# Transcript

### Quinn Barnette:

All right, thank you, Patrick. Welcome, everyone, to the RECOVER Research Review or R3 Seminar. My name is 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&A feature in your Zoom menu. After today's panel, our speakers will answer as many questions as possible.

A Q&A document will also be posted with the recording of this 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 any questions about individual clinical care.

I'm pleased to share that our presenters today are Dr. Ann Bruno, Dr. Chengxi Zang, and Dr. Torri Metz, and our discussant will be Dr. Valerie Flaherman. Dr. Bruno is a woman's reproductive health research, K12 scholar, and an assistant professor in the Department of Obstetrics and Gynecology in the Division of Maternal-Fetal Medicine at University of Utah Health. Her clinical care focuses on management of high-risk pregnancies, and her clinical and research interests include venous thromboembolism and thrombotic disorders in pregnancy, vaginal birth after caesarian, hypertensive disorders of pregnancy, and COVID-19.

Dr. Bruno is joined by Dr. Zang who is an instructor in the Department of Population Health Sciences at Weill Cornell Medicine, and faculty in the Weill Cornell Medicine Institute of AI for Digital Health. His research focus is using AI machine learning and data-driven methods to generate robust and generalizable real world evidence for clinical decision making, drug discovery and development. He works with PCORI EHR adult cohorts to develop computational phenotyping tools, subphenotyping tools, predictive models, and repurposing drugs for long COVID among general adults as well as for pregnant populations.

Dr. Metz is vice chair for research and an associate professor of obstetrics and gynecology at the University of Utah Health. She's a practicing maternal-fetal medicine subspecialist, and is the PI for the Utah center of the Eunice Kennedy Shriver NICHD Maternal-Fetal Medicine Units Network, where she leads their study examining the effects of COVID-19 on serious maternal morbidity and mortality. She's also leading NHLB-funded four-year longitudinal study on long COVID in mothers and their offspring as part of the trans-NIH RECOVER consortium.

Finally, Dr. Flaherman is an epidemiologist and pediatrician at the University of California, San Francisco, where she's professor of pediatrics, epidemiology, and biostatistics, and core faculty at the Institute for Health Policy Studies. Her research program focuses on exposures and preventive interventions during infancy and early childhood. And she is managing director of the Better Outcomes through Research for Newborns Network. For the past four years, Dr. Flaherman has assessed the long-term impacts of COVID-19 on children, first as co-PI of the pregnancy and coronavirus registry study, and currently as co-PI of the RECOVER-UCSF Pregnancy cohort.

The topic of today's seminar is SARS-CoV-2 infection during pregnancy and development of long COVID. Today's speakers will present findings from the RECOVER-Pregnancy observational cohort and EHR cohort about the association between SARS-CoV-2 infection during pregnancy and development of

long COVID. Please welcome all of our speakers. And with that, I will turn it over to our first presenter, Dr. Bruno.

### Dr. Anne Bruno:

Thank you for the intro, and thank you for the opportunity to present this morning. As identified, my name is Ann Bruno, and I'm an assistant professor at the University of Utah. I'm very happy to be presenting this morning on pregnancy and PASC at the RECOVER Research Review Seminar Series. Listed here are my co-authors, who I am presenting on behalf of as well. Our table of contents for the next 1 to 20 minutes will be to go over a little bit of background, discuss the RECOVER PCORnet electronic health record dataset as the data source for our analysis, talk through our research question looking at pregnancy and interval PASC development, talk through the methods and results of our analysis, and talk briefly about future direction.

To begin with, when thinking about long COVID, complications of acute SARS-CoV-2 infection are increasingly well described, therefore attention has turned to better understanding post-acute sequelae as SARS-CoV-2 infection or PASC. The World Health Organization or WHO defines PASC as symptoms occurring by three months post-SARS-CoV-2 infection lasting for at least two months, and not explained by an alternative diagnosis. And the National Institutes of Health Researching COVID to Enhance RECOVERy or RECOVER Initiative, the focus is dedicated to studying the long-term effects of COVID-19 in the form of PASC or long COVID.

The RECOVER structure is outlined briefly here. At the base is the NIH. Within that are these several different cores. So the RECOVER consortium, the research infrastructure, and RECOVER participants and research studies. Through this core and then building out to the larger RECOVER consortium and research studies, several different populations have been the focus of the variety of studies, including adult populations, pediatric populations, pregnant populations, which we'll hear more from later with Dr. Metz, tissue pathology and immunology, and then real world data.

Our analysis today focuses on the real world data aspect of this through the PCORnet EHR dataset. This is a patient-centered clinical research network, or PCORnet, electronic health record dataset, which essentially is a single unified electronic health record repository to study PASC underneath the umbrella of the RECOVER Initiative. Within the PCORnet EHR dataset is data from inpatient and outpatient encounters, including for things such as demographics, diagnoses from inpatient and outpatient admissions identified through the use of insurance and billing codes, medications, and laboratory results. Overall, this reflects about 10 million patients across 19 US health systems. And these data are refreshed quarterly to allow for updated analyses over time within those up-to-date data population, reflecting the changes in the pandemic [inaudible 00:07:04].

The PCORnet PASC team has already worked together previously to identify a definition of PASC within the PCORnet EHR dataset. This is just briefly reflecting the work of our collaborators, including Dr. Zang who will be on the panel a little bit later. But essentially, their team began by looking at approximately 6,000 codes, including medications and insurance diagnostic codes, to identify 137 condition categories that may contribute to PASC. This was then taken through an iterative process using literature, clinician input, and overlap from different data sources to take 137 conditions through this process and select 44 PASC categories and then assess on a baseline population within the PCORnet dataset, varying incidence and significance.

In their primary analysis, this was done using data primarily from New York City and Florida, and refined the overarching 137 conditions down to a refined risk of 25 conditions. In their publication in Nature Communications, they presented this EHR cohort of about 35,000 adults aged greater than or equal to 20 years with SARS-CoV-2 infection, and identified those 25 conditions that most contributed to

the definition of PASC. This is called the PCORnet PASC computable phenotype which we used in our analysis, which we'll talk about more today.

[Inaudible 00:08:40] identified as the 25 conditions that they included in defining PASC when considering EHR datasets. You can see that they're different conditions-classed organ systems, including neurologic, genito-urinary, digestive, respiratory, circulatory, and endocrine system. Taking that and applying both the EHR dataset as well as prospective dataset, PASC has been studied across populations to identify risk factors and protective factors as it relates to the interval development of PASC. Retrospective studies have identified risk factors for the development of PASC to include severe COVID-19 disease, female sex, middle age, presence of pre-existing comorbid health conditions such as diabetes, obesity, obstructive sleep apnea, and chronic lung disease, as well as a strong antibody response to SARS-CoV-2 infection.

The most prevalent protective factor that's been identified across datasets has been COVID-19 vaccination. So it's ongoing work for us to define PASC and elucidate these risk factors and protective factors across different populations. One such population is pregnant individuals, which has been rather minimally assessed thus far in evaluating long-term development of PASC. That leads us to our research question, which was to ask, "Does the risk for interval development of PASC differ between acquiring SARS-CoV-2 infection during a pregnancy as compared with acquiring SARS-CoV-2 infection outside of a pregnancy?"

And this is relevant because pregnant populations differ somewhat from the baseline population as it relates to immunologic responses as well as other comorbid complications that can come up in pregnancy. When thinking about pregnancy and acute infection, acquiring SARS-CoV-2 infection during pregnancy has been associated with worse perinatal outcomes and increased maternal morbidity. In a study done by Dr. Metz et al, highlighted here, was a retrospective cohort study of about 14,000 individuals delivering across 17 US hospitals in 2020. And those with SARS-CoV-2 infection compared to no infection in pregnancy were more likely to experience maternal mortality and morbidity from complications such as hemorrhage, infection, and hypertensive disorders of pregnancy.

Other studies have found similar associations between SARS-CoV-2 infection during pregnancy and an increased risk for things such as ICU admission, need for mechanical ventilation, and cardiovascular complications, as well as rate of preterm birth. Our goal from our current analysis that we'll present today was to focus rather on... instead of the pregnancy and active infection, we'll still look at pregnancy and long-term respiratory development of PASC. When thinking about this question, one thing I will highlight in advance is that there are physiologic change in the pregnancy. And in general, pregnancy is often defined as an immune tolerant state. There are alterations in cytokine, complement and T cell regulation, as well as changes at the uterine-placenta interface.

All of these are meant to accommodate fetal protection. And these immune changes may alter the risk of PASC following SARS-CoV-2 infection in pregnancy, and therefore was the basis for our question. The objective of our current analysis was to evaluate the association between acquiring SARS-CoV-2 infection during pregnancy and the development of PASC compared with acquiring SARS-CoV-2 infection outside of pregnancy, specifically in the RECOVER Initiative EHR dataset. Our hypothesis was that the physiologic changes of pregnancy would have a protective effect resulting in a lower incidence of PASC following SARS-CoV-2 infection acquired in pregnancy.

The method for analysis specifically utilized a retrospective cohort study designed within the PCORnet EHR dataset which we discussed earlier. We included females aged 18 to 49 years of age with lab-confirmed SARS-CoV-2 infection from March of 2020 through June of 2022. We considered baseline characteristics of the population included, utilized the EHR algorithm and datasets to access medical and obstetrics history, and then used these same datasets to define the interval development of PASC

conditions identified using the insurance and diagnosis codes as outlined earlier. This RECOVER EHR Initiative was IRB approved previously through the Biomedical Research Alliance of New York.

In our analysis, the exposure was acquiring SARS-CoV-2 during pregnancy as compared to acquiring it outside of pregnancy. In order to do this, we used a validated algorithm to identify pregnancies and define a gestational window for each individual included. The outcome of interest was PASC, which we identified as, or defined as occurrence of the 25 conditions within the computable phenotype previously defined by the PCORnet EHR team after our laboratories confirmed SARS-CoV-2 infection. So we utilized that previously established definition from an adult population and applied it within pregnant or reproductive-aged females.

We will highlight that we removed anemia as one of the conditions of priority because of the known high prevalence among pregnant and postpartum populations for anemia to be preexisting. So ultimately, our PASC definition included 24 rather than 25 conditions that contribute to the computable phenotype. Here is demonstrating how we did this, from the previous slide. So the top figures here demonstrates that we looked at data from three years, prior to COVID onset. This defined our baseline period to allow us to look for confounders. So during this period, we identified individual demographics as well as medical history.

We then looked at the onset of the SARS-CoV-2 infection and the acute period within 30 days afterwards. And then ultimately, the PASC period was defined at 30 to 180 days after the incident infection. Similarly, we used a validated algorithm to define pregnancy utilizing gestational ages from 20 to 42 weeks as the pregnancy period, and then an additional 42 days postpartum period. We then overlaid these as demonstrated in this box, where we looked at the incident pregnancy period as well as the incident SARS-CoV-2 infection period.

The pregnancy periods in green, or these three that are highlighted, were those individuals that were included. Individuals that experienced the SARS-CoV-2 infection during the postpartum period only were excluded. And individuals that experienced the SARS-CoV-2 infection prior to the onset of pregnancy were also excluded. We then completed univariable comparisons between characteristics of individuals of SARS-CoV-2 infection acquired during pregnancy and outside of pregnancy, and used stabilized inverse probability of treatment weighting adjusted for baseline differences and estimated the association between expiring SARS-CoV-2 infection during pregnancy and the interval outcome of PASC.

This is reported as adjusted hazard ratio and 95% confidence intervals. And we did complete an adjustment for multiple comparisons. For our results, here you can see a flow diagram of the population that we considered. Across the time period that we looked at, there were 1.5 million individuals with data available within PCORnet EHR datasets. As we [inaudible 00:16:40] our restrictions looking at females and then classifying individuals as pregnant or non-pregnant with SARS-CoV-2 infection, we ended up with about 5,000 individuals that's SARS-CoV-2 positive status with a pregnancy, and then around 84,000 individuals that were SARS-CoV-2 positive, but in a non-pregnant population.

Here you can see the baseline characteristics as we compared them between individuals with SARS-CoV-2 infection during pregnancy, as compared to those who acquired SARS-CoV-2 infection outside of pregnancy. Here you can see the rates of the various outcomes or the median with interquartile ranges. And then we utilized the standardized mean difference using a value of greater than 0.1 OS than -0.1 to indicate a meaningful effect size. Notably and [inaudible 00:17:33], we can appreciate the females with SARS-CoV-2 acquired outside of pregnancy as compared to those who acquired it during pregnancy were more likely to be non-Hispanic, white, to be of older age, and to have comorbid health conditions such as chronic kidney disease and diabetes.

Here we can see that among individuals that were pregnant at the time of their SARS-CoV-2 infection, they were more likely to be admitted to the intensive care unit, as seen in the top row. We can also see that individuals who had SARS-CoV-2 infection acquired during pregnancy were less likely to

be fully vaccinated against COVID-19. In the bottom, you can also see that we looked at SARS-CoV-2 infection over time to understand potential viral variants as a surrogate marker using time periods. In our prior analysis acquiring SARS-CoV-2 infection during pregnancy was associated with a lower incidence of PASC in the subsequent 30 to 180 days compared with acquiring SARS-CoV-2 infection outside of the pregnancy.

This was identified as 25.5% of the population amongst pregnant individuals who had acquired SARS-CoV-2 infection, as compared to 33.9% in those with SARS-CoV-2 infection outside of pregnancy. Stated another way, we also looked at this as a cumulative incidence of PASC, where we found that approximately 31 per 100 persons among those with SARS-CoV-2 infection in pregnancy went on to develop PASC, as compared to approximately 36 per 100 persons among those with SARS-CoV-2 infection outside of pregnancy. These are the subcomponents. So as identified before, we ultimately used a computable phenotype defined as 24 conditions, excluding anemia, to do the primary analysis.

Here are the subconditions of the 24 different conditions that were considered. And you can see in utilizing their rates and an adjusted hazard ratio here that some conditions were more likely or others were less likely following SARS-CoV-2 infection in pregnancy. Some of it were a higher risk for those identified such as thromboembolism as well as abdominal pain, whereas other conditions were at a lower incidence than contributing to the overall primary analysis. So in conclusion, our key findings were that in this population based retrospective cohort study of COVID-19 survivors, SARS-CoV-2 infection acquired during pregnancy were associated with a lower risk of developing PASC at 30 to 180 days after infection, compared with SARS-CoV-2 infection acquired outside of pregnancy.

This current study is the first to describe a lower incidence of PASC following acquisition of SARS-CoV-2 infection in pregnancy. When we consider our findings in the context of prior alert, overall, the available studies and data to date have been rather limited. Our prior prospective cohort study in 2020 of pregnant and postpartum individuals who had SARS-CoV-2 infection, either during pregnancy or postpartum up to six weeks afterwards, identified that 26% of those with SARS-CoV-2 went on to report persistent symptoms at eight weeks after infection. In another cross-sectional study published in 2022 of pregnant and non-pregnant females in Ecuador, an anonymous 37-item online questionnaire identified that 48.5% of them self-reported long COVID symptoms such as fatigue, hair loss, and difficulty concentrating.

So overall, these prior studies demonstrate somewhat of similar findings to our work. And as you will hear shortly, the RECOVER-Pregnancy Cohort has prospectively included pregnant individuals exposed to SARS-CoV-2 infection during pregnancy and gone on to evaluate PASC, which Dr. Metz will report on shortly. As far as limitations and strengths of our analysis then, some of the limitations including that this was a database study which utilized insurance codes, which always risks the potential for misclassification and under ascertainment. We also had insufficient sample size for sub-analyses such as by-COVID variants, severity, or vaccination status.

Our findings are not generalizable to individuals of pregnancy at less than 20 weeks gestational age, as our inclusion algorithm required individuals to have ongoing pregnancy beyond 20 weeks for inclusion. We also did not adjust the indication for testing within the population, so we potentially had individuals who were tested and screened positive for SARS-CoV-2 infection, even though they were potentially asymptomatic. Strengths are that this was a novel analysis where we were able to report on PASC following pregnancy, which was not previously done. We used a large sample of representatives of the geographic and racial diversity of the United States, increasing the generalizability of our findings. And we used robust modeling using inverse probability of treatment weighting.

So for the future, overall we've been able to identify that pregnancy may function as a protective factor against interval PASC. And this differs from the well-described association between COVID-19 in pregnancy and worse acute findings and perinatal outcomes. This might be explained by

immunologic adaptations of pregnancy, and future work may work to focus on this. The current findings [inaudible 00:23:12] inform patient counseling and help to direct our future work. Right now, we are continuing this effort with a collaboration with the National COVID Cohort Collaborative, or N3C, to repeat our analysis in a second electronic health record dataset. And then, further prospective study will be necessary to confirm these findings, some of which has already been done through the work of Dr. Metz.

So I'll hand it over to her to present on her prospective cohort. But thank you for your time. And when we get to the Q&A and panel session, I'm happy to answer any questions.

## Dr. Torri Metz:

Okay.

## Speaker X:

I'm sorry. Yeah, thank you.

## Dr. Torri Metz:

Thanks so much for joining us today. I am going to talk a little bit about the prospective RECOVER cohort and talk about the development of post-acute sequelae of SARS-CoV-2 after infection during pregnancy, or the NIH RECOVER-Pregnancy Cohort. I do have two disclosures. I was a site PI or site principal investigator for a Pfizer study of the COVID-19 vaccination in pregnancy, and money was paid to my institution to conduct that study. I was also the site principal investigator for a Pfizer study of the pharmacokinetics of Paxlovid in pregnancy for the treatment of mild to moderate COVID-19. And similarly, money was paid to the institution to conduct that work.

So what is the RECOVER-Pregnancy Observational Cohort? The RECOVER-Pregnancy Cohort will enroll maternal and child dyads to investigate the effects of SARS-CoV-2 acquired during pregnancy on the long-term health of both the pregnant person and their offspring who were exposed to SARS-CoV-2 in utero. So it's unique in enrollment of dyads, maternal-child dyads. This is just a graphical figure, just to give you a little bit more perspective the RECOVER-Pregnancy Cohort and what it means when I'm talking about this. So we aim to enroll 2,300 pregnant individuals and their offspring. You can see the photos of the two there. And we are enrolling both people who had SARS-CoV-2 during pregnancy, and their children who are thus exposed to SARS-CoV-2 in utero, which is on the top, 1,867 of them, and those who did not have SARS-CoV-2 during pregnancy and unexposed children so that we can make comparisons, really specifically for the neurodevelopmental outcomes, which I'm going to talk about on the next slide.

Actually, two slides from now, sorry. So in terms of the adults, so the mothers that are enrolled in this study, we are going to follow the study procedures of the adult cohort, and have been doing that. This means that there's three tiers of different studies that are done as part of the RECOVER adult cohort. And basically, there's deeper phenotyping by tier. And so, the first tier is really a lot of symptom-based surveys. Tier two gets until a bit more invasive testing. And then, tier three is really in-depth testing for specific organ systems. We did have to make some modifications for the pregnancy and the postpartum state. For example, we did not want weight loss among postpartum people that trigger certain tests.

So there's certain tests specifically looking more the GI system that had been triggered by people losing weight, and so we noticed at some point that while we're triggering these and the reason we're triggering them is because people have become postpartum. It's not that they're having abnormal weight loss or having physiologic weight loss. So we did have to make some modifications the triggers

for the tiered tests. Similarly, there's some things that we just don't do in pregnancy. We don't typically perform exercise, treadmill testing when people are pregnant. We also don't typically perform some imaging studies, specifically those with radiation, like CT scans when people are pregnant. So we weren't doing those and pregnant people.

These is just a summary of the adult study procedures. This is not a slide that I expect anybody to read. But really, it's just a reminder overview or a familiar realization for people that aren't otherwise familiar with the adult RECOVER cohort, that there are a number of time points that we're in contact with participants in our cohort. It's actually the baseline visit. And then in that first two years, it's every three months, and then it starts to decrease a little bit in frequency in terms of their in person visits subsequently. But really collecting detailed data on the people who are enrolled in RECOVER-Pregnancy that are doing all the same procedures as the RECOVER adults.

This is a slide I thought was previously coming next. Apologies. We are also doing offspring neurodevelopmental testing, and so I think the thing that's really unique about the pregnancy cohort is that we're enrolling the adult mothers and then their offspring. So the real primary focus of the offspring study procedures in RECOVER-Pregnancy are looking at neurodevelopmental testing, and we're doing that starting at 12 months. We do it again to 18, 24, 36, and 48 months. And we are trying to pass all of our participants who are enrolled in RECOVER-Pregnancy's offspring to what we are calling our tier two tests. The tier two tests are in person neurodevelopmental testing, including the Bayley-4 exam and the Differential Ability Skills II exam.

We're also measuring their growth, and we're collecting blood specimens for future research if the parents consent to that. Prior to those tier two tests, we are also collecting very valuable data remotely from participants using the Ages and Stages Questionnaire, which is sent to participants at 12 months of age. And then also looking at M-CHAT, which is a screening tool for autism at 18 months of age. So today, we're going to focus more on the adult side. We hope to have the offspring results forthcoming soon as well. But the first thing we're able to really examine is the adults and the pregnant people who acquired SARS-CoV-2 during pregnancy. So in terms of background, and Dr. Bruno talked about a little bit of this already, but SARS-CoV-2 we know increases the risk for serious maternal morbidity, stillbirth, preterm birth, and hypertensive disorders of pregnancy, or high blood pressure during pregnancy.

We also know that pregnant people are at higher risk of developing severe COVID-19, having ICU admissions, and dying of COVID-19. And we do see this with other viruses as well, so this was not unique to SARS-CoV-2. We know that about 10 to 25% of non-pregnant adults infected with SARS-CoV-2 develop post-acute sequelae of SARS-CoV-2, also known as PASC or long COVID. And we do see increased risk with early variance, higher disease severity, medical comorbidities, and among those who are unvaccinated at the time of infection. And this really is a new public health crisis, which has really led to the Congressional funding and the RECOVER Initiative that hopefully is going to be able to answer a lot of these questions.

So it really remains unclear though how pregnancy affects PASC. And as Dr. Bruno stated, the publication that came out from the EHR cohort is really the first to draw attention to the fact that it might be different in pregnancy than it is outside of pregnancy. The NIH RECOVER Cohort is designed to really understand the prevalence and pathophysiology of PASC. And we established the RECOVER-Pregnancy Cohort to follow people that had SARS-CoV-2 during pregnancy in order to determine if they develop PASC. And we thought and hypothesized that perhaps we would observe a differential prevalence or differential risk factors for PASC after getting SARS-CoV-2 during pregnancy.

So the objective of this initial work that I'm going to share with you today is to estimate the prevalence of post-acute sequelae of SARS-CoV-2 infection, PASC or long COVID after an infection with SARS-CoV-2 during pregnancy among people in the RECOVER-Pregnancy Cohort and to characterize the

associated risk factors. The design is a multicenter observational cohort study, or the RECOVER-Pregnancy Cohort study. Participants were enrolled from December 2021 through September 2023 across 46 states, plus Washington DC. In person study visits were performed at the 26 sites that are participating in the Maternal-Fetal Medicine Units Network, and remotely nationwide by the University of California, San Francisco. Participants completed surveys about their PASC symptoms and the symptom severity.

We included participants in the RECOVER-Pregnancy Cohort who were pregnant at the time of index SARS-CoV-2 infection. And we excluded those with no available study visit with a PASC symptom survey six months or more from the index infection. Our primary outcome was PASC at the first study visit six months or more from the index infection. And for this particular analysis, PASC was defined using the same NIH-RECOVER Adult PASC scoring system that had previously been developed based on the presence and severity of self-reported symptoms. Scores range from zero to 34. And participants with a score greater than or equal to 12 were considered to be PASC positive, and the others were considered to be PASC indeterminant. And this is the same cutoff that was used in the initial JAMA publication by the RECOVER-Pregnancy Cohort with the recognition that this is really a research definition, and that some people who have PASC or long COVID would not have a score greater than 12. But we do know that those who do have a score greater than 12 are highly likely to have PASC or long COVID. And so we feel like this is still a valuable research measure.

We looked at risk factors for development of PASC as well. And the sociodemographic risk factors that we considered were insurance status at enrollment, self-reported difficulty covering expenses and paying bills, self-reported experience of discrimination as measured by the Everyday Discrimination Scale. We also looked at preexisting clinical characteristics, including maternal vaccination status and self-reported comorbidities such as tobacco use, obesity in the year prior to infection, high blood pressure, hypertension, and depression or anxiety disorder. Similarly, we looked at risk factors that came from their index SARS-CoV-2 characteristics, so things like initial infection severity, the trimester at the time of SARS-CoV-2 infection during the pregnancy, and the calendar time of index infection as a proxy for the variant of SARS-CoV-2.

In terms of our statistical analysis, we performed unadjusted and adjusted... odds ratios were calculated between each risk factor, and the past status was estimated using multivariable logistic regression. Missing covariant information was addressed using a process called multiple imputation, where we use other covariates to basically fill in that missing data. And a sensitivity analysis was performed, excluding the study visits when the patients were still pregnant or within 12 weeks postpartum, meaning that we reperformed these analyses and took out all the people that were still pregnant or within 12 weeks postpartum when we were measuring their symptoms of PASC, because a lot of the symptoms of PASC are overlapping with those that we see in normal pregnancy and postpartum. Things like fatigue or brain fog. And so we wanted to make sure that we weren't just seeing symptoms of pregnancy and being postpartum, and that we were indeed seeing symptoms of PASC.

We also did a complete case analysis to assess our handling of missing data, meaning that we looked only at those who didn't have any missing data to make sure that we were getting the same results as as we did when we actually imputed the missing data, meaning we filled in that missing data with other information that we knew about the participants that could predict the things that were missing. So here are our results. Overall, there are 14,636 participants in the NIH-RECOVER Adult Cohort. We excluded people who identified as male, intersex, or missing sex, those who are over age 45 or age unknown, and those who are not infected with SARS-CoV-2, our control population. We focused in on patients who are infected, identified as female between 18 and 45 years of age. So thinking about the reproductive age period.

We excluded people who were not pregnant or didn't have pregnancy information, and focused on people who were pregnant at the time of their index SARS-CoV-2 infection, which was 1,612 patients. We then excluded those who didn't have a six-month study visit because we weren't able to assess them for PASC or the outcome, which resulted in a final cohort of 1,502 participants for this analysis. 61% of them had an index SARS-CoV-2 infection on or after December 1, 2021, meaning that they had an infection during the period of Omicron variant dominance. 48% had an index infection during the third trimester. 51% were fully vaccinated more than two weeks prior to next infection, meaning that we felt like the vaccination had taken full effect at that time. 24% reported obesity in the year prior to infection. And 29% had medical comorbidities that they self-reported.

This is our primary outcome, which was the prevalence of PASC. 9.3% of our cohort met criteria for PASC. You can see on the right there, a graph that shows the PASC scores of those who met criteria for PASC, so those that had a score of 12 or more, and how frequently those different scores showed up in our cohort. And so you can see that having a score of exactly 12 is actually the most prevalent score that we saw. But you can see patients with scores as high as 31. The median time from index date to our PASC-defining study visit was 10.3 months. So we know that the prevalence of PASC is going to change over time. And so we just think it's important to note that, in general, the median for these patients was 10 months, is when we were assessing them for PASC and looking at their symptoms of PASC.

The most the most common PASC symptoms were post-exertional malaise, fatigue, gastrointestinal symptoms, dizziness, and brain fog. And these are similar to the adult cohort that contains also non-pregnant adults. We were able to identify some risk factors that were associated with PASC, that we put everything into our multivariable logistic regression model. And the things that remained in the model, as being associated with the development of PASC, were that patients reported covering expenses was difficult in the past 30 days. They reported that they self-reported a diagnosis of obesity in the year prior to infection, self-reported diagnosis of depression or anxiety in the year prior to infection. And they reported that they had higher severity of initial infection, meaning that they required oxygen for their acute infection.

We also found that infection pre-Omicron, not being fully vaccinated, having a higher discrimination index, and having medical comorbidities were associated with PASC in our unadjusted models. But once we adjusted them for all the other risk factors, we saw that those results were no longer significant, meaning that that 95% confidence interval in parentheses in the far right column starts to cross one. It doesn't mean for sure that these would never be associated. It just means that when we looked at this in the sample size that we had available, and adjusted for all the other things, that these things were no longer associated. But will certainly warrant further investigation because we did see a signal in the unadjusted modeling.

We also did the two sensitivity analyses that I spoke about. Our results were similar in the sensitivity analysis in which we excluded those who were still pregnant, and those within 12 weeks postpartum at their PASC-defining study visit. Our results were also similar in the complete case analysis where we only analyzed people that didn't have any missing data. In terms of limitations of this work, our PASC outcome definition is based on an algorithm that creates an overall PASC score. People experience different symptoms and different symptom severity. Some PASC symptoms can be common, nonspecific, and can overlap with those seen during pregnancy or postpartum. And we really cannot estimate the true population prevalence of PASC using this methodology, because people came to us and wanted to enroll in the study, in addition to us seeking them out. And it's possible that those who came to us wanting to enroll in study already knew that they were affected by PASC.

The strengths are that this is a multicenter and diverse population. The PASC symptoms were collected prospectively and rigorously. Sampling was not limited to those previously identified as having PASC. I think more so in the pregnancy cohort, we really didn't seek to identify patients for our RECOVER

cohort from those who were already seeking care in places like long COVID clinics. We were just looking in the electronic medical record for patients who had been pregnant during that timeframe, patients who had a positive SARS-CoV-2 test during the pregnancy, and then through social media advertisements, just saying, "Have you been pregnant during the pandemic? Would you be interested in enrolling in a study?"

We also established a scoring system to identify those with PASC... Or sorry, we used an established scoring system to identify those with PASC that has already been previously published by the adult cohort. And we were using the same surveys and severity assessments as the adult cohort. So in conclusion, we think about one and 10 individuals with SARS-CoV-2 during pregnancy will develop PASC. Symptoms include post-exertional malaise, fatigue, and GI symptoms predominantly. We did identify socioeconomic and clinical characteristics that are associated with the development of PASC. And we note that the rates of PASC among pregnant populations may be lower than non-pregnant adults.

In the initial RECOVER publication of RECOVER adults, the range of PASC prevalence was from 10 to 25%. It was 10% among those in the RECOVER cohort who were enrolled acutely with their SARS-CoV-2 infection, then followed longitudinally to see if they develop PASC, and was 25% overall. So we're getting a rate around 9%, which is slightly lower and is consistent with the data from the EHR cohort. And so, it's starting to be a little bit more of a body of work demonstrating that, potentially, patients who acquire SARS-CoV-2 in pregnancy have a lower incidence of PASC subsequently. I'll like thank all of the RECOVER-Pregnancy sites who enrolled patients for this study. Many of these are part of the NICHG, Maternal-Fetal Medicines Units Network, and also UCSF School of Medicine who recruits patients remotely across the whole United States.

We would also like to thank the participants ant patient representatives who have contributed to the NIH-RECOVER Initiative. Certainly, without them this work would not be possible. Thank you so much, and I'm happy to take questions afterwards. Thank you.

## Dr. Valerie Flaherman:

Thank you so much to both of the panelists for presenting these fascinating results. I think what you've highlighted is that the physiologic state of pregnancy is really unique. And from the results that you've shared about long-term COVID outcomes among pregnant people, we have the opportunity to learn information that's relevant not only to our pregnant population, but also to inform understanding of the mechanisms by which PASC develops in this immune tolerant state of pregnancy. So I think your work has broad applicability, both, of course, to the important public health questions related to pregnancy itself. And more broadly to looking at PASC in general, and how we can develop effective therapies.

I just wanted to start today with one of the questions that I noticed in the chat. A crucial question we have all been waiting to learn the answer to is how does infection during pregnancy impact the offspring? And practicing during the early pandemic, this was a great worry at that time and a huge focus of public health efforts. What do we know about that, currently? And can you perhaps say just a bit about the plans that your teams have to examine these questions in the future?

## Dr. Torri Metz:

Yeah, I think I can probably take that one. So, I did review a little bit on one of my slides, really, the offspring neurodevelopmental assessments that we're doing as part of RECOVER-Pregnancy. We do have a very robust set of neurodevelopmental assessments that we are completing on the offspring of these participants. Those will lag behind the adult data, just because we have to wait until the children

are old enough to assess them. So the last RECOVER-Pregnancy participants delivered in December of 2023, And so all of them will reach one year of age by December of 2024. So we are starting to look at those data and are really interested in seeing them.

There are a couple of publications looking at offspring assessments, outside of RECOVER, using data from other large administrative datasets, examining if offspring have basically abnormal neurodevelopmental diagnoses in their medical records is how they did that that work. And they did find a signal that those who had been exposed to SARS-CoV-2 in utero did appear to have a higher rate of those diagnoses. I think it's hard to know whether they were just more closely followed. They were certainly more likely to be born premature. And those children are often followed in specialty clinics where those diagnoses just may be made more often. So I think that it's a really interesting work that's already been published, but it will be important to validate that work in a prospective cohort, like the RECOVER cohort.

There was another publication also looking at just using the Ages and Stages Questionnaire, which we are also using in RECOVER and examining outcomes. They did use some control groups of children who were born prior to the pandemic. And it seems like it's going to be really important to sort out what are pandemic effects of children being born during the pandemic, being born in a period where patients were masked, where people were masked, where there was less social contact, how that affects neurodevelopment in socio-emotional development in comparison to is it the SARS-CoV-2 itself, that exposure and that inflammatory response that influences that? So I think it's really important questions that we're excited about examining, and I think probably Dr. Flaherman can also maybe pitch in there since she's involved in the pediatric aspect of this cohort as well.

## Dr. Valerie Flaherman:

Yes, I think this is something that RECOVER, I think, was... it has really focused on. In our prospective pregnancy cohort, we are doing these careful assessments of the offspring through four years of age. And one thing I'm really hoping to be able to look at is how exposure to SARS-CoV-2 affects the developmental trajectory of children over time. And I think one thing that RECOVER is very suited for is adjusting for those effects of the pandemic itself, because we have those actual controls that are contemporaneous to the exposed participants. So I think there will be some great things in the future. And I'm glad to see that there seems to be some audience interest in it. So hopefully, we'll see you all at another seminar, not too far from now.

Okay. So overall, as Dr. Bruno and Dr. Metz, as you were presenting today, it was great to hear about the important research question being addressed simultaneously in the two different RECOVER cohorts. So looking at the impact of SARS-CoV-2 during pregnancy in our prospective RECOVER cohort where we're enrolling participants and following them with a combination of remote and in-person outcomes, as well as in the electronic health record cohort. Is it possible to say in a general way for the overall recover project, what are the benefits and advantages of the prospective data collection, and the benefits and advantages of the EHR data collection? These are two unique data sets that might have different sorts of biases. And pregnancy could be a good opportunity maybe to think about the unique contributions of each cohort.

## Dr. Chengxi Zang:

Right. Maybe I can start with the EHR cohort. I think one of the biggest trends is sample size of the EHR cohorts and those potentially more generalizable real world evidence. Actually, based on Ann Bruno's work, we are continually our efforts to collect him a bigger cohort. Currently, we are targeting five to 10 times bigger cohort to study more, so try to find analysis by different variants of cancers,

different trimesters, and so on so forth. I think that's the first [inaudible 00:49:48] we have a bigger sample size. And potentially, we can generate more helpful evidence or hypotheses in a more timely way, right? This is a more timely, cost-effective than the prospective cohort. And of course, this is a real world evidence we are collecting to the real world of treatment and real world outcomes. Which of course, we [inaudible 00:50:09] informed data collection of the prospective cohorts and of course vise versa. And prospective cohorts will also informs the EHR analyses.

### Dr. Torri Metz:

I guess I could just speak to the prospective cohort a little bit. I mean, I think that Chengxi is exactly right. It is super helpful to really get that large population based capture that we can get with the electronic medical records. I alluded a little bit to, with the prospective observational cohorts, we do worry a little bit more about bias in terms of people who were already affected with PASC, then wanting to enroll, not surprisingly so, in a study that's investigating, PASC. And so we worry about that inflating the the prevalence a little bit in the observational cohort. I do think, as I noted, that there's a little less concern about that, I think, in the pregnancy cohort, just because the way we did our recruitment, and that we really weren't recruiting specifically for many long COVID clinics.

But I think that is a concern that the EHR cohort can fill and really complement the two. I think the advantage of the prospective cohort is that we can really collect detailed data on every single participants, really make sure that we understand all of their past medical history very well, take laboratory assessments, really extensive symptom surveys, things that we just can't get from just pulling information from a medical record. And so, they really do work synergistically to try to get us research answers.

### Dr. Valerie Flaherman:

Great, thank you. I hope that as the seminar series continues, we have a continuing opportunity to present the EHR and prospective data of the various cohorts in the context of each other. Because I think they're both a real opportunity to learn about the field. Another thing I think is really interesting about this work is the role of vaccination in modulating PASC and the overall impact during pregnancy. And this also received a huge amount of public health attention in 2021, in 2022, as vaccination was rolling out. Have your groups looked at some of the risks and benefits of COVID vaccination during pregnancy? And how do you think about that in terms of recovered data?

### Dr. Torri Metz:

Dr. Bruno, you want to take that one?

### Dr. Anne Bruno:

Yeah, happy to. So I would just say outside of the two studies that Dr. Metz and I presented today, there is quite a bit of literature now supporting COVID-19 vaccination in pregnancy. As you stated earlier, in the pandemic, this was a big worry. Just like when there's any vaccination, or medication, it's very important to include pregnant and postpartum individuals in those analyses and studies. And over time, that has successfully been completed and the overwhelming evidence support the safety of COVID-19 vaccination in the course of pregnancy and the postpartum period. Both won without any evidence of teratogenicity or other specific complications in pregnancy. But also, as highlighted in some of the prior work of Dr. Metz, to try to reduce some of the acute risks related to SARS-CoV-2 infection in pregnancy.

And then we also are starting to see that in some of these longer term studies looking at PASC and the EHR data set, we did include documentation of vaccination and analyses. In general, we identified that pregnant individuals were less likely to be fully vaccinated. That likely reflect some of the time period that we were utilizing, because it crossed to the period before we had as robust of data around safety for vaccination. And that's something that's also been included in the ongoing prospective cohort with Dr. Metz. So I think we'll continue to get more and more data from that aspect. I will say clinically, that we as maternal-fetal medicine physicians, our national societies all highly support the use of COVID-19 vaccination before and during pregnancy. And so, it's also nice to see that those recommendations are bearing out in data now to support that those are again, likely safe and demonstrate long-term protective ability as well. But I think future analyses that are more specific and focused on COVID-19 vaccination to look at PASC will be necessary within this population.

## Dr. Valerie Flaherman:

Thanks. That kind of leads well into my next question, which I see was echoed by one of the live questions in the Q&A. Thinking about the question of PASC in pregnancy, have we flipped the research question to look at pregnancy in participants who actually have PASC? So future pregnancy among people who have PASC diagnosis, and they know that this is a concern for many people in the patient community, individuals who are interested in pregnancy and know that they have a pre-existing health condition. Has RECOVER started to look at that? And if so, what is that? What's the state of our investigation?

## Dr. Torri Metz:

Yeah, thanks for that question. So this has come up. All of these cohorts have sort of coordinated committee groups that meet, and we have patient representatives that are part of those committees and help lead the work that RECOVER's doing. It actually has come up there where they have asked, "What can we look at? What about..." Now that somebody has a diagnosis of PASC or long COVID, and they want to get pregnant, how is that subsequent pregnancy going to be affected? How is their fertility going to be affected? And I think that those are really important questions that are definitely on our radar. I don't have any data to share about that today. But do know that it has been brought up in our group that is really helping to lead this work, and that we we definitely think it's an important question.

I think we can get at it somewhat, for sure, with the prospective observational data. And that we do collect subsequent pregnancies on all of the adult participants, so not just those in the pregnancy cohort. But any adult participant who was enrolled, we have information about when they had met a diagnosis of PASC, and if they had any subsequent intervening pregnancies after that time. And we've talked about trying to get into how many participants actually have had a subsequent pregnancy. But I also think it's something that will be very ripe for investigation in the EHR cohort, where we take these patients that now we have done this computational phenotyping for and have identified them as people who have made PASC, and then looking at subsequent pregnancy in them.

## Dr. Chengxi Zang:

Right. To add one point... It's a great question, right? Actually, currently, we must acknowledge that our current analysis focuses on the incident of PASC, which means they were not all happening the previously and we checked against the conditions. And this is more about the PASC scan as they are relapsing or worsening or some consequences on the practicing outcomes. These are still open questions and they need more research. And also, another challenge is how to distinguish between the

PASC and the common conditions in gestational period or postpartum period, which might cause for revising our definition of existing PASC, which are derived from general population from the incident conditions. We can see the gap there.

## Dr. Valerie Flaherman:

It's interesting, because many of these questions seem to really relate in part to the physiology of pregnancy and the physiology of PASC, and how they interact. Has there been thought given to the different stages, or perhaps trimesters of pregnancy, and how this may impact the physiology of the individual, and the outcome of the outcome of PASC?

## Dr. Anne Bruno:

I can take that one. So that is something I think that's of interest. In our analysis that we presented today, while we did have a large sample size, which is a major positive of using this data source, we were still limited in our ability to complete sub-analyses looking at by trimester of infection. That is something that we are working on for future work in a larger electronic health record data set. So considering how we might be able to consider what we've highlighted earlier about vaccination status a bit further.

Also considering bivariants of SARS-CoV-2 infection has been of some interest. And then as it relates specifically to pregnancy, thinking about the trimester of infection and how that might alter the interval development of PASC. So that is something that we are working on currently. And so, we'll hopefully have more information in the future. But I think highlights an important question that comes up as we think about pregnancy and whether it matters at what point during pregnancy an infection occurs as it relates to interval PASC.

## Dr. Valerie Flaherman:

Yes. I'm so glad you also brought up the question of variant because I think that's a common question that I hear from folks is, "Since SARS-CoV-2 has changed over time in its acute form, would it be reasonable to think that PASC itself might also be changing? And if it is, how can we track that in the data?" And I think that's a question for all of us to address on an ongoing basis.

## Dr. Torri Metz:

Yeah. I think, for sure, it's a question to address on an ongoing basis. I mean, I think, it does seem like earlier variants, people are more associated with PASC. But perhaps that's because of how we've defined PASC. And I think keeping an eye open to we may see differential symptoms in severity of PASC with different variants. I think uniquely with pregnancy, there were definitely variants, I mean specifically the Delta variant, that was particularly harmful for pregnancies. As in the general population, lot higher rates of ICU admission, but we also saw much, much higher rates of stillbirth and placental effects of that particular variant of the virus. And so also, I think it is important to look at differences in the offspring outcomes by variant differences and PASC by variant.

And those are all things that I think are certainly at the forefront of people's minds when we're thinking about this. Pregnancy is a little tricky, because we presented data showing you that people who are pregnant who got SARS-CoV-2 are more likely to be admitted to the ICU and die. I mean, that definitely epidemiologically is true and has has borne out over and over in the literature. And it's probably because their immunologic response is a little bit different than people who aren't pregnant. And that's why we also see with other viruses, pregnant women tend to get more ill. And that's because they're a little more immune tolerant in pregnancy. They have to tolerate a fetus that doesn't have their

DNA. And so in order to do that, a lot of changes happen with the immune system that adapt, that allow more tolerance, which then results in sicker patients.

So then you'd say, "Well, if they got sicker, why isn't their PASC worse?" Well, maybe it's all interrelated, that even though they got sicker, it was because they didn't have quite as robust of an inflammatory response perhaps that's involved in the pathophysiology. I think next steps, if this continues to be demonstrated that there's a lower prevalence among people who had SARS-CoV-2 in pregnancy, we'll be examining why. And can we look pathophysiologically? Can we look back at the bio-specimens that we've collected, and really demonstrate if there's differences there?

### Dr. Chengxi Zang:

And also, it's a prevalence in the same term, so the PASC can be varied by different SARS-CoV-2 variants suggested by our epidemiology study. For example, in New York's data, we just found a more bigger hazard ratio, bigger access burden of the pulmonary arteries, and some GI conditions in [inaudible 01:03:33], compared to the ancestral variants. But as these are knowledge from the general population, I just think it'll be question mark for the pregnant cohort, how they evolve over time. It's a big question mark.

### Dr. Valerie Flaherman:

Great, thank you so much. This has been such an educational presentation. And I really look forward to hearing from the audience on what most interests them. So I'll maybe turn it over now to Quinn.

### Quinn Barnette:

All right. Thanks so much, everyone, for such a rich discussion. Now we'd like to open our audience Q&A with a few questions that we received in advance. And just as a reminder, any questions that we aren't able to get to will be posted in the Q&A document on recovercovid.org. Our first question is for all the panelists, "Are there any known or hypothesized risks about getting pregnant while currently experiencing long COVID symptoms?"

### Dr. Torri Metz:

Yeah, I think that's one that we addressed a little bit in the discussion. I mean, I think that's definitely a question of high interest. I am not aware of any data on that. It is definitely something that's come up in our group as an area that will be really important in terms of future investigation.

### Quinn Barnette:

Thank you. You both spoke a little bit about the physiological changes that happen during pregnancy that might be implicated in the differential risk of PASC, that you both demonstrated in your studies. Could you talk a little bit more about the specific indications, such as the immune changes, and why that might be hypothesized to be a protective factor during long COVID?

### Dr. Anne Bruno:

I can take that one. So in prior evaluations of other infections in pregnancy, there has been data supporting that there can be immune changes. Both Dr. Metz and I sort of talked through that a little bit, that in the presence of a developing fetus, that there are natural physiologic immune changes that allow for a tolerant state, because there is "foreign DNA" in the setting of the fetus as well as other immune regulatory aspects. So while that is a hypothesis, because it's been borne out with other infections, it's

still technically a hypothesis. So as Dr. Metz highlighted, I think future work will be interesting to be able to use bio-specimens to look more specifically at cell regulation and the pathology within specimens to try to confirm or deny that a bit further. But because of existing data for other infections and the the hypothesis from a biologic plausibility standpoint, that is something that would make sense to us clinically.

## Quinn Barnette:

Thank you. Regarding the apparent lower incidence of PASC among people who were pregnant during infection, do you think this could have been influenced by the perception of fatigue and brain fog that's associated during the postpartum period?

## Dr. Torri Metz:

We were worried, for sure, about overlapping symptoms that we see between a lot of the PASC symptoms that people have as well as what is more just being postpartum, feeling fatigued, obviously, from interrupted sleep with a newborn. And the vast majority of our cohort, their pregnancy did result in live births, about 96%. And actually, we're trying to enroll people whose pregnancies resulted in live birth, just because we want to also follow their offspring. But I think that we do see that, which is why we... For the analysis that we did in the prospective observational cohort, we did that second sensitivity analysis where we took out anybody who was being assessed for PASC while they were either still pregnant or while they were within the first 12 weeks postpartum, and just tried to make sure that we were still seeing the same prevalence of PASC, which we did.

I think it is important to try to tease those things out. Also, our comparison group is other people who'd had a pregnancy who didn't develop PASC, and so similarly, those people also have a newborn at home and would, in theory, have similar symptoms related just being postpartum. And so, I think we do have an appropriate comparison group for that. And we also did that additional analysis where we looked only at people who are assessed further out from their birth.

## Quinn Barnette:

Thank you. I think the next question will also be for you, Dr. Metz. Your study uses the definition of PASC that was from the recent JAMA article. Can you talk about if that included pregnant individuals in their algorithm, and if there's any distinguishing symptoms that are seen in the pregnant sub-cohort that maybe might not be as frequent in the rest of the population?

## Dr. Torri Metz:

Yeah, thank you for that question. Yes, the initial publication did include pregnant individuals, and so they did help drive that initial PASC score development. Although, I will say that it is only about 10% of the overall adult cohort population, and so that was not largely driving that. It was largely driven by people who had SARS-CoV-2 outside of pregnancy. But we really have been trying to just on general principle and broadly say pregnant people should be included in analyses, they should be included in research, they should be included in studies. And I think, across the whole RECOVER consortium, unless we have a really good rationale for excluding them from these analyses, they are being included.

I think more broadly, in terms of the symptoms that we saw, they really were the same in terms of the most prevalent symptoms between the initial adult RECOVER population and the subset of this pregnancy population. We looked at it specifically. Really very much the same most-prevalent symptoms in both cohorts. We didn't see a difference in those, which might be a little bit surprising because you may think that you would see a difference in those, especially with what we've been talking about in

terms of just differences being postpartum and being pregnant. But they really were consistent across the two cohorts.

### Quinn Barnette:

Thank you. I'd like to move on to a couple of questions we got regarding breastfeeding and related issues with infants. Is there a discernible impact on breastfeeding success or failure rates related to perinatal COVID infection or postpartum long COVID that you're aware of?

### Dr. Valerie Flaherman:

Maybe I can take that question. This was something that RECOVER is very focused on answering. And we do have a good assessment of breastfeeding practices in our infant outcomes. It was a major concern of pediatricians in the early pandemic, when mothers who delivered with SARS-CoV-2 were actually separated from their infants. And there was a lot of concern about breastfeeding during SARS-CoV-2 infection. So I'm very happy to say that there... Of course, as I think everyone knows at this point, breastfeeding is very much to be encouraged. But we really want to look into what happened at that time, and whether there was an impact of early infection on breastfeeding. So I look forward to hopefully presenting that later this year.

### Quinn Barnette:

Thank you. And related to sequelae for offspring, has there been a... The focus on neurodevelopmental evaluation on offspring. Are there other aspects of development that should be considered in evaluating? And why was there such an emphasis on the neurodevelopment measures?

### Dr. Torri Metz:

I can maybe answer that from an obstetrician perspective, then maybe Valerie can answer from a pediatrician perspective. So from an OB perspective, we worry a lot with infections that we see a lot of. We can see maternal fever, we can see maternal inflammation. And all of those things in other conditions have been associated with adverse neurodevelopment in the fetus. And so, that's the rationale for really focusing on that. I think early in the pandemic, there was a lot of concern for vertical transmission of SARS-CoV-2, meaning the virus actually crossing the placenta and infecting the fetus. We have found that that is extraordinarily rare for that to actually happen.

And so, I think that allows us to shift our attention a little bit more to not those acute effects of the fetus actually being infected with the virus, but the effects of the fetus being in an inflammatory maternal environment with things like a fever that can really affect that neurodevelopment. And that's why we wanted to focus on that from an OB perspective. I don't know if you want to add anything from the pediatric side, Valerie.

### Dr. Valerie Flaherman:

Yeah. I mean, I think just to say that because of the risk factors that Dr. Metz was describing, it is very difficult to assess child neurodevelopment through, for example, an electronic medical record, especially in early childhood. And we didn't want to wait 10 years until these kids were in the middle of their school age and we could actually demonstrate a drop in test scores, or something like that. We wanted to do the assessment early so that we can really inform public health preparedness for the future. And the only way to do that was to do this detailed neurodevelopmental assessment that really has not been done with the sample size that RECOVER is going to be able to do it.

Having said that, we are also looking at a wide variety of other childhood outcomes, including growth, body mass index, child health services utilization, sleep quality, behavior, different aspects of child well-being that we'll be able to report on. And I think one of the unique things about RECOVER is that we do have this detailed information on both the pregnant individual and the child, and we have the ability to follow them together, which is really unique across cohorts. So I think we will see... That cohort will have to age somewhat before we can do our final neurodevelopmental assessments. But I think we should be able to get some of the highest quality data on this topic of any studies that I'm aware of.

### Quinn Barnette:

Thank you. Our next question is, "How do you hypothesize that sequelae of SARS-CoV-2 infection during pregnancy might influence trends and severe maternal morbidity and mortality?" So things like trends in cardiovascular, mental health, and substance use outcomes.

### Dr. Torri Metz:

Do you guys want to take that? I can take that. I mean, it's definitely an area of interest for me and research for me. The CDC has released data about maternal mortality across... now starting to be in the period of the pandemic as well, and definitely did see an increase initially in maternal deaths during the pandemic. Which, if you really broke down that analysis in detail, could be largely attributed to SARS-CoV-2 itself, so COVID-19 itself. But I think in the pregnant population, like any population, we also saw increases and just all-cause mortality.

And certainly for things like mental health disorders, suicide, drug overdoses have gone up in the pregnant population, just like they have in the non-pregnant population. So certainly ongoing concerns with that. The very most recent maternal mortality data that have come out actually did start to show a decline again. But we certainly saw an increase over the early pandemic years, related largely to COVID-19 and maternal deaths from that, but also other causes of mortality that were influenced by just living in the time of the pandemic.

### Quinn Barnette:

Thank you. And then related to that, what supports can we offer women at risk for long COVID and the transition from antepartum to postpartum care? Perhaps, Dr. Bruno, would you like to answer that one?

### Dr. Anne Bruno:

Yeah. I mean, I think that's a great question in regards to how do we apply clinical research to our actual clinical practice? And so I think that is one piece that's exciting about these findings, from both of the studies presented today, is how those can be utilized to counsel patients. And while I do think there's a lot of additional work still needed, as we have sort of highlighted to see future prospective work and hopefully replication of our findings, I do think that these data can be utilized to start to counsel patients on what we have identified as far as associations between COVID-19 during pregnancy versus outside of pregnancy and interval PASC.

Currently, I think that there's somewhat limited availability of long COVID clinics, as it relates to postpartum patients. Because for many of these other reasons discussed from our research as well as clinical aspects, unfortunately sometimes our pregnant patients fall out of some of those mechanisms of support. And so I think these findings also can lend support to policy change as far as available resources

through hospitals, communities, and wider policy around that. So hopeful that that would be a change that we could see.

### Quinn Barnette:

Great, thank you. I think we'll have time for maybe a couple more questions. And this might be a question for both Dr. Metz and Dr. Bruno, but has there been any interest or have you seen any differences in findings based on the multiparity of your participants that are reporting symptoms? The notion behind this is a previous pregnancy might affect their reporting of symptoms.

### Dr. Anne Bruno:

We could maybe both answer. I think from the electronic health record dataset, that is more difficult for us to get at in regards to considering prior pregnancy history while we have obstetric history as it relates to prior history of certain health conditions. Our ability to understand how that might alter presentation as far as symptomology is somewhat limited when we're using electronic health record diagnoses. So that, I think, going back to the pluses and minuses of different datasets or data sources is as something that's of a benefit, thinking about the prospective cohort.

### Dr. Torri Metz:

Yes, and we definitely are collecting pregnancy history in the prospective cohort in terms of both just whether people have had pregnancies in the past and also if they've had pregnancy complications. Because pregnancy complications can predispose or unmask underlying tendencies to other comorbidities, things like diabetes or high blood pressure. We did not examine that specifically in the analysis that we have already done, but I think that's a that's a great question and something we should definitely keep in mind.

### Quinn Barnette:

Is there any interest or any current evidence that the length of time that someone has long COVID might differ for pregnant populations versus the general adult population?

### Dr. Torri Metz:

That's a great question. I did put one answer just in the Q&A that I felt like we didn't do a good job of answering with the variant question, but just about trajectory of PASC. And I think that's a really... That is a focus currently of RECOVER broadly. The RECOVER adult cohort has a writing group that's working specifically on that question now, "What does the trajectory of PASC look like?" Which would be a great opportunity to also look at it in the subset of pregnant participants to see if it actually differs in our pregnant population. But really, RECOVER broadly is just starting to do that work related to trajectory?

I think I emphasized a little bit in my presentation, but want to reemphasize here. I mean, we really are looking at a snapshot in time and at a median time of 10 months after the infection. But that time differed from as soon as four months to as late as a year. Or even a year and a half actually, I think, in one of the participants. So really, it's these little snapshots we're getting. And I think as RECOVER, with all the thousands of participants that it has, with these really robust analyses and interactions with participants every three months, we're really going to be able to get a much better look at what does that trajectory look like over time as we gather data. And I think is going to be super interesting. It's a really important question, and we are actively working on it.

## Quinn Barnette:

All right, thank you. I think we have one last question, which might be pretty quick. Is there any evidence that offspring from mothers who are infected during pregnancy might be more likely to be infected with COVID, as newborns or as offspring?

## Dr. Valerie Flaherman:

I think I could take that question. I have not seen that. But one of the things that we are collecting data on in RECOVER is offspring infections. And we actually assess those periodically throughout follow-up, most recent infection. So we'll be able to look at whether infants whose mothers had SARS-CoV-2 during pregnancy are more or less likely to get it in the first years after birth.

## Dr. Torri Metz:

Yeah. I would just add briefly that we do know that maternal vaccination is protective against neonatal infection, and so that's just circling back a little bit to the vaccine conversation earlier. I mean, that data has been published demonstrating that moms who've been vaccinated, their neonates have a lower risk of being hospitalized for COVID-19. But we have that information too, in terms of vaccinations. It's gonna be interesting to look at both of those things.

## Quinn Barnette:

Great. Well, thank you so much to all of our presenters, and thank you to our audience for attending the seminar and engaging with the Q&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&A document that has responses to all the questions that we received today, including those that we did not have time to address. We are planning seminars in June and July, and we'll post registration information on the RECOVER website when those are available, so please check the R3 page at recovercovid.org for updates. In a moment, you'll see a short survey that will come up on your screen which will ask for your feedback on the seminar. We would appreciate if you could take just a minute to fill out that brief survey. But thank you so much to all of our panelists for such a rich discussion. Thank you to our audience for your Q&A. And I hope everyone has a great day.