

Long COVID-19: Long-Term Complications of COVID-19

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Financial Relationships

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Learning Objectives

After attending this presentation, learners will be able to:

- Summarize the current understanding of the epidemiology of post-acute sequelae of COVID-19 (PASC)
- Describe the long-term health consequences of COVID-19

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Long COVID = Long Hauler = Post COVID Conditions [CDC] = Post Acute Sequelae of SARS-CoV-2 Infection (PASC) [NIH]

As reports of long-term COVID-19 symptoms emerged, the need for scientific research about long COVID has intensified.

Newsweek
1 Out of 5 Months Ago and Still Have Symptoms

ABC News
The New York Times
For Long-Haulers, Covid-19 Takes a Toll on Mind as Well as Body

NBC
The many strange long-term symptoms of Covid-19, explained

CNN
SCIENTIFIC AMERICAN
U.S. Millions Now ill and healthy before COVID-19 in a condition 'long hauler' says

ABC News
Continuing survivors plagued by long-term ailments

ABC News
What's It Like To Be A COVID-19 'Long Hauler'?

ABC News
The Problem of 'Long Haul' COVID

Often referred to as 'Long COVID', these symptoms, which can include fatigue, shortness of breath, 'brain fog', sleep disorders, fevers, gastrointestinal symptoms, anxiety, and depression, can persist for months and can range from mild to incapacitating. In some cases, new symptoms arise well after the time of infection or evolve over time. -NIH

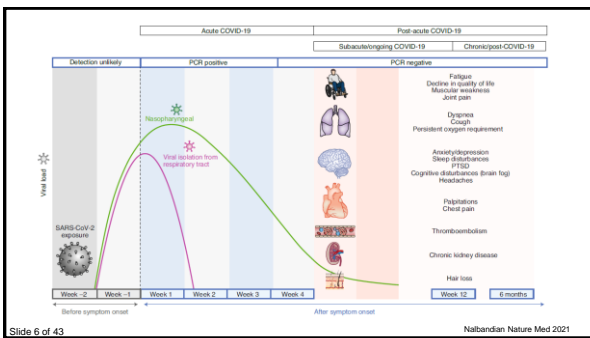
Preliminary reports indicate some patients may develop a so-called 'post-acute COVID-19 syndrome,' in which they experience persistent symptoms after recovering from their initial illness. The syndrome appears to affect those with mild as well as moderate-to-severe disease. The incidence, natural history and etiology of these symptoms is currently unknown. -CDC

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State of the Science

- Accepted case definition lacking
- True prevalence not established; multiple published cohort studies but almost all lack control groups without ongoing signs/symptoms
- Reports include patients throughout the age and disease spectrum (mild → severe), previously healthy, pregnant people and children
- Risk factors and pathophysiology under investigation
- Management strategies in evolution; no specific therapies identified to date

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Definition

- CDC uses the term **post-COVID conditions** to describe health issues that persist **more than four weeks** after first being infected with the virus that causes COVID-19
- **Types of Post-COVID Conditions**
 - **Long COVID** - range of symptoms
 - **Multisystem effects** - can affect most body systems and include [multisystem inflammatory syndrome \(MIS\)](#) and autoimmune conditions
 - **Effects of COVID-19 Treatment or Hospitalization** – post ICU syndrome, PTSD

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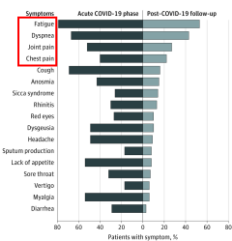
ARS Question 1

- What proportion of patients with confirmed COVID-19 develop long term symptoms/organ dysfunction?
- 1. 5%
- 2. 10%
- 3. 25%
- 4. 75%
- 5. I don't know

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Persistent Symptoms in Patients After Acute COVID-19

JAMA. 2020;324(6):603-605. doi:10.1001/jama.2020.12603



- N=143 patients hospitalized in Italy
- Mean age 56.5y
- 53% female
- 12.6% ICU admission

Post-acute COVID-19 follow-up characteristics	
Days since symptoms onset, mean (SD)	60.3 (13.6)
Days since discharge, mean (SD)	36.1 (12.9)
Persistent symptoms, No. (%)	18 (12.6)
None	18 (12.6)
1 or 2	46 (32.2)
≥3	79 (55.2)
Worsened quality of life, No. (%) ^a	63 (44.1)

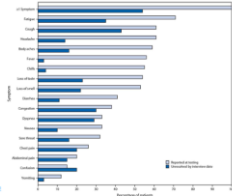
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Lingering symptoms reported by participants of a multi-state phone study in the USA

Symptoms which may persist:

- Fatigue
- Cough, congestion or shortness of breath
- Loss of taste or smell
- Headache, body aches
- Diarrhea, nausea
- Chest or abdominal pain
- Confusion

Self-reported symptoms at the time of positive SARS-CoV-2 testing results and unresolved symptoms 14-21 days later among outpatients (N = 274) United States, March–June 2020



Source: https://www.cdc.gov/mmwr/wwmm/wwmm0111a1.htm#r1_dhtml

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COVID symptom study

- An app into which >4 million people in the US, UK and Sweden have entered symptoms
- Data suggest some 10-15% of individuals with COVID-19 – even mild cases – do not recover quickly
- In a subset: long COVID was more likely with increasing age and body mass index and female sex
- > 5 symptoms in first week associated with long COVID (odds ratio = 3.53 (2.76-4.50))

<https://doi.org/10.1038/s41591-021-01292-y>

<https://covid.joinzoe.com/us-2>

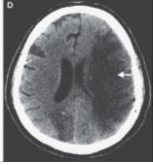
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Epidemiology Conclusions

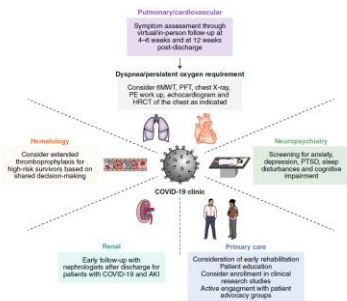
- Incidence/prevalence data cover a broad range, depending on definitions and methods used
- All studies confounded to varying degrees by lack of control groups **without** lingering signs and symptoms
- Therefore, interpret with caution
- However, US has reported > 32m cases
 - So if prevalence only 10%, this = 3,200,000 people

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Clinical Manifestations



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COVID-19 and the heart

- **Manifestations:**
 - Myocarditis
 - Ventricular arrhythmias
 - Cardiomyopathy
- **Pathogenesis:**
 - Direct invasion by the virus
 - Inflammation
 - Blunting of ACE2 receptors
- **Long-term consequences:**
 - Will there be an increase in heart failure as a result?

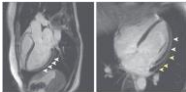


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JAMA Cardiology | Original Investigation

Outcomes of Cardiovascular Magnetic Resonance Imaging in Patients Recently Recovered From Coronavirus Disease 2019 (COVID-19)

- German study, n=100 patients
- Cardiac MRI performed median 71 days after COVID-19 diagnosis
- Cardiac involvement in 78%
- Ongoing myocardial inflammation in 60%
- Presence of chronic comorbidities, duration and severity of acute COVID-19, time since original diagnosis did not correlate with findings



Non-random sample likely biased toward cardiac findings.

Slide 16 of 43 Puntmann VO et al. JAMA. Cardiol. 2020 Jul 27:e2030557.

JAMA Cardiology | Brief Report

Association of Cardiac Infection With SARS-CoV-2 in Confirmed COVID-19 Autopsy Cases

Diana Lindner, PhD, Antonia Fiebel, MD, Hanna Birkhäger, MS, Ganna Anetcheva, PhD, Caroline Eder, MD, Kira Meisner, Katharina Scherschel, PhD, Paula Kirchhof, MD, Felicia Escher, MD, Heinz Peter Schulthess, MD, Stefan Blankenberg, MD, Klaus Püschel, MD, Dirk Westermann, MD

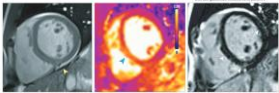
- Cardiac tissue from 39 consecutive autopsy cases included
- SARS-CoV-2 could be documented in 61.5%.
- Viral load above 1000 copies per µg RNA could be documented in 41%.
- A cytokine response panel consisting of 6 proinflammatory genes was increased in those 16 patients compared with 15 patients without any SARS-CoV-2 in the heart.
- Comparison of 15 patients without cardiac infection with 16 patients with more than 1000 copies revealed no inflammatory cell infiltrates or differences in leukocyte numbers per high power field.

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RESEARCH LETTER

Cardiovascular Magnetic Resonance Findings in Competitive Athletes Recovering From COVID-19 Infection

Rajpal S et al. JAMA. Cardiol. 2020 Sep 11:e204916.



Persistent cardiac abnormalities identified not only in the elderly with multimorbidity but also among healthy young athletes.

- 26 competitive college athletes diagnosed with COVID-19 (RT-PCR)
- None were hospitalized
- Majority did not report symptoms
- 12 (46%) had evidence of myocarditis or prior myocardial injury by cardiac magnetic resonance imaging routinely performed for positive testing results (range, 12-53 days)

Slide 18 of 43 Rajpal S et al. JAMA. Cardiol. 2020 Sep 11:e204916.

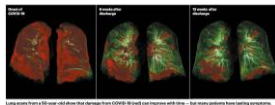
COVID-19 and the lungs

- **Manifestations:**
 - Chronic cough
 - Fibrotic lung disease
 - Bronchiectasis
 - Pulmonary vascular disease
- **Pathogenesis:**
 - Inflammation → Fibrosis
 - Thromboembolic disease
- **Long-term consequences:**
 - Will there be an increase in cases of COPD and/or pulmonary fibrosis as a result?



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Pulmonary sequelae



Long-term effects of our old friend that damage from COVID-19 look not unlike with this – but many patients have lasting symptoms.

Photo: 11/18/2020 11:13:20 AM

• Acute manifestations

• Pneumonia, ARDS, hypoxic respiratory failure

• Post-acute manifestations = Sx/signs of restrictive lung disease

• After hospital discharge:

30d = 53% decreased DLCO, 49% diminished respiratory muscle strength

3mo = 25% decreased DLCO

3mo = 71% with radiographic evidence of interstitial thickening and fibrosis

If compounded on cardiovascular comorbidity, persistent decline in pulmonary function could have significant consequences

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Zhao YM et al. EClinicalMedicine. 2020;25:100463.

Huang Y. Respir Res. 2020;21(1):1163.

COVID-19 and the brain

- **Manifestations:**
 - Headaches
 - Dizziness
 - Trouble concentrating
 - Confusion
 - Hallucinations
 - Stroke
- **Pathogenesis:**
 - Inflammation
 - Direct viral invasion of brain
 - Hypoxemia
- **Long-term consequences:**
 - Will there be an increase in "COVID brain"?



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Anosmia:

SARS-CoV2 receptor: ACE2 in non-neuronal cells

Olfactory pathway

89 yrs male 39 yrs

Age Group	% ACE2+ sustentacular cells
89 yrs male	~10
39 yrs	~25

Expression of ACE2 in Sustentacular cells

Brann et al., Science Advances
2020

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Long Term Neurologic Symptoms

More than one quarter of patients developed new neurological symptoms after their acute COVID-19 illness.
 COVID-19 symptoms among 70 non-hospitalized patients, France

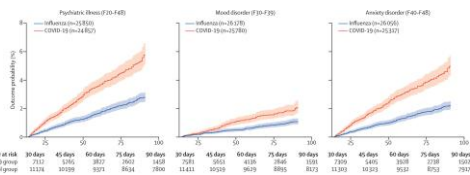
Symptom	Acute symptoms (%)	Persistent symptoms (%)
Fatigue or muscle weakness	~75	~65
Sensory disturbances	~65	~55
Chest pressure or pain	~55	~45
Dyspnea	~45	~35
Palpitations/tachycardia	~35	~25
Headaches	~25	~15
Cognitive neurological disorders	~15	~5
Problems with taste or smell	~5	~15
Other neurological signs	~5	~10

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Emotional health & wellbeing

At-risk of a global mental and behavioral health crisis given sheer number of COVID-19 cases

New diagnoses of anxiety, insomnia, dementia and mood disorders as well as psychiatric disorders in general, were increased after COVID-19 illness



Univ Oxford [www.thelancet.com/psychiatry](https://doi.org/10.1016/S2215-0366(20)30462-4) Published online November 9, 2020 [https://doi.org/10.1016/S2215-0366\(20\)30462-4](https://doi.org/10.1016/S2215-0366(20)30462-4)

Emotional & behavioral concerns

- A diagnosis of COVID-19, and subsequent need for physical distancing, has been associated with feelings of isolation and loneliness
- COVID-19-related stigma has become pervasive and can result in a sense of hopelessness
- Increasing reports of lingering malaise and exhaustion akin to chronic fatigue syndrome may leave patients with physical debility and emotional disturbance
- Individuals recovering from COVID-19 may be at even greater risk (than general population) of depression, anxiety, PTSD, substance use disorder

Galea S. JAMA Intern Med. 2020;180(6):817-818.

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Management of Long COVID

- No proven management strategies/therapies yet
- CT.GOV search for "long COVID"
 - 449 studies
 - 217 interventional
- Many comparing various rehab strategies
- Some with cytokine antagonists (monetlukast, IL-7)
- Other random agents eg naltrexone, hyperbaric oxygen
- Anticipate many more to come

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ARS Question 2

Can COVID-19 vaccines improve long COVID symptoms?

- 1. yes
- 2. no
- 3. maybe
- 4. I don't know

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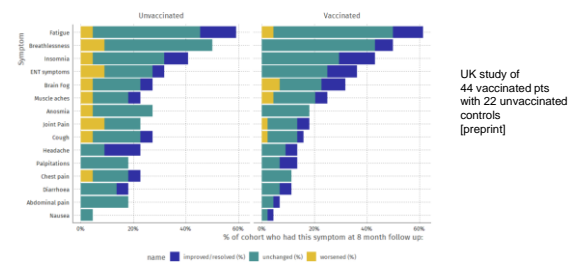
Does Vaccination Help?

- Anecdotal reports
- Biologically plausible



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Figure 1: Symptoms at 8-month follow up with change following vaccination (or matched timepoint in unvaccinated group)



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<https://doi.org/10.1101/2021.03.11.21253225>

NIH Clinical Research Strategy to Understand and Treat Post-acute Sequelae of COVID-19

Note: includes existing and new efforts

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Conclusions

- Likely large numbers of patients will experience long-term sequelae
- Multidisciplinary care approach will be needed
- Access for underserved populations is critical, including case management support for housing and food
- Listen to patients –
 - MH care for anxiety and depression
 - Referrals for counseling and peer support
- Rigorous observational and interventional trials required
- Public Health Messaging to avoid infection—it's not all about COVID Mortality

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Question-and-Answer Session

Thanks to Carlos Del Rio and Avi Nath for multiple slides
