

# Long COVID

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Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection, post-acute sequelae of COVID-19 (PASC), chronic COVID syndrome (CCS) and long-haul COVID, is a theorized condition, proposed to be characterized by long-term sequelae; persisting after the typical convalescence period of coronavirus disease 2019 (COVID-19). The exact nature of symptoms and number of people who experience long-term symptoms is unknown and varies according to the population being studied, the definition used and the time period used in the study. A preliminary survey by the UK Office of National Statistics estimated that approximately 10% of people who tested positive for SARS-CoV-2 experienced one or more symptoms for longer than 12 weeks. In peer-reviewed literature and public discussion, persistent symptoms are being reported among COVID-19 survivors. These persistent symptoms pose new challenges to patients, healthcare providers and public health practitioners. Research is underway to differentiate symptoms of a prolonged course of COVID-19 illness from sequelae following resolution of acute SARS-CoV-2 infection.

Post-COVID-19 care centers are opening at academic medical centers in the United States, bringing together multidisciplinary teams to provide a comprehensive and coordinated treatment approach to COVID-19 aftercare. The National Institutes of Health have published interim guidelines for the medical management of COVID-19 external icon, including a section on persistent symptoms or illnesses after recovery from acute COVID-19. Study of 6-month consequences of COVID-19 in patients discharged from hospital revealed that most patients exhibited at least one symptom, particularly fatigue or muscle weakness, sleep difficulties and anxiety or depression. More severely ill patients had increased risk of pulmonary diffusion abnormality, fatigue or muscle weakness and anxiety or depression. The seropositivity and titers of the neutralizing antibodies were significantly lower than at acute phase.<sup>1</sup> These data confirm that the toll of COVID-19 extends well beyond hospitalization. Collectively, these findings suggest that better models to support COVID-19 survivors are necessary. While

long COVID is observed after infection, it has not been reported after vaccination, with over 100,000 participants included in vaccine trials as of December 2020.

### Terminology and definitions

While studies into various aspects of long COVID are under way, as of January 2021, the definition of the illness is still unclear and it is too early to draw conclusions on the mechanism. Nonetheless, the illness is not well-characterized, has no understood mechanism nor fixed diagnostic criteria and therefore, is considered an idiopathic disease and a diagnosis of exclusion. Long COVID is a patient-created term which was reportedly first used in May 2020 as a hashtag on Twitter by Elisa Perego, an archaeologist at University College London. Long COVID has no single, strict definition. One rule of thumb is that long COVID represents symptoms that have been present for longer than two months, though there is no reason to believe that this choice of cutoff is specific to infection with the SARS-CoV-2.

### British definition

The British National Institute for Health and Care Excellence (NICE) divides COVID-19 into three clinical definitions:

1. **Acute COVID-19** for signs and symptoms during the first 4 weeks after infection with SARS-CoV-2; new or ongoing symptoms 4 weeks or more after the start of acute COVID-19, which is divided into:
2. **Ongoing symptomatic COVID-19** for effects from 4 to 12 weeks after onset and
3. **Post-COVID-19 syndrome** for effects that persist 12 or more weeks after onset.

NICE defines post-COVID-19 syndrome as “Signs and symptoms that develop during or after an infection consistent with COVID19, continue for more than 12 weeks and are not explained by an alternative diagnosis. It usually presents with clusters of symptoms, often overlapping, which can fluctuate and change over time and can affect any system in the body. Post COVID-19 syndrome may be considered before 12 weeks while the possibility of an alternative underlying disease is also being assessed”.

Long covid, the name commonly used to explain lasting effects of COVID-19, may actually be four different syndromes, according to a review by the National Institute for Health Research (NIHR).<sup>2</sup>

A team of researchers and doctors reviewed current evidence and interviewed post-hospitalised and non-hospitalised patients and reported that long COVID did not seem to fit as one syndrome. They suggested that people experiencing long term effects of COVID-19 may have different syndromes such as post-intensive care syndrome, post-viral fatigue syndrome and long term COVID syndrome. Elaine Maxwell, review author and content lead for NIHR's Centre for Engagement and Dissemination, said, "We are not saying that we have identified four definitive syndromes".

### U.S. definition

In February 2021, the National Institutes of Health said symptoms of Long COVID can include fatigue, shortness of breath, "brain fog", sleep disorders, intermittent fevers, gastrointestinal symptoms, anxiety and depression. Symptoms can persist for months and can range from mild to incapacitating, with new symptoms arising well after the time of infection. NIH Director Francis Collins said the condition can be collectively referred to as Post-Acute Sequelae of SARS-CoV-2 infection (PASC).

### Incidences

As of January 2021, the precise incidence was unknown. The incidence declines over time, as many people slowly recover. Some early studies suggested that between 20% and 33% of people with COVID-19 experienced symptoms lasting longer than a month. A telephone survey in the US in the first half of 2020 showed that about 35% of people who had tested positive for SARS-CoV-2 experienced a range of symptoms that lasted longer than three weeks. As of December 2020, the Office of National Statistics in the UK estimated that, of all people with a positive test for SARS-CoV-2, about 21% experienced symptoms for longer than five weeks and about 10% experienced symptoms for longer than 12 weeks. Some studies have suggested that some children experience lingering symptoms of SARS-CoV-2 infection.

Although anyone who gets infected can develop long COVID, people who become so sick that they require hospitalization take longer to recover. A majority (up to 80%) of those who were admitted to hospital with severe

disease experience long-term problems including fatigue and shortness of breath. Patients with severe initial infection, particularly those who required mechanical ventilation to help breathing, are also likely to suffer from post-intensive care syndrome following recovery. A study of patients who had been hospitalised in Wuhan found that the majority still had at least one symptom after six months. Patients who had been more severely ill still showed severe incapacity in lung function. Among the 1733 patients who had been discharged from hospital and followed up about six months later, the most common symptoms were fatigue or muscle weakness (63%), sleep difficulties (26%) and anxiety or depression (23%). Some people suffer long-term neurologic symptoms despite never having been hospitalized for COVID-19; the first study of this population was published in March 2021. Most frequently, these non-hospitalized patients experienced prominent and persistent 'brain fog' and fatigue that affect their cognition and quality of life. In January 2021, a study in the UK reported that 30% of recovered patients were readmitted to hospital within 140 days and 12% of the total died. Many patients had developed diabetes for the first time, as well as problems with heart, liver and kidneys. The mode of insulin failure was at that point unknown. In March 2021, the Indonesian Doctors Association, in a survey of 463 people, suggested that 63.5% of respondents self-reported lingering symptoms after SARS-CoV-2 infection. The exact set of symptoms was not specified, however, according to the article, fatigue and cough were the most commonly reported symptoms, followed by muscle pain and headache. NHS England has estimated that up to 5 June, more than 95000 patients had been admitted to hospitals across England with COVID-19 and it assumed 45% would need ongoing support. Figures from the UK Covid Symptom Study app—which has more than four million regular users—suggest that a significant number of people report symptoms for a month and between 10% and 20% report complications for longer.

### Etiology

Causes (presumed): It is currently unknown why most people recover fully within two to three weeks and others experience symptoms for weeks or months longer. A review by the United Kingdom's National Institute for Health Research hypothesized that ongoing long COVID symptoms may be due to four syndromes:

1. Permanent damage to the lungs and heart,
2. Post-intensive care syndrome,

3. Post-viral fatigue, also known as Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS), and
4. Continuing COVID-19 symptoms.

Other situations that might cause new and ongoing symptoms include: a. the virus being present for a longer time than usual, due to an ineffective immune response; b. reinfection (e.g., with another strain of the virus); c. damage caused by inflammation and a strong immune response to the infection; d. physical deconditioning due to a lack of exercise while ill; and e. post-traumatic stress or other mental sequelae, especially in people who had previously experienced anxiety, depression, insomnia or other mental health difficulties.

### **Risk factors**

According to a King's College London study initially posted on 21 October 2020 risk factors for long COVID may include:

- a. Age – particularly those aged over 50
- b. Excess weight
- c. Asthma
- d. Symptoms of presentation: Reporting more than five symptoms (e.g. more than cough, fatigue, headache, diarrhoea, loss of sense of smell) in the first week of COVID-19 infection; five is the median number reported
- e. Women gender are less likely to develop severe acute COVID but more likely to develop long COVID than men. Some research suggests this is due primarily to hormonal differences, while other research points to other factors, including chromosomal genetics, sex-dependent differences in immune system behavior, and non-biological factors may be relevant
- f. Co-morbidities: Risk factors for persistence of symptoms may high blood pressure, obesity, mental health conditions.

In children, a study in Italy, which analyzed 129 children under the age of 18, examined health data obtained via a questionnaire between September 2020 and January 1, 2021, 53% of the group experienced COVID-19 symptoms more than 120 days after their diagnosis.

### **Pathophysiology**

Characterization of late sequelae is underway and may reflect organ damage from the acute infection phase, manifestations of a persistent hyperinflammatory state, ongoing viral activity associated with a host viral reservoir or an inadequate antibody response. Factors in addition to acute disease that may further complicate the picture include physical deconditioning at baseline or after a long disease course, pre-COVID-19 comorbidities and psychological sequelae following a long or difficult disease course as well as those relating

to lifestyle changes due to the pandemic. Likely, the persistent sequelae of COVID-19 represent multiple syndromes resulting from distinct pathophysiological processes along the spectrum of disease.

### **Signs and symptoms**

The surveys showed there are a wide range of recurring symptoms experienced by patients, regardless of whether they were hospitalised, affecting the respiratory system, the brain, cardiovascular system and heart, the kidneys, the gut, the liver and the skin. The report said these symptoms range in intensity and duration, and do not necessarily present in a linear or sequential manner. It is unclear if all have the same phenomenon. Many researchers and healthcare professionals are cautious about attributing all the reported problems to a single diagnosis.

### **List of symptoms**

A wide range of symptoms are commonly discussed, including fatigue, headaches, shortness of breath, anosmia (loss of smell), muscle weakness, low fever and cognitive dysfunction. Symptoms reported by people with long COVID include: General: extreme fatigue, long lasting cough, muscle weakness, low grade fever. Neuropsychiatrics: inability to concentrate (brain fog), memory lapses, changes in mood, sometimes accompanied by depression and other mental health problems, sleep difficulties, headaches, needle pains in arms and legs. The most common signs and symptoms that linger over time include: fatigue, shortness of breath, cough, joint pain, chest pain etc.

### **More serious complications**

Cardiovascular: myocardial inflammation, ventricular dysfunction. Respiratory: pulmonary function abnormalities. Renal: acute kidney injury. Dermatologic: rash, alopecia. Neurological: olfactory and gustatory dysfunction, sleep dysregulation, altered cognition, memory impairment. Psychiatric: depression, anxiety, changes in mood.

### **Organ damage caused by COVID-19**

This organ damage may increase the risk of long-term health problems. Organs that may be affected by COVID-19 include:

**Heart.** Imaging tests taken months after recovery from COVID-19 have shown lasting damage to the heart muscle, even in people who experienced only mild COVID-19 symptoms. This may increase the risk of heart failure or other heart complications in the future.

**Lungs.** The type of pneumonia often associated with COVID-19 can cause long-standing damage to the tiny air sacs (alveoli) in the lungs. The resulting scar tissue can lead to long-term breathing problems.

**Brain.** Even in young people, COVID-19 can cause strokes, seizures and Guillain-Barre syndrome — a condition that causes temporary paralysis. COVID-19 may also increase the risk of developing Parkinson's disease and Alzheimer's disease.

**Blood clots and blood vessels.** COVID-19 can make blood cells more likely to clump up and form clots. While large clots can cause heart attacks and strokes, much of the heart damage caused by COVID-19 is believed to stem from very small clots that block tiny blood vessels (capillaries) in the heart muscle.

Other parts of the body affected by blood clots include the lungs, legs, liver and kidneys. COVID-19 can also weaken blood vessels and cause them to leak, which contributes to potentially long-lasting problems with the liver and kidneys.

### **Problems with mood and fatigue**

People who have severe symptoms of COVID-19 often have to be treated in a hospital's intensive care unit, with mechanical assistance such as ventilators to breathe. Simply surviving this experience can make a person more likely to later develop post-traumatic stress syndrome, depression and anxiety. Many people who have recovered from SARS have gone on to develop chronic fatigue syndrome, a complex disorder characterized by extreme fatigue that worsens with physical or mental activity, but does not improve with rest. The same may be true for people who have had COVID-19. Much is still unknown about how COVID-19 will affect people over time. However, researchers recommend that doctors closely monitor people who have had COVID-19 to see how their organs are functioning after recovery.

### **Health system responses**

#### **United States**

Dr. Anthony S. Fauci has described long-term Covid-19 as "...a phenomenon that is really quite real and quite extensive" but also said that the number of cases is unknown. On February 23, 2021, National Institutes of Health Director Francis Collins announced a major initiative to identify the causes and ultimately the means of prevention and treatment of people who are suffering

from long COVID. Part of this initiative includes the creation of the COVID-19 Project which will gather data on neurological symptoms associated with PASC.

#### **United Kingdom**

Future clinical guidelines were announced, with further research on 10,000 patients planned and a designated task-force to be set up, along with an online rehabilitation service – "Your Covid Recovery". The clinics include a variety of medical professionals and therapists, with the aim of providing "joined-up care for physical and mental health". The National Institute for Health Research has allocated funding for research into the mechanisms behind symptoms of long COVID. In December 2020, University College London Hospitals (UCLH) opened a second long COVID clinic at the National Hospital for Neurology and Neurosurgery for patients with post-Covid neurological issues. The first clinic had opened in May, primarily focused on respiratory problems, but both clinics refer patients to other specialists where needed, including cardiologists, physiotherapists and psychiatrists. On 18 December 2020, the National Institute for Health and Care Excellence (NICE), the Royal College of General Practitioners (RCGP) and the Scottish Intercollegiate Guidelines Network (SIGN) published a guide to the management of long COVID.

### **Conclusions**

Many large medical centers are opening specialized clinics to provide care for people who have persistent symptoms or related illnesses after they recover from COVID-19. Some people experiencing long COVID have formed groups on social media sites. There is an active international long COVID patient advocacy movement which includes research led by patients themselves. Long COVID is yet an unresolved issue for physicians and health care professionals who render services to COVID-19 patients. Ongoing efforts around the globe could explore the reality.

### **REFERENCES**

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