Dunedin Multidisciplinary Health & Development Study

Concept Paper Form

Provisional Paper Title: Kidney function trajectories from young adulthood to midlife: Findings from a five-decade longitudinal study
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P.I. Sponsor: Richie Poulton
Today's Date: September 2020

Objective of the study:

Understanding normative patterns of change in kidney function over the life course and the factors that influence such change is essential for the differentiation of healthy versus unhealthy kidney aging. This is essential for the development of policies and interventions designed to prevent or slow the onset of kidney disease or dysfunction. Population-based prospective longitudinal studies provide one of the best methods for characterising these patterns of change as they enable control of important covariates, including between-person differences. However, most longitudinal or meta-analytic studies that include prospective data have to date focused on monitoring changes in kidney function only after middle age (e.g., de Boer et al., 2009; Eriksen et al., 2020; Hemmelgarn et al., 2006; Rifkin et al., 2008; Salimi et al., 2018; Sesso, Prado, Vicioso, & Ramos, 2008). As a result, little is known about common patterns of change in kidney function earlier in adulthood.

It is important to understand potentially problematic patterns of change in kidney function early in adulthood as preventive policies and interventions will be most effective when implemented before disease becomes manifest. Given the current dearth of good quality information on population-level patterns of change in kidney function prior to middle age, the aims of the proposed study are to use data from the five-decade Dunedin longitudinal birth cohort study to: model common trajectories of kidney function from age 32y to 45y; understand the early life factors that are linked to healthy or unhealthy trajectories; identify factors that modify kidney function from young adulthood to early middle age; and examine the associations between trajectories and kidney health-related outcomes at age 45y.

Data analysis methods:

MEASURES OF KIDNEY FUNCTION

Glomerular filtration rate (GFR) is one of the most important indicators of overall kidney function, but is time consuming and expensive to measure directly. Estimated GFR (eGFR) is a good proxy commonly used in clinical and research settings, and can be calculated using the standardized Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations that incorporate blood markers (serum creatinine and/or cystatin C levels) and demographic variables (Inker et al., 2012; Levey et al., 2009).

GFR estimated from serum creatinine (crGFR) is the most common measure of kidney function used in clinical settings, but can provide a misleading picture as it has high inter-individual variability, which is influenced by a number of factors including lean muscle mass (Chew-Harris et al., 2014), diet, drugs that inhibit tubular secretion of creatinine or the renin-angiotensin aldosterone system, and other hemodynamic reductions in renal blood flow (Endre, Pickering, & Walker, 2011). GFRs estimated from cystatin C (cyGFR) or the combination of creatinine and cystatin C (crcyGFR) are preferred in research settings as they have been shown to be more accurate and reliable (Husain et al., 2018; Inker et al., 2012; Shlipak et al., 2013; Stevens et al., 2008; Willey et al., 2020).

In the proposed study, our primary measure of kidney function will be crcyGFR. As a separate methodological contribution to the current literature, we will also seek to replicate our analyses using crGFR and cyGFR.

ANALYSIS APPROACH

Replicating the approach Theodore et al. (2015) used to understand blood pressure trajectories in Dunedin study members, we will use group-based multi-trajectory modelling (Nagin, Jones, Passos, & Tremblay, 2018) to identify clusters of study members (trajectory groups) that show distinct patterns of change in eGFR from age 32 to 45 years. Note that the groups are not predetermined: model fit statistics will help to identify the most parsimonious division of participants into trajectory groups.

Once the trajectory groups have been identified, we will use standard regression techniques to identify:

1. Early life predictors of trajectory group membership, including intrauterine, sociodemographic, childhood cardiovascular risk, and familial risk factors (see 'Variables needed at which ages' section for more details).
2. Physical and psychosocial factors in adulthood that modify trajectories.
3. The association between particular trajectories and kidney health-related outcomes in midlife (i.e., at age 45y).

Variables needed at which ages:

Variables		Phase				
Topic	**Type**	**Birth**	**Childhood composite**	**32**	**38**	**45**
Measures of kidney function - ages 32 to 45y						
Serum creatinine	Continuous			✓	✓	✓
Serum cystatin C	Continuous			✓	✓	✓
Creatinine-derived eGFR (crGFR)	Continuous			✓	✓	✓
Cystatin C-derived eGFR (cyGFR)	Continuous			✓	✓	✓
Creatinine & cystatin C-derived eGFR (crcyGFR)	Continuous			✓	✓	✓
Risk factors for trajectory group membership - ages 0 to 15y						
Sex	Binary	✓				
Intrauterine risk factors (≥1 of maternal diabetes or pre-diabetes, or maternal hypertension)	Binary	✓				
Birth weight	Continuous	✓				
Socioeconomic status (SES)	Ordinal		✓			
Childhood body mass index (BMI)	Continuous		✓			
Childhood blood pressure	Continuous		✓			
Familial risk (≥1 of family history of chronic kidney disease, cardiovascular disease, or diabetes)	Binary			✓		
Trajectory modifiers - ages 32 to 45y						
Physical factors						
BMI	Continuous			✓	✓	✓
Blood pressure	Continuous			✓	✓	✓
Inflammation (composite measure combining high sensitivity c-reactive protein, fibrinogen, and white blood cell counts)	Continuous			✓	✓	✓
Glycated haemoglobin	Continuous			✓	✓	✓
Taking medications that affect kidney function	Binary			✓	✓	✓
Psychosocial factors						
Current smoking	Binary			✓	✓	✓
Average weekly alcohol consumption	Continuous			✓	✓	✓
SES	Ordinal			✓	✓	✓
Kidney-related health outcomes at age 45						
Proteinuria (high urine albumin-creatinine ratio)	Binary					✓
Low cyGFR relative to crGFR	Binary					✓
Blood pressure	Continuous					✓
Metabolic syndrome (≥3 of high waist circumference, high blood pressure, high total cholesterol, low HDL, high triglycerides, or high glycated haemoglobin)	Binary					✓
Self-reported health	Ordinal					✓
Life satisfaction	Ordinal					✓

Significance of the Study (for theory, research methods or clinical practice):

The proposed study will be the first to provide high quality general population information about longitudinal changes in kidney function from young adulthood to midlife. Strengths include measurement of eGFR by both creatinine and cystatin C at multiple time points, allowing individual kidney trajectories to be observed.

By identifying common healthy and unhealthy trajectories of change in kidney function across the first twenty years of adulthood, as well as the physical and psychosocial factors that modify those trajectories, the proposed study will help to inform the development and early implementation of public health policies and interventions aimed at protecting kidney health and preventing disease before it becomes manifest.

The proposed study will also make an important methodological contribution to the kidney health literature by showing how the use of different estimates of GFR (crGFR, cyGFR, crcyGFR) influences the observed patterns of age-related changes in kidney function, or the factors that might modify those trajectories.

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Data Security Agreement

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Please keep one copy for your records and return one to the PI Sponsor

Please initial your agreement: (customize as necessary)

✓	I am current on Human Subjects Training [CITI www.citigrogram.org] or equivalent.
✓	My project is covered by the Dunedin Study's ethics approval OR I have /will obtain ethical approval from my home institution (please specify).
✓	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: • encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) • password-protected • configured to lock-out after 15 minutes of inactivity AND • has an antivirus client installed as well as being patched regularly.
✓	I will not "sync" the data to a mobile device.
✓	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact my PI Sponsor or Study Director, Richie Poulton (richie.poulton@otago.ac.nz).
✓	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
✓	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. The Dunedin Study Members have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to your PI Sponsor or Richie Poulton for strategies for achieving compliance with data-sharing policies of journals.*
✓	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. The data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.

Signature: Hayley Guiney