Transcript

Quinn Barnette:

Welcome everyone to the RECOVER Research Review, or R3 Seminar. My name's Quinn Barnette. I'm an epidemiologist with the RECOVER Administrative Coordinating Center, and I'll be your moderator for today's session. The goal of this seminar series is to catalyze a shared understanding of the research within the RECOVER Consortium. I want to start by thanking everyone who submitted questions in advance, and remind everyone that you can submit any questions during today's presentation using the Q and A feature in your Zoom menu.

After today's panels, our speaker will answer as many questions as possible. A Q and A document will also be posted with the recording of the seminar on recovercovid.org. The document will include the answers for submitted questions relevant to today's presentations. Questions about other scientific topics will be addressed in future seminars, and answers to broader questions about RECOVER will be available in the FAQs found at recovercovid.org. As a reminder, we cannot answer questions about individual clinical care.

I'm pleased to share that our presenters today are Dr. Melissa Stockwell, Dr. Tanayott Thaweethai, Dr. Rachel Gross, and our discussants will be Ms. Megan Carmilani and Dr. Andrea Foulkes. Dr. Stockwell is the chief of the Division of Child and Adolescent Health and the Felice K. Shea Professor of Pediatrics in the Department of Pediatrics at Columbia University's College of Physicians and Surgeons, and a Professor of Population and Family Health in the Department of Population and Family Health at the Mailman School of Public Health. She's also the founding director of the Department of Pediatrics Center for Children's Digital Health Research. Dr. Stockwell serves as contact PI for Columbia University's NIH RECOVER Study Hub and chair of the RECOVER Pediatric Coordinating Committee.

Dr. Gross is a general academic pediatrician, a clinical research investigator, and an associate professor of pediatrics and population health at the NYU Grossman School of Business. She's the principal investigator and director of pediatric research for the RECOVER Clinical Science Corps, leading the implementation of the Pediatric Observational Cohort Study.

Dr. Thaweethai is the Associate Director of Biostatistics Research and Engagement in Massachusetts General Hospital Biostatistics. He's also an instructor in medicine at Harvard Medical School, and an instructor in the Department of Biostatistics at the Harvard T.H Chan School of Public Health. And he serves as lead statistician in the Data Resource Corps for the RECOVER initiative. He's also co-investigator of an NHLBI-funded RO1, titled Statistical Methods in COVID-19 Clinical Research.

Ms. Carmilani is the founder and president of Long Covid Families, a non-profit organization dedicated to supporting children with long COVID and their families. With over 20 years of experience in patient advocacy and a background as a former public school teacher, she's navigated the challenges of living with poorly understood infection-associated conditions for over 30 years. She's a member of the RECOVER Initiative Pediatric Coordinating Committee and contributes to the RECOVER National Community Engagement Group to ensure that research addresses the needs of patients, caregivers in the community.

Finally, Dr. Foulkes is Director of Biostatistics at Massachusetts General Hospital, professor of Medicine at Harvard Medical School, and the professor in the Department of Biostatistics at Harvard T.H Chan School of Public Health. She serves as principal investigator of the Data Resource Corps for the RECOVER Initiative, where under her leadership, the Data Resource Corps has contributed to novel breakthroughs in ever-evolving comprehension of COVID-19 through applied statistical analysis on patient data and prior clinical research.

The topic of today's seminars is Characterization of Long COVID Among Children and Adolescents, Pediatric Cohort Insights. Today's speakers will present some early findings from the RECOVER Pediatric Observational Cohort Study, and they'll present a symptoms-based approach for identifying children and adolescents with long COVID from a study recently published in the Journal of the American Medical Association. Please welcome all of our speakers. And with that, I will turn it over to our first presenter, Dr. Stockwell.

Dr. Melissa Stockwell:

Thank you so much, and we're really excited to be here today to share with you some of our really hot off the press findings. Next slide. I'm going to briefly give a background on long COVID in children and what sort was known before, a little bit about the RECOVER Pediatric Study, and then I'm going to turn it over to my colleagues who will go into the analysis from this paper. And then we'll finish up with some next steps for RECOVER-Pediatrics. Next slide.

So, what is currently known about long COVID in Children? Next slide. Most of what we know about long COVID is actually from adults. And when it comes to long COVID in children, there really were many and are many more questions than answers. So there was an early misconception, if you remember back in 2020, that children and adolescents didn't get COVID. And we knew that wasn't true.

And similarly, there's a current misconception that children and adolescents don't get long, or if they do, that their symptoms are the same as adults. And we sort of knew the first part wasn't true, that they definitely do get long COVID, but not a lot was known about what their symptoms will look like. And that has led, unfortunately, to a really large-level under recognition of long COVID in this population. Next slide.

We really do like to always bring it back to patients and their families. So I'm just going to read two quotes from RECOVER Families. So the first was, "My daughter had COVID in December 2022, and months later she was really struggling. She's been out of school for six weeks with debilitating fatigue, pain and brain fog, none of which show any signs of letting up. All in all, COVID has been a devastatingly difficult journey for my family. It's not one I wish on anyone." And we really feel like our mandate in RECOVER overall, but also for the Pediatric Cohort, is really to find some relief for these families and children and adolescents. Next slide.

This is from another person in RECOVER. "When my daughter tested positive for COVID in October 2021, she had pain in several parts of her body, along with fatigue. The fatigue failed to immediately subside and the pain, which went away for about a week, returned worse than before, preventing her from being touched at all. After months of physical and occupational therapy,

acupuncture and massage treatment, she's now 100%, although I think sometimes emotionally she's a little bit different."

This quote is actually really interesting for me to look back on now that actually we have some of the results from our study, but also to understand that even when children and adolescents have gotten better, and we hope that they do, there is and always maybe a residual effect that things may not totally go away. Or if they do, there's always a concern that they could come back. Next slide.

So what are some unique challenges in understanding long COVID in children? The first is that there's difficulties in assessing symptoms in children, especially younger ones. There could be inconsistent manifestations of symptoms. The assessments of conditions could be dependent on developmental stage. So again, looking different for different ages, and obviously there could be issues with recall.

And there's limitations of the current research that had been out there. The first was that many lacked a comparison group. And that's really important for pediatric and adolescent studies, because although everybody was affected by the pandemic, children and adolescents were very much affected by everything that went on. And so it's really important to tease out what it may be from an infection itself versus what was by being a child during the pandemic, both of which are incredibly important, but it's really important that we separate them out.

We also lack a standardized definition across studies. What is long COVID in children? There can be time varying from infection, there can be small sample sizes, and that's a real problem if we really want to understand differences based on age, there can be selection biases and misclassification bias, and then there's been limited to no follow-up for recovery and relapse. And so that longitudinal part is incredibly important. Next slide.

So if we're sort of thinking about long COVID in children, it's important to kind of think about, they're four potentially broad categories. The first are children who have an underlying condition that could have gotten exacerbated during an infection, then continues at a worsened level. There can be persistent of symptoms that happen in an acute infection, and then there can be de novo conditions, so children and adolescents, who after the COVID infection, develop new conditions. And then there's obviously the MIS-C, which we're going to kind of put aside here, which I think there's a lot more information about. And what we really need to do is understand more about the long COVID part of it. Next slide.

The prevalence of long COVID in children has been something that's been hard to pin down. There are early reports suggested 4 to 58% affected children have persistent symptoms. There are some meta-analyses where it was 2 to 70%, another one that's at 25.2%, another one that looked at 2 to 5%. That's because, again, there hasn't a definition. There's difference in terms of how long the time points that we're using.

But I think what's really important to understand is that even if we're going to use a lower end of this, say 2 to 10% and we're saying that's 1.4 million children, or if we're going to say 10% of all the children who are antibody-positive, which there are 65 million, and that's 6 million children, a disease is considered to be rare when it affects less than 200,000 children in the US. So no matter what, long

COVID is not in children and adolescents, is not a rare disease, but this is something that's really important that we understand. Next slide.

So up until this point, there have been papers that have sort of looked at different constellations of symptoms. Some of these will look very familiar to you, potentially from the adult literature. So, neurologic changes, mental health changes, cardiorespiratory, and then really lots of things in different organ systems. But it was really unclear how these symptoms might vary by children's age. And so again, do children and adolescents look different from each other and do they look different than adults? Next slide.

So, what is RECOVER Pediatrics and how do we seek to fill this critical research gap or gaps? Next slide. So I think everybody at this point knows what RECOVER stands for. It's a research project that aims to learn about long-term health effects of COVID. And obviously, the end goal is to better prevent and treat long COVID in the future, and it's an observational study. Next slide.

For RECOVER-Pediatrics, there are 103 enrolling sites all across the US and these are the hubs that are listed, and then these are our amazing cores. Next slide. And the Pediatric Study questions include, how many children are getting long COVID? Why do some children get long COVID and others do not? What symptoms do children feel when they get long COVID? How long are they sick for? What causes long COVID to happen? And then really important to us is, how does long COVID effect later physical health, mental health and development in children? And this is this, again, longitudinal part of the developmental part, and the life course impact is really important in this cohort. Next slide.

There are four parts to the RECOVER Pediatric Study. The first we call the Main Cohort. Those are children and adolescents and young adults who are 0 to 25 years old. They get enrolled either during an acute infection, post-acute, they've been uninfected as far as they know. We also enroll their caregivers. And there's the ABCD Cohort, which is adolescent only. They are children who are in the NIH Adolescent Brain Cognitive Development Study who cross enroll into RECOVER. And those two groups are who are the groups that we're going to focus on today for this analysis. Just wanted to mention there are other two. There's our Congenital Cohort, which you've probably heard about in other seminars, and then our MIS-C Cohort as well. Next slide.

Just very briefly, we have three tiers in the RECOVER Pediatric Cohort. The first tier one is fully remote, answers a lot of survey questions, and have some blood and saliva testing. And this study right now is focused on these tier one survey responses. We're also in the middle of tier two, where families answer more survey questions. They come in in person, have some simple exams, more blood tests and long and breathing tests and other tests. And then our tier three is our more in-depth imaging, echocardiogram, MRIs of brain and cardiac MRI, exercise testing, EEG, and lots of neurocognitive tests as well. Next slide.

So we think sort of conceptually about our analysis, our main analytic comparator is we're looking, again, at these children who were infected versus uninfected. Again, to try and tease apart what may be the infection versus being in the pandemic. This analysis, this seminar today is focusing on this first box, characterizing long COVID based on symptomatology by age and looking at the symptoms.

And we are very much actively working in on this right side as well. We're trying to understand and characterize phenotype, which you'll hear about a little bit today, but also evaluating risk and resiliency factors, really trying to understand mechanism and pathophysiology. And ultimately we all want to get to developing and evaluating interventions, that is most important to us. Next slide. I will stop here and hand it over to Rachel who will... Oh no, Tony. Rachel. Sorry, Rachel, who is going to going to kick us off. Thank you.

Dr. Rachel Gross:

Great. Thank you so much, Melissa. Thank you all for having us today. We are so excited to share with you our first main analysis and manuscripts from the Pediatric Observational Cohort Study. And as Melissa said, this is a study really characterizing long COVID in both school-age children and adolescents.

So, this tells us what our three main objectives were for this analysis. So first, we were trying to identify common prolonged symptoms and to understand how these symptoms might vary by age group. And in this paper, we were looking at two specific age groups. First, we looked at school-age children who are between 6 and 11 years old, and we looked at adolescents or teenagers who are between 12 and 17 years old. A.

Nd then we wanted to determine how symptoms that children were experiencing in combination could be used to a data-driven index, really to help researchers to consistently assess whether long COVID is present or to be able to identify children who may probably have long COVID. And then we also wanted to understand, are there ways that symptoms are clustering or grouping together in what we call phenotypes or potentially different types of long COVID? Next slide.

So, for this study we did a cross-sectional analysis looking at data that was collected in our baseline survey for the Pediatric Study. And we were comparing prolonged symptoms between two groups of children. We were looking at those with a reported history of a SARS-CoV-2 infection. For the purposes of the presentation, we refer to this group as infected, and those without a known history of a SARS-CoV-2 infection.

And to verify this, we did assess antibody levels in all of these children. And to be included in this group, they needed to have negative nucleocapsid antibodies. And for this talk, we refer to this group as uninfected. And so looking at the two groups of children and teenagers, we aimed to characterize long COVID based on the symptoms that the caregivers were reporting for these two different age groups. Next slide.

So, our main variables, looking at what are these prolonged symptoms, was based on a comprehensive symptom survey that was delivered remotely or by an interviewer, if a family needed, really using health literacy-informed principles and very plain language to really make these symptoms relatable to children and their families.

And they were age-appropriate symptoms that were occurring and lasting at least four weeks, then they started or worsened since the beginning of the pandemic, and for those with a COVID infection since their COVID infection occurred. And they were also still present at the time of their

enrollment into the study, which was for a minimum at least three months since their COVID infection. But many of our children had their COVID infections much longer than that. And we assessed up to almost 74 different symptoms across nine different body systems, and these were caregiver-reported symptoms. Next slide.

So I'm not going to read through all of these, but it gives you a sense of the diverse range of symptoms that we asked about, from general symptoms, to symptoms that affected the ear, nose and throat, heart and lungs, the skin, the GI or stomach systems, muscles and skeletal and bones, as well as neurologic symptoms and feelings and behavior. And so I'm going to turn it over to Tony to start to share with you the results that we found.

Dr. Tanayott Thaweethai:

Thanks, Rachel. So, I wanted to, again, thank the organizers for putting this together and inviting us to present the findings from this paper that we've been working on. So, I'm statistician, the lead statistician for this study, and I'll be walking through, as Rachel said, some of the key findings and results, and then hand it back to Rachel to kind of the findings from the paper.

So the first, we have this summary table of the demographics of the study cohort. So, in total, there were just under 900 children, who we're calling school-age children, who were ages 6 to 11 when they enrolled into RECOVER, 84% of whom had a history of infection. And then there were nearly 4,500 adolescents aged 12 to 17 who were in the study, 69% of whom were infected. And so many of the analyses that I'll be describing, compared infected versus uninfected participants, as Rachel described. And as Melissa introduced earlier, our adolescent cohort is very large due to participation in RECOVER from the ABCD Cohort, who contributed a lot of very useful data to this analysis.

So, just to summarize briefly this demographics table, there was almost even distribution of male and female participants. RECOVER, thanks to the efforts of our recruiting sites, is a diverse cohort with the demographic distribution of race and ethnicity, which is a select all that apply form described here. About a third, roughly, of the participants were from a medically underserved area. And this last row is telling us about the timing of participants' infection. So about half had their first experience with COVID prior to December 1st, 2021, which is, we think, of as roughly the time that Omicron began. So this analysis really encompasses both children who have been infected during the whole range of the pandemic. Next slide.

So, I'm going to walk through the three different phases of the analysis that were outlined earlier. And the first was to identify common prolonged symptoms and how these symptoms vary by age group. So looking in these two age groups. And so in order to identify symptoms that were associated with long COVID and could help us characterize what long COVID is in children and adolescents, the way that we did that is we looked at each symptom and then we compared how common that symptom was for infected versus uninfected participants. So here, in this first analysis, we looked at each symptom individually. And we did that, jumping into the little bit of the statistical details here by calculating odds ratios from logistic regression, where we looked at whether this predictor, a history of having been infected with SARS-CoV-2, was associated with each symptom, and we adjusted these models for sex and race, ethnicity.

So on the next slide we can move. Thank you. So we did this analysis first within the roughly 900 school-age children. And so this is the first figure that's in the paper, where we look... This is what's called a forest plot, which summarizes the odds ratios that we estimated for each individual symptom visually. And so there were many symptoms that we looked at. And here, we identified that there were 18 symptoms that were more common in infected than uninfected school-age children, indicating that they were in fact associated with long COVID.

And you can see that in this figure here where the lines and the dots represent the odds ratio, the point estimate of the odds ratio and then the confidence interval around them. So we found that there were 18 that were deemed statistically significant here. And so we found that these symptoms affected many different body systems, that they were not limited to only certain areas, and as I go through more slides, we'll see how different participants had different combinations of symptoms. So first, 18 symptoms that were more common in this age group in infected than uninfected. Next slide.

In adolescents, which we analyzed separately, we found that there were 17 symptoms. Again, affecting many different body systems that were associated with long COVID because we saw that they were more common in infected than uninfected participants. And some of these confidence intervals are a bit smaller because our sample size was considerably larger for the adolescents.

So the next slide summarizes the findings of the forest plot in slightly more digestible fashion, where we're seeing that there were 17 symptoms associated with long COVID in the school-age children, 18 in the adolescents, there was actually a lot of overlap. So 14 symptoms were more common in both age groups, and those are enumerated in the middle column here, with symptoms affecting feelings and behavior, nerves and brain, and general symptoms and so on, with the symptoms that are unique to each age group on the left and the right side. So those are summarized here, where we're seeing specific things about feelings and behavior, heart and lungs, skin, hair and nails for the younger children in the study. And then other symptoms I want to highlight, change or loss of smell or taste in the older kids in the study that they were experiencing that the younger kids were not experiencing.

Next slide. Okay. So that was looking at all the symptoms kind of individually. And so the question next was, how can we use all of this really rich symptom data that we have in combination as a way to actually say, "Does this child or adolescent have long COVID or not based on their symptom presentation?"? And so what we did is we tried to derive an empirically derived index, so sort of data-driven way that could be used as a research tool to identify the likely presence of long COVID in these groups of participants.

And so the way that we did this is we used LASSO, which is a penalized regression approach to identify which symptoms are best at identifying those who had a history of infection. So here, we're kind of flipping things, where now we're trying to say which symptoms could predict whether you had COVID. And then the symptoms that are most predictive of having COVID are going to be the ones that are most associated with long COVID, and can be used to identify children and adolescents who have it. Next slide.

So, using this statistical approach, in school-age children, we identified 10 symptoms that were most associated with a history of having long COVID, which are listed here. And so they're listed in descending order, where the higher score within this research index suggests that there's more evidence

that this participant does have long COVID, or as sometimes referred to as PASC, or post-acute sequelae of SARS-CoV-2 infection. So, we'll be using those terms interchangeably here, long COVID and PASC.

So, this paper, which established this PASC research index, lists these symptoms with associated scores with each symptom. And then for an individual, you would calculate the research index by adding up the scores for the prolonged symptoms that are present for that participant. So they had to have been experiencing them for four more weeks since their infection, and then also needed to have it at the time of the survey.

And so if a participant had a score of 5.5 or greater, they were classified as PASC-probable. And if the score was less than 5.5, they're categorized as PASC-unspecified. We're not saying PASC-negative here because there may be other presentations of long COVID or PASC in participants, but based on the symptom-based rule, this is how we would identify participants we think as being very likely to have PASC for the purposes of research. So, we can see that the symptoms that are emphasized here, there are cognitive difficulties, there are some symptoms related to stomach pain, nausea or vomiting, as well as some specific behavioral symptoms as well that were characterizing really long COVID in this population. Next slide.

So here, we did some sort of internal validation to see how the PASC score related to PROMIS measures. So these questions that all the participants were asked about related to overall health, quality of life and physical health. So, the way that you can kind of read this, is that as the PASC research index increased, as you go along the x-axis within each of these figures, people tended to report worse, give worse responses to these PROMIS questions, suggesting that higher PASC research indices were correlated with worse PROMIS scores on all of these three domains that we looked at. Next slide.

We repeated this analysis in adolescents, identifying here eight symptoms that were most associated with history of COVID. The symptom that was the most strongly associated with the history of COVID was change or loss in smell or taste, which is something that has been well known to be a sign of long COVID in adults. And so here, the threshold for identifying participants who are PASC-probable was five, and then less than five was PASC-unspecified. But other symptoms here that appeared, tiredness, sleepiness, being tired after walking and so on. Next slide.

And overall, we saw similar trends, where if you had a higher score according to PASC research index, that was correlated, again, with worse PROMIS scores, suggesting that there is a relationship. If you have a higher on the PASC research index, it was likely that you had worse responses to these questions about overall health, quality of life and physical health in adolescents as well. Next slide.

So, this figure from the paper summarizes what the result of applying this algorithm for identifying PASC-probable participants does. So there's a lot of information here, but I want to focus on primarily the third column on the left and then the first column on the right, so the purple columns here. And so this is a heat map that's summarizing how common all of these symptoms are in participants who were classified as PASC-probable, compared to participants... So the second column on the left half of the slide is infected participants who were classified as PASC-unspecified, and then the farthest to the left, that first column, is uninfected participants.

And what we're seeing is that using this scoring algorithm, this research index, uninfected and infected PASC-unspecified participants had very low rates of symptoms, all of these symptoms that we looked at here, but then the group that was identified as PASC-probable had higher rates of all of these symptoms. And so these blue and purple dots are referring to which symptoms were part of the PASC research index.

And so this is telling us that even though we only looked at a subset of all the symptoms to identify PASC-probable participants, we still picked up or captured a lot of other symptoms. So even though a symptom like feeling anxious was not part of the PASC research index, this method still captured many participants who had high rates of these other symptoms, showing that this was able to, again, pick up other symptoms that we are finding that may be associated with long COVID. Okay, next slide. And so finally, to the third part of the analysis, looked at how symptoms clustered into phenotypes. So how did these symptoms appear together? And so we used clustering analyses to identify distinct symptom patterns and profiles. Next slide.

So, to answer this question of whether there's different types of long COVID in children and adolescents, we did clustering analyses and found four clusters or groups in the school-age children, and then three clusters in the adolescents. And so the next slide, if we move to that, kind of summarizes the findings here, where again, there's four clusters that are on the left side, two that were in school-age children, only two that were shared. And then on the right, in adolescents, there were three clusters total. Again, two shared, and then one on its own in adolescents.

And what we saw, is that in school-age children there was a cluster that had issues with nerves and brain, a cluster that gastrointestinal issues, so symptoms related to stomach and intestines, and those were unique to school-age children. And then in adolescents, there was this unique cluster of participants who had a change or loss or smell or taste. And then in the middle, we saw a cluster that was common in both age groups, where they had many symptoms across many organ systems, and then a cluster that was characterized by pain and fatigue or being very low energy. So there were distinct groups, but then some groups that overlapped between the two age groups. Next slide. Great. Okay, so that wraps up the presentation of the methods and results, and I'll hand it back to Rachel to summarize some next steps and conclusions.

Dr. Rachel Gross:

Thank you so much, Tony, for walking us through those results. So I know we talked about a lot today, and so I wanted to just summarize what we found. And this RECOVER Study is really the first of its kind to look at long COVID symptoms in children across different age groups in such a large national sample. And what we found, was that these long COVID symptoms occur in almost every organ system of the body, and that many children are experiencing these symptoms in many different organ systems.

We also found that these patterns, while similar across different ages or compared to adults, there are distinguishable differences across these age groups. We also developed this new research tool to help us identify children who are most likely to have long COVID so that we can continue to study them in these research studies and to learn more. We learned that these symptoms can cluster together into distinct types of long COVID, that not all of long COVID may look the same in different children, and

we need to understand what that looks like, and that we saw four different types in the school children and three different types in the teenagers. Next slide.

I also wanted to highlight that the index, which brings together the symptoms, is really a framework to set the stage for future research studies. It will allow us to study children and these symptoms over time in order to understand, why are we seeing these differences? Why are we seeing differences at different ages and why are we seeing these types of groupings? So that we can identify the underlying mechanisms and the trajectory of long COVID over time. So we can study how are these symptoms persisting over time? How are they recovering? And even how are they coming and going and relapsing over time?

I wanted to highlight that this is not a tool intended for clinical practice at this time. And we know from the work, that even one symptom that a child is experiencing may be sufficient to indicate long COVID in any given child, and no way is intended to minimize the importance of the many other symptoms that children may be experiencing. And this is really highlighted by that last figure that Tony shared, that even these symptoms in the index are really identifying children that have so many other important symptoms. And that this is really a first step into developing a future tool that can help us to identify and screen for children with long COVID, and we expect that to evolve and change and expand over time as we do more research to learn more about long COVID over time. Next slide.

So I just wanted to highlight a few limitations. One, is that we are basing this work so far on caregiver-reported symptoms. [inaudible 00:37:15] maybe some difficulty recalling symptoms or interpreting symptoms, but we do this very deliberately because we know that caregivers and families spend the most time with children, and they are really there to see changes, even subtle changes that are happening over time. And their point of view is so critically important, especially as children are growing and especially for younger children. But we know that we want to start to incorporate other more objective data. So next steps are really to include the checkups and tests that we're doing at in-person visits, as well as ultimately to be look at findings that we're doing from the different samples that we're collecting.

I also wanted to highlight that we are comparing groups of children with a history of a SARS-CoV-2 infection to those with no known history, and there may be some misclassification. For the infected groups, we don't require children to have had a test to show that they had a [inaudible 00:38:31]. We also did that very deliberately because we knew, especially in the earlier stages of the pandemic, that it was very difficult for people, but especially children, to get testing for COVID. And this really aligns with the newer definitions of long COVID that are coming out that don't actually require a test to prove the infection. So that's the reason that that was the case.

Also, for our uninfected group, while we are checking for antibodies to provide evidence that these children may not have had a COVID infection or have no known COVID infection, it's possible that we may be missing infections, or children's antibodies waned or that they didn't develop a response. But because we're seeing these differences between these two groups, it's likely that this misclassification is minimal. Next slide.

So, despite these limitations, why are these study findings important? Well, to start, these study findings are really important because they're really laying the groundwork to help clinicians, to help

healthcare teams, as well as families, to really raise awareness about long COVID, in showing that children can develop long COVID, and that their symptoms may be different from those of adults, as well as for those of children in different age groups.

And this is so important because many children who are experiencing these prolonged symptoms may be missed because their symptoms aren't identified as long COVID, or they may be misdiagnosed. And so what these findings highlight, is that even some symptoms that we commonly see in other health conditions for children, such as prolonged headaches or stomach pain, may actually be long COVID.

We also think next steps are to really understand why these age differences are happening so that we can create future treatments for children that may need to be age-specific. And so this data really starts to show us that a one-size-fits-all approach is not likely to be effective in both identifying children with long COVID and developing screening tools, or also for future treatments, and that these may actually need to be tailored for specific age groups. Next slide.

So, I wanted to highlight that all of these findings were published in the Journal of American Medical Association. I have a link here at the bottom. And has also received media attention in these venues here. And so these are things that you can look at for more information and for spreading awareness about long COVID in children. Next slide.

And so when we go back to the bigger picture about what our next steps are for the Pediatric Study, we will build on this research related to symptoms and start to integrate the additional longitudinal data that we're collecting in order to further understand the different types of long COVID that may be happening, what are those underlying mechanisms, and how do we move towards development and evaluating critically needed treatments, and continuing to refine what we learn as more research is happening. Next slide.

So, to conclude, here, we focused on school-aged children and adolescents, but our RECOVER Study really focuses on the whole lifespan. So next, we're going to be looking at what about our youngest children? What about the children between birth to five years old? What will their symptoms look like? How will long COVID look different in this early group? And building on the underlying mechanisms, the pathophysiology, setting the stage for needed therapeutics and critically needed clinical trials in children.

And I want to end with how important it is to raise this awareness because long COVID in children is truly a public health crisis. And as a general pediatrician, I know and we know, that child health in this early period, experiencing a chronic illness, experiencing adverse conditions, can really affect children as they grow and develop and as they even become adults. And so we are likely to see the impact of long COVID in children for decades to come. Next slide.

And so before I end, I do want to highlight that we are still enrolling children and young adults, particularly those who either know that they have long COVID, but also children and young adults who may be experiencing prolonged symptoms and they're not feeling well even after having a COVID infection, and even if they're not sure why. And so we're enrolling these children through the end of the calendar year through December 31st. There is a QR code here and this website, RECOVERcovid.info. If

you or you know anyone who might be interested, please spread this and share this with them. Next slide.

So, I want to end by thanking everyone involved, because this is really a huge effort with so many important people that contribute to this work. I especially want to thank all of the participants and their families, all of the sites and staff around the United States, the patient, caregiver, and community representatives that contribute so much, as well as all of the institutions that you see here. Next slide. Thank you so much. Thank you.

Dr. Andrea Foulkes:

Well, thank you so much. I want to just begin by thanking you, Melissa, Rachel and Tony, for sharing with us the results of this truly groundbreaking study of long COVID in children. As you've described, this work was particularly challenging due to the inconsistent manifestations of long COVID, and that really further, are dependent on the age of a child, making it a particularly complex problem to address. And yet, you've successfully not only collected this very complex data so carefully, but you leveraged these RECOVER data to perform a rigorous and comprehensive analysis.

And through that, specifically, you provided an improved understanding of the breadth of long-term physical and mental health outcomes in both school-age children as well as adolescents. And additionally, you've generated this novel, validated and reproducible index that will be a critical first step, as you've described, in supporting further research, including studies of the mechanism of long COVID, as well as clinical trials of novel interventions. So, really fantastic work and wonderful to hear your summary today. I'd like to turn now to Megan to get her perspective. And thank you Megan for joining us for this seminar today. So to begin, I'm wondering if you can talk to us about the importance of these research findings for families and children affected by long COVID?

Ms. Megan Carmilani:

Yeah, absolutely. I'm going to use my notes to help me. And I'm sharing that because it's an accommodation that I use all the time to support me and my work. And it's something that could be appropriate for kids in school settings, and I really want to help normalize the use of accommodations. So, I know there are some kids listening or will be watching this, so if you need your notes, you use your notes, guys. Okay?

So, the research are incredibly important for families. This is the first large-scale study that truly begins to map out the range of symptoms and experiences our children have endured. For so long, many families have struggled to get the recognition and validation for what their children have been going through. Now, with this research, the medical community is finally catching up to what our families have known all along.

Children display a range of serious symptoms that may vary by age. Knowing the most predictive symptoms of pediatric long COVID will help identify children sooner, leading to earlier interventions and better outcomes. And I want to emphasize that because we've seen this in the community for over four years now, that when children are identified early as having long COVID and we intervene, they have better outcomes.

These findings should serve as a wake-up call, not just for pediatricians but also for schools, public health officials and policymakers. The impact of long COVID on children is significant and this research highlights the urgent action, the need for urgent action in terms of healthcare, educational support, and broader policy decisions. With the release of this research, I hope policymakers and public health experts will see that pediatric long COVID is a real and present danger to our most precious natural resource, our kids, and act now to take it seriously.

Dr. Andrea Foulkes:

Thank you, Megan. I really appreciate the response, and also your candor with respect to accommodations and the importance of all of us acknowledging those and respecting those. So, related to your answer, I'm wondering what you see as the challenges for families, particularly in navigating their children's education. What would families like schools to better understand about long COVID and how can the school environment support students who've been affected by long COVID?

Ms. Megan Carmilani:

Sure. There's a range of challenges that families are facing in navigating their children's education. One of the biggest difficulties is the way long COVID symptoms, such as low energy, sleep disturbances, memory problems, even we didn't talk about much today, but school refusal was noted as a symptom, how that impacts a child's ability to participate in school.

So, just to mention school refusal. A lot of times children in our community, they don't have the language to communicate they don't feel well. So one of the earliest signs that families will report is their child refuses to go to school. But if you had fatigue, if you had post-exertional malaise, if you were experiencing chronic migraines as our children are experiencing, it makes sense that they wouldn't want to go to school.

And one of the things we'd flag is that we need to be curious about that and not just simply assume that the child's trying to get out of something. Maybe look at it as an invitation to look more closely about what's going on with the child. Long COVID symptoms can be unpredictable and they may fluctuate from day to day, often making consistent attendance and academic progress a real struggle.

Families often find themselves the ones educating schools on what long COVID is, while simultaneously having to advocate for accommodations, while also dealing with emotional and physical toll that long COVID takes on their children. It is a heavy burden that the community is taking on right now, and we need schools to really partner with us to raise awareness about long COVID in children.

I think ultimately, what we want schools to understand, is that long COVID is real and its effects can be long-lasting and profound. It's crucial for educators to recognize that these symptoms are not simply short-term setbacks, but ongoing issues that affect learning, concentration, and even social interactions. Children with long COVID may need breaks. They need flexible schedules or adjustments to assignments, or testing to keep up academically without compromising their health. And really, to support our students, schools need to create a more inclusive environment by offering flexible attendance, extending deadlines, and providing personalized learning plans that take their fluctuating health into account. Long COVID is a dynamic disability. It fluctuates day to day.

Importantly, schools should approach children with compassion and understanding, and acknowledging that their struggles are real and that they need support in such a way the child knows and understands that they're being supported, because our children are reporting that they feel like a burden. By working closely with families and offering the necessary resources and flexibilities, schools can help children affected by long COVID continue their education while managing their health.

Dr. Andrea Foulkes:

Thank you, Megan, several really important points that you've made there, and also really highlighting what Rachel mentioned earlier about the importance of awareness and increasing awareness more broadly. And again, a plug for the audience here to do what they can in helping with increasing. So thank you for that.

And again, mentioning the importance of flexibility, accommodations within the school environment. So in terms of next steps, we heard a bit from the panelists already about out what their plans are for future research. We'll hear a little bit more about that as well, but first, I want to hear from you. What would you say are families' priorities for further research?

Ms. Megan Carmilani:

Sure. Well first, I'll acknowledge that our community stays really well-informed on the research, because it's really essential for us to be able to advocate for our children. And while there are many areas that we would like to see explored, our concerns really boil down to five key questions. One, what is happening with our children's immune systems? Why do they constantly get sick? Because we know it's not normal. Two, what's going on with our children's brains? They seem to be facing cognitive challenges and really struggling. We want to know why.

Three, why are younger children struggling to thrive and missing developmental milestones after infection? Four, studies have shown persistent infection in children. What are the long-term health implications? And five, we often see reinfections worsening symptoms in our children. What is the impact of ongoing rapid reinfection that we are experiencing? So these are the questions we urgently need answers to. And I will tell you, our community is very worried.

Dr. Andrea Foulkes:

Yeah, I hear that and everything that you're saying, and really appreciate that. And also, really appreciate the succinct clear goals moving forward, both in terms of advocacy and support that you've articulated, but also in terms of research that needs to be done going forward. Also, really grateful for, as you mentioned, the engagement of the community and patient representatives in the Pediatric Cohort. And I really want to emphasize how important that has been, going both from the very beginning of collecting data, all the way through the analyses and the interpretations of findings that we heard about today. So, I'm really pleased that you mentioned the commitment that we've, of course, seen every day of the patient reps and community reps in advancing the science and understanding. So thank you for that.

Ms. Megan Carmilani:

No, thank you.

Dr. Andrea Foulkes:

So, turning back to Melissa, Tony and Rachel, question I have for all of you that I hope you can each comment on, is a little bit more about what's next for RECOVER-Pediatric and what do you see as the most pressing scientific and clinical questions on the horizon and what are you planning specifically to address next?

And thinking maybe in terms of what Megan was just talking about, really understanding mechanism, whether it's the immune system, what's going on in the brains, the developmental challenges some of our younger children are experiencing, the why of that. And then also, the implications of things like reinfections. We're hearing in the chat about boosting. So, what do you think are the most important priorities going forward?

Dr. Melissa Stockwell:

Thanks. [inaudible 00:57:20] to cover. I think we're going to try and kind of split up for that. I think I just wanted just to first, again, to thank Megan and the other patient representatives. Really, as you mentioned, a really incredible part of our group from the very beginning, from study design, to gathering data, to analyzing data to think about it, and always bringing that patient and family voice, I think has just been... I've not experienced that in other sites that I've been in, and it's something that's incredibly unique to RECOVER. And again, just to publicly thank Megan and her, there are other representatives as well who are amazing, who are part of our group, because it really is such an important part of what we're doing in RECOVER.

I think just to focus first on what the next phase is. So I had mentioned briefly the sort of tier three part of it, which is really our foray into to understand, so mechanism and pathophysiology, in part by doing some more intense imaging. So we're really looking forward to taking our very affected children and really trying to understand a little bit more intently what is going on, as well as more analyses looking at our tier two data. So again, we're bringing kids in in person, so not only focusing on the symptoms, but also focusing on what we might be seeing physically in them.

And not only overall, but again by age, by symptomatology, and really understand what's happening over time. And so I think that that's probably one of the most important things on the horizon, is really that pathophysiology of the mechanism, because we all want to get to treatments, we want to understand it, we want to prevent it, and we want to treat long COVID in kids. So I think that's first and foremost on our next steps. And I'll turn to Tony for some of more the analytic things that we're focusing on now.

Dr. Tanayott Thaweethai:

Thanks. Yeah. So as I mentioned, we've spent so much time today talking about how symptomatology is between 6 to 11-year-olds compared to 12 to 17-year-olds. RECOVER has recruited

children who are younger than that. And so, one of the key objectives going forward is going to be to understand the experiences of even younger children. Our symptom surveys ask different types of questions towards different age groups. And so we'll be looking at the experience of infants who have COVID, what long COVID can look like in children as young as two years old, or even younger than two years old, and then preschool age children as well, to understand whether and how symptomatology differs in those age groups.

Additionally, so RECOVER, all the data, as Rachel mentioned, as she introduced the presentation, has been cross-sectional. We've been looking at participants' responses to the remote surveys, and we've tried to understand their... And this is kind of the tier one part of the survey that was mentioned earlier, and participants progress to tier two and then the tier three. And so we are collecting longitudinal data on participants to understand these trajectories.

And so I think there's something we'll also be working on is understanding how symptoms change over time, especially acknowledging that symptoms wax and wane, that we may be capturing symptoms on a day that somebody is feeling a little better or a little worse. And so having a more longitudinal picture of that is going to really illustrate what long COVID looks like over a period of years rather than just at one time point.

And so, both understanding kind of the natural progression of long COVID, but then also to understand what risk factors there are, and again, interventions that may influence whether somebody recovers from their symptoms over time, if there's anything that can help alleviate symptoms over time. Of course, the presentation, and we're talking today about the RECOVER Observational Cohort, so there are of course many statistical epidemiological challenges to try to draw conclusions about these symptoms when interventions are not randomized and stuff like that.

And so we're trying to make sure that we are drawing conclusions that are sound, respecting the way in which the data were collected, since it's not a randomized study. But we think that there's a lot that we can learn about risk factors and other factors that may influence the experience of children in long COVID. Particularly clinical risk factors, pre-existing comorbidities, pre-existing health problems, as well as other non-clinical factors such as social determinants of health, things like related to economic stability, access to healthcare. And how all these other factors may also capture things that you don't get if you just look at somebody's health record, and how these may have a big impact on whether a child develops long and whether they're able to recover from it. So I'll pause there, but I think those are just, again, some of the avenues we're exploring. There's so much more that's ahead with the data that's being collected in RECOVER.

Dr. Rachel Gross:

Thank you. I think what everyone has said is so important. And what I would add, is that we know that children are not just little adults, that they are different, and that they are growing and developing over time. And we also know that the school-age children of today will become teenagers in a few years. And so that's why this longitudinal part of RECOVER, where we're following children over time, is going to be so important.

And so some of the next steps are to understand why are we seeing these different symptoms in different ages? So, are there differences in immunologic factors that are happening? Is there a difference with relate to hormones and children entering puberty? What are the underlying causes? And so that's where a lot of the effort is needed. And how does this change as children transition from one age and grow to be older? How does that affect the symptoms they're feeling and how is that changing over time?

And we really need this information as we think about how to identify targets that will help children with the long COVID that they're experiencing, both to help them with the symptoms themselves, but also really to help with the underlying causes for why this is happening. And as I mentioned earlier, this is likely not to be a one-size-fits-all. Why do some of these school-age children have primarily stomach symptoms as their long COVID, where others are having symptoms in almost every organ system? What is it that's causing those differences? Because those children may need different treatments. And so this is really to lay the foundation for clinical trials in children. And so that's why this work is so critically important.

Dr. Andrea Foulkes:

Thank you. Thank you all for such a comprehensive answer to that. And I think all of you were sort of reiterating what Megan was mentioning about the importance of understanding mechanism, but also at the same time, pointing to the real challenges when we're talking about a disease that has very different manifestations in different people within the same age group, but of course, across different ages as well. So, thank you all for the work that you've been doing. We have lots of questions, so I'm going to be turning it over to Quinn now to take some questions from the audience for you. And thank you again.

Quinn Barnette:

All right. Well, thank you so much everyone for that really, really important presentation and rich discussion. I'd like to open up our audience Q and A with our few questions that we received in advance and then I'll move into questions that we've been receiving during the seminar. But just as a reminder, we will post a Q and A document on recovercovid.org after the seminar. Our first question is for Rachel and Melissa and it asks, "What do children and adolescent long COVID symptoms have in common with those of older populations, and how might they differ?"

Dr. Melissa Stockwell:

Do you want to start? I think what we found was, I think to me was really interesting, was sort of this, it's almost like a gradation, right? And so there's sort of this overlap, the adult findings, and there's an adolescent overlap, particularly with the loss of taste and smell. And then there's some of those that overlap with the school-age children.

And so I think, to me, that makes sense, and goes along with what, Rachel, we're seeing, in terms of as children are growing and developing, their symptoms could look different. And so that makes sense why there's going to be some overlap with adolescent adults and then some overlap with

school-age and adolescent as well. And so I think that that kind of take-home finding is interesting, and I think will also help as we're sort of trying to tease apart the pathophysiology and the biology behind it.

As well as when we talk about the clustering and the phenotypes, that some of the phenotypes, again, there was this overlap between children and adolescents, but then there were these phenotypes that were very different in school-age. And are a lot of things that Megan would talk about, that families and long-COVID, families are seeing that they see in school-age kids, that they're not seeing adolescents. And there's some that in adolescents that we just weren't seeing that phenotype among the younger kids as well.

Dr. Rachel Gross:

Yeah, thank you. Just when we think about the clusters of groups of symptoms that we described, we are seeing the first grouping where children, teenagers, even adults, are experiencing symptoms in almost every organ system of the body. So, that particular type seems to be crossing all of the ages, but where we are starting to see these similar but distinguishable differences, or when we're seeing types of long COVID that may involve fewer symptoms, but that they may be more specific to different stages of development.

Ms. Megan Carmilani:

Can I also add, that in addition to the difference in symptoms, children express symptoms just differently, and I think that's really important to pay attention and highlight. And so some of the common things that we've been hearing is that a child may say that their legs hurt. And what they're trying to explain is that they feel fatigued. Or a child will say, "I can't think." And they're trying to explain cognitive difficulties or they'll say that their head hurts. And what they're really trying to say is, "I can't think. I'm having a hard time." A very common one is that a child will talk about not being able to breathe, and it turns out to be more heart palpitations or a tachycardia, which is a rapid heartbeat.

And so part of what we've learned in our community of trying to help long COVID kids is really paying attention to the way they express things and not insert an adult perspective on what that means. Really try to figure out what the chat's saying. Another common one is that children have often said that their throat hurts, but if you ask them where on their body, they'll point to the back of their head. And we've learned that's a common way for little ones to say they have a migraine. So really, just pay attention and try to think of it through the eyes of a child and what they're trying to communicate about the symptoms. Thanks.

Quinn Barnette:

Yeah, thank you, Megan. Our next question is also for Rachel and Melissa, and it asks, "Are there current or future plans to capture related illnesses and measures of long COVID prevalence? So for example, people with mild ME/CFS or those with related complications such as mast cell disease?"

Dr. Rachel Gross:

Yes. Thank you for that really important question. We collect a lot of diverse data about all of our participants in the study. And so while this first analysis focused on the symptoms that are being experienced by the children, many of our next steps are to look more broader at that conceptual model that Melissa talked about from the review paper. That we are collecting data about other medical problems, specifically the ones mentioned in the question, as well as a diverse range of other past medical history and special healthcare needs that children are experiencing, to see how these influence the development of long COVID, but also how they develop over time. So we ask about the emergence of new conditions over time as well so we can begin to look at this as we're following children over time.

Dr. Melissa Stockwell:

And then I think just to add, that importantly, it's symptoms but also, again, those phenotypes are beginning to emerge. Because as Rachel had mentioned, it may be that one of the GI symptoms, I'm going to quote Megan, might be associated more with certain underlying conditions or certain things, and it might be the grouping that might be multi-system might be different. And so I think we're really trying to look by age, but again, by symptom, cluster as well. Understand, as Rachel said, it's not going to be a one-size-fits-all by age, but also with the phenotypes as well and kind of really interrogating at that level.

Quinn Barnette:

Thank you. I think I'll jump to a question we received today during the seminar, and this one will be directed for Tony. "Are there any plans for the PASC research index to be independently validated externally before moving forward with more research?

Dr. Tanayott Thaweethai:

Yeah, it's a great question. It kind of is like we have the RECOVER data, we have developed this research index for identifying participants who are likely to have PASC. We will be, as the other panelists have mentioned, looking at how other clinical tests may correspond to having higher scores on this PASC index. So looking at other physical assessments, things like that, that we could look at how they relate to the PASC index.

But I think my answer to the question, really is that the purpose of this presentation is to open the door to other people who are studying long COVID, who have patient data, who can validate what we've found. To examine looking at the symptoms that we've identified as being most important, if you ask participants about these symptoms and you calculate their PASC research index as we've outlined it, does that correspond to whether your clinical diagnosis, perhaps, of long COVID in other populations?

And so that's really important. And we're so excited. We're hoping that people will do that, that they will take what we've presented here and validate that in their populations that they're studying. And I think that will help us better understand. I think importantly, this is a definition, or rather an index and an algorithm that's used to identify people for research. And I think it would require additional validation in other groups, in other cohorts, before we can approach a way to truly diagnose in the

clinic. And so I think that will be a really essential part on the path towards being able to diagnose people in a clinical setting.

Dr. Melissa Stockwell:

And can I just add one thing? I think also one important part about the research index, is because it's a smaller number of items and isn't like 88 questions. I think that part of the point was for us being able to use something, and again, we would love for other people to use it and validate it and look at other contexts for research, is it's easier to ask some shorter number of questions than to ask 88.

In part as a researcher, but also for the patients and participants, because it is a lot of information to be asking them over time. And obviously, we do know that we have many dyads where the caregiver and the child has long COVID. And so just we always think about the participant burden. For the caregiver, if they're filling it out for their child and they also have long COVID, or if it's a young adult who's filling it out for themselves. And so this sort of shorter list of questions to be able to use for research, we hope will also be helpful for others.

Quinn Barnette:

Thank you. This next question I think is for the whole panel, and asks, "How do you view the progress in developing diagnostic tools for the condition? Do you believe a quantitative biomarker would be the most effective method for assessment? And what do you think are the main challenges and advancements for diagnostics?" Rachel, would you like to start?

Dr. Rachel Gross:

Yeah, thank you for that question. I think it is such an important one, and really what this type of foundational work is aiming to help with. Because we need a way to be able to easily identify, in clinical practice, a way to diagnose long COVID, acknowledging that it is a very heterogeneous condition, meaning that people's long COVID looks different from other people. And I'm hopeful that we will be able to identify a biomarker in the future, but it's unclear right now what exactly that is. And so, one of the things that we're trying to do in RECOVER is we do collect blood and other specimens from children, as well as the adult study does a similar, so that we can do the foundational research to try to identify such a biomarker, based on the underlying mechanisms and pathophysiology that we can identify as we follow these participants and families over time. I don't know, Melissa, if you want to add anything?

Dr. Melissa Stockwell:

Yeah, no, I think we all would love to get to a place there is a biomarker. I think in the interim, I do think even, if I think from the pediatrician perspective, even just understanding what are some of the common symptoms that we saw in school-aged children. So even if we're putting aside the research index part of it, but even sort of first part that Tony outlined, just that information, I think is incredibly important for pediatricians and families to know. I think one thing that's great about kids, is in general, oftentimes whenever there are symptoms, they're self-limited. But in this case, these kids, it's not self-limited.

So if you're seeing a child who's having prolonged symptoms in these groupings or not, and they had a COVID infection, many of them have had, and it doesn't have to be that they had a COVID infection today and this started a week later, put that together and I can't tell you how many times I've had that conversation with pediatricians and there's this aha moment of like, "Oh." And Rachel's nodding and she's had this too, "I didn't think that those could be related. That all make sense now." And I think it's what families have been trying to say. And I think while we want to and hopefully get to a biomarker, in the meantime, even just sharing these symptoms, and we are trying to get that information out there, is incredibly important for families and for pediatricians as well in the interim part of it.

Dr. Tanayott Thaweethai:

Yeah, I would add that, just to address one of the challenges, I think, of finding a biomarker. I think something we've mentioned, kind of has been a theme throughout, has been the idea that it presents in many different ways. And so it suggests that there may be different mechanisms of disease here that may mean that there are different biomarkers. And so it's related to this one-size-fits-all, but I think what we've discussed is that long COVID doesn't look the same in all kids across age groups, but even within the same age group, long COVID still looks different.

And so trying to do an analysis, I'm imagining as for trying to plan what an analysis would be, it might be pertinent to think about specific types of long COVID and whether there are specific biomarkers that are associated with particular types, rather than kind of looking at everything in aggregate, which is challenging. And so I don't know what we'll eventually find about a single biomarker, but I think it's possible that the story could be quite complicated.

Quinn Barnette:

Thank you. The next question I think is also going to be directed to you, Tony. "In this analysis or in other analysis that you've done, did you find any differences in prevalence or phenotype by sex similar to what's been seen in the adult populations?"

Dr. Tanayott Thaweethai:

That's a great question. For the present analysis, we accounted for sex in fitting the statistical models, but we didn't specifically look at whether the symptomatology was very different by sex of the participant. And so, I think what we know, that a lot of emerging evidence is in adults, is that participants assigned female at birth tend to have higher rates of long COVID. I think that would be worth investigating in pediatric populations as well, but unfortunately, I don't have a concrete answer to that at this time.

Quinn Barnette:

All right, thank you. Sorry, Rachel?

Dr. Rachel Gross:

Yeah, I was just going to say that really some of our next steps in this work is to try to understand why some children are experiencing these long prolonged symptoms and others are not. And so some of our next manuscripts that we will be working on and publishing are related to those very questions. So are there sex differences? How do vaccines play a role in these? What are the other factors that might influence the development of these symptoms or not? And so that is one of the main questions that we are also working on within the RECOVER Pediatric Study.

Quinn Barnette:

Thank you. This question is also for Rachel and Melissa. "Is RECOVER doing any assessments of downstream effects of long COVID in children and adolescents, such as functional outcomes and schooling outcomes, for example?"

Dr. Melissa Stockwell:

Yeah, thank you for that question. It's very important for us. So one of the things that in our tier two, we're seeing families more often, so 6 months, 12 months, 24 months, is we do ask them both some functional questions, but also about school. And to really understand both about days missed from school, but also if they have an IEP or not, how they're doing in school, as well as understanding impact of physical activity and nutrition and other sort of issues for them. So it's really important.

I think one of the nice things about RECOVER, because we can ask participants directly, we can capture a lot of things that a medical-based study may not necessarily capture. And so those include the kind of educational outcomes as well. And I would say that's probably one of the most important things that we want to be focusing on also going forward. We do worry a lot about how kids are doing right now, but again, as it's been mentioned, how kids do as they develop and are they able to be in school as much as they can? Are they able to learn? Or also, how is this school accommodating them? I know there's some questions in the chat about accommodations. We can definitely tell, just from our participants, that when kids are not granted accommodations, it really also affect their trajectory as well. So that's important for us to be looking at.

Dr. Rachel Gross:

Yeah, and one of the main assessments that we are doing at every time children are coming in overtime, is extensive look at neurocognitive development. And these are things that can be subtle, even. So we are doing assessment of memory, we're doing assessment of language, of motor skills, of executive functioning. And so these are things that people, schools, teachers, families, physicians, they may not necessarily pick up as a change that's happening over time. And we're hoping that having these extensive assessments at every time point will really help to answer some of those questions.

Quinn Barnette:

Thank you. I think we'll have time for one more question, which is for the whole panel, but perhaps I'll start with Megan with this question. "How are findings raising awareness of the impact of

COVID infections on child and adolescent health and informing policy to help address better screening for it and treatment?

Ms. Megan Carmilani:

I'm sorry, how is what? I didn't catch it.

Quinn Barnette:

"How are findings raising awareness of the impact of COVID on children and adolescent health, and informing policy to help address screening and treatment and accommodations for children?"

Ms. Megan Carmilani:

So as far as informing policy, we are very, very early stages. So we are, I would say, two to three years behind where the adult population is as far as awareness in general. So we're still in the awareness phase, and that's why we're emphasizing it so very much. We're still having debates with policymakers about whether or not long COVID is real in children.

That's where we are, unfortunately. And there may be potentially six million children out there that are waiting on us to find some solutions for them. So, I would invite everybody listening to help us to raise awareness. Knowing the symptoms that have been outlined today has been really, really helpful. We have heard from both families and educators and other doctors in the community. And so we can start there and with awareness, then we can start pushing for the policies our families need.

Quinn Barnette:

All right. Would anyone else like to add to that or? I know we're at time. Okay.

Dr. Melissa Stockwell:

I think we'll give Megan the last-

Ms. Megan Carmilani:

Thank you.

Quinn Barnette:

Sounds great. That was a great final answer. Well, thank you so much to our presenters, and thank you again to our audience for attending this seminar and engaging with the Q and A. As a reminder, a recording of today's seminar will be available on recovercovid.org within a few weeks, and we'll also be posting a Q and A document that has responses to the questions we received today, including some that we did not have time to address.

We are planning seminars in October and we'll post registration information on the RECOVER website when those are available. So please check the R3 page at recovercovid.org for those updates. And you will see a short survey come up on your screen in just a moment which asks for your feedback on this seminar. We would appreciate if you'd take a few minutes to fill out this survey. And thank you so much to our panelists and our audience, and have a great day.