Post-COVID Syndrome

Marissa M. Alejandria, MD, MSc, FPCP, FPSMID

University of the Philippines

College of Medicine

Disclosures

- No financial disclosures related to this presentation

Outline

- Definitions
- Prevalence and symptoms
- Risk Factors
- Pathophysiology
- Management

There are many terms used to refer to Post-COVID Syndrome

Long COVID – Commonly used

Post-COVID Condition(s) – CDC and WHO

Post-Acute Sequelae of SARS-CoV-2 (PASC) – NIH terminology

Post-acute COVID-19

Long-term effects of COVID

Post-acute COVID syndrome

Chronic COVID

Long-haul COVID

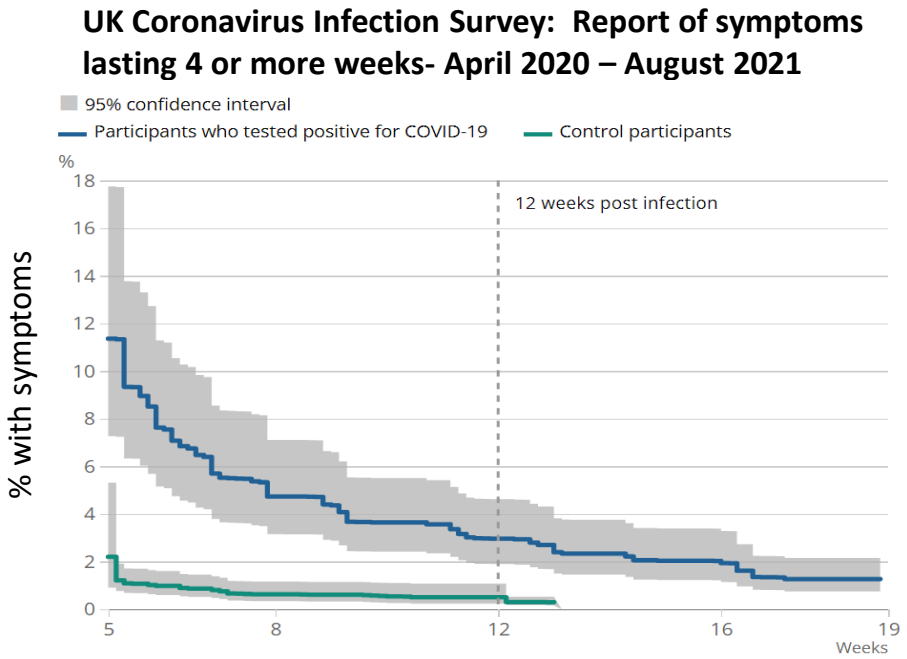
Late sequelae

Definitions: Post COVID-19 Condition (PCC)

Broad	• lack of return to a usual state of health following acute COVID-19 illness.
WHO (October 2021)	• PCC occurs in individuals with **a history of probable or confirmed SARS- CoV-2** infection, **usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.** • Common symptoms: **fatigue, shortness of breath, cognitive dysfunction** and generally have an **impact on everyday functioning.** • Symptoms may be **new onset** following initial recovery from an acute COVID-19 episode or **persist** from the initial illness. • Symptoms may also **fluctuate** or **relapse** over time.
CDC	• umbrella term for the wide range of physical and mental health consequences that can be present **four or more weeks** after infection with SARS-CoV-2 (**new, returning or ongoing symptoms**)

Duration of post-COVID conditions can vary

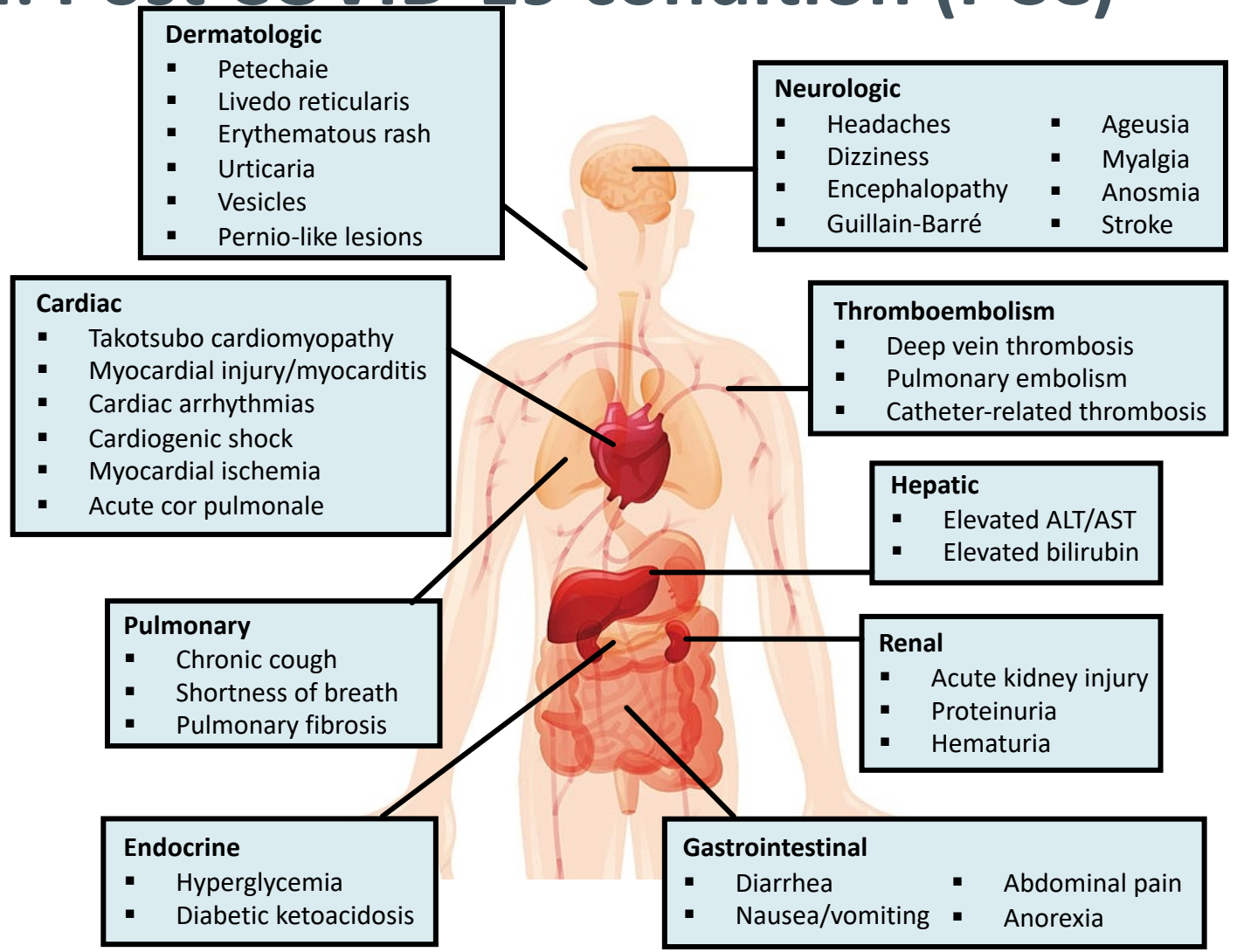
- Most patients recover in 4 weeks and the proportion reporting symptoms decreases between 4-12 weeks
- Improvement slows around 12 weeks after infection
- Majority of cases are self-limited and resolve or improve in 3-6 months
- Prolonged relapsing symptoms may last > 6 months
- Women and men follow same pattern, but more women report symptoms



Source: Office for National Statistics - Coronavirus Infection Survey

Harmonized definition: Post COVID-19 condition (PCC)

- **New symptoms** that affect everyday function, emerge within 4 wk to 3 mo after first being infected and **last for at least 2 months**
  - Symptoms may fluctuate over time
  - Overlap with prolonged symptoms post hospitalization
  - Cannot be explained by an alternative diagnosis



www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1.
www.cdc.gov/coronavirus/2019-ncov/long-term-effects/index.html.

Slide credit: clinicaloptions.com

Core Outcome Set for Adults with Post COVID-19 Condition

Physiological or clinical outcomes

1 Cardiovascular functioning, symptoms, and conditions
2 Fatigue or exhaustion
3 Pain
4 Nervous system functioning, symptoms, and conditions
5 Cognitive functioning, symptoms, and conditions
6 Mental functioning, symptoms, and conditions
7 Respiratory functioning, symptoms, and conditions
8 Post-exertion symptoms

Life impact outcomes

9 Physical functioning, symptoms, and conditions
10 Work or occupational and study changes

Survival

11 Survival

Outcome from previous COS

12 Recovery*

Munblit D, et al
Lancet Respir Med 2022; 10: 715–24

Challenges in understanding Post Covid Conditions

- Includes a wide range of physical and mental health consequences experienced by some patients
  - Spectrum of physical, social, and psychological consequences
  - Conditions are heterogenous and attributable to different underlying pathophysiologic processes
- Studies include different patient populations
- Assessments of occurrence of symptoms and conditions are done at varying time points following acute infection, often only once
- Many studies do not include control groups
- Severity and impact of symptoms on quality of life or daily activities not consistently reported

Prevalence varies widely

- Self- reported symptoms range from 13.3% at ≥ 1 month to 2.5% at ≥ 3 months
- Based on electronic health data
  - Of non-hospitalized adults with COVID-19, 7.7% experienced one or more of 10 identified late-onset conditions 1 to 4 months post infection
  - Frequency of at least one symptom at 6 months differs by severity of acute COVID:
    - Overall: 73.4/1,000 patients
    - Non-hospitalized: 44.5/1,000 patients
    - Hospitalized: 217.1/1,000 patients
      - ICU: 360.5/1,000 patients

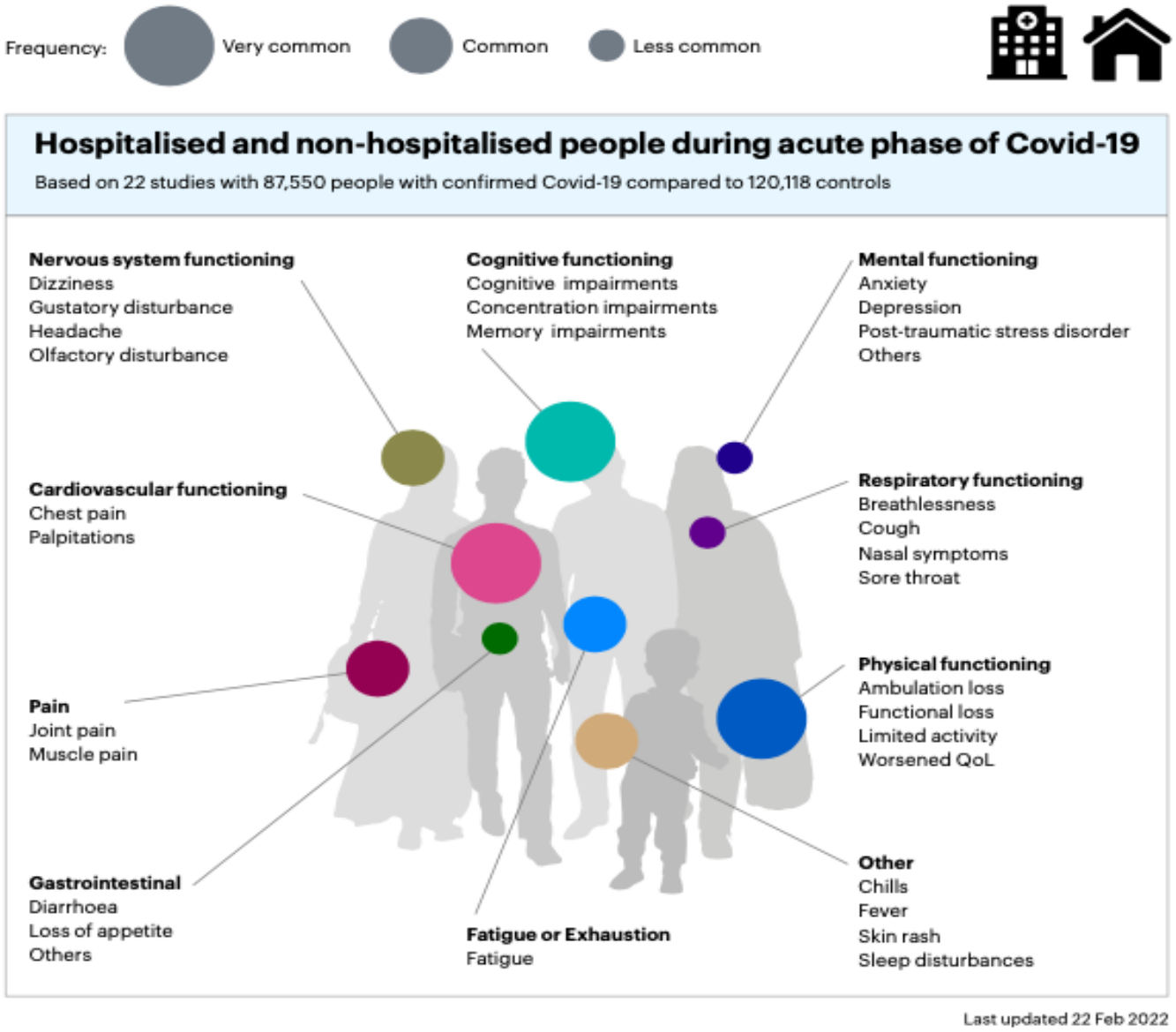
Sudre CH et al Nature Medicine 27, 626-631 (2021)
Chevinsky JR et al. Clinical Infectious Diseases 73 (S1) 2021
Xie Y et al. Nature Communications 12, 6571 (2021)

Characterizing Long Covid: a living systematic review update with controlled studies

- 28 studies included up to Feb 2022: 20 cohort, 5 case-controls, 3 cross-sectional
- With at least 100 people with confirmed or clinically diagnosed COVID; with onset of symptoms reported at an average of 12 weeks or more post COVID
- 242,715 with Covid-19 and 276,317 controls in 16 countries; 56% female
- Most were of moderate quality (71%). Only 2 in LMIC countries and few included children (18%).
- Longest mean follow-up time: 419.8 (SD 49.4) days post-diagnosis.
- COVID-19 infection is associated with increased risk (RR 1.53, 95% CI: 1.50 to 1.56) of experiencing persistent or new symptoms that can last for a year or more compared with controls

Michelin M, et al. Posted Aug 2022 medRxiv

Long Covid symptoms and signs



Core outcomes with highest increased risk:

Cardiovascular (RR 2.53 95% CI: 2.16 to 2.96)

Cognitive (RR 1.99; 95% CI: 1.82 to 2.17)

Physical functioning (RR 1.85; 95% CI: 1.75 to 1.96)

Michelin M, et al. Posted Aug 2022 medRxiv

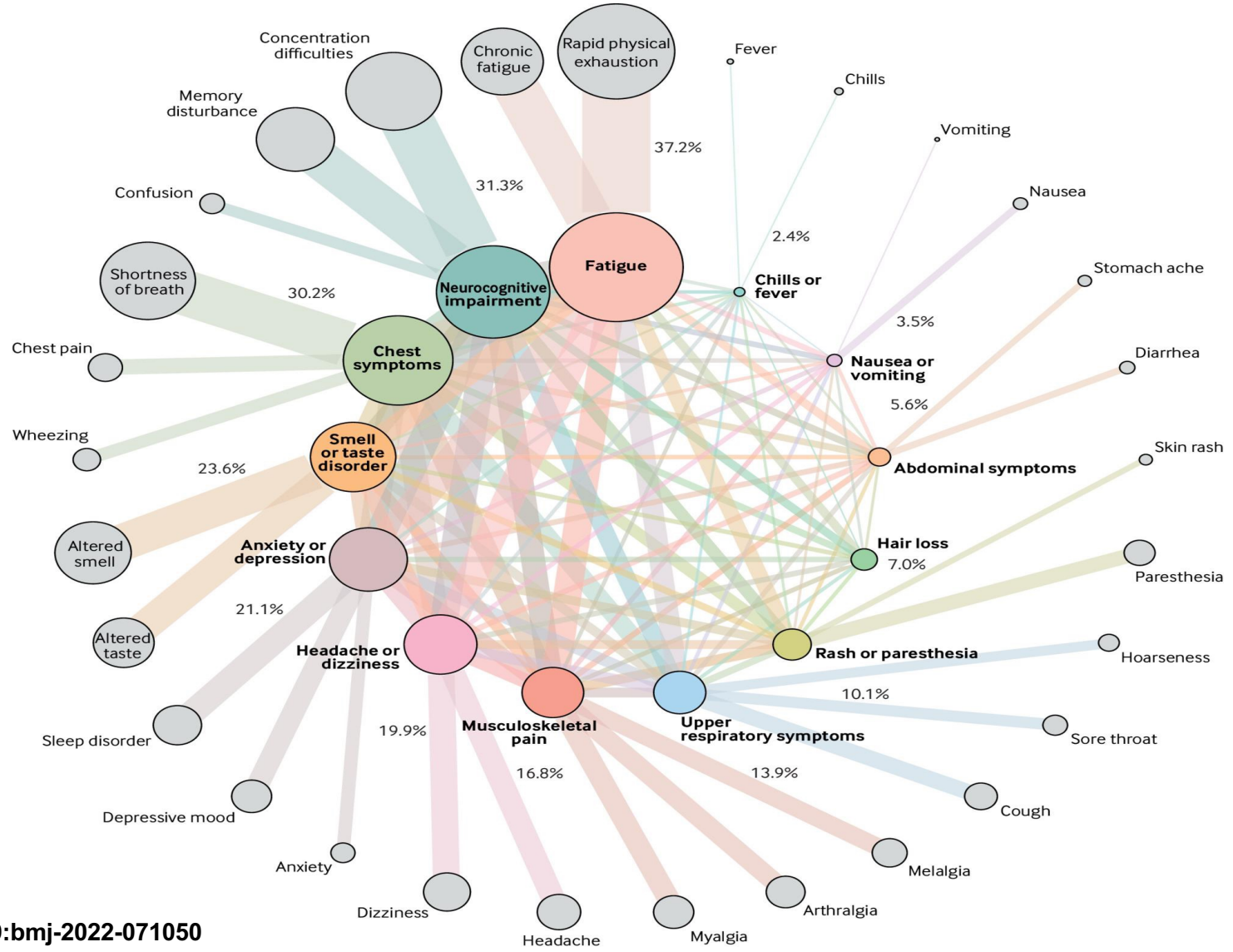
Post-acute sequelae of covid-19 six to 12 months after infection: population-based study

- Adults 18-65 years with confirmed SARS-CoV-2 infection between October 2020 and March 2021 in 4 regions in southern Germany.
- N=11, 710 participants; 58.8% female; mean age 44.1 years; 3.6% previously admitted with covid-19; mean follow-up time 8.5 months
- New symptom clusters: **fatigue, neurocognitive impairment, chest symptoms, smell or taste disorder, and anxiety/depression** persist beyond six to 12 months after acute SARS-CoV-2 infection
- The three most frequent clusters (fatigue, neurocognitive impairment, chest symptoms) often interfere with daily life and activities and often co-occur
- Long term smell and taste disorders are reported relatively independently of other complaints

Raphael S Peter et al. BMJ 2022;379:bmj-2022-071050

thebmj

Co-occurrence network of symptom clusters 6-12 months after acute infection.

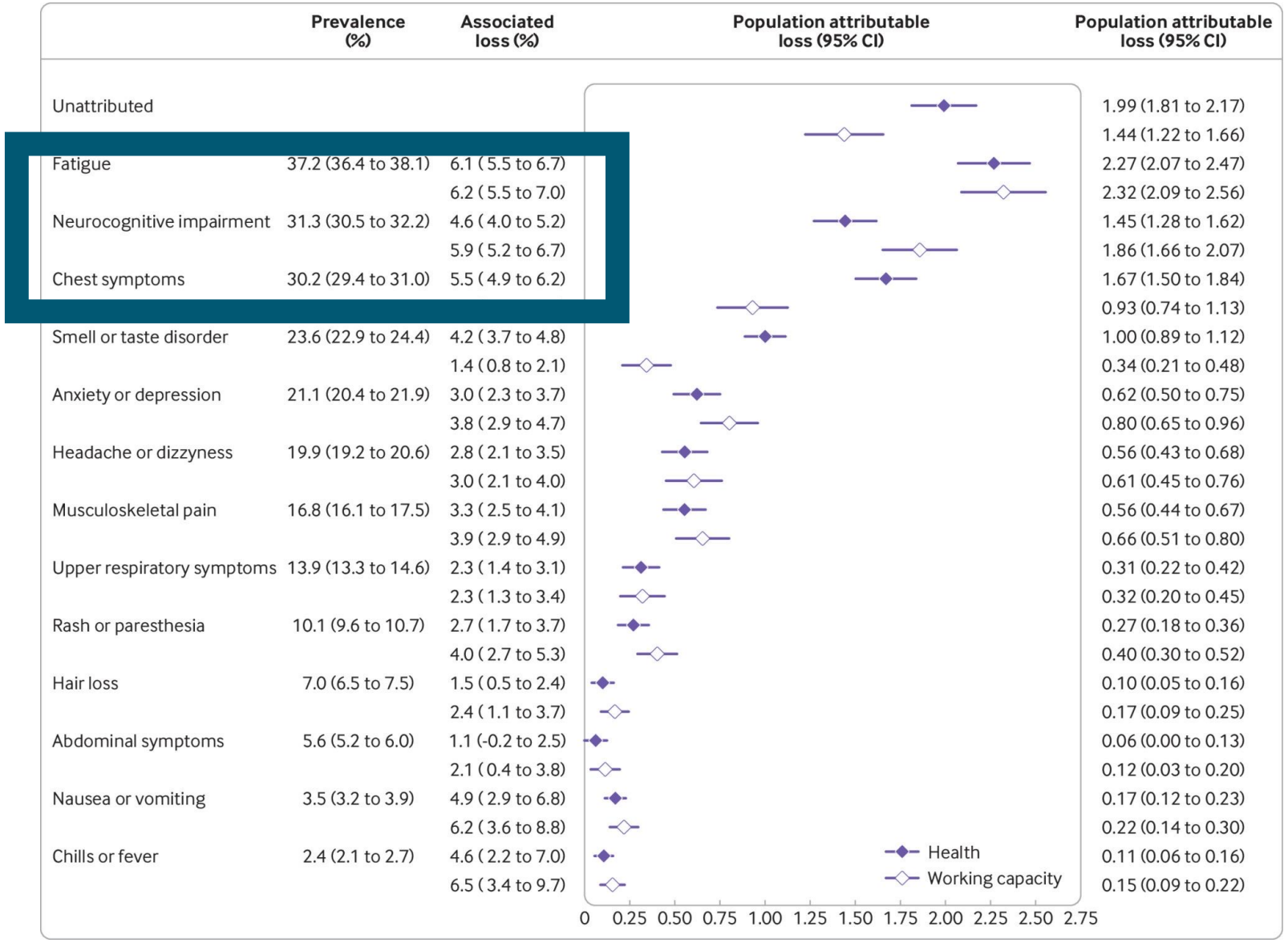


Raphael S Peter et al. BMJ 2022;379:bmj-2022-071050

Prevalence of symptom clusters 6-12 months after acute infection and associated loss (%) and population attributable loss (%) of general health and working capacity

N=10 268
Average **overall loss of general health 11.5%,** 95% CI 11.2% to 11.7%

N=10 324
Average **overall loss of working capacity 10.7%,** 95% CI 10.4% to 11.0%

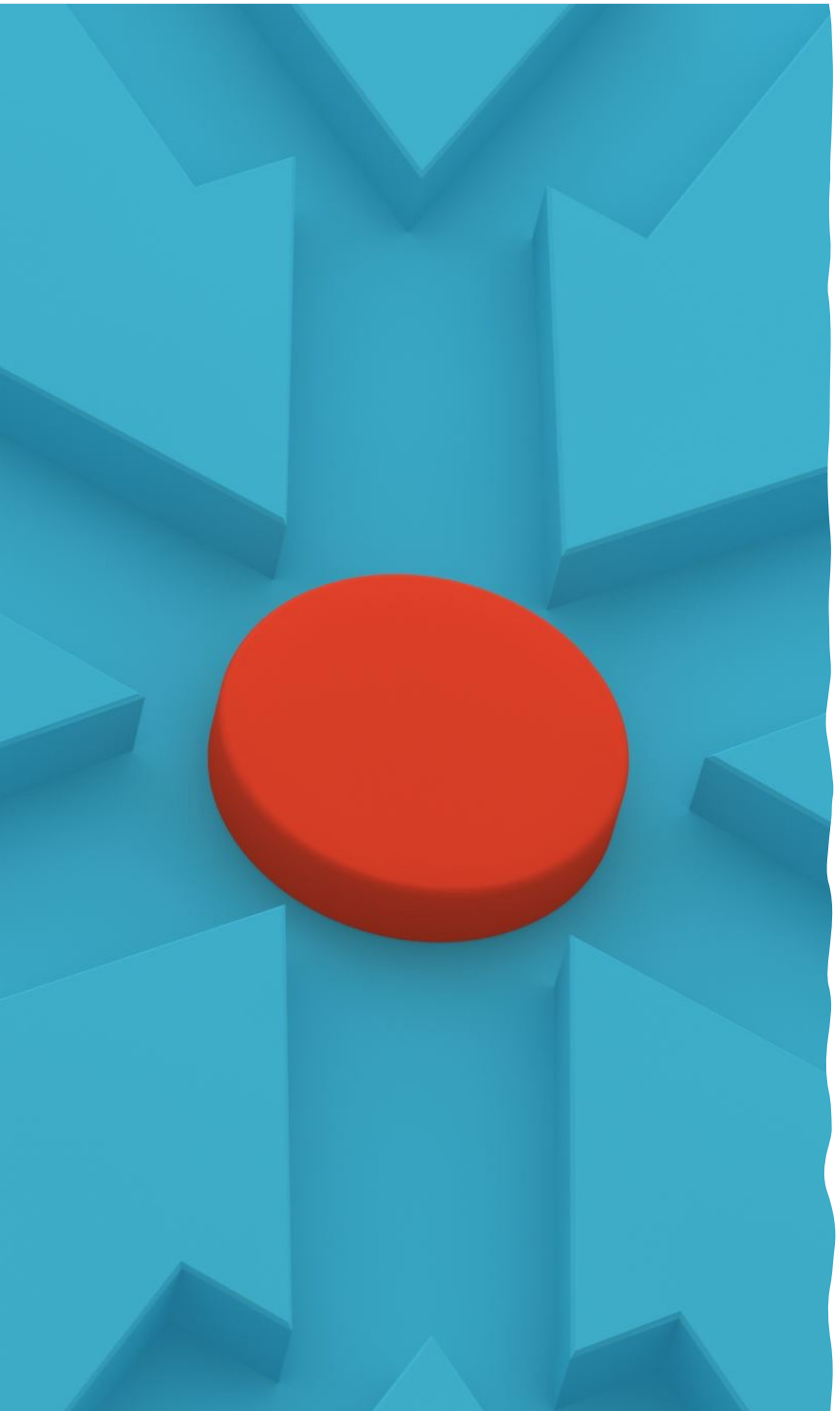


Raphael S Peter et al. BMJ 2022;379:bmj-2022-071050

Focus on cognitive symptoms

- Often described as "**brain fog**" by patients
  – Includes difficulty thinking clearly and concentrating, forgetfulness, and memory loss
- The most common impairments reported are in:
  - **Memory: 92.2%**
  - **Attention: 76.5%**
  - Fluency: 29.4%
  - Executive Function: 25%
- Frequently reported in post-COVID studies of both **hospitalized** and **non- hospitalized patients**
  – 18% moderate to severely ill (including hospitalized) reported cognitive symptoms, 9% mildly ill
  – 25% report cognitive symptoms at 1 year follow-up
  – Cognitive deficits in 18% after 1 year (more among hospitalized)

1.Caspersen et al. European Journal of Epidemiology 2022
2.Rass et al. European Journal of Neurology 2022



Risk Factors

Factors associated with an increased occurrence of post-COVID conditions

- Severity of initial infection
- Female sex
- Pre-existing conditions – DM, heart/lung disease, obesity, mental health disorders, multimorbidity
- Older age
  - Increased occurrence among older adults compared to younger adults
  - Increased occurrence among adults compared to children
- Infection without evidence of vaccination
  - Lower occurrence among adults with infection after vaccination

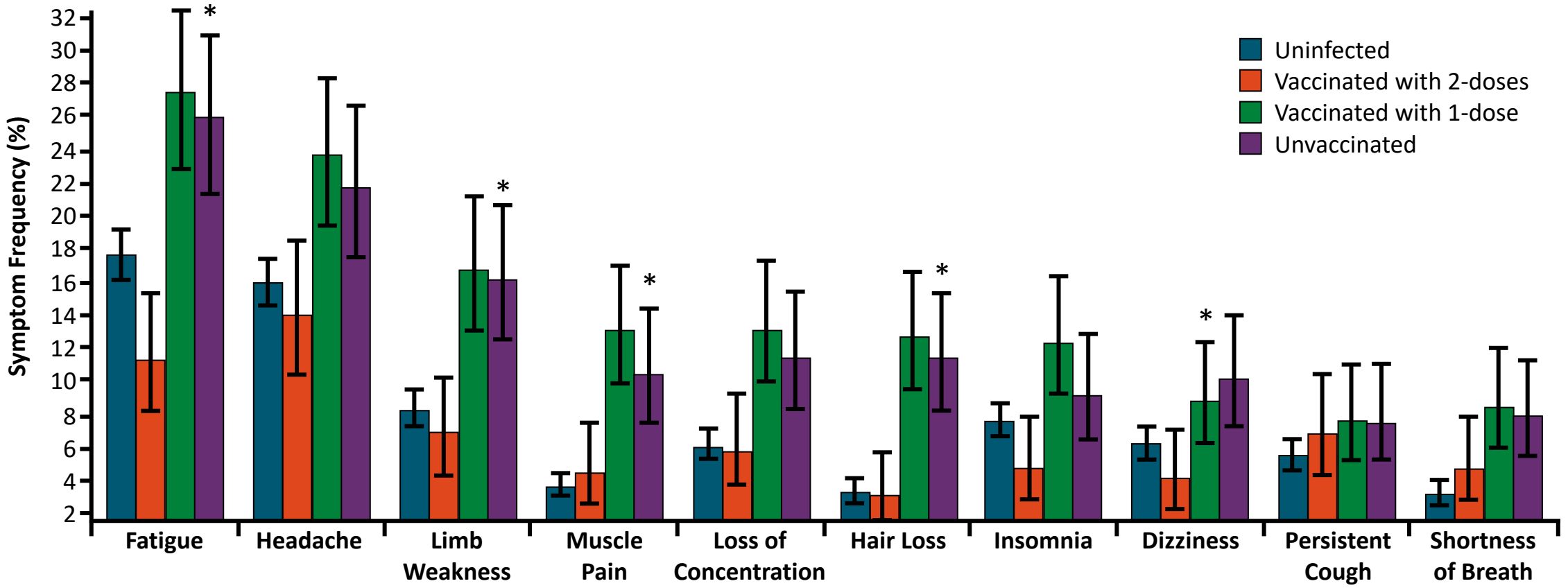
1Thompson et al. medRxiv doi: 10.1101/2021.06.24.21259277
2Koudi et al. medRxiv doi: 10.1101/2022.01.05.22268800
3 Raphael S Peter et al. BMJ 2022;379:bmj-2022-071050

Post-COVID conditions may occur after vaccine breakthrough infections

- Study of infections after vaccination among healthcare workers in Israel found vaccine breakthrough cases were generally mild or asymptomatic, but **19% (7/36) had persistent symptoms at >6 weeks** in the setting of alpha variant
- UK Case–Control Study (n=906, 1:1 match): individuals with infections after vaccination are **less likely to report** prolonged symptoms (**≥ 28 days**) compared to persons who are unvaccinated (**OR 0.51, 95% CI 0.32, 0.82**)
- US Dept of Veterans Affairs database: Compared to people with SARS-CoV-2 infection who were not previously vaccinated (n = 113,474), people with BTI had lower risks of death (HR = 0.66, 95% CI: 0.58, 0.74) and incident post-acute sequelae (HR = 0.85, 95% CI: 0.82, 0.89).
- **Vaccines prevent post-COVID conditions by decreasing transmission**, and lower the occurrence of post-COVID conditions in persons with infection after vaccination (who tend to have milder infections) than infections in persons who are unvaccinated
  - Whether this association changes with the emergence of new variants is unknown

1.Bergwerk NEJM 2021
2.Antonelli Lancet ID 2021
3. Al-Aly Nature Medicine 2022

Symptom Frequency in Vaccinated and Unvaccinated Individuals



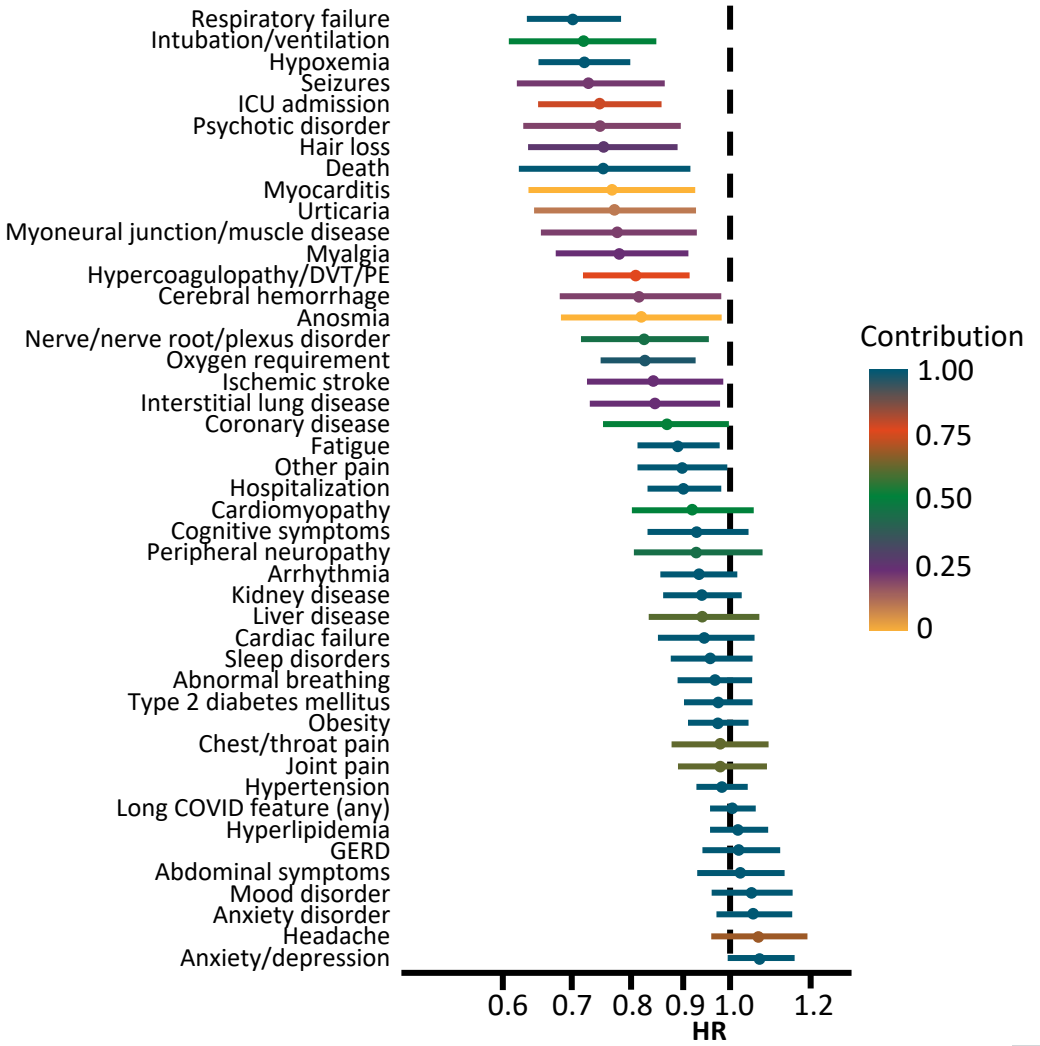
*Significantly less frequent among those vaccinated with two doses compared to those unvaccinated

Kuodi. medRxiv. 2022;[Preprint]. Note: this study has not been peer reviewed.

Slide credit: clinicaloptions.com

Long COVID and COVID-19 Vaccination

- Long COVID can occur after a breakthrough infection, but rates are consistently lower in vaccinated vs unvaccinated persons
- 2 doses of SARS-CoV-2 vaccine is protective against *some* postacute sequelae of COVID-19, but not all



Kuodi. medRxiv. 2022;[Preprint]. Note: this study has not been peer reviewed.
Taquet. medRxiv. 2021;[Preprint]. Note: this study has not been peer reviewed.

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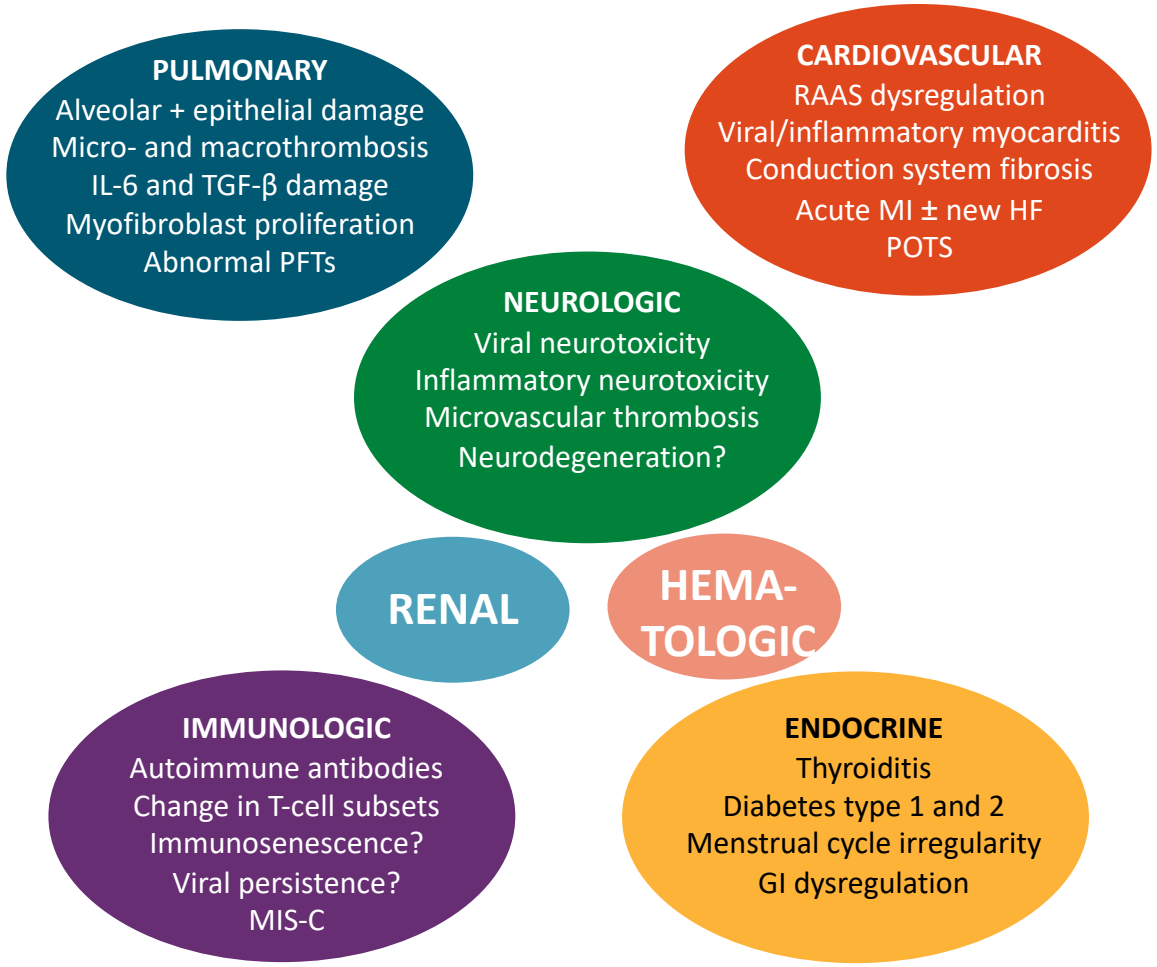
Pathophysiology

Potential Causes of Long COVID - Pathophysiology

- Direct neuro-invasion
- Dysregulated immune response
- Auto-inflammation
- Lingering virus in immunologically privileged sites
- Endothelial injury, ongoing endothelial dysfunction
- Post-ICU syndrome



Akselrod. IDWeek 2021. Chasing the Sun presentation.
www.sciline.org/covid-19/emerging-challenges/. Proal. Front Microbiol. 2021;12:698169.

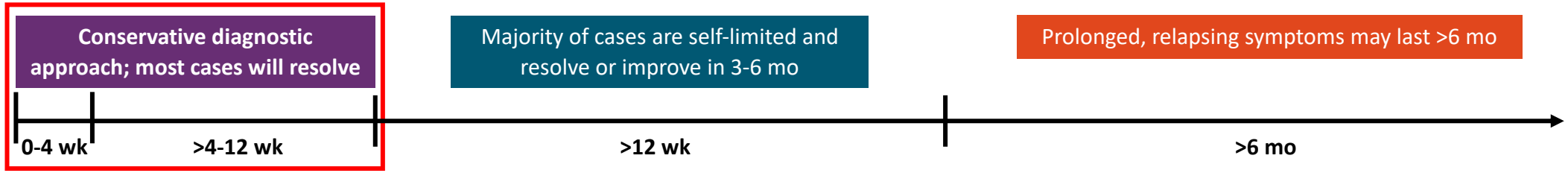
Slide credit: clinicaloptions.com

MARCO DI LAURO/GETTY

Management of Post COVID Conditions

Clinical Management of Long COVID

- Long COVID conditions can be managed by primary care providers
  - Patient-centered approaches to optimize QoL and function
- Laboratory values and imaging are not the only measure of a patient's well-being
  - Lack of abnormalities does not invalidate a patient's symptoms



- Set achievable goals via shared decision-making
  - Specific symptom amelioration
  - Management plan to improve physical, mental, and social well-being

www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-clinical-eval.html.
www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-management.html.

Slide credit: clinicaloptions.com

Table 1a. Basic diagnostic laboratory testing to consider for patients with post-COVID conditions

Category	Laboratory Tests
Blood count, electrolytes, and renal function	Complete blood count with possible iron studies to follow, basic metabolic panel, urinalysis
Liver function	Liver function tests or complete metabolic panel
Inflammatory markers	C-reactive protein, erythrocyte sedimentation rate, ferritin
Thyroid function	TSH and free T4
Vitamin deficiencies	Vitamin D, vitamin B12

Table 1b. Specialized diagnostic laboratory testing to consider for patients with post-COVID conditions

Category	Laboratory Tests
Rheumatological conditions	Antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide, anti-cardiolipin, and creatine phosphokinase
Coagulation disorders	D-dimer, fibrinogen
Myocardial injury	Troponin
Differentiate symptoms of cardiac versus pulmonary origin	B-type natriuretic peptide

Table 2a. Selected assessment tools for evaluating people with post-COVID conditions

Category	Tools
Functional status or quality of life	• Patient-Reported Outcomes Measurement Information System (PROMIS) (e.g., Cognitive Function 4a) • Post-Covid-19 Functional Status Scale (PCFS) • EuroQol-5D (EQ-5D)
Respiratory conditions	• Modified Medical Research Council (mMRC) Dyspnea Scale
Neurologic conditions	• Montreal Cognitive Assessment (MoCA) • Mini Mental Status Examination (MMSE) • Compass 31 (for dysautonomia) • Neurobehavioral Symptom Inventory
Psychiatric conditions	• Generalized Anxiety Disorder-7 (GAD-7) • Patient Health Questionnaire-9 (PHQ-9) • PTSD Symptom Scale (PSS) • Screen for Posttraumatic Stress Symptoms (SPTSS) • PTSD Checklist for DSM-5 (PCL-5) • Impact of Event Scale-Revised (IESR) • Hospital Anxiety and Depression Scale (HADS)
Other conditions	• Wood Mental Fatigue Inventory (WMFI) • Fatigue Severity Scale • Insomnia Severity Index (ISI) • Connective Tissue Disease Screening Questionnaire

Long COVID Treatments Under Consideration

- Investigational agents for long COVID
  - LYT-100
    - Deuterated pirfenidone
  - Leronlimab
    - CCR5 antagonist
  - LMWF5A
    - Anti-inflammatory peptide
  - SNG001
    - Inhaled interferon beta

- Currently available drugs being studied to treat long COVID
  - Budesonide (inhaled)
  - Colchicine
  - Fluvoxamine
  - Monoclonal antibodies
  - NSAIDS
  - SARS-CoV-2 vaccination
  - Sirolimus
  - Statins
  - Vitamin D

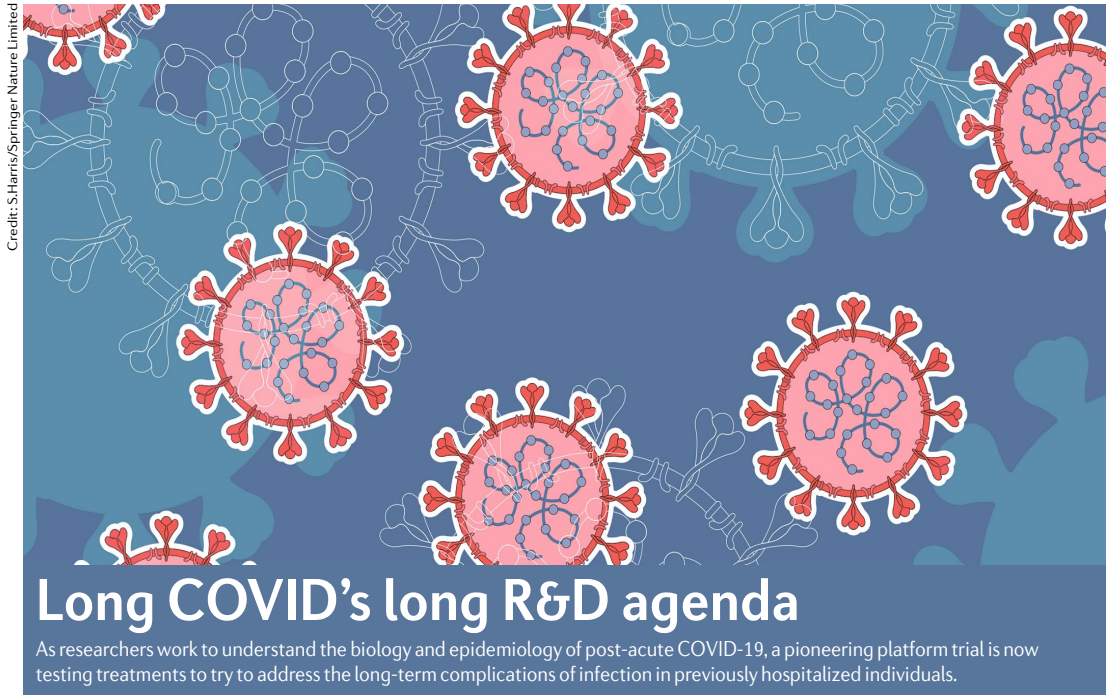
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8277229/

Slide credit: clinicaloptions.com

In the pipeline

HEAL-COVID will recruit and randomize 2,000 hospitalized COVID-19 survivors who are on track to be discharged. Volunteers will receive standard of care or one of three treatments.

- **Apixaban**, a factor Xa-inhibiting anticoagulant
- **Atorvastatin**, a lipid-lowering HMG-CoA reductase inhibitor with pleiotropic effects, might provide benefit by acting as an anti-thrombotic, an anti-inflammatory and by improving endothelial function.



Research on biomarkers, genetic and immune mechanisms

- **GINCO Cohort e-ASIA**

Preventing Long COVID

Protect yourself and others from becoming infected.

- Stay up to date with vaccines. Boost immunity with vaccines.
- Improve air quality by opening windows and using adequate filtration
- Wear mask in crowded areas
- Hand hygiene

Thank you!