An Introduction to Long COVID

Rachel Nicoll PhD

What is Long COVID?

- Both NICE and NHS England define Long COVID as '**signs and symptoms that develop during or following an infection consistent with COVID-19 which continue for more than 12 weeks and are not explained by an alternative diagnosis**.'
- But you should be aware that other organisations and studies define Long COVID as symptoms which persist for >4 weeks, when it is known as **post-acute COVID**.
- Long COVID can also be called **post-COVID syndrome, post-acute sequelae of COVID-19 (PASC), chronic COVID syndrome (CCS) and long-haul COVID**. People living with Long COVID are sometimes known as 'long haulers'.
- 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.

(https://www.england.nhs.uk/coronavirus/post-covid-syndrome-long-covid/; https://www.nice.org.uk/news/article/nice-sign-and-rcgp-set-out-further-details-about-the-uk-guideline-on-management-of-the-long-term-effects-of-covid-19; https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-effects-of-coronavirus-long-covid; https://en.wikipedia.org/wiki/Long_COVID; https://commonslibrary.parliament.uk/research-briefings/cbp-9112/)

What is the government doing about Long COVID?

- **£18.5 million for 4 research studies** to better understand and address the longer-term effects of COVID on physical and mental health. Government funding for the projects approved in partnership with the National Institute for Health Research (NIHR) and UK Research and Innovation (UKRI). They aim to identify the causes of long COVID and effective therapies.
- They have allocated **funding to set up a number of Long COVID clinics** but there is the inevitable **problem accessing them**. Some only see patients who had been **admitted to hospital with acute COVID-19**.
- Anecdotally, some of these clinics are offering graded exercise therapy.
- According to a survey of UK GPs in 2020, 67% were looking after patients with COVID-19 symptoms lasting longer than 12 weeks but only 23% had access to a Long COVID clinic that they could refer into.
- However, the UK has provided some of the largest and most comprehensive surveys, including the **ONS (Office for National Statistics) survey and the Zoe app study**.

(https://www.england.nhs.uk/2020/10/nhs-to-offer-long-covid-help/; https://www.yourcovidrecovery.nhs.uk/; Royal College of General Practitioners, 2020)

How have Long COVID clinics and GP services worked out in practice? NIHR patient survey

The National Institute for Health Research (NIHR) carried out a survey in early 2021, which revealed that:

- 15% of respondents with Long Covid had not sought any healthcare advice;
- 32% had not been able to access all of the healthcare they thought they needed.
- GP practices were the most frequently accessed service, with 37% of respondents saying they listened and helped them develop a management plan.
- 49% said that although they were sympathetic, GPs were not able to offer much help.
- Only 16% had accessed a psychologist or mental health service and only 11% had seen a physiotherapist.
- Many complained of fragmented care and 23% of our survey respondents wanted a case worker/key worker to co-ordinate care.
- 77% of our survey respondents wanted a one-stop Long Covid clinic.

(https://evidence.nihr.ac.uk/themedreview/living-with-covid19-second-review/)

Is Long COVID ‘Our next National Health Disaster’?

- A New England Journal of Medicine paper predicted that patients with long Covid will face ‘a difficult and tortuous experience with our multispecialty, organ-focused health care system’, in light of the complex and ambiguous clinical presentation and natural history of long Covid.
- There is currently no clearly delineated consensus definition for the condition
- There are no currently accepted objective diagnostic tests or biomarkers.
- The symptoms may affect a number of organ systems, occur in diverse patterns and frequently get worse after physical or mental activity.
- The pathophysiology is unknown, though there are several hypotheses.
- One camp believes that long Covid is a new pathophysiological syndrome that merits its own thorough investigation, while the other believes it is a mental illness.

(Phillips S, Williams MA. Confronting Our Next National Health Disaster - Long-Haul Covid. N Engl J Med. 2021 Aug 12;385(7):577-579)

One problem is the lack of uniformity in the Long COVID studies

Comparative analysis, as in meta-analysis, is very difficult because of:

- **Lack of an agreed definition of Long COVID.**
- **Differing lengths of follow-up,** and lack of consistency in measuring time elapsed from date of diagnosis, date from hospital discharge or date from end of viral shedding. This will affect whether the patient has 'long COVID' or 'post-acute COVID'.
- Some researchers **only study patients discharged from hospital**, while others include those who have received a positive test. Some rely on **blood tests and scan results, while others focus on patient symptoms**.
- **Problems with relying on testing as evidence of COVID infection**:
  - **Many patients may never have taken a COVID-19 test** as they were not initially available.
  - **COVID tests are known to produce false positives and negatives; participants may be wrongly allocated to 'cases' and 'controls' (where controls exist)**
  - Some studies rely on **antibody testing**, but some patients are known never to produce antibodies or they may have waned.
- Researchers **do not evaluate consistent symptoms or markers** and may fail to include many symptoms that are relevant. Difference in terminology for the symptoms can lead to confusion.
- **Study design is different** (e.g. prospective versus retrospective): many are patient-led or survey-based, with differences in questionnaires; these may exclude a large number of patients who are unwilling to or cannot participate (men, the elderly, ethnic minorities).
- **Lack of control groups**.

Duration of Long COVID?

- **No-one has any idea!** I could find no study that lasted longer than 1 year.
- The **ONS survey** reported that **among those who still had symptoms at 12 weeks**, **42% still had symptoms at 1 year**.
- **Patients who reported symptoms lasting for longer than 6 months** following acute infection experienced an average of **14 symptoms in month 7**, and **86% of patients experienced relapses** during the period assessed, with exercise, physical or mental activity, and stress reported as common triggers.
- The UK PHOSP-COVID study assessing patients after hospital discharge found that only 25.5% were fully recovered at 5 months but at 1 year the percentage had only increased to 29%; **the authors noted the minimal improvement between 5 months and 1 year**.
- **The known existence of relapses in Long COVID (it is a relapsing and remitting condition) makes it difficult to determine the true duration.**
- A 1-year study of hospitalised adults found that fatigue or muscle weakness was the most frequently reported symptom at 12 months, while almost half of patients reported having at least one symptom, such as sleep difficulties, palpitations, joint pain, or chest pain at 12 months. The proportion of COVID-19 survivors who had anxiety or depression slightly increased between 6 months and 12 months.

(https://www.independentsage.org/independent-sage-report-on-long-covid/; Davis HE, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:101019; Huang L, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021 Aug 28;398(10302):747-758; Evans, https://www.medrxiv.org/content/10.1101/2021.12.13.21267471v2; https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/3february2022)

But the good news is that the existence of Long COVID is now widely known (even by the BBC!)

Why your health may never be the same after Covid-19 (2 May 2020)

‘But recovering from the initial onslaught of the virus on the body may only be the start of long-term health issues for some patients.

You've survived. But what happens next?’

(https://www.bbc.co.uk/news/uk-scotland-52506669)

Long COVID symptoms

- Long COVID usually presents with **clusters of symptoms, often overlapping, which may change over time and can affect any body system**. Many the same symptoms they had during their initial COVID-19 infection but some (76% in one study) may develop **new symptoms** as well.
- Symptoms can be **continuous or relapsing and remitting** in nature. After discharge from hospital, 43% had a symptom-free interval before relapsing. A survey found that 86% experienced relapses in an irregular pattern or in response to specific triggers (such as physical or mental activity, stress, menstruation, heat, or alcohol).
- The Zoe App study reported that in general, fatigue was present all the time while headaches came and went; approximately 16% reported relapse.
- **Rehospitalisation and death can also occur during Long COVID**.

(Salmon-Ceron D, et al. Clinical, virological and imaging profile in patients with prolonged forms of COVID-19: A cross-sectional study. J Infect. 2021;82(2):e1-e4; Davis HE, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:101019; Ziauddeen, https://www.medrxiv.org/content/10.1101/2021.03.21.21253968v2; Anaya JM, et al. Post-COVID syndrome. A case series and comprehensive review. Autoimmun Rev. 2021 Nov;20(11):102947; https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/news/news/2021/2/new-policy-brief-calls-on-decision-makers-to-support-patients-as-1-in-10-report-symptoms-of-long-covid/understanding-and-managing-long-covid-requires-a-patient-led-approach; Aiyegbusi OL, et al. Symptoms, complications and management of long COVID: a review. J R Soc Med. 2021 Sep;114(9):428-442; Sudre CH, et al. Attributes and predictors of long COVID. Nat Med 27, 626–631 (2021)

Long COVID symptoms recognised by the NHS

- extreme tiredness (fatigue)
- shortness of breath (dyspnoea)
- pain or tightness
- memory and concentration impairment (brain fog)
- difficulty sleeping (insomnia)
- heart palpitations
- dizziness
- pins and needles
- joint/muscle pain
- depression and anxiety
- tinnitus, earaches
- feeling sick, diarrhoea, stomach aches, loss of appetite
- a high temperature, cough, headaches, sore throat, changes to sense of smell or taste
- rashes

https://www.gov.uk/government/news/185-million-to-tackle-long-covid-through-research#:~:text=Long%20COVID%20can%20present%20with,people%20experience%20organ%20damage.)

Other symptoms reported

- Post-traumatic stress disorder (PTSD)
- Loss of feeling in the extremities, blue finger nails
- Sudden loss of body weight
- Persistent fever with chills and sweats, swollen glands, sneezing, flushing
- Impaired consciousness, altered mental state, confusion, stroke
- Skin: papulosquamous eruptions, in particular pernio- or chilblain-like lesions
- Impaired balance and gait, tremor
- Poor glycaemic control, thyroid problems
- Bone demineralisation, hair loss
- Visual impairment, ear pain
- Gut dysbiosis, vomiting
- Reduced quality of life

References:

Malik P, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. J Med Virol. 2022 Jan;94(1):253-262

Evans RA, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021 Nov;9(11):1275-1287;

van Kessel SAM, et al. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. Fam Pract. 2022;39(1):159-167.

Ramakrishnan RK, et al. Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19. Front Immunol. 2021;12:686029;

Raveendran AV. Long COVID-19: Challenges in the diagnosis and proposed diagnostic criteria. Diabetes Metab Syndr. 2021;15(1):145-146.

Rodríguez-Alfonso B, et al. 18F-FDG-PET/CT in SARS-CoV-2 infection and its sequelae. Rev Esp Med Nucl Imagen Mol (Engl Ed). 2021;40(5):299-309.

Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021;53(10):737-754.

Conditions reported by the UK Doctors Long COVID group

- myocarditis/pericarditis,
- microvascular angina,
- cardiac arrhythmias including atrial flutter and atrial fibrillation,
- dysautonomia including postural orthostatic tachycardia syndrome,
- interstitial lung disease,
- thromboembolic disease (pulmonary emboli or cerebral venous thrombosis),
- myelopathy,
- neuropathy,
- neurocognitive disorders,
- renal impairment,
- hepatitis and abnormal liver enzymes,
- new onset allergies, anaphylaxis and dysphonia

- UK doctors #longcovid group
- https://doctors-in-distress.org.uk/
- https://www.bma.org.uk/news-and-opinion/a-problem-shared-support-for-doctors-with-long-covid
- Gorna R, et al. Long COVID guidelines need to reflect lived experience. Lancet. 2021 Feb 6;397(10273):455-457
- Problems accessing the support group, email Robin Gorna rgorna@gmail.com

Hospital readmission and new onset conditions

- The January 2021 **UK ONS survey** of hospitalised patients reported that **29% of recovered patients were readmitted to hospital and 12% died within 5 months**, particularly those who had been admitted to intensive care.
- Many of these patients were readmitted with a **new diagnosis**.
- According to the Mayo Clinic, the principal new onset conditions are:
  - Psychiatric conditions
  - Diabetes
  - Neurodegenerative: Parkinson's and Alzheimer's diseases

(Ayoubkhani D, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021 Mar 31; 372: n693; https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/2september2021; https://www.mayoclinic.org/diseases-conditions/coronavirus/in-depth/coronavirus-long-term-effects/art-20490351)

New onset psychiatric diagnosis

- A survey of 69 million individuals found a new onset psychiatric condition between 14 and 90 days, **particularly anxiety disorders, insomnia and dementia** (Taquet M, et al. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med. 2021 Sep 28;18(9):e1003773)
- **Cognitive dysfunction tended to increase over the first 3 months** in all age groups; over half of those who experienced symptoms for over 6 months went on to have memory deficits in month 7 (Davis HE, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:101019).
- However, those with a psychiatric diagnosis in the previous year were reported to be at a 65% greater risk of being diagnosed with COVID-19, suggesting that mental ill health could be both a risk factor and a complication of COVID-19 (i.e the effect is bi-directional). (https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/in-the-wake-of-the-pandemic-preparing-for-long-covid-2021)
- Of GPs surveyed by the Royal College of General Practitioners in the United Kingdom, 76% described patients reporting sleep disorders or mood changes (https://elearning.rcgp.org.uk/mod/page/view.php?id=11512).

New onset diabetes diagnosis

- A systematic review and **meta-analysis reported 14% of Long COVID patients experienced new onset type 2 diabetes** (Sathish T, et al. Proportion of newly diagnosed diabetes in COVID-19 patients: A systematic review and meta-analysis. Diabetes Obes Metab. 2021 Mar;23(3):870-874).
- New onset insulin-requiring diabetes children with COVID-19 has been reported in multiple studies and appears to persist after recovery from acute infection. (Rubino F, et al. Neonset diabetes in Covid-19. N Engl J Med. 2020;383(8):789–790; Cariou B, et al, CORONADO Investigators. Phenotypic characteristics and prognosis of newly diagnosed diabetes in hospitalized patients with COVID-19: results from the CORONADO study. Diabetes Res Clin Pract. 2021;175:108695)
- There has also been reporting **of new-onset type 1 diabetes** with presentation of dry cough, nausea, vomiting, fever and elevated blood glucose levels (Nassar M, et al. The association between COVID-19 and type 1 diabetes mellitus: a systematic review. Diabetes Metab Syndr. 2021;15(1):447–454; Rubino F, et al. New-Onset Diabetes in Covid-19. N Engl J Med. 2020 Aug 20;383(8):789-790; Yan Z, et al. Long COVID-19 Syndrome: A Comprehensive Review of Its Effect on Various Organ Systems and Recommendation on Rehabilitation Plans. Biomedicines. 2021 Aug 5;9(8):966)
- Studies have shown an increased rate of new onset hyperglycaemia in hospitalised COVID-19 patients with nearly 35% exhibiting persistent hyperglycaemia for up to 6 months. Patients with new-onset hyperglycaemia exhibited a higher clinical score and required a longer in-hospital stay. Thus, new-onset hyperglycaemia in COVID-19 patients may predispose patients to increased risk of poor clinical outcomes and long-term hyperglycaemia. (Ramakrishnan RK, et al. Unraveling the Mystery Surrounding Post-Acute Sequelae of COVID-19. Front Immunol. 2021 Jun 30;12:686029)
- Pre-existing cardiometabolic conditions are a risk factor for severe COVID-19 disease and mortality and may be a feature of new-onset Long COVID, making this another bi-directional condition (Singh AK, et al. Diabetes in COVID-19: Prevalence, pathophysiology, prognosis and practical considerations. Diabetes Metab Syndr. 2020;14(4):303-310).

Implications of Long COVID for the State

- An international survey found that **45% of Long COVID sufferers had reduced their workload and 22% were still unable to work.**
- Long COVID can be severely disabling with implications for sufferers' ability to work. This has implications for **labour force productivity and the cost of long-term sickness absence**. In some, impaired activities of daily living (ADLs) such as walking, bathing or dressing have been found.
- 45% of those who did not recover within three months following COVID-19 reported needing a reduced work schedule and 22% were not working six months later.
- 15% of working people were off sick when followed up four to six weeks after discharge from hospital (rising to 38% in those who had an ICU admission).
- A US study of the implications of CFS/ME found that household productivity declined by 37% and labour force productivity by 54%. The annual lost productivity in the USA was US$ 9.1 billion, representing about US$ 20,000 per person with CFS.

(Torres-Castro R, et al. Functional Limitations Post-COVID-19: A Comprehensive Assessment Strategy. Arch Bronconeumol. 2021;57:7-8.; Davis HE, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:101019; Aiyegbusi OL, et al. Symptoms, complications and management of long COVID: a review. J R Soc Med. 2021 Sep;114(9):428-442; Reynolds KJ, et al. The economic impact of chronic fatigue syndrome. Cost Eff Resour Alloc. 2004 Jun 21;2(1):4. doi: 10.1186/1478-7547-2-4; Malik P, et al. Post-acute COVID-19 syndrome (PCS) and health-related quality of life (HRQoL)-A systematic review and meta-analysis. J Med Virol. 2022 Jan;94(1):253-262Halpin, S.J., et al, (2021) Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. Journal of medical virology, 93(2), pp.1013-1022)

Implications of Long COVID for the individual

- Long COVID can also affect patients' **social lives, quality of life and daily living ability, with possible need for carers**. Symptomatology is likely to lead to increased social isolation, affecting mental health. The inability to work or reduced hours will have a **financial impact** on household finances.
- The latest **ONS Survey found that Long COVID symptoms adversely affected the day-to-day activities of 63%** of those with self-reported long COVID, with 18% reporting that their ability to undertake their day-to-day activities had been "limited a lot".
- A Belgian survey noted that among those **not admitted to hospital**, **11 weeks after the infection 44% newly needed help with personal care, with 31% meeting the threshold for being care-dependent.**
- 18% of people previously independent prior to infection had some degree of dependency on others 3 months after hospital discharge.

(https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/3february2022; Vaes AW, et al. (2020) Care dependency in non-hospitalized patients with COVID-19. Journal of Clinical Medicine, 9(9), p.2946; Venturelli S, et al., (2021). Surviving COVID-19 in Bergamo Province: a post-acute outpatient re-evaluation. Epidemiology & Infection, 149, e32, pp.1-9)

Diagnosing Long COVID

NHS patient information: seeing your GP with suspected Long COVID

Symptoms of long COVID List of symptoms – see earlier slide

What happens at your appointment:

- Your doctor will ask about your symptoms and the impact they're having on your life.
- They may suggest some tests to find out more about your symptoms and rule out other things that could be causing them.
- These might include:
    - blood tests
    - checking your blood pressure and heart rate
    - a chest X-ray

Treatment and support

- Your doctor will talk to you about the care and support you might need.
- You may be given advice about how to manage and monitor your symptoms at home.
- If the symptoms are having a big impact on your life, you may be referred to a specialist rehabilitation service or a service that specialises in the specific symptoms you have.

(https://www.nhs.uk/conditions/coronavirus-covid-19/long-term-effects-of-coronavirus-long-covid/)

What does this mean in practice?

- Long COVID is a diagnosis of **exclusion of other causes**
- There are **no GP tests to diagnose Long COVID; instead the GP must run usual blood tests based upon signs and symptoms**.
- A survey of long Covid patients reported that around **two-thirds of who had undergone GP blood testing reported normal results.** (Davis HE, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021 Aug;38:101019)
- But the essential thing is that **as long as sufferers have at least one symptom on the Long COVID list and no other cause, the GP should diagnose them with Long COVID, i.e. the patient should be believed**.
- This is in stark contrast to the battle to have CFS/ME recognised as a medical condition! So one small benefit to come out of the pandemic (but not for the patient, obviously!).
- The GP refers to a specialist if necessary and otherwise discusses ‘care and support’ and gives ‘advice about how to manage and monitor’ the symptoms.
- However, specialist scans such as chest X-ray and ECG don’t seem to pick up Long COVID damage. An MRI or CT scan is normally required.

What does the Royal College of General Practitioners (RCGP) say?

- ‘No laboratory test is required for a diagnosis and patients don’t need a positive PCR or antibody test to be diagnosed with Long COVID.’
- Prior to 12 weeks following diagnosed or suspected COVID, the GP can consider Long COVID but must rule out other potential causes first.
- RCGP recommends, in addition to specialist testing for suspected conditions:
  - Full blood count
  - Kidney and liver function tests
  - C-reactive protein
  - Ferritin
  - Thyroid function
- ‘When seeing a patient with Post-COVID symptoms….don’t dismiss their symptoms as a psychological problem or anxiety’.

(https://elearning.rcgp.org.uk/mod/scorm/view.php?id=12135)

And the WHO agrees

- ‘There is no simple symptom or test for diagnosing Long COVID.’
- ‘Long COVID is a clinical diagnosis, based on a history of COVID-19 and a failure to fully recover, with development of some of the symptoms listed.’
- ‘Although a positive swab or antibody test for COVID-19 is helpful, it is not a prerequisite for diagnosis.’

(https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/in-the-wake-of-the-pandemic-preparing-for-long-covid-2021)

Long COVID prevalence: The UK ONS survey

- Based on **self-reported (not clinically diagnosed)** long Covid in responses to the UK COVID-19 Infection Survey (CIS) and extrapolated to the whole population, an estimated 1.3 million people living in the UK (**2.1% of the population**) were experiencing long COVID (symptoms persisting for **more than four weeks** after the first suspected COVID-19 infection that were not explained by something else, as of 2 January 2022.
- Of those self-reporting with Long COVID, 21% first had (or suspected they had) COVID-19 less than 12 weeks previously, **71% had (or suspected they had) COVID-19 at least 12 weeks previously and 42% first had (or suspected they had) COVID-19 at least one year previously.**
- Note that the September 2021 ONS survey estimated that 1.5% of the population had symptoms persisting >12 weeks, while a 2020 ONS survey found that 10% were symptomatic after 12 weeks. **So the prevalence fluctuates according to which ONS survey is used.** The Sep 2021 survey predicted that 0.06% of the population had symptoms persisting for >1 year.
- **Fatigue continued to be the most common symptom reported** as part of individuals' experience of long COVID (50% of those with self-reported long COVID), **followed by shortness of breath** (37%), loss of smell (37%), and loss of taste (28%).
- As a proportion of the UK population, prevalence of self-reported long COVID was greatest in **people aged 35 to 69 years, females,** people living in more deprived areas, those working in health care, social care, or teaching and education, and those with another activity-limiting health condition or disability.
- **Raising questions about whether Long COVID exists:** The Sep 2021 survey showed that among those who tested positive for COVID-19, **5% reported one or more of 12 common symptoms at least 12 weeks after infection. However, 3.4% of the control group also reported such symptoms, suggesting that the coronavirus may not be to blame in the majority of cases.**

(https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/3february2022;
https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/2september2021)

Other UK studies: The King's College Symptom study (Zoe App)

- The King's College COVID Symptom (ZOE App) study followed 4,182 people who had laboratory-confirmed COVID and compared them to matched negative test controls (problematic in itself!). Among diagnosed cases:
  - 12.5% had symptoms lasting over 28 days
  - 5% had symptoms lasting over 8 weeks
  - 2% had symptoms lasting over 12 weeks.
- Those with symptoms lasting longer than 4 weeks were also more susceptible to symptom relapses (16%) than those whose symptoms resolved within 10 days (8.4%).
- The researchers did point out that those using the app were not necessarily representative of everyone getting COVID-19. They had more women, fewer people over 70, and fewer people from ethnic minorities than in the general population but they were able to adjust for this. However, they could not take account of the possibility that those who did experience persisting symptoms would be more or less likely to continue to report symptoms than those whose symptoms resolved.
- Patients report that their symptoms often fluctuate in intensity and frequency, with approximately 16% in the King's College COVID Symptom (ZOE App) reporting relapse, with new symptoms appearing at different stages of their illness (Sudre CH, et al. Attributes and predictors of long COVID. Nat Med 27, 626–631 (2021).
- To put these numbers in context, only 10% of people who get the flu are still sick after 14 days. (https://academic.oup.com/cid/article/62/4/448/2463108)

Long COVID risk factors

Age and gender: Females but no clear consensus on age

- In contrast to the initial infection, which particularly affected elderly males, the ONS survey reported that there is a greater prevalence of Long COVID among females aged 35-69, and particularly between the ages of 50-69.
- The Zoe App study (which is self-reported) showed that 10% of subjects aged 18–49 years were sufferers but this rose to 22% in those aged above 70 years. The difference in gender was most apparent in the 50-60 age group, which contained 15% females but 10% males. There was no gender difference in those aged >70.
- The UK PHOSP-COVID study found that the young and old recover more completely, with the middle-aged having the highest proportion of failure to recover; Long COVID was more prevalent in women under the age of 50.
- The National Institute for Health Research (NIHR) 2nd Review found that young people and children were disproportionately affected, despite experiencing much less severe COVID-19.
- The WHO and other international reviews, however, reports that Long COVID increases with age.
- Most studies agree that Long COVID is more prevalent among females.

(https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/6january2022; Sudre CH et al. Attributes and predictors of long COVID. Nat Med 27, 626–631 (2021); Evans RA, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021 Nov;9(11):1275-1287; https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/in-the-wake-of-the-pandemic-preparing-for-long-covid-2021; Aiyegbusi OL, et al. Symptoms, complications and management of long COVID: a review. J R Soc Med. 2021 Sep;114(9):428-442; https://evidence.nihr.ac.uk/themedreview/living-with-covid19-second-review/)

Ethnicity: no clear consensus

- The REACT study found that Asian people had a lower risk of long COVID, whereas SAGE goes as far as to say that non-whites are less likely to suffer Long COVID.
- Similarly the UK PHOSP-COVID study found that failure to recover fully was associated with white ethnicity.
- Nevertheless, one review found that ethnic minorities suffered a disproportionate prevalence of Long COVID, while another found no difference between ethnicities.
- A UK study reported that individuals belonging to the BAME community were more likely to experience breathlessness than white individuals at 4–8 weeks post-discharge, although rates of PTSD were not different.

(Whitaker, https://spiral.imperial.ac.uk/handle/10044/1/89844; https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1007511/S1327_Short_Long_COVID_report.pdf; Evans RA, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021 Nov;9(11):1275-1287; Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811; Garg, M., et al. (2021) The Conundrum of 'Long-COVID-19': A Narrative Review. International journal of general medicine, 14, 2491–2506; Halpin SJ, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: A cross-sectional evaluation. J Med Virol. 2021 Feb;93(2):1013-1022)

Correspondence with COVID-19 risk factors: no clear consensus

- The ONS survey reports that those with other health conditions (co-morbidities) and those working in health or social care were more likely to suffer Long COVID.
- The UK PHOSP-COVID study found that failure to recover fully was associated with two or more co-morbidities, although Carvalho-Schneider et al found that the number of comorbidities did not predict Long COVID.
- A review confirmed that a high number of comorbidities was a risk factor for Long COVID. However another found that pre-existing conditions including obesity, diabetes and cardiovascular disease showed no association with Long COVID development.
- SAGE reports that those with overweight/obesity and pre-existing asthma, are more likely to suffer both severe COVID-19 infection and Long COVID.

(https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/6january2022; Carvalho-Schneider C et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect. 2021 Feb;27(2):258-263; https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1007511/S1327_Short_Long_COVID_report.pdf; Evans RA, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021 Nov;9(11):1275-1287; Whitaker, https://spiral.imperial.ac.uk/handle/10044/1/89844; Aiyegbusi OL, et al. Symptoms, complications and management of long COVID: a review. J R Soc Med. 2021 Sep;114(9):428-442; Crook H, et al. Long covid-mechanisms, risk factors, and management. BMJ. 2021 Jul 26;374:n1648; Cabrera Martimbianco AL, et al. Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. Int J Clin Pract. 2021;75(10):e14357. doi:10.1111/ijcp.14357)

Pre-existing mental health

- Studies found those with a **pre-existing diagnosis of depression, anxiety or any psychiatric disorder had a higher prevalence of Long COVID.**
- A SAGE report showed that those with pre-pandemic poor physical and mental health are more likely to suffer both severe COVID-19 infection and Long COVID.

(Townsend L, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One. 2020 Nov 9;15(11):e0240784; Poyraz BÇ, et al. Psychiatric morbidity and protracted symptoms after COVID-19. Psychiatry Res. 2021 Jan;295:113604; https://www.gov.uk/government/publications/ons-short-report-on-long-covid-22-july-2021)

Severity of initial COVID-19 symptoms: No clear consensus

- The ONS survey and other surveys have shown that although those asymptomatic for COVID-19 can still suffer Long COVID, in general it is more prevalent in those who experienced symptoms, and particularly among those with a high viral load during their initial infection. SAGE and other reviews confirm that those hospitalised for COVID-19 infection, particularly those given oxygen, transferred to ICU and given mechanical ventilation are more likely to have Long COVID.
- Those who had been hospitalised for COVID-19 were 3.5 times more likely to be readmitted to hospital and 7.7 times more likely to die within 140 days than those not hospitalised. The risk of readmission was greater for people under 70 than those over 70 years, and for ethnic minority groups than for the white population.
- The Zoe App study, confirmed by several others, found that the more symptoms a person experienced within the first week of illness, the more likely they were to develop long COVID; one study found that >5 symptoms was the single, strongest predictive factor, while another noted >10. Key symptom predictors of Long COVID were hoarseness of voice, shortness of breath and hospital admission. This study also found that among those over 70, the leading risk factors were loss of smell, early fever, hoarseness of voice and comorbidities, particularly those involving the heart and lung. Nevertheless, others found that the presence of initial symptoms (chest pain, dyspnoea, fever, anosmia, ageusia) did not predict Long COVID.
- However, the WHO and other global reviews concluded that the chances of having long-term symptoms is not linked to COVID-19 severity or duration of the acute phase.

(https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1007511/S1327_Short_Long_COVID_report.pdf; https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/2september2021; ; Aiyegbusi OL, et al. Symptoms, complications and management of long COVID: a review. J R Soc Med. 2021 Sep;114(9):428-442; Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis (Lond). 2021;53(10):737-754.; Ayoubkhani D, et al. Post-covid syndrome in individuals admitted to hospital with covid-19: retrospective cohort study. BMJ. 2021 Mar 31;372:n693; Sudre CH et al. Attributes and predictors of long COVID. Nat Med 27, 626–631 (2021; Evans RA, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. Lancet Respir Med. 2021 Nov;9(11):1275-1287; https://www.euro.who.int/en/health-topics/health-emergencies/coronavirus-covid-19/publications-and-technical-guidance/2021/in-the-wake-of-the-pandemic-preparing-for-long-covid-2021); Carvalho-Schneider C et al. Follow-up of adults with noncritical COVID-19 two months after symptom onset. Clin Microbiol Infect. 2021 Feb;27(2):258-263; Cabrera Martimbianco AL, et al. Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. Int J Clin Pract. 2021;75(10):e14357. doi:10.1111/ijcp.14357; Moreno-Pérez O, Merino E, Leon-Ramirez JM, et al. Post-acute COVID-19 syndrome. Incidence and risk factors: A Mediterranean cohort study. *J Infect*. 2021;82(3):378-383. doi:10.1016/j.jinf.2021.01.004; Stavem K, et al. Persistent symptoms 1.5-6 months after COVID-19 in non-hospitalised subjects: a population-based cohort study. Thorax. 2021 Apr;76(4):405-407; Greenhalgh T et al. Management of post-acute covid-19 in primary care. BMJ. 2020 Aug 11;370:m3026)

Test results on hospital admission or discharge: No clear consensus

- A UK study showed that among patients with abnormal test results on hospital discharge, those with Long COVID had persistently elevated d-dimer and C reactive protein (CRP). 9% of patients in a Long Covid clinic had X-rays showing deterioration seven to eight weeks after discharge from hospital, suggesting the possibility of lung fibrosis development.
- Another UK study found no association with COVID-19 severity or laboratory markers of inflammation or cell turnover and Long COVID development.
- A review found that the majority of people with Long COVID are PCR negative, indicating microbiological recovery.
- Long COVID development was not associated with earlier antibody test result.

(Mandal S, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. Thorax. 2021 Apr;76(4):396-398; Townsend L, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One. 2020 Nov 9;15(11):e0240784; Raveendran AV, et al. Long COVID: An overview. Diabetes Metab Syndr. 2021;15(3):869-875. doi:10.1016/j.dsx.2021.04.007; Anaya JM, et al. Post-COVID syndrome. A case series and comprehensive review. Autoimmun Rev. 2021 Nov;20(11):102947)

Relationship of current test/scan results to symptoms

- Some studies show no association of current test or scan results with symptoms.
- **But, even among patients asymptomatic for COVID-19, MRI scans revealed cardiac problems in 78% of Long COVID patients and ongoing myocardial inflammation in 60%.**
- **These were independent of pre-existing conditions, severity and overall course of COVID-19, and the time from the original diagnosis.**

(D'Cruz RF, et al. Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia. ERJ Open Res. 2021 Feb 8;7(1):00655-2020; Puntmann VO, et al. Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Nov 1;5(11):1265-1273)

Impact of vaccination

- The UK Health Security Agency (UKHSA) has undertaken a rapid evidence review looking at the effects of vaccination against Long COVID or post-COVID symptoms. The review includes 15 UK and international studies that were undertaken up until January 2022.
- **Eight studies in the review looked at the effect of vaccinations administered before infection. Most of these studies suggest that vaccinated people (1 or 2 doses) were less likely to develop symptoms of long COVID** following infection compared with unvaccinated people – in the short term and long term (4 weeks up until 6 months after infection).

(https://www.pslhub.org/learn/coronavirus-covid19/data-and-statistics/the-effectiveness-of-vaccination-against-long-covid-a-rapid-evidence-briefing-february-2022-r6159/)

Medications as risk factors for Long COVID: mostly steroids

- A Korean study found that those with subsequent lung fibrosis had longer duration of pulsed steroid therapy and antiviral therapy. (Yu M, et al. Prediction of the Development of Pulmonary Fibrosis Using Serial Thin-Section CT and Clinical Features in Patients Discharged after Treatment for COVID-19 Pneumonia. Korean J Radiol. 2020;21(6):746-755)
- Agents used in acute COVID-19, such as tocilizumab, can result in thrombosis, even after the resolution of the acute infection. (Atallah B, et al. Thrombotic events following tocilizumab therapy in critically ill COVID-19 patients: a Facade for prognostic markers. Thromb J 2020; 18 :22)
- Some of the medications currently in use to treat COVID-19, particularly steroids and antibiotics, have the potential to detrimentally affect skeletal muscle (Piotrowicz K et al. Post-COVID-19 acute sarcopenia: physiopathology and management. Aging clinical and experimental research vol. 33,10 (2021): 2887-2898).
- Steroid therapy contributes to bone loss and sarcopenia. (Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021 Sep-Oct;6(9):796-811)
- Some pancreatitis may be drug-induced, particularly in patients taking NSAIDs and glucocorticoids (Liu F, et al. ACE2 Expression in Pancreas May Cause Pancreatic Damage After SARS-CoV-2 Infection. Clin Gastroenterol Hepatol. 2020;18(9):2128-2130.e2)
- High dose corticosteroid therapy causes severe hyperglycaemia, electrolyte imbalance and myopathy. (Raveendran AV, et al. Long COVID: An overview. Diabetes Metab Syndr. 2021 May-Jun;15(3):869-875)
- Some dermatological eruptions may be COVID drug-related (Suchonwanit P, et al. Cutaneous manifestations in COVID-19: Lessons learned from current evidence. J Am Acad Dermatol. 2020;83(1):e57-e60).

Children/Adolescents and Long COVID

- A comprehensive review of 14 studies (published Aug 2021) found that **although the risk of severe COVID-19 is low, there may be a greater risk for Long COVID**. Prevalence varied widely from 4% to 66%, making the risk difficult to quantify. **Symptoms rarely persisted beyond 12 weeks in children and adolescents.**
- **BUT poor quality studies are a problem.** Of the only 5 studies which had a control group, 2 did not find persistent symptoms to be more prevalent in children and adolescents with evidence of COVID-19 infection.
- The authors commented that **long COVID symptoms are difficult to distinguish from pandemic-associated symptoms resulting from school closures, not seeing friends and being unable to do sports and hobbies.**
- Some studies showed that older age and being female were the most common risk factors but a UK study found that the majority of children were male and 43% were non-white.
- The most common reported symptoms were headache, fatigue, sleep disturbance, concentration difficulties, abdominal pain, myalgia/arthralgia, congested or runny nose, cough, chest tightness or pain, loss of appetite or weight, disturbed smell (anosmia) and rash.
- Other reviews have found that the children with Long COVID may be either symptomatic or asymptomatic with COVID-19. There was a consistently higher prevalence of Long COVID in adults compared to children.

(Zimmermann Pet al. How Common is Long COVID in Children and Adolescents?. Pediatr Infect Dis J. 2021;40(12):e482-e487; Garg M et al. (2021). The Conundrum of 'Long-COVID-19': A Narrative Review. International journal of general medicine, 14, 2491–2506; Jiang DH, et al. Postacute Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 Infection: A State-of-the-Art Review. JACC Basic Transl Sci. 2021;6(9):796-811; Swann OV, et al. Clinical characteristics of children and young people admitted to hospital with covid-19 in United Kingdom: prospective multicentre observational cohort study. BMJ. 2020 Aug 27;370:m3249; https://www.gov.uk/government/publications/ons-short-report-on-long-covid-22-july-2021)

The CLoCK Study

- The CLoCK study**, the world's largest study on Long Covid in adolescents, led by UCL and Public Health England researchers**, reported that among young people aged 11-17 followed up after 3 months, 66.5% of those with a baseline positive PCR test and 53% of those with a negative PCR test had at least 1 symptom, whilst 30% of PCR-positive and 16% or PCR-negative had at least 3 symptoms. Headaches and unusual tiredness were the most common complaints.
- The authors concluded that the results meant that **those with a positive baseline PCR test had a similar symptom profile to those with a negative PCR test** but had a higher prevalence of single and multiple symptoms 3 months later.
- One of the researchers commented on Twitter: '…nearly all symptoms in the test-positives were also reported among test-negatives at 3 months, **making it nearly impossible to attribute any symptoms or groups of symptoms specifically to the effects of COVID-19'**.
- The researchers proposed 3 possible reasons for why high numbers of young people who tested negative reported symptoms at 3 months:
  - symptoms such as tiredness are common in this age group generally.
  - the timing of the survey coincided with the return of school following lockdown and a likely increase in infections.
  - only 13% of those sent a survey actually responded – it is possible that these respondents were more likely to have poor health than those who did not respond.
- This study has engendered some criticism and a re-analysis of the data allegedly came up with a different result.
- But a similar result was seen in a large US study of children when only a positive PCR test was considered but when serologic evidence (antibodies) was included, then 100% had a positive result. Since the UCL team did not include serologic testing, this also calls into question their conclusion that the symptoms cannot be attributed to COVID-19.

(Stephenson https://www.researchsquare.com/article/rs-798316/v1; Godfred-Cato Set al. COVID-19-Associated Multisystem Inflammatory Syndrome in Children - United States, March-July 2020. MMWR Morb Mortal Wkly Rep. 2020 Aug 14;69(32):1074-1080; https://twitter.com/ShamezLadhani/status/1480114954061508608; https://www.ucl.ac.uk/news/2021/sep/first-findings-worlds-largest-study-long-covid-children)

Could he have Long COVID ‘delirium and confusion’?

- Is Putin suffering 'delirium and confusion' due to Long COVID? Questions arise over Russian leader’s mental state.
- Vladimir Putin, 69, could be suffering from hubris syndrome, according to expert. This is associated with a loss of contact with reality and inability to weigh up risk
- Rumours of Putin's poor health have been circulating for years.

(https://www.dailymail.co.uk/femail/article-10551251/Did-Covid-send-Putin-mad.html)