Hearing Intervention, Cognition, & Brain Health: Results from the Aging & Cognitive Health Evaluation in Elders (ACHIEVE) Randomized Trial*

Frank Lin, MD PhD
Johns Hopkins University
For the ACHIEVE Collaborative Research Group

* Published in Lancet, July 18, 2023

ACHIEVE study www.AchieveStudy.org

Funded by National Institute on Aging: R01AG055426, R01AG060502

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ACHIEVE Collaborative Research Group

THE UNIVERSITY of NORTH CAROLINA at CHAPEL HILL
Data coordinating center

JOHNS HOPKINS BLOOMBERG SCHOOL of PUBLIC HEALTH
Study governance unit & Washington County field site

UMMC The MIND Center
Jackson field site

WAKE FOREST UNIVERSITY
Forsyth County field site

SCHOOL OF PUBLIC HEALTH UNIVERSITY OF MINNESOTA
Minneapolis field site

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USF UNIVERSITY OF SOUTH FLORIDA
Hearing intervention design

UNIVERSITY OF PITTSBURGH
Health education control intervention design

MAYO CLINIC
MRI reading center

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ACHIEVE Trial Presentation

Outline

- Background on hearing loss & dementia
- Study design, methods, & ACHIEVE cohort characteristics
- Evidence for hearing intervention target engagement
- Effects of hearing intervention on global cognitive decline
- Effects of hearing intervention on brain MRI structure
- Summary & conclusion

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BACKGROUND

What we studied & why

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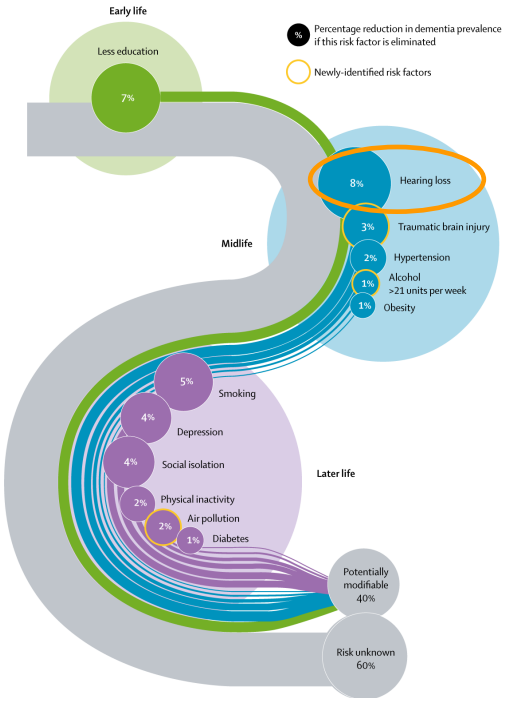
2020 Lancet Commission on Dementia Prevention, Intervention & Care

Potentially Modifiable Risk Factors for Dementia



Hearing loss in mid & late life identified as the single largest potentially modifiable risk factor for dementia

G. Livingston et al., Lancet 2020

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Hearing Loss, Cognitive Decline & Dementia

Hypothesized Mechanistic Pathways

- Cognitive load ("information degradation hypothesis")
  - Hearing loss imposes a constant load on cortical resources that otherwise could have buffered against other pathological contributors to dementia (AD, vascular disease)
- Direct effects on brain structural integrity ("sensory deprivation hypothesis")
  - Hearing loss contributes to accelerated brain atrophy & other pathologic brain changes (white matter tracts, altered functional connectivity)
- Social isolation/loneliness
  - Multiple factors could be involved—less physical activity & cognitively-stimulating activities, stress/inflammation, adherence to medical care, etc.

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F. Lin & M. Albert, Aging & Mental Health, 2014

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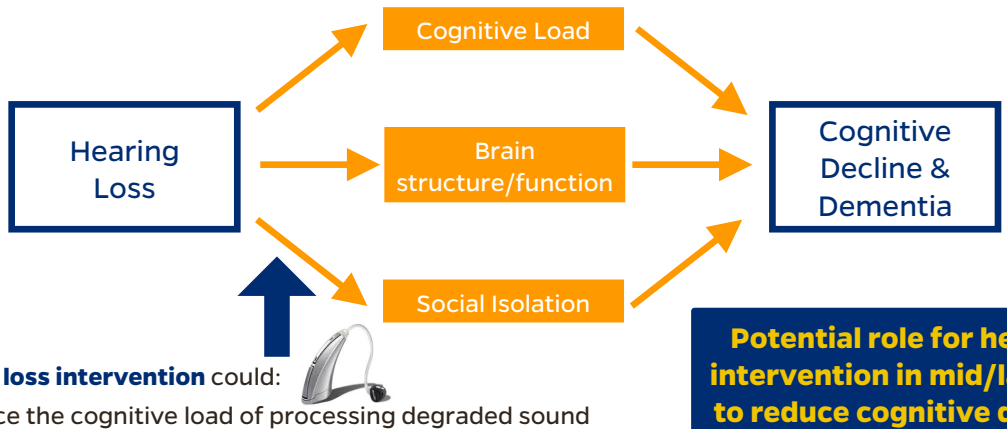
Hearing Loss & Dementia

Hearing Loss as a Modifiable Risk Factor



Hearing loss intervention could:

- Reduce the cognitive load of processing degraded sound
- Provide increased brain stimulation
- Improve social engagement

Potential role for hearing intervention in mid/late life to reduce cognitive decline & dementia

F. Lin & M. Albert, Aging & Mental Health, 2014

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The question of whether treating hearing loss could reduce cognitive decline remained unknown

- Question cannot be definitively answered through observational studies because of bias from residual confounding (e.g., health behaviors, income, etc.)
- Recent meta-analysis of observational studies (Yeo et al, JAMA Neurology, Feb 2023): Hearing aid use associated with 19% decreased hazard of long-term cognitive decline
- No prior randomized controlled trial has ever investigated effect of hearing intervention on long-term cognitive decline or other functional outcomes (e.g., social isolation, loneliness, etc.)

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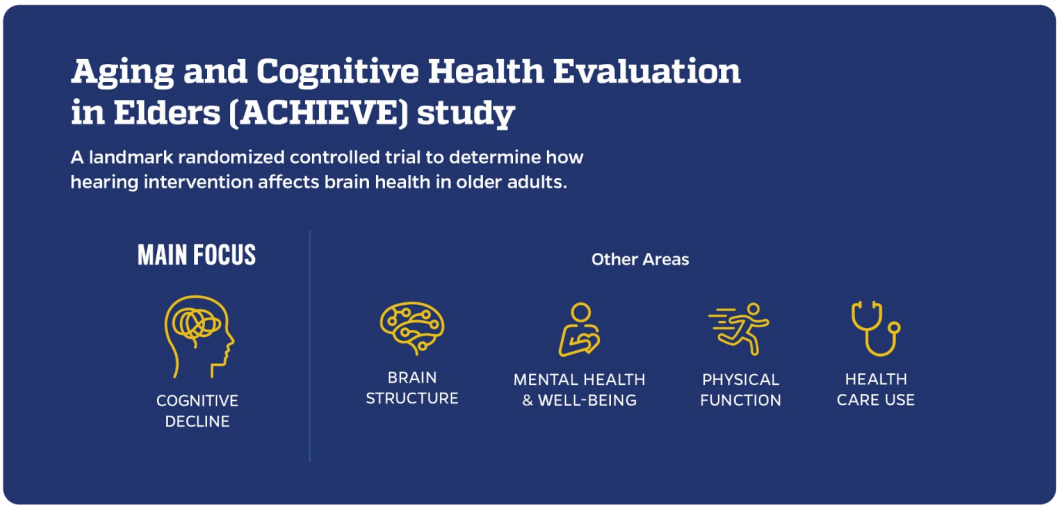
Can treating hearing loss reduce cognitive decline over 3 years in older adults with hearing loss without substantial cognitive impairment?



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STUDY DESIGN

Study design, methods, & ACHIEVE cohort characteristics

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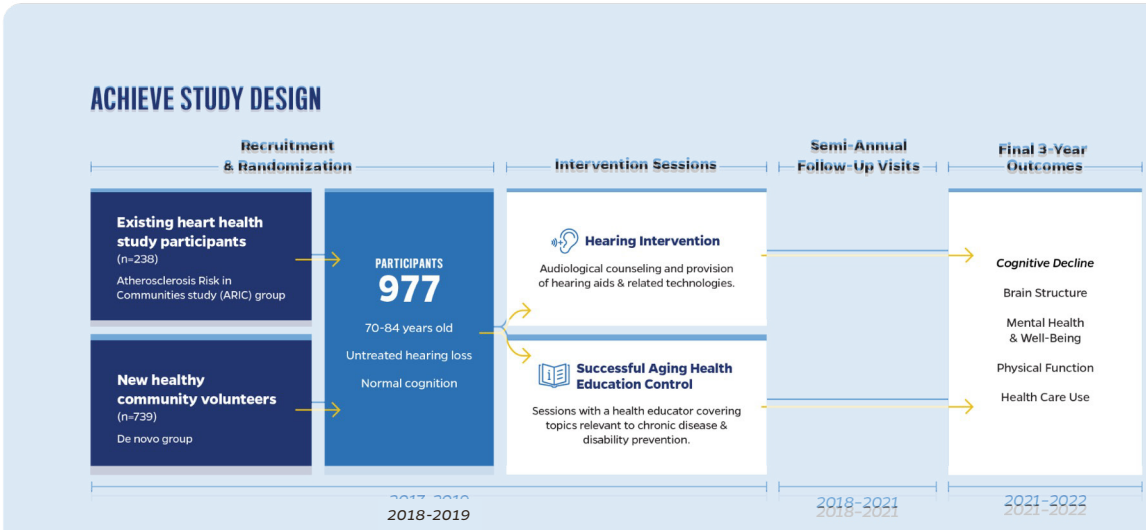

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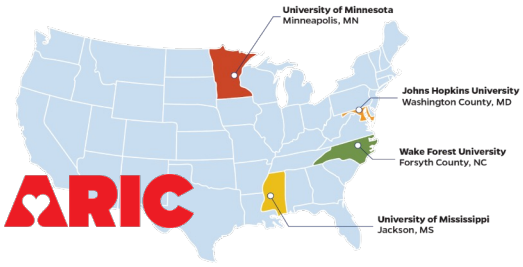
The ACHIEVE study was based within the scientific & physical infrastructure of the Atherosclerosis Risk in Communities (ARIC) study*



- ARIC study – Ongoing longitudinal observational study of 15,792 adults followed for over 30 years at 4 dedicated field sites across the U.S.
- ARIC participants - Random sample of the communities at the 4 sites who were ages 45-64 when recruited in 1987-89
- Original goal of the ARIC study was to understand how mid-life risk factors are associated with later life cardiovascular disease & brain health

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***ARIC funded through multiple NHLBI contracts & grants along with additional support from NINDS, NIA, and NIDCD**

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The ACHIEVE study cohort (n = 977) was recruited from two distinct study populations at each site

- **ARIC Cohort** (n = 238)
  - ARIC participants were a randomly recruited sample of the field site communities followed since 1987
- **De novo cohort** (n = 739)
  - New healthy volunteers responded to advertisements about a clinical trial focused on interventions for healthy aging
- All participants informed they would be randomized to one intervention & offered the other intervention after Year 3

Main Inclusion Criteria:
- 70-84 years-old
- MMSE ≥ 23 for high school degree or less; ≥ 25 for some college or more
- Untreated hearing loss with 0.5-4 kHz pure tone average ≥30 and <70 dB in the better-hearing ear
- Word recognition in quiet ≥ 60% correct in the better-hearing ear
- Community-dwelling

Main Exclusion Criteria:
- Self-reported disability in 2+ ADL
- Presenting near visual acuity worse than 20/63 (14-point font)
- Permanent conductive hearing loss

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Design: Randomization & Interventions

- Eligible participants randomized 1:1 to hearing intervention versus health education control, stratified by severity of hearing loss, recruitment source (ARIC vs de novo) & field site

Hearing Intervention	Health Education Control
• Best-practices hearing intervention provision with a certified study audiologist • 4 sessions to receive hearing loss education and hearing aids & related technologies (streamers, remote mic, etc.) • Semiannual visits thereafter for 3 years to receive booster sessions	• Established program (10 Keys) to promote understanding of key health topics (nutrition, etc.) important for healthy aging • 4 sessions with a certified health educator to cover healthy aging topics • Semiannual visits thereafter for 3 years to receive booster sessions

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Design: Study Outcomes

- Baseline & every 6 month in-person visits for intervention delivery & outcome assessments for 3 years
- **Primary endpoint:** Change from baseline to Year 3 in a global cognition standardized factor score derived from a comprehensive neurocognitive battery administered annually
- Secondary cognitive outcomes:
  - Domain-specific cognitive function (memory, executive function & language)
  - Incident cognitive impairment
- Other pre-specified outcomes
  - Hearing Handicap Inventory for the Elderly* (HHI; measure of self-reported communication impairment); Cohen Social Network Index*, UCLA Loneliness Scale*; Brain MRI; depression; physical functioning/activity & accelerometry; falls; hospitalizations; health care costs

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ACHIEVE Neurocognitive Battery

Verification of speech understanding conducted before cognitive test administration

1. ***Digit Span Backwards (DSB)**
2. **Boston Naming Test (BNT)**
3. **Word Fluency Test (WFT)**
4. **Animal Naming Score (ANS)**
5. **Digit Symbol Substitution (DSS)**
6. **Trail Making Test A (TMTA)**
7. **Trail Making Test B (TMTB)**
8. **Incidental Learning (ILR)**
9. ***Logical Memory Test (LMT)**
10. **Delayed Word Recall (DWR)**

* Indicates tests with only auditory stimuli

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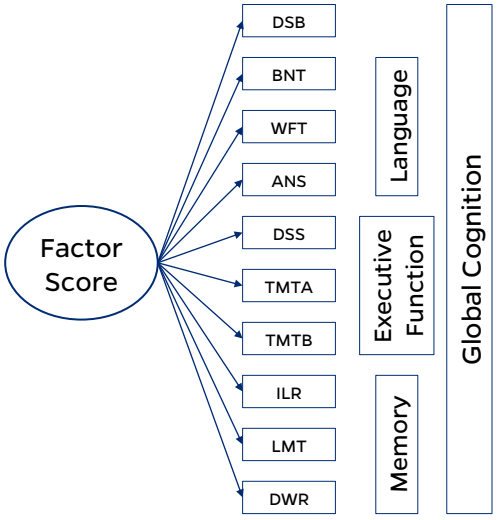
ACHIEVE Cognitive Factor Scores



All 10 tests are used to compute a factor score of global cognition (Primary outcome)

3 tests are used to compute factor scores for each cognitive domain (Secondary outcomes)

Latent factors are standardized to the ACHIEVE baseline.

Change over time is in standard deviation units relative to baseline.

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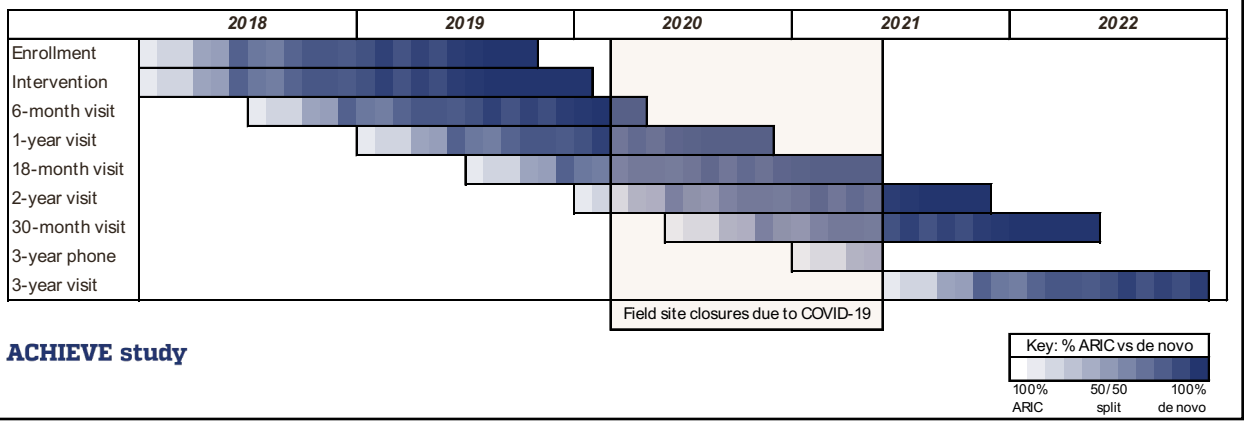
Impact of COVID-related field site closures – Baseline & 3-year outcomes were unaffected

- Study procedures were adapted for phone-based intervention delivery & outcome assessments from March 2020 to June 2021
- Initial provision of study interventions and baseline & Year 3 in-person neurocognitive assessments were unaffected



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Statistical Analysis – Cognitive outcomes

- Estimated effect of assignment to hearing intervention versus control on change in global cognition from baseline to Year 3 (primary outcome)
  - Mixed effects models adjusted for baseline hearing (PTA <40 vs 40+ dB), recruitment source, field site, age, sex, education, presence of APOE ε4 allele(s), & covariate x time interactions
- Multiple imputation by chained equations used to estimate missing Year 3 cognitive factor scores & covariates using a prespecified model
- Main analysis used only baseline and Year 3 in-person neurocognitive scores. Year 1 or 2 in-person scores only used when a participant died prior to Year 3.
- Pre-specified sensitivity analyses:
  - **Replication of primary analyses stratified by study population (ARIC, De novo)**
  - Other variations of the analytic model parameters (e.g., per protocol, CACE)

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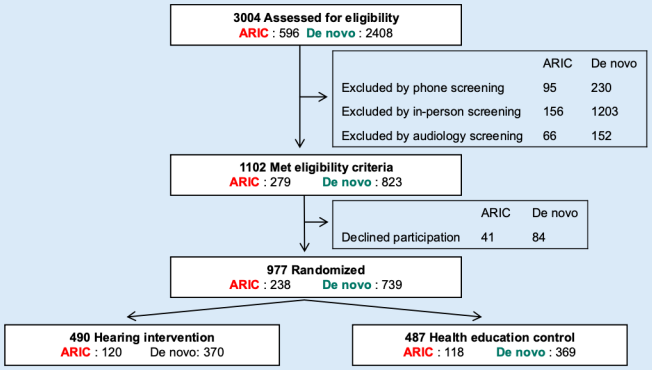
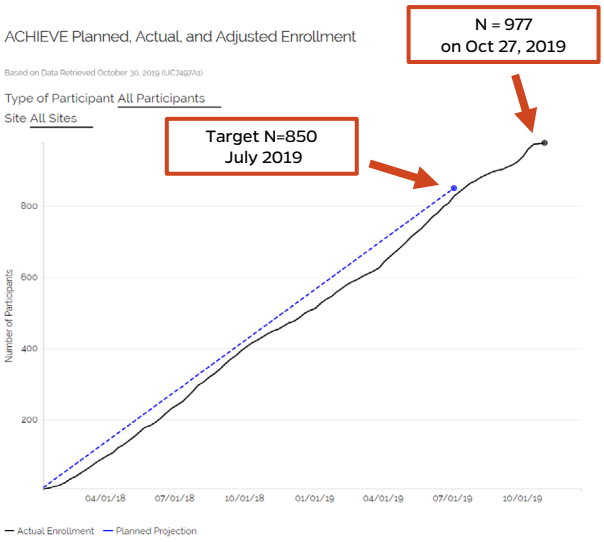
ACHIEVE Study Cohort

Recruitment





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Follow-Up Visits

Complete Year 3 follow-up data available on **90%** (877/977) of participants.

490 Hearing intervention
ARIC: 120 De novo: 370

ARIC	Year 1	De novo
114	Assessed in-person	320
0	Assessed by phone	39
5	Incomplete assessment	5
0	Lost to follow-up	4
0	Withdrew	1
1	Deceased	1

ARIC	Year 2	De novo
79	Assessed in-person	95
28	Assessed by phone	255
4	Incomplete assessment	7
2	Lost to follow-up	3
2	Withdrew	0
4	Deceased	4

ARIC	Year 3	De novo
97	Assessed in-person	336
4	Assessed by phone	3
5	Incomplete assessment	3
0	Lost to follow-up	9
2	Withdrew	1
3	Deceased	5

487 Health education control
ARIC: 118 De novo: 369

ARIC	Year 1	De novo
115	Assessed in-person	296
1	Assessed by phone	48
1	Incomplete assessment	4
0	Lost to follow-up	3
0	Withdrew	17
1	Deceased	1

ARIC	Year 2	De novo
80	Assessed in-person	101
33	Assessed by phone	235
3	Incomplete assessment	4
0	Lost to follow-up	1
0	Withdrew	1
1	Deceased	6

ARIC	Year 3	De novo
106	Assessed in-person	323
1	Assessed by phone	7
3	Incomplete assessment	5
2	Lost to follow-up	0
1	Withdrew	1
3	Deceased	4

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Baseline Characteristics by Recruitment Source

De novo cohort has fewer risk factors for cognitive decline than **ARIC**

Baseline characteristics	All Participants (N=977)	ARIC Cohort (N=238)	De novo Cohort (N=739)
*Age, mean (SD), y	76.8 (4.0)	78.9 (2.9)	76.1 (4.0)
*Female sex, No. (%)	523 (53.5)	147 (61.8)	376 (50.9)
*Black race, No. (%)	112 (11.5)	68 (28.6)	44 (6.0)
*Education, No. (%)			
Less than high school	37 (3.8)	22 (9.3)	15 (2.0)
High school, GED, or vocational school	418 (42.8)	96 (40.5)	322 (43.6)
College, graduate, or professional school	521 (53.4)	119 (50.2)	402 (54.4)
*Income, No. (%)			
Under $25,000	147 (15.5)	60 (26.7)	87 (12.0)
$25,000-$49,999	283 (29.8)	77 (34.2)	206 (28.4)
$50,000-$74,999	210 (22.1)	47 (20.9)	163 (22.5)
$75,000-$100,000	140 (14.7)	21 (9.3)	119 (16.4)
Over $100,000	170 (17.9)	20 (8.9)	150 (20.7)

*indicates statistically significant difference between groups

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Baseline Characteristics by Recruitment Source (cont'd)

De novo cohort has fewer risk factors for cognitive decline than **ARIC**

Baseline characteristics	All Participants (N=977)	ARIC Cohort (N=238)	De novo Cohort (N=739)
One or more apolipoprotein E ε4 alleles, No. (%)	224 (24.7)	59 (25.7)	165 (24.3)
*Diabetes, No. (%)	195 (20.0)	68 (28.6)	127 (17.2)
Hypertension, No. (%)	651 (66.8)	169 (71.9)	482 (65.2)
*Living alone, No. (%)	290 (30.0)	83 (35.9)	207 (28.1)
Pure tone average, mean (SD), dB	39.4 (6.9)	39.1 (6.7)	39.5 (7.0)
*Hearing handicap inventory, mean (SD)	15.3 (9.8)	12.0 (9.5)	16.3 (9.6)
*Mini-mental state exam, mean (SD)	28.2 (1.6)	28.0 (1.8)	28.3 (1.6)
*Global cognition, mean (SD)	0.000 (0.926)	-0.379 (1.042)	0.123 (0.851)
*Executive function, mean (SD)	-0.001 (0.888)	-0.318 (0.999)	0.102 (0.824)
*Language, mean (SD)	0.000 (0.837)	-0.395 (0.924)	0.127 (0.765)
*Memory, mean (SD)	0.000 (0.909)	-0.191 (0.937)	0.061 (0.892)

*indicates statistically significant difference between groups

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HEARING INTERVENTION TARGET ENGAGEMENT

Hours of hearing aid use & self-reported communication impairment

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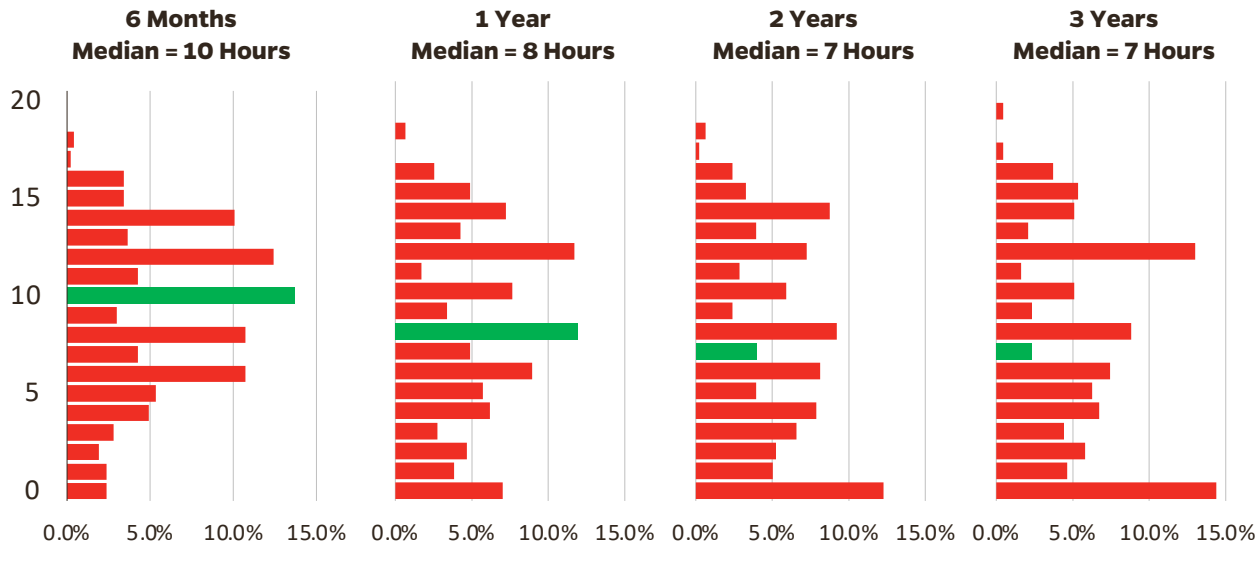
Hearing Intervention Participant Self-Reported Hours of Hearing Aid Use Over 3 Years



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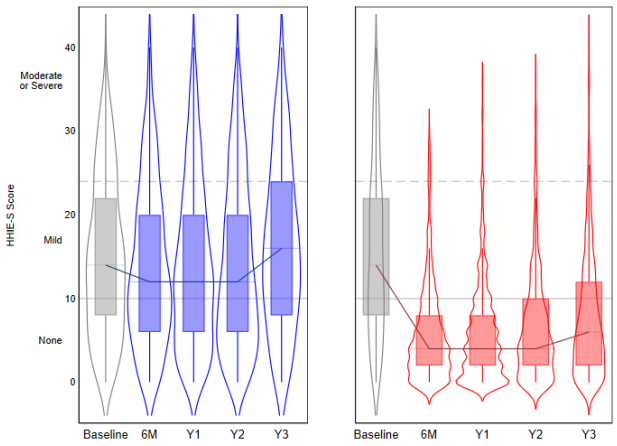
Self-perceived communicative impairment† (Hearing Handicap Inventory) significantly decreases with hearing intervention



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† Hearing Handicap Inventory for the Elderly-Screening * p < 0.001

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3-YEAR COGNITIVE OUTCOMES

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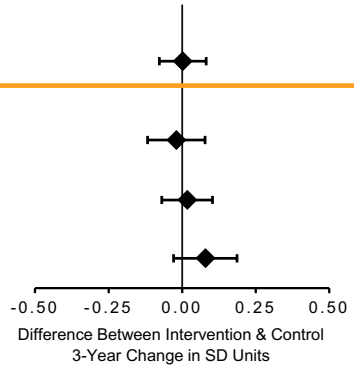
3-Year Change in Global & Domain-Specific Cognition

Main Analysis of the Total Cohort (ARIC & De novo)

Primary & Secondary Outcomes

Total (N = 977^)	3-Year Change in SD Units β (95% CI)	Difference Between Intervention & Control 3-Year Change in SD Units β (95% CI)
Primary Outcome:		
Global Cognition		
Control	-0·202 (-0·258, -0·145)	0·002 (-0·077, 0·081)
Intervention	-0·200 (-0·256, -0·144)	p=0·96
Secondary Outcomes:		
Executive Function		
Control	-0·248 (-0·315, -0·181)	-0·020 (-0·118, 0·078)
Intervention	-0·268 (-0·339, -0·197)	p=0·69
Language		
Control	-0·155 (-0·214, -0·096)	0·017 (-0·070, 0·104)
Intervention	-0·138 (-0·199, -0·077)	p=0·70
Memory		
Control	-0·054 (-0·128, 0·020)	0·079 (-0·029, 0·187)
Intervention	0·025 (-0·053, 0·103)	p=0·15



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In the total combined cohort, hearing intervention had no effect on reducing cognitive decline within 3 years

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3-Year Change in Global & Domain-Specific Cognition

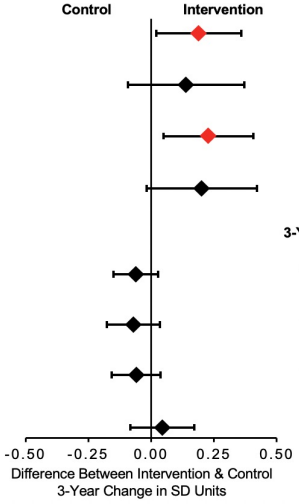
Pre-Specified Sensitivity Analysis Stratified by ARIC & De novo

ARIC Cohort

ARIC (N=238^)	3-Year Change in SD Units β (95% CI)	Difference Between Intervention & Control 3-Year Change in SD Units β (95% CI)
Global Cognition*		
Control	-0·402 (-0·536, -0·267)	0·191 (0·022, 0·360)
Intervention	-0·211 (-0·349, -0·073)	p=0·027
Executive Function		
Control	-0·387 (-0·578, -0·197)	0·139 (-0·092, 0·370)
Intervention	-0·248 (-0·434, -0·062)	p=0·24
Language*		
Control	-0·344 (-0·488, -0·201)	0·229 (0·050, 0·408)
Intervention	-0·116 (-0·264, 0·032)	p=0·012
Memory		
Control	-0·154 (-0·335, 0·027)	0·201 (-0·019, 0·421)
Intervention	0·047 (-0·132, 0·227)	p=0·073

De novo Cohort

De Novo (N=739^)	3-Year Change in SD Units β (95% CI)	3-Year Change in SD Units β (95% CI)
Global Cognition*		
Control	-0·151 (-0·215, -0·087)	-0·061 (-0·151, 0·028)
Intervention	-0·213 (-0·277, -0·148)	p=0·18
Executive Function		
Control	-0·202 (-0·273, -0·131)	-0·070 (-0·176, 0·035)
Intervention	-0·272 (-0·351, -0·194)	p=0·19
Language*		
Control	-0·111 (-0·178, -0·044)	-0·059 (-0·156, 0·037)
Intervention	-0·170 (-0·241, -0·100)	p=0·23
Memory		
Control	-0·032 (-0·118, 0·055)	0·044 (-0·082, 0·171)
Intervention	0·013 (-0·081, 0·106)	p=0·49



3-way interaction
GC: p = 0.010
EF: p=0.077
L: p=0.005
M: p=0.29

In the ARIC cohort, hearing intervention reduced 3-year global cognitive decline by 48%

No effect of hearing intervention observed in the De novo cohort

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3-Year Change in Global & Domain-Specific Cognition

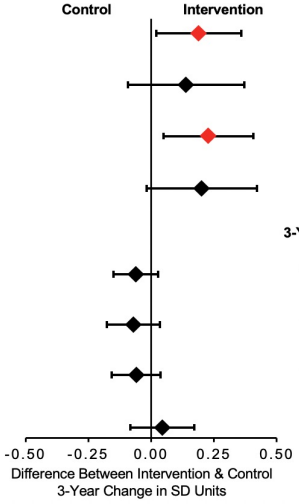
Pre-Specified Sensitivity Analysis Stratified by ARIC & De novo

ARIC Cohort

De novo Cohort

3-way interaction
GC: p = 0.010
EF: p=0.077
L: p=0.005
M: p=0.29

	ARIC (N=238^) 3-Year Change in SD Units β (95% CI)	De Novo (N=739^) 3-Year Change in SD Units β (95% CI)	Difference Between Intervention & Control 3-Year Change in SD Units β (95% CI)
Global Cognition*			
Control	-0·402 (-0·536, -0·267)	-0·151 (-0·215, -0·087)	0·191 (0·022, 0·360) p=0·027
Intervention	-0·211 (-0·349, -0·073)	-0·213 (-0·277, -0·148)	
Executive Function			
Control	-0·387 (-0·578, -0·197)	-0·202 (-0·273, -0·131)	0·139 (-0·092, 0·370) p=0·24
Intervention	-0·248 (-0·434, -0·062)	-0·272 (-0·351, -0·194)	
Language*			
Control	-0·344 (-0·488, -0·201)	-0·111 (-0·178, -0·044)	0·229 (0·050, 0·408) p=0·012
Intervention	-0·116 (-0·264, 0·032)	-0·170 (-0·241, -0·100)	
Memory			
Control	-0·154 (-0·335, 0·027)	-0·032 (-0·118, 0·055)	0·201 (-0·019, 0·421) p=0·073
Intervention	0·047 (-0·132, 0·227)	0·013 (-0·081, 0·106)	
			-0·061 (-0·151, 0·028) p=0·18
			-0·070 (-0·176, 0·035) p=0·19
			-0·059 (-0·156, 0·037) p=0·23
			0·044 (-0·082, 0·171) p=0·49



Rates of cognitive change ~3x slower in **De novo** than **ARIC** controls

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Hearing Intervention & 3-Year Cognitive Outcomes

Summary

- In the total combined cohort, hearing intervention had no effect on reducing cognitive decline within 3 years
- Strong effects in ARIC (48% reduction) suggests that hearing intervention might reduce cognitive decline within 3 years in populations at increased risk for cognitive decline
- No effect observed in De novo → Slow rate of cog. change would limit ability to observe any positive effect of hearing intervention within just 3 years
  - Slow cognitive decline likely reflects self-selection of "healthy volunteers" in the de novo cohort (vs. ARIC participants coming from a randomly selected cohort recruited 30+ years ago)

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Hearing Intervention & 3-Year Cognitive Outcomes

Limitations

- Effects of hearing intervention on populations at decreased risk of cognitive decline & on rates of cognitive impairment (dementia) will require follow-up beyond 3 years
- Control participants could perform more poorly on tests comprising only auditory stimuli (2/10 tests). However, strongest effects in ARIC observed in language domain which did not consist of any auditory-only tests
- Participants & study staff could not be feasibly masked to intervention assignment

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BRAIN HEALTH

Exploratory effects of hearing intervention on brain structure

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Preliminary Unpublished Results

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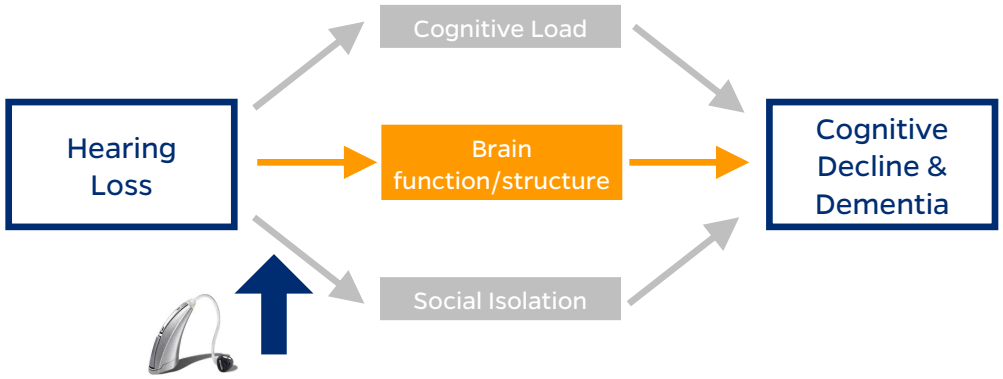
Hearing Loss & Dementia

Hearing Loss as a Modifiable Risk Factor



Does hearing intervention with hearing aids reduce brain atrophy over 3 years?

F. Lin & M. Albert, Aging & Mental Health, 2014

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Hearing Loss & Brain Function/Structure

Background

- Peripheral auditory inputs are integrated across multiple brain regions & neural networks (default mode network, salience network, etc.)
- Hearing loss (impoverished auditory encoding) associated with*:
  - Functional changes in both resting state & task-activated patterns of neural activity and cross-modal plasticity
  - Increased structural atrophy in whole brain, temporal lobe regions, cingulate cortex, superior frontal gyrus, & DMN regions
- Hearing aid use for 6 months in adults associated with reversal of cross-model reorganization of auditory cortex**
- Broader & long-term effects of hearing aid use on brain function/structure are unknown

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**Review by Z. Jafari, Ann NY Acad Sci, 2021; ** Glick et al., Front Neurosci, 2020*

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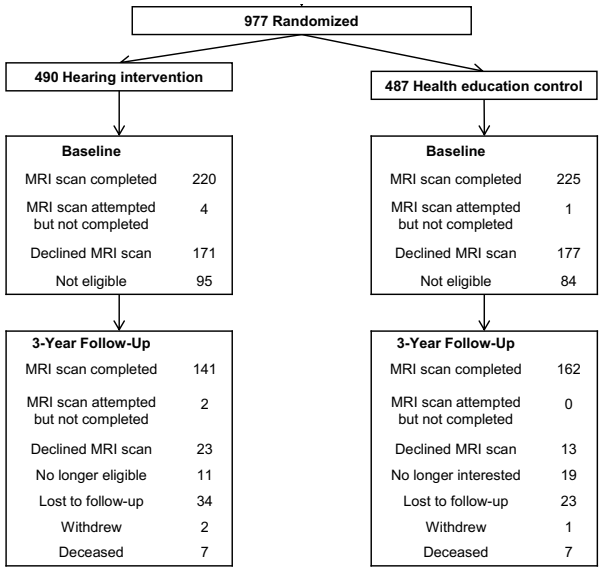
ACHIEVE MRI Substudy

- Half-sample at baseline (n = 445) & n = 303 at Year 3
- 3D scans performed on 3 Tesla Siemens scanners
- Regions of interest defined using Freesurfer atlas. Cortical thickness measured for each region



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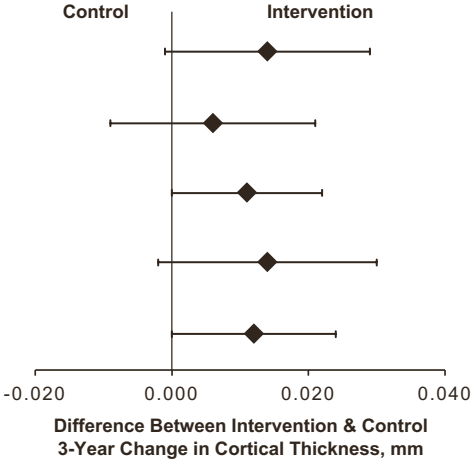
Adjusted, Intention-To-Treat Analysis of Three-Year Change in Cortical Thickness in Millimeters (N=445)

	3-Year Change in Cortical Thickness, mm β (95% CI)	Difference Between Intervention & Control 3-Year Change in Cortical Thickness, mm β (95% CI)	Cohen's D
Frontal Lobe			
Control	-0.011 (-0.021, -0.001)	0.014 (-0.001, 0.028) p=0.066	0.110
Intervention	0.003 (-0.008, 0.014)		
Temporal Lobe			
Control	-0.035 (-0.047, -0.024)	0.006 (-0.009, 0.022) p=0.44	0.047
Intervention	-0.029 (-0.040, -0.018)		
Occipital Lobe			
Control	-0.007 (-0.015, 0.000)	0.011 (0.000, 0.023) p=0.051	0.113
Intervention	0.004 (-0.004, 0.011)		
Parietal Lobe			
Control	-0.006 (-0.016, 0.004)	0.014 (-0.002, 0.029) p=0.082	0.109
Intervention	0.008 (-0.003, 0.019)		
Whole Brain			
Control	-0.014 (-0.023, -0.006)	0.012 (0.000, 0.024) p=0.057	0.105
Intervention	-0.003 (-0.011, 0.006)		



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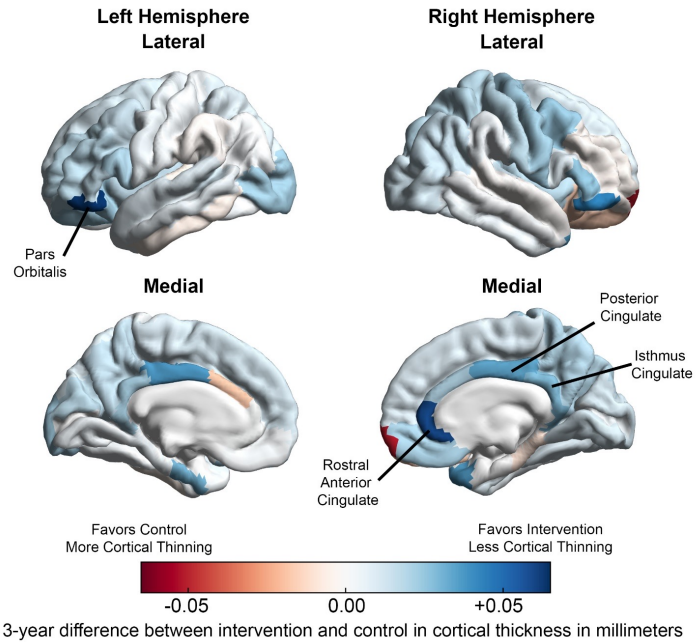
Difference in 3-Year Change in Brain Cortical Thickness in Intervention vs Control



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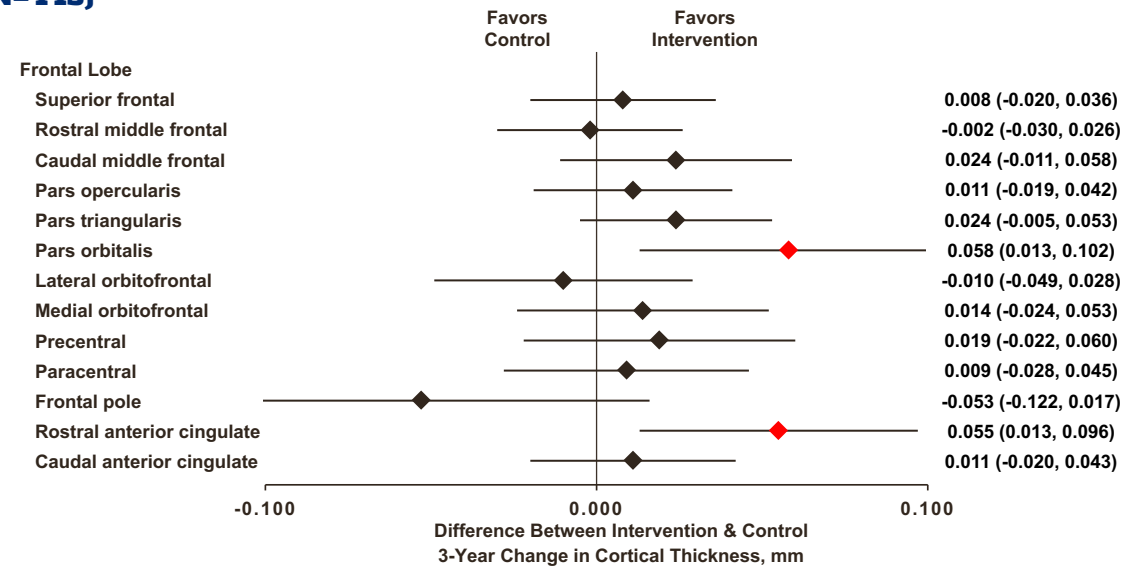
FRONTAL LOBE - Adjusted, Intention-To-Treat Analysis of Three-Year Change in Cortical Thickness of *Dominant* Hemisphere in Millimeters (N=445)



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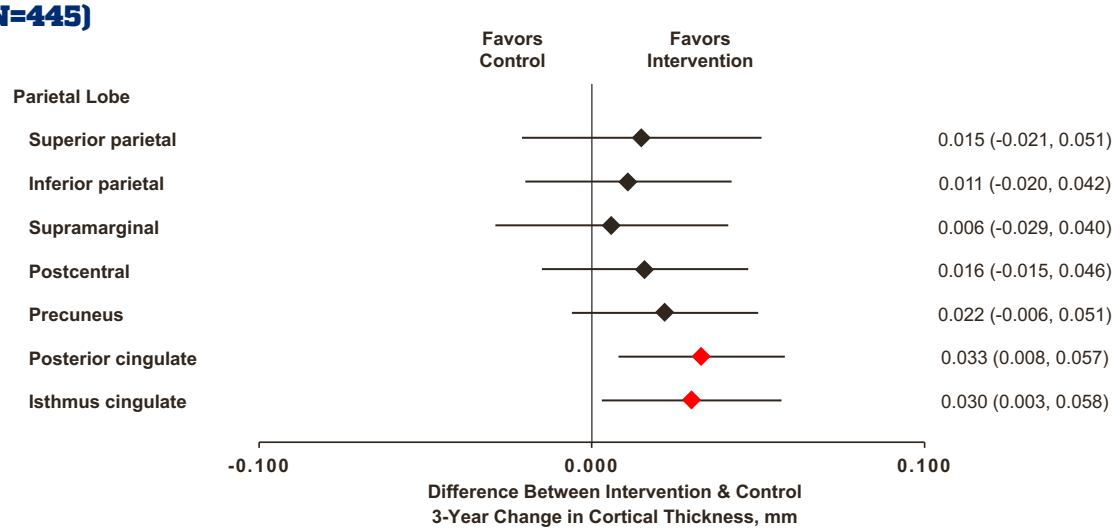
PARIETAL LOBE - Adjusted, Intention-To-Treat Analysis of Three-Year Change in Cortical Thickness of *Dominant* Hemisphere in Millimeters (N=445)



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Hearing Intervention & Brain Cortical Atrophy

Summary

- Analyses demonstrate a clear signal of hearing intervention being associated with reduced cortical thinning over 3 years in whole brain & certain lobar regions
- Pattern of findings suggest that hearing intervention may have greatest effects in the pars orbitalis & cingulate cortices and not in the temporal lobe
- Potential mechanisms could include effects of hearing intervention on sustained alterations in patterns of neural activity, increased social & physical activity, etc.

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SUMMARY & CONCLUSION

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ACHIEVE Study – Key Findings

- High adherence to & satisfaction with hearing intervention sustained over 3 yrs with positive effects on self-perceived communication impairment
- Exploratory MRI analyses suggest biomarker effects of hearing intervention on reducing cortical thinning within 3 years
- Strong effects of hearing intervention (48% reduction) on 3-year global cognitive decline in the ARIC cohort that came from a random sample of the population
  - Slow rate of cognitive change in healthy de novo volunteers would limit any apparent cognitive benefits of hearing intervention within just 3 years
- Key inference: Hearing intervention could reduce cognitive loss within 3 years for populations of older adults at increased risk for cognitive decline.

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ACHIEVE Study – Implications for Clinical Care

- Clinical recommendations always require extrapolating scientific evidence to the individual while balancing risk vs. benefit
- Clinical - Is a patient at increased risk of cognitive decline (more like the ARIC or De novo cohort)? What about patients with severe hearing loss who could benefit from a cochlear implant?
- My approach – I focus conversation on the tangible proximal outcomes of hearing intervention on communication and social function. I only mention potential downstream effects on supporting cognitive/brain health as an afterthought.

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What's next for ACHIEVE?

- Determining 3-year effects on other outcomes gathered in the ACHIEVE study: brain MRI structure, health-related quality of life, depression, hospitalizations, physical activity & functioning, health care costs
- Longer term follow-up of the entire cohort needed to observe for hearing intervention effects on those at decreased risk (de novo cohort) & risk for cognitive impairment (e.g., adjudicated dementia)
  - 6-year follow-up study (2022-2027) is underway (NCT05532657, R01AG076518)

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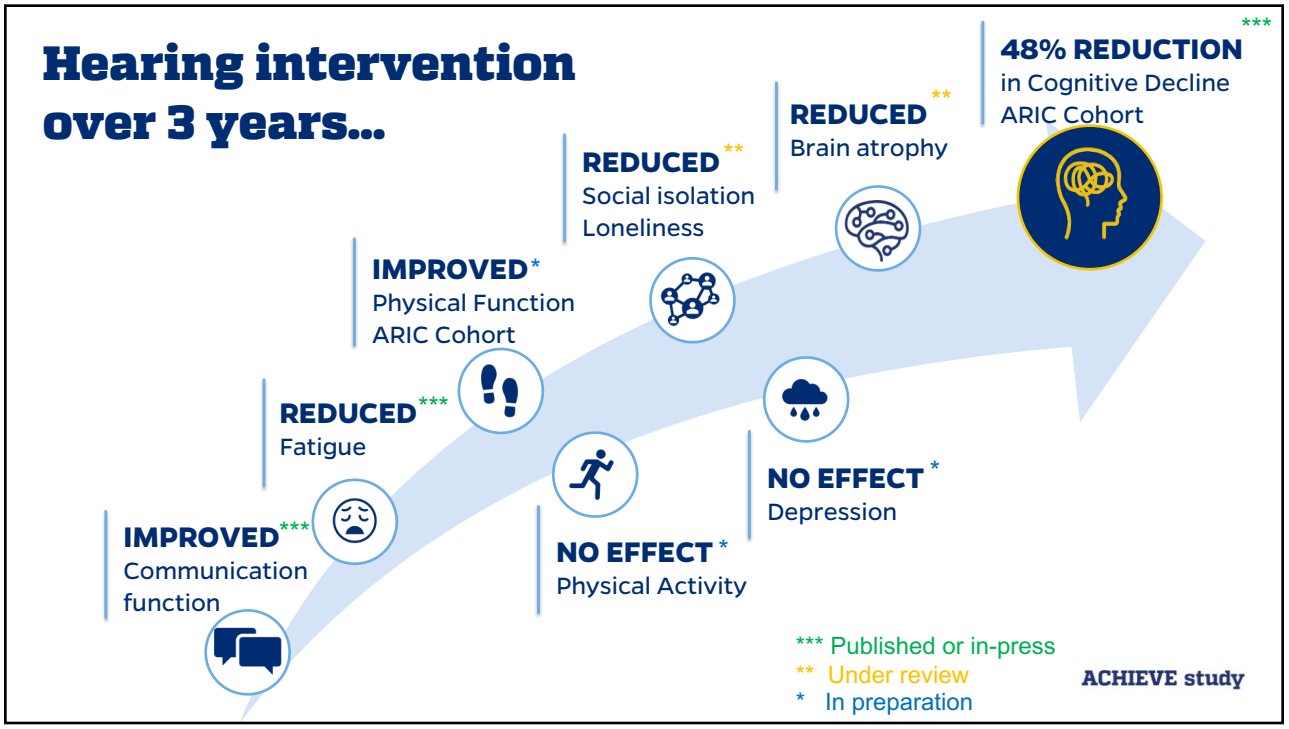
Hearing intervention over 3 years...
IMPROVED*** Communication function
REDUCED*** Fatigue
IMPROVED* Physical Function ARIC Cohort
REDUCED** Social isolation Loneliness
NO EFFECT * Physical Activity
NO EFFECT * Depression
REDUCED** Brain atrophy
48% REDUCTION*** in Cognitive Decline ARIC Cohort
*** Published or in-press
** Under review
* In preparation
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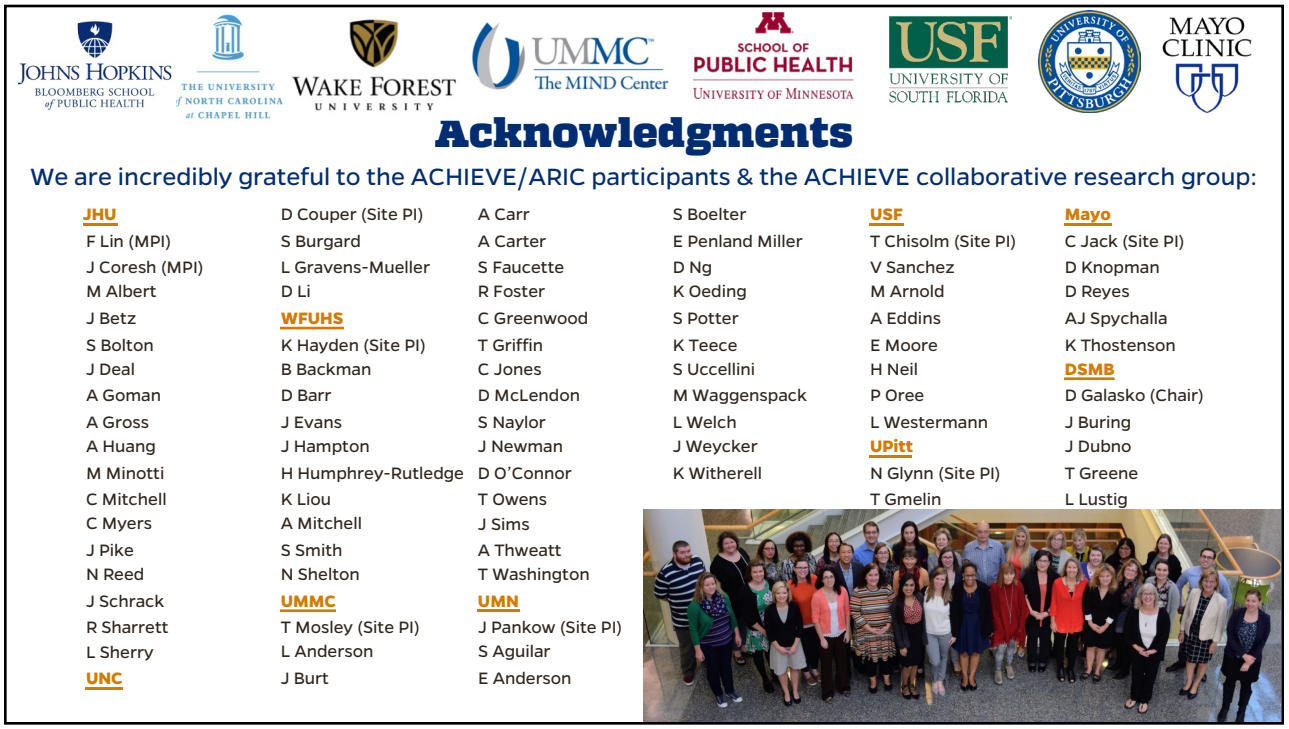
Acknowledgments
We are incredibly grateful to the ACHIEVE/ARIC participants & the ACHIEVE collaborative research group:
JHU
F Lin (MPI)
J Coresh (MPI)
M Albert
J Betz
S Bolton
J Deal
A Goman
A Gross
A Huang
M Minotti
C Mitchell
C Myers
J Pike
N Reed
J Schrack
R Sharrett
L Sherry
UNC
D Couper (Site PI)
S Burgard
L Gravens-Mueller
D Li
WFUHS
K Hayden (Site PI)
B Backman
D Barr
J Evans
J Hampton
H Humphrey-Rutledge
K Liou
A Mitchell
S Smith
N Shelton
UMMC
T Mosley (Site PI)
L Anderson
J Burt
A Carr
A Carter
S Faucette
R Foster
C Greenwood
T Griffin
C Jones
D McLendon
S Naylor
J Newman
D O'Connor
T Owens
J Sims
A Thweatt
T Washington
UMN
J Pankow (Site PI)
S Aguilar
E Anderson
S Boelter
E Penland Miller
D Ng
K Oeding
S Potter
K Teece
S Uccellini
M Waggenspack
L Welch
J Weycker
K Witherell
USF
T Chisolm (Site PI)
V Sanchez
M Arnold
A Eddins
E Moore
H Neil
P Oree
L Westermann
UPitt
N Glynn (Site PI)
T Gmelin
Mayo
C Jack (Site PI)
D Knopman
D Reyes
AJ Spychalla
K Thostenson
DSMB
D Galasko (Chair)
J Buring
J Dubno
T Greene
L Lustig

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Funding & support

- ACHIEVE main trial: NIA/NIH grant R01AG055426
- ACHIEVE MRI ancillary study: NIA/NIH R01AG060502
- Pilot study: NIA/NIH R34AG046548 & the Eleanor Schwartz Charitable Foundation
- ARIC:
  - NHLBI contracts HHSN268201700001I, HHSN268201700002I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I
  - Neurocognitive data: NIH grants 2U01HL096812, 2U01HL096814, 2U01HL096899, 2U01HL096902, 2U01HL096917 (NHLBI, NINDS, NIA and NIDCD)
  - Previous brain MRI examinations: NHLBI grant R01HL70825
- Hearing aids & related technologies and training support of study audiologists provided in-kind by Sonova/Phonak through a materials transfer agreement with Johns Hopkins

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Thank you!

www.AchieveStudy.org

Frank Lin
flin1@jh.edu

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