Lifecourse Risk Factors for AD/ADRD: The Need for Multidisciplinary Evidence Triangulation

Maria Glymour, Boston University School of Public Health

November 11, 2025

Outline

- What do we know about dementia?
- What does it tell us about prevention?
- How can we improve on our current approaches/
- What expertise do we need to borrow across fields?

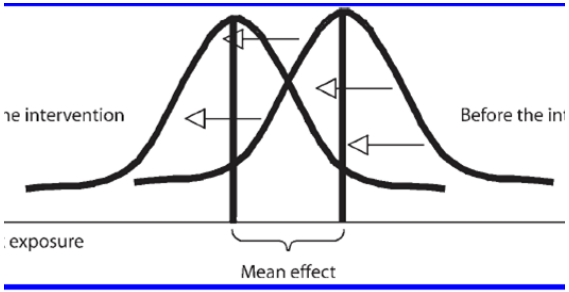
What do we know about dementia?

- It is common -- nearly ⅓ of people who live to age 65 likely to experience dementia -- but unequal
- Dementia is a functional outcome caused by many diseases
- Long, insidious development of disease with no clear moment of onset: delayed diagnosis is typical
- Numerous, deeply socially patterned confounders across the lifecourse

What do these facts imply about prevention?

- Dementia is common & unequal →
  - We need population approaches
  - Shifting the distribution of risk >> larger impact than targeting high-risk individuals
  - Prioritize differentially distributed risks

- Dementia is caused by many diseases →
  - Many possible strategies for prevention
  - If 'multiple hits' are necessary to cause dementia, preventing *any* hit may be sufficient to prevent dementia



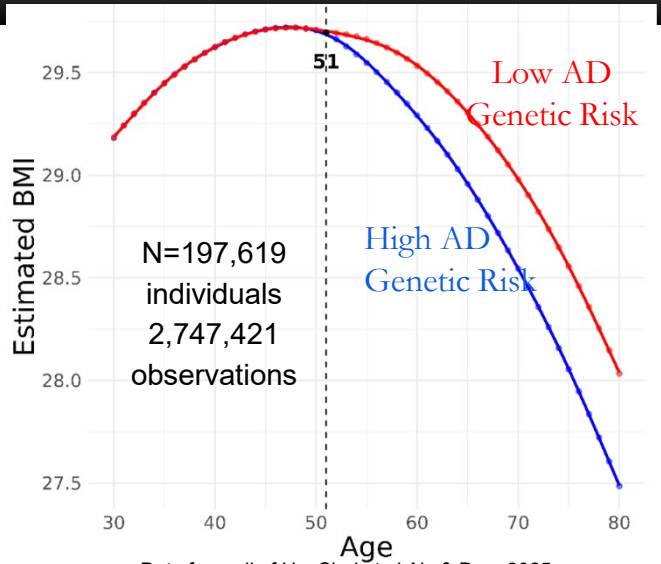
ate where the lines of the distribution would be after a population-level approach.

ypothetical homogenous effect of a population-approach intervention on the dist ılation.

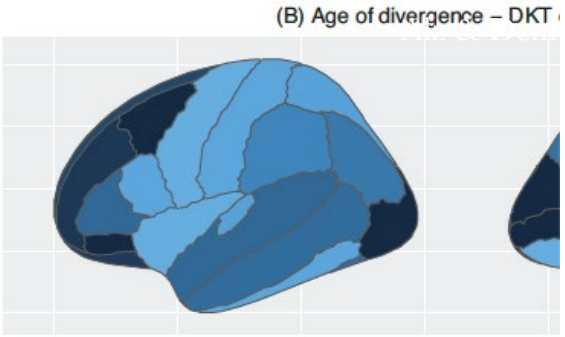
Frohlich & Potvin, 2008

What do these facts imply about prevention?

- Long, insidious development of disease with no clear moment of onset: delayed diagnosis typical
- Numerous confounders across the lifecourse are deeply socially patterned
  - Physiologic & cognitive changes detectable by ~age 50
  - People diagnosed with AD *this year* probably had the earliest stage of disease *before* human in vivo amyloid imaging was available.
  - Every risk factor I have evaluated is associated with childhood SES and cognition.
  - Cognitive scores as early as age 11 predict diagnoses of late onset



Data from all of Us: Choi et al Alz & Dem 2025.

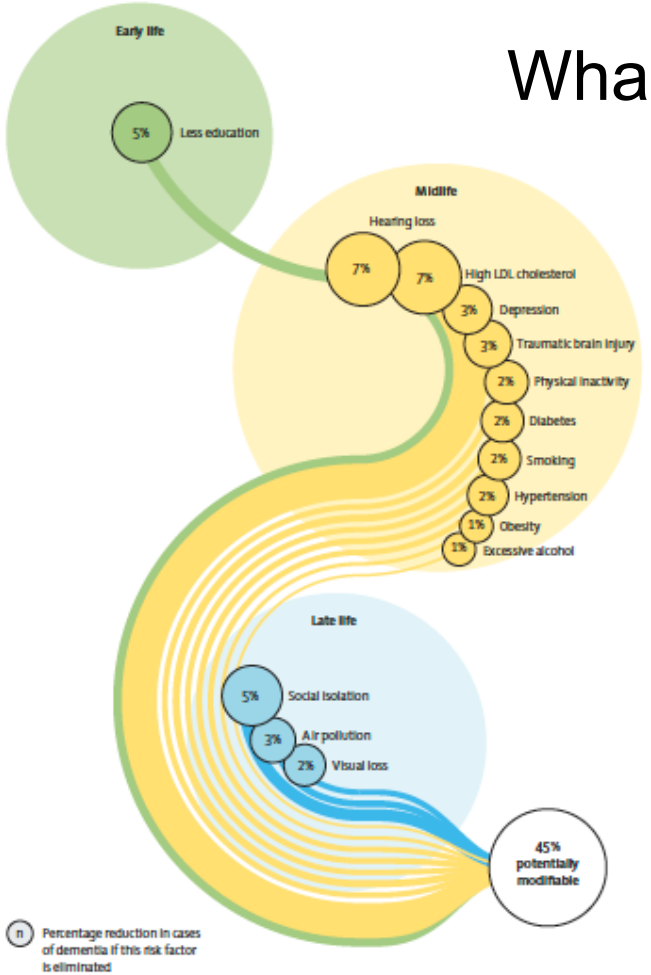


Data from UK Biobank: Buto et al..

What do these facts imply about prevention?

- Long, insidious development of disease with no clear moment of onset: delayed diagnosis typical
- Numerous confounders across the lifecourse are deeply socially patterned
  - Primary prevention must begin 30ish years before diagnosis.
  - Intentionally designed RCTs cannot tell us about primary prevention
  - Secondary prevention - preventing clinical impacts of disease pathology - is critical
  - Need alternative methods to establish causality

What does Lancet report get right?



Focus on population impact

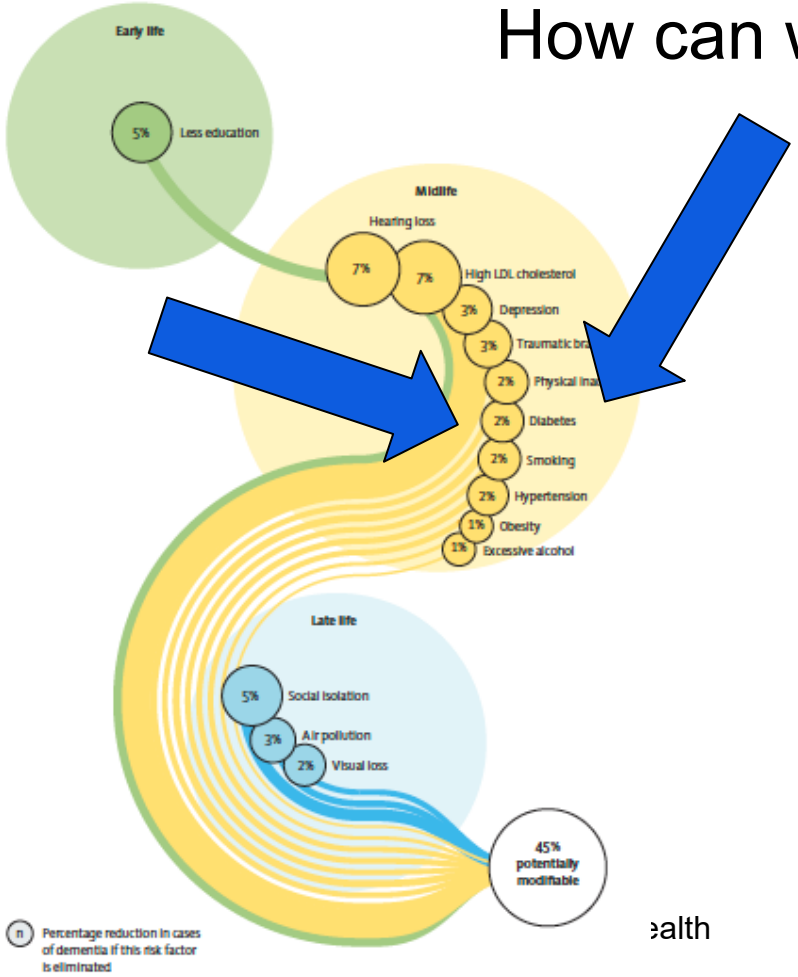
Consideration across the lifecourse

"A large number of people exposed to a low risk is likely to produce more cases than a small number of people exposed to a high risk." - Rose, 1981

ealth

BOSTON UNIVERSITY

How can we improve?



1. Consider the causes of causes.

Midlife obesity, diabetes, smoking, hypertension, and alcohol use are not randomly assigned.

Eg Diabetes and obesity are shaped by converging forces that promote unhealthy eating and discourage physical activity.

ealth

BOSTON UNIVERSITY

How can we improve?

2. Question individual-level solutions.

They are expensive, hard to scale, and can exacerbate disparities.

When you think about POINTER, ask: what are the population level interventions to move these risk factors?

Take models from other public health achievements.

Smoking; Cessation counseling is important, but taxes and bans in public places were critical.

Lead exposure: Getting the lead out of gas and paint.

POINTER:
38 facilitated peer team meetings:
physical exercise,
MIND diet,
BrainHQ cognitive training,
other intellectual and social activities,
regular health review and goal-setting with a study.

How can we improve?

3. Incorporate population differences in risk factor distributions and impacts

This is happening! Bravo!

Nianogo, Suemoto, too many others to keep track of, often with support from original lancet team.

How can we improve?

4. Address causality and uncertainty head-on:

We will have to live with non-RCT evidence.

There is a lot of work on causal inference without randomization!

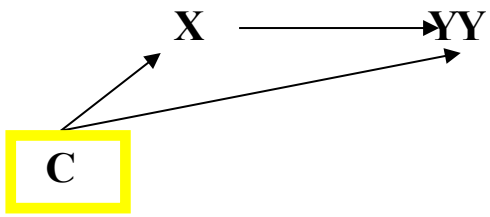
Replication without triangulation only modestly improves the evidence.

- Contrast bilingualism in settings where it is a high SES phenomenon versus a setting where it is common in low SES individuals

This is a major adjustment in the field:

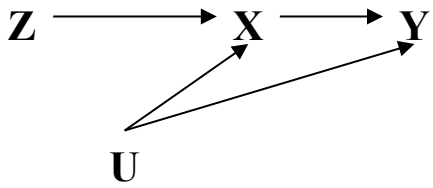
- Understanding that imperfect studies are valuable,
- Talking about limitations - especially if others can address - is part of the science
- Systematically interrogate uncertainty

How can we improve?



4. Address causality.

- There are only 3 basic approaches to causal inference, with 4 million variations on those 3:
  - Condition on all confounders (98% of dementia epi)
  - Find a random/arbitrary variation in exposure
    - (RCTs, quasi-experiments, Mendelian Randomization, policy IVs)
  - Measure all mediating pathways
    - (almost never used… but increasingly promising)
- Complement these by approaches to correcting imperfect analyses: QBA, quantifying reverse causation



Triangulation approaches to build on a conventional confounder-controlled regression study

Dr. Sirena Gutierrez

Meta-analyses: Combining multiple studies with similar designs and measures.

Meta-regression: Using features of contributing studies to evaluate sources of heterogeneity in meta-analyzed research

Cross-Context Comparisons

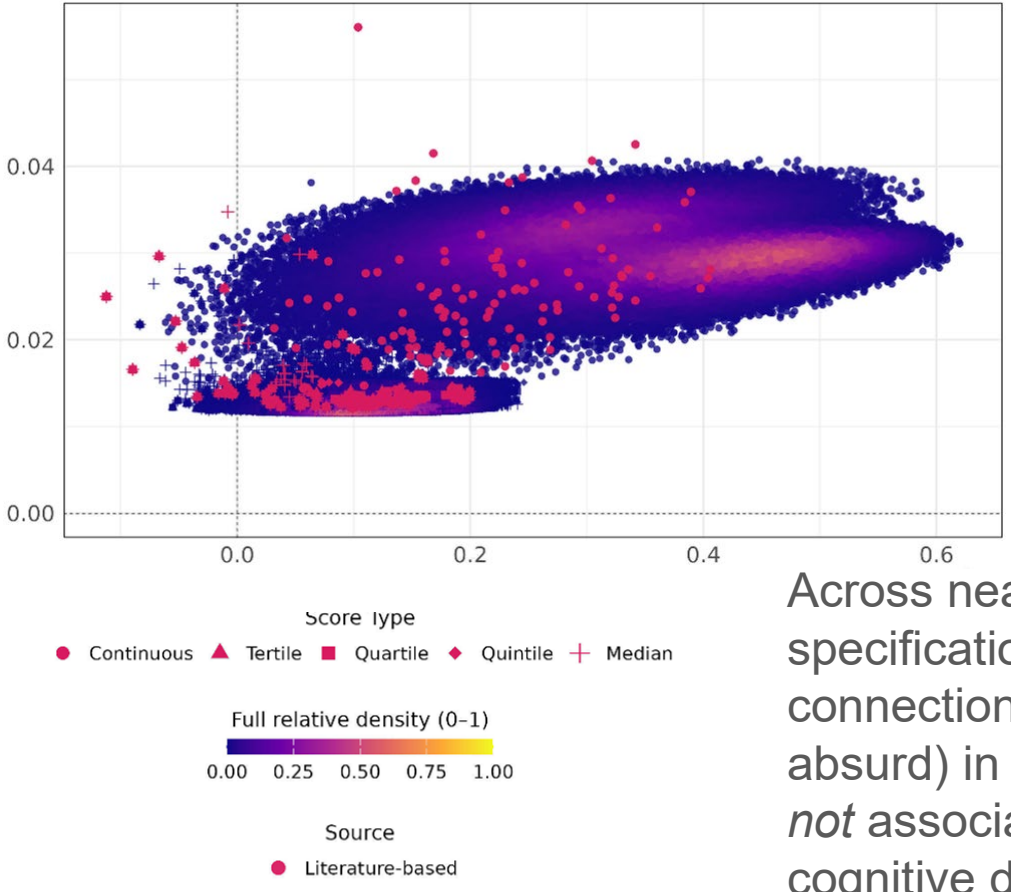
Instrumental Variables (IV)

Bias demonstration and quantification

- Positive and Negative Controls
- Evaluation of reverse causation (reverse MR)
- Multiverse analyses
- QBA

Gutierrez, Glymour, and Davey Smith, Eur J Epi, 2025

Systematically interrogate uncertainty: multiverse



Across nearly every possible specification of social connection/ isolation (some absurd) in HRS, <2% were *not* associated with slower cognitive decline.

Dr. Ruijia Chen, Dylan Tran (MS student) & Andrew Philips (MS student, not shown)

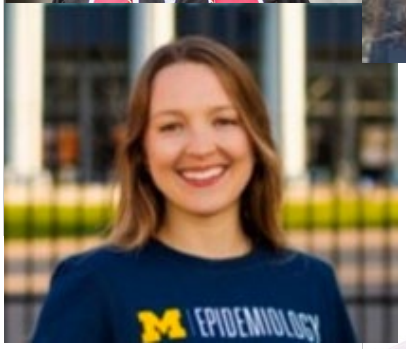
What expertise do we need?

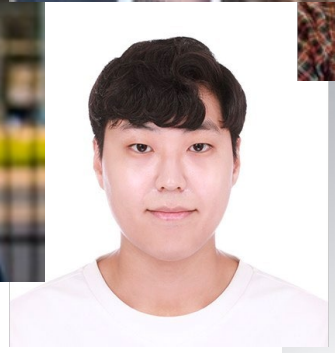
- Public health practitioners with experience on population level interventions
- Better data, more data: informatics specialists, computer scientists
- Better measurement: neuro disciplines but also exposure side disciplines, environmental health, social scientists, behavioral health, plus psychometrics and other measurement foci
- Better computational tools
- Causal inference tools: causal revolution emerged in computer science, taken up in epidemiology and economics



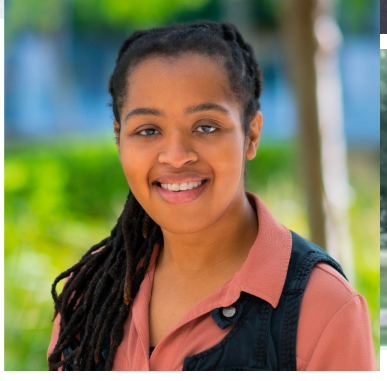










NIA!

MELODEM

Advanced Psychometric Methods in Cognitive Aging

P01AG082653 (Glymour/Gilsanz/Torres)

RF1AG059872 (Glymour)

RF1AG069259 (Schaefer/Glymour/Krauss)

RF1AG055486 (Zeki Al Hazzouri/Glymour)

RF1AG052132 (Whitmer/Gilsanz/Mayeda/Glymour)