ECHO-Bateman Horne Series
September 20, 2022

Pediatric Long COVID

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Disclosures and Conflicts of Interest

- Eryka Pawlak: None

- Dongngan Truong:
  - Grant Support: NIH
  - Co-PI on research that receives funding from NHLBI Pediatric Heart Network and Pfizer

Objectives

- Understand pediatric long COVID in the spectrum of other post-viral syndromes
- Better understand pediatric long COVID
  - Prevalence
  - Who gets pediatric long COVID
  - Clinical symptoms/manifestations
- Inform of Primary Children's Hospital Long COVID Navigation Clinic

Post-Acute Sequelae of COVID-19 (PASC)/Post COVID Syndromes

- New or persistent symptoms after the acute COVID-19 infection
- Pediatric PASC
  - Multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C)
  - Long COVID
- Much less data on pediatric long COVID than
  - MIS-C
  - Adult long COVID

Long COVID vs Other Pediatric Post-Viral Sequelae

- The concept of post-viral syndromes and persistent sxs is not new to peds

Table 1. Established long-term sequelae and complications by organ system for common pediatric infectious diseases according to available literature.

Parameters	Chronic fatigue	Lungs	Heart	Kidneys	Immune system	Brain	Cancers
RSV	–	✓	–	–	–	–	–
EBV	✓	–	–	–	✓	✓	✓
Measles	–	–	–	–	✓	✓	–
Poliomyelitis	✓	✓	✓	–	–	–	–
Influenza virus	✓	–	–	–	–	–	–
HIV	✓	✓	✓	✓	✓	✓	✓
Streptococcus pyogenes	–	–	✓	✓	–	✓	–
Dengue virus	✓	–	–	–	–	–	–
Chikungunya virus	✓	–	–	–	–	–	–
SARS-CoV-2	✓	✓	✓	✓	?	✓	–

For patients' experience refer to Box 1, for literature details refer to the Supplementary Box.

Buonsenso D et al. Long-term outcomes of pediatric infections: from traditional infectious diseases to long Covid. Future Microbiol. 2022 May;17:551-571.

Differences Between Peds/Adult COVID/Long COVID

- Most children and adolescents had mild disease (some asymptomatic)
  - Most were not hospitalized with COVID-19, even less in ICUs
- Children were/are less likely to be tested for COVID-19 than adults, even when testing was more widely available
  - Waning antibodies for testing can also be hard to interpret in dx long COVID
- <18 year old population encompasses wide spectrum of development
- Reliance on parents/other caregivers for care, symptom evaluation
- Much of current and future research will most likely focus on adults
  - Treatment strategies

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Limitations to Pediatric Long COVID Research

- Lack of standard definition in research (and clinically)
  - No specific pediatric definition
  - Varying duration of symptoms, typically 4-12 weeks post acute infection
- Inclusion of children without confirmed SARS-CoV-2 infection
- Variable follow-up times

- WHO case definition:

"Post COVID-19 condition occurs in individuals with a history of probable or confirmed SARS CoV-2 infection, ***usually 3 months from the onset of COVID-19 symptoms*** *and that* ***last for at least 2 months*** *and* ***cannot be explained by an alternative diagnosis****... 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."*

https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1

Limitations to Pediatric Long COVID Research

- Reliance on self- or parent-reported sxs
  - Often without clinical assessments
  - No standardized testing assessment
- Absence of control groups
- Denominators are unknown
- Bias
  - Selection
    - Those affected more likely to respond
    - Higher SES with access to apps and internet
  - Non-response
  - Recall

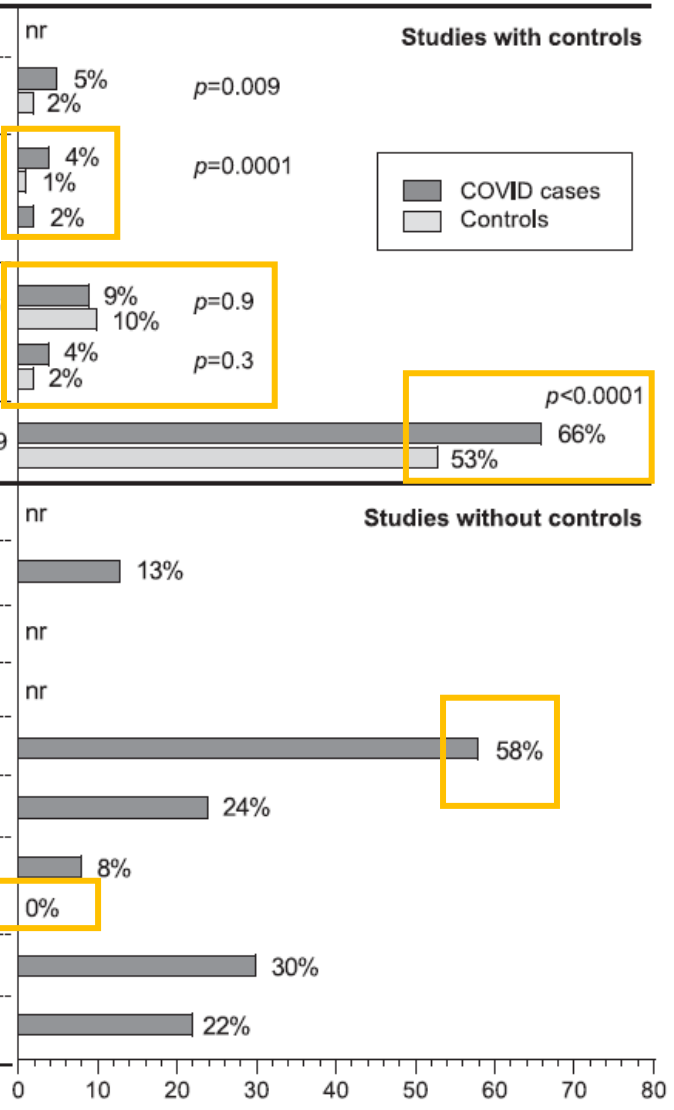
Prevalence

- Prevalence of pediatric long COVID has been highly variable
- Early data suggested that the prevalence of long COVID may be >50%
- Subsequent studies note this is more likely up to about 4-6%
- Accurate determination plagued by limitations

Taquet M, et al. Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med. 2021 Sep 28;18(9)

Zimmermann P, et al. How Common is Long COVID in Children and Adolescents?, The Pediatric Infectious Disease Journal: December 2021 - Volume 40 - Issue 12 - p e482-e487

First author	Country	Study	Age (y)[a]	Timing	Cases	Controls	Prevalence of patients with persisting symptoms
Blankenburg	Germany	CS	median 15 (14-16)	nr	nr	nr	nr
Miller	UK	PCS	nr, ≤17	4w	8/174	72/4504	5% vs 2%, p=0.009
Molteni	UK	PCS	median 13 (10-15)	4w	77/1734	15/1734	4% vs 1%, p=0.0001
				8w	25/1734	nr	2%
Radtke	Switzerland	PCS	median 11 (nr)	4w	10/109	121/1246	9% vs 10%, p=0.9
				12w	4/109	28/1246	4% vs 2%, p=0.3
Stephenson	UK	PCS	range 11-17	12w	2038/3065	1993/3739	66% vs 53%, p<0.0001
Ashkenazi-Hoffnung	Israel	PCS	mean 12 (5)	[b]	90	-	nr
Blomberg	Norway	PCS	median 8 (6-12)	5m	2/16	-	13%
Brackel	Netherlands	CS	median 13 (9-15)	nr	89	-	nr
Buonsenso	UK, USA	CS	mean 10 (3.8)	4w	510	-	nr
Buonsenso	Italy	CS	mean 11 (4.4)	[c]	75/129	-	58%
Osmanov	Russia	PCS	median 10 (3-15)	5m	126/518	-	24%
Say	Australia	PCS	mean 3.7 (3.5)	4w	12/151	-	8%
				12w	0/151	-	0%
Smane	Latvia	RCS	mean 9.2 (5.2)	[d]	9/30	-	30%
Sterky	Sweden	PCS	nr, ≤18	16w	12/55	-	22%



[a] mean (SD), median (interquartile range), or range;
[b] median 112d after infection, range 33–410d
[c] mean 163d after infection, SD 114d
[d] mean 101d after infection, SD 17d

Zimmermann P, et al. How Common is Long COVID in Children and Adolescents?, The Pediatric Infectious Disease Journal: December 2021 - Volume 40 - Issue 12 - p e482-e487

Pediatric Populations at Risk

- Factors that have been associated with long COVID development in <18 yo
  - Older age
  - Female sex
  - PMHx of allergic diseases
  - Worse pre-COVID physical or mental health
  - In those hospitalized, longer hospitalization correlated with >severe, persistent sxs

Zimmermann P, et al. How Common is Long COVID in Children and Adolescents?, The Pediatric Infectious Disease Journal: December 2021 - Volume 40 - Issue 12 - p e482-e487

Symptoms

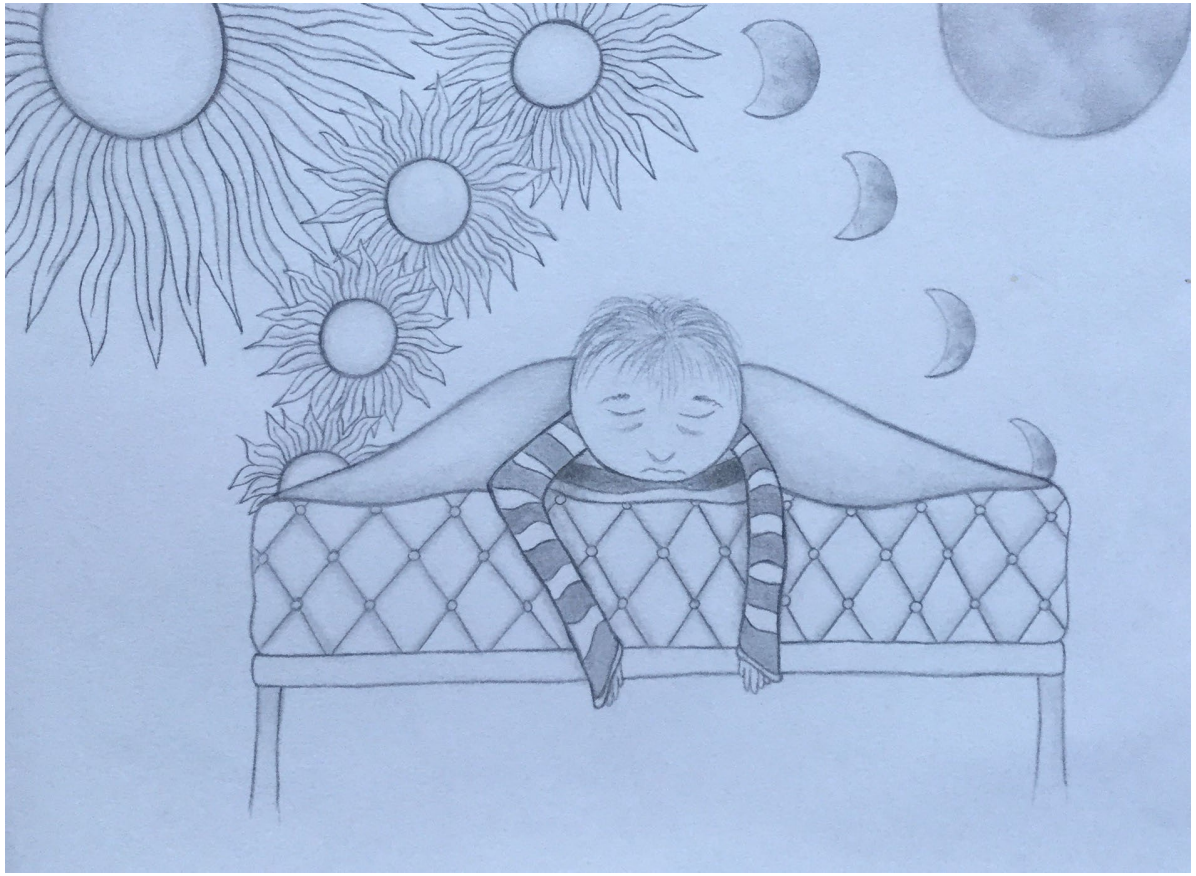
- Fatigue and malaise (general and post-exertional)
- Headaches
- Brain fog, attention problems
- Sleep disturbance
- Tachycardia and palpitations
- Chest pain
- Dysautonomia
  - POTS
  - Orthostatic intolerance

- Nausea*
- Abdominal pain*
- Rash
- Depression
- Anxiety
- Shortness of breath
- Chronic cough
- Fevers

Buonsenso D et al. Long-term outcomes of pediatric infections: from traditional infectious diseases to long Covid. Future Microbiol. 2022 May;17:551-571.

Pediatric Long COVID vs. Myalgic Encephalitis/Chronic Fatigue Syndrome

- Overlap of symptoms
  - Fatigue, post-exertional malaise, sleep disturbance, cognitive impairment, lightheadedness
- Cerebral blood flow reductions during upright posture
- Females>males
- No diagnostic test
- Sxs management is focus of tx
- BUT Dx ME/CFS requires 6 mos sxs
  - Separate entity vs. trigger?



"Lilly Klontz, age 16, from OK, created this artwork in response to a contest prompt asking participants to depict how having ME/CFS makes people feel." https://www.parentcenterhub.org/me-cfs/

Morrow AK et al. Long-Term COVID 19 Sequelae in Adolescents: the Overlap with Orthostatic Intolerance and ME/CFS. Curr Pediatr Rep. 2022;10(2):31-44

Long COVID, Pandemic Effects, or Both?

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

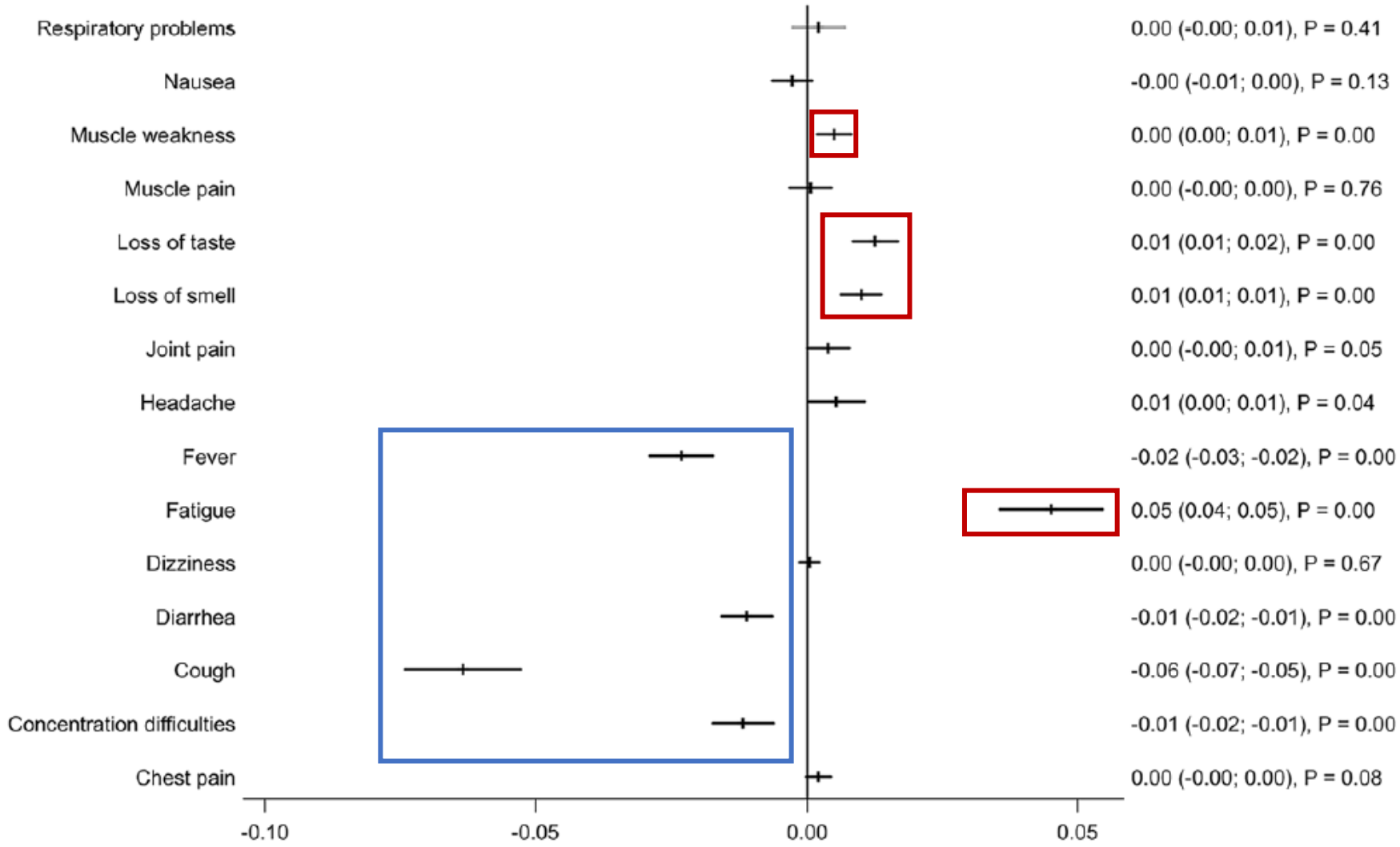
ORIGINAL ARTICLE

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

Luise Borch[1] · Mette Holm[2] · Maria Knudsen[3] · Svend Ellermann-Eriksen[4] · Soeren Hagstroem[5,6]

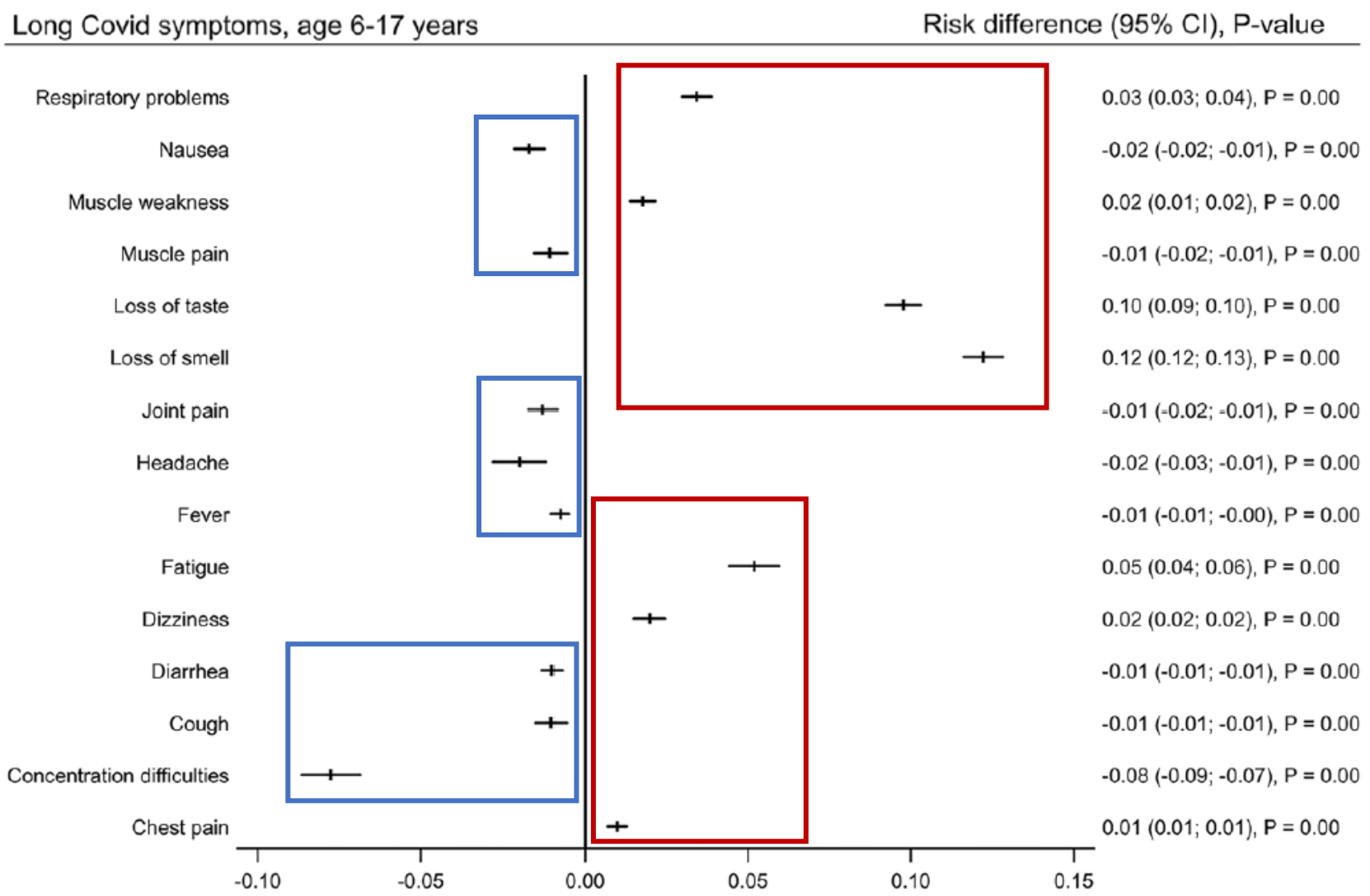
- Denmark (<18 yo): 37,522 COVID PCR+ vs. 78,037 controls (not tested +)
  - 44.9% (N=16,836) vs. 21.3% (16,642) response rates (cohorts: 15,041 vs. 15,080)
  - 0-5 yo: 14.8% COVID+ vs. 17.6% controls had sxs >4 weeks (p=0.001)
  - 6-17 yo: 28% vs. 27.2% had sxs >4 weeks (p=0.02)

Panel **B**



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

Panel **C**



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

scientific reports

Check for updates

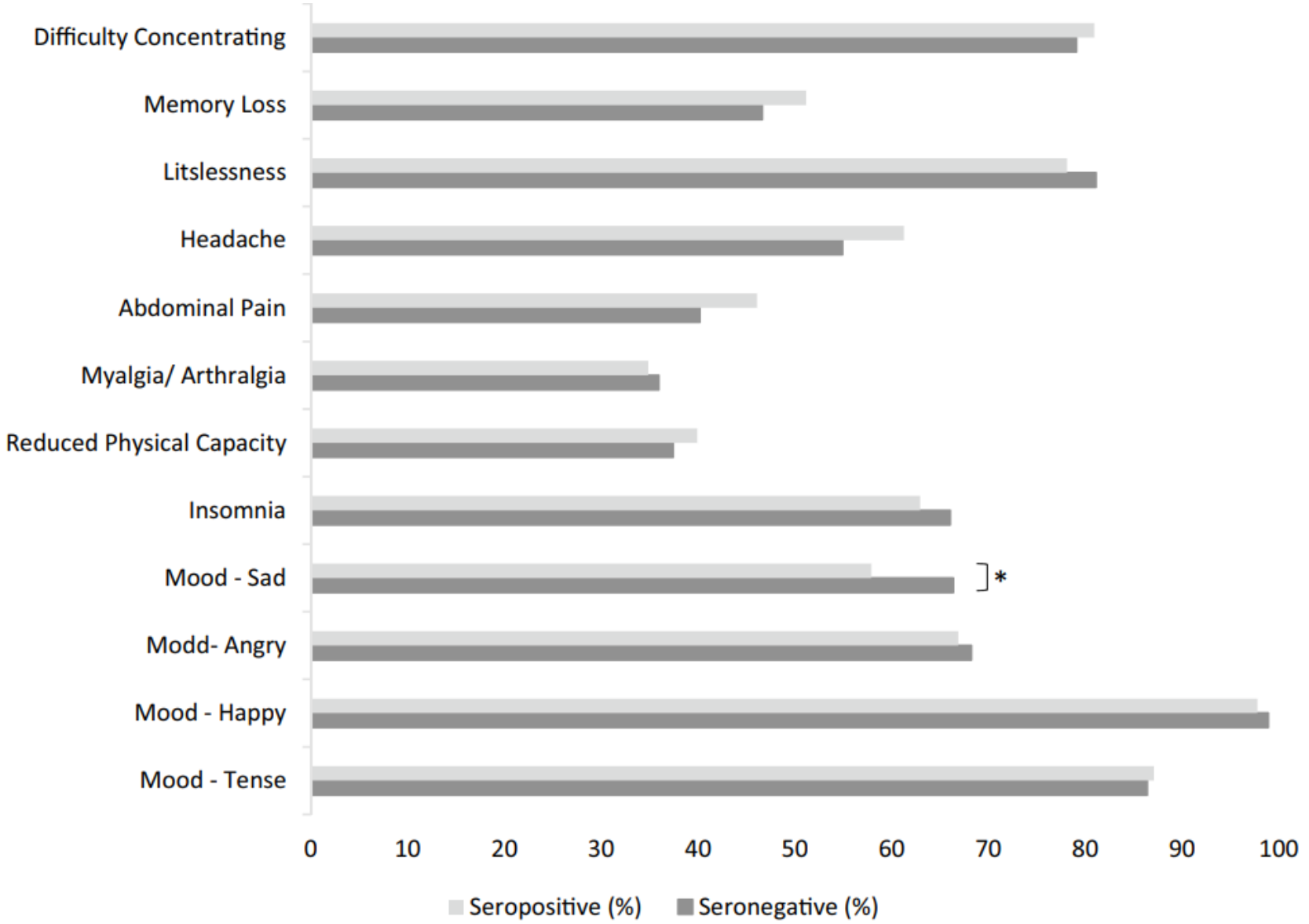
OPEN

Comparison of mental health outcomes in seropositive and seronegative adolescents during the COVID19 pandemic

Judith Blankenburg[1], Magdalena K. Wekenborg[2], Jörg Reichert[1], Carolin Kirsten[1], Elisabeth Kahre[1], Luise Haag[1], Leonie Schumm[1], Paula Czyborra[1], Reinhard Berner[1] & Jakob P. Armann[1]✉

- 1560 teens (median age 15 yo)
- 188 (12%) seropositive vs. 1365 (88%) seronegative (serial testing)
- 12 question long COVID-19 survey from Symptom Checklist-90-R, the Somatic Symptom Scale, and questionnaire about stress/stress management during March/April 2021 visit (SchoolCOVID19 study)

Blankenburg J, et al. Comparison of mental health outcomes in seropositive and seronegative adolescents during the COVID19 pandemic. Sci Rep. 2022 Feb 10;12(1):2246.



Blankenburg J, et al. Comparison of mental health outcomes in seropositive and seronegative adolescents during the COVID19 pandemic. Sci Rep. 2022 Feb 10;12(1):2246.

Research is Underway

- https://recovercovid.org/
- https://childrensnational.org/news-and-events/childrens-newsroom/2021/cnh-and-niaid-launch-large-study-on-long-term-impacts-of-covid-19-and-mis-c-on-kids

Primary Children's Long COVID Navigation Clinic

The Heart Center
At Primary Children's Hospital

U HEALTH UNIVERSITY OF UTAH

Intermountain Primary Children's Hospital

Rationale

- Anticipated the need within the pediatric population
- Lots of questions from families/providers if a long-COVID clinic would be established for children/adolescents
- Unknowns and considerations
  - How great will the need be, and how can we adapt quickly as the need becomes clearer?
  - Navigation clinic vs. multidisciplinary subspecialty clinic?
  - Separating long-COVID from other entities?
- Major aim: To support children and adolescents with long COVID and help them return to functional status
  - Return to school and activities

Care Team

Eryka Pawlak, NP-C
Clinic Nurse Practitioner (0.5 FTE)

Dongngan Truong, MD, MS
Medical Director

Shaylnn Mackie, MA PRN

Corrine Espinoza, Psychologist (0.1 FTE)

- Starting October 2022

PCH Long COVID Navigation Clinic

- Opened in mid April 2022
- Help to evaluate for alternative diagnoses
- Refer as needed to specialist care and assist in the management of symptoms
- **Telehealth clinic** that can virtually see patients <18 years old in Utah, Nevada, Idaho and Montana
  - We hope to see patients from Wyoming soon
- Patients need to be referred by their PCP, 2 ways:
  - Electronically through iCentra
  - Via fax at 385-297-2750

PCH Long COVID Navigation Clinic

- Half-day clinic a week
  - 60 minute appointments
- We use WHO definition for clinic (though no one has been turned away)
- Red Cap Survey, to be completed ahead of time
  - Past medical & surgical history
  - Family history
  - COVID 19 history with current symptoms
  - Functional status and behavioral health
    - Functional disability index
    - SSS8
    - Mental fatigue screening
    - Day of clinic PHQ-9 depression screening

Who We Have Seen

- Total new patients seen in clinic: 43
- Follow- ups: 10
- Female: 31 (72%)
- Age range: 5 months to 17 years
- Most common symptoms: fatigue, orthostatic intolerance/dysautonomia symptoms, pain-abdominal, chest, muscle/joint, and headaches, brain fog, sleep problems, exercise intolerance, anxiety & depression
- Most common referrals we have made
  - Integrative Medicine, Behavioral Health, Physical Therapy, Cardiology (for Orthostatic Intolerance Symptoms)

Next Steps

- Broaden our reach to Wyoming
- Website, getting the word out
- Working on physical space to see some patients in-person
- Hoping for future collaborations with the new PAUSE clinic
  - Similar goals
  - Similar patient populations
  - Resource sharing
  - Alignment of treatment modalities and practices
  - Uniform education

A Typical Scenario

- 17 yo presented 5/12/2022 (COVID-19 infection 11/2020)
- Initial sxs: Headache; tested because father texted positive
  - No hospitalization, no meds; no persistent sxs
- 2nd COVID infection: Sxs around 2/1/2022, Ab testing + 2/26/2022
  - Fatigue, headaches; resolved then restarted
- No COVID-19 vaccination
- Sxs at initial appt
  - Brain fog, memory loss, confusion, difficulty concentrating, dizziness, depression, anxiety, problems sleeping, heart palpitations, racing heart- followed by dizziness then passing out on a regular basis, shortness of breath, generalized weakness without focal weakness , fatigue, abdominal pain, and nausea
  - Worst sxs: Tachycardia, syncope, fatigue

Initial Questionnaire Results

Functional Disability Inventory= 36 (severe)

Sleep Disturbances= 27 (high)

PHQ Depression Scale 2a90
4/27/22 (Parent): 19 (mod severe) No thoughts of harming self or wanting to be dead
5/12/22 (Patient):16 No thoughts of harming self or wishing to be dead

Parent Pain Pcs= Total score 0

Checklist Individual Strength- Mental Fatigue= 15 (moderate)

Somatic Symptom Scale (SSS8)= 17 (very high)

9 out of 10 debilitation score

25% baseline mood

0% baseline activity participation

50% baseline for school function

Prior Work-up and Referrals by PCP

- Normal labs: Celiac Disease Dual Antigen Screen, CRP, CMP, ESR, CBC (except for elevated lymphocytes at 69%), ferritin, free T4, TSH
- Strep A cx: NEG
- SARS COV2 IgG Antibody: Positive
- Referral to Behavioral Health

What We Recommended

- Testing
  - Labs: Vitamin B12, Vitamin D levels (never obtained)
  - ECG: Normal
- Referrals
  - Cardiology: dx'd with orthostatic intolerance
    - Increase fluids and salt intake
    - Regular exercise/stretching if tolerated
    - If sxs not improving in 2-3 months, consider ivabridine
  - Behavioral Health
  - Integrative Medicine

- Symptom management recommendations
  - Sleep hygiene
  - Brain fog advice
  - Pacing
  - Stay involved with family, friends and activities but modified to as tolerated
  - Journal symptoms for 2 weeks
  - Follow up in 2 months

Follow-up 3 Months Later…

Functional Disability Inventory= 31 (severe; was 36)

PHQ Depression Scale 2a90 (patient)= 13 (mild-mod; was 16). No thoughts self-harm, wishing for death

Checklist Individual Strength- Mental Fatigue= 18 (moderate; was 15)

Somatic Symptom Scale (SSS8)= 22 (very high; was 17)

- Reported that she has seen "a whole lot" of improvement since her last appointment
- Feels like her symptoms are better and more manageable than they previously were

5 out 10 debilitation score (last appt 9 out of 10)

50 % baseline mood (last appt 25%)

25% baseline activity participation (last appt 0%)

75% baseline for school function (last appt 50%)

What We Did at Follow-up

- Tests: Re-ordered Vit B12, and Vit D levels
  - Ordered ferritin and Iron
- Referrals
  - Speech Therapy for cognition evaluation
- Symptom Management Recs
  - Continue pacing; avoiding push-crash cycle
  - Drink 2-3L of non-caffeinated fluid/day, salty snacks
  - Consider compression socks, particularly with marching band
- Symptom Management Recs
  - Sleep hygiene
  - Breathing exercises (John Hopkins) daily
  - Constipation management & trial peppermint oil or Heather's Tummy Tamers for abdominal pain
  - Vaccinate against COVID-19
  - Wrote 504, including the following accommodations: use of elevator, bathroom pass, access for water and salty snacks, ability to take a break for 15 minutes as needed (in RN office if possible) for fatigue, no heavy lifting over 15 lbs
  - Plan for follow up with Long COVID Navigation Clinic in the next 2-3 months or sooner if needed

In Summary

- Similar to adults, pediatric long COVID is a complex disease with much to be learned
- Need for pediatric specific definitions, large studies with testing, trials
- Separating long COVID from pandemic effects will be difficult, but in general, many children/adolescents are struggling
- The PCH Long COVID Navigation Clinic is here to support the children and adolescents of the Intermountain West with long COVID

Questions?