental health,[67] while periods of isolation and the inability to work can cause anxiety, loneliness, and financial concerns, and living through a global health crisis can lead to avoidance behaviors and behavioral changes.[113] The mental health of the older population is greatly affected by social distancing and similar measures. By assessing the associations between loneliness, physical activity, and mental health both before and during the pandemic, one study found that negative changes of these factors were not solely owing to longitudinal situations before 2020, therefore the pandemic exerted extra unfavorable effects on loneliness, physical activity, and mental health.[114] People living in care homes, including people with dementia, are vulnerable to covid-19 and to other impacts of the pandemic. Those with dementia in care homes have been observed to become more depressed, anxious, agitated, and lonely.[115] Protracted social isolation has resulted in exacerbation of neuropsychiatric and behavioral disturbances, including apathy, anxiety, agitation, boredom, and confusion in dementia patients living in care homes, to a greater degree than for care home residents without dementia.[116 117]

Sleeplessness is also commonly reported following recovery from covid-19, with many studies finding poor sleep quality and sleep disturbances to be frequent following recovery from acute illness.[16 25 31 44 118 119] Furthermore, a retrospective study of medical records of covid-19 patients treated in Seoul, South Korea, found that after prescriptions to treat fever, cough, and rhinorrhea, medications for sleep problems were the next most prescribed treatments.[120] Knowledge of the covid-19 death toll also has a negative impact on quality of sleep, stress, anxiety, and other negative emotions,[121] and sleep problems have been shown to be associated with covid-19 related loneliness.[122] This leads us to question whether post-covid-19 sleep disturbances are a result of covid-19 infection, the negative effects of the pandemic, or a combination of both.

Possible mechanisms

Coronaviruses including SARS-CoV-2 can infect the central nervous system (CNS) via hematogenous or neuronal retrograde neuro-invasive routes.[123] The entry mechanism and subsequent CNS infection may explain the high incidence of neuro-inflammation seen in patients with covid-19, and may result in damaging long term effects, with associations of viral infections and chronic neuro-inflammation with neurodegenerative and psychiatric disorders already elucidated.[123 124] SARS-CoV-2 may also affect the permeability of the blood-brain barrier, which would enable peripheral cytokines and other blood derived substances to enter the CNS and further drive neuro-inflammation.[125] Thrombo-inflammatory pathways may be the cause of the increased prevalence of stroke in covid-19,[126] while "brain fog" may evolve from PTSD or deconditioning following critical illness and invasive treatment.[127] Evidence suggests that a direct viral encephalitis, systemic inflammation, peripheral organ dysfunction, and cerebrovascular changes may contribute to the development of long term sequalae following covid-19.[128] Figure 2 outlines the potential mechanisms occurring within the CNS.

Olfactory and gustatory dysfunction

Abnormalities of smell and taste have been reported to persist following recovery from covid-19. The ONS estimated the 5 week prevalence of loss of smell and loss of taste as 7.9% and 8.2% of all people who have had covid-19, respectively.[53] Other studies have found varying prevalence of olfactory and gustatory dysfunction, ranging from 11% to 45.1% of cohorts of patients who have recovered from acute covid-19.[22 39 47]

Possible mechanisms

Non-neuronal expression of the ACE2 receptor may enable entry of the SARS-CoV-2 virus into olfactory support cells, stem cells, and perivascular cells. This local infection could cause an inflammatory response which subsequently reduces the function of olfactory sensory neurons. Additionally, by damaging the support cells responsible for local water and ionic balance, SARS-CoV-2 may indirectly reduce signaling from sensory neurons to the brain,[129] resulting in a loss of sense of smell.

ACE2 receptors are also expressed on the mucous membrane of the oral cavity, particularly on the tongue,[130] therefore SARS-CoV-2 has a direct route of entry into oral tissue, which may result in cellular injury and dysfunction. Moreover, SARS-CoV-2 may bind to sialic acid receptors,[131] causing an increase in gustatory threshold and resulting in degradation of gustatory particles before they can be detected.[132] Another possible mechanism of gustatory dysfunction in covid-19 and long covid concerns the functional link between taste and smell, whereby gustatory perception is reduced because of antecedent olfactory sensory dysfunction.[133]

Other commonly reported manifestations

Covid-19 infection can result in multi-organ impairment in individuals with low or high risk for severe acute disease.[2 13] Studies show the presence of acute kidney injury in discharged patients who have recovered from covid-19.[134-136] Although the long term effects of covid-19 on the kidneys are not fully elucidated, a study assessing kidney function in patients with covid-19 found that 35% had decreased kidney function at 6 months post-discharge.[50]

Acutely, pancreatitis triggered by SARS-CoV-2 has been seen in people with covid-19,[6 137] while serum amylase and lipase levels have been observed to be higher in people with severe illness compared with mild cases, and computed tomography images have shown pancreatic injury.[138] A cross sectional study found that 40% of patients with covid-19 who were at low risk of severe disease, assessed 141 days following infection, had mild impairment of the pancreas. This impairment was associated with diarrhea, fever, headache, and dyspnea.[13] Postmortem and case studies have highlighted the impact that covid-19 has on the spleen, including atrophy of lymphoid follicles, a decrease in T and B lymphocytes leading to lymphocytopenia, and thrombotic events such as infarcts.[139-141] A cross sectional study found mild impairment of the spleen in 4% of those assessed at 141 days following clearance of covid-19.[13] Other organs and tissues, such as the liver, gastrointestinal tract, muscle, and blood vessels express the ACE2 receptor and are susceptible to direct damage from SARS-CoV-2 and indirect damage through elevated systemic inflammation.[142-144] Alterations in gut microbiota[145] and subacute thyroiditis[142] have been observed following covid-19 infection.

Possible mechanisms

Kidney injury may occur through several mechanisms associated with covid-19, including sepsis[143] and lung injury leading to hemodynamic changes and hypoxemia.[144] The ACE2 receptor is highly expressed in the pancreas,[4] perhaps to a greater level than in the lungs[138]; however, it is unclear whether pancreatic damage is a direct result of viral infection within the pancreas, or caused by the systemic inflammatory response seen during covid-19. [146] The spleen also expresses ACE2 receptors[6] and may be directly attacked by the virus, rather than the intense systemic inflammation being the primary cause of splenic damage.[139] Chronic systemic inflammation is frequently observed long after the clearance of acute covid-19 infection,[13] therefore, it is likely that this elevated inflammatory state causes long term complications in multiple organs in people with long covid.

Risk factors

Risk factors for severe covid-19 and hospital admission, and risk factors for death as a result of covid-19 include older age, male sex, non-white ethnicity, being disabled, and pre-existing comorbidities including obesity, cardiovascular disease, respiratory disease, and hypertension.[2 13 19 147 148] Linked to risk of covid-19 severity and possibly the risk of long covid, the role of immune suppression is still being debated. Immune suppression may have protective effects against long term effects of covid-19 infection[149-151]; however, these findings are conflicted.[152 153]

The risk factors for developing long covid are less appreciated. To explore the characteristics associated with symptoms of long covid, 274 non-hospitalized patients who had covid-19 were interviewed between 14 and 21 days following their positive test. Risk factors for not returning to "usual health" included age (P=0.01), with the ≥50 years age group having the greatest odds ratio, and number of pre-existing medical conditions (P=0.003), with a greater number of conditions associated with a greater odds ratio of not returning to "usual health." Of the pre-existing conditions, having hypertension (odds ratio (OR)=1.3, P=0.018), obesity (OR=2.31, P=0.002), a psychiatric condition (OR=2.32, P=0.007), or an immunosuppressive condition (OR=2.33, P=0.047) corresponded with the greatest odds of not returning to "usual health."[18]

A cross sectional study identified an association between the severity of acute covid-19 infection and post-recovery manifestations in people who have had covid-19, showing that a more severe acute phase may transform into the development of more severe symptoms of long covid.[43] A cohort study, meanwhile, corroborated this finding, with patients with more than five symptoms during the initial covid-19 infection and those that required hospital admission more likely to experience long covid symptoms.[34]

Although certain factors may increase the risk of both severe covid-19 and long covid, some factors associated with covid-19 do not also increase risk for long covid. Male sex and older age are associated with an increased risk of severe covid-19, however, the ONS reported that the prevalence of any long covid symptoms is higher in women compared with men (23.6% versus 20.7%), while the age group estimated to be most greatly affected by long covid symptoms is 35-49 years (26.8%), followed by 50-69 years (26.1%), and the ≥70 years group (18%).[53] Furthermore, a prospective cohort study assessing recovered patients found no baseline clinical features associated with the subsequent development of long covid symptoms.[154] Male sex, age, and pre-existing conditions including obesity, diabetes, and cardiovascular disease have shown no association with the risk of developing long covid. However, pre-existence of asthma has been found to be significantly associated with long covid.[34]

Treatment and management of long covid

WHO and the Long Covid Forum Group agree that research priorities for long covid include improving clinical characterization and the research and development of therapeutics.[155 156] Clinical characterization of patients with long covid is essential to provide appropriate treatment options. Gaining an understanding of why certain disease phenotypes arise in different individuals is an important piece of the puzzle. A review, which included perspectives from patients with long covid, suggested that the condition may actually be four different syndromes.[102] Recognizing which patients belong to which subgroup of long covid, and understanding the pathophysiology, will be important in deciding the treatment they receive.

Guidelines

Various guidelines focus on treating and managing long covid, or have included recommendations for long covid in their guidelines for treating covid-19.[9] Guidelines recommend how to identify, refer, and treat patients with long covid. The holistic assessment, investigation, and management approaches suggested by NICE[9] are outlined in fig 3. In January 2021, WHO updated its covid-19 guidance to include a new chapter focused on caring for patients post-covid-19.[157] These guidelines go into little detail about long covid, however. Similarly, the NIH has released treatment guidelines for covid-19,[158] but little guidance on managing long covid. The CDC is expected to release guidance on long covid management soon.[159] The European Society of Cardiology has also released guidelines on the diagnosis and management of cardiovascular disease during the pandemic.[160] The guidelines for treating and managing long covid will undoubtedly evolve as new evidence comes to light; however, other general guidelines, such as Evidence Based Medicine's guidance on post-infectious syndromes may be useful for treating long covid.[161]

Pulmonary symptoms

Pulmonary symptoms are common during long covid. NICE recommends that breathlessness may be investigated using an exercise tolerance test suited to the person's ability, for example the one minute sit-to-stand test, and treatment and management should be multidisciplinary, with advice and education given on managing breathlessness. Furthermore, the guidelines recommend offering patients with continuing respiratory symptoms a chest radiograph by 12 weeks after infection.[9] Blood oxygen levels can be monitored using a pulse oximeter.

Recommendations from the Mayo Clinic suggest that shortness of breath can be self-managed by limiting factors that exacerbate dyspnea, including stopping smoking, avoiding pollutants, avoiding extremes in temperature, and exercising,[162] however, chronic shortness of breath may require further intervention. Recognized non-pharmacological strategies for managing dyspnea include breathing exercises,[163] pulmonary rehabilitation,[164] and maintaining optimal body positioning for postural relief.[165] Meanwhile, a systematic review has found that oral opioids can be used to treat dyspnea,[166] therefore this class of drugs may prove useful for treating the condition in people with long covid.

Patients with pulmonary fibrosis resulting from covid-19 should be managed in accordance with NICE guidelines on idiopathic pulmonary fibrosis,[167] while antifibrotic therapies may be advantageous.[168] Exacerbations of bronchiectasis should be treated

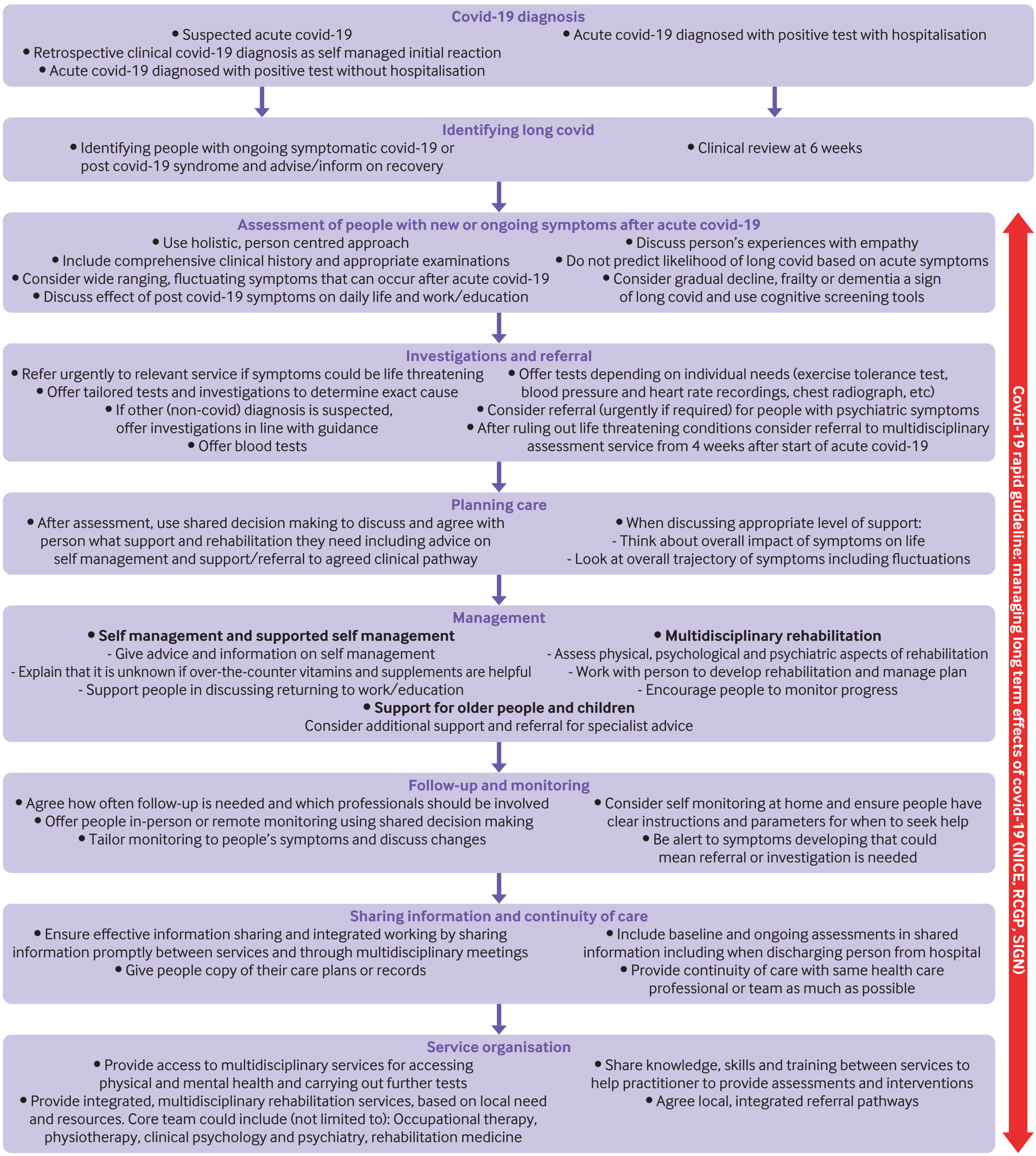

Fig 3 | Overview of the NICE rapid guideline: managing the long term effects of covid-19

with antimicrobial prescribing,[169] while non-antimicrobial therapies, including airway clearance, may be considered.[170] Modified rehabilitation practices, including stretching, body rotations, acupressure, and massage have shown beneficial long term effects on respiratory symptoms in mild covid-19 patients in a small trial.[171]

Cardiovascular symptoms

The NICE guidelines on long covid state that exercise tolerance tests may be undertaken to measure heart function, while lying and standing blood pressure and heart rate recordings should be performed if postural orthostatic tachycardia syndrome (POTS) is suspected.[9] Urgent referral should occur for people that have symptoms of a life threating complication, such as cardiac chest pain.

The European Society of Cardiology has released comprehensive guidance for the diagnosis and management of cardiovascular disease during the covid-19 pandemic.[160] The range of cardiovascular conditions that can manifest in long covid translates to a wide range of potential therapeutic options, therefore, ongoing investigation and observation of cardiac biomarkers is important. NICE guidelines recommend β blockers for several cardiac complaints, including angina,[172] cardiac arrhythmias,[173] and acute coronary syndromes,[174] therefore, β blockers may be useful in the treatment of cardiovascular manifestations of long covid. Myocarditis may resolve naturally over time; however, supportive and/or immunomodulating therapy may improve recovery, as a systematic review describes.[175] A review has also suggested that anticoagulants may be used to reduce the risks associated with hypercoagulability.[176] Meanwhile, advice and education, agents to maintain vascular tone, and agents to manage palpitations have been shown by a randomized controlled trial and discussed in a review to be advantageous in the treatment of POTS.[89 177]

Treating fatigue, cognitive, and neuropsychiatric symptoms

Chronic fatigue is a common manifestation of long covid. NICE recommends that self-management and support are important in managing fatigue, owing to the poor availability of covid-19 specific treatment.[9] A condition that may overlap with long covid fatigue is myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), therefore, the treatment algorithm designed for treating ME/CFS may prove useful in treating post-covid-19 fatigue. NICE has specific guidelines that outline how to refer and treat ME/CFS patients; these include cognitive behavioral therapy (CBT) and graded exercise therapy (GET).[178] Following backlash over these guidelines from the ME Association,[179] however, NICE aims to publish revised guidelines in August 2021.[180]

Randomized controlled trials have shown that CBT is beneficial in the treatment of chronic fatigue,[181] however, this is conflicted by findings from a re-analysis of a Cochrane review which question its effectiveness and show a high incidence of adverse events. This re-analysis study states that if a trial of a drug or surgical procedure demonstrated similarly high rates of adverse effects, then it would not be accepted as a safe treatment option, therefore CBT should have to adhere to the same level of scrutiny.[182]

Another management strategy for fatigue is pacing, whereby patients manage tasks and activities to avoid over-exertion and exacerbating fatigue. NICE guidelines for ME/CFS[178] describe pacing as a self-management strategy, however guidance and education from healthcare professionals may be useful for patients. Evidence from randomized controlled trials for the use of pacing in long covid is yet to be seen.

The implementation of group therapy via videoconferencing in people with early psychosis during the covid-19 pandemic shows promising results, with a pilot study showing improvements in psychotic symptoms and self-esteem,[183] however, a review article provides information to suggest that CBT is ineffective in reducing long covid symptoms, including fatigue, with only 10% of participants achieving clinically meaningful improvements.[184]

GET is a structured intervention plan consisting of physical activities with a therapeutic goal.[185] A systematic review of exercise therapy for CFS concluded that patients with ME/CFS generally feel less fatigued and have improved sleep and physical function following completion of exercise therapy, to a greater degree than following a program of either adaptive pacing or supportive listening.[186] The NICE guidelines on ME/CFS recommend GET; however, in July 2020 NICE released a statement urging caution when implementing GET for people recovering from covid-19, stating that with guidelines currently being updated, these recommendations may change.[187] This statement accompanies concerns over the potential negative effects of GET, including post-exertional malaise.[188]

Evidence specific to covid-19 is lacking, therefore cognitive impairment should be managed with support, including setting tailored, achievable goals and implementing validated screening tools.[9] Managing cognitive impairment will require a holistic approach, however, patients should be advised that most people gradually recover from cognitive impairment following severe illness.[106 189] The holistic approach to treatment should extend to the services offered, with professionals including occupational and speech and language therapists addressing cognitive changes.[190] Cognitive impairment in long covid, sometimes called "brain fog," has been compared to "chemobrain."[191] The Mayo clinic recommendations suggest strategies to manage chemobrain including repeating exercises, tracking what influences deficits, and using stress relief and coping strategies. Furthermore, medications including methylphenidate, donepezil, modafinil, and memantine may be considered.[192] These strategies may prove useful for long covid. Specific to long covid, luteolin, a natural flavonoid, may alleviate cognitive impairment by inhibiting mast cell and microglia activation,[191] but clinical trials are required.

Sleep disturbances may be managed by following relevant guidelines on insomnia,[193] and a range of treatment strategies can be considered.[194-197] Patients with mental health problems alongside or as a result of long covid can be managed following the relevant guidelines: depression,[198] anxiety,[199] PTSD,[200] obsessive-compulsive disorder,[201] and other mental health problems.[202] Care home residents, including those with dementia, who acquire long covid have additional needs.[116] Discussing mental health problems with patients requires compassion and understanding.[203]

Treating other organ impairments

Current evidence for the recovery of renal function following covid-19 is lacking. Considering that early and close follow-ups with nephrologists have previously been beneficial,[204] post-covid-19 patients with renal dysfunction may benefit from early and ongoing monitoring. Covid-19 can disrupt and alter the microbiome of the gut, which may allow for opportunistic infections.[145] Covid-19 associated destructive thyroiditis can result in incident hyperthyroidism, which can be treated with corticosteroids.[142] Overall, close follow-up of patients with long covid and adequate investigative procedures should be kept up to accurately diagnose and treat specific symptoms.

Repurposing drugs for long covid

Antihistamines have been implicated as a possible treatment for covid-19, with a study that employed cellular experiments suggesting that histamine-1 antagonists may be able to reduce the covid-19 infection rate by inhibiting SARS-CoV-2 from entering ACE2 expressing cells.[205] Systematic reviews and molecular studies have suggested that histamine-1 and histamine-2 antagonists are viable candidates for further clinical trials in covid-19.[206-208] It remains to be seen whether antihistamines have potential for treating long covid. Antidepressants have been proposed to reduce the effects of long covid. Antidepressant use has been associated with reduced risk of intubation or death in covid-19,[209] while a meta-analysis of antidepressant drug treatment for major depressive disorder has shown that use of antidepressants, including serotonin-norepinephrine reuptake inhibitors and selective serotonin reuptake inhibitors, results in a reduction in peripheral inflammatory markers.[210]

Emerging treatments

Clinical trials exploring the efficacy of hyperbaric oxygen (NCT04842448), montelukast (NCT04695704), and deupirfenidone (NCT04652518) to treat respiratory conditions in long covid are ongoing. A trial of breathing exercises and singing is also under way to assess their utility in improving breathing abnormalities in patients with long covid (NCT04810065).

A trial to assess the effectiveness of an 8 week exercise program in patients with long covid and fatigue is ongoing (NCT04841759). Vitamin C supplementation may prove useful in treating fatigue in patients with long covid, with a systematic review concluding that high dose intravenous vitamin C could be a beneficial treatment option.[211] LOVIT-COVID (NCT04401150) is an ongoing clinical trial aimed at assessing the effects of high dose intravenous vitamin C on hospitalized patients with covid-19.

Two trials examining the effects of nicotinamide riboside, a dietary supplement, are ongoing (NCT04809974, NCT04604704) with the expectation that the molecule reduces cognitive symptoms and fatigue by modulating the pro-inflammatory response.[212]

A clinical trial is currently ongoing assessing the effectiveness of a probiotic supplement to normalize the composition of the gut microbiome and reduce inflammation in long covid (NCT04813718). The understanding of long term sequalae of covid-19 infection in the gastrointestinal tract will evolve, with studies currently ongoing (NCT04691895), which will subsequently affect treatment.

Other potential treatments are molecules that suppress the intense inflammatory response seen in covid-19. Leronlimab is a monoclonal antibody that blocks the function of CCL-5. It has been shown to be effective and safe in HIV[213] and reduces plasma interleukin-6 levels in covid-19.[214] Clinical trials are ongoing to evaluate the efficacy of leronlimab post-covid-19 (NCT04343651, NCT04347239, NCT04678830). Another antibody treatment, tocilizumab, blocks interleukin-6 receptors and has shown efficacy in a small trial of patients with covid-19 patients.[215] Trials to explore the effects of tocilizumab are ongoing (NCT04330638). The anti-oxidative and anti-inflammatory function of melatonin may also be useful in treating long covid.[216] Lastly, adjuvant treatments, such as adaptogens, are being explored for their effectiveness in treating long covid (NCT04795557).

Conclusion

With many people having been infected and continuing to be infected with covid-19, the long term implications are of increasing concern. Here, we have reviewed the studies that have explored the persisting symptoms of long covid, and have addressed the possible risk factors associated with developing long covid and the treatment options that may be useful in alleviating its symptoms. Currently, long covid remains enigmatic and, with the question of the impact that new variants of covid-19 will have on the incidence and severity of long covid still looming large, it is important that research continues to explore post-covid-19 syndrome. Greater understanding of the pathogenesis, risk factors, symptoms, and methods of treating long covid is required to reduce the strain and demand on people with the condition and the healthcare systems that will endeavor to support them.

RESEARCH QUESTIONS

- What is the precise epidemiology of long covid and how will novel variants of covid-19 affect the epidemiology and severity of long covid?
- What are the major risk factors for long covid and how do we best reduce an individual's risk of developing long term post-covid-19 symptoms?
- Which symptoms, or set of symptoms, can we use to classify long covid, clinically and phenotypically, with the aim of improving diagnosis and management?
- What is the optimal treatment and management strategy for long covid and is this strategy non-specific or will it require targeting and tailoring to specific patients?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Members of a long covid focus group were contacted and requested to review the initial drafts of this article. The feedback received assisted in developing and focusing our review towards the experiences of different symptoms experienced by patients with long covid. Cognition and mental health were of particular interest to patients, which we have addressed in this article.

Contributors: HC, SR, JN, and MY performed the primary literature search and drafted parts of the manuscript; HC was the first author of the manuscript who drafted the manuscript and revised it; PE was responsible for the concept and design of the work. PE reviewed and revised the manuscript. PE is the guarantor.

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