Responses to Participants' Questions

The overarching goal of the RECOVER Research Review (R3) Seminars is to catalyze a shared understanding of the research being conducted by the scientific stakeholder community within the RECOVER Consortium. The R3 Seminars and the Q&As typically feature highly scientific material intended for researchers and clinicians. For other audiences interested in these topics, a link to the National Library of Medicine's MedlinePlus medical dictionary is provided at the end of the Q&As as a resource to help in understanding the scientific terminology.

This document provides responses (edited for clarity) to questions raised by seminar participants related to the following presentations at the R3 Seminar *Long COVID in Older Adults: Insights from the RECOVER Adult Observational Cohort* held on October 28, 2025 (videos for this and previous seminars are available from the Seminar Series page on the RECOVER website):

- ***Long COVID in Older Adults***

  Samantha Russell, MD
- ***Long COVID Update—Overview of the National RECOVER Study***

  Janko Nikolich, MD, PhD, MSc

All Presenters: Questions and Responses

Q: Were the findings of lower incidence of Long COVID in older adults surprising? How are these findings consistent or inconsistent with what we know about other post-viral conditions in older adults?

Response:

Dr. Nikolich: They were somewhat surprising because much of the literature was suggesting incidence in older adults may be higher. But when we think about the mechanisms, and when we think about what you mentioned about other post-viral syndromes, we are seeing similar curves of incidence, certainly in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and Long Lyme. I think that the issue of relatedness to other post-infection syndromes is really, really important. In fact, my group has gotten some funding to study that very topic. We're not thinking that Long COVID is the same as ME/CFS, but they do share many features, so distinguishing what is similar and what is not similar, particularly at the level of molecular signatures and the potential mechanisms of the disease, is going to be very important going forward.

Q: What are the priorities for future research related to Long COVID in older adults?

Response:

Dr. Nikolich: One would be to go to the weaknesses of our study, the limitations, and try to correct as many of those as we can. One of those would be to study this very same group at another couple of time points, because fortunately, with RECOVER being a longitudinal study, we do have more time points. We know about the evolution of symptoms. A Long COVID trajectories manuscript will be published soon. I don't know how much the authors specifically focused on age, and that's certainly something to revisit. The second limitation is about age-sensitive questions, where we could re-contact and re-ask some of our participants and make sure that we don't miss some of the things that Dr. Russell mentioned. For example, was a respondent too tired answering question number 75 on the questionnaire, or was there some other reason why they didn't want to go any further? The third really important one is that, mechanistically, we think that lower responsiveness of their immune system and their inflammatory system could be protecting older adults from Long COVID, and we can study that based on the results of the samples that were collected across the study. So that is one of the things that we're continuing to do and hope to do in greater granularity.

Q: How can these findings be helpful for clinicians who are seeing older adults to recognize or to diagnose Long COVID?

Responses:

Dr. Russell: I think when you're caring for an older adult, one of the biggest things is to not anchor on any particular diagnosis. The clinical picture for everyone is very different and sometimes very complicated. It's really important to always have Long COVID as a possibility, but also make sure you're not ruling out other things. One of the examples I gave during my talk is whether brain fog could be a side effect of a medication. You wouldn't want to miss that, so I think it's important to understand the symptom clusters and know that it's definitely a possibility, but I think it's also important to really take a step back and look at the whole patient when making these diagnoses to make sure you're not missing anything.

Dr. Nikolich: Having these symptoms you mentioned might lead a practicing physician to think about if somebody's presenting with a prolonged history of loss of smell and taste that wasn't there before, they should probably consider Long COVID as part of their diagnostic set. But I couldn't agree more that one of the worst things that you can do is say, oh, I read this in a textbook, and this is how it's going to be for this patient. For our geriatric patients, that's almost never the case. You really have to keep an open mind.

Q: Although these studies today didn't cover treatments, do you have any knowledge of new insights or treatments for Long COVID in older patients specifically?

Responses:

Dr. Russell: I can start by saying that a lot of the management strategies are individualized now, based on focusing on symptom relief and rehabilitation and multidisciplinary care. There are studies looking at potential pharmacologic management of Long COVID, but they really are investigational at this point, so I know that there's some research, and perhaps Dr. Nikolich can go into more detail looking at things like metformin, low-dose naltrexone, and colchicine.

Dr. Nikolich: The first round of RECOVER-based clinical trials has still not been unblinded, meaning that we don't know the results yet, and those were targeting virus and viral persistence, which is a difficult topic to study because the virus is not very obvious. It's actually hiding, and if it is still present, you need very sensitive laboratory measures to detect it. If we don't get a signal from that study, it may not mean that we have conclusively set that issue aside. In the meantime, however, you mentioned many other studies, Dr. Russell, that metformin has shown some anecdotal and early trial promise. Naltrexone has relieved symptoms in many people, and RECOVER-TLC is prioritizing it for the next generation of clinical trials. Another important and interesting drug is baricitinib, which is an immune suppressant. This drug trial could support (or not) our hypothesis that Long COVID may be immune mediated, at least in some people. If so, baricitinib should quiet things down, and it may bring those high-risk groups of 40 to 49 or 50 to 59 lower and closer to the older adults in how they manifest their symptoms. But for all these treatments—first, none of them are specifically targeting older adults as of now. Second, one of the problems that we're facing in general with geriatric medicine is that in many clinical trials, older adults are underenrolled. We don't have enough of them, and they're not targeted as a population. That is something that we need to very carefully think about and make sure that any forward-going studies, particularly within RECOVER, enroll enough people of the appropriate age groups. That goes for children as well. Pediatricians will tell you that children don't get enrolled enough, but older adults are even more underenrolled than children in many cases, so we really need to understand what's happening in these vulnerable groups. Eventually, what we would like to do, which is completely consistent with what you have heard from Dr. Russell, is that we need to go to this level of individualization and precision medicine, not only at the level of treatments, but also of enrollment into the trials. In other words, by clinical symptoms and by molecular biomarkers, we need to know exactly what people's profiles are, and these different profiles are going to require different treatments. If people are coming with 200 to 300 symptoms, it's unlikely that a single drug treatment will take care of all of them. We're very likely to need combinations of treatments, and we're very likely going to need different combinations of treatments for different clusters of symptoms and maybe biomarker signatures as well.

Q: What older age categories were in the study, and how does that compare to the literature from your review?

Responses:

Dr. Russell: Speaking from our literature review standpoint, we were looking at papers that categorize patients aged 65 or older. Sixty-five-plus is generally considered older. I did come across one paper in our literature review that classified older than age 35 as older, which made me roll my eyes. But, generally speaking, 65 or above is considered older.

Dr. Nikolich: I would add that aging is a continuous process. The first age-related change that happens in our body happens to the gland called the thymus that sits above our heart; it's making T cells. That gland basically loses 90% of its mass and of its production of new T cells by the time we're in puberty. Somebody could argue that this is the beginning of aging, and immunologically, it probably is, actually. But 65 has always been considered a definition that probably came more from the Social Security Administration than from anybody in science. Immunologically, when people ask me, when is your immune system starting to age? Well, we know that at 45, it's starting to age, so not at 35. But if you analyze the death curves from these outbreaks of new infections, which is the best and the most sensitive index for older adults, with coronavirus, West Nile virus, and a bunch of other infections including SARS-CoV-1, you start seeing that the group of 45 to 54 is about 2 to 3 times more likely to die than those younger than them. Then that gets worse and worse. It's this logarithmic curve that goes very high up very quickly, so as I mentioned, by the time you're 85 with SARS-CoV-2 or other infections, you'd be 2 to 300 times more likely to die than people in the 18 to 39 age group.

Q: Is there anything in the literature about the influence of autoimmune disease before acute infection and how this could potentially impact Long COVID symptoms?

Response:

Dr. Nikolich: I have been, during acute COVID, very much on the forefront of that type of research, and it's interesting. People with autoimmune diseases are more likely to have exaggerated immune reactions. A Long COVID story in that group, surprisingly, did not really show an enormous association. It was checkered. Some people had it, and some people didn't. Even when you look at their responses to the vaccine, they were not uniformly compromised. So it's a really interesting topic to study. I intend to bring this back to my colleagues and see if we can mine the RECOVER study and figure out some of these answers from the vast datasets that we have. It's not a clearly settled issue. There's not a clear link; there is no doubt that in the complex diseases, like Long COVID, ME/CFS, and others, there will be a genetic component. There will be people who are predisposed. Those would be the people who typically reacted to other infections even before Long COVID, with a lot of symptoms,

like Guillain-Barré syndrome, for instance, and many others. But it's not a simple association, and there is much to learn.

Q: If you could leave clinicians and policymakers with a message about Long COVID in older adults, relevant to research or policy objectives from your work, what would that message be?

Responses:

Dr. Russell: One of the biggest things is just to make sure that you're listening to your patients. Patients know their bodies and what's normal for them, and if they're experiencing a symptom that is frustrating or causing them difficulties, it's important to really listen to it and think about the underlying cause, because I think it's common for older patients to feel like their concerns are not being heard. That's the biggest message I'd want to leave: make sure you're really working with your patients and creating a plan that is supporting them moving forward.

Dr. Nikolich: I would just amplify that because this point really cannot be overemphasized in many ways. A patient did not come to your office today to complain and waste your time. They came because they're miserable. I think what Dr. Russell has mentioned is that older adults are very often not heard for their own complaints. Long COVID patients, certainly many of them, have been told that a lot of this is in their head, and that this is not real. This is extremely real. It's debilitating, it's devastating, and it can really change and ruin people's lives in many ways. We have seen this over and over; so for everybody, for decisionmakers, for clinicians, do not ignore this one. We have literally millions of people who are disabled with this disease, and in any age stratum, and we don't even know how this is going to play out with kids with Long COVID. Are they going to be really incapable of fully functioning down the line, and to what extent? What can we do to make sure that they're not and that we can help them? I think across the board, this is an extremely serious disease, an extremely debilitating disease. The other point to remind everybody of is that, although there will be some differences between Long COVID, Long Lyme, long flu, ME-CFS, fibromyalgia, and so on; there will be a common basis as well for most of these people. People with ME-CFS, fibromyalgia, and so on will tell you that there was a particular infection after which things went downhill. But in all these diseases, the infecting microorganism may not be known, and even if it is, there simply are not enough cases happening at the same time so that one can study them in a systematic way. For Long COVID, on the other hand, this is the only group where we know that there was a virus, and which virus it was, and then right after that virus, there were huge numbers of people who are disabled. So, the benefit of understanding how the virus causes this prolonged and disabling disease in the case of Long COVID will definitely have positive impacts on all these other diseases and should allow us to hopefully understand them deeper.

Q: How strong are the data that a severe case of COVID increases the risk of Long COVID, given that patients with a severe acute illness of any kind may suffer from tissue damage and reconditioning?

Responses:

Dr. Russell: I reviewed my notes from writing our literature review—approximately 4 to 5 papers supported severe acute infection as a risk factor for every 1 paper that stated it wasn't a risk factor. But you are correct—no matter the severity of acute infection, patients are still suffering damage that puts them at risk of Long COVID.

Dr. Nikolich: The chances of developing Long COVID after severe COVID were between 40% and 70%. It was less, and overall down to 5% to 10%, in milder disease. But it was still happening in those with mild and even asymptomatic disease.

Q: Is there any indication that Long COVID is a root cause of severe dental issues in older adults?

Response:

Dr. Nikolich: I am not aware of this type of data.

Q: Did you notice a difference when you additionally crossed age by sex? I'm curious how menopausal transition might contribute to higher prevalence in 40s and 50s.

Response:

Dr. Nikolich: There are ongoing studies, including a published one from RECOVER, but the interaction of age and sex was not specifically investigated. Females have a stronger predilection for autoimmunity, which peaks in middle age (40–55), so that fits with our results of potentially lower incidence in older adults.

Q: Could the lower number of reporting 70 or older be attributed to less agility and experience with IT?

Response:

Dr. Russell: Absolutely. This is a common limitation for geriatric research in a world that is so driven by online surveys and technology.

Q: Why not just treat age as a near-continuous variable rather than binning? What's the advantage?

Response:

Dr. Nikolich: We have run the analysis in both ways with similar results.

Q: Could the requirement of no potential alternate explanation not have the same impact across ages so that older adults appear to have less Long COVID because there are more potential alternate explanations? That seems to be likely to me and a problem with the diagnosis of exclusion approach.

Response:

Dr. Russell: That is one of the aspects that makes diagnosing Long COVID in older adults so difficult and why it is so important to get a better understanding of how Long COVID more specifically presents in older adults.

Q: Did Dr. Nikolich find different symptom clusters across the lifespan?

Response:

Dr. Nikolich: Yes. We found that older adults dominantly had milder clusters.

Q: Might the relatively lower rate of Long COVID in older adults be explained by the higher mortality rate of COVID among older adults?

Responses:

Dr. Russell: Absolutely. A high fatality rate is one of the key factors that naturally reduces the prevalence of a disease and is a theory we have discussed when looking at the data.

Dr. Nikolich: Indeed. We have flagged this explanation in the "discussion" section of our paper.

Q: How do this study and other research programs have an impact on treatments for these participants? Developing treatments are missing from practitioners in smaller cities/communities!

Response:

Dr. Nikolich: By helping us formulate hypotheses that will be tested in clinical trials. We are in communication with RECOVER-TLC on these issues.

Q: Is there any study being done that looks at Long COVID interaction with long-term HSV?

Response:

Dr. Nikolich: Yes. These are in progress (we are directly studying herpesvirus reactivations).

Q: Are you aware of research indicating anything about intravenous immunoglobulin (IVIG) for Long COVID treatment?

Response:

Dr. Nikolich: Yes. The RECOVER-AUTONOMIC trial was done with IVIG. Results are still being analyzed.

Q: Did your study separate out time of onset of health conditions to know better the connection of symptoms with SARS-CoV-2 versus an earlier exposure?

Response:

Dr. Nikolich: Yes.

Q: Which biomarkers should we be examining next in research?

Response:

Dr. Nikolich: Many inflammatory and immune parameters are now being routinely examined in mechanistic studies and will be studied in clinical trials.

Q: Any research on the virus causing worse Long COVID each time you are infected?

Response:

Dr. Nikolich: Yes. Reinfection is being studied as a separate risk factor.

Q: Given the persistent oxidative stress, endothelial injury, and microvascular dysfunction seen in Long COVID, I wonder if there's potential value in studying extracorporeal blood oxygenation and ozonation or ultraviolet blood irradiation therapies. Some small non-randomized studies in chronic infections and autoimmune conditions have suggested redox modulation and immune recalibration effects. Has there been any consideration of exploring these modalities in Long COVID patients, especially older adults?

Response:

Dr. Nikolich: This is an interesting possibility; it would need some piloting to support a full trial.

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