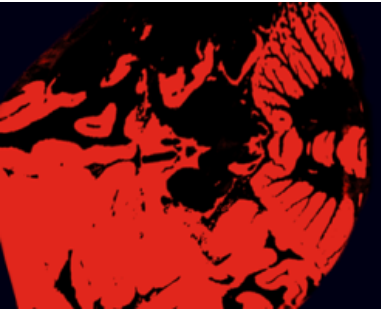


BRAINWEEK™ twenty 21 | Live Virtual Conference | MAY 7–9

I Can't Hear You: Association of Subclinical Hearing Loss with Cognitive Performance

Justin S. Golub, MD, MS
Associate Professor
Otology, Neurotology, and Skull Base Surgery
Department of Otolaryngology—Head and Neck Surgery
Columbia University Vagelos College of Physicians and Surgeons
New York-Presbyterian/Columbia University Irving Medical Center

Disclosures

- Consulting Fee (eg, Advisory Board): Oticon Medical, Auditory Insight, Optinose, Abbott, Decibel, Alcon
- Contracted Research:
  Storz, Stryker, Medtronic, Acclarent, 3NT, Decibel
- Honoraria:
  Oticon Medical, Auditory Insight, Optinose, Abbott, Decibel, Alcon
- Other: travel expenses for industry-sponsored meetings from Advanced Bionics, Oticon Medical, Alcon

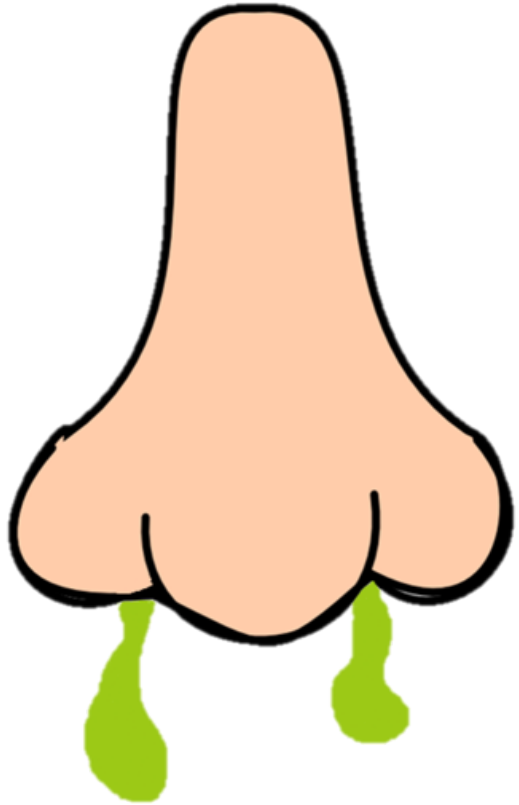
Learning Objectives

- Review the cause, prevalence, and treatment prevalence of age-related hearing loss
- Discuss evidence relating age-related hearing loss and cognition
- Identify proposed mechanisms related age-related hearing loss to cognition
- Describe the level of evidence relating subclinical age-related hearing loss and cognition

What Am I?

Otolaryngology—Head and Neck Surgery

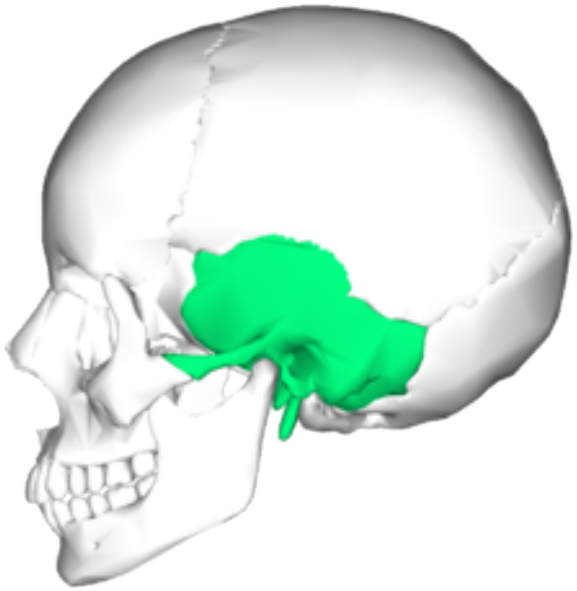
Ear



Nose

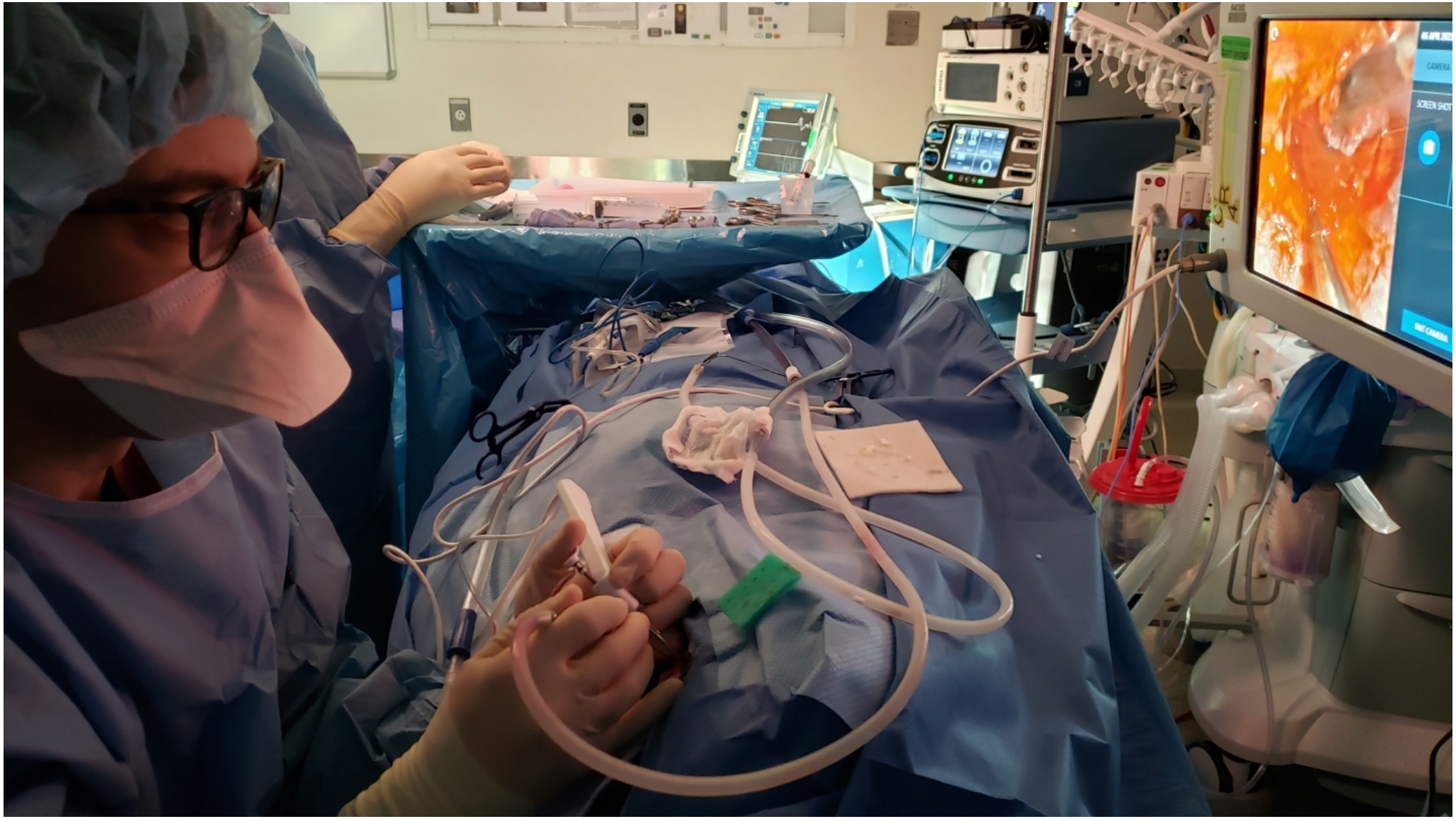
Throat

Otology/Neurotology



(ENT)

Otology/Neurotology

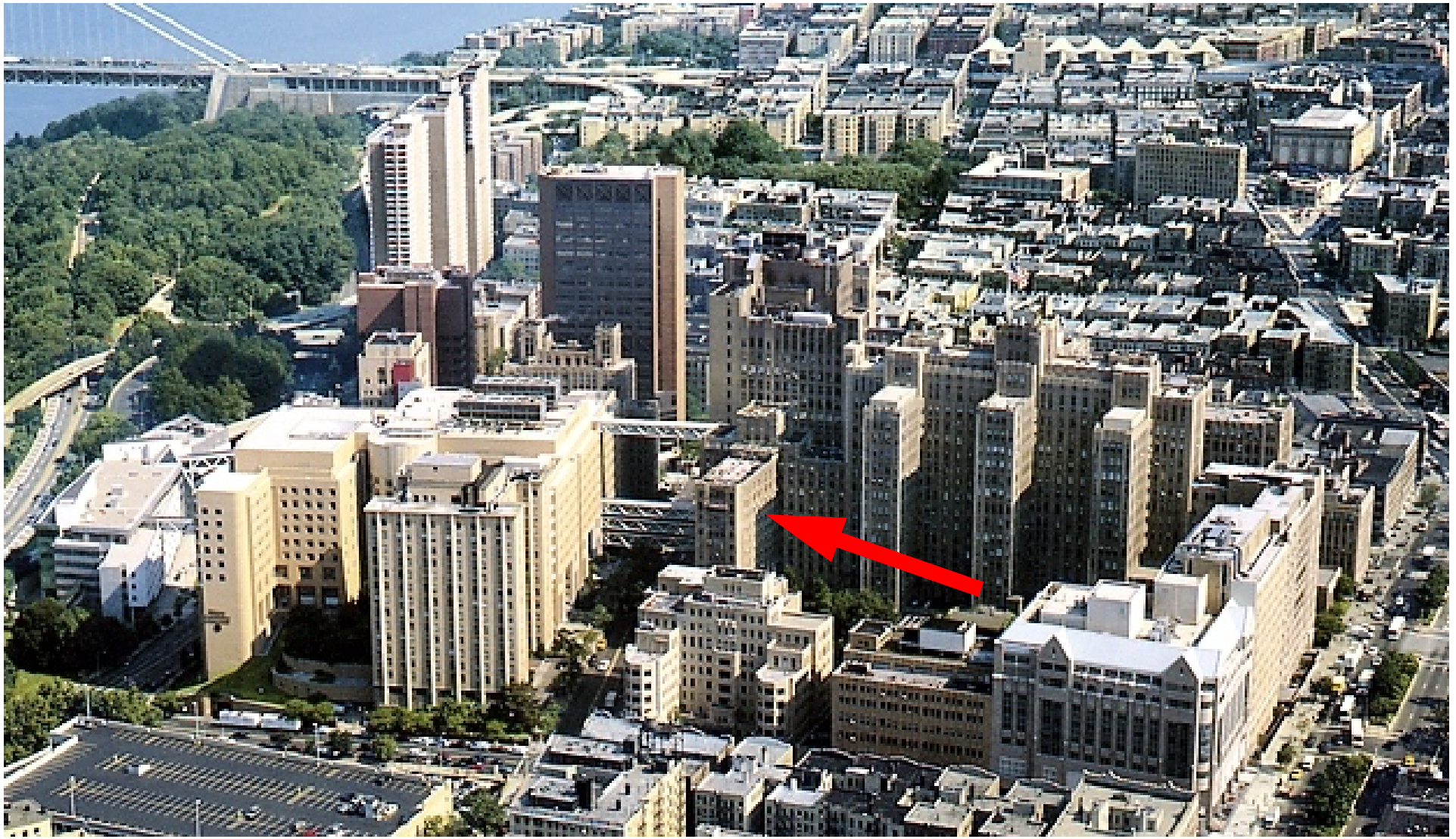


Age-Related Hearing Loss Researcher

> Golub Lab

Age-Related Hearing Loss Researcher

Columbia University Irving Med Center

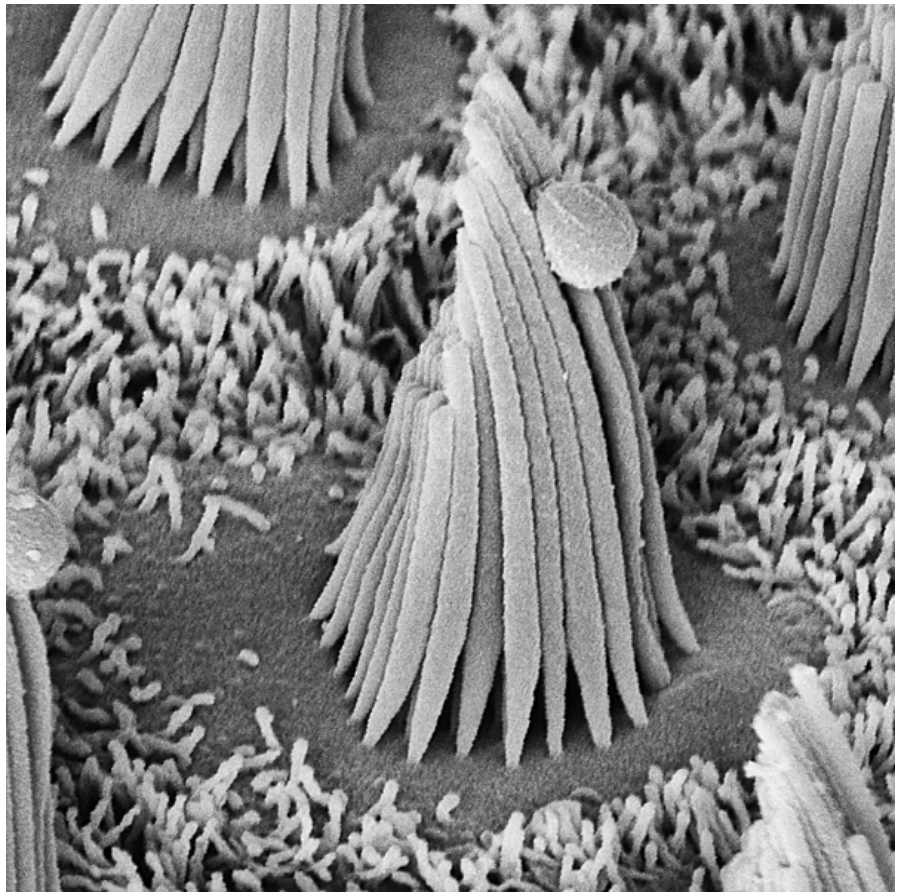


Outline

- What's Age-Related Hearing Loss?
- Hearing Loss ⟷ Cognition
- Mechanisms
- Subclinical Hearing Loss ⟷ Cognition
- Conclusion & Next Steps

- **What's Age-Related Hearing Loss?**
- Hearing Loss ↔ Cognition
- Mechanisms
- Subclinical Hearing Loss ↔ Cognition
- Conclusion & Next Steps

Age-Related Hearing Loss: Cause



- Death of inner ear **hair cells**
- A **sensorineural hearing loss**
- Etiology unknown and irreversible

Age-Related Hearing Loss: Treatment

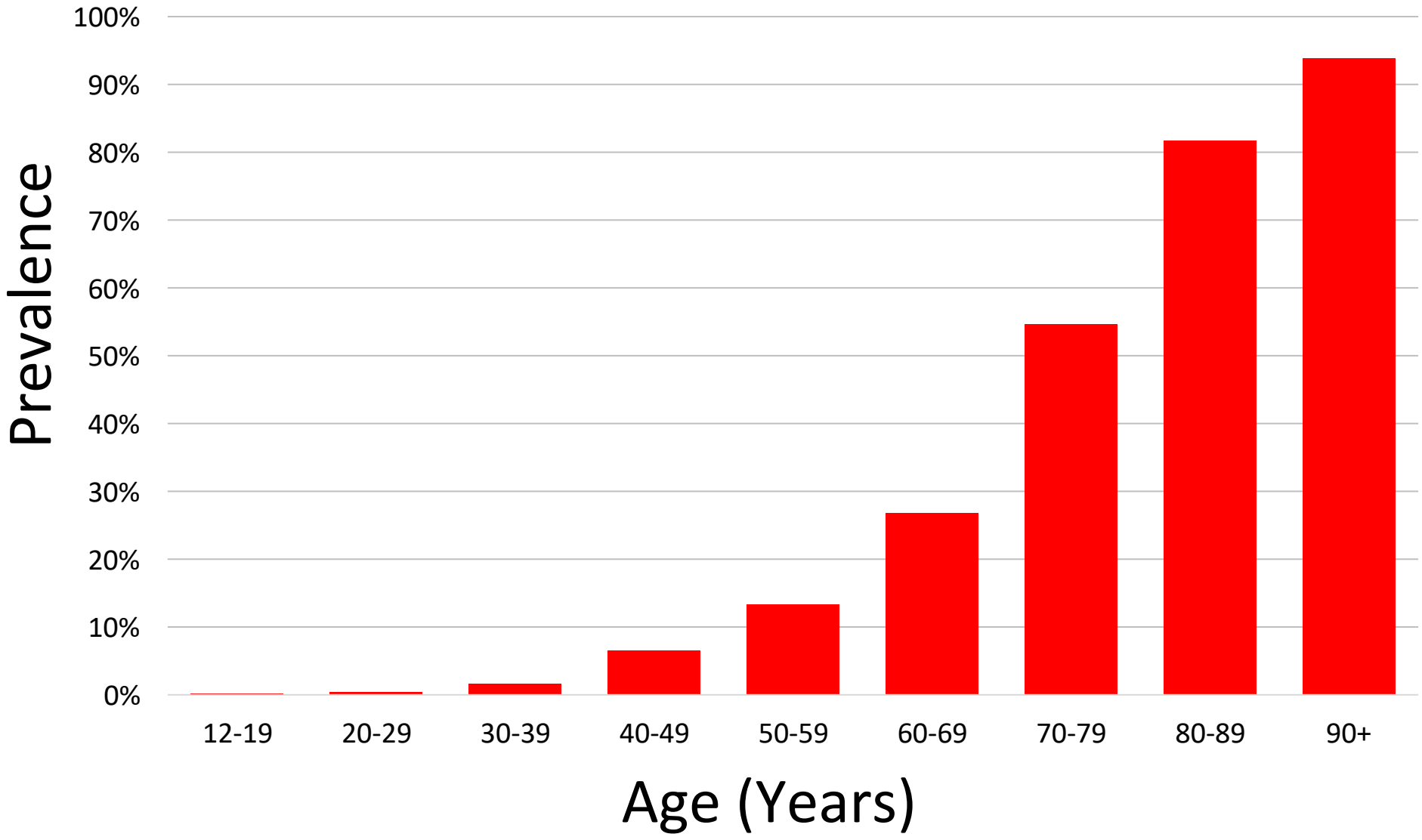
- Treat with devices

Rare!

Hearing aids:

Cochlear implant:

Age-Related Hearing Loss: Prevalence



Sharma 2020; Goman 2016. (NHANES)

How Do We Measure Hearing Loss?

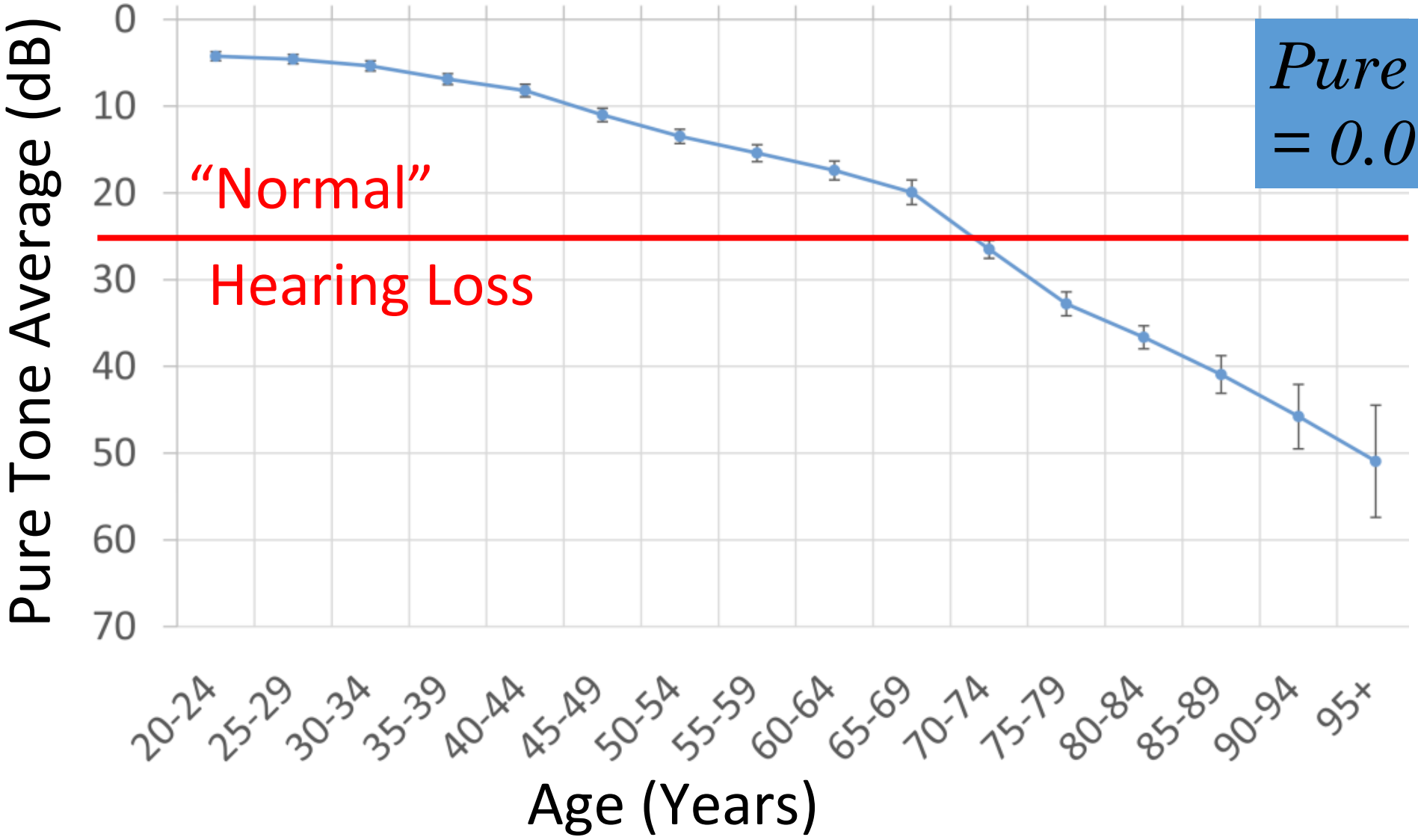
- Unit: **dB** (decibel)
- How loud a tone is to hear it

0 dB ← **25** dB — **40** dB —— **70** dB → **100** dB

Normal | Mild | Moderate | Severe, Profound

- **Pure tone average**:
  mean dB at several frequencies (pitches)

Age-Related Hearing Loss: Prevalence

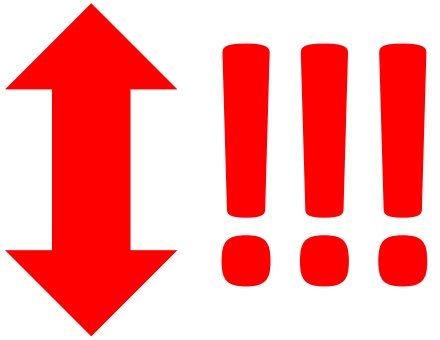


Pure tone average $= 0.0052 \times age^2$

Sharma 2020a
Sharma 2020b

Summary

- **High prevalence** (**>80%** of 80+ y/o)



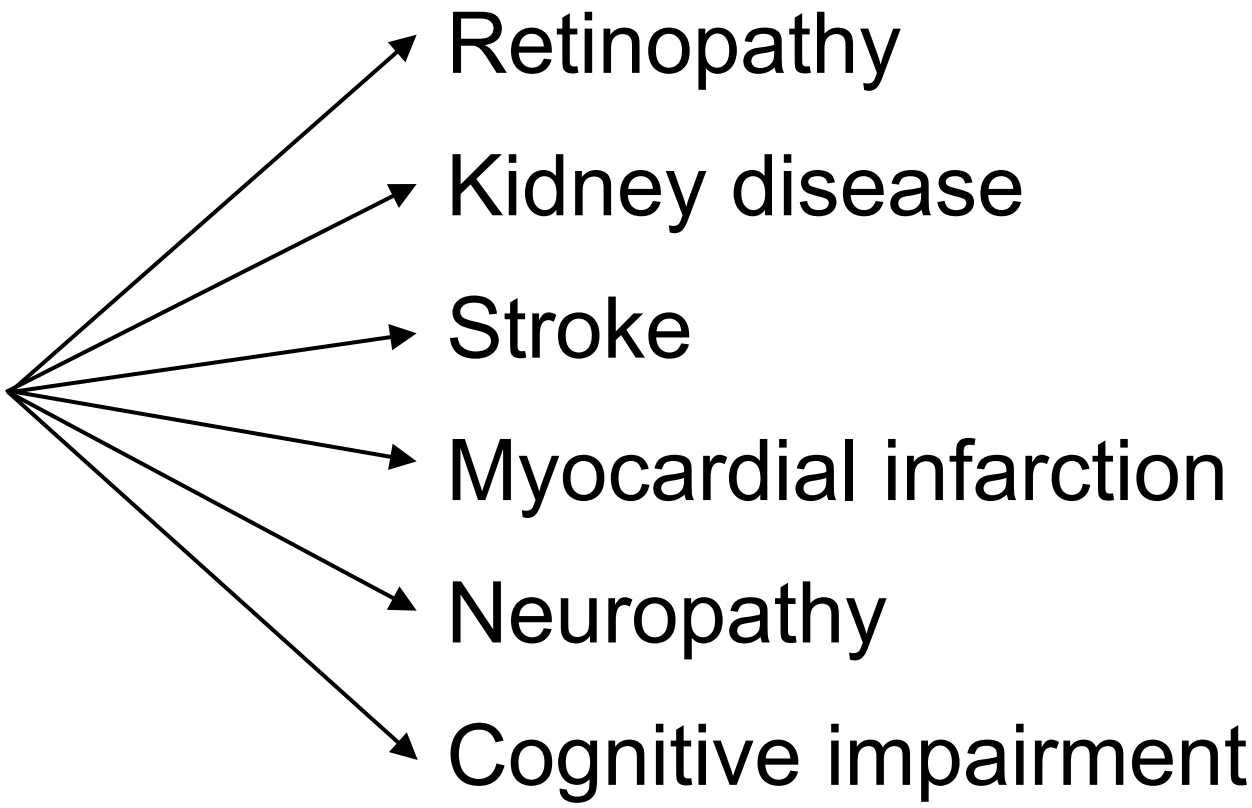
- **Low treatment** (**<25%** of 80+ y/o)

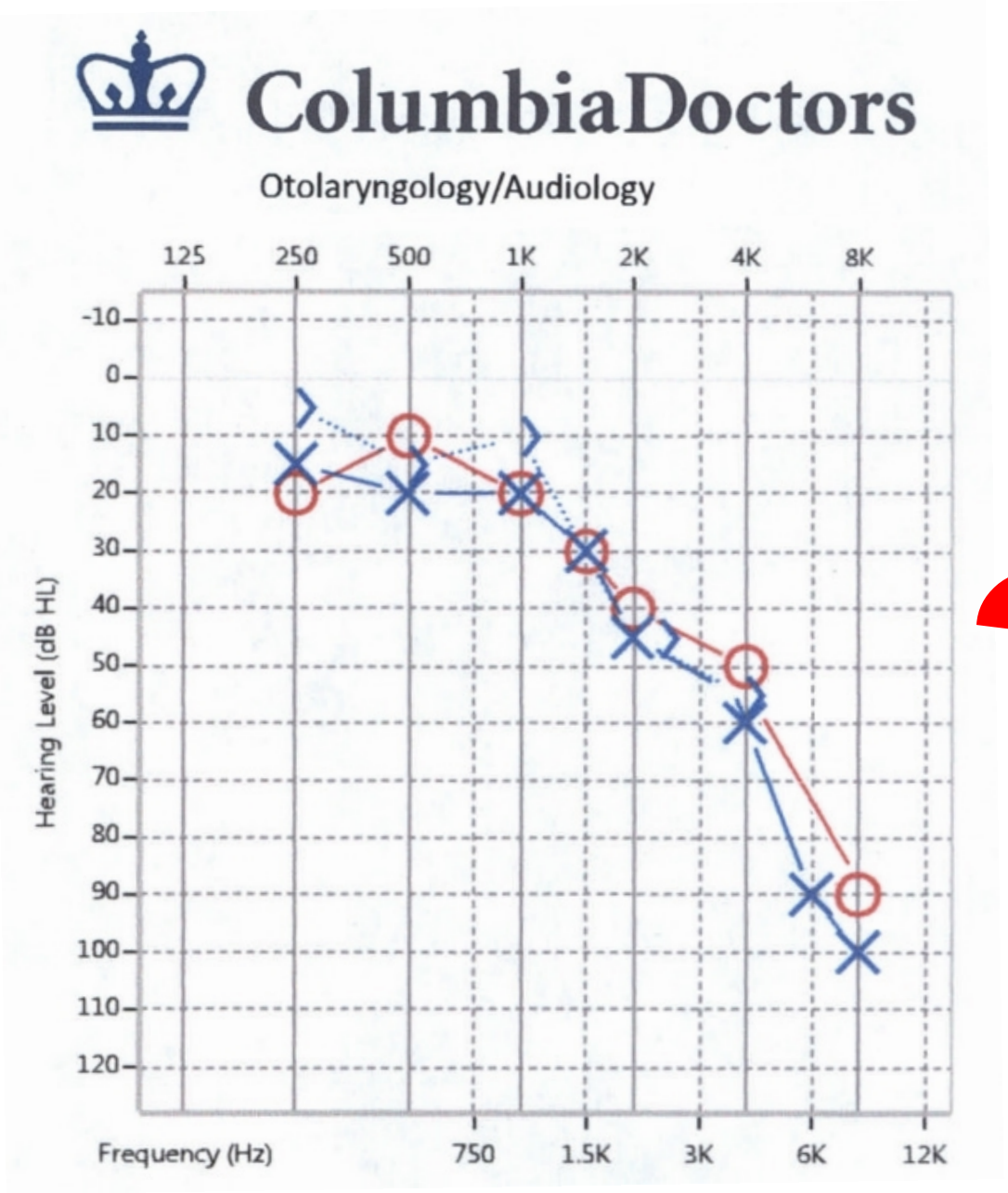
Goman 2016
Chien 2012

Lab	Value
Glucose	280

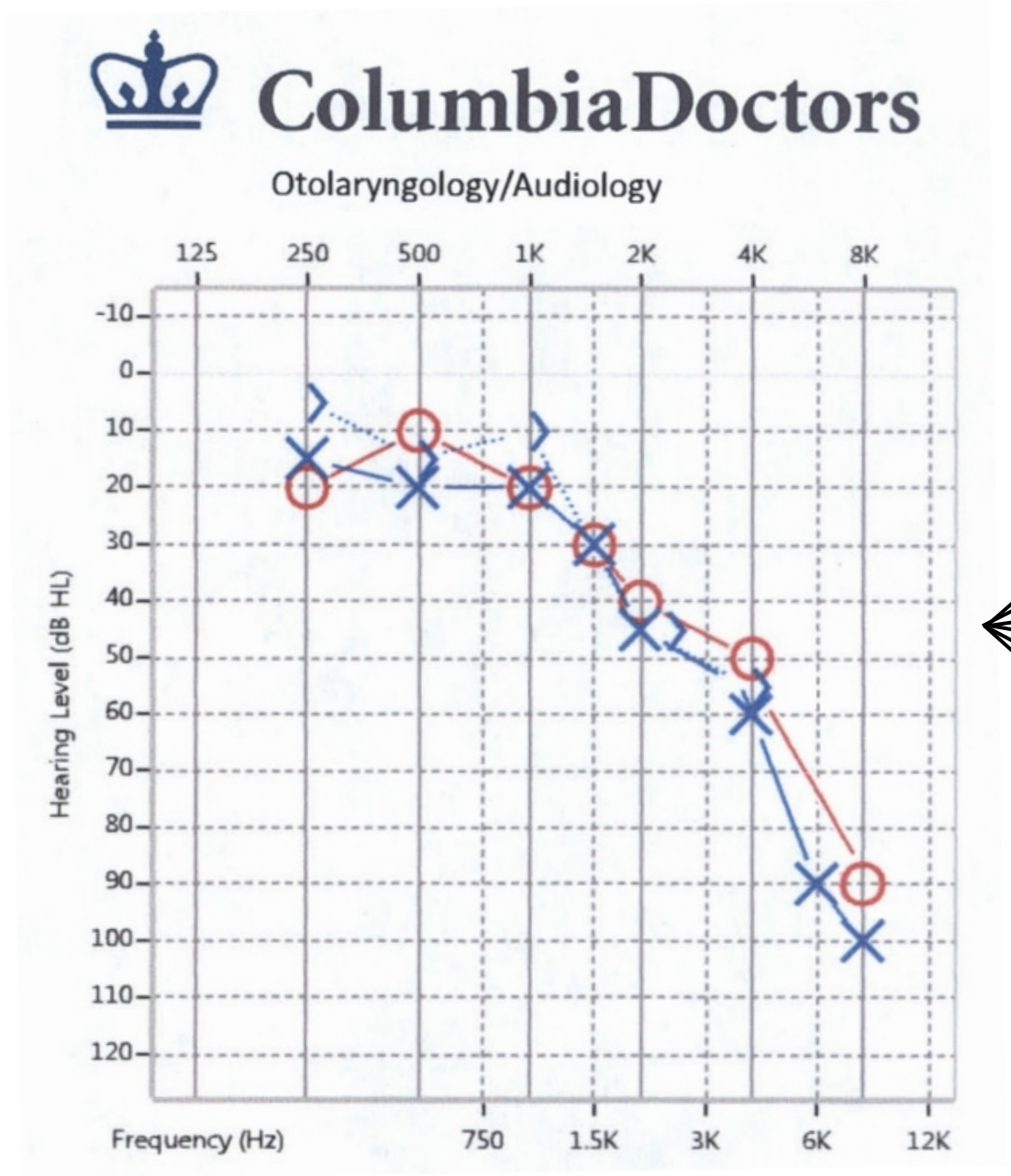
?

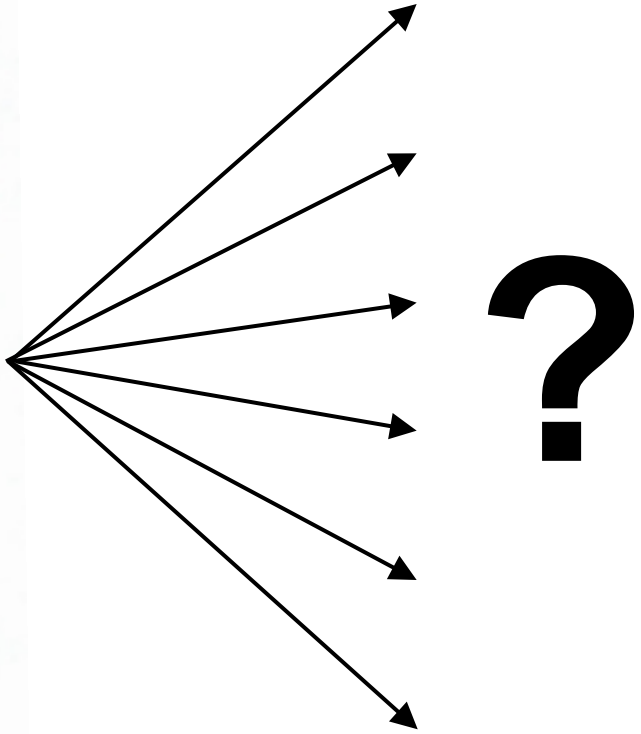
Lab	Value
Glucose	280




ColumbiaDoctors
Otolaryngology/Audiology
125
250
500
1K
2K
4K
8K
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
Hearing Level (dB HL)
Frequency (Hz)
750
1.5K
3K
6K
12K

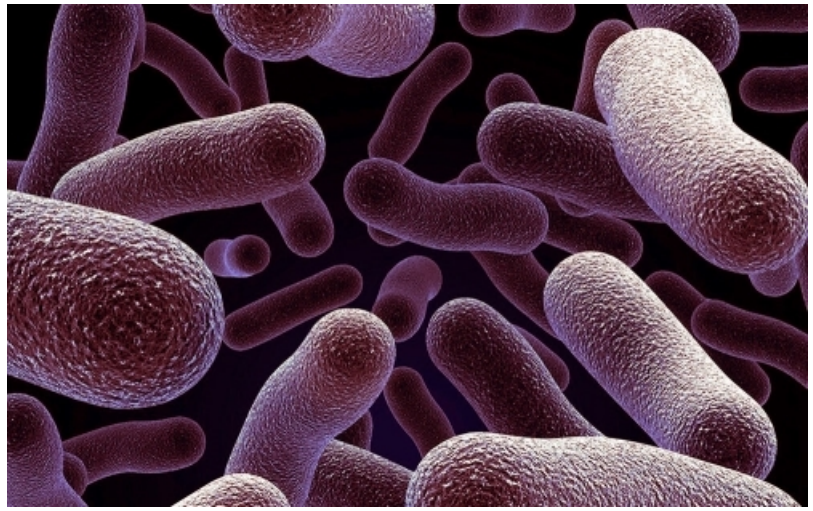
?


ColumbiaDoctors
Otolaryngology/Audiology
125
250
500
1K
2K
4K
8K
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
Hearing Level (dB HL)
Frequency (Hz)
750
1.5K
3K
6K
12K



?

Exposure → (Outcome) Disease



Hearing Loss as the Disease

Exposure → Disease

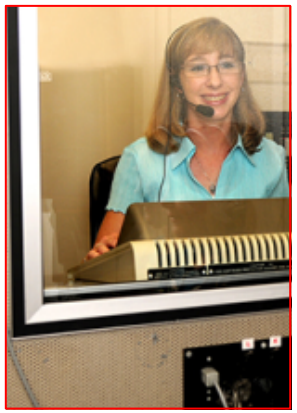
Genetics → Hearing loss?
Ototoxicity → Hearing loss?
Noise → Hearing loss?

Do something about this…
…to *prevent* hearing loss

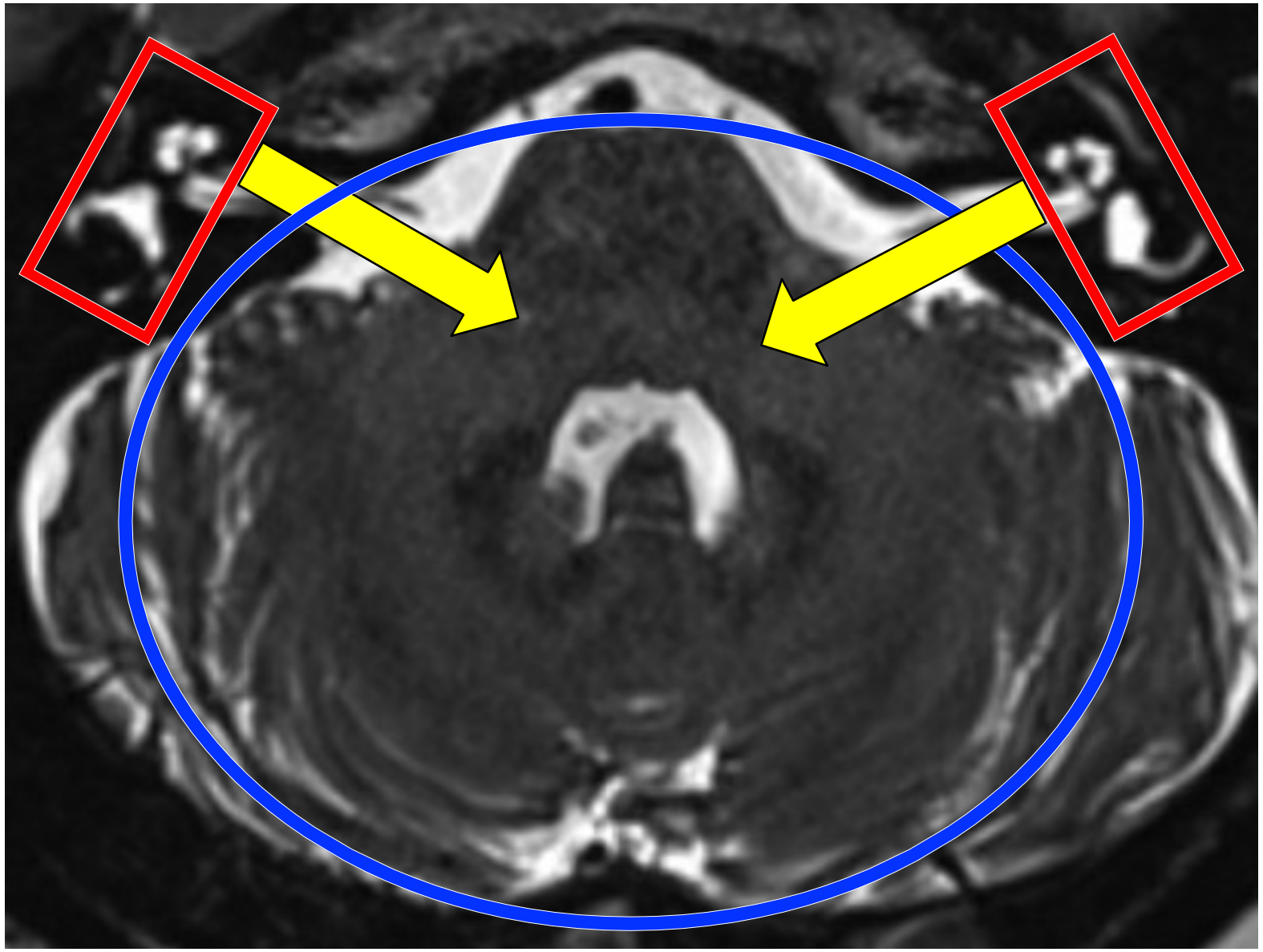
Hearing Loss as the Exposure

Exposure → Disease

Hearing loss → Cognitive impairment?
Hearing loss → Dementia?
Hearing loss → Depression?



Ear



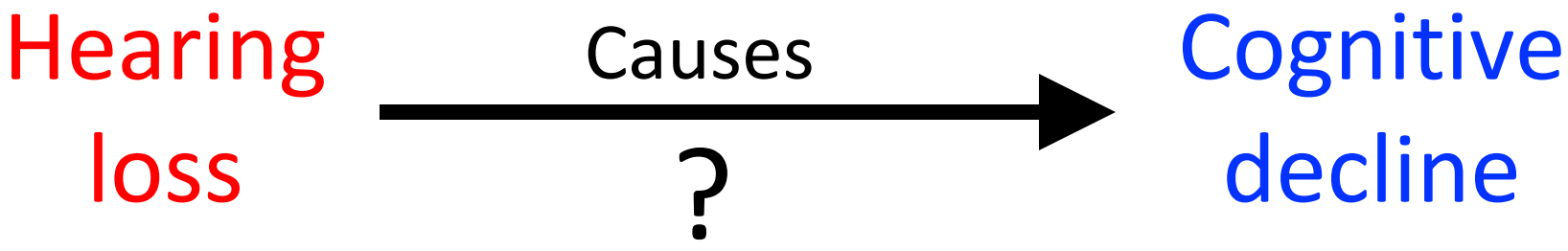
Ear

Brain

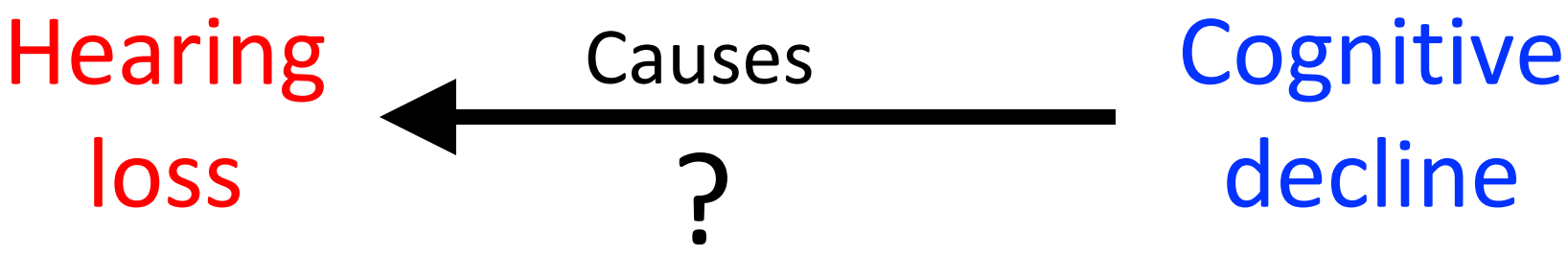
Epidemiology 101

Association

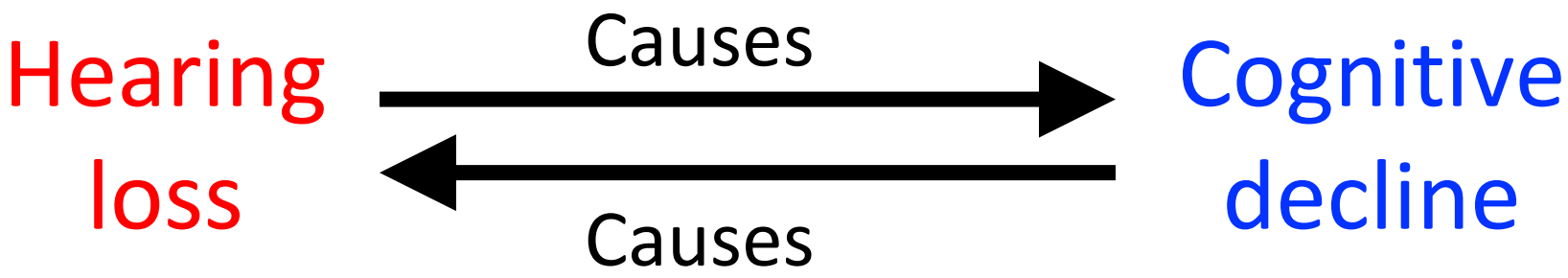
Epidemiology 101



Epidemiology 101

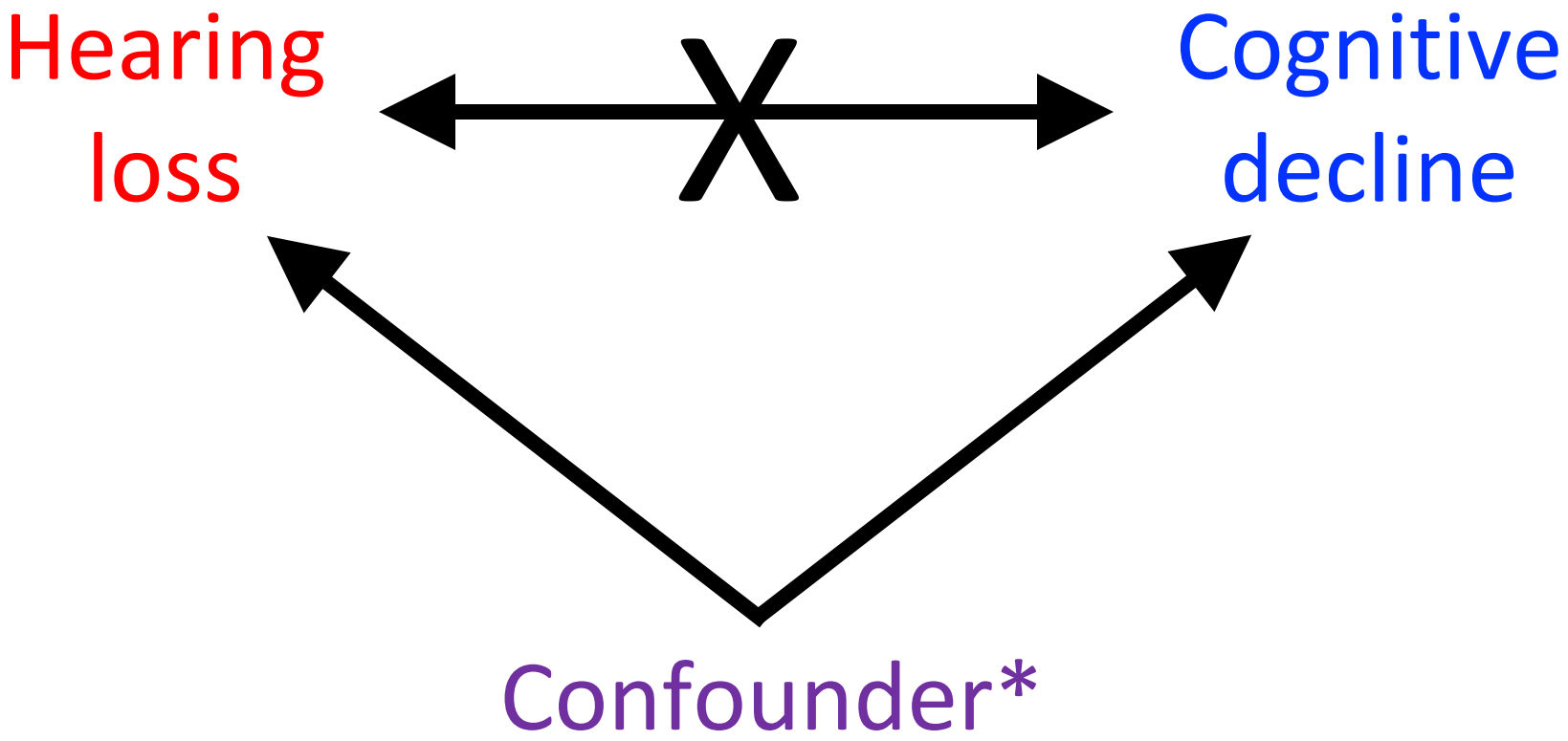


Epidemiology 101



?

Epidemiology 101



***Adjusting** in statistics reduces confounding possibility

Epidemiology 101

Does Hearing Loss Cause Dementia?

- Association ≠ causation (hard to prove)

Impossible

- **Proof:**
  Randomize hearing *loss* → *get* dementia?

$$$ + Rare

- **Proxy for proof:**
  Randomize hearing *treatment* → *avoid* dementia?

- **Suggestive evidence:**
  Naturally occurring hearing loss → get dementia?

- What's Age-Related Hearing Loss?
- **Hearing Loss ↔ Cognition**
- Mechanisms
- Subclinical Hearing Loss ↔ Cognition
- Conclusion & Next Steps

Review: How Hearing Loss is Measured

- Unit: **dB** (decibel)
- How loud a tone is to hear it

0 dB ← **25** dB — **40** dB —— **70** dB → **100** dB

Normal | Mild | Moderate | Severe, Profound

- **Pure tone average**:
  mean dB at several frequencies (pitches)

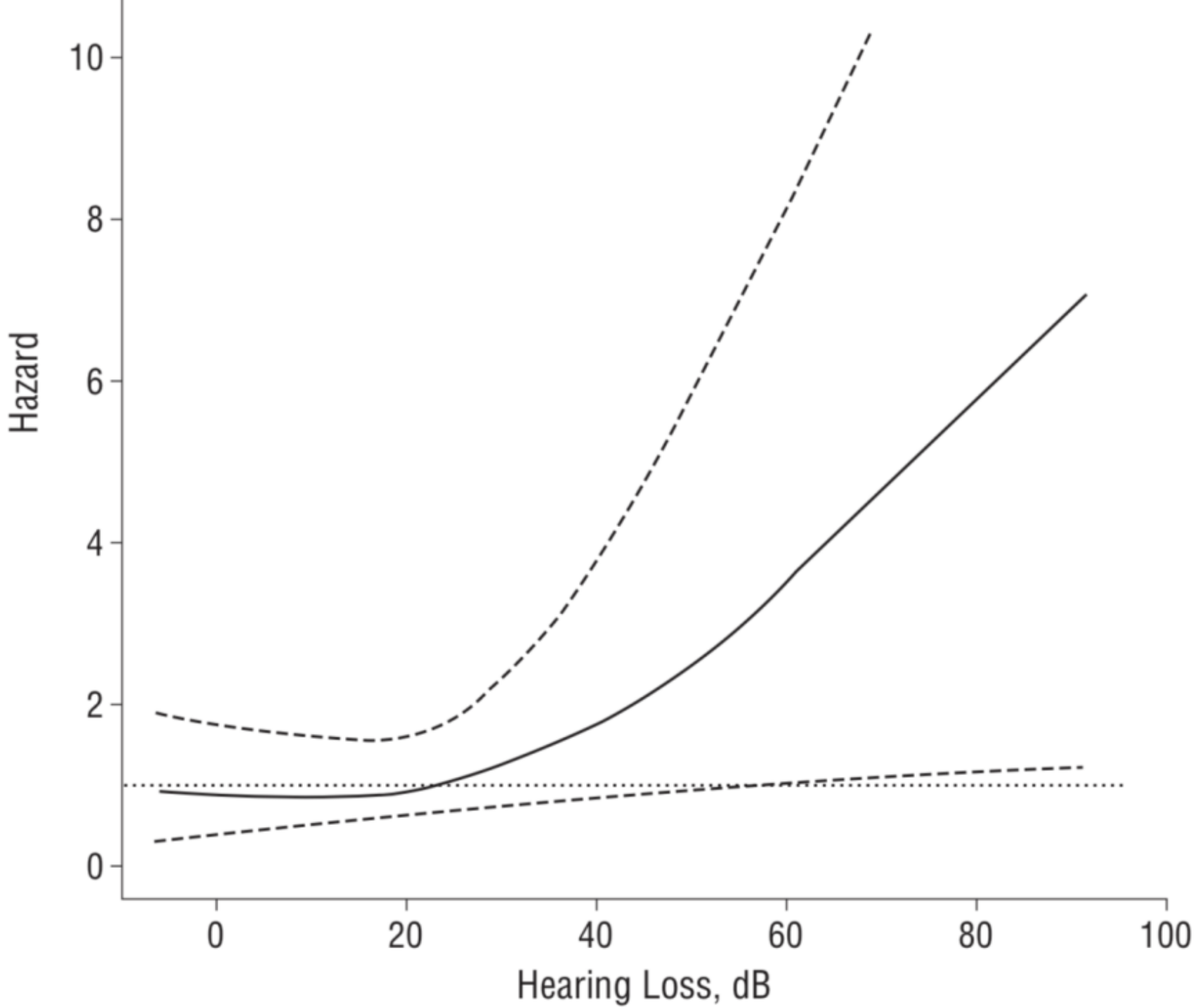
Hearing Loss ↔ Dementia

Lin 2011

- Exposure: pure tone average (**audiometry**)
- Outcome: incident dementia
- Cohort: Baltimore Longitudinal Study of Aging
- n=639
- Longitudinal (12 yrs)
- Adjusted: age, demographics, CV risk factors

- HR = **1.27** per 10 dB HL increase ($p<0.01$)

Lin 2011



*Adjusted

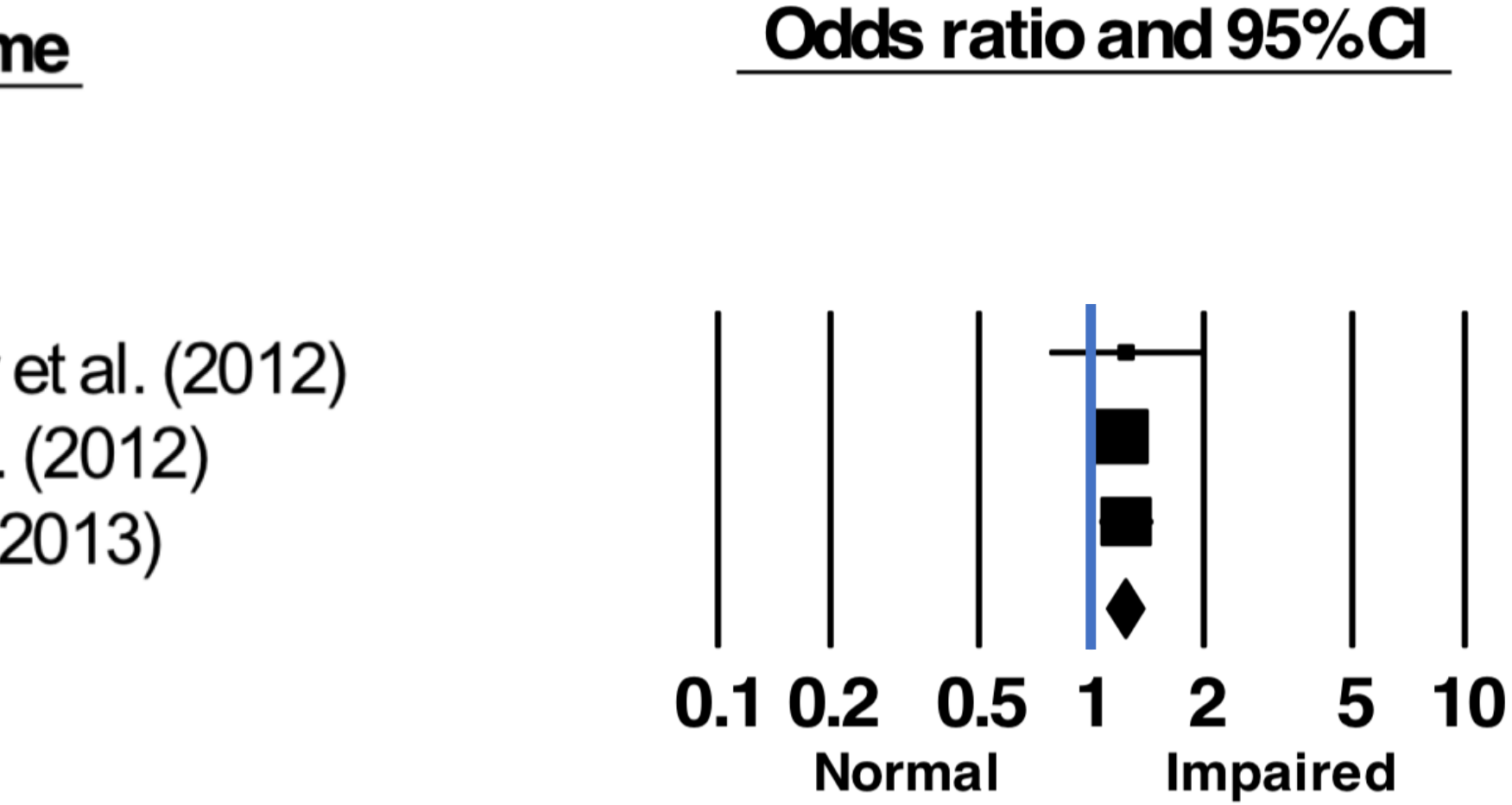

JAMA
REUTERS
CBS NEWS
The New York Times
FOX NEWS
CNN
The Washington Post
@jsgolub

Hearing Loss ↔ Cognition/Dementia

Loughrey 2018

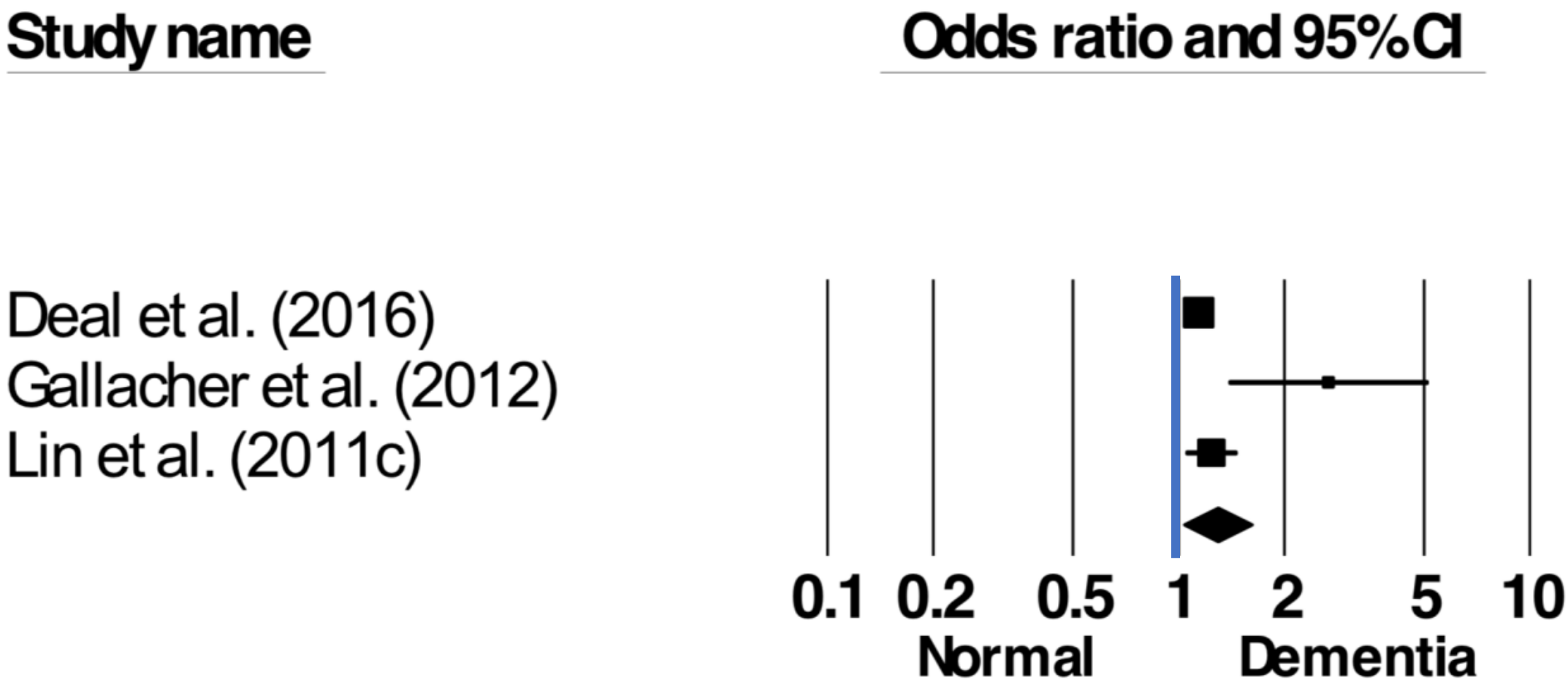
- **Meta analysis**
- 1,824→ 36 papers (n=20,264)
- Excluded: no audiometry
- 37 eTables, 73 eFigures

Cognitive Impairment for Cohort Studies



Loughrey 2018

Dementia for Cohort Studies



Loughrey 2018

The Lancet Commissions

Dementia prevention, intervention, and care: 2020 report of the *Lancet* Commission

8% reduction in **dementia prevalence** if hearing loss was eliminated

Hearing Aid RCT in Veterans

Mulrow 1990

Design

- Intervention: Unilateral hearing aid vs waitlist
- Outcome: Disease-specific QOL (HHIE)
- Population: Veterans
- Age (mean): 72
- Size: n=194
- Duration: 4 months

Hearing Aid RCT in Veterans

Mulrow 1990

Results

- Significant improvement in **disease-specific QOL** (HHIE, QDS)

Limitations

- Unilateral hearing aid
- 30+ year old tech
- Cognition not really assessed
- Mostly white male veterans

Hearing Aid RCT in Alzheimer's Disease

Nguyen 2017

Design

- Intervention: Hearing aid vs placebo hearing aid
- Outcome: ADAS Cog
- Population: Alzheimer's (community)
- Age (mean): 83 y/o
- Size: n = 51 → 38
- Duration: 6 mos, then 6 more mos crossover

Hearing Aid RCT in Alzheimer's Disease

Nguyen 2017

Results

- **No significant differences** between groups (1º and 2º outcomes)

Limitations

- Hearing intervention design
- Small n
- Self-report of compliance

Hearing Aid RCTs

Cochrane Library

Fergusson 2017

Methods

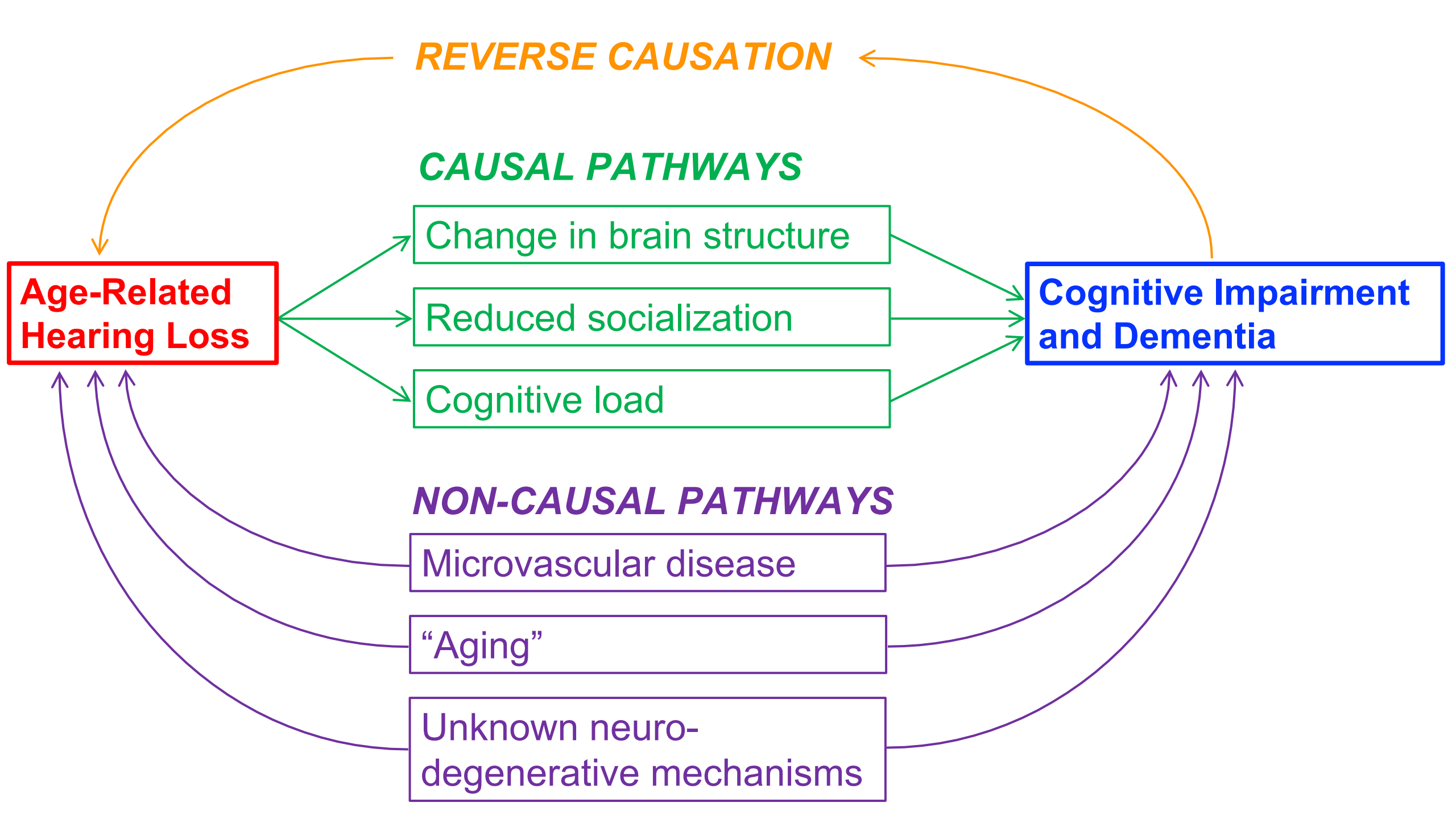
- Mild-moderate age-related hearing loss
- 5 RCTs, n=825

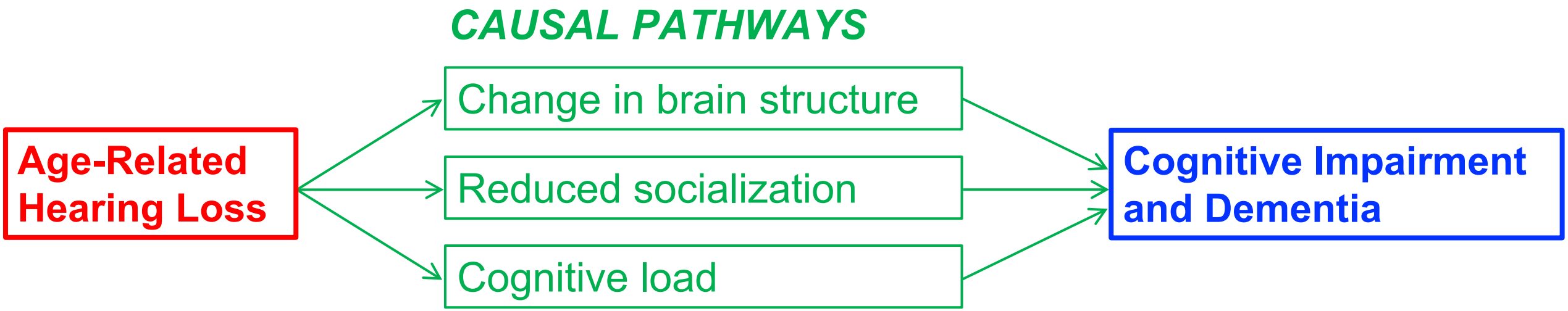
Hearing aids improve:

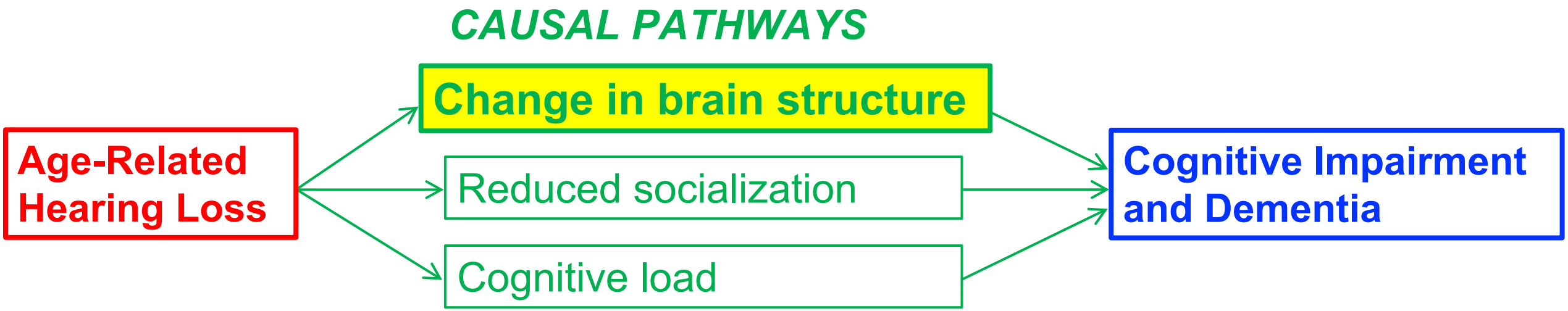
- Hearing-specific QOL
- General QOL
- Listening abilities

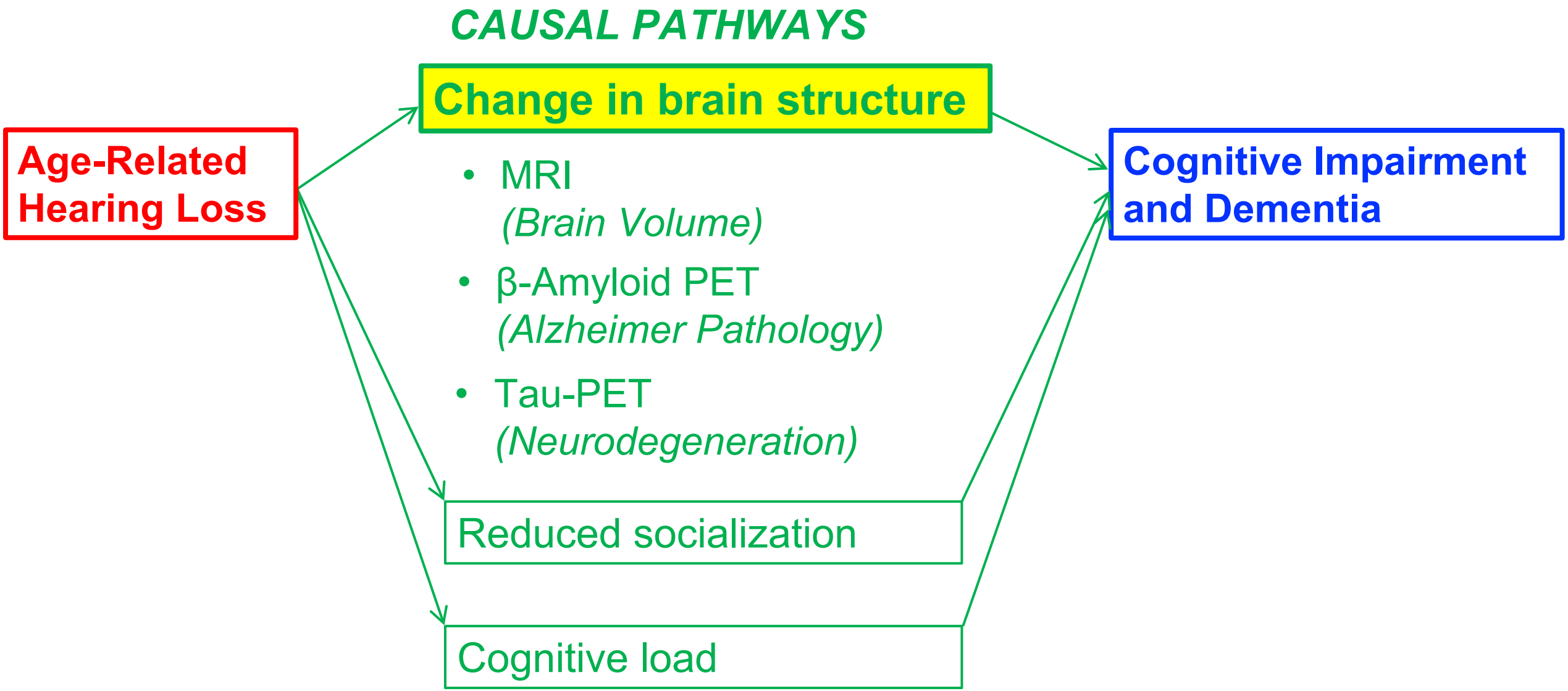
Nothing (yet) beyond *hearing* or *QOL*

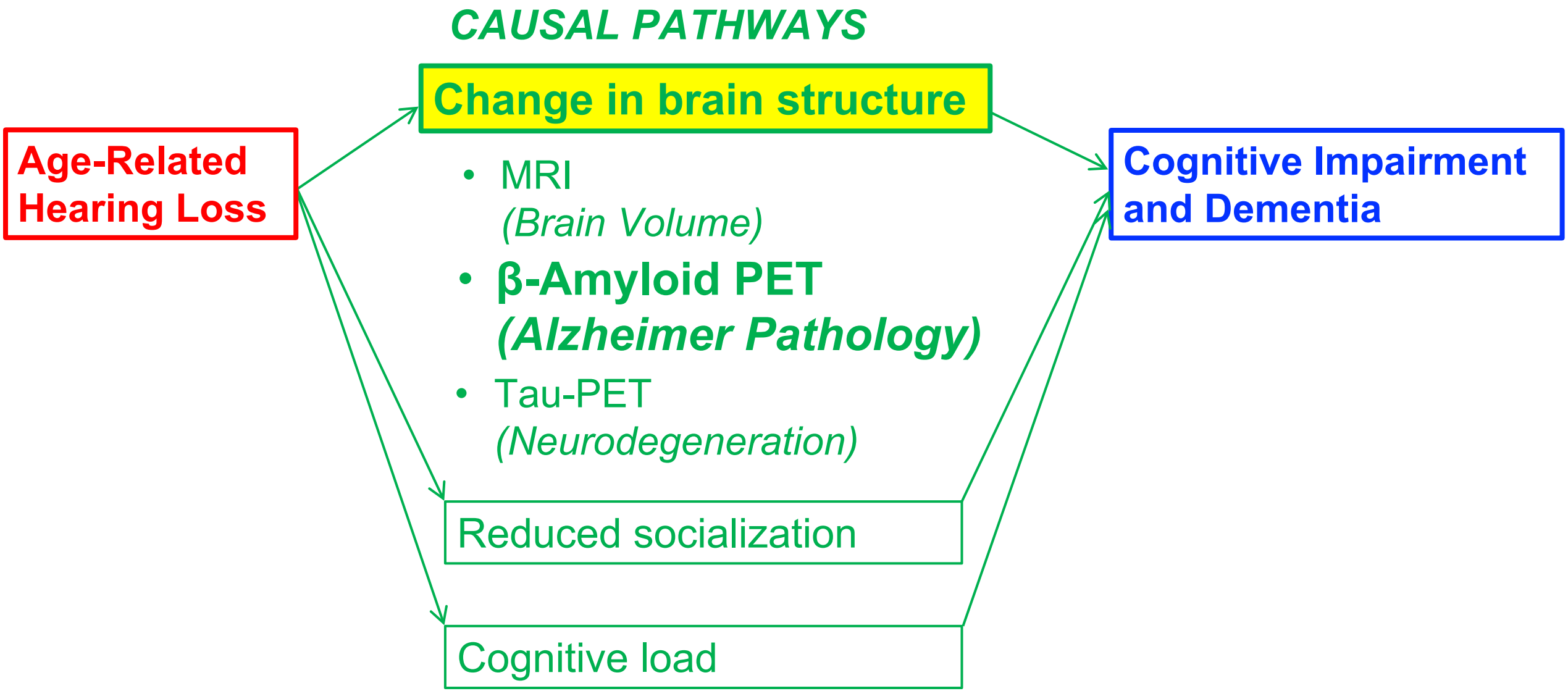
- What's Age-Related Hearing Loss?
- Hearing Loss ⟷ Cognition
- **Mechanisms**
- Subclinical Hearing Loss ⟷ Cognition
- Conclusion & Next Steps


REVERSE CAUSATION
CAUSAL PATHWAYS
Change in brain structure
Reduced socialization
Cognitive load
Age-Related Hearing Loss
Cognitive Impairment and Dementia
NON-CAUSAL PATHWAYS
Microvascular disease
“Aging”
Unknown neuro-degenerative mechanisms

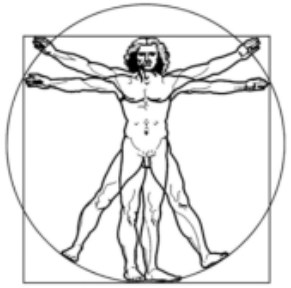

CAUSAL PATHWAYS
Age-Related Hearing Loss
Change in brain structure
Reduced socialization
Cognitive load
Cognitive Impairment and Dementia


CAUSAL PATHWAYS
Change in brain structure
Age-Related Hearing Loss
Reduced socialization
Cognitive load
Cognitive Impairment and Dementia


CAUSAL PATHWAYS
Age-Related Hearing Loss
Change in brain structure
• MRI (Brain Volume)
• β-Amyloid PET (Alzheimer Pathology)
• Tau-PET (Neurodegeneration)
Reduced socialization
Cognitive load
Cognitive Impairment and Dementia


CAUSAL PATHWAYS
Change in brain structure
Age-Related Hearing Loss
• MRI
(Brain Volume)
• β-Amyloid PET
(Alzheimer Pathology)
• Tau-PET
(Neurodegeneration)
Reduced socialization
Cognitive load
Cognitive Impairment and Dementia

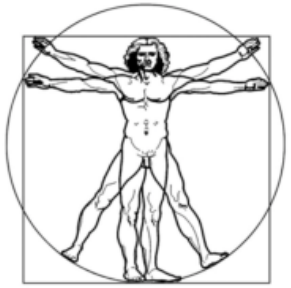
How Can We Study This?



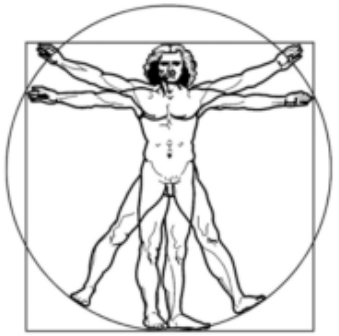
NOMEM
Northern Manhattan Study of Metabolism and Mind

Luchsinger, PI
R01AG050440
RF1AG051556
R01AG055299
R56AG061817

Grants



NOMEM-H
Northern Manhattan Study of Metabolism and Mind—Hearing



NOMEM-H

Northern Manhattan Study of Metabolism and Mind—Hearing

- Community
- Late-middle age volunteers
- Hispanic > black, white
- **Added: audiogram**
- Target n=500

Pilot Study

Question:

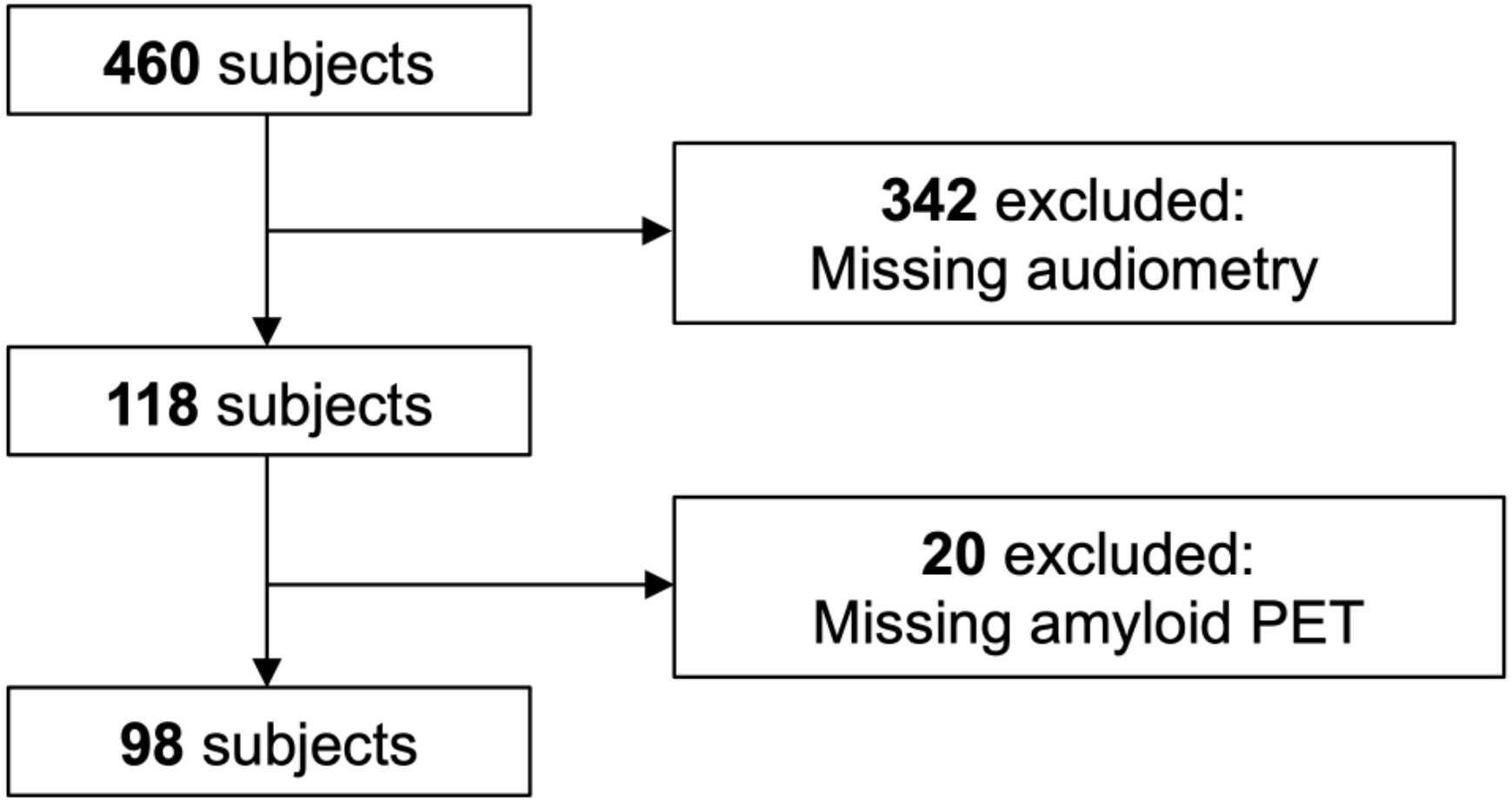
Is hearing loss cross-sectionally associated with brain β-amyloid in late-middle age community volunteers?

Hearing loss: Pure tone average (dB)

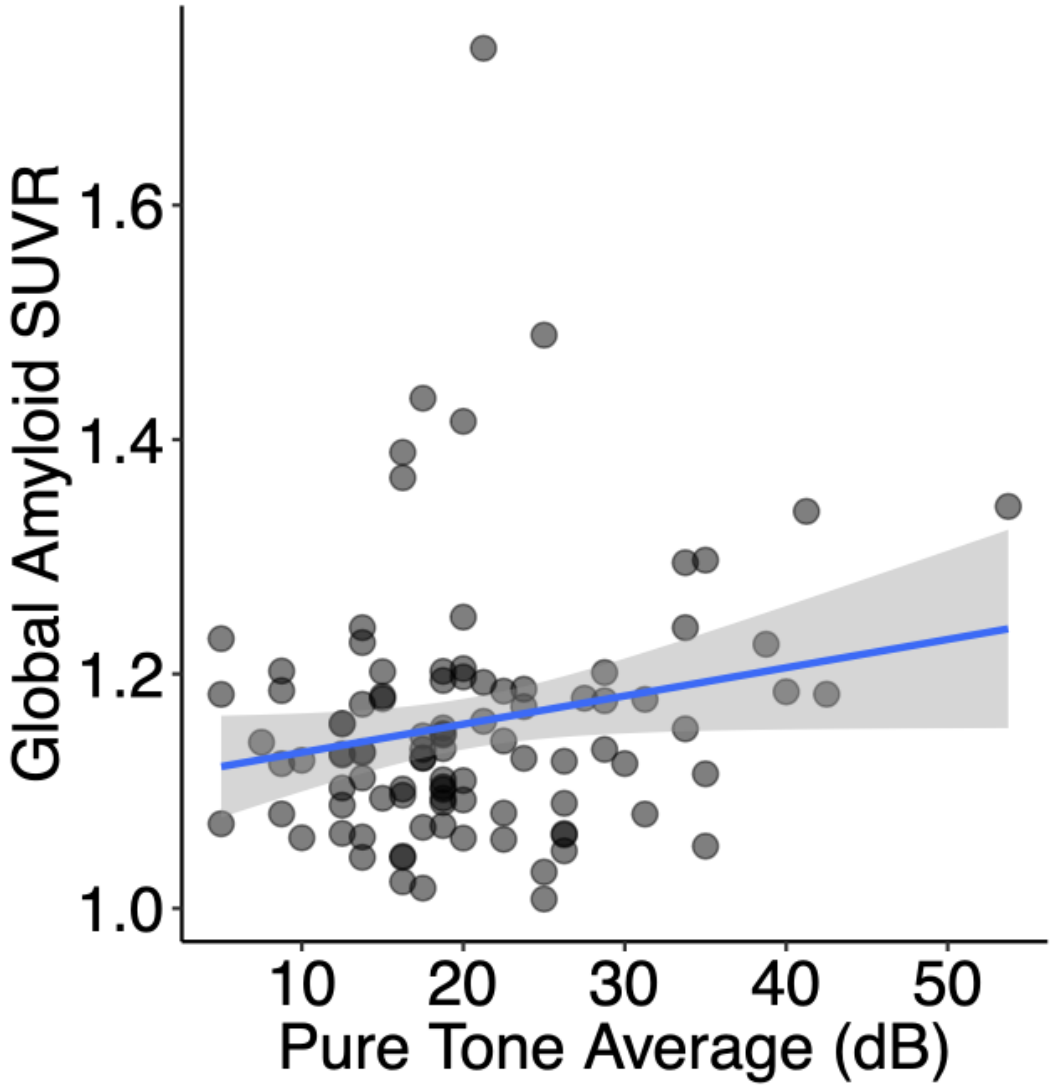
Word recognition score (%)

Brain β-amyloid: Intensity (SUVR) on PET

Enrollment


460 subjects
342 excluded:
Missing audiometry
118 subjects
20 excluded:
Missing amyloid PET
98 subjects

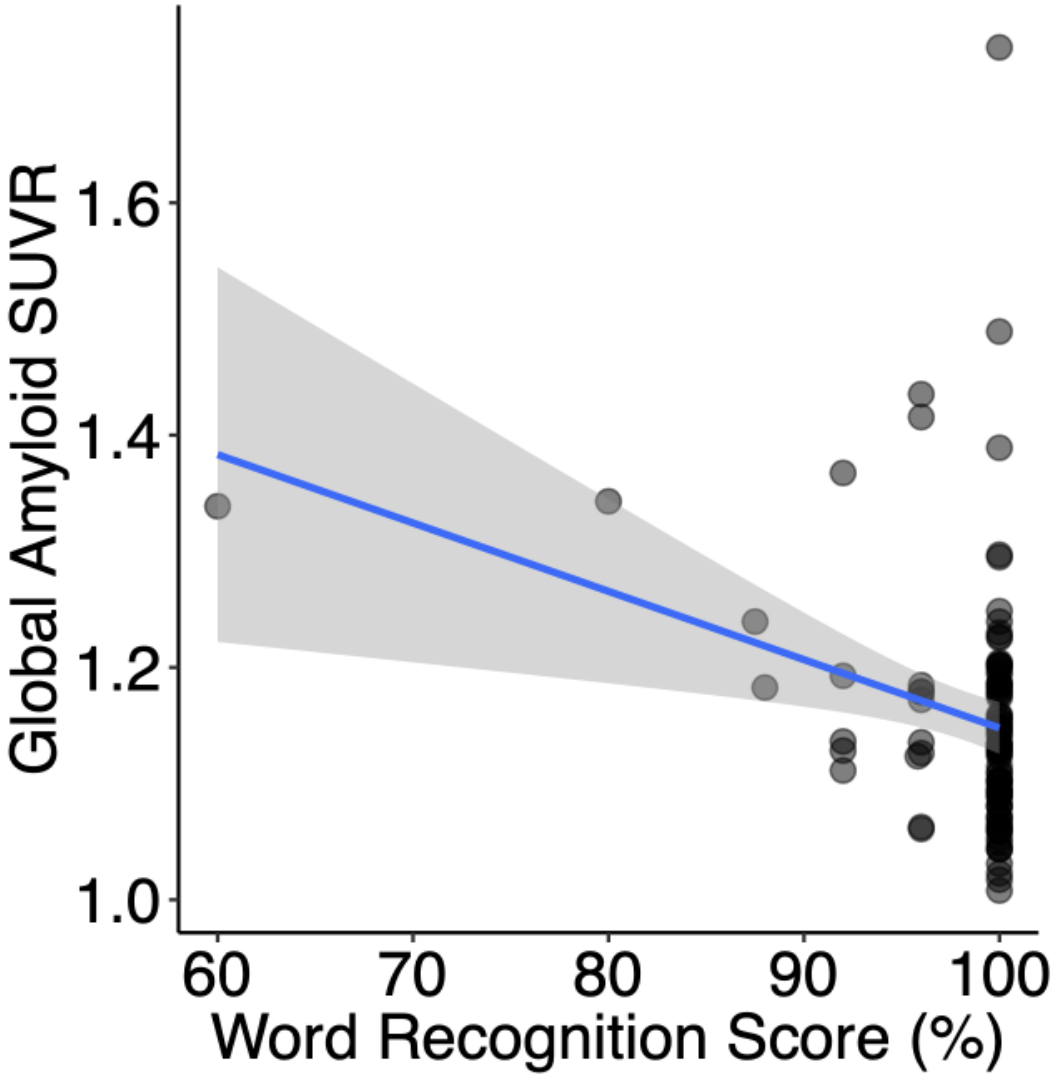
Brain β-Amyloid vs Pure Tones



Model	Global Amyloid SUVR Difference Per 10 dB Worsening Pure Tone Avg (95% CI)	P
Univariable	0.024 (0.00, 0.049)	0.054
Multivariable*	0.029 (0.003 0.056)	**0.030**

*adjusted for: age, gender, education, CV disease, hearing aid

Brain β-Amyloid vs Word Recognition



Model	Global Amyloid SUVR Difference Per 10 %B Worsening Word Recog (95% CI)	P
Univariable	0.059 (0.017, 0.101)	**0.006**
Multivariable*	0.061 (0.009, 0.112)	**0.021**

*adjusted for: age, gender, education, CV disease, hearing aid

...Really?

Prior Studies

Hearing loss related to….

- **Yes:** Smaller brain volumes[1,2,3]
- **Yes:** CSF tau[4]
- **No:** CSF amyloid or amyloid PET[4]
- **No:** Dementia pathology on autopsy[5]

First study to show association between hearing and ***β-amyloid: hallmark pathology of Alzheimer's***

[1]Lin 2014, [2]Armstrong 2019, [3]Eckert 2012, [4]Xu 2019, [5]Neff 2019

Limitations

- Cross-sectional
- Regional

Next Steps

- **Replication** including longitudinally
- **How** could hearing loss cause amyloid?

- What's Age-Related Hearing Loss?
- Hearing Loss ⟷ Cognition
- Mechanisms
- **Subclinical Hearing Loss ⟷ Cognition**
- Conclusion & Next Steps

But What *is* Hearing Loss?

- Pure tone average >25 dB
- Arbitrary

Q Do associations with cognitive impairment begin with **subclinical hearing loss** (pure tone average 1-25 dB)?

Methods: Subjects

- Hispanic Community Health Study
- Multicentered
- Cross-sectional, 2008-2011
- ≥50 y/o
- “Normal” hearing (≤25 dB)
- n=4,347

Methods: Analysis

Exposure:
Pure Tone Average

Multivariable Linear Regression

Outcome:
Cognition

- Digit Symbol Substitution Test
- Word Frequency Test
- Spanish-English Verbal Learning Test
- Six-item Screener

Adjusted for: demographics, hearing aids, cardiovascular disease

Results

- **Age**: mean **58 y/o**
  (Range = 50 to 75)

- **Pure tone average**: mean **14 dB**
  (Range = -2.5 to 25)

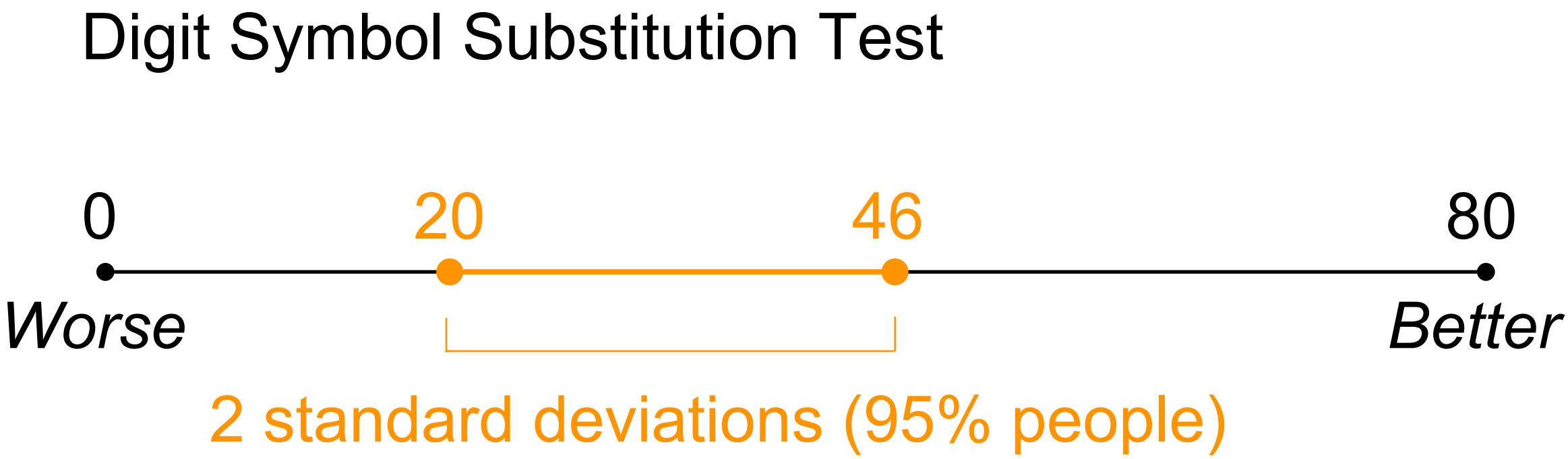
Results

In subclinical HL, 10 dB worse hearing associated with:

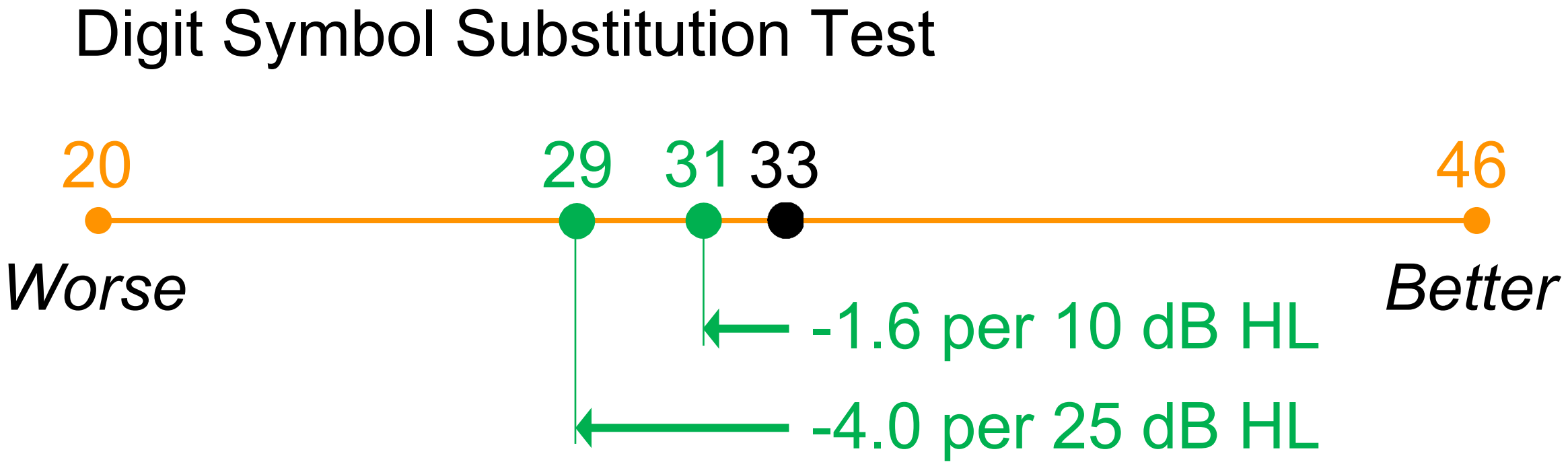
Score Change (95% CI)	Cognitive Test
-1.61 (-2.18, -1.04)*	Digit Symbol Substitution
-0.71 (-1.07, -0.35)*	Word Frequency Test
-0.67 (-0.95, -0.40)*	SEVLT 3 trials
-0.40 (-0.55, -0.25)*	SEVLT 3 recall
-0.08 (-0.12, -0.03)*	Six-Item Screener

*$p<0.001$

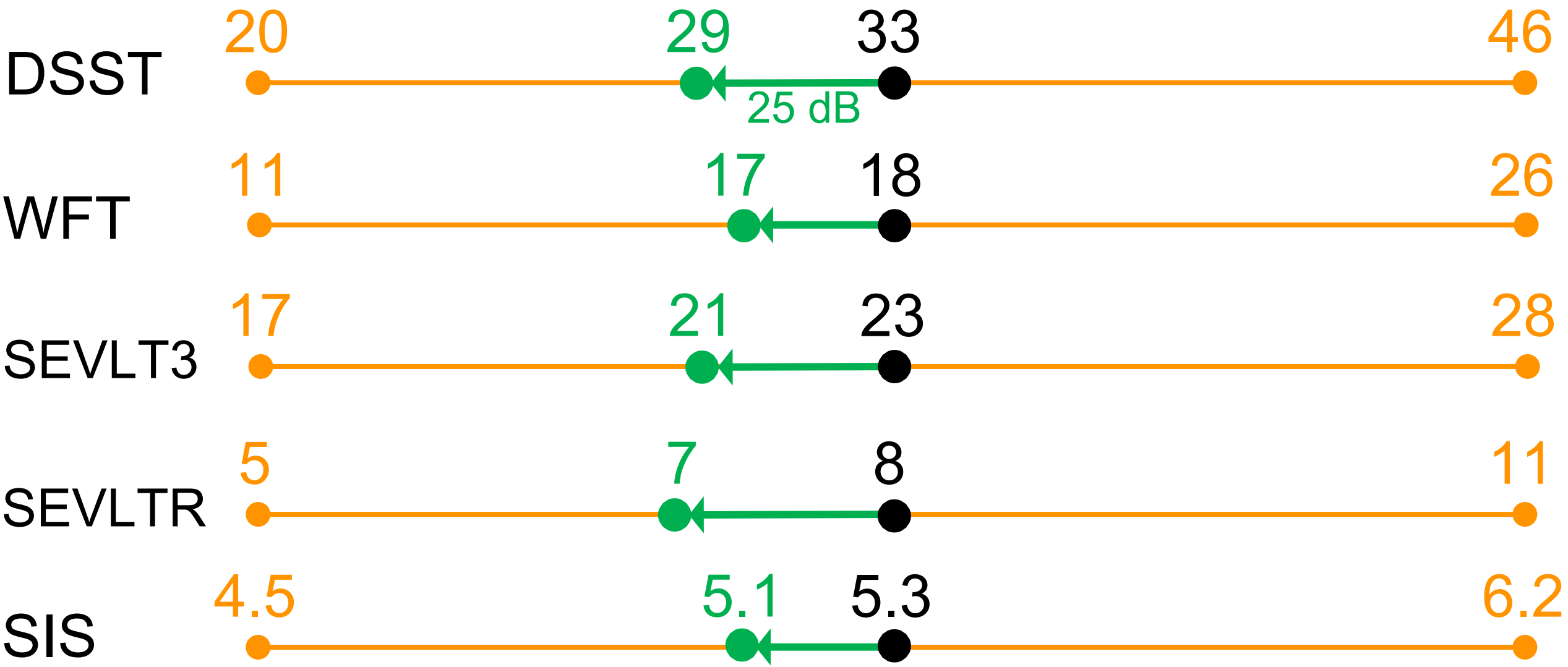
Is That Clinically Meaningful?



Is That Clinically Meaningful?



Is That Clinically Meaningful?



Conclusion

- Worse hearing was associated with lower cognition among adults **with subclinical hearing loss** (PTA 1-25 dB)
- Hearing-cognition relationship may begin earlier than previously realized
- >25 dB definition for adult HL too high?

The New York Times

Gracia Lam

PERSONAL HEALTH

For Better Brain Health, Preserve Your Hearing

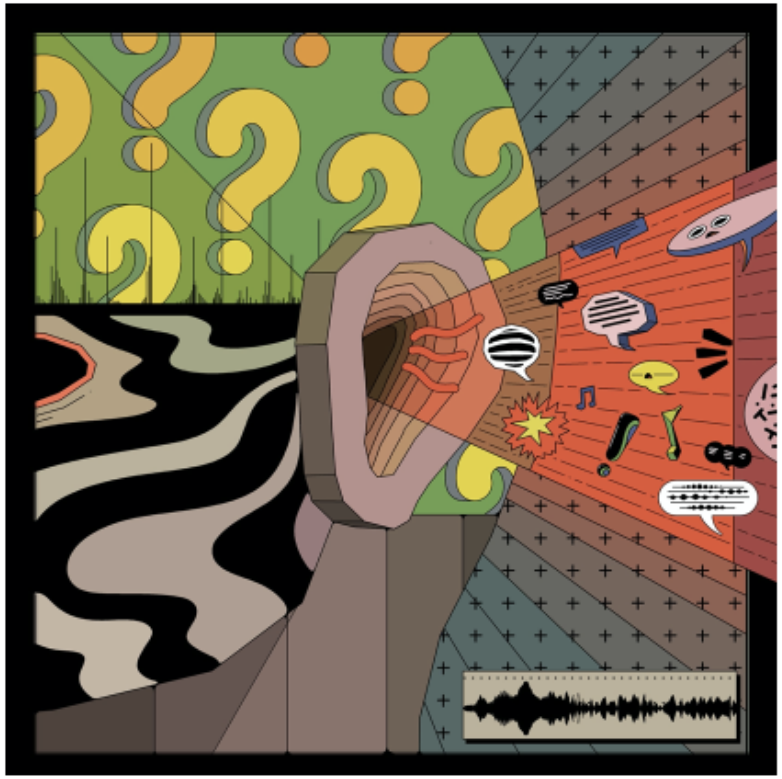
Hearing loss is the largest modifiable risk factor for developing dementia, exceeding that of smoking, high blood pressure, lack of exercise and social isolation.

By Jane E. Brody

Dec. 30, 2019

544

The New York Times



Illustrations by Ori Toor

STUDIES SHOW

Can Hearing Aids Help Prevent Dementia?

By Kim Tingley

Feb. 20, 2020

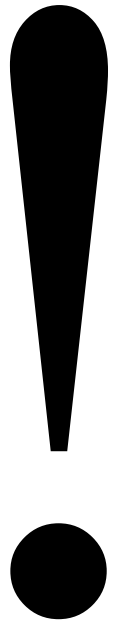
Hearing loss has long been considered a normal, and thus acceptable, part of aging. It is common: Estimates suggest that it affects two out of three adults age 70 and older. It is also rarely

- What’s Age-Related Hearing Loss?
- Hearing Loss ⟷ Cognition
- Mechanisms
- Subclinical Hearing Loss ⟷ Cognition
- **Conclusion & Next Steps**

Conclusions

- Hearing loss unquestionably **associated** with cognitive impairment
- Hearing loss *might* **cause** cognitive decline
- Hearing aids *might* **prevent** cognitive decline
- Association may begin with **subclinical** hearing loss
- Needs RCTs and mechanistic studies

Recommendations



Given risk/benefit ratio:

- Test hearing
- Recommend treatment

Next Steps

Coming Soon

IN THE SENATE OF THE UNITED STATES

DECEMBER 1, 2016

A BILL

To provide for the regulation of over-the-counter hearing aids.

Next Steps

ACHIEVE
HEALTHY AGING

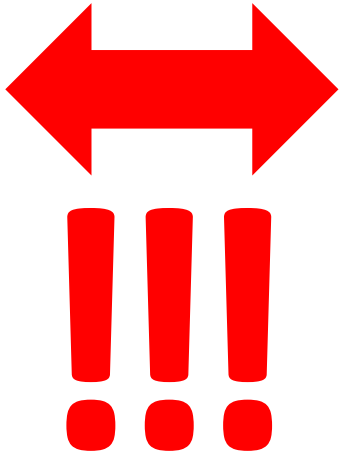
Cognition (plus much more) RCT

Depression pilot RCT

NOMEM-H

Neuroimaging observational

Status Quo: When Hearing is Treated



Children

Always and immediately!

Adults

Late or never.

Thank You

@jsgolub

Katharine K. Brewster, MD
Adam M. Brickman, PhD
Jessica Campbell
Adam J. Ciarleglio, PhD
Alexander L. Chern, MD
Alexandria Irace
Ana Kim, MD
Anil K. Lalwani, MD
José A. Luchsinger, MD, MPH
Jack Rowe, MD
Bret Rutherford, MD
Nicole Schupf, PhD
Rahul Sharma

Cochlear Center team: Frank R. Lin, MD, PhD; Adele Goman, PhD; Nick Reed, PhD; Jennifer Deal, PhD; Carrie Nieman, MD; Jonathan Suen

NIH/NIA K23AG057832, NIH/NIA Loan Repayment Program Award L30AG060513, Gerstner Scholars Award, Triological Society Career Development Award; Triological Society/American College of Surgeons Clinician-Scientist Award; Columbia Irving Institute for Clinical & Translational Research UL1TR001873/ UL1TR000040

References

1. Sharma RK, Lalwani AK, Golub JS. Prevalence and Severity of Hearing Loss in the Older Old Population. *JAMA Otolaryngol Head Neck Surg.* 2020.
2. Sharma RK, Lalwani AK, Golub JS. Modeling Hearing Loss Progression and Asymmetry in the Older Old: A National Population-Based Study. *The Laryngoscope.* 2020.
3. Golub JS, Brickman AM, Ciarleglio AJ, Schupf N, Luchsinger JA. Association of Subclinical Hearing Loss With Cognitive Performance. *JAMA Otolaryngol Head Neck Surg.* 2019.
4. Goman AM, Lin FR. Prevalence of Hearing Loss by Severity in the United States. *Am J Public Health.* 2016;106(10):1820-1822.
5. Lin FR, Metter EJ, O'Brien RJ, Resnick SM, Zonderman AB, Ferrucci L. Hearing loss and incident dementia. *Arch Neurol.* 2011;68(2):214-220.
6. Loughrey DG, Kelly ME, Kelley GA, Brennan S, Lawlor BA. Association of Age-Related Hearing Loss With Cognitive Function, Cognitive Impairment, and Dementia. *JAMA Otolaryngology–Head & Neck Surgery.* 2018;144(2).
7. Chien W, Lin FR. Prevalence of hearing aid use among older adults in the United States. *Arch Intern Med.* 2012;172(3):292-293.

References

8. Golub JS, Sharma RK, Rippon BQ, Brickman AM, Luchsinger JA. The Association Between Early Age-Related Hearing Loss and Brain beta-Amyloid. *Laryngoscope.* 2020.
9. Lin FR, Ferrucci L, An Y, et al. Association of hearing impairment with brain volume changes in older adults. *Neuroimage.* 2014;90:84-92.
10. Armstrong NM, An Y, Doshi J, et al. Association of Midlife Hearing Impairment With Late -Life Temporal Lobe Volume Loss.*JAMA Otolaryngol Head Neck Surg.* 2019.
11. Eckert MA, Cute SL, Vaden KI, Jr., Kuchinsky SE, Dubno JR. Auditory cortex signs of age-related hearing loss. *J Assoc Res Otolaryngol.* 2012;13(5):703-713.
12. Xu W, Zhang C, Li JQ, et al. Age-related hearing loss accelerates cerebrospinal fluid tau levels and brain atrophy: a longitudinal study. *Aging (Albany NY).* 2019;11(10):3156-3169.
13. Neff RM, Jicha G, Westgate PM, Hawk GS, Bush ML, McNulty B. Neuropathological Findings of Dementia Associated With Subjective Hearing Loss. *Otol Neurotol.* 2019;40(9):e883-e893.