Identification of Factors Associated with Alzheimer's Disease Diagnosis Over Complex Large-scale Longitudinal Health Data

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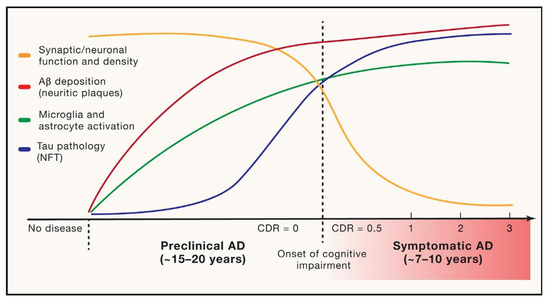
Motivation

Risk of Alzheimer's disease (AD) doubles every 5 years after age 65. An estimated 14 million Americans will have AD by 2050. With no disease modifying treatment or prevention in sight, we aim to:

- Identify factors associated with pre-clinical AD i.e. 10 or more years prior to disease diagnosis using electronic health records.
- Discover novel causal associations for AD using graphical causal methods.



Long JM, Holtzman DM. Cell 2019. doi: 10.1016/j.cell.2019.09.001

Project Description

1. Cases - patients with ICD-10 AD diagnosis since 2016 and with UPMC visits 10+ years prior to their diagnosis.
2. Controls (8 controls to 1 case) - patients matched on age, sex, and other factors who were not diagnosed with AD but do have UPMC visits 10+ years prior.
3. Case-control & machine learning analyses to identify early markers of AD.
4. Knowledge graphs and graphical causal methods to address confounding and suggest mechanisms.

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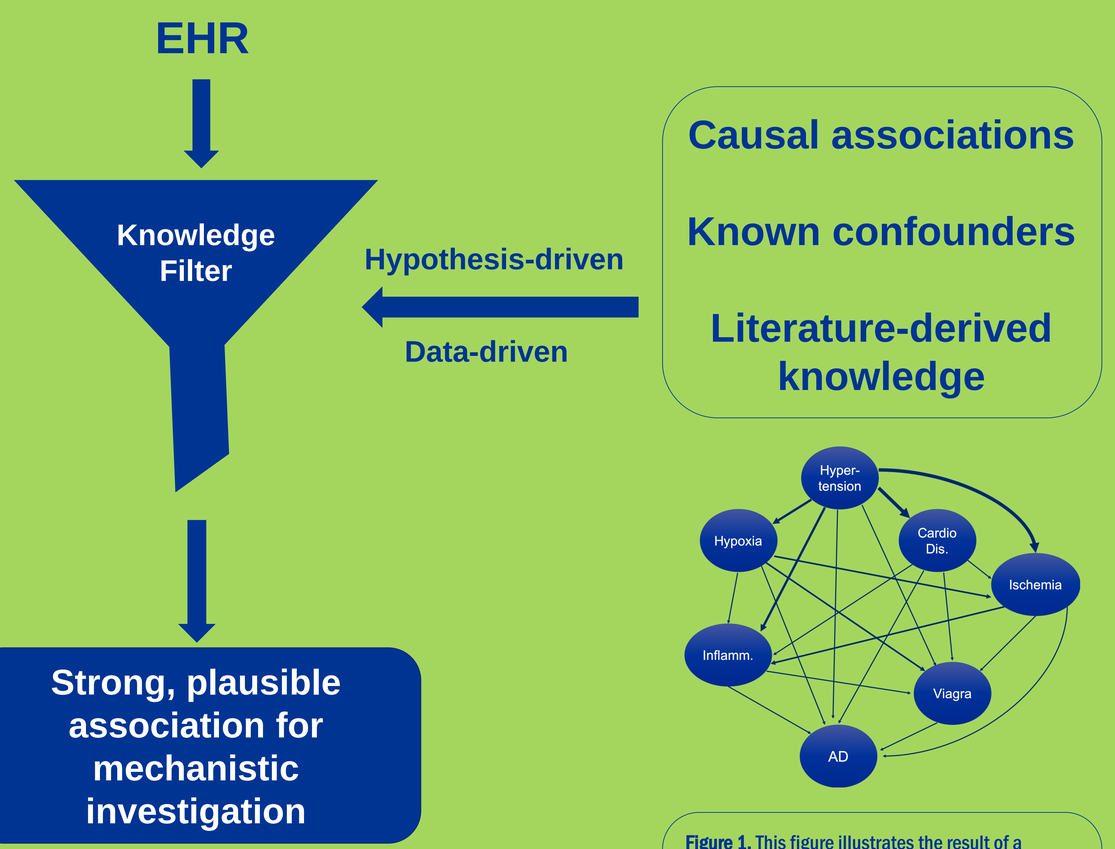
We aim to **discover novel clues** in large-scale electronic health records (EHR) to **prevent the onset of Alzheimer's disease.**



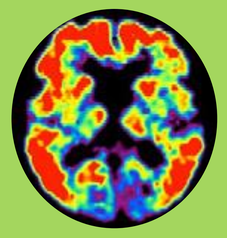


Figure 1. This figure illustrates the result of a literature-informed graphical causal model answering the causal question: "Does sildenafil (Viagra) affect AD?" Semantic MEDLINE database was used as the knowledge repository to identify confounders depicted in the graph. Arrow thickness represents strength of the association.

Source: Mathis CA, Lopresti BJ, Klunk WE. *Nucl Med Biol*. 2007.

Context

- **Type of analysis**

First analysis of its kind:

- Associations 10+ prior to a diagnosis of Alzheimer's disease
- Inpatient + outpatient data
- Complete EHR data - medical history, medications, lab results, family history, procedures, demographics, and vitals.
- Integrates detailed control of confounders identified through both typical literature review and machine reading of the literature

- **Scale of analysis**

> 9,000 cases and >72,000 controls

- **Team**

Multidisciplinary members from three schools (Medicine, Public Health, Computing & Information)

Project Deliverables

- Data mart of UPMC EHR data with both cases and controls
- Case-control and machine learning analyses for AD and associated factors
- Preliminary results on causal associations through knowledge graphs
- Abstracts and manuscripts with results
- National Institute of Ageing (NIA) R01 grant proposal for long-term funding

Potential Impact

Provide novel hypotheses to advance research on prevention of AD

- Identify potential disease-course-altering markers for further investigation
- Long-term research plans (using follow-on funding) will generate much-needed disease trajectories & mid-level mechanistic models of great value to AD research community
- A new data mart for use by the wider community of AD researchers

Collaborators

Dr. Arthur Levine
Michelle Kienholz
Dr. Howard Aizenstein
Dr. William Klunk
Brian McLay and the R3 team