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### Allergic Reactions and Cardiac Concerns: Exploring the Heart Disease Link

#### Dr. Butler:

You're listening to *Heart Matters* on ReachMD. I'm Dr. Javed Butler, and joining me today to discuss his research from the article, titled "Allergic Responses to Common Foods Could Significantly Increase the Risk of Heart Disease and Cardiovascular Death," that was published on UVA Health in November 2023 is Dr. Jeffrey Wilson. He's an allergist and immunologist in the Department of Medicine's Division of Asthma, Allergy, and Immunology at the University of Virginia.

Dr. Wilson, welcome to the program.

#### Dr. Wilson:

Thank you, Dr. Butler. It's great to be here.

#### Dr. Butler:

So let's jump right into it. I'm a cardiologist, and I have never thought about food allergies and cardiovascular disease. So what made you do this study or think about this topic?

#### Dr. Wilson:

It's a great question, and really, there's a number of reasons that we got into this. One is that I think a lot of us don't realize, but there's actually a pretty good body of literature already linking allergic immunity with heart disease. There's a number of studies that have invoked mast cells in heart disease. So we know that there's a lot of mast cells in the heart, and we know that there are mast cells in atherosclerotic lesions in people who have coronary artery disease. We know that IgE, which is a bread and butter marker of allergies and something we're talking about today, but if you just measure total IgE levels, they tend to be higher when you look at cohorts who have heart disease in the subacute setting of people who are having MIs and things like that. We also know, if you just do population-based studies and you look at folks who have asthma or atopic dermatitis, that those things also have associations with heart disease. So overall, there's like a decent body of evidence that says that allergic immune responses could have connections with heart disease. Obviously, there's a lot of gaps and things we don't know.

The next thing that is a lead-in for this specific article is that our group at UVA reported about five years ago a connection between IgE to an unusual meat allergen, called Alpha-gal, in the severity of coronary artery disease. And so Alpha-gal is the tick-acquired red meat allergy, and this has a number of features that make it different from a lot of bread-and-butter food allergy that people think about with those things being more like peanut and tree nuts and milk and eggs. But here at UVA, we have a lot of interest in Alpha-gal. We studied the question, and we did find a significant association with the severity of heart disease. Interestingly, that observation has subsequently been replicated by a larger cohort study in Australia where Alpha-gal is also common. So those are important pieces of the backdrop.

And then there's little pieces of information that are also helpful to understand the specific question here, and it's really just thinking about, is there consequences when we make individuals who make specific immune responses to food? Even if that doesn't manifest clinically with obvious allergic symptoms or anaphylaxis, could that have other health implications? Could that be contributing to subclinical inflammation? And the reason that matters is because we know people who have food allergies, they make the allergic antibodies to food, and then they can have the allergic reactions; but that's really the tip of the iceberg because something on the order of 80 to 90 percent of people who make IgE to food never have obvious over-allergic reactions, and we know that a lot or probably most of these people are routinely consuming the food to which they make this specific and unique immune response. And so it just raises the question—could there be consequences of making a specific immune response to a food? And heart disease is one of the things we've

looked at here.

**Dr. Butler:**

This is simply fascinating. So let's dig a little bit into the study. So what were your objectives?

**Dr. Wilson:**

So this is obviously a human study, and our objective here was to identify large observational studies where we had access to blood samples or we already knew information about whether people made the IgE-allergic antibodies to some common foods. We wanted studies where we had information about dietary habits because we were interested to know whether people were consuming these foods to which they made the specific IgE antibodies to. And then we wanted to have fairly long-term outcome data available, and so to be able to follow out 10, 15, 20 years and ask questions about outcomes. Our specific outcome here is cardiovascular death. And so the two studies we're looking at here are called NHANES and MESA.

**Dr. Butler:**

Can you tell us a little bit about your design and some of the characteristics of the patient population for our colleagues who don't know about NHANES and MESA studies?

**Dr. Wilson:**

Sure. So NHANES is a population-based cross-sectional study. I think it's carried out about every two years by the CDC. And so the specific study that we work with here is the 2005 to 2006 study. And NHANES looks at both children and adults, but here we limited our study to adults 20 years and older. Serum was obtained from all of the adults who participated in the study. And actually, a different group a number of years ago measured the IgE antibodies to a large panel of food and also other respiratory allergens. And so in total in NHANES, we ended up being able to study a little over 4,400 adults. And again, these all had follow-up information that extended out about 14 years on average.

And MESA, so MESA is an NIH-funded cohort study, and it was specifically set up maybe 20 years ago with the objective of trying to find and discover new subclinical risk factors for the development of heart disease. And so what they did is they recruited adults age 45 to 84 from six sites across the country, and in this case, they were looking for folks who did not have known heart disease, and the objective was to follow them over time and see who developed heart disease. And so the parent study in MESA involves over 6,600 adults from six different sites, but the current study we had access to individuals who were recruited to the site in North Carolina, specifically from Wake Forest.

**Dr. Butler:**

For those just joining us, you're listening to *Heart Matters* on ReachMD. I'm Dr. Javed Butler, and I'm speaking with Dr. Jeffrey Wilson about his study on allergic responses to common foods and how it could be associated with heart disease and cardiovascular death.

So how did you design your study, and what were the questions and the associations you were looking for?

**Dr. Wilson:**

Yeah. So for NHANES, of the 4,400 adults that were studied, over that about 14 years, actually, it was 874 deaths in total, and 229 of those were from cardiovascular causes. And then MESA over about 18 years of follow-up, there was 290 deaths, and 56 were from cardiovascular causes. So here, our primary outcome is cardiovascular death.

And then the variables that we were really interested to understand if they had associations with a cardiovascular death again was whether people made the IgE-allergic antibodies to food. And the specific foods that were available for both studies were cow's milk and peanut. NHANES we also had information about IgE to shrimp and to egg. And in both cohorts, we also had information about whether they made IgE to a number of respiratory allergens.

**Dr. Butler:**

And what did you find?

**Dr. Wilson:**

And so starting off with how many of these folks make IgE antibodies to the food—in both cohorts about four percent were making IgE to the cow's milk, and about seven percent were making IgE to peanut. When you look at the number who make IgE to respiratory allergens, it's a bigger number, and so that's what the situation looked like at the beginning.

We also know that the majority of those especially who are making IgE to milk were routinely consuming cow's milk, so over 90 percent. And then when we generated Cox proportional hazards models including adjustment for important things like race and ethnicity, sex, age, education, smoking, asthma, as well as known cardiovascular risk factors, such as hypertension, obesity, diabetes, and high cholesterol, we found a significant association between the presence of IgE to cow's milk and cardiovascular death. The hazard ratio in

NHANES was about two, and the hazard ratio in MESA was a little bit over three.

So for IgE to milk, we saw a significant association with cardiovascular disease with all-comers. For IgE to peanut, we didn't see a significant association at first, but interestingly, if you limit it to those people who frequently consume peanut, then you saw the association. One of the differences there is there's more variability in who consumes and doesn't consume peanut as compared to milk, so there's more non-consumers of peanut. The same thing is actually true of shrimp, which we only measured in NHANES. But IgE to shrimp in the initial analysis was not associated with cardiovascular death, but if you limit it to the people who routinely eat shrimp, it was. And so it sets up a situation that is actually consistent with our initial hypothesis and idea that it's actually an interaction between two things. It's an interaction between a specific immune response and routine exposure to that relevant allergen in your diet. It seems like it's the intersection of those two things that would confer risk.

**Dr. Butler:**

So can you tell us what are the implications of your findings to our patients today? And what further research needs to be done?

**Dr. Wilson:**

Yeah, it's a great question. I think it's just really important to emphasize right now that this is very early research. We think the findings are interesting and provocative, but it's almost hypothesis-generating at this point, and so there's a lot more to do. The other thing is I think it's important to emphasize that our study is actually really less about food allergy and more about precision nutrition. And the reason for that is because people who have bona fide food allergy are not likely to be regularly consuming the food to which they make IgE, so in many ways it's those other folks. It's the 80 or 90 percent of the people who make IgE to food and don't know they had—like it's a subclinical immune marker.

And so it's really early. We have a lot more to do. I think one of the next steps is to try to go into even bigger cohorts to see if we can get more information, we can look at more food allergens, we can follow out for a longer period of time, and we can also try to get more specific information about the specific causes of cardiovascular death. Cardiovascular death is a pretty big umbrella, and so could this be coronary artery disease? Is this heart failure? Is this arrhythmia? There's a whole host of questions embedded in here that we need to tease out, and so I think trying to leverage some bigger data will be helpful. And for anything like this, I also think it's going to be important probably to start doing some mechanistic studies that could well involve animal models to get a better handle on what's actually driving this association.

**Dr. Butler:**

This has been really an important conversation on how food allergies could lead to an increased risk of heart disease and cardiovascular death, and we certainly look forward to further research coming out of Dr. Jeffrey Wilson's work.

Dr. Wilson, thank you for sharing your insights with us today.

**Dr. Wilson:**

Thank you, Dr. Butler.

**Dr. Butler:**

For ReachMD, I'm Dr. Javed Butler. To access this and other episodes in our series, visit *Heart Matters* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening.