



Long-term sequelae of COVID-19

Post-acute COVID syndrome

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Reports of post-acute symptoms emerged in the media early in the pandemic

The logo for Vox, featuring the word "Vox" in a white, serif font on a dark purple rectangular background.

The emerging long-term complications of Covid-19, explained

"It is a true roller coaster of symptoms and severities, with each new day offering many unknowns."

By Lois Parshley | May 8, 2020, 1:10pm EDT

The logo for Science, featuring the word "Science" in a white, serif font on a black rectangular background.

From 'brain fog' to heart damage, COVID-19's lingering problems alarm scientists

By Jennifer Couzin-Frankel | Jul. 31, 2020, 1:30 PM

The logo for The New York Times, featuring the words "The New York Times" in a black, gothic-style serif font.

Surviving Covid-19 May Not Feel Like Recovery for Some

Debilitating symptoms can last long after a person's body has gotten rid of the coronavirus, a reality Italians are now confronting.

The logo for NPR, featuring the letters "n", "p", and "r" in white, lowercase, sans-serif font, each inside a colored square (red, black, and blue respectively).

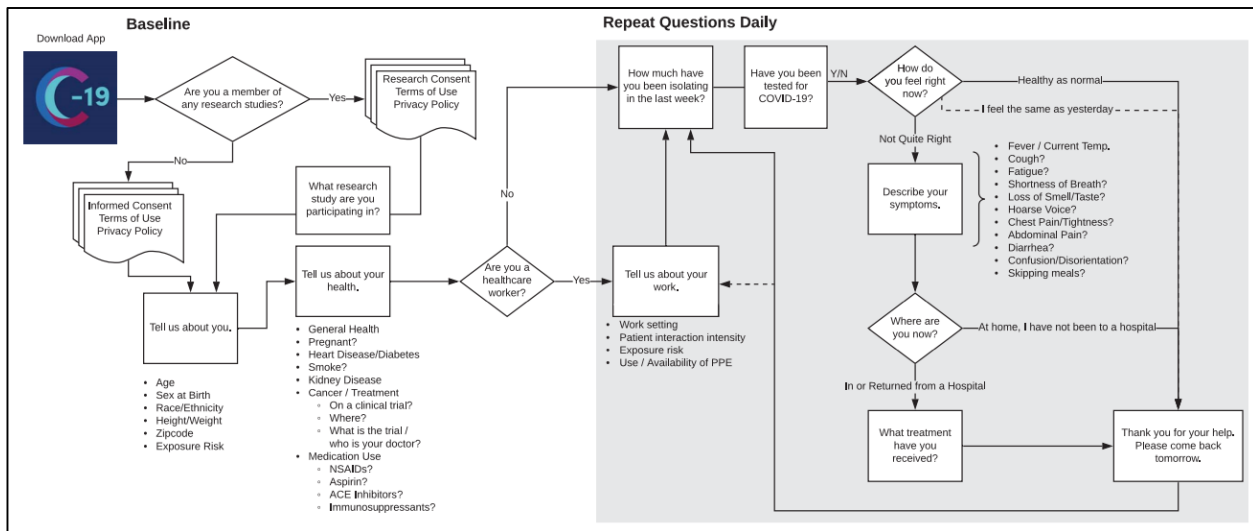
PRESS PLAY WITH MADELEINE BRAND

Think COVID-19 lasts 2 weeks? This patient has been suffering for months

Hosted by Madeleine Brand • Jul. 24, 2020 CORONAVIRUS

Rapid implementation of mobile technology for real-time epidemiology of COVID-19

David A. Drew^{1*}, Long H. Nguyen^{1*}, Claire J. Steves^{2,3}, Cristina Menni², Maxim Freydin², Thomas Varsavsky⁴, Carole H. Sudre⁴, M. Jorge Cardoso⁴, Sebastien Ourselin⁴, Jonathan Wolf⁵, Tim D. Spector^{2,5†}, Andrew T. Chan^{1,6†‡}, COPE Consortium[§]

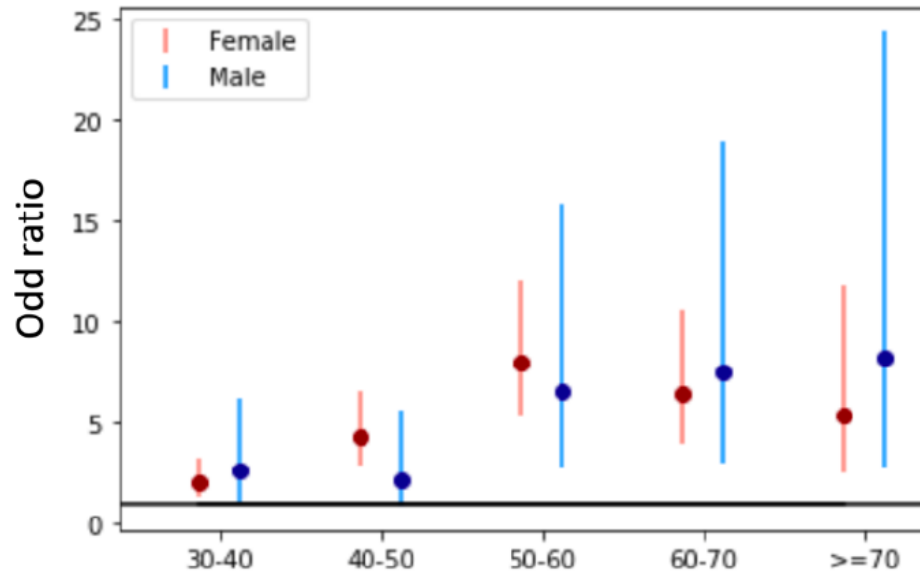


- The COVID Symptom Study uses an app into which over 4 million of people in the US, UK and Sweden have entered their symptoms
- 4182 incident cases (all self-described as “normal” prior to infection)
 - Symptoms > 4 weeks: 13.3%
 - Symptoms > 8 weeks: 4.5%
 - Symptoms > 12 weeks: 2.3%

Carole H. Sudre^{1,2,3}, Benjamin Murray³, Thomas Varsavsky³, Mark S. Graham³, Rose S. Penfold⁴, Ruth C. Bowyer⁵, Joan Capdevila Pujol⁵, Kerstin Klaser³, Michela Antonelli³, Liane S. Canas³, Erika Molteni³, Marc Modat³, M. Jorge Cardoso³, Anna May⁵, Sajaysurya Ganesh⁵, Richard Davies⁵, Long H Nguyen⁶, David A. Drew⁶, Christina M. Astley⁷, Amit D. Joshi⁶, Jordi Merino^{8,9,10}, Neli Tsereteli¹¹, Tove Fall¹², Maria F. Gomez¹¹, Emma L. Duncan⁴, Cristina Menni⁴, Frances M.K. Williams⁴, Paul W. Franks^{4,11}, Andrew T. Chan⁶, Jonathan Wolf⁵, Sebastien Ourselin^{3,8}, Tim Spector^{4,8}, Claire J. Steves^{4,8*}

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Comparator group: Age 20-30

- Predictors of long-COVID (> 28 days) versus transient disease (< 10 days)
 - Sex (female)
 - Age
 - Symptomatic acute infection (> 5 sx): OR 3.53
 - BMI
- Free text: late delay of cardiac and neurologic symptoms

What are the long-term sequelae?

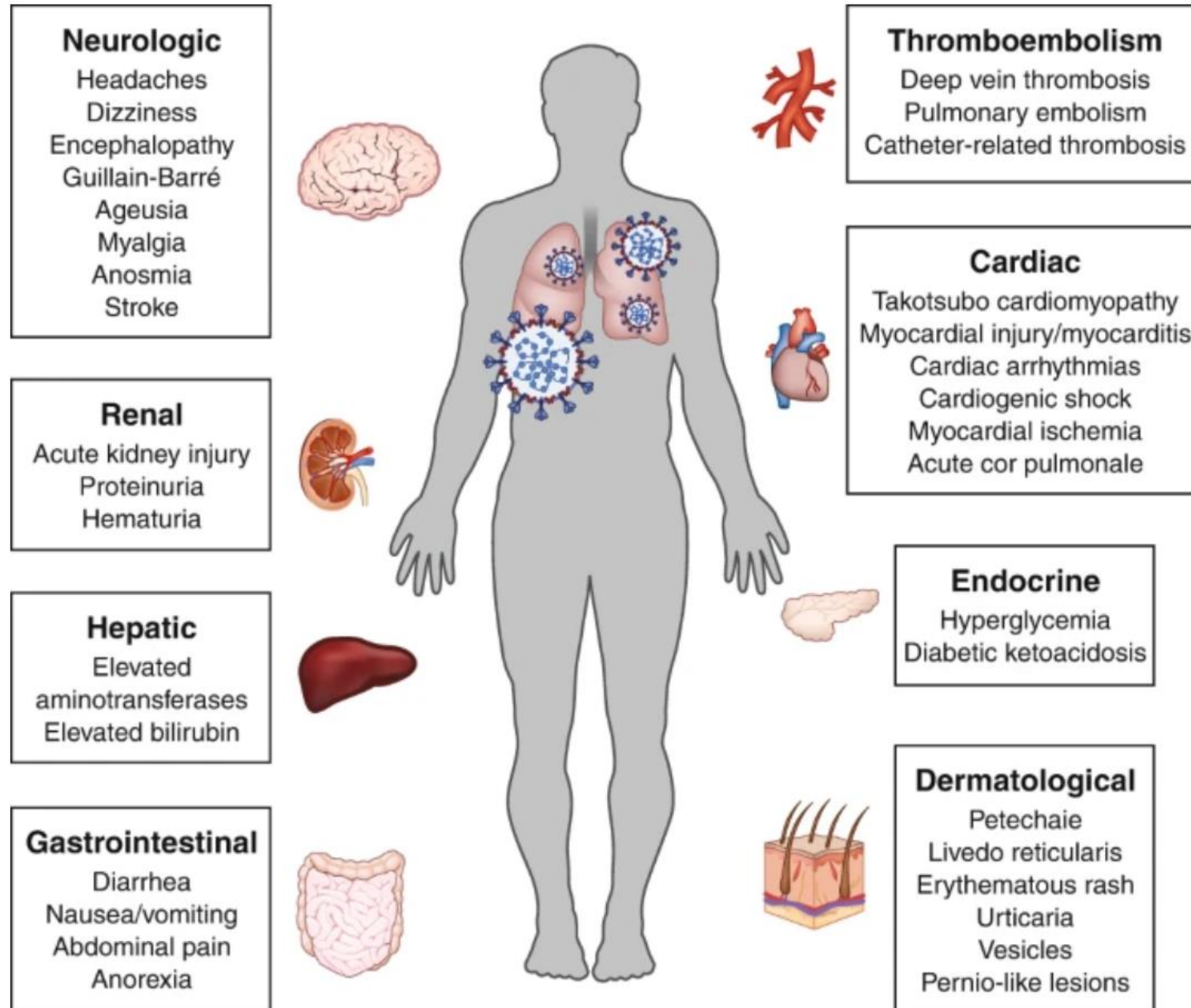
The COVID Symptom Study

Six Emerging Clusters

1. ('flu-like' with no fever): Headache, loss of smell, muscle pains, cough, sore throat, chest pain, no fever
2. ('flu-like' with fever): Headache, loss of smell, cough, sore throat, hoarseness, fever, loss of appetite
3. (gastrointestinal): Headache, loss of smell, loss of appetite, diarrhea, sore throat, chest pain, no cough
4. (severe level one, fatigue): Headache, loss of smell, cough, fever, hoarseness, chest pain, fatigue
5. (severe level two, confusion): Headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain
6. (severe level three, abdominal and respiratory): Headache, loss of smell, loss of appetite, cough, fever, hoarseness, sore throat, chest pain, fatigue, confusion, muscle pain, shortness of breath, diarrhea, abdominal pain

Extrapulmonary manifestations of COVID-19

Aakriti Gupta^{1,2,3,20}, Mahesh V. Madhavan^{1,2,20}, Kartik Sehgal^{4,5,6,20}, Nandini Nair⁷, Shiwani Mahajan^{3,8}, Tejasav S. Sehwat⁹, Behnood Bikhdeli^{1,2,3}, Neha Ahluwalia¹⁰, John C. Ausiello⁷, Elaine Y. Wan¹, Daniel E. Freedberg¹¹, Ajay J. Kirtane², Sahil A. Parikh^{1,2}, Mathew S. Maurer¹, Anna S. Nordvig¹², Domenico Accili⁷, Joan M. Bathon¹³, Sumit Mohan^{14,15}, Kenneth A. Bauer^{4,6}, Martin B. Leon^{1,2}, Harlan M. Krumholz^{3,8,16}, Nir Uriel¹, Mandeep R. Mehra¹⁷, Mitchell S. V. Elkind^{12,15}, Gregg W. Stone^{2,18}, Allan Schwartz¹, David D. Ho¹⁹, John P. Bilezikian⁷ and Donald W. Landry¹⁴✉



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

Valentina O. Puntmann, MD, PhD; M. Ludovica Carerj, MD; Imke Wieters, MD; Masia Fahim; Christophe Arendt, MD; Jędrzej Hoffmann, MD; Anastasia Shchendrygina, MD, PhD; Felicitas Escher, MD; Mariuca Vasa-Nicotera, MD; Andreas M. Zeiher, MD; Maria Vehreschild, MD; Eike Nagel, MD

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

Diana Lindner, PhD; Antonia Fitzek, MD; Hanna Bräuninger, MS; Ganna Aleshcheva, PhD; Caroline Edler, MD; Kira Meissner; Katharina Scherschel, PhD; Paulus Kirchhof, MD; Felicitas Escher, MD; Heinz-Peter Schultheiss, MD; Stefan Blankenberg, MD; Klaus Püschel, MD; Dirk Westermann, MD

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

- **Recent “severe” infection (n=100, median 71 days post-recovery): Most (78%) had abnormal cardiac MR findings, including active myocarditis (60%) and tissue damage (fibrosis)**
- **Endomyocardial biopsy: Active lymphocytic inflammation**
- **Autopsy study: Viral RNA in cardiomyocytes**
- **Myocarditis reported in 15% of college athletes (many with mild/asymptomatic disease)**

The New York Times

Opinion

Covid-19 Is Creating a Wave of Heart Disease

Emerging data show that some of the coronavirus’s most potent damage is inflicted on the heart.

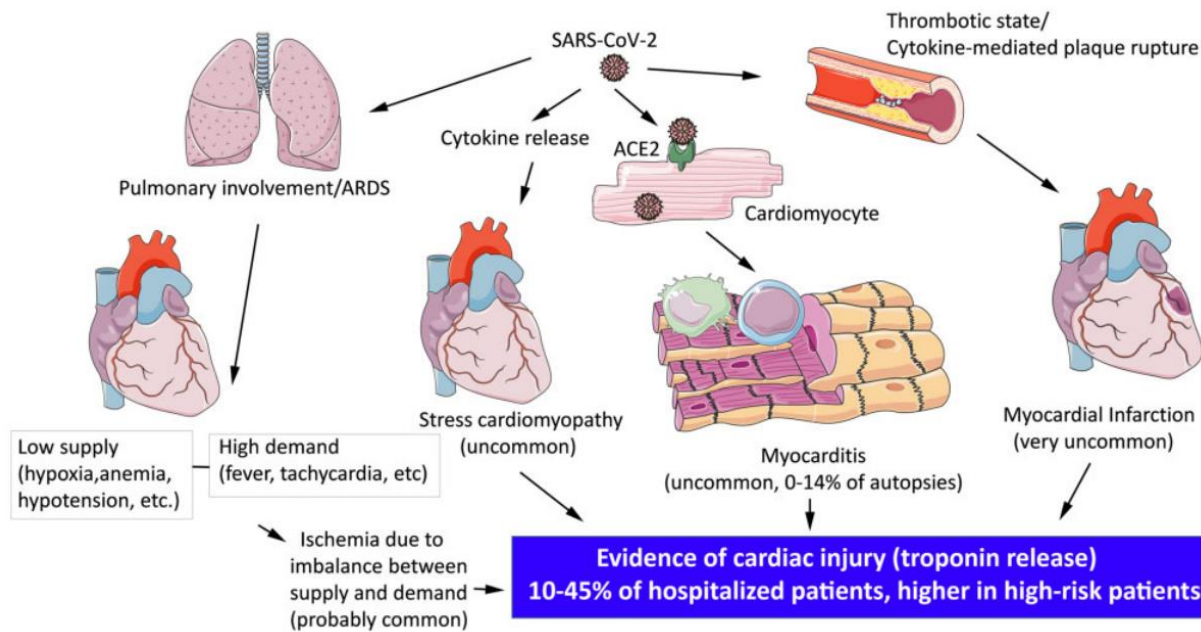
By Haider Warraich
Dr. Warraich is a cardiologist.

Pathological features of COVID-19-associated myocardial injury: a multicentre cardiovascular pathology study

Cristina Basso ^{1†}, Ornella Leone ^{2†}, Stefania Rizzo ¹, Monica De Gaspari¹, Allard C. van der Wal³, Marie-Christine Aubry⁴, Melanie C. Bois ⁴, Peter T. Lin ⁴, Joseph J. Maleszewski ⁴, and James R. Stone ^{5*}

The significance of COVID-19-associated myocardial injury: how overinterpretation of scientific findings can fuel media sensationalism and spread misinformation

Nikolaos G. Frangogiannis ^{*}



Autopsy study (n=21): Macrophage infiltration common, myocarditis/thrombi rare

Myocardial injury (troponin leak) common (10-45% of cases)

Most cardiovascular harm may be related to supply/demand, in contrast to early reports that SARS-CoV-2 infection “ravages the heart”

Long-term impact of COVID on heart is unknown

Pulmonary sequelae



Lung scans from a 50-year-old show that damage from COVID-19 (red) can improve with time — but many patients have lasting symptoms.

- Symptoms/signs of restrictive lung disease common among those who had been hospitalized
 - 30d = 53% decreased DLCO, 49% diminished respiratory muscle strength
 - 3mo = 25% decreased DLCO
 - 3mo = 71% with radiographic evidence of interstitial thickening and fibrosis

COVID-19 and the brain

- Severe COVID-19 infection triggers a complex inflammatory response that may result in cytokine storm syndrome, stroke, hypoxia, and/or delirium (Cohran et al, Brain Behav Imm)
- Past pandemics have demonstrated that diverse types of neuropsychiatric symptoms, such as encephalopathy, mood changes, psychosis, neuromuscular dysfunction, or demyelinating processes, may accompany acute viral infection, or may follow infection by weeks, months, or longer in recovered patients

Does COVID-19 cause diabetes?

- Diabetes is associated with an increased risk of severe COVID-19
- Incident diabetes mellitus (DKA, hyperosmolar coma) and acute worsening variably reported to be common in those with acute infection
- ACE2 receptors are present on pancreatic islet cells, adipose tissue and the small intestine
- Is there a “diabetogenic” effect of COVID-19?
 - CoviDIAB Registry: covid diab.e-dendrite.com

**What are the putative mechanisms
that might contribute to this
syndrome?**

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

Diana Lindner, PhD^{1,2}; Antonia Fitzek, MD³; Hanna Bräuninger, MS^{1,2}; [et al](#)



Unspecific post-mortem findings despite multiorgan viral spread in COVID-19 patients

[Myriam Rimmelink](#), [Ricardo De Mendonça](#), [Nicky D'Haene](#), [Sarah De Clercq](#), [Camille Verocq](#), [Laetitia Lebrun](#), [Philomène](#)



Neuroinvasion of SARS-CoV-2 in human and mouse brain

Song E, ... Iwasaki A. 2020.

Viral RNA can be detected in autopsy tissues weeks after acute infection

Longitudinal analyses reveal immunological misfiring in severe COVID-19

<https://doi.org/10.1038/s41586-020-2588-y>

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 Check for updates

Carolina Lucas^{1,7}, Patrick Wong^{1,7}, Jon Klein^{1,7}, Tiago B. R. Castro^{2,17}, Julio Silva¹, Maria Sundaram³, Mallory K. Ellingson³, Tianyang Mao¹, Ji Eun Oh¹, Benjamin Israelow^{1,4}, Takehiro Takahashi¹, Maria Tokuyama¹, Peiwen Lu¹, Arvind Venkataraman¹, Annsea Park¹, Subhasis Mohanty⁴, Haowei Wang⁴, Anne L. Wyllie³, Chantal B. F. Vogels³, Rebecca Earnest³, Sarah Lapidus³, Isabel M. Ott³, Adam J. Moore³, M. Catherine Muenker³, John B. Fournier⁴, Melissa Campbell⁴, Camila D. Odio⁴, Arnau Casanovas-Massana³, Yale IMPACT Team*, Roy Herbst⁵, Albert C. Shaw⁴, Ruslan Medzhitov^{1,6}, Wade L. Schultz^{7,8}, Nathan D. Grubaugh³, Charles Dela Cruz⁹, Shelli Farhadian⁴, Albert I. Ko^{3,4}, Saad B. Omer^{3,4,10} & Akiko Iwasaki^{1,6}✉


Sex differences in immune responses that underlie COVID-19 disease outcomes

<https://doi.org/10.1038/s41586-020-2700-3>

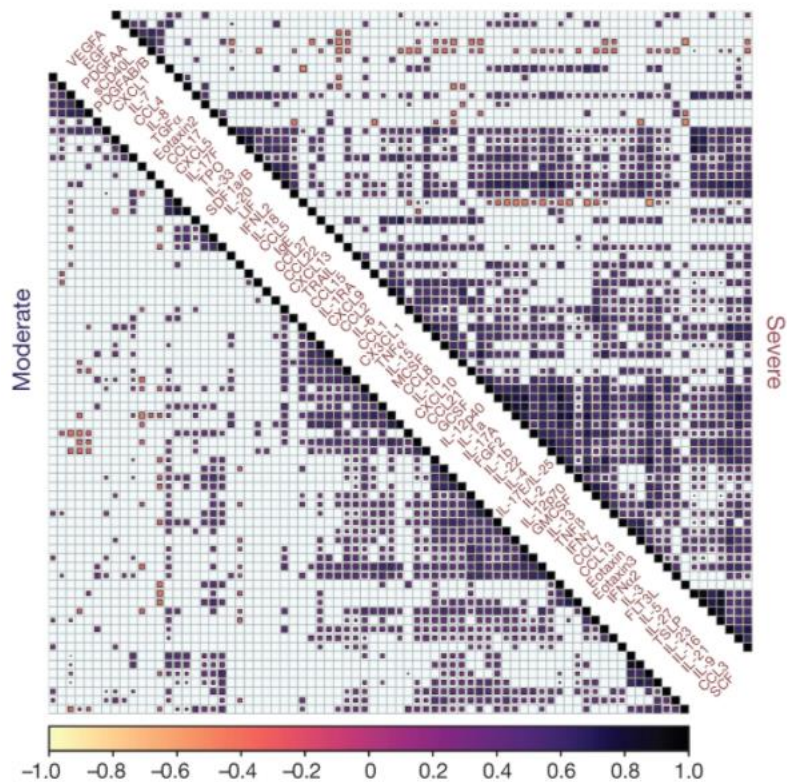
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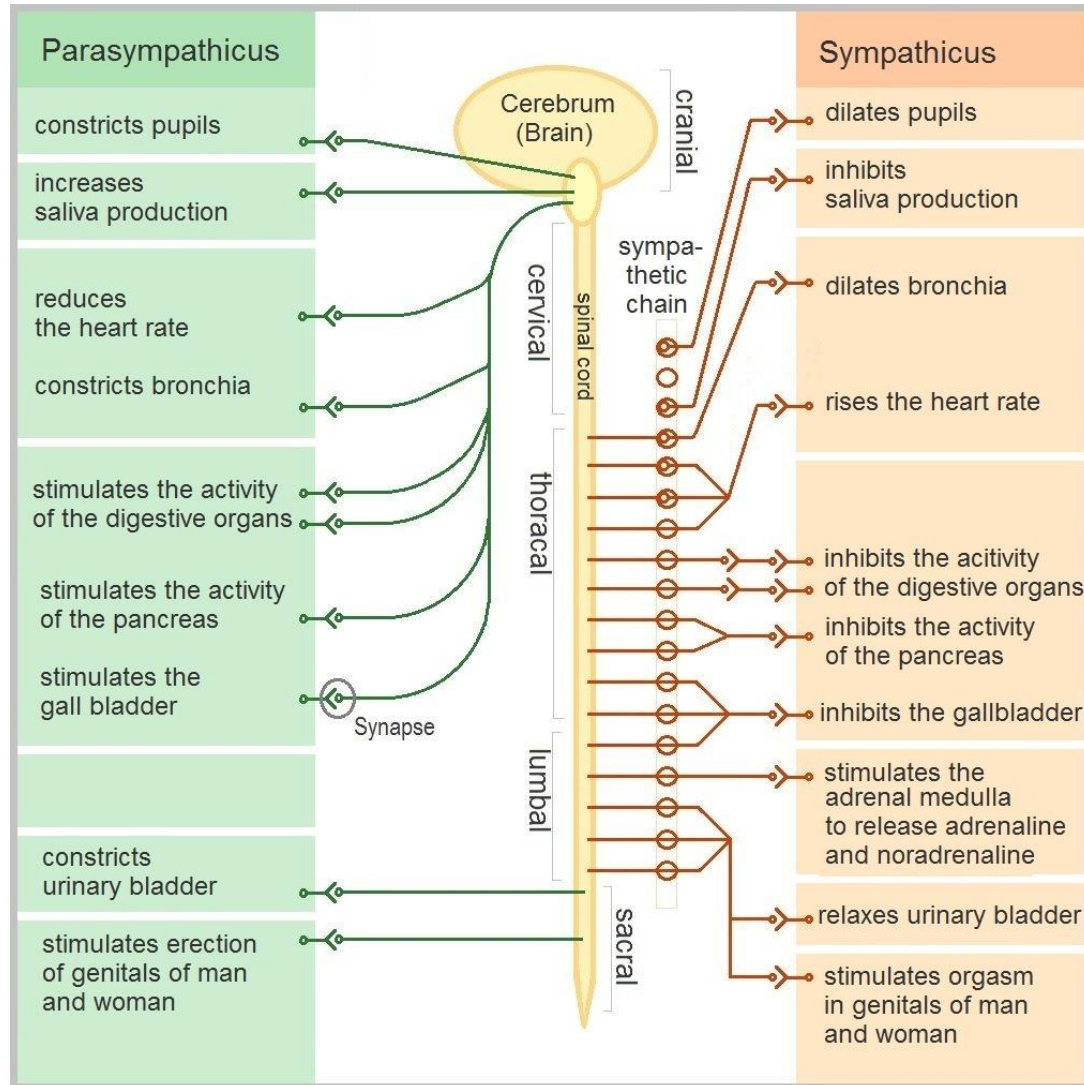
Takehiro Takahashi^{1,21}, Mallory K. Ellingson^{2,21}, Patrick Wong^{1,21}, Benjamin Israelow^{1,3,21}, Carolina Lucas^{1,21}, Jon Klein^{1,21}, Julio Silva^{1,21}, Tianyang Mao^{1,21}, Ji Eun Oh¹, Maria Tokuyama¹, Peiwen Lu¹, Arvind Venkataraman¹, Annsea Park¹, Feimei Liu^{1,4}, Amit Meir⁵, Jonathan Sun⁶, Eric Y. Wang¹, Arnau Casanovas-Massana², Anne L. Wyllie², Chantal B. F. Vogels², Rebecca Earnest², Sarah Lapidus², Isabel M. Ott^{2,7}, Adam J. Moore², Yale IMPACT Research Team*, Albert Shaw³, John B. Fournier³, Camila D. Odio³, Shelli Farhadian³, Charles Dela Cruz⁸, Nathan D. Grubaugh², Wade L. Schultz^{9,10}, Aaron M. Ring¹, Albert I. Ko², Saad B. Omer^{2,3,11,12} & Akiko Iwasaki^{1,13}✉



Endothelial injury

- Endothelium: single cell layer of cells that covers pro-thrombotic connective tissue
 - ACE2 levels high on endothelial cells
- Vicious circle of injury and reaction leading to microvascular thrombosis
 - Pre-existing disease: diabetes, hypertension and other common COVID risk factors
 - Direct infection: target for SARS-CoV-2 infection
 - Inflammation: release of multiple pro-coagulant factors (VWF, others)
- Consequences: small vessel ischemia (digit necrosis), strokes, cardiovascular events

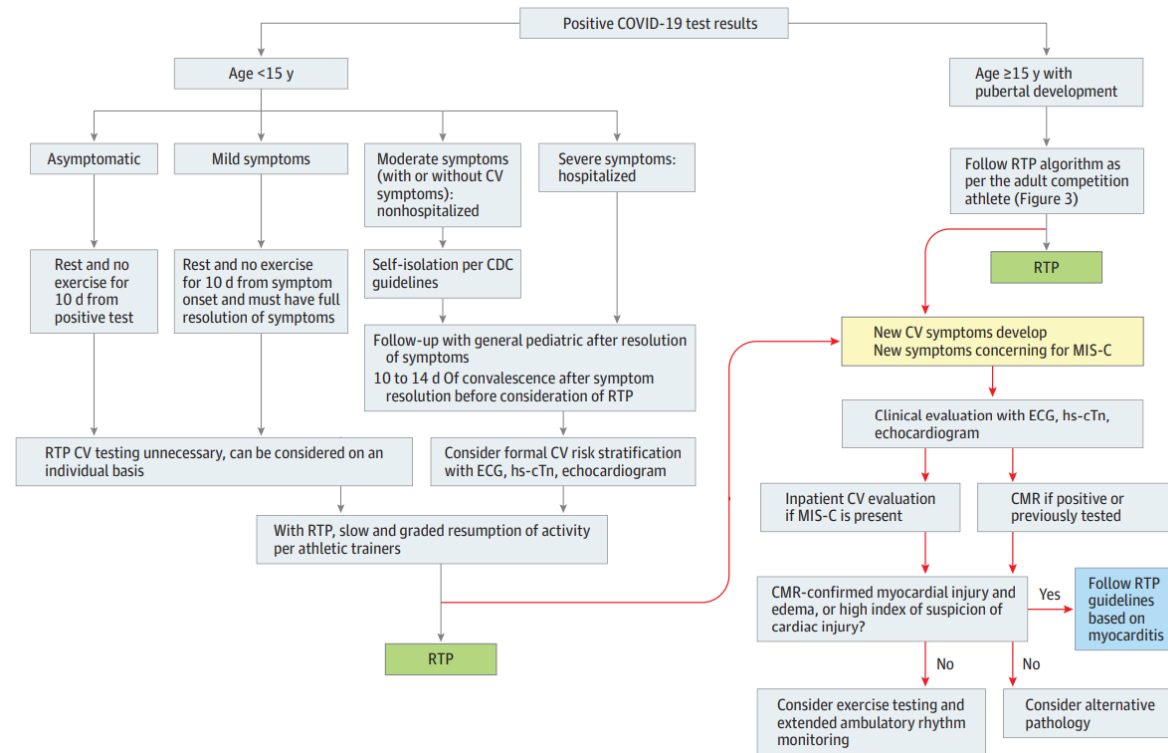
Dysautonomia (autonomic nervous system dysfunction) might explain multiple symptoms



**How should these complications
be managed?**

Coronavirus Disease 2019 and the Athletic Heart Emerging Perspectives on Pathology, Risks, and Return to Play

Jonathan H. Kim, MD, MSc; Benjamin D. Levine, MD; Dermot Phelan, MD, PhD; Michael S. Emery, MD, MS; Mathew W. Martinez, MD; Eugene H. Chung, MD, MSc; Paul D. Thompson, MD; Aaron L. Baggish, MD



Return to Play for Athletes After Coronavirus Disease 2019 Infection— Making High-Stakes Recommendations as Data Evolve

James E. Udelson, MD; Michael A. Curtis, MEd, CSCS; Ethan J. Rowin, MD

- Complex algorithms published for high school athletes, adult engaged in recreational sports, and professional athletes
- Slow escalation of activity recommended for those with mild COVID and no CV symptoms
- Aggressive work-up (ECG, troponins, echocardiogram) for those with CV symptoms (particularly syncope), progressing to CMR as needed

"Long covid" in primary care

Assessment and initial management of patients with continuing symptoms

Post-acute covid-19 appears to be a multi-system disease, sometimes occurring after a relatively mild acute illness. Clinical management requires a whole-patient perspective. This graphic summarises the assessment and initial management of patients with delayed recovery from an episode of covid-19 that was managed in the community or in a standard hospital ward.

An uncertain picture



The long term course of covid-19 is unknown. This graphic presents an approach based on evidence available at the time of publication.

However, caution is advised, as patients may present atypically, and new treatments are likely to emerge.

Managing comorbidities

Many patients have comorbidities including diabetes, hypertension, kidney disease or ischaemic heart disease. These need to be managed in conjunction with covid-19 treatment. Refer to condition specific guidance, available in the associated article by Greenhalgh and colleagues.

Safety netting and referral

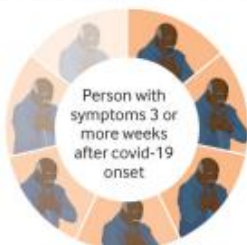
The patient should seek medical advice if concerned, for example:

- Worsening breathlessness
- PaO₂ < 96%
- Unexplained chest pain
- New confusion
- Focal weakness

Specialist referral may be indicated, based on clinical findings, for example:

- Respiratory** if suspected pulmonary embolism, severe pneumonia
- Cardiology** if suspected myocardial infarction, pericarditis, myocarditis or new heart failure
- Neurology** if suspected neurovascular or acute neurological event.

Pulmonary rehabilitation may be indicated if patient has persistent breathlessness following review.



Person with symptoms 3 or more weeks after covid-19 onset

Clinical assessment

Full history
From date of first symptom

Current symptoms
Nature and severity

Examination, for example:

- Temperature
- Heart rate and rhythm
- Blood pressure
- Respiratory examination
- Functional status
- Pulse oximetry
- Clinical testing *if indicated*

Medical management

- Symptomatic, such as treating fever with paracetamol
- Optimise control of long term conditions
- Listening and empathy
- Consider antibiotics for secondary infection
- Treat specific complications as indicated

Self management

- Daily pulse oximetry
- Attention to general health
- Rest and relaxation
- Self pacing and gradual increase in exercise **if tolerated**
- Set achievable targets

Social, financial, and cultural support

Prolonged covid-19 may limit the ability to engage in work and family activities. Patients may have experienced family bereavements as well as job losses and consequent financial stress and food poverty. See the associated article by Greenhalgh and colleagues for a list of external resources to help with these problems.

Mental health

- In the consultation:**
 - Continuity of care
 - Avoid inappropriate medicalisation
 - Longer appointments for patients with complex needs (face to face if needed)
- In the community:**
 - Community linkworker
 - Patient peer support groups
 - Attached mental health support service
 - Cross-sector partnerships with social care, community services, faith groups

Investigations

Clinical testing is not always needed, but can help to pinpoint causes of continuing symptoms, and to exclude conditions like pulmonary embolism or myocarditis. Examples are provided below:

Blood tests

- Full blood count
- Electrolytes
- Liver and renal function
- Troponin
- C reactive protein
- Creatine kinase
- D-dimer
- Brain natriuretic peptides
- Ferritin – to assess inflammatory and prothrombotic states

Other investigations

- Chest x ray
- Urine tests
- 12 lead electrocardiogram

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PRACTICE POINTER

Management of post-acute covid-19 in primary care

Trisha Greenhalgh,¹ Matthew Knight,² Christine A'Court,¹ Maria Buxton,³ Laiba Husain¹

The establishment of one-stop clinics that address the the multisystem nature of COVID-19 are emerging, providing patients with access to support and potentially treatment, as well as becoming a critical infrastructure for understanding the nature of this syndrome

Planning for the Post-COVID Syndrome: How Payers Can Mitigate Long-Term Complications of the Pandemic

David H. Jiang, B.A.¹  and Rozalina G. McCoy, M.D., M.S.^{1,2}

Long-term Sequelae of COVID-19

Post-COVID syndrome, long COVID, long haulers

- Limited peer-reviewed data focused on the occurrence or prevalence of COVID-19–related long-term sequelae
 - Most of the agenda driven by anecdotes and media stories
 - Publication bias likely real
- Reasonable to anticipate manifestations based on established knowledge of SARS-CoV-2 pathophysiology, other acute viral infection outcomes
 - Entry receptor ACE2 expressed across extrapulmonary tissue
 - Inflammation
 - Hypercoagulability and clotting
- Among patients recovering from severe SARS-CoV or MERS-CoV infection, long-term complications were not uncommon
- Although there was initial skepticism, the consensus now seems to be that this is real and will need to be addressed