IHME
Measuring what matters

Alzheimer's disease and other dementias: The Global Burden of Disease Project

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Outline

1. Overview of the Global Burden of Disease Study
2. Case definition for Alzheimer's disease and other dementias
3. Recent results
4. Methodological challenges and ongoing work
   - Diagnostic heterogeneity and challenges related to case definition
   - Data sparsity and improvements using item response theory methods
   - Biases in vital registration data: previous solutions and future improvements

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What is the Global Burden of Disease Study?

- A ***systematic, scientific*** effort to quantify the ***comparative*** magnitude of ***health loss*** from all major diseases, injuries, and risk factors by age, sex, and population, and over time.
- *Fundamental premise*: Policy should be informed by **valid**, **reliable** and **timely** data; poor quality data → poor decisions → lost opportunities to improve population health

- *Key principles*:

  - comprehensiveness;

  - informed estimates better than no estimates;

  - comparability (across locations, time, diseases, injuries, risk factors, age and sex)

GBD: standardized solution to global health measurement challenges

Challenges:

1. Inconsistent coding and case definitions
2. No data
3. Conflicting data
4. Sampling and non-sampling measurement error

GBD solutions:

1. Quality review of all sources and corrections for garbage coding
2. Cross-walking different case definitions, diagnostic technologies, recall periods, etc., using statistical methods
3. Statistical methods to deal with missing data, inconsistent data, and measurement error

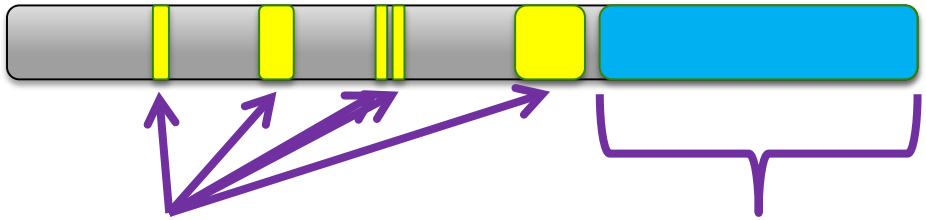
Multiple metrics for health to facilitate different types of uses

1) **Traditional metrics:** Disease and injury prevalence and incidence, death numbers and rates.
2) **New metrics:**
   - Years Lived with Disability (YLD)
   - Years of Life Lost (YLL)
   - Disability Adjusted Life Years (DALYs)

DALY = YLL + YLD

YLL = years of life lost due to premature death

YLD = years of life lost to disability



YLD: the number of years of life spent unwell, weighted according to the severity of illness or injury

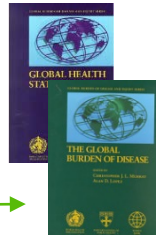
YLL: the number of years of life expectancy remaining at time of death

Over 20 years of innovation on GBD

1991: **GBD originated** by the World Bank and WHO

1993: **Prelim. results published** in World Development Report

1996-7: Final results published



2007: **IHME established** to catalyze new era of GBD innovation

2015: **WHO and IHME sign MOU; European BoD Network formed**

2016: IHME begins **annual updates to GBD as global public good**

2018: IHME and WHO sign new MOU to strengthen GBD efforts and uptake

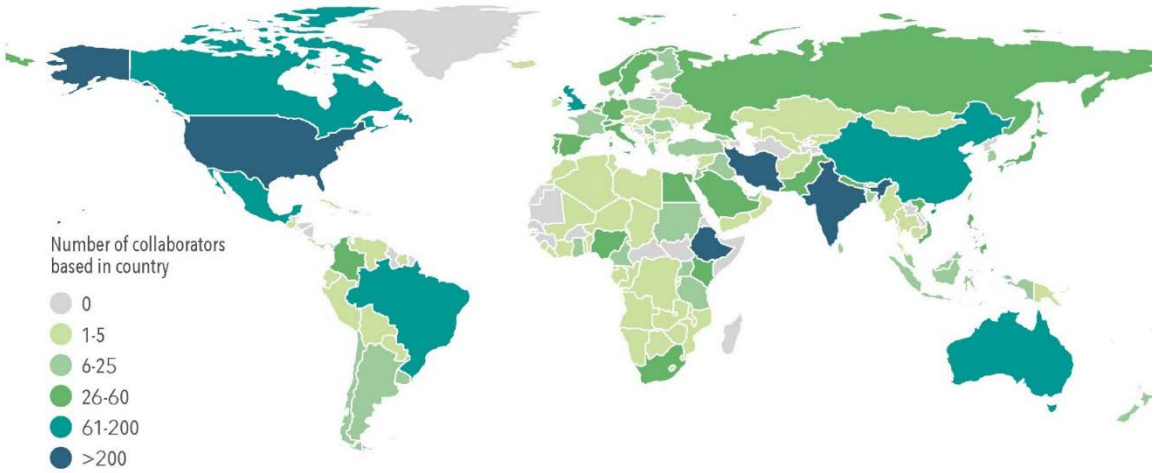
1990 2000 2010 Today

★ Publication of updated GBD results

GBD Collaborator Network

- GBD Collaborators are specialists in a range of topic areas related to the GBD enterprise, including: researchers, clinicians, epidemiologists, global health practitioners, demographers, health economists, and policy-makers.

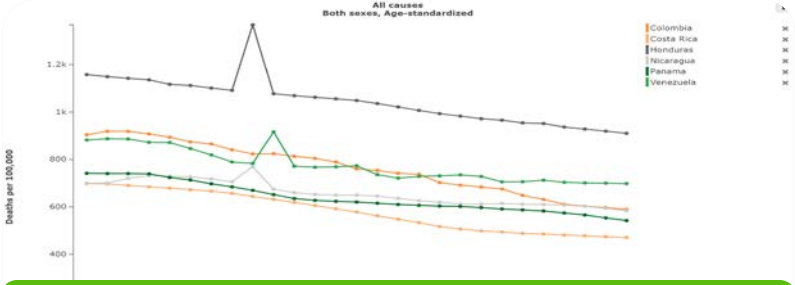
- Collaborators are critical throughout the process - from data analysis to policy uptake and impact – and participate in a range of ways.



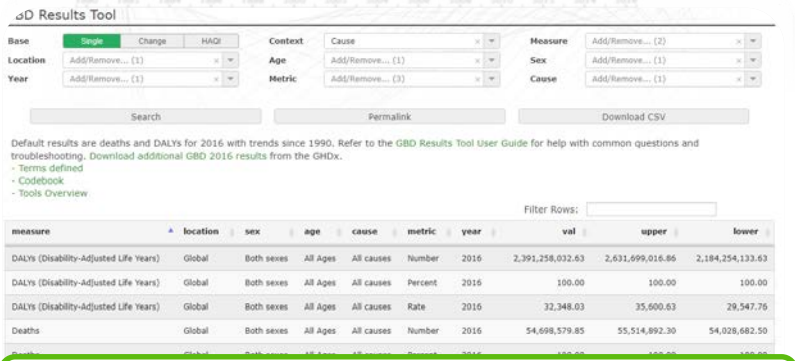
The Collaborator Network is made up of **3,366 collaborators** from **141 countries and territories**

Scope of Global Burden of Disease Today

- Today covers 195 countries and territories from 1990 to present. Sub-national assessments for some countries including Brazil, China, Ethiopia, India, Indonesia, Iran, Japan, Kenya, Mexico, New Zealand, Norway, Russia, South Africa, Sweden, UK, and US
- 359 diseases and injuries, 3,228 clinical sequelae, 84 risk factors or clusters of risk factors.
- Time series from 1990 to most recent year updated annually
- Findings published in major medical journals, policy reports, and online data visualizations.



Visualization Tools



Database Query Tool

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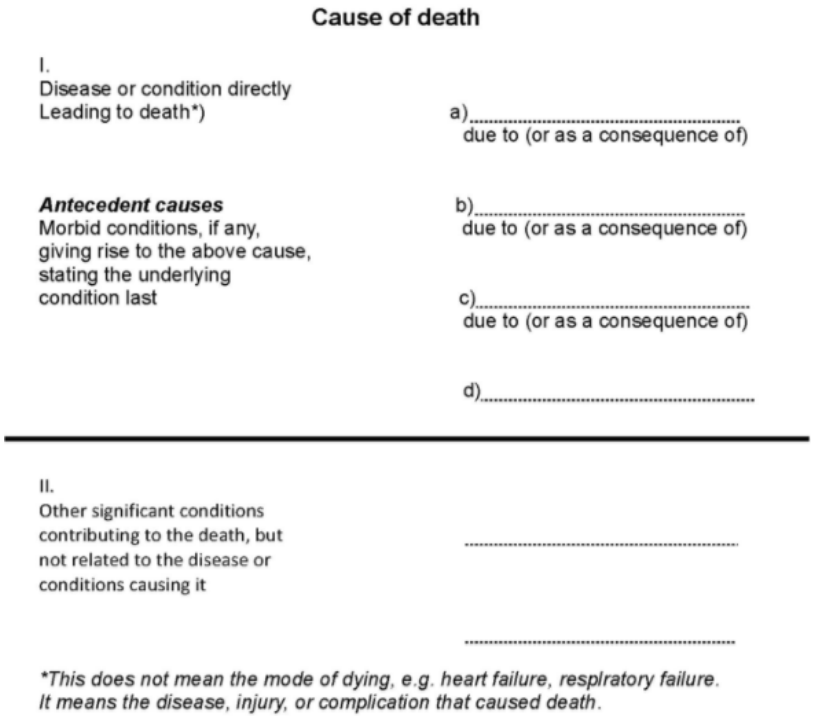
Dementia Case Definition

- The gold standard case definitions for dementia are the DSM-III, DSM-IV, DSM-V definitions or ICD definitions from representative surveys
  - DSM-IV:
    - **Multiple cognitive deficits** manifested by both memory impairment and one of the following: aphasia, apraxia, agnosia, disturbance in executive functioning
    - Must cause **significant impairment** in occupational functioning and represent a significant decline.
    - Course is characterized by **gradual onset** and continuing cognitive decline
    - Cognitive deficits are not due to other psychiatric conditions
    - Deficits do not occur exclusively during the course of a delirium
  - ICD definition is very similar, designed with input from DSM-IV work group

Conceptual Basis for Underlying Causes of Death

- GBD attributes each death to a single underlying cause, in line with ICD principles
- Deaths are assigned to the **underlying** rather than immediate cause
- If someone has dementia, and because of this ends up bedridden and gets a UTI, which leads to death, this is a death **due to** dementia



Cause of death

I.
Disease or condition directly Leading to death*)

a)..... due to (or as a consequence of)

Antecedent causes
Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last

b)..... due to (or as a consequence of)

c)..... due to (or as a consequence of)

d).....

II.
Other significant conditions contributing to the death, but not related to the disease or conditions causing it

.....

.....

**This does not mean the mode of dying, e.g. heart failure, respiratory failure. It means the disease, injury, or complication that caused death.*

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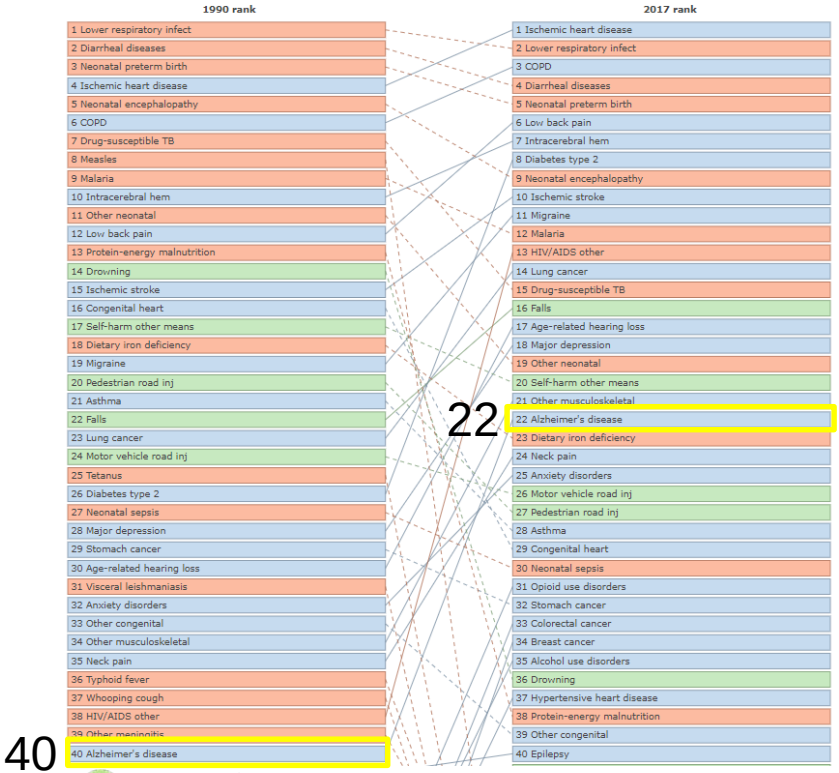
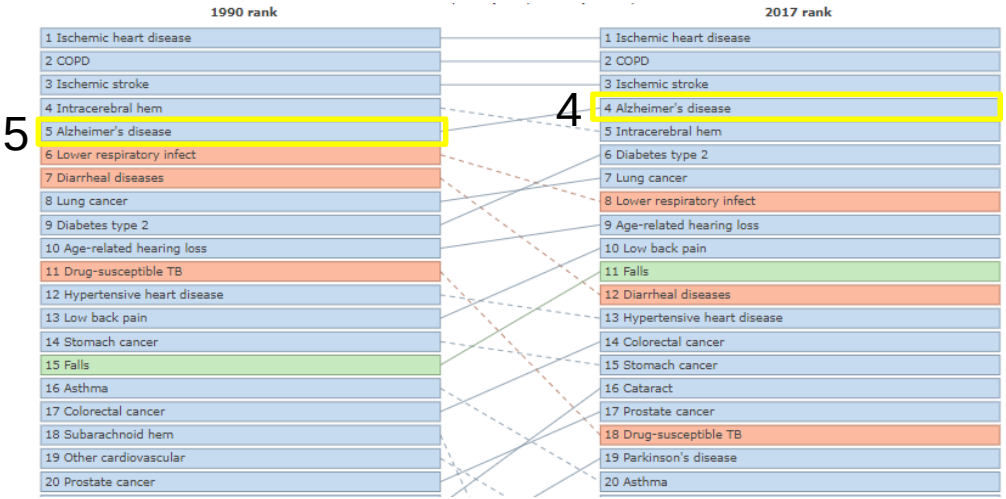
Change in rank over time (DALYs)

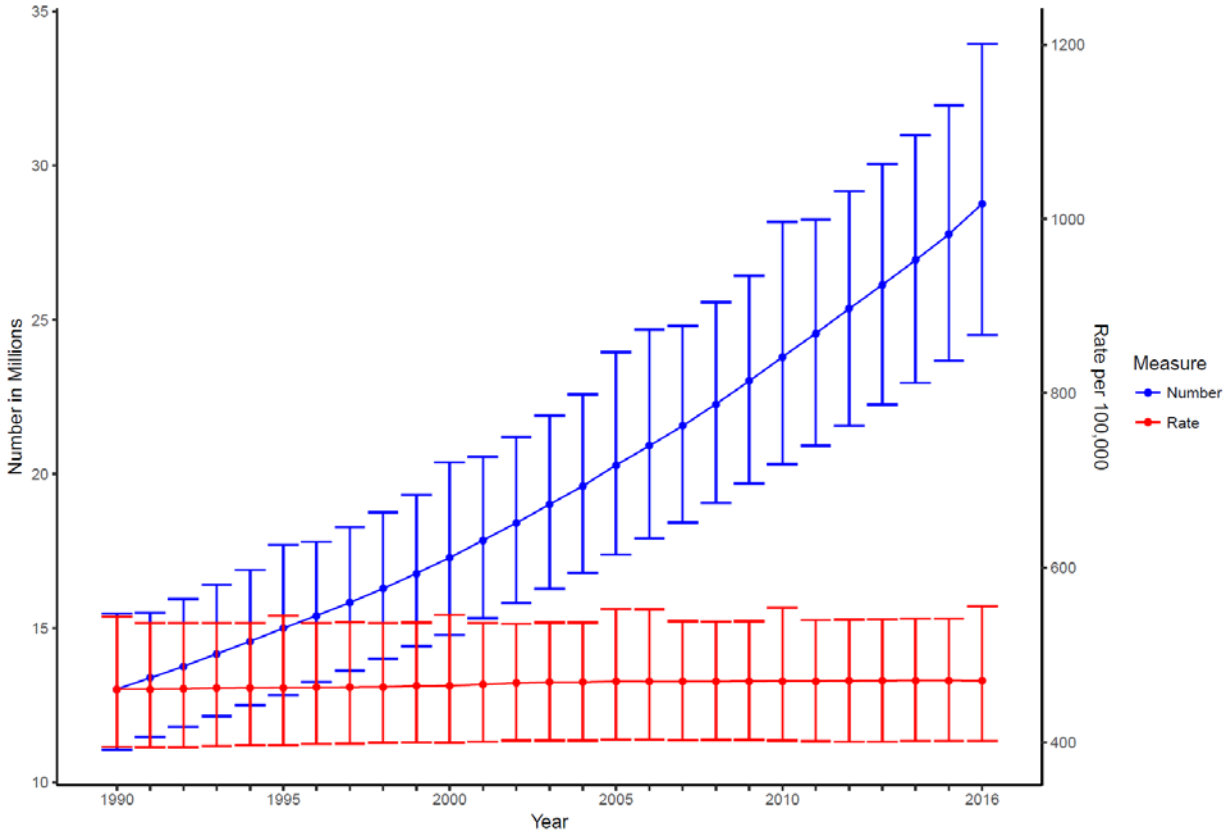
All Ages



Over 70

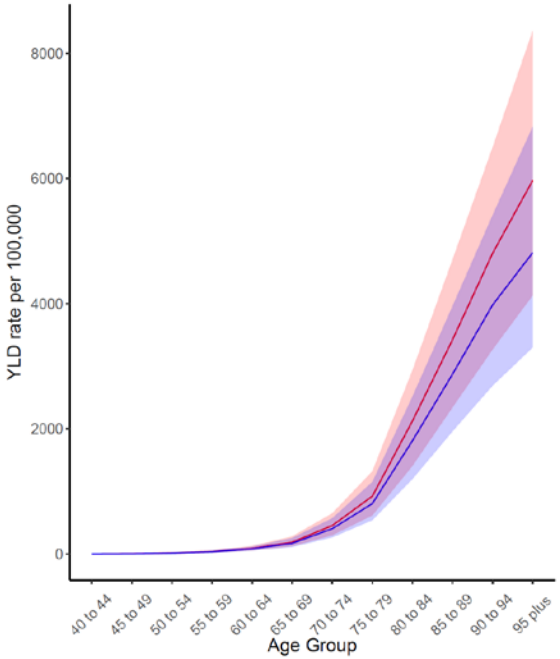


Counts and Age-Standardized Rates of DALYs due to Dementia Over Time

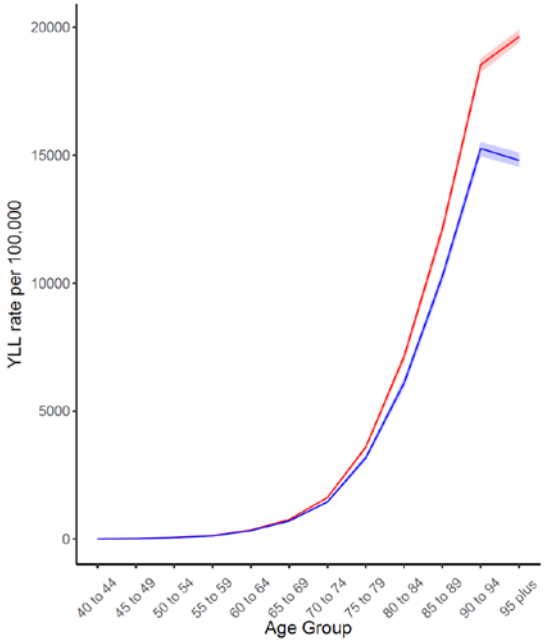


Patterns by Age and Sex (2017 Global Estimates)

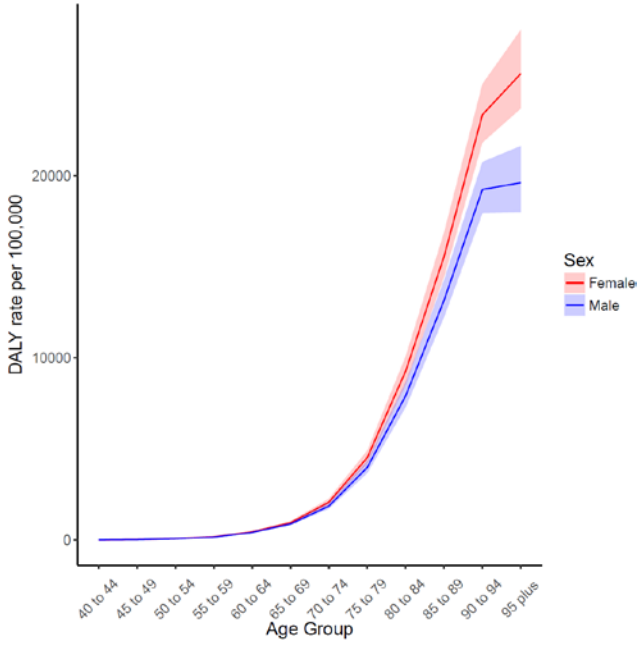
YLDs



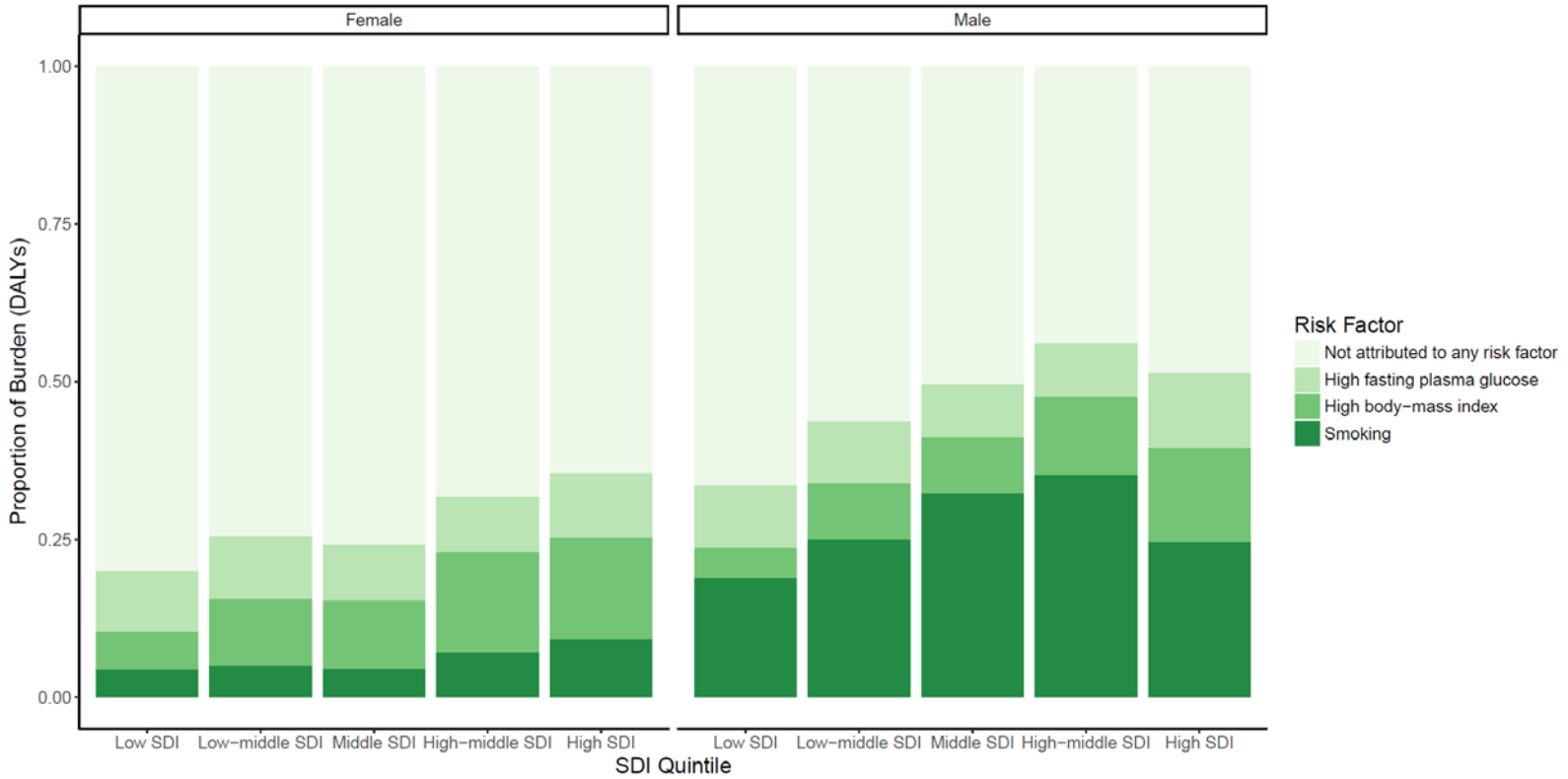
YLLs



DALYs



Risk Factors by SDI Quintile (2017)



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Case Definition Continued

- **BUT …** This definition includes dementia cases where the dementia was caused by other GBD causes including HIV, stroke, Parkinson's disease, Down's syndrome and TBI
  - These cases need to be subtracted out to prevent double counting within the GBD cause hierarchy
- We need a method for the calculation of the proportion of cases that are due to these etiologies and subtract these from the total when we report on dementia in the neurological cause group
  - GBD will still also report on the total aggregated burden of dementia as well
- Proposed Method:
  - Review of the literature and meta-analyses on the proportion of each disease that results in dementia

Preliminary Evidence from ADAMS study

Analysis Plan:

1. Use data from the Aging Demographics and Memory study to fit logistic regression models predicting the outcome of dementia based on whether individuals have each condition
2. Calculate the relative risk of dementia given each exposure at various ages using predictions from the models
3. Using data on relative risk and prevalence of each condition (from GBD), calculate the Population Attributable Fraction (PAF)
   - Proportion of the total dementia prevalence attributable to each condition
4. Multiply these fractions by dementia prevalence to get the amount of dementia prevalence to place under each cause

Logistic Regression in the ADAMS study

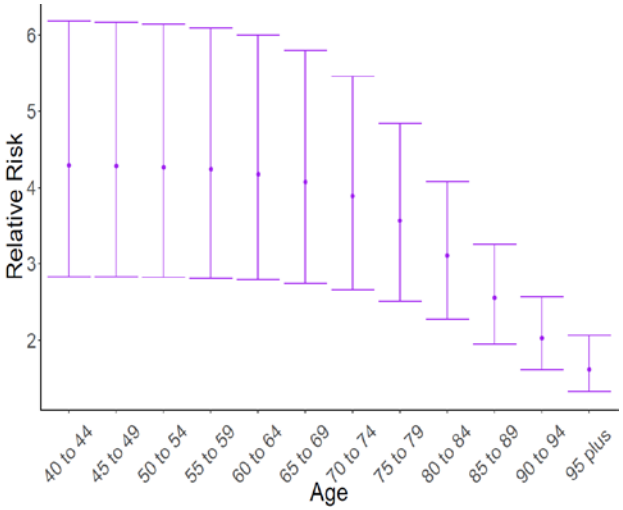
Evaluate the relative risk of dementia given an exposure for each cause of dementia measured in ADAMS (Stroke, TBI, PD)

- For the stroke analysis we also tried controlling for potential confounders (BMI, smoking, blood pressure etc.) but none of these were significant in the expected direction

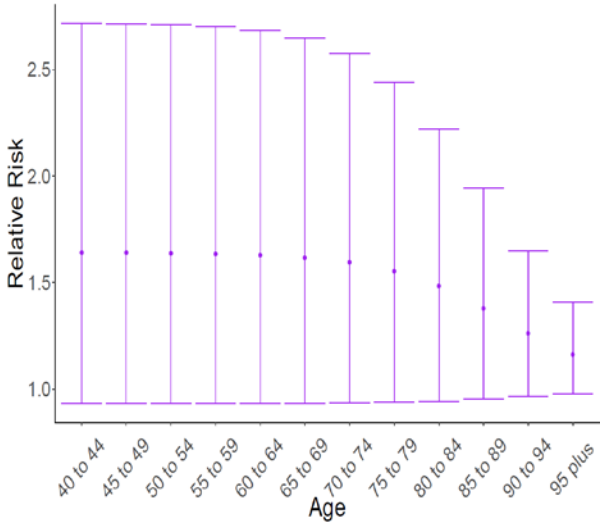
Regression	Condition Effect (SE)	Age Effect (SE)
Stroke Regression	4.2 (1.24)	1.15 (1.02)
PD Regression	5.74 (2.47)	1.16 (1.02)
TBI Regression	1.59 (1.31)	1.16 (1.02)

Relative Risk Results

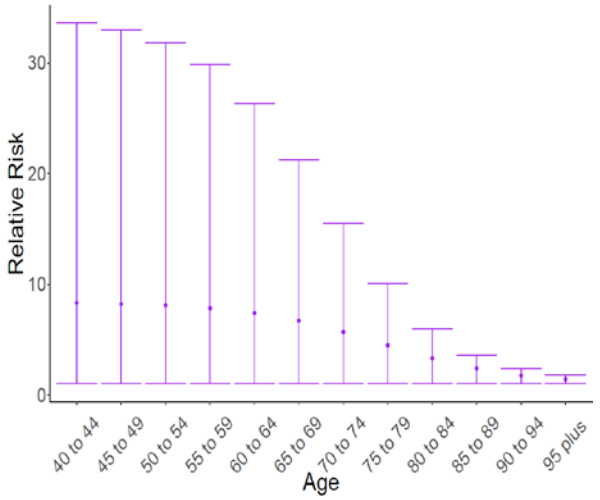
Stroke



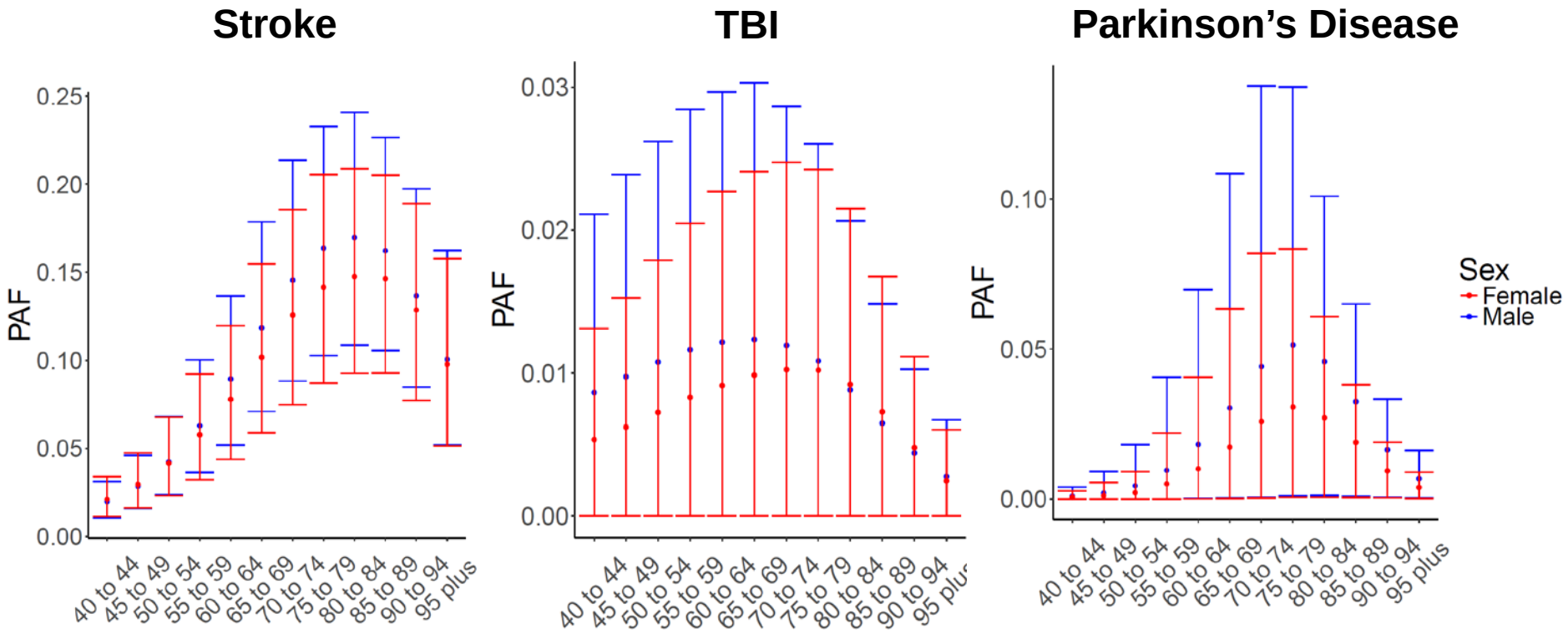
TBI



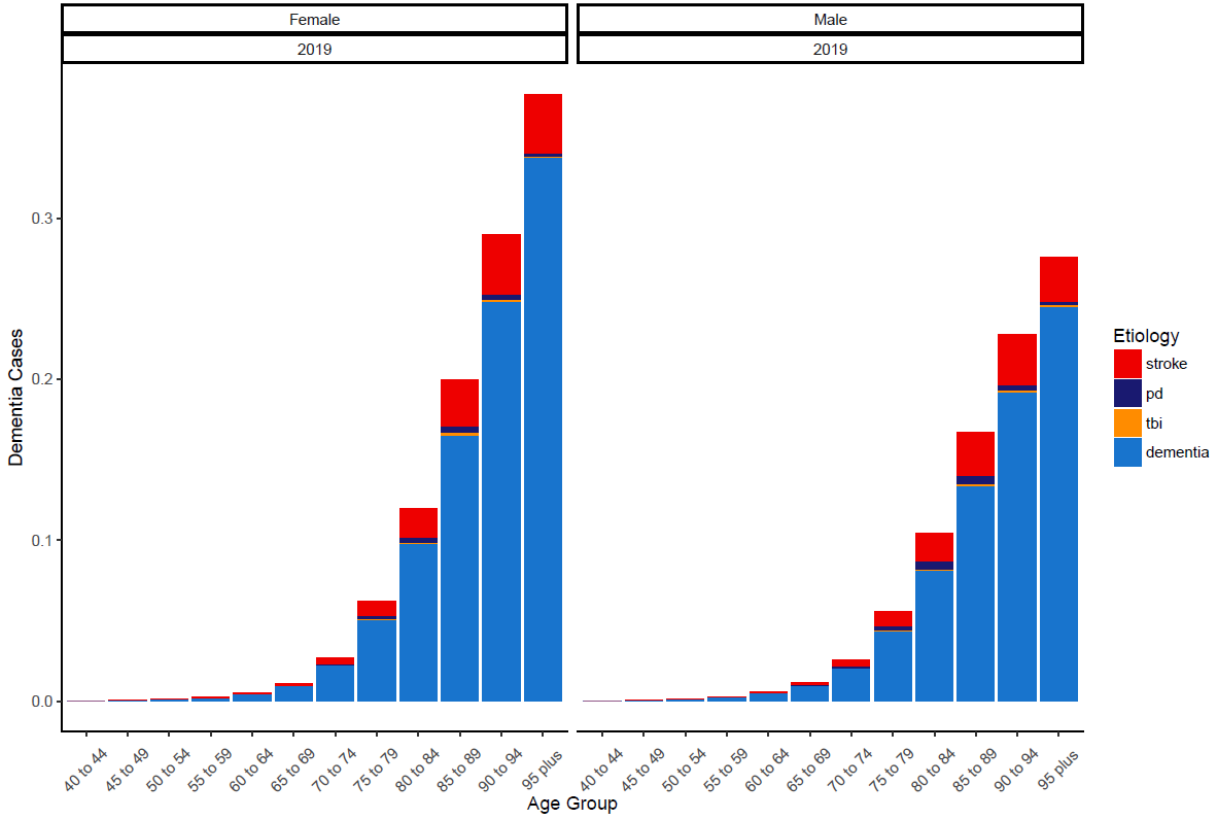
Parkinson's Disease



PAF Results: Canada Example



Prevalence Results: Canada Example



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Data Sparsity

Global Data Coverage

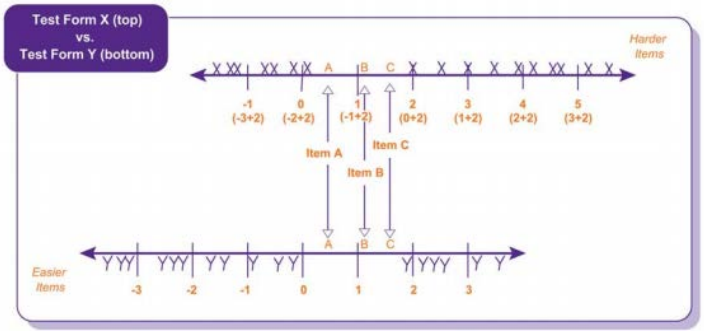
Leverage Information from Aging Surveys

- Would allow for expanded data availability and global data coverage
- Currently only include data that does a full diagnostic work-up but this is cost prohibitive and many larger survey series use shorter cognitive instruments
- Information on cognitive impairment and functional limitations may be able to be translated to predictions of dementia

HRS and HRS Sister Studies

Analysis Plan

1. Harmonize the cognitive instruments on different surveys of aging
   - Use Item Response Theory Methods: allows for the harmonization of tests that contain a set of common items

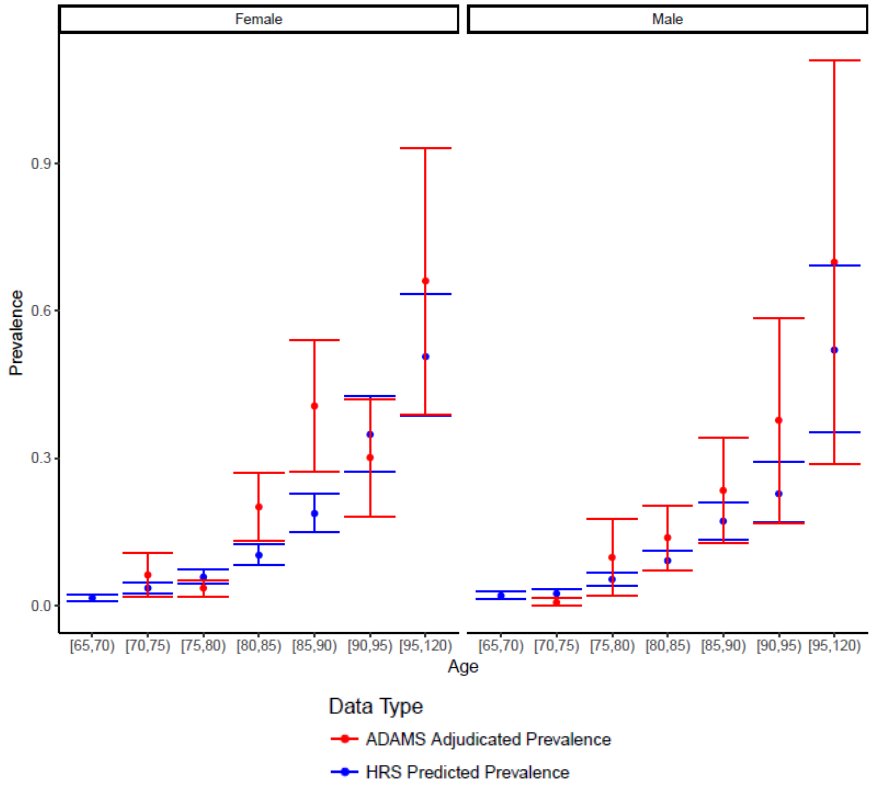


   - Two factor model incorporates information on both cognition and functional limitations

2. Leverage samples with both cognition data and adjudicated dementia diagnosis to develop an algorithm to predict dementia status from other surveys

Initial Results: HRS and ADAMS

	Multidimensional IRT	Langa-Weir Approach
Sensitivity	0.83 (0.77 to 0.87)	0.637
Specificity	0.89 (0.86 to 0.91)	0.86



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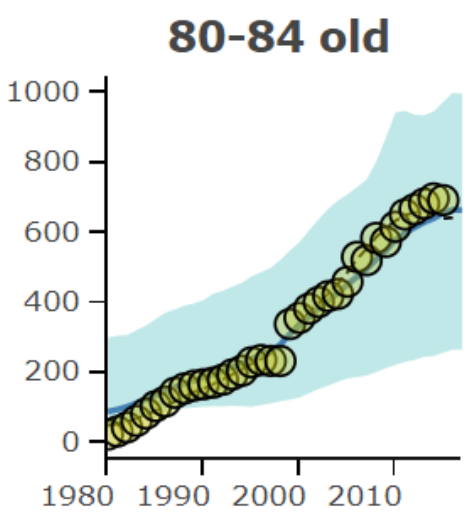
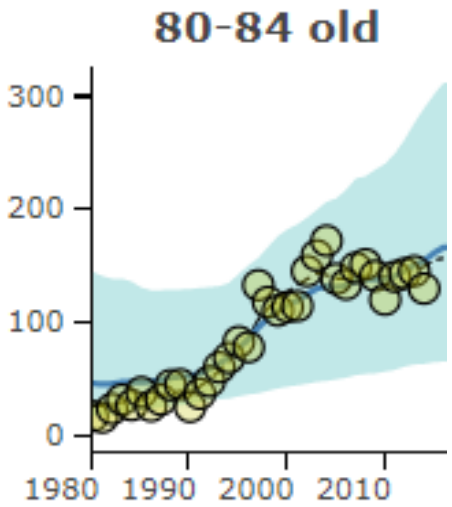
Vital Registration Data

Cause-Specific Mortality Rate per 100,000

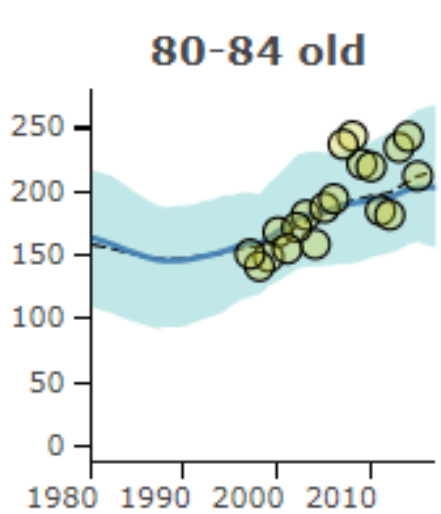
United States



Argentina

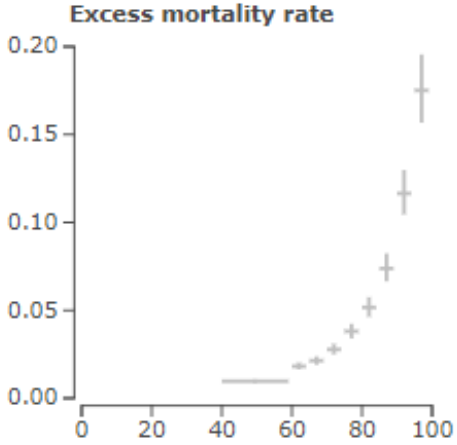


South Africa



Previous Strategy (GBD 2017 and earlier)

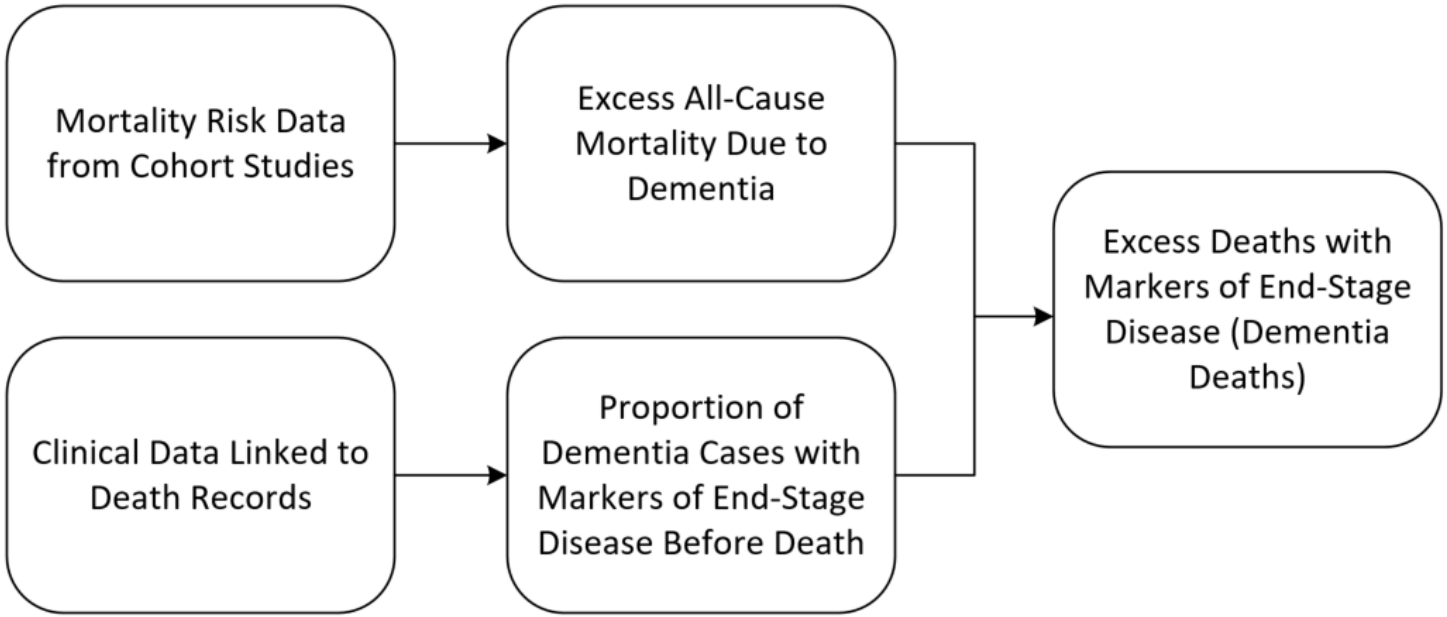
1. Estimate excess mortality
   - Use initial estimates of prevalence and mortality to determine countries most likely to code deaths to dementia per prevalent case
   - Predict excess mortality by age and sex using data from these countries in the most recent year
2. Use these excess mortality estimates and prevalence estimates to predict mortality



Limitations:

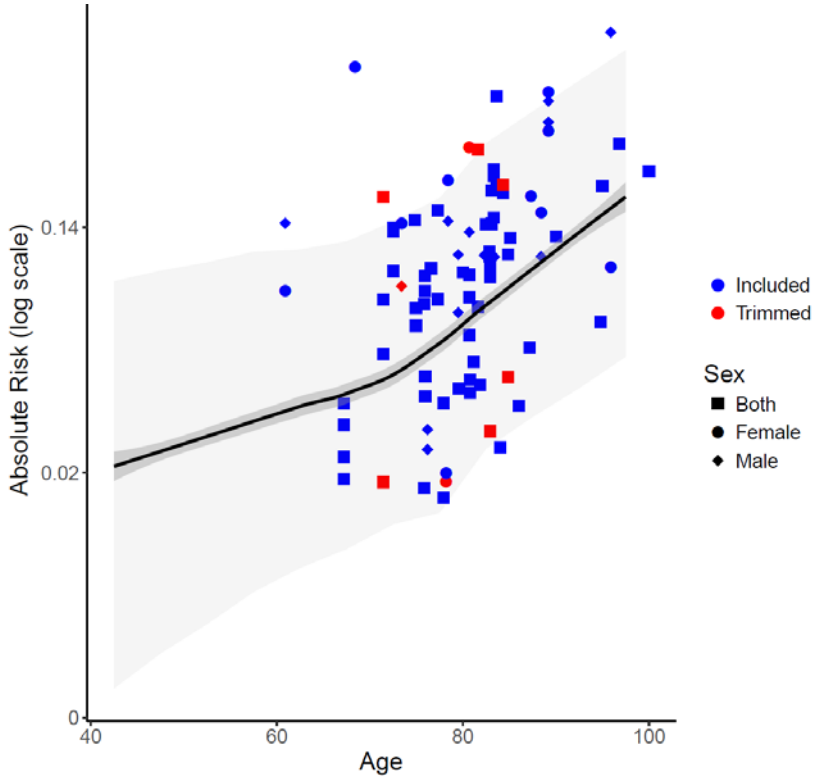
- We rely heavily on prevalence estimates from sparse heterogeneous data
- The method is sensitive to the choice of how many countries to include
- We do not allow excess mortality to vary over time and location
- We assume the highest observed excess mortality is correct, but there may be over-coding

New Strategy



Meta-Regression Model on Attributable Risk Data

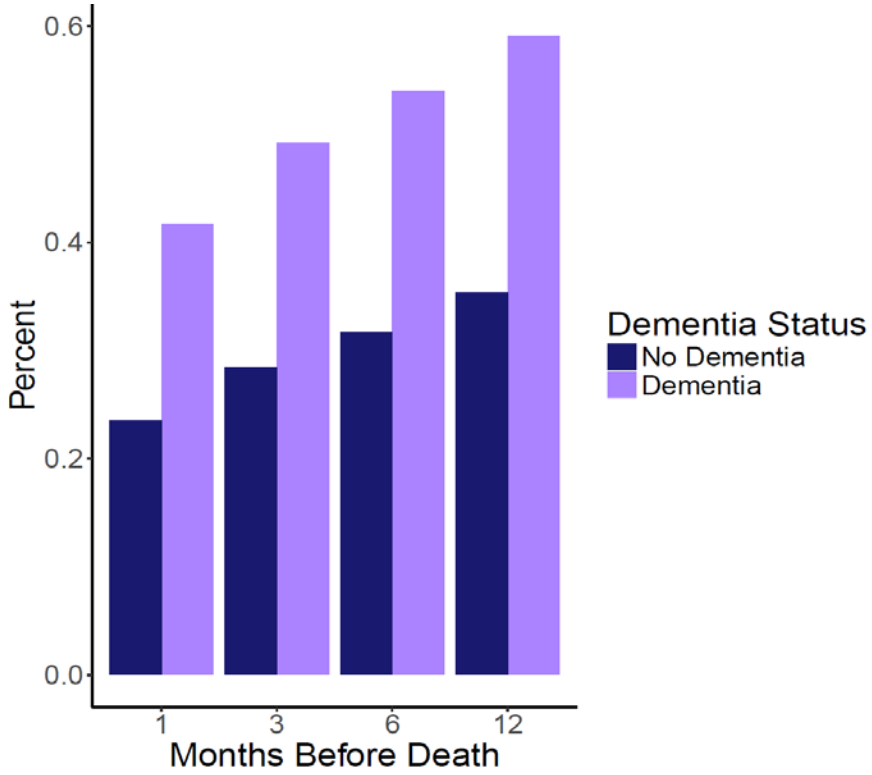
- Bayesian framework
- Trimming- outlier detection as part of the likelihood function
- More accurately estimates between-study heterogeneity
- Cubic spline on age with four knots



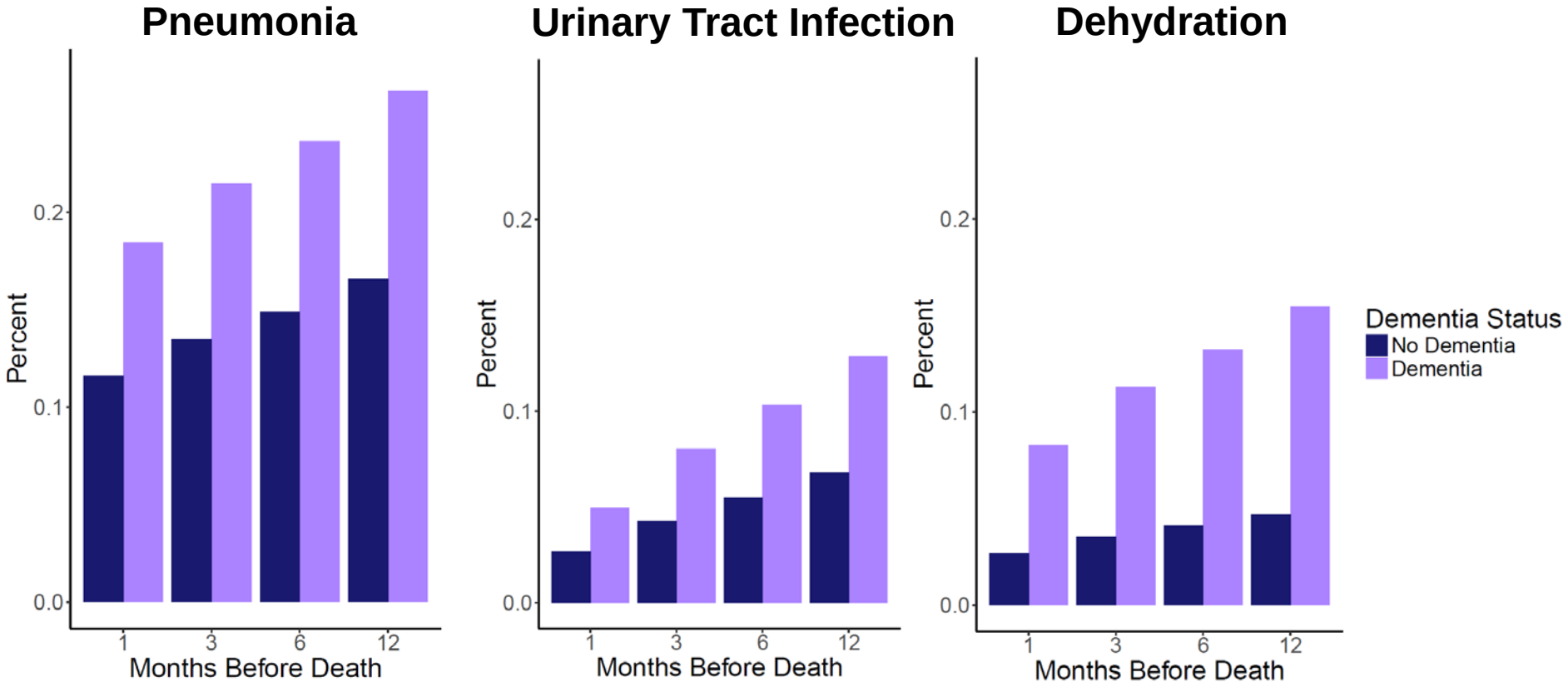
End Stage Proportions: Any Condition

Conditions Included:

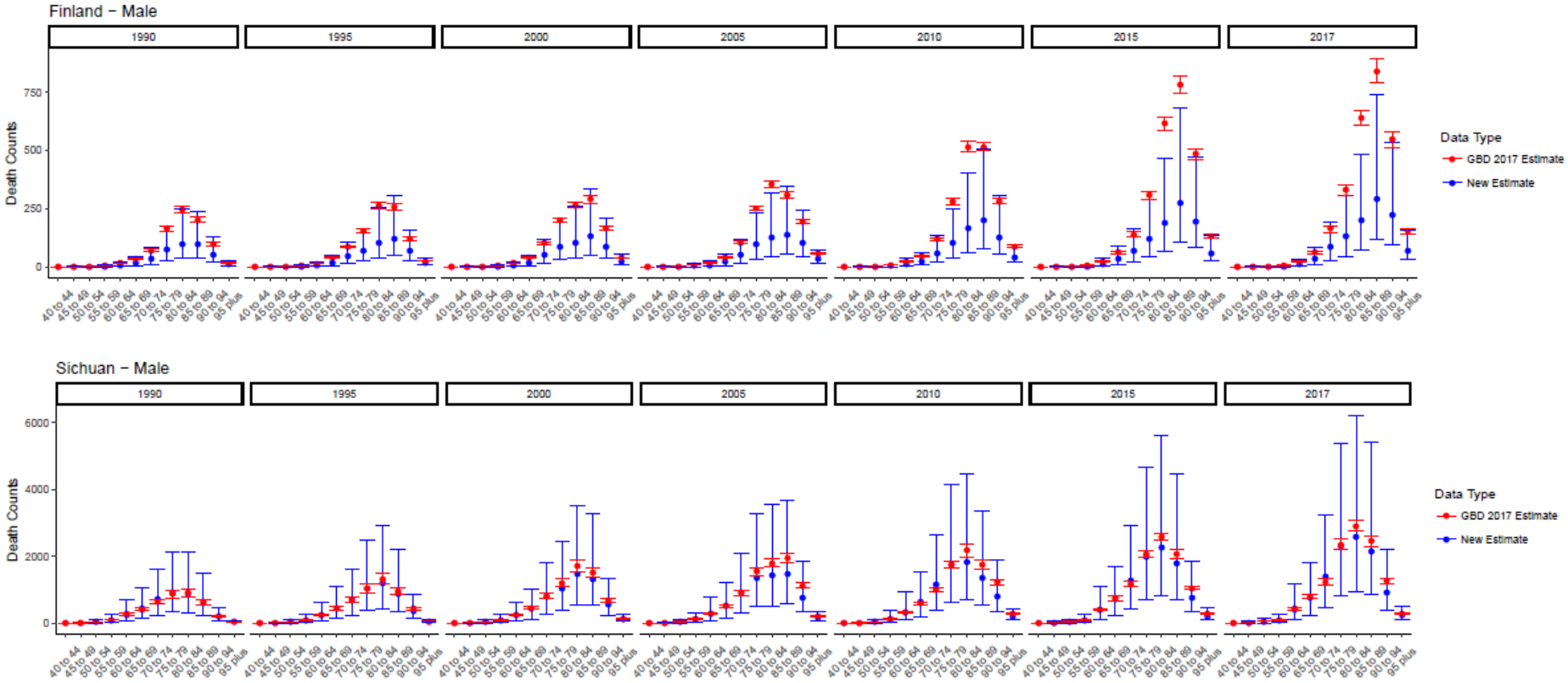
- Decubitus ulcer
- Malnutrition
- Muscular Wasting
- Pneumonia
- Dysphagia
- Dehydration
- Hip Fracture
- Sepsis
- Urinary Tract Infection
- Bronchitis
- Septicemia
- Bedridden
- Senility



Top Conditions



Example Results



In Conclusion

- GBD provides a rigorous scientific framework for measuring health loss and making comparisons between different diseases and risk factors
- Dementia is an important contributor to health loss globally, and the burden due to dementia will likely continue to increase with current trends in population growth and population aging
- Because of biases in cause of death data, data sparsity and heterogeneity, the estimation of dementia is subject to a number of critical methodological challenges
- With new GBD updates, there will be ongoing methodological innovation and improvements to global dementia estimates

IHME
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Thank you

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