“Causal Inference Methods: Applications in Studies of Aging-Related Health Outcomes”

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Causal Inference Methods

- What are marginal effects?
- How do we identify and estimate them from observed data?
- What is their significance in epidemiologic practice?
Traditional vs. Causal Inference Methods

In contrast to traditional methods (e.g., association model) which provide stratum-specific (conditional) effects

\[ E(Y \mid A, W) = \beta_0 + \beta_1 A + \beta_2 W_1 + \beta_3 W_2 + \ldots + \beta_k W_k \]

Causal methods can be used to identify and estimate marginal (population-level) effects, for example, with marginal structural models (MSMs):

\[ E(Y_a) = \beta_0 + \beta_1 a \]

e.g., \( a \)=brain glucose metabolism (i.e., metabolic activity) and \( E(Y_a) \) is population-level distribution of cognitive function
Assessing marginal effects would be equivalent to modeling an outcome under one set of conditions for everyone, and comparing it to an outcome under another set of conditions.

E.g., the marginal effect $\beta_1$ in the model

$$E(Y_a) = \beta_0 + \beta_1 a$$

represents the difference in expected outcome, summed over all subjects, if everyone experienced metabolic activity level $a = 1$ vs. $a = 0$, i.e.,

$$E(Y_1) - E(Y_0) = \beta_1$$
Causal Inference Methods

- Given observed data, one would not observe all conditions for a given subject and the effect of interest is likely related to other covariates.
Among patients with mild cognitive impairment, what are the independent, individual effects of brain glucose metabolism, hippocampal volume, and whole brain volume at any given time on a progressive clinical measure of AD (e.g., ADAS-Cog)?
Hypothesized relationships between biomarkers and clinical AD

Brain glucose metabolism measured using FDG-PET imaging

Assumptions

- Potential (Counterfactual) outcomes exist
- Consistency Assumption
- Temporal Ordering
- Sequential Randomization Assumption (SRA)
  - Treatment (e.g. metabolic activity level) is randomized with respect to outcome
- Positivity Assumption
Sequential Randomization Assumption

- At each time \( k \), model probability, or density, of “\( A \)” — e.g., metabolic activity conditional on covariates and past activity levels \( A(k-1) \)

\[
Sw(t) = \prod_{k=0}^{t} \frac{\Pr(A(k) \mid \overline{A}(k - 1), V)}{\Pr(A(k) \mid \overline{A}(k - 1), L(k))}
\]

\( Sw(t) \) represents weight in MSM regression

- Model could contain several covariates and interactions between these covariates
  - High-dimensional analytical problem to select model
Positivity Assumption

- All treatment levels must be present given covariates--e.g., poor health cannot determine treatment level
  - Required for “experimentation” and making comparisons to identify causal effects
Individual Effects of AD Biomarkers on ADAS-Cog

Univariable Model:

$$E[Y_a(t)] = \beta_0 + \beta_1 a(t)$$

where ‘a’ represents one biomarker – e.g., hippocampal volume

$\beta_1$ effect (95% CI) represents population-level increase in biomarker level (1 SD) on expected ADAS-Cog

Expected ADAS-Cog=12 if contrary to fact, subjects biomarker level = median of biomarker distribution
Inidividual and Joint Effects of AD Biomarkers on ADAS-Cog
Study Summary

- Greater FDG-PET, a marker of brain glucose metabolism, and greater hippocampal volume independently decrease AD progression in MCI patients.

- Greater total brain volume does not decrease AD progression accounting for the other biomarkers.

- FDG-PET and hippocampal volume represent biologic markers to investigate potential interventions and treatment strategies in MCI patients.
Study of Physical Functioning
Research Question

- What are the independent effects of leisure-time physical activity and body composition on physical functioning over time in the elderly?
Study of Physical Functioning

- **Body composition**
  - Direct measure: bioelectric impedance (BI) data
  - Prediction equations from dual-xray absorptiometry (DEXA) and BI in subsample
  - Lean mass, fat mass, and **lean mass: fat mass ratio**

- **Physical Function**
  - Self-report: difficulty on tasks related to lower/upper body strength, mobility, etc
  - 1= ≥ 1 limitation on task ; 0=No limitation

- **Physical Activity**
  - Self-report: type of activity, frequency, duration
  - Derived measure of energy expenditure
  - Grouped based on public health recommendations
Physical Functioning Outcome

- Outcome space of functional limitation over \( t \) in the population

\[
\Omega(\overline{Y}) = \begin{pmatrix}
0 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 \\
0 & 0 & 1 & 1 \\
. & . & . & . \\
1 & 1 & 1 & 0 \\
1 & 1 & 1 & 1 \\
\end{pmatrix}
\]

- Each row represents a pattern of physical function for 4 evaluations over an 8-year period

\((0,0,0,0) = \text{limitation-free at all 4 visits}\)

- Estimate the distribution in the population if contrary to fact everyone experienced a change in Lean: Fat Mass ratio and/or levels of physical activity (Mets/week) from observed levels

\[
\Pr(\overline{Y}_a) = \prod_{1}^{4} \Pr(Y_a(1), Y_a(2), Y_a(3), Y_a(4)) = \prod_{1}^{4} \Pr(Y_a(t) | \overline{Y}_a(t-1))
\]

where \( a = \text{joint effect of Lean:Fat Mass ratio and physical activity} \)
## Results

Proportions of selected patterns of functional limitation in women over 4 surveys for four counterfactual scenarios

<table>
<thead>
<tr>
<th>Selected Transitions</th>
<th>Selected Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No Activity</td>
</tr>
<tr>
<td></td>
<td>Observed Lean:Fat</td>
</tr>
<tr>
<td>Pr (0,0,0,0)</td>
<td>0.38</td>
</tr>
<tr>
<td>Pr (1,1,1,1)</td>
<td>0.15</td>
</tr>
<tr>
<td>Pr (0,0,0,1)</td>
<td>0.13</td>
</tr>
<tr>
<td>Pr (1 to 0)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* Proportions do not sum to 1 given selected transitions.
** Confidence Intervals excluded.

Haight et al. (2005) AJE 162(7): 607-617
Study Summary

- Lean: Fat mass ratio establishes and maintains levels of physical functioning in the elderly

- Higher levels of physical activity reduce the risk of future physical limitation and increase the probability of recovery from limitation

- Incremental increases in physical activity and lean mass: fat mass ratio confer similar benefits as high physical activity levels to reduce the risk of future physical limitation
History-Adjusted Marginal Structural Models

- Given changes over time in elderly populations, it is important to assess effects of potential interventions given these changes.

- Changes may occur in the form of physician-diagnosed health status, subclinical disease, and other physiologic/environmental factors.

- In this regard, we can better understand patients' responsiveness/non-responsiveness to treatment, and identify the factors involved, which can potentially inform RCTs.
Hypothetical Study of 5-year risk of Cardiovascular Mortality

- Assess the benefits of future leisure-time physical activity (LTPA) on mortality risk in subgroups defined by age, prior exercise history, clinical CVD (e.g. MI), and subclinical disease (e.g., based on electrocardiogram)
Hypothetical Study of 5-year risk of Cardiovascular Mortality

- Given timepoints \( j=1,\ldots,5 \), define parameters for the probability of CVD-related mortality in a 5-year period, if contrary to fact, everyone in the population followed leisure-time physical activity (LTPA) regimen: 

\[
a = (a(j), \ldots, a(j+4))
\]

At baseline \( j=1 \), define parameter, where \( T_a \) is the counter-factual failure time, \( t_0 \) is the desired time frame of 5 years to assess mortality, and \( V_0 = \nu \) represents subgroups to contrast differences in the causal effect of LTPA

\[
\theta(a, \nu) = \Pr(T_a \leq t_0 \mid V_0 = \nu)
\]
Hypothetical Study of 5-year risk of Cardiovascular Mortality

- For each follow-up survey, until time $j=5$, define parameters to correspond with the mortality risk at each of these surveys:

\[
\theta(a, v, j) = \Pr(T_{A(j-1)a}^- \leq M_j + t_0 \mid T_{A(j-1)}^- \geq M_j, V(j) = v)
\]

- For each survey $j$, we define the counterfactual probability of CVD-related mortality if subjects who survived up to given survey $M_j$ were allowed to follow their observed LTPA up to survey $j$, but, contrary to fact, followed LTPA regimen $a = (a(j), ..., a(j+4))$ for 5 years starting with $j$.

- Obtain “average” 5-year risk based on effects at each $j$. 
Implications

- Methods can be used to address a variety of questions

- Methods allow for more direct focus on causal questions of interest—i.e., confounding is dealt with separately

- Potential to yield useful information for interventions in older populations and subgroups in those populations
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