Responses to Participants' Questions

This document provides responses* to questions raised by webinar participants related to the following presentations:

- **Presentation 1: Metabolic Dysfunction and PASC: An Overview of the Evidence**
  Clifford Rosen, MD
- **Presentation 2: Why Are We Concerned about COVID Interacting with Diabetes?**
  Jane Reusch, MD
- **Presentation 3: Health Disparities in Diabetes and RECOVER**
  Emily Gallagher, MD, PhD
- **Discussants: Philipp Scherer, PhD and Lucio Miele, PhD**

* Responses may have been edited for clarity.

All Presenters: Questions and Responses

Q1. I have a question regarding potassium depletion. I understand that our minerals are all getting skewed with Long COVID, but I don't quite understand what the mechanism is that's depleting the potassium.

Response:

Dr. Rosen: I'm not aware of anything beyond acute COVID illness that can cause multiple mineral changes, particularly as patients are acutely ill. If patients are being treated with insulin, their potassium can go down. There are also multiple other factors, like diuretics, that can change potassium. I'm not aware of any changes in magnesium other than what we see in acute illness. I've not seen any data in Long COVID as to what potential mineral elements are there. We do measure calcium in Tier 1 of RECOVER, but there's no evidence currently that certain calcium levels are low. One thing that has been reported, which received a lot of press, was a report of hypercalcemia, which is very high calcium, for an individual getting more than 100,000 units of vitamin D a day for Long COVID. So, there is a risk of developing side effects from medications that probably are not effective.

Q2. Are there known or studied methods for repairing the endothelial injuries caused by an acute infection, at least beyond the body's natural cellular healing mechanisms, which may be hindered by the multisystemic injuries?

Response:

Dr. Reusch: It may sound counterintuitive, but the best method is exercise. Additionally, there is a method using inspiratory pressure that's been used in very sick dialysis patients to improve endothelial function. It's an inspiratory exercise of the diaphragm that has had systemic improvements in endothelial markers in aging as well

as in dialysis populations. But again, exercise has been proven to improve endothelial health. It's been shown in PAD (peripheral arterial disease), diabetes, hypertension, and more. There are also drugs, like the thiazolidinediones, that can be used.

Q2a. To follow up on the response to my endothelial repair question, exercise intolerance is a common symptom of Long COVID. This is understood to be related to an overreactive sympathetic response. Is the inspiratory device more of a parasympathetic-supportive form of exercise? Can this paradox be addressed a bit?

Response:

Dr. Reusch: This is a big question that our lab is trying to unravel in diabetes. I would say that the device does appear to increase parasympathetic tone, or at least R-R variation. I haven't yet used this method—but we have a proposal in, so we may be testing it with youth with type 2 diabetes patients—but it seems that when you're taking a relatively frail or deconditioned population it's good to start with an exercise intervention that's both portable and not overwhelming to them. So, I like the chances of it potentially being useful. The push in R-R variation from the aging population was statistically significant, but it's harder to say whether it was clinically significant.

Q3. Is there a list of Long COVID symptoms?

Response:

Dr. Miele: Yes, there is now and it's an extensive list. There's a very nice paper by Jordan Reese and coworkers on the N3C data set that has identified a series of ICD 10 codes.[1] So this is very relevant from the standpoint of primary care. These codes are associated with Long COVID manifestations. Reese and colleagues broke it down into 3 major groups: gastrointestinal/metabolic, cardio-respiratory, and neurological. There's a root ICD 10 code and a series of codes in association with that can tell you how likely it is that someone has Long COVID.

Q4. Will those in RECOVER with preexisting ME/CFS be utilized as a cohort for the metabolomic studies?

Response:

Dr. Reusch: The ICD code for ME/CFS is the same as the code for the symptom of chronic fatigue, unspecified; meaning, it can't be separated out by code. This will be fixed in October 2022, but old records will not be automatically fixed, so it will be challenging to use these codes.

Q5. How can these findings from these presentations be helpful to a primary care doctor in the treatment of a long-haul [COVID] patient now?

Responses:

Dr. Miele: We don't yet know how to treat Long COVID, but we hope to learn how through RECOVER. At this stage, treatment should be targeted to the specific consequences of Long COVID. So, if somebody develops diabetes as a result, then the diabetes needs to be managed and supported. We simply don't yet have a treatment for Long COVID.

Dr. Rosen: An awareness of what dysfunction could occur—such as endocrine dysfunction besides glucose intolerance and multiple other factors that we've outlined—could be important. I think for primary care providers it's important to do a full workup, pretty much what we're doing in RECOVER, in terms of trying to identify potential pathogenic factors that could contribute to symptomatology.

Dr. Gallagher: From a primary care perspective, it's important to realize that in young people, sometimes diabetes is the first symptom of COVID. If somebody comes in with no known history of diabetes and suddenly has symptoms like hypoglycemia, then they may have COVID.

Q6. There has been interesting work recently on the role of mitochondria in Long COVID and other post-infection conditions. Will that be discussed in another webinar?

Responses:

Dr. Reusch: When you have so much sarcopenia post COVID, you would expect that you would have decreased mitochondrial function. And that's where Dr. Miele's data on the metabolic profiles, specifically on the semitargeted metabolic profiling, may offer some key insights.

Dr. Gallagher: I remember that early on there were papers on the mitochondrial effects of metformin. Does anyone have a comment on those?

Dr. Reusch: Carolyn Bramante, who is part of the N3C diabetes domain, has a paper regarding metformin and a 1,500 person cohort that she'll be reporting on soon. The news reports before the official FDA paper release look exciting.[2]

Q7. A lot of the data shown were associated with the early COVID-19 variants. Is there any evidence that this can be extrapolated to the newer [COVID-19] Omicron variants? Symptomology is very different. Is there the same incidence of diabetes, stratification of severity, and PASC risk based on race and age, etc.?

Responses:

Dr. Miele: The short answer is that we don't yet know because the Omicron variant is still changing. We just saw what might be the first instances of two of the newest subvariants around here. This is going to have to be looked

at retrospectively, but there is work ongoing on matching clinical phenotypes on subvariants. I can say that even within subvariants of Omicron there are key differences, so their immunogenics are going to be different. This will require a lot of work.

Dr. Reusch: There was a recent paper suggesting that PASC is slightly less common with the Omicron variant at 6 months, but does that mean it will be less common or that it just hasn't happened yet? I think that these types of questions point to the fact that RECOVER is not an epidemiological study and consequently will not be able to answer this question. RECOVER research will provide information on mechanisms of disease and we have to keep focused on the goal here. A lot of time and resources are being invested into RECOVER and we need make sure that we are pursuing whatever questions we can address with RECOVER.

Dr. Gallagher: We saw from a paper by Elo and colleagues that looked at mortality statistics across different waves that mortality rates decreased among the oldest groups as time went on.[3] However, that was probably related to vaccinations.

Dr. Rosen: Right, and it's still not clear whether vaccination reduces the risk of Long COVID.

Q8. Is the N3C list accessible through NCATS or elsewhere?

Response:

Dr. Miele: The N3C list is available through the National Center for Advancing Translational Sciences. Here is a link to the Long COVID paper: https://pubmed.ncbi.nlm.nih.gov/34839263/.[4]

Q9. Will there be any research into disorders of the gut-brain axis for PASC?

Response:

Dr. Rosen: Yes, in the RECOVER Pathobiology research recently awarded there is work on the gut microbiome and the brain.

Q10. Is there any research completed or ongoing regarding weight gain in Long COVID patients [that is] unexplained by other factors?

Responses:

Dr. Scherer: I think that will be a difficult question to answer. Because there are so many things coming together in Long COVID, it is nearly impossible to put a finger on specific Long-COVID–induced weight gain. I think it's very likely, but it will be difficult to convincingly prove a direct relationship.

Dr. Miele: To the extent that it has been looked at in the N3C cohort, new onset obesity was one of the codes that was part of the metabolic constellation of Long COVID. However, the mechanisms would be multiple. It could simply be caused by inactivity due to fatigue. So, we really don't know if there is a direct link, but that's something certainly worth studying.

Dr. Scherer: There have been several studies focusing on weight gain over the course of COVID, without a consensus at the end of the day. There are papers that argue for an increase in overall weight, but I think there are just as many papers that argue that the net increase in weight gain or loss is no different from a period of the 3 years preceding COVID. So, I think it will be a very difficult question to answer because it's a heterogeneous response as well; unquestionably, some individuals have gained weight and others have lost weight. Whether this is the result of infection or lifestyle changes over the time beyond that will be a tough question to tease out.

Dr. Reusch: The only group where obesity has been a little more consistent is youth. In kids, not specifically related to the burden of whether they had a COVID infection, but just overall, there has been more weight gain in kids during the pandemic.

Q11. Are you seeing a high number of [COVID] long haulers being diagnosed with reactivated EBV [Epstein-Barr virus], and does it have any impact on the gastrointestinal health?

Response:

Dr. Rosen: There is a relationship with COVID and EBV, but the cause and effect has not yet been established.

Q12. For patients experiencing constipation post COVID, besides IBS [irritable bowel syndrome] treatments such as Linzess (linaclotide) and MiraLAX, are there any other recommended treatments?

Response:

Dr. Rosen: At the present time there are no other treatments. However, studies are currently underway to discover other treatments.

Q13. Could slow colon motility be caused by dysautonomia? Does this also cause slow metabolism?

Response:

Dr. Rosen: Yes, dysautonomia can certainly lead to slow gut motility.

Webinar Slides

To request a copy of the R3 Webinar slides, please email RECOVER_ACC@rti.org.

To Learn More

- **Information about RECOVER research and to volunteer for studies:** https://recovercovid.org/research
- **Frequently Asked Questions about RECOVER and PASC:** https://recovercovid.org/faqs
- **CDC information: Information for the general public and for healthcare providers about post-COVID conditions:** https://www.cdc.gov/coronavirus/2019-ncov/long-term-effects/

References

1. Reese J, Blau H, Bergquist T, et al. Generalizable Long COVID subtypes: Findings from the NIH N3C and RECOVER Programs. *medRxiv.* [Preprint]. May 25, 2022. doi: 10.1101/2022.05.24.22275398

2. Bramante CT, Huling JD, Tignanelli CJ, et al. Randomized trial of metformin, ivermectin, and fluvoxamine for Covid-19. *N Engl J Med.* 2022;387:599-610. doi: 10.1056/NEJMoa2201662

3. Elo IT, Luck A, Stokes AC, Hempstead K, Xie W, Preston SH. Evaluation of age patterns of COVID-19 mortality by race and ethnicity from March 2020 to October 2021 in the US. *JAMA Netw Open.* 2022;5(5):e2212686 doi:10.1001/jamanetworkopen.2022.12686

4. Deer RR, Rock MA, Vasilevsky N, Carmody L, et al. Characterizing Long COVID: Deep phenotype of a complex condition. *EBioMedicine.* 2021;74:103722. doi: 10.1016/j.ebiom.2021.103722. Epub 2021 November 25, 2021.