

# The enduring grip of covid-19

Contrary to medical expectation, many people with covid-19 are still experiencing symptoms weeks or even months later. **Linda Geddes** investigates what's going on

**W**ITHIN 24 hours of asking an online covid-19 support group if anyone had been experiencing prolonged or unusual symptoms, I had been messaged by 140 people. The list was mind-boggling and deeply upsetting. "I feel like I'm in the middle of a waking nightmare," said Zoe Wall, who was previously fit and healthy. Two months after developing covid-19-like symptoms, she was still experiencing chest pains and "fatigue beyond description".

Harry's symptoms started with a terrible headache and itchy body, followed by shortness of breath. He was still experiencing breathing difficulties, chest pain, numbness in his arm and bloating 10 weeks later. Jenn had had no sense of smell or taste since testing positive for covid-19 on 31 March. Abbi had minimal respiratory symptoms, but very bad gastric ones and lost 19 kilograms

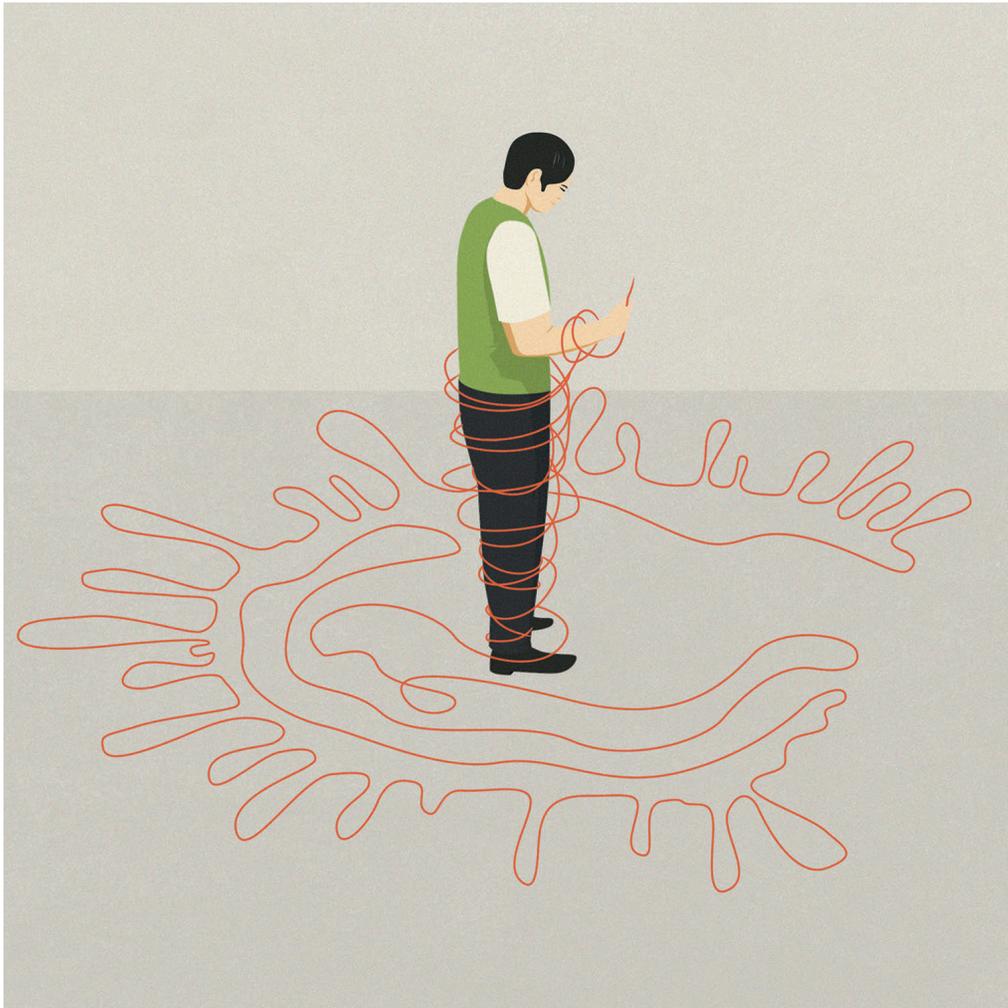
in two months. Others reported fatigue, headaches, tingling fingertips and brain fog.

As the months tick by since the start of the coronavirus pandemic and we learn more about covid-19, it is becoming increasingly evident that even mild cases can have distressing and long-lasting effects. "There's clearly something going on here. It is not their imagination or hypochondria. It doesn't even seem to be linked to how severely they had the disease, as far as I can see," says Danny Altmann, an immunologist at Imperial College London. All this means we need to rethink how we diagnose and treat covid-19. The long list of symptoms also seems to suggest there might even be several subtypes of the disease, which could help us predict which cases will become serious.

When the pandemic was announced in early March, the prevailing view was that we

were dealing with a respiratory infection that had symptoms similar to flu, and that while a minority of people would develop pneumonia and need breathing support, most would experience a mild illness characterised by a cough, fever and shortness of breath, which would be over in a couple of weeks.

Some of the first clues that the coronavirus behind covid-19, SARS-CoV-2, might trigger more widespread disease began to emerge in February, when the outbreak in the Chinese city of Wuhan was at its peak and doctors in the Lombardy region of Italy were also experiencing a surge in cases. As their emergency department colleagues fell sick, doctors like Sebastiano Recalcati, a dermatologist at Alessandro Manzoni Hospital in Lecco, Italy, began taking over the care of those hospitalised with covid-19. He noticed skin problems in around 10 per



cent of the covid-19 patients he encountered. Some symptoms, like a flat red rash on people's torsos, could have had other causes besides the virus, but others were more specific: some patients developed small blisters on their torso or around their mouth – similar to those seen in chickenpox, except that they weren't itchy.

Since then, he and others have documented other skin symptoms, including a reddish-purple rash, caused by tiny clots in blood vessels, and chilblain-like lesions on the toes. Unlike the earlier rashes and blisters that Recalcati spotted, which seem to strike at the time of infection, these additional symptoms occur several weeks later. "We think they may be a delayed immune response, whereas the other types of rash may be a direct viral response," he says.

**“Hardly anyone’s symptoms are the same the whole way through”**

That was just the start. By mid-March, the virus had spread across Europe and many countries were announcing lockdowns. As epidemiologist Tim Spector packed up his lab at King's College London, he pondered how he might continue his research, on the health differences between twins, from home. Together with the technology company Zoe, Spector developed an app to allow the twins in his study – and maybe the general population – to log and track any potential covid-19 symptoms they developed, so they could be monitored over time.

The Covid Symptom Tracker app launched on 23 March – the start of the UK's own lockdown. Within 36 hours, it had been downloaded by 1 million people, and by 29 March they had 1.5 million users, of whom 1702 reported having been tested for covid-19. "That's when we started to see this lack of ➤



smell coming up as the top feature, present in 60 per cent of people who had positive tests,” says Spector. This is higher than fever or cough, in predictive terms, he says, because some of those who tested negative for the coronavirus also had fever or cough. Studies in China and Italy have also found loss of smell and taste to be quite common in people with covid-19. As a result, loss of smell and taste are now recognised as a key symptom by several health bodies including the NHS.

Other predictors currently being investigated are severe muscle pain, which seems to differ from the general aches and pains you get with the flu – “it can be very acute and very painful”, says Spector – and loss of appetite, which may be connected to the loss of taste or smell. Spector himself lost 3 kilograms within a week of developing relatively mild covid-19.

**“The extreme fatigue is like being hit over the head with a cricket bat”**

The list of unexpected symptoms doesn’t stop there. Other covid-19-associated gastrointestinal problems, such as diarrhoea, nausea and vomiting, have been reported by researchers in California and Hong Kong, and many doctors are reporting neurological symptoms ranging from headaches and dizziness to seizures and hallucinations. There have also been reports of covid-19 patients being discharged from hospital, only to return several weeks later with a deep vein thrombosis or blood clot on the lung, says James O’Donnell, director of the Irish Centre for Vascular Biology in Dublin.

Some relatively young and healthy people with mild covid-19 are having heart attacks or strokes with unusual features. “The strokes seem to involve multiple different parts of the brain, and some of them are occurring and progressing despite patients being on

standard blood thinners,” says O’Donnell. “This started off as a respiratory illness, but within the space of a couple of months we’ve now got this kind of multi-system phenotype that we don’t really understand very well.”

Then there is the extreme fatigue. Paul Garner, who had to stop working after coming down with covid-19 in mid-March, likens the feeling to being hit over the head with a cricket bat. “Calling it post-viral fatigue isn’t helpful because the fatigue has been there from day one, and runs alongside some quite nasty, life-threatening conditions,” he says. “It also implies we know what’s happening and that the virus has gone – but we don’t know any of this stuff really.” Now, three months later, he can only work for 20 minutes at a time before needing to lie down, and will soon return to work for an hour a day. Garner says his symptoms are the same as chronic fatigue syndrome, with one difference – CFS is defined as not having a cause. “This clearly has a cause,” he says.

Garner speaks with authority. A professor of infectious diseases at Liverpool School of Tropical Medicine, he has experienced many of the diseases he studies first-hand. The only one that is vaguely comparable, he says, is dengue – a mosquito-borne illness characterised by bouts of exhaustion long after the virus clears. “The weird thing with covid-19 is how it sort of goes away, and you feel a bit muggy and a little bit drained and then you feel a bit better and then, whack, it comes at you again from another direction.”

It is this persistent nature of some cases of covid-19 that troubles many of those who contacted me via the online support group. A big frustration is the sense that because they don’t require hospital treatment, their symptoms aren’t taken seriously, and they are largely left to fend for themselves. “We keep being dismissed as anxious people who haven’t yet given their bodies time to heal,” said Wall. This lack of medical support really does make her anxious. “I feel utterly abandoned and left on my own,” she says.

Not everyone is surprised that SARS-CoV-2 is causing such varied and persistent symptoms. Julian Hiscox is a virologist at the University of Liverpool, UK, who has been

working with coronaviruses since the early 90s, including the one that causes MERS. “Nothing that we are seeing with this coronavirus has not been seen with other coronaviruses,” he says. “We know from animal studies that the same coronavirus can cause many different types of clinical disease. We also know from our experience with SARS and MERS that some people are fine, whereas others are worse off.”

## Immune reset

The same applies to longer-term health issues. Around 28 per cent of people who had SARS were still experiencing impaired lung function 18 months after SARS symptoms started, affecting their ability to exercise and their overall quality of life. And a recent meta-analysis suggested that depression, anxiety, insomnia and fatigue were all found in about 10 to 20 per cent of patients in the months following recovery from SARS. “If covid-19 plays out anything like SARS and MERS, there will be quite a bit of this longer-term mental illnesses and fatigue,” says Ed Bullmore, a neuroscientist at the University of Cambridge and author of *The Inflamed Mind*.

This isn’t just about the psychological trauma of being seriously ill. According to Bullmore, it is a product of our immune system’s response to infection. When our

immune cells encounter an invader, they release signalling molecules called cytokines to rally further immune help. Some of these cross into the brain and trigger further cytokine secretion and inflammation. “People who get infected with this new coronavirus often have this hyper-intense inflammatory reaction and being in such an inflamed state will have a negative impact on brain health,” says Bullmore. Specifically, it can damage nerve cells in areas of the brain responsible for emotion regulation.

Inflammation may persist long after SARS-CoV-2 has been cleared from the body. “The healthy response to this virus is to have massive immune cell activation,” says Altmann. “It would not at all surprise me if that could slightly reset the set point of your immune response in a slightly pathological and chronic way.”

Exhaustion could also be linked to vascular symptoms, such as blood clots, which may be caused by the immune system or by the virus infiltrating the cells that line blood vessels. Microclots in the lungs could reduce oxygen supply by restricting the movement of oxygenated blood through the lungs. “We think we’ve probably got a positive feedback loop going on where we’ve got pneumonia followed by micro-clots in the lungs, followed by low blood oxygen, and those things go round and round in a circle,” says O’Donnell. ▶



Public health messaging in England and Wales on symptoms doesn’t fit with the way many people experience covid-19

STU FORSTER/GETTY IMAGES

It is unclear whether microclots are occurring in people with mild cases of covid-19, but if the body isn't getting enough oxygen, this could cause many of the long-term symptoms people are experiencing, such as shortness of breath, headache and exhaustion.

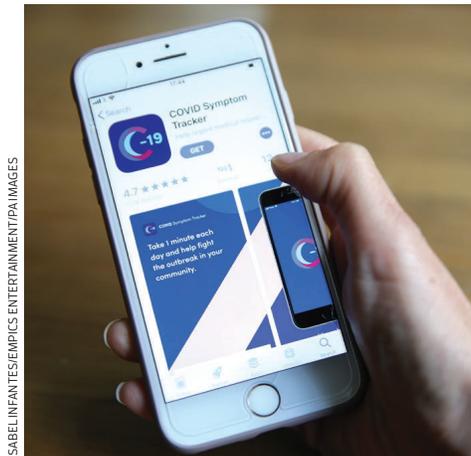
Another source of prolonged inflammation could be the gut. Cells lining the gastrointestinal tract have a receptor called ACE2 on their surface – the same receptor that SARS-CoV-2 uses to gain access to lung cells – which suggests they could become infected and inflamed. Researchers in Hong Kong have also identified an altered gut bacteria profile in people infected with the virus, characterised by large numbers of harmful bacteria and the depletion of beneficial ones. These changes persisted even after the virus had been cleared from the body.

"It's this prolonged phase of disruption that I'm worried about," says Siew Ng at the Chinese University of Hong Kong, who led the research. "If the bacteria in your gut have not recovered, you may have some lasting fatigue, discomfort or loss of appetite, and it may also make you more susceptible to other infections."

One question raised by many of those experiencing persistent symptoms is whether they are still infectious. Kim Clarke, who lives in Surrey, UK, has repeatedly tested positive for the coronavirus in her blood since losing her sense of smell on 1 April. She has been caring for her three children at home, despite severe and ongoing breathlessness, fatigue and headaches. "They're saying, because I've had the virus for so long, that I can't still be infectious, but I don't think anyone knows anything really," she says. "At least it helps explain why I still feel so rough. I can't leave the house because I can't walk, I can't breathe."

The fact that viral RNA can be detected in some people weeks after diagnosis could imply the presence of some active virus, says Hiscox. However, "whether there is enough of it to cause an infection in someone else, we just don't know at this stage".

Another question is what proportion of those infected with the coronavirus are experiencing prolonged symptoms – and



ISABEL INFANTE/EMPICS ENTERTAINMENT/PA IMAGES

Millions have used the COVID Symptom Tracker app

**“People are destroyed by this. They never expected it to be long term”**

how long these can be expected to last. Here, Spector has some insights. Having now tracked some 2000 people with positive tests, he has found that the median duration of symptoms was 10 days, but they sometimes endured for extended periods. One in 10 people had symptoms lasting longer than three weeks, and one in 20 had experienced symptoms for longer than a month.

"Hardly anyone's symptoms are the same the whole way through, and we think we are actually seeing six different subtypes of disease, based on the groupings of symptoms and their timings," says Spector. The clustering of these symptoms may even help to predict who is more likely to need hospitalisation. "It looks like illness with a really acute and more classic flu-like start seems to be over quickly and people recover, whereas these other ones that are a bit more complex seemed to linger on more – but we need a bit more data to be completely confident," he says.

Further studies on the aftermath of covid-19 are urgently needed. "We are desperate to get our lab studies in place to understand some of these longer-term symptoms and the consequences of this infection," says Altmann. "I've had lots of contact with people who are really destroyed by this. They never expected it to be a long-term chronic problem."

Until now, much of the response to covid-19 has been about preventing deaths, but hospitals are beginning to establish clinics to follow-up the survivors – including those who are still ill. "I'm certainly hoping that if folks like us can work out some of the biological mechanisms of this disease, there will be therapeutic ways of getting around it," says Altmann.

For Wall, this won't come a moment too soon. "My life has changed so dramatically. I don't know how to adjust to this. I don't know that I want to. I just want my life back." ■



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