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### I LONG COVID

#### A. The puzzle of long COVID

SARS-CoV-2 is the virus that can cause the disease called COVID-19. This virus belongs to a family of viruses called coronaviruses.

Most people infected with SARS-CoV-2 have mild symptoms or none at all. However, a minority of people can develop severe symptoms, including difficulty breathing and pneumonia, and require hospitalization. And then there are some people infected with SARS-CoV-2 who have mild or serious initial symptoms and later develop a long-lasting disorder commonly called "long COVID."

People with long COVID can experience a wide range of symptoms because different organs and systems in the body appear to be affected. Due to the serious and even debilitating nature of long COVID, some affected people may be unable to do normal everyday activities and have difficulty working.

As SARS-CoV-2 and COVID-19 are relatively new, and long COVID is even newer, there is much that remains unknown. Major research institutions such as the U.S. National Institutes of Health are beginning to invest in research on long COVID. However, it will take time for scientists and doctors to understand the many issues that bedevil people with long COVID, such as the following:

- Why do some people infected with SARS-CoV-2 develop long-term complications?

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- How long will post-COVID-19 complications last?
- What can be done to help people with long COVID get better?

Scientists must be able to firmly understand the cause of long COVID before it is possible to find effective remedies. In this issue of *TreatmentUpdate*, we report on a limited range of research associated with long COVID.

### More than one syndrome?

Because so many different organ systems can be affected in long COVID, some scientists think that long COVID is not one disorder but instead may represent a syndrome, with different people developing different manifestations of it.

### Is autoimmunity an issue?

Scientists at several research centres, including Yale University, have found that infection with SARS-CoV-2 seems to cause the immune system to attack itself (a phenomenon called autoimmunity). Specifically, the immune system attacks a key molecule that plays a role in the early defence against viruses and other germs. This molecule is called interferon-alpha. By causing the immune system to attack interferon-alpha with its own antibodies, SARS-CoV-2 is better able to infect people.

### Not just interferon-alpha

In addition, emerging research has found that people who develop COVID-19 tend to have antibodies that attack a wide range of the body's proteins and organs. These antibodies can interfere with how organs communicate and function, particularly the brain. The full implications of this emerging research are not clear (and require confirmation). However, one example provided by scientists at Yale University is that these antibodies attack a receptor called orexin that plays a role in "regulating wakefulness and appetite."

Hopefully, additional research will uncover other cellular communication pathways that are affected by long COVID. Identification of such pathways could potentially explain why so many different organ systems are affected and give rise to interventions to help people recover. However,

it is important to note that the immune system turning on the body might not explain all aspects of long COVID. This suggests that the drivers of long COVID may be complex.

### Inflammation and the immune system

There is a high level of inflammation and activation of the immune system in people with COVID-19. Initially, this can be useful in helping to contain an infection. However, persistent inflammation can injure tissues.

Some cells of the immune system circulate throughout the body and while on patrol for germs and tumours can take up residence within an organ system. If these roving cells of the immune system are not functioning normally, they can release chemical signals that incite inflammation in organ systems. Some researchers think that lingering inflammation and immune activation may contribute to the symptoms that manifest in long COVID.

### Fragments of a virus

There may be pieces of SARS-CoV-2 (viral RNA) or certain proteins from this virus that linger deep within some organs and tissues. This could be another potential contributor to long COVID. It does not mean that people with long COVID are infectious with SARS-CoV-2, as there is zero evidence for that.

Experiments with mice infected with other coronaviruses have found that viral RNA lingers in the brains of these animals after acute infection. This viral RNA persists without any infectious coronavirus present in the mice. Scientists are not certain why this virus persists.

### At the National Institutes of Health (NIH)

NIH virologist Dr. Avi Nath, MD, is one of many leading scientists who are starting research on long COVID. In an interview with the journal *Nature Methods*, he discusses his preliminary findings after reviewing data from more than 200 people with long COVID. He says that people with long COVID can be divided into three broad groups based on grouping their symptoms:

## 1. Problems with the autonomic nervous system (dysautonomia)

The autonomic nervous system connects parts of the brain with many important organs and systems. Usually, the autonomic nervous system functions without most people being aware of it. This system affects functions such as heart rate, breathing, digestion, urination, and so on. In cases of dysautonomia, the autonomic nervous system does not function normally. Symptoms of dysautonomia can include the following: dizziness upon sitting up or standing up as blood pressure temporarily falls, erectile dysfunction in men, and difficulty digesting food.

## 2. Brain fog

In people with long COVID who have this condition, Dr. Nath has found that “they are unable to remember names of people and objects, and they lose a sense of time. They can recount what they had for breakfast but fail to recall if it was today’s breakfast or last week’s.” Some people may also experience changes in mood, including the development of severe depression.

## 3. Exercise intolerance

There may be many reasons for an intolerance to exercise, ranging from injury to the lungs, heart and blood vessels to other issues. Exercise intolerance can sometimes also arise from injury to the autonomic nervous system (dysautonomia). Dr. Nath gave the example of a cardiologist with long COVID. She becomes exhausted after climbing a flight of stairs and has to spend the rest of the day in bed recovering. He said that after extensive investigation her doctors were unable to find any obvious causes to explain her symptoms.

## Hiding in the brain

Many viruses attack and live inside cells in the brain. As mentioned earlier, another coronavirus that can infect mice persists in their brains. Coronaviruses belong to a larger family of viruses called RNA viruses. Other RNA viruses, including dengue virus, Zika virus and HIV, can also invade the brain. So, it is plausible that SARS-CoV-2 can also enter the brain.

Measles virus can infect unvaccinated children (causing measles). Dr. Nath notes that “months, even years, after recovering from measles, some children develop a deadly condition called subacute sclerosing panencephalitis (SSPE).” While scientists

can’t find measles virus in the blood of affected children at autopsy, Dr. Nath says, “you look in the brain, it’s loaded with virus.” He says that in such cases the measles virus has mutated significantly and does not behave like the strain of measles that originally infected the child. It can’t form new viruses, just some proteins and viral RNA. This severely mutated virus causes infection within the brains of children with SSPE in a limited form, moving from one brain cell to another.

Based on these findings with measles, Dr. Nath says that it is possible that SARS-CoV-2 may have mutated significantly within the brains of people with long COVID. This significantly mutated virus is not infectious to other people. However, the virus has adapted to living in the brain (or another organ) of an affected person and slowly replicates there. Note that this idea of fragments of SARS-CoV-2 lurking in the brain is a theory, as Dr. Nath and his team attempt to make sense of why some people have long COVID. One proposed NIH study will use powerful magnetic resonance imaging (MRI) technology to try to detect traces of SARS-CoV-2 in the brains of people with long COVID.

## For the future

Long COVID represents a puzzle to scientists as they race to find its cause and possible treatments. The ideas and associated research reported in this section of *TreatmentUpdate* are preliminary. Much more research lies ahead as scientists try to confirm their preliminary findings on long COVID.

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## B. Some people's perspectives on long COVID

Researchers at Sheffield Hallam University in Sheffield, England, recruited people for interviews who were experiencing long COVID. Using a database and an algorithm, researchers randomly selected a sample of 18 people of different ages, genders and ethnicities and asked them about their experience with long COVID and how they dealt with physical activity.

### Results

Participants described a range of trajectories of illness. However, they all reported that long COVID was associated with debilitating fatigue, lasting weeks or months. One person described her experience as follows:

“The slightest thing was an effort in a way I’ve never ever conceived before, it’s the most fatigued I have ever been ... things like changing my bedding, I did in stages like one pillowcase and then later in the day I’d do another pillowcase, it was that sort of level of difficulty with day-to-day tasks.”

Long COVID can encompass draining and disturbing physical and psychological symptoms, as another person stated:

“I do something physical, I suffer. If I walk, I suffer in my legs. If I do something with my hands, I suffer with my hands. If I start to think too much, I then get a foggy head. If I type an email on the computer and it goes on too long, I then can’t think enough to shut the computer down.”

### Advice about physical activity

Health systems, doctors and nurses have been overwhelmed by the crisis nature of successive waves of the COVID-19 pandemic. This disease is new and, not surprisingly, many people reported being unable to get the advice they needed from healthcare providers or health systems. As a result, the researchers found that many participants had turned to online forums and social media. In general, this helped them to better understand their condition as other people with long COVID shared their experiences.

### Relapse

The trajectory of long COVID is unpredictable. Some people reported setbacks or relapse when they engaged in physical or cognitive activity. One woman stated:

“As much as I’m enjoying [walking the dog], it has the knock-on effect. But that is getting less and less, so the more I’m doing, the better I’m feeling afterwards. I think [relapses are] all part of it, just got to get on with it and push myself a little bit harder and then hopefully I’ll get better quicker. It doesn’t put me off.”

### The importance of pacing oneself

Participants felt discouraged about engaging in physical activity because of their own symptoms or from reading about other people’s negative experiences online. They also found pacing themselves to be challenging.

The researchers stated: “Most participants established personal strategies for managing physical activity [PA] based on trial and error. All described a limited energy reserve that must



be used wisely, planning their days according to personal schedule and priorities. Activities tended to be selected based on their benefit to well-being and/or responsibilities, for example, walking, getting outdoors and fulfilling caring duties.”

One person told the researchers the following:

“Everything that you read is pace yourself, pace yourself. But that’s really hard to do, because until you’ve overdone it you don’t know how much you can do without overdoing it, if you see what I mean, so learning by default. Which isn’t the best way, but I guess what’s enough for me might not be enough for somebody else.”

### Life altering

Many participants found the impact of long COVID to be what the researchers called “life-altering,” as the disability caused by the disorder was distressing. The researchers found that older participants used their pre-COVID-19 life experience to help them adjust, as one participant stated:

“I’m self-aware when it comes to my health and my mood and I think I’m just accepting of it rather than wanting to change it or be negative about it.”

Younger people without this experience seemed to struggle more with coping. One young person despaired, saying the following:

“I just want my life back, it’s getting a bit tedious. I see myself just becoming a burden, I don’t want to live my life like that.”

The researchers found that many participants were able to get support from friends and family: “While participants’ symptoms were severe and physical function was most disrupted, friends and family acted as informal carers, supporting self-care activities such as cooking. They also provided emotional support, although as with medical professionals, this was sometimes contingent on an understanding and awareness of long COVID that developed gradually. Over time, family and friends became important PA companions, often adjusting their own PA behaviour to match the level of the person with long COVID and providing a reassurance that fostered confidence in activities such as walking.”

### Bear in mind

The researchers noted that their findings underscore the severe impact that long COVID can have on people’s energy and their ability to engage in routine daily activities (such as housework and child care).

The researchers also stated:

“Our findings indicate that people experiencing long COVID need better support to manage their symptoms, especially fatigue, while also helping them safely pursue the potential benefits of PA. As in previous research, 11 participants reported that guidance about PA was not always tailored to the complexity of long COVID. In particular, they lacked support on how to establish a baseline and upper threshold for activity which accommodated the erratic relapse–recovery cycle common to our participants’ experience. Our research suggests that pacing needs to be individualised, considering biographical factors such as life stage as well as current physical function and activity history. Many people will also require monitoring (either via professional or self-monitoring tools) to provide reassurance about the safety of PA while experiencing other symptoms like rapid heartbeat or breathlessness.”

### REFERENCE:

Humphreys H, Kilby L, Kudiersky N, et al. Long COVID and the role of physical activity: a qualitative study. *BMJ Open*. 2021 Mar 10;11(3):e047632.

### C. Veterans Affairs study explores long COVID

Although many people hospitalized with acute COVID-19 have died, many have also survived. After their recovery from acute COVID-19, some people have persistent symptoms. Researchers have recently begun to study these survivors.

### Veterans Affairs

A team of researchers in the U.S. has investigated databases that collect health-related information on veterans. The researchers focused on people who survived 30 days after their initial diagnosis of COVID-19. Specifically, they assessed subsequent

diagnoses of complications, laboratory tests and medicines that were initiated and other measures.

The researchers compared information from different groups of people. First, they compared more than 73,000 people who survived at least 30 days after a diagnosis of acute COVID-19 and who were not hospitalized with nearly 5 million other people who did not have COVID-19 and who were also not hospitalized. They also used data from about 26,000 hospitalized people with and without COVID-19.

The researchers found that survivors of COVID-19 had health issues that affected different organ systems for up to six months after recovery from acute COVID. (Note that other, longer studies have found longer durations of long COVID.) Affected organs and systems in the present study included the following:

- brain and nerves
- bone marrow
- gastrointestinal system
- lungs
- metabolism

Common issues included the following:

- fatigue
- anemia
- bone and muscle pain

Researchers noted that after people recovered from acute COVID-19 some received certain categories of prescription medicines for the first time, as follows:

- anti-anxiety drugs
- antidepressants
- drugs to treat high blood pressure
- drugs to treat diabetes
- drugs to ease breathing

Research is urgently needed to find out why some people who develop acute COVID-19 subsequently develop persistent, late-stage complications.

### Study details

The researchers analyzed data from two main groups of people, as follows:

- non-hospitalized people – 73,435 people diagnosed with COVID-19 who survived at

least 30 days after their diagnosis and 4,990,835 people who did not have COVID-19

- hospitalized people – 13,654 people diagnosed with COVID-19 who survived for at least 30 days after being admitted to hospital and 13,997 people who were also hospitalized but who did not have COVID-19

Participants were already part of the Veterans Affairs database for at least a year before December 31, 2019. People who tested positive for SARS-CoV-2 had their tests done between March 1, 2020 and November 30, 2020. Participants were monitored until January 31, 2021.

The researchers assessed data for up to six months after participants left the hospital.

### Results

Among people who recovered from acute COVID-19, whether or not they had been hospitalized, the researchers found that they developed a “broad array” of conditions affecting many organ systems.

Researchers grouped categories of illnesses that appeared in long COVID as follows:

#### Lungs

- problems breathing, coughing

#### Brain and nervous system

- The researchers found that there was an increase in diagnoses of headache, problems with memory and thinking clearly, loss of sense of smell and an increased risk for stroke.

#### Mental health

- problems with sleep, anxiety and depression

#### Metabolism

- high cholesterol, high blood sugar

#### General

- fatigue, muscle pain and weakness, anemia

#### Heart and circulatory system

- high blood pressure, abnormal heart rhythm, chest pain

#### Gastrointestinal system

- problems swallowing, abdominal pain, nausea, excess stomach acid, constipation in some people and diarrhea in others

#### Other issues

- The researchers found that there was an increased risk for blood clots in the lungs, and additional problems unrelated to clots: skin disorders, bone and joint pain and infections (including urinary tract infections).

### Survival

The researchers found an increased risk of death among people who survived the first 30 days after a diagnosis of acute COVID-19. This elevated risk was highest among participants who were previously hospitalized for COVID-19. Also, among people who had been diagnosed with COVID-19 but who were not hospitalized, there was also an increased risk of death even if they survived the first 30 days of their illness.

### Bear in mind

The present analysis, which found an increased risk for a wide range of persistent complications one month or more after a diagnosis of acute COVID-19, is sobering. This problem of long COVID occurred whether or not participants were initially hospitalized for COVID-19. Among participants who survived their first 30 days after a diagnosis of acute COVID-19, whether or not they were hospitalized within those first 30 days, there was a remarkably increased risk of death over the next six months.

The researchers stated that, overall, their findings about the long-term consequences of COVID-19 “highlight the need for holistic and integrated multidisciplinary long-term care for patients with COVID-19.”

### Many potential causes

As explained earlier in this issue of *TreatmentUpdate*, scientists are exploring several leads as they seek to uncover the causes of long COVID. The present team is not certain why long COVID occurs, but

due to the broad nature of long COVID, they suggested the following possibilities:

- fragments of SARS-CoV-2 persist deep inside the body, such as in the central nervous system (the brain and spinal cord)
- the immune system remains highly activated and inflamed
- the immune system attacks parts of the body

In addition to the biological issues mentioned above, the researchers suggested that social factors and other issues may indirectly contribute to the poor health of some people with long COVID:

- reduced social contact and loneliness
- loss of employment
- changes to diet and reduced exercise

### Notes about the study

Although the present study is an important step forward, it does have some limitations:

- Due to the study’s design, it is not clear which manifestations of long COVID are direct or indirect consequences of SARS-CoV-2.
- Participants in the study were overwhelmingly male, while other studies suggest that long COVID may be common among women.
- As SARS-CoV-2 mutates and more people become vaccinated, it is possible that the manifestations of long COVID may change over time.

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### D. Long COVID found even in people who initially were diagnosed with mild COVID-19

Many people who developed serious complications of COVID-19 were hospitalized. Some of the people who survived have gone on to develop long-term complications (called long COVID).

Two separate teams of scientists in the U.S. have done studies on long COVID and reported that it can develop even in people who had mild or uncomplicated COVID-19. The most common manifestation of long COVID in both studies was fatigue.

These and other studies add to the emerging research on long COVID and underscore the need to investigate this issue and develop interventions to help people with long COVID recover.

### Study 1

In the first study, a team at Stanford University in California conducted research with 118 participants who had recovered from acute COVID-19. Their average age was 43; 53% were men and 43% were women. A total of 22 participants had required hospitalization when they were diagnosed with COVID-19.

Three to four months after their initial diagnosis of acute COVID-19 (when any hospitalizations would have occurred), researchers found that many participants had symptoms of long COVID, distributed as follows:

- formerly hospitalized people – 82%
- not hospitalized – 64%

Common symptoms of long COVID were as follows:

- fatigue
- shortness of breath
- loss of sense of taste and/or smell
- muscle pain or soreness
- memory problems
- chest pain
- loss of hair

Having shortness of breath at the onset of COVID-19 was linked to a greater risk of subsequently having two or more symptoms of long COVID.

Many participants had some degree of impairment caused by symptoms of long COVID that affected their productivity at work.

### Study 2

Another team of scientists, this time at the University of Washington in Seattle, has been monitoring 177 participants with and without COVID-19 for up to nine months. Their average age was 57; 57% were men and 43% were women.

The researchers categorized participants as follows:

- formerly hospitalized with COVID-19 – 16 people
- diagnosed with COVID-19 but not hospitalized because of mostly mild symptoms – 150 people
- diagnosed with SARS-CoV-2 infection and remained symptom free – 11 people

Over the course of the study, about 30% of people who were first diagnosed with acute COVID-19 had persistent symptoms of long COVID. This figure was similar regardless of whether or not they had been hospitalized.

Common symptoms of long COVID in this study were as follows:

- fatigue
- loss of sense of smell and/or taste

Four people reported problems with thinking clearly and memory (brain fog).

Nearly 30% of people with long COVID reported poor health-related quality of life.

Although both studies are relatively small, they confirm general findings from other studies and reports that long COVID can occur later even in some people who had a mild course of COVID-19.

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  2. Logue JK, Franko NM, McCulloch DJ, et al. Sequelae in adults at 6 months after COVID-19 infection. *JAMA Network Open*. 2021 Feb 1;4(2):e210830.
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## E. A large U.S. study uncovers a wide range of complications linked to long COVID

Many survivors of COVID-19 have long-term complications that are commonly called long COVID. Some studies that have been done with these people were not able to dig deeper into the data collected to explore the difference in the manifestations of long COVID between genders or between younger and older people.

Now, a research team in the U.S. has conducted a study comparing health-related information from 266,000 people who became infected with SARS-CoV-2 with about 9 million people who did not. The researchers also reviewed data from other years to compare health and use of medical resources in another group of people.

The researchers found more than 50 different manifestations of long COVID occurring in 14% of participants. Common persisting health issues included the following:

- problems breathing
- abnormal heart rhythms
- excessive formation of blood clots
- brain inflammation
- injured nerves
- memory problems
- diabetes
- liver inflammation
- heart inflammation
- anxiety
- fatigue

The researchers found that the greatest risk for developing long COVID was in people with the following factors:

- older than 50
- having underlying health conditions
- hospitalization for acute COVID-19

Though people outside these groups were at risk for developing long COVID, their risk was lower than that of people with the above-listed factors. Furthermore, the researchers found differences in the distribution of manifestations of long COVID between men and women.

## Study details

Researchers reviewed several databases with a health insurance plan called UnitedHealth Group. Using data from 9,247,505 people, the researchers created two main groups for comparison:

- number of people who tested positive for SARS-CoV-2, some of whom developed COVID-19 – 266,586
- number of people who were not diagnosed with SARS-CoV-2 infection – 8,980,919

The main focus of the study was data collected over the period of January through October 2020. For purposes of comparison, the researchers assessed health-related information collected in 2019 and 2017 from people who developed lung infections due to influenza and other causes.

All participants were between 18 and 65 years (average age was 42) and the proportions of men and women were the same.

## Results

Among the people with SARS-CoV-2, 8.2% were hospitalized and 1% were admitted to an intensive care unit.

## Focus on long COVID

The vast majority of participants (86%) who became infected with SARS-COV-2 did not develop long COVID 21 days after their positive test result (14% did develop long COVID). This figure of 14% is similar to that found by the Office of National Statistics in the UK.

Among the 14% of participants who did develop long COVID, the distribution of symptoms was as follows:

- 10% – one symptom of disease
- 4% – more than one symptom of disease

All 14% required medical care for these symptoms.

## Time

Although the risk for developing a serious complication was greatest one month after having a positive test result for SARS-CoV-2, the researchers

found that even up to six months after infection, people were at heightened risk for the following:

- high blood pressure
- diabetes
- sleep apnea
- fatigue

Although the risk of symptoms of long COVID was greatest in people over the age of 50, researchers found that people between the ages of 18 to 34 had a modestly elevated risk for at least the following conditions:

- high blood pressure
- abnormal heart rhythms
- excessive blood clots
- memory problems
- diabetes
- fatigue

### **Mental health**

The risk for developing a mental health condition was increased among all people regardless of age or presence of underlying conditions.

### **Gender**

In general, the researchers did not find many differences in the symptoms of long COVID by gender, except for the following:

- women were more likely to have fatigue and loss of sense of smell
- men were more likely to have heart inflammation, excess blood clots, kidney injury and sleep apnea

### **Bear in mind**

Viral illness, including severe bouts of the flu, can cause medium- and long-term problems. However, the depth of issues faced by people with long COVID seems much greater than the consequences of many other acute viral infections. For instance, the researchers analyzed data from people diagnosed with influenza in 2019, when COVID-19 was largely unknown. They found that people who were diagnosed with COVID-19 in 2020 generally had two times as many long-term complications as people who had influenza and other respiratory viral infections in 2019.

### **Imperfections and strengths**

The present study reviewed data for one purpose (an administrative database) and reanalyzed it for another purpose—to find out more about COVID-19 and long COVID. Such a study design may inadvertently cause biased interpretation of the data.

It is possible that the full breadth of long COVID symptoms was not captured by the study. The researchers cautioned that some patients may not have reported all of their symptoms and some doctors may not have recorded all of the reported symptoms.

There was a lack of individual level data on race/ethnicity.

Despite its imperfections, the present study's findings align with those of other studies. Another study from the British Office of National Statistics found that about 14% of people who survived acute COVID-19 developed long COVID. This is strikingly similar to what the current study has found. The present study also echoed findings from other studies that suggest that long COVID affects women more than men as well as people with low income.

### **Unpredictability**

Commenting on the present U.S. study in the journal *BMJ Open*, scientific advisor Elaine Maxwell stated in an editorial:

“It is too early to predict how long the [symptoms of long COVID will persist] but the symptoms clearly create a major personal burden for many people, with some individuals experiencing difficulty returning to work and [being] unable to care for dependents.”

She added: “One of the peculiarities of long COVID is its non-linear progression, hampering attempts to predict who will develop particular symptoms and when. Risk factors differ for different new diagnoses of [long COVID symptoms], suggesting that a variety of mechanisms could be subdivided into more specific phenotypes.”

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## F. A Mayo Clinic study explores long COVID and attempts at rehabilitation

As mentioned earlier in this issue of *TreatmentUpdate*, some people who have been diagnosed with acute SARS-CoV-2 infection can develop long-term symptoms, called long COVID, a month or more after symptoms of the acute infection have resolved.

The Mayo Clinic in Rochester, New York, has developed a COVID-19 Activity Rehabilitation Programme (CARP). This program is designed to evaluate and treat people who have long COVID.

Researchers with CARP produced a report on the first 100 people who entered the program from June through December 2020.

Participants were relatively young (45 years) and a majority were women (68%). Most participants (75%) had never been hospitalized for acute COVID-19.

Common symptoms of acute COVID-19 included the following:

- fatigue
- breathing problems
- neurological issues
- sleeping problems
- mental health issues

About 34% of participants had difficulty with household chores because of fatigue and 67% had not returned to full-time work. Strikingly, many routine laboratory blood test results were within the normal range. Note that a different study of people with long COVID that used MRI scans of key organ systems has found signs of tissue injury.

## Study details

CARP was developed from a program that doctors had created for interventions with earlier outbreaks of coronavirus-related diseases such as SARS (2003-2004) and MERS (2012 and later).

CARP has three main aims:

1. to actively assess for associated conditions and detect problems arising from COVID-19 when people are recovering
2. to help people improve their overall functioning and health, using physical and occupational therapy
3. to facilitate a safe return to work

Participants received an extensive series of assessments, including laboratory analysis of blood samples, ultrasound and CT scans.

Here are some common pre-existing conditions found in the first 100 participants in the program:

- history of depression or anxiety – 34%
- asthma and other breathing issues – 23%
- high blood pressure – 19%
- chronic fatigue – 4%
- diabetes – 3%

## Results

Here are common issues participants had upon entry to CARP:

- fatigue – 80%
- breathing problems – 59% (the most common was shortness of breath)
- neurological problems – 59% (the most common was headache)

Participants also reported other issues, most commonly the following:

- problems with memory and thinking clearly
- problems with sleep
- symptoms of anxiety and/or depression

About 84% of participants reported difficulty with the following:

- household chores
- driving a car

- exercise
- complex tasks at work

Prior to becoming infected with SARS-CoV-2, 91% of participants were employed. At the time they sought help with CARP, 63 people had returned to work. Of these 63, 46% did not need to limit their activity at work because of long COVID.

### Assessments

According to the CARP researchers, “interestingly, most tests were within normal limits.” Only two of 31 ultrasound scans of the heart found abnormalities. Tests of lung function found only a few people with abnormalities.

### The autonomic nervous system

An exception was found in testing of the autonomic nervous system. The autonomic nervous system connects parts of the brain with many important organs and systems. Usually, the autonomic nervous system functions without most people being aware of it. This system affects functions such as heart rate, breathing, digestion, urination, and so on. In cases of dysautonomia, the autonomic nervous system does not function normally. Some symptoms of dysautonomia can include the following: dizziness upon sitting up or standing up as blood pressure temporarily falls, erectile dysfunction in men, and difficulty digesting food.

At the time of publication of the Mayo Clinic study, 15 participants had completed assessments of their autonomic nervous system reflexes. Doctors found that 12 of these 15 people had abnormalities. All 12 patients were referred to neurologists for further help.

### Bear in mind

Most people in the present study were relatively young (45 years) and had not been hospitalized for COVID-19, yet they had long COVID.

Three times as many women as men sought help for long COVID. The researchers stated that they did not have enough data to explain why long COVID appeared to affect more women than men. However, they noted that a similar imbalance in gender has been found in people recovering from

infection caused by a member of the herpes virus family, EBV (Epstein Barr Virus).

Many routine laboratory tests and even CT scans did not find serious abnormalities in people with long COVID. This suggests that routine tests are inadequate at helping doctors diagnose the underlying drivers of long COVID.

The Mayo Clinic researchers stated: “Patients reported that their cognitive and mood symptoms were often minimized or dismissed by healthcare providers, which is concerning since many [long COVID] symptoms are similar to prolonged [consequences] of traumatic brain injury for which prolonged or permanent inability to return to work has been recorded.”

The researchers also stated that their findings “provide impetus for a thorough assessment and consideration of all symptoms and their impact on financial capacity both at work and at home.”

### Interventions – caution with exercise

CARP offered brain rehabilitation as well as physical and occupational therapy. Doctors cautiously introduced exercise into the lives of patients, as the CARP researchers stated that past research with SARS, MERS and chronic fatigue syndrome found that “excessive activity can result in prolonged worsening of symptoms and function.”

The researchers stated that psychosocial support “was heavily emphasized.” They offered such support because participants expressed feelings that the researchers described as “abandonment, guilt and frustration” during their first visit with the CARP team. Furthermore, the researchers found that more than 25% of participants “reported increased anxiety and depression symptoms compared to [their medical records before they were diagnosed with acute COVID-19].” Psychosocial support included referrals for counselling and mental health specialists.

Note that the present study was relatively small and participants entered the study via self-referral. Its findings may not be generalizable. However, its finding about more women getting long COVID is in alignment with some other studies. Also, the high level of autonomic nervous system disorders has been seen as part of an ongoing study by the U.S. National Institutes of Health.



Long COVID is not well understood and research in this area is in its infancy. It will take time to find answers to this often disabling and mysterious condition.

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## G. Can muscle inflammation explain some of the symptoms of long COVID?

Some people with post-acute complications of COVID-19 (called long COVID) can experience intense fatigue and muscle weakness. Scientists are exploring possible reasons for these issues. Studies in Germany and the U.S. suggest that people who died from COVID-19-related complications had muscle inflammation. Emerging research suggests that the muscle inflammation is likely caused by intense immunological reactions. Such reactions occur during acute COVID-19 in some people.

It is at least plausible that some people with long COVID also have muscle inflammation, but research needs to be done to confirm this and to find possible causes of such inflammation.

### Study 1 – Berlin

Scientists at Charité Hospital (a leading biomedical research centre) in Berlin have reported findings from a study that compared muscle tissue taken at autopsy from two groups of people:

- 43 people who died from COVID-19-related complications
- 11 people who died from complications unrelated to SARS-CoV-2 infection

The vast majority of these people had been admitted to an intensive care unit (ICU) in the hospital prior to their death. People who died from

COVID-19-related complications did so between March 2020 and February 2021.

#### Key findings

- Muscle biopsies from people who had recently died from COVID-19 showed signs of inflammation and injury.
- Generally, these muscle samples had higher-than-normal levels of CD8+ T-cells and natural killer cells inside of them.
- Use or non-use of corticosteroids before death did not seem to affect inflammation of muscles.

The finding about the infiltration of cells of the immune system into muscle tissue suggests that the immune system played a role in their inflammation and possibly tissue injury. The researchers could not find SARS-CoV-2 in the muscle tissue samples they analyzed. Some muscles (such as those of the heart) have a protein on their surface called ACE2. This protein is used by SARS-CoV-2 to infect cells, and other studies have found SARS-CoV-2 in muscle cells in the heart. Other muscles, such as those that are connected to the skeleton (skeletal muscles), do not appear to have ACE2, and this may account for the difficulty the scientists had in finding any virus in the biopsies of muscle tissue. The scientists did not find a similar degree of muscle inflammation in people who were not infected with SARS-CoV-2 and who died. Also, most people who died from COVID-19 did not have antibodies that attacked their muscles. Therefore, the scientists suspect that the muscle injury that arises in COVID-19 may be due to the intense inflammation that is a key part of severe COVID-19.

### Study 2 – Harvard University hospital system

Another team of scientists at Boston hospitals affiliated with Harvard University has analyzed muscle and associated nerves biopsied from 35 people who died from COVID-related complications and 10 other people who died but who did not have SARS-CoV-2 infection. Participants died between April and mid-June 2020.

#### Key findings

- 25 of the 35 people in the Boston study had biopsies that found inflammation in muscles and nerves.
- SARS-CoV-2 could not be found in these biopsies.

- The researchers think that the muscle and nerve inflammation found in their study was due to the immune system. Specifically, such injury was a consequence of an intense inflammatory reaction as the body attempted to defend itself from SARS-CoV-2 infection.

### **Bear in mind**

Both teams of scientists in Germany and the U.S. have found that people who died from COVID-19 had muscles that were inflamed. In addition to muscle inflammation, the U.S. team also found nerve injury arising from inflammation in their autopsies.

The scientists from both countries suspect that some people who develop SARS-CoV-2 undergo intense inflammatory reactions as the body attempts to defend itself from this virus. The intense inflammatory reactions may help reduce virus levels in muscles and nearby nerves, but, as a side effect, they cause tissue injury—in this case, injury to skeletal muscles and associated nerves. The Harvard University scientists stated that “viral RNA may be cleared from muscle and nerve tissue due to efficient type I interferon response or other mechanisms, but may not be cleared from higher burdened organs like the lungs”

This potential explanation for the findings of muscle and nerve injury seems incomplete. There are many chemical messengers (cytokines) associated with inflammation that have been found in other studies of people with COVID-19, including the following:

- IL-1 (interleukin-1)
- IL-6 (interleukin-6)
- TNF (tumour necrosis factor)
- GM-CSF (granulocyte-macrophage colony-stimulating factor)

Unfortunately, neither the German nor the U.S. scientists were able to access blood samples to analyze levels of cytokines in the people they studied.

The research from Germany and the U.S. is a good first step in identifying a problem that occurs in some people with COVID-19—inflammation-related injury of muscles and nerves. The inflammation appears to be indirectly caused by the immune system.

Additional research is needed to explore the issue of muscle and tissue injury in people who are living with long COVID. In these people, analysis of biopsies may be useful in providing insight into the health of their muscles and peripheral nerves.

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## **H. UK study uses MRI scans to uncover organ impairment in long COVID**

Many people with long COVID experience disabling symptoms. A source of frustration for patients and their doctors is that many routine blood tests and other assessments can be within the normal range despite the obvious suffering of patients. This hampers the ability of doctors to discover the drivers of long COVID.

Researchers at universities in the UK are conducting a study based on assessments, including MRI (magnetic resonance imaging) scans of key organs, of about 200 people who have long COVID.

Initial analysis of the data collected so far has found that many people with long COVID have ongoing health issues and reduced quality of life. What was novel about this study was its use of MRI scans. These scans helped researchers uncover that 70% of participants had at least one organ impaired in the months after they had been diagnosed with acute COVID-19. Key affected organs included the following:

- liver
- heart
- lungs
- kidneys
- spleen

This study advances the field of long COVID research and shows that there is something happening deep within the body’s organs. Now other researchers need to confirm these findings of organ impairment. Also, researchers need to find

out why different people with long COVID have different organs that have been impaired and what can be done about this.

### Study details

There were 201 people who had acute COVID-19 in the past and who entered the present study nearly four months after their initial diagnosis.

The average profile of participants upon study entry was as follows:

- age – 41 years
- 71% women, 29% men
- major ethno-racial groups: white – 88%; South Asian – 4%; Black – 2%
- body mass index (BMI) – 26 kg/m<sup>2</sup>
- 19% had been hospitalized with acute COVID-19

Among healthy people who had never been hospitalized for COVID-19, their average age was 39; 60% were men and 40% were women. This group's average BMI was 23.

### Results

The most commonly reported symptoms of long COVID (whether or not people had been hospitalized) were as follows:

- fatigue – 98%
- shortness of breath – 88%
- muscle ache – 87%
- headache – 83%

According to the researchers, “99% of people [with long COVID] had four or more [symptoms] and 42% had 10 or more symptoms.”

### MRI findings

Organ impairment was more common in people with long COVID than in healthy people. According to the researchers, 70% of people with long COVID “had impairments in at least one organ and 24% had multi-organ impairment, with overlap across multiple organs.”

Below are some of the findings from the MRI scans indicating the proportion of people with

impairment of each organ and the type of impairment described by the researchers:

- pancreas – 40%; inflammation, excess fat
- liver – 28%; inflammation, excess fat
- heart – 26%; inflammation, weakened pumping action
- lungs – 11%; reduced ability to inhale/exhale
- kidneys – 4%; inflammation
- spleen – 4%; inflammation

### Severe long COVID

Researchers found that people with severe symptoms of long COVID were more likely to report the following symptoms:

- shortness of breath
- headache
- chest pain
- abdominal pain
- wheezing

People with severe long COVID were two times more likely to have heart inflammation than people who had moderate symptoms of long COVID.

### Syndromes

As with several other research teams, the British researchers involved in the present study think that long COVID may be a syndrome with different manifestations in different people.

### Bear in mind

The present study was imperfect; it could not prove that specific organ impairment resulted in specific symptoms. However, the study is an important step forward and has uncovered ongoing organ impairment in many people with long COVID. Why such impairment occurs and differs from one person to another is not clear.

Additional research is needed to find out more about the underlying biological issues that drive the symptoms associated with long COVID.

### REFERENCE:

Dennis A, Wamil M, Alberts J, et al. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open*. 2021 Mar 30; 11(3):e048391.

## I. Rehabilitation and long COVID

Researchers at the regional Centre for Exercise and Rehabilitation in Leicester, England, have reported promising results in a pilot study with people who have long COVID.

### Study details

Researchers reported on the first 32 people who completed a six-week rehabilitation program.

Participants were referred by their family doctors and the researchers stated that they excluded people if they had “acute symptoms or were not medically stable or had only symptoms that were not modifiable from a rehabilitation program (such as loss of sense of taste only).”

All participants were screened for cardiovascular disease.

The program consisted of two supervised sessions each week that had the following elements:

- aerobic exercise – walking on a treadmill
- strength training of upper and lower limbs
- educational discussions – addressing long COVID symptoms

Researchers noted that participants were cautioned to pace themselves so as not to become exhausted.

Additionally, validated surveys were used to assess changes in endurance, functional ability, fatigue, mental health, brain issues and quality of life.

The average profile of participants upon study entry was as follows:

- age – 58 years
- 52% men, 48% women
- 26 participants had previously been hospitalized (because of acute COVID-19) for 10 days. Five of these people required mechanical ventilation during their hospitalization.

Overall, 30 people completed the program. Two participants left due to what the researchers called unspecified “social circumstances.”

## Results

No one had to stop or leave the program because of worsening symptoms. Researchers found significant improvements with the following issues:

- walking capacity
- fatigue
- cognition
- breathing

### Concern about exercise

Some rehabilitation specialists and people with long COVID have raised concerns that exercise therapy may inadvertently make fatigue worse. However, the exercise component of the program was supervised by staff who were experienced with lung and heart rehabilitation. The intensity of exercise was gradual and tailored to each person’s capacity. The researchers did not report any relapse or serious side effects due to exercise.

Most participants reported decreased symptoms of fatigue and improved exercise capacity as a result of the intervention. However, five people did not improve or had mixed results, as follows:

- one person had no improvement in exercise capacity or fatigue due to a previous stroke
- four people had improvement in their exercise capacity but also experienced fatigue

### For the future

The research team concluded by stating:

“Rehabilitation programmes should aim to provide a holistic and multi-faceted approach to managing post-COVID symptoms. Clinicians should aim to individualise programmes and to monitor adverse events and symptoms, given the limited evidence in the field.”

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## J. Safety of COVID-19 vaccination in people with long COVID

To investigate the safety of COVID-19 vaccination in people who have long COVID, researchers in Bristol, England, conducted an observational study of 36 people who had been hospitalized for acute COVID-19. Overall, vaccination was safe and did not make symptoms of long COVID worse or degrade quality of life.

### Study details

Researchers recruited participants who had symptoms of long COVID about eight months after they were hospitalized for acute COVID-19. Participants were vaccinated between January and February 2021.

The average profile of participants at the start of the study was as follows:

- age – 54 years
- 58% men, 42% women
- major ethno-racial groups: 86% white; 14% people of colour
- body mass index (BMI) – 32 kg/m<sup>2</sup>

The vaccine was distributed as follows:

- 18 people received the Pfizer-BioNTech vaccine
- 18 people received the Oxford-AstraZeneca vaccine

### Results

Participants had what researchers called “a high burden of persistent symptoms [of long COVID],” usually four symptoms per person. The most common symptoms were as follows:

- fatigue – 75%
- breathlessness – 61%
- sleeping problems – 53%
- brain fog – 40%

At the start of the study, analysis of quality of life and mental well-being assessments found that participants had lower ratings than what would have been obtained from healthy people.

### Vaccination

One month after vaccination, participants were surveyed and researchers found that mental well-being and health-related quality of life were stable.

Overall, 72% of participants reported vaccination-related side effects. These were temporary (usually lasting a couple of days) and were as follows:

- fever – 44%
- muscle aches – 22%
- headache – 19%

No major safety issues were reported.

Overall, the impact of vaccination on symptoms of long COVID was modest. One month after vaccination, participants reported the following:

- 23% of symptoms had improved
- 71% of symptoms stayed the same
- 6% grew worse

### For the future

People with long COVID need interventions to help them recover. There have been anecdotal reports that COVID-19 vaccines have improved the health of some people with long COVID. However, the design of the present study precludes drawing firm conclusions about the effectiveness of using these vaccines as a potential intervention for long COVID. For instance, this was not a randomized controlled clinical trial.

Still, the report from Bristol is a good step forward and demonstrates the safety of COVID-19 vaccines in a small group of people with long COVID.

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### Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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