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RESEARCH ARTICLE

Cognitive benefits of hearing intervention vary by risk of cognitive decline: A secondary analysis of the ACHIEVE trial

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Abstract

INTRODUCTION: Results from the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) trial suggest hearing intervention may not reduce 3-year cognitive decline in all older adults with hearing loss but may be beneficial in certain groups. This secondary analysis investigated if participants with multiple risk factors for cognitive decline received greater benefits.

METHODS: We used a sample of dementia-free participants (N = 2692) from the Atherosclerosis Risk in Communities (ARIC) cohort to develop a predictive model for cognitive decline. The model was applied to baseline measures of ACHIEVE participants (N = 977) to estimate predicted risk. We tested an interaction between predicted risk and randomization to hearing intervention or health education control.

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RESULTS: Among ACHIEVE participants in the top quartile of predicted risk, 3-year cognitive decline in the hearing intervention was 61.6% (95% confidence interval [CI]: 33.7%–94.1%) slower than the control.

DISCUSSION: The effect of hearing intervention on reducing 3-year cognitive decline was greatest among individuals with multiple baseline risk factors associated with faster cognitive decline.

Trial Registration: ClinicalTrials.gov Identifier: NCT03243422

KEYWORDS
aging, cognition, cognitive decline, dementia, hearing, hearing aids, hearing loss, memory, presbycusis, randomized control trial

Highlights

- The Aging and Cognitive Health Evaluation in Elders (ACHIEVE) trial tested the effect of hearing intervention on cognitive decline.
- Participants were recruited from the Atherosclerosis Risk in Communities (ARIC) cohort or de novo from the local community.
- A 48% reduction in cognitive decline was observed in ARIC cohort participants.
- In this secondary analysis, there was an interaction between hearing intervention and predicted risk of cognitive decline.
- Among participants in the top quartile of predicted risk of cognitive decline, hearing intervention slowed cognitive decline by 62%.

1 | BACKGROUND

Current global estimates suggest that more than 55 million adults live with dementia.[1] By 2050, the number is projected to rise to more than 150 million,[1] underscoring the urgent need for interventions capable of modifying risk factors for dementia. Among the potentially modifiable risk factors, hearing loss is a promising target.[2] Meta-analyses of longitudinal observational studies have found that hearing loss is associated with greater risk of cognitive decline[3,4] and incident dementia.[4–6] In addition, meta-analyses of observational studies indicate that hearing intervention may reduce the risk of cognitive decline.[7]

The Aging and Cognitive Health Evaluation in Elders (ACHIEVE) trial[8] was the first randomized controlled trial to investigate the 3-year effects of hearing intervention on cognitive decline in older adults with untreated hearing loss and without cognitive impairment. Although a protective effect was not observed in the full sample, differences were detected across the two populations that comprised the sample. Among participants from the Atherosclerosis Risk in Communities (ARIC) cohort who enrolled in the ACHIEVE trial, the hearing intervention slowed cognitive decline by 48%. Among healthy community volunteers recruited de novo, cognitive decline was slower than the rate observed in participants recruited from the ARIC cohort and the hearing intervention had no effect.

One explanation for this difference is that the 3-year benefits of hearing intervention were evident only in individuals with multiple risk factors associated with faster cognitive decline.[8] Prior research suggests hearing loss interacts with such factors as age,[9] chronic disease,[9,10] and social isolation[11–13] to accelerate cognitive decline. Given that participants from the ARIC cohort were more likely to be older, have a chronic disease, and live alone,[8] it may be the case that the ACHIEVE trial hearing intervention reduced 3-year cognitive decline by mitigating these interactions.

To assess whether ACHIEVE trial participants with multiple risk factors for cognitive decline received the greatest benefit from hearing intervention, we conducted a two-stage analysis. In the first stage, we developed a model that predicted cognitive decline. In the second stage, we tested an interaction between the predicted risk of cognitive decline and randomized treatment assignment to hearing intervention or health education control.

2 | METHODS

2.1 | Data sources

Each stage of the analysis used a different dataset. The first stage used data from 2692 ARIC cohort participants who did not participate in the

ACHIEVE trial. The second stage used data from 977 ACHIEVE trial participants.

2.2 | First data source: ARIC cohort

ARIC is a prospective cohort study originally focused on the etiology of atherosclerotic disease in a middle-aged sample of largely Black and White participants.[14,15] Between 1987 and 1989, participants were randomly sampled from four U.S. communities (Washington County, Maryland; Forsyth County, North Carolina; selected suburbs of Minneapolis, Minnesota; and Jackson, Mississippi). A total of 15,792 participants were assessed at baseline. The baseline assessment was followed by Visit 2 (1990–1992, N = 14,348), Visit 3 (1993–1995, N = 12,887), Visit 4 (1996–1998, N = 11,656), Visit 5 (2011–2013, N = 6538), Visit 6 (2016–2017, N = 4214), Visit 7 (2018–2019, N = 3589), Visit 8 (2020, N = 3226), and Visit 9 (2021–2022, N = 2105). In addition to clinic-based assessments performed at each visit, ARIC cohort participants or their proxies completed annual (through 2011) and semi-annual (starting in 2012) phone-based assessments, and granted access to hospitalization records and death certificates. The study protocol was approved by the institutional review boards at Johns Hopkins University, Wake Forest University, University of Mississippi Medical Center, the University of Minnesota, and the University of North Carolina at Chapel Hill. Written informed consent was obtained from each participant or their legal representative at each visit.

ARIC cohort participants who completed Visit 6 were included in the dataset used to develop a predictive model for cognitive decline (Figure 1). Completion of this visit was an inclusion criterion because Visit 6 was the first time a comprehensive audiological assessment was performed. Participants were excluded from the dataset if they enrolled in the ACHIEVE trial (N = 232), did not complete a neurocognitive examination (N = 63), or were classified with mild cognitive impairment or dementia at or before Visit 6 (N = 1016).

2.3 | Second data source: ACHIEVE trial

ACHIEVE is a parallel-group, unmasked, randomized controlled trial[8,16] that investigated the effects of a best-practice hearing intervention versus a health education control on 3-year cognitive change among older adults with hearing loss and without cognitive impairment (ClinicalTrials.gov identifier: NCT03243422). The trial was partially nested within the ARIC cohort and conducted at the four ARIC field sites. Participants were recruited from the ARIC cohort or newly recruited (de novo) from the local community. Recruitment methodologies,[17] screening procedures,[16,17] selection criteria,[8,16] 1:1 randomization,[8] and baseline characteristics[17,18] have been reported. Briefly, 3004 participants were screened for eligibility and 977 participants underwent randomization (Figure 2). Participants enrolled in the ACHIEVE trial were 70- to 84 years of age, had age-related bilateral hearing loss (HL; better-ear 4-frequency [0.5–4 kHz] pure tone average ≥30 dB hearing level (dB HL) and <70 dB HL), did not use hearing aids, and had no substantial cognitive impairment at enrollment (Mini-Mental State Examination [MMSE][19] score ≥23 for participants with a high school degree or less; ≥25 for participants with some college education or more). Written informed consent was obtained from each individual using a protocol approved by the institutional review boards at each field site and academic center.

Participants randomly assigned to the hearing intervention[16,20,21] completed four, 1 h sessions with an audiologist over 2–3 months following randomization. Participants received bilateral hearing aids fitted to prescriptive targets using real-ear measures and other hearing-assistive technologies to pair with the hearing aids, such as devices that stream from smartphones and televisions. An orientation on device use and instructions for self-management and communication strategies were provided. Reinstruction was given during booster sessions held every 6 months post-randomization.

The health education control was modeled on 10 Keys to Healthy Aging,[22] an evidence-based health education program for older adults. Similar to the hearing intervention, participants completed four, 1 h sessions over 2–3 months post-randomization followed by booster sessions every 6 months. Each session included a didactic education component and a 5–10 min upper body stretching program.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed published articles on the association of hearing loss and hearing intervention with cognitive decline and incident dementia.
2. **Interpretation**: A secondary analysis of the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) randomized controlled trial found that participants with multiple risk factors for cognitive decline at baseline had greater predicted risk of cognitive decline and received the greatest benefit from hearing intervention in reducing cognitive decline. Among participants in the top quartile of predicted risk of cognitive decline, the 3-year rate of cognitive change in the hearing intervention was 61.6% (95% confidence interval [CI]: 33.7%–94.1%) slower than the health education control.
3. **Future directions**: Treating hearing loss may reduce 3-year cognitive change in older adults without cognitive impairment but with multiple risk factors for cognitive decline. Future investigations should examine long-term effects in older adults without cognitive impairment and short-term effects in older adults with multiple risk factors including mild cognitive impairment.

FIGURE 1 Flowchart for ARIC cohort participants, 2016–2022. ACHIEVE, Aging and Cognitive Health Evaluation in Elders; ARIC, Atherosclerosis Risk in Communities.

2.4 | Measures shared by the ARIC cohort and ACHIEVE trial

Multiple measures were administered during ARIC Visit 6 (2016–2017) and the baseline of the ACHIEVE trial (2018–2019). Only shared measures were included in the predictive model for cognitive decline.

2.4.1 | Demographic

Date of birth, sex, race (Black, non-Black), education (less than high school, high school or equivalent, or greater than high school), and annual income (<$5000, $5000 to $7999, $8000 to $11,999, $12,000 to $15,999, $16,000 to $24,999, $25,000 to $34,999, $35,000 to $49,999, $50,000 to $74,999, $75,000 to $99,999, or ≥$100,000) were self-reported. Date of birth was used to calculate age at ARIC Visit 6 or the baseline of the ACHIEVE trial. The field site each participant was recruited by was documented.

2.4.2 | Genetic

The Human Genetics Center at the University of Texas, Houston analyzed DNA extracted from blood samples[23] provided by participants. The TaqMan assay (Applied Biosystems, Foster City, CA) detected apolipoprotein E (*APOE*) variants at codons 130 and 176 and determined the presence of 0, 1, or 2 ε4 alleles.

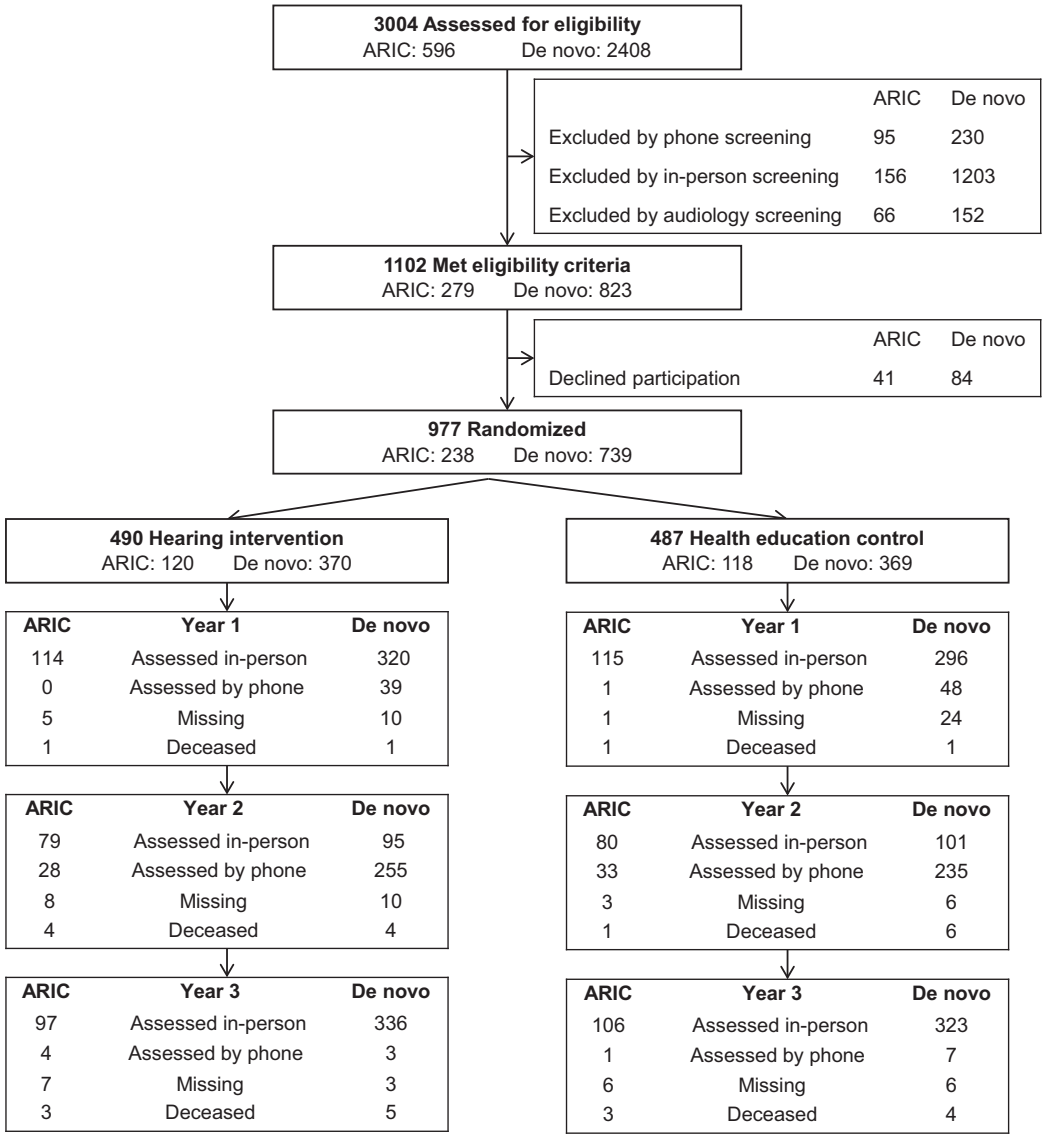

FIGURE 2 Flowchart for ACHIEVE trial participants, 2018–2022. ACHIEVE, Aging and Cognitive Health Evaluation in Elders; ARIC, Atherosclerosis Risk in Communities.

2.4.3 | Hearing

Objective hearing was quantified through audiometry performed in sound attenuating rooms. Pure tone air and bone-conduction thresholds were assessed in each ear using a modified Hughson–Westlake[24] psychophysical bracketing method.[25] Pure tone average was defined as the mean in the better-hearing ear across the frequencies 0.5, 1, 2, and 4 kHz. Communicative function was measured by the 10-item screening version of the Hearing Handicap Inventory for the Elderly.[26,27] Loud noise exposure was quantified based on self-reported lifetime exposure to firearms, job-related loud noise for more than 10 h per week, or very loud noise for more than 10 h per week outside of a job.[28] Speech in noise ability was measured by the Quick Speech in Noise (QuickSIN) test.[29]

2.4.4 | Anthropometric

Body weight was measured to the nearest 0.1 kg, and height was measured to the nearest centimeter. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Waist circumference was measured to the nearest centimeter using the smallest circumference between the lower ribs and iliac crests and hip circumference was measured using the greatest circumference between the

iliac crest and thighs. The ratio of the waist-to-hip circumference was computed.

2.4.5 | Cardiovascular

Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using the Omron HEM-907 XL oscillometric automated sphygmomanometer (Omron Healthcare, Kyoto, Japan). Resting heart rate was calculated from a 2 min supine 12-lead electrocardiogram recording using standardized methods.[30]

2.4.6 | Medical conditions

Hypertension was defined as SBP ≥140 mmHg, DBP ≥90 mmHg, use of anti-hypertensive medication, or self-reported physician diagnosis. Diabetes was defined as fasting glucose ≥126 mg/dL, non-fasting glucose ≥200 mg/dL, use of glucose-lowering medication, or self-reported physician diagnosis. Stroke, coronary heart disease, and myocardial infarction were determined by self-reported physician diagnosis in the ACHIEVE trial. In the ARIC cohort, self-reported information was supplemented by data abstracted from medical records.[15,31,32] In both studies, the Neuropsychiatric Inventory[33,34] was used to document self-reported physician diagnosis of Parkinson's disease, traumatic brain injury, and seizures.

2.4.7 | Mental Health

Depressive symptomology was measured using the 11-item Center for Epidemiologic Studies Depression Scale[35,36] validated for older adults.[37]

2.4.8 | Lifestyle

Current, former, or never use of cigarettes or alcohol was ascertained by self-report. Leisure-time and sport-related physical activity were measured by the Baecke questionnaire.[38]

2.4.9 | Physical Function

Lower extremity function was quantified from repeated chair stands, balance tests (side-by-side, semi-tandem, tandem), and a 4-meter walk.[39] A value was assigned using population-based norms and summed into a composite Short Physical Performance Battery (SPPB) score.[40]

2.4.10 | Functional Status

Functional limitations[41,42] were measured by five items that determined whether the participant had difficulty walking a quarter mile, walking up 10 steps, bending their body (stooping, crouching, or kneeling), lifting or carrying, or standing up. Participants also self-reported whether they needed a walking aid, a special eating utensil, or devices to help dress themselves. Difficulty with instrumental activities of daily living[43] was measured by three items that ascertained whether the participant was able to do chores, prepare meals, or manage money on their own. A fourth item asked if the participant needed help with chores. Activities of daily living[44] were assessed by four items that asked about the participant's ability to walk between rooms, get out of bed, eat, and dress themselves. Participants also self-reported whether they needed help with personal care.

2.4.11 | Cognition

Cognition was assessed by the MMSE[19] and a 10-test cognitive battery (**eMethods: Cognitive Battery**). The battery included the Digit Span Backwards,[45] Boston Naming Test,[46] Word Fluency Test,[47] Animal Naming Score,[47] Digit Symbol Substitution,[45] Trail Making Tests A and B,[48] Incidental Learning,[49] Logical Memory Test,[45] and the Delayed Word Recall.[50] Scores from the 10-test cognitive battery were used to compute a factor score of global cognition.[51] The factor score was standardized to either ARIC Visit 6 or the baseline of the ACHIEVE trial. A factor score was chosen over other summary measures, such as weighted averages, since it mitigates measurement error,[52] improves precision,[53] has interval-level properties,[54] and has minimal floor or ceiling effects.[55] Select tests were used to compute separate factor scores[51] for predefined cognitive domains[51,56] of executive function (Digit Symbol Substitution, Trail Making Tests A and B), language (Boston Naming Test, Word Fluency Test, and Animal Naming Score), and memory (Incidental Learning, Logical Memory Test, Delayed Word Recall).

2.5 | Mitigating bias from informative attrition in the ARIC cohort and ACHIEVE trial

Because estimates of cognitive decline can be biased by informative attrition,[57] multiple imputation by chained equations (MICE)[58] was performed in Stata (version 18.0). The ARIC cohort imputation model included all shared measures from Visit 6 plus time-varying measures of cigarette use, BMI, SBP, DBP, hypertension, diabetes, stroke, coronary heart disease, myocardial infarction, MMSE, the six-item screener,[59] self-reported health,[60] the use of a proxy during in-person or phone-based assessments, the number of hospitalizations since the last in-person assessment, and incident dementia defined by adjudicated review, telephone interviews, informant interviews, hospitalization records, and death certificates.[61,62] The ACHIEVE trial imputation model was identical to the prespecified version[8] described in the statistical analysis plan (https://clinicaltrials.gov/study/NCT03243422) except that the model was expanded to include two-way and three-way interactions between predicted risk of cognitive decline, randomized treatment assignment, and time. One hundred imputed datasets

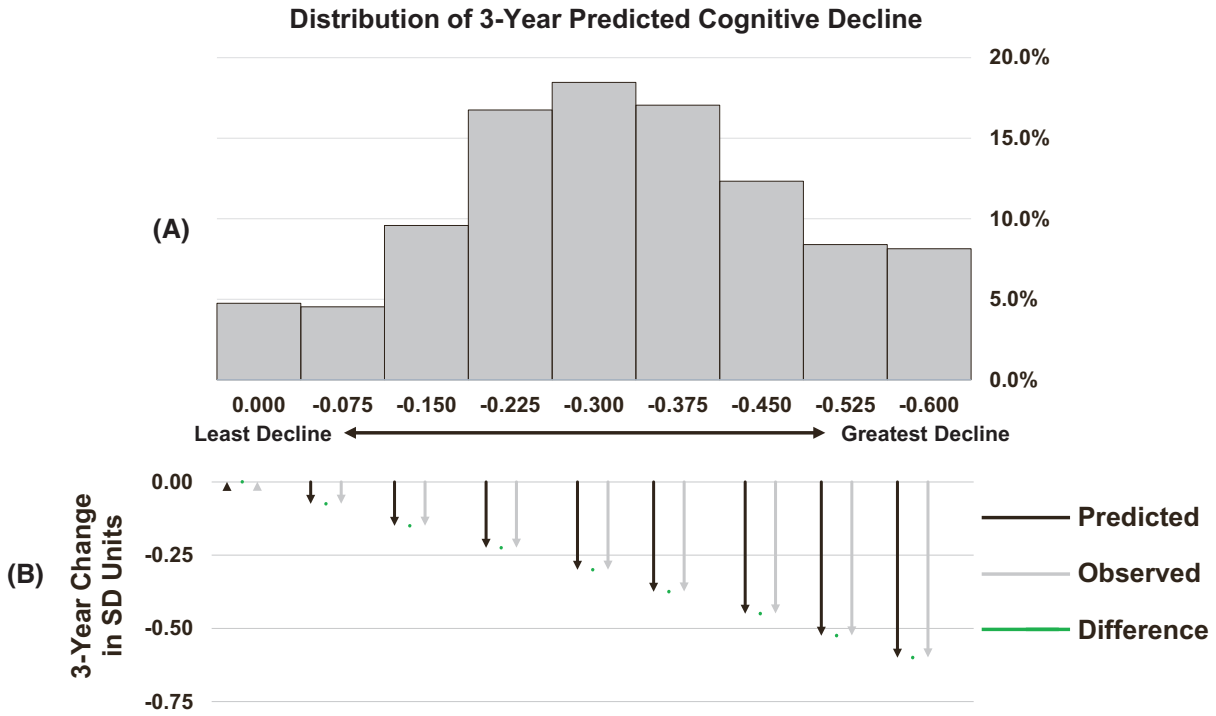

FIGURE 3 Distribution of 3-year predicted risk score for cognitive decline in ARIC cohort participants with a comparison between predicted and observed cognitive decline ($N = 2692$). ARIC, Atherosclerosis Risk in Communities; SD, standard deviation. (A) Depicts the distribution of the predicted risk score for cognitive decline in the ARIC cohort. (B) Depicts the difference between predicted cognitive decline and observed cognitive decline in each increment displayed in A. The minimal differences suggest that there was no systematic bias in the predictive model.

were generated for the ARIC cohort and ACHIEVE trial even though a quadratic formula[63] indicated that sufficient precision would be attained with only 18 imputations. Only pre-death factor scores were imputed.

2.6 | Developing a predictive model for cognitive decline in the ARIC cohort

All shared measures administered during ARIC Visit 6 were incorporated into a linear mixed-effects model in SAS (version 9.4) that estimated cognitive change from Visit 6 (2016–2017) to Visit 9 (2021–2022). An interaction was specified between each shared measure and time from Visit 6. The model included a random intercept to allow for subject-specific variation in cognition at Visit 6 and a random time slope to allow for variation in the rate of cognitive change. An unstructured variance–covariance matrix was employed to optimize model fit. Restricted maximum likelihood was used to reduce bias in the variance components of the matrix.

The linear mixed-effects model explained 81.9% of the variance in cognitive change over time. The model was used to generate a predicted risk score for each ARIC cohort participant. Predicted risk scores had a modest right skew (Figure 3A). The difference between predicted and observed cognitive change in the ARIC cohort was minimal (Figure 3B), suggesting that there was no systematic bias in the predictive model.

In a sensitivity analysis, least absolute shrinkage and selection operator (LASSO) was used to identify the minimum number of shared measures required to explain at least 80% of the variance in cognitive change. The resulting parsimonious predictive model of cognitive change included age, race, the presence of one or more *APOE* ε4 alleles, pure tone average, sport-related physical activity, SPPB, depressive symptomology, functional limitations, activities of daily living, MMSE, each measure from the 10-test cognitive battery, and an interaction between each variable and time. The parsimonious model explained 80.9% of the variance in cognitive change. The distribution of predicted risk scores was normal (Figure S1A). However, differences observed among participants with the least predicted cognitive decline (Figure S1B) suggest that the parsimonious model overestimated the rate of decline among participants with fewer risk factors. Both the full model and parsimonious model were applied to baseline measures from the ACHIEVE trial to generate predicted risk scores for each ACHIEVE participant.

2.7 | Testing an interaction between predicted risk of cognitive decline and randomized treatment assignment in the ACHIEVE trial

Descriptive statistics compared the ARIC cohort ($N = 2692$) and ACHIEVE trial ($N = 977$). Utilizing χ^2 tests, *t*-tests, and Cochran–Armitage trend tests, *p* values were calculated. The ARIC cohort

sample was stratified by the top quartile of predicted risk to identify measures associated with cognitive decline. The ACHIEVE trial sample was stratified by randomization and each quartile of predicted risk to evaluate whether measures were balanced between the hearing intervention and health education control within strata of predicted risk.

Predicted risk scores were added to intention-to-treat analyses previously performed for the ACHIEVE trial.[8] The effect of random treatment assignment on 3-year cognitive change was estimated by fitting a three-level mixed-effects model. The model had an unstructured variance–covariance matrix and used restricted maximum likelihood with a Kenward–Roger correction to generate parameter estimates, 95% confidence intervals (CIs), and *p* values. A random intercept and time slope was specified at Level 2 for participants, and a random intercept was specified at Level 3 for spouses or partners randomized as a unit. The unadjusted model included predicted risk of cognitive decline, randomized treatment assignment, and time from baseline plus two-way and three-way interactions between each variable. The covariate-adjusted model added baseline measures of hearing loss (pure tone average <40 dB vs 40 + dB), recruitment source (ARIC cohort vs de novo), field site, age, sex, education, and the presence of one or more *APOE* ε4 alleles, and it specified an interaction between time and each covariate except education. Separate models were fit for global cognition, executive function, memory, and language.

The initial intention-to-treat model used restricted cubic splines to visualize the three-way interaction between predicted risk of cognitive decline, randomized treatment assignment, and time. Knots were placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the predicted risk score. A nonlinear interaction was observed in the top quartile of predicted risk of cognitive decline. Based on this visualization, the predicted risk score was dichotomized into a binary variable in which the top quartile denoted an increased risk of cognitive decline and the bottom three quartiles indicated a decreased risk of cognitive decline. An interaction between the dichotomized predicted risk and randomized treatment assignment was tested to determine if participants with multiple risk factors for cognitive decline received the greatest benefit from hearing intervention. Statistical significance for the interaction was defined as $p < .05$.

A series of sensitivity analyses was performed to assess the robustness of the results. The first sensitivity analysis replicated the intention-to-treat analysis but examined complete case data rather than imputed data. The second sensitivity analysis dichotomized the predicted risk score at the top quintile. The third sensitivity analysis generated per protocol and complier average causal effect (CACE) estimates of 3-year change in global cognition. The CACE analysis was performed by using a logistic regression model to estimate the propensity of treatment adherence.[64,65] The propensity model included baseline measures of hearing loss, recruitment source, field site, age, sex, education, the presence of one or more *APOE* ε4 alleles, cigarette use, alcohol use, global cognition, executive function, memory, language, and predicted risk of cognitive decline. An interaction was specified between each baseline measure and the predicted risk of cognitive decline. The estimated propensity of treatment adherence was used to create time-invariant unstabilized inverse probability weights that were integrated into mixed-effects models.

The fourth sensitivity analysis repeated the intention-to-treat, per protocol, and CACE analyses of global cognition but used the predicted risk score from the parsimonious model of cognitive decline. The fifth sensitivity analysis replicated this process but used the risk score from a predictive model that included only baseline cognitive measures, which explained 80.9% of the variance in cognitive change, or a predictive model that explained 54.0% of the variance by using all measures except those related to hearing and cognition. The sixth sensitivity analysis examined whether a single measure could be used as a proxy for the predicted risk score. Each measure shared by the ARIC cohort and ACHIEVE trial was dichotomized and tested for a three-way interaction with randomized treatment assignment and time. Parkinson's disease and seizures were not examined due to small sample sizes.

3 | RESULTS

3.1 | Characteristics of ARIC cohort and ACHIEVE trial participants

Among the 2692 participants in the ARIC cohort used to develop a predictive model for cognitive decline, the median (interquartile interval [IQI]) follow-up time was 4.7 years (4.2, 5.1). Among the 977 participants in the ACHIEVE trial, the median (IQI) follow-up time was 3.1 years (3.0, 3.2). Compared to ARIC cohort participants (Table 1), ACHIEVE trial participants were younger (76.8 vs 79.7 years, $p < .0001$), less likely to be female (53.5% vs 60.3%, $p = .0003$), less likely to be Black (11.5% vs 24.1%, $p < .0001$), and less likely to die within 3 years (3.5% vs 7.4%, $p < .0001$). Mean 3-year change in global cognition was similar when comparing ACHIEVE trial participants in the health education control to ARIC cohort participants (−0.230 vs −0.239, $p = .69$) but slower when comparing ACHIEVE trial participants in the hearing intervention to ARIC cohort participants (−0.179 vs −0.239, $p = .009$).

ARIC cohort participants in the top quartile of predicted risk of cognitive decline were more likely to be older, Black, have fewer years of formal education, have a lower annual income, have one or more *APOE* ε4 alleles, have worse measures of hearing, have one or more medical conditions, have low physical function, have functional limitations, have difficulty with activities of daily living, have greater depressive symptomology, and have lower scores on tests of cognitive function (Table S1). Among ACHIEVE trial participants, there were almost no statistically significant measurement imbalances between the hearing intervention and health education control within quartiles of predicted risk of cognitive decline (Table S2).

TABLE 1 Characteristics of the ARIC cohort (*N* = 2692) and the ACHIEVE trial (*N* = 977) participants.

	N	ARIC Cohort (*N* = 2692)	*N*	ACHIEVE Trial (*N* = 977)	*p*
Age, mean (SD), y	2692	79.7 (4.7)	977	76.8 (4.0)	< .0001
Female sex, no. (%)	2692	1622 (60.3)	977	523 (53.5)	.0003
Black race, no. (%)	2692	650 (24.1)	977	112 (11.5)	< .0001
White race, no. (%)	2692	2034 (75.6)	977	858 (87.8)	< .0001
Field site, no. (%)					
Forsyth County, North Carolina	2692	632 (23.5)	977	236 (24.2)	.48
Jackson, Mississippi		582 (21.6)		243 (24.9)	
Minneapolis suburbs, Minnesota		802 (29.8)		236 (24.2)	
Washington County, Maryland		676 (25.1)		262 (26.8)	
Education, no. (%)					
Less than high school	2686	310 (11.5)	976	37 (3.8)	< .0001
High school, GED, or vocational school		1130 (42.1)		418 (42.8)	
Some college, graduate, or professional school		1246 (46.4)		521 (53.4)	
Annual income, no. (%)					
Under $5000	2455	38 (1.5)	952	6 (0.6)	< .0001
$5000 to $7999		36 (1.5)		4 (0.4)	
$8000 to $11,999		101 (4.1)		18 (1.9)	
$12,000 to $15,999		151 (6.2)		36 (3.8)	
$16,000 to $24,999		282 (11.5)		84 (8.8)	
$25,000 to $34,999		331 (13.5)		117 (12.3)	
$35,000 to $49,999		421 (17.1)		167 (17.5)	
$50,000 to $74,999		530 (21.6)		210 (22.1)	
$75,000 to $99,999		261 (10.6)		140 (14.7)	
$100,000 and over		304 (12.4)		170 (17.9)	
One or more *APOE* ε4 alleles, no. (%)	2608	683 (26.2)	908	224 (24.7)	.37
Pure tone average, mean (SD), dB	2558	32.5 (14.2)	977	39.4 (6.9)	< .0001
Hearing handicap inventory score, mean (SD)	2647	3.7 (4.3)	970	15.3 (9.8)	< .0001
Noise exposure, no. (%)					
Use of firearm	2614	1098 (42.0)	975	477 (48.9)	.0002
Work related	2608	636 (24.4)	976	260 (26.6)	.17
Non–work related	2609	192 (7.4)	976	107 (11.0)	.0005
Quick Speech-in-Noise, mean (SD)	2436	20.0 (5.9)	972	18.4 (5.2)	< .0001
Diabetes, no. (%)	2692	821 (30.5)	977	195 (20.0)	< .0001
Body mass index, mean (SD), kg/m^2	2659	28.5 (5.5)	972	29.0 (5.5)	.045
Waist-to-hip ratio, mean (SD)	2591	0.9 (0.1)	967	0.9 (0.1)	.0006
Hypertension, no. (%)	2692	2303 (85.5)	974	651 (66.8)	< .0001
Systolic blood pressure, mean (SD), mmHg	2680	135 (18.9)	968	131 (17.3)	< .0001
Diastolic blood pressure, mean (SD), mmHg	2680	67.2 (10.4)	851	65.0 (10.1)	< .0001
Heart rate, mean (SD), bpm	2681	63.1 (10.2)	968	66.3 (10.5)	< .0001
Stroke, no. (%)	2692	89 (3.3)	973	79 (8.1)	< .0001
Coronary heart disease, no. (%)	2610	359 (13.8)	972	148 (15.2)	.26
Myocardial infarction, no. (%)	2692	175 (6.5)	974	73 (7.5)	.29

(Continues)

TABLE 1 (Continued)

	N	ARIC Cohort (N = 2692)	N	ACHIEVE Trial (N = 977)	p
Cigarette use, no. (%)					
Current	2692	183 (6.8)	977	25 (2.6)	< .0001
Former		1368 (50.8)		443 (45.3)	
Never		1141 (42.4)		509 (52.1)	
Alcohol use, no. (%)					
Current	2638	1370 (51.9)	977	560 (57.3)	.023
Former		751 (28.5)		238 (24.4)	
Never		517 (19.6)		179 (18.3)	
Sport-related physical activity, mean (SD)	2456	2.6 (0.8)	971	2.6 (0.8)	.78
Leisure time physical activity, mean (SD)	2454	2.2 (0.6)	973	2.2 (0.6)	.32
Short physical performance summary score, mean (SD)	2360	9.2 (2.6)	954	9.9 (2.1)	< .0001
	N	ARIC Cohort (N = 2692)	N	ACHIEVE Trial (N = 977)	p
Functional limitations, no. (%)					
Difficult to walk a quarter mile	2416	815 (33.7)	966	255 (26.4)	< .0001
Difficult to walk up 10 steps	2402	587 (24.4)	968	162 (16.7)	< .0001
Difficulty with stooping, crouching, or kneeling	2410	1492 (61.9)	967	570 (58.9)	.11
Difficulty with lifting or carrying	2416	546 (22.6)	971	160 (16.5)	.0001
Difficulty standing up	2428	692 (28.5)	976	184 (18.9)	< .0001
Need walking aids	2434	335 (13.8)	975	91 (9.3)	.0004
Need special eating utensils	2435	7 (0.3)	975	4 (0.4)	.57
Need aids or devices when dressing	2434	148 (6.1)	975	39 (4.0)	.016
Difficulty with instrumental activities of daily living, no. (%)					
Doing chores	2389	523 (21.9)	963	163 (16.9)	.0013
Preparing meals	2379	164 (6.9)	959	33 (3.4)	.0001
Managing money	2374	79 (3.3)	960	43 (4.5)	.11
Need help with chores	2434	181 (7.4)	975	50 (5.1)	.015
Difficulty with activities of daily living, no. (%)					
Walking between rooms	2469	106 (4.3)	977	35 (3.6)	.34
Getting out of bed	2432	268 (11.0)	975	55 (5.6)	< .0001
Eating	2435	80 (3.3)	977	25 (2.6)	.27
Dressing	2432	257 (10.6)	976	63 (6.5)	.0002
Need help with personal care	2435	45 (1.8)	975	10 (1.0)	.085
Depressive symptomology, mean (SD)	2566	2.6 (2.7)	977	2.5 (2.5)	.36
Parkinson's disease, no. (%)	2660	16 (0.6)	908	6 (0.7)	.84
Traumatic brain injury, no. (%)	2626	366 (13.9)	894	154 (17.2)	.017
Seizures, no. (%)	2651	60 (2.3)	903	22 (2.4)	.76
Mini-Mental State Examination score, mean (SD)	2692	28.3 (2.0)	977	28.2 (1.6)	.52
Digit Span Backwards, mean (SD)	2537	5.6 (2.0)	973	6.1 (2.0)	< .0001
Boston Naming Test, mean (SD)	2536	25.9 (4.3)	973	27.0 (3.4)	< .0001
Word Fluency Test, letter F, mean (SD)	2666	11.8 (4.3)	976	12.0 (4.4)	.34
Word Fluency Test, letter A, mean (SD)	2667	10.1 (4.4)	976	10.6 (4.1)	.0004
Word Fluency Test, letter S, mean (SD)	2667	12.3 (4.7)	976	12.8 (4.5)	.004
Animal Naming Score, mean (SD)	2679	16.6 (4.6)	972	17.6 (5.0)	< .0001
Digit Symbol Substitution, mean (SD)	2613	39.0 (11.4)	977	41.6 (10.2)	< .0001

(Continues)

TABLE 1 (Continued)

	N	ARIC Cohort (*N* = 2692)	*N*	ACHIEVE Trial (*N* = 977)	*p*
Trail Making test A, mean (SD)	2621	47.5 (25.5)	972	40.0 (16.8)	< .0001
Trail Making test B, mean (SD)	2574	130 (61.0)	964	116 (57.2)	< .0001
Incidental Learning Test, symbols, mean (SD)	2610	6.3 (1.5)	976	6.6 (1.4)	< .0001
Incidental Learning Test, digit-symbol pairs, mean (SD)	2610	3.4 (2.2)	973	3.7 (2.3)	.0084
Logical Memory Test, story A, immediate recall, mean (SD)	2523	11.7 (3.8)	971	12.4 (3.9)	< .0001
Logical Memory Test, story B, immediate recall, mean (SD)	2522	11.6 (3.8)	971	12.4 (3.8)	< .0001
Logical Memory Test, story A, delayed recall, mean (SD)	2523	9.4 (4.1)	971	10.4 (4.2)	< .0001
Logical Memory Test, story B, delayed recall, mean (SD)	2522	9.8 (4.2)	971	10.7 (4.2)	< .0001
Delayed Word Recall, mean (SD)	2662	5.6 (1.5)	976	5.8 (1.6)	.0028
Global Cognition, mean (SD)					
Baseline	2692	0.204 (0.753)	977	0.000 (0.926)	< .0001
Three-year change[a]	2407	−0.239 (0.433)	916	−0.205 (0.574)	.066
Executive function, mean (SD)					
Baseline	2629	0.080 (0.826)	977	−0.001 (0.888)	.011
Three-year Change[a]	2216	−0.158 (0.499)	914	−0.281 (0.666)	< .0001
Language, mean (SD)					
Baseline	2691	0.145 (0.800)	977	0.000 (0.837)	< .0001
Three-year change[a]	2272	−0.166 (0.613)	916	−0.142 (0.601)	.30
Memory, mean (SD)					
Baseline	2688	0.205 (0.667)	977	0.000 (0.909)	< .0001
Three-year Change[a]	2274	−0.129 (0.719)	916	−0.021 (0.745)	.0002

Note: Univariate differences in study variables assessed using χ^2 tests, *t* tests, and Cochran–Armitage trend tests.
Abbreviations: ACHIEVE, Aging and Cognitive Health Evaluation in Elders; *APOE*, apolipoprotein E; ARIC, Atherosclerosis Risk in Communities; bpm, beats per minute; dB, decibels; GED, general educational development credential; kg, kilogram; m, meter; m/s, meters per second; mmHg, millimeter of mercury; SD, standard deviation; y, year.
[a]In the ARIC cohort, 3-year change across multiple cognitive assessments was calculated from subject-specific linear regression models that included time from baseline as a covariate. In the ACHIEVE trial, 3-year change across two cognitive assessments was calculated as the difference between the baseline and follow-up assessment divided by the time between assessments.

3.2 | Interaction between predicted risk of cognitive decline and randomized treatment assignment in the ACHIEVE trial

The predictive model generated using a sample of ARIC cohort participants overestimated cognitive decline among ACHIEVE trial participants (Figure 4A, B). The discrepancy between predicted and observed cognitive decline was greatest among ACHIEVE trial participants randomized to the intervention that had the greatest predicted risk of cognitive decline (Figure 4B). Visualizing the nonlinear interaction between predicted risk, time, and treatment assignment revealed that the hearing intervention had the greatest effect among participants in the top quartile of predicted risk (Figure 4C). This finding was empirically supported by intention-to-treat models of 3-year change in global cognition (Table 2). In these models, the two-way interaction between the top quartile of predicted risk and time was statistically significant, indicating a more rapid cognitive decline in individuals with higher predicted risk. The two-way interaction between treatment assignment and time was not statistically significant, suggesting that the hearing intervention did not reduce cognitive decline in participants who were at minimal risk of cognitive decline. The three-way interaction between the top quartile of predicted risk, time, and treatment assignment was statistically significant, signifying that individuals with the highest predicted risk of cognitive decline received the greatest benefit from the hearing intervention. More precisely, covariate-adjusted estimates indicated that the three-way interaction between predicted risk, time, and treatment assignment was equivalent to a 61.6% (95% CI: 33.7%–94.1%) reduction in cognitive decline. A similar pattern of effects was observed in each cognitive domain, although the three-way interaction was statistically significant for language ($p = .04$), but not executive function ($p = .27$) or memory ($p = .14$).

The pattern of effects observed in models fit to imputed data was replicated in sensitivity analyses that examined complete case data (Table S3), although estimates were attenuated. Analyses that exam-

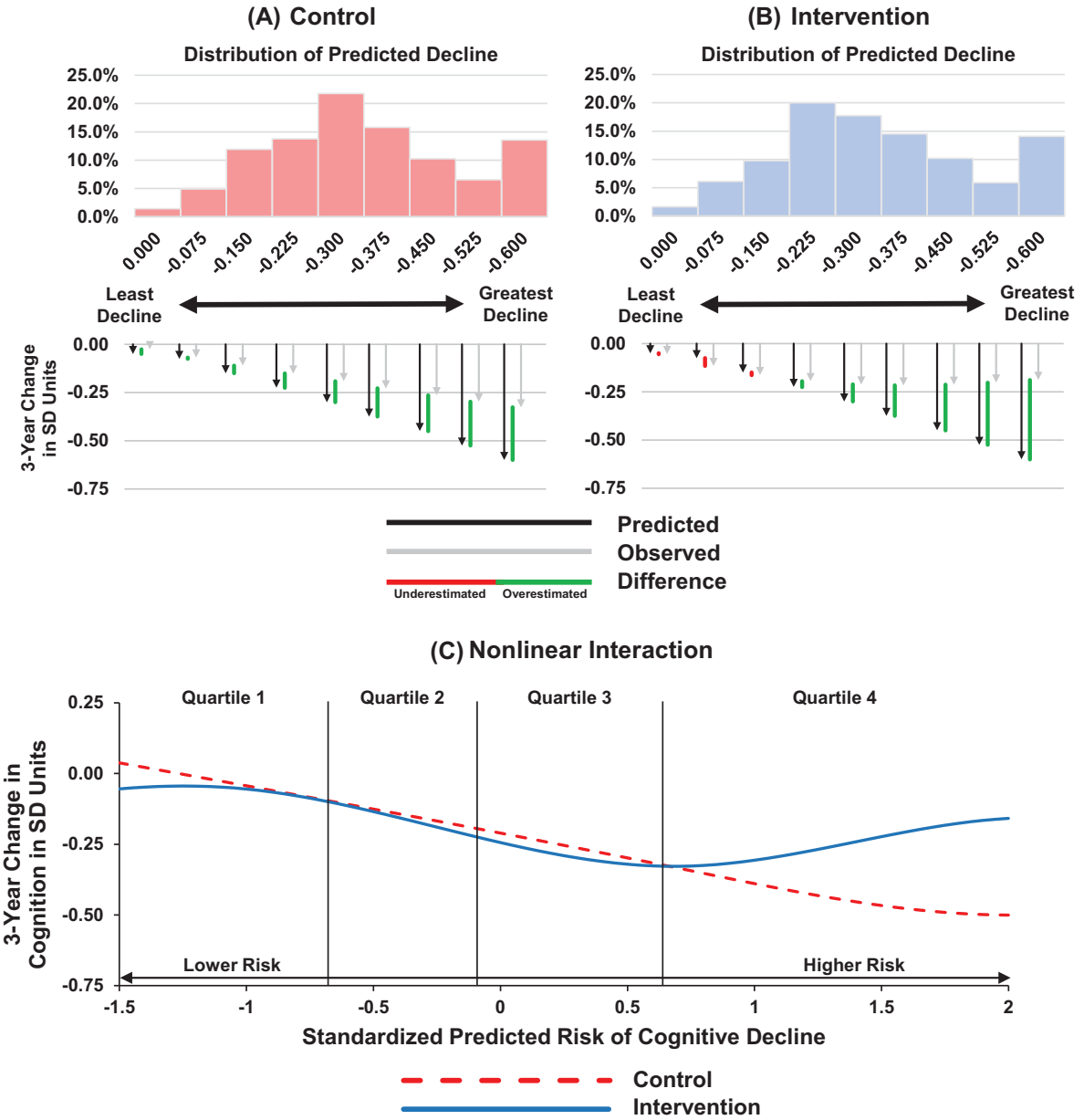

FIGURE 4 Three-year change in global cognition by predicted risk score for cognitive decline in ACHIEVE trial participants with comparison between predicted and observed cognitive decline by randomized treatment assignment ($N = 977$). (A) Depicts the distribution of the predicted risk score for cognitive decline among ACHIEVE trial participants randomized to the control and the difference between predicted and observed cognitive decline. The differences observed in A suggest that the predictive model based on the ARIC cohort overestimates the rate of cognitive decline among ACHIEVE trial participants. (B) Depicts the same information as A but among ACHIEVE trial participants randomized to the intervention. The differences between A and B suggest that the discrepancy between the predicted and observed cognitive decline is greater among ACHIEVE trial participants randomized to the intervention who have a predicted risk score ≤-0.450. (C) Visualizes the 3-year change in global cognition across different values of the predicted risk score for cognitive decline. A nonlinear interaction between randomized treatment assignment and predicted risk of cognitive decline is observed in the top quartile. ACHIEVE, Aging and Cognitive Health Evaluation in Elders; SD, standard deviation.

ined the top quintile of predicted risk produced comparable results (Table S4) as did per protocol and CACE analyses (Table S5). Analyses that utilized predicted risk scores from the parsimonious predictive model replicated the prior findings (Figure S2), except that the three-way interaction between predicted risk, time, and treatment assignment was only statistically significant in the top quintile of risk (Table S6).

In analyses that used the predicted risk score derived only from cognitive measures (Table S7), the three-way interaction was not statistically significant. Likewise, when the predicted risk score was gen-

TABLE 2 Intention-to-treat analysis of 3-year cognitive change among ACHIEVE trial participants estimated from models with interactions between predicted risk score for cognitive decline and randomized treatment assignment, 2018–2022 ($N = 977$).

	Unadjusted		Covariate-Adjusted	
	3-Year Change in SD Units		3-Year Change in SD Units	
	β (95% CI)	*p*	*β* (95% CI)	*p*
Global Cognition				
Intervention × time	−0.038 (−0.132, 0.057)	.43	−0.047 (−0.141, 0.047)	.32
Top quartile of predicted risk × time	−0.307 (−0.443, −0.172)	< .0001	−0.265 (−0.408, −0.122)	< .0001
Top quartile of predicted risk × intervention × time	0.202 (0.012, 0.392)	.03	0.208 (0.020, 0.397)	.03
Executive Function				
Intervention × time	−0.037 (−0.144, 0.071)	.50	−0.043 (−0.150, 0.065)	.44
Top quartile of predicted risk × time	−0.216 (−0.369, −0.062)	< .0001	−0.169 (−0.332, −0.007)	.04
Top quartile of predicted risk × intervention× time	0.123 (−0.098, 0.344)	.27	0.125 (−0.095, 0.345)	.27
Language				
Intervention × time	−0.028 (−0.126, 0.069)	.57	−0.031 (−0.128, 0.067)	.54
Top quartile of predicted risk × time	−0.123 (−0.265, 0.019)	.08	−0.085 (−0.236, 0.065)	.27
Top quartile of predicted risk × intervention × time	0.211 (0.009, 0.412)	.04	0.204 (0.003, 0.404)	.04
Memory				
Intervention ×time	0.044 (−0.077, 0.166)	.47	0.033 (−0.087, 0.153)	.59
Top quartile of predicted risk × time	−0.311 (−0.485, −0.138)	< .0001	−0.305 (−0.487, −0.123)	< .0001
Top quartile of predicted risk × intervention × time	0.166 (−0.085, 0.417)	0.19	0.185 (−0.063, 0.433)	.14

Note: Linear mixed-effects models fit to imputed data estimated the intention-to-treat effect of a hearing intervention on 3-year change in cognition moderated by the predicted risk for cognitive decline. The unadjusted model included randomized treatment assignment, the predicted risk score, time from baseline, a two-way interaction between the predicted risk score and randomized treatment assignment, a two-way interaction between the predicted risk score and time, a two-way interaction between randomized treatment assignment and time, and a three-way interaction between time, the predicted risk score, and randomized treatment assignment. The covariate-adjusted model added baseline measures of hearing loss (pure tone average <40 dB vs 40+ dB), recruitment source, field site, age, sex, education, and the presence of *APOE* ε4 alleles. An interaction with time was specified for each covariate except education.

Abbreviations: ACHIEVE, Aging and Cognitive Health Evaluation in Elders; *APOE*, apolipoprotein E; CI, confidence interval; SD, standard deviation.

erated from a model that excluded measures of hearing and cognition (Table S8), the three-way interaction was not statistically significant in most models. In models that examined whether a single measure could be used as a proxy for predicted risk of cognitive decline (Tables S9–S40), none of the three-way interactions were statistically significant for global cognition. Collectively, this suggests that the three-way interaction observed in the primary analysis (Table 2) was not caused by a single risk factor for cognitive decline but rather collective risk from multiple factors, with baseline cognitive performance playing a major role in the prediction of risk.

4 | DISCUSSION

In this first-in-kind study investigating whether older adults without cognitive impairment but with multiple risk factors for cognitive decline received the greatest benefit from hearing intervention in a randomized controlled trial, we found that among participants in the top quartile of predicted risk the 3-year rate of cognitive decline in the hearing intervention was 62% slower than the health education control. This protective effect is larger than the 48% reduction previously reported among ARIC cohort participants enrolled in the ACHIEVE trial[8] and was not limited to participants recruited from the ARIC cohort. These findings clarify the characteristics of older adults with hearing loss who are most likely to experience 3-year cognitive benefits from hearing intervention. Additional observation time is needed to determine if there are cognitive benefits among participants with fewer risk factors and a slower rate of cognitive decline.

Measures retained in the parsimonious predictive model for cognitive decline (Section 2.6) included age, depressive symptomology, physical function, functional limitations, and difficulties with activities of daily living. Prior research suggests that cognitive decline may be accelerated by the interaction between hearing loss and age,[9] depressive symptomology,[66] physical function,[67,68] and greater difficulty engaging in leisure activities.[69] In the context of the current findings, it is plausible that the 3-year effects previously reported for the ACHIEVE trial hearing intervention[8] may operate by mitigating these interactions.

A surprising finding from the current investigation is that among ACHIEVE trial participants in the top quartile of predicted risk of cognitive decline, the distribution of individuals recruited from the

ARIC cohort (25.8%) and de novo (74.2%) was similar to the distribution in the full cohort. If the risk factors in the predictive model for cognitive decline were the only factors that interacted with the hearing intervention, then the previously reported 48% reduction among ARIC cohort participants in the ACHIEVE trial[8] would likely not have been observed. One explanation is that hearing loss among ARIC cohort participants in the health education control of the ACHIEVE trial interacted with additional risk factors known to accelerate cognitive decline such as loneliness[12] and social isolation.[11,12,13] Although measures of social networks and loneliness were administered at the ACHIEVE trial baseline, they were not administered during ARIC Visit 6 and, therefore, could not be included in the predictive model for cognitive decline. This limitation should be explored in future studies.

Another surprising finding is that the three-way interaction between predicted risk of cognitive decline, time, and randomized treatment assignment was only statistically significant for the cognitive domain of language. A plausible explanation for this difference is that during the administration of the 10-test cognitive battery, cognitive load was reduced by the hearing aid worn by participants in the hearing intervention. This reduction in cognitive load may have led to improved performance on tests with an auditory component, such as the Animal Naming Score and Word Fluency Test. Another possibility is that a healthy volunteer effect among de novo participants[8] may have diminished the overall amount of cognitive decline in the sample. This reduction would have decreased the power needed to detect a statistically significant interaction across all three cognitive domains and explain why the pattern of effects is consistent across domains. Longer term follow-up of ACHIEVE trial participants is presently underway and may provide the power needed to detect a protective effect of hearing intervention on memory and executive function.

An important limitation is that selection bias may have had unanticipated effects on the current findings. Compared to national estimates of older adults with hearing loss in the United States,[70] participants in the ARIC cohort had more years of formal education and higher annual income. This discrepancy intensified in the de novo sample, which had participants who were more educated and had a higher annual income than participants in the ARIC cohort. These differences hinder generalizability and may have caused the protective effect of the hearing intervention to be underestimated or overestimated, since education and income alter the risk of incident cognitive impairment and access to and utilization of hearing aids, which affected eligibility for the ACHIVE trial.[71] Future studies that examine the effect heterogeneity of hearing interventions in additional randomized controlled trials[72] and observational studies[73] are needed to evaluate the reproducibility of the findings.

Results from this secondary analysis of the ACHIEVE trial[8] provide additional evidence that hearing intervention may reduce cognitive decline[7] and risk for dementia.[2] Such evidence should be considered alongside recent estimates from the ARIC cohort[74] suggesting treating hearing loss in late life may result in a 32% reduction of dementia cases. Given the magnitude of this reduction and the fact that hearing interventions confer little or no medical risk,[8] supporting policy measures that address age-related hearing loss[75] such as expanding Medicare to include hearing care,[76] may be a safe and efficacious way of reducing the global burden of dementia.

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CONFLICT OF INTEREST STATEMENT

Lin reports research grants from the U.S. National Institutes of Health and Eleanor Schwartz Charitable Foundation; consulting fees from Frequency Therapeutics and Apple; payment for expert testimony and participation on a scientific advisory board for Fondation Pour L'Audition and Sharper Sense; being a volunteer board member for Access Hearing Health Equity through Accessible Research & Solutions (HEARS); donation in-kind from Sonova/Phonak to Johns Hopkins University for hearing technologies used in the present study; and being the director of a public health research center funded in part by a philanthropic donation from Cochlear to the Johns Hopkins Bloomberg School of Public Health. Hayden reports consulting fees from Fred Hutchinson Cancer Research Center; travel support from the National Institute for Health Center for Scientific Review and Hebrew Senior Life; and participation on the Wake Forest School of Medicine DSMB (unpaid) and the TEMPO trial DSMB (paid). Huang reports paid presentations for MoCA Cognition "MocA Talk" and Together Senior Health Boost Your Brain Health study. Reed reports being Editor of the *American Journal of Audiology* (paid) and Scientific Chair of the American Academy of Audiology, Advisory Board Member with stock options for Neosensory, and being a member of the Scientific Advisory Board

for Shoebox. Sanchez reports consulting fees and industry-sponsored clinical research contract (to institution) to support research activity from Otonomy, Frequency Therapeutics, Pipeline Therapeutics, Aerin Medical, Oticon Medical, and Helen of Troy; consulting fees from Autifony Therapeutics and Boehringer Ingelheim; honoraria from Oticon Medical, Sonova Holding, and Phonak USA; and hearing technology devices donated for educational or research purposes from Sonova Holding and Phonak USA. Pike, Arnold, Chisolm, Couper, Deal, Glynn, Goman, Mitchell, Mosley, Pankow, Sullivan, Tan, and Coresh report no conflicts of interest. Author disclosures are available in the Supporting Information.

CONSENT STATEMENT

All ARIC cohort and ACHIEVE trial participants provided written informed consent prior to participation.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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