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

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Chronic Renal Insufficiency Cohort Study (CRIC)

- 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

- $1 : \text{SBP} < 120$ mm Hg
- $2 : 120 \leq \text{SBP} < 130$ mm Hg
- $3 : 130 \leq \text{SBP} < 140$ mm Hg
- $4 : \text{SBP} \geq 140$ mm Hg

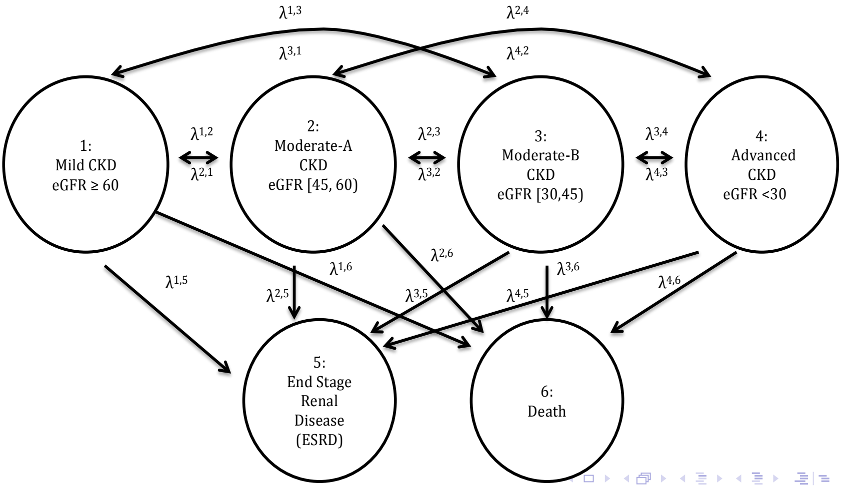
Outcome Levels

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

- 1: eGFR ≥ 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



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 presssure/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 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 mm Hg) blood pressure?

Multistate Marginal Structural Models (MS-MSMs) and Estimation

- **Model:** Longitudinal marginal stuctural 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

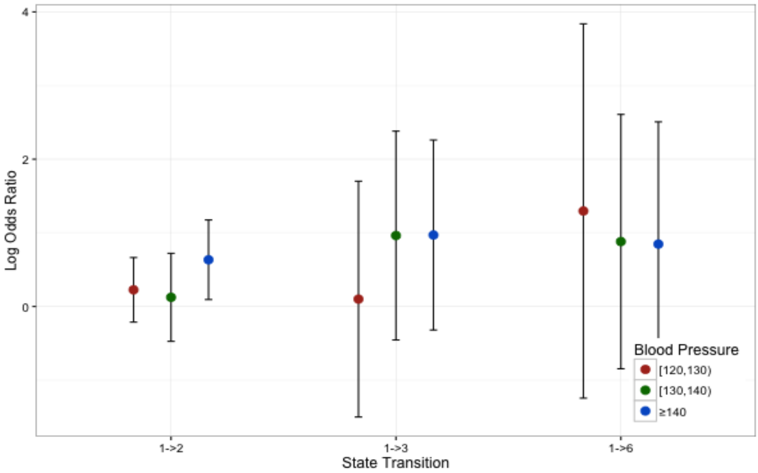
Aggregate Observed Transitions Among eGFR-defined States

For modeling, several rare transitions set to 0 probability

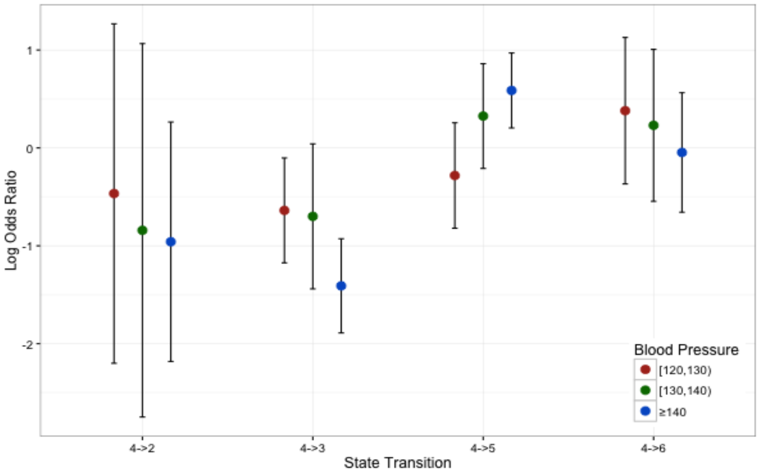
- $1 \to 4, 5$
- $2 \to 5$
- $4 \to 1$

	Y_{j+1}					
Y_j	≥ 60	$[45, 60)$	$[30, 45)$	$(0, 30)$	ESRD	Death
≥ 60	2139	473	42	**0**	**1**	27
$[45, 60)$	478	2332	844	54	3	50
$[30, 45)$	34	543	2941	921	47	120
$(0, 30)$	**1**	20	347	2428	547	146

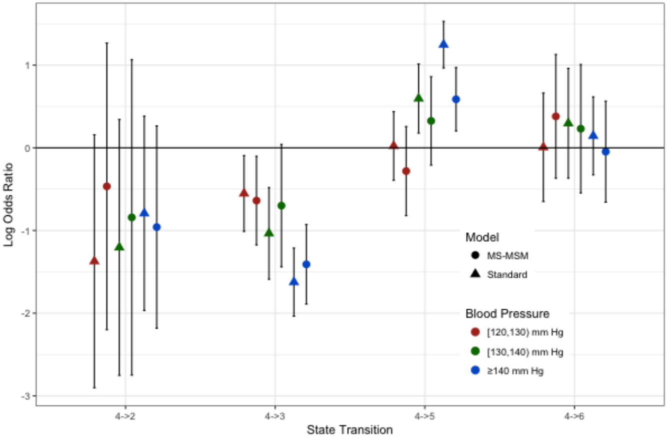
Log Odds Ratios of Blood Pressure Effects for Transitions from State 1 from MS-MSM



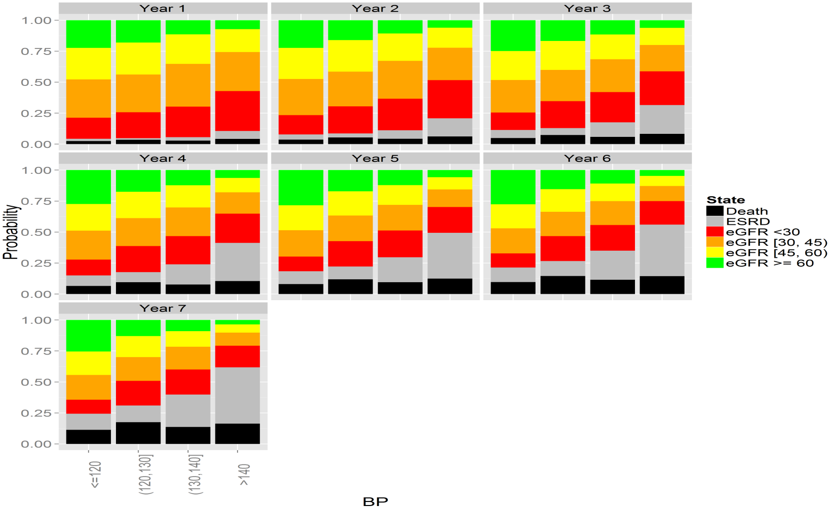
Log Odds Ratios of Blood Pressure Effects for Transitions from State 4 from MS-MSM



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

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

- 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

Conclusion

- 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

Acknowledgements

CRIC Study Team Members

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Potential Confounders and Censoring

Baseline:
Sex, race, education, hypertension awareness, baseline values of all time-dependent covariates

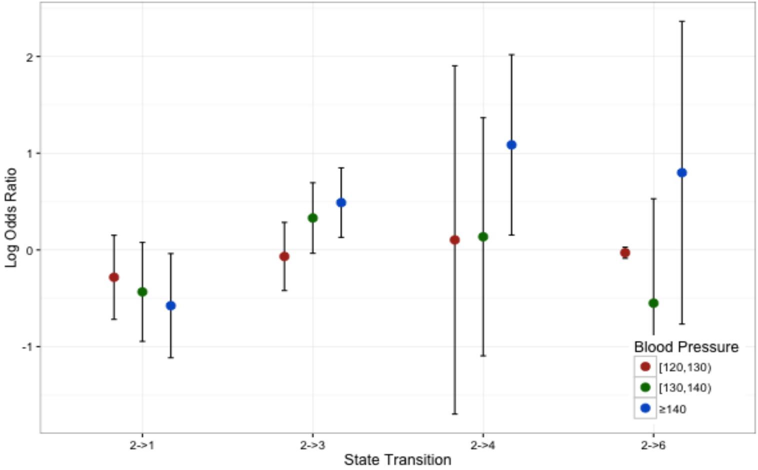
Time-Dependent:
Age, cardiovascular disease, diabetes, BMI, use of ACEs or ARBs, number of antihypertensive medications, proteinuria, current eGFR

Censoring Events:
Loss to follow up

Unweighted marginal probabilities

	eGFR Level				Absorbing	
SBP	≥ 60	$[45, 60)$	[30,45)	< 30	ESRD	Death
< 120	27.4	19.9	20.6	10.9	9.3	11.9
	(25, 30)	(18, 22)	(18, 23)	(9, 12)	(7, 11)	(9, 14)
$[120, 130)$	14.2	18.1	20.2	19.7	13.3	14.5
	(11, 18)	(15, 21)	(17, 24)	(16, 23)	(10, 17)	(11, 18)
$[130, 140)$	8.0	12.4	18.3	20.7	26.4	14.2
	(5, 11)	(10, 15)	(15, 22)	(17, 25)	(21, 32)	(10, 19)
≥ 140	2.1	4.7	8.1	15.1	53.9	16.1
	(1.2, 3.0)	(3.6, 5.8)	(6.8, 9.4)	(13, 17)	(50, 58)	(13, 19)

Log Odds Ratios of Blood Pressure Effects for Transitions from State 2



Log Odds Ratios of Blood Pressure Effects for Transitions from State 3