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

Jennifer A. Deal, PhD

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ACHIEVE study Johns Hopkins University

Jennifer A. Deal, PhD

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  - 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

Learning Outcomes

After this course, participants will be able to:

- Summarize the results of a randomized controlled trial to determine if a best-practices hearing intervention vs. health education control delays cognitive decline in older adults with untreated mild-to-moderate hearing loss.
- Explain the strengths and limitations of the study design that may impact study findings.
- Discuss how to interpret and discuss study findings with patients.

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

USF UNIVERSITY OF SOUTH FLORIDA
Hearing intervention design

UNIVERSITY OF PITTSBURGH
Health education control intervention design

MAYO CLINIC
MRI reading center

MPI's: Frank R. Lin, MD PhD & Josef Coresh, MD PhD

ACHIEVE Trial Presentation
Outline

- Motivation: Background on hearing loss & dementia
- Study design and methods
- Effects of hearing intervention on cognitive decline
- Interpreting ACHIEVE results in the clinic
- Summary & conclusion

Background

What we studied & why

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

Lancet Commission on Dementia Prevention, Intervention & Care

- **Hearing loss – 8%**
- Less education – 7%
- Smoking – 5%
- Depression, Social Isolation – 4%
- Traumatic brain injury – 3%
- Air pollution, Physical inactivity, Hypertension – 2%
- Obesity, Diabetes, Heavy Alcohol Use – 1%

Livingston G. Lancet. 2020 Aug 8;396(10248):413-446.

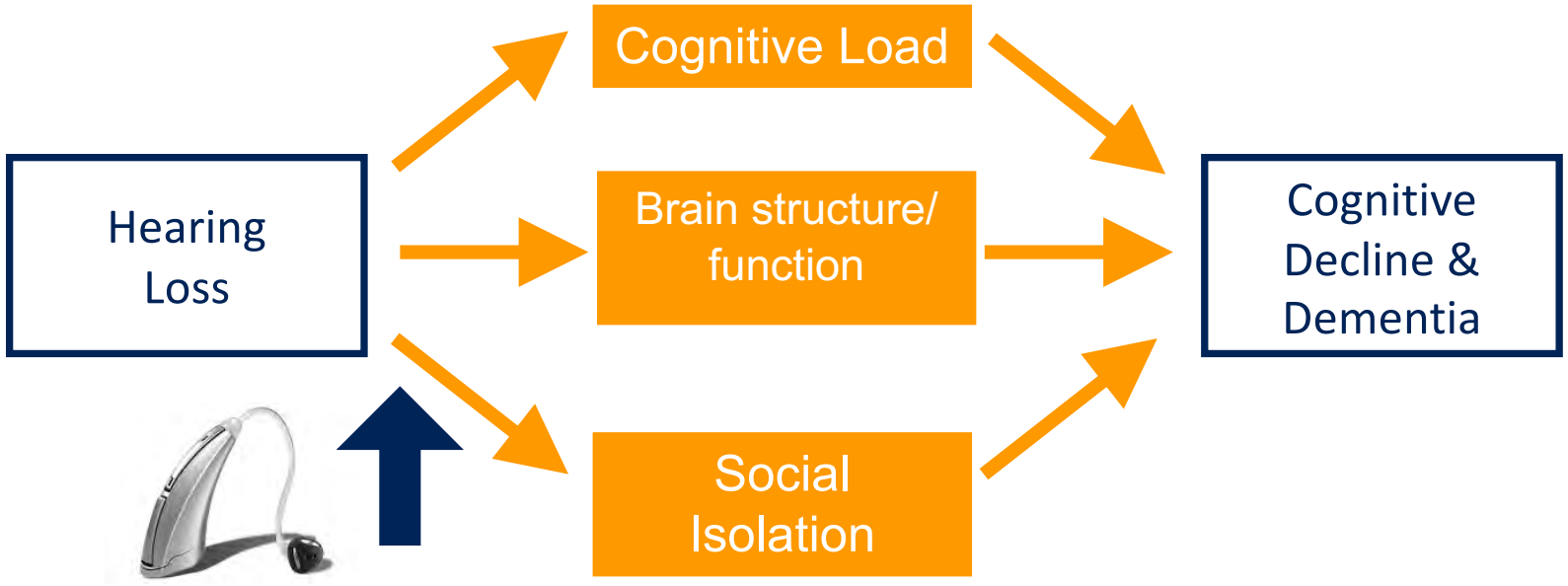
Hearing Loss, Cognitive Decline & Dementia
Hypothesized Mechanistic Pathways

- **Cognitive load ("information degradation")**
  - Constant load on cortical resources that otherwise could have buffered against pathological contributors to dementia (
- **Direct effects on brain structural integrity ("sensory deprivation")**
  - Accelerated brain atrophy & other pathologic brain changes (white matter tracts, altered functional connectivity)
- **Increased social isolation/loneliness**
  - Less physical activity & cognitively-stimulating activities, stress/inflammation, adherence to medic

Lin FR, Albert M. Aging Ment Health. 2014;18(6):671-3.

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

Lin FR, Albert M. Aging Ment Health. 2014;18(6):671-3.

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

- Recent meta-analysis of observational studies*: hearing aid use associated with 19% decreased hazard of long-term cognitive decline
- But question cannot be definitively answered through observational studies

Why?

*Yeo BSY, et al. JAMA Neurol. 2023 Feb 1;80(2):134-141.

Challenges to Interpreting Observational Studies

- Bias exists in all observational studies
  - Data generation (measurement)
  - Participant selection
  - Other factors (confounding)

- If we find an association, we must consider all possible reasons we see that association, including bias

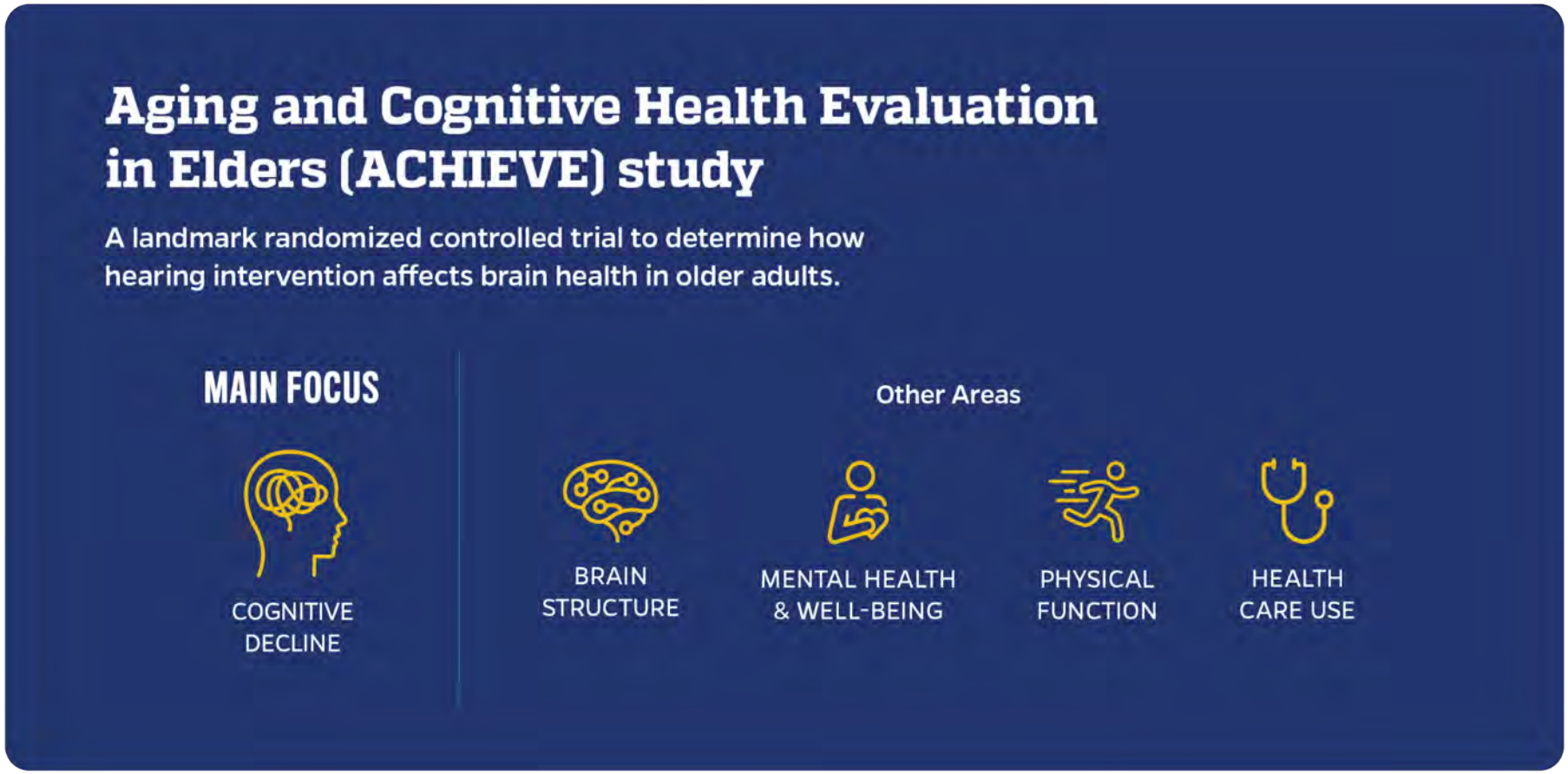
Deal JA, et al. Semin Hear. 2021 Feb;42(1):3-9.

Benefits of Randomized Trials

- Intervention is randomized
  - Not linked to any patient characteristics (e.g., age, race/ethnicity, etc.)
  - Therefore, no bias in allocation of treatment
- Increases the likelihood that the treatment groups are balanced on factors related to the outcome
- Therefore, any observed different in the outcome comparing treatment to control can be ascribed solely to the treatment

Deal JA, et al. Semin Hear. 2021 Feb;42(1):3-9.

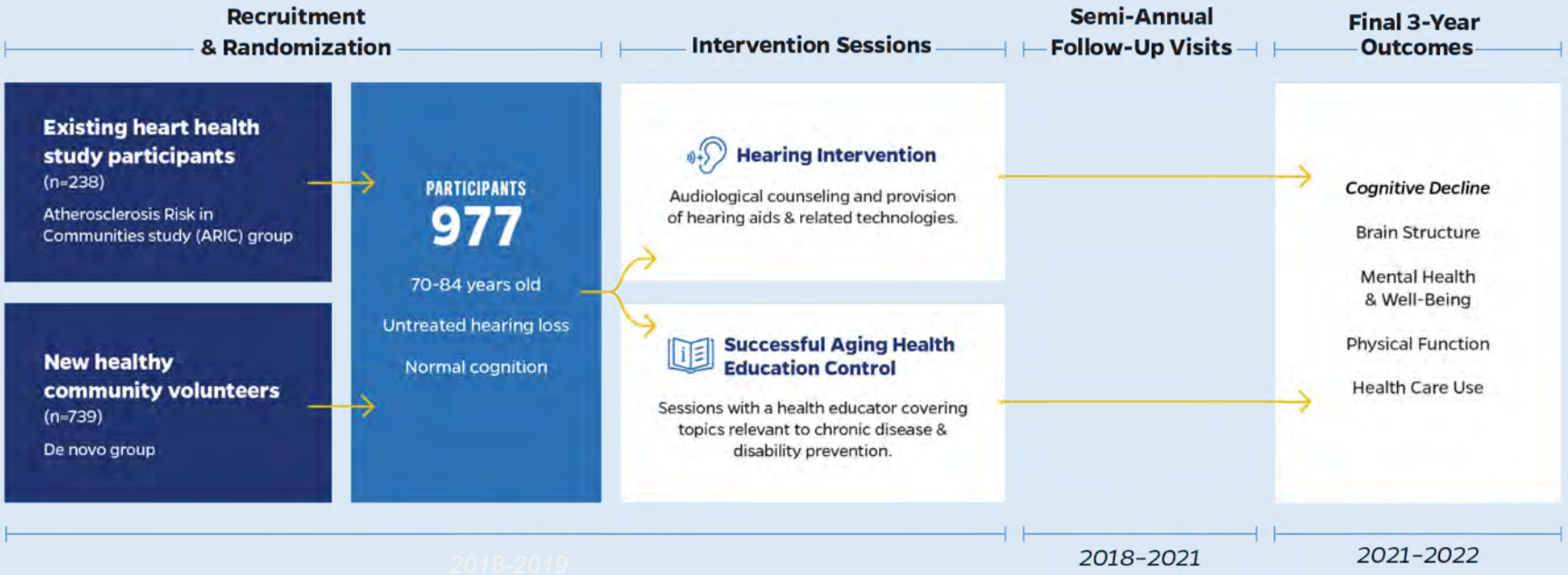
Can treating hearing loss reduce cognitive decline over 3 years in older adults with hearing loss without substantial cognitive impairment?



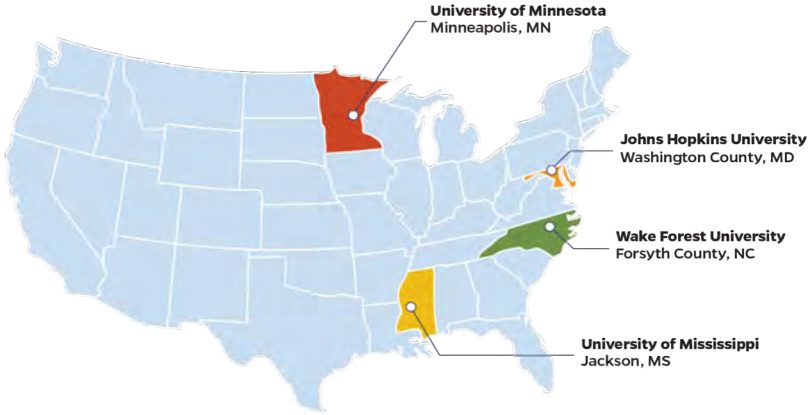
Study design

Study design, methods, & ACHIEVE cohort characteristics

ACHIEVE STUDY DESIGN



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 aged 45-64 recruited in 1987-89 from a random sample of the communities at 4 sites
- ARIC's focus on heart disease & stroke was expanded in 2011 to include neurocognitive assessment & hearing loss
- ACHIEVE recruited & randomized participants at the 4 ARIC field sites
  - ARIC – Participants eligible based on audiometric & cognitive assessment
  - De novo - Healthy community volunteers

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

- ARIC Cohort (n = 238)
  - ARIC participants have been followed to the present day with 6 visits prior to ACHIEVE
- De novo cohort (n = 739)
  - New 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

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

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

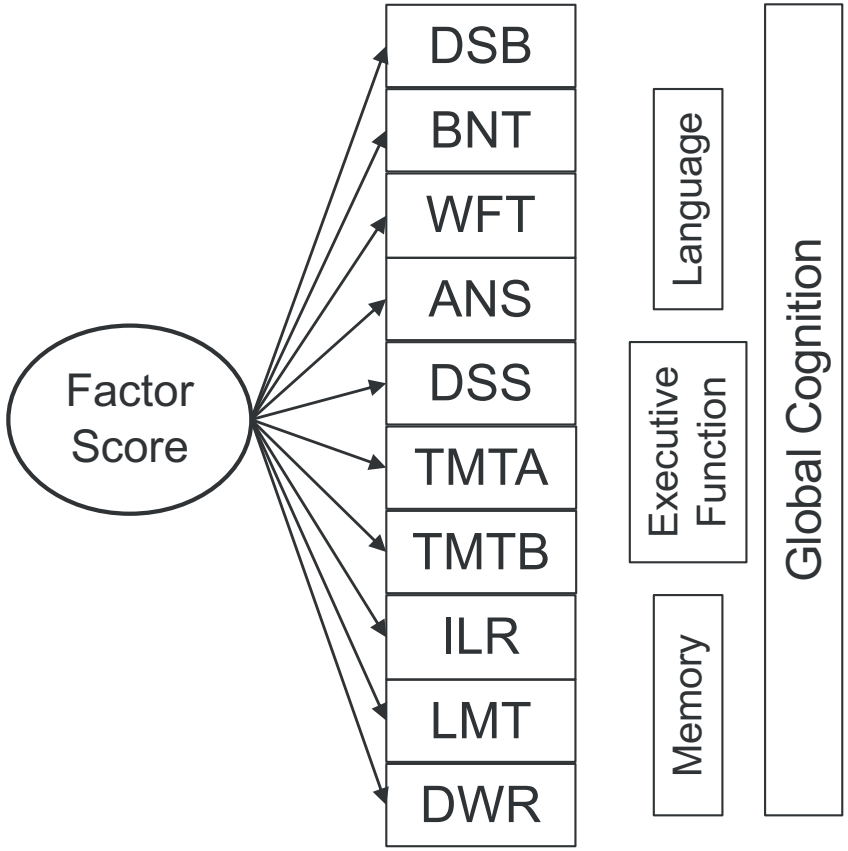
ACHIEVE Neurocognitive Battery

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

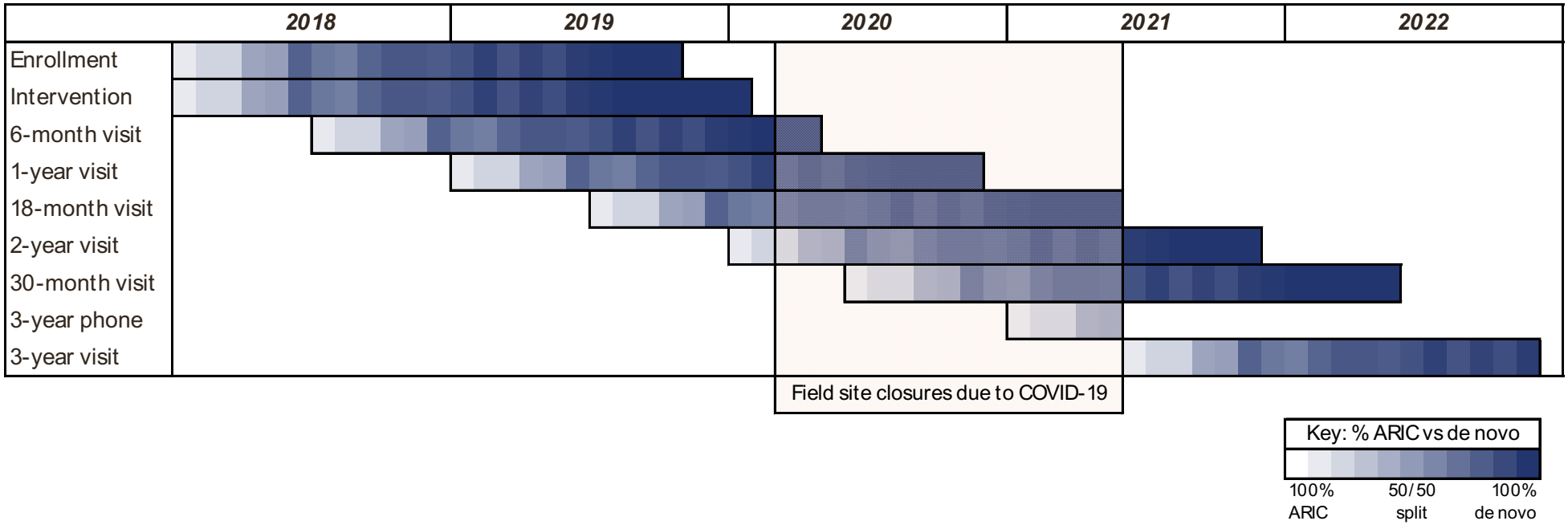
ACHIEVE Cognitive Factor Scores



- 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.

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



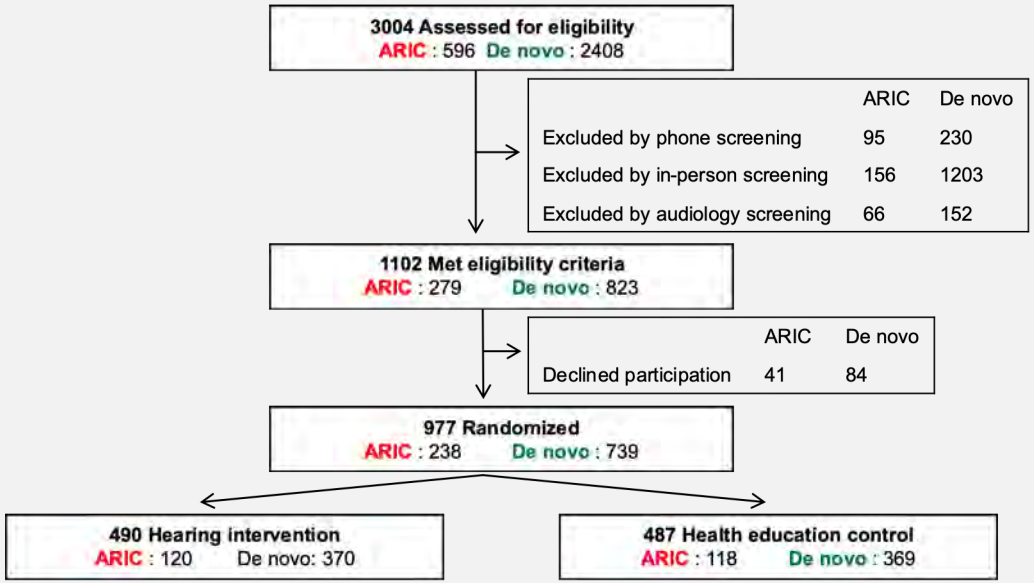
Statistical Analysis – Cognitive Outcomes

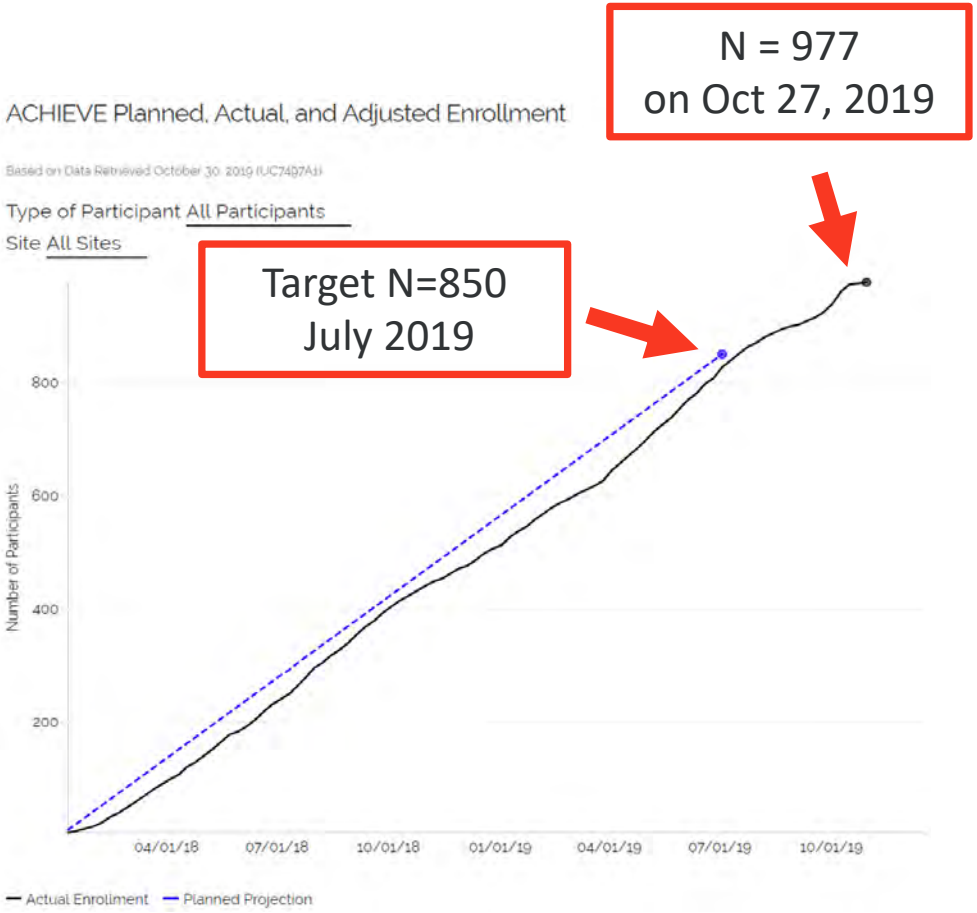
- Estimated effect of assignment to hearing intervention versus control on change in global cognition from baseline to Year 3 (primary outcome)
  - Mixed effects models adjusted for baseline hearing (PTA <40 vs 40+ dB), recruitment source, field site, age, sex, education, presence of APOE ε4 allele(s), & 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)

Statistical Analysis – Secondary Cognitive Outcomes

- For secondary cognitive domains, same analytic model as primary outcome
- Statistical significance
  - **Primary outcome defined as a two-tailed α<0·05**
  - For 4 secondary outcomes: Hochberg modification to the Bonferroni adjustment → Estimates are considered significant if the largest p-value is <0·05. If the largest p-value >0·05, then the second largest value is evaluated at <0·025 (0·05/2), etc.
  - Same approach applied post-hoc to stratified analyses by ARIC & de novo

ACHIEVE Study Cohort *Recruitment*





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

3-year Cognitive Outcomes

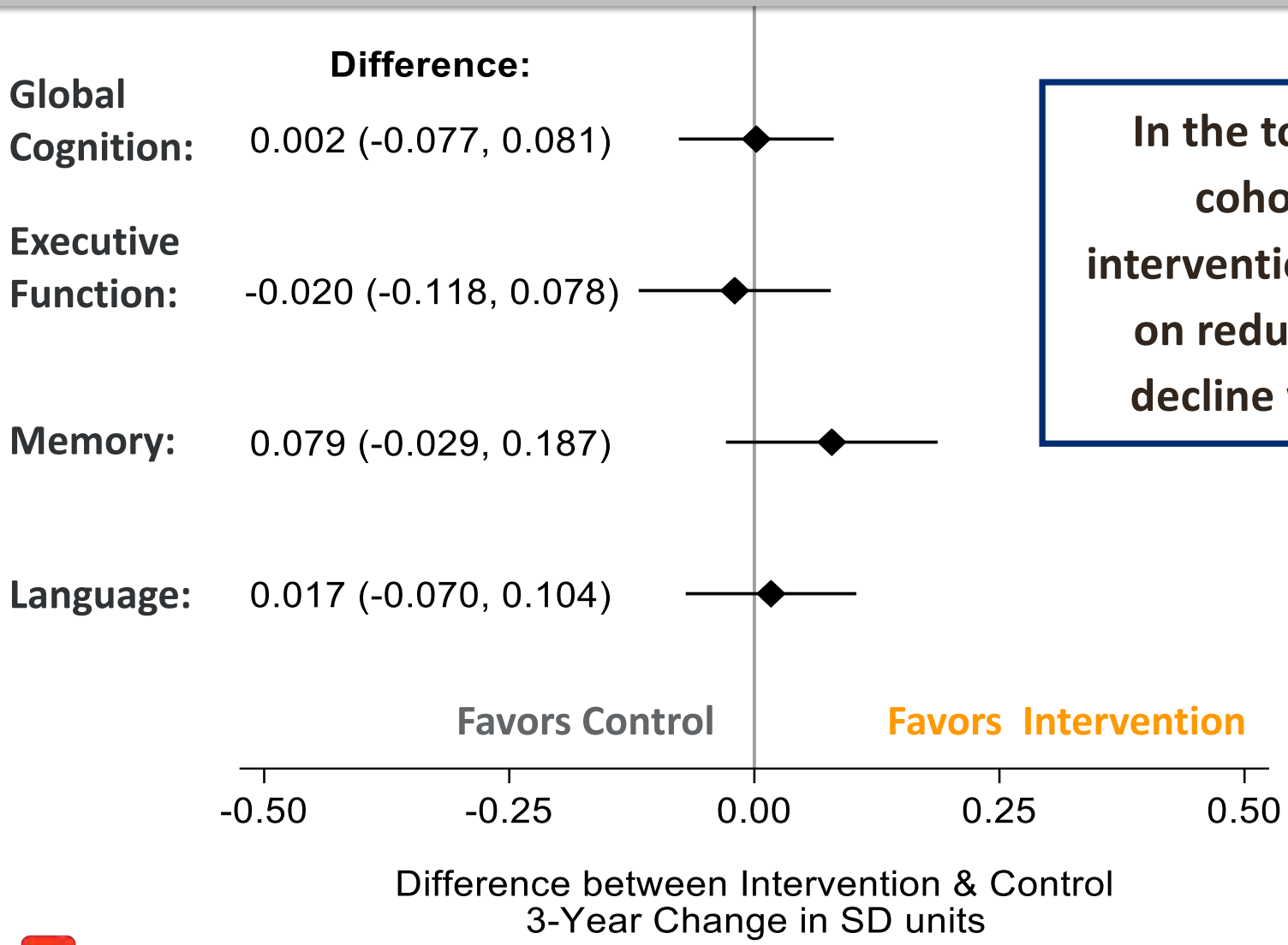
3-Year Change in Global & Domain-Specific Cognition

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

		3-Year Change (SD units)
Global Cognition	Control	-0.202 (-0.258, -0.145)
	Intervention	-0.200 (-0.256, -0.144)
Executive Function	Control	-0.248 (-0.315, -0.181)
	Intervention	-0.268 (-0.339, -0.197)
Memory	Control	-0.054 (-0.128, 0.020)
	Intervention	0.025 (-0.053, 0.103)
Language	Control	-0.155 (-0.214, -0.096)
	Intervention	-0.138 (-0.199, -0.077)

3-Year Change in Global & Domain-Specific Cognition

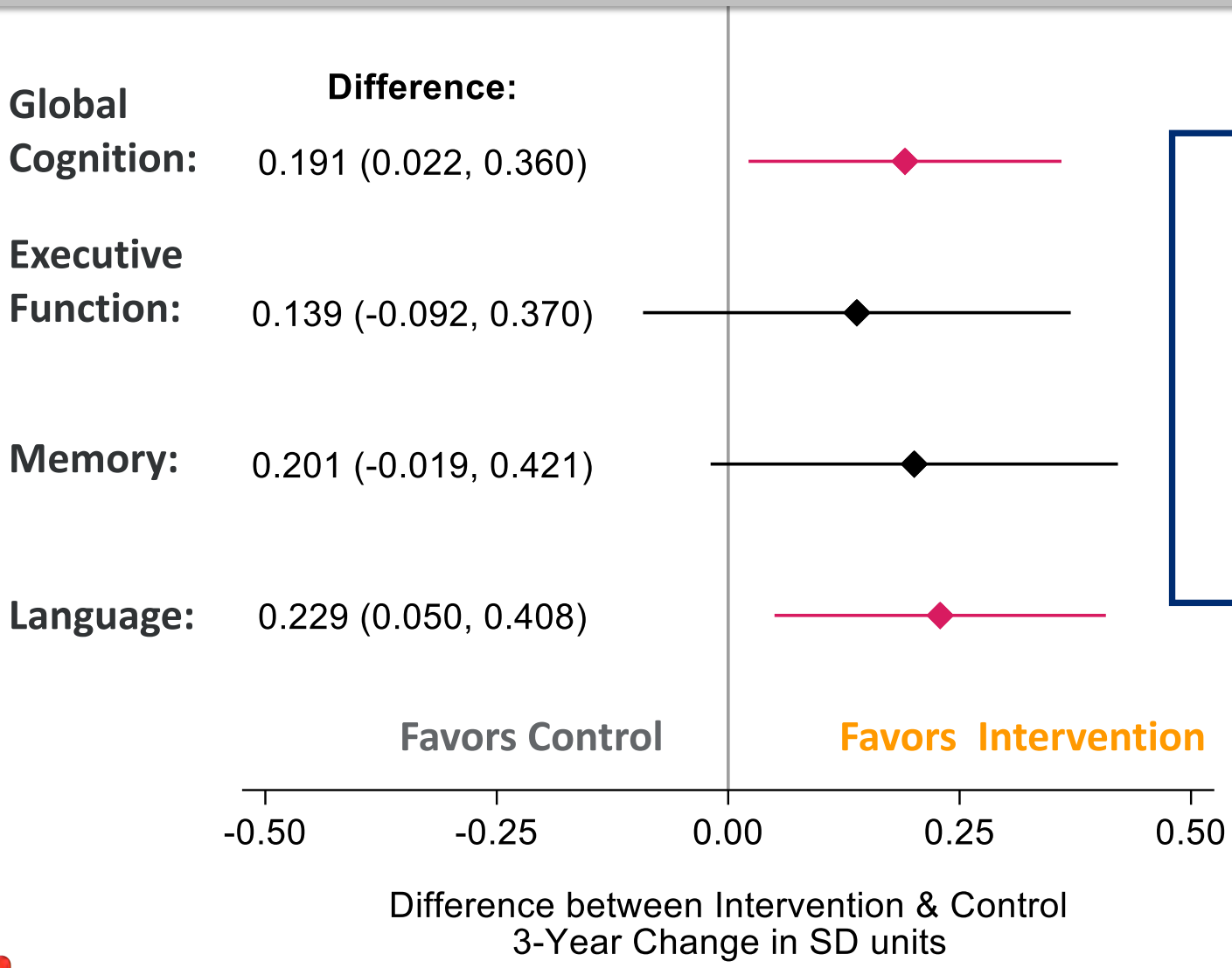
Main Analysis of the Total Cohort (ARIC & De novo)



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

3-Year Change in Global & Domain-Specific Cognition

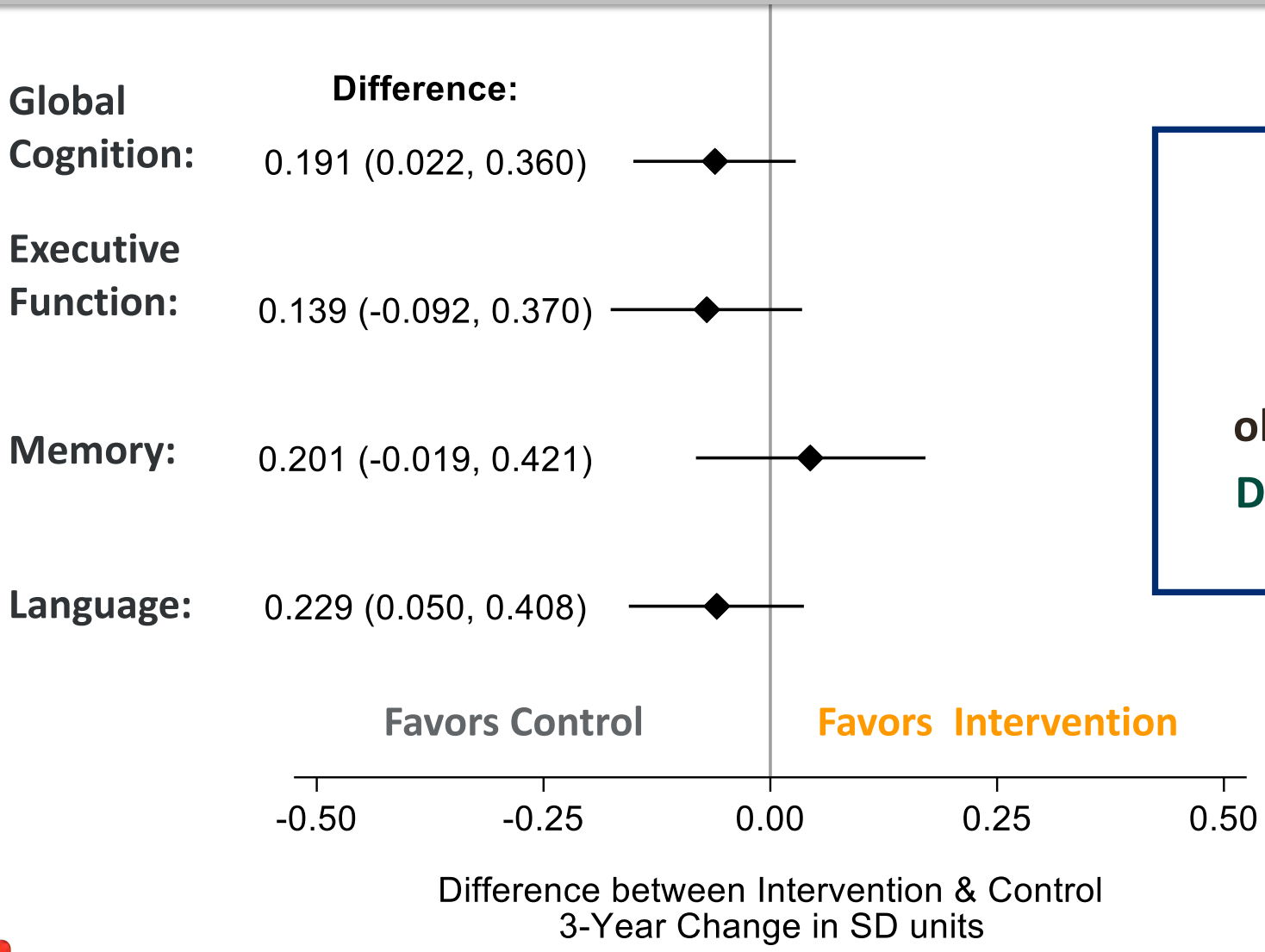
Pre-Specified Sensitivity Analysis Stratified by Cohort - ARIC



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

3-Year Change in Global & Domain-Specific Cognition

Pre-Specified Sensitivity Analysis Stratified by Cohort – De Novo



No effect of hearing intervention observed in the De novo cohort

Why Might the Intervention Work in the ARIC Cohort, but Not in the De Novo?

Baseline Characteristics by Recruitment Source ARIC cohort has more risk factors for cognitive decline than De novo

Baseline characteristics	All Participants (N=977)	ARIC Cohort (N=238)	De novo Cohort (N=739)
Age, mean (SD), years	76.8 (4.0)	78.9 (2.9)	76.1 (4.0)
Female, %	53.5	61.8	50.9
Black race, %	11.5	28.6	6.0
<High school education, %	3.8	9.3	2.0
Income under $25,000, %	15.5	26.7	12.0
Living alone, %	30.0	35.9	28.1
Diabetes, %	20.0	28.6	17.2

Baseline Characteristics by Recruitment Source
ARIC cohort is less concerned about their hearing than De novo

Baseline characteristics	All Participants (N=977)	ARIC Cohort (N=238)	De novo Cohort (N=739)
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)

Does this speak to motivation for participating in the study? De novo group worried about their hearing but doing well in terms of their health and cognition? “Worried well”? Primarily healthy volunteers?

Baseline Characteristics by Recruitment Source
ARIC cohort has lower cognitive performance than De novo

Baseline characteristics	All Participants (N=977)	ARIC Cohort (N=238)	De novo Cohort (N=739)
	Mean (SD)	Mean (SD)	Mean (SD)
Mini-mental state exam	28.2 (1.6)	28.0 (1.8)	28.3 (1.6)
Global cognition,	0.000 (0.926)	-0.379 (1.042)	0.123 (0.851)
Executive function	-0.001 (0.888)	-0.318 (0.999)	0.102 (0.824)
Memory	0.000 (0.909)	-0.191 (0.937)	0.061 (0.892)
Language	0.000 (0.837)	-0.395 (0.924)	0.127 (0.765)

ARIC Cohort Experienced Fasters Rates of Cognitive Change over 3 Years than De novo

	3-Year Change (SD units)		
		ARIC	De Novo
Global Cognition	Control	-0.402 (-0.536, -0.267)	-0.151 (-0.215, -0.087)
	Intervention	-0.211 (-0.349, -0.073)	-0.213 (-0.277, -0.148)
Language	Control	-0.344 (-0.488, -0.201)	-0.111 (-0.178, -0.044)
	Intervention	-0.116 (-0.264, 0.032)	-0.170 (-0.241, -0.100)

Hearing Intervention & 3-Year Cognitive Outcomes *Summary*

- Overall, hearing intervention did not reduce 3-year cognitive decline
- 48% reduction in cognitive decline in ARIC
  - Because of the greater number of risk factors for cognitive decline?
  - Because of the observed faster rates of cognitive change in this cohort?
- No effect observed in De novo
  - Because of the lower number of risk factors for cognitive decline?
  - Because of slow rate of cognitive change in this cohort?

More work is needed to understand who might (and who might not) benefit

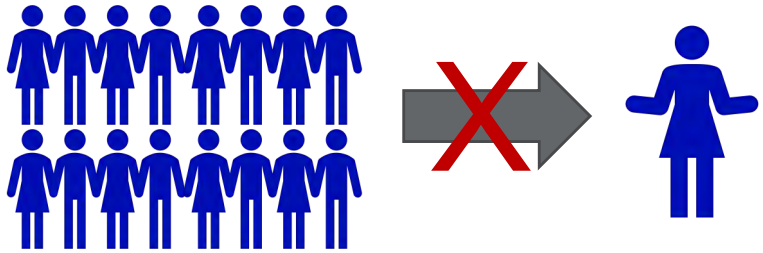
Interpreting ACHIEVE Results in the Clinic

Interpreting Clinical Trials vs. Observational Studies

- Because randomized trials have protections from bias that observational studies do not, we can determine cause from randomized studies
- We cannot determine cause from any observational study

Interpreting Population-Level Studies for Patients

- We cannot determine individual risk from epidemiologic studies, which are, by nature, an average across the population



- An individual's risk of the outcomes is 0 or 1 – they will get it or not
- This is true for observational studies and clinical trials!

Talking About ACHIEVE Study Results

- How do you explain ACHIEVE findings to a patient considering whether to get hearing aids?
- Hearing aids slowed cognitive decline for some people, but not for all people in the study. If they are worried about cognitive decline, hearing aids may help, but they may not.
- How similar is your patient to the patients in the cohort that benefited (ARIC)? Are there other reasons they may benefit from treatment?

Summary & Conclusion

ACHIEVE Study – Key Findings

- Strong effects (48% reduction) on 3-year global cognitive decline in ARIC but not in de novo
  - Slow rate of cognitive change in healthy de novo volunteers may limit any apparent cognitive benefits of hearing intervention within just 3 years
  - In secondary analysis, hearing intervention delayed cognitive decline in language in ARIC cohort
- Key inference: Results add to our understanding of the impact of hearing treatment to delay cognitive decline, but more work is needed to understand who might (and who might not) benefit

ACHIEVE Study – Limitations

- Effects of hearing intervention may require follow-up beyond 3 years
- Participants & study staff could not be feasibly masked to intervention assignment

What's next for ACHIEVE?

- Determining 3-year effects of hearing aids on dementia
- Determining 3-year effects of hearing aids on other outcomes gathered in the ACHIEVE study (e.g., brain MRI structure, health-related quality of life, depression, hospitalizations, physical activity & functioning, etc.)
- Longer term effects of the hearing intervention
  - 6-year follow-up study is underway (NCT05532657, R01AG076518)

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Thank you!

ACHIEVE study

www.AchieveStudy.org

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