The EPAD Approach: Using Longitudinal Data for Selection into Dementia Trials

Graciela Muniz -Terrera
Craig Ritchie
Centre for Dementia Prevention
University of Edinburgh

www.ep-ad.org
Consensus exists that the genesis of AD pathology predates dementia onset by over 20 years.

This presents an opportunity for disease course modification in the prodromal phase and even prior to appearance of clinical symptoms.

So, the accurate identification of high risk, non demented individuals to join secondary prevention trials is crucial.
EPAD project seeks to:

- develop disease models for risk prediction at earlier phases of the disease process
- create a readiness cohort as a source for participant selection into trials; resource to be used for selection into trials

www.ep-ad.org
EPAD funnel
EPAD resource

Parent cohorts

- PREVENT
- Generation Scotland
- Others
- UK Biobank

EPAD Register (N~ 24,000)

EPAD Cohort (N~6000)
Cognition, Imaging, Blood, CSF, other markers

Trials

Modelling!

www.ep-ad.org
EPAD LCS information

- Data from EPAD comprise:
  - cognitive outcomes RBANS total and domain specific scores
  - biomarkers CSF (e.g. amyloid beta, t-tau, p-tau), neuroimaging data (MRI) (e.g. hippocampal and whole brain volume, vascular burden)
  - risk factors (APOE, family history of AD/dementia), socio demographic factors (age, sex, education, etc)

Aim is to make best use of this rich information to identify individuals at higher risk of AD
Existing dementia risk models recently reviewed and multiple limitations identified:

- no internal validation, no model transportability, *usually developed in samples “closer” to disease manifestation*
- methodologically limited (upcoming presentations)
- most ignore information about change in markers, which is at the core of the process that we are aiming to predict

To sum: *traditional methods may not be right tools for identification of higher risk individuals at an early stage for dementia*
we will consider a latent class model to identify groups of individuals whose trajectories over time are similar.

we will define a latent variable that reflects information from multiple markers that are being tracked (cognitive scores, biomarkers, etc)

these are assumed to be different noisy measurements of a single underlying AD process (unobserved)

additional information (observed markers, risk factors) will also be considered within declining group
will employ a latent class model that reflects information from multiple markers that are being tracked (cognitive scores, biomarkers, etc.) via a latent variable. The latent variable represents the "process" of interest and accounts for the correlation between the various markers of the process. Individuals who are assigned by the model to the declining group will be selected to enter trials. Additional information (observed markers, risk factors) will also be considered within the declining group.

Conceptual Diagram

- Risk Factors \( X \)
- Latent Class \( C \)
- Underlying AD Process \( U \)
- Cognitive Outcomes
  - \( Y_1 \)
  - \( Y_2 \)
  - \( \ldots \)
  - \( Y_k \)
  - \( Y_{k+1} \)
  - \( \ldots \)
  - \( Y_K \)
- Biomarkers
- Time to AD Dementia \( T \)
Joint latent class model for multivariate outcomes & *time-to-event*

- **Latent class membership model**, \( P(C_i = c | X_{0i}) \)
  - Multinomial logistic with covariates \( X_{0i} \)
- **Structural model** for underlying AD process, given class \( c \)
  \[
  U_{ci}(t) = X_{1i}(t)^T \beta_c + Z_i(t)^T u_{ic}
  \]
- **Outcome-specific observation model**, given class \( c \)
  \[
  h(Y_{kij}; \eta_k) = U_{ci}(t_{kij}) + X_{2i}(t_{kij})^T \gamma_{kc} + b_{kci} + \epsilon_{kij}
  \]
- **Time-to-event model**, given class \( c \)
  - Class-specific proportional hazards or parametric model with covariates \( X_{3i}(t) \)
• individuals who are assigned by the model to the declining group will be selected to enter trials

• models & risk scores will be continuously updated as new information is collected over time

• approach will not only identify “high risk” individuals, but will also allow to tease out what the contributors are for each individual

• participants being recruited to EPAD LCS. Limited influence of disease modelling in early stages of EPAD LCS (need data!), but will increase over time

• currently, we are in “testing mode” using existing data (ADNI), though only limited information available
Opportunities

- substantive work and results from variety of trials run using EPAD data will generate new knowledge about AD
- it is also a fantastic platform for sub studies
- dataset incredibly rich resource for methodological developments

- Contact me if interested.