Challenges and opportunities in statistical methods for studies of aging and dementia

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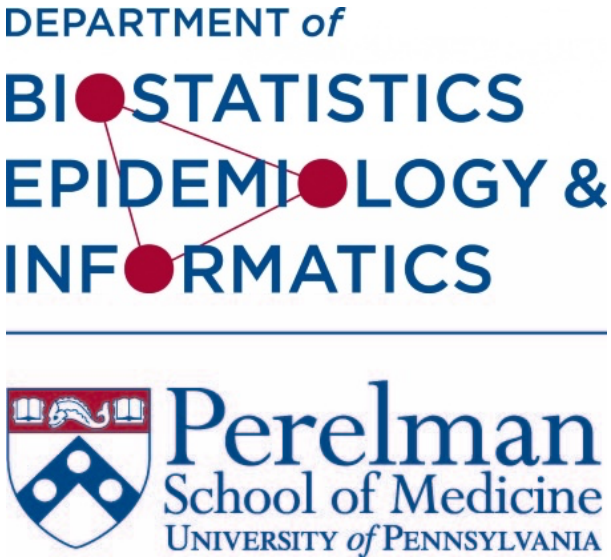


Intro

- Cognitive decline associated with dementia results in loss of independence creating often devastating burdens for patients, caregivers, and society
- Because dementia is strongly age related, demographic changes in the age structure of the population raise concerns about future increases in dementia prevalence and associated healthcare demands
- Changes in population-level risk factors and development of novel therapeutics have the potential to mitigate the impact of an aging population
- This creates an opportunity for high impact biostatistics to: identify risk factors, characterize changes in the course of disease, identify surrogates for pathologic outcomes that can be used in trials, model the impact of interventions on population health outcomes

Objectives

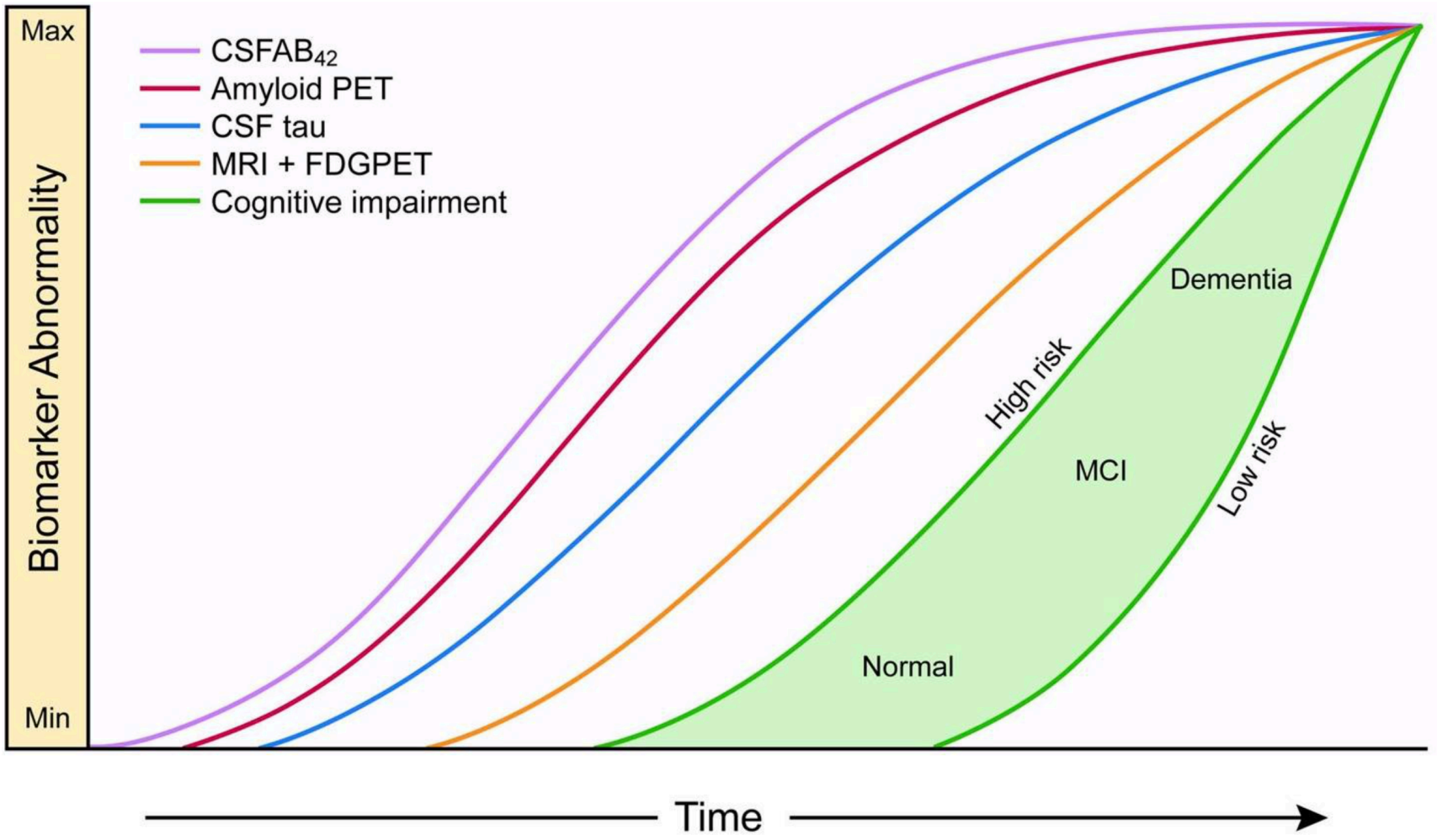
Discuss active research areas in which statistical contributions have the potential to accelerate knowledge creation

1. Characterizing natural history of disease using longitudinal biomarker and neuroimaging data
2. Identifying risk factors vis novel linkages to EHR data
3. Developing simulation models to project population health impacts

Etiology

- natural history of disease
- evolution of understanding of etiology
- Jack model overview
- need for multidimensional trajectory models

Jack model of natural history of disease

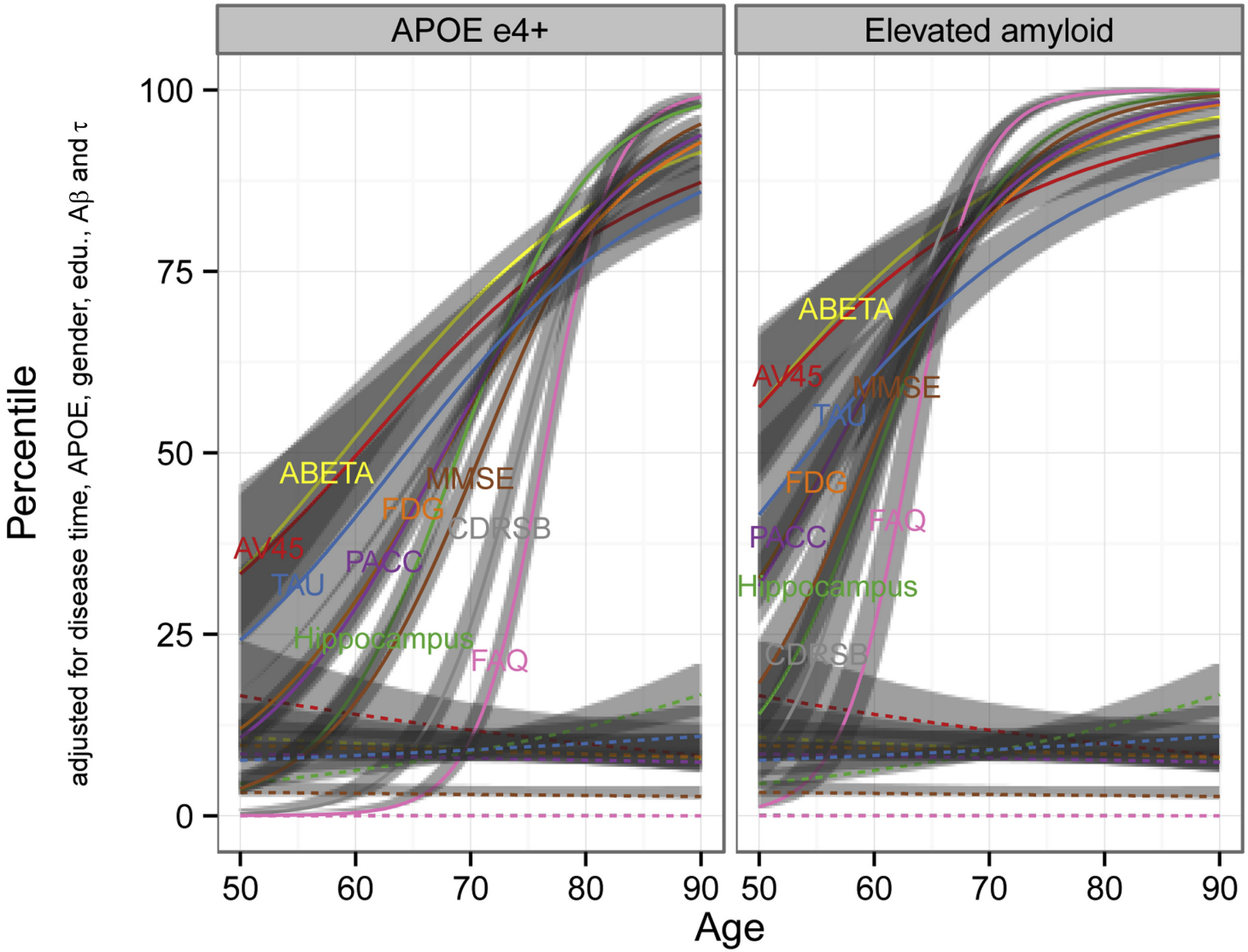


Jack Jr CR et al. Update on hypothetical model of Alzheimer's disease biomarkers. *Lancet Neurology*. 2013;12(2):207.

Summary of ADNI analysis

- summary summary

Jack model of natural history of disease



Beckett LA et al. The Alzheimer's Disease Neuroimaging Initiative phase 2: Increasing the length, breadth, and depth of our understanding. *Alzheimer's & Dementia*. 2015;11(7):823-31.

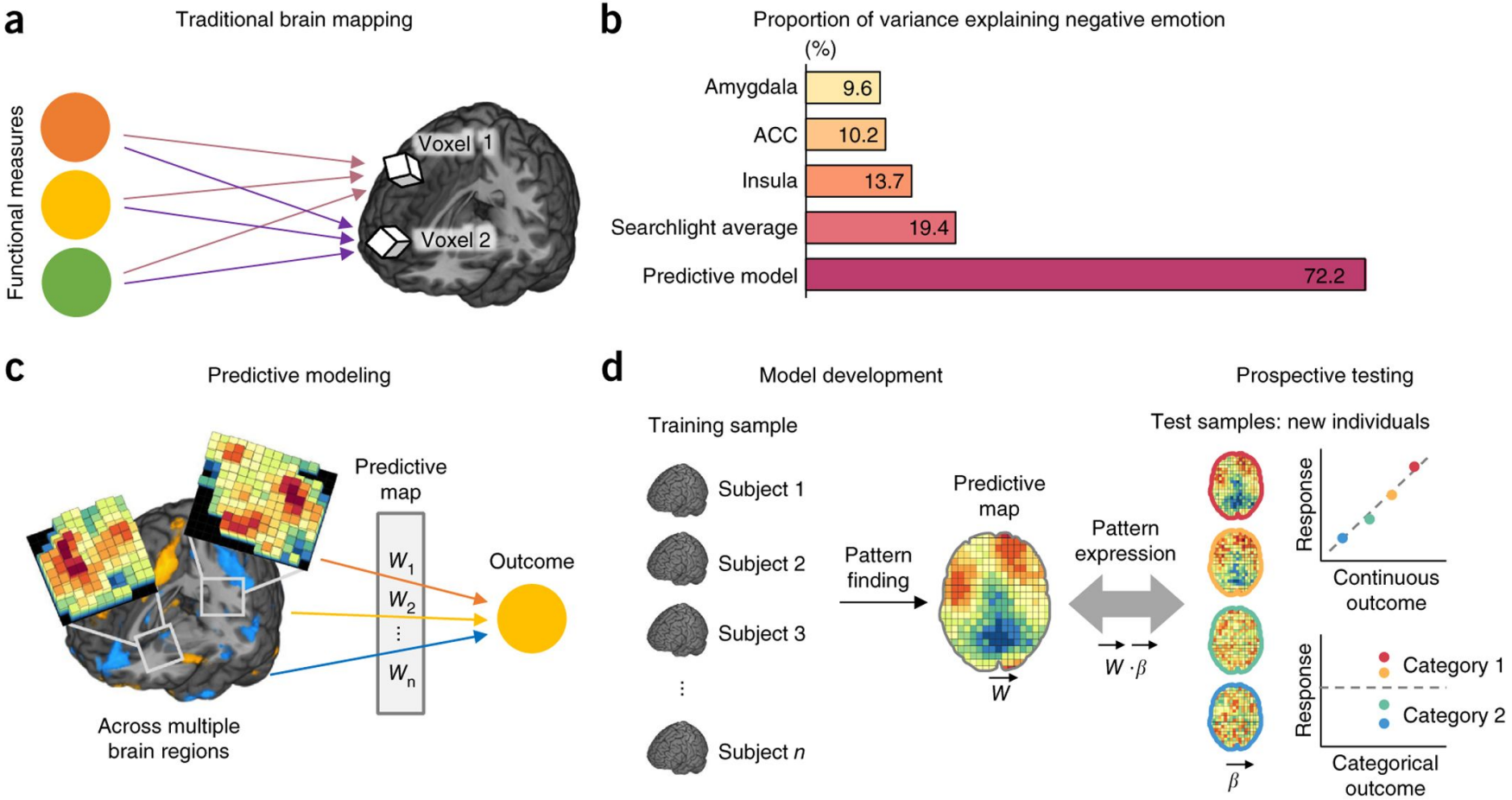
Future directions

- for disease etiology/early detection models

Neuroimaging

- One avenue for improvement in early identification and better characterization of natural history is via neuroimaging
- As additional imaging modalities become available interest has centered on development of imaging biomarkers
- Imaging biomarkers have the potential for non-invasive characterization of AD pathological changes in the brain and early diagnosis

Advances in translational neuroimaging



Woo CW et al. Building better biomarkers: brain models in translational neuroimaging. *Nature neuroscience*. 2017;20(3):365-377.

Neuroimaging

- Modern approaches to AD classification using neuroimaging data are leveraging recent developments in prediction modeling using machine learning
- Additional challenges include
  - Methods that can address small sample sizes, particularly in light of heterogeneity of the AD disease process
  - Need for methods to integrate multiple imaging modalities as well as imaging data and genetics, cognitive test scores, biomarkers (mulit-view data)

Leveraging EHR data to identify novel risk factors

- Linkage to EHR data can expand the reach of a traditional cohort study
- Advantages of this data source include
  - Breadth of data
  - Relative efficiency (cost and time) of creating data sets
- Despite these strengths, EHR data have numerous limitations including data quality, availability, and provenance

Stronger together?

- The strengths and weaknesses of EHR data and longitudinal cohort data are complementary

EHR data	Cohort data
▸ Inconsistent data quality	▸ High quality data
▸ Data collection schedule unspecified	▸ Specified data collection schedule
▸ Broad data availability	▸ Limited data availability
▸ Cheap	▸ Expensive

- Analyses of combined data must account for limitations due to source of individual data elements

Incident AD and glycemia

- We were interested in investigating the association between AD and glycemia
- We know that a clinical diagnosis of AD is an imperfect representation of the underlying neuropathology
- The design of the ACT study provide data on AD neuropathology for a subset of participants
- This allows us to characterize operating characteristics (sensitivity and specificity) of the clinical outcome, which can be incorporated into analysis

Analysis of imperfect time to event outcomes

- Bias in HR estimates using naive analysis depends on operating characteristics of imperfect outcome
- Several approaches to analysis of imperfect time to event outcomes have been developed
- Discrete time survival approaches leverage panel study design of ACT, treating AD status at each study visit as a possibly misclassified binary outcome
- We used the approach of Meier et al. (2003) based on discrete time likelihood incorporating known sensitivity and specificity to give adjusted HRs

Meier, A. S., Richardson, B. A., & Hughes, J. P. (2003). Discrete proportional hazards models for mismeasured outcomes. *Biometrics*, 59(4), 947-954.

Comparison of results

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	HR Diff	Rel CI width
No diabetes				
Q2 (95.9-100.9)	1.04 (0.72 1.50)	1.82 (0.80 4.17)	0.78	4.3
Q3 (100.9-107.8)	1.21 (0.85 1.73)	1.84 (0.72 4.72)	0.63	4.5
Q4 (>107.8)	1.28 (0.90 1.82)	2.13 (0.82 5.55)	0.85	5.1
Diabetes				
Q2 (149.5-167.0)	0.86 (0.40 1.86)	0.30 (0.02 5.48)	-0.56	3.7
Q3 (167-187.7)	0.59 (0.25 1.41)	0.68 (0.08 5.59)	0.09	4.8
Q4 (>186.7)	1.19 (0.54 2.62)	2.41 (0.42 13.76)	1.22	6.4

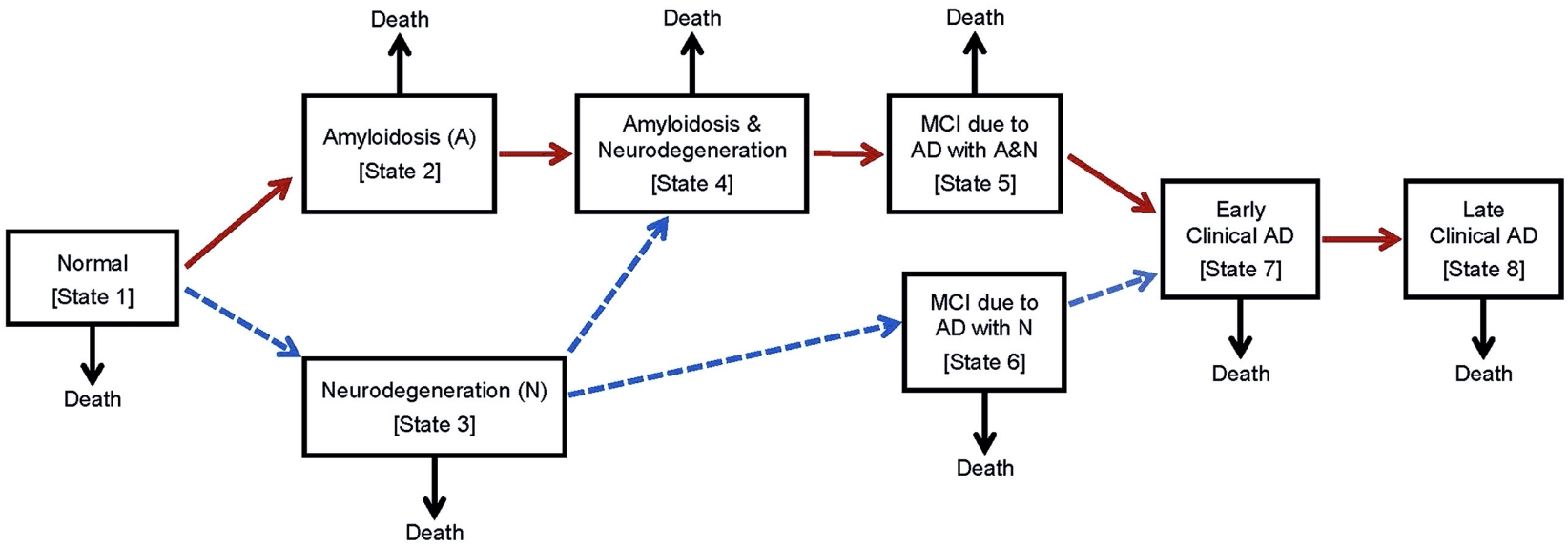
Remarks

- Important to account for operating characteristics of the surrogate outcome
- Unadjusted results tend to be attenuated towards the null
- Unadjusted results also substantially overstate the precision of our analysis by failing to outcome for error in AD assessment

Population models

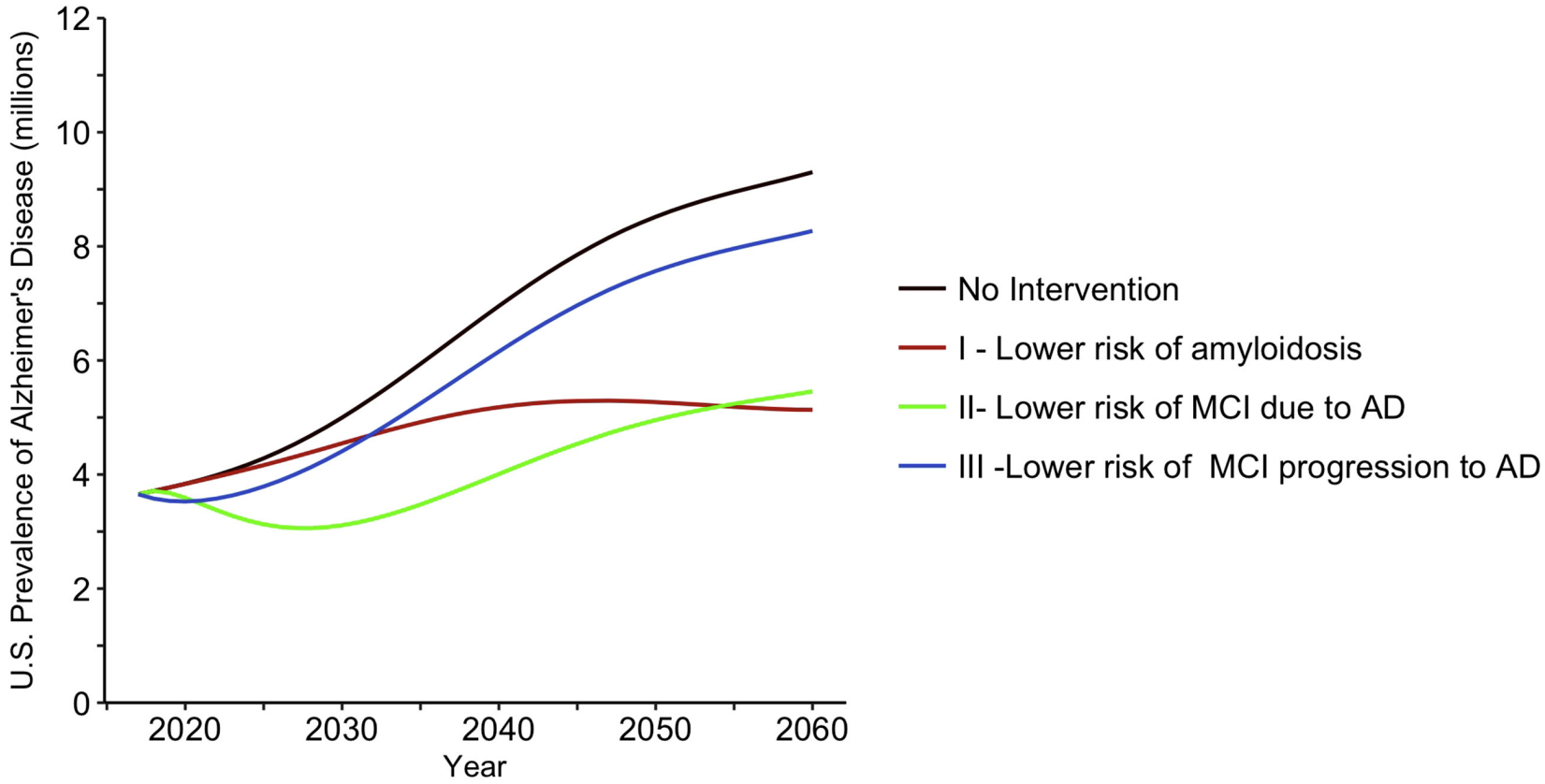
- summarize currently available models for projecting population burden of dementia/AD and life expectancy
- what are the limitations of currently available models?

Brookmeyer multi-state model for MCI and AD



Brookmeyer R et al. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. Alzheimer's & Dementia. 2018;14(2):121-9.

Population projections for burden of disease



Brookmeyer R et al. Forecasting the prevalence of preclinical and clinical Alzheimer's disease in the United States. Alzheimer's & Dementia. 2018;14(2):121-9.

Conclusions

- Many opportunities for statisticians to make an impact in this field
- Opportunities to contribute to early identification of disease and development of potentially disease modifying therapies
- Understanding population health impacts of changes in risk factor and age distribution of population important for resource allocation and public health planning
- Statistical understanding of prediction and inference as well as tools for modern data sources critical for advancement

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https://www.med.upenn.edu/ehr-stats/