Interest Group 12: The Intersection of Obesity, COVID-19, and Chronic Disease

Diane Birt: Welcome again to Interest Group 12: Nutrition, Diabetes, and Obesity. Our program is on the intersection of obesity, COVID-19, and chronic disease. I'm Diane Birt, and I chair the Interest Group Planning Committee. Barbara Hansen is on, and she is the co-chair. Also very engaged has been Connie Weaver in the planning of this as our past chair.

Now, we'll turn to Connie Weaver for introduction of speakers.

Connie Weaver: I think you'll be impressed and delighted with our program today. Not any of us are long-time experts with COVID, but the two speakers have done more than many of us in relating COVID to their interests.

I'm going to introduce the first two speakers together. First up is Philip Calder. He is Professor of Nutritional Immunology at the University of Southampton, and he's an internationally recognized researcher with 700 scientific publications. I first encountered Philip's wonderful work when he presented the lecture for the Danone International Prize for Nutrition he received in 2016. He is currently the president of the Federation of European Nutrition Societies, and he's been a fellow of the Association for Nutrition since 2012. He's going to speak to us on obesity, immunity, and COVID.

Then we're going to have a presentation by Scott Solomon, MD. He's the Edward D. Frolich Distinguished Chair Professor of Medicine at Harvard Medical School, Director of Noninvasive Cardiology, and senior physician at Brigham and Women's Hospital. His research has focused on changes in ventricular function and structure following myocardial injury, modifiers of risk and influences of outcome in patients following myocardial infarction, and with chronic heart failure, cardiovascular safety of nonvascular cardiovascular therapies, factors that influence the transition from hypertension and heart failure, and heart failure itself.

He has authored more than 400 peer-reviewed articles, and he has authored two textbooks of cardiac imaging. He's the Cardiac Section Editor and International Associate Editor at the *European Heart Journal*. He will be speaking to us about COVID-19 and cardiovascular disease; no surprise with those credentials.

I turn it over to Professor Calder, who is speaking on obesity, immunity, and COVID. Philip?

Philip Calder: Thanks very much, Connie, and thanks to the organizers for inviting me to this really important meeting. I'm just sharing my screen now; hopefully that's gone okay, Connie.

I want to address the issue of obesity and immunity, and where that impacts susceptibility to and severity of COVID-19. First of all, a few slides about the immune system, just to get everybody on the same page. The immune system is a cell and tissue system that protects the host, the individual, from harmful organisms, harmful bacteria, viruses, and so on. Of course, harmful organisms are termed *pathogens*.

We know that a well-functioning immune system is key to providing robust defense against pathogens, and we've heard a lot about that in the last 2 years or so, because we know people with compromised immunity are at increased risk of infectious disease and of infectious disease becoming more severe.

The four general functional features of the immune system are listed here. Firstly, it acts as an exclusion barrier to keep pathogens out. Secondly, it's able to identify organisms and recognize whether they're harmful or harmless. Thirdly, it acts to eliminate those organisms identified as being harmful. Finally, it has a memory component, so that those immunological encounters are remembered immunologically often for decades, sometimes even for the entire life.

The point of the memory response is that reinfection or re-exposure generates a faster and more vigorous response than the first exposure. The memory response is the basis of vaccination, which is really topical right now.

The immune system is pretty complex, it's pretty sophisticated—it can recognize, it can eliminate, and it can remember. These sophisticated capabilities come about because of the many different particularly cellular components within the immune system, which generally speaking are divided into innate immunity, which includes the barrier functions, and acquired immunity.

We have all of these different cell types within both innate and acquired immunity; these different cell types have specialized functions. For example, we have phagocytic cells that can engulf and digest bacteria intercellularly; we have natural killer cells that kill virally infected cells and tumor cells; cytotoxic T cells do that as well; B cells are the cells that produce antibodies; we have regulatory cells, and so on.

So we have specialized cell functions, but obviously to mount an effective immune response, all of these different cellular components have to be working together in an integrated and coordinated way. I picture that in this more complicated figure that I'm not going to go through in detail, but simply showing the different cellular interactions that are involved in antiviral immunity, with the aim being to kill virally infected cells, to block the replication of viruses, and to neutralize viruses with antibodies. We see important cytokines, like the interferons that I'll come back to later on, which are key to antiviral protection. We see these proteins perforin and granzyme that are key to the lysis of virally infected cells. We see, overall, lots of different cells involved in eliciting effective antiviral immunity.

But if we strip this back, we have these two general functional capabilities. We have the barrier function to keep pathogens out, and then we have these powerful cellular components of innate and acquired immunity to deal with pathogens if they breached the barrier.

Mostly, people think of immune cells circulating in the bloodstream, the white blood cells, but in fact only about 2% of our immune cells are in the bloodstream at any time. Most of our immune cells are actually locked away in tissues, places like the spleen, the lymph nodes, and the Peyer’s patches and the gut wall. These are places where immune cells come together, they interact with one another, and these are the places where the immunological decisions are made.

Just to remind you what I already said, that weak immunity results in poor defense against harmful organisms that results, in turn, in infections and inability to control infections. Since early 2020, weak immune systems have been exposed as a major public health challenge in places where there wasn't such concern about communicable diseases. Of course, there are geographies where there's always

been a big concern about communicable diseases, but certainly they were considered less important or more controlled in North America and Europe, for example, than the noncommunicable diseases.

Obesity has emerged as a major risk factor for severe COVID-19. I'm going to come back to that many times over. The key to this, perhaps, is that obesity impairs immunity. Obesity results in a weak immune system, a weak immune response. In fact, obesity impairs the activity of many important immune cells, some of which I've mentioned already. It reduces antibody responses, reduces the production of these important interferons involved in antiviral and antibacterial infection.

There's no doubt that people with obesity have a weakened immune response. They're also more susceptible to many infections—that's well documented—and also they don't respond so well to some vaccinations. I'm going to come back to these things a few times during my talk.

In the H1N1 flu pandemic of 2009, it was identified that people with obesity had delayed and weak antiviral responses and they recovered poorly from disease compared to normal-weight individuals. In fact, they have a prolonged period of flu virus shedding, and new, more virulent strains of the flu virus emerge in people with obesity because of their inability to control the virus. As I'll show you later, vaccinated individuals (vaccinated with the seasonal flu vaccine) with obesity still have a higher risk of influenza than normal-weight people, meaning the vaccines just don't work so well in people with obesity.

This is an example of some of the sorts of studies that have been done. This is an in vitro study where cells were taken from the blood of healthy-weight individuals, overweight individuals, and obese individuals. (This is an American study.) Those cells were incubated in culture with the influenza vaccine, so the influenza vaccine elicited an immune response in vitro. The researchers looked at different readouts of immune factors that are important in antiviral immunity: activation of cytotoxic T cells, which are the key cells to destroy virally infected cells; production of protein granzyme that's involved in lysis of virally infected cells; and production of interferon gamma. What you see is that the cells taken from people with obesity have much weaker responses than cells taken from people with a healthy weight, with cells from overweight individuals somewhere in-between. This is a study suggesting defective cytotoxic T-cell activation and function in people with obesity.

This is a busy slide, but it's exactly the same study design. Cells were taken from people of healthy weight, overweight, and obese. This time they were incubated with the flu virus, the pandemic H1N1 virus. The previous slide was with the flu vaccine; this is with the actual virus. Unstimulated cells are in the open bar, cells stimulated or exposed to the flu virus are in the dark bars. What you'll see is on some of these panels—these are all different immune cell subtypes—on some of these panels, cells from individuals with obesity show a weaker response to the virus than cells from healthy people, with the cells from overweight people in-between.

This is a good example here. These are interferon gamma and granzyme B-producing cells, and you see there are reduced numbers with obesity, perhaps a 50% reduction, with overweight being in-between. These are interferon gamma–producing cytotoxic T cells; again, reduced with obesity. This is an indication that cells from people with obesity have weaker responses to viruses than cells taken from normal-weight people, with overweight being somewhere in-between.

The cells have a weaker response. This is a paper, which is currently available as a preprint. What this is doing is looking at the types of antibodies that are produced upon flu vaccination in obese people compared with normal weight people. Essentially, what these researchers showed was that not only is the vaccination response impaired in obese people compared to normal weight, but also the types of antibodies, the actual proteins that are produced, have a different structure in obese people compared to normal-weight people. Their whole response to vaccination immunologically is different; they produce different antibodies.

We know that the antibodies to the flu vaccine decline over time. What this study is doing is documenting the relationship between body mass index and loss of anti-flu vaccine antibodies. This is the decline, this is the loss of antibodies, as a function of BMI. What you see is the higher the BMI, the greater the decline. If you divide those individuals by healthy weight or obese, and you look at the decline to each of the three components of the trivalent seasonal influenza vaccine, you see that—this is percentage of people with a greater than fourfold decrease in antibodies over the follow-up period—you see that people with obesity are more likely to lose antibodies than people of normal weight. I think that's a way to summarize it. They have a weak response, they produce different antibodies in terms of structure, and then the loss of antibodies is faster with obesity compared to normal weight.

If you put all that together, it's maybe no surprise that vaccines don't work so well in people with obesity. This is a study that looked at the likelihood of individuals developing influenza-like illness or lab-confirmed influenza after vaccination for seasonal flu in obese compared to normal-weight individuals. They showed that the obese individuals were about twice as likely to develop flu post vaccination as normal-weight individuals, confirming this poor vaccination response and this more rapid loss of antibodies.

The immune response is weak in people with obesity. We also know that adipose tissue becomes inflamed with obesity; there's infiltration of cells like macrophages and also T cells, and there's an inflammatory response within the adipose tissue with production of classic inflammatory cytokines. This is a picture you see in nice review articles; this is the real thing taken by one of my students, showing the macrophages here surrounding the adipocytes and interacting with the adipocytes.

What my student did was transcript on adipose tissue taken from normal-weight and obese individuals, and she found almost 4,500 genes were differentially expressed in obesity; 600 were regulated at least twofold compared to normal weight, and 175 downregulated at least twofold compared to normal weight.

And these are the 25 most affected pathways and, if you look at this, almost all of these pathways are to do with immunity and inflammation. We've got regulation of the immune response, acute phase response singling, IL-8 signaling, IL-6 signaling. These are all—NFκB is down here somewhere—I think about 23 out of these 25 pathways have to do with inflammation and immunity, a couple have to do with metabolism.

Adipose tissue and obese individuals has ramped up inflammation and the result of that is that people with obesity have higher blood levels of inflammatory markers compared to non-obese. This is P-selectin, interleukin-6, and TNF-α in obese compared to non-obese women, and you see the concentrations are significantly higher.

The adipose tissue itself is inflamed; you've seen that. Blood levels of inflammatory markers are higher. What this means is adipose tissue is exporting its inflammation, and as a result of that we get a few like secondary inflammation in places like liver and skeletal muscle and elsewhere. We get in the end, our whole-body systemic inflammation and insulin resistance.

Another interesting thing that happens is changes in the thymus with obesity. The thymus is the organ where T cells mature. Of course, the thymus shrinks as we age, the process of thymic involution, but it turns out that people with obesity also have smaller thymuses. What that means is they have less capability to put out new T cells. This is the relationship between thymus size and body mass index, and this is thymus size and fatness. I think there is a phenomenon like fatty liver, which is a fatty thymus, and I think this could be impairing the ability of obese people to generate T cell–mediated immune responses. Obesity is linked to a weak immune response and increased low-grade inflammation.

I'm going to turn now to COVID-19. This is the relationship in meta-analysis between infection with coronavirus in obesity compared with non-obese individuals. You see that obese people, according to this meta-analysis, are somewhere between two-and-a-half and three times more likely to be infected with coronavirus compared to non-obese individuals. I think part of this could be due to this immune impairment seen in obese individuals.

Obesity could make people more susceptible to infection because their immune systems can't cope so well to exposure to bacteria and viruses, that is, their immune systems are weak.

This is COVID-19 data looking at anti-coronavirus antibodies as a function of BMI. What this is showing is the higher the BMI, the lower the level of the antibodies. This would be consistent with a weaker immune response in obese people; they just can't cope with coronavirus infection, so they're not generating sufficient antibody concentrations.

Now, of course, poor outcome from COVID-19 is partly related to weak immunity and is partly related to excessive inflammation; of course, there are other things involved as well. This is an early study from China looking at interleukin-6 as a marker of inflammation and blood lymphocytes as a marker of immunity. Those individuals who were—these were all severe COVID-19 patients: the individuals who survived, they're in blue; those who didn't survive are in red—and you see the nonsurvivors have much greater inflammation, and the nonsurvivors have lower lymphocytes numbers—so weaker immunity. It's possible that people with obesity are immunologically predisposed to poor outcome from COVID-19 because of weak immunity and higher low-grade inflammation.

There's been an enormous number of studies on obesity and COVID-19 outcomes; in fact, there are already more than 50 published meta-analyses of obesity and COVID-19 outcomes, which is pretty phenomenal. I'm going to show you data from some of these meta-analyses: This is the relationship of obesity and severe outcomes from COVID-19 showing that obesity increases the risk of severe COVID-19, increases risk of acute respiratory distress syndrome, increases risk of hospitalization with COVID-19 compared to normal-weight individuals. Likewise, obesity increases risk of the need for invasive mechanical ventilation and increases risk of ICU admission. The increases in risk are typically between about 1.5 and 3 times.

A similar meta-analysis, again these a univariate associations just comparing obese and non-obese, showing increased risk of hospitalization, increased risk of ICU admission, increased risk of invasive

mechanical ventilation, increased risk of mortality in obese compared to non-obese individuals as a dichotomy.

This is a multivariate association, so taking into account some other factors, but all of these are increased risks with obesity hold up in the multivariate association. Something like a two-and-a-half-fold increase, two-and-a-half times increase, in risk of hospitalization, ICU admission, mechanical ventilation, and mortality.

Now the meta-analysis: fewer studies here, but again showing the same thing for these sorts of outcomes from severe COVID-19.

Again, another study showing the same sort of picture.

So those are all studies looking at obese compared to normal weight. It's interesting to look at the continuum of body mass index. This is data from nearly 7 million people here in England looking at the relationship between BMI and admission to hospital, admission to the ICU, and mortality. We've already seen that obesity increases the risk of these outcomes compared to normal weight, but what these data from England are showing is really that from a BMI of let's say about 25 or so, there's basically a linear relationship between BMI and these more severe outcomes.

You're all from the US. These are data from the American Heart Association registry, slightly more complicated data than what I just showed you. Here we have three different outcomes: in black squares is death or need for mechanical ventilation; the blue is death alone; and the red is mechanical ventilation alone according to overweight and obesity. Again you see, I think, a dose-response relationship, if you like, between body mass index and these severe outcomes either individually or when they're put together as the combination of death or need for mechanical ventilation (in black). These are the relationships according to age and according to BMI for each of those outcomes. I think that data are pretty similar to the data from England, where essentially there's a dose-response relationship between BMI and poor outcome from COVID-19.

A question is, how does the effect of obesity compare with other risk factors that we've heard about, like aging and being male? This is a meta-analysis that looked at the effect of being aged more than 75 years, that looked at the effect of being male rather than female, and looked at severe obesity compared to normal weight. What this meta-analysis shows is that for all three of these factors individually, there's actually a roughly similar increase in risk, which is somewhere between two- and two-and-a-half-fold. Over 75 is about two-fold higher risk of severe COVID-19 compared to under 75 male in this meta-analysis, about twice the risk as female, and severe obesity about 2.6 times the risk compared to normal weight.

So far I've talked about susceptibility to COVID-19 and severity of COVID-19. Another consequence, which you might imagine from what I said earlier in my talk, another consequence of obesity-associated immune weakness, as I'm calling it, would be poor response to COVID-19 vaccines. In fact, there are a couple of papers on that now.

This is the effect of obesity on the antibody response to the first shot of the COVID-19 vaccine. What they showed was a significantly better response. This is antibody response to the first shot of the Pfizer vaccine in underweight or normal-weight individuals compared to those with overweight or obesity, so a suggestion that overweight and obesity impair the vaccination response.

This is the relationship between waist circumference and antibodies to after the second shot of the Pfizer vaccine. This is showing that as waist circumference increases, the antibody concentration in the blood goes down. These are two studies suggesting that obesity impairs the response to theCOVID-19 vaccination.

What are the links between obesity, susceptibility to COVID-19, and severity of COVID-19? One of them could be, what I've sort of proposed to you, is that obesity weakens immunity. People with obesity, per se, are at greater risk of infection, and they can't control the infection so it's more likely to become severe.

The second is that it's actually all to do with the pro-inflammatory environment of obesity. This enables or creates an environment to enable the disease to become more and more severe in individuals who are infected. Related to this, perhaps, but it's a slightly different way of viewing it, is actually that this is because adipose tissue in obese individuals produces factors that somehow influence immunity and inflammation; so it's not the obesity, per se, but it's the factors that the adipose tissue is producing. One of these might be leptin, so of course there's a relationship between leptin concentrations and body mass index. In fact, leptin is a cytokine. It's highly related to interleukin-6, and this is just to show you that leptin has a receptor, binds to its receptor, and juices signaling. That signaling triggers inflammation and also has impacts on the immune response. So, it may be something to do with factors produced by adipose tissue and obese individuals, that is the link here.

Now, of course, there might be some other things. Maybe it's not obesity at all; maybe it's the obesogenic diet and lifestyle that increases risk. Both sugar and saturated fat have been shown to enhance inflammation. Many obesogenic diets are poor in essential nutrients, and the micronutrients in particular are vital to immune function and inflammation control. Being physically fit also supports the immune system. So maybe it's to do with the diet and the lifestyle of obese individuals, that those things are impacting their immune systems.

Some people have said, actually it's all about low vitamin D, because vitamin D is important to antiviral immunity and protects against respiratory illness. There are studies on vitamin D and COVID-19 infection and susceptibility. So maybe it's simply that obese people have low vitamin D, and it's all about vitamin D.

Others have argued it's gut dysbiosis. Gut dysbiosis occurs in people with obesity. It's associated with weak immunity and low-grade inflammation. so maybe it's gut dysbiosis that's the player here. It's important to note that there is a gut–lung axis so gut dysbiosis is linked with respiratory inflammation and respiratory illness.

Of course, this may be nothing to do with immunity at all. It could be because obesity weakens pulmonary function, for example. Or it could be actually that it's not obesity, it's the comorbidities of obesity that are posing the risk; I think we're going to hear a little bit more about that in the next talk.

This is a figure of what sort of catches those ideas that I've just presented to you: Obesity results in a state of a weakened immune system; chronic inflammation; obviously metabolism is messed up in obesity; there are effects on the endothelium; but also there are the comorbidities related to the airways and what have you, and there are other things going on obesity. You put that together with exposure to a virulent pathogen like coronavirus—which has the capacity to produce severe disease,

cytokine storm, respiratory illness, what have you—and these factors—one or more of them, maybe it's all of them—linked to obesity increase the likelihood of these things happening and them being more severe. This, together, is what I've actually been talking about, the link between obesity and COVID-19.

What I've told you is: A well-functioning immune system is required for effective defense against pathogens; impaired immunity predisposes to infections and it weakens vaccine responses. I've told you in a lot of detail that the immune system is weakened with obesity; I think this is an underrecognized result of obesity, and we really need to find out more about that. Obesity is accompanied by low-grade inflammation; this links obesity with its comorbidities and the adverse response to infection. There is a lot of evidence now; as you've seen there's already 40 meta-analyses at least, there's maybe even more now since I prepared my talk, on that obesity increases the risk of infection, more serious infection, poor recovery from infection, weaker response to vaccination—that's all pre COVID literature, increases risk of being infected with coronavirus, increases risk of more severe COVID-19 hospitalization, ICU need, ventilator need, and mortality. Lastly, I talked about the fact there's actually many mechanisms linking obesity with risk of and more severe COVID-19.

Thanks very much for your attention.

Diane Birt: Okay, thank you for an outstanding presentation, Dr Calder. We're now ready for questions. I think with a number of people on we probably can use the hand raise function, so click on the hand raise if you have a question, or you can put it in chat. For those of those who are on the streaming and can't use chat or hand raise, you could send me an email.

We have a hand raised from John Werdman.

John Werdman: I have a question. Can the level of the amount of vaccine used partially overcome the negative effects of obesity?

Philip Calder: That's a good question. I haven't I haven't heard that proposed. I have a feeling that probably wouldn't work very well. This vaccine wasn't trialed great before it was put into practice, but I think most vaccines are designed to provide pretty good stimulation of the immune system in healthy normal-weight people, and indeed that's what happens. So I don't think that would be a strategy; I think we have to find other ways to support the immune response, John.

I think it's really important to say that the vaccines actually do work quite well, even in people with obesity, even in older people who have weak immune responses. The vaccines are providing protection, at least, to a lot of people. It's not that they don't work at all, but I think they could be a bit more effective. I mean we see this every year with the flu vaccine anyway in older people, but I think this is a signpost that this is something to really focus on to find out how we can remedy the situation.

Venkat Narayan: Thank you. This is Venkat Narayan. Again, a very nice presentation, Philip.

My question is kind of related to the first question; I've got two parts to it. Firstly, should we be considering different dosage and different periodicity of vaccination for obese individuals, number one. Secondly, more importantly, with the long-term in mind, if the vaccination has nonspecific other benefits in terms of improving the immune function, you see potential for vaccination to mitigate the adverse consequences of obesity in the future.

Philip Calder: Those are great questions.

What we know is many vaccines wear off, so we lose the antibodies to many vaccines. Some of them, actually, we can get lifetime protection from some vaccinations. You've seen data that with the flu vaccine, the antibodies wear off over time in everybody; the influenza virus is mutating and changing, so we need new vaccines anyway. But I think the evidence is that antibodies to the flu vaccine disappear more quickly in people with obesity than normal weight, so I think a strategy could be, for the seasonal flu vaccine, could be, as you suggest, giving the vaccine again, perhaps.

We know with COVID-19, for most of the vaccines, we needed two vaccinations to get antibody levels up anyway; that was quite well-documented. Now we're seeing those antibodies are going away, and people need another vaccination; some people have had that already. It may be that for at-risk groups like older people, maybe people with obesity, maybe some others, more frequent vaccination could be a strategy, for sure. I think in the long-term, this is one reason why we have to try to push to reduce obesity. Of course, we already have the individuals with obesity, so we have to find ways of helping their immune response, maybe with other strategies. They could be nutritional strategies; they could be other things.

Diane Birt: Allen, please ask your question.

Allen Spiegel: Thank you.

There was a U-shaped relationship between BMI and some of the severe COVID outcomes; you didn't comment on the effects of low BMI that's been seen, with mortality in general as an endpoint. Is this really just a confounding effect of people with chronic diseases—cancer metastases, etc? What is the mechanism of low BMI?

Philip Calder: Allen, I didn't comment on that because I was focusing on obesity rather than underweight or frailty or whatever. We know that underweight is known to be associated with increased susceptibility to infection, increased mortality from infection; this is well-described in the field, but also in hospitalized patients in settings in in North America and Europe.

I think, again, this is weakened immunity. There are interesting data showing that frailty is associated with weak responses to the seasonal flu vaccination. I think at that end of BMI, again, we have weak immune systems that are not feeling very well. The reasons may be a little bit different from obesity. It may be insufficient essential nutrients in general; it could be the loss of lean mass isn't enough to

support a good immune response. Certainly, that's a phenomenon that occurs. It may also, as you mentioned, include individuals who have serious morbidities that are affecting body weight and that might also affect their susceptibility to infection.

Diane Birt: Question from George Arlene: It's not clear why the increased inflammation in the obese predispose them to an increased risk of infection or decreased response to vaccination.

Philip Calder: This is really complicated. That's a great question, George.

Inflammation is part of our immune response, and when we are infected or, indeed, when we receive a vaccination, we trigger an inflammatory response. Most of the symptoms that people report post vaccination—and you might have had these if you've had your COVID-19 vaccines—are due to your inflammatory response kicking off. It turns out that there are aspects of inflammation that impair T-cell function and B-cell function. Inflammation weakens immunity in its own right, and therefore increased inflammation could predispose to infections getting out of hand. The other thing is that inflammation causes adverse respiratory effects, for example, so it predisposes people to those consequences of viruses that infect the airways.

Diane Birt: I think this will have to be our last question. From David Metzler: Is it known whether the relationship of obesity to COVID risk varies by race?

Philip Calder: David, that is a great question, but I don't know the answer. I'm sorry. That answer may be out there. I'm sure there will be studies, particularly from the US, from your country, where people have looked at looked at ethnicity and obesity separately and as an interaction. I'm not aware of the data; I'm really sorry.

You mentioned vitamin D as part of your question [in the chatroom]. People have used vitamin D as an explanation for the susceptibility of different ethnic groups to infection.

Diane Birt: And then we have one last comment about the poor outcomes in underweight people may be very important to the low- and middle-income countries. That's from Venkat.

Philip Calder: Agreed.

Diane Birt: Connie, did you have one final short comment?

Connie Weaver: No, I was going to transition to the next speaker. Is that alright?

Diane Birt: That is perfect.

Philip Calder: Great. Thanks so much.

Connie Weaver: Thank you, Professor Calder, that was really fantastic. Now we look forward to hearing Dr Scott Solomon on COVID-19 and drilling into cardiovascular disease, specifically. Dr Solomon?

Scott Solomon: Do you see my slides alright?

Connie Weaver: Yes.

Scott Solomon: Perfect.

I just want to thank The National Academy and the organizers of this meeting for this invitation to address this extremely important topic that has impacted all of our professional lives, our personal lives, and, importantly, the lives of our patients and billions of people around the world.

Here are my disclosures. By way of full disclosure, I need to say that I'm a cardiologist and a cardiovascular researcher who has by necessity had to shift the fair amount of my own research focus over the past year to understanding how COVID affects the cardiovascular system and cardiovascular patients. I also want to caution all of you that this is a rapidly evolving field, and anything that I might say might very well be out of date in a few short months; we're really just beginning to understand some of these relationships.

It was hubris to think that we had essentially conquered infectious disease as a public health threat, and that in the cardiovascular field we could focus exclusively on diseases of overabundance and aging that have been the price that we've paid for relative prosperity and better health care and longer lives. Throughout history, our species has been plagued by pandemics. Influenza, in particular, has struck us in pandemic form four times in the past century, starting with the 1918 flu—50 to 100 million deaths worldwide and an eerily familiar series of infectious waves.

Pandemic flu, as you know, occurs every 20 to 50 years. It stems from a viral strain that differs antigenically from previous strains due to a sudden genetic reassortment between two closely related strains, and the overall lack of immunity in the population correlates with disease severity and excess mortality.

Indeed, while the majority of the morbidity and mortality associated with both endemic and pandemic influenza has been pulmonary, there's been a growing recognition that influenza in particular and viral

illnesses in general, could contribute to cardiovascular morbidity, even in the absence of pandemics. For example, in the data shown on the left from a large Canadian administrative database, flu was linked to a six-fold increase in the risk of acute myocardial infarction in the days following a laboratory-confirmed infection. Similarly, hospitalizations for heart failure in the ARIC surveillance communities were temporarily related to regional influenza activity. In parallel, there's been a growing recognition of the mechanistic links between influenza infection, we heard a little bit about this on the last talk, and cardiovascular disease.

Now coronaviruses have been much less appreciated as human pathogens until much more recently. In fact until 2003, only two coronaviruses had been identified, both of which as causes of the common cold. The SARS epidemic of 2003 was a wakeup call to these novel viruses. About 8,000 people around the world ended up infected, with a 10% overall death rate; this was followed by MERS in 2012. As you know, both epidemics burned out fairly quickly. Until 2019, all other known coronaviruses have been associated with self-limited upper respiratory infections.

But as you know, in late 2019, a cluster of 27 cases of pneumonia was reported in Wuhan, China. Within weeks, the viral genome for this novel virus was published, and it was shown to be 79% homologous with the 2003 SARS virus.

Coronaviruses are composed of a shell-like, fatty protective membrane studded with these crown-like spike proteins on their surface—that's from which they get their name. These spiked proteins mediate the attachment of the virus to the host through ACE2 receptors, and they're also the epitopes that are most immunogenic and the targets of both natural- and vaccine-induced antibodies. Inside the protective membrane is a single strand of RNA in addition to other structural proteins. I don't need to tell anybody here that it's been 22+ months, 228 million cases worldwide, 4.7 million deaths worldwide, and a world economic impact of $4 trillion.

It was quickly recognized after the start of the pandemic that the severity of illness with this disease varied widely from asymptomatic, from minimally symptomatic, to severe or critical disease. As reports started coming out of China, Italy, and New York City, we began to recognize that, while the majority of the morbidity and mortality with the severe cases was pulmonary, other organ systems were involved. The link to the cardiovascular system seemed particularly important, both because of the cardiovascular manifestations that we were seeing in our patients and the fact that cardiovascular risk factors were emerging as important determinants of disease.

It became pretty clear that from very early on in the pandemic that cardiovascular risk factors appeared to be the same risk factors for COVID-19 disease, not necessarily for becoming infected with COVID, but for severity of illness once infected—hypertension, obesity and cardiometabolic disease playing the major role.

As you saw in the last talk, in study after study, several demographic features and comorbidities became linked to severe disease. Black race, for example, has consistently been associated with increased risk and, by the way, that is even with adjusting for other comorbidities like obesity. Male sex has emerged for an important risk factor for reasons that we're not clear about at all. Age appears to act synergistically with other comorbidities to modify risk.

When we look closely at the risk factors for mortality in COVID-19, several patterns begin to emerge. First, there's a clear gradient with age; we're all aware that especially early on and pre-vaccine, the most vulnerable of our patients were indeed the elderly. Second, a similar gradient was apparent with BMI, with increased risk in those who are severely or morbidly obese as we heard about extensively in the last talk. Other risk factors that have stood out and held up include male sex, history of myocardial infarction, other cardiovascular comorbidities.

Obesity, as we heard from Dr Calder, is not just a risk factor for mortality in COVID but also for hospitalization, for the need for ICU care, for the need for invasive mechanical ventilation. What we see is that this risk associated with obesity actually appears to be greater in younger individuals, as this is a risk factor that appears to become diluted by other risk factors in the older patients. Importantly, if we look at the risk related to obesity for each of these endpoints and patients over and under 65 years of age, we see attenuation of the effect in these older patients in whom many other risk factors compete.

Why might patients with obesity be at increased risk for severe COVID-19? We certainly heard a number of reasons in the last talk. Various hypotheses have been proposed; I suspect the jury is, to a large extent, still out. There are data suggesting that obesity results, as we just heard, in low-grade inflammatory state that may have direct negative effects on both and innate and adaptive immunity. Obese patients, as Dr Calder mentioned, are known to have elevation and pro-inflammatory cytokines—like TNF-α, MCP-1, IL-6—mainly produced by visceral and subcutaneous adipose tissue that may contribute to this dysregulated, pro-inflammatory response.

Patients with obesity also often have compromised respiratory function, characterized by decreased lung volumes, decreased diaphragmatic strength, increased airway resistance, impaired gas exchange; these factors exacerbate the ventilation profusion mismatch, which is already impaired in COVID-19, and makes these obese patients who require invasive ventilation much harder to ventilate.

In addition, ACE2 expression in adipose tissue appears to be higher than that in lung tissue. This shared viral tropism for both tissues may favor prolong SARS-CoV-2 shedding in obese individuals.

We've known for a long time that thrombosis is enhanced in obese patients, and this may be synergistically increasing the risk of prothrombtic events in severe COVID-19; I'm going to talk more about that in a second. Lastly, there's evidence that widespread microvascular endothelial dysfunction, which we know to be the case in obesity, appears to be exacerbated by SARS-CoV-2 infection.

In addition to obesity, other cardiovascular risk factors have emerged as important, including hypertension. This is an early series of 1,000 patients from China, in which the prevalence of hypertension in patients presenting with severe disease in the absence of other risk factors was really quite striking.

This observation about this relationship between hypertension and severity of disease led to the speculation that the link between blood pressure and hypertension and severe disease might indeed be ACE2, which of course is the enzyme by which the virus gains entry. Normally, ACE2 serves as a counter-regulatory enzyme mitigating the effects of renin–angiotensin system activation. Unfortunately, some poorly controlled observational studies early in the pandemic suggested that the use of renin–angiotensin system inhibitors, which are by the way, commonly used in patients with cardiovascular disease, with hypertension, with heart failure, might be associated with an increased risk of

upregulation of ACE2, leading to a possible increased likelihood of viral entry and potentially increase disease severity. Fortunately there was actually little evidence to support that hypothesis, and in fact, counter-hypotheses emerged suggesting that dysregulation of the local renin–angiotensin system, due to the virus, might be contributing to worsening disease. Virtually all of the major cardiovascular societies came out strongly discouraging patients stopping or physician stopping medications like ACE inhibitors and angiotensin-receptor blockers in patients with hypertension and especially heart failure. Subsequently two randomized trials of withdrawal of these types of medication showed there was no effect on the course of disease. This is a great example of how poorly controlled observational data led to the wrong conclusions; this is a problem, unfortunately, that we've had throughout the pandemic and that certainly has contributed to some of the morbidity that we've seen.

The link between COVID and the cardiovascular system has been further strengthened by data showing that the primary biomarkers we use to evaluate risk and cardiovascular disease are elevated in hospitalized COVID patients. High-sensitivity troponin, which is a marker of myocardial injury, may be elevated in as many as 30% of patients admitted with COVID-19 to hospital, and it’s associated with increased mortality regardless of whether patients have underlying cardiovascular disease. Shown in the right, our data from 12,000 patients with natriuretic peptides like NT-proBNP or BNP measured upon hospitalization—this showed a three-fold adjusted increased risk of mortality in those with the highest compared to the lowest quartile even in the absence of known cardiovascular disease.

Although we're seeing evidence of myocardial injury in patients with COVID-19, the question has remained: Was this due to the virus attacking the heart directly, or simply due to the increased myocardial oxygen demand in the setting of severe illness? Much of the evidence suggests that, in most cases, the heart is a bystander and it's usually not targeted directly by the virus. Despite early reports of a lot of acute myocarditis in the setting of COVID-19, the actual incidents of pathologically proven true myocarditis in COVID appears to be quite low. There have been limited data that the virus directly infects the heart.

We are seeing now what appears to be a low risk of myocarditis and pericarditis following some COVID vaccines, particularly the mRNA vaccines. The data suggest that this risk is greatest in young men; whether this is due to an idiopathic immunologic phenomenon or a more nonspecific effect of inflammation induced by the vaccination is as yet unknown.

There's also been evidence that acute atherosclerotic events, such as myocardial infarction and ischemic stroke, are increased in the setting of COVID. In these data in over 5,000 patients from Denmark, where researchers have access to the health records of virtually the entire country in near real time, COVID patients who were used as their own controls had a nearly 13-fold increased risk of ischemic stroke and a six-fold increased risk of acute myocardial infarction in the 2 weeks following a diagnosis with COVID compared with the 6 months preceding infection.

The disease and the pandemic are affecting our most vulnerable cardiovascular patients, such as those with heart failure, disproportionately. In this large series of over 2 million hospitalizations, patients with a diagnosis of heart failure who were hospitalized with COVID had a nearly two-fold increased risk of death compared to those without heart failure. The risk of a heart failure patient dying during a COVID admission was 12 times the risk of their dying during a heart-failure exacerbation.

It's important to remember that the pandemic has taken a huge toll, not just on those who can track the disease but has influenced cardiovascular death more broadly in the population. In fact, in the early COVID surge in Boston in the first spring in 2020, we saw a 40%–50% decreased incidence of hospitalization for acute MI or heart failure compared to previous years. That was also seen in many other locations. This wasn't because these diseases had been cured. On the contrary, this was likely due to a combination of patients ignoring symptoms, delaying seeking appropriate medical care. No surprise, during this time we saw many complications due to delayed care, such as increased risk of ischemic cardiomyopathy or myocardial rupture—both complications of acute myocardial infarction when care is delayed.

Unfortunately, the reduction in hospitalizations was paralleled with an increase in the number of out-of-hospital cardiac deaths and cardiac arrests as shown here in the US, in Italy on the right, and New York City, where out-of-hospital deaths attributed to cardiovascular disease peaked during their 2020 surge.

One of the many paradoxes of this disease is that, while many people recover from acute infection in about 7 to 10 days, in some—and clearly way too many patients—the disease progresses to hypoxia, shortness of breath, and in the most severe cases, acute respiratory distress syndrome and organ dysfunction. There are several pathophysiological processes that seemed to be at play in the development of severe disease that tie into the cardiovascular system.

The first, as we heard about in the last talk, is the abnormal activation of the inflammatory response. Inflammation is an integral part of the innate immune response to infection, but normally inflammation is expected to be proportional to the pathogen burden. Infection with COVID seems to trigger a robust and even exaggerated systemic inflammatory response, sometimes referred to as cytokine storm, with an overproduction of a wide variety of inflammatory mediators, including IL-6, IL-1α, IL-1β, TNF, and many others. Many of these markers of inflammation have been shown to predict poor outcome in the disease.

The second pathophysiologic theme is increased thrombosis—both macrovascular thrombosis and microvascular thrombosis, which autopsy series have shown occur very commonly in COVID-19 even when these were not recognized pre-mortem. Venous thrombosis, such as deep venous thrombosis and pulmonary embolism as shown on the left, have occurred more commonly than expected. Microthrombosis appears to be playing an important pathophysiologic role in the severe lung disease of COVID.

In this comparison of patients who died of COVID, influenza, and uninfected controls, patients with COVID demonstrated severe endothelial injury, disruption of endothelial membranes, occlusion of endothelial capillaries, and even new vessel growth. Taken together, these findings have suggested that acute endothelial injury, what has been termed *endotheliitis,* likely plays a broad role in this disease.

This is probably due to the fact that the release of pro-inflammatory cytokines during infection can lead to the loss of the antithrombotic, vasodilatory, and antioxidant properties of the normal endothelium. Also, as you know, endothelial cells, when triggered, release endothelial granules, which contain von Willebrand factor and P selectin, both of which can facilitate platelet aggregation and thrombosis. Nearly all of the risk factors that we talked about earlier in the talk have been associated with endothelial dysfunction, suggesting that the endothelium may be the link between these risk factors and severe COVID disease.

Another really fascinating emerging pathophysiologic concept in COVID-19 is immunothrombosis. This is the process by which immunologic triggers can cause thrombosis, which in normal settings may be part of the body's normal protective response to infection. One emerging key player in this process is neutrophil extracellular traps, or NETs. This is a fabulous acronym, because NETs are these multimolecular, DNA-based structures that are expelled from neutrophils in response to infections and actually look like nets. Unfortunately, net formation can be both thrombogenic and cytotoxic, can damage endothelial and vascular integrity, and may be contributing to rapid pulmonary dysfunction and other complications that we see in COVID.

There are many other factors that I haven't had time to go into, including genetic factors and our pre-COVID viral exposure history, which may be very important in influencing the host response to infection. We're just beginning to understand these.

Putting all these data together suggests that comorbidities that are truly synergistic with viral disease, in fact, augment risk; that activation of platelets and the endothelium seems to predispose patients to more severe disease. This is much more likely to happen in patients with preexisting cardiovascular risk factors and morbidities. I think this helps explain why, even with the greater infectivity of the Delta variant and the shifts that we've seen over the past several months in the demographics of this disease, with more younger patients being infected, it's still quite rare for a young person without comorbidities to develop severe disease.

Unfortunately, some patients continue to have symptoms for weeks and months after seeming to recover from the acute phase of the disease. The symptoms of so-called long-COVID syndrome, which has now been renamed post acute sequelae of COVID, or PASC, are highly variable in variety, in severity, in duration. Preliminary studies suggest that up to about 30% of patients may report symptoms as long as 9 months after acute infection. Of course, we don't know what the tail on this is yet. These include fatigue, reduced functional capacity, exercise intolerance, and shortness of breath, and have been linked to various organ systems, including the cardiovascular system.

There now several reports of patients with no known prior cardiovascular disease, at months post acute infection, with evidence of both myocardial edema and fibrosis detected by cardiac MRI. Clearly understanding the scope of this problem is going to be challenging because of the inherent bias of patients presenting with persistent symptoms. Clearly, we are going to need to apply solid epidemiologic methods to truly understand the extent of this problem.

Well, as I mentioned, the demographics of this pandemic are changing rapidly. Shown on the left is the age distribution of the new COVID cases in Massachusetts as Delta began to surge in the US this summer. By far the largest group of patients infected were young people between the ages of 15 and 30. Fortunately, as I said, young people are way less likely to be hospitalized with COVID, but those who do get hospitalized are generally quite sick. In a survey of nearly a quarter of the hospitals in the US, when young people between ages of 18 to 35 or admitted to the hospital for COVID, 20% of them required ICU care, 10% of them required ventilation, and 3% of them died. Even in the very young, cardiovascular risk factors that we've been discussing—obesity, hypertension, and diabetes—markedly increased their risk of this sequelae.

In 1889 a pandemic emerged in Central Asia and then one globally, with fatigue, fever, and severe respiratory symptoms, killing an estimated million people worldwide. This was dubbed the “Russian flu,”

but a lot of new circumstantial evidence suggests that this actually might not have been the flu but might have been a coronavirus. It was likely a coronavirus that was isolated in the 1960s; it's now widely known as a cause of the common cold.

About 20% to 30% of common colds are caused by four circulating coronaviruses. The epidemiology of this 1889 disease and the symptomatology were very similar to what we've seen with COVID-19, including relative sparing of young patients, which is different from what we see with influenza, and symptoms like anosmia that have become pathognomonic of COVID-19.

Viruses have emerged throughout our history and will continue to emerge. If SARS-CoV-2 follows the same playbook as other coronaviruses that circulate currently in humans, it is very likely this virus will become endemic, causing mild disease in children first exposed to it, with older individuals who develop immunity early in life being relatively protected. Nevertheless, as we know, common colds do reinfect us frequently due to antigenic shifts caused by mutations in the virus. We know this virus is mutating. It's likely that even when the pandemic phase of COVID-19 is over, the endemic phase will continue to engender risk in high-risk individuals, just as influenza does year after year.

Exactly 30 years ago this month, two large storms collided in the North Atlantic not far from where I am now in Boston, causing what we typically refer to as “the perfect storm,” for those of you who read the book or saw the movie. We're now witnessing a perfect storm that was born from the intersection of these two pandemics: the pandemic of obesity and of cardiometabolic disease in COVID-19.

We've seen that the severity of COVID-19 is influenced by known cardiovascular risk factors, including hypertension, metabolic disease, obesity, which is increasing in pandemic form across the globe. It is likely that endothelial disease and dysfunction represents the crucial link between cardiovascular risk factors and severe COVID-19 through its effects on the inflammatory, immune, and thrombotic systems. As the demographics of COVID-19 disease change, risk factors such as obesity, increasingly prevalent in our young patients, appear to play an ever-greater role in influencing disease severity. We're just beginning to understand the role of cardiometabolic risk factors and disease in determining the severity of pathogen-induced diseases. Understanding this intersection is the key to the preparedness for the next perfect storm.

Thank you very much for your attention.

Diane Birt: Thank you for an outstanding presentation, Dr Solomon.

Unfortunately, we have very little time now for questions. Maybe we'll push things back and take just a couple of quick questions. Can we get people to use a hand raise function if they have questions here? I have on the chat function.

How can post acute persistent symptoms be distinguished between COVID versus what you would have with adverse effects anyway? That's Connie, you want to explain that question?

Connie Weaver: By his nodding his head, I think he gets it. People were saying that they have these things because they once had COVID; how do you know if it's due to the COVID or if they would have gotten them anyway?

Scott Solomon: This is a great question. By virtue of the fact that so many of these patients who have COVID also have cardiovascular risk factors.

The real way we're going to have to assess this is obviously through good epidemiologic studies. We can't just look at the enumerators; we can't just look at the patients who come to our clinics and say they're having palpitations or chest pain. I can tell you that I spend most of my clinic sessions seeing patients like that anyway, and we're going to have to really understand to what extent we're seeing this in the match controls to know that these symptoms are indeed due to persistent effects of the virus and not symptoms that people are simply more aware of. I think that there is sort of a hyper acute time post disease when we're thinking about everything that's happening in our bodies. There is going to be some degree of selection bias there. It's going to require some very good epidemiology. The NIH has been supporting assessment of post acute sequelae in large epidemiologic cohorts where we also know about people prior to the pandemic.

Diane Birt: We have a question from Henry Brem regarding cardiovascular effects of vaccine. Would you like to ask that, Henry?

Henry Brem: The FDA raised the issue of the Moderna booster, that there's concerns that they're not sharing yet with the public from Europe that there are cardiovascular effects of the booster. The question that’s coming up from patients is, how real is that, and how much….

Scott Solomon: I mentioned this briefly. There have been cases, relatively small numbers of acute myocarditis and pericarditis following vaccination, usually 3 to 5 days post usually the second vaccination of the series. It's on the order of 1 in 1 million people, so very small numbers. It seems to be much higher in young men between the ages of roughly 18 to 35.

I believe this is real but very uncommon. The risk is relatively low. Most of these patients recover, so the risk of actually getting cardiovascular effects if you have COVID is actually considerably higher than the risk of having this problem post vaccine. It's interesting that it's really only being seen with the mRNA vaccines, both Moderna and Pfizer, not so much with, for example, the J&J vaccine. Whether this is due to an idiopathic, immunological response or more nonspecific information, we don't know.

Henry Brem: Would a person who has a previous history of myocarditis be more at risk of myocarditis secondary to the vaccine, let's say, or to COVID, for that matter?

Scott Solomon: It's a great question. I don't think we know the answer to that, because that will be a very small number, but I've not seen any data to support that somebody who has either cardiovascular disease or a history of myocarditis would be increased risk for the vaccine-related myocarditis. Maybe that would be a reason that you might want to think about a non-mRNA virus vaccine instead of an mRNA vaccine, but I have to say this based on no data whatsoever.

Diane Birt: One final question, and we'll make it very brief here. Looking at comorbidities, is there any known contribution of social determinants? This is from James Gavan.

Scott Solomon: It's a really great question.

One thing that neither of us really talked about were some of the enormous health disparities that we see in COVID-19. We know that Black patients, patients of color in general, and ethnic minorities were at markedly increased risk for infection.

It's hard to sort that out from the other comorbidities in those groups. When you adjust for other things, you do still see increased risk, in general, in these groups. Interestingly, when you get to the hospital stage, our own data support suggests that you've kind of equalized everything. While, for example, Black patients are at increased risk for developing COVID, they may not be at increased risk for death if they've been hospitalized with COVID-19 compared to others. This is an area that we're really going to have to understand much better through the use of good epidemiologic techniques.

Diane Birt: Just as a final follow-up from our first speaker, Philip Calder. He said, yes, social determinants likely will be very important for infection.

Thank you, all. I hate to rush, but I think we need to get to our third speaker. Connie, you want to give a brief introduction so we can move forward?

Connie Weaver: It's my pleasure to introduce Dr Holly Nicastro, who's been a program officer with both NHLBI and NIDDK. We invited her today to talk about her role as coordinator for Nutrition for Precision Health Powered by the All of Us Research Program. She's going to bring us updates in the developments from NIH on precision nutrition, obesity, and diabetes. We're pleased you could join us today, Holly.

Holly Nicastro: Great, thank you for having me. Good afternoon or good morning, everybody.

I have been tasked with giving updates from the NIH, specifically on precision nutrition, obesity, and diabetes. I am a program director in the relatively new NIH Office of Nutrition Research. This office was formally established by Dr Francis Collins, NIH director, just in January of this year, 2021. Our office's mission is to advance nutrition science to promote health and reduce the burden of diet-related diseases.

You probably know, our office in some form has been around. Most of the current staff had been in the NIDDK Office of Nutrition Research. We had a similar charge of coordination of some trends, NIH nutrition activities, but now with the establishment of the NIH Office of Nutrition Research, we're in a much stronger position to advance our goals.

Key responsibilities of our office include advising NIH leadership on matters relating to nutrition research, coordinating the implementation of the strategic plan for NIH nutrition research (more on that will come in the next slide), and leading and representing NIH on various government-wide committees related to nutrition.

The establishment of ONR followed the release of the first-ever strategic plan for NIH nutrition research. This plan was released in May 2020, so I hope you've all heard of it; our timing wasn't great here with the newness of the COVID-19 pandemic at the time. If you haven't seen it, I highly recommend you take a look.

The plan is broken up into four major goals, and each goal has accompanying objectives. Each objective could read as if it could be a future initiative or RFA. Now, that's not a plan, that's not a promise, but rather these objectives under the four goals identify areas in which NIH may need to take the lead, or where accomplishing these goals may require efforts beyond individual investigator-initiated R01s, for example.

To be clear, investigator-initiated projects remain a major driving force, if not the major driving force of innovation at NIH. Our task as program directors is to identify areas where increased coordination funds or other pushes in the right direction might be needed.

The unifying theme of the plan is precision nutrition. When we say precision nutrition at NIH, what we mean is the goal of developing individualized, actionable dietary recommendations that help everyone figure out what, when, why, and how to eat to optimize health and quality of life.

Besides the unifying theme of precision nutrition, there are also five cross-cutting areas woven throughout all of the goals and objectives. These include minority health and health disparities; the health of women; rigor and reproducibility; data science, system science, and artificial intelligence; and training the scientific workforce.

What's not mentioned in the strategic plan but very much on everyone's mind is the COVID-19 pandemic. Our office and the strategic plan have only ever existed in COVID's world. We hear the word *syndemic*, we use that frequently now, and we know the COVID-19 pandemic is exacerbating nutrition-related health issues like food insecurity, access to food, hunger, food quality, the supply chain, and so on. We know, and heard very well earlier, that diet and nutrition and diet and nutrition-related diseases like obesity, diabetes, heart disease, chronic kidney disease, can all influence one's risk of severity of COVID-19 and its complications.

Even though it's not in our strategic plan, COVID-19 and its complications are being considered in the implementation of the strategic plan. Our office is coordinating the implementation of the plan, primarily of the seven different working groups and a few outside initiatives that I'll talk about. These working groups are developing short- and long-term goals on their respective topics and developing workshop concepts, guidance documents, transformation initiatives, or grand challenges.

Another activity our office is doing that I want to make you all aware of is our NutRitioNaLS, or listening sessions. As COVID hit and travel and in-person meetings stopped, we lost our opportunities to have informal and extremely valuable conversations with our extramural stakeholders. With this effort, anyone can request a session. Our office director, Chris Lynch, will attend as well as any relevant NIH subject-matter experts or program directors.

I just want to now highlight three efforts thate represent the very beginning of implementation of the strategic plan. First, hopefully you've heard of this in some way or another, this project is my baby, this is Nutrition for Precision Health Powered by the All of Us Research Program. The goal of this program is to develop algorithms to predict individual responses to foods and dietary patterns, with the idea that these algorithms can then be used to develop personalized or individualized dietary recommendations. We plan to do this by using a comprehensive set of inputs—microbiome, genomics, physiological measures, metabolic, behavioral, cognitive, contextual, electronic health records, survey data, environmental data. We'll do this in the largest and most diverse population study to date in a precision nutrition study. We'll accomplish that, we'll engage that large and diverse population, by being the first ancillary study to the All of Us Research Program.

This is the 10,000-foot view of the Nutrition for Precision Health, or NPH, study. It's a modular discovery science study. In the first of three modules, we'll enroll 10,000 All of Us participants and look at their baseline diet for 2 weeks, so what they're already eating out there in the wild on their own, and study their physiological responses to meal challenges.

Module 2 is a controlled feeding study of 1,500 to 2,000 participants who first completed module 1. We'll look at responses to three different short-term intervention diets. The exact diets will be determined by our investigators and our steering committee. These will be free-living studies, meaning participants will receive all of their food through the study but will otherwise carry on with their regular lives—live at their house, go to work, etc.

Module 3 is a domiciled feeding study. We'll study the same three diets as in module 2, but participants will check into the study centers for each of the three 2-week intervention periods.

In all three modules, we'll collect the same potential predictive measures, conduct the same next-meal challenges, and collect the same outcome measures, all to be determined and finalized by the investigators.

And then module 2, module 3 in particular, we'll provide additional opportunities for more detailed and more rigorous sample collection and data collection. Then we'll use machine learning and artificial intelligence to develop the algorithms that will predict various health-related responses to foods.

I'll pause here and just say, you'll notice that despite my charge today to address updates in diabetes and obesity, that most of what I'm really talking about is disease or condition agnostic, or perhaps disease or condition inclusive. The exclusion criteria for this study for NPH will be minimal, and we aim to include an incredibly diverse population, including diversity in disease and conditions like obesity and diabetes. We want people with every BMI, people without diabetes, people with diabetes, people with pre-diabetes. We'll also be studying endpoints relevant to these, like blood glucose responses, blood pressure, blood lipids, satiety, and more, to be determined by the steering committee.

The timeline for this program is that we are close to making initial awards for the program. We expect that to happen around December of this year, and it will be funded for an initial 5 years.

Another effort, this one very newly announced, is a T32 program called advanced training in artificial intelligence for precision nutrition science research, or AIPrN. This concept was recently cleared at the NIH Council of Councils meeting in September. The goal here is to build a future workforce that will be able to make pivotal discoveries using an increasingly complex landscape of big data and a wide array of data tools to tackle complex biomedical challenges in nutrition science and diet-related chronic diseases.

This was concept cleared. What that means is, there's not yet a timeline or a budget attached to it, but our intent to develop this program is now public. We're hopeful that the timing of several AIPrN trainees will coincide with the release of the public data set and the tools from nutrition for precision health.

And one final effort I want to highlight is our recent workshop on food insecurity, neighborhood food environment, and nutrition health disparities. This happened a few weeks ago in September. I do have the link in the notes of the slide deck, or if you email me, I'll send you this link. Right now, anybody can go and register to access the materials from this workshop whether or not you attended the workshop live or not.

Thank you for your attention through my whirlwind tour of NIH nutrition activities. If you want to go deeper in any topics, I'm happy to take questions if time remains. Or you're always welcome to reach out by email: holly.nicastro@nih.gov. Thank you!

Diane Birt: Thank you very much, Holly, for a wonderful summation of what's happening at NIH particularly related to nutrition. I see that Allen Spiegel has his hand up, so Alan, first question.

Allen Spiegel: Thank you very much for that interesting overview. I suspect that this has kind of fallen by the wayside, sadly, because of the COVID pandemic. I think it's very important that you try to disseminate through a variety of channels information about this plan.

My question, which is not directed at you in a negative sense or even at my former colleagues at the NIH; I'm speaking from perspective of being the NIDDK director from 2000-2006, of co-chairing the obesity strategic research plan.

If, for example, when we're studying lung cancer and/or cardiopulmonary disease in the late 20th century and was going to frame a plan to do that without directly tackling the role of the tobacco industry, that would be really ludicrous. I'm not being naïve; I'm sure there are huge political challenges here. But how can one launch this plan without really directly looking at the fast-food industry, sugared beverage industry, all of the industry that is so powerfully, and again I'm not jumping to conclusions. It's very difficult, lacking really rigorous data, to say that the obesity epidemic is due largely or solely to the effect of industry, particularly with regard to health disparities and the inequities that we see with regard to a prevalence of fast-food chains, etc.

This is my question: I didn't see any of what you're outlining directly confronting this issue.

Holly Nicastro: That's fair. Directly confronting, no, I can't list for you any immediate initiatives coming out that might directly tack on to that. I will say our partnerships with our other federal partners, so FDA, CDC, USDA, and others, really have been strengthened now that we have a central NIH nutrition research office. We also do have a group that is focused on implementation of nutrition-related programs, practices, and behaviors, and that's where maybe some of these policy-related issues might fall.

We have a couple of calls out, I think, led by NIDDK I believe, on fast response, rapid response. If a policy related to obesity is about to be implemented, maybe a soda tax or something, you can quickly send in an application, have expedited peer review, expedited Council clearance, so that you can get in, collect baseline data before that program or policy takes effect, and then collect your posted data as well. It allows people to move quickly to study these natural experiments or to study policies.

That's probably the closest we have to something underway right now to tackle this. I think tackling the food environment, these industries, will require all of the federal partners and not just NIH.

Diane Birt: Thank you, Holly. We have time for a couple more questions. Use the hand raise function or put it in chat. Or if you're part of the web, you can send an email. Last chance, I'm not seeing anything else come up.

Well, thank you again, Holly. Thank you to all of our speakers. The session has been outstanding. Great questions; great talks.

We want to thank all of the public participants for joining us.