# Evaluating relationships of hearing and cognition with Bradford Hill criteria for causation

Lauren K Dillard, PhD, AuD, MS

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# Acknowledgements

Co-authors: Gabrielle Saunders, Graham Naylor, Oliver Zobay



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PVARF and NCRAR

# Outline & Approach

- Introduction to Bradford Hill criteria
- Purpose
- Proposed mechanisms of hearing & cognition relationship
  - Mechanisms not necessarily mutually exclusive!
- Approach
  - Draw on published research (meta-review) & supporting studies
  - Datasets
- 9 Bradford Hill criteria
- Discussion & implications

# Bradford Hill criteria for causation

Framework for causal inference consisting of 9 ‘viewpoints’ to help determine if epidemiologic associations can be described as causal.

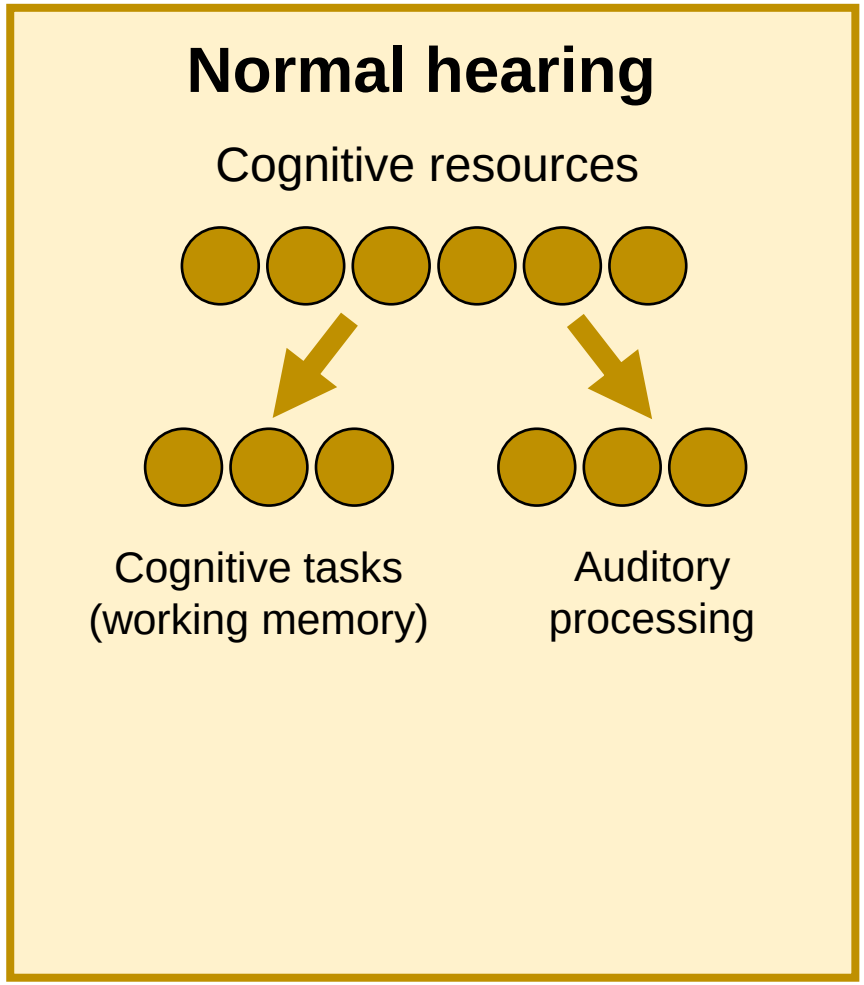
*Not a rigid ‘checklist’ and should evolve alongside modernizing scientific methods and understanding.*

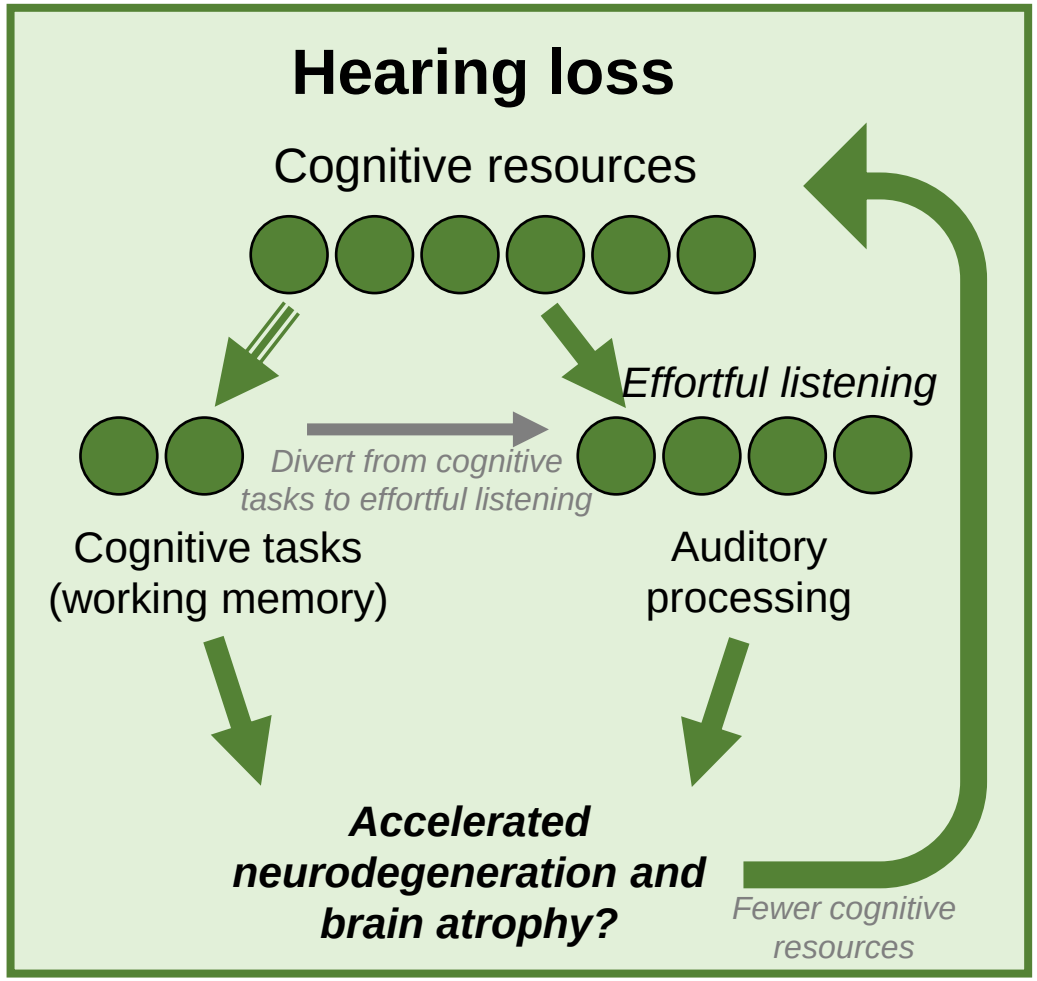
Bradford-Hill, 1965

# Purpose

Contextualize the current state of research focused on hearing and cognition with the Bradford Hill criteria for causality, in order to understand whether or not causal inferences can be made from current observed associations.

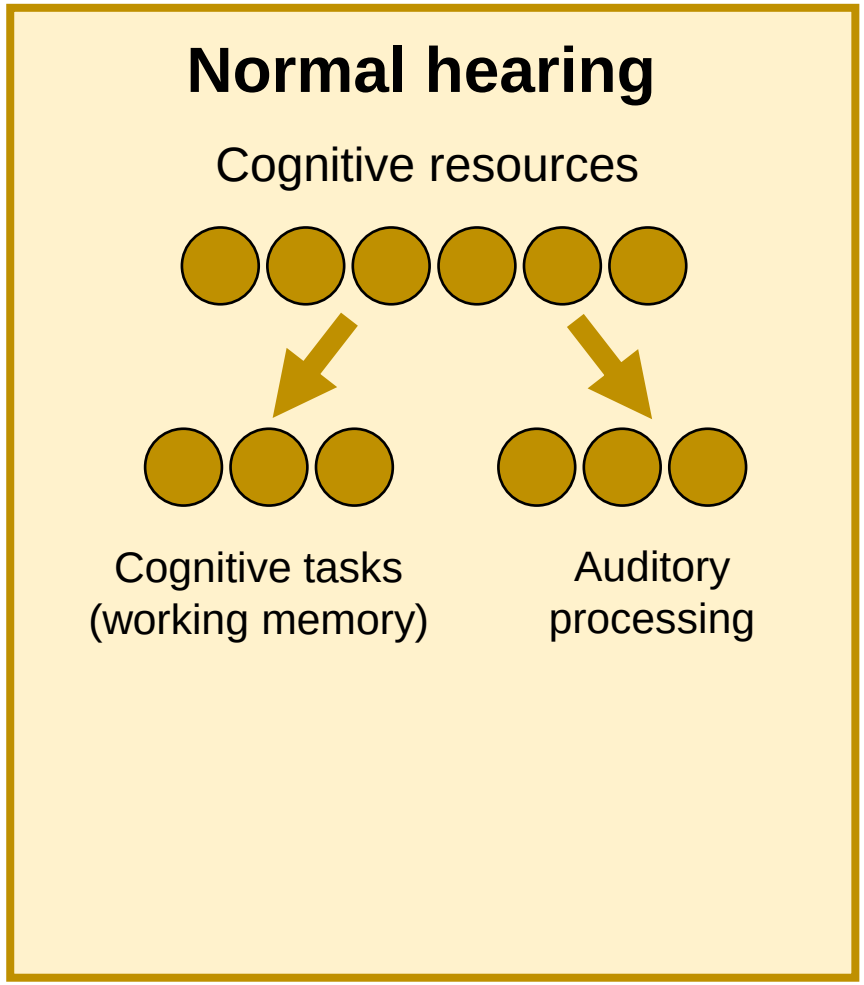
# Proposed mechanisms: Cognitive load

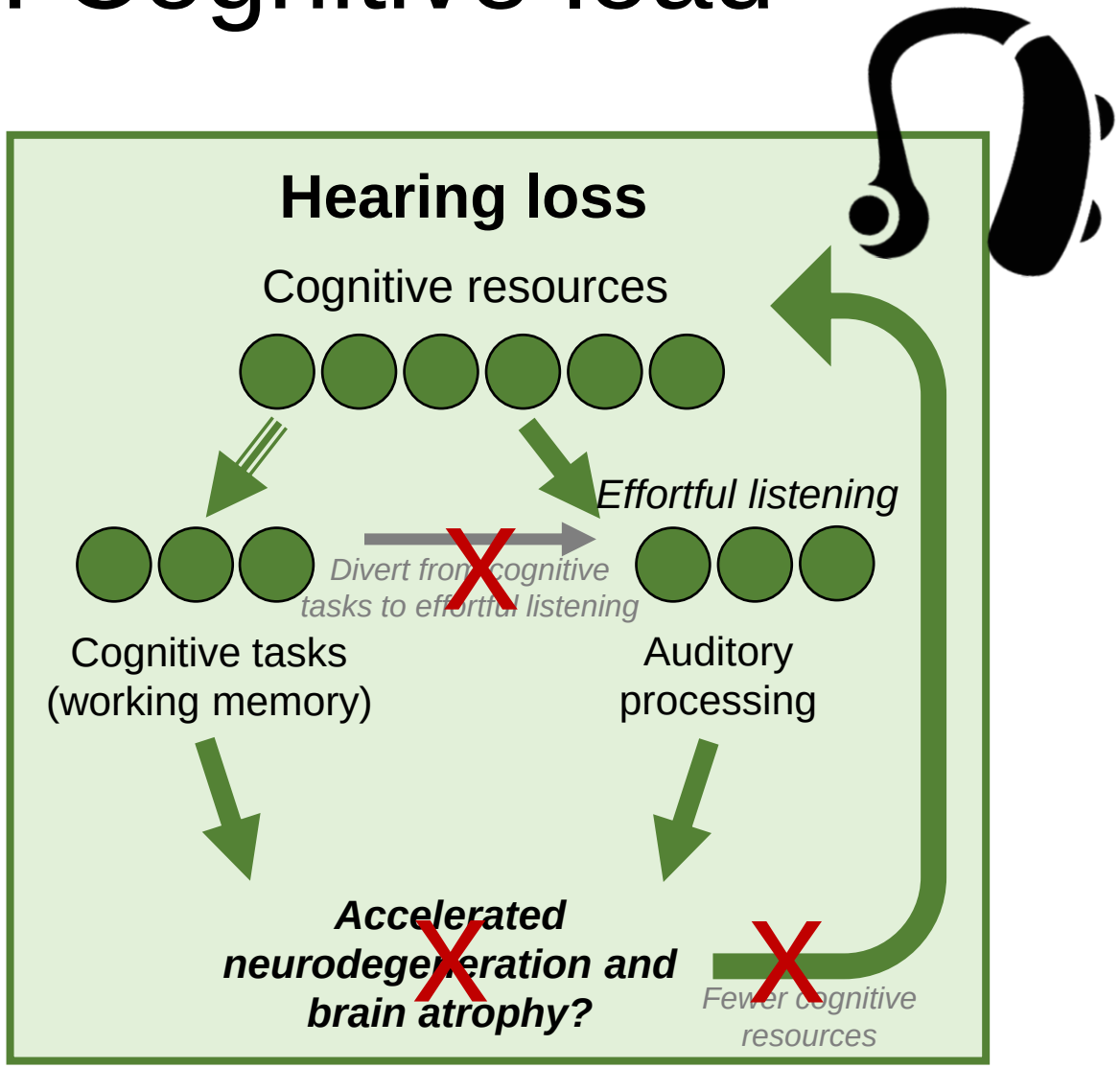



Uchida et al., 2020

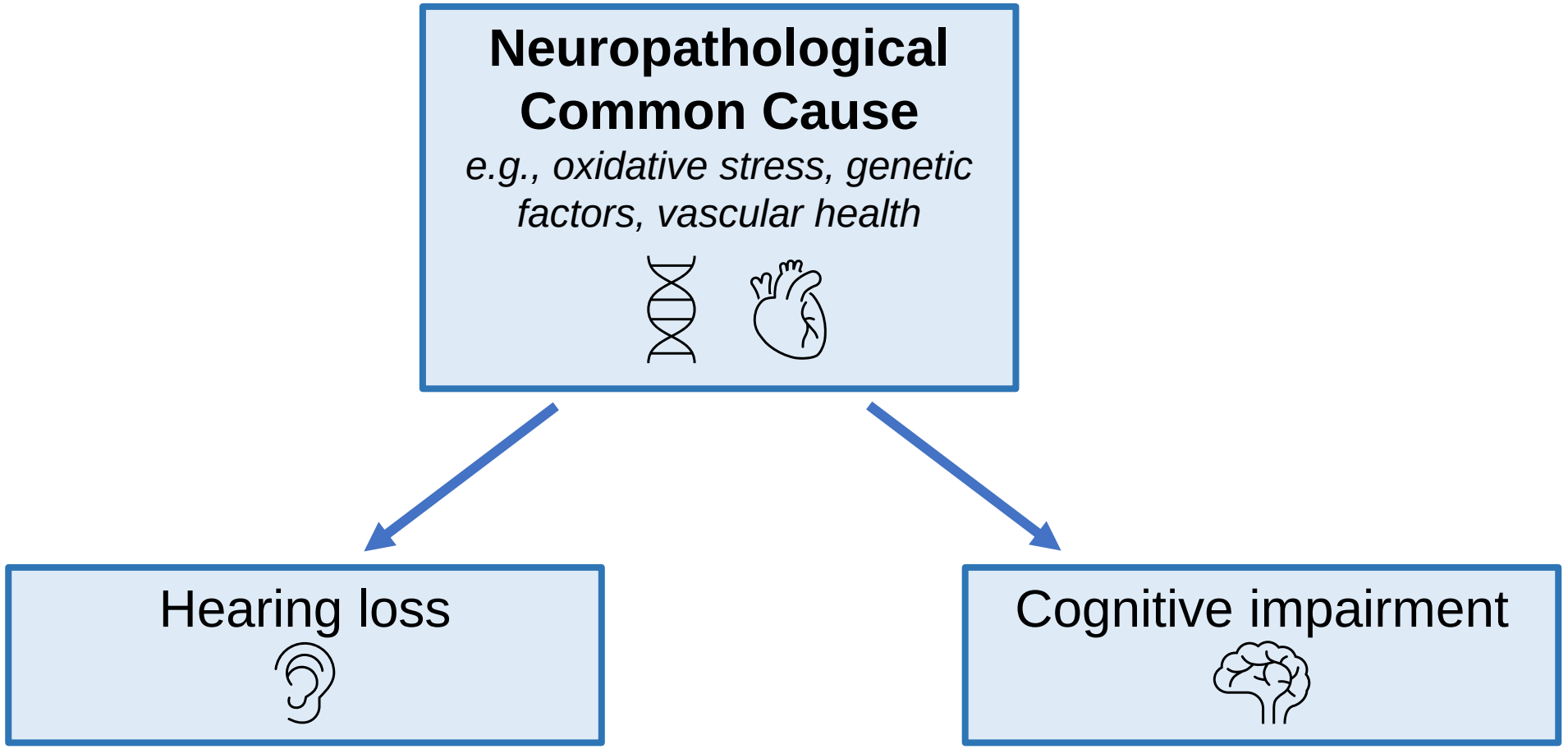
# Proposed mechanisms: Cognitive load




Uchida et al., 2020

# Proposed mechanisms: Common cause




Uchida et al., 2020

# Proposed mechanisms: Common cause

Nothing changes

**Neuropathological Common Cause**

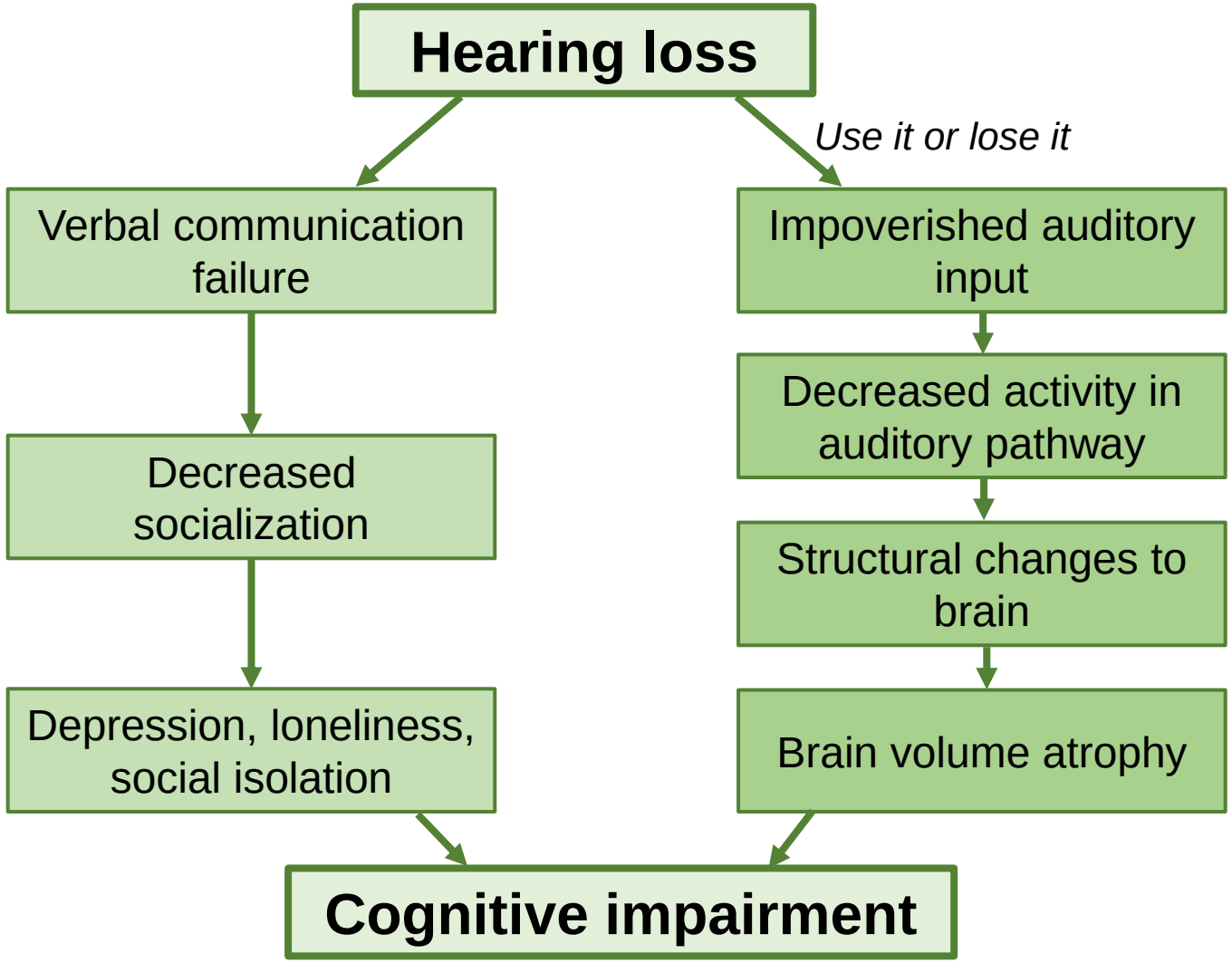
*e.g., oxidative stress, genetic factors, vascular health*

Hearing loss

Cognitive impairment

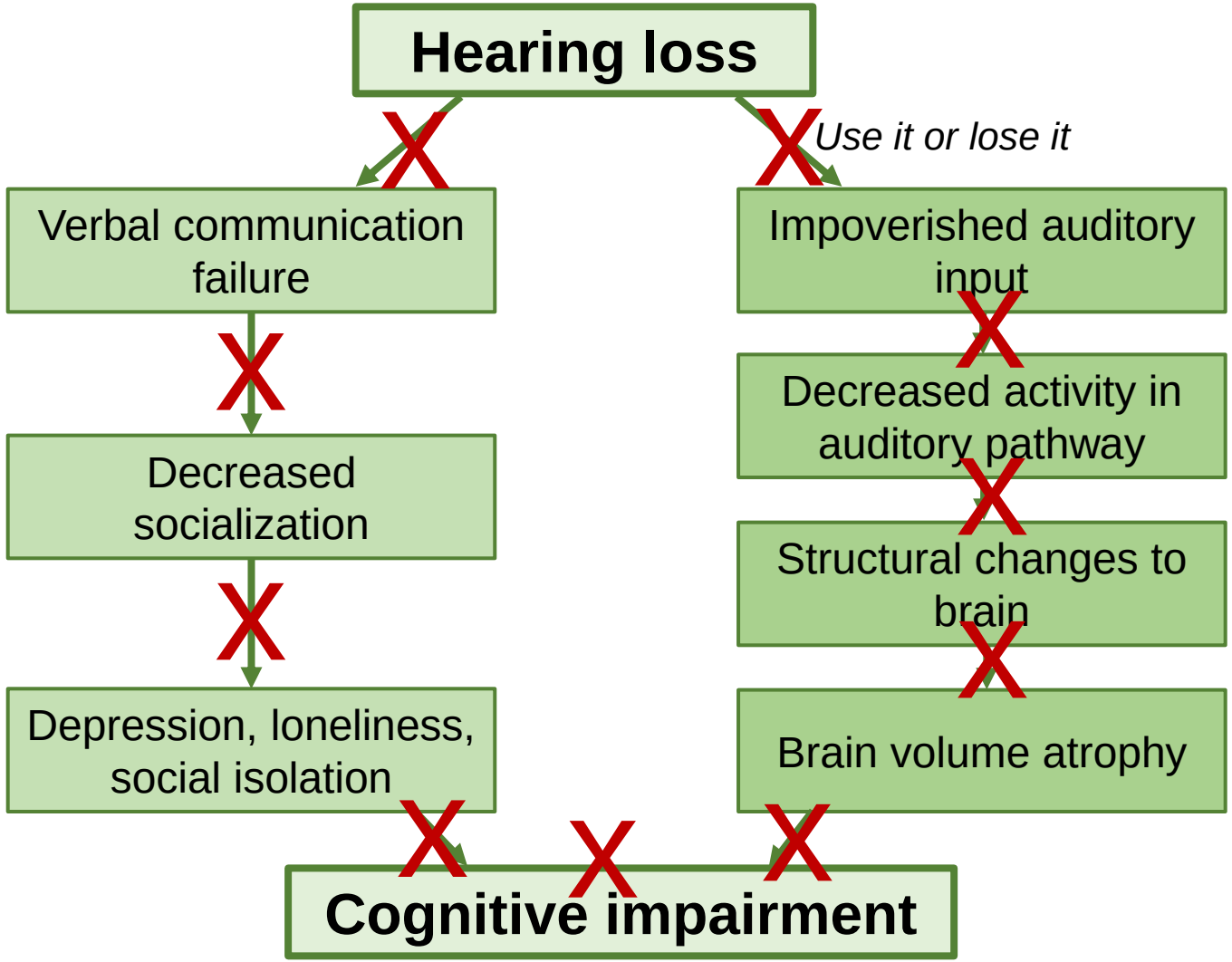
Uchida et al., 2020

# Proposed mechanisms: Cascade



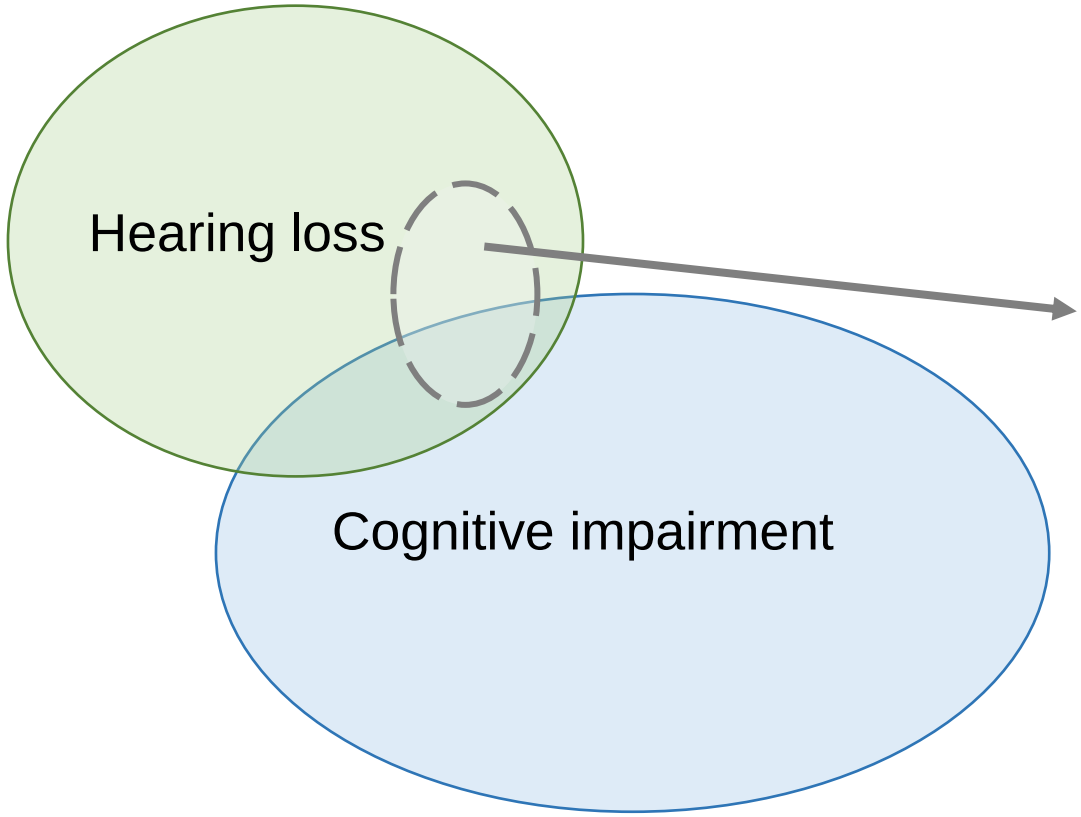

Uchida et al., 2020

# Proposed mechanisms: Cascade




Uchida et al., 2020

# Proposed mechanisms: Overdiagnosis




Over or misdiagnosis of cognitive impairment due to impacts of hearing loss on cognitive test performance.

Uchida et al., 2020

# Proposed mechanisms: Overdiagnosis

Hearing loss

Cognitive impairment

X a: Over or misdiagnosis of cognitive impairment due to impacts of hearing loss on cognitive test performance.

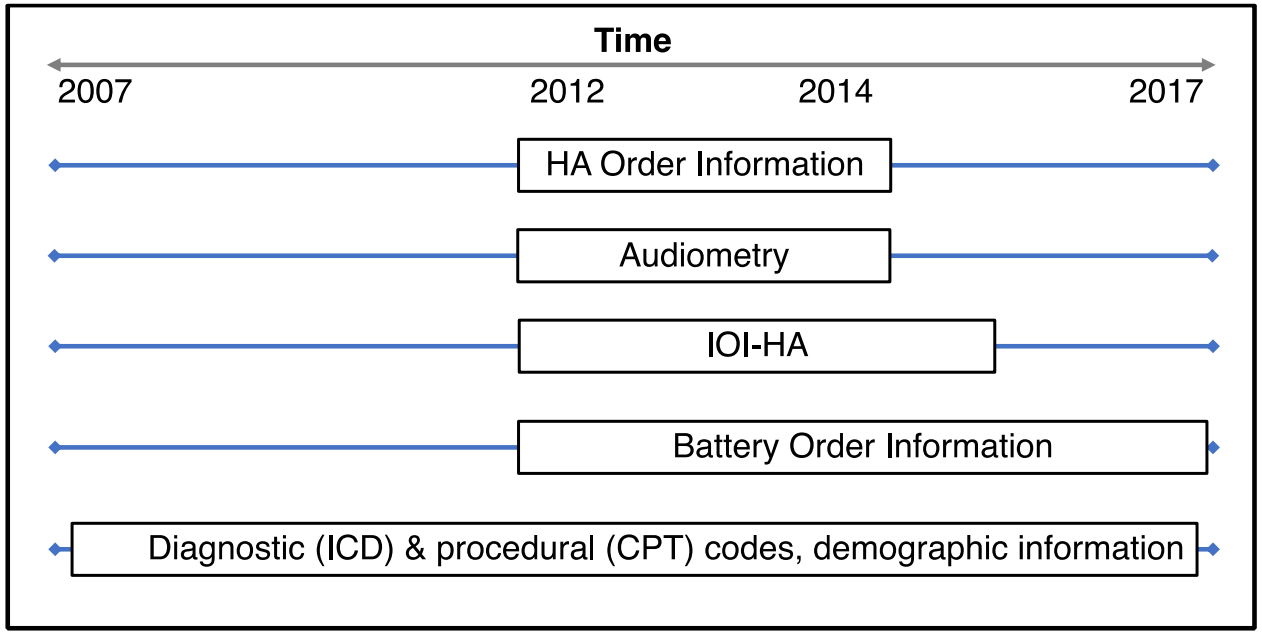
Uchida et al., 2020

# Other relevant definitions

- **Cognitive function or decline (domains):**
  - Memory and learning
  - Language
  - Executive function (e.g., working memory, adaptable thinking, self-monitoring/control, organization)
  - Complex attention
  - Perceptual and motor functions
- **Mild cognitive impairment (MCI):** memory or thinking problems that may progress to dementia
- **Dementia:** umbrella term characterized by severe loss of memory and other thinking abilities.
  - **Alzheimer's**: Most common cause of Dementia.

# Dataset: VA Electronic Health Records

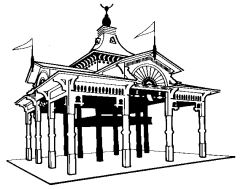
Patients with hearing aid order (n=731,213; 98.9% male)




IOI-HA: International Outcome Inventory for Hearing Aids; ICD: International Disease Classification codes; CPT: Current Procedural Terminology codes

Dillard et al., 2020; Saunders et al., 2021; Zobay et al., 2021; Naylor et al., 2022

# Dataset: Longitudinal Cohort Studies

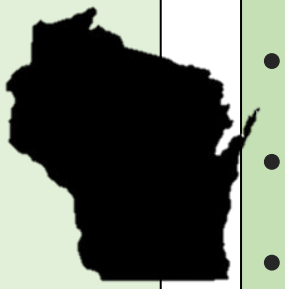


Beaver Dam Offspring Study

MUSC Medical University of South Carolina Hearing Research Program

## Epidemiology of Hearing Loss Study (EHLS)

- 1993-2020
- n=3500
- Older



## Beaver Dam Offspring Study (BOSS)

- 2005-current
- n=3300
- Middle-aged
- Offspring of EHLS

## MUSC Longitudinal Study

- 1988-current
- n=1775
- Older

Pooled (n=3574) middle-aged to older adults

Cruickshanks et al., 1998, 2003, 2015; Nash et al., 2011; Dubno et al., 2008

# Bradford Hill criteria for causation

1. Strength of association
2. Consistency of evidence
3. Specificity
4. Temporality
5. Biologic gradient
6. Plausibility
7. Coherence
8. Experimental evidence
9. Analogy

Intervention with hearing aids

Bradford-Hill, 1965; Rothman, 2005

# 1. Strength of Association

The larger the association, the more likely to be a causal relationship.

Weak associations may be more easily explained by undetected biases.

Bradford-Hill, 1965; Rothman, 2005

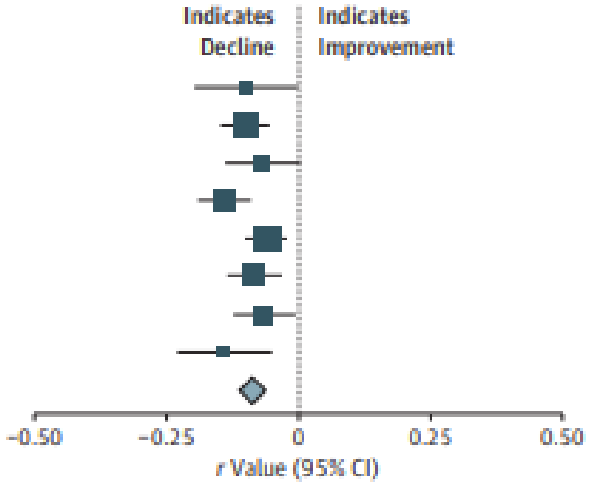
# 1. Strength of Association

The larger the association, the more likely to be a causal relationship.

**Correlations of hearing loss and cognitive domains (longitudinal studies)**

**-0.06 to -0.14**

| Outcome | No. of Participants/ Events | *r* Value (95% CI) |
|---|---|---|
| Attention | 391/1 | −0.10 (−0.20 to 0.00) |
| Delayed recall | 1774/4 | −0.10 (−0.15 to −0.05) |
| Fluency | 1233/4 | −0.07 (−0.14 to 0.01) |
| Global cognition | 4227/6 | −0.14 (−0.19 to −0.09) |
| Immediate recall | 4225/6 | −0.06 (−0.10 to −0.02) |
| Processing speed | 6462/10 | −0.08 (−0.14 to −0.03) |
| Reasoning | 1057/1 | −0.06 (−0.12 to 0.00) |
| Semantic memory | 707/1 | −0.14 (−0.23 to −0.05) |
| Summary | 8233/33 | −0.09 (−0.11 to −0.07) |




Note: Present results from one systematic review/meta-analysis related to hearing loss. Other meta-analyses returned similar results.

**Longitudinal associations of risk factors (separate meta-analyses) with dementia**

| | HR | 95% CI |
|---|---|---|
| **Hearing loss** | **1.22** | **(1.09, 1.36)** |
| Education (low vs high) | 1.99 | (1.30, 3.04) |
| Smoking (history vs never) | 1.37 | (1.23, 1.52) |
| Physical activity (high vs low) | 0.58 | (0.49, 0.70) |
| Homocysteine (high vs low)[a] | 1.93 | (1.50, 2.49) |

[a]amino acid identified as risk factor for Dementia

Loughrey et al., (2018); Beydoun et al., (2014)

# 1. Strength of Association

The larger the association, the more likely to be a causal relationship.

**Magnitude of association is relatively small and is smaller than other risk factors for cognitive decline or dementia.**

# 2. Consistency of evidence

A variety of locations, methods, and populations show same results.

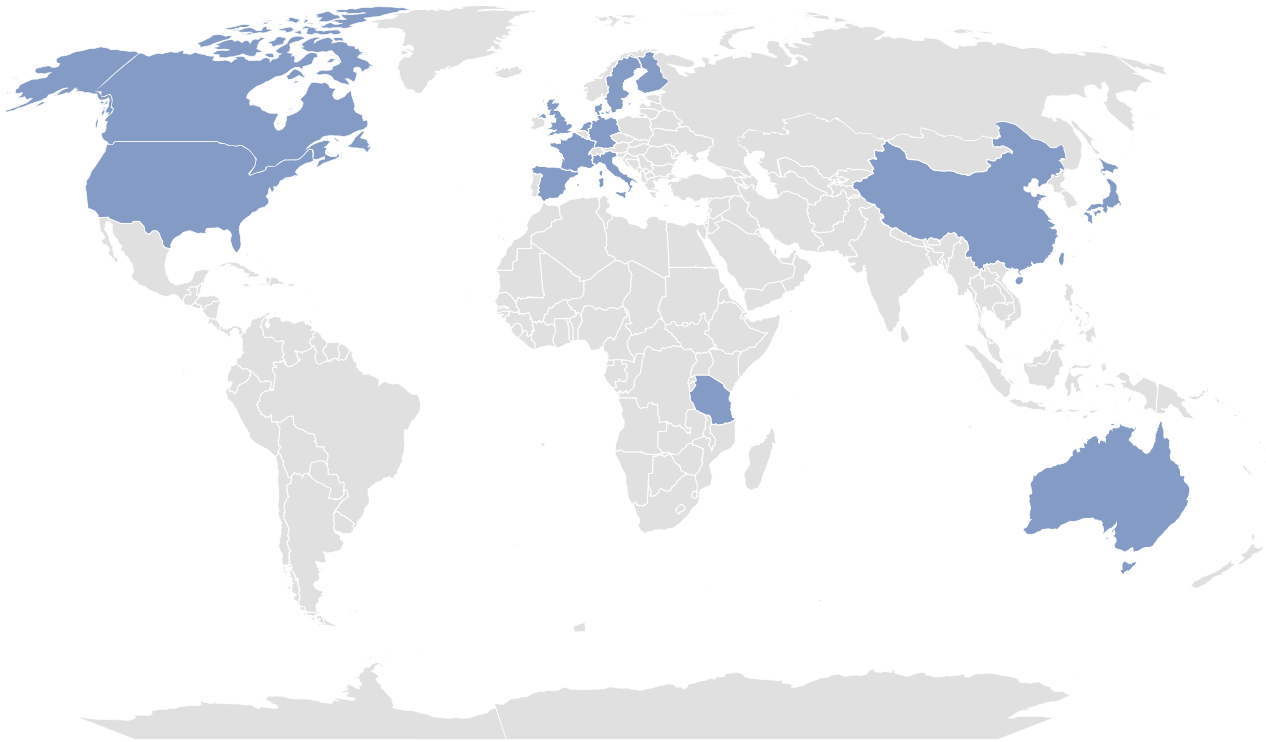
Rules out hypothesis that the association is attributable to some factor that varies across studies.

Bradford-Hill, 1965; Rothman, 2005

# 2. Consistency of evidence

A variety of locations, methods, and populations show same results.

- Several countries (most high income) show similar results
- Many (not all) definitions/ methods show similar results
- Types of cohorts
  - Community dwelling
  - Health care recipients
  - Medical records



Loughrey et al., (2018); Ford et al., (2018); Zheng et al., (2017); Tarawneh et al., (2017); Fu et al., (2023); Lau et al., (2022); Liang et al., (2021); Taljaard et al., (2016)

# 2. Consistency of evidence

A variety of locations, methods, and populations show same results.

**Associations are generally consistent.**

# 3. Specificity

Exposure causes only one disease outcome.

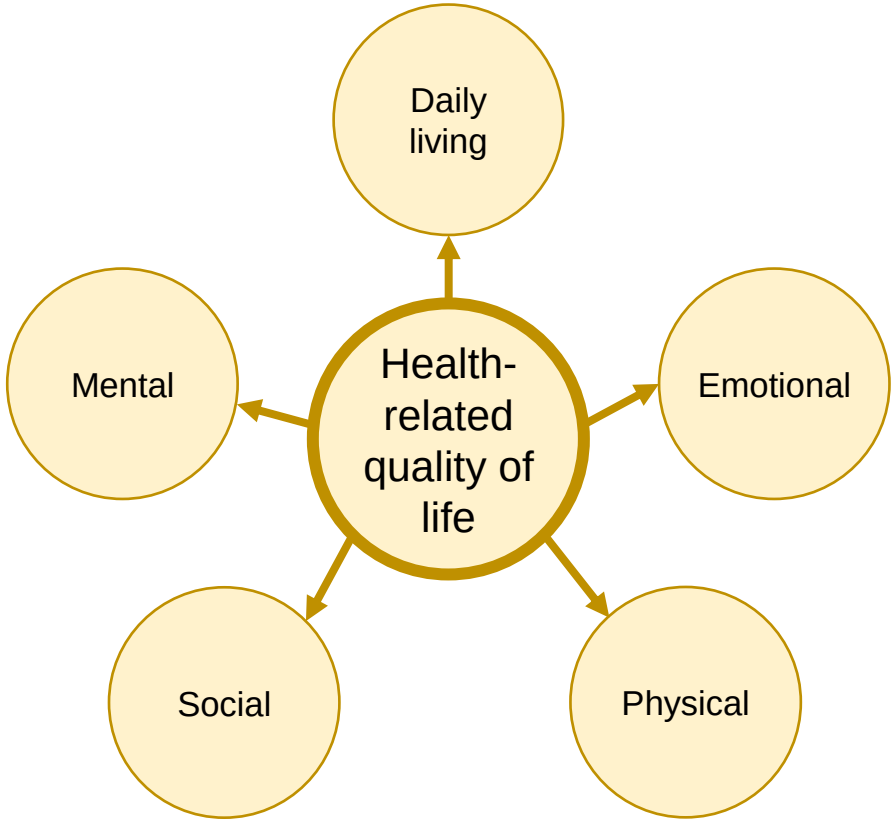
If present, the greater the specificity between an exposure and outcome, the greater the probability of causality.

Bradford-Hill, 1965; Rothman, 2005

# 3. Specificity

Exposure causes only one disease outcome.

- Most studies focus on associations of hearing loss with health-related quality of life
- Some evidence suggests hearing is associated with depressive symptoms or physical frailty




Lawrence et al., 2020; Tian et al., 2021

# 3. Specificity

Exposure causes only one disease outcome.

**It is difficult to apply this criterion to hearing loss.**

??

# 4. Temporality

Time of the exposure precedes the disease outcome.

Inarguable criterion!

Bradford-Hill, 1965; Rothman, 2005

# 4. Temporality

Time of the exposure precedes the disease outcome.

**Cross-Sectional Studies**

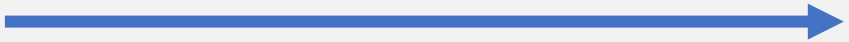
Time

Hearing loss (exposure)

Cognitive function or decline (outcome)

**Cannot determine temporality**

**Longitudinal Studies**



Time

Hearing loss (exposure)

Cognitive function or decline (outcome)

**6 to 18 years**

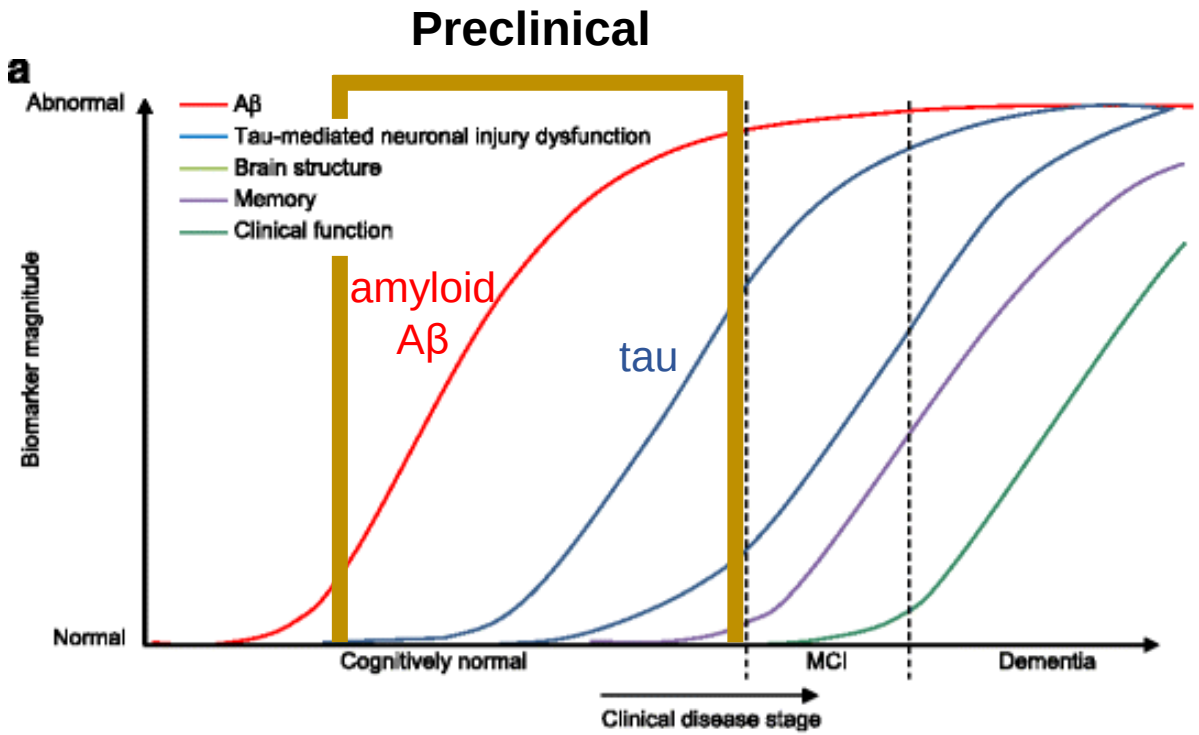
**Need to consider when in disease course measurements are made, frequency and duration of follow-up**

Loughrey et al., (2018)

# 4. Temporality

Time of the exposure precedes the disease outcome.

Dementia has long pre-clinical phase and biomarkers (e.g., amyloid Aβ, tau) can be observed before clinical stage




Aisen et al., (2017)

# 4. Temporality

Time of the exposure precedes the disease outcome.

**Longitudinal studies confirm temporality yet vary in the frequency and methods of data collection. Understanding temporality is complicated given preclinical stages of disease.**

# 5. Biologic gradient

Dose/response relationships between exposure and outcome.

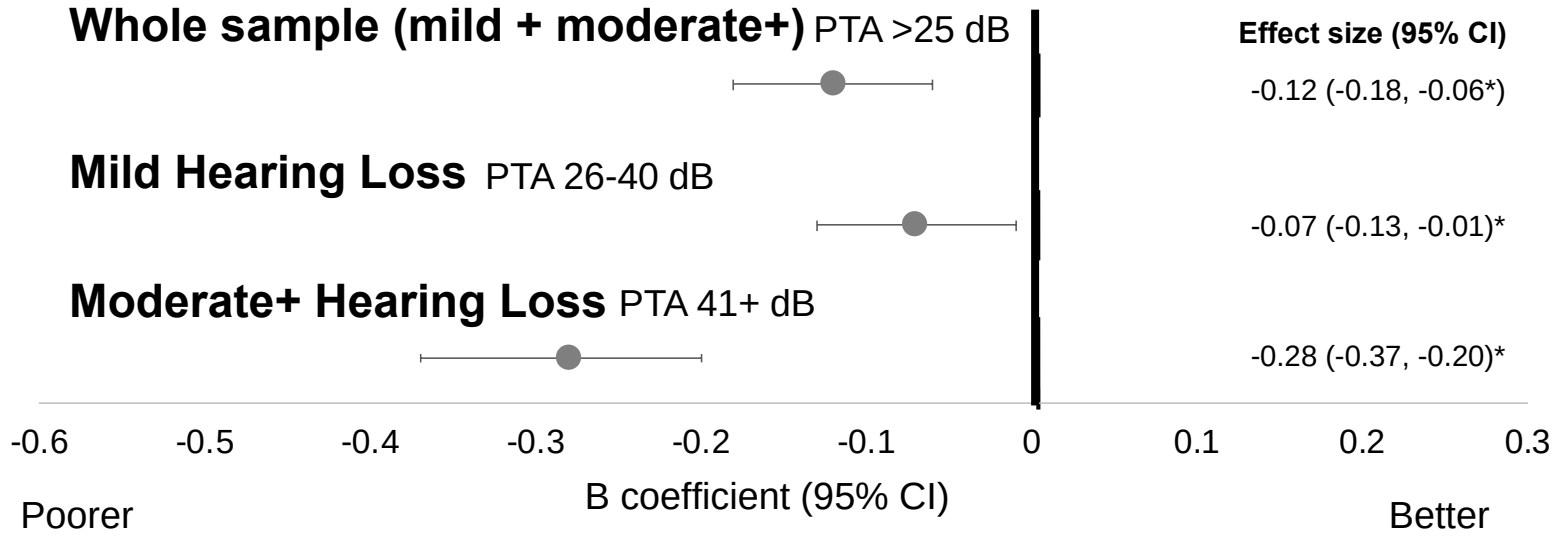
Helpful to establish association but is not expected from all causal relationships.

Bradford-Hill, 1965; Rothman, 2005

# 5. Biologic gradient

Dose/response relationships between exposure and outcome.

**EHLS and BOSS (n=3574): Cognition measured by a principal component analysis**




Scores standardized (M=0, SD=1)

Cognitive domains:

- Memory
- Language
- Processing speed
- Executive function

Referent group = normal hearing
Adjusted for: age, sex, education, marital status, visual impairment, atherosclerotic plaque, diabetes
PTA: 0.5-4.0 kHz, better ear

Dillard et al., 2022

# 5. Biologic gradient

Dose/response relationships between exposure and outcome.

**More severe hearing loss is associated with higher odds or risk of poorer cognition or dementia.**

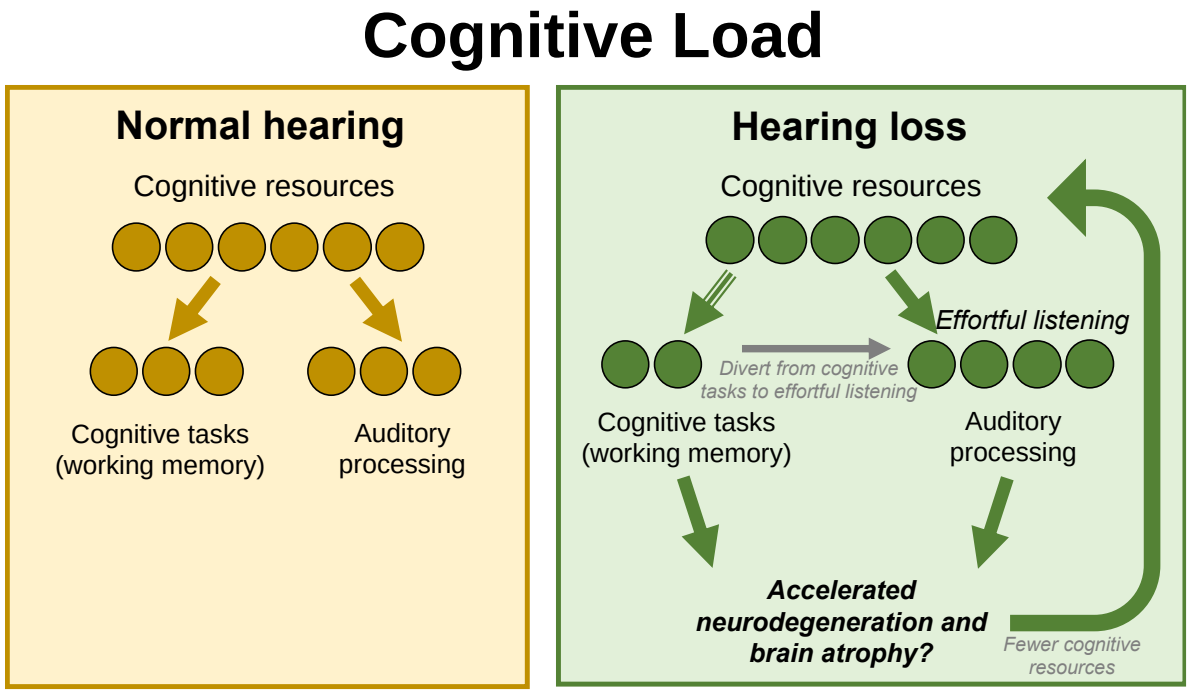
# 6. Plausibility

Association consistent w/ biological, psychological, or social models.

Bradford-Hill, 1965; Rothman, 2005

# 6. Plausibility

Association consistent w/ biological, psychological, or social models.



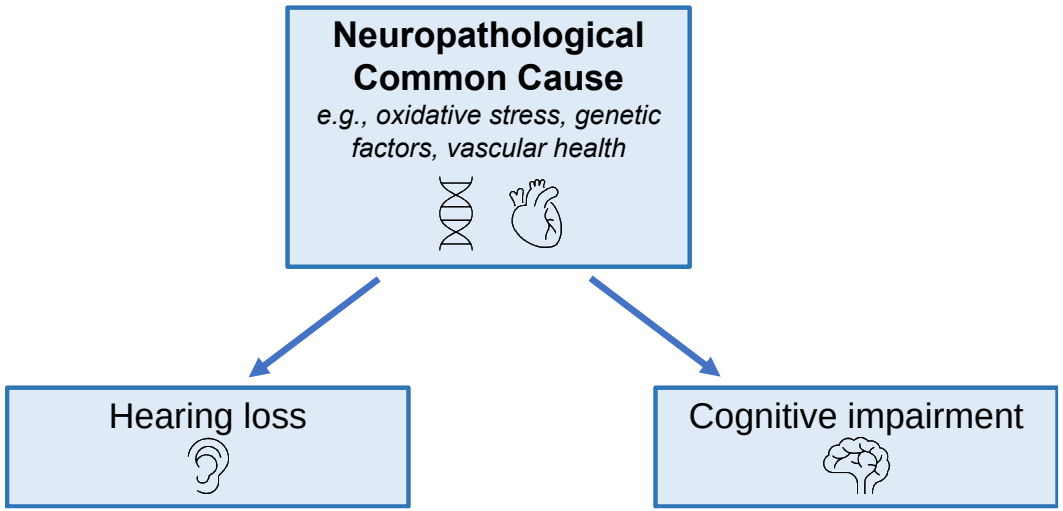

- Inconsistent evidence that hearing loss increases listening effort

Ohlenforst et al. (2017); Uchida et al., 2020

# 6. Plausibility

Association consistent w/ biological, psychological, or social models.

**Common cause**

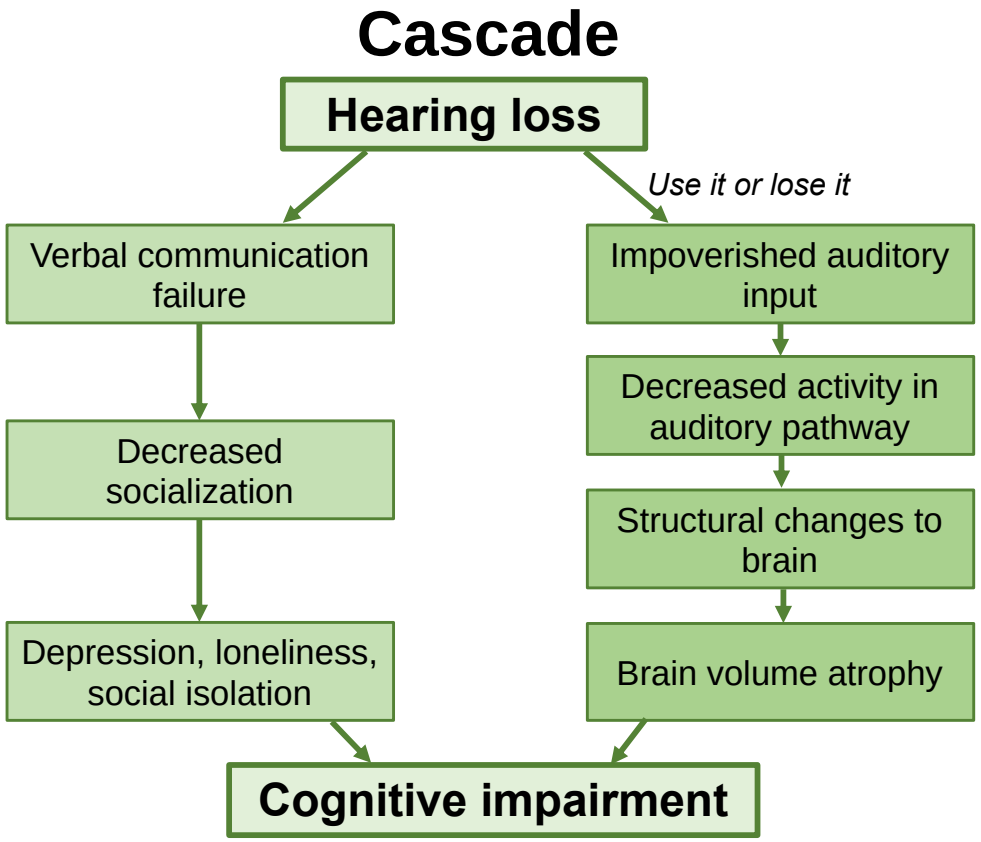



- Associations often persist after controlling for shared risk factors
- Difficult to rule out residual or uncontrolled confounding

Uchida et al., 2020

# 6. Plausibility

Association consistent w/ biological, psychological, or social models.



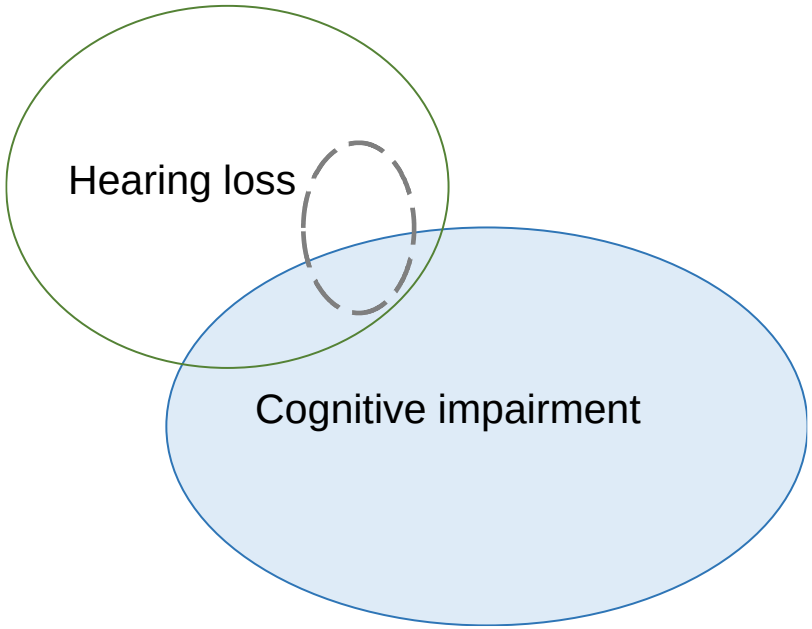

- Inconsistent evidence that hearing loss leads to depression, loneliness, and social isolation
- Hearing loss has been associated with smaller brain volume yet there is evidence for cross-modal plasticity

Uchida et al., 2020; Bott & Saunders, 2021; Lin et al., 2014; Rigters et al., 2017

# 6. Plausibility

Association consistent w/ biological, psychological, or social models.

**Overdiagnosis**




- Associations of hearing loss with cognitive function are shown on verbal and non-verbal tasks

Uchida et al., 2020; Füllgrabe, 2020

# 6. Plausibility

Association consistent w/ biological, psychological, or social models.

**Associations are plausible, but mechanistic frameworks were developed based on plausibility.**

# 7. Coherence

All available evidence supports the cause-effect relationship and does not conflict with what is known about the natural history and biology of disease.

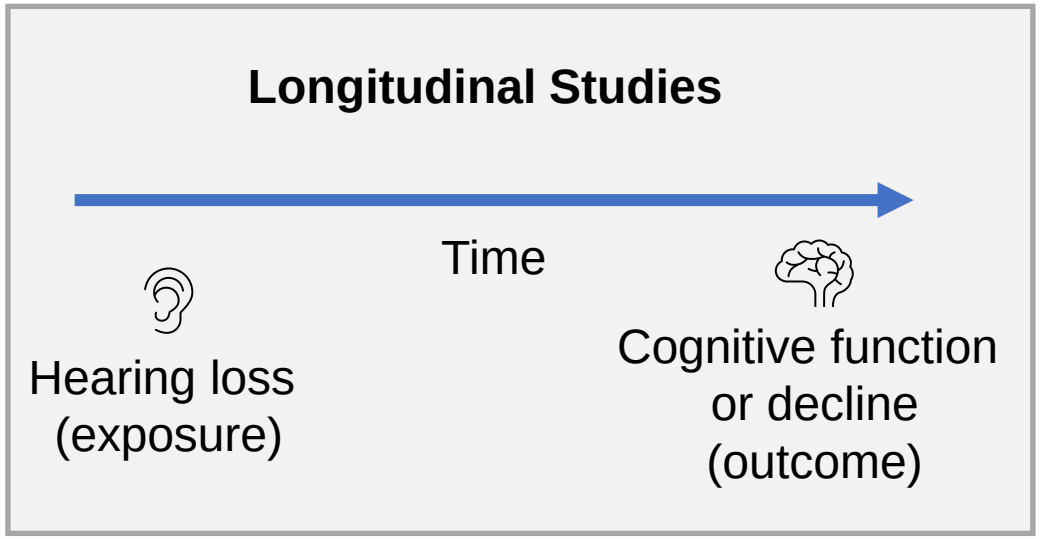
Conflicting information may undermine a hypothesis.

Bradford-Hill, 1965; Rothman, 2005

# 7. Coherence

All available evidence supports the cause-effect relationship and does not conflict with what is known about the natural history and biology of disease.

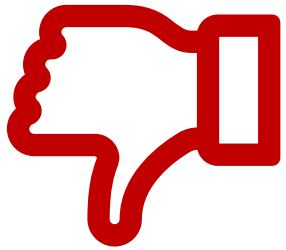
- Few longitudinal studies of hearing
- All evidence towards the proposed mechanisms have some supporting, conflicting, and missing information.
- More high-quality data (from human and animal studies) and improved understanding of mechanisms will help establish or refute coherence.



# 7. Coherence

All available evidence supports the cause-effect relationship and does not conflict with what is known about the natural history and biology of disease.

**Evidence supporting causality is inconsistent. High quality data, including longitudinal and cross-disciplinary data, are needed to improve understanding of mechanisms.**



# 8. Experimental Evidence

Intervention reduces exposure, thereby reducing risk of the disease.

Bradford-Hill, 1965; Rothman, 2005

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Intervention reduces exposure, thereby reducing risk of the disease.

## Hearing aid fitting (meta-analysis of pre/post studies)

### Studies with no control group

| Cognitive Domain | No significant change - | Significant change + |
|---|---|---|
| Brief mental status | ●● | ●● |
| Motor function | ● | |
| Executive function | | ●●●●●●●● |
| Complex attention | ●●●●● | ●● |
| Language | ●● | |
| Learning & memory | ●●● | |

### Studies with control group

| Cognitive Domain | No significant change - | Significant change + |
|---|---|---|
| Brief mental status | ● | ● |
| *General intelligence* | | ● |
| Executive function | ●●● | ●●●● |
| Complex attention | ●●●●●●●●● | |
| Language | ●●●●● | |
| Learning & memory | ●●●● | ●● |

*Circles represent number of studies*

Sanders et al., 2021

SUPPORTING STUDY: 2-WAY STREET

# Cognitive impairment ⟷ hearing aid use

**Hypothesis 1**: Hearing aid (HA) use is protective against dementia onset

*(Association of persistent hearing aid use with incident dementia)*

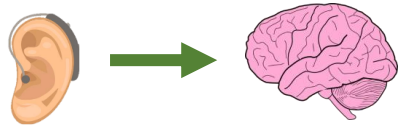

**Hypothesis 2**: Cognitive dysfunction makes HA use challenging, so HA are rarely or never used

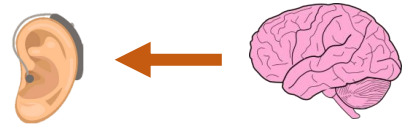
*(Association of prevalent dementia with persistent hearing aid use)*

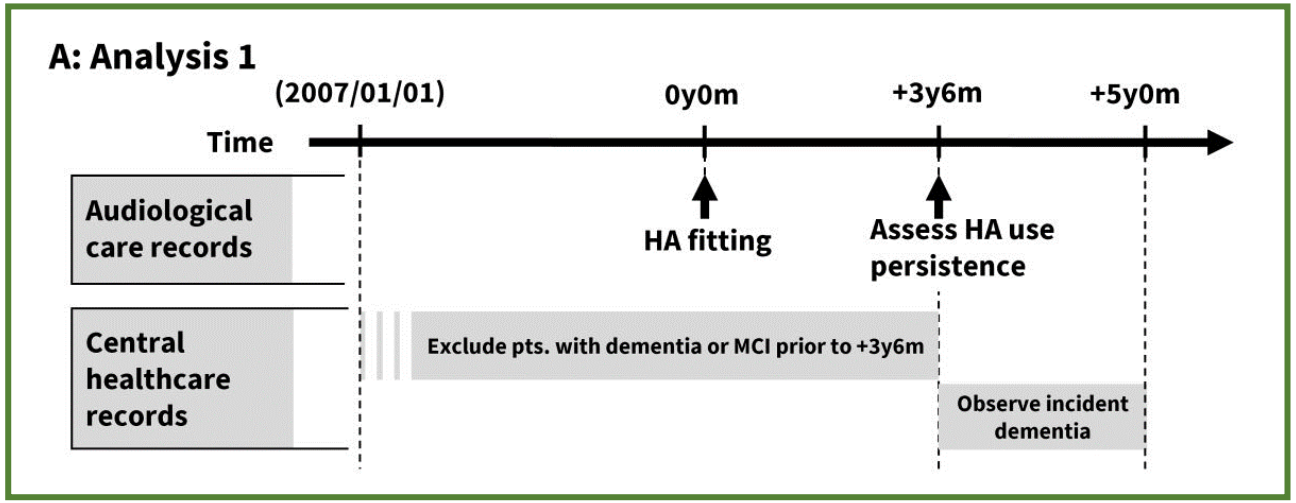
SUPPORTING STUDY: 2-WAY STREET

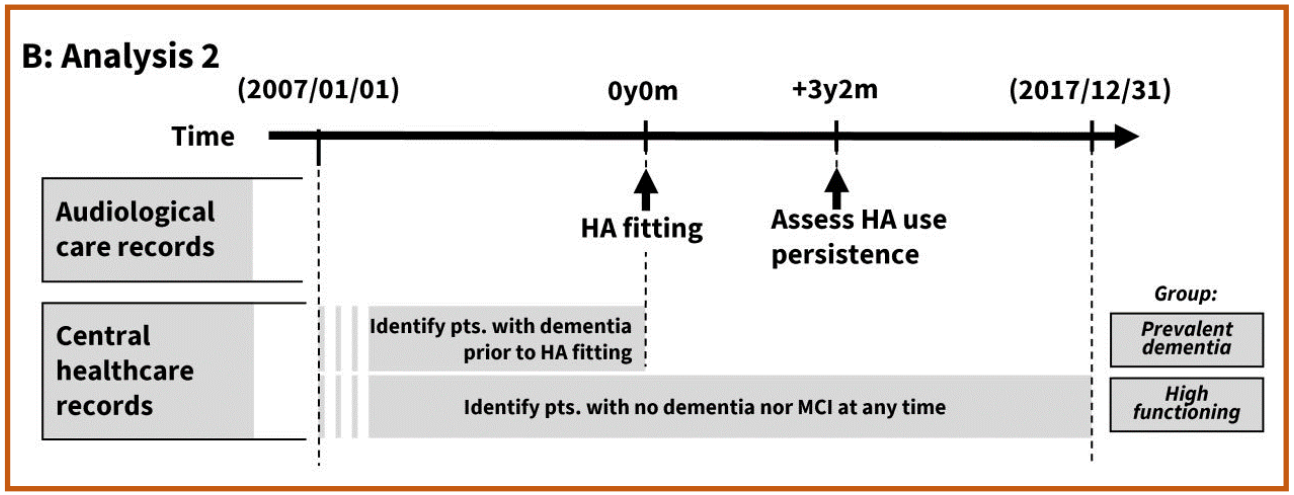
# Methods: VA Health Records

Isolated pathways

**FORWARD PATH** 

**REVERSE PATH** 

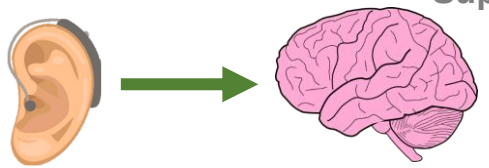



Zulman et al., 2015; Healthcare Cost and Utilization Project, 2016; Saunders et al., 2021; Zobay et al., 2021; Naylor, et al., 2022

# Results

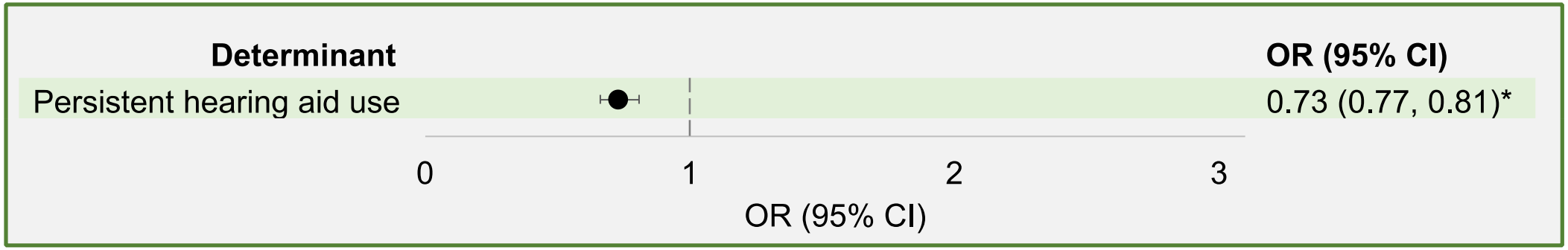
## FORWARD PATH



exposure → outcome

✓ **Hypothesis 1**: HA use is protective against dementia onset

**n=72,180**



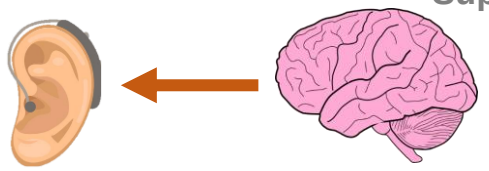

**Persistent HA use is associated with reduced odds of incident dementia**

Referent group = non persistent hearing aid use
Adjusted for: age, PTA, obesity, stroke, diabetes, depression, bipolar, hypertension

SUPPORTING STUDY: 2-WAY STREET

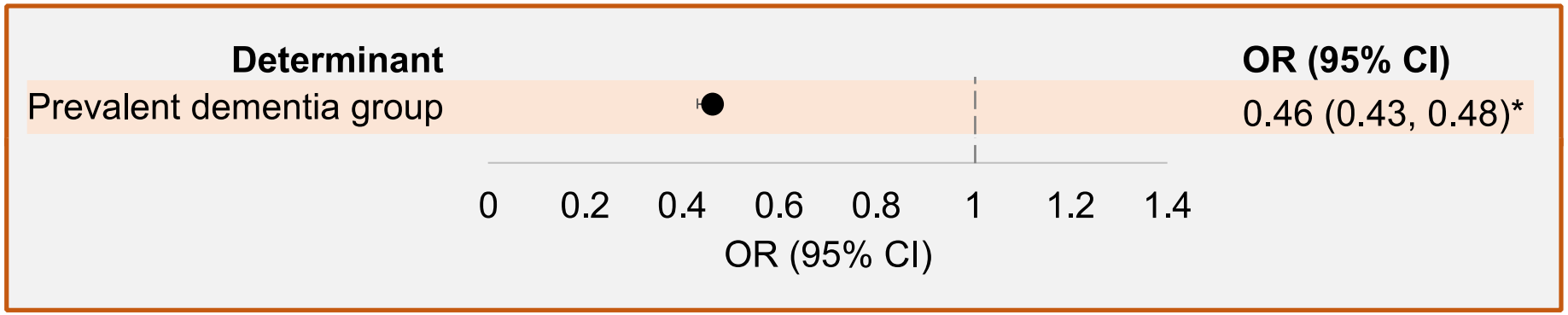
# Results

## REVERSE PATH



exposure → outcome

✓ **Hypothesis 2**: Cognitive dysfunction makes HA use challenging, so HA are rarely or never used **n=350,918**




**Prevalent dementia is associated with reduced odds of HA persistence**

Referent group = non persistent hearing aid use
Adjusted for: age, PTA, new vs experienced HA users, chronic disease

Naylor, et al., 2022

# Hearing aid use and cognition in the general population

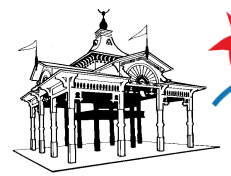
**EHLS:** Older; 25-yr longitudinal study

**BOSS:** Middle-aged; 20-yr longitudinal study

→ Pooled samples (n=3574) middle-aged to older adults

**Cognitive measure:** Principal component analysis of cognitive tests measuring memory, language, processing speed, executive function.

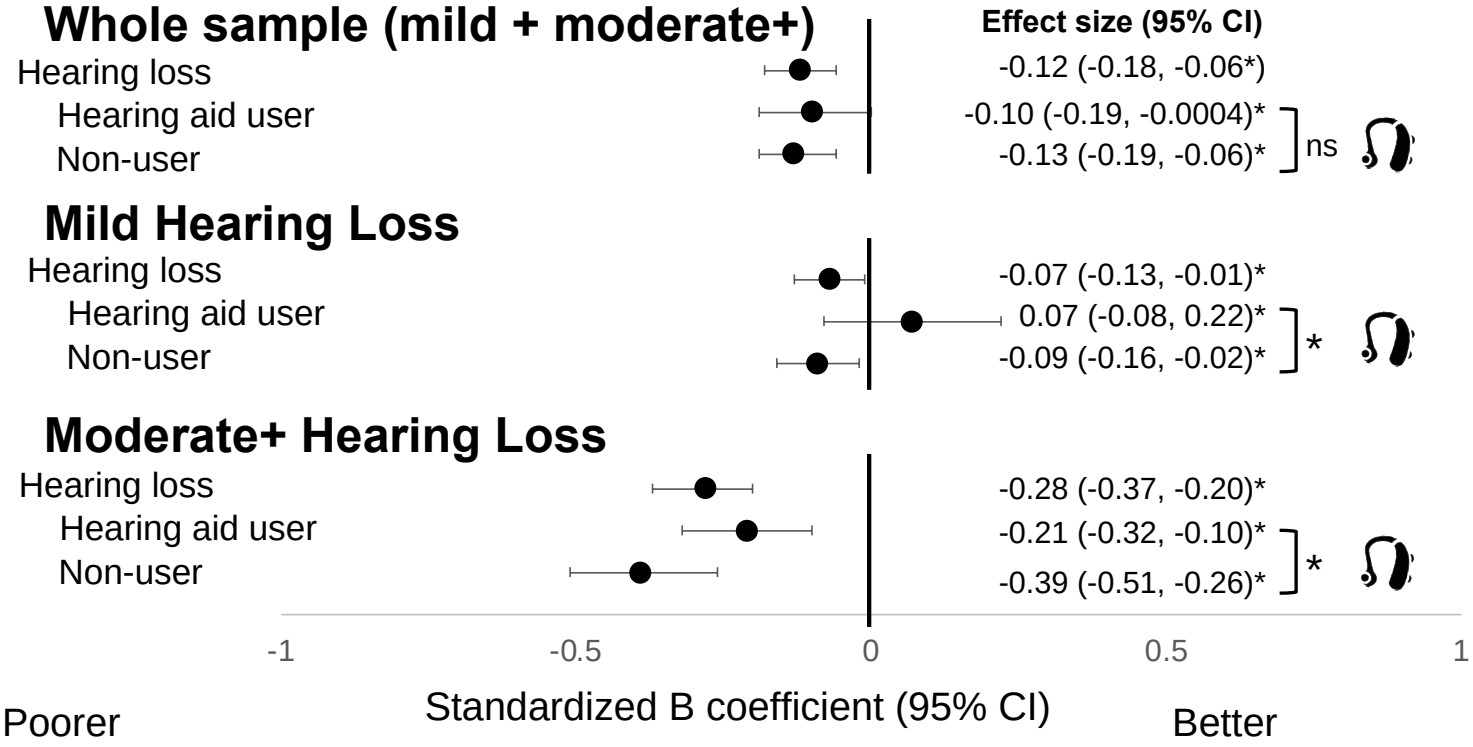
# Hearing aid use and cognition in the general population



Beaver Dam Offspring Study

## Cognitive Function

Referent = normal hearing



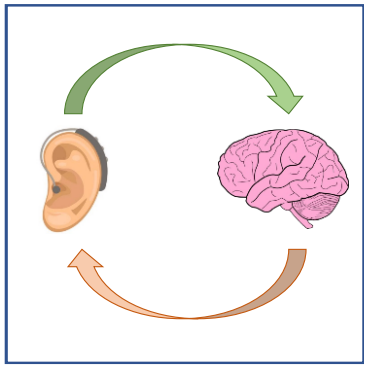

*p<0.05; Adjusted for: age, sex, education, marital status, visual impairment, atherosclerotic plaque, diabetes

Associations related to hearing aid use and cognitive function vary by hearing loss severity.

Dillard et al., 2022

# Supporting studies conclusions

- Research should consider potential for **reverse causality** between hearing aid use and cognition
- Hearing aid users vs non-users show differences in cognitive function which are likely influenced by hearing loss severity
  - Global neurodegeneration?
  - Limitations of hearing aids to overcome listening effort or excess cognitive load?
- Need to determine influence of earlier intervention with hearing aids as a determinant of benefit



Naylor, et al., 2022; Dillard et al., 2022

# 8. Experimental Evidence

Intervention reduces exposure, thereby reducing risk of the disease.

**It is unclear whether hearing aid use reduces the risk of cognitive decline.**

# 9. Analogy

Weaker evidence is acceptable if a stronger causal relationship has been established between a similar agent and a similar disease.

May provide a source of more elaborate hypotheses about the associations.

Bradford-Hill, 1965; Rothman, 2005

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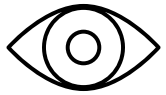
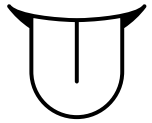


Associated with incident dementia; role of correction (i.e., eyeglasses) unclear

Associated with incident MCI and progression to Alzheimer's



Less, but some evidence of a link between taste and cognitive impairment.

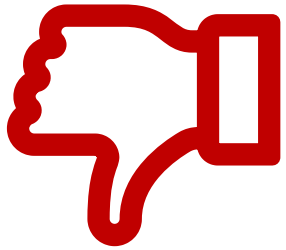
**Often cite similar mechanisms**

Behrman et al., 2014; Robert et al., 2016; Roalf et al., 2017; Windon et al., 2019; Brenowitz et al., 2020; Vu et al., 2021; Tian et al., 2023

# 9. Analogy

Weaker evidence is acceptable if a stronger causal relationship has been established between a similar agent and a similar disease.

**Sensory disorders may provide an analogy. *Stronger causal* relationships between other sensory disorders and cognitive decline have not been established and mechanisms are unclear.**



# Discussion: Overview

| Criterion | | Takeaways |
|---|---|---|
| 1. Strength of association |  | Magnitude of associations relatively small |
| 2. Consistency of evidence |  | Associations generally consistent |
| 3. Specificity | ?? | Limited relevance to hearing and cognitive relationships |
| 4. Temporality |  | Requires additional knowledge on mechanisms & disease processes |
| 5. Biologic gradient |  | Worse hearing is associated with poorer cognition |
| 6. Plausibility |  | Associations are plausible |
| 7. Coherence |  | Not all available evidence supports causality; more data are needed |
| 8. Experimental evidence |  | The role of intervention (e.g., hearing aid use) is unclear |
| 9. Analogy |  | Analogous (sensory) conditions have not established causality. |

# Future research needs

- High quality longitudinal data
  - Diverse samples
  - Quality measures of hearing and cognition
  - Evaluate early intervention as a determinant
- Randomized controlled trials to determine role of hearing aids
- Cross-disciplinary research to improve understanding of mechanistic pathways

# Conclusions

- Bradford Hill criteria provide a framework for evaluating state of evidence yet must be interpreted carefully
  - Most criteria cannot be considered necessary to determine causality
  - No criteria can be considered sufficient to determine causality
- Meta analyses are only as good as the studies included in them
  - Need to carefully interpret scientific evidence in terms of sources for bias

**The available evidence does not support claims that hearing loss causes cognitive decline.**

# Marketing claims for hearing aids

**Causal claims featured on 6 of 16 hearing aid websites.**

"The **returns on an investment** in **quality hearing instruments** include better performance at work, a deeper, richer social life, and more resistance to the anxiety, depression and **dementia associated with long-term hearing loss**."

"**Treating hearing loss <u>early</u>** on can reduce the stress that straining to hear puts on the brain, thus **decreasing your risk** of developing serious conditions like depression, **dementia**, and more."

"To **do something about your hearing loss** and help **lessen the risk of dementia**, **consult with a hearing health care professional**. To do that, **simply call**...or **click here** and we can help schedule a consultation with a provider near you."

"**Acting at the first sign** of hearing loss is a great way to avoid future health difficulties such as **dementia**."

Blustein et al., 2020

- Bradford Hill criteria are a helpful tool to evaluate state of scientific evidence in terms of causality
- Doing so highlights gaps in evidence and reiterates there is ***inadequate evidence to claim hearing loss causes cognitive decline***

# Questions?

dillalau@musc.edu

MUSC MEDICAL UNIVERSITY of SOUTH CAROLINA HEARING RESEARCH PROGRAM