Transcript

Disclaimer: *This transcript has been generated using AI technology and lightly edited. It is intended to provide an accurate, verbatim representation of the language used by the speakers during the RECOVER Research Review (R3) seminar. Please note that some errors or omissions may have occurred due to the limitations of automated transcription. Videos for this and previous seminars are available on the RECOVER R3 Seminar Series web page.*

Patrick Ahearn:

So good afternoon and good morning, everyone. Welcome to today's session of the R3 Seminar Series: Long COVID in Older Adults: Insights from the RECOVER Adult Observational Cohort. My name is Patrick Ahearn with RTI, and I'll be helping out with the virtual room today. So just a few housekeeping notes before we get started. When you log in, your microphone and web camera will be automatically muted. But if you have any questions for our presenters today, please submit those into the Q&A window at any time. And if you run into any technical issues, please let me know in the Q&A window as well. Closed captions are available during today's webinar. Just click on the show captions button on your main Zoom toolbar to turn those on. So, at this time, I'll turn things over to Quinn to introduce today's session. Thank you.

Quinn Barnette:

All right. Good afternoon and welcome everyone to the RECOVER Research Review R3 seminar. My name's Quinn Barnette. I'm an epidemiologist for the RECOVER Administrative Coordinating Center, and I'll be your moderator for today's session. The goal of the R3 Seminar Series is to share the RECOVER Initiative's research findings with researchers and the public. The seminars accelerate scientific discovery by allowing experts to share their insights on Long COVID and related conditions. In today's seminar, the panelists represent their research on Long COVID frequency and symptoms in older adult populations. These findings further our understanding of how age-related changes may impact the clinical manifestations of Long COVID.

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

I'm pleased to share that our panelists today are Dr. Samantha Russell and Dr. Janko Nikolich. Dr. Russell is a board-certified internal medicine physician specializing in geriatric medicine and hospice and palliative medicine and assistant clinical professor at the University of Arizona at Tucson. Her research includes publications on topics such as Long COVID in older adults and interventions for symptom reduction and myeloproliferative neoplasms. With a commitment to improving quality of life for older adults and patients with serious illness, Dr. Russell provides compassionate patient-centered care that emphasizes dignity, quality of life, and support. She's dedicated to empowering patients and their families, their education, shared decision-making, and personalized care strategies.

Dr. Nikolich is the director of the Aegis Consortium for a Pandemic-Free Future, Bowman professor and head of the Department of Immunobiology, and co-director of the Arizona Center on Aging at the University of Arizona College of Medicine in Phoenix. He's an internationally recognized leader in immunology and gerontology with long-term research interests in the basic mechanisms of T-cell function, immunity to acute viral infection in older adults, persistent virus interactions over the lifespan, vaccines and biomarkers of declining immunity in the elderly, and the impact of inflammation and nutritional intervention in aging, immunity, and metabolic disorders. The topic of today's seminar is Long COVID in Older Adults: Insights from the RECOVER Adult Observational Cohort. Today's speakers will present recent findings from the RECOVER Adult Observational Cohort about Long COVID frequency and symptoms in older adults. They'll also discuss current understanding of the biological mechanisms of Long COVID as they relate to older adults. Please welcome all of our speakers, and with that, I will turn it over to our first speaker, Dr. Russell.

Dr. Samantha Russell:

Thank you, Quinn. I'm just going to pull up my slides. Can you see it okay?

Quinn Barnette:

Yes, we can.

Dr. Samantha Russell:

Great. Alrighty. So good morning, everyone. Thank you so much for the privilege of being able to speak to you today. My name is Samantha Russell. I'm assistant clinical professor at the University of Arizona in Tucson, where I now practice full-time as a geriatrician. And I have the pleasure of discussing our literature review focused on COVID and Long COVID in older adults. I do not have any conflicts of interest to disclose. And really, I'm here today because I had the wonderful opportunity to partner with Dr. Nikolich during my geriatric medicine fellowship to write a comprehensive literature review covering what was known about Long COVID in older adults at that time, and more importantly, to figure out what was not known and where we needed future research.

So, for the next 20 minutes, I plan to first take a step back and talk about why it's important to focus on older patients. What are the changes our bodies go through as we age that make us more vulnerable to things like COVID, and how might this impact why older adults present with Long COVID compared to younger patients? I'll briefly define Long COVID in the context of our literature review, and I would also like to highlight some of our findings before I hand the mic over to Dr. Nikolich to discuss further research in this area. So aging is a biological process that we all experience, whether we want to or not.

At a cellular organ and tissue level, it can be defined as the progressive decline in deterioration of functional properties that can lead to a loss of homeostasis, a decreased ability to adapt to stressors, and ultimately, an increased vulnerability to things like disease and mortality. To add a level of complexity, aging is extremely heterogeneous, meaning that the onset rate and extent of the aging process varies, not only between individuals, but also across the different organ systems within the same individual. And although aging is often associated with decline, it's important to mention here that there's a lot of positive aspects to aging as well. So, with age, we gain wisdom and experience, thereby enhancing decision-making abilities, empathy, and understanding. We gain increased emotional stability and a greater capacity to cope with stress.

We may prioritize meaningful relationships, which foster stronger social connections. We generally develop a deeper appreciation for life and its blessings. And with age, we can gain a greater acceptance of ourselves and our life experiences, leading to a greater sense of fulfillment and peace. So, there's a lot to be said behind the common saying "aging like a fine wine." So, a lot of research has gone into identifying the molecular and cellular mechanisms that underlie the aging process, looking for that silver bullet of aging or that fountain of youth. And as far as I know, we haven't found it yet, but they have identified what is known as the hallmarks or pillars of aging. And so as presented as in López-Otín's 2023 review paper, there are 12 proposed mechanisms thought to drive the aging process on a cellular level. So, let's start with some of the root causes of damage that can initiate age-related decline.

One example is genomic instability. So essentially this means the DNA in our cells accumulate damage over time, either from internal sources like replication errors or external sources like ultraviolet radiation, which can lead to dysfunction. Telomere attrition is another example. So, telomeres are the protective caps on the end of our chromosomes, and every time a cell divides, they get shorter. And when they become too short, the cell actually stops dividing. Epigenetic alterations is another example. So, changes in how the genes switch on and off can disrupt normal cell function as we age. Loss of proteostasis is when the body becomes less able to fold and clean up and recycle proteins properly. So, think about it leading to toxic buildups. So, one example would be the amyloid plaques that develop in the brains of patients with Alzheimer's dementia, and disabled macroautophagy is another example. So, a decline in the cell's ability to self-clean and recycle damaged parts, which can contribute to aging and decline.

There's also a number of processes in the body that start off as protective but eventually become harmful with becoming overactive with age. One example is dysregulated nutrient sensing. So, aging can affect how cells respond to nutrients and energies, and this can contribute to diabetes and other age-related diseases. Mitochondrial dysfunction, so mitochondria, as we all know, is the powerhouse of the cell, but over time, it can become less efficient and can actually generate more harmful byproducts like free radicals that can damage cells. Cellular senescence is another example. So damaged cells will stop dividing, but they don't die. So, they just sit there releasing inflammatory signals which can harm nearby cells. And finally, what are some of the results of this accumulated damage? One example is stem cell exhaustion. So, stem cells are the cells in our bodies that repair and regenerate when tissue is damaged.

And over time, we get a decrease in number and a decrease in function of these cells. Altered intercellular communication is another example. So, aging disrupts how cells talk to each other, which can lead to chronic inflammation, a weakened immunity and tissue breakdown. Chronic inflammation is another example. So persistent low-level inflammation or what we call inflammation can occur, which is now recognized as a key driving factor for many age-related diseases. And then dysbiosis, so an age-related imbalance and gut microbiome can disrupt metabolism and immunity and even brain function. So these are only a few of the proposed mechanisms that drive aging, but what does it mean clinically? Why does it matter? It matters because the process of aging changes our body's ability to respond to stressors like infections. It decreases the body's reserve to recover from significant events like a fracture or hospitalization. And these changes make our bodies more vulnerable to things like medication side effects or delirium.

And with aging, we see an accumulation of chronic diseases, which usually leads to polypharmacy or multiple prescription medications or over-the-counter medications and various other geriatric syndromes like malnutrition and falls. And all of these impact how older adults function and how we need to approach an older adult in a clinical setting. Let's talk about an example of how aging

impacts a clinical approach to patient care. It's a known fact that adults can and regularly do present with different symptoms compared to younger adults who present with the same disease. Let's take a heart attack for an example. A younger patient who's having a heart attack might come to the hospital describing symptoms of crushing chest pain. This symptom immediately raises red flags for the doctors to consider the possibility of a heart attack. And so thereby immediately sending that patient down the path for timely diagnosis and treatment.

An older patient, however, might present with symptoms of dyspnea or breathlessness or confusion, which may not trigger that same immediate response to consider a heart attack, thereby risking a delay in diagnosis and treatment. Another example is when an older individual with pneumonia might present with generalized weakness and falls instead of the more well-known symptoms of fever and cough that you might see in a younger person. So long story short, if a medical provider is not aware of how an older person might typically present with certain diseases or illnesses, they may consider their symptoms "atypical," which may lead to delayed or even misdiagnoses. So aging changes the way that patients present with diseases, it changes the symptoms that they report or don't report, and it can impact how they receive diagnoses in addition to how their bodies might respond to treatments.

Now that we know how aging can impact the body and how it complicates disease response and presentation in our older patients, let's circle back and talk about it in the context of Long COVID. This is a table from our review paper outlining some of the challenges faced when evaluating Long COVID in older adults. So, like other diseases, we expect some atypical presentations. We anticipate some confounding baseline symptoms, for example, maybe someone has shortness of breath at baseline due to their chronic lung disease. Is there persistent dyspnea due to Long COVID or worsening of their COPD? Or perhaps they have developed brain fog from a new medication. Could this be mistaken as Long COVID instead of stopping the offending agent? Maybe our older adults have some cognitive decline that makes it difficult to identify or describe new symptoms. Perhaps an older adult is downplaying the severity of their symptoms, attributing it just to old age, or maybe they're afraid to report worsening weakness or brain fog in fear of losing their independence, or perhaps they just have trouble responding to online questionnaires because they have trouble using their new smartphone.

So, you can see how all of these factors make it difficult not only to define symptoms of Long COVID in our older adults, but also to identify the prevalence. The purpose of our literature review was to try to identify the gaps in our knowledge and to prioritize future areas of research, specifically looking at things like epidemiology, risk factors, molecular mechanisms and immune picture, clinical setting and symptoms, and ultimately, we were hoping to better characterize the impact of Long COVID in older adults. Now, in 2023, a large RECOVER study was published, which provided a lovely definition of Long COVID, but unfortunately, many of the papers that we were reviewing were published before this.

So, one of the difficulties we faced upfront writing this paper was that there was a lack in consistency of the definition of what Long COVID actually was, and there wasn't even agreement in the terminology. So, some papers called it Long COVID, others called it post-acute sequelae of SARS-CoV-2, others post-COVID condition, others post-COVID syndrome. There's also a wide variation in the criteria for the diagnosis between different organizations like the CDC versus the World Health Organization, but there were common themes amongst the criteria, like the symptoms had to occur after an acute COVID-19 infection. They needed to continue or develop within 4 to 12 weeks after the infection, and really the big one is they couldn't be explained by any other diagnosis.

So, we ended up reviewing close to 80 to 90 papers, and what we found was that the incidence of Long COVID in older adults varied greatly, so anywhere from 4% to 80% in the literature. There was a lot of variability in study designs, definitions, uniform data quality, so we did our best to try to find some

trends and overall agreements between the manuscripts. And generally speaking, some of the risk factors we found included older age, female sex, Black, American, Indian, Hispanic ethnicity, multiple comorbidities, especially chronic kidney disease, lung disease, and diabetes. Some elevated BMI, smoking, and the severity of the acute COVID infection, in addition to whether or not someone required hospitalization or a stay in the intensive care unit. Interestingly, there were some protective factors identified too, including higher education, being physically active prior to the acute COVID infection, and most importantly, vaccination status. But given the variability and the data, more research was needed to provide a little bit more clarity.

Now, arguably, one of the most interesting sections of our paper discussed the molecular mechanisms of Long COVID and how it changes in the older adult. And this section was authored mainly by Dr. Laskowski and Dr. Nikolich. So, I'm slightly embarrassed to present it with my simplified understanding condensed in one slide, but I'll do my best. So, one mechanism of Long COVID is believed to be virus driven. So perhaps prolonged viral replication in cells or persistent presence of viral components within the cells can result in accumulated damage over time. We know that with aging, we see a decline in immune function that can impact our body's ability to completely clear a virus and its particles at baseline. So, this would put our older patients at higher risk for this mechanism of damage. There's also a hypothesis that the virus can induce senescence, meaning they can induce the cell to stop dividing, which can dysregulate tissue homeostasis and organ function. And finally, COVID-19 has been found to reactivate other persistent viral infections that are lying dormant in tissues such as cytomegalovirus and Epstein-Barr virus, which can lead to a more severe acute COVID-19 infection.

And as we know from our previous slide, a more severe acute COVID-19 infection puts people at higher risk for developing Long COVID down the road. Another mechanism thought to play a role is immunoinflammation. From my own personal experience treating patients in the ICU with acute COVID-19 infections, the sheer amount of inflammation that this virus caused in my patients was astounding and so damaging. So, I was not surprised to see that inflammation was a possible mechanism leading to Long COVID and infections. We know that prolonged and dysregulated immune responses can injure tissues. We know that in an attempt to fight an infection, our body can injure tissues or normal healthy tissues around it as collateral damage. And then finally, a process driven by antigen or inflammation, our immune cells can get a little bit confused and actually start attacking our own healthy tissues, spurring an autoimmune reaction. So, with aging, we see a process called immunosenescence, meaning we developed impaired immune responses, impaired functional immune cells, and chronic inflammation with age, all of which makes our older patients more vulnerable to this mechanism of damage induced by COVID-19.

And finally, endothelial cell dysfunction. So endothelial cells are the cells that line the blood vessels. They play a pivotal role in vascular function and viral interactions. They even have a receptor that's thought to be a primary target for COVID-19 entry into the cells. So viral infections result in inflammation and a cascade that induces what we call thromboinflammation. So, a fancy term for creating an environment full of inflammatory cytokines and mediators that promote clot formation. Dysregulated blood clotting, either microvascular clots or macrovascular clotting events like a heart attack or a stroke, are believed to play a significant role in the aftermath of COVID-19, especially in our older patients who likely already have underlying vascular disease and damage that puts them at baseline risk of clotting. And likely, there's no single mechanism for Long COVID, but actually an overlap of all of these mechanisms because it's probably more complicated than just one cause.

One of our goals for this review paper was to characterize the typical clinical presentation of Long COVID in older adults. That proved to be very challenging due to limited data, a highly

heterogeneic clinical picture described in the literature. In general, fatigue, dyspnea, cognitive changes, joint and muscle pain appear to be the most endorsed symptoms. Cognitive impairments were nearly two to three times more likely in older adults with Long COVID than younger counterparts, which not surprisingly had a negative impact on functional status and also physical decline. In reality, with the extremely heterogeneic nature of Long COVID, in addition to the common overlap with symptoms from non-COVID-related diseases, more research is needed to clarify the clinical picture, and also medical providers will need a high index of suspicion for making a diagnosis of Long COVID in the older adult. Taking a step back, let's look at the big picture. So, our population is aging significantly and rapidly, and we are seeing an increase in clinical complexity in our patients as they live longer.

So having a good understanding of the biology and clinical picture of Long COVID in our older patients is important, not only for proper and timely diagnosis, but also for implementing interventions and hopefully, in the near future, treatments. So, in summary, after reviewing all of these papers, our group decided that we know that we don't know much, meaning when it comes to Long COVID in older adults, we have hypotheses and correlations, theories, some supporting papers and even almost as many conflicting papers and very few studies that specifically focused on the older adult. There were many limitations in our review, including the large variability in study designs, many lacking control groups or were underpowered and no consensus about Long COVID definition, or even no agreement on what age was considered old. So even though older age has been implicated as an important contributor to Long COVID, more research needs to be done. And so, with that, I'd like to thank you for your time, and I'd like to thank my co-authors for our review paper, and I will hand the mic over to Dr. Nikolich to talk about some future further research.

Dr. Janko Nikolich:

Well, wonderful. Thank you, Dr. Russell. So, Quinn, we're not going to take questions now. Is it going to be all at the end?

Quinn Barnette:

Correct. We'll take questions after your presentation.

Dr. Janko Nikolich:

All right, sounds great. So let me then share my slides and take it from there. So hopefully everyone can see them now in the full view. So, this is the overview from our very recently published paper. In fact, it appeared in print yesterday. And before I proceed with any of this, let me just see if I can hide my meeting controls. I would like to really acknowledge, most of all, the participants of the RECOVER study and the RECOVER committee patients and caregiving representatives who have been tremendous in guiding the study, as well as providing their direct input of their experiences. And then all of the people that I had a pleasure to work with. I was until recently the site PI of the Arizona site. Since I have now moved from Tucson to Phoenix, I have relinquished that role, but I'm still one of the multiple PIs of the Arizona study, which is one of the 13 participants in the National RECOVER Study.

And I'm also a co-chair of the RECOVER Pathobiology Committee, which is the committee that's trying to integrate our understanding of the mechanisms of this particular disease, which is quite challenging and urgently needs to progress. So, we'll talk some more about all of this. I have no disclosures, and you have heard about this. I will just very quickly go through all of these symptoms that basically Long COVID can produce more than 200, probably closer to 300 symptoms. And that while we're talking about the operational definitions and the research definitions and about when are we

fairly certain that some of [them] are highly likely to have had Long COVID, a lot of these definitions also acknowledge very clearly that people who may have fewer symptoms, that are not meeting the statistical cutoff, still very well may have Long COVID. And so therefore, all of our classifications classify people into Long COVID likely or Long COVID indeterminate. And indeterminate means that we cannot conclusively determine whether their symptoms are due to Long COVID or not.

But again, most certainly we're not ruling out that they might. And so this goes across the body, as you have heard from Dr. Russell, and we wanted to know specifically in the older adults going through the RECOVER study, which was the largest study ever set up for Long COVID, and it involves a phenomenal infrastructure of many centers and sites and was set to both study the disease, but also to have an interventional arm and to start the interventions. And we can talk about that down the line. This is the study that managed to assemble more than 15,000 adult participants and many pediatric participants that are, I think, approaching almost 20,000 now, as well as the pregnancy cohort, the autopsy cohort, and so forth. So, in other words, this was a true national mobilization at the time to try to understand Long COVID, and many of you know very well about this study.

This was the question that we tried to understand in this particular paper and in this particular part of the RECOVER study, which is what is happening with Long COVID in older adults? And again, going back to Dr. Russell's wonderful introduction, you have to remember that up until this point, first of all, there has been no really large studies of older adults. Most of the review of the literature that we have done came from groups of a few tens to maybe about a hundred here and a hundred there and so forth. The RECOVER study has the power of both being prospective and being set up in that way so that there are concurrent control uninfected people, but also in sheer numbers so that we can actually hopefully get a much better signal of what's happening in different segments of the population. So again, I would really love to, again, thank every RECOVER participant, patient, representative, caregiver, and all of our RECOVER colleagues, because without them, this would not be possible.

This paper alone took a coordinated effort of about 49 people, including the core writing group that I have led that included some 11 colleagues. And these were the questions that we were asking. What is the prevalence of Long COVID in different age categories? And for that, we have used that *JAMA* paper that Dr. Russell referred to in 2023 that managed to show that by the use of about 12 main symptoms, you can fairly reliably define who was likely to have had Long COVID. And then we had control groups as well, and there were other people in that group that were COVID indeterminate. We also wanted to know what symptoms are characterizing Long COVID in older adults. Are they different from those found in the general and younger population groups? And then also, the Thaweethai paper showed that there were some preferential clusters, groups of symptoms that if a person had certain types of symptoms, they were more likely to have some other types of symptoms, whereas some other folks had a different set of symptoms.

So, which of these might be dominating in older adults? How does that distribution compare to younger demographics? And in terms of our expectations, as Dr. Russell mentioned, many of the papers in the field were suggestive that older adults may be having higher prevalence and perhaps maybe a more severe clinical picture of Long COVID, because certainly they were the population that was the most vulnerable to acute COVID. So that was our expectation, that was our hypothesis at the beginning. So, when we started the study, this is how we designed the study. We analyzed our community-dwelling participants over 60 years old. We had more than 2,600 of them with infection, and we had some almost 500 controls that did not have the disease, and all of them were enrolled in the RECOVER adult cohort, and we studied them more than 135 days post-onset. Almost everybody, most of our participants were studied 180 days, so 6 months post-onset, which meets very easily every definition

around, including the NASM and the WHO and the CDC definitions of the time elapsed since the disease itself.

Now, we compared these people over 60 to the people 18 to 59 years old, and we had 7,500 of those and 700 plus controls. And again, the same time from onset. These people were recruited from 83 sites to 33 states, as well as the territories of Puerto Rico and Washington, DC. So very highly diverse, very representative of the US population. We analyzed responses to about 41 symptoms that were covering many organs and symptoms, including allergy and immunology, neurological, including pain and sleep, psychiatric, cardiopulmonary, gastrointestinal, genitourinary, musculoskeletal. And I'll show you the list of all of the symptoms that we have surveyed. And then we reported the results for the study and the initial infection by age group. And our age groups were our younger control. This was our index group, 18 to 39. And then we bend other age groups by decades, 40 to 49, 50 to 59.

And then 60 and above, we analyzed as one group, but we also broke them between 60 to 69 and 70 and above. Then we calculated a proportion of the participants who reported each symptom within each age group, as well as by infectious. So, whether the infected people had a certain symptom more frequently than the uninfected, of course, that was the main point. And everything was referred to our reference category of people that were uninfected and of younger age. So that was our control control, although there have been controls by age group as well. And so, then we really wanted to evaluate potential differences in the definition of Long COVID for older adults for the interaction between the symptom and age. And then when you do these types of studies, you have to adjust for sex and race and ethnicity and so on and so forth.

So that, for instance, because you have inadvertently enrolled many more males than females, your results are all of a sudden biased and they're actually reflecting an impact of sex rather than the impact of age. So, our brilliant statisticians, led by Tanayott Thaweethai and Andrea Foulkes, have done all of that work for us. And these were the 41 symptoms that showed the most discrimination between Long COVID and uninfected folks. And so many more symptoms were surveyed, but in the group setting, in the larger setting of the RECOVER study, they did not show the signal that they can reliably distinguish in a statistically robust way between people that were infected and uninfected. Again, it doesn't mean that people with other symptoms do not have Long COVID, but this is what was reliable for us to proceed with our analysis. So, the main findings from our group, contrary to what we expected was that the prevalence of Long COVID was the highest in 40 to 49 and 50 to 59 years of age.

And then it declined progressively in the 60 to 69 and even more so in the 70-plus-year-olds. And so that was definitely a surprise. Many Long COVID symptoms, including the problems with hearing and chest and joint pain were less prominent in infected older adults. And the reason for that was that even though these symptoms distinguished the infected from uninfected individuals in younger [populations], they were less useful to define Long COVID or PASC in those aged over 70, for whom some symptoms such as hearing loss or chest pain and joint pain may be common also in the uninfected group. So, we basically lost our discrimination at that point. Again, we'll discuss this and how and why this is important. So how did this look graphically? So, in our group, general prevalence in the RECOVER cohort was fairly high because three-quarters of our people were self-referred and self-enrolled in the study, and those were more likely the people that would have high symptoms.

But that was true across all of these age groups. And so, you can see here that if our reference level in 18 to 39 was about 20%, that went up and was statistically significant in 40 to 49, 50 to 59 starting to decline. This is now significantly declining relative to here, but about the same level as in the reference group. And then 70 plus were definitely below what our reference group had. The other important point was that by symptom clustering, older adults exhibited qualitative shifts, and we had

these five clusters, and the clusters four and five were the most severe ones. And actually, sorry, three and four, whereas clusters one and two were a little milder. So interestingly, older adults had more loss of taste and smell and more of GI and chronic cough and palpitations, but they did not have loss of smell and taste.

Whereas they had much less of cluster three, which was brain fog, but no loss of smell and taste. Or four, which was the most severe cluster, which has basically a mix of all symptoms, but very prominent, joint pain, brain fog, muscle pain, hearing issues, and a lot of exhaustion. So, this is how that looked graphically. Again, if you look at these distributions, this is cluster one, one of our two milder ones. And cluster two, you can see that folks over 70 were quite frequently in these groups and much more than some of the others. But then when it came to cluster three and cluster four, particularly cluster four, was quite dramatically reduced in older adults. So again, what were the limitations of our studies? They certainly were several. We had relatively fewer older adults. So, for the 70-plus group, we had close to 800. That's again, a lot more than other studies, but we would've preferred to have more. We did not have enough of them to analyze separately the group of 80 plus, so we really cannot tell how the picture might look in people over 80.

This was also a study where we have analyzed a single time point, so we did not have a trajectory. This study of trajectories is coming up and hopefully will be published pretty soon. The other caveat here that we worried about is the so-called survivor effect, and that is the fact that we have lost huge numbers of older adults to acute COVID. That group was up to 200 times more vulnerable and more likely to die, almost 300 times more likely to die in the people over 85 relative to the people 18 to 39. So did we lose all of the people that would've been sensitive and if they recovered, they may have developed Long COVID? That we don't know. That's a possibility. And it's also possible what you have heard from Dr. Russell is that older adults may have under-reported certain symptoms because they may have been already present in those people before, like the joint pain, for example, and so forth.

So, with all of these caveats, the other problem that I have already alluded to was that our study could have been biased by self-enrollment of the people that we call post-acute participants. We had folks that were enrolled in the study because they have already been experiencing symptoms. Those people were much more motivated than any other group to enroll, and therefore, our high prevalence of about 20% even in the index group of 18 to 39 could have been ascribed to that. But that would have to selectively bias the older participants towards a milder, longer COVID phenotype, which would've been unlikely. The other way that we have countered this potential limitation is that we have analyzed people who got Long COVID and enrolled within the first 30 days of the symptoms, where this biasing was much less likely. So, they were enrolled between 7 days and 30 days after testing positive. And when we analyzed that group, we got, again, the same type of result where effectively, the results and the symptoms in folks over 70 in particular were both less frequent and less severe in that group.

It's possible that we may have underenrolled older participants with severe Long COVID because of the demands of the study protocol. That's particularly possible for the post-acute where they just were not able to meet the frequent visits. And this needs to be, again, redone in certain types of analysis. But with all that being said, what we can conclude is that adults older than 60 are less likely to be classified as having Long COVID and in particular over 70. And even when classified as Long COVID positive, they're less likely to have highly symptomatic and highly debilitating symptomatic forms of disease with more of a loss of smell and taste and GI problems, and relatively speaking, less fatigue, less post-exertional malaise, certainly much less brain fog and so forth. Again, with a caveat that maybe some of them thought that some brain fog is normal and okay. Alternatively, it's also possible that they

would exhibit entirely different flavors of Long COVID that were not captured by our study, but this is very unlikely because our questionnaire was very symptom dense.

We had started with lots of symptoms. The 41 that I have shown you were the ones that we honed in on, but there were many other symptoms assessed as well. And because we saw lower risk of individual symptoms in infected older participants versus uninfected compared to the risk in younger groups, this is again, speaking against this possibility of totally different symptoms in older adults. Finally, how do we interpret these findings relative to the mechanisms of Long COVID and what may be causing Long COVID? These findings are consistent with the decline of immune responsiveness in older adults. And in this particular case, while this would've been and is devastating in dealing with an acute infection, it might be protective against certain immune and inflammation-mediated Long COVID mechanisms. So, if you are having the flavors of Long COVID that rely on autoimmunity and excessive inflammation and your immune system is a little more quiet because you're a little older, then this may be good in this case.

And we know that there are similar age peaks of other likely post-viral syndromes or post-infection syndromes like ME/CFS and so forth. And with that, this is of course leading us to think about what next studies we will do. And we certainly would want to corroborate this hypothesis about the immune relatedness of these symptoms and lighter picture in older adults. So, this is certainly one of the main things that is up to us to do now. And I will stop now and let you ask the questions and maybe return to this particular topic about what else we would like to do and how going forward. Thank you very much. I'll stop sharing now.

Quinn Barnette:

All right. Sounds great. Thank you both so much for those great and important presentations. I'm going to turn us now to our audience Q&A with some questions that we received in advance and in the Q&A chat during your presentations. Just as a reminder to the audience that we will also post a Q&A document on recovercovid.org with answers to any questions that we get to during this session. I want to start us off with some general questions to get some of your reflections about this work. Our first question is, were the findings of lower incidence of Long COVID in older adults surprising and how are these findings consistent or inconsistent with what we know about other post-viral conditions in older adults? And I think this is for both of you, but maybe I'll pass it to Janko to start us off.

Dr. Janko Nikolich:

Yeah, I think as I mentioned, they were somewhat surprising because much of the literature was suggesting that there may be higher incidence in older adults. 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 any CFS, I think in long Lyme as well. And 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 very interested. We're not thinking that Long COVID is the same as ME/CFS, but they do share many features. And so, distinguishing what is similar and what is not similar, particularly at the level of molecular signatures and the potential mechanisms of the disease, I think is going to be very important going forward.

Quinn Barnette:

All right, thank you. I think you touched on this a little bit, Janko, but my next question is, what are priorities for future research related to Long COVID in older adults?

Dr. Janko Nikolich:

Well, so 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 just 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. There is a trajectories manuscript. I don't know if you know off the top of your head whether that has been published yet or not. I think it's not yet published, but I don't know how much they have specifically focused on age, and that's certainly something to revisit.

The second one is to think about age-sensitive questions that we can recontact and re-ask some of our participants and make sure that we don't miss some of the things that Dr. Russell mentioned in terms of, is this because somebody was too tired answering question number 75 on the questionnaire or whether there was some other reason why they just had enough of this study, didn't want to go any further. And the third really important one is mechanistically, we think that this will relate to lower responsiveness of their immune system and their inflammatory system, and we can definitely study that based on the results on 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 a greater granularity.

Quinn Barnette:

All right, thank you. Our next question asks, how can these findings be helpful for clinicians who are seeing older adults to recognize or to diagnose Long COVID? Maybe I'll direct this one to Samantha.

Dr. Samantha Russell:

There we go. I got my mic muted. I think when you're caring for an older adult, one of the biggest things is to not anchor on any particular diagnosis. I think because 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 making sure you're not ruling out other things. One of the examples I gave during my talk is, could brain fog be a side effect of a medication? You wouldn't want to miss that. And 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.

Quinn Barnette:

All right, thank you.

Dr. Janko Nikolich:

Yeah. And I think what I would want to add is having these symptoms mentioned would 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, that 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 like, "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.

Quinn Barnette:

Thank you. We're getting a lot of interest, of course, in potential treatments for Long COVID in older adults and generally. And I know that these studies today didn't cover that, but I wonder if you

have any knowledge of new insights or treatments for Long COVID in older patients specifically at this time.

Dr. Samantha Russell:

I can—

Dr. Janko Nikolich:

Yeah, go ahead.

Dr. Samantha Russell:

I can start off by just saying that a lot of the management strategies are individualized right now based on focusing on symptom relief and rehabilitation, multidisciplinary care. There are studies looking at potential pharmacologic management of Long COVID, but they really are investigational at this point. And 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, but at this point in time, nothing is used clinically that I'm aware of, but maybe Dr. Nikolich can add a little more.

Dr. Janko Nikolich:

Yeah. So 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. So, if we don't get a signal from that study, it may not mean that we have really conclusively set that issue aside. In the meantime, however, there are many other studies that you have mentioned, and that metformin has shown some both anecdotal and early trial promise. Naltrexone has relieved symptoms in many people, and it will be going into the TLC next generation of studies, clinical trials. One important one that will be interesting is baricitinib, and that one is the immune suppressant. It's the one that's supposed to quiet down the immune system.

And again, from the standpoint of older adults, that one may speak somewhat to our hypothesis at the end of the study, which is that if people in which this is immune mediated, this should quiet things down and it may bring those high groups of 40 to 49, 50 to 59, maybe lower and closer to the older adults in how they manifest their symptoms. But again, for all of these treatments, first of all, none of them are specifically targeting older adults as of now. Second of all, one of the problems that we're facing in general in geriatric medicine is that in many clinical trials, older adults are under enrolled. We don't have enough of them, and they're not targeted as a population. And 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. And that goes for children as well. I mean, pediatricians will tell you that children don't get enrolled enough. Older adults are even worse than children in many cases. And so, we really need to understand what's happening in these vulnerable groups.

So that's where things stand. Eventually, what we would like to do, which is completely consistent with what you have heard from Sam, 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, both by clinical symptoms and by molecular biomarkers, we need to know exactly where the people's profiles are, and these different profiles are going to require different treatments. So, we are very... Given that if you think about it, if people are coming with 200 to 300 symptoms, it's quite

unlikely that a single drug treatment will take care of all of them. We're very likely going 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. In fact, I would bet that that's how it will be in the end.

Quinn Barnette:

Great. Thank you. We've received a couple of questions about what constitutes older age as a risk factor, and I know that you touched on this in your presentations, but I thought it might just bear repeating on what older age categories were in the study and maybe how this compares to the literature from your lit review.

Dr. Samantha Russell:

Speaking from our literature review standpoint, generally, we were looking at papers that categorize patients 65 years and older. 65 is generally speaking, older than 65 considered older. I did come across one paper in our literature review that classified over the age of 35 as older, which made me roll my eyes, but generally speaking, 65 and above is considered older. And then Dr. Nikolich classified it further in his study.

Dr. Janko Nikolich:

So, what I would add to that is 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 and it's making T-cells. And that gland basically loses 90% of its mass and production of new T-cells by the time we're in puberty. So, 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 really the beginning, so not at 35. But if you analyze the death curves from these outbreaks of new infections, which is what is the best and the most sensitive index for older adults, both with coronavirus, West Nile virus, and a bunch of others, SARS-1 as well, you start seeing the group of 45 to 54 is about two to three times more likely to die than everybody before them, and then that gets worse and worse and worse. It's like this logarithmic curve that goes very high up very quickly so that as I mentioned, by the time you're 85, of SARS-Coronavirus too, but also of other infections, you'd be two to 300 times more likely to die than people in the group of 18 to 39. So, pick your definition of aging and your fountain of youth and let us know.

Quinn Barnette:

All right, thank you. We did get a question about the influence of autoimmune disease prior to acute infection and how this could potentially impact Long COVID symptoms. I'm not sure if you're aware of anything in the literature about that, Janko.

Dr. Janko Nikolich:

Yes. So, I have been during acute COVID very much on the forefront of that type of both research and the numbers. And it's interesting. So, people with autoimmune diseases are more likely to have exaggerated immune reactions. The Long COVID story in that group surprisingly did not really show up an enormous association. It was checkered. Some people had it, some people didn't. Even when you

look at their responses to the vaccine, they were not uniformly compromised really. So, it's a really good topic.

I don't know actually, but this is something that I intend to go 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's no doubt that in the complex diseases like Long COVID, ME/CFS, and others, there will be a genetic component. There will be people that are predisposed. Those would be the people that typically reacted to other infections even before Long COVID with a lot of symptoms like Guillain-Barre syndrome, for instance, and many others. But it's not a simple association.

Quinn Barnette:

Okay. I think we're approaching the end of our questions. So, I'll wrap up the Q&A with a final question and a reflection. 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? And maybe I'll start with Janko here.

Dr. Janko Nikolich:

I was going to defer to Sam first.

Quinn Barnette:

Sure, Sam.

Dr. Samantha Russell:

I think 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 is causing them difficulties, it's important to really listen to it and really think about what's the underlying cause. Because I think it's common for older patients to feel like their concerns are not being heard. And I think that's the biggest message I'd want to leave is just make sure you're really working with your patient and creating a plan that is supporting them moving forward.

Dr. Janko Nikolich:

Yeah, I would just amplify that because this is the point that 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. And I think what Sam has mentioned is 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. And this is extremely real. It's debilitating. It's devastating. It can really change and ruin people's lives in many ways. We have seen this over and over. So, for everybody, for decision makers, for clinicians, do not ignore this one. We have literally millions of people that 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?

And what can we do to make sure that they're not, 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 again, while there will be some differences between Long COVID, long Lyme, long flu, ME/CFS, fibromyalgia, whatever, there are common... For most of these people, they will tell you

that there was a particular infection after which things went downhill. And this one gives us an opportunity to really understand it because everybody else was like, even if it's not one-off, it might be a hundred off or a thousand off here, that's not enough for people to go and study this disease because there's no funding, there's no rallying cry. This is the only group where we know that there was a virus. And then right after that virus, there were huge numbers of people that are disabled. And that benefit of understanding it now for Long COVID will definitely have positive impacts on all of these other categories as we hopefully understand them deeper.

Quinn Barnette:

All right. Well, I will wrap us up there on that great note. So thank you so much to both of you for those really important presentations and discussion. And thank you again to our audience for attending the seminar and engaging with this Q&A. As a reminder, a recording of the seminar will be available on recovercovid.org in about a week. And then later, we'll also post a recap of the seminar as well as a Q&A document that has responses to the questions we received today.

Dr. Janko Nikolich:

I'd like to thank our audience as well. Wonderful to have you all around.

Quinn Barnette:

Yes. And then before we conclude, I also want to let you know about a two-part webinar series that we're going to learn more about accessing and using RECOVER data to continue advancing our understanding of Long COVID. Part one of that seminar series will be held on Tuesday, December 9, and it will focus on accessing and using RECOVER observational study data points such as data that were collected during study visits and symptom surveys. And then part two of the series will be held on Tuesday, January 13, and it will focus on accessing and using biosamples from the RECOVER observational studies and ancillary studies. We'll include the link to register for both of those seminars in the chat, but you can also use the QR code on your screen to navigate to that registration page.

These upcoming webinars are also related to a recent research opportunity announcement from NIH. Researchers both within and outside of RECOVER can apply to use RECOVER data and biosamples in their research studies. This includes data from three RECOVER observational studies, adults, including pregnant adults, pediatric, and autopsy. NIH encourages researchers to submit proposals that investigate the mechanisms of Long COVID. We'll post a link to a research opportunity announcement in the chat as well. To learn more and apply, you can visit the link in the chat or go to recovercovid.org/funding. Additionally, as you'll have seen, there's a short survey that will come up on your screen, and we ask for your feedback on the seminar, so if we'd appreciate if you just take a quick minute to fill out this brief survey. And with that, thank you again to our presenters for those fantastic presentations and to our audience for being here today, and have a great rest of your day. Thank you.

Dr. Janko Nikolich:

Thank you.