Pediatric Long COVID: What to know about diagnosis and management

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Objectives

- To understand how to diagnose pediatric long COVID
- To report common symptoms and presentations of pediatric long COVID
- To describe guidance on assessment and treatment options for children with long COVID

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Long COVID

Long COVID
PASC (Post Acute Sequela of SARS-CoV-2)
Long-haul COVID
Post-COVID Conditions

WHO: Post COVID-19 condition in **children and adolescents** occurs in individuals with a history of **confirmed or probable SARS-CoV-2 infection**, when experiencing **symptoms lasting at least 2 months** which initially occurred within 3 months of acute COVID-19.

OLD CDC: post-COVID conditions as an umbrella term for the wide range of health consequences that are present **four or more weeks** after infection with SARS-CoV-2.

NEW CDC: **Long COVID** is a chronic condition that occurs after SARS-CoV-2 infection and is present for at **least 3 months**. Long COVID includes a **wide range of symptoms** or conditions that may improve, worsen, or be ongoing.

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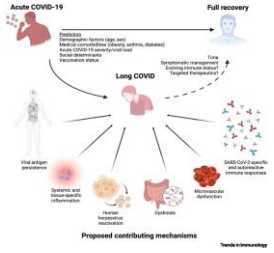
Possible Long COVID mechanisms



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Peluso and Deeks. Early clues regarding the pathogenesis of long-COVID: Trends in Immunology (cell.com) 2022

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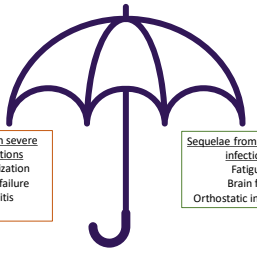
Long COVID



Sequelae from severe acute infections
ICU hospitalization
Respiratory failure
Myocarditis
MIS-C

Sequelae from mild acute infections
Fatigue
Brain fog
Orthostatic intolerance

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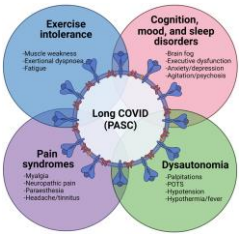
Long COVID: Phenotypes



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Brain, Volume 144, Issue 12, December 2021, Pages 3576–3588, https://doi.org/10.1093/brain/awab302.

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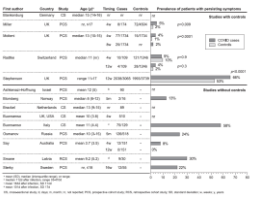
Prevalence of Long COVID in Pediatrics

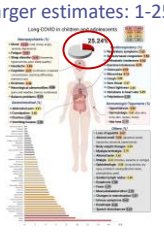
Prevalence estimates:

Individual studies: 4-66%



Zimmerman et al. 2021

Larger estimates: 1-25%



Lopez-Leon et al. 2022

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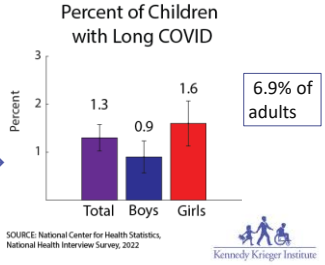
Prevalence of Long COVID in Pediatrics

Long COVID was defined as: "Any symptoms lasting 3 months or longer that you did not have prior to having COVID-19?" among those who reported receiving either a positive test or a doctor's diagnosis of COVID-19 and were symptomatic.

73 million children in the US → 950,000 children that had or currently have long COVID



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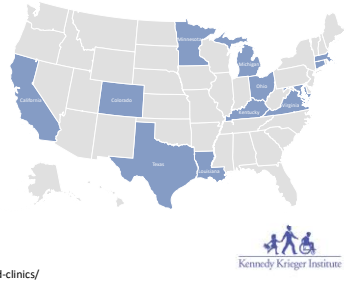
Limited Pediatric Long COVID Clinics

- 14 pediatric COVID clinics in the US
  - Some focus on follow-up of hospitalized or MIS-C patients only
  - Many children rely on pediatricians only for healthcare services



https://longcovidfamilies.org/healthcare/pediatric-covid-clinics/

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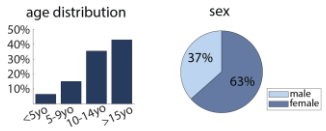
Clinic Demographics



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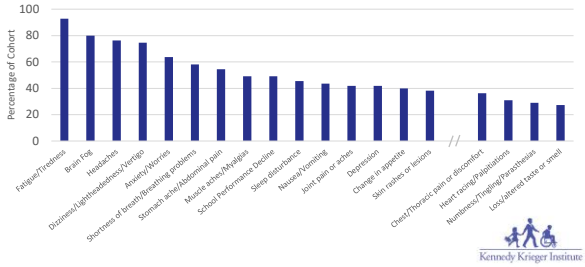
Most Common Pediatric Long COVID Symptoms at KKI



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Long COVID in Pediatrics: Time Course

Table 3. Children's experience of COVID-19 by confirmation of infection and pre-existing conditions.

Characteristics	All (N = 510)	Clinical diagnosis (N = 156)	Positive test (N = 145)	Unconfirmed but suspected (N = 209)	Pre-existing conditions (N = 287)	No pre-existing conditions (N = 223)
Constant symptoms, n (%)	129 (25.3)	45 (28.8)	50 (34.5)	34 (16.3)	76 (26.5)	53 (23.8)
Alternating recovery/symptoms, n (%)	252 (49.4)	78 (50)	66 (45.5)	108 (51.7)	144 (50.2)	108 (48.4)
Long period of wellness followed by symptoms, n (%)	97 (19)	21 (13.5)	24 (16.6)	52 (24.9)	46 (16)	51 (22.9)
Undetermined, n (%)	32 (6.3)	12 (7.7)	5 (3.4)	15 (7.2)	21 (7.3)	11 (4.9)

Results were not significantly affected by age, comorbidities or sex ($p > 0.05$).

Buonsenso et al. 2022

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Children with long COVID can benefit from multi-disciplinary care

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- Multidisciplinary team-based approach:
  - Medical
  - Psychosocial
  - Cognitive
  - Physical
- Goal to improve patients' overall functioning:
  - Day to day tasks
  - Physical activity
  - School
  - Extracurricular activities & social engagement

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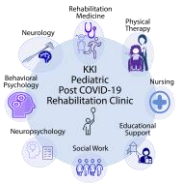
- Interdisciplinary team approach:
  - Medicine
    - Neurology
    - Pediatric Rehabilitation
  - Physical Therapy
  - Behavioral Psychology
  - Social Work
  - Nursing
- Direct, expedited referrals within 1-2 weeks of visit:
  - Neuropsychology
  - Education Specialist



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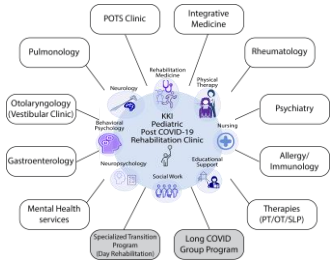
Pediatric Post COVID-19 Rehabilitation Clinic



- Directed referrals to additional subspecialists

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Long COVID can have a significant impact on the lives of children and their families

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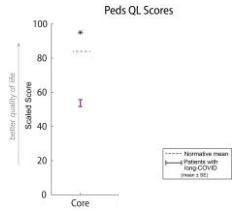
Effects on child's quality of life



- Minimal clinically meaningful difference: 4-5 points (Varni et al. 2007, Hilliard et al. 2013)

Chen, Morrow & Malone, *AJPMR*, 2023

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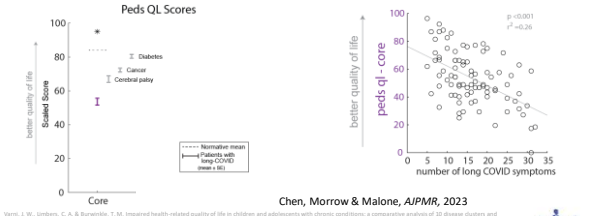
Effects on child's quality of life



Chen, Morrow & Malone, *AJPMR*, 2023

Varni, J. W., Limbers, C. A. & Burwinkle, T. M. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. *Health Qual. Life Outcomes* **5**, 43 (2007).
Varni JW, Burwinkle TM, Katz ER, Meeske K, Dickinson P. The PedsQL™ in pediatric cancer. Cancer. 2002;94(7):2090–106.
Varni JW, Burwinkle TM, Jacobs JR, Gottschalk M, Kaufman F, Jones KL. The PedsQL in type 1 and type 2 diabetes: reliability and validity of the Pediatric Quality of Life Inventory Generic Core Scales and type 1 Diabetes Module. Diabetes Care. 2003 Mar;26(3):631–7.
Varni JW, Burwinkle TM, Berrin SJ, Sherman SA, Artavia K, Malcarne VL, et al. The PedsQL in pediatric cerebral palsy: reliability, validity, and sensitivity of the Generic Core Scales and Cerebral Palsy Module. Dev Med Child Neurol. 2006 Jun;48(6):442–9.

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Long COVID has effects on the child and their family

Chen, Morrow & Malone, *AJPMR*, 2023

Varni, J. W., Limbers, C. A. & Burwinkle, T. M. Impaired health-related quality of life in children and adolescents with chronic conditions: a comparative analysis of 10 disease clusters and 33 disease categories/severities utilizing the PedsQL 4.0 Generic Core Scales. *Health Qual. Life Outcomes* **5**, 43 (2007).
Varni, J. W., Burwinkle, T. M. & Sherr, L. S. The PedsQL Multidimensional Fatigue Scale in pediatric rheumatology: reliability and validity. *J. Rheumatol.* **31**, 2494–2500 (2004).
Bernister TB, Brooks BL, Dyck RH, Kirton A. Parent and family impact of raising a child with perinatal stroke. BMC Pediatr 2014;14:1–11. https://doi.org/10.1186/1471-2431-14-182.

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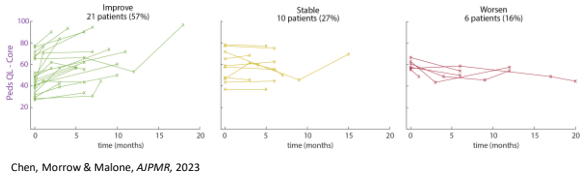
Trajectories vary but most children improve over time



Chen, Morrow & Malone, *AJPMR*, 2023

Most children recovered over time, but 1-in-20 of those with long COVID at 3 months reported persistent symptoms 18 months post-Sars-CoV-2 infection. (Morello et al. 2023)

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How do we treat long COVID?

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Treatment approach


PM&R WILEY

Clinical Guidance | Free Access

Multi-disciplinary collaborative consensus guidance statement on the assessment and treatment of postacute sequelae of SARS-CoV-2 infection (PASC) in children and adolescents

Laura A. Malone MD, PhD, Amanda Morrow MD, Yuxi Chen MD, Donna Curtis MD, MPH, Sarah D. de Ferranti MD, MPH, Monika Desai MD, Talya K. Fleming MD, Therese M. Giglia MD, FAHA, Trevor A. Hall PsyD, ABPdN, Ellen Henning PhD, Sneha Jadhav MD, Alicia M. Johnston MD, Dona Rani C. Kathirithamby MD, Christina Kokorelis MD, Catherine Lachenauer MD, Lilun Li MD, Henry C. Lin MD, Tran Locke MD, Carol MacArthur MD, Michelle Mann MD, Sharon A. McGrath-Morrow MD, Rowena Ng PhD, Laurie Ohlms MD, Sarah Risen MD, S. Christy Sadreameli MD, MHS, Sarah Sampsel MPH, S. Kristen Sexson Tejtel MD, PhD, MPH, Julia K. Silver MD, Tregony Simoneau MD, Rasha Srouji DNP, Sanjeev Swami MD, Souraya Torbey MD, Monica Verduzco Gutierrez MD, Cydni Nicole Williams MD, MCR, Lori Allison Zimmerman M.D., Louise Elaine Vaz MD, MPH ... See fewer authors

First published: 28 September 2022 | https://doi.org/10.1002/pmrj.12890

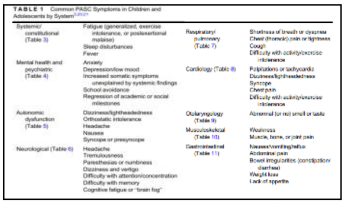
TABLE 1 Common PASC Symptoms in Children and Adolescents by System

Systemic/constitutional (Table 3)	Fatigue (generalized, exercise intolerance, or postexertional malaise) Sleep disturbances Fever
Mental health and psychiatric (Table 4)	Anxiety Depression/low mood Increased somatic symptoms unexplained by systemic findings School avoidance Regression of academic or social milestones
Autonomic dysfunction (Table 5)	Dizziness/lightheadedness Orthostatic intolerance Headache Nausea Syncope or presyncope
Neurological (Table 6)	Headache Tremulousness Paresthesias or numbness Dizziness and vertigo Difficulty with attention/concentration Difficulty with memory Cognitive fatigue or "brain fog"
Respiratory/pulmonary (Table 7)	Shortness of breath or dyspnea Chest (thoracic) pain or tightness Cough Difficulty with activity/exercise intolerance
Cardiology (Table 8)	Palpitations or tachycardia Dizziness/lightheadedness Syncope Chest pain Difficulty with activity/exercise intolerance
Otolaryngology (Table 9)	Abnormal (or no) smell or taste
Musculoskeletal (Table 10)	Weakness Muscle, bone, or joint pain
Gastrointestinal (Table 11)	Nausea/vomiting/reflux Abdominal pain Bowel irregularities (constipation/diarrhea) Weight loss Lack of appetite

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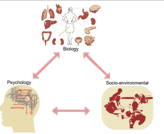
Treatment approach

- Evaluate for other etiologies of symptoms (e.g., anemia for fatigue)
- Symptom management
  - Primary with lifestyle and rehabilitation-based interventions
    - Hydration
    - Regular meals, sodium
    - Exercise & physical activity (physical therapy referrals)
    - Sleep
    - Stress management (therapist, counselor referrals)
    - Nonpharmacologic therapies (yoga, acupuncture, relaxation therapies with deep breathing exercises)
  - Medications as needed to treat symptoms (e.g., pain, POTS)

Biopsychosocial framework



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Fatigue

- **Characterization/patterns and screening for **Crashes****

Post-exertional malaise (PEM)
Worsening of symptoms after minor physical, cognitive, or emotional exertion

- Evaluate sleep
- Rule out other medical causes of fatigue


ADOLESCENT MEDICINE (MA GOLDSTEIN, SECTION EDITOR)

Long-Term COVID 19 Sequelae in Adolescents: the Overlap with Orthostatic Intolerance and ME/CFS

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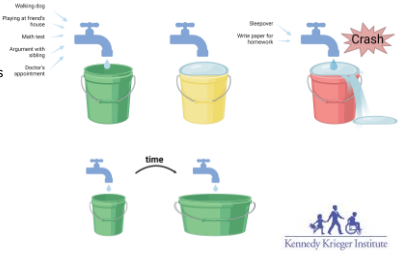
Fatigue Treatment Strategies

- Optimize physical activity through **PACING**
  - Energy conservation/energy bucket
  - Gradual increase in exercise as tolerated
  - AVOID PEM or post-exertional symptom exacerbation
- Support mental health
  - Validate symptoms
  - It's NOT "all in your head"
  - CBT may help with comorbid mood concerns, coping with physical symptoms, structuring routine, prioritizing activities



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Dizziness/Lightheadedness

Orthostatic

- With standing
- Worse with standing in line, hot environments
- Improves with sitting or lying down

Screen for OI and POTS

Vestibular

- With standing
- Worse with positional head changes
- Gait/balance difficulties
- Tinnitus or hearing loss

Hearing/vestibular evaluation and vestibular PT

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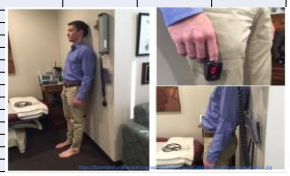
Standing Tolerance Test

SUPINE	Heart Rate	Blood Pressure	Dizziness (N/10)	Headache (N/10)	Blurry Vision (N/10)	Fatigue (N/10)	Other
1 min							
2 min							
3 min							
4 min							
5 min							
STANDING							
1 min							
2 min							
3 min							
4 min							
5 min							
6 min							
7 min							
8 min							
9 min							
10 min							
SUPINE							
1 min							
2 min							



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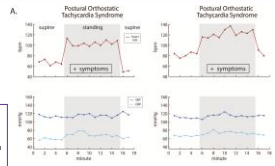
Standing Tolerance Tests

Orthostatic intolerance: (Stewart 2018)
- Abnormal autonomic response
- Symptoms develop in an upright posture and improve in supine position

Postural orthostatic tachycardia syndrome (POTS):
- Diagnostic criteria <20 years of age (Roma 2018):
  - Within 10 minutes of standing:
    - -Heart rate increase of >=40 beats per minute (bpm)
    - OR
    - -An upright heart rate of at least 120 bpm
    - PLUS
    - -Worsening of orthostatic symptoms



Morrow, Villatoro, Kokorelis, Rowe & Malone, *Clinical Pediatrics,* 2024

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Cognitive difficulties

- "Brain fog":
  - Concentration difficulties
  - Memory problems
  - Attention issues
  - Declining school performance
- Semi-flexible brief neuropsychological screening protocol was administered

Cognitive Constructs	3 - 4 years	5 - 7 years	8 - 15 years	16-17 years	18+ years
Verbal Skills	DAS-II Naming Vocabulary	DAS-II Naming Vocabulary (5 to 6 years);or WASI-II Vocabulary (6 years+)	WASI-II Vocabulary		
Nonverbal Reasoning	DAS-II Matrices	DAS-II Matrices (5 to 6 years);or WASI-II Matrix Reasoning (6 years+)	WASI-II Matrix Reasoning		
Working Memory	DAS-II: Digits Forward		WISC-V: Digit Span	WAIS-IV Digit Span	
Attention	—	TEA-ch Score (6+ years)	TEA-ch Score and Score DT	CMS Sequences (16 years), BTA (17 years)	TEA Elevator Counting and Elevator Counting with Distractors
Processing Speed	—	NEPSY-II Inhibition - Naming	Oral SDMT		
Executive Function	—	NEPSY-II Inhibition and Switching	DKEFS Verbal Fluency		
Verbal Memory	—	CHAMP List			CVLT-3
Performance Validity Indicator	—	MVP Verbal			
Questionnaires (Caregiver-Report)	3 - 4 years	5 - 7 years	8 - 15 years	16-17 years	18+ years
Psychosocial and Behavior	Conners Early Childhood (2.5 years+)	Conners Early Childhood (5 years), CBRS (6+years)	CBRS		BASC-3, CAARS
Executive Functioning	—	BRIEF			
Behavioral Screeners	—	ADHD-RS-5 (5 years+), VBRS ODD/CD (6+years), RCADS – Anxiety, Depression, OCD subscales (6 years+)			
Questionnaires (Self-Report)	3 - 4 years	5 - 7 years	8 - 15 years	16-17 years	18+ years
Anxiety	—	RCMAS-2 (6 to 7 years), MASC-2 (8+ years)			BAI
Depression	—	CDI-2 (7-17 years), BDI-2 (13+ years)			BDI-2

Ng, Vargas, Jashar, Morrow & Malone, *Arch Clin Neuropsychol,* 2022

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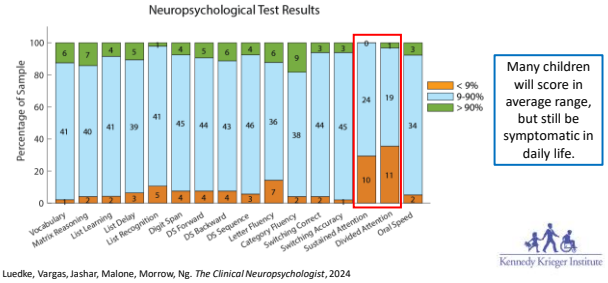
Cognitive evaluation



Many children will score in average range, but still be symptomatic in daily life.

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Luedke, Vargas, Jashar, Malone, Morrow, Ng. *The Clinical Neuropsychologist*, 2024

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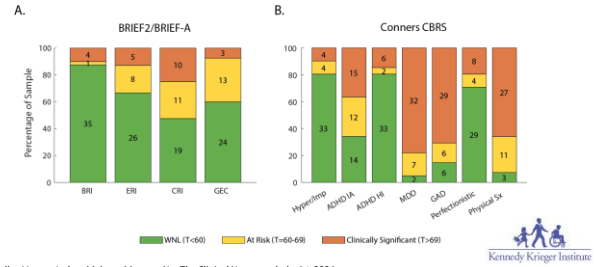
Cognitive evaluation



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Luedke, Vargas, Jashar, Malone, Morrow, Ng. *The Clinical Neuropsychologist*, 2024

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School & Activity Accommodations

Important to have a meeting with school to discuss accommodations & obtain collateral from multiple sources (e.g., 504, individualized education program [IEP], individualized health plan)

Possible Interventions

- Prioritizing academic demands & excuse/limit nonessential classwork/homework
- Increased time for exams or assignments (i.e., x1.5, x2.0) & rest breaks during instruction
- Copies of teacher notes prior to start of class/note taker in class
- Adjusted school days (i.e., shortened/alternative)
- Adapted PE or reduced demands during physical activity
- Allow access to water/salty snacks

Pacing both with physical and cognitive activity!

Make lifestyle interventions accessible at school

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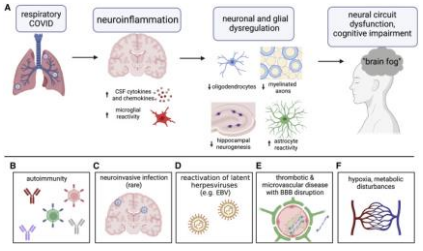
Possible mechanisms of Cognitive Dysfunction



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Monje & Iwasaki, Neuron, 2022

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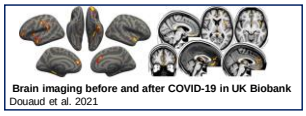
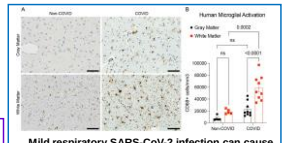
Mechanisms of Cognitive Dysfunction



Brain imaging before and after COVID-19 in UK Biobank
Douaud et al. 2021

	Cognitive PASC	Cognitive Controls
CSF abnormality	77% (10/13)	0% (0/4)
Elevated CSF protein	15% (2/13)	0% (0/4)
Abnormal OCB patterns	69% (9/13)	0% (0/4)
Matched bands CSF/serum	89% (8/9)	--

Risk factors and abnormal cerebrospinal fluid associate with cognitive symptoms after mild COVID-19
Apple et al. 2022



Mild respiratory SARS-CoV-2 infection can cause multi-lineage cellular dysregulation and myelin loss in the brain
Fernández-Castañeda et al. 2022

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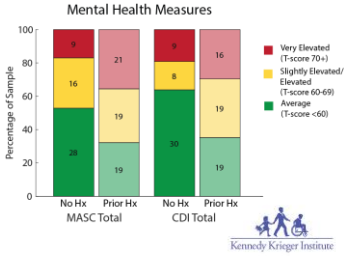
Mood/psychological symptoms

- Important to screen for comorbid mood/psychological concerns
  - Anxiety and depressive symptoms common in: (Bould et al. 2011, Anderson et al. 2014, Yriondi et al. 2017)
    - ME/CFS
    - OI/POTS
    - Mild traumatic brain injury
- Recommendations:
  - Identify additional resources for coping, support
  - Outpatient psychotherapy (biopsychosocial framework)
  - Psychiatry referrals as needed



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Possible Mechanisms of Mood Symptoms

- Multiple underlying mechanisms may contribute to mental health sequelae (Brackel et al., 2021; Uzunova, 2021)
  - Neuroinflammation/impact of COVID-19 on nervous system
  - Biological vulnerability/genetics
  - Impact of physical symptoms on daily life
  - Presence of psychosocial stressors

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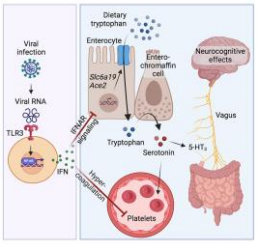
Low serotonin levels in long COVID



Wong et al., Cell, 2023

- Long COVID is associated with reduced circulating serotonin levels
- Serotonin depletion is driven by viral RNA-induced type I interferons (IFNs)
- IFNs reduce serotonin through diminished tryptophan uptake and hypercoagulability
- Peripheral serotonin deficiency impairs cognition via reduced vagal signaling

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Conclusions

- Pediatric long COVID can affect the physical, mental, and social well-being of children's lives. Early recognition is key!
- Many children improve over time but need treatment and support throughout recovery.
- Multidisciplinary integrated care can be beneficial to manage long COVID.
- School accommodations may be necessary to enable continued attendance at school.
- The mechanism underlying long COVID is still being researched but it is likely multifactorial.

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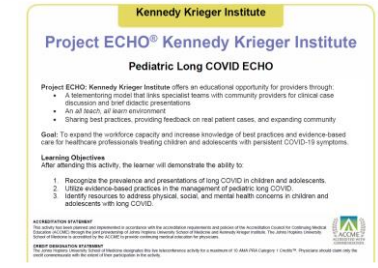
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Project ECHO® Kennedy Krieger Institute

Pediatric Long COVID ECHO

Project ECHO: Kennedy Krieger Institute offers an educational opportunity for providers through:

- A telementoring model that links specialist teams with community providers for clinical case discussion and brief didactic presentations
- An all teach, all learn environment
- Sharing best practices, providing feedback on real patient cases, and expanding community

Goal: To expand the workforce capacity and increase knowledge of best practices and evidence-based care for healthcare professionals treating children and adolescents with persistent COVID-19 symptoms.

Learning Objectives
After attending this activity, the learner will demonstrate the ability to:

1. Recognize the prevalence and presentations of long COVID in children and adolescents.
2. Utilize evidence-based practices in the management of pediatric long COVID.
3. Identify resources to address physical, social, and mental health concerns in children and adolescents with long COVID.

ACCREDITATION STATEMENT

CREDIT DESIGNATION STATEMENT

Meeting time: Fall 2024 (September 10th)

Venue: Zoom live videoconference

Target audience: Primary care providers (MD, DO, PA, NP), school nurses, school educators, physical therapists, occupational therapists, and mental health providers (psychologists, social workers)

Kennedy Krieger ECHO Pediatric Long COVID website:
https://www.kennedykrieger.org/training/programs/project-echo/current-echo-series/pediatric-long-covid-echo

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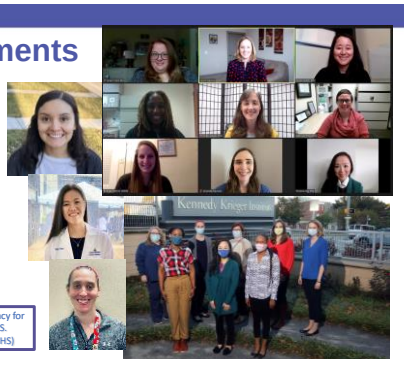
Acknowledgements



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