What the ACHIEVE randomized trial tells us about hearing intervention to delay cognitive decline

Presenter: Jennifer A. Deal, PhD Associate Professor | Epidemiology | OtolaryngologyHead and Neck Surgery

- [Christie] It's my pleasure to welcome back Dr. Jennifer Deal. Today she'll be presenting to us the results of the ACHIEVE Study. If you'd like to learn more about Dr. Deal, you can read about her bio on the course registration page. At this time, we'll hand the mic over to you, Dr. Deal.

- Thank you so very much, Christie. It's really a delight to be back here today. As Christie mentioned, we're gonna be talking about the ACHIEVE Study results today and what it tells us about using hearing intervention to delay cognitive decline in older adults. These are my disclosures and I do wanna acknowledge some funding from the NIH, as well as hearing aids and related technologies, which were provided in kind by Sonova Phonak for this study. These are our learning outcomes for today. And I do wanna begin by just acknowledging that there's a very large group who made all of this work happen from a number of different sites across the US. So just wanna start by acknowledging all of the collaborators that made this possible.

So today in the presentation, we'll start by doing just a little bit of the motivation, the background about what we know about hearing loss and dementia on the question we were trying to address. We're gonna spend a lot of time talking about the study design and the methods for the ACHIEVE randomized trial. We'll talk about the primary results, the effect of hearing intervention on cognitive decline. We'll spend a little bit of time talking about how we might talk about these results with patients, And then at the end we'll have a summary and conclusion. So starting with the background. the Lancet Commission on Dementia Prevention, Intervention and Care first released a report in 2017, and then they updated that in 2020.

And part of the goal of that report was to understand just what modifiable risk factors might contribute to dementia and how they might change across the life course. It was really, I think, a surprise for dementia researchers in that 2017 report because many of us knew about education, we knew about cardiovascular disease, we knew about a lot

of risk factors for dementia, but I think many of us at that time were not yet thinking about hearing loss. And actually, that report identified hearing loss as potentially the single greatest contributor to dementia cases worldwide. So it estimated that about 8% of dementia cases in the world are due to hearing loss. And that means if hearing loss causes dementia, that if we treat hearing loss, then potentially we could prevent up to 8% of dementia cases.

So that really was big news at the time, and part of what motivated us to conduct this study. We do think that there are some potentially causal ways that hearing loss might lead to dementia. Certainly it may just be associated with some kind of common cause like increased inflammation, for example, maybe that's causing the hearing loss, it's also causing the dementia. So we do have to be concerned about that. But we do have some pathways by which we think hearing loss may actually cause dementia. The first is cognitive load, and this is also known as the information degradation hypothesis in the literature. And this just means that when you have that garbled signal coming in from the ear into the brain, that, that puts this constant load on those cortical resources that otherwise may have helped and buffer against the pathological contributors to dementia.

And we know the primary pathology for dementia, it's either Alzheimer's type, so those plaques and tangles, or cerebral vascular disease is very important. There also may be direct effects on the brain in terms of structural integrity, and this is called the sensory deprivation hypothesis. And there have been some studies to suggest that there is accelerated brain atrophy in people with hearing loss compared to people without, and this was particularly true when we think about the parts of the brain that we know are associated with hearing, so the superior temporal lobe, for example, where the primary auditory cortex is located. And then also when we think about social isolation and loneliness, hearing loss could potentially increase those through decreased communication.

Maybe if someone is having a hard time hearing a noise, they may stop attending the social events that they used to. And then we do know that social isolation and loneliness are really important for cardiovascular health. They're associated with cardiovascular health, stroke, myocardial infarction. They're also associated with cardiovascular mortality. And we know that anything that's good for the heart is also good for the brain. So this is another potential causal pathways. I see a question in the chat that's asking about isolating social isolation from hearing loss. And the comment is, "In our experience, most of our older patients with moderately severe or more loss tend to isolate themselves. And the one who waited too long already had significant symptoms of dementia.

" So I think this is probably going back to the Lancet Commission report. I will say that report was based on observational data. There were three studies included in that report, and there were several who did try to adjust for social isolation. So we were looking, I would say, at the independent effect, but certainly you worry that you can't tease all of that out in an observational study. I think it's a very astute question and it really is one of the reasons why we need the clinical trial, right? So that will help us better determine cause and better control for some of these factors like social isolation compared to the observational data. So an astute observation and good question.

Thank you. So then when we think about the pathways by which hearing loss may cause cognitive decline in dementia, it's these three primary pathways, increased cognitive load, changes to brain structure and function, potentially increased social isolation. I think what's really important to think about is that amplification could potentially intervene on all of these pathways. So hearing loss intervention could potentially reduce that cognitive load of the processing that degraded auditory signal. It could potentially provide increased brain stimulation. So we help protect against that atrophy that we've seen in some studies, and then potentially it could improve social

engagement. The question of whether hearing loss could reduce cognitive decline was unknown when we set about designing this study.

There was a recently published meta-analysis. So this is using observational data, looking at the potential impact of hearing aids on cognition and dementia. And I will say that the observational literature is consistent. So when people tend to ask that question, they tend to find that hearing aids seem to be protective. So individuals with hearing loss who use hearing aids tend to have protection against cognitive decline or at least delayed cognitive decline compared to people with hearing loss who don't use hearing aids. But the question really can't be definitively answered through observational studies. And part of the reason why is that we know that people who use hearing aids are just different fundamentally from people who don't use hearing aids.

And a lot of that has to do with the cost of hearing aids. It may have to do with access to care. It may have to do with socioeconomic status. So people who have hearing aids tend to have better education, higher educational attainment, more socioeconomic resources, better access to care, or least more consistent access to healthcare, and all of those things can protect against dementia. And so in the observational data, we do our best to try to make sure that we're accounting for those factors, trying to keep them constant, because we really wanna just understand the impact of hearing loss. But the truth is, in any observational study, there's bias. So we've talked a little bit about why we're worried about hearing aid use tracks with a lot of other factors that we know are protective for dementia.

We're worried we just can't disentangle the impact of hearing aid use from the impact of those other protective factors. And so there are challenges to interpreting observational studies, and this is what I do for a living. So I just want the caveat that observational studies tell us a lot of really good information. They are a valid study design. We can learn a lot, but there is bias in all studies, and we just have to start by

acknowledging that. And so we can have bias in observational studies based on the way that we're generating our data. And so this has to do with the measurement of our exposures, our outcomes, any other factors in our study. Sometimes you'll see this referred to as information bias or measurement bias or misclassification.

Certainly we worry about that. There's also a type of bias that's related to participant selection and that can be either into or out of the cohort. That's a selection bias. And then there's also potential bias, or at least you worry that you're not getting the correct measure association, so your relative risk isn't quite correct because of confounding. And if you've heard of that term, it just means that it's a third factor. It's associated with the exposure, it causes the outcome. It's not on the causal pathway between the exposure and the outcome. And if we don't account for it, what happens is the effect of our exposure for, in this case, we're interested in hearing aid use as a protective factor against dementia, that effect of hearing aid use gets kind of mixed up with the effects of these other things like we were just talking about.

Increased socioeconomic status, better educational attainment, those types of things. So we do have to worry about all those types of bias in an observational study. And so when we're interpreting our studies, they have to be within that context. Now, randomized trials have some benefit compared to observational studies, which is why they're called the gold standard. Now they're not perfect. Sometimes people in our discipline call them the bronze standard, but they do have some potential benefits and protections from bias. And the reason why is that the intervention, the exposure is randomized. And when you randomize, that means you break the link between any participant characteristics. So imagine that you are in an observational study, it's observational because you're just doing.

.. Living your everyday life and you're being followed up by some researchers to understand associations between exposures and outcomes. You are making the

decisions on what types of interventions you're doing. Are you being physically active? Are you getting all of your immunizations that you should be? Are you eating well? Are you making sure that if you are a current smoker, are you working towards smoking cessation, for example? And all of those factors are your choice. And you can imagine that people who choose to be healthy in one area may choose to be a little bit healthier in others, right? So people who are physically active tend to also eat well comparatively. Now that's not always the case, but a lot of times those factors tend to go together.

And so when you randomize, now it's no longer my choice, you are breaking that link. So now whether I get hearing aids is not related to my socioeconomic status, it's not related to my education level. So we're breaking that link. And so what that means is there's no bias in who gets which treatment, whether you get the intervention or you get the control. There's nothing else that's tracking with that. And so fundamentally, ultimately that means that the likelihood that the two treatment groups we're comparing are gonna be balanced on factors that we know relate to the outcome. So in the case of our ACHIEVE trial, people who use hearing aids and people who don't, because it was randomized, now hearing aid use, again, it's not linked to socioeconomic status, for example.

That means that any observed difference in the outcome when we compare the treatment to the control group really can be ascribed solely to the treatment. And so that really is one of the benefits of randomized trials compared to observational studies. And so that's what we set out to do using a randomized controlled design, we asked the question about treating hearing loss and whether it can reduce cognitive decline over three years in older adults who have hearing loss but don't have substantial cognitive impairment. So no one had dementia at the time of our study, but we wanted to pick an age range where they were old enough potentially to be at risk for cognitive decline over the study period.

So a little bit more details about the design of the ACHIEVE study. So we started out by recruiting two different types, two different cohorts of participants. Some were already actively involved in an ongoing observational study called the Atherosclerosis Risk in Community Study. And then some were healthy volunteers that were living in the community and they were also interested in participating in our study. Our total number of participants was 977. They were randomized one-to-one to get either a best practices hearing intervention or a successful aging health education control. We then had follow-up visits, semi-annual and annual follow-up visits. And then at the end of three years, that's when we concluded the study and measured cognition for the last time, as well as some of our other outcomes.

The ACHIEVE study really did have an unusual design in that it was nested within an ongoing observational study. And I mentioned the name of that study already, the Atherosclerosis Risk in Community Study or ARIC, A-R-I-C study. This is a study that's been ongoing since the late 80s in four communities in the United States. So we have Minneapolis, Minnesota, Jackson, Mississippi, Hagerstown, Maryland, and then also Wake Forest, so in North Carolina as well. It started out by being a cohort of nearly 16,000 participants that were randomly sampled from those communities. The goal when it first started was really thinking about what are risk factors for cardiovascular health and how might they vary by geography, sex, and race.

Over time, as the study participants aged, the study really became a study of aging, not just cardiovascular health, and really started to focus on brain health, thinking about cognitive decline and dementia. And that expansion really started in 2011 with the ARIC Neurocognitive study, or ARIC NCS study. ACHIEVE then recruited from those four field sites, So from the ARIC NCS participants, we already had hearing measured on them because we were already measuring it in ARIC. As I said, the study had become really a study of cognition, so we already had cognition on them. So we

were able to kind of pre-screen our ARIC participants and reach out to them if we thought they would be eligible to participate in the study.

Many of them had been involved in the study, in the ARIC study for over 35 years. And so they may have chosen to participate because we reached out to them with another opportunity to participate in research and that's something they felt very passionate about. That's in contrast to the de novo group, And de novo just means there are healthy volunteers that were recruited from the community. So we had things like flyers and TV advertisements and web-based advertisements to try to recruit individuals that were living in the community. We told them when we recruited them that we were doing a study on cognition. We didn't talk about it being a study on hearing. So then the cohort was recruited from, again, those two distinct populations, the ARIC and the de novo.

In the end, we ended up having 238 participants recruited from ARIC, so about a quarter, and then 739 recruited de novo from the community. Our inclusion criteria, 70 to 84 years old. So we wanted people to be at risk for cognitive decline. Also, we know that hearing loss is common in this age group. We did wanna have people be cognitively intact at baseline. So we had education stratified mini mental state exam score that we used for screening untreated hearing loss, four frequency, pure tone average greater than or equal to 30 and less than 70 dB HL. We had a word recognition IN quiet score greater than or equal to 60% in the better ear, and then community dwelling. They also had to be willing to be randomized for the study.

Exclusion criteria is if they had any activity of daily living disability, they had presenting near vision acuity that we didn't think they would be able to participate in the cognitive testing, or if they had permanent conductive hearing loss. Now, if it was something that could be treated and they were still interested in participating, we had them go get medical clearance and then would reevaluate them. But if they had permanent

conductive loss, they were ineligible. When we recruited individuals, we made sure everyone understood the randomization process. So we had written informed consent. We also let them know that we would be giving them whatever intervention that they didn't get the first time around, They would get at the end of three years.

So if you were initially randomized to the health education control, then you would get the hearing intervention at the end of the three years of follow up. So again, we had a one-to-one randomization. We did stratify by severity of hearing loss, recruitment source and field sites. So we just wanted to make sure that we had the randomization worked across all those strata. The hearing intervention was best practices. It was developed with colleagues at the University of South Florida. It was provided by a certified study audiologist, a research audiologist with us. There were four sessions. They received hearing aids. They also had education and hearing aid-related technologies, anything that really would help them meet their hearing goals.

So it was very much driven by what the goals were for the individual participant. We then had semi-annual visits thereafter and some booster sessions as well. The health education control was designed with collaboration from colleagues from the University of Pittsburgh. It was based on an established program that's called the "10 Keys to Successful Aging". And the purpose of that program is to understand key health topics, things like nutrition, physical activity, immunization, smoking cessation, those types of things that are all important in order to maintain our health as we age. We were matched in terms of the amount of time that individuals spent with someone. So there were four sessions with the audiologist if you had the hearing intervention or there were four sessions with the health educator if you got the successful aging intervention.

And then we had, again, the same touches. So visits, semi-annual visits thereafter and for three years. And also the same number of booster sessions. Our study outcome. So with any randomized trial, you pick one primary outcome and you power on that

outcome. And it's really important because everything else should be viewed as secondary. We're not powered to look at the secondary outcomes. Now we will still look and we still have it as part of our statistical analysis plan, but I just wanna emphasize that when we interpret the chief findings, we really only wanna interpret the primary outcomes with any level of certainty because that's the outcome that we powered for. So we had baseline and six-month visits for the intervention delivery and the outcome assessments.

The primary outcome was change in global cognitive function from baseline to year three. I'll talk a little bit more about the test used and how we derived the primary outcome, which was what we call a cognitive factor score. We do have some secondary cognitive outcomes, and those include cognition that were domain specific, so not global, but domain. So executive function, memory, and language. I will present those results today. We also have incident cognitive impairment and dementia and that's something that we'll be continuing to review as we continue the analysis of this data. And then we have a lot of other pre-specified outcomes, some of which may be of interest to you. So I list them here.

A lot of these analyses are still ongoing. So we'll have updated results about some of these outcomes I hope very soon. But just a reminder that these are secondary outcomes. So we were not powered to detect differences in the hearing intervention versus control for these outcomes. So the ACHIEVE neurocognitive battery was really complete. It takes an hour to complete this cognitive test battery. It's 10 different tests and they do measure a wide range of domains, memory, language, and executive function. We also did make sure that individuals were able to recognize and register speech before we had any of the cognitive tests. Many of these cognitive tests are just pen and paper, but some do require kind of auditory interaction.

And so we just had a test upfront that we made sure individuals were able to hear us and register what was being said before we moved forward with cognitive testing. I'm not presenting it today, but we did do some sensitivity analysis that looked just at tests that relied only on pen and paper. So it was not auditory in terms of the way that you engage with the test material. And we found similar results. So I just wanna make sure everyone is clear that it's not just that you had hearing aids in and so could hear the test better in terms of the results that we're showing today. So a factor score is just... It's based on an advanced statistical technique.

In this case, we did a confirmatory factor analysis that really looks at common covariation among these different cognitive tests. And so what it does is it creates an overall score that we then standardize. So all of the outcomes that'll be talking about today are presented in terms of standard deviation units. This methodology has been used quite commonly. We use it a lot in the ARICs cohort. And so it really has just meant using these latent methods, factor methods. It's just a more advanced technique to kind of summarize the data. So I'll be talking about the factor scores. It's just a summary of all the 10 different scores using this advanced technique. When we look at change over time, that is all relative to baseline.

So for example, if the change over time is 0.5, then it would be 0.5 standard deviation change from baseline to year three in whatever group we're talking about. When we first started this study and we're recruiting, it was really we were wrapping up recruitment in the summer and fall of 2020 and so... Or 2019 really for the fall and then summer, and then obviously we had the pandemic shut down. We were able to get everyone in for their screening for their first baseline visit where we had cognition measured. Everyone was able to come into the clinic so it was all done in person. We then had the pandemic shut down. Now we pivoted and started having telephone assessments so that we didn't lose individuals over time, we didn't lose that data.

But it was a different mode of administration and then we were able to be fully back in the clinic by the time that the study wrapped up. So really in terms of the study, we were, I'd say fortunate that the pandemic did not hit until after we had been able to have everyone in for their full baseline visit. The statistical analysis. So any randomized trial has to have a very clear statistical analysis plan. We have to stick to it, we can't deviate from that. This is a plan that is designed at the beginning of the study before anyone has seen data. And so we looked at the effect of hearing intervention versus the control using an advanced technique, a mixed effects model.

And then we also used standard adjustment factors or standard adjustment recommendations for randomized trials. So we should have balance on these factors, but we go ahead and adjust just to make sure there's no imbalance and what we're actually seeing is the true causal effect of the hearing intervention on the outcome. We did have multiple imputation and that's just an advanced technique. If you have missing data, if someone doesn't come back for the visit, to try to understand based on all of the other information we have on them, what their scores would've been. And that was something that we do quite commonly because if you ignore missing data, oftentimes people who leave your study are doing worse.

And so it actually makes it seem like maybe the intervention is not quite as strong because people aren't coming back who actually were at higher risk for cognitive decline. So that's just another advanced technique we used. Because of COVID and the change of modality for the way that we administered the cognitive battery during the shutdown, we did have a primary analysis that just used baseline in year three, so change from baseline to year three, and that's what I'll be presenting today. And then we also had some pre-specified sensitivity analyses looking at the results stratified by whether you were recruited from the ARIC study or de novo, and then other variations like whether you were per protocol.

So if you were assigned to the hearing intervention but didn't wear your hearing aids, we would've analyzed you as being in the control group. That's also common in randomized trials to do it both ways. But our primary was intention to treat. For secondary cognitive domains, we had the same model as for the primary outcome. And then for statistical significance, so it was two-tailed, alpha less than 0.05. And then we did do some adjustment for multiple comparisons because we're looking at a lot of other factors and we don't want a finding just due to chance. So we had advanced techniques to try to control for that as well. In terms of the recruitment, so we screened 596 participants from ARIC and 2,408 participants de novo from the community that started with the telephone screening.

Just over 1,100 met our inclusion criteria. We ended up having 977 randomized, where it was 490 were randomized to the hearing intervention and 487 to the healthy education control intervention. You can see actually on the right, this is a graph of our recruitment and enrollment, and it really is amazing that we were able to meet our recruitment goals as tightly as we were. So the dash line is what we were aiming for. The kind of wavy line underneath is what we were actually able to attain. And I think the fact that we were able to meet our recruitment goal really speaks to the fact that we nested within ARIC because we did have a lot of information on those participants.

They were already pre-screened, and so we were able to understand whether or not they might be eligible for this study. So we were really able to do some additional screening and recruitment and randomization of the participants that came from the ARIC cohort early on as we were ramping up recruitment efforts in the community. And then we started getting more people from the community. And in fact, we met our target. We originally were powered for 850 individuals in the study, but we met and surpassed our recruitment target and there was no reason to think why our power calculations would've changed. But the truth is we still had more time and we knew

that probably a trial like this would never be repeated, especially with over the counter hearing aids coming out.

So then you start to worry about equipoise, whether it's okay to withhold hearing aids from someone in terms of the ethics of the trial design. And so we were able to talk to the NIA, the National Institute on Aging, and secure additional funding for additional recruitment. And that's how we were able to get up to 977 participants by the end of October in 2019. In terms of our follow-up, so we actually had really good retention in the study as well, despite COVID. It was over 90% of all participants that were enrolled ended up staying in the study for the full three years. So we were quite happy with the retention rate as well. Okay, so for the primary results, the cognitive outcomes, so these are the three-year change in the global domain score.

This is looking at the entire cohort together. Global cognition was our primary outcome of interest. Executive function, memory, and language were secondary outcomes. So we were not powered on those, but I know they might be of interest. What I'm showing here is the change in standard deviations from baseline to year three for the control and the intervention group for each of these different domains. So for global cognition, the control group declined over three years 0.2 standard deviations. That may not seem like a lot, but it actually is. Depending on the age level for different groups, sometimes you expect to see something even like 0.04 standard deviation changes per year. And so we were actually seeing standard deviation changes for cognition that did suggest that there was decline in the study population over time.

But you can see then right underneath the intervention group, the mean change in the global cognitive factor score over three years was almost identical. It was -0.2. So their declining by 0.2 standard deviations. So these are the absolute rates of change for the two groups. And I present them just to show that generally speaking, we did see declines in all of the domains except maybe in memory for the intervention group. But

what really is most helpful is thinking about the comparison of intervention versus control. And so what I'm showing here are the differences. So I had the absolute numbers in the prior slide. Here are the differences comparing intervention to control. We can see 0.002 was the difference comparing hearing intervention to control for global cognition.

Any number subtracted from itself is zero. So zero is the null value. And you can see on the plot there's the line there showing kind of the null value. That estimate is as close to null as you will ever get. So overall, in the total combined cohort for ARIC and de novo, the hearing intervention did not make a difference on cognitive decline. The rates of change in both the hearing intervention group and the control group were the same over the three years. In executive function, we see again something that's very close to the null, that kind of dot, that estimate is almost on the null line. The confidence interval does overlap the null value. So even though it was -0.

020, that's a very small difference in the rates of change over time. And so again, we would conclude that there's no association that hearing intervention versus education control did not impact executive function change over three years. Same for memory and same for language. So even though the effect estimate for memory suggests maybe that intervention, it favors the intervention where the intervention group maybe declined at a slower rate. It's not statistically significantly different between the two groups. So I just wanna highlight again that this is the primary result of this trial, that there was no impact of the hearing intervention versus education control on cognition in any domain. But we did, and you'll recall when we talked about the methods, we did have some things that at the very beginning of the study we said we were gonna do.

We were gonna look at ARIC and de novo separately, as well as some other subgroups. And so we do find interesting results when we look at the two cohorts separately. So this is data showing the ARIC cohort. It again is highlighting the

difference. So I'm not now showing the absolute rates of change, just the difference. So you take the rate of change in the intervention group and subtract from the control group. And so here we see a difference of 0.191 for global cognition. And that does suggest that individuals who had the hearing intervention, who were recruited from ARIC versus individuals who got the control, who were recruited from ARIC, did have slower rates of change and it was slower by 0.

19 standard deviation. That's really starting to get into a small to moderate effect size estimate, and we can convert that to thinking about it being a percent change. And the way we do that is by taking the difference between the two groups, we divide it by the rate of change in the control group and then we get a percent change. And that percent change was 48%. So we could also say that in ARIC, participants who got the hearing intervention had a 48% slower rate of cognitive decline in global cognition compared to people who got the intervention group. And that was statistically significant, and I think a very, very interesting and important finding of the study. For executive function, you'll see there is the suggestion that the estimate favors the intervention, but that confidence interval is very wide.

So we can't say there's a statistically significant difference. The same from memory, although that confidence interval really does just barely cross the null value. If this were an observational study, I would be much looser in my interpretation, but here it's a trial so we have to be clear with what we said we would do. So it crosses the null value. So it's not associated, but we do see associations with language. And so individuals in ARIC who received the hearing intervention had a slower rate of change in language over time compared to individuals who had the control. And that rate of change was similar to global cognition. It was slower by about 0.23 standard deviations over the three-year time period.

So that was in the ARIC cohort. Now if we look in the de novo cohort, we see there's no effect of the hearing intervention compared to control on rates of three-year change for any of the cognitive domains, for global, executive function, memory, or language. So really we saw this protective effect in ARIC that is not being replicated in the de novo group. And so of course the question is why might we see that? Why might that be the case? So here is some just baseline characteristics looking at recruitment source. So we're comparing ARIC to de novo. Overall, broadly, our two groups, whether you got the hearing intervention or you got the control, they were balanced on all of these factors.

But when we look at the ARIC versus de novo, we do see differences. And the differences are that people from ARIC had more risk factors for cognitive decline, and these are known risk factors. So they were older. So the ARIC cohort, the mean age was 78.9 compared to 76.1 for the de novo cohort. We did have a higher proportion female, 62% versus 51%. We had a real difference in terms of black race participants. So it was about 29% from ARIC and only 6% de novo. And I'm not meaning to say that black race is a biological risk factor for dementia here, just that it's a social factor, it's a social construct that tracks with a lot of known risk factors. For example, access to care, socioeconomic status, access to healthcare or education, that type of thing.

We also see that our ARIC cohort had a higher proportion of individuals with less than a high school education, nine compared to 2% in the de novo. A higher proportion of individuals with low income, so income under 25,000, 27% compared to 12% in the de novo. A higher proportion of people living alone, 36% compared to 28%. And then also some additional risk factors, cardiovascular risk factors that we know are important for cognition, including diabetes. So there were a higher proportion of individuals with diabetes. In the ARIC cohort, that was 29% compared to 17% in the de novo cohort. Now I do wanna point out that even though the ARIC cohort had a greater proportion

of what we would consider general risk factors for dementia, their hearing level was the same.

So when you look at the pure tone average comparing ARIC to de novo, the means were the same. It was right around 39 for that four frequency pure tone average. Now what is different is the hearing handicap for the inventory... Hearing handicap inventory for the elderly screening that we did, and it was a higher score for the de novo group. So the de novo group was actually more concerned about their hearing than the ARIC cohort, even though their levels of audiometric hearing loss were the same. And so one way to kind of think about this is does it actually speak to motivation for participating in this study? We've been working with these ARIC participants for over 35 years.

They were dedicated to research. They feel like it's important, it's an important way that they give back broadly to their community and to the world. And so they were not interested in trying to protect their cognitive health or protect their hearing health. They just participated in our study because we reached out to them and asked if they would be interested in participating. That's different from the de novo group. We advertise this study as a study to try to understand ways in which to prevent or delay cognitive decline. And so you do have individuals then potentially reaching out to participate because they're concerned about their cognition. And a lot of times this is what we see in studies.

Sometimes you see it referred to as a healthy volunteer effect. Sometimes you see it kind of referred to as the worried well. So individuals who are actually doing quite well in terms of their health but do have concerns or they don't wanna see their health worsen over time, and so they're trying to be really proactive. And so I think this probably speaks to we're recruiting from two very different sources. ARIC is probably more akin to just the general US population. Now it's not completely, but it's more akin to that compared to the de novo group who's probably more motivated to join this

study because they were concerned about their health. And then another, I think really important reason why we may have seen this difference where hearing intervention made a difference for the ARIC cohort but not for the de novo, is that ARIC participants had lower cognitive scores at baseline.

And so here I'm showing the mini mental state exam comparing ARIC to de novo. Those scores are almost identical, but the mini mental state exam is not designed to look at subtle differences in cognition. It really is designed to be a screener for dementia. And so if you don't have dementia, you score pretty well on the MMSE. But then when we look at the different factor scores, global cognition, executive function, memory, and language, we see negative numbers for our ARIC cohort, positive numbers for our de novo. That means that all of our ARIC participants on average were scoring more poorly, so they're starting from a lower place in terms of their cognition. The other thing that's really important is that they started at a lower place at baseline and then they had much faster rates of change in their cognition over time.

So here I'm just showing global cognition and language and I'm restricting to those two because that's where we saw intervention effects. So if we look at the rate of change in the control group, comparing ARIC to de novo, that's the top line on the table. For ARIC, it was -0.402 in terms of the mean change from year or from baseline to year three. In terms of cognition for the de novo, it was 0.151. So you can see that it's over twice as fast in terms of rates of decline for the ARIC group compared to the de novo group. And if you're gonna be comparing rates of change between individuals who are getting an intervention and individuals who aren't, you first have to have some decline.

You have to have enough decline so that you can actually detect differences between the groups. And so that could be another possibility that here we had people performing well at baseline in terms of their cognition, and then they just weren't declining that much over the three-year time period. And so we weren't able to actually

detect a difference that the hearing intervention might have made for them. And so I think the conclusion from this is that probably three years was not enough follow-up time for them and we're gonna continue to follow them. And so maybe we'll be able to see something down the line as well. So in terms of a summary of these findings overall, and this is the primary finding if anyone asks you.

I know it's very exciting to look at the subgroup analyses and these were subgroup analyses that we said a priori we would do. But really the primary finding, the trial, what we set out to ask, what we were powered to ask was overall in the entire cohort, and overall in the entire cohort, we did not see changes. So hearing intervention did not slow cognitive decline. But we did, especially in global cognition and language, we did see change or differences where the hearing interventions slowed rates of change compared to the control and it was by 48% for global cognition, which is something that I think is meaningful to individuals. I think the question is why? Was it because there were a greater number of risk factors for cognitive decline that they had lower cognition at baseline because of these observed faster rates of cognitive decline?

These are all reasons why we think we saw the difference, but we can't say for sure those are the reasons why we saw the difference. So it's kind of post hoc speculation for why we're seeing the differences that we are. And then again just highlighting that we did not see any effect in the de novo group. Again, we think because they had less risk factors because they had slower rates of decline overall. And so we just weren't able to pick up any difference within the three-year time period. So really, I would say more work is needed to understand who might and who might not benefit. So we have some suggestions by the subgroup analysis that if you have lower cognition to start with, a greater number of risk factors, maybe hearing intervention would help you.

And I think that makes sense based on what we think about the way in which hearing might impact dementia risk or cognitive decline. So we really think it's not through the

typical dementia pathways, right? So I don't think we have any reason to think that hearing loss is going to increase the number of beta amyloid plaques in your brain for example. But if you are facing that challenge already where you do have maybe what's starting to be a significant burden of plaques and tangles in your brain, maybe you have some microvascular or small vessel disease in the brain that could be leading to some changes in cognition over time. If you are someone who's already maybe at high risk, then maybe hearing loss just is what pushes you over the edge in terms of having faster rates of decline and greater incidence of dementia.

And so it may be that hearing aids for that group could really be beneficial. But I do have to say that, again, this is speculation that's post hoc because we did not find an association in the entire study. So we do need some additional work here to disentangle what was really going on and who is really most likely to benefit. I wanted to spend just a minute because I know many of you are in the clinic and probably talking with your patients about this. How do you interpret those results for your patients? And I would say just generally speaking, taking a step back, we can think about how we interpret results from a clinical trial versus an observational study.

So we've talked already about how randomized trials, now if they're well designed, if they're well conducted, if they're adequately powered, if they've made the right decisions about the amount of time that you need to have the intervention, for example, there's a lot of caveats here, but they do have protections against bias and against confounding that observational studies just don't. And so if we find an association in a randomized trial, we actually can say that an exposure causes the outcome, right? And that's different from observational studies. In observational studies, we can talk about associations between an exposure and an outcome. But if we're actually able to show in a trial, if we lower blood pressure, for example, to a target and then we're able to show that decreases risk of whatever outcome we're studying, then we know that blood pressure is a cause of that outcome.

And so we can conclude cause from a trial where we can't from any observational design. Sometimes in the literature you'll just see people say cross-sectional studies that you can't determine causation. That's not true. Any observational study, even a really well-designed cohort study, you still can't determine causation. So we just can't determine cause from any observational study. So that is a difference to keep in mind when talking about study results with patients. But regardless of whether you're looking at a trial or you're looking at an observational study, these are studies that are conducted at the population level and the inference is also at the population level. We can never determine individual risk from studies because by nature, they're an average across the population.

So on average in ARIC, we saw that people who got the hearing intervention had slower rates of cognitive decline compared to people who didn't. But that doesn't mean that everybody had slower rates, right? That is the average difference. And so whether or not you would be someone who would have a slower rate or not is something that we just can't determine from our study. So we can't have individual risk prediction from these types of studies. I think it's also really important. We're used to thinking about risk for something as a percentage. So if it's a 50% chance, if it increases, let's say dementia or hearing loss increases dementia risk by 50%, so if I have hearing loss, then my risk for dementia is increased by 50%.

And that is the wrong interpretation because again, that's a population average. For you as an individual, you'll never have a 50% risk. Your risk will always be zero. You will not get the disease or 100% you will. And there's no in-between for an individual just at the population level. And we're used to thinking about percent chances of rain and things like that. But really what that means is if it's an 80% chance of rain, that on average, with weather conditions like we're seeing today, 80 out of 100 times it rains,

right? It doesn't mean that it will 80% chance rain that day, right? It's gonna rain or it's not. And so really that's something else important to keep in mind too.

And that is true regardless of whether you're talking about an observational study or a trial. The benefit of a trial is that we can say, look, we found a result that means that our intervention is working and the exposure we were trying to intervene on is a cause of the outcome. But it doesn't mean that everyone who gets the intervention is gonna benefit from it even if you can determine cause. And so in terms of thinking about how we actually have these conversations, 'cause these are tough conversations to have with patients and with others who are really concerned about their health, right? We know that hearing aids slowed cognitive decline for some people, but they didn't for everybody.

And if someone is worried about their cognition, hearing aids may help, but they may not. There's lots of other things that we also recommend for cognition. Things like staying socially active, staying physically active, eating well, smoking cessation, right? We do have some recommendations for things that you can do if you're worried about your cognition. Hearing aids may help some people, but they're not necessarily a cure all. They're not gonna help everybody. And just because someone gets hearing aids does not mean that they're still not gonna get dementia. They still might down the line. And so what is the art of interpreting this for patients is starting to think about, I have a patient sitting in front of me, what are their characteristics?

Are they more similar to the ARIC group where we did see benefit or are they more similar to the de novo group? And so they may not see at least a short-term benefit, right? And so those are conversations that you can have. And certainly we know that hearing aids provide benefits over and above cognition and it's always appropriate to talk about those. Increased quality of life, better communication, all of those types of things. We know that hearing aids help with that. I think we just wanna be very careful.

It's not appropriate to say hearing aids are gonna prevent cognitive decline in that person. We just don't know. But it is possible if they're worried about it, that it might help.

If they have characteristics that are similar to those ARIC participants, they might be especially helped. So just to kind of summarize the discussion in terms of the key findings, we saw no overall effect of hearing intervention versus health education control on three-year cognitive change in the entire group. We did see a strong effect of 48% reduction in three-year cognitive decline in the ARIC cohort, but not in the de novo cohort. That slow rate of cognitive change in our healthy de novo participants may just not have let us see any difference. And maybe as we continue to follow them for longer than three years, maybe then we will see a difference. And so we are continuing to follow them up.

I do also just wanna point out that we did see associations with language in the ARIC cohort in addition to global cognition. And so overall, I would say these findings really do add to our understanding of the impact of hearing treatment. It may be beneficial in some but not in others in terms of delaying cognitive decline. We just need additional work to really understand who are those individuals who are going to benefit and who's not, at least in the short term. So we're talking about short-term benefit. There certainly are limitations to any study. I think this was a very well-designed study. We had a lot of amazing collaborators, but again, we may just have had too short a follow-up time to see a difference in the overall cohort and in that de novo group specifically.

Another limitation is that we couldn't mask. So you knew whether you got the hearing aid, but what we did do was in terms of kind of any adjudication process, when we're thinking about dementia adjudication or something like that, anyone making that call was masked to whether someone had received a hearing aid or not, or the hearing intervention as part of this study. In terms of what's next, so we are going to be looking

at three-year effects on dementia down the line and longer term effects. We have a lot of other secondary outcomes that we're in the process of analyzing the data now. So we're looking at brain structure as measured on MRI, magnetic resonance imaging.

We've got health liquidated quality of life, we've got physical functioning, we have depressive symptoms, hospitalizations, we have a lot of different secondary outcomes, and so we're working on all of those papers right now. And then we do have additional funding to continue to follow these individuals up. And so we'll be able to look at longer term effects of the hearing intervention. So a big acknowledgement to the entire team. This was a huge team. The NPIs of this grant and this study are Joe Coresh here at Johns Hopkins, as well as Franklin here at Johns Hopkins. And we had just amazing team that we worked with over the course of... It really was, I mean, almost 10 years now from the start of when we started thinking about the observational work and designing the pilot study and then actually designing, conducting the study and then analyzing the study.

It really has been almost a full 10-year effort. So a huge thank you to everyone and thank you so much to you for listening as well. My information is here if you'd like to talk a little bit more, have any additional questions. And then the ACHIEVE Study website is listed here as well, AchieveStudy.org. And I know we have just a couple minutes left, so I'll pause and take any questions that you may have. Thank you.

- [Christie] Thank you so much, Dr. Deal. We'll go ahead and open up the floor. Any comments or questions for Dr. Deal, please send them through to that Q&A chat box in the lower right hand corner of your screen and we'll go ahead and just wait a few more minutes. I wanted to thank Dr. Deal for coming back on and sharing the results of this study. I know it was a lot of information, but really important and really great findings that you had there, Dr. Deal.

- [Dr. Deal] Thank you. I think they're very... I think we were hoping for a different outcome that we would see something overall, but I do think that these findings are really important. I think that they give us some additional information that we didn't have before and some new avenues to pursue in terms of the research as well. So thank you. They're encouraging. They're encouraging findings.

- [Christie] Well, we don't have any questions at the moment, but we do have a nice comment from Ann. Ann just says thank you to Dr. Deal for the presentation. We'll go ahead and close the classroom at this time. Again, thank you so much for joining us on Audiology Online. We know that you have a choice on where you earn your continuing education, and we just are honored and thankful that you've chosen us as your provider. Thank you to Dr. Deal for sharing her time and her expertise with us. And have a great day, everyone.

- [Dr. Deal] Thank you. Take care.