Understanding the Hearing Loss-Dementia Relationship: What Epidemiologic Studies Can and Cannot Tell Us

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- [Moderator] It is my pleasure to introduce our guest presenter today, Dr. Jennifer A. Deal, who is an epidemiologist and gerontologist with expertise in hearing loss and cognitive aging. Dr. Deal is an assistant professor of epidemiology and otolaryngology-head and neck surgery at Johns Hopkins University as well as core faculty and associate director for academic training with the Johns Hopkins Cochlear Center for Hearing and Public Health. Dr. Deal is trained in the epidemiology of aging and she studies how hearing loss and vascular factors impact the aging brain and cognition to provide insight into pathways involved and to inform development of public health prevention strategies. Thank you so much for being with us today, Dr. Deal, and at this time, I hand the mic over to you.

- Thank you so much. It's really my pleasure to be here today. I really appreciate the opportunity, thank you. And I wanted to just put my webcam on just at the beginning to say hello. I think, especially with now all this virtual communication, that that kind of face to face is still so important for engagement. So, hello again. I am an epidemiologist, I trained in epidemiology, and then I came to the hearing loss side later. And so that really is the focus of today's presentation, thinking about what we know about hearing loss and dementia and then thinking about really how we interpret that. That's really the goal of today. This is the course description. Again, we'll talk about the evidence that exists currently for thinking that there is a relationship between hearing loss and risk for dementia. And then, really, we're gonna focus on the interpretation of that population-level data. And I really wanna also have a chance to talk a little bit about the interpretation not only in the sense of, is the finding true, but also what does it mean for you as practicing audiologists when you're meeting with a patient in your clinic. So, no disclosures, except an honorarium. And these are our outcomes. By the end of this presentation, you'll be able to summarize and interpret epidemiologic evidence, that population-level evidence, for relationship between hearing loss and dementia and cognitive decline in older adults. We'll be evaluating potential explanations for why we have those findings in the literature. And then we're also gonna talk about some important questions that we don't know yet, and so we still

need to be addressing. And here's our agenda. So, we're gonna talk with just a brief overview of epidemiology, we're gonna review that literature and we're really gonna spend the bulk of our time in thinking about how we interpret it. So, probably, I'm going to go ahead now and turn the webcam off. Thank you again. Appreciate that. So, this is really the motivation for the talk today. And this is a headline that you have probably seen in many different forms, in many different publications. This is one that came from The New York Times. The headline is, "For Better Brain Health, Preserve Your Hearing." And underneath, they say, "Hearing loss is the largest modifiable risk factor for developing dementia, exceeding that of smoking, high blood pressure, lack of exercise, and social isolation." That's a strong statement. And I think the question that we really have to address is, is it true? Is that, actually, correct? Is that the right message we should be sending to the public and to our patients? And in order to really evaluate that, we have to understand where the evidence is coming from, we have to know the limitations of that evidence, and know how to correctly interpret that evidence.

So, to start out with our first section, I just wanna talk a little bit about epidemiology and its role in public health. This is the definition of epidemiology. It's taken directly from a dictionary of epidemiology. Yes, there is such a thing. When we graduate, we all have a copy sitting on our shelves. Epidemiology is the study of how disease is distributed in populations and what factors influence or determine that distribution. And there are a couple of key things that I wanna highlight in this definition. And the first is, here, we're talking about the study of disease. That's true, but it can also be other health states. It could be the absence of disease. Anything related to health, essentially, is what we study. And probably a little bit more important is that, really, it's distributed in populations. What distinguishes epidemiology from other disciplines, who may be asking the same research question, is that we study groups of individuals. What's interesting to us is not the variability in a person. We try to get rid of all that variability so that the only thing that differs in the groups that we're comparing is their exposures status. And because we're looking at this population level, we're looking

kind of at an average in the population, our inference and our interpretation really also has to be at the population level. And I think that's something, for someone who hasn't trained in epidemiology, that's kind of a tough concept for thinking about what's the average in a group and then how does that relate to an individual? So, why is epidemiology important? What are some of its uses? So, we can do several things. We can look at the burden of disease, the number of cases, the proportion of people with the disease, for instance. This is something, of course, that's going on right now. Very timely, thinking about COVID-19. Every day, we're seeing a number of cases. And what we really still are trying to understand is the denominator, how many people have been exposed and have not become a case. That's something that we do. We try to determine causes of disease. And epidemiology really has a population-based science, is the science of public health, which is the study of health and populations, of course. We try to determine causes of disease in populations, in groups within the population so that we can prevent the disease. That's really the goal.

We can look at natural history and prognosis of disease. We can evaluate interventions. And that can include treatment, that can include interventions that are designed to prevent something from occurring. Those first kind of bullet points really have to do with the questions that we address and the science that we do, but another really important aspect of epidemiology is how we communicate those findings. Those last two, inform policy and inform the public, really have to do with, once we learn something, how do we communication that effectively? We have really two main types of studies in epidemiology. One is the experimental and one is the observational study. Experimental studies, you've heard of these other randomized controlled trials. These are where individuals are randomized to received one treatment over the other. It has nothing to do with their preference for treatment, it has nothing to do with me as the investigator. I don't have a say, it's a completely random process. But for most of our studies, we don't perform randomized trials. Sometimes it's just not ethical to randomize. Certainly, we couldn't randomize someone to have hearing loss, for example. So, what we're left with is what we call observational studies. These are

called that because we just let people take their natural course during their lives and observe what happens. And we are very, very fortunate that they agree to participate and work with us in our studies. Different designs that you'll hear that fall under the observational context include case-control studies, cohort studies. Those are really the primary cross-sectional studies sometimes you'll see as a design as well. And these are observational where people are selecting to participate in certain behaviors. And then we follow them over time and see who develops the disease. As a group in epidemiology, sometimes we're really successful and we've made great strides that have really made an impact for people's lives. And I think one of the greatest public health and epidemiologic successes is thinking about smoking. Cigarette smoking, the picture here on the left, this is the surgeon general report from the United States from 1964. That was the first time that it was really acknowledged at the government level that cigarette smoking was harmful. Before that, there was a lot of debate. And even some epidemiologists and statisticians came down on the side that we didn't actually know that it was harmful. Smoking back then in 1964, and I think we've continued to make progress there too.

Now, of course, vaping is the more recent concern. But I really think that's a great public health epidemiology success story. And then sometimes we're just wrong. We get the wrong answer. And this really is within the observational study context. One example is the Women's Health Initiative. It's now been about 20 years or so. This was a hugely influential randomized trial. All of the work that had come before that had been observational suggested that women who took hormone therapy had better cardiovascular outcomes than women who didn't when they we're undergoing menopause. This was a trial that, actually, randomized women to receive hormone therapy or a placebo, and it, actually, had to be stopped early. And it had to be stopped early because among women who were assigned to the hormone therapy group, they were having greater rates of cardiovascular events and greater breast cancer incidents. It, actually, looked like it may be harmful to take hormone therapy, whereas before it had been thought that it would be protective. So, sometimes the

observational studies and the randomized trials don't agree. And sometimes, and most often now, who really knows? So, this is one headline, "Foods that are surprisingly bad for your cholesterol." Here, they're talking about coffee drinking, increasing your bad cholesterol levels, your LDL cholesterol levels. More recently, within the past several years, there have been some large studies that have suggested that coffee is beneficial. And, in fact, one big review recently said that up to five cups a day help protect against cardiovascular disease and mortality. So, here, we're saying it's bad for your cholesterol, then we get some studies that say, "No, it's good, and, actually, may help prevent cardiovascular disease." And then after that, there's another ruling that comes out. "California judge rules that coffee requires a cancer warning." And that's because there's a chemical produced when the beans are roasted that may be potentially harmful, it may be a carcinogen. And so when we're faced with all these studies, how do we interpret that, how do we use that, what's the messaging that we would give to our patients?

So, within that context, it was epidemiologic studies that gave rise to all of those conflicting headlines. I think it's just worth pausing and taking a step back and saying, "Is epidemiology useful? If so, why?" And to do that, I'm gonna take you just a little bit back in time, back into the 1600s with John Graunt who was born in London, he was a businesses man, he was a haberdasher, but he is really known now as the forefather, perhaps the first demographer. And, certainly, in epidemiology we sometimes count him as potentially the first epidemiologist as well. And the reason that we do that is because in 1662, he published a book, which you can see pictured on the left, "Natural and Political Observations" made upon the bills of mortality. Bills of mortality were their mortality records. He went back over 50 years and looked at the different causes of death. This table is very small and it really is just meant to show the types of data that would be there. But, essentially, he has causes of death down the left-hand side, he's got years across the top, and the account of the number of people who died given that certain cause for every year. And these can be quite entertaining to read. Some of the causes, we don't have to worry so much about now. For example, the very last cause

that's listed there is wolf. And, unfortunately, there were eight people who died by wolf during a given year over this time period. But what was really powerful, and why I bring this up, is that this was the first time that anyone had looked across a population. And it's still true. Predicting a cause of death for an individual is incredibly difficult. We don't know what that person will die from. But when you look at a population level, suddenly, patterns start to emerge. And so at a population, we can see and even predict, and very accurately predict, patterns that we just can't see at an individual level. And I don't mean to discount the individual at all. Individual's very important, but it's kind of almost like you could think about what happens in one individual being almost anecdotal versus what happens in a population is really a pattern. That's really the first time that this was recognized and why we consider him, potentially, the first epidemiologist. I will say too, the fact that he was able to see this allowed just, it was so eye-opening. When we think about epidemics now, and, of course, we're in the midst of a very important epidemic, we define an epidemic as a case of disease that's greater than the usual number.

And we have to understand what the usual number is. So, we have to have this type of perspective in order to even be able to define an epidemic. So, his work has been incredibly influential. Again, just kind of going back to why epidemiology, what's the purpose? I think one of our main purposes, and where we get into the most trouble, and so what I wanna spend the rest of the time talking about today is when our goal is to try to think about determining causes. The truth is our methods really aren't designed to determine cause. So, I think we have to be honest with ourselves and upfront with the people we're communicating with. And we'll talk a little bit about why that is coming up. And then informing the policy, informing the public, that communication piece is so critical, but we can also get into trouble where we highlight results from individual studies, and those results aren't consistent over time and then people tire of the messaging and aren't sure really what the right approach is. So, I think we have to be very careful in terms of the way that we present those results too. Okay. So, when thinking about, a study comes out, it's a large study, maybe published

in a prestigious journal, and thinking about the interpretations, I just wanna highlight, of course, that there are a lot of different perspectives, and all are equally important. The patient is critical, their family, health care providers, journalists, epidemiologists, statisticians, policy makers. So, we all kind of need different information and different levels of interpretation and understanding that findings from that particular study. On one extreme, if we're looking, for example, at the relationship between hearing loss and dementia, we have a study comes out, well-designed, well-conducted, we find an association, we could say, "Well, that's a cause." So, hearing loss now causes dementia, and so we should be treating everyone for hearing loss or preventing hearing loss from occurring in the first place. So, that's one extreme. I think the other extreme is that it's not worth anything. That is just junk. And I think we tend to accentuate that interpretation, again, when we have these headlines coming out over and over with these conflicting results. And a lot of times, what you'll hear people say about epidemiology is that it's just a correlation. And that it's not true.

Our methods are well-designed to answer the questions that we can answer. And I think the issue is that we tent to overstep sometimes in terms of the interpretation, or at least the communication of that interpretation. So, like I said, epidemiology, we try to get rid of all the variability in individuals at the population level. We want the only thing to differ between the groups that we're comparing, we only want that to differ by exposure levels. For example, level of hearing loss. We want everything else to be the same. We have regression methods where we can account for factors that might affect that relationship. We think carefully about what should be included, how we're measuring things, lots of important things. The way I talk to my students about this is, really, we just need to be informed. When we're thinking about our inference and our interpretation, we don't wanna jump to either side right away, we wanna be more measured in terms of thinking about this relationship. So, kind of then to summarize, epidemiology is the science of public health. It has real value because we can look, again, at that population level and see those patterns that we just can't at the individual level. It is more than a correlation, but it's also not always a cause, and often my not be

a cause. That's something to keep in mind too. And that was really why we need to have care in interpreting the results, we need to balance the uncertainty that's inherent because of the design against the needs of those different stakeholders and those different perspectives in terms of interpretation. I haven't seen any questions come through, which is great. I'm sorry, it seems like a couple of you lost audio, but are back again. But if you do have questions, please feel free to post and I'll be happy to address as we go through. Now, having that little bit of a background about what epidemiology is, why it's valuable, I'd like now to just turn to a review of the evidence. What do we know about the relationship between hearing loss and dementia? And I would like to start with this quote because I think it gives some also very important perspective. This was from the Lancet Commission on dementia prevention, intervention, and care. It was published in July 2017, so about three years ago now. And what they said is, "Dementia is the greatest global challenge for health and social care in the 21st century." And there were several reasons why they made this claim. I am a dementia researcher, I agree with it.

One thing is just the high prevalence, the incredibly high burden of people with dementia, and that is increasing as our population ages. Another important issue is the cost of dementia, and that's both the monetary cost, and with dementia, of course, there's the cost for the care, but there's also the caregiving costs and some of those more intangible costs for people who may have to go to part-time working instead of full-time because they need to be at home for instance. So, there's kind of that monetary cost that's not taken into account. But, for me, I think the most important cost to talk about is that personal cost of dementia. And this is a paper from The New York Times again, and it was, I thought, so poignant. There was a woman who was diagnosed with dementia and then very bravely allowed a reporter into her home to be with her husband as they kind of grappled with what that diagnosis meant. Dementia is a culminating experience of cognitive decline, you've had change in your cognitive function from a prior level and it is now bad enough or severe enough that it is impacting your everyday life. I'm seeing a question here about cognitive decline and

dementia related. Yes, absolutely, they are. I don't have a picture here, but you can think of dementia as being a very long process. Dementia really occurs probably over 20 years or so. I think the average time between the onset of initial cognitive symptoms where someone might notice that they're having issues with their cognition, memory complaints are common, and the time that someone, actually, receives a dementia diagnosis is 10 to 12 years. And that really is because it is a gradual process. And as cognition slowly changes over time, then it starts to impact the activities and the ability for someone to be independent. That's when the diagnosis of dementia comes. So, we often times, in our studies, think about cognitive decline and dementia on a continuum. And if we look at cognitive decline, that's very important because that's what really predicts whether someone could potentially end up with that dementia diagnosis. And what's tricky with dementia and with cognitive decline is that we don't have treatment. It's not completely true. We have treatments and they have made a difference in clinical trials, small points in terms of small changes in terms of the increment of someone's cognitive performance.

But the truth is that it doesn't really impact the disease. As far as the natural history goes, the treatments may slow the cognitive decline, the progressive decline a little bit at the beginning, but over time the person, essentially, catches up to where they would've been had they never taken the drugs. And the drugs have a lot of very negative side effects as well. So, we don't have a cure and we don't have any treatments that really prolong life or alter the natural history of dementia, which is really disheartening. But it really highlights then this public health perspective, the importance of prevention. So, if we can't treat it, when someone has it, what we can do is try to prevent it from occurring in the first place, and that gets in again to cognitive decline. Can we slow the rate of cognitive decline over time? And that may help prevent dementia. I mentioned that Lancet Commission report at the very beginning. So, they looked at a number of risk factors and what we call modifiable risk factors, meaning that we can change them. We can either prevent them or we have treatments, effective treatments for them. And they looked at them across the world. So, from a

global perspective. I've listed them here in order in terms of what they found. And I will say this was very surprising for a lot of dementia researchers because hearing loss was associated with the greatest risk. And I do just wanna take a minute to interpret that number because it's an interesting statistic. It's called the population attributable risk percent, which isn't important for you to know, but it has this lovely interpretation for thinking about prevention. And so the interpretation of that number is that 9% of dementia cases in the world are due to hearing loss. And they could've been prevented if no one had hearing loss, or, potentially, if everyone had treated hearing loss. That's incredibly powerful. We have a chance to really make, potentially, a huge difference in terms of dementia. But there are some really important caveats. It means there can't be bias or confounding. We'll talk a little bit more about what I mean by that soon. But it also assumes that hearing loss is a cause of dementia, and we don't yet know if that's really true. Why that number, why was it so huge? Hypertension was only 2%, for example. Well, it's so large because hearing loss impacts a really large number of older adults, a very high proportion.

So, if you're thinking about intervention at a population level, if a lot of people have that hearing loss and we treat them all, then we can make a bigger impact than something that maybe only impacted a small proportion. And it was also so large because the association between hearing loss and dementia is stronger than has been estimated for other risk factors. But I do have to give the caveat that this study and that number was really based on only three studies. Now, I will say there have been a lot more studies that have been conducted since that time. There have been additional systematic reviews and kind of synthesis of the evidence. But at the time, these were really the three highest quality studies that the authors from the Lancet felt they should include in their work. I'm giving here the study title for each as well as the relative risk, and then the overall risk. So, just to interpret that for you, for example, for the study that we conducted, the Deal et al. 2016, the relative risk is 1.55. So, that would be an estimated 55% increase in the risk of dementia. And this was following individuals over nine years, comparing people who had a moderate or greater hearing loss compared

to normal hearing. Overall, when they combined these estimates, the estimated risk was 1.94. That's a 94% increase in the right of dementia for people with hearing loss compared to no hearing loss. I'm really just focusing on that Lancet report because I do still think it's the strongest summary that we have. But I will say there is a wide variety of studies that have been conducted, and what's wonderful is that they are consistent. We're seeing a relationship across all these different studies across different populations that hearing loss is associated with increased risk of dementia. I firmly believe there is an association. And now I wanna take a step back, go back a little bit to that discussion of epidemiology we have and really talk about how we interpret those studies. There is an association, but how do we interpret it? So, let's evaluate the evidence. Here's the tricky thing, and this is why I said, "Epidemiology in terms of our observational studies, we were really just not designed to determine cause." And the reason we're not is because of these reasons.

So, if we see an association, it might be a false association. It might fall into that junk category, and some reasons for that include bias and chance. And bias, typically, we think about three types of bias. The first is selection bias. This has to do with how people are enrolled into our study or if they leave the study early, for example. Information bias is the second type of bias. This has to do with how we measure things within our study. If we measure them without error. And then confounding is such an important consideration. Confounding is, actually, something that exists in the real world. There is a third factor, for example, that is related to the exposure that causes the outcome. If we don't consider it, the impact of that third factor kind of mixes with our exposure, and we're not able to understand, is the association we see with our outcome, is it due to the exposure or is it due to that other factor? A simple example might be thinking about age and hearing loss. Of course, if we think about hearing loss as our outcome, age as an exposure, we know that as people get older, they are at higher risk for hearing loss. But something to think about, if you didn't know it was really age or something just simple like white hair. You will see an association between gray hair, white hair, and hearing loss. But that's not because of the hair color, that's

because of the increasing age. So, that's a very simple example. We have to think carefully about how our exposure interacts with other factors in the world and could some of that interaction be explaining our association? So, that's really what we mean by confounding. And then chance is the final. And this is something that's really important to think about. From a statistics perspective, this is where we start thinking about confidence intervals and p-values. The smaller the study we have, the more likely we are to find an association just due to chance. Once we start getting larger populations, chance is less of a concern. But we always have to consider that, it's always a possibility. And that's why we use the statistical methods that we do. I just wanna highlight, it's not just that bias occurs at one part of the study, it's true that it occurs at all levels. It can occur when we're designing the study. Maybe we didn't appropriately design the study. When we conducted it, maybe we didn't do everything we should have and bias got introduced. We can introduce bias again when we conduct our analysis, and even when we interpret those findings. So, it's across all levels of the study that bias can be introduced.

And so you can see that it starts to become a real concern in terms of whether or not it's influencing our association that we estimated. From a kind of evaluation perspective, epidemiologists and researchers conducting this population-based research, think about those types of bias, like in biased information, bias in confounding. Clinical knowledge is so key. I really love working with fellow audiologists and other researchers, clinician researchers for understanding what those possible confounding factors are. That's so critical. And then, again, statistics is really what we use to help evaluate the role of chance. So, we have expertise to evaluate the potential for bias, and the trick is we just always need to do that and effectively communicate that. Finally, if an association isn't due to these other things, it could be a cause. And so that's kind of at the bottom of the list for reasons why we might see an association between an exposure and an outcome. In terms of thinking about cause, I went back again to the dictionary of epidemiology, how do we define a cause? Another word for cause is etiology. This is their definition, "Literally, the science of causes, causality; in

common usage, cause." It's not useful at all. And when we go and look at cause, try to look up cause in the dictionary of epidemiology, it's not there. The reason it's not there is because it, actually, is quite difficult to describe. There are some philosophical reasons for that, and there are whole courses that think about causal inference and causal reasoning and what is a cause within the context of epidemiologic studies. From my perspective, and this is my definition, is if I have a factor A, and I change A, does that change B? That's what we mean by a cause. It's really because epidemiology, again, is the science of prevention. And so if we wanna prevent an outcome from occurring, like dementia, and hearing loss is a cause of dementia, then I would say we know hearing loss is a cause of dementia if we treat hearing loss and that impacts dementia risk. That's how we know that it's a cause. And it seems obvious, but, again, it's something that epidemiologists, typically, talk about characteristics of causes and don't do a great job at defining cause itself. Our methods just weren't designed for it. But there are some important things that we can consider when we're thinking about trying to interpret results from a study. This is Sir Bradford Hill. We talked about smoking as a big public health success story.

Sir Bradford Hill was really, along with Richard Doll, one of those individuals who made that case. He studied smoking and lung cancer and recognized that that was an important association. And he gave an address and here he, as part of that address, he talked about some guidelines and, at the time, he called them criteria. We try to avoid that terminology now. But he talked about some guidelines for trying to judge if an association is causal. So, we see a relationship between hearing loss and dementia, does that mean hearing loss causes dementia? And so these were nine things that he recommended. The one here that's highlighted is, number one, the temporal relationship. That's the only guideline that you absolutely have to have. And all that means is that the exposure precedes the outcome. So, if we're gonna change A to impact B, A has to come first. It has to come before B. And so that's really the only thing that has to be met. Otherwise, strength of the association is important. We talked about the relationship between hearing loss and dementia. That's estimated right now

as 1.9. But something like the relative risk or the odds ratio for thinking about the relationship between smoking and lung cancer, that's 20. That's huge. That's so large that it probably, even if there's some bias happening, it's not gonna account for everything, there probably is still a true relationship there. So, the larger estimate we see, the stronger the relationship, the less likely it is due to chance alone. Dose-response means that as you increase levels of the exposure, the risk of the outcome increases. This is something that we see with hearing loss and dementia. Someone who has mild hearing loss compared to normal may be at slightly increased risk for dementia. But if you look at moderate or greater hearing loss compared to normal hearing, that's a much stronger relative risk.

So, we see this increase in risk as the exposure levels increase. Replication of the findings, we talked a little bit about this already, and I'll highlight it again later because it's so important. I sometimes talk to reporters, and a common question will be, "Well, what surprised you about this study?" And my answer is always, "Nothing because I'd go in with a very strong hypothesis. And if I don't have a strong hypothesis, I don't believe that association and I wouldn't even have necessarily published the paper." Replication of the findings, we have to have a strong hypothesis, we have to have the association of one group, and then we have to see it in other groups, in other populations, in different time periods in order to be sure that it's not just something unique to that population we studied, that it, actually, is a true relationship that exists out there in the world. Cessation of the exposure, an example could be if someone has hearing loss and we treat them effectively, and kind of stop that hearing loss exposure. Smoking cessation is another example. Biological plausibility, we'll talk a little bit more about in just a moment. And then considering alternate explanations, that's thinking about possible sources of bias, confounding, chance, like we just talked about before. Consistency with other knowledge means that across disciplines, you are studying the same question, we're finding the same answer. So, is the evidence in animal model supportive of what we're seeing in a population of individuals in a human population? Specificity of the association is really not one that's critical. That's mostly for infectious

disease. And so he gave us kind of this list of things to consider if we have an association within a study. I do just wanna talk a little about biological plausibility. I said before, and I'll emphasize it again, we don't know at this time if hearing loss is a cause of dementia or cognitive decline. But we do have some biological pathways and mechanisms through which we think it might. I just wanted to take a moment to talk about those. So, our big question overall, is hearing loss related to dementia? And one reason why we could see this is that there is that common cause that leads both to hearing loss and to dementia. So, something like this, something associated with increasing age. Increased levels of information, for example, or increased systemic cardiovascular disease. All of those things could be common causes for both hearing loss and dementia. Another way to think about this is that these are the confounders of the relationship. And what's tricky here with the cause or why it's so critical for us to make sure that it's not just a common cause is that if it is the third factor that's leading to both, if we treat hearing loss, that won't do anything to impact someone's dementia risk.

And so we really need to make sure that there are some causal pathways by which hearing loss and dementia could be associated. The first pathway that we think may be causal is an increase in cognitive load. And, of course, this is a term that you all know well. I'm grossly oversimplifying here, and I know you know that, but just thinking very simply, with hearing, we've got the two steps, right? We have the step that occurs within the ear where you have that peripheral transduction of sound in the cochlea. It's transduced into a neural signal. And then it's sent to the brain. So, the first step happens in the ear, the second step happens in the brain. And if we have cochlear impairment, we have that decreased sensitivity, there's distortion in the sound encoding. So, that sound, when it gets sent to the brain, is not clear, it's not crisp, it's garbled, it's a mess. And that means the brain has to work that much harder to kinda decode that signal. And that comes at the expense we think of doing other things like forming a memory. So, that increase in cognitive load, that effortful listening where you really have to work hard to understand what's being said is one mechanism by which

hearing loss can potentially cause dementia and cognitive decline. The second one is really one that I'm very interested in, and this is through changes to the brain. And so direct impact on the brain structure. And if you change the structure, the you'll change the function. There have been some very interesting studies that have started to investigate this. We know in terms of the brain that hearing loss is associated with lower grey matter volumes, so smaller volumes, in the primary auditory cortex. Maybe not surprising, right? So, that's the area of the brain, of course, where sound is processed. So, if you have hearing loss and you're not using that part of the brain, maybe it would tend to atrophy more. I think that's not so surprising. But what's really interesting and what we're trying now to get a better understanding of is that in some imaging studies, what we, actually, see is that there are networks that seem to be recruited outside of that primary auditory cortex area to help someone try to interpret.

So, if you put someone in an imager who has hearing loss and give them sentences, it's not just the primary auditory cortex that lights up, it's these other networks as well. We don't know exactly what that means, but it's at least a route through which hearing loss could be impacting the brain more generally and not just in that primary auditory cortex. And then there have been a couple of studies that have, actually, looked at rates of brain atrophy over time and its relationship with hearing loss. And what they found is that there have been faster rates of atrophy in the temporal lobe which is where that primary auditory cortex is located, but also in the whole brain. And so, again, there's this idea that someone with hearing loss, their brain may be shrinking faster than persons without. And it's been proposed and called the Double Hit model. So, we know in terms of thinking about dementia and cognitive decline, there are some really important brain pathology that leads to those changes. One is kind of the classic Alzheimer's neuropathology. This is the amyloid plaques and the tau tangles. Individuals would have this pathology. All of us, and starting actually at a young age, actually, start to have amyloid build up in our brain. It doesn't mean that we're all going to get dementia, but it is something that's pretty common. And, again, it can start, they've identified it even in people as young as 20 years of age. The presence of those

plaques and tangles is characteristic of Alzheimer's disease. Then cerebrovascular disease, that would occur from a stroke or from a ministroke. All of those are also important in terms of thinking about cognitive function. And the idea is if you have this pathology that's already occurring in the brain, which does so commonly, and then you add hearing impairment on top of that, that may, actually, be kind of the point that tips you over the scale in terms of how well you're doing. So, you could think of it kind of as a double hit, the second hit in addition to the cerebrovascular disease and Alzheimer's pathology, that really sets someone on the path to dementia diagnosis. And, finally, the third pathway would be from hearing loss to increased social isolation to dementia. And I don't really have another slide to talk about this because I think this is the pathway that is most intuitive and, clinically, I know that you see this a lot in your patients where they may tend to withdraw as their hearing worsens over time. And we know from a lot of studies, isolation, loneliness, large risk factors for things related to cardiovascular disease, cardiovascular mortality, and mortality generally.

So, social isolation is a big risk factor for some important outcomes including dementia. So, those are kinda the biological reasons why we think there would be an association. And I kinda wanna wrap up this discussion by going back to Sir Bradford Hill who proposed those nine criteria that we can consider. And I think he voiced it so eloquently as part of his speech. He said, "Here then are nine different viewpoints from all of which we could study association before we cry causation. What I do not believe, and this has been suggested, is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required. What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question, is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?" This is not a checklist. It's not something that will give us a definitive answer. It really is just kind of a viewpoint, a way of thinking about the association to try to understand whether it's causal. Take-home messages, there's no

checklist for understanding how to interpret the results of any one study. We can't say cause. It's not like three out of a nine and we get to say cause. Each study has strengths and limitations. They have to be considered and we need to be thinking about those alternate explanations like bias and chance. And no study is ever perfect. But, again, they can be informative, especially when we think about the larger body of work and the way that we can synthesize all that information. I hope that's not too disheartening. But it begs the question, where does that leave us, where do we go? Is it really still worth doing those epi studies? And I think the answer is yes. It's just that we have to recognize that one study by itself isn't enough and that there's, actually, a long chain of events that needs to happen if we're moving from generating this evidence to, actually, taking some sort of public health or clinical action. We start by developing the evidence. That's epidemiologic work, it's a human experiment, it's other research.

All of that goes together to develop the evidence base. Then we need to synthesize. We're gonna have conflicts, it's not gonna be consistent throughout. So, which studies do we trust more and why? We have to evaluate, and those guidelines can help us evaluate. Expert judgment is so critical there too. Finally, then we make the decision, the inference. Do we think this is a cause? If it is, then there needs to be a decision on what we do with that leading to action. And, again, kind of the place of epidemiology is very early on. Certainly, epidemiologists can be thinking about this evaluation and moving into decision and action, especially when we're talking about just individual studies. This is the first step. And we can't take action without kinda proceeding along this whole pathway. I really wanna highlight, for these reasons that we've been talking about, there are some rare cases of definitive clinical trails. The Women's Health Initiative is one, although there are still controversies surrounding that finding today. But except in the rare of some studies, we can never ever determine cause from one single population-based epi study. And so that's really key. So, when you see the headline comes out that says, "Whatever may be good for your health," it doesn't mean that you should start doing whatever they told you to say, right? More study is

needed, and, again, we need that kinda synthesis of the evidence to, actually, know whether it will make a difference. So, just to kind of summarize, we don't know if hearing loss causes dementia, but we do see multiple studies, consistent findings from multiple populations, the estimated association is strong, the association is stronger as hearing loss increases, we have these biological pathways that have been hypothesized that may give rise to a causal relationship, and we thought about some of these alternate explanations. It doesn't mean we're perfect, but we are trying to hit kind of all those Hill's guidelines to get us closer. And my own take right now is that the observational evidence is pretty strong that there is a relationship there. So, in the last 10 or 12 minutes or so, I just wanna talk a little bit then about what does this mean, what are the implications for practice, and what kind of questions still need to be addressed? I wanna go back to this idea of interpretation. We've been talking about, how do I interpret an association from the perspective of, is it true, is it a cause? But I wanna take another perspective that I think is equally important, and even more important, arguably, from a clinical perspective.

So, let's assume that we have an epidemiologic study and we estimate absolutely the truth. It's a valid study, we get the true relative risk for the relationship between an exposure and a disease. There's no bias, there's no confounding, we know it's a causal relationship, so we can trust that it's right. So, how do we interpret that relative risk for a patient? Let me give you an example. I'd like your participation in a poll to get your thoughts. Let's assume that the true relative risk for hearing loss and dementia in older adults is 1.9. That's what the Lancet estimated. How do we interpret that finding? So, we could say if an older adult has hearing loss, they have a 90% increased risk of developing dementia. So, if you saw your patient, you would say, "You have hearing loss, your increased risk of developing dementia is 90%." The other one would be that older adults with hearing loss have, on average, a 90% increased risk of developing dementia compared to older adults without hearing loss. I ask you to go ahead. I see the results. I think you guys don't see it yet in terms of the broadcast. I'll give it just another couple seconds. It looks like we're up to maybe about half who have

participated. Okay, I'm gonna go ahead and broadcast the result so everyone can see. Hopefully, that's working. If it doesn't, let me know. But it looks like majority have chosen the second version. We'll go ahead and end the poll now. Thank you. And that's what I would say too. Now, I will say on an exam if a student interpreted a relative risk for me, if they gave the answer for A, I would still count it as correct. But I think it's a little bit misleading and maybe a little bit dangerous in terms of the interpretation. And the reason why I say that is because we can't determine individual risk from an epidemiologic study because by nature they're an average across the population, like thinking back to the introduction of John Graunt's work. Because of that, we can't take the results that we get in a population and directly apply it to one individual. I also think it's a little bit tricky because we're used to thinking about things in terms of percent. Like the weather person will say, "There's a 30% increased risk of rain today." But the truth is it's not 30%, it's on average for days with these types of conditions, it'll rain 30% of the time. That's the truth. If it rains, it rains. If it doesn't rain, it doesn't.

So, for that individual day, it's gonna be a zero or a one. It's not gonna rain, or it's gonna rain. So, an individual's risk is gonna be zero or one, we just don't know what it is until it happens. They'll get it or not. And hearing loss may increase the risk, but it doesn't mean that everyone with hearing loss will get dementia. And it also, the converse is true. So, even if hearing loss is treated, the patient may still develop dementia because hearing loss is not the only risk factor. Family history is important, levels of education is important, cardiovascular risk is important. So, all of those things play in. Even if they have hearing loss that's effectively treated, they still may go on to develop dementia. I see a question here in the chat. Does that mean minus other factors such as cardiovascular disease, sorry, and Alzheimer's, the effect of hearing loss might be lesser in terms of causing dementia? I'm not sure if I quite understand the question. I think I maybe missed context with which it came up. Maybe it was within the double hit context. I think the idea is everyone has a different constellation of risk factors. If someone did not have cardiovascular factors and did not have

Alzheimer's disease, it still could be that hearing loss could cause dementia through those other mechanisms. I think the idea with that double hit hypothesis was really just like, "Look, as we get older, we already know that brains are becoming more vulnerable based on the pathology that's occurring within the brain, and hearing loss may be that kind of extra factor, again, that tips the scales." But each would contribute their own amount of risk. If you had hearing loss without any amyloid plaques, if you had hearing loss without any evidence of cerebrovascular disease, that still could potentially be enough to lead to dementia. We don't know that, but they could also work independently. Hopefully, that answered your question. Please let me know if it didn't. Okay. So, thinking a little bit then, returning to the slides, thinking about future research needs. Even if all of Hill's guidelines are met, we can still get it wrong. Again, think back to that example of the Women's Health Initiative.

The question is just why, why do we still get the wrong answer? And the answer is because we can't always account for bias. There's lots of bias that we just won't be able to account for, either because we didn't measure something that was important in our study, or we didn't realize we needed to measure something that would've been important. And I think an important question that kind of illustrates this gap where we can't always account for bias is this question of whether hearing aids prevent dementia. And we don't know. And why don't we know that? What's really the concern? I will say there have been a lot of studies who are interested in this from a population-based perspective. Some of them have quite an interesting design. Looking at an individual's cognitive trajectory before they got hearing aids and how it compares to after hearing aids, for example. And I will say that the findings that have been published are pretty consistent, that hearing aids look like, you know, if someone has hearing loss but uses hearing aids, it looks like they are at less risk for dementia than someone who has hearing loss and is not using hearing aids. So, the association is there and it's consistent. But the concern is one that we really can't get around with that observational design. It's that hearing aid users are fundamentally different from nonusers. And that's based the way that we have access to care and access to hearing

aids. Hearing aids for some can be the third most expensive purchase in their life compared to a house and a car, right? So, they're just fundamentally different from nonusers in a lot of important ways. Tend to have higher education, tend to have higher socioeconomic status, so higher wealth, they tend to be greater utilizers of healthcare, have greater access to healthcare, and all of these things are really important because they also protect against dementia. People who have hearing aids, by nature, being able to afford hearing aids, may already have these other protective factors that help protect them against getting dementia. And so that may be why the relationship looks the way it does. The fundamental issue is that we can't disentangle the effect of a hearing aid from the effect of those other factors. Randomization, the randomized trial is really what may help. That's really the type of study that we're going to need, I think, in order to be able to answer this question.

Because randomization where we, it's a random process which treatment someone is assigned to, and masking means that they don't know what treatment they're assigned to. That can really help protect against bias. We're gonna have to wait and see. There are several randomized studies that are underway right now thinking about whether hearing aids protect against cognitive decline and dementia. We're running one at Johns Hopkins. And our results, we'll have results by 2022. So, we have to wait and see, but those results are coming. And then, finally, kind of the last consideration distinct from bias, so even if a study is free from bias, it's important because the population that we study just may differ from other groups. So, if we study only nurses, they're fundamentally different on a number of factors compared to the general U.S. population. And so it may mean that even though we have valid results, within that group of nurses for example, those results don't apply to everybody else. They're unique to them. And we called generalizability. The results are valid, but they just don't generalize to the U.S. population. And so the take-home there is just like we can't directly apply results from one study to an individual. We also can't just necessarily apply them to other groups. Maybe we can, but we might not be able, and we have to carefully consider that too. And so kind of finally, in summary for this section, I think

results from population studies cannot generally be applied to an individual. So, it's not an individual risk. And they may not always apply to other populations. We don't know right now if hearing aids will prevent dementia, but we need more studies, randomized trials that will help us determine that. I think we're, actually, great on time. We have just a couple of minutes left it looks like. And I would be happy at this time to take any additional questions. Thanks so much again for having me. I've really enjoyed being here this afternoon. My email is here, if you have any questions, as well as my Twitter, I'd be happy to talk with you in those forms as well as any questions that you may have here. Thank you.

- [Moderator] Thank you so much, Dr. Deal. I can say that this has served as a very valuable resource for us clinicians, and coming from a great perspective as well. So, thank you for coming on today and sharing your wealth of knowledge with us. We have about one minute left before the top of the hour. So, if there's any comments or questions, feel free to type them in that chat box in that Q&A box just below the slides. And we do have a couple of thank yous here from members.

- [Dr. Deal] Thank you so much too. I've learned recently, especially moving to the online format, it's about nine seconds that we always need to allow to make sure that someone doesn't have a question coming in. So, that's why I was pausing there, silence.

- [Moderator] Wonderful presentation, Dr. Deal. Thank you so much for sharing with us your time and your expertise. We're gonna go ahead and wrap up today's course. We hope that you guys all enjoyed today's presentation. If you have any questions, feel free to reach out to Dr. Deal. She's provided her contact information there. We hope you have a wonderful day, and thank you so much for joining us on Audiology Online.

- [Dr. Deal] Thank you, take care.