Post-COVID Syndromes in Children

Tess Barton, MD, FAAP, CTropMed
Associate Professor
Pediatric Infectious Diseases

UT Health
San Antonio

Disclosures

I have no conflicts of interest to disclose

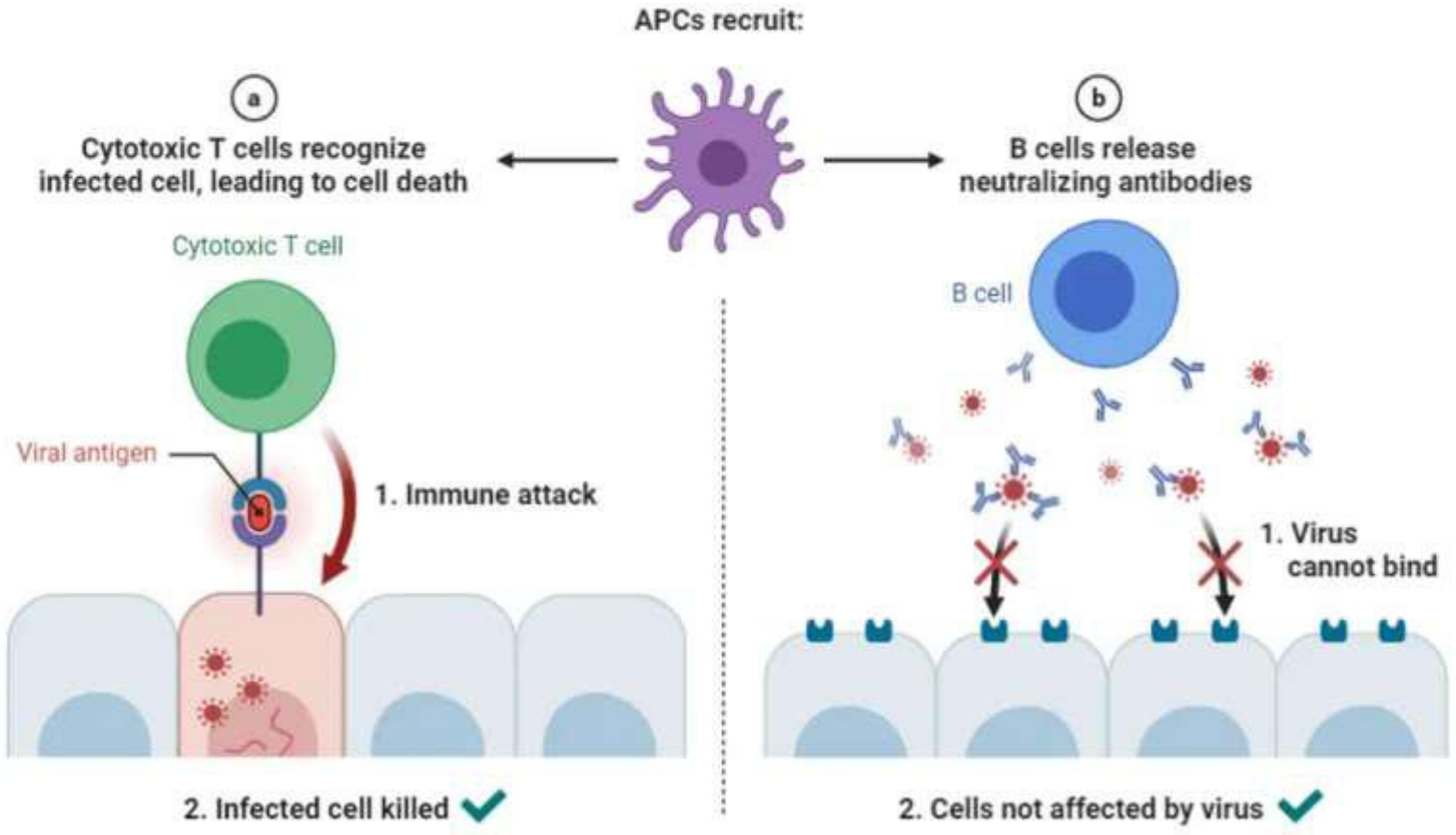
I am not a PM&R specialist, Cardiologist, Neurologist, Psychiatrist

I am (at best) an Adolescent Medicine dilettante

Objectives

- Describe the immune response to SARS CoV-2 virus, and its contribution to complication of COVID-19 illness.
- Review features of “Long COVID” syndrome.
- Identify strategies to facilitate recovery from post-viral syndromes.

Immune Response to SARS-CoV-2 Infection



Akiko Iwasaki, MD, https://app.biorender.com/biorender-templates/t-5f178d344f5fad00a7792332

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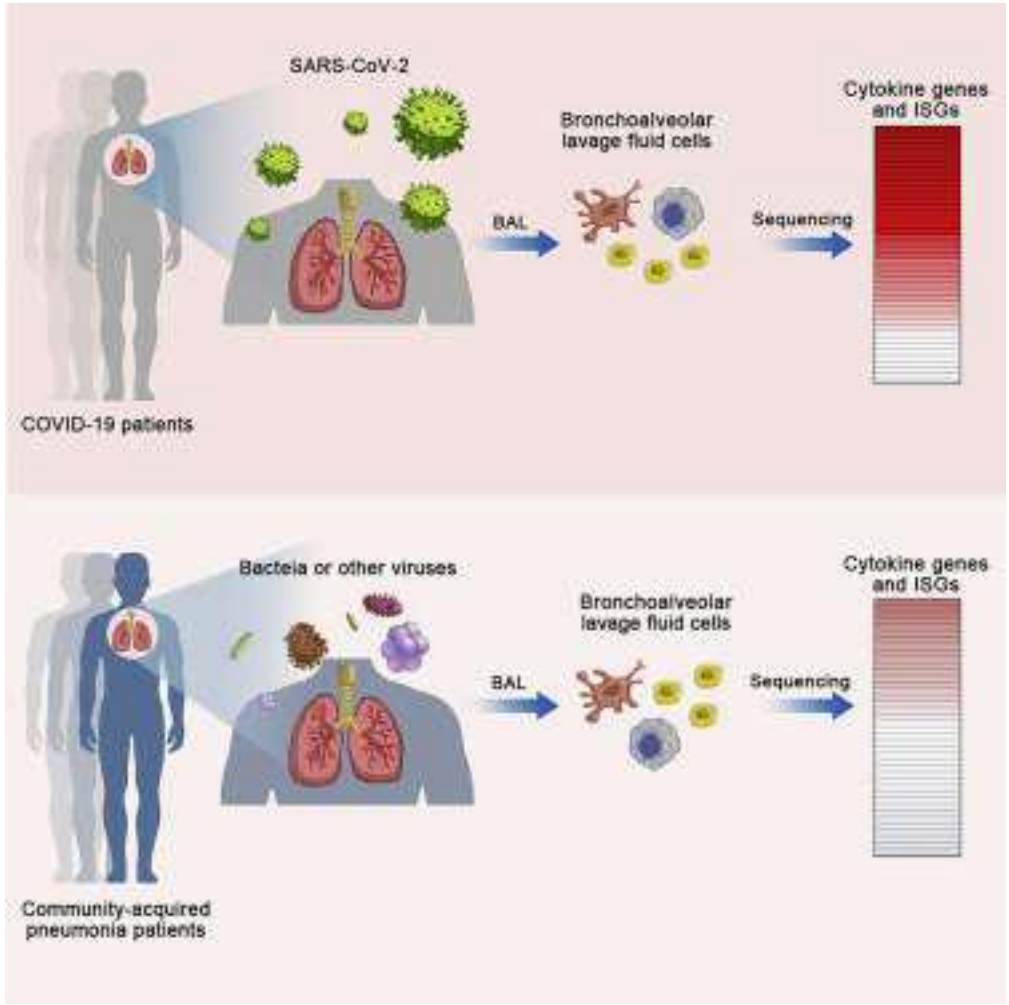
Immune Response to SARS-CoV-2 Infection



Zhou Z, et al. Heightened Innate Immune Responses in the Respiratory Tract of COVID-19 Patients. Cell Host Microbe. 2020 Jun 10;27(6):883-890.e2.

- Cytokine storm associated with severe respiratory disease
- Cellular immune responses (CD4+ lymphocytes) coordinate immune responses
  - Secrete cytokines
  - Down-regulation
- Persistent activation, or inappropriate responses, may lead to prolonged disease
- No evidence for persistent viral infection (or is there?)

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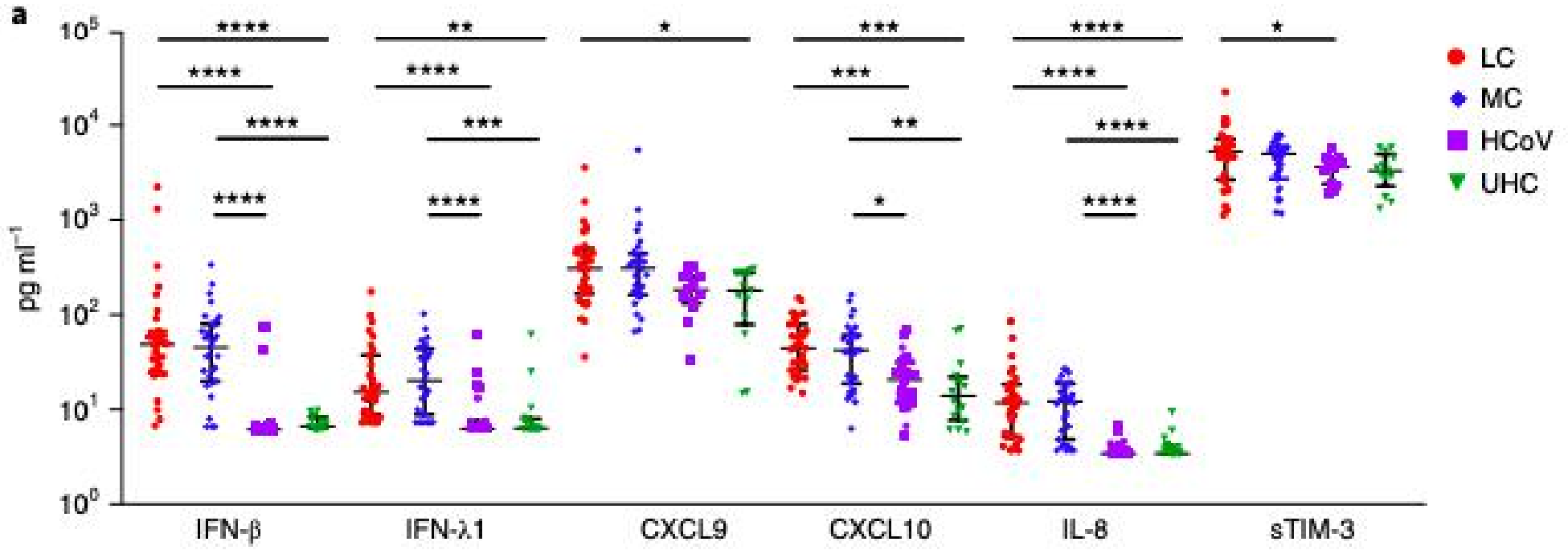
LETTERS
https://doi.org/10.1038/s41590-021-01113-x
nature immunology
Check for updates

Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection

Chansavath Phetsouphanh[1,7]✉, David R. Darley[2,7], Daniel B. Wilson[3], Annett Howe[1], C. Mee Ling Munier[1], Sheila K. Patel[4], Jennifer A. Juno[5], Louise M. Burrell[4], Stephen J. Kent[5,6], Gregory J. Dore[1,2], Anthony D. Kelleher[1,2,7]✉ and Gail V. Matthews[1,2,7]✉

LC = Long COVID
MC = COVID Asymptomatic matched controls
HCoV = Other coronaviruses
UHC = Unxeposed/uninfected



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 Feb;23(2):210-216.

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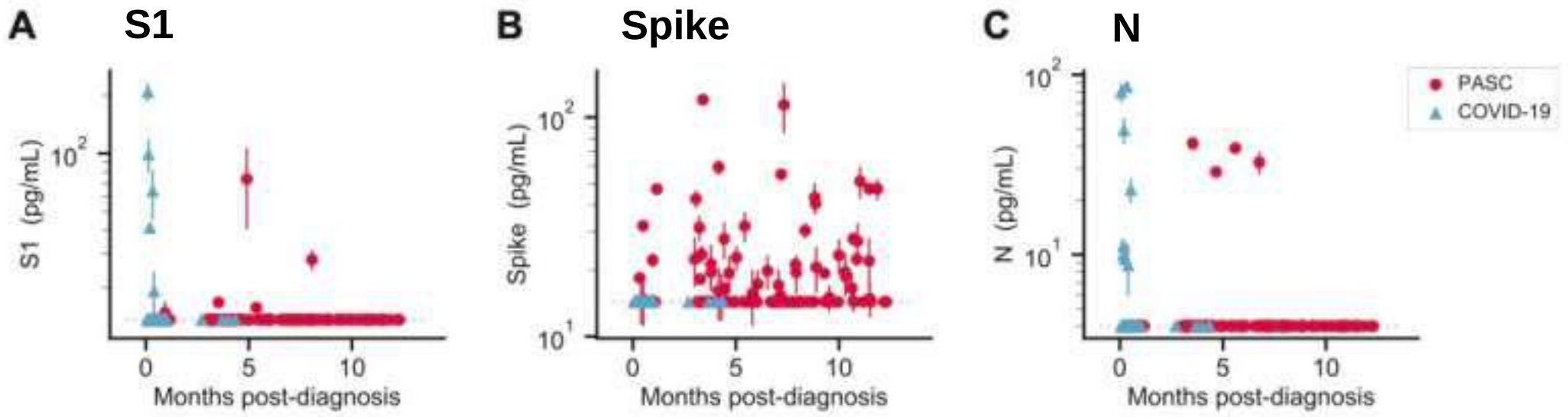
Persistence of SARS CoV-2 Antigens

60% of PASC subjects (n=63) vs. none of the non-PASC subjects (n=26) had detectable spike protein antigen ≥5 months after infection



Zoe Swank, Yasmeen Senussi, Galit Alter, David R. Walt. Persistent circulating SARS-CoV-2 spike is associated with post-acute COVID-19 sequelae medRxiv 2022.06.14.22276401; doi: https://doi.org/10.1101/2022.06.14.22276401

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Thromboembolic Complications

Myocarditis

Autoimmune Diseases

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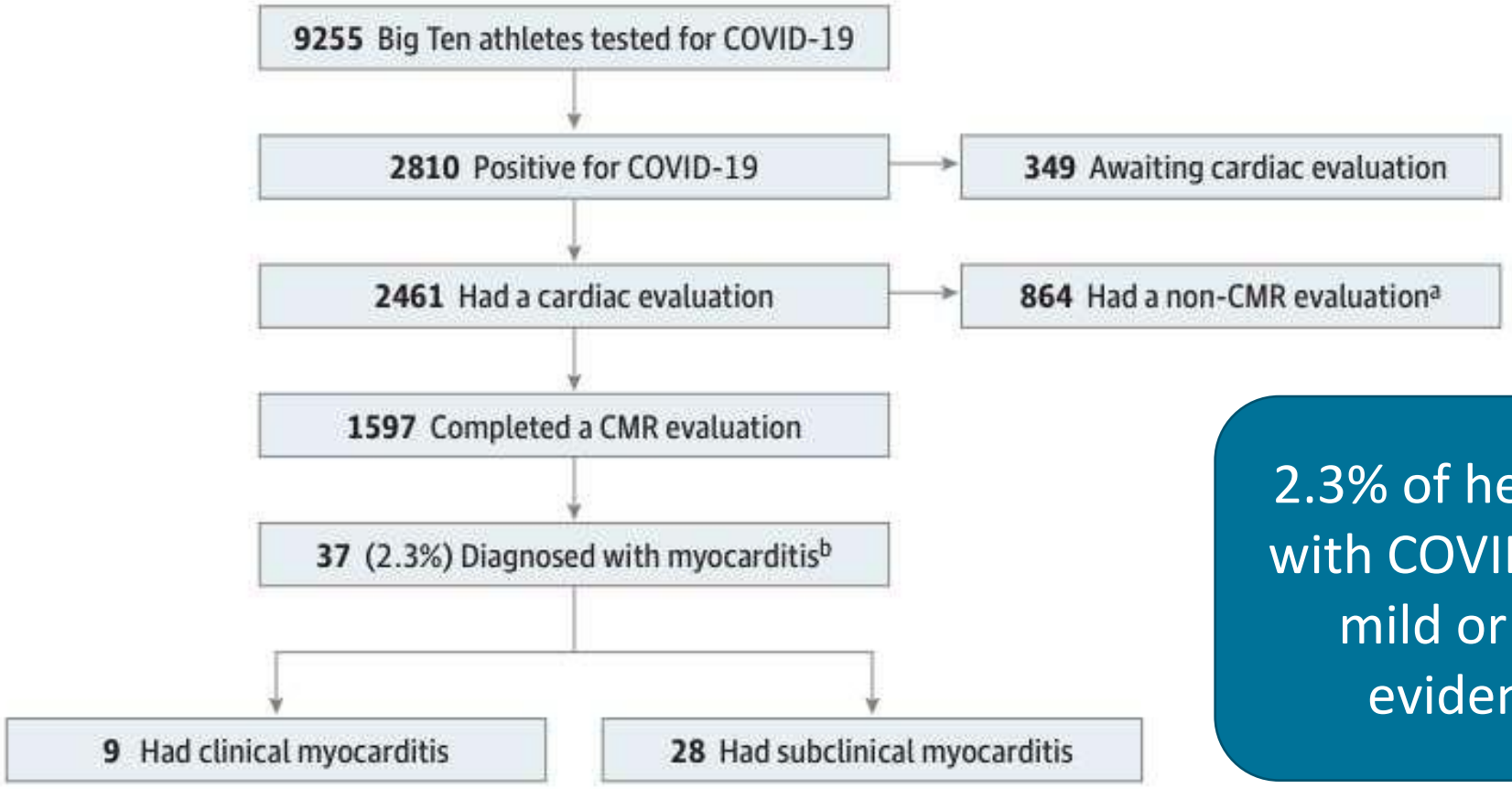
Big Ten Study

JAMA Cardiology | Original Investigation

Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes With Recent SARS-CoV-2 Infection

Results From the Big Ten COVID-19 Cardiac Registry



2.3% of healthy college athletes with COVID infection (most with mild or no symptoms) had evidence of myocarditis

Daniels CJ, Rajpal S, Greenshields JT, et al. Prevalence of Clinical and Subclinical Myocarditis in Competitive Athletes With Recent SARS-CoV-2 Infection: Results From the Big Ten COVID-19 Cardiac Registry. *JAMA Cardiol.* Published online May 27, 2021. doi:10.1001/jamacardio.2021.2065

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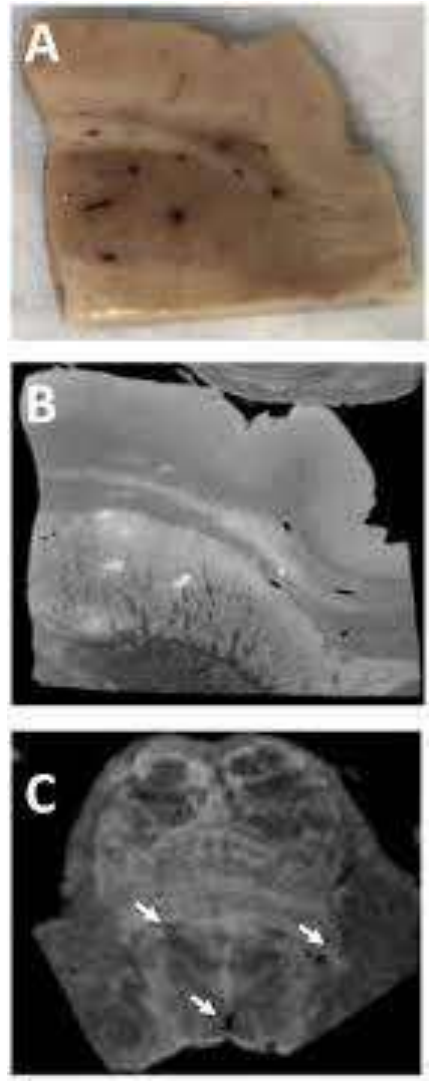
Neuropathogenic Mechanisms

Acute Neurologic Syndromes	Proposed Mechanism
Anosmia/ageusia	Direct viral infection of olfactory bulb
Stroke	Hypercoagulability Endothelial damage
Encephalitis	Viral neuro-invasion Autoimmunity
Encephalopathy	Metabolic derangements Hypoxia/ischemia Cerebral microthrombi Cytokine storm
Peripheral neuropathy	Molecular mimicry
Myositis	Autoimmune Cytokine storm



Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain. 2021 Dec 31;144(12):3576-3588.

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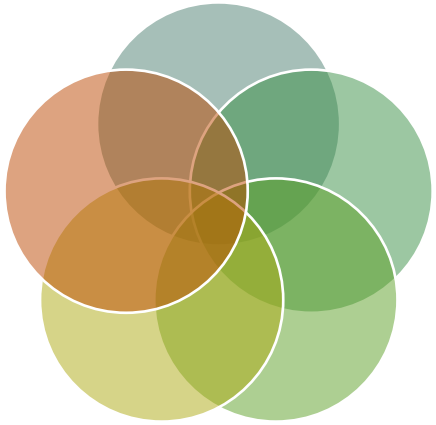
What Is “Long COVID?”

- Long COVID – Various persistent symptoms and health effects, weeks or months after infection
- Long Hauler – COVID-19 survivor with lingering effects
- Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) - New syndrome announed by NIH in 2021
- Post-COVID Condition – New, returning, or ongoing symptoms ≥4 weeks after infection
- Post-Viral Fatigue Syndrome
- Chronic Fatigue Syndrome
- Myalgic Encephalitis



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Post-Acute Sequelae of SARS-CoV-2 Infection (PASC)

Symptom onset or persisting ≥4 weeks after COVID-19 infection

Fatigue + various other symptoms

- Post-exertional fatigue a dominant feature

Intrusive into daily activities

Not explained by other conditions

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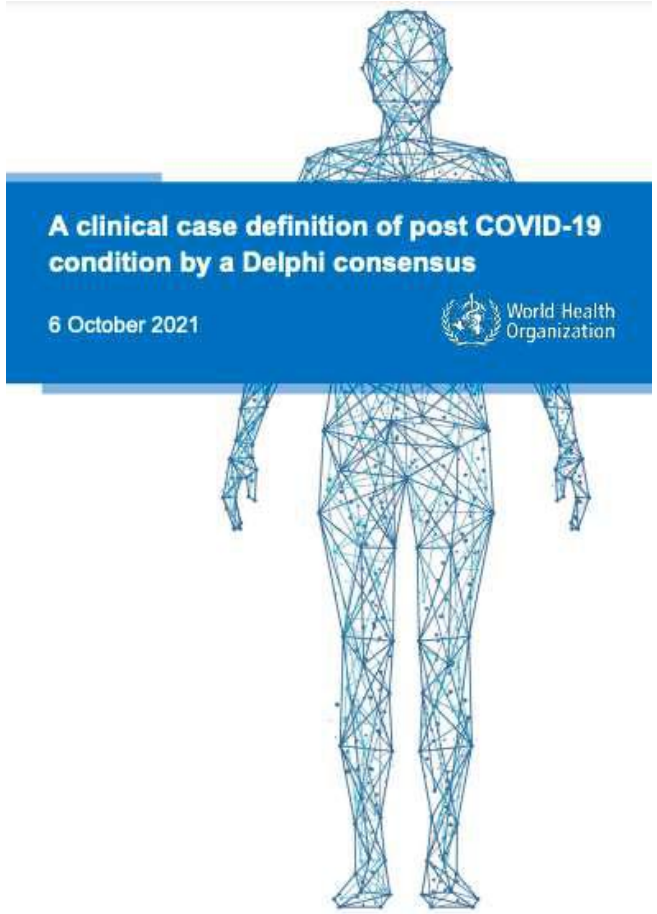
Proposed Definition



History of probable or confirmed SARS-CoV-2 infection

3 months from the onset of COVID-19

Symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.

Common symptoms include fatigue, shortness of breath, cognitive dysfunction and generally have an impact on everyday functioning.

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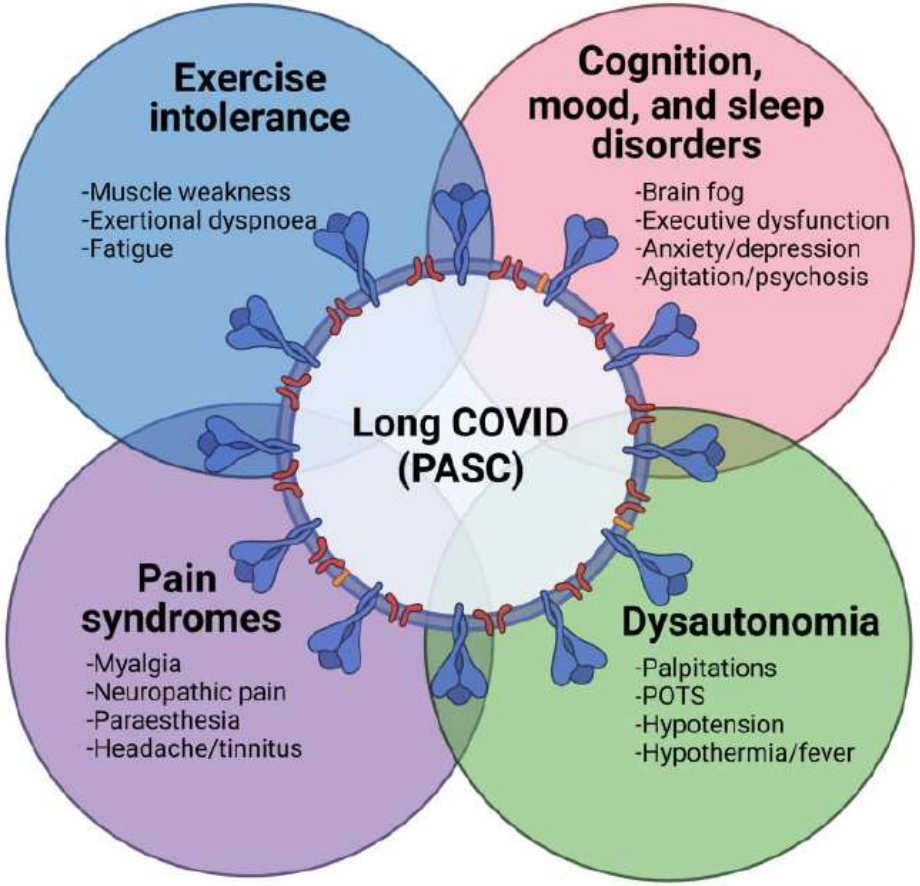
Neurologic Sequelae of COVID-19



Balcom EF, Nath A, Power C. Acute and chronic neurological disorders in COVID-19: potential mechanisms of disease. Brain. 2021 Dec 31;144(12):3576-3588.

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Are There Predictive Factors?

Maybe?

Severe disease

ICU stay

Pulmonary embolism

Myocardial dysfunction

Incidence of PASC in Children & Adolescents

- Pediatric studies report 8–58% of SARS-CoV-2 infected children experience “long COVID” symptoms
  - Uncontrolled studies may over-estimate by not accounting for other illnesses, or pandemic stress
- Controlled cohort studies consistently show higher prolonged symptoms, but wide variability
  - 1.7% vs 4.6%
  - 0.9% vs 4.4%
  - 53.4% vs 66.5%

Asadi-Pooya AA, Nemati H, Shahisavandi M, et al. Long COVID in children and adolescents. *World J Pediatr WJP.* 2021;17:495–499.

Ashkenazi-Hoffnung L, Shmueli E, Ehrlich S, et al. Long COVID in children: observations from a designated pediatric clinic. *Pediatr Infect Dis J.* 2021

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European Journal of Pediatrics (2022) 181:1597–1607
https://doi.org/10.1007/s00431-021-04345-z

ORIGINAL ARTICLE

Long COVID symptoms and duration in SARS-CoV-2 positive children — a nationwide cohort study

Children 0-17, Danish Health Data Authority, linked to national laboratory database

Questionnaire sent to 78,037 children's families

15,041 COVID+ vs. 15,080 never COVID controls

"Long COVID" cohort = symptoms lasting >4 weeks

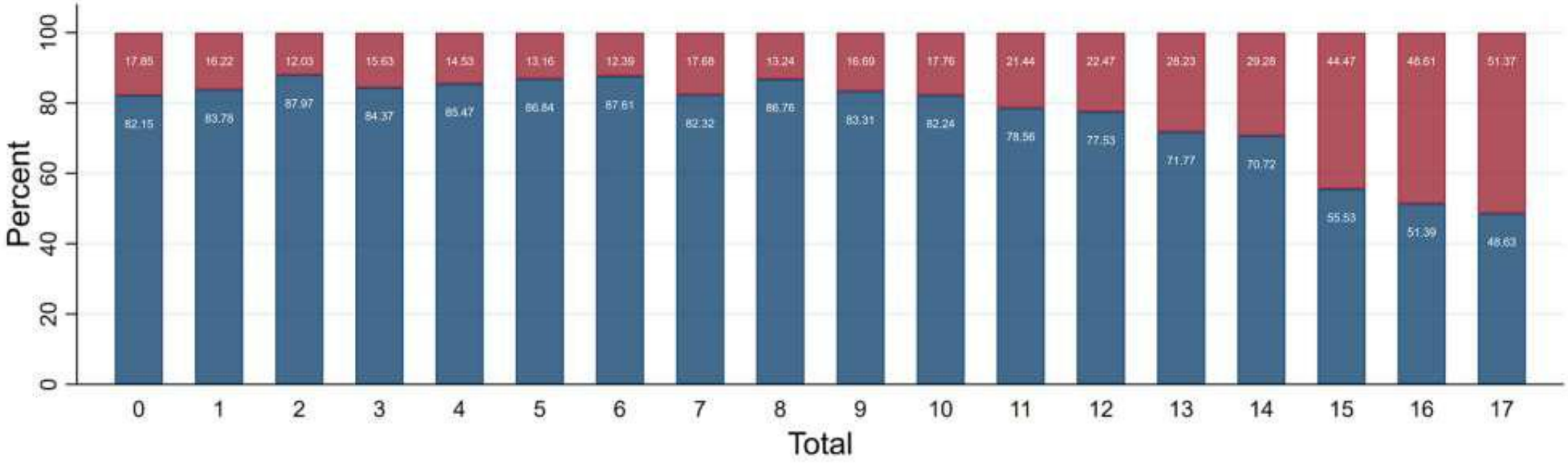
25.3% of COVID cohort reported symptoms >4 weeks

22.8% of children in CONTROL group reported symptoms >4 weeks ($p<0.0001$)

7% of long COVID children were asymptomatic during acute COVID

Borch L, et al. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. Eur J Pediatr. 2022 Apr;181(4):1597-1607.

Danish Long COVID Cohort



Adolescents have higher rates of prolonged symptoms (up to 51% of 17 year-olds)

Borch L, et al. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. Eur J Pediatr. 2022 Apr;181(4):1597-1607.

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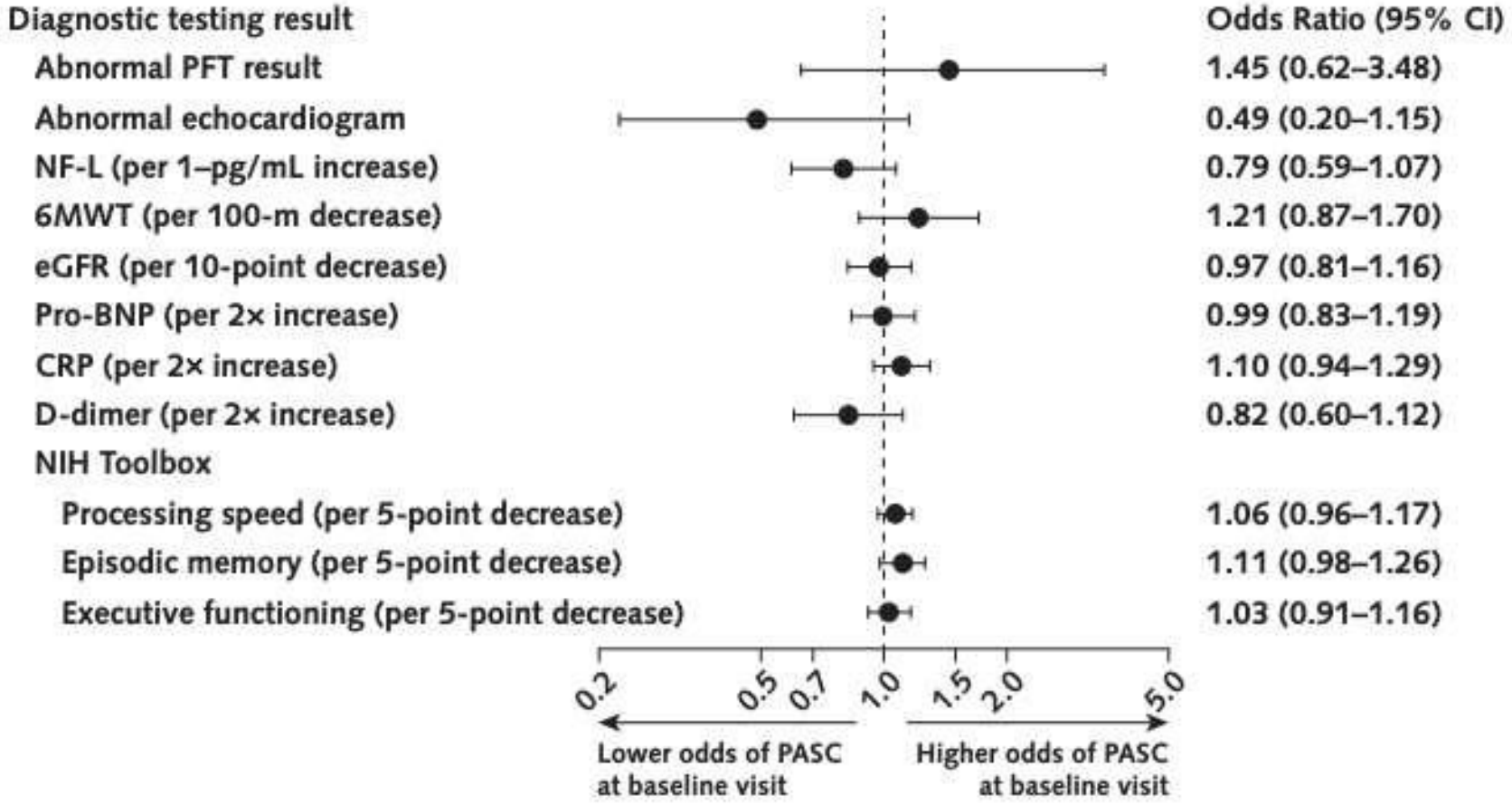
Evaluations to Consider

- Rule-out cardiomyopathy
- Rule-out thromboembolic complications (CVA, PE)
- Screen for autoimmune diseases
- Think about mimics (hypothyroidism, diabetes, depression)
- Mental heath assessment

Lab Values, PASC vs Control



No major differences in inflammatory labs, pulmonary function, cardiac function, cognitive function

Sneller MC, et al. A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings. Ann Intern Med. 2022 May 24:M21-4905.

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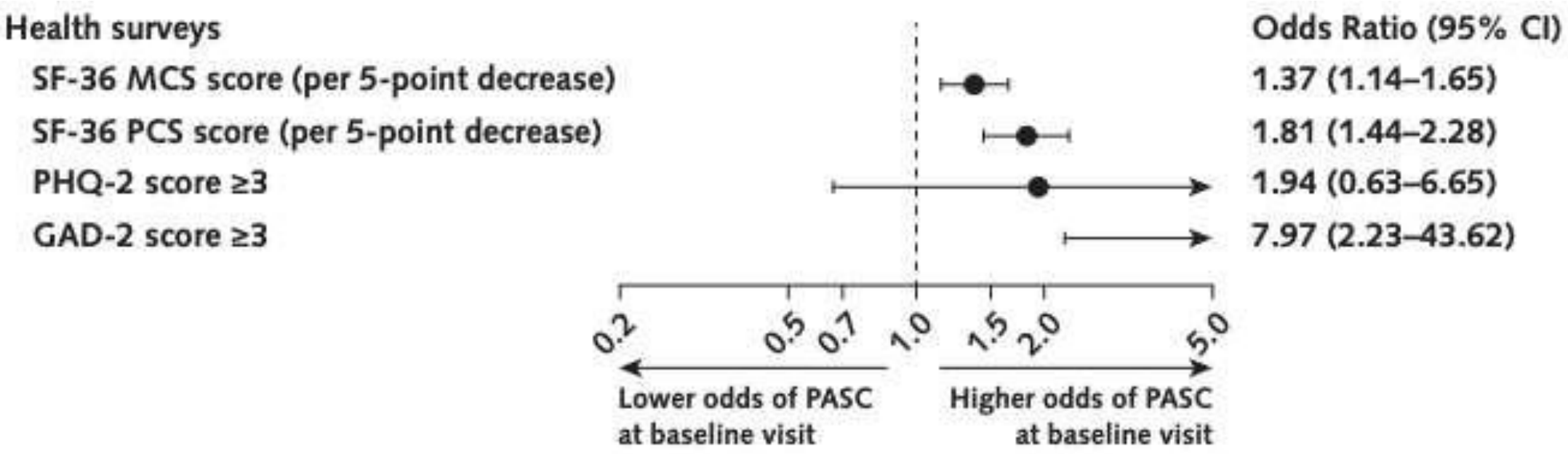
Quality of Life, Mental Health Assessments



Sneller MC, et al. A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings. Ann Intern Med. 2022 May 24:M21-4905.

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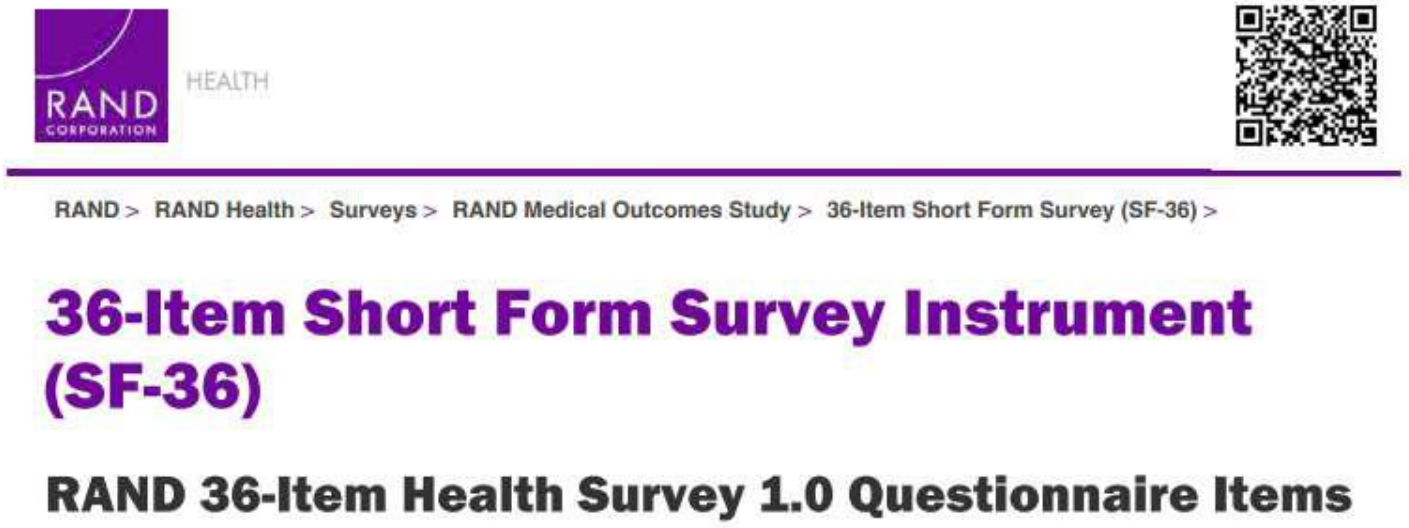
https://www.rand.org/health-care/surveys_tools/mos/36-item-short-form/survey-instrument.html



GAD-2

Over the **last 2 weeks**, how often have you been bothered by the following problems?

1. Feeling nervous, anxious or on edge

2. Not being able to stop or control worrying

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Management

Clinical Guidance | Free Access

Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients

Correction(s) for this article

Joseph E. Herrera DO, William N. Niehaus MD, Jonathan Whiteson MD, Alba Azola MD, John M. Baratta MD, MBA, Talya K. Fleming MD, Soo Yeon Kim MD, Huma Naqvi MD, Sarah Sampsel MPH, Julie K. Silver MD, Monica Verduzco-Gutierrez MD, Jason Maley MD, Eric Herman MD, Benjamin Abramoff MD, MS

Herrera JE, et al. Multidisciplinary collaborative consensus guidance statement on the assessment and treatment of fatigue in postacute sequelae of SARS-CoV-2 infection (PASC) patients. PM&R. 2021 Sep;13(9):1027-1043.

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Management

- Set achievable goals
- Focus on specific symptoms (e.g., headache) or conditions (e.g., dysautonomia)
- Improving physical, mental, and social well-being

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Supportive Care – Sleep/Wake Cycle

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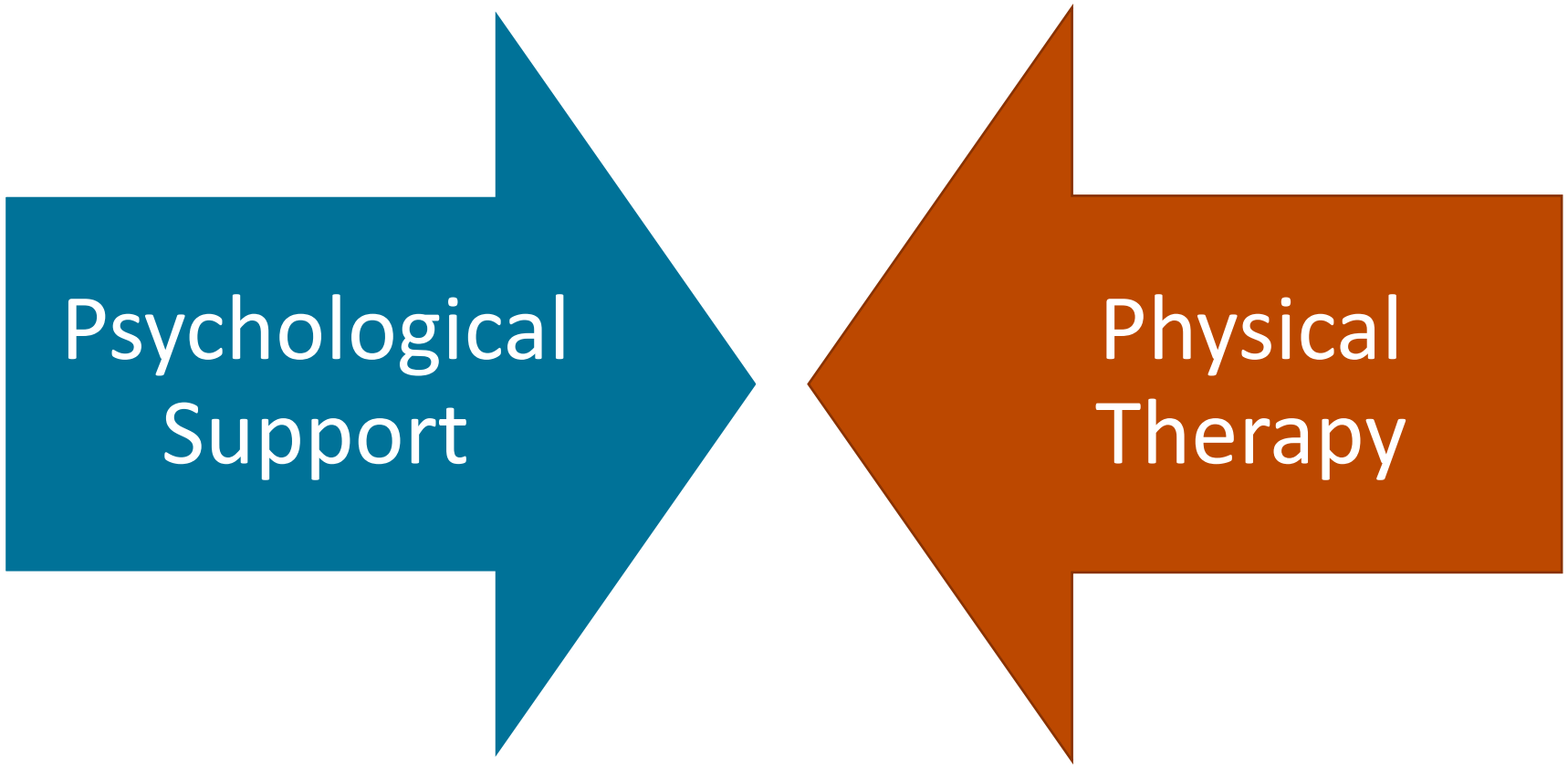
Coping & Restoring Normal



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Pediatric PASC (pPASC) Management

Specialty	Indications for evaluation	Assessment tools	Management strategies
Primary care	Diagnosed with acute COVID-19	Initial post-COVID follow-up (4 weeks)	Validation, early pacing discussions, referral to multidisciplinary pPASC clinic
		Subsequent post-COVID follow-up (12 weeks)	
		Basic screening laboratory tests: CBC with differential, CMP, CRP, ESR, Ferritin, TSH ± Free T4, vitamin D, Epstein Bar virus antibody panel	Olfactory retraining

Brugler Yonts, Alexandra, et al. "A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19." Pediatric Annals, vol. 51, no. 11, Nov. 2022

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Olfactory Training

- Studied in the setting of loss of taste and smell after various infections and is currently being studied in clinical trials in patients with post–COVID-19
  - www.clinicaltrials.gov: NCT04764981, NCT04710394, NCT04361474, NCT04657809, NCT04406584, NCT04495816, NCT04569825, NCT04789499, NCT04528329
- A variety of odors (essential oils, etc)
- Sniff twice daily (preferably once in the morning before breakfast and once in the evening before going to bed) for at least 20 to 30 seconds on each of the four scents separately
  - Constantly sniff for 20 to 30 seconds on each odor without a break.
- Typically, for at least 24 weeks.

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Pediatric PASC (pPASC) Management

Physical rehabilitation	All pPASC	Orthostatic vitals	Aerobic exercise or reconditioning program
		Functional history and examination	Energy conservation strategies
		6-minute walk test	Dietary counseling
Psychology	All pPASC	Comprehensive psychosocial history	Anxiety management strategies (relaxation, cognitive-behavioral therapy techniques)
		Validated self-report and parent proxy psychosocial questionnaires (eg,	Behavioral activation
		PROMIS Pediatric Profile)	Support groups

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Pediatric PASC (pPASC) Management

Cardiology	Hospitalized for acute COVID-19		
	Persistent palpitations or syncopal episodes	ECG, troponin, CRP, brain natriuretic protein for myopericarditis symptoms	Dysautonomia syndrome management: fluids, electrolytes, compression, midodrine, fludrocortisone, propranolol
	Chest pain that occurs with exercise; radiates to the back, jaw, left arm, or shoulder; and/or increased when lying down	Echocardiogram, cardiac MRI, stress test if appropriate	Admission and supportive care for myopericarditis if applicable

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Pediatric PASC (pPASC) Management

Neurology	New or worsening persistent or daily headaches	MRI ± EEG	Headache management (fluids, sleep hygiene, abortive or preventive medications)
	Focal neurological signs	Vitamin and heavy metal levels ± lumbar puncture for CSF cytokines, cell count, neuroimmune studies	Coenzyme Q10, vitamin B complex, magnesium
Pulmonary	Hospitalization for acute COVID-19 infection	Pulmonary function tests ± Chest x-ray	Bronchodilators as applicable
	Persistent cough, wheezing or increased work of breathing	CT chest if studies abnormal	

Brugler Yonts, Alexandra, et al. "A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19." Pediatric Annals, vol. 51, no. 11, Nov. 2022

Pediatric PASC (pPASC) Management

Otolaryngology	Hoarseness, stridor, or change in vocal quality	Laryngoscopy	Breathing exercises
	Shortness of breath in the absence of pulmonary findings	Spirometry	Speech pathologist referral
			Vocal retraining
Pain medicine	Paresthesias	Quantitative sensory testing	Tricyclic anti-depressants
	Dysautonomia	Skin biopsy for small fiber neuropathy	Anti-epileptics
	Chronic pain		Topical lidocaine, other analgesics IVIG

Brugler Yonts, Alexandra, et al. "A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19." Pediatric Annals, vol. 51, no. 11, Nov. 2022

PEDIATRIC ANNALS

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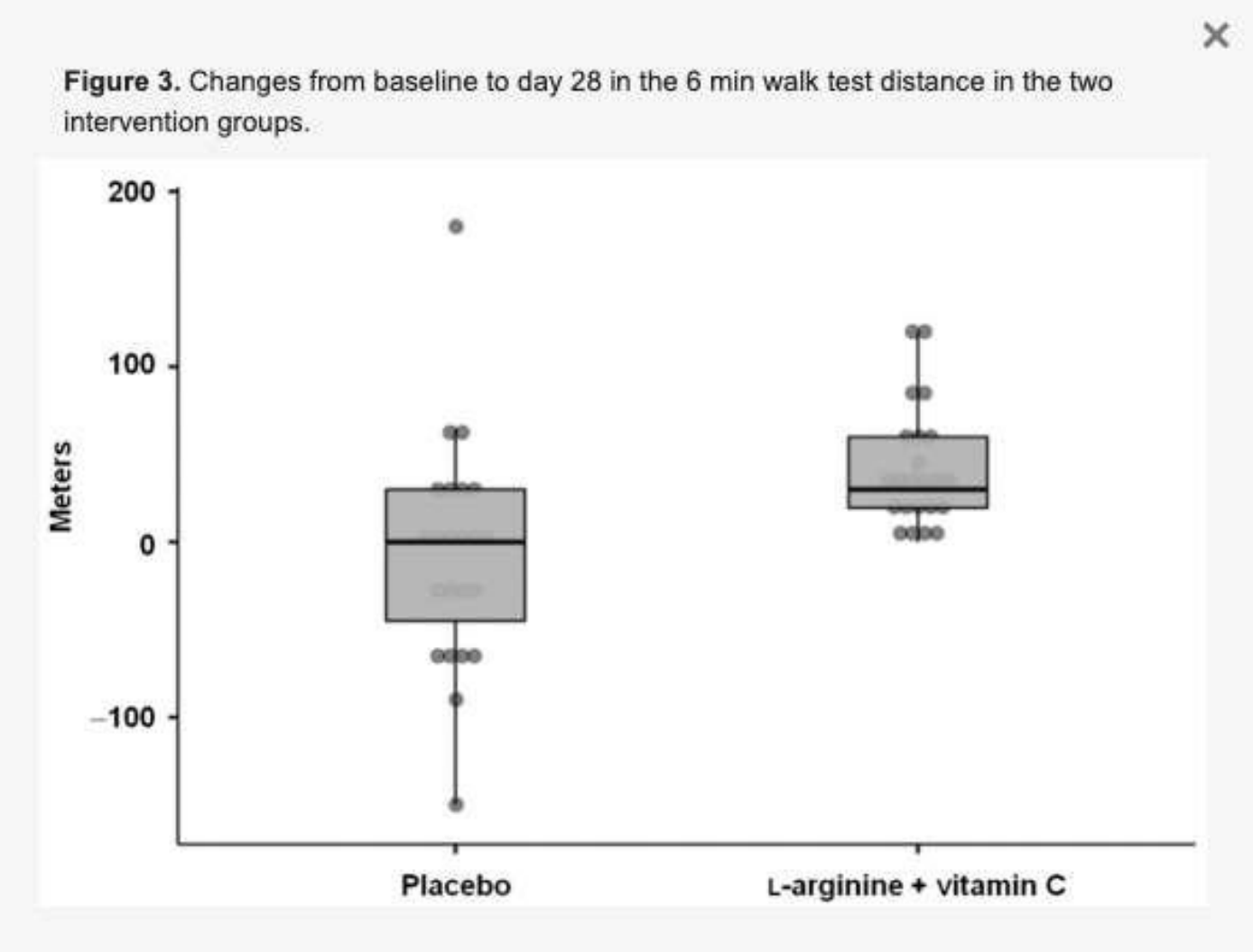
A Review of Current Evaluation and Management Strategies in Pediatric Postacute Sequelae of COVID-19

Alexandra Brugler Yonts, MD, Justin Burton, MD, and Linda Jones Herbert, PhD

Published Online: November 01, 2022 · https://doi.org/10.3928/19382359-20220913-08

Supplements?



- Randomized 1:1 (n=46, 23 per group)
- BID 1.66 g L-arginine + 500 mg liposomal vitamin C vs. placebo for 28 days
- Improved 6-minute walking distance, hand grip, fatigue at 28 days

Tosato M, et al. Nutrients. 2022; 14(23):4984. https://doi.org/10.3390/nu14234984

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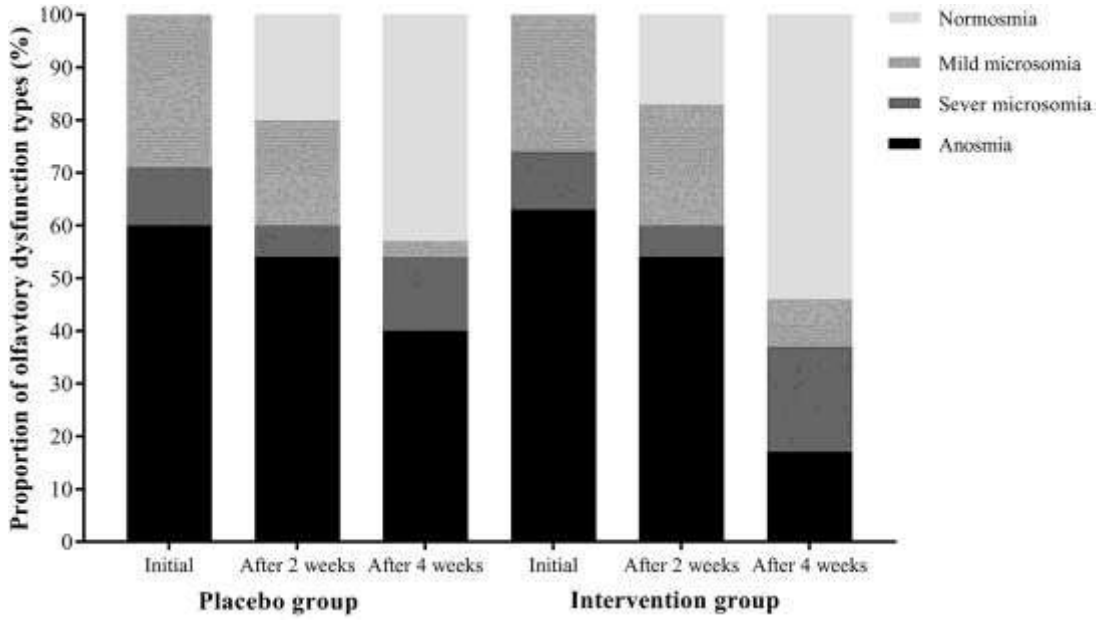
Intranasal Mometasone for Anosmia?



- Persistent anosmia or severe microsmia for more than 4 weeks due to COVID-19
- Mometasone furoate nasal spray vs. sodium chloride intranasal spray x 4 weeks
- Not significant difference
- 22% reduction in anosmia with treatment (powered to detect 45% difference)

The Laryngoscope, Volume: 132, Issue: 11, Pages: 2209-2216, First published: 25 August 2022, DOI: (10.1002/lary.30353)

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Expected Timing of Remission

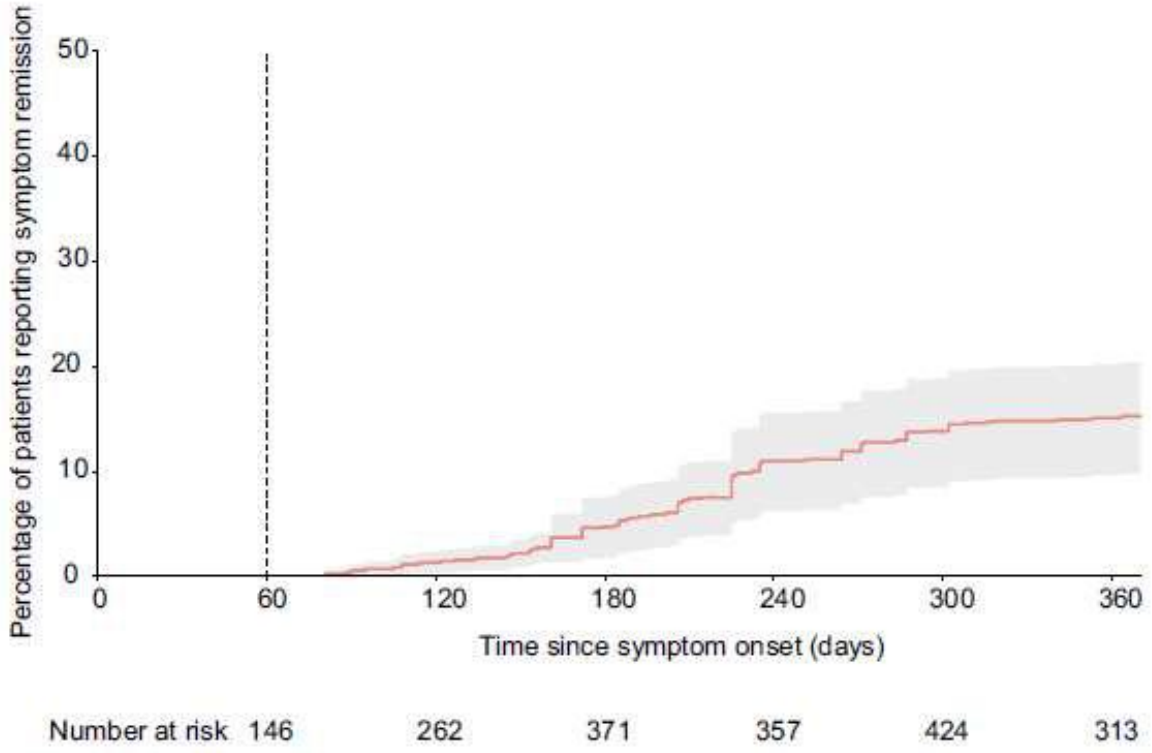

Fig. 2 Cumulative event curve for remission of post COVID-19 symptoms.

Tran, VT., Porcher, R., Pane, I. et al. Course of post COVID-19 disease symptoms over time in the ComPaRe long COVID prospective e-cohort. Nat Commun 13, 1812 (2022).

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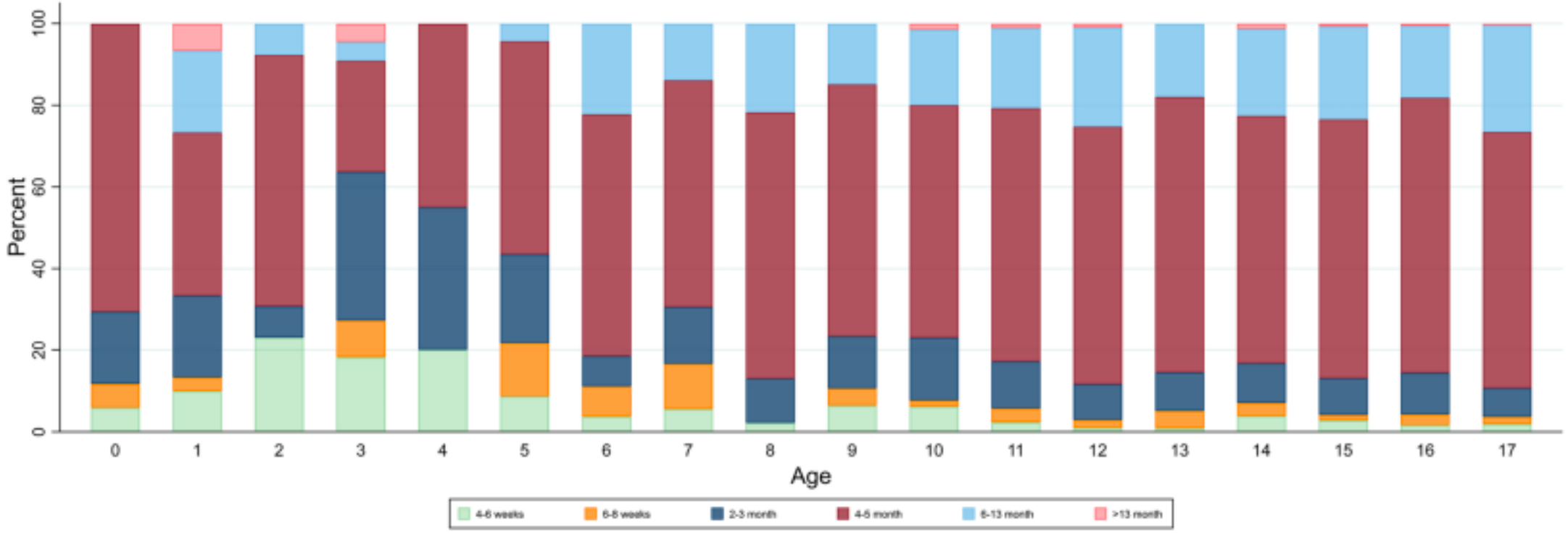
Ongoing Prolonged Symptoms in Children (Danish Cohort)



54-75% had symptom resolution within 1-5 months. About 20% had symptoms 6-13 months.

Borch L, et al. Long COVID symptoms and duration in SARS-CoV-2 positive children - a nationwide cohort study. Eur J Pediatr. 2022 Apr;181(4):1597-1607.

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Case

- 14 year-old boy, previously healthy
- COVID vaccine x 2 doses
- Whole family had COVID January, 2022 – all mild infections
- February, 2022 – still feeling tired all the time
  - Excessive naps
  - Unable to play basketball like before
  - Lots of aches/pains; chest tightness during sports
- Physical exam totally normal
  - Heart exam normal, Neuro exam normal, Joint exam normal

Evaluations to Consider

- Rule-out cardiomyopathy – EKG, ECHO, refer to Cardiology
- Rule-out thromboembolic complications (CVA, PE)
- Screen for autoimmune diseases
- Think about mimics (hypothyroidism, diabetes, depression)
- Mental heath assessment

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Management

- Set achievable goals
- Focus on specific symptoms (e.g., headache) or conditions (e.g., dysautonomia)
- Improving physical, mental, and social well-being

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Supportive Care – Sleep/Wake Cycle

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