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Hearing, Hearing Aids, and Cognition: An Audiologist's Guide to Evaluating Evidence, in partnership with the American Academy of Audiology

Nicholas S. Reed, AuD PhD

Nicholas Reed, AuD, PhD

Dr. Nicholas Reed serves as faculty in the Departments of Otolaryngology-Head & Neck Surgery and Population Health and in the NYU Langone Health Optimal Aging Institute. His training is in clinical audiology (AuD, Towson University) and public health with a focus in epidemiology (PhD, Johns Hopkins University) which uniquely position him to approach his research on hearing loss and aging from both a clinical and population level. Dr. Reed's research focuses on direct-to-consumer hearing care, understanding hearing aid use in the United States, the relationship between hearing loss and health care outcomes/interactions (e.g., satisfaction with care, inpatient safety, quality of care, delirium, etc.), and whether interventions targeting hearing loss can mitigate these associations.

Currently, Dr. Reed leads a first-in-kind Audiology Core, founded in 2018, that aims to support and lead the integration of hearing measures into epidemiologic studies of aging (e.g., protocol development, quality assurance, quality control) and has directly supported hearing data collection in over 25000 participants across numerous large cohort studies including the Atherosclerosis Risk in Communities Neurocognitive Study, the Baltimore Longitudinal Study of Aging, National Health Aging and Trends Study, and the Longitudinal Aging Study of India-Diagnostic Assessment of Dementia.

Dr. Reed believes that research should make a difference in the lives of people, and he has strived to be a conscious communicator of his work to the public and policy professionals.

Disclosures

- **Presenter Disclosure**: Financial: Nicholas Reed is employed by New York University Langone Health and receives grant funding from the National Institute on Aging and the National Institute on Deafness and Other Communication Disorders within the National Institutes of Health. He is an adjunct faculty at Johns Hopkins University and a former member of Neosensory scientific advisory board (2021-2023). He received an honorarium for this webinar. Non-financial: Nicholas Reed has no relevant non-financial relationships to disclose.
- **Content Disclosure**: This learning event does not focus exclusively on any specific product or service.
- **Sponsor Disclosure**: This course is presented in partnership with the American Academy of Audiology.

Limitations/Risks

- The applicability and accuracy of the course content may vary by the clinical, geographical, and cultural context; you should evaluate the course accordingly.
- As healthcare is rapidly evolving, new findings may change the validity of the information presented in this course. Providers should always consult the latest research and guidelines from professional associations.
- The interventions discussed in this course may be limited in generalizability, requiring practitioners to consider specific individual and population factors.
- The course may not cover all possible risk factors, diagnostic methods, or treatment options, and complex cases may require additional considerations.
- Healthcare providers should apply cultural competence and sensitivity to ensure effective and respectful care based on their patients' diverse needs.
- Providers should always evaluate the limitations of diagnostic and screening tools, considering their potential for false results as well as any ethical implications.
- It is the responsibility of course participants to critically evaluate the evidence from multiple sources to guide professional practice.

Learning Outcomes

After this course, participants will be able to:

- Describe the plausibility of a causal association between hearing loss and cognitive decline among older adults.
- Identify bias within the current literature on the association of hearing loss with cognitive decline and dementia among older adults.
- Describe the impact, or lack thereof, of treating hearing loss on cognitive decline based on observational and prospective trial results.

Public Health and Hearing Loss

Hearing Loss and Age in the United States

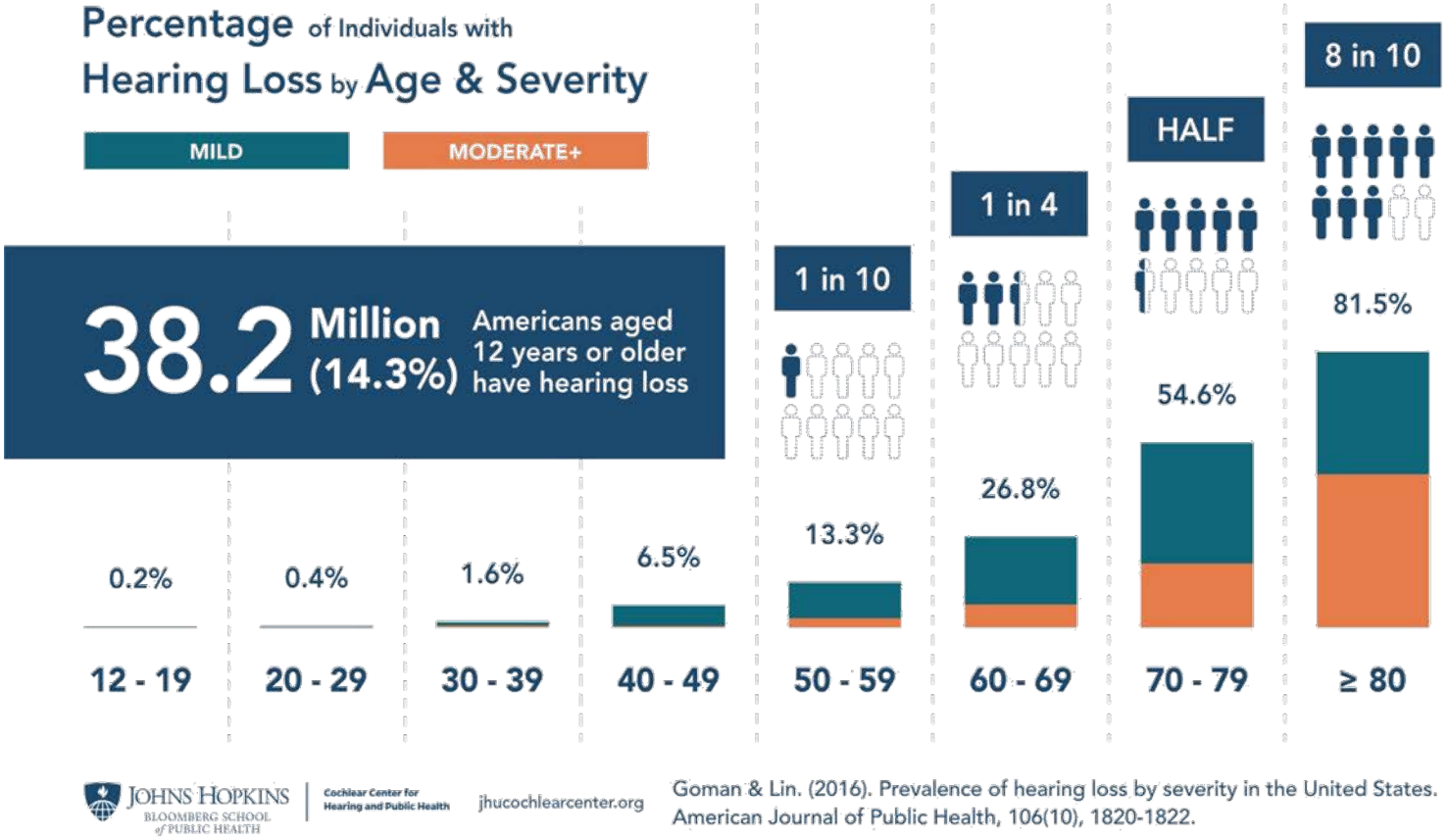
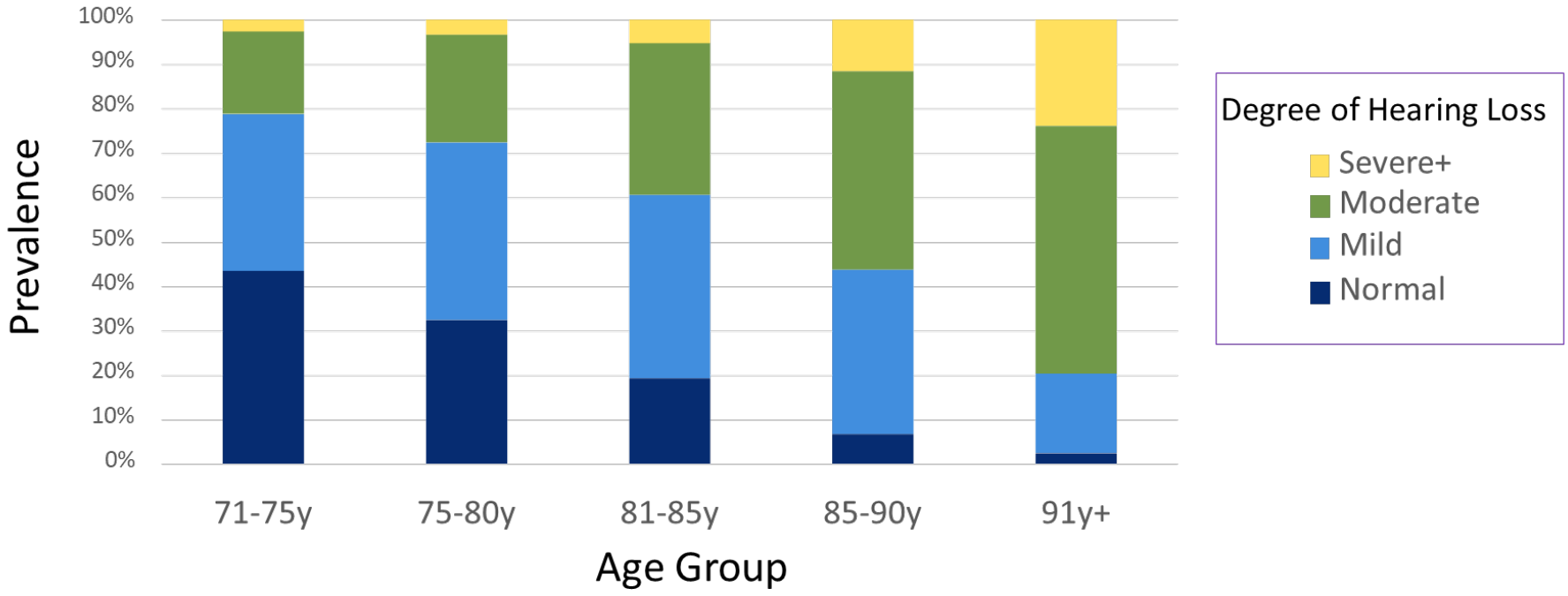
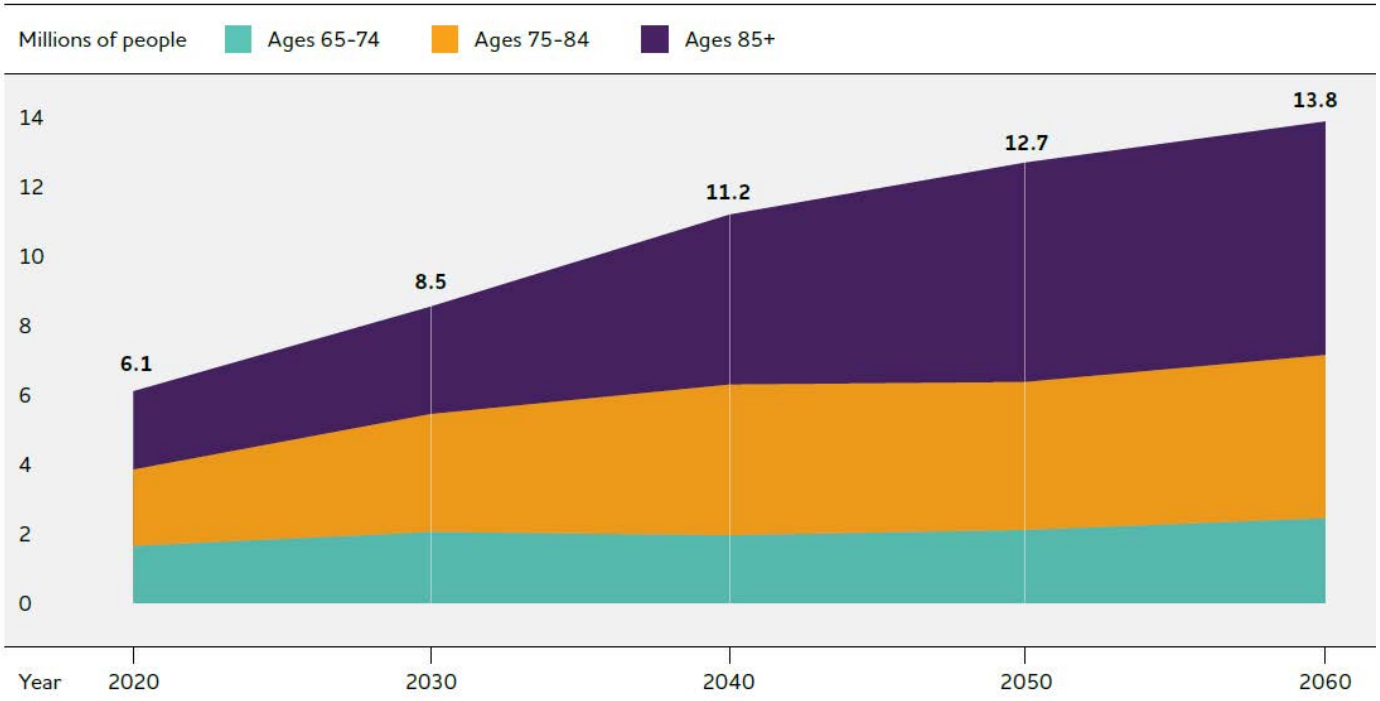


Image courtesy of the JHU Cochlear Center; used with permission.

Prevalence of Hearing Loss in Adults Aged ≥71 Years in the United States: National Health & Aging Trends Study



Projected Number of People Age 65 and Older (Total and by Age) with Alzheimer's Dementia, U.S., 2020 to 2060



Created from data from Rajan et al.[A6,224]

What is Dementia?

- Clinical Diagnosis!
- Cognitive or behavioral (neuropsychiatric) symptoms that:
  - Interfere with the ability to function at work or at usual activities; and
  - Represent a decline from previous levels of functioning and performing; and
  - Are not explained by delirium or major psychiatric disorder
- At least 2 domains of cognitive function (e.g., memory, language, executive function)
- Significant interference in the ability to function at work or in usual daily activities
  - Differentiates dementia from MCI

The Cost of Dementia

- Substantial health care costs (↑$1 trillion/year global)
- Personal Stories

Studying Senses in Aging: Input for the Brain

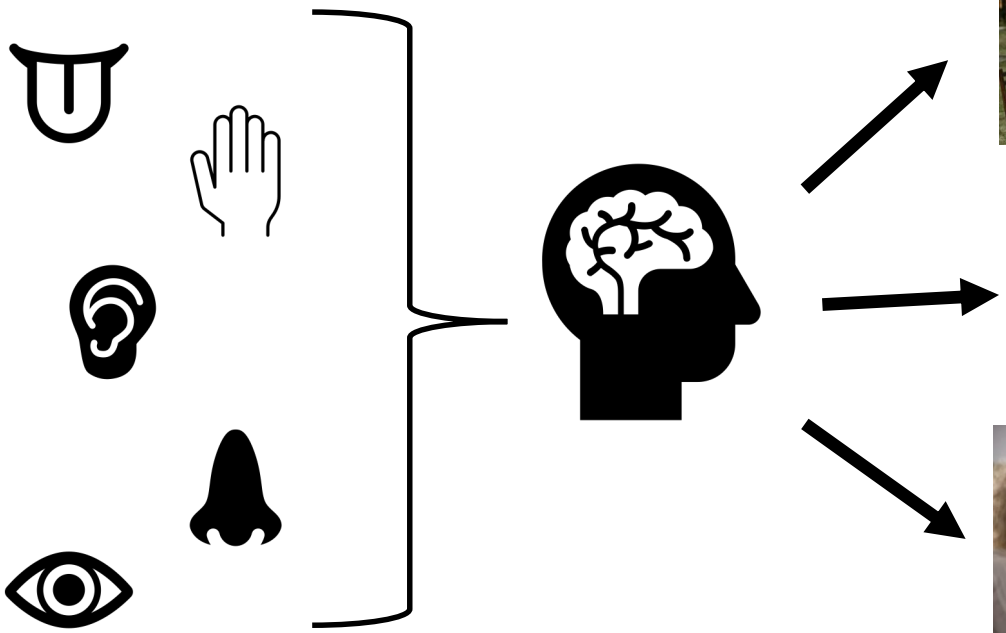


Image by cottonbro studio, via pexels.com

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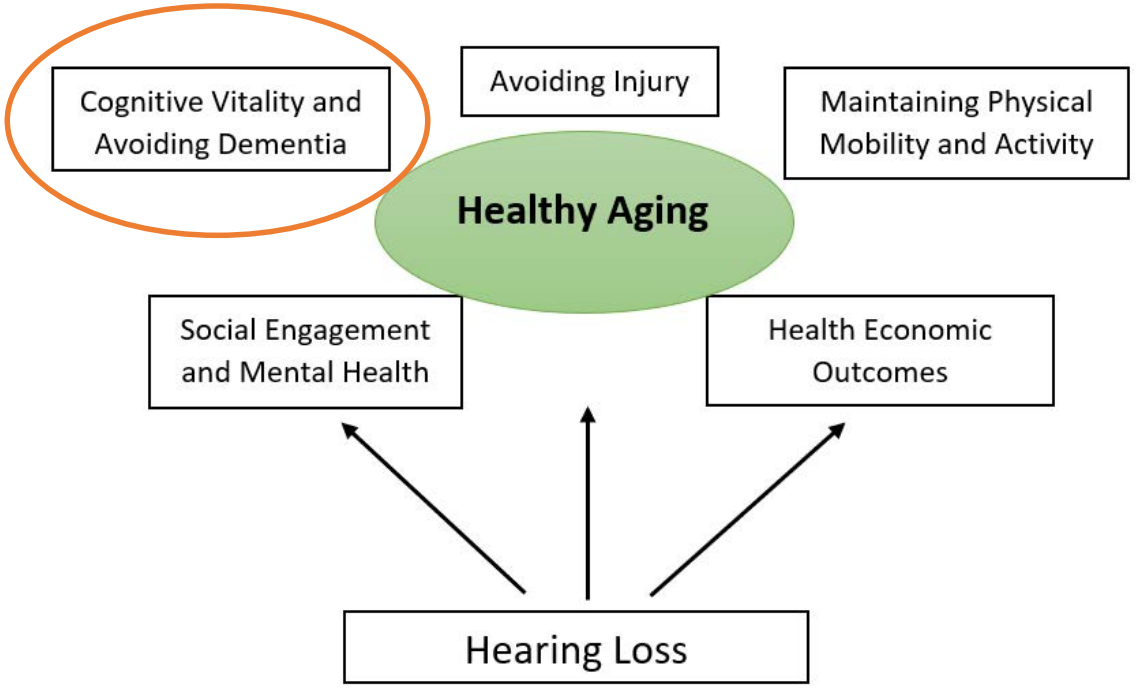
Hearing & Healthy Aging



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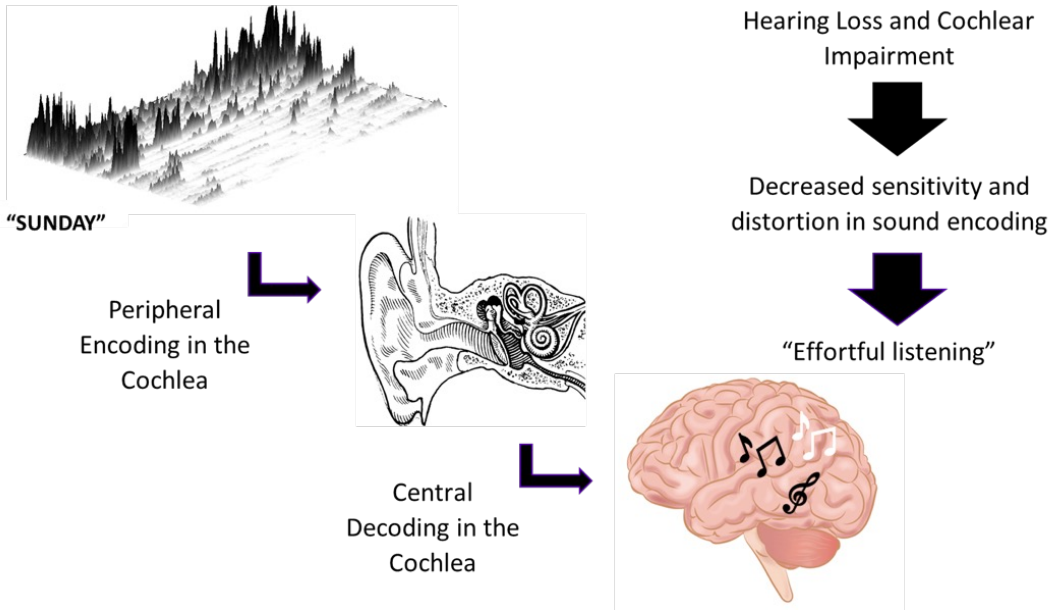
Hearing Loss and Cognitive Decline: An Explosion in Evidence

How We Hear: Peripheral Encoding & Central Decoding



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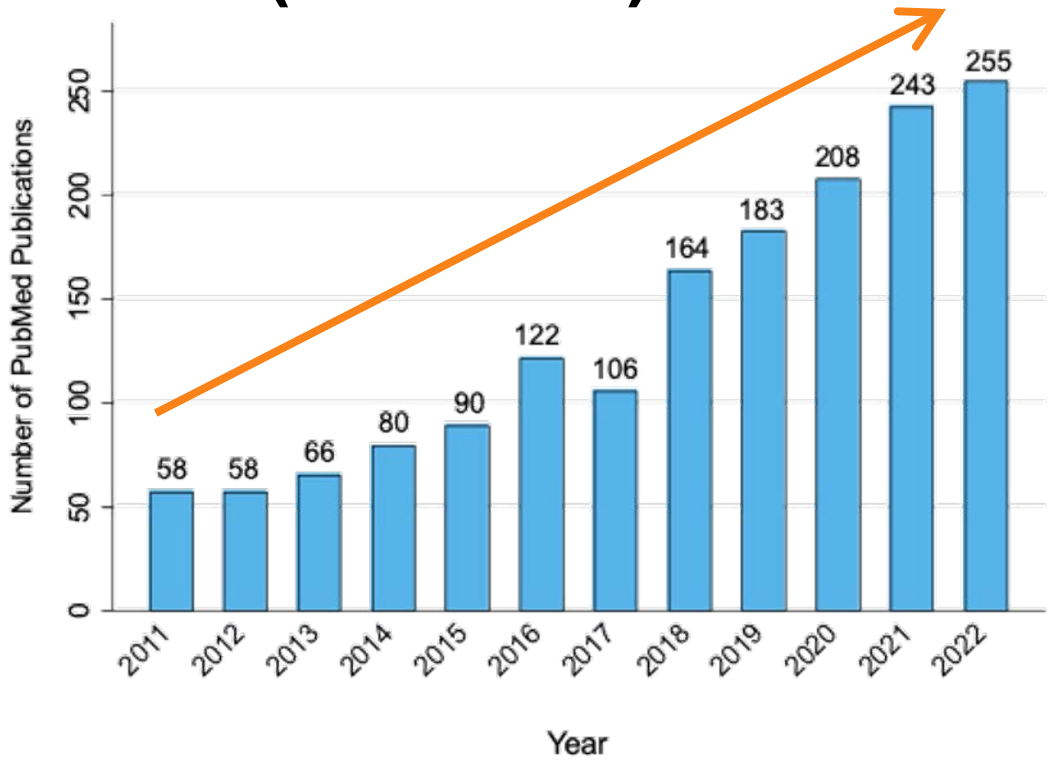
Increase in Age-Related Hearing Loss Literature Over Time (Pubmed)



Hearing Loss & Cognition Timeline

Relationship of Hearing Impairment to Dementia and Cognitive Dysfunction in Older Adults

Richard F. Uhlmann, MD, MPH; Eric B. Larson, MD, MPH; Thomas S. Rees, PhD; Thomas D. Koepsell, MD, MPH; Larry G. Duckert, MD, PhD

1989

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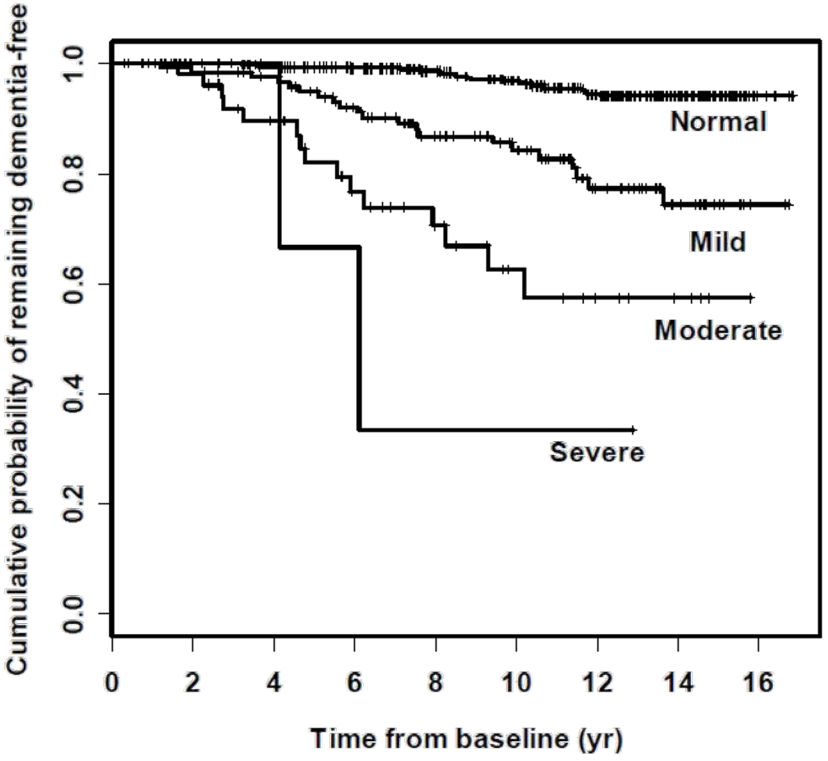
Hearing Loss and Incident Dementia

Frank R. Lin, MD, PhD; E. Jeffrey Metter, MD; Richard J. O'Brien, MD, PhD; Susan M. Resnick, PhD; Alan B. Zonderman, PhD; Luigi Ferrucci, MD, PHD

Hearing Loss and Incident Dementia



639 adults followed for >10 years Baltimore Longitudinal Study on Aging

Risk of All-Cause Dementia*			
	HR	95% CI	p
Mild	1.89	1.00 – 3.58	0.05
Moderate	3.00	1.43 – 6.30	.004
Severe	4.94	1.09 – 22.4	.04

*Compared to normal hearing

Adjusted for age, sex, race, education, diabetes, smoking, & hypertension

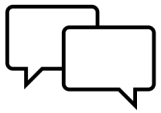
Hearing Loss and Cognitive Decline

Lin et al. (2013) examined adjusted Modified Mini Mental State & Digit Symbol Substitution scores by years of follow-up and hearing loss status in 1,966 adults > 70 years followed for 6 years (Health ABC study)

41% faster rate of cognitive decline in 3MS scores in HL vs. NH

↓

Requires oral (auditory) communication to complete the task



VS

32% faster rate of cognitive decline in DSS scores in HL vs. NH

↓

Can be completed *without* auditory input

Independent association of cognitive decline and hearing loss even on cognitive assessment without auditory input

Hearing Loss & Cognitive Decline

Hearing Impairment and Cognitive Decline: A Pilot Study Conducted Within the Atherosclerosis Risk in Communities Neurocognitive Study

Jennifer A. Deal*, A. Richey Sharrett, Marilyn S. Albert, Josef Coresh, Thomas H. Mosley, David Knopman, Lisa M. Wruck, and Frank R. Lin

Hearing Loss & Cognition Timeline

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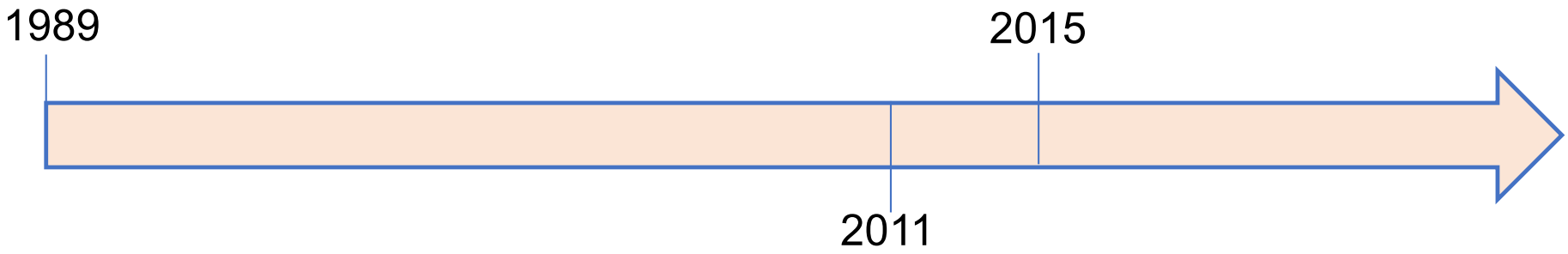


Hearing Loss and Incident Dementia

Frank R. Lin, MD, PhD; E. Jeffrey Metter, MD; Richard J. O'Brien, MD, PhD; Susan M. Resnick, PhD; Alan B. Zonderman, PhD; Luigi Ferrucci, MD, PHD

Quiz Hint

Q6

Refining Estimates of Hearing Loss and Incident Dementia

Deal et al. (2017) characterized incident dementia by hearing status among 1889 adults followed for 9 years Health Aging and Body Composition Study

Risk of Dementia				
	N (%)	HR	95% CI	p
No Hearing Loss	80/786 (10%)	Ref	-	-
Mild Hearing Loss	79/716 (11%)	1.02	0.75-1.40	0.89
≥Moderate Hearing Loss	70/387 (18%)	1.55	1.10-2.19	0.01
4-Frequency PTA (per 10 dB increase)		1.14	1.03-1.26	0.01

Adjusted for age, sex, race, education, study site, smoking status, hypertension, diabetes, stroke

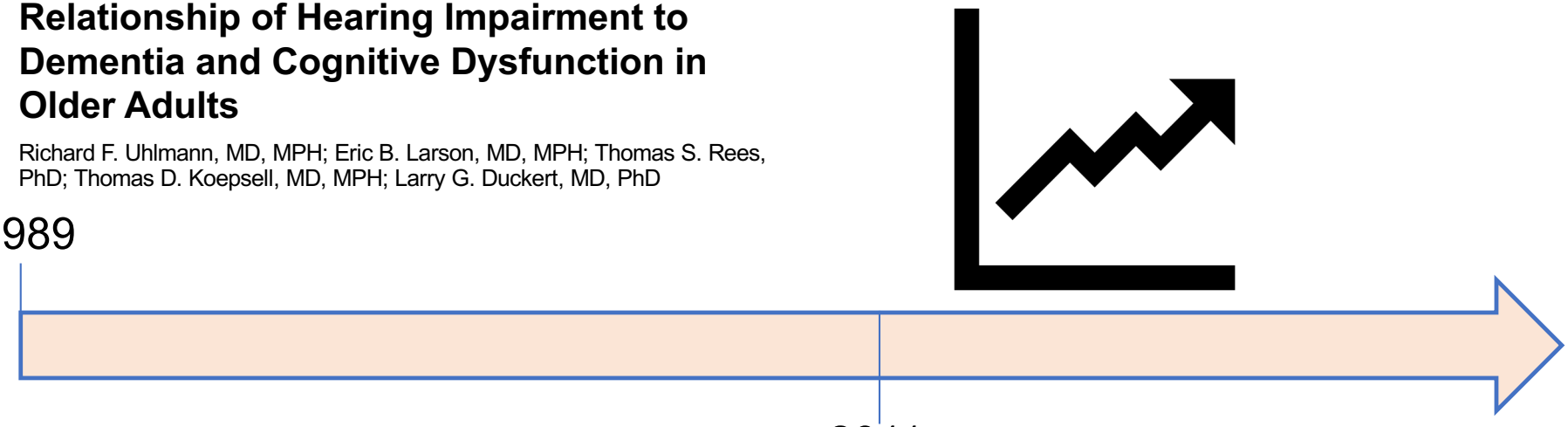
Abbreviations: PTA, pure tone average

Hearing Loss & Cognition Timeline

Relationship of Hearing Impairment to Dementia and Cognitive Dysfunction in Older Adults

Richard F. Uhlmann, MD, MPH; Eric B. Larson, MD, MPH; Thomas S. Rees, PhD; Thomas D. Koepsell, MD, MPH; Larry G. Duckert, MD, PhD

1989



2011

Hearing Loss and Incident Dementia

Frank R. Lin, MD, PhD; E. Jeffrey Metter, MD; Richard J. O'Brien, MD, PhD; Susan M. Resnick, PhD; Alan B. Zonderman, PhD; Luigi Ferrucci, MD, PHD

Hearing Loss &
Cognitive Decline

Observational Studies Agree:

Hearing Loss is Associated with Dementia & Cognitive Decline

Hearing Loss and Dementia: A Meta-Analysis of Prospective Cohort Studies
Zhen Liang, Ao Li, Yuanyuan Xu, Xiaoyun Qian, & Xia Gao

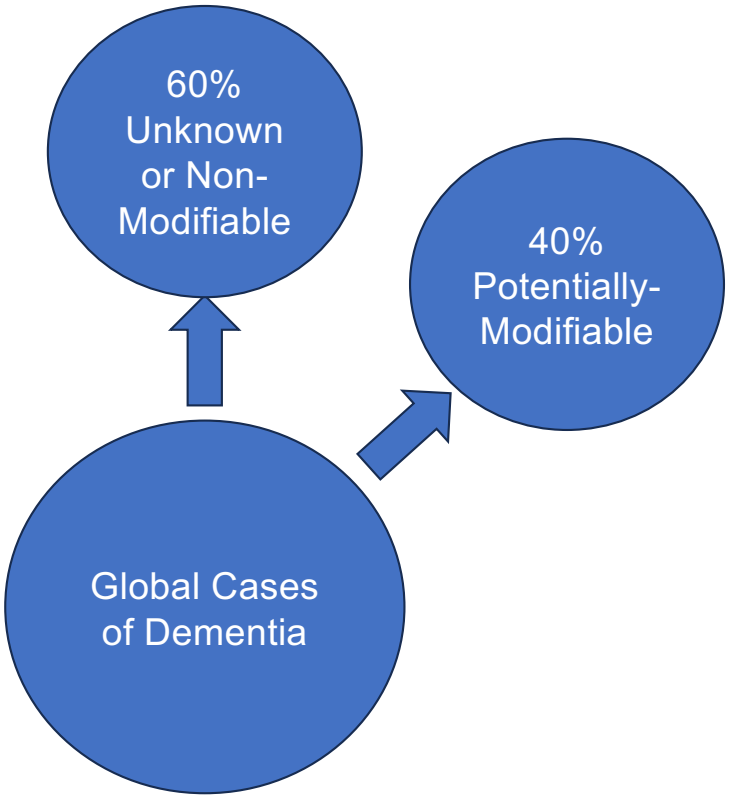
Association of Age-Related Hearing Loss With Cognitive Function, Cognitive Impairment, and Dementia
A Systematic Review and Meta-Analysis
David G. Loughrey, Michelle E. Kelly, George A. Kelley, Sabina Brennan, & Brian Lawlor

Dementia Prevention, Intervention, and Care: 2020 Report of the Lancet Commission
Gill Livingston, Jonathan Huntley, Andrew Sommerlad, David Ames, et al.

Quiz Hint

Q1

State of Dementia Prevention



Proportion of Risk Due to Specific Factors

Hearing Loss – 8%

Less education – 7%

Smoking – 5%

Depression, Social isolation – 4%

Traumatic brain injury – 3%

Air pollution, Physical inactivity, Hypertension – 2%

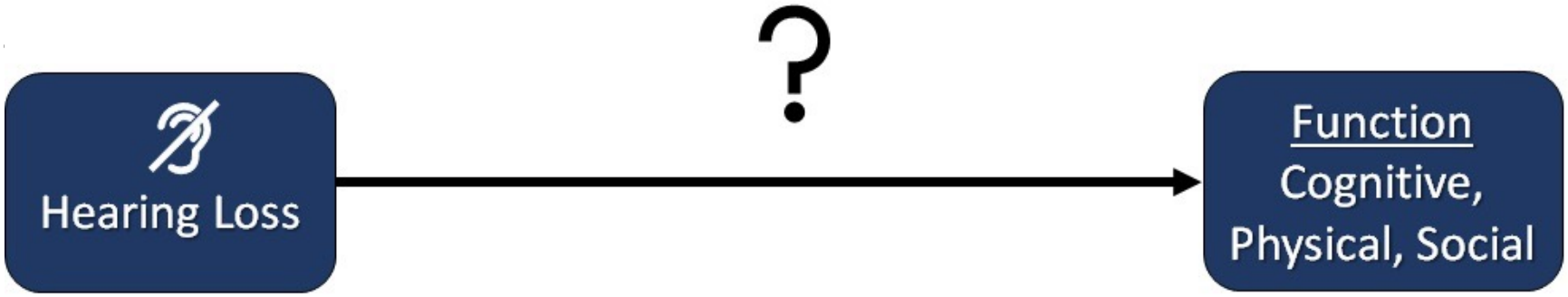
Obesity, diabetes, heavy alcohol use – 1%

Interpretation:
If all hearing loss cases were eliminated, then 8% of dementia cases would be eliminated

Livingston et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet. 2020 Aug 8;396(10248):413-446. doi: 10.1016/S0140-6736(20)30367-6.

Linking Hearing Loss and Cognitive Decline

Does Hearing Loss Lead to Decreased Function in Older Adults?

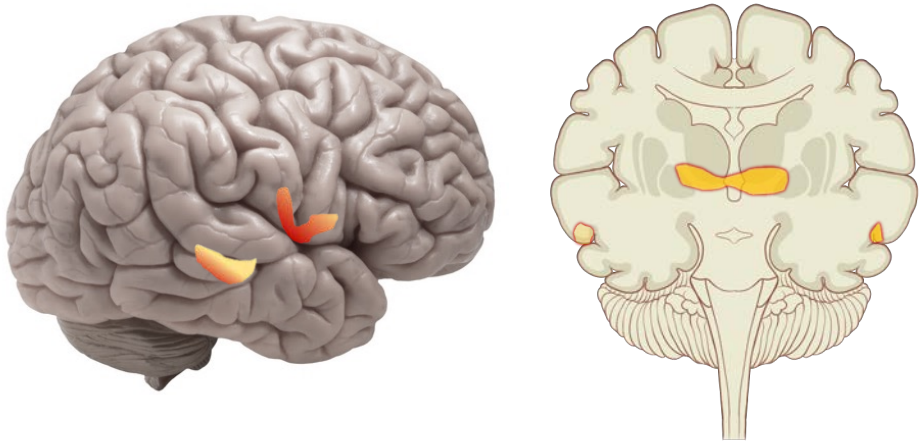


- We don’t know for certain (no complete mediation analyses)
- Several mechanistic pathways have been hypothesized

Hearing Loss & Cognitive Load

Poorer hearing is associated with:

A. Reduced language-driven activity in primary auditory pathways



B. Increased compensatory language-driven activity in pre-frontal cortical areas

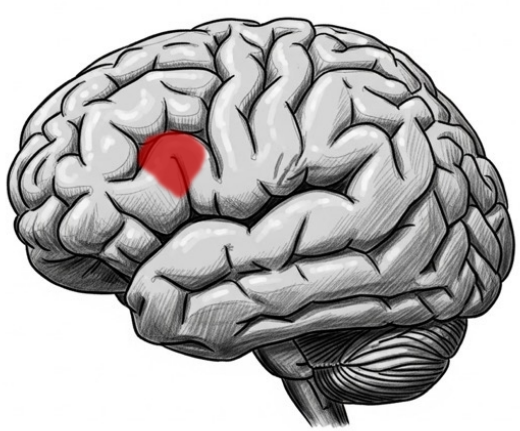


Image adapted from Easy-Peasy.AI. https://easy-peasy.ai/ai-image-generator/images/digital-sketch-human-brain-prefrontal-cortex

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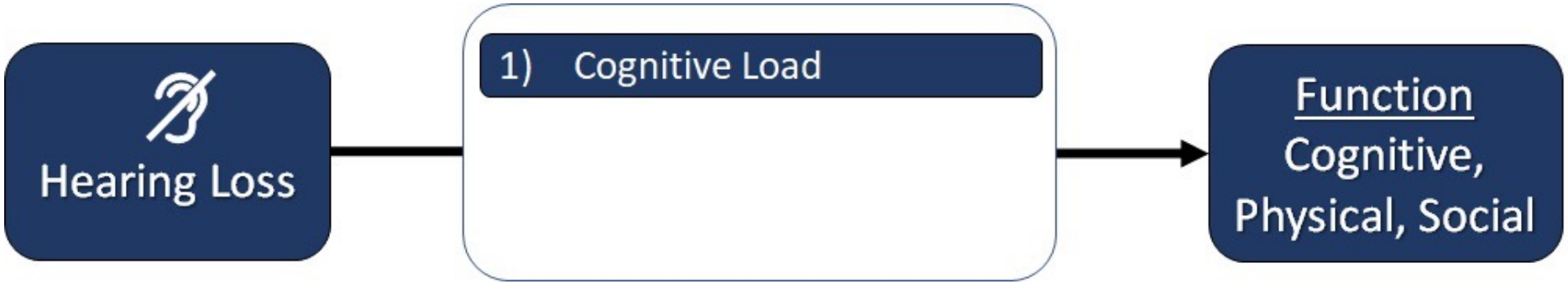
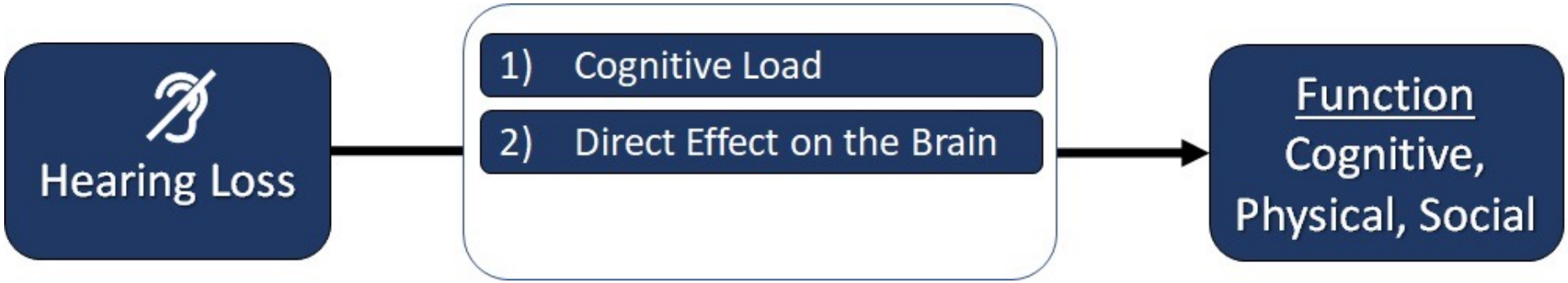
Does Hearing Loss Lead to Decreased Function in Older Adults?



- **Cognitive Load ("Information Degradation")**
  - **Hearing involves (1) peripheral transduction of sound (encoding) in the cochlea & (2) central processing (decoding) in the brain**
  - **With cochlear impairment, decreased sensitivity & distortion in sound encoding**
  - **"Effortful listening"**

Changes in Brain Structure

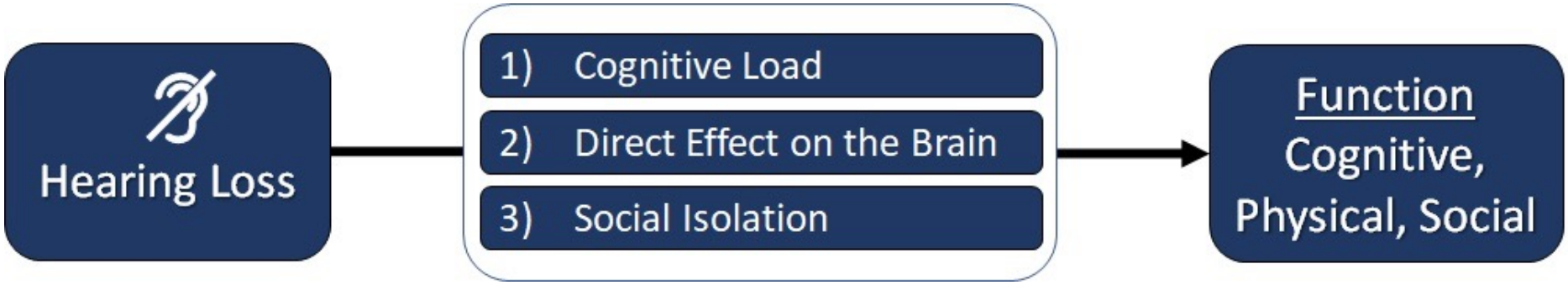


- **Direct Effects on the brain ("Sensory deprivation")**
  - **Lower grey matter volume in the auditory cortex**
  - **Recruitment of executive networks (outside primary auditory cortex)**
  - **Faster rates of brain atrophy & poorer white matter integrity in temporal lobe**
  - **Impacts on the brain are independent of Alzheimer's pathology ('second hit')**

Quiz Hint

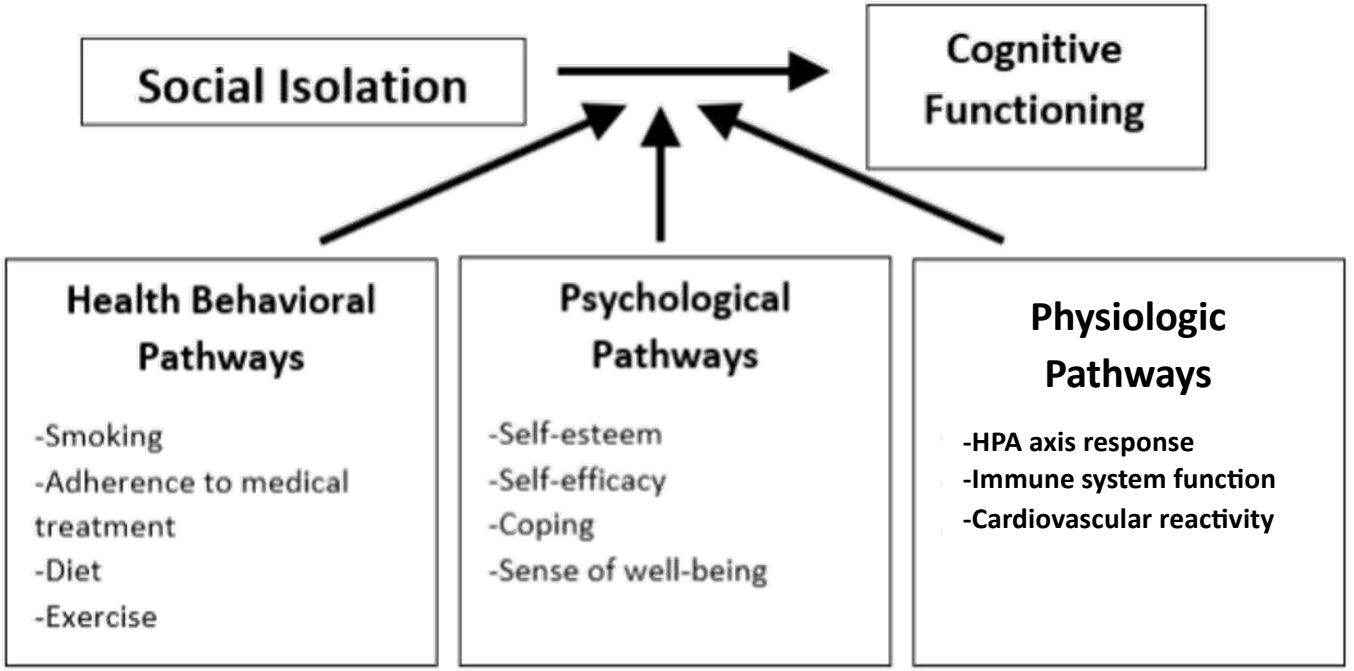
Q5

Social Isolation and Loneliness



- **Associated with many adverse health outcomes, including cognition, cardiovascular disease and mortality**
- **Has also been shown to have biological effects (e.g., increased inflammation, upregulation of pro-inflammatory cytokines)**

Sensory Loss and Cognition: Social Isolation

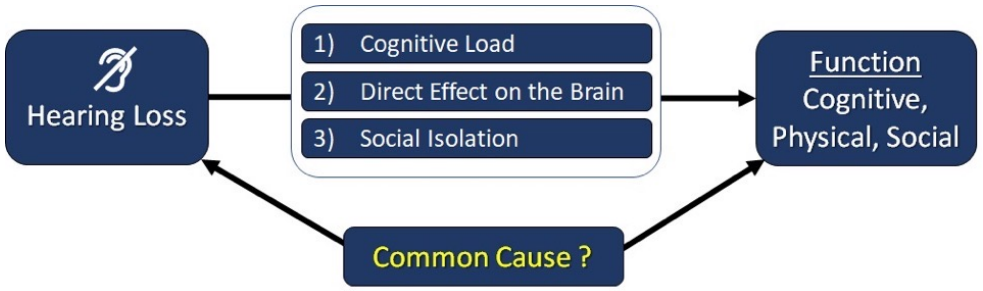


Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. *Soc Sci Med*. 2000;51(6):843-857. doi:10.1016/s0277-9536(00)00065-4

Potential Non-Causal Mechanisms?

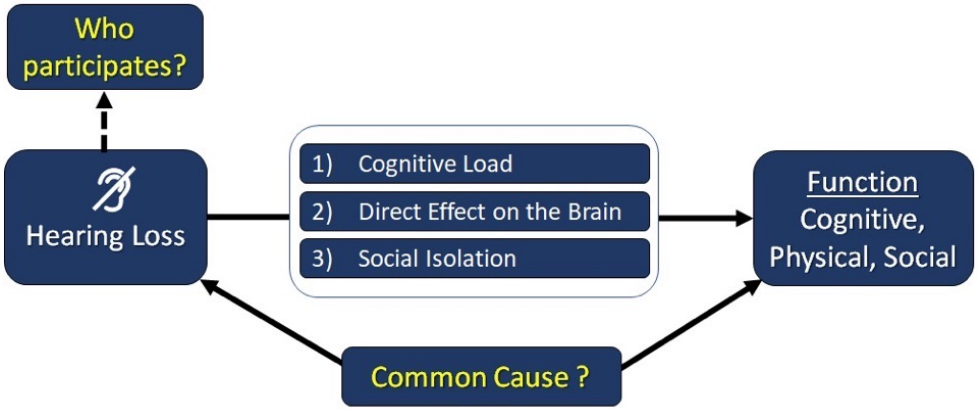
- Everything presented thus far assumes a clear, causal association but other “bias” and “confounding” could be at play

Non-Causal: Common Cause



- **Common Cause**
  - **e.g., inflammation, vascular disease**
  - **“Confounding”**
  - **If true, intervening on hearing loss will *not* prevent dementia**

Non-Causal: Selection Bias

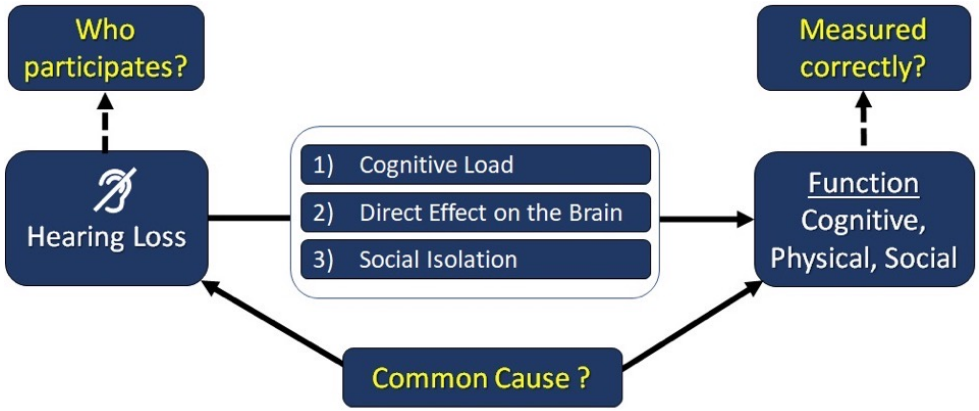


- **Who participates?**
  - **"Selection bias"**
    - Systematic error due to the way in which participants selected to participate in the study or to be included in the analysis
  - **Important for hearing aid research**
    - Hearing aid users are fundamentally different from non-users (higher education, SES, etc.)

Quiz Hint

Q7

Non-Causal: Information Bias



- **Measured Correctly?**
  - **"Information bias"**
    - Systematic error in the measurement of the exposure, outcome, or other factors in the study
  - **Example: Persons with hearing loss do poorly on a cognitive test because they did not hear it**

Can we measure hearing in people with dementia? –Yes!

Test-Retest Reliability of Audiometric Assessment in Individual With Mild Dementia
JAMA Otolaryngology-Head & Neck Surgery
Katrina McClannahan, Yi-Fang Chiu, Mitchell Sommers, Jonathan Peelle

- *"Test-retest reliability for hearing measures obtained from participants with mild dementia was comparable to that obtained from cognitively normal participants."*

McClannahan KS, Chiu Y, Sommers MS, Peelle JE. Test-Retest Reliability of Audiometric Assessment in Individuals With Mild Dementia. *JAMA Otolaryngol Head Neck Surg.* 2021;147(5):442–449. doi:10.1001/jamaoto.2021.0012

Summary:

Cause	Not a cause
• Increased cognitive load • Direct effect on brain structure & function • Increased social isolation & loneliness	• Common cause • Selection bias • Information bias

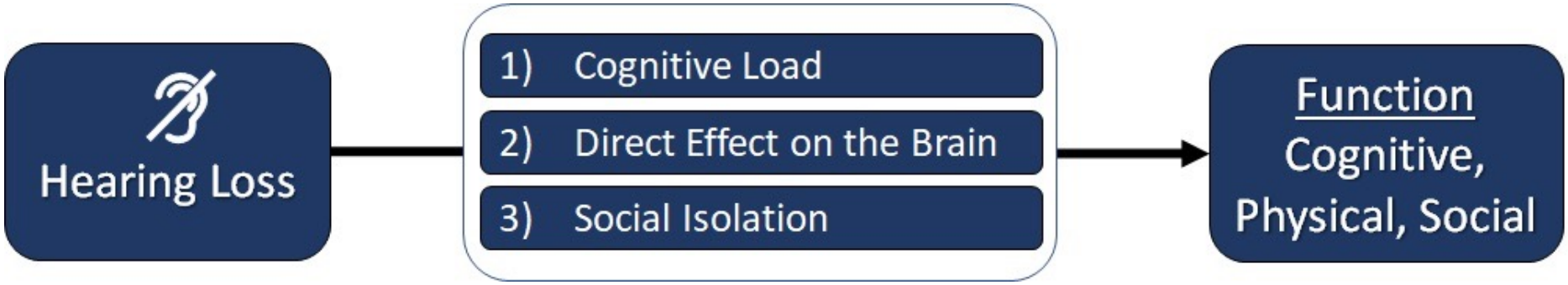
We think hearing loss *causes* functional decline through several pathways but we don't know that this is true

Interpreting Epidemiologic Studies

- Including and beyond what was covered, Factors to Consider:
  - Design (e.g. ,prospective vs. cross-sectional)
  - Reverse causation
  - Selection bias
  - Measurement of hearing loss
  - Measurement of outcome
  - Other sources of bias?
  - Generalizability?
  - Impact of treatment? (selection bias…)

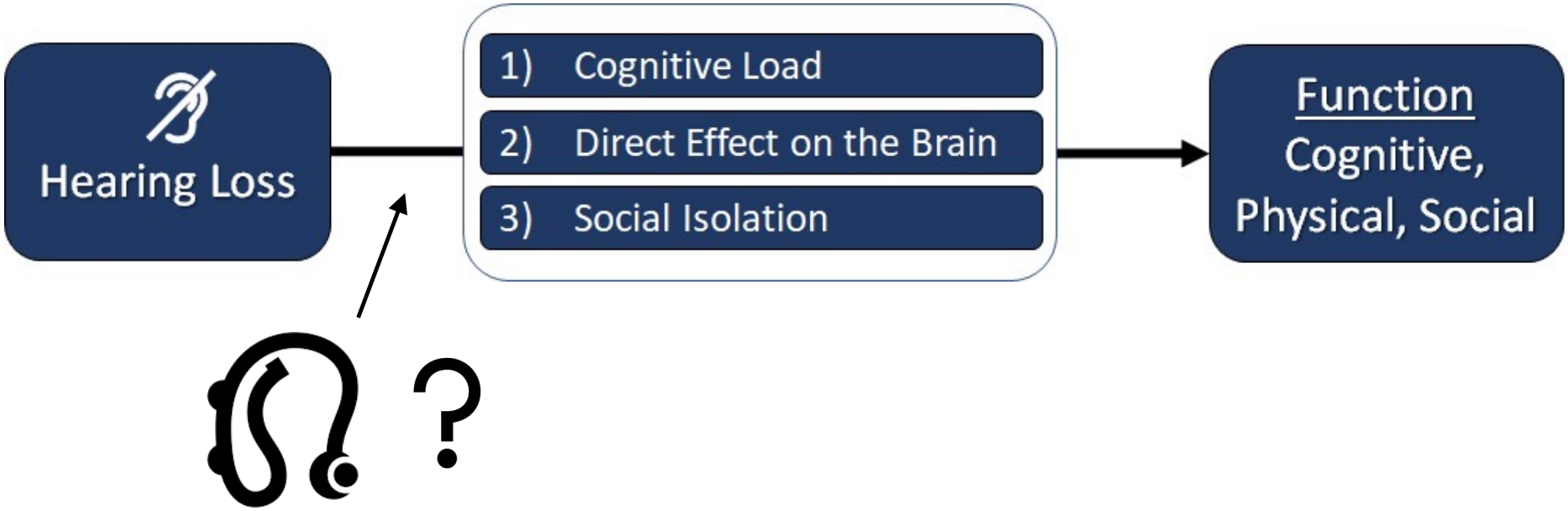
Hearing Care to Reduce Cognitive Decline: Observational Evidence

Modifying the Pathway from Sensory Loss to Cognition & Dementia



Whitson HE et al. American Geriatrics Society and National Institute on Aging Bench-to-Bedside Conference: Sensory Impairment and Cognitive Decline in Older Adults. J Am Geriatr Soc. 2018 Nov;66(11):2052-2058. doi: 10.1111/jgs.15506. Epub 2018 Sep 24.

Modifying the Pathway from Sensory Loss to Cognition & Dementia



Whitson HE et al. American Geriatrics Society and National Institute on Aging Bench-to-Bedside Conference: Sensory Impairment and Cognitive Decline in Older Adults. J Am Geriatr Soc. 2018 Nov;66(11):2052-2058. doi: 10.1111/jgs.15506. Epub 2018 Sep 24.

Reduce Cognitive Decline

Before definitive evidence was available as to whether hearing aids reduced cognitive decline, media outlets jumped to treatment

The New York Times
12/30/2019

For Better Brain Health, Preserve Your Hearing

Hearing loss is the largest modifiable risk factor for developing dementia, exceeding that of smoking, high blood pressure, lack of exercise and social isolation.

The Washington Post
10/20/2022

Hearing loss is a major risk factor for dementia. Hearing aids can help.

Hearing aids, now available over the counter, may address hearing loss and help prevent cognitive decline.

Do Hearing Aids Prevent Dementia?

Association between hearing aid use and all-cause and cause-specific dementia: an analysis of the UK Biobank cohort

Fan Jiang, Shiva Raj Mishra, Nipun Shrestha, Akihiko Ozaki, Salim Virani, Tess Bright, Hannah Kuper, Chengchao Zhou, a& Dongshan Zhu

Retracted by Authors

Original Published Findings

	Hazard Ratio (95% CI)
No hearing loss	1.0 (Referent)
Hearing loss	
No hearing aids	1.28 1.42 1.57
Hearing aids	0.98 1.04 1.10

Noted that the variables were coded incorrectly (backward) but does this suggest that **hearing aid use is actually associated with increased risk of dementia?**

Reference Groups Matter

- Can we assess the effect of hearing aids compared to adults without hearing loss? – Not Likely!
  - To assess a therapeutic effect of X → Y, all groups should be at risk to experience the proposed association between X → Y
  - Appropriate model is to limit to only those with hearing loss

Hearing Loss, Dementia, Hearing Aids in Observational Data

Hearing Loss and Dementia Prevalence in Older Adults in the US
JAMA 2022
Huang AR, Jiang K, Lin FR, Deal JA, Reed NS

Older adults with hearing loss who reported using hearing aids had lower risk of dementia

Multivariable-Adjusted Association Between Hearing Loss, Hearing Aid Use, and Dementia in the National Health Aging Trends Study (2021)

	Weighted prevalence of dementia (%)	Prevalence Ratio	95% CI	p
No Hearing Loss	6.19%	Ref	-	-
Mild Hearing Loss	8.93%	1.08	0.72-1.63	0.71
≥Moderate Hearing Loss	16.52%	1.61	1.09-2.38	0.02
4-Frequency PTA (per 10 dB increase)		1.16	1.07-1.26	<0.001
Hearing Aid Use Among Those with ≥Moderate Hearing Loss				
No	21.53%			
Yes	11.46%	.68	0.47-1.00	.05

Huang AR, Jiang K, Lin FR, Deal JA, Reed NS. Hearing Loss and Dementia Prevalence in Older Adults in the US. JAMA. 2023;329(2):171–173. doi:10.1001/jama.2022.20954

Are Hearing Aid Users the Same as Non-Users?

- People with hearing loss who use hearing aids are different to those with hearing loss who do not use hearing aids
  - Income
  - Education
  - Health seeking behaviors
  - Perception of hearing loss
- Observational data can miss details (ownership ≠ use)

Are Hearing Aid Users the Same as Non-Users?

Preventing dementia through correcting hearing: huge progress but more to do
Lancet Public Health 2023
Livingston & Costafreda

"Observational findings might be confounded, as those who use hearing aids might have better access to financial, social, or cognitive resources to look after their health compared with those with hearing loss without hearing aids"

The question of whether treating hearing loss could reduce cognitive decline remained unknown based on Observational Literature

- Question cannot be definitively answered through observational studies because of bias from residual confounding (e.g., health behaviors, etc.)
- Meta-analysis of observational studies suggest hearing aid use associated with 19% decreased hazard of long-term cognitive decline
- **Randomized controlled trials** were needed to investigated effect of hearing intervention on long-term cognitive decline or other functional outcomes (e.g., social isolation, loneliness, etc.)

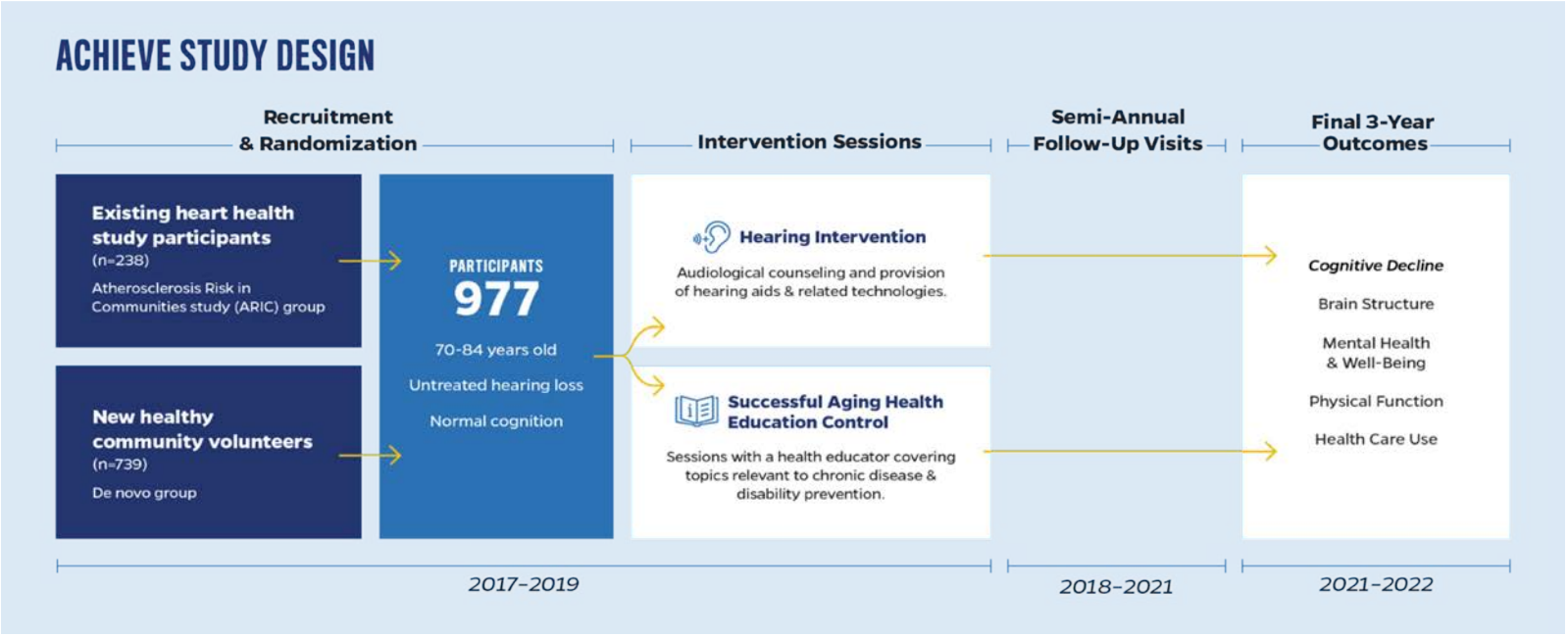
Randomized Trials to Examine Hearing Care on Cognition

Effects of hearing intervention on cognitive decline:

Results of the Aging & Cognitive Health Evaluation in Elders (ACHIEVE) randomized trial

- PIs: Frank Lin, MD PhD & Josef Coresh, MD PhD
- Can treating hearing loss reduce cognitive decline over 3 years in older adults with hearing loss without substantial cognitive impairment?

Study Design



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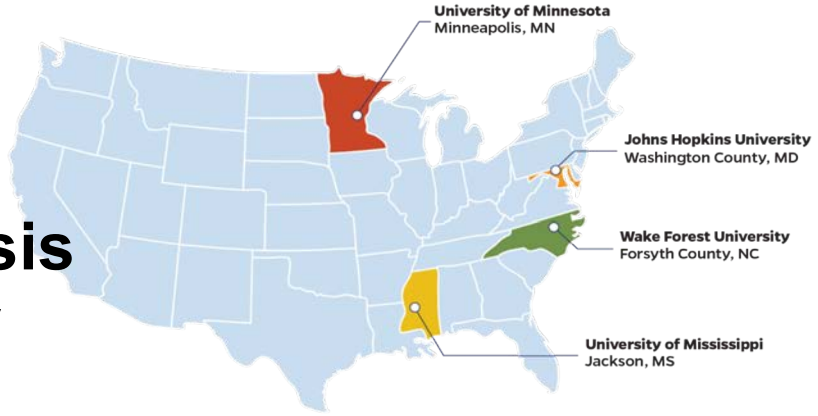
Randomized Trials

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 ages 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

Image courtesy of the JHU Cochlear Center; used with permission.

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

Randomization

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

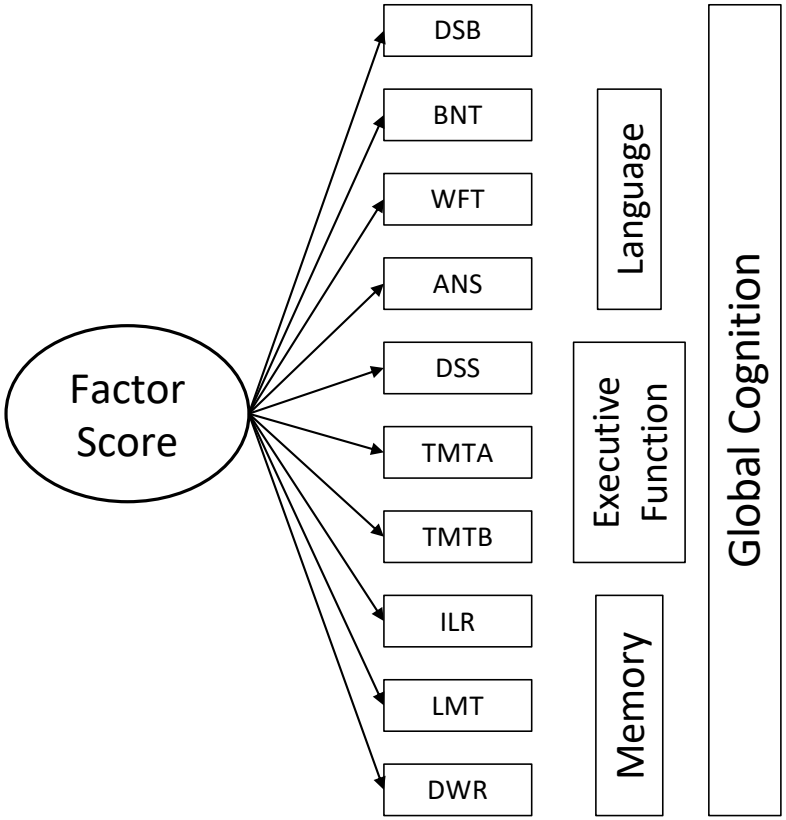
- Baseline & every 6 month in-person visits for intervention delivery & outcome assessments for 3 years
- **Primary endpoint**: Change from baseline to Year 3 in a global cognition standardized factor score derived from a comprehensive neurocognitive battery administered annually
- Secondary cognitive 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



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

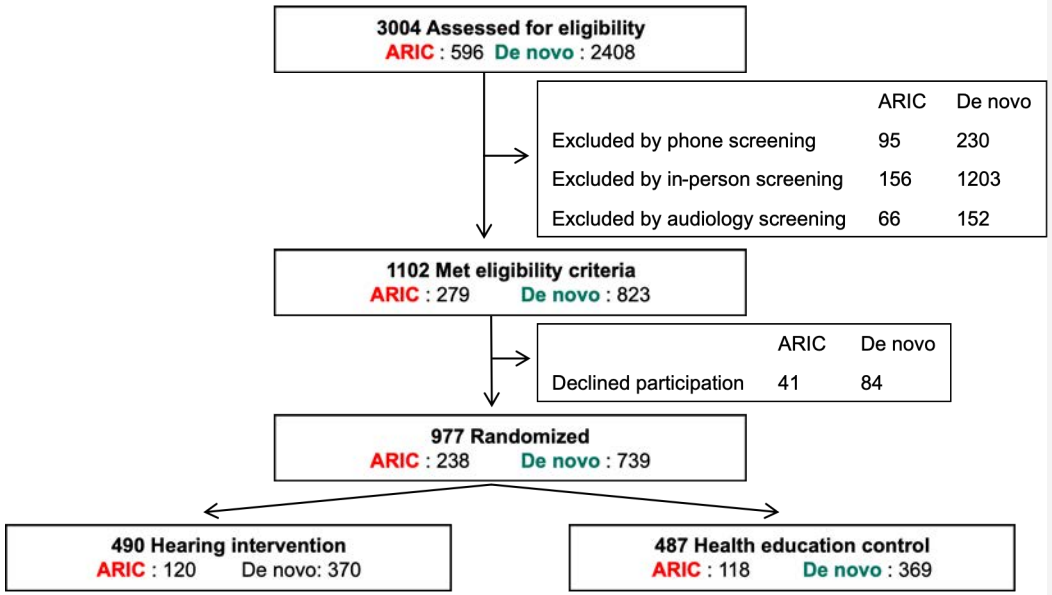
3 tests are used to compute factor scores for each cognitive domain (Secondary outcomes)

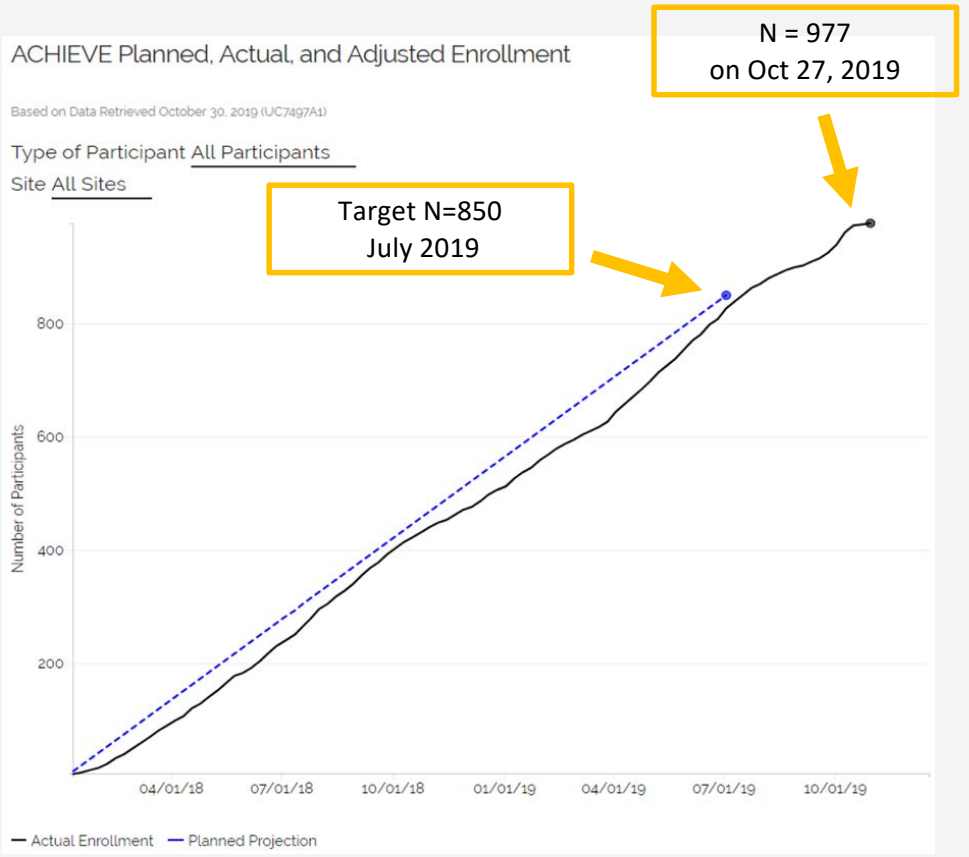
Latent factors are standardized to the ACHIEVE baseline.

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

Randomized Trials

Recruitment





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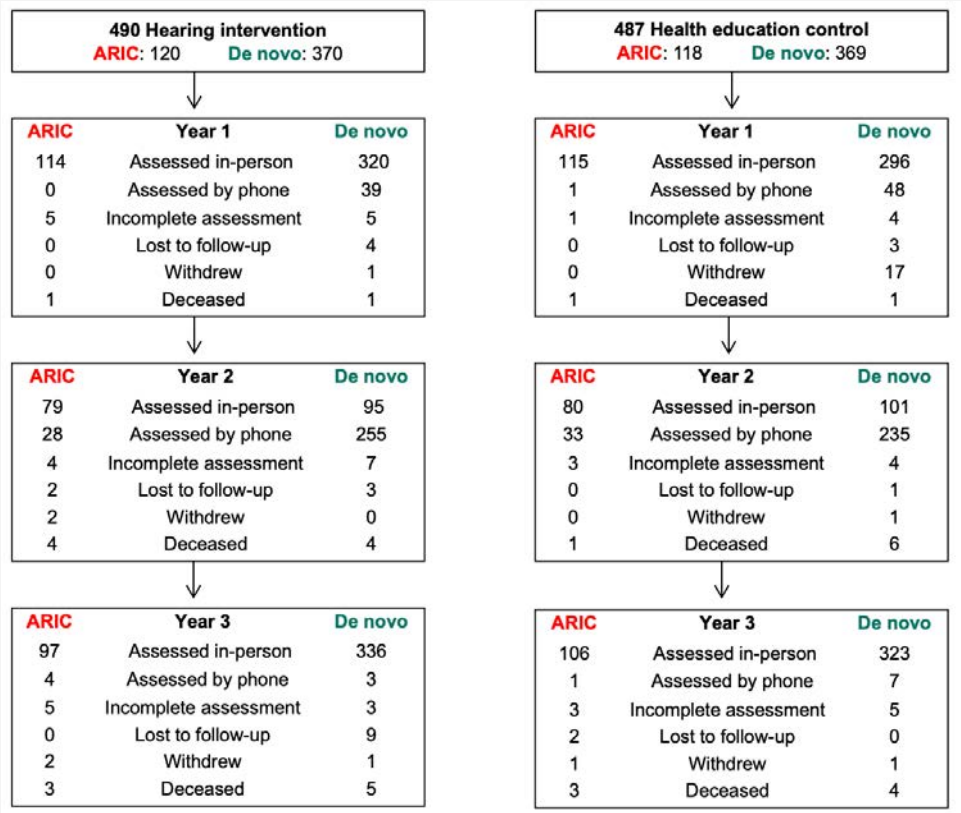
Randomized Trials

Recruitment

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

Covid-related shutdowns occurred between baseline visits (end of intervention) and 3rd year visits



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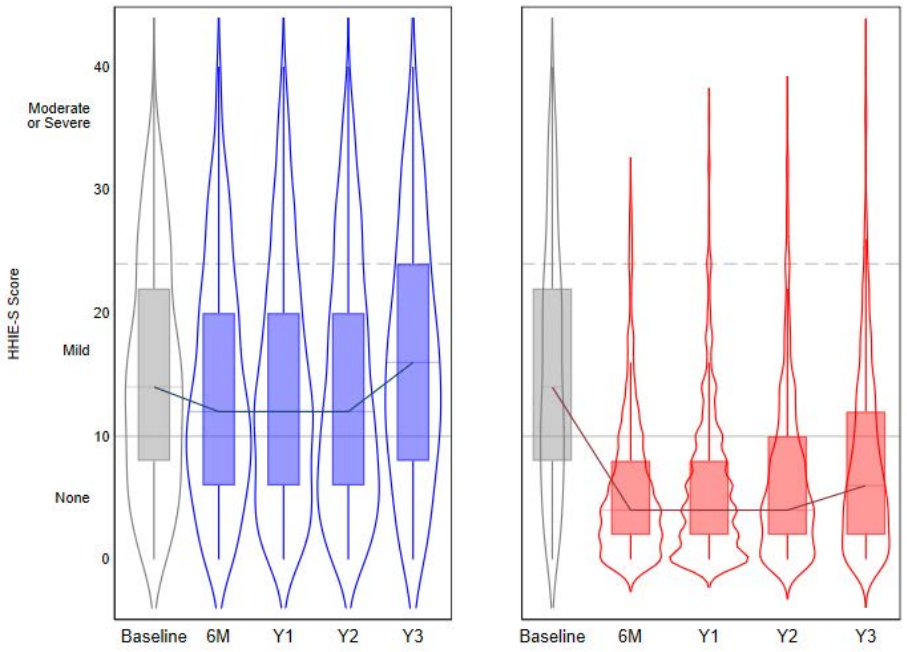
Effect on Hearing Outcome

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

Total (ARIC & De novo)
Continuous Score



Health Education Control

Hearing Intervention

Image courtesy of the JHU Cochlear Center; used with permission.

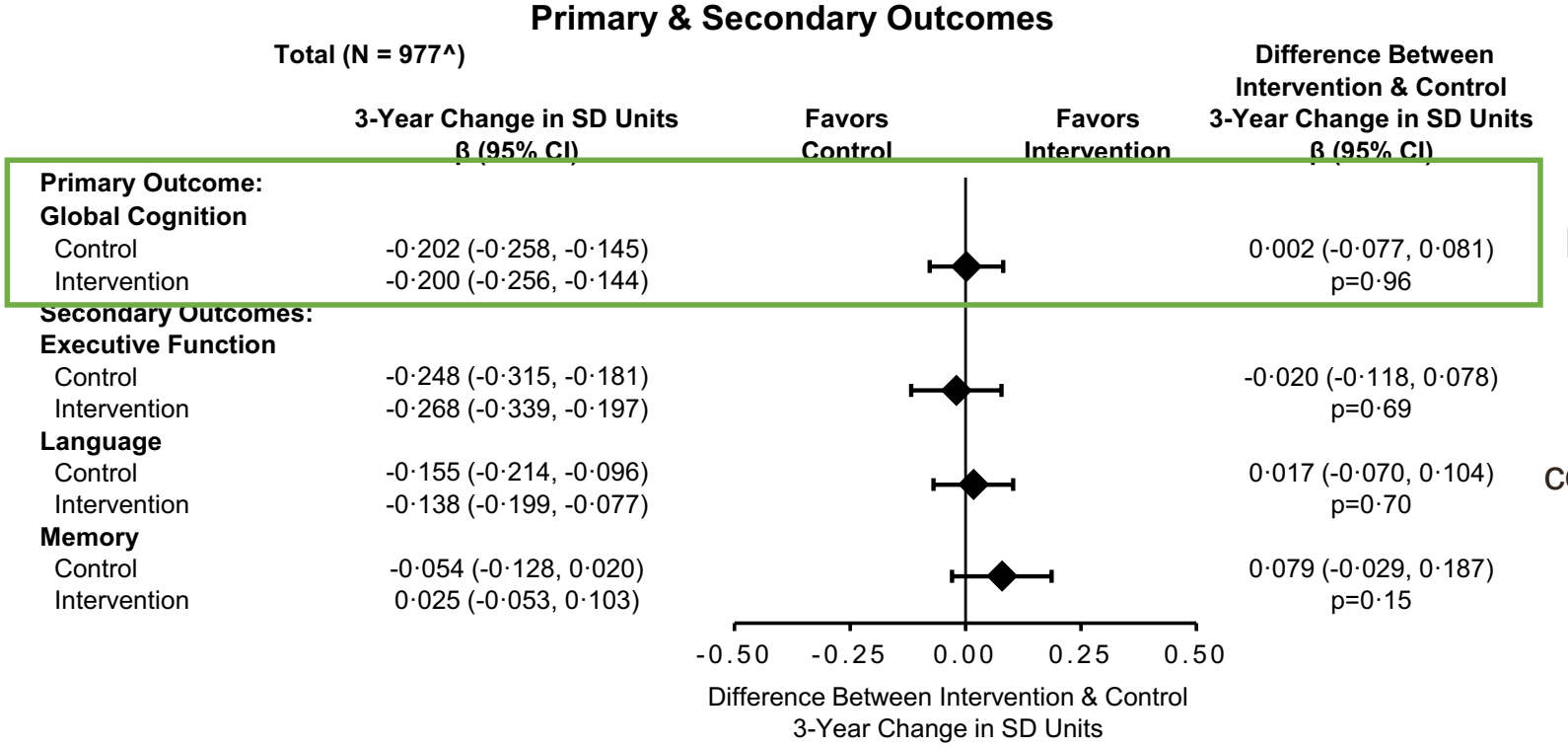
Effect on Hearing Outcome

Hearing Intervention Participant Self-Reported Hours of Hearing Aid Use

Hours of Hearing Aid Use/Day Mean (SD)	All Hearing Intervention Participants (N=490)	ARIC Cohort (N=120)	De novo Cohort (N=370)
Year 1	8.1 (4.6)	7.2 (4.4)	8.3 (4.7)
Year 2	7.1 (5.0)	6.8 (4.8)	7.2 (5.1)
Year 3	7.2 (5.2)	5.8 (5.0)	7.6 (5.2)

Main Outcome

3-Year Change in Global & Domain-Specific Cognition

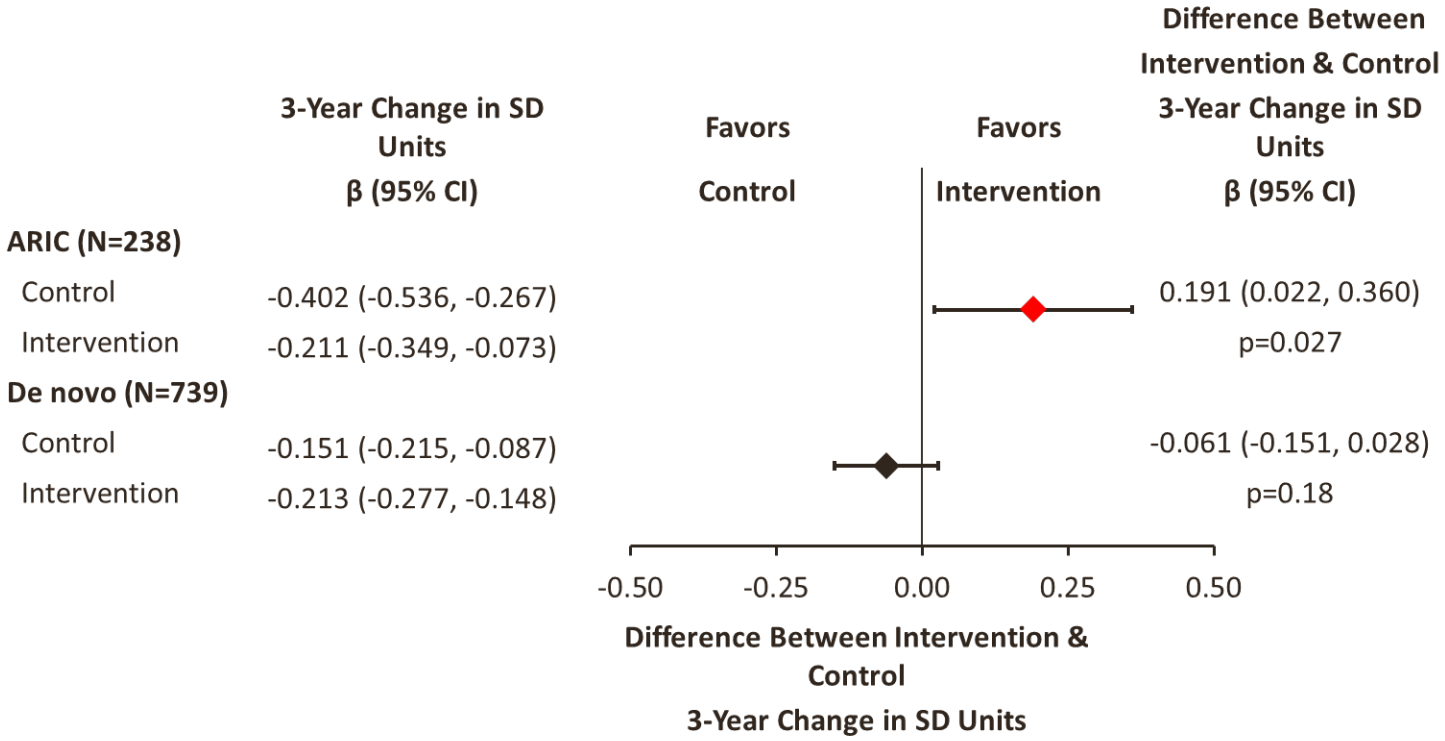


In the total combined cohort, hearing intervention had no effect on reducing cognitive decline within 3 years

Quiz Hint

Q3

3-Year Change in Global Cognition by Recruitment Source



Hearing intervention reduced 3-year global cognitive decline by 48% in the ARIC Subgroup

Baseline Characteristics by Recruitment Source

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)**
One or more apolipoprotein E ε4 alleles, No. (%)	224 (24.7)	59 (25.7)	165 (24.3)
***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)**

Trial Results 3-Year Change in Cognition

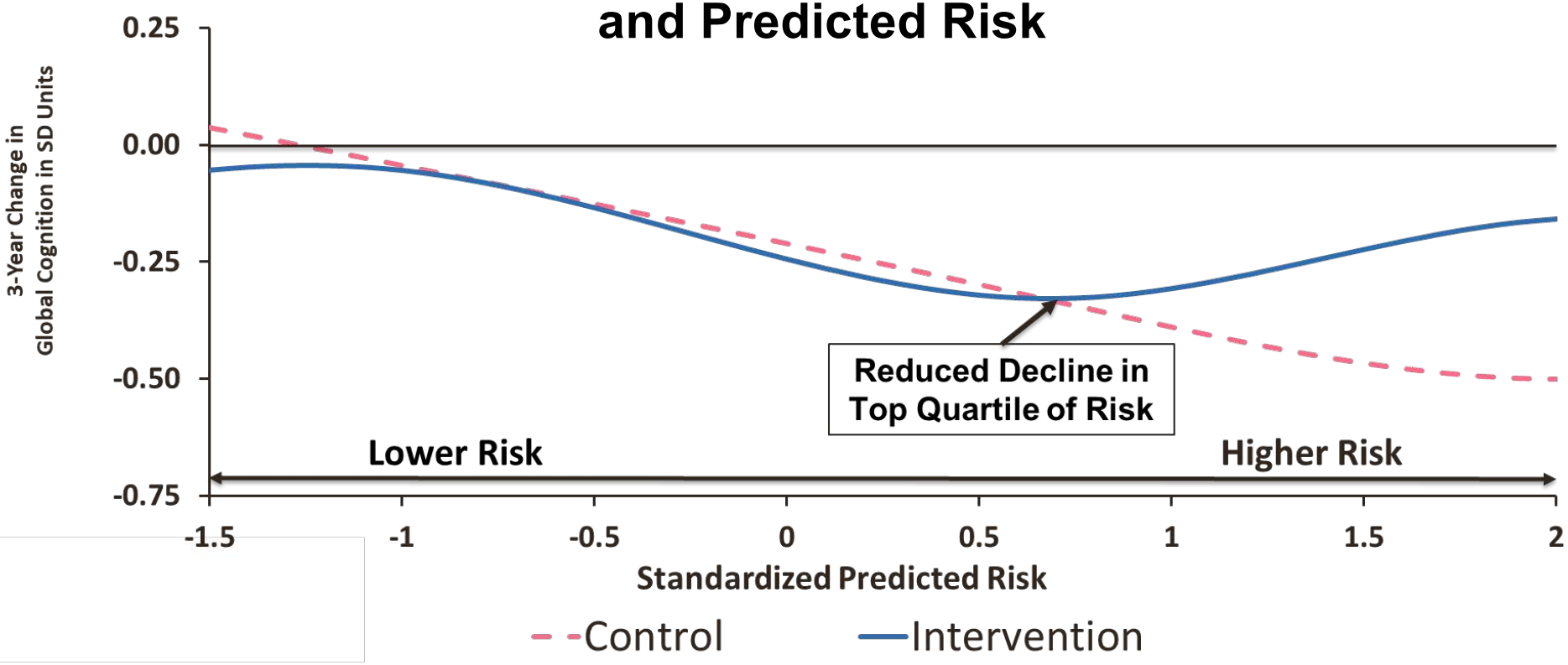
- **No effects in the full population**
- **Secondary analyses suggest…**
  - **in the less healthy, existing volunteers (ARIC), hearing intervention reduced 3-year global cognitive decline by 48%**
  - **No effect in the healthier, new volunteers (de novo)**

INTERPRET WITH CAUTION!

Predicted Risk vs. Observed Effect in ACHIEVE

- Goal: Use the parent ARIC study (population-based epidemiologic study of each site) to inform predicted risk scores of cognitive decline to apply to ACHIEVE design
- Hypothesis: Participants with the ***greatest risk*** who were randomized to the hearing intervention will have the ***greatest reduction*** in cognitive decline compared to participants randomized to the health education control.

Cognitive Decline in ACHIEVE Estimated From Mixed Effects Model Examining Nonlinear Interaction Between Intervention and Predicted Risk



Quiz Hint

Q10

3-Year Change in Cognition by Predicted Cog Risk

	Unadjusted 3-Year Change in SD Units ß (95% CI)	p	Covariate-Adjusted 3-Year Change in SD Units ß (95% CI)	p
Intervention X Time	-0.038 (-0.132, 0.057)	0.43	-0.047 (-0.141, 0.047)	0.32
Top Quartile of Risk X Time	-0.307 (-0.443, -0.172)	<0.0001	-0.265 (-0.408, -0.122)	<0.0001
3-Way Interaction	**0.202 (0.012, 0.392)**	**0.03**	**0.208 (0.020, 0.397)**	**0.03**

Among participants in the top quartile of risk, cognitive decline in the intervention group was 61.6% (95% CI 33.7%, 94.1%) slower than the control group

ACHIEVE Study Cognition Take Aways

- Hearing and cognition derives from population-based studies and should not be interpreted or messaged on an individual level
- The ACHIEVE trial is null and should be framed as such
- Secondary analyses suggest a signal exists for a non-linear association between hearing intervention and cognitive trajectory
  - Need for work on bi-directional synergies, increased diversity, and consideration for objective markers

Causality: Evidence for a Causal Link Between Hearing Loss and Cognition

Defining Cause is Hard!

- Animal, in vitro models (cell culture) are extrapolated to humans
- We rely on observations and randomized experiments in humans
- Ethical considerations are important
- Epidemiology relies on a sum of evidence

Study Designs

Study Type	Characteristics
Experimental (RCT)	• Investigator actively manipulates which groups receive the study agent • Studies prevention and treatment of disease
Observational	• Studies associations, prevention and treatment for diseases • Investigator watches as natures takes its course
Cohort	• Examines multiple health effects of an exposure • Participants defined by exposure levels and follow for disease occurrence
Case-control	• Typically examines multiple exposures in relation to a disease • Subjects are defined as cases and controls and exposure histories compared
Cross-sectional	• Examine relationship between exposure and disease prevalence in a defined population at one point in time
Ecological	• Examines association between exposure and disease with population-level data (rather than individual data)

Quiz Hint

Q9

Observational vs. Randomized Trial

- Non-causal associations is a primary concern in observational trials due to chance or bias (selection, information, measurement error, confounding)
- Randomized trials:
  - Establish Temporality
  - Removes selection bias and balance confounder via allocation of treatment
  - Masking reduces information bias (e.g., removes beliefs about treatment)

We can’t just rely on randomized trials

- Unethical to randomize harmful effects
- Trials lack generalizability
- Trial populations are also subject to selection and participation bias (Healthy Volunteer Effect!)

Causal Inference

- Judging all the evidence to establish likelihood of a causal relationship
  - Animal and in vitro models
  - Epidemiologic and statistical evidence
  - Randomized trials

Quiz Hint

Q2

Austin Bradford Hill's Considerations for Causality

1. **Temporal relationship***
2. Strength of the association
3. Consistency
4. Specificity
5. Biological gradient
6. Biological plausibility
7. Coherence
8. Experiment
9. Analogy

*must be met

"Here then are nine different viewpoints from all of which we should study association before we cry causation. What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect. None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis … What they can do, with greater or less strength, is to help us to make up our minds on the fundamental question – is there any other way of explaining the set of facts before us…"

Hill AB. Proc R Soc Med 1965;58:295-300.

Temporality

- Does the exposure precede the outcome?
- Temporality is the one causal guideline that must be met for a factor to cause a disease
- **Does Dementia cause Hearing Loss?**
  - Peripheral vs Central

Strength of the Association

- How strong is the measure of association (e.g. OR, RR) between a factor and an outcome?
- Compared to weak associations, strong associations may be less likely to be explained only by bias, confounding or chance
- **Relative Risk with Hearing?**
  - Between .20-.60

Consistency

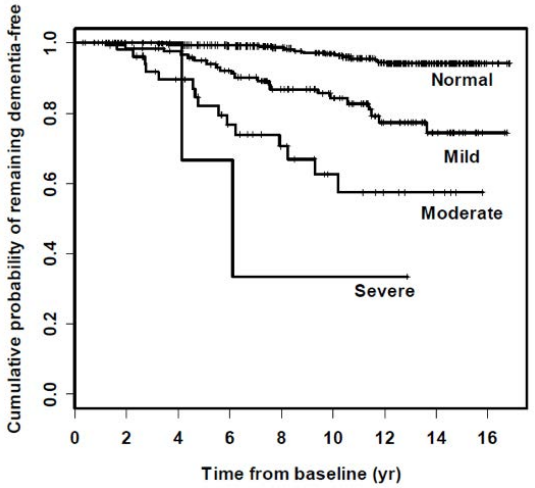
- Has this association been observed in epidemiologic studies in different places, populations and times?
  - If causal, it should be replicated across populations
- Evidence from systematic reviews and meta-analyses

Specificity

- Is the exposure associated with only one disease and is the disease associated with only one exposure?
- Specificity simpler for infectious disease, but difficult in evaluating multi-factorial chronic diseases
- **Hearing is not specific**

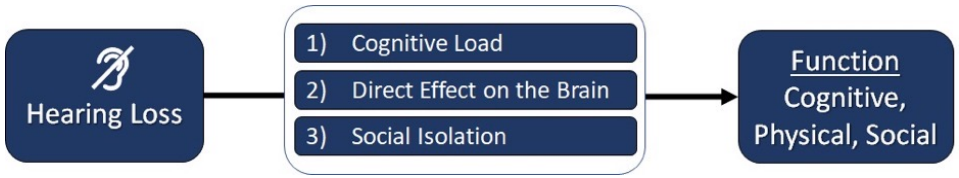
Biologic Gradient

- Does risk of disease increase as the exposure to the factor increases?
- ‘dose-response’



Biologic Plausibility

- Is current biological knowledge consistent with a causal association?



Coherence

- Is a casual association consistent with what is known from scientific investigations from other disciplines?
- An association should not conflict with what is known about the natural history and biology of the disease

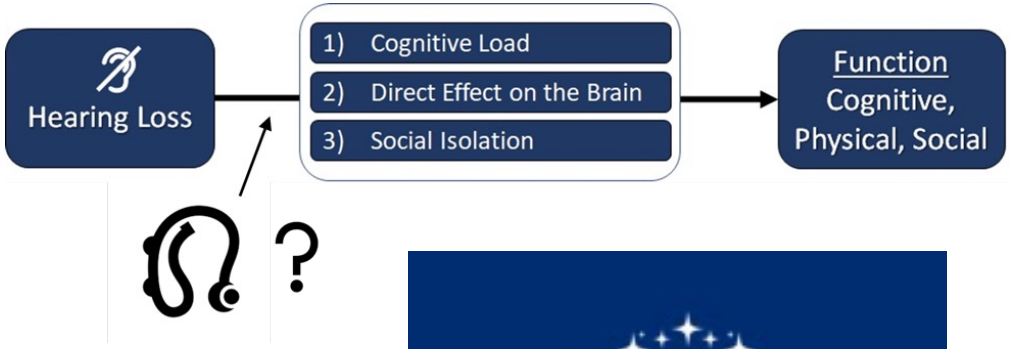
Analogy

- Is there a similar (analogous) association that is known to be causal?
- For example, a drug is known to cause birth defects; if a similar drug is associated with birth defects, that association may also be causal
- **Vision and Hearing?**

Experiment

- If preventive actions regarding an exposure are taken, is the disease, in fact, prevented?

- Can be an unplanned, or ‘natural’ experiment



ACHIEVE
HEALTHY AGING

Key Take Aways

Key Take Aways

Strength of Evidence

- **The association (READ: Relationship) between hearing and cognition meets most criteria for a causal framework**
  - Most of Bradford Hill's Criteria met to some degree:
    - Temporality, Strength of Association, Consistency, Biological Gradient, Biological Plausibility, Coherence, Experiment, Analogy
- **Evidence for intervention is in an early stage**
  - ACHIEVE overall is null with important sensitivity findings to guide future work
    - 'One trial a conclusion does not make'
      - Need: precision in group that benefits, enrichment of populations, longer observation period

Key Take Aways

Individual versus Population Stats

- **Trial and observational data should be interpreted on a population level and not at the individual level**
  - Like other health areas, risk of any outcome is a larger sum of genetic and lifestyle factors. Every individual is different.
- **Messaging hearing aids for an *individual* to prevent dementia is an incorrect interpretation**
  - Hearing aids have many other benefits for an individual that are more proximal and likely to be observed at that level (e.g., social engagement)
  - Population level data is key for changing policy (e.g., Medicare, Medicaid, etc)
  - Deep need for translational work to estimate individual effect in the real-world
    - 'Precision Audiology'

Thank You!

Nicholas S. Reed, AuD PhD

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