More information on long-term outcomes in Covid-19 patients (including children)

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Game plan

- Examine some new articles on Covid-19 long haulers, including children…an area with far fewer published findings
- Revisit a JAMA article on long-term outcomes among Covid-19 survivors, among both outpatient and hospitalized patients (a summary report)

Objectives

- Recognize that long-term complications from even mild cases can be measured weeks to months post recovery, including in children
- Describe some of the abnormalities among Covid-19 survivors in major organ systems (pulmonary, neurologic, cardiac)…both signs and symptoms, for adults and children
- Pass a take-home test at the end

Take home messages

- SARS-CoV-2 effects multiple organ systems and can have long-term consequences...we do not know yet how long they can last, and the true definition of 'long-haulers'
- Even among mildly ill Covid-19 patients, cardiovascular, neuro, and pulmonary abnormalities can be measured many months post recovery…including in asymptomatic younger patients and children
- A multidisciplinary approach to management of 'long-haulers' may be indicated for your clinic patients...including mental health experts with pediatric experience

Introduction

- Most of the published reports to date have been focused on short term complications post Covid-19 in adults
- Several case reports and case series suggest SARS-CoV-2 affects CV, neuro and pulmonary systems in the 'short haul'—some new studies take us out to 8 months
- Mechanisms proposed for many outcomes: ex: for CV long-term: plaque rupture, stent thrombosis, Increased cardiac output leading to stress of muscle, endothelial cell inflammation
- 2020 Italian study post Covid-19, only 12.6% of adult patients were symptom- free after two months…similar findings from Wuhan
- Lots of TV news coverage on pediatric long-haulers, mostly anecdotal reports…few published studies on kids

Case series on long Covid in children in Sweden (Ludviggson, 2021)

- Series included 5 children ages 9-15 years
- Early signs/sxs included fatigue, SoB, palpitations, chest pain, headache, difficulty concentrating, weakness, dizziness, sore throat
- All in the series had at least one symptom or sign at 6-8 months
- (Author could not find any other papers in his systematic review of this topic, at that time)

Long Covid in children in Italy
(Buonsenso et al, 2021)

- Cross sectional survey
- Two pediatricians interviewed caregivers or study participants
- One hospital in Rome (Gemelli)
- Part of a 24 month study (cohort)

Results from Italian study

- N=129 participants with Covid-19, aged 18 or less
- Mean age 11 years
- Assessments done average of 5.3 months post dx
- 40% recovered/36% 1 or 2 symptoms/23% with 3 or more sxs
- Thus, over half had symptoms at 4 months
- Persistent symptoms more common among hospitalized kids
- MIS-C in 2.3% of children
- Next slides show symptom prevalence at 5.3 months (average), by symptom status at time of positive Covid test

Persisting symptoms	N 129	Asymptomatic N 33	Symptomatic N 96	P value
Fatigue (compared to before Covid-19 diagnosis)				0.453
Less	1 (0.8%)	0 (0%)	1 (1%)	
A bit less	16 (12.4%)	2 (6.1%)	14 (14.6%)	
Same	98 (75.9%)	29 (87.9%)	69 (71.9%)	
A bit more	13 (10.1%)	2 (6.1%)	11 (11.5%)	
More	1 (0.8%)	0 (0%)	1 (1%)	
Nasal congestion/rhinorrhea	16 (12.4%)	1 (3%)	15 (15.6%)	0.112
Chest tightness	8 (6.2%)	0 (0%)	8 (8.3%)	0.196
Chest pain	4 (3.1%)	1 (3%)	3 (3.1%)	1
Persistent cough	7 (5.4%)	1 (3%)	6 (6.2%)	0.796
Persistent muscle pain	13 (10.1%)	1 (3%)	12 (12.5%)	0.221
Joint pain or swelling	9 (6.9%)	1 (3%)	8 (8.3%)	0.525
Headache	13 (10.1%)	1 (3%)	12 (12.5%)	0.221
Alternated smell	6 (4.6%)	0 (0%)	6 (6.2%)	0.321
Alternated_taste	4 (3.1%)	0 (0%)	4 (4.2%)	0.542
Lack of concentration	13 (10.1%)	1 (3%)	12 (12.5%)	0.221

Insomnia	24 (18.6%)	2 (6.1%)	22 (22.9%)	0.059
Hypersomnia	4 (3.1%)	2 (6.1%)	2 (2.1%)	0.579
Weight loss	10 (7.7%)	2 (6.1%)	8 (8.3%)	0.965
Diarrhoea	2 (1.5%)	0 (0%)	2 (2.1%)	0.985
Stomach/abdominal pain	3 (2.3%)	0 (0%)	3 (3.1%)	0.72
Constipation	8 (6.2%)	1 (3%)	7 (7.3%)	0.647
Skin rashes	9 (6.9%)	3 (9.1%)	6 (6.2%)	0.876
Palpitations	5 (3.8%)	1 (3%)	4 (4.2%)	1

Sydney cohort, Long Covid in adults (Darley et al, 2021)

- 99 PCR positive patients from one hospital, followed forward
- Part of a 2 year cohort
- This report focuses on the 8th month post infection
- Questionnaires on health and mental health
- Simple analyses thru logistic regression (univariate)

Results, Sydney study

- 40% had one or more symptoms at 8 months
- Most common persistent symptoms were fatigue and SOB
- Among those with long Covid at 4 months, most had no changes or very little change at 8 months
- RR for long Covid included female sex and history of hospitalization for Covid-19 (see table following)
- Mental health issues associated with long Covid were (predictably) frequently reported

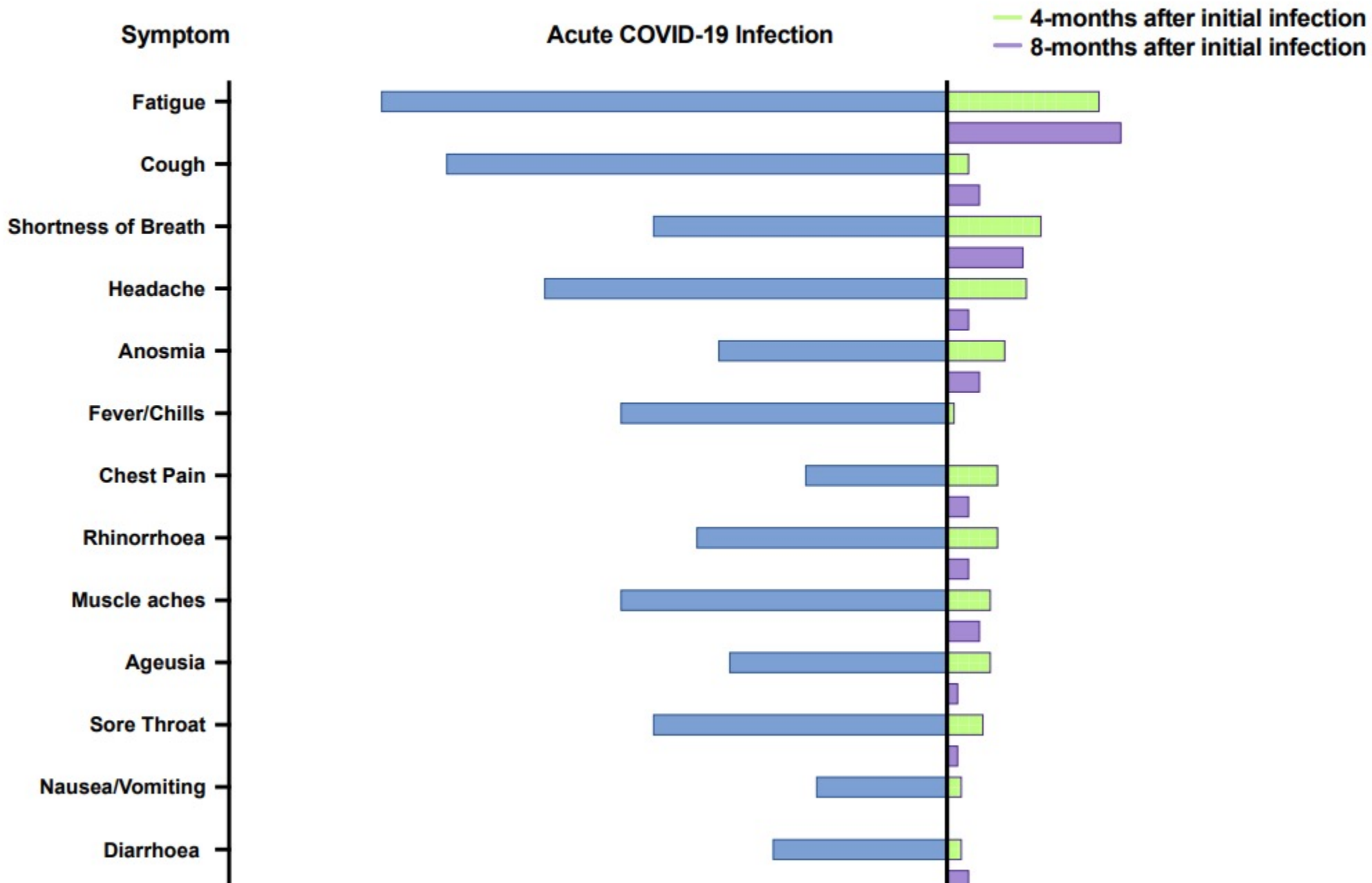
Variable	Univariable Odds Ratio (95%CI)	P value	Multivariable Odds Ratio (95% CI)	P value
Gender - Female - Male	 2.7 (1.2-6.3) Reference	 0.02	 3.2 (1.3-7.8) Reference	 **0.01**
Hospitalisation - Yes - No	 2.9 (0.9-9.4) Reference	 0.09	 3.8 (1.1-13.6) Reference	 **0.04**
Age at diagnosis (1-unit)	1.0 (1.0-1.0)	0.35		
Hospital Length of Stay	1.7 (0.9-3.1)	0.08		
Co-morbidities - Yes - No	 0.9 (0.4-2.2) Reference	 0.87		

Table 3. Comparison of recovery Likert questionnaire in patients with Long COVID at 8-month assessment compared to those without (n=98).

Variable	Total Cohort (n=98)	Long COVID (n=39)	Without Long COVID (n=59)	p-value
I have fully recovered from after COVID-19 - Slightly Agree, Agree or Strongly Agree (n, %-total)	78/98 (80%)	21/39 (54%)	57/59 (97%)	<0.001
I feel confidence returning to pre-COVID-19 work - Slightly Agree, Agree or Strongly Agree (n, %-total)	88/98 (90%)	30/39 (77%)	58/59 (98%)	<0.001
I have returned to my usual activities of daily living - Slightly Agree, Agree or Strongly Agree (n, %-total)	89/98 (91%)	31/39 (80%)	58/59 (98%)	0.002
I have returned to my normal exercise level - Slightly Agree, Agree or Strongly Agree (n, %-total)	76/98 (78%)	23/39 (59%)	53/59 (90%)	<0.001

COVID-19 = Acute coronavirus disease 2019

infection compared with 8 months after assessment (n=66).



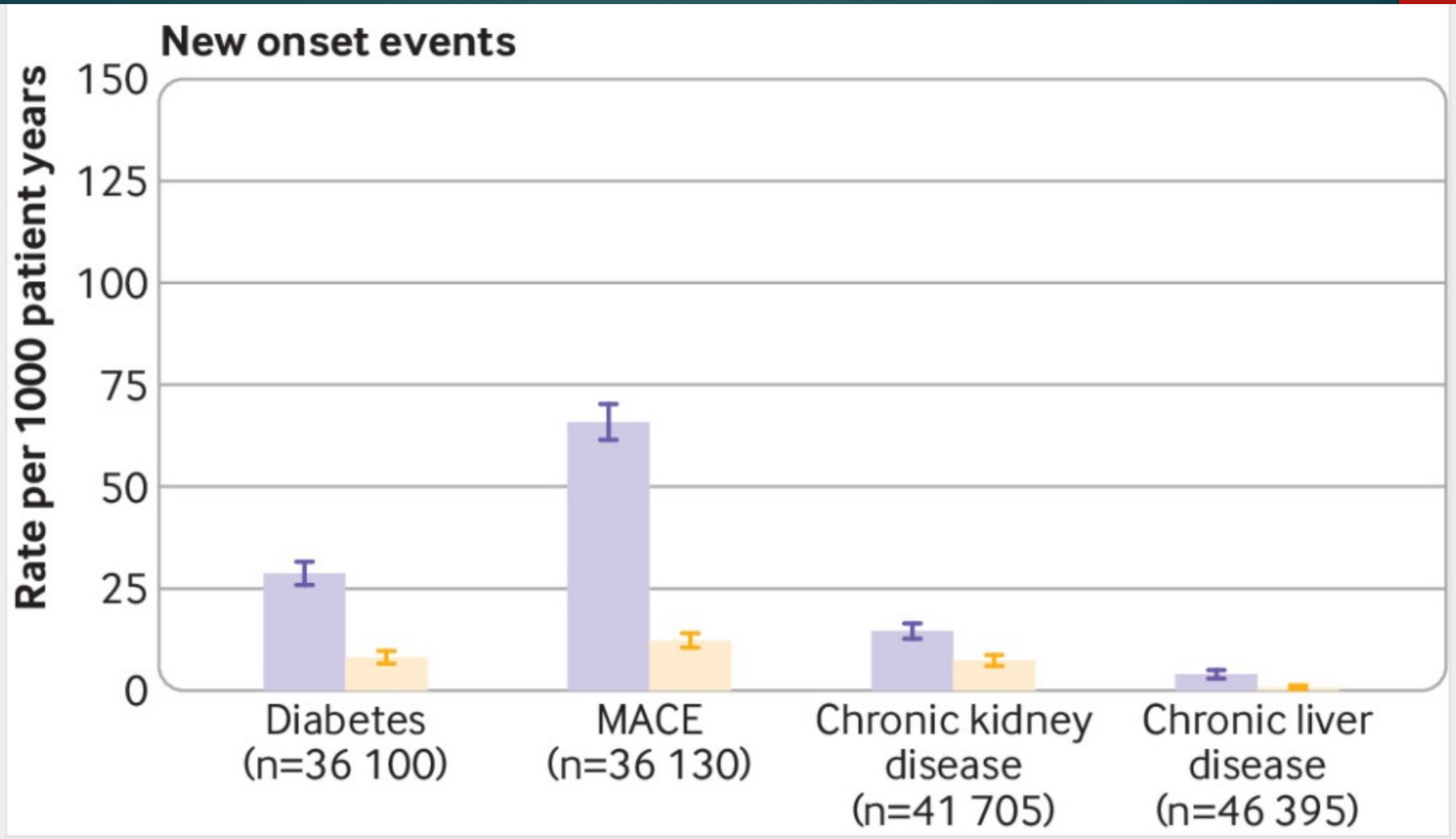
Post-Covid syndrome: retrospective cohort (Ayoubkhani et al, BMJ, 2021)

- 47780 Covid-19 survivors in UK followed for 5 months post d/c
- Comparison cohort of randomly selected UK citizens, matched on a few key factors, not diagnosed with Covid-19
- Mean age 65 years
- Study participants followed (electronically) for outcomes
- Endpoints were all cause mortality, cause-specific mortality, admissions for organ-specific disease (including new events)

- Caution: the authors mis-use terms…cohort studies do not include controls, they include exposed and unexposed persons.

Principal findings

Three major findings were found in this large study examining post-covid syndrome in 47 780 patients admitted to hospital with covid-19 in England, matched to controls. Firstly, admission to hospital for covid-19 was associated with an increased risk of readmission and death after discharge compared with individuals with similar personal and clinical characteristics in the general population over the same period. After admission to hospital for covid-19, 29% were readmitted and 12% died within a mean follow-up of 140 days. Secondly, rates of multiorgan dysfunction after discharge were raised in individuals with covid-19 compared with those in the matched control group, suggesting extrapulmonary pathophysiology. Diabetes and major adverse cardiovascular event were particularly common,


New onset events
Rate per 1000 patient years
150
125
100
75
50
25
0
Diabetes (n=36 100)
MACE (n=36 130)
Chronic kidney disease (n=41 705)
Chronic liver disease (n=46 395)

‘Long-hauler’ article, Del Rio et al, JAMA (review of multiple studies)

- CDC phone survey, n=292, all 18 years or older
- All had positive test for SARS-CoV-2
- 35% reported sub-normal health after 12 weeks
- Higher percent of abnormalities reported with increasing age
- Most commonly reported symptoms: fatigue, dyspnea, joint pain, chest pain

Behavioral health/mental health

- The JAMA review by Del Rio touches on the importance of long-term consequences for patients and clinicians who care for them
- Washington Post did article on this issue for children months ago, with an additional article more recently
- Chronic fatigue is a frequent post-Covid-19 long-term complaint (Nature, 2020), with similar picture in children (tho fewer data)
- Providers and health care planners may want to start ramping up for this set of outcomes, in addition to long-term physiological clinical management challenges…in kids as well as adults

Additonal ongoing research in this arena, in children

- UK, King's Hospital (so far, at the one month mark, 15% of kids less than 16 years old had one persistent symptom)
- Norton Hospital in Louisville, KY
- Childrens Hospital in Omaha

Ongoing research in this arena, among adults

- Large (10,000) Covid-19 patient cohort now followed in UK with goal of monitoring multiple outcomes for one year
- Similar but smaller study in US
- US Veterans study
- Rhineland Study in Bonn: 5,000 participants…immune system focus related to long-term outcomes in multiple organ systems (genes, environment, behavior considerations). Not all are Covid survivors.
- Norwegian Mother-child cohort, also immune system focus
- Iceland genetic studies, immune system focus, 50,000 participants
- Citizen-Scientist Covid-19 surveys (US and UK)
- Post hospitalization survey Covid-19 (UK)

Take home test

- What advice would you give parents of a 9 year old who was recently shown to have a PCR positive test for SARS-CoV-2, with mild Covid symptoms, related to long term effects?
- This long-term outcome is the most common symptom reported in most follow-up studies. What is it for children?
- True or false: behavioral health issues, including anxiety, depression, substance use disorder, are likely to increase the further we progress into the Covid-19 pandemic
- True or false: Cohort studies typically include controls in the design and implementation of such studies

References

- "Limited recovery from post-acute sequelae of SARS-CoV-2 (PASC) at eight months of a prospective cohort," Darley et al. Preprint available at *medRxiv*. https://www.medrxiv.org/content/10.1101/2021.03.29.21254211v1
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- Thanks to Grazia for peds article

- Buonsenso et al. 2021 https://www.medrxiv.org/content/10.1101/2021.01.23.21250375v1.full-text

- "Post-acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT," Ball et al. Preprint available at *medRxiv*. https://www.medrxiv.org/content/10.1101/2021.03.29.21254588v1

- Ludvigsson. Acta Peds 2021:110; 1914