Blood Pressure and the Risk of Chronic Kidney Disease Progression Using Multistate Marginal Structural Models in the CRIC Study

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Joint work w/ Wei Yang, Andrew Spieker, Tom Greene, and Marshall Joffe
CRIC: Prospective, multicenter, observational study of 3,708 adult patients with mild to moderate chronic kidney disease

Duration of follow up: Annually from 0 to 7 years, median of 5.7 years

Study Question: How does systolic blood pressure affect disease progression among 6 possible disease states?
Exposure Levels

SBP modeled in 1 of 4 categories at each year

- 1: SBP < 120 mm Hg
- 2: 120 ≤ SBP < 130 mm Hg
- 3: 130 ≤ SBP < 140 mm Hg
- 4: SBP ≥ 140 mm Hg
Outcome Levels

Disease states: Defined by levels of estimated Glomerular Filtration Rate (eGFR), ESRD, and death at each year

- 1: eGFR $\geq 60$
- 2: eGFR $[45, 60)$
- 3: eGFR $[30, 45)$
- 4: eGFR $(0, 30)$
- 5: End Stage Renal Disease (Absorbing)
- 6: Death (Absorbing)
Chronic Kidney Disease Progression

- Patients transition among states at each annual follow up

1: Mild CKD
eGFR ≥ 60

2: Moderate-A CKD
eGFR [45, 60]

3: Moderate-B CKD
eGFR [30,45]

4: Advanced CKD
eGFR <30

5: End Stage Renal Disease (ESRD)

6: Death

λ1,2, λ1,3, λ2,1, λ2,3, λ2,4, λ3,1, λ3,2, λ3,4, λ4,2, λ4,3, λ4,4, λ4,6, λ5,6
Chronic Kidney Disease and Blood Pressure

Relationship between hypertension and CKD complex and challenging to measure

- Hypertension both a cause and effect of CKD
- Several time dependent confounders (eg proteinuria or use of ACEs/ARBs) exist for the blood pressure/CKD relationship
- Standard regression analyses fail to provide unbiased estimates of causal joint exposure effects in the presence of time-dependent confounding, even if all relevant confounders are measured
Marginal Structural Models (MSMs)

- Developed by Robins (1997) to estimate causal contrasts in the presence of time-dependent confounding by covariates.
- Model for the marginal mean of outcomes that would have been observed if everyone in the population had a particular exposure sequence.
- Accounts for time-dependent confounding by using inverse probability weights (IPW) to remove confounding effect of time-varying covariates.
Approach

Extend MSMs to Multistate Models:
- Estimate the effect of time-varying blood pressure on probability of transition among mild and severe CKD states
- Estimate the effect of time-varying blood pressure on marginal probability of being in a given state at the end of follow up
- Avoid composite endpoints that may present challenges for interpretation
- Avoid treating death as a censoring event
Parameters of Interest

- **Transition probability**: the probability of potential outcome state under a specified SBP sequence given the outcome state in the previous year
  - What’s the population probability of transitioning from mild CKD to ESRD at a given time if everyone were to always have well controlled blood (\( \leq 120 \text{ mm Hg} \)) pressure up until that time?

- **Marginal probability**: the marginal probability of potential outcome state at the end of follow up under a specified SBP sequence
  - What proportion of the population has advanced CKD by the end of followup if all individuals were to always have well controlled blood pressure versus always having high (\( > 140 \text{ mm Hg} \)) blood pressure?
Multistate Marginal Structural Models (MS-MSMs) and Estimation

- **Model**: Longitudinal marginal structural baseline-category logit model
  - Effect of SBP sequence for a single transition time characterized by odds ratios

- **Estimation of Transition Probability**: Weighted estimating equations
  - Weights are the inverse probability of an individual’s observed SBP sequence
  - Weights estimated by multinomial regression of SBP categories onto time dependent confounders cardiovascular disease, diabetes, BMI, use of ACEs or ARBs, number of antihypertensive medications, proteinuria, current eGFR

- **Estimation of Marginal Probability**: matrix product of estimated CKD transition probability matrices under a specified SBP sequence
Aggregate Observed Transitions Among eGFR-defined States

For modeling, several rare transitions set to 0 probability

- $1 \rightarrow 4, 5$
- $2 \rightarrow 5$
- $4 \rightarrow 1$

<table>
<thead>
<tr>
<th>$Y_j$</th>
<th>$\geq 60$</th>
<th>$[45, 60)$</th>
<th>$[30, 45)$</th>
<th>$(0, 30)$</th>
<th>ESRD</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\geq 60$</td>
<td>2139</td>
<td>473</td>
<td>42</td>
<td>0</td>
<td>1</td>
<td>27</td>
</tr>
<tr>
<td>$[45, 60)$</td>
<td>478</td>
<td>2332</td>
<td>844</td>
<td>54</td>
<td>3</td>
<td>50</td>
</tr>
<tr>
<td>$[30, 45)$</td>
<td>34</td>
<td>543</td>
<td>2941</td>
<td>921</td>
<td>47</td>
<td>120</td>
</tr>
<tr>
<td>$(0, 30)$</td>
<td>1</td>
<td>20</td>
<td>347</td>
<td>2428</td>
<td>547</td>
<td>146</td>
</tr>
</tbody>
</table>
Log Odds Ratios of Blood Pressure Effects for Transitions from State 1 from MS-MSM
Log Odds Ratios of Blood Pressure Effects for Transitions from State 4 from MS-MSM
Contrast of Log Odds Ratios of Blood Pressure Effects for Transitions from State 4 for MS-MSM and Standard Regression
Yearly Marginal Probabilities of CKD State by Blood Pressure Trajectory
### Differences in Marginal Probabilities of CKD State by End of 7 years for MS-MSM versus Standard Regression

<table>
<thead>
<tr>
<th>SBP</th>
<th>Standard (Unweighted)</th>
<th></th>
<th></th>
<th></th>
<th>MS-MSM</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eGFR ≥ 60</td>
<td></td>
<td></td>
<td></td>
<td>eGFR ≥ 60</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 120</td>
<td>27.4</td>
<td></td>
<td>9.3</td>
<td>25.5</td>
<td>13.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(25,30)</td>
<td></td>
<td>(7,11)</td>
<td>(24, 31)</td>
<td>(7.3, 11)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[120, 130)</td>
<td>14.2</td>
<td></td>
<td>13.3</td>
<td>12.9</td>
<td>13.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(11,18)</td>
<td></td>
<td>(15,21)</td>
<td>(10, 18)</td>
<td>(9.7, 17)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>[130, 140)</td>
<td>8.0</td>
<td></td>
<td>26.4</td>
<td>9.1</td>
<td>26.1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5, 11)</td>
<td></td>
<td>(21, 32)</td>
<td>(4.8, 12)</td>
<td>(19, 34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 140</td>
<td>2.1</td>
<td></td>
<td>53.9</td>
<td>3.5</td>
<td>45.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(1.2,3.0)</td>
<td></td>
<td>(50,58)</td>
<td>(1.2, 3.2)</td>
<td>(49, 58)</td>
<td></td>
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</tr>
</tbody>
</table>

- Calculated under the exposure sequence where subjects stay in the indicated SBP category for the duration of follow up
- 95% CI calculated by bootstrap percentile method
Formulated marginal structural models for multistate outcomes

Demonstrated an effect of systolic blood pressure on transitions among multiple CKD states

- Higher SBP results in greater likelihood of ESRD and lower likelihood of mild CKD
CRIC Study Team Members
Dawei Xie
Amanda Anderson
Sally Thompson
Qiang Pan
Baseline:
Sex, race, education, hypertension awareness, baseline values of all time-dependent covariates

Time-Dependent:
Age, cardiovascular disease, diabetes, BMI, use of ACEs or ARBs, number of antihypertensive medications, proteinuria, current eGFR

Censoring Events:
Loss to follow up
Unweighted marginal probabilities

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<td>≥ 140</td>
<td>8.0</td>
<td>12.4</td>
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Note: SBP values are in mmHg, eGFR levels are in mL/min/1.73m², and absorbing probabilities are in percentage.

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<tr>
<td>[130, 140)</td>
<td>8.0</td>
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</tr>
<tr>
<td>≥ 140</td>
<td>2.1</td>
<td>(1.2, 3.0)</td>
</tr>
</tbody>
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Log Odds Ratios of Blood Pressure Effects for Transitions from State 2
Log Odds Ratios of Blood Pressure Effects for Transitions from State 3