In brief

Long COVID

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Question

What is the evidence on the prevalence, presentation and management of long-COVID?

Background

- The World Health Organization defines long COVID (or 'post COVID-19 condition', 'post-acute sequelae of COVID infection' (PASC)) as an illness that occurs in people who have a history of probable or confirmed SARS-CoV-2 infection; usually within three months from the illness onset, with symptoms and effects that last for at least two months. The symptoms and effects of long COVID cannot be explained by an alternative diagnosis.[1, 2]
- The definition of long COVID and the approaches to estimating prevalence vary considerably across studies.[1] Researchers have called for consensus in definitions.[2]
- Many studies have weak designs – many are cross-sectional, rely on self-reported symptoms for enrolment and subsequent self-reported outcomes or often do not have a control group.[3]

Summary

Prevalence

- Estimates of long COVID prevalence vary. More recent, large and rigorous studies report between 3.7% and 20.0% of people will develop long COVID after acute infection.[1, 4-8]
- Prevalence estimates may be linked to study rigour (with a meta-analysis finding that higher study quality was associated with lower prevalence).[9]
- Studies suggest lower prevalence of long COVID following infection with Omicron (4.5%) than with Delta (10.8%), especially among double vaccinated individuals and irrespective of time elapsed between infection and most recent vaccination.[7, 10] In triple vaccinated individuals, the prevalence was similar for Delta (5.0%), Omicron BA.1 (4.5%) and Omicron BA.2 (4.2%) infections.[10]
- In children, COVID-19 infection (pre-Omicron) was associated with an increased risk of reporting at least one symptom lasting more than two months than controls (absolute risk difference: 12.8% for 0-3 years; 4.4% for 4-11 years; 4.7% for 12-14 years).[11] Other studies (pre-Omicron) estimate a prevalence of around 1.7% for long COVID symptoms in non-hospitalised children at three months post-infection.[12, 13]

Symptoms

- Symptoms may:
  - range from mild to severe
  - be singular or multiple
  - be continuous or episodic
  - be chronic sequelae of acute COVID-19 disease (such as loss of smell or cough) [14, 15]

  - include fatigue, shortness of breath or difficulty breathing, memory, concentration or sleep problems, persistent cough, chest pain, trouble speaking, muscle aches, loss of smell or taste, depression or anxiety and fever[1]
  - predominantly include mood symptoms, fatigue and sleep disorders for children.[16]
- Numerous studies have proposed subtypes or phenotypes of long COVID, however, their conclusions differ considerably and as yet there is no international consensus.[17-22]
- There are a number of chronic sequelae of severe acute COVID-19 disease that will lead to persistent impairment and may result in chronic disease:[23]
  - pulmonary fibrosis secondary to acute lung injury (pre-print)[24]
  - myocarditis which may lead to persistent cardiac dysfunction[25]
  - pulmonary thromboemboli[26, 27]
  - diabetes[28]
  - cardiovascular and cerebrovascular disease.[29, 30]

Risk and protective factors

- Risk factors for long COVID may include: number of initial COVID-19 symptoms; certain comorbidities, such as hypertension, diabetes, obesity and asthma; and certain demographic factors, such as being older and living in more deprived areas.[4, 5, 31-35]
- A more severe initial COVID-19 infection may be associated with persistent illness, however, the available studies are low quality.[32, 36] People admitted for acute infection have been noted to recover slower from long COVID symptoms than those with a milder acute illness.[8]
- According to most studies, women are more likely to develop long COVID than men.[5, 31-33, 37]
- Protective factors for long COVID include vaccination and young age.[12, 38-40]

Mechanisms

- Little is known about the underlying cause of long COVID, as per most post-acute infection syndromes.[41] Other respiratory illnesses, such as influenza, have also been associated with persistent symptoms of a similar nature.[42]
- The mechanisms for ongoing symptoms are proposed to be due to viral persistence, persistent immune activation or autoimmunity, [15, 43-46] however, these are not proven hypotheses.

Diagnosis and assessment

- In a clinical setting, there is no definitive test for long COVID. Diagnosis is based on ruling out other similar conditions.[47]
- A growing range of assessments, such as brain imaging or plasma samples to identify persistent SARS-CoV-2 viral reservoirs, may act as a useful biomarkers of long COVID.[48, 49]
- Differential diagnosis is critical, since the clusters of symptoms associated with long COVID can overlap with other post-acute infection syndromes, such as post intensive care syndrome.[47, 50-57]
- A Delphi consensus study has recently confirmed a core outcome set to be suggested for use in clinical practice and research.[58] A patient-reported outcome measure for long COVID has recently been developed and proposed.[59]

- Guidelines advocate for a holistic, person-centred approach to diagnosis, including a comprehensive clinical history and an examination that involves assessing physical, cognitive, psychological and psychiatric symptoms, as well as functional abilities.[47, 51]

Management

- Regarding management of long COVID, high quality, **evidence-based guidelines are not yet available**.[60]
- Recent available guidelines recommend:
    - A medically-led, multidisciplinary approach[61]
    - Clinicians work with the person (and their family or carers) to develop a personalised rehabilitation and management plan[47]
    - Patients be given advice and information on self-management[47]
    - Symptom management in primary care or referral to specialised care as required.[51] Relevant local guidelines should inform onward referral for anxiety and mood disorders or other psychiatric symptoms.[47]
    - A graded and individualised approach to exercise.[62, 63] High level evidence on the role of exercise and its impact on post-exertional malaise is scant, even in conditions such as chronic fatigue or myalgic encephalitis.[64, 65]

Method

To inform this brief, PubMed and Google Scholar searches were conducted using terms related to long COVID, on 01 August 2022.

References

1. World Health Organization. Coronavirus disease (COVID-19): Post COVID-19 condition [Internet]. Switzerland: World Health Organization; 2021 [cited 2022 May 26]. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19-condition.
2. Munblit D, O'Hara ME, Akrami A, et al. Long COVID: aiming for a consensus. Lancet Respir Med. 2022;10(7):632-4. DOI: 10.1016/S2213-2600(22)00135-7
3. Sneller MC, Liang CJ, Marques AR, et al. A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings. Ann Intern Med. 2022. DOI: 10.7326/M21-4905
4. Bull-Otterson L, Baca A, Saydah S, et al. Post–COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021 [Internet]. United States: Centers for Disease Control and Prevention; 2022 [cited 2022 May 26]. Available from: https://www.cdc.gov/mmwr/volumes/71/wr/mm7121e1.htm?s_cid=mm7121e1_w.
5. Thompson EJ, Williams DM, Walker AJ, et al. Long COVID burden and risk factors in 10 UK longitudinal studies and electronic health records. Nat Commun. 2022 Jun 28;13(1):3528. DOI: 10.1038/s41467-022-30836-0
6. van der Maaden T, Mutubuki EN, de Bruijn S, et al. Prevalence and severity of symptoms 3 months after infection with SARS-CoV-2 compared to test-negative and population controls in the Netherlands. medRxiv. 2022:2022.06.15.22276439. DOI: 10.1101/2022.06.15.22276439
7. Antonelli M, Pujol JC, Spector TD, et al. Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2. Lancet. 2022;399(10343):2263-4. DOI: 10.1016/S0140-6736(22)00941-2
8. Wulf Hanson S, Abbafati C, Aerts JG, et al. A global systematic analysis of the occurrence, severity, and recovery pattern of long COVID in 2020 and 2021. medRxiv. 2022:2022.05.26.22275532. DOI: 10.1101/2022.05.26.22275532

9. Alkodaymi MS, Omrani OA, Fawzy NA, et al. Prevalence of post-acute COVID-19 syndrome symptoms at different follow-up periods: a systematic review and meta-analysis. Clin Microbiol Infect. 2022 May;28(5):657-66. DOI: 10.1016/j.cmi.2022.01.014
10. Office for National Statistics. Self-reported long COVID after infection with the Omicron variant in the UK: 18 July 2022 [Internet]. United Kingdom: Office for National Statistics; 2022 [cited 2022 Jul 20]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/selfreportedlongcovidafterinfectionwiththeomicronvariant/18july2022.
11. Kikkenborg Berg S, Palm P, Nygaard U, et al. Long COVID symptoms in SARS-CoV-2-positive children aged 0-14 years and matched controls in Denmark (LongCOVIDKidsDK): a national, cross-sectional study. Lancet Child Adolesc Health. DOI: 10.1016/S2352-4642(22)00154-7
12. Kostev K, Smith L, Koyanagi A, et al. Post-COVID-19 conditions in children and adolescents diagnosed with COVID-19. Pediatr Res. 2022 2022/05/14. DOI: 10.1038/s41390-022-02111-x
13. Funk AL, Kuppermann N, Florin TA, et al. Post–COVID-19 Conditions Among Children 90 Days After SARS-CoV-2 Infection. JAMA Network Open. 2022;5(7):e2223253-e. DOI: 10.1001/jamanetworkopen.2022.23253
14. Mehandru S, Merad M. Pathological sequelae of long-haul COVID. Nat Immunol. 2022 2022/02/01;23(2):194-202. DOI: 10.1038/s41590-021-01104-y
15. Morrow AJ, Sykes R, McIntosh A, et al. A multisystem, cardio-renal investigation of post-COVID-19 illness. Nat Med. 2022 2022/05/23. DOI: 10.1038/s41591-022-01837-9
16. Lopez-Leon S, Wegman-Ostrosky T, Ayuzo Del Valle NC, et al. Long-COVID in children and adolescents: a systematic review and meta-analyses. Sci Rep. 2022 Jun 23;12(1):9950. DOI: 10.1038/s41598-022-13495-5
17. Bowyer RCE, Huggins C, Toms R, et al. Characterising patterns of COVID-19 and long COVID symptoms: Evidence from nine UK longitudinal studies. medRxiv. 2022:2022.06.20.22275994. DOI: 10.1101/2022.06.20.22275994
18. Kenny G, McCann K, O'Brien C, et al. Identification of Distinct Long COVID Clinical Phenotypes Through Cluster Analysis of Self-Reported Symptoms. Open Forum Infect Dis. 2022;9(4). DOI: 10.1093/ofid/ofac060
19. Reese J, Blau H, Bergquist T, et al. Generalizable Long COVID Subtypes: Findings from the NIH N3C and RECOVER Programs. medRxiv. 2022 May 25. DOI: 10.1101/2022.05.24.22275398
20. Yong SJ, Liu S. Proposed subtypes of post-COVID-19 syndrome (or long-COVID) and their respective potential therapies. Rev Med Virol. 2022 Jul;32(4):e2315. DOI: 10.1002/rmv.2315
21. Zhang H, Zang C, Xu Z, et al. Machine Learning for Identifying Data-Driven Subphenotypes of Incident Post-Acute SARS-CoV-2 Infection Conditions with Large Scale Electronic Health Records: Findings from the RECOVER Initiative. medRxiv. 2022:2022.05.21.22275412. DOI: 10.1101/2022.05.21.22275412
22. Mayer N, Meza-Torres B, Okusi C, et al. Developing a long covid phenotype for post-acute COVID-19 in a national primary care sentinel cohort: an observational retrospective database analysis. JMIR Public Health Surveill. 2022 Jul 19. DOI: 10.2196/36989
23. Mehandru S, Merad M. Pathological sequelae of long-haul COVID. Nature Immunology. 2022 2022/02/01;23(2):194-202. DOI: 10.1038/s41590-021-01104-y
24. Stewart I, Jacob J, George P, et al. Interstitial lung damage following COVID-19 hospitalisation: an interim analysis of the UKILD Post-COVID study. medRxiv. 2022:2022.03.10.22272081. DOI: 10.1101/2022.03.10.22272081
25. Haryalchi K, Olangian-Tehrani S, Asgari Galebin SM, et al. The importance of myocarditis in Covid-19. Health Sci Rep. 2022 Mar;5(1):e488. DOI: 10.1002/hsr2.488
26. Katsoularis I, Fonseca-Rodríguez O, Farrington P, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after covid-19: nationwide self-controlled cases series and matched cohort study. BMJ. 2022 Apr 6;377:e069590. DOI: 10.1136/bmj-2021-069590
27. Miró Ò, Jiménez S, Mebazaa A, et al. Pulmonary embolism in patients with COVID-19: incidence, risk factors, clinical characteristics, and outcome. Eur Heart J. 2021 Aug 31;42(33):3127-42. DOI: 10.1093/eurheartj/ehab314

28. Rezel-Potts E, Douiri A, Sun X, et al. Cardiometabolic outcomes up to 12 months after COVID-19 infection. A matched cohort study in the UK. PLOS Medicine. 2022;19(7):e1004052. DOI: 10.1371/journal.pmed.1004052
29. Raman B, Bluemke DA, Lüscher TF, et al. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. Eur Heart J. 2022 Mar 14;43(11):1157-72. DOI: 10.1093/eurheartj/ehac031
30. Xie Y, Xu E, Bowe B, et al. Long-term cardiovascular outcomes of COVID-19. Nature Medicine. 2022 2022/03/01;28(3):583-90. DOI: 10.1038/s41591-022-01689-3
31. Ayoubkhani D, Munro M. Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK: 6 May 2022 [Internet]. United Kingdom: Office for National Statistics; 2022 [cited 2022 May 26]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/6may2022.
32. Whitaker M, Elliott J, Chadeau-Hyam M, et al. Persistent COVID-19 symptoms in a community study of 606,434 people in England. Nat Commun. 2022 2022/04/12;13(1):1957. DOI: 10.1038/s41467-022-29521-z
33. Kersten J, Wolf A, Hoyo L, et al. Symptom burden correlates to impairment of diffusion capacity and exercise intolerance in long COVID patients. Sci Rep. 2022 2022/05/25;12(1):8801. DOI: 10.1038/s41598-022-12839-5
34. Chan Sui Ko A, Candellier A, Mercier M, et al. Number of initial symptoms is more related to long COVID-19 than acute severity of infection: a prospective cohort of hospitalized patients. Int J Infect Dis. 2022 May;118:220-3. DOI: 10.1016/j.ijid.2022.03.006
35. Kulenovic A, Lagumdzija-Kulenovic A. Using Logistic Regression to Predict Long COVID Conditions in Chronic Patients. Stud Health Technol Inform. 2022 Jun 29;295:265-8. DOI: 10.3233/shti220713
36. Han Q, Zheng B, Daines L, et al. Long-Term Sequelae of COVID-19: A Systematic Review and Meta-Analysis of One-Year Follow-Up Studies on Post-COVID Symptoms. Pathogens. 2022;11(2). DOI: 10.3390/pathogens11020269
37. Pelà G, Goldoni M, Solinas E, et al. Sex-Related Differences in Long-COVID-19 Syndrome. J Womens Health (Larchmt). 2022 May;31(5):620-30. DOI: 10.1089/jwh.2021.0411
38. Bossley CJ, Kavaliunaite E, Harman K, et al. Post-acute COVID-19 outcomes in children requiring hospitalisation. Sci Rep. 2022 2022/05/17;12(1):8208. DOI: 10.1038/s41598-022-12415-x
39. Nygaard U, Holm M, Hartling UB, et al. Incidence and clinical phenotype of multisystem inflammatory syndrome in children after infection with the SARS-CoV-2 delta variant by vaccination status: a Danish nationwide prospective cohort study. Lancet Child Adolesc Health. 2022. DOI: 10.1016/S2352-4642(22)00100-6
40. Byambasuren O, Stehlik P, Clark J, et al. Impact of COVID-19 vaccination on long COVID: a systematic review and meta-analysis. medRxiv. 2022:2022.06.20.22276621. DOI: 10.1101/2022.06.20.22276621
41. Choutka J, Jansari V, Hornig M, et al. Unexplained post-acute infection syndromes. Nat Med. 2022 2022/05/01;28(5):911-23. DOI: 10.1038/s41591-022-01810-6
42. Taquet M, Dercon Q, Luciano S, 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 Medicine. 2021;18(9):e1003773. DOI: 10.1371/journal.pmed.1003773
43. Phetsouphanh C, Darley DR, Wilson DB, et al. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. Nat Immunol. 2022 2022/02/01;23(2):210-6. DOI: 10.1038/s41590-021-01113-x
44. Berry C, Mangion K. Multisystem involvement is common in post-COVID-19 syndrome. Nat Med. 2022 2022/05/23. DOI: 10.1038/s41591-022-01838-8
45. Buonsenso D, Piazza M, Boner AL, et al. Long COVID: A proposed hypothesis-driven model of viral persistence for the pathophysiology of the syndrome. Allergy Asthma Proc. 2022 May 1;43(3):187-93. DOI: 10.2500/aap.2022.43.220018

46. Martínez-Salazar B, Holwerda M, Stüdle C, et al. COVID-19 and the Vasculature: Current Aspects and Long-Term Consequences. Frontiers in cell and developmental biology. 2022;10:824851-. DOI: 10.3389/fcell.2022.824851
47. National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19 [Internet]. United Kingdom: National Institute for Health and Care Excellence; 2021 [cited 2022 May 30]. Available from: https://www.nice.org.uk/guidance/ng188.
48. Petersen M, Nägele FL, Mayer C, et al. Brain imaging and neuropsychological assessment of individuals recovered from mild to moderate SARS-CoV-2 infection. medRxiv. 2022:2022.07.08.22277420. DOI: 10.1101/2022.07.08.22277420
49. Swank Z, Senussi Y, Alter G, et al. Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae. medRxiv. 2022:2022.06.14.22276401. DOI: 10.1101/2022.06.14.22276401
50. Cocconcelli E, Bernardinello N, Giraudo C, et al. Characteristics and Prognostic Factors of Pulmonary Fibrosis After COVID-19 Pneumonia. Front Med (Lausanne). 2021 2022-Jan-31;8:823600. DOI: 10.3389/fmed.2021.823600
51. Sisó-Almirall A, Brito-Zerón P, Conangla Ferrín L, et al. Long Covid-19: Proposed Primary Care Clinical Guidelines for Diagnosis and Disease Management. Int J Environ Health Res. 2021;18(8):4350. DOI: 10.3390/ijerph18084350
52. Espinosa Rodríguez P, Martínez Aguilar A, Ripoll Muñoz MP, et al. [Long COVID: Is it really myalgic encephalomyelitis? Bibliographic review and considerations]. Semergen. 2022 Jan-Feb;48(1):63-9. DOI: 10.1016/j.semerg.2021.03.006
53. Poenaru S, Abdallah SJ, Corrales-Medina V, et al. COVID-19 and post-infectious myalgic encephalomyelitis/chronic fatigue syndrome: a narrative review. Ther Adv Infect Dis. 2021 2021/01/01;8:20499361211009385. DOI: 10.1177/20499361211009385
54. Nakanishi N, Liu K, Kawakami D, et al. Post-Intensive Care Syndrome and Its New Challenges in Coronavirus Disease 2019 (COVID-19) Pandemic: A Review of Recent Advances and Perspectives. J Clin Med. 2021;10(17):3870. DOI: 10.3390/jcm10173870
55. Rousseau A-F, Minguet P, Colson C, et al. Post-intensive care syndrome after a critical COVID-19: cohort study from a Belgian follow-up clinic. An Intensive Care. 2021 2021/07/29;11(1):118. DOI: 10.1186/s13613-021-00910-9
56. Peach BC, Valenti M, Sole ML. A Call for the World Health Organization to Create International Classification of Disease Diagnostic Codes for Post-Intensive Care Syndrome in the Age of COVID-19. World Medical & Health Policy. 2021;13(2):373-82. DOI: 10.1002/wmh3.401
57. US Centres for Disease Control and Prevalence. Long COVID or Post-COVID Conditions [Internet]. United States: Centres for Disease Control and Prevalence; 2022 [cited 2022 May 30]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html.
58. Munblit D, Nicholson T, Akrami A, et al. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. Lancet Respir Med. 2022;10(7):715-24. DOI: 10.1016/S2213-2600(22)00169-2
59. Sivan M, Preston N, Parkin A, et al. The modified COVID-19 Yorkshire Rehabilitation Scale (C19-YRSm) patient-reported outcome measure for Long Covid or Post-COVID-19 syndrome. J Med Virol. 2022 Sep;94(9):4253-64. DOI: 10.1002/jmv.27878
60. Yelin D, Moschopoulos CD, Margalit I, et al. ESCMID rapid guidelines for assessment and management of long COVID. Clin Microbiol Infect. 2022 2022/02/17/. DOI: 10.1016/j.cmi.2022.02.018
61. Nurek M, Rayner C, Freyer A, et al. Recommendations for the recognition, diagnosis, and management of long COVID: a Delphi study. Br J Gen Pract. 2021;71(712):e815-e25. DOI: 10.3399/bjgp.2021.0265
62. NSW Agency for Clinical Innovation. Exercise and Long COVID [Internet]. Agency for Clinical Innovation, NSW Health; 2022 [cited 2022 Jul 15]. Available from: https://aci.health.nsw.gov.au/__data/assets/pdf_file/0010/735562/Evidence-Check-Exercise-and-long-COVID.pdf.
63. Compagno S, Palermi S, Pescatore V, et al. Physical and psychological reconditioning in long COVID syndrome: Results of an out-of-hospital exercise and psychological - based

rehabilitation program. Int J Cardiol Heart Vasc. 2022 Aug;41:101080. DOI: 10.1016/j.ijcha.2022.101080

64. Barhorst EE, Boruch AE, Cook DB, et al. Pain-Related Post-Exertional Malaise in Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME/CFS) and Fibromyalgia: A Systematic Review and Three-Level Meta-Analysis. Pain Med. 2022 May 30;23(6):1144-57. DOI: 10.1093/pm/pnab308

65. Wormgoor MEA, Rodenburg SC. The evidence base for physiotherapy in myalgic encephalomyelitis/chronic fatigue syndrome when considering post-exertional malaise: a systematic review and narrative synthesis. J Transl Med. 2021 Jan 4;19(1):1. DOI: 10.1186/s12967-020-02683-4

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