Examining the breadth and burden of chronic kidney disease in community-dwelling older adults

Trinity College Dublin
Coláiste na Tríonóide, Baile Átha Cliath
The University of Dublin

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Dr. Mark Canney

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The Irish Longitudinal Study on Ageing
Mercer's Institute for Successful Ageing
St. James's Hospital
Dublin 8

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Dissemination of Thesis

Manuscripts accepted for publication

1. The relationship between kidney function and quality of life among community-dwelling adults varies by age and filtration marker
   Mark Canney, Eithne Sexton, Katy Tobin, Rose Anne Kenny, Mark A. Little and Conall M. O'Seaghdha
   Clinical Kidney Journal. 2017 DOI: 10.1093/ckj/sfx084 (published August 4 2017)

2. Graded association between kidney function and impaired orthostatic blood pressure stabilization in older adults
   Mark Canney, Matthew D.L. O'Connell, Donal J. Sexton, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha
   Journal of the American Heart Association. 2017 DOI: 10.1161/JAHA.117.005661 (published May 4 2017)

3. Kidney function estimated from cystatin C, but not creatinine, is related to objective tests of physical performance in community-dwelling older adults
   Mark Canney, Donal J. Sexton, Matthew D.L. O'Connell, Rose Anne Kenny, Mark A. Little and Conall M. O'Seaghdha
   The Journal of Gerontology: Medical Sciences. 2017 Oct 12;72(11):1554-1560
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4. Single agent antihypertensive therapy and orthostatic blood pressure behaviour in older adults using beat-to-beat measurements: The Irish Longitudinal Study on Ageing
   Mark Canney, Matthew D.L. O'Connell, Catriona M. Murphy, Neil O'Leary, Mark A. Little, Conall M. O'Seaghdha, Rose Anne Kenny
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1. Examining the clinical utility of cystatin C as a confirmatory test of chronic kidney disease across the age range in community-dwelling older adults
   Mark Canney, Donal J. Sexton, Neil O'Leary, Martin Healy, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha

2. Longitudinal association between kidney function and objective tests of physical performance in community-dwelling adults
   Mark Canney, Daniel Carey, Matthew D.L. O'Connell, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha

Abstracts

1. Kidney function is not associated with an accelerated decline in objective tests of physical performance in older adults
   Mark Canney, Daniel Carey, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha
   Poster presentation at the American Society of Nephrology annual scientific meeting (ASN Kidney Week), New Orleans, November 2017

2. Kidney function is not an independent predictor of falls among community-dwelling older adults
   Mark Canney, Daniel Carey, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha
   Poster presentation at the American Society of Nephrology annual scientific meeting (ASN Kidney Week), New Orleans, November 2017

3. Graded association between kidney function and postural blood pressure instability
   Mark Canney, Matthew D.L. O'Connell, Donal J. Sexton, Neil O'Leary, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha
   Oral presentation at the American Society of Nephrology annual scientific meeting (ASN Kidney Week), Chicago, November 2016

4. Kidney function and objective markers of frailty in community-dwelling older adults
   Mark Canney, Donal J. Sexton, Matthew D.L. O'Connell, Neil O'Leary, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha
   Poster presentation at the American Society of Nephrology annual scientific meeting (ASN Kidney Week), Chicago, November 2016

5. Distribution of cystatin C and creatinine with advancing age
   Mark Canney, Donal J. Sexton, Neil O'Leary, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha
   Poster presentation at the American Society of Nephrology annual scientific meeting (ASN Kidney Week), Chicago, November 2016

6. The relationship between estimated glomerular filtration rate and quality of life in community-dwelling older adults
   Mark Canney, Eithne Sexton, Rose Anne Kenny, Mark A. Little, Conall M. O'Seaghdha
   Poster presentation at the Irish Nephrology Society annual scientific meeting, Dublin, March 2016

7. The association between antihypertensive agents and postural blood pressure responses using beat-to-beat data: Results from The Irish Longitudinal Study on Ageing
   Mark Canney, Matthew D.L. O'Connell, Catriona M. Murphy, Neil O'Leary, Mark A. Little, Conall M. O'Seaghdha, Rose Anne Kenny
   Poster presentation at the American Society of Nephrology annual scientific meeting (ASN Kidney Week), San Diego, November 2015

Invited speaker

1. World Kidney Day – are Irish kidneys ok?
   Plenary session, Irish Nephrology Society annual scientific meeting, Dublin, March 2016

2. Exploring the impact of a diminished GFR in an older adult population
   13th European Peritoneal Dialysis (EuroPD) Meeting, Dublin, October 2017

Summary

Chronic kidney disease (CKD), characterised by reductions in glomerular filtration rate (GFR) and/or proteinuria, is associated with several adverse outcomes including cardiovascular disease, premature mortality and progression to end stage kidney disease. The general population of older adults has by far the highest prevalence of CKD, however the relative risks of these outcomes are lower in older compared to younger individuals. Whether reductions in GFR reflect kidney ageing or a true disease has been debated in the literature. There is a pressing need to better characterise the clinical phenotype of CKD in older people in order to understand the importance of detecting reduced levels of kidney function, beyond risk associations with hard outcomes. The overarching aim of this thesis was to investigate the burden of reduced GFR on the health and well-being of middle-aged and older individuals, by examining the association between GFR and more proximal or person-centred outcomes. The thesis used data from the first three waves of The Irish Longitudinal Study on Ageing (TILDA), a large cluster-sampled national cohort of community-dwelling adults aged 50 years and over.

Chapter 1 provides a brief overview of the thesis including specific aims and objectives, and how these objectives are addressed in later chapters. Chapter 2 describes the current classification of CKD and summarises the evidence that supports the use of GFR thresholds to define and stage the severity of CKD. The relative strengths and weaknesses of GFR estimating equations using the filtration markers creatinine and cystatin C are evaluated. Chapter 2 concludes by addressing the concerns of diagnosing CKD in older people, and provides a rationale for changing the outcome measure in this population from a hard outcome such as mortality, to outcomes that are more pertinent to an older person such as physical function and quality of life. Methodological aspects of the thesis are discussed in Chapter 3, including a detailed description of the sampling frame and the various methods of data collection employed in TILDA.

Chapters 4 to 8 represent the 5 empirical studies in this thesis. Chapter 4 examined the distribution of creatinine, cystatin C and GFR estimated from either biomarker as a function of age. The shape of the cystatin C distribution was markedly different to that of creatinine, exhibiting a sharp rise beyond the age of 65. This contributed to a higher predicted probability of confirming CKD using cystatin C at older age, as high as 80% at age 80. The weighted prevalence of CKD (GFR <60 mL/min per 1.73m^2) varied between 14% and 19% depending on the GFR estimating equation, and demonstrated a steep age gradient. Prevalence estimates using cystatin C exceeded 70% for participants aged ≥80. Plots of predicted GFR per year of age were generated for men and women, designed to be representative of the target population.

Chapter 5 investigated the cross-sectional relationships between GFR and three objective tests of physical performance – gait speed, timed-up-and-go (TUG) and grip strength. The use of cubic splines to model GFR illustrated the non-linear association between creatinine-based GFR and physical function outcomes, due to variable generation of creatinine from age-related declines in muscle mass. GFR estimated from cystatin C demonstrated more linear associations with all outcomes, a pattern which became more evident at older ages. These findings were explored further in Chapter 6, using mixed effects models to determine the longitudinal association between GFR and repeated measures of gait speed and TUG. Unadjusted models suggested that lower levels of GFR were associated with comparatively greater declines in both outcomes over time, indicated by a statistically significant interaction between time (wave) and GFR. This interaction did not retain statistical significance after adjusting for demographic variables.

Chapter 7 examined the association between GFR and quality of life using an instrument that encompasses both positive and negative aspects of life at older age. GFR estimated from cystatin C, but not from creatinine, predicted lower quality of life scores, especially in participants aged 50-64 years compared to older age categories. The multivariable association between GFR and quality of life, while statistically significant, was modest from a clinical perspective. Chapter 8 explored the relationship between GFR and postural blood pressure responses, captured by beat-to-beat blood pressure measurements during an active stand test. This novel association appeared to be graded across levels of GFR, and was robust to adjustment for cardiovascular risk factors and antihypertensive medications.

Chapter 9 provides a detailed summary of the findings from the 5 empirical studies and their clinical implications. The changing distribution of cystatin C with age, and the high pre-test probability of confirming CKD at older ages, question the utility of cystatin C as a confirmatory test of CKD across the age range. The plots of expected GFR per year of age may prove useful to clinicians when explaining the implications of a GFR result to an older person, by framing their GFR in the context of population-representative data. The findings suggest that GFR is a marker, rather than a driver, of declines in physical performance. However, a reduced GFR does not appear to substantially affect the quality of life of an older person. The depth and quality of objective health data in TILDA facilitates the exploration of novel research questions in older adults, such as the observed relationship between GFR and postural blood pressure behaviour. Future studies will interrogate the hypotheses generated in this thesis, and leverage the rich longitudinal data in TILDA to better characterise the phenotype of CKD in older people.

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List of abbreviations

ACR	Albumin to creatinine ratio
AIC	Akaike information criterion
BCPE	Box-Cox Power Exponential
BMI	Body mass index
BP	Blood pressure
BSV	Between subject variability
CAPI	Computer assisted personal interview
CASP-19	Control, autonomy, self-realisation and pleasure scale
CCB	Calcium channel blocker
CI	Confidence interval
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology collaboration
cm/s	Centimetres per second
CV	Cardiovascular
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DBP	Diastolic blood pressure
eGFR	Estimated glomerular filtration rate
ELSA	English Longitudinal Study on Ageing
ESKD	End stage kidney disease
GAMLSS	Generalised additive model for location shape and scale
GFR	Glomerular filtration rate
GFRcr	Glomerular filtration rate estimated from creatinine
GFRcys	Glomerular filtration rate estimated from cystatin C
HbA1c	Glycated haemoglobin
HDL	High density lipoprotein
Health ABC	Health, Aging and Body Composition study
HRS	Health and Retirement Survey
InCHIANTI	Invecchiare in Chianti, aging in the Chianti area
IQR	Interquartile range
IRR	Incidence rate ratio
KDIGO	Kidney Disease Improving Global Outcomes
K/DOQI	Kidney Disease Outcomes Quality Initiative
Kg	Kilograms
LDL	Low density lipoprotein
LR	Likelihood ratio
MDRD	Modification of Diet in Renal Disease

MMSE	Mini-mental state examination
MOCA	Montreal Cognitive Assessment
NHANES	National Health and Nutrition Examination Survey
OH	Orthostatic hypotension
OR	Odds ratio
PD	Parkinson Disease
QoL	Quality of life
RAAS	Renin angiotensin aldosterone system
REGARDS	REasons for Geographic and Racial Differences in Stroke
SART	Sustained Attention to Response Task
SBP	Systolic blood pressure
SCQ	Self-completion questionnaire
SD	Standard deviation
SHARE	Survey of Health, Ageing and Retirement in Europe
TILDA	The Irish Longitudinal Study on Ageing
TUG	Timed-up-and-go
WSV	Within subject variability

1 Introduction

1.1 Overview

Recent decades have witnessed dramatic changes in the age profile of the population. Not only is the world's population increasing, but life expectancy is improving all the time. One of the consequences of this demographic shift is that people are living longer with chronic health conditions. How, as a society, we are going to deal with this growing burden of chronic disease among the most vulnerable members of the population is a huge challenge. It is a challenge that has motivated the creation of prospective studies of ageing in representative populations around the world, collectively aiming to better understand the ageing experience in health and disease in order to inform future research priorities and public health policy.

Chronic kidney disease (CKD) is a good example of an age-related chronic health condition with important public health implications. The prevalence of CKD is high in the general population, affecting about one in ten adults (1), and demonstrates a steep age gradient (2). From middle age, the lifetime risk of developing CKD has been estimated at 40%, and may be even higher in the presence of another risk factor such as obesity or high blood pressure (3). Making a diagnosis of CKD is quite straight-forward in primary care, either from a blood or urine test. Circulating kidney biomarkers can be measured, and their results converted into an estimate of kidney function called glomerular filtration rate (GFR), standardised to body surface area. CKD is defined by (i) the presence of kidney damage e.g. protein in the urine (specifically albumin), blood in the urine (in the absence of a urological cause such as stones or malignancy), radiological evidence of a structural problem, or laboratory evidence of tubular dysfunction, and/or (ii) reduced kidney function, specifically a GFR below 60 mL/min per 1.73m^2 (4). The most abundant kidney biomarker is creatinine. Because creatinine is generated by muscle cells, it can be an unreliable biomarker in older people due to age-related changes in muscle mass. A low creatinine level, suggesting excellent kidney function, could also reflect a diminished muscle mass due to co-existent illness. This phenomenon manifests as a U-shaped relationship between creatinine level and mortality risk (5). Alternative biomarkers have been proposed in this population, circulating proteins whose generation is less influenced by nutritional status or muscle mass. One such biomarker, cystatin C, has gained favour as a potentially preferable marker of kidney function to creatinine, principally due to better discrimination of the risk of

kidney-related and cardiovascular outcomes (6). For this reason, cystatin C has entered clinical guidelines as a confirmatory test of CKD.

The risks associated with CKD, principally end stage kidney disease (ESKD) and premature death (7, 8), are not uniform across age (9, 10). The majority of older adults with CKD have GFR values which fall just below the diagnostic threshold, in the range of 45-59 mL/min per 1.73m^2. It is far more likely that an older individual with a GFR in this range will die from another cause before progressing to ESKD (11). This presents something of a quandary – the segment of the population with the highest prevalence of CKD is also the group with the lowest incidence of the end-point of the disease. Whether a reduction in GFR is an inevitable consequence of ageing or truly represents a distinct disease entity among older people is a theoretical argument that has been debated several times in the literature (12, 13). This debate is not particularly helpful on a practical level when discussing the clinical implications of a reduced GFR. An older person may ask what impact a reduced level of kidney function might have on their overall health and well-being, beyond associations with an outcome like mortality. They might want to know where their GFR lies compared to others of the same age in the general population, or if the presence of a reduced GFR will hamper their functional status or quality of life. These questions, which are perhaps more meaningful to the individual, have not been as extensively investigated as the risk relationships between GFR and hard outcomes.

This thesis uses data from The Irish Longitudinal Study on Ageing (TILDA), a cluster-sampled national cohort of Irish adults aged 50 years and over who are resident in the community. Several factors make TILDA an excellent setting in which to study the association between kidney function and outcomes that are pertinent to an older individual. The dataset is enriched for the population of interest i.e. middle-aged and older community-dwelling adults with mild to moderate reductions in GFR. TILDA was designed to comprehensively describe the health of its participants by employing complementary methods of data collection. The questionnaire captures potentially important confounding variables such as traditional cardiovascular risk factors, other chronic conditions and a comprehensive list of medications. The health assessment component of the study has generated exceptionally detailed objective information, including granular measures of cardiovascular and autonomic function, thus facilitating exploration of novel research questions. A powerful aspect of the study is the ability to follow the same cohort over time and investigate the longitudinal relationships between kidney function and outcomes in an older adult population.

1.2 Aims and objectives

The overarching aim of this thesis is to examine the burden of a reduced level of kidney function on the health and well-being of middle-aged and older community-dwelling adults. I hypothesise that lower levels of GFR will be associated with reduced quality of life, declines in physical function and a greater likelihood of orthostatic hypotension.

The specific objectives of this thesis are as follows:

1. Investigate the epidemiology of CKD in the TILDA cohort
    - Define the prevalence of CKD (GFR <60 mL/min per 1.73m^2) using different GFR estimating equations incorporating creatinine, cystatin C, or both
    - Generate expected values of GFR per year of age in men and women
2. Examine the clinical utility of cystatin C as a confirmatory test of CKD
    - Model the distributions of creatinine and cystatin C as functions of age
    - Estimate the predicted probability of confirming CKD with cystatin C across the age range
3. Perform an in-depth assessment of the association between reductions in GFR and the physical functioning of older adults
    - Compare cystatin C and creatinine as predictors of objective tests of physical performance, including grip strength, gait speed and timed-up-and-go (TUG)
    - Investigate whether baseline GFR predicts an accelerated decline in lower extremity physical performance
4. Examine the association between GFR and overall quality of life
5. Explore the relationship between GFR and postural blood pressure responses using novel beat-to-beat blood pressure measurements

1.3 Outline of thesis

Chapter 2 describes the structure and function of the kidney, and how that function is quantified at a population level with the use of GFR estimating equations. The current classification system for CKD is discussed, along with some of the controversial issues regarding the diagnosis of CKD in older individuals. Chapter 3 provides details of the study population, in particular the sampling frame employed in TILDA and the specific types of data collected in the various components of the study. This chapter also describes specific statistical approaches used in later chapters, over and above the level of detail provided in the methods section of the relevant chapters. Chapters 4 to 8 represent the five empirical studies in this thesis, which are tied to the study objectives described above.

Chapter 4 aims to address the first two study objectives. The primary aim of this study is to examine the clinical utility of cystatin C as a confirmatory test of CKD across the age range in the TILDA sample. We do this by robustly modelling the distribution of cystatin C as a function of age, and compare this distribution to that of creatinine. Secondly, we estimate the "pre-test" probability of confirming CKD using cystatin C in the subgroup of participants with creatinine-based GFR values between 45 and 59 mL/min per 1.73m^2. The secondary aims of Chapter 4 are to estimate the prevalence of CKD by gender and age category, and to generate population-representative plots of expected GFR per year of age for men and women.

Chapter 5 seeks to address the first part of the third study objective. This study describes the cross-sectional association between GFR and three objective tests of physical performance – grip strength, gait speed and TUG. We compare creatinine and cystatin C as predictors of each outcome by modelling cubic splines of GFR estimated from either filtration marker. We further explore if the relationship between GFR and gait speed varies by age. Building on these observations, Chapter 6 employs a mixed effects model to investigate the longitudinal association between GFR (estimated from cystatin C) and repeated measures of gait speed and TUG over the first three waves of TILDA. The parameter of interest in this study is the interaction between time (wave) and GFR, seeking to answer the question "Do reductions in GFR contribute to an accelerated decline in tests of physical performance?"

Chapter 7 addresses the fourth study objective by investigating the cross-sectional relationship between GFR and quality of life using a questionnaire that was specifically developed for community-dwelling adults in early old age. The CASP-19 instrument captures both positive and

negative aspects of quality of life across four domains: control, autonomy, self-realisation and pleasure. The study compares cystatin C and creatinine as predictors of quality of life, and further investigates the relationship between GFR and quality of life scores within age strata.

The final study objective is addressed in Chapter 8, which describes a novel association between GFR and postural blood pressure behaviour, the latter captured by beat-to-beat data during an active stand test at the Wave 1 health assessment. Impaired stabilisation of blood pressure after standing is highly prevalent at older ages (14), and is emerging as an important predictor of outcomes such as falls (15) and cognitive dysfunction (16). This is the first study to describe the relationship between postural blood pressure responses and the kidney using beat-to-beat blood pressure data.

The thesis concludes with a summary of the key findings in Chapter 9, along with their clinical and theoretical implications. This chapter discusses some of the methodological considerations from the five empirical studies, as well as future research directions.

1.4 Statement of authorship

Apart from the kidney biomarker data, the datasets used in this thesis had already been collected by members of the TILDA team. I was responsible for checking existing variables for accuracy and coding errors, and generating derived variables for the analyses. Creatinine and cystatin C were measured in a central laboratory in the Biochemistry Department of St. James's Hospital in Dublin. I was responsible for (i) checking the accuracy of the data for raw values of creatinine and cystatin C prior to merging the variables with the Wave 1 dataset, and (ii) developing the syntax to create the GFR variables from these filtration markers using published GFR estimating equations.

I conducted the literature review and generated the research questions, study aims and objectives. I planned and, unless otherwise stated, conducted the statistical analyses. Along with my supervisors Dr. Conall O'Seaghdha and Professor Mark Little, I interpreted the output from these analyses. Dr. Neil O'Leary (Chapters 4 and 8), Dr. Matthew O'Connell (Chapters 5 and 8), Dr. Daniel Carey (Chapter 6) and Dr. Katy Tobin (Chapter 7) provided statistical support where required. I wrote all of the manuscripts arising from this thesis. All co-authors on these manuscripts met criteria for authorship by contributing to data analysis and/or interpretation, revising manuscript drafts and approving the final versions of the manuscripts.

1.5 Funding

TILDA is supported by the Irish Government, the Atlantic Philanthropies and a charitable gift from Irish Life plc. I received a Research Training Fellowship for Healthcare Professionals (HPF/2014/540) from the Health Research Board of Ireland to conduct this research. I also received a research bursary from the Irish Nephrology Society in 2014. The funders had no role in the design or execution of the studies, analysis or interpretation of data, or in the preparation of this thesis.

2 Chronic Kidney Disease

2.1 Structure and function of the kidney

The functioning unit of the kidney is called the nephron. Each kidney has, on average, approximately 1 million nephrons, but the number in a given individual can range between 200,000 and 2.5 million (17). The nephron is a complex structure, consisting of a network of capillaries called the glomerulus and a long tubule made up of a number of highly specialised segments (Figure 2.1). The glomerulus is responsible for filtering fluid from the blood, and this fluid is then converted into urine as it passes along the tubule. The final portions of the renal tubules interconnect to form collecting ducts, which continuously drain urine into the renal pelvis. The urine is delivered through the ureters to the bladder, where it is stored until the need for micturition. The kidneys excrete approximately 1.5 litres of urine per day, an amount that can vary substantially depending on the needs of the body. However, because the kidneys receive 20% of the cardiac output, the glomeruli filter about 180 litres of blood each day. This ultrafiltrate undergoes substantial modifications as it passes through the tubule, including reabsorption of substances back into the bloodstream and secretion of other substances into the tubule. As such, the kidneys play a pivotal role in governing body homeostasis.

The glomerular capillaries are covered by epithelial cells, and the entire glomerulus is housed within a structure called Bowman's capsule. The interface between the blood and the kidney is the glomerular filtration barrier, consisting of fenestrated endothelial cells on the blood side, highly specialised epithelial cells called podocytes on the kidney side, and a basement membrane in between. The filtration barrier is permeable to water, solutes and very low molecular weight proteins, but under normal circumstances will not allow larger proteins or red blood cells to pass through. The glomerular filtration rate represents the average filtration rate in each nephron multiplied by the number of nephrons in both kidneys, and has long been considered the best marker of kidney function. GFR is standardised to 1.73m^2 body surface area, to account for differences in kidney size, which is proportional to body size. Young healthy men and women would be expected to have a GFR of 130 mL/min per 1.73m^2 and 120 mL/min per 1.73m^2 respectively (18). An individual's GFR is determined by the glomerular surface area available for filtration, the pressure promoting movement of water from the vascular space into the kidney (net ultrafiltration pressure), and the integrity (permeability) of the filtration barrier. Generally, conditions affecting either glomerular surface area, glomerular haemodynamics or

the integrity of the filtration barrier will manifest as a reduction in GFR and/or leakage of protein into the urine – the hallmarks of kidney disease (19).

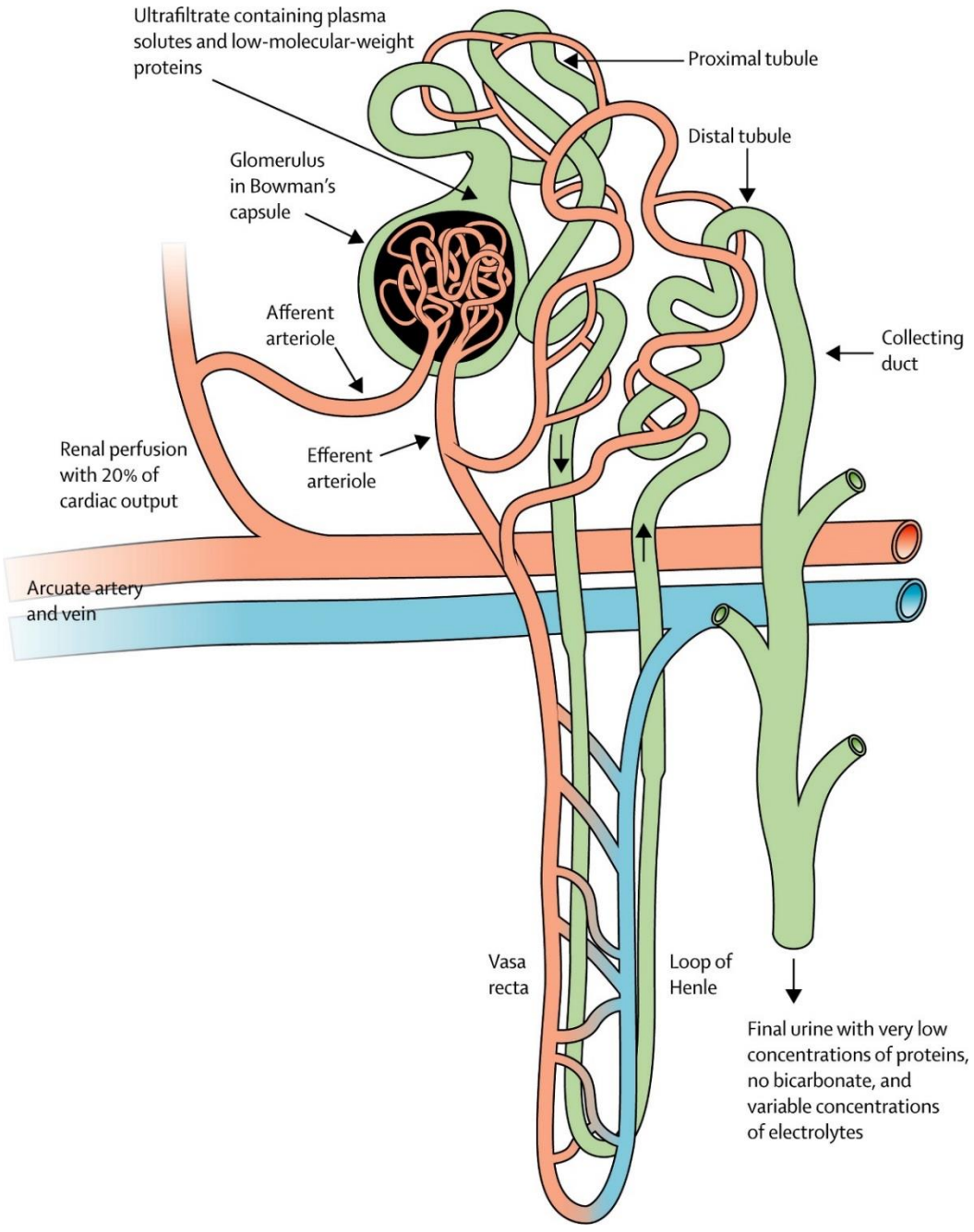


Figure 2.1: The structure of the nephron
Reproduced from Eckardt et al. (19)

2.2 Measurement of glomerular filtration rate

It is not possible to directly measure an individual's GFR. Instead, a filtration marker is measured to assess clearance of that marker from the circulation, as an indirect measure of GFR (20). The ideal filtration marker is freely filtered at the glomerulus and excreted unchanged in the urine, neither selectively reabsorbed nor secreted by the tubular epithelium as it travels through the nephron. Exogenous filtration markers fulfil that role and the gold standard measurement is clearance of inulin, a 5200-dalton fructose polymer. Other examples of exogenous filtration markers include iothalamate and iohexol. Regardless of the exogenous marker chosen, the procedure of measuring GFR is expensive, technically challenging, and onerous on the patient, necessitating a continuous intravenous infusion and simultaneous timed plasma and urine specimens. Measured GFR has therefore not entered routine clinical practice, outside of specific circumstances such as evaluation of a potential living kidney donor, and principally remains a research tool.

An alternative approach is to measure plasma or urinary clearance of an endogenous filtration marker. By far the most widely measured endogenous marker is creatinine, a 113-dalton amino acid derivative. Creatinine clearance can be calculated from a 24-hour urine collection in tandem with a single plasma sample. Although this approach removes the need for administration of an exogenous marker, timed urine collections are frequently prone to measurement error due to over- or under-collection. Furthermore, unlike exogenous markers, endogenous filtration markers are subject to a variety of factors other than glomerular filtration that influence their serum or urine concentration (non-GFR determinants). Creatinine is freely filtered at the glomerulus but is also secreted into the tubule by proximal tubular cells. Creatinine clearance will therefore systematically over-estimate GFR. Creatinine is a by-product of muscle catabolism, and so variation in creatinine levels between individuals can be high. In the acute setting, creatinine levels can rise following exercise or high dietary protein intake. In the chronic setting, variability in creatinine generation between individuals is principally due to differences in muscle mass. For example, an older female Caucasian would be expected to have far lower creatinine generation than a young male of African ancestry. These large reference ranges for creatinine, reflecting wide variations between normal individuals, mean that by the time an individual's creatinine exceeds the upper reference value, they might have already lost as much as half of their GFR (21).

2.3 Estimation of glomerular filtration rate

GFR estimating equations attempt to overcome the limitations of endogenous filtration markers by incorporating demographic variables such as age, sex, race and body weight to approximate their non-GFR determinants. The earliest estimating equation was developed by Cockcroft and Gault in 1973 using data from 249 men who had a creatinine clearance ranging between 30 and 130 mL/min (22). The equation estimated creatinine clearance from serum creatinine, age, sex and body weight. The Cockcroft-Gault formula has a number of limitations: women were not included in the derivation cohort (the formula arbitrarily reduces the result by 15% for females); it is an estimate of clearance rather than GFR, and is thus susceptible to bias from tubular secretion of creatinine (resulting in over-estimation of GFR); by including body weight, it over-estimates the clearance of creatinine in the setting of obesity or oedema; it is not standardised to body surface area.

The first estimating equation which used measured GFR as the reference was published in 1999 from the Modification of Diet in Renal Disease (MDRD) study (21). The MDRD study was a randomised clinical trial which set out to investigate the effects of dietary protein restriction and tight blood pressure control on slowing the progression of kidney disease in a study population with clinical evidence of kidney disease (23). While the trial is recognised as one of the first studies to investigate blood pressure targets in CKD, the study is perhaps better known for generating the MDRD equation to calculate estimated GFR (eGFR). A total of 1628 trial participants had their GFR measured using renal clearance of ^{125}I-iothalamate, normalised to 1.73m^2 body surface area. This enabled the investigators to derive a formula to predict GFR from serum creatinine and several other variables including age, sex, race and laboratory measures such as serum albumin. The MDRD equation was found to be a more accurate estimate of GFR than either creatinine clearance or the Cockcroft-Gault formula (21).

The original MDRD equation had a number of limitations owing to the entry criteria for the trial. Exclusion criteria included type 1 diabetes or insulin-requiring type 2 diabetes, age over 70 years, and the presence of serious comorbid conditions. The generalisability of the MDRD equation was further limited to those with an underlying diagnosis of kidney disease. It therefore could not be extrapolated to general population cohorts because it lacked precision at higher GFR values. Another factor that hampered widespread clinical use of the equation was that the creatinine assay needed to be calibrated to the laboratory that developed the equation. This issue was addressed in 2006 with the development of an updated MDRD equation which

incorporated a standardised creatinine assay (24). The updated formula was also more parsimonious than the original, including just four variables: creatinine, age, sex and race.

An alternative GFR estimating equation was published in 2009 by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (25). The CKD-EPI equation was developed in a more diverse population than the MDRD equation, and included individuals with and without evidence of kidney disease. The equation was developed and internally validated in 8254 participants from 10 studies, and subsequently externally validated in 3896 participants from 16 other studies. The CKD-EPI equation was shown to be as accurate as the four-variable MDRD equation at lower levels of kidney function (GFR < 60 mL/min per $1.73m^2$), and to demonstrate less bias than the MDRD formula at higher levels of kidney function (GFR > 60 mL/min per $1.73m^2$). An important limitation of the CKD-EPI derivation study was the relatively small sample size for adults over 70 years of age.

2.4 Clinical application of GFR estimating equations

Around the same time as GFR estimating equations were being developed and refined, there was a move by the Kidney Disease Outcomes Quality Initiative (K/DOQI) to standardise both the definition of kidney disease and the laboratory markers used for clinical assessment of kidney function. Efforts to better understand and treat kidney disease in the research and clinical arenas had historically been hampered by a lack of consensus on the terminology of what constituted kidney disease (26). Whereas kidney failure requiring renal replacement therapy in the form of dialysis or a kidney transplant was an unambiguous diagnosis of severe kidney disease, many more patients had less severe forms of kidney disease which were not felt to be clinically important until the need for dialysis or transplantation arose (19). As a consequence, kidney disease often went undiagnosed until its late and sometimes irreversible stages.

In 2002 a series of clinical practice guidelines on CKD were published by K/DOQI (27) and were subsequently disseminated in a landmark publication by Levey *et al.* (4). This represented a paradigm shift in the approach to diagnosis and classification of kidney disease. The new paradigm recognised that kidney damage could be detected at an early stage, even before overt reductions in kidney function, which could facilitate early diagnosis and treatment to prevent disease progression (Figure 2.2). It also highlighted that complications could arise at any point along the spectrum of kidney disease severity. The K/DOQI working group put forward a novel

framework for the diagnosis and classification of CKD based on two principal outcomes: progressive loss of kidney function and the development of complications, namely cardiovascular disease. Importantly, the framework facilitated a diagnosis of CKD in all individuals irrespective of the underlying cause.

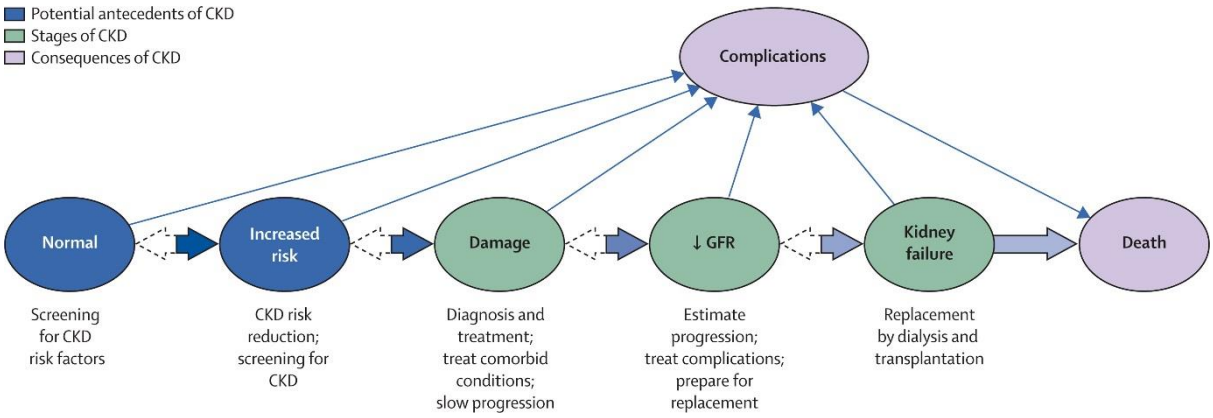


Figure 2.2: Conceptual framework of chronic kidney disease
Reproduced from Levey *et al*. (28)

The working group defined CKD as "either kidney damage or decreased kidney function (decreased GFR) for 3 or more months." Markers of kidney damage included protein in the urine (specifically albuminuria), blood in the urine (haematuria), radiological evidence of renal structural abnormalities, and electrolyte or other abnormalities indicative of renal tubular dysfunction. They proposed that kidney function be determined using GFR estimating equations rather than creatinine alone. A staging system was developed based on categories of GFR. Stages 1 and 2 included individuals with markers of kidney damage but who had relatively preserved function as determined by a GFR greater than 60 mL/min per 1.73m^2. Even in the absence of proteinuria or other markers of kidney damage, a diagnosis of CKD could be made based on having a GFR below a threshold value of 60mL/min per 1.73m^2. This staging system has since been revised by Kidney Disease Improving Global Outcomes (KDIGO) to provide a more granular risk stratification based on the cross-classification of GFR stage and degree of albuminuria (Figure 2.3).

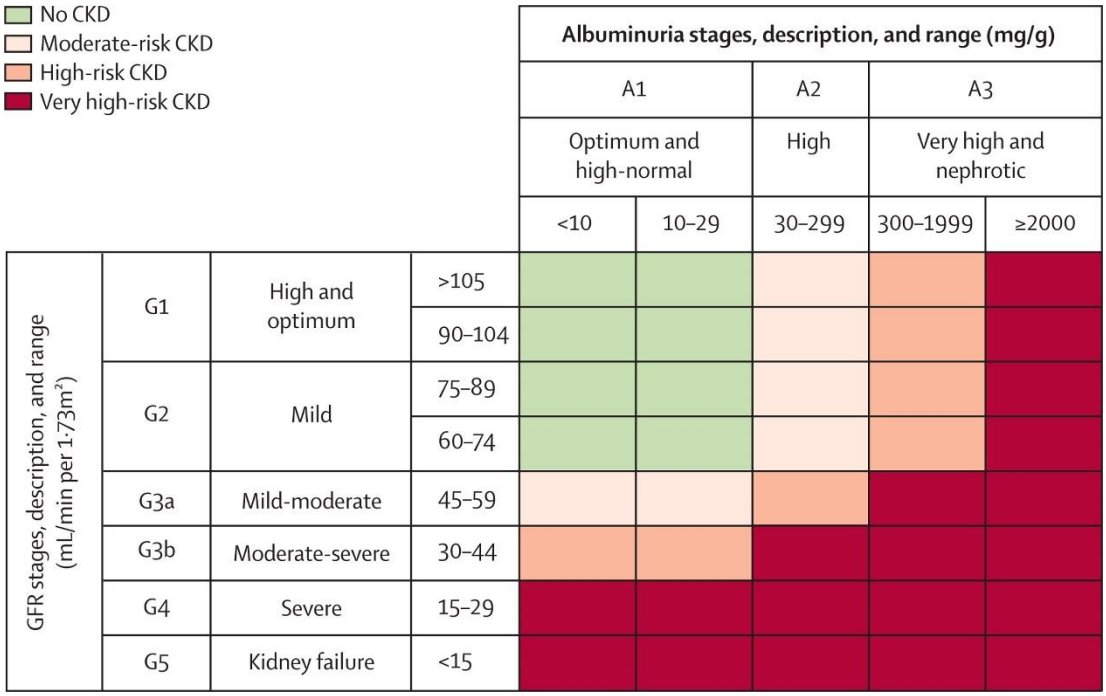


Figure 2.3: Prognosis according to level of glomerular filtration rate and degree of albuminuria
Reproduced from Levey *et al*. (28)

This conceptual change to the diagnosis and staging of CKD has facilitated a global research effort to better understand and combat kidney disease. A number of key concepts have emerged from this work, all of which have highlighted CKD as an important public health challenge.

2.5 The public health challenge of chronic kidney disease

2.5.1 High prevalence in the general population

International comparisons estimate the prevalence of CKD across all ages to be over 10% (1). Prevalence of CKD in the United States rose from 10% in the period 1988-1994 to 13.1% in the period 1999-2004 based on a cross-sectional analysis of National Health and Nutrition Examination Surveys (NHANES) data (2). The increase was thought to be at least partly explained by increases in rates of risk factors such as diabetes, hypertension and advancing age. The prevalence of CKD exhibits a steep age gradient, with prevalence estimates in the general population exceeding 30% among women over 70 years of age (29). Among general population cohorts in Europe, the prevalence of CKD varies widely. For example, the prevalence of any stage of CKD in individuals aged 20-74 years varied between 3.3% in Norway and 17.3% in Germany, despite the use of a single definition for CKD (30). It should be noted that considerable heterogeneity exists among studies reporting the prevalence of CKD, for example varying sample sizes and response rates, use or non-use of a sampling frame to define the study population, and lack of standardisation in the assays used to measure creatinine (31). Despite these differences in study methodology, it is likely that there are population-specific factors contributing to these varying prevalence estimates. Therefore, it is important to define the prevalence of CKD in well-characterised, nationally representative samples.

2.5.2 Risk of adverse clinical outcomes

The fundamental concept behind the use of GFR to diagnose and stage CKD is that it is built on the risk of hard outcomes. CKD associates strongly with premature mortality, in particular from cardiovascular disease. A seminal paper by Go *et al*. in 2004 illustrated the graded association between categories of GFR and the risks of cardiovascular and all-cause mortality and hospitalisation (32). The risk of death increased as GFR fell below 60 mL/min per 1.73m^2 and rose sharply below a GFR of 45 mL/min per 1.73m^2. A number of studies from the Chronic Kidney Disease Prognosis Consortium have provided evidence to support the threshold GFR value of 60 mL/min per 1.73m^2 to define those at increased risk. A collaborative meta-analysis of 21 general population cohort studies demonstrated that both GFR and proteinuria (either dipstick proteinuria or an elevated albumin to creatinine ratio [ACR]) were independently associated with higher cardiovascular and all-cause mortality (7). The risk of mortality increased steadily below a GFR of 75 mL/min per 1.73m^2 and became statistically significant at approximately 60

mL/min per 1.73m^2 (Figure 2.4). Similarly, the presence of albuminuria was linearly related to mortality risk at ACR values ≥10mg/g. A second meta-analysis incorporating both general population (N=845,125) and high risk (of kidney disease, N=173,892) cohorts demonstrated an exponential increase in the risk of ESKD below a GFR of 60 mL/min per 1.73m^2, which was independent of traditional cardiovascular risk factors (8). Subsequent meta-analyses of data from over 2 million participants have demonstrated that while the risks of cardiovascular mortality, all-cause mortality and ESKD do vary somewhat by age and gender, these risks are consistently higher with decreasing GFR at all ages and in both sexes (9, 33).

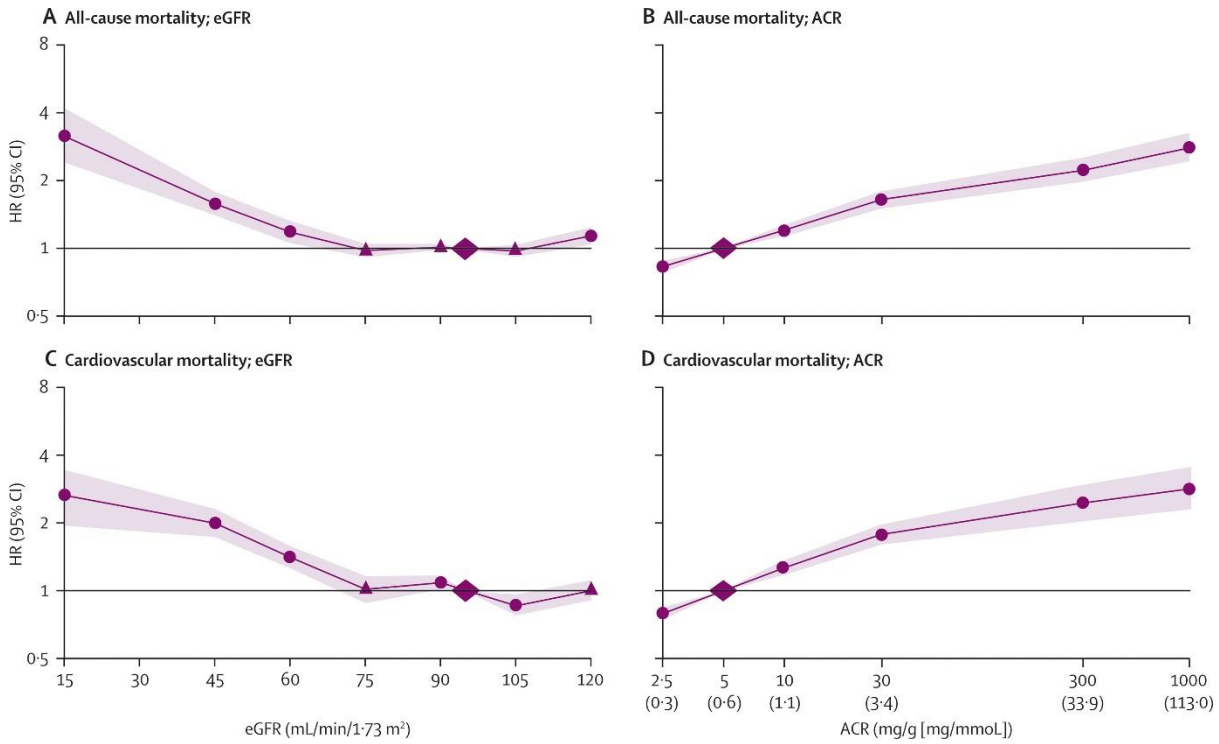


Figure 2.4: Risk of mortality associated with lower estimated glomerular filtration rate and higher albumin to creatinine ratio
Reproduced from Matsushita *et al*. (7)

2.5.3 Burden and complications

CKD is one of several non-communicable diseases whose burden is anticipated to increase as a consequence of population growth, longer life expectancy and increasing rates of risk factors such as hypertension, diabetes and obesity. The Global Burden of Disease study quantifies this burden in terms of mortality and morbidity, the latter captured as disability adjusted life years (DALY) (34). Between 1990 and 2013, the age-standardised death rate due to CKD increased from 11.6 per 100,000 people to 15.8 per 100,000 people (35). This increase was driven by a 107% increase in the death rate from CKD due to diabetes. Over the same time period, global DALYs due to CKD have increased from 19 million to 33 million, in keeping with growing numbers of the population living with chronic diseases (35). Consistent with the previously described association between GFR and cardiovascular disease endpoints, more than half of global deaths attributed to reduced GFR in 2013 were cardiovascular deaths, strengthening the case for early detection and awareness of CKD (36).

Reductions in GFR and the presence of albuminuria are cardinal risk factors for acute kidney injury (37-39), which is itself associated with increased risk of morbidity and mortality (40), particularly from cardiovascular disease (41). The development of acute kidney injury may contribute to de-novo CKD, progression of underlying CKD and an increased risk of ESKD (42). The presence of CKD is also a complicating factor for hospital-based investigations such as the administration of contrast agents, drug dosing and potential drug-drug interactions. Finally, CKD places enormous economic strain on health care resources. Based on United States Renal Data System data, 41 billion dollars were spent treating CKD and its complications in 2010 (43).

2.6 Filtration markers as predictors of risk

2.6.1 Comparison of GFR estimating equations

A meta-analysis of studies including 1.1 million adults from 45 cohorts (25 general population, 7 high-risk cardiovascular and 13 CKD cohorts) compared the MDRD and CKD-EPI equations with respect to all-cause mortality, cardiovascular mortality and ESKD (44). In general population cohorts, the mean GFR was higher using the CKD-EPI compared to the MDRD equation (88.9 versus 81.5 mL/min per 1.73m^2), resulting in a lower prevalence of CKD using CKD-EPI (6.3% versus 8.7%). Using the CKD-EPI formula, 25% of individuals were reclassified to a different GFR category (Figure 2.5). The majority (24.4%) were reclassified to a higher GFR category. These people were more likely to be younger, female and non-black with fewer co-morbidities, and they had a lower risk of all outcomes. Overall, the results suggested that the CKD-EPI equation performed better than MDRD in terms of risk stratification across heterogeneous populations.

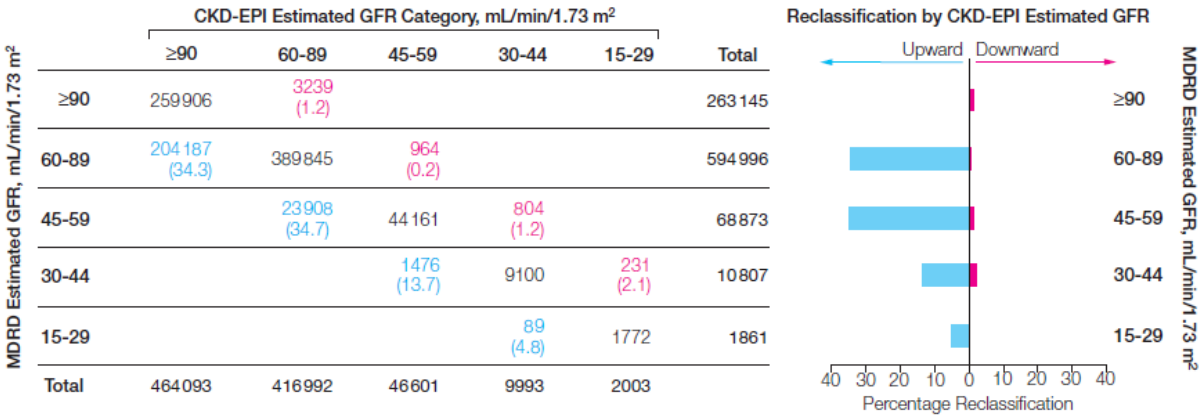


Figure 2.5: Reclassification to higher (blue) or lower (pink) GFR category using the CKD-EPI equation
Reproduced from Matsushita *et al*. (44)

When compared to measured GFR, the CKD-EPI equation has been shown to have better specificity than MDRD (less likely to classify an individual as having CKD when measured GFR >60 mL/min per 1.73m^2) (45). On the other hand, the MDRD formula exhibits greater accuracy at lower GFR i.e. in established CKD (46). Although the total prevalence of CKD across all age groups is lower using the CKD-EPI formula, the prevalence of CKD amongst older adults is increased as compared to MDRD (47). The key advantage of both estimating equations is the ease with which they can be used for reporting of GFR, given that only basic demographic data are required by the reporting laboratory. Nevertheless, despite refinement of the equations over time, they are still subject to the limitations of creatinine as a filtration marker. The precision of GFR estimating equations remains limited at values of GFR above 60 mL/min per 1.73m^2, suggesting that age, sex and race do not account for all of the variation in non-GFR determinants of creatinine. A number of alternative biomarkers have been examined, in the hope of improving precision of GFR estimating equations from endogenous filtration markers. The biomarker that has gained most traction as an alternative to creatinine is cystatin C.

2.6.2 Cystatin C as a marker of filtration

Cystatin C is a cysteine proteinase inhibitor encoded by the CST3 gene, a so-called "house-keeping" gene. It is thought to be produced by all nucleated cells in the body at a constant rate. Cystatin C is a small protein (13kDa) and therefore freely filtered by the kidney at the level of the glomerulus, before being reabsorbed by the proximal renal tubule. These properties of cystatin C were expected to overcome the limitations of creatinine as a marker of kidney function, specifically the bias associated with confounding by muscle mass. The earliest studies comparing cystatin C and creatinine as predictors of measured GFR supported this hypothesis. The correlation between the inverse of cystatin C and GFR was stronger than the correlation between the inverse of creatinine and GFR (Figure 2.6) (48). A subsequent meta-analysis of GFR measurement studies, incorporating 54 datasets, provided convincing evidence that cystatin C was a superior marker of GFR than creatinine (49).

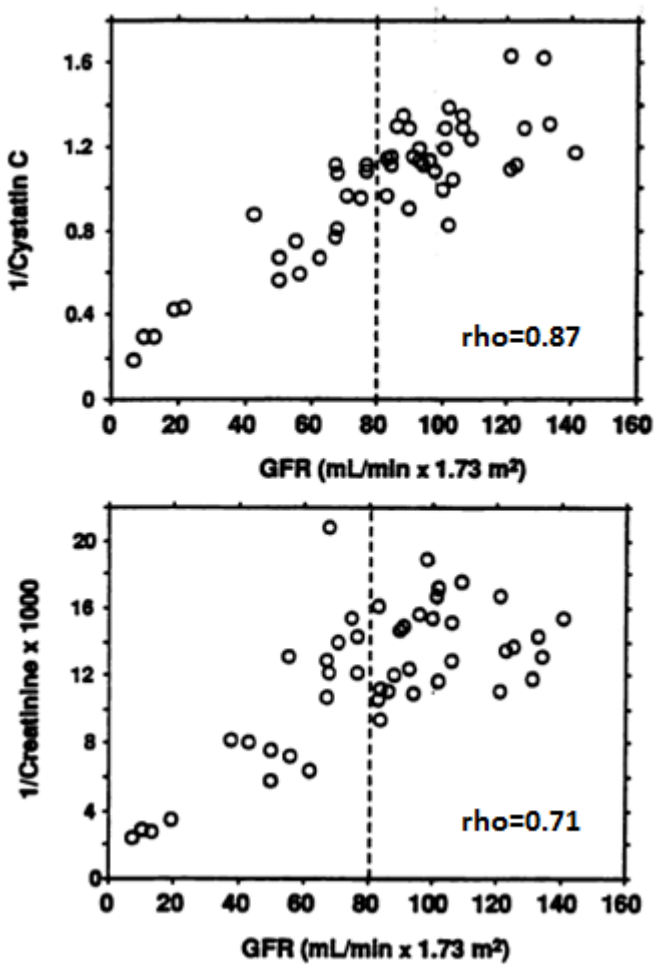


Figure 2.6: Correlation between filtration markers and measured glomerular filtration rate
Adapted from Kyhse-Anderson *et al* (48)

With the advent of GFR estimating equations, cystatin C (without adjustments for demographic variables) compared favourably to GFR estimated from creatinine (GFRcr) as a predictor of measured GFR (50, 51). More recently, equations have been developed to estimate GFR from cystatin C (GFRcys), using similar methodologies to GFR estimating equations that use creatinine. Whereas adjusting for non-GFR determinants of creatinine generation (i.e. age, gender and race) greatly improves the correlation between GFRcr and measured GFR, the same adjustments for cystatin C only minimally improve its performance as a predictor of measured GFR (52). The net result is that using GFRcys rather than GFRcr produces little or no additional gain, if accurate estimation of GFR is the primary objective (53). For this reason, as well as higher cost and limited availability of assays, cystatin C struggled to gain traction as a viable long-term alternative to creatinine as an endogenous marker of kidney function (54). The landscape changed, however, when cystatin C was investigated, and compared to creatinine, as a marker of risk of kidney-related and cardiovascular outcomes.

2.6.3 Cystatin C as a marker of risk

Early studies of cystatin C showed it to be a stronger predictor of all-cause mortality and cardiovascular mortality than either creatinine or GFRcr, while risks of ESKD were similar with all three biomarkers (55). Data from the Cardiovascular Health Study demonstrated cystatin C to be a much stronger predictor of incident heart failure (56) and mortality among those with existing heart failure (57). Further studies from this cohort of community-dwelling elderly adults showed cystatin C to be a stronger predictor of all-cause death and cardiovascular events than either creatinine alone or GFRcr (5). The association between cystatin C and death was linear as opposed to the U-shaped association observed with creatinine (Figure 2.7), the latter reflecting poorer outcomes and over-estimation of GFR among individuals with low muscle mass. In elderly participants without CKD at baseline (GFRcr ≥60 mL/min per 1.73m^2), cystatin C associated strongly with cardiovascular and all-cause mortality, incident stroke and cardiac events. The authors coined the term "preclinical kidney disease" to describe this higher risk profile identified by cystatin C, but not detected by either creatinine or GFRcr (6).

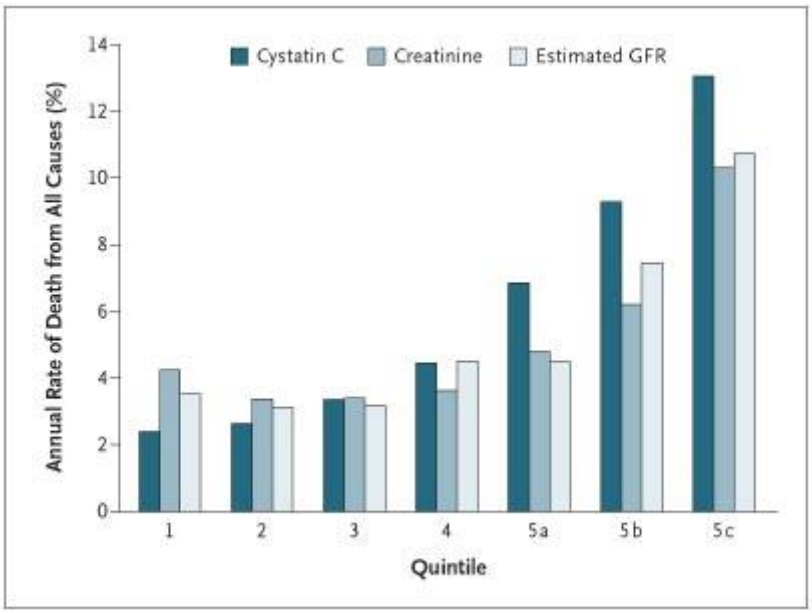


Figure 2.7: All-cause mortality according to quintiles of creatinine, glomerular filtration rate estimated from creatinine, and cystatin C
Reproduced from Shlipak *et al*. (5)

More recent studies have availed of GFR estimating equations using cystatin C (52, 53) to examine the association between GFRcys and clinical outcomes. Peralta *et al* demonstrated that in adults diagnosed with CKD as defined by GFRcr <60 mL/min per 1.73m^2, the risks of ESKD and mortality were limited to those individuals who also had a GFRcys <60 mL/min per 1.73m^2 (58). In fact, study participants who had CKD based on creatinine alone had a similar risk profile to those without any evidence of CKD. Individuals diagnosed with CKD based on both creatinine and cystatin C were older and had higher rates of hypertension and diabetes mellitus. This group had a very high risk of developing ESKD (hazard ratio [95% confidence interval] 23.82 [12.68, 44.76]), almost ten-fold the risk observed in participants with decreased GFRcr alone. As the risk of adverse outcome was restricted to participants with GFRcys <60 mL/min per 1.73m^2, the authors suggested that cystatin C could have clinical utility as a confirmatory test of CKD, with the aim of distinguishing between a high risk and a low risk of these outcomes.

The role of cystatin C as a determinant of risk was further illustrated by Shlipak *et al* in a meta-analysis of 11 general population studies and 5 CKD cohort studies with over 90,000 participants (59). This study sought to investigate the prognostic value of reclassifying study participants from their GFRcr stage to a higher or lower GFR category based on their GFRcys value. Compared to GFRcr, GFRcys demonstrated stronger and more linear risk relationships with cardiovascular and all-cause mortality. Reclassification of participants to a higher GFR using cystatin C was associated with a substantially reduced risk of cardiovascular mortality, all-cause mortality and ESKD. Similarly, reclassification to a lower GFR was associated with a higher risk of all three outcomes (Figure 2.8). The potential for cystatin C to refine an individual's risk profile associated with their kidney disease led to cystatin C being incorporated into KDIGO clinical practice guidelines, primarily as a confirmatory test in people with a GFRcr of 45-59mL/min per 1.73m^2 (Stage 3a CKD) but without other evidence of kidney damage (60).

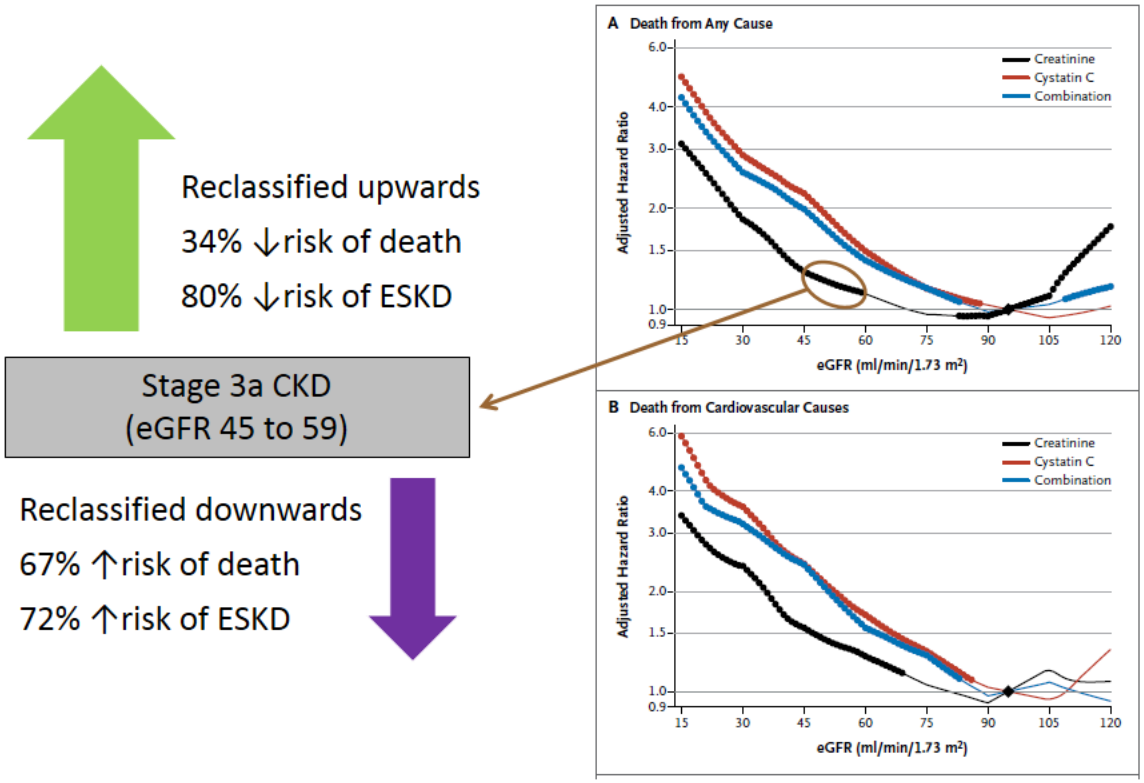


Figure 2.8: Reclassification of Stage 3a chronic kidney disease with cystatin C
Adapted from Shlipak *et al*. (59)

2.6.4 Potential limitations of cystatin C

Despite its advantages over creatinine, cystatin C is not a perfect filtration marker and can be biased in certain circumstances, for example states of high cell turnover such as hyperthyroidism (61, 62) and with the use of corticosteroids (63). A number of studies have identified potential non-GFR determinants of cystatin C, which may be contributing to the risk relationships between cystatin C and cardiovascular outcomes. Mathisen *et al*. reported the cross-sectional associations between traditional cardiovascular risk factors and GFR estimated from creatinine or cystatin C in a Norwegian general population cohort (N=1627 participants aged 50 to 62 years) without known cardiovascular disease, diabetes mellitus or kidney disease (64). The key strength of this study was the availability of measured GFR using iohexol clearance. The authors found that, after adjusting for measured GFR, GFRcr was only associated with current smoking. The direction of association was positive i.e. smokers had, on average, higher values of GFRcr (lower values of creatinine). Conversely, GFRcys was inversely associated with several cardiovascular risk factors including body mass index, low density lipoprotein cholesterol and triglyceride levels.

These observations were consistent with previous studies which had identified GFR-independent positive associations between cystatin C and smoking (65), and between cystatin C and body mass index (66), suggesting that estimates of association between cystatin C and cardiovascular endpoints could be confounded by these non-GFR determinants of cystatin C. Indeed, long-term outcome data from the MDRD study demonstrated cystatin C to be a stronger predictor of cardiovascular mortality than either all-cause mortality or ESKD, after adjusting for measured GFR and cardiovascular risk factors (67). It is possible that the residual associations between GFRcys and cardiovascular risk, after controlling for measured GFR in the same model, could be explained by multicollinearity or residual confounding of measured GFR due to measurement error.

These potential issues were investigated by Rule *et al*. in a study of 1093 participants from two cohorts who had complete data available for measured GFR, GFR estimated from creatinine or cystatin C, and CKD risk factors (68). The authors compared two analytical approaches. Firstly, they examined the age- and sex-adjusted associations between each risk factor and estimated GFR in a linear regression model with measured GFR included as a covariate. Similar to previous studies, both GFRcr and GFRcys had strong residual associations with several risk factors such as hypertension, body mass index and dyslipidaemia. In the second approach, the authors investigated how much the associations between estimated GFR and each risk factor deviated from the associations between measured GFR and the same risk factors. While GFRcr had associations with CKD risk factors that were similar in direction and magnitude to those with measured GFR, GFRcys had much stronger associations with these risk factors after accounting for measured GFR. In a subset of participants with repeated kidney function measures, measured GFR had comparable within-subject variability to GFRcr, and lower variability compared to GFRcys, arguing against measurement error as a contributing factor to the residual associations between CKD risk factors and GFRcys.

A second study from the Norwegian cohort (69) examined inflammatory markers as non-GFR determinants of GFRcr or GFRcys, using the approach advocated by Rule *et al* (68). After accounting for the measured GFR association with these markers, C-reactive protein and soluble tumour necrosis factor receptor 2 were strongly associated with both GFRcr and GFRcys, but in opposite directions. These discordant findings suggested that both estimates of GFR are biased by non-traditional vascular risk factors. The question remains whether the improved discrimination of cardiovascular and mortality risk by cystatin C relates to its role as a marker of

glomerular filtration, or to its GFR-independent correlation with traditional and non-traditional cardiovascular risk factors (Table 2.1).

Table 2.1: Comparison of measurement and prognostic studies of GFR

	Measurement studies	Prognosis studies
Outcome	Glomerular filtration rate	Risk of death or ESKD
Study population	Volunteers, convenience samples, trial participants	Heterogeneous cohorts: general population, CKD, high vascular risk
Sample size	< 10,000	> 2 million
Biomarker performance	Cystatin C > creatinine Cystatin C ~ GFRcr GFRcys ~ GFRcr	Cystatin C > creatinine Cystatin C > GFRcr GFRcys > GFRcr
Uncertainty	External validity	Contribution of non-GFR determinants to risk

GFRcr, glomerular filtration rate estimated from creatinine; GFRcys, glomerular filtration rate estimated from cystatin C; ESKD, end stage kidney disease

2.7 Chronic kidney disease in older adults

While the use of GFR and/or albuminuria to diagnose and stage the severity of CKD has harmonised the terminology of kidney disease and facilitated a standardised approach to defining the disease, the classification system has come under scrutiny due to the high prevalence of CKD among older adults. Several studies have observed a steep age gradient in the prevalence of CKD stages 3 to 5 (GFR <60 mL/min per 1.73m^2), even in apparently healthy adults without manifest cardiovascular disease (Figure 2.9) (29). Table 2.2 reports the prevalence of CKD stages 3 to 5 among European general population cohorts aged ≥65 years, extrapolating data from the European CKD Burden Consortium (30). Although estimates vary between these studies, half of studies reported CKD prevalence of over 40% among the oldest old (≥75 years). The clinical importance of detecting a reduced level of kidney function in older individuals has been vigorously debated in the literature.

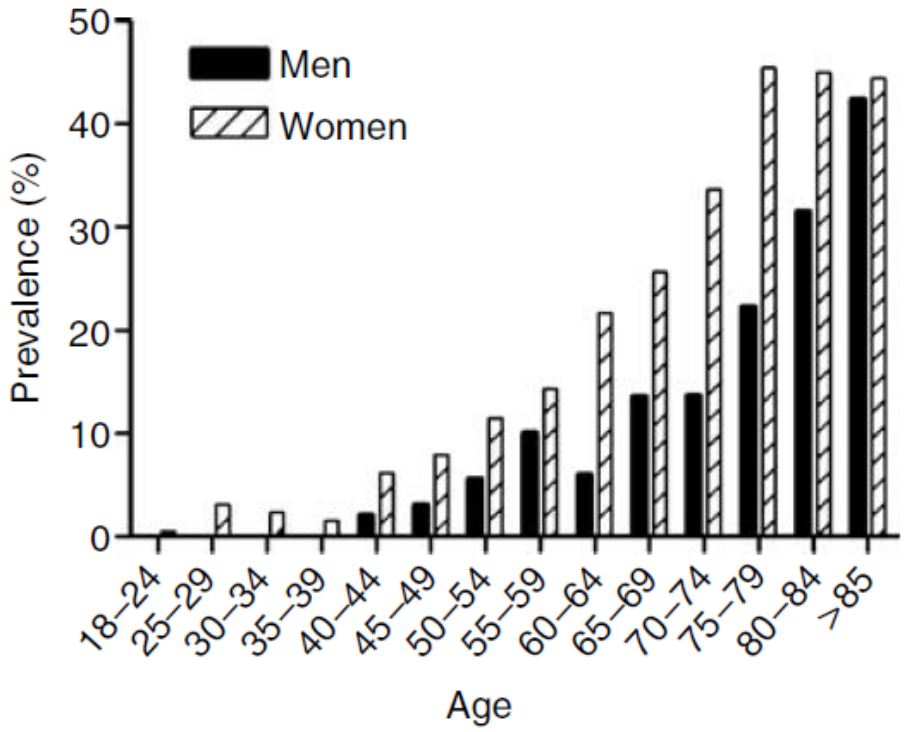


Figure 2.9: Prevalence of CKD stages 3 to 5 by age category in apparently healthy adults
Reproduced from Wetzels *et al*. (29)

Table 2.2: Prevalence of CKD Stage 3 to 5 in general population cohorts aged ≥65 years

Study†	Country	Sampling frame	N	Prevalence Age 65-74	Prevalence Age 75-84
SHIP	Germany	Population register	984	25.5 (22.2-28.8)	44.8 (39.1-50.4)
ActiFE	Germany	Population register	1506	20.8 (17.9-23.6)	43.2 (39.1-47.4)
EPIRCE	Spain	Census data	578	20.0 (16.1-23.9)	42.5 (34.7-50.3)
SLAN	Ireland	Postal residential lists	386	19.1 (14.6-23.5)	56.6 (46.0-67.3)
PIVUS	Sweden	Population register	1016	17.9 (15.6-20.3)	
FINRISK	Finland	Population register	501	11.0 (8.2-13.7)	
INCIPE	Italy	GP lists	1301	10.1 (8.1-12.1)	29.0 (24.6-33.5)
HUNT	Norway	Census data	15658	8.7 (8.2-9.3)	21.8 (20.7-22.9)
Three City	France	Electoral rolls	8705	7.4 (6.7-8.1)	20.7 (18.2-23.2)
LifeLines	Netherlands	GP lists	6983	6.5 (5.9-7.1)	14.1 (10.5-17.6)
MATISS	Italy	Electoral rolls	626	4.7 (2.9-6.5)	
Bus Santé	Switzerland	Population register	1435	4.1 (2.9-6.5)	18.6 (17.2-19.9)
MRC	UK	GP lists	13179		64.4 (63.5-65.3)

†All reported studies used creatinine assays traceable to isotope dilution mass spectroscopy except the MRC study

GP, general practitioner; UK, United Kingdom

Study acronyms: SHIP, Study of Health in Pomeranzia; ActiFE, Activity and Function in the Elderly in Ulm study; EPIRCE, Estudio Epidemiológico de la Insuficiencia Renal en España; SLAN, Survey of Lifestyle, Attitudes and Nutrition in Ireland; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors Study; FINRISK, Finland Cardiovascular Risk Study; INCIPE, Initiative on Nephropathy, of relevance to public health, which is Chronic, possibly in its Initial stages, and carries a Potential risk of major clinical Endpoints; HUNT, Nord-Trøndelag Health Study; LifeLines, LifeLines Cohort and Study Biobank; MATISS, Malattie cardiovascolari ATerosclerotiche Istituto Superiore di Sanita; MRC, Medical Research Council trial of assessment and management of older people in the community

2.7.1 Criticisms of the CKD classification system

A number of arguments have been put forward to support a refinement of the CKD classification system and, specifically, the adoption of a classification that can be calibrated for age (13). Underpinning these arguments is the belief that the current CKD framework, which diagnoses CKD irrespective of age and cause of disease, inappropriately captures a substantial proportion of older adults in whom a diminished GFR reflects "normal" kidney ageing rather than a disease process per se (70). The concept that GFR declines with age was postulated several decades ago in measurement studies of volunteers (71, 72). Contemporary population studies of apparently healthy adults have demonstrated a gradual fall in GFR with advancing age (29), supporting this notion. This age-related fall in GFR eventually dips below the threshold of 60 mL/min per 1.73m^2, resulting in a steep age gradient in the prevalence of undifferentiated CKD in the general population (29, 73, 74).

This high prevalence of CKD in the older adult population is not accompanied by a similarly high risk of kidney-related outcomes. For example, in one general population cohort, approximately 1% of all individuals with CKD (GFR less than 60 mL/min per 1.73m^2) developed ESKD within 8 years (75). The risk of ESKD was even lower after the age of 70 and among those with a GFR of between 45 and 59 mL/min per 1.73m^2 at initial screening, the range of GFR the majority of older people find themselves in. Conversely, the risk of death from cardiovascular disease was higher with diminishing GFR, even in the 45-59 mL/min per 1.73m^2 range. One of the reasons, therefore, that older individuals with CKD have a low risk of progression to ESKD is that they are more likely to die from another cause, principally cardiovascular disease. In a large study of US veterans with CKD, the authors estimated the threshold GFR below which the risk of ESKD would be expected to exceed the risk of all-cause mortality as a function of age (11). This threshold was 45 mL/min per 1.73m^2 in individuals aged 18 to 44 years, but fell to 15 mL/min per 1.73m^2 in those aged 65 to 84 years (Figure 2.10). It is possible that the presence of CKD is simply a surrogate for an adverse vascular phenotype. In a study of almost 17000 Icelandic adults without manifest vascular disease, the incorporation of CKD into risk prediction models for coronary artery disease provided little prognostic information over and above traditional risk factors (76). Specifically, the net reclassification improvement associated with CKD was one-sixth that associated with current smoking.

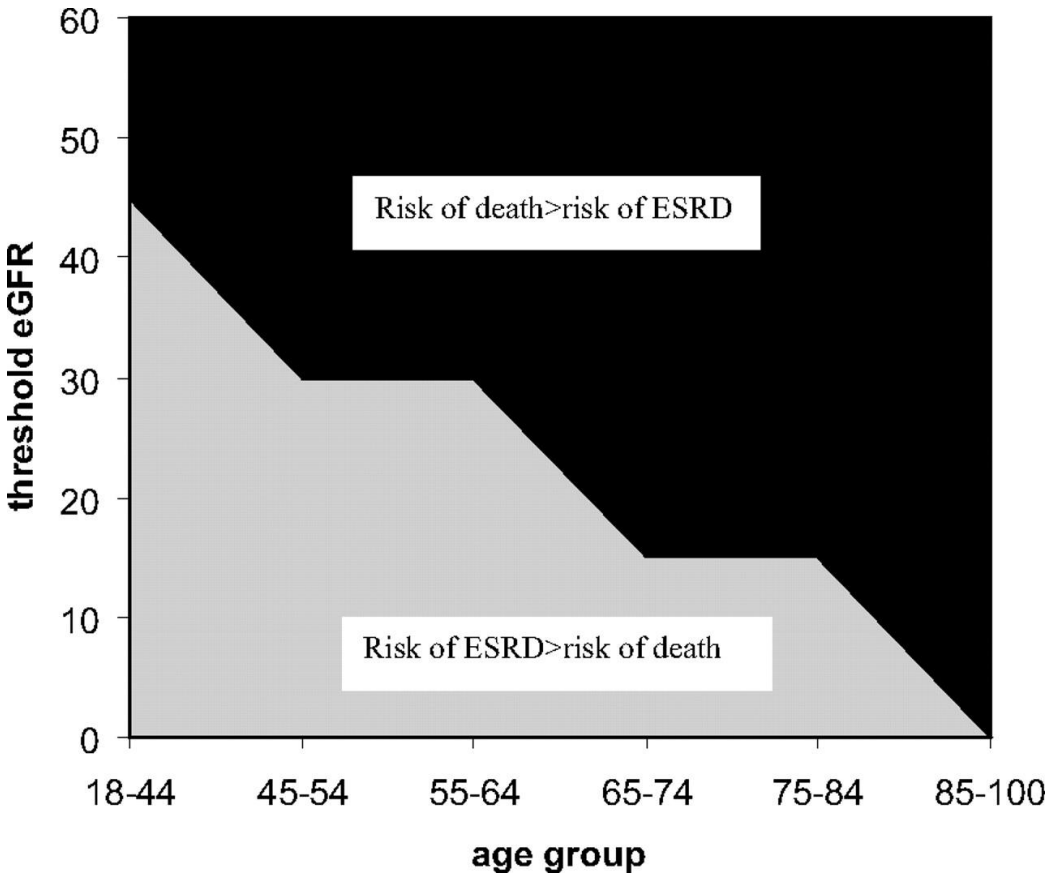


Figure 2.10: Threshold of estimated glomerular filtration rate below which the risk for end stage renal disease exceeded the risk of death for each age category
Adapted from O'Hare *et al*. (11)

An intriguing population in which to study kidney ageing are individuals who donate one of their kidneys. Living kidney donors undergo a rigorous multi-system evaluation of their overall health including comprehensive testing of kidney function to ensure that (i) the donor is a suitable candidate to donate, and (ii) the transplanted kidney is sufficiently healthy to maximise the health gain to the recipient. The kidney evaluation includes both measured GFR and a biopsy at the time of engraftment, thus facilitating an in-depth assessment of age-related structural and functional changes in the kidney in a subgroup of the population without kidney disease or traditional risk factors for CKD. The proportion of sclerosed (scarred) glomeruli increases steadily with age in living donors, from approximately 19% in 18 to 29 year olds to 82% in 70 to 77 year olds (77). Other histological changes evident in these biopsies include arteriosclerosis, tubular atrophy and interstitial fibrosis, collectively referred to as nephrosclerosis. Although nephrosclerosis appears to increase linearly with age, this association is not explained by age-related declines in GFR or CKD risk factors (77). The use of GFR to define CKD assumes that a falling GFR is reflective of a disease process in the kidney. These micro-anatomical changes of nephrosclerosis in healthy living kidney donors, however, appear to represent a subclinical

phenomenon of natural ageing. Put another way, the decline in GFR with age does not appear to be explained by nephrosclerosis (78). Whether the same is true of an unselected general population is unknown, as a kidney biopsy is seldom performed in older adults with isolated reductions in GFR. Even in healthy kidney donors, GFR (measured or estimated) declines with age in a predictable fashion, thereby questioning a single GFR cut-off for the diagnosis of CKD regardless of age (79).

2.7.2 Arguments in favour of the CKD classification system

Although the vast majority of older adults with CKD are unlikely to ever require dialysis or a kidney transplant, the presence of CKD nevertheless puts them at risk of premature death, in particular from cardiovascular disease (80). The association between CKD and cardiovascular mortality does not vary by the presence or absence of hypertension and diabetes, arguing against a clustering of traditional risk factors as the underlying explanation for the link (81, 82). A meta-analysis of 14 studies of general population cohorts with over 100,000 participants demonstrated that seemingly modest reductions in GFR (45 to 59mL/min per 1.73m^2) were associated with all-cause and cardiovascular mortality, even in the absence of albuminuria (7). The higher mortality risk did not vary by age, however the age variable for interaction analyses was crude (over or under 65 years).

A subsequent meta-analysis of over 2 million participants specifically addressed the question of effect modification by age in the association between GFR and the risk of mortality or ESKD (9). Among 33 general population and high risk (of vascular disease) cohorts, age was found to modify the relationship between GFR and mortality risk. Relative risks of mortality and ESKD were reduced at older age, while absolute risk differences were higher. Despite evidence of an interaction, GFR was independently associated with mortality and ESKD across all age categories. The increased risk of mortality generally became evident in the GFR range of 60 to 74 mL/min per 1.73m^2, except in the oldest age group (≥75 years) in whom the hazard ratio (with 80 mL/min per 1.73m^2 as the reference) started to become statistically significant below a GFR of 56 mL/min per 1.73m^2. In 13 CKD cohorts, the relationship between GFR and risks of ESKD and mortality did not vary substantially by age. The consistent association between CKD, as currently defined by a threshold GFR value of 60 mL/min per 1.73m^2, and hard adverse outcomes make a strong case for maintaining that diagnostic threshold irrespective of age (12).

2.8 Alternative outcomes in older adults

While the prevalence of CKD is high in the general population of older adults, and risks of important hard outcomes are increased at lower levels of GFR, it is clear that not all older adults with reduced GFR are at risk of these outcomes. A key unanswered question is how best to identify those older individuals in whom a diminished GFR represents a significant health problem. An alternative approach in this population is to change the outcome measure from a hard outcome like mortality to a more proximal outcome that would be expected to have a significant bearing on the well-being of an older individual. This thesis examines the relationship between kidney function and a number of such outcomes: physical performance, quality of life, and postural blood pressure responses.

2.8.1 Frailty and physical performance

Frailty is a concept characterised by cumulative declines across multiple organ systems and limited physiological reserve to withstand stressors, culminating in increased vulnerability to adverse outcomes (83). There is no single, universally accepted definition of frailty. The frailty instrument most often used in the kidney disease literature was developed by Fried and colleagues. This phenotypic definition of frailty was operationalized in a large cohort of community-dwelling older adults, and validated by way of its association with adverse outcomes including falls, hospitalisations and death (83). Five components are included in the Fried model, three or more of which are required for the diagnosis of frailty: unintentional weight loss, muscle weakness, exhaustion, low physical activity and slow gait. The prevalence of frailty is extremely high among patients with ESKD requiring dialysis. The dialysis population are at high risk of premature mortality, and yet frailty has been shown to independently predict mortality in these patients (84).

The Fried phenotype has gained favour among clinicians and researchers, and has been validated in several other research settings. There are disadvantages to the Fried model however. As it employs a rules-based approach, the specific combination of factors required to make the diagnosis may not be appropriate for each individual (85). The frailty components were chosen based on the specific self-reported and objectively gathered data captured in the Cardiovascular Health Study. They are therefore not immediately reproducible across other cohort studies, which have instead modified the criteria to suit the needs of their particular study. This has contributed to varying estimates of frailty prevalence in CKD populations (86,

87). Objective markers of physical performance, such as gait speed and TUG are useful tests of frailty that can be easily standardised and reproduced across different study populations. Furthermore, these simple tests can be used to predict outcomes. Decreased gait speed is a powerful predictor of mortality among community-dwelling adults aged 65 years and older, providing similar prognostic information to more complex models incorporating multiple health-related variables (88). Slower gait speed is also associated with new-onset disability and dependence for activities of daily living (89). Similar observations have been made for poorer performance in the TUG test (90). Patients with CKD attending out-patient clinics have weaker grip values, longer TUG times and slower walking speeds compared to age-matched peers in the general population (91). Relatively little is known about the relationship between GFR and physical performance tests in the general population of middle-aged and older adults, the demographic with the highest prevalence of CKD.

2.8.2 Quality of life

Similar to frailty and physical performance, most studies to date that have assessed the relationship between kidney disease and quality of life (QoL) have been restricted to those with advanced kidney disease such as the dialysis population or those referred to CKD out-patient clinics. These studies have suggested much poorer QoL scores among CKD patients compared to the general population. Patients with advanced CKD encounter numerous specific complications of their disease, along with high rates of comorbidity and polypharmacy, and as such represent a fairly unique population. For older persons in the general population with much less severe reductions in GFR, assessment of their QoL could offer insights into whether a diminished GFR contributes to poorer QoL. A positive correlation would strengthen the argument that the detection of seemingly modest declines in GFR has important consequences to an older individual, whereas lack of a correlation would suggest that a reduced GFR is part of a constellation of health problems that accumulate with advancing age and contribute to an older person's well-being. A number of studies have investigated the link between kidney function and QoL in the general population. In general, the exposure variable has been a dichotomous CKD variable (GFR above or below 60mL/min per 1.73m^2) rather than GFR. Most studies have used a health-related QoL instrument such as the Short Form-36 or a modification of it. These instruments place a large emphasis on physical determinants of QoL, which may not be appropriate in older people who could have a good QoL despite physical health challenges. A more holistic QoL instrument called CASP-19 was specifically developed in older community-dwelling adults to capture positive and negative aspects of QoL across four dimensions: control,

autonomy, self-realisation and pleasure (92). The relationship between kidney function and CASP-19 has not been evaluated among community-dwelling older adults.

2.8.3 Postural blood pressure responses

Orthostatic hypotension (OH) refers a drop in blood pressure on standing from a sitting or lying position. Similar to CKD, OH prevalence increases with age and is associated with several cardiovascular endpoints including coronary artery disease, heart failure and stroke (93-96). Methods for detecting OH in clinical practice are rather crude, involving two or three blood pressure (BP) measurements and binary BP thresholds to define the presence or absence of OH (97). Beat-to-beat BP data are increasingly being used to better characterise dynamic BP responses after standing. Such measurements have identified a greater prevalence of impaired BP stabilisation than previously detected by conventional testing for OH (14). Failure to adequately stabilise one's BP after standing is a predictor of injurious falls (15) and all-cause mortality (98). Given the reliance on the glomeruli for consistent regulation of blood flow to maintain adequate pressure for filtration, the kidney may be vulnerable to periodic bouts of low blood pressure due to orthostasis. On the other hand, CKD is associated with greater degrees of autonomic dysfunction, which could contribute to a greater risk of OH. Despite high prevalence of both conditions at older age, there is surprisingly little known about the relationship between OH and reduced kidney function. One previous study demonstrated an association between baseline OH and incident CKD (99). No study to date has investigated the association between postural BP responses and the kidney using beat-to-beat data.

2.9 Summary

The uniform system for the diagnosis and staging of CKD has stimulated global research at a population level to better understand the burden and clinical implications of CKD. It is hoped that this research will translate into improved outcomes for people living with CKD, and earlier detection of CKD in people with underlying risk factors. One of the key drivers of the growing population burden of CKD is the rapidly changing age demographic. An increasing number of older adults are being diagnosed with CKD based on reductions in their GFR. The risks of cardiovascular mortality, all-cause mortality and ESKD attributable to reductions in GFR are not uniform across age, which has led to debate about the appropriateness of diagnosing a large proportion of the older general population with CKD. This debate often centres on the question of whether declines in GFR in this population represent "normal aging" or a disease. This

question, although important, cannot ultimately be answered. An alternative question is how much does the presence of a reduced GFR contribute to outcomes other than hard endpoints such as mortality in older people. The assessment of outcomes such as frailty or quality of life may be more meaningful to an older person, and could inform the debate about the importance of detecting a reduced GFR at older ages.

3 Methods

3.1 Study population

This thesis uses data from the first three waves of The Irish Longitudinal Study on Ageing, a prospective, population-representative cohort of older adults who are resident in the Republic of Ireland. TILDA was founded in 2006 with the overarching aim of improving the ageing experience for Irish adults. At that time, there was a paucity of population-level data regarding the health, social and economic circumstances of older persons in Ireland. This lack of robust population data was compounded by a rapidly changing age distribution. Similar to other developed countries, Irish people are living longer, even in the presence of chronic diseases, with the result that older people represent an increasingly larger proportion of the total Irish population. It has been projected by the Irish Central Statistics Office that the population of adults aged 65 years and over will increase from approximately 500,000 to 1,400,000 between 2011 and 2046. The most rapidly growing subpopulation is the oldest old, those aged over 80 years, in whom the population looks set to treble over that time period. This dramatic change in age distribution will undoubtedly create public health and societal challenges.

TILDA was established with the following objectives (100):

- Provide comprehensive baseline economic, social and health data on the Irish general population of older adults
- Collect longitudinal data to better understand the complex processes of the ageing transition and how they interact with one another
- Inform and improve policy and planning with respect to Ireland's ageing population
- Raise awareness of ageing as a public issue of major importance
- Create an infrastructure for ageing research in Ireland and further afield by providing an anonymised dataset for national and international researchers

TILDA is a member of a family of cohort studies of ageing around the world, which started with the Health and Retirement Study (HRS) in the United States in the early 1990s. Studies from the HRS family have been designed to meet the specific needs of the populations they represent. The studies share core elements in study methodology and data collection, thereby enabling harmonisation of data and facilitating international comparisons. The TILDA questionnaire was specifically designed to be comparable with three studies: The English Longitudinal Study on

Ageing (ELSA), the Survey of Health, Ageing and Retirement in Europe (SHARE), and the HRS. The cohorts in the HRS family also differ in terms of the depth and type of information collected. TILDA has a particular emphasis on health and is unique among its peers with respect to the extent of objective health data captured, and the use of novel health technologies in the assessment of study participants.

3.2 Sample Design

3.2.1 Target population

The target population chosen for TILDA were individuals aged 50 years and over who were living in the Republic of Ireland and resident in the community at the time of recruitment. People living in nursing homes or other institutions were therefore excluded. Sampling of the target population was performed at the household level using the Irish Geodirectory, a comprehensive and continually updated list of residential addresses in the Republic of Ireland, as the sampling frame. The RANSAM computer-based sampling system, developed by the Economic and Social Research Institute, was employed to generate a probability sample of addresses (101). The sample was designed in such a way as to provide an equal probability ("epsem") sample of addresses containing a member of the target population, and of individuals within that target population. This process involved three stages (102).

Firstly, the national population of addresses was grouped into 3155 geographical clusters, each one containing between 500 and 1180 addresses. 640 of these clusters were then chosen at random, using three dimensions of proportionate stratification: all addresses were pre-sorted by socio-economic position (percentage in a professional or managerial occupation), age structure (percentage of the population in the cluster aged 50 years and over), and geographical location (the RANSAM procedure ordered clusters within each of the 26 counties from north to south). The probability of selection was proportional to the size of the cluster, defined as the estimated population of addresses in the cluster containing a person aged 50 years or more.

Secondly, a probability sample of 50 addresses was selected from each of the 640 clusters. This generated a potential list of 32,000 addresses, each with an equal probability of selection. This list was randomly divided into two groups: an initial sample of 25,600 addresses (40 addresses chosen at random from each of 640 clusters), and a reserve sample of 6,400 addresses (10 addresses randomly selected from each of 640 clusters). An invitation letter was sent by post to

each of the selected unique addresses. Rural areas can have a high proportion (up to 50%) of addresses which are not unique and only identifiable by the resident's name, which is not available in the Geodirectory. An advantage of the RANSAM system is the availability of a geocode for each address. For non-unique addresses, invitation letters were delivered by hand to the selected address, aided by the use of satellite navigation devices. One week after sending the letter, each selected household was visited by a member of the field staff to ascertain if that household contained a potentially eligible participant.

Finally, all household resident aged 50 years and over, and their spouses or partners of any age, were invited to participate in the study. Despite not being in the target population, spouses younger than 50 years were nevertheless interviewed with the aim of capturing data at the couple or household level. For the purposes of this thesis, which examines person-level data, spouses younger than 50 years (N=329) have been excluded from the analysis.

3.2.2 Response rate

Two pilot studies were conducted in 2008 (July to October) and 2009 (April to July). Between January 2009 and February 2011, 8175 interviews of respondents aged 50 years and over were successfully conducted from 6279 households. The household response rate was 62%, defined as the proportion of selected households containing an eligible respondent (N=10128) from which an interview was conducted (N=6279).

3.3 Methods of data collection

There are three components to data collection in TILDA: a computer-assisted personal interview (CAPI), a self-completion questionnaire (SCQ), and a health assessment (103). The CAPI and SCQ are performed at each wave. A health assessment was conducted at Wave 1 and Wave 3.

3.3.1 CAPI data

The CAPI is administered in the respondent's home by a trained professional social interviewer. Interview responses are inputted directly into a laptop computer. The interview is wide-ranging and includes information on demographics, social circumstances, employment, income and wealth, lifestyle and behaviour, physical, mental and cognitive health, and health care utilisation (Table 3.1).

3.3.2 SCQ data

On completion of the interview, and in their own time, participants are asked to fill out a paper-and-pencil self-completion questionnaire (SCQ) and return it by free post to the study site. At Wave 1, 84.6% of participants (7196 out of 8504) returned a SCQ. The SCQ contains more personal or sensitive information, such as anxiety and stress, alcohol consumption, relationship quality, and perceptions of aging (Table 3.1). The SCQ also contains the CASP-19 quality of life instrument.

Table 3.1: Data collected in the interview and self-completion questionnaire at Wave 1

Demographics	**Physical health**
Age and gender	Self-rated health
Educational attainment	Self-reported physician-diagnosed conditions
Childhood health	Falls/fear of falling
Migration history	Medical screening
Marital status	Sensory function
Social circumstances	Disability
Activities of daily living	**Mental health**
Helpers	Self-reported mental health
Social participation	Depression
Employment	Anxiety and worry (SCQ)
Current occupation	Loneliness (SCQ)
Job history	Perceived stress (SCQ)
Retirement planning	Quality of life (SCQ)
Income and assets	**Cognitive health**
Health care utilisation	Memory
Health insurance	Orientation
Medical card	Recall
Visits to family doctor	Verbal fluency
Hospitalisations	**Ageing perceptions (SCQ)**
Community-based supports	**Behavioural health**
Medications	Smoking
Including supplements	Physical activity
	Alcohol consumption (SCQ)

SCQ, self-completion questionnaire

3.3.3 Health variables

In the physical and cognitive health section of the CAPI, respondents are shown a card with a list of conditions on it and asked "Has a doctor ever told you that you have any of the conditions on this card?" Both cardiovascular and non-cardiovascular chronic conditions are captured in a similar fashion. The conditions listed on the card shown to respondents are detailed in Table 3.2.

Table 3.2: Conditions listed on cards shown to respondents

Cardiovascular conditions	Other chronic conditions
High blood pressure or hypertension	Chronic lung disease (bronchitis or emphysema)
Angina	Asthma
A heart attack (myocardial infarction or coronary thrombosis)	Arthritis (osteoarthritis or rheumatism)
Congestive heart failure	Osteoporosis
Angioplasty or stent	Cancer or malignant tumour
Open heart surgery	Parkinson's Disease
Stroke (cerebrovascular disease)	Emotional, nervous or psychiatric problems such as depression or anxiety
Mini-stroke or TIA	Alcohol or substance abuse
Diabetes or high blood sugar	Alzheimer's Disease
High cholesterol	Dementia
Abnormal heart rhythm	Serious memory impairment
Heart murmur	Stomach ulcers
Any other heart trouble (specify)	Varicose ulcers
	Cirrhosis or serious liver damage

The presence of hypertension was defined as a self-reported doctor's diagnosis and/or regular use of anti-hypertensive medications. The presence of diabetes was defined as a self-reported doctor's diagnosis and/or regular use of anti-diabetes medications. Medication use (up to 20 medications or supplements) was recorded during the home interview and cross-checked with medication labels. All medications were then coded according to the World Health Organisation Anatomical Therapeutic Chemical Classification (ATC) (104). Richardson *et al*. previously demonstrated a good or very good level of agreement between interview-ascertained medication use in TILDA and pharmacy records for 15 out of 19 medication classes (105). Specifically, kappa scores varied between 0.77 and 0.86 for anti-hypertensive and anti-diabetes medications.

3.3.4 Health assessment data

All participants who completed the CAPI at Wave 1 were invited to take part in a comprehensive health assessment at one of two dedicated research centres in Cork and Dublin (106). The assessment was conducted by trained nursing staff utilising standard operating procedures for all tests. These two areas were chosen on the basis of transport infrastructure and population density. The centre-based assessment takes approximately 150 minutes to complete and encompasses five domains (106): cognitive performance, vision, gait and balance, strength and bone density, and cardiovascular fitness (Table 3.3). The first pilot study of the health assessment showed that respondents who attended the health centre tended to be in better health than the average health status of the overall cohort (the CAPI sample). A second pilot study included the option of a home-based health assessment for participants who were unable or unwilling to travel to the research centre. This modified version of the centre-based assessment was carried out by trained research nurses. Data from the second pilot study confirmed that the "home" population was qualitatively different to the "centre" population – they were older, had less educational attainment, and poorer self-rated health (107). Therefore, a home health assessment was incorporated into the first wave of data collection to counteract bias from systematic over-representation of younger and healthier participants in the centre-based health assessment. Components of the home health assessment are also detailed in Table 3.3. At Wave 1, a total of 5275 respondents took part in a centre-based health assessment, and a further 875 respondents completed a home assessment.

3.3.5 Ethical considerations

Ethical approval for TILDA was granted by the Research Ethics Committee of Trinity College Dublin. All respondents provided informed signed consent. All experimental procedures were adherent to the Declaration of Helsinki. Separate consent was obtained from participants who agreed to have a health assessment. Participants who agreed to provide a blood sample required further informed consent for the immediate analysis (for a lipid profile) and long-term storage of their sample, the latter to be used for future unspecified medical research.

Table 3.3: Data captured in the TILDA health assessment at Wave 1

Variable	Centre	Home	Measurement	Equipment
Height	Yes	Yes	1	Wall-mounted measuring rod
Weight	Yes	Yes	1	Electronic floor scale
Waist size	Yes	Yes	2	Tape measure
Hip size	Yes	Yes	2	Tape measure
Cuff BP	Yes	Yes	2 seated, 1 standing	Digital automatic BP monitor
Phasic BP	Yes	No	1	Beat-to-beat BP monitor
Heart rate variability	Yes	No	10-minute recording	Holter recorder
Pulse wave velocity	Yes	No	2	Non-invasive monitor
Visual acuity	Yes	No	Both eyes separately	Logmar chart
Macular pigment optical density	Yes	No	12	Densitometer
Retinal photograph	Yes	No	Both eyes	Nonmydriatic automatic camera
Global cognition	Yes	Yes	1	MMSE, MOCA
Attention	Yes	Yes	1	SART
Executive function	Yes	No	1	Timed colour trials I & II
Processing speed	Yes	No	1	Choice reaction time
Grip strength	Yes	Yes	2	Hydraulic hand dynamometer
Timed-up-and-go	Yes	Yes	1	Chair, tape measure, stop watch
Gait speed	Yes	No	3 walks	Sensored mat
Bone density	Yes	No	1	Ultrasound machine
Blood sample	Yes	Yes	25mL volume	Standard materials

Adapted from Cronin *et al*. (106)

BP, blood pressure; MMSE, mini-mental state examination; MOCA Montreal cognitive assessment; SART, sustained attention to response time

3.3.6 Follow up waves of data collection

Further waves of data were collected between February 2012 and March 2013 (Wave 2), and between April 2014 and December 2015 (Wave 3). Wave 2 encompassed a CAPI and SCQ, along with a limited health assessment in the respondent's home which included the TUG test. At Wave 3, respondents completed a CAPI and SCQ, and were invited to participate in either a home- or centre-based comprehensive health assessment (Figure 3.1). The components of the Wave 3 health assessment were very similar to those measured at Wave 1. Gait speed and TUG were measured using the same standard operating procedures at both Wave 1 and Wave 3.

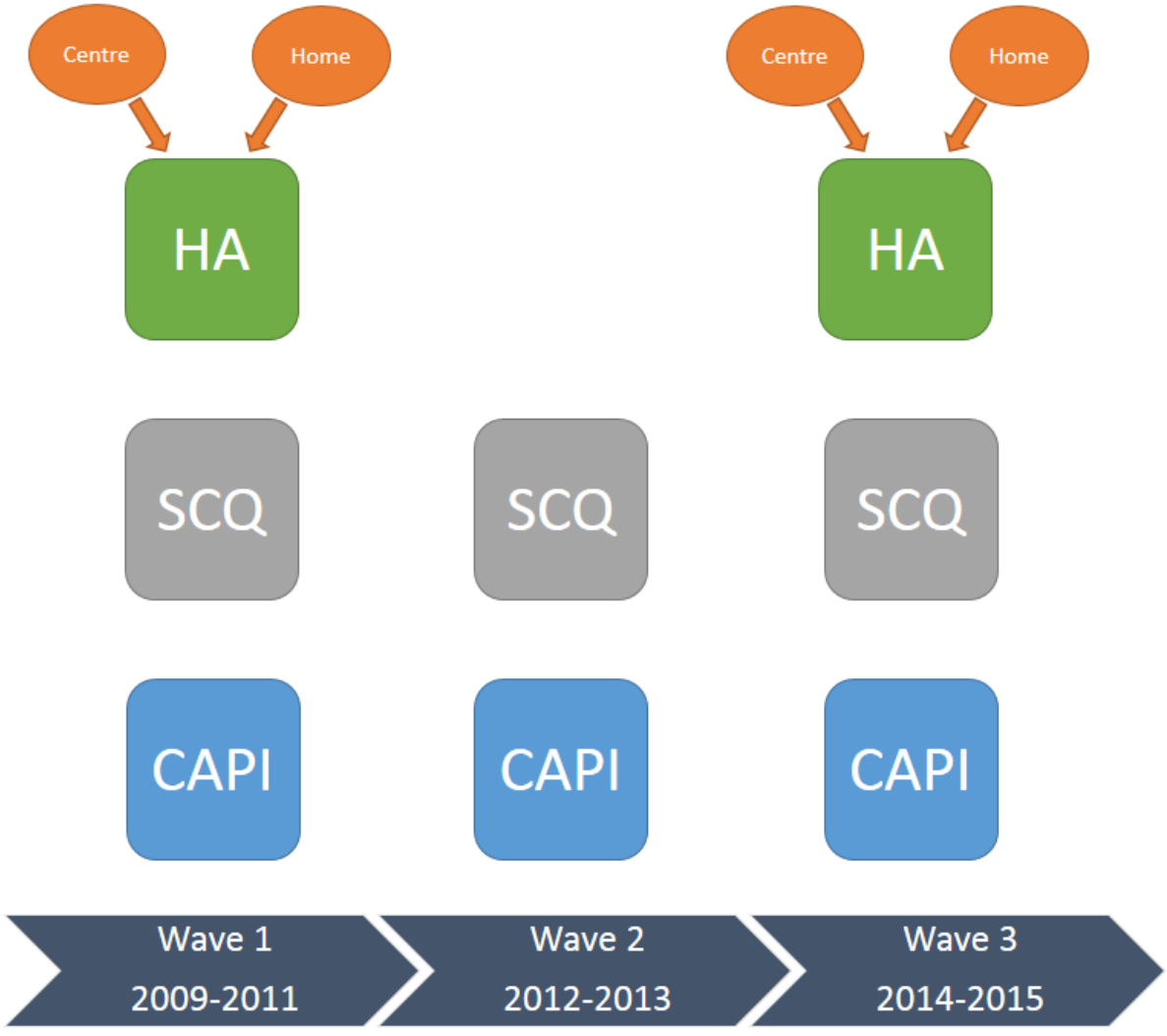


Figure 3.1: Methods of data collection in the first three waves of TILDA
CAPI, computer assisted personal interview; HA, health assessment, SCQ, self-completion questionnaire

3.3.7 Measurement of filtration markers

A 25 millilitre venous blood sample was collected from each participant who provided written informed consent during the Wave 1 health assessment. Blood samples were taken during the home assessment as well as the centre-based assessment. All samples were transported to a central laboratory in temperature-controlled shipping boxes for processing within 48 hours. Each sample was centrifuged and aliquoted into 10 bar-coded cryovials which were then stored at -80 degrees Celsius. Cystatin C and creatinine were measured simultaneously from frozen plasma. Cystatin C was measured using a second generation particle enhanced immunoturbidimetric assay (Roche Tina-quant™) on a Roche Cobas 701 analyser. This assay has a measuring range of 0.40 – 6.80 mg/L and is traceable to the European reference standard material (ERM-DA471/IFCC) for cystatin C (108). Creatinine was measured using an enzymatic method traceable to isotope-dilution mass spectrometry (Roche Creatinine plus ver.2, Roche Diagnostics, Basel, Switzerland).

3.3.8 Estimation of glomerular filtration rate

The equations used to estimate GFR from creatinine, cystatin C, or the combination of creatinine and cystatin C are detailed in Table 3.4. Participant race was presumed to be Caucasian in all cases. Participant age was calculated as the age (to the nearest year) on the day the blood sample was taken, rather than age at the time of the household interview.

Table 3.4: Equations used to estimate GFR from creatinine, cystatin C or both

MDRD equation (24)
$175 \times (Cr/88.4)^{-1.154} \times Age^{-0.203}$ (x 0.742 if female)
CKD-EPI creatinine equation (25)
$143.538 \times (Cr/61.88)^{-0.329} \times 0.993^{Age}$ *if female & Cr ≤61.88µmol/L*
$143.538 \times (Cr/61.88)^{-1.209} \times 0.993^{Age}$ *if female & Cr >61.88µmol/L*
$141 \times (Cr/79.56)^{-0.411} \times 0.993^{Age}$ *if male & Cr ≤79.56µmol/L*
$141 \times (Cr/79.56)^{-1.209} \times 0.993^{Age}$ *if male & Cr >79.56µmol/L*
CKD-EPI cystatin C equation (53)
$133 \times (Cys/0.8)^{-0.499} \times 0.996^{Age}$ (x 0.932 if female) if Cys ≤0.8mg/L
$133 \times (Cys/0.8)^{-1.328} \times 0.996^{Age}$ (x 0.932 if female) if Cys >0.8mg/L
CKD-EPI combination equation (53)
$130.815 \times (Cr/61.88)^{-0.248} \times (Cys/0.8)^{-0.375} \times 0.995^{Age}$ *if female & Cr≤61.88µmol/L & Cys≤0.8mg/L*
$130.815 \times (Cr/61.88)^{-0.248} \times (Cys/0.8)^{-0.711} \times 0.995^{Age}$ *if female & Cr≤61.88µmol/L & Cys>0.8mg/L*
$130.815 \times (Cr/61.88)^{-0.601} \times (Cys/0.8)^{-0.375} \times 0.995^{Age}$ *if female & Cr>61.88µmol/L & Cys≤0.8mg/L*
$130.815 \times (Cr/61.88)^{-0.601} \times (Cys/0.8)^{-0.711} \times 0.995^{Age}$ *if female & Cr>61.88µmol/L & Cys>0.8mg/L*
$135 \times (Cr/79.56)^{-0.207} \times (Cys/0.8)^{-0.375} \times 0.995^{Age}$ *if male & Cr≤79.56µmol/L & Cys≤0.8mg/L*
$135 \times (Cr/79.56)^{-0.207} \times (Cys/0.8)^{-0.711} \times 0.995^{Age}$ *if male & Cr≤79.56µmol/L & Cys>0.8mg/L*
$135 \times (Cr/79.56)^{-0.601} \times (Cys/0.8)^{-0.375} \times 0.995^{Age}$ *if male & Cr>79.56µmol/L & Cys≤0.8mg/L*
$135 \times (Cr/79.56)^{-0.601} \times (Cys/0.8)^{-0.711} \times 0.995^{Age}$ *if male & Cr>79.56µmol/L & Cys>0.8mg/L*

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cr, creatinine; Cys, cystatin C; MDRD, Modification of Diet in Renal Disease

3.4 Strengths and limitations of the TILDA sample

A key strength of TILDA is that it can provide estimates of disease prevalence that are robust and representative of the Irish general population aged 50 years and over. The survey instruments such as the CAPI have been harmonised with other cohort studies of ageing to facilitate international comparisons of the ageing experience. The questionnaire collects vast amounts of information spanning economic, socio-demographic and health domains, allowing for comprehensive adjustment of relevant confounding variables. The SCQ captures more sensitive information that is important to an older person but which might otherwise be neglected. What makes TILDA unique among its peers in the HRS family is the depth and richness of objective physiological data measured at the health assessment, for example beat-to-beat blood pressure during postural change. The inclusion of a modified health assessment in the respondent's home reduces bias from the recruitment of younger and fitter participants into the health centre assessment. Finally, the longitudinal study design provides a framework for addressing important research questions regarding the trajectory of health declines as we age.

The sample also has some limitations. Only individuals with a residential address were invited to participate, and therefore the findings are not generalisable to individuals in a nursing home or other institution. The sample is also likely to under-represent individuals with significant cognitive impairment or dementia, as the primary respondent was required to provide written informed consent when visited by the social interviewer. Comparisons with the Irish population using census data from the Quarterly National Household Survey and the Central Statistics Office have demonstrated evidence of differential non-response across certain strata such as educational attainment and some age categories e.g. under-representation of women over 75 years. When response rates vary by subgroups of the population this can contribute to bias, for example in estimates of disease prevalence. In an effort to reduce this potential bias, sampling weights have been applied to such estimates.

3.5 Statistical analysis

3.5.1 Description of inverse probability weight for kidney biomarkers

Chapter 4 provides estimates of CKD prevalence and expected values of GFR by age for the target population. An inverse probability weight was created to reduce bias from (1) non-response at the initial recruitment stage, and (2) non-participation in the health assessment and/or inability or refusal to provide a blood sample for estimation of GFR. For (1), the characteristics of the TILDA cohort at Wave 1 were compared to the national population of Irish residents aged 50 years and over (N=1,273,087) using 2011 national census data (Central Statistics Office, http://www.cso.ie) and post-stratification weights were generated (109, 110). Sampling fractions were compared in the cross-classifications of the following stratifying variables in the sample and the population: age (in 5-year age bands, with ≥80 as the upper band), sex, location (urban/rural), educational attainment (3 levels), marital status (4 levels). The ratio of these fractions was used to derive a calibration weight – the inverse of the probability that a person in each stratum of the population would be selected and participate in TILDA at Wave 1.

Subsequently, the probability of Wave 1 TILDA participants having a venous blood sample taken ("blood test weight") was estimated by performing logistic regression on this binary outcome in the TILDA Wave 1 sample with a set of independent variables including demographics, socio-economic and educational status, health behaviours, chronic health conditions and disabilities (110). The latter model also included 2- and 3-way interactions between socio-demographic variables. The final weight was created by multiplying the TILDA weight by the blood test weight. At both stages of weight generation, in order to reduce biases from (1) and (2), weights were trimmed at their 99th centile to avoid large weights increasing the standard errors of estimates. This analysis was conducted by Dr. Neil O'Leary.

3.5.2 Description of inverse probability weight for longitudinal data

Chapter 6 describes the longitudinal association between GFR and repeated measures of physical performance across the first three waves of data collection. For each outcome (gait speed and TUG), separate survey weights were derived that were specific to the sample under study. The TUG sample were those with GFR and TUG measurements at Wave 1, and at least one further TUG measurement at a subsequent wave. The gait speed sample were those with gait speed and GFR measurement at Wave 1, and gait speed measurement at Wave 3. The TUG weight was calculated by multiplying the blood test weight (described above) by the inverse of

the probability that a participant met the TUG sample criteria. This probability was calculated from a logistic regression model using predictors from Wave 1 including: age, gender, marital status, urban-rural residence, socio-economic position, employment status and disability. The gait speed weight was calculated by multiplying a previously derived weight for completion of a health centre assessment at Wave 1 by the inverse of the probability that a participant met the gait speed sample criteria. This probability was calculated from a logistic regression model using the same Wave 1 predictors (age, gender, marital status, urban-rural residence, socio-economic cluster, employment status and disability). Participants who did not meet the necessary criteria for the sample, or had exited the study following Wave 1, were assigned weights of zero. All weights were trimmed at the 95th percentile to remove extreme values, and were re-scaled relative to the total of the base TILDA weight at Wave 1, with attrition included in the scaling. This analysis was performed by Dr. Daniel Carey.

3.5.3 The Box-Cox Power Exponential distribution

Chapter 4 compares the age-related distributions of creatinine and cystatin C. Like most laboratory measures, creatinine and cystatin are strictly positive and highly skewed variables, demonstrating a long right-hand tail. The Box Cox Power Exponential (BCPE) distribution provides a flexible means of modelling such heavy-tailed outcomes whose values are greater than zero (111). The BCPE has four parameters: location (central tendency, represented by μ), dispersion (a variance parameter denoted by σ), skewness (ν) and kurtosis (τ). With four parameters that can vary, as opposed to two parameters in a normal distribution (mean and standard deviation), the BCPE distribution has greater scope to model any observed data. As more distributional parameters are allowed to change, the BCPE distribution becomes progressively more complicated in shape. In the theoretical example below (Figure 3.2), only the location (median) parameter is held constant, while the values of one or more of the other three parameters are changing.

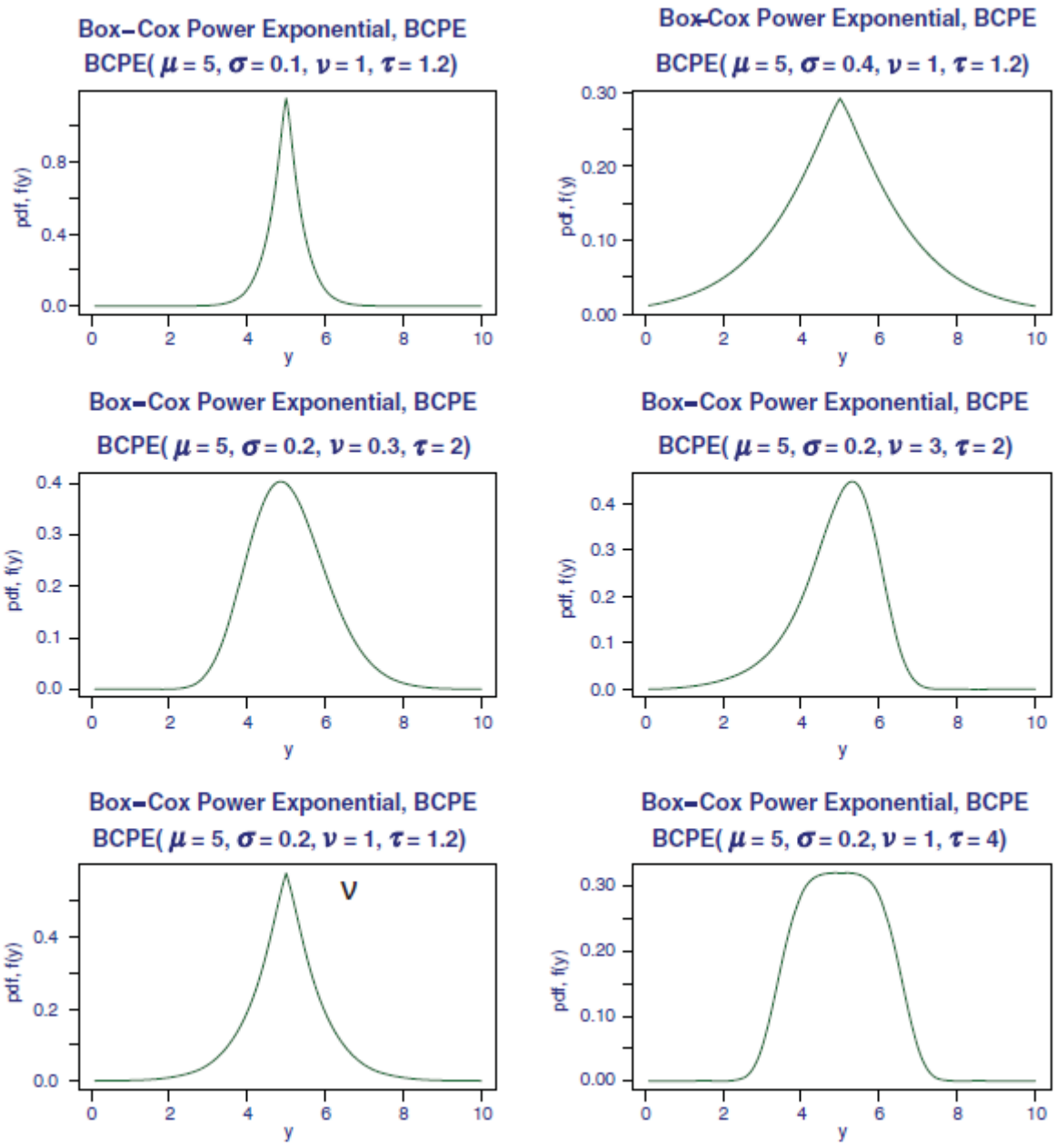


Figure 3.2: Examples of BCPE distributions
In each panel, the location (μ) parameter remains constant while the scale (σ), skewness (ν) and kurtosis (τ) parameters are allowed to change.
Reproduced from Voudouris et al. (16)

When examining the relationship of kidney biomarkers with age, in a simple spline regression only the mean would be modelled as a function of age. Using an approach such as the generalised additive model for location, shape and scale (GAMLSS) (112) facilitates modelling the change in all parameters of a distribution with age. In the case of the BCPE, this includes specifying changes not only in the central tendency (μ), but also in the dispersion (σ) and shape (ν and τ) of the distribution across age for males and females, either jointly or separately. Each BCPE parameters is modelled using natural cubic splines. Increasing the number of knots in the creation of these splines might improve model fit, but at a potential cost of increasing the complexity of the model. A set of models can be fitted with varying complexity of each distributional parameter in terms of its relationship to age and sex, including age-sex interaction terms. Fit statistics such as the Akaike Information Criterion (AIC) are used to weigh up the balance between optimising model fit and sacrificing degrees of freedom in more complicated models. The AIC is calculated as follows, where k is equal to the number of model parameters:

$$AIC = -2*\log(likelihood) + 2*k$$

The second term therefore acts as a penalty for increased model complexity. A lower AIC indicates a better fitting model. These models were fitted in R by Dr. Neil O'Leary.

3.6 Conclusion

This chapter described the sampling frame, study design and methods of data collection employed in TILDA. Key strengths of the study are the household level sampling of participants and the depth and quality of the information collected at each wave, in particular the extent of objective physiological data captured at the health assessment. Chapters 4 to 8 leverage this data to describe the relationship between kidney function and a variety of health outcomes in TILDA participants. We start by investigating the distribution of kidney biomarkers across the age spectrum.

4 Distribution of kidney biomarkers and prevalence of reduced kidney function in community-dwelling older adults

4.1 Introduction

Among older individuals with CKD, the majority have relatively modest reductions in GFR, in the range of 45 to 59 mL/min per 1.73m^2 (Stage 3a CKD). While a proportion of this group is at increased risk of ESKD and cardiovascular events (9), many more are left with a diagnosis that carries an uncertain clinical significance (70). Furthermore, it is well recognised that creatinine is a sub-optimal filtration marker in this demographic due to variable generation of creatinine in the setting of declining muscle mass, and evidenced by U-shaped associations with clinical outcomes (5). The need for better risk-stratification within this heterogeneous older population with mild CKD has fuelled interest in alternative filtration markers that are less influenced by nutrition or muscle mass. One such candidate biomarker is cystatin C, a 13kDa molecule released by all nucleated cells and freely filtered at the glomerulus. Cystatin C is a better predictor of measured GFR than creatinine (48). GFR estimating equations incorporate variables that predict differences in muscle mass between individuals such as age, sex and race. The inclusion of these factors greatly improves the accuracy of creatinine-based GFR equations, but does little to enhance the accuracy of cystatin C-based equations (54). As a result, GFR estimating equations that use cystatin C have similar accuracy to equations that use creatinine (53).

Where cystatin C out-performs creatinine is in risk prediction. Recent landmark studies have demonstrated that reclassification of CKD using cystatin C can substantially alter an individual's risk profile for major clinical endpoints (58, 59, 113). For this reason, cystatin C has entered KDIGO clinical guidelines as a confirmatory test of CKD. Recommendation 1.4.3.5 "suggests measuring cystatin C in adults with creatinine-based estimated GFR 45-59 mL/min per 1.73m^2 who do not have markers of kidney damage, if confirmation of CKD is required (2C). If the cystatin C-based estimated GFR is also <60 mL/min per 1.73m^2, the diagnosis of CKD is confirmed. If the cystatin C-based estimated GFR is ≥60 mL/min per 1.73m^2, the diagnosis of CKD is not confirmed." The suggested use of cystatin C is thus not to confirm an individual's GFR, but rather to better inform their risk profile. It is unclear whether this reclassification of risk solely reflects the role of cystatin C as a kidney function biomarker, or if other factors governing cystatin C production may be confounding the observed risk relationships between cystatin C and clinical outcomes. These potential non-GFR determinants of cystatin C, which include

adiposity (64) and inflammation (69), are also age-related. The distribution of cystatin C could therefore vary with increasing age, which could in turn influence its utility as a discriminator of risk at older ages. This question is most pertinent among community-dwelling older adults, in whom the KDIGO guideline is likely to be most applicable.

Where along the range of GFR the diagnostic threshold for CKD should lie has been the source of much debate in the literature (12, 13), with some advocating a lower threshold (<45 mL/min per 1.73m^2) for adults over the age of 60 years (13). Choosing a dichotomous criterion to define the presence or absence of disease may not be all that informative on an individual level. For example, an older adult might transition from a GFR of 61 mL/min per 1.73m^2 (and therefore "disease-free") to a GFR of 59 mL/min per 1.73m^2 (and therefore diagnosed with CKD) in the course of a year or two by virtue of an age-related loss in GFR. This example, of course, does not take into account the variability associated with GFR estimating equations, but it highlights the limitations of collapsing a continuous metric of organ function into a binary variable to classify disease status. For the case described, it may be helpful to frame that person's GFR result in the context of what would be expected for their age-matched peers in the general population. The aim of such an approach would not be to replace the established CKD classification system, which has been built on the risk of hard adverse outcomes, but rather to inform discussions with the individual patient who may want to know where their kidney function lies relative to others of the same age.

The present study utilises data from a large, population-representative cohort of middle-aged and older adults. Our primary aims were to compare the distributions of creatinine and cystatin C with advancing age, and estimate the predicted probability of confirming CKD using cystatin C as a function of age. Our secondary aims were to provide expected values of GFR per year of age for men and women, and define the prevalence of CKD (GFR <60 mL/min per 1.73m^2) in this sample using different GFR estimating equations.

4.2 Methods

4.2.1 Participants

This was a cross-sectional analysis from Wave 1 (June 2009 to June 2011) of The Irish Longitudinal Study on Ageing. A total of 5386 participants had a blood sample taken for measurement of creatinine and cystatin C at Wave 1 (Figure 4.1). Within this group, the majority of participants had a blood sample taken during the course of a centre-based health assessment, but a substantial number of participants (650, 12%) had their blood sample taken during a modified health assessment in their home.

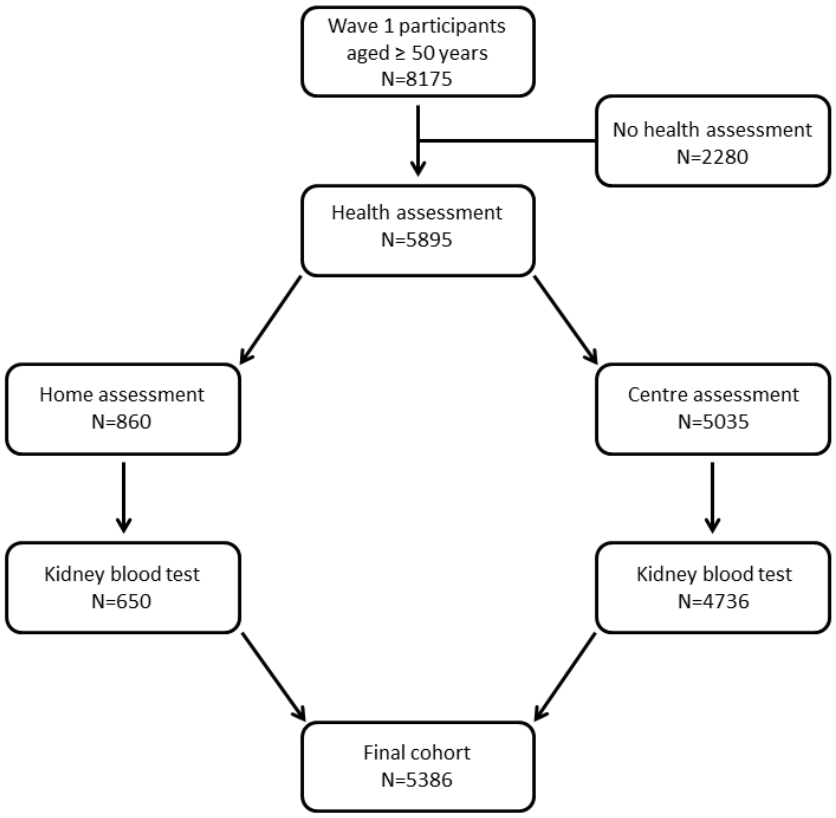


Figure 4.1: Flowchart of TILDA participants who had their kidney function tested at Wave 1

4.2.2 Health variables

The CAPI captured information on age, gender, smoking history, and self-reported physician-diagnosed conditions. Medication use was recorded during the interview and cross-checked with medication labels. Glycated haemoglobin (HbA1c) was measured from frozen buffy coat samples as described previously (114). We defined diabetes mellitus as one or more of the following: a self-reported physician's diagnosis; receiving insulin or oral hypoglycaemic medications; HbA1c level ≥48mmol/L. We defined hypertension as a self-reported physician's diagnosis of hypertension and/or receiving anti-hypertensive medication. We defined cardiovascular disease as the number (0, 1, 2 or more) of self-reported physician-diagnosed conditions: angina, heart failure, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischaemic attack or stroke. Body mass index (BMI) and waist circumference were measured objectively at the health assessment. Blood pressure was measured by a nurse according to a standard protocol using a digital automated BP monitor (Omron M10-IT, Omron Inc. Kyoto, Japan) and recorded as the average of two seated measurements.

4.2.3 Estimation of glomerular filtration rate

GFR was estimated in each participant from the Chronic Kidney Disease Epidemiology equations for creatinine (25), cystatin C (53) and the combination of creatinine and cystatin C (53). For comparative purposes we also estimated GFR from the MDRD formula (24), as this is the equation most commonly reported in laboratories in the Republic of Ireland. Cystatin C and creatinine were measured simultaneously from frozen plasma using standardised assays as described previously (Chapter 3 Section 3.3.7 "Measurement of filtration markers").

4.2.4 Statistical analysis

Analyses were performed using R (115) and Stata version 14.1 (StataCorp, College Station, TX). Continuous variables are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]) as appropriate. Categorical variables are presented as count (percentage).

The distributions of creatinine, cystatin C and GFR estimated from either filtration marker were modelled using the BCPE distribution (see Chapter 3 Section 3.5.3 "The Box-Cox Power Exponential distribution"). The BCPE includes four parameters - location (μ), dispersion (σ), skewness (ν) and kurtosis (τ), providing a flexible model for skewed and heavy-tailed outcomes whose values are greater than zero (111). An identity (linear) link was used for the μ and ν BCPE distributional parameters as functions of age and sex, whereas a log-link was used for the σ and τ parameters. This ensured values always greater than zero for the latter two. Natural cubic splines were used to model the BCPE distribution as a function of age, with knots set at given quantiles to ensure equal sample sizes between knots. For each biomarker, the optimal model for each BCPE distribution was sought using the GAMLSS package in R (112). Selection of the best-fitting model was based on the Akaike Information Criterion. The search space allowed models to contain anywhere from 3-5 knots for the μ BCPE parameter, and 0-2 knots for the other 3 BCPE parameters. Models with BCPE parameters, as functions of age, without an additional sex term, with a sex term, and stratified by sex were explored. The details of the parameters governing the age and sex relationships in the best-fitting model for each variable are given in the table below.

Table 4.1: Summary of best fitting models for BCPE distribution of cystatin C, creatinine and GFR estimated from either filtration marker

Variable	Mean (μ)		Scale (σ)		Skewness (ν)		Kurtosis (τ)	
	Stratified by sex	Number of knots	Stratified by sex	Number of knots	Stratified by sex	Number of knots	Stratified by sex	Number of knots
Cystatin C	Yes	5	Yes	2	Yes	2	Yes	2
Creatinine	No	3	No	2	Yes	2	Yes	2
GFRcys	Yes	5	Yes	2	Yes	2	Yes	2
GFRcr	No	3	No	2	Yes	2	Yes	2

GFRcr, GFR estimated from creatinine; GFRcys, GFR estimated from cystatin C

Based on the fitted BCPE models, plots were produced of the predicted 5th, 25th, 50th, 75th, and 95th centiles of the target population as continuous curves across the age range (50 to 85 years) for males and females for creatinine, GFRcr, cystatin C and GFRcys. Plots were also produced of the predicted proportion of the male and female populations across the same age range with GFR <60 mL/min per 1.73m^2. To ensure estimates were representative of the target population, all models incorporated an inverse probability weight as described in Chapter 3 (Section 3.5.1 "Description of inverse probability weight for kidney biomarkers"). Standard errors and confidence intervals accounted for the two-stage clustered sampling of participants (households within geographical regions and individuals within households).

Finally, we estimated the likelihood of GFRcys <60 mL/min per 1.73m^2 as a function of age in the subgroup of participants with CKD Stage 3a defined by GFRcr 45 to 59 mL/min per 1.73m^2 (N=463). Probability estimates by year of age, stratified by sex, were obtained using the post-estimation *margins* command in Stata.

4.3 Results

4.3.1 Participant characteristics

Characteristics of the study population, overall and by gender, are provided in Table 4.2. The median (IQR) age of the cohort was 62 (55-69) years and 53.5% of participants were female. One quarter of the participants (n=1291) were aged 70 years or over. Median (IQR) GFRcys and GFRcr were 80 (67-93) mL/min per 1.73m^2 and 82 (69-92) mL/min per 1.73m^2 respectively. The age distribution was similar in men and women. Male participants had a higher prevalence of diabetes (10.6% versus 6.2%) and hypertension (45.7% versus 39.9%) compared to female participants. Male participants also reported a greater burden of physician-diagnosed cardiovascular conditions.

4.3.2 Distributions of creatinine and cystatin C with age

The relationship between creatinine and age is illustrated by way of plots of the predicted population limits in Figure 4.2 for male and female participants. The trajectory of this slope was relatively flat. In both sexes there was some evidence of greater dispersion in the distribution of creatinine with advancing age. This change in the distribution pattern with age appeared to be more prominent in women. In contrast to creatinine, the relationship between cystatin C and age was strongly positive and non-linear (Figure 4.3). Beyond the age of approximately 65 years, cystatin C levels rose sharply in both sexes. The distribution of cystatin C changed markedly with advancing age, such that an individual aged 80 years had a strikingly different distribution to that of a 50 year old. As well as having an increased median level with age, older participants demonstrated progressively greater variability in cystatin C levels. The shape of the distributions of creatinine and cystatin C at specific ages are illustrated in the side panels of Figures 4.2 and 4.3. These distributions are presented in a larger scale in Appendix Figure 4.1 and Appendix Figure 4.2 for creatinine and cystatin C respectively

Table 4.2: Characteristics of study participants

Variable	Total (N=5386)	Men (N=2505)	Women (N=2881)
Age in years, median (IQR)	62 (55-69)	62 (56-69)	61 (55-69)
Age category, N (%)			
50-64 years	3265 (60.6)	1468 (58.6)	1797 (62.4)
65-74 years	1428 (26.6)	718 (28.7)	710 (24.6)
≥ 75 years	693 (12.9)	319 (12.7)	374 (13.0)
Smoking, N (%)			
Current	841 (15.6)	395 (15.8)	446 (15.5)
Former	2112 (39.2)	1178 (47.0)	934 (32.4)
Never	2433 (45.2)	932 (37.2)	1501 (52.1)
BMI (kg/m^2), median (IQR)	28.1 (25.3 - 31.3)	28.7 (26.2 – 31.5)	27.5 (24.6 – 31.0)
Waist (cm), mean (SD)	95.3 (13.8)	101.6 (11.9)	89.9 (13.0)
Diabetes, N (%)	442 (8.3)	264 (10.6)	178 (6.2)
Hypertension, N (%)	2295 (42.6)	1145 (45.7)	1150 (39.9)
SBP (mmHg), mean (SD)	135.6 (19.8)	139.2 (18.6)	132.4 (20.3)
DBP (mmHg), mean (SD)	82.3 (11.2)	83.4 (11.2)	81.4 (11.1)
CV conditions, N (%)			
None	4797 (89.1)	2128 (85.0)	2669 (92.6)
One	430 (8.0)	264 (10.5)	166 (5.8)
Two or more	159 (3.0)	113 (4.5)	46 (1.6)
GFRcr, median (IQR)	82 (69 – 92)	82 (70 – 92)	81 (69 – 93)
GFRcys, median (IQR)	80 (67 – 93)	81 (68 – 94)	79 (66 – 92)

BMI, body mass index; CV, cardiovascular; DBP, diastolic blood pressure; GFRcr, glomerular filtration rate estimated from creatinine; GFRcys, glomerular filtration rate estimated from cystatin C; SBP, systolic blood pressure

Data were missing for waist circumference (N=21), body mass index (N=14), diabetes (N=52) and blood pressure (N=30)

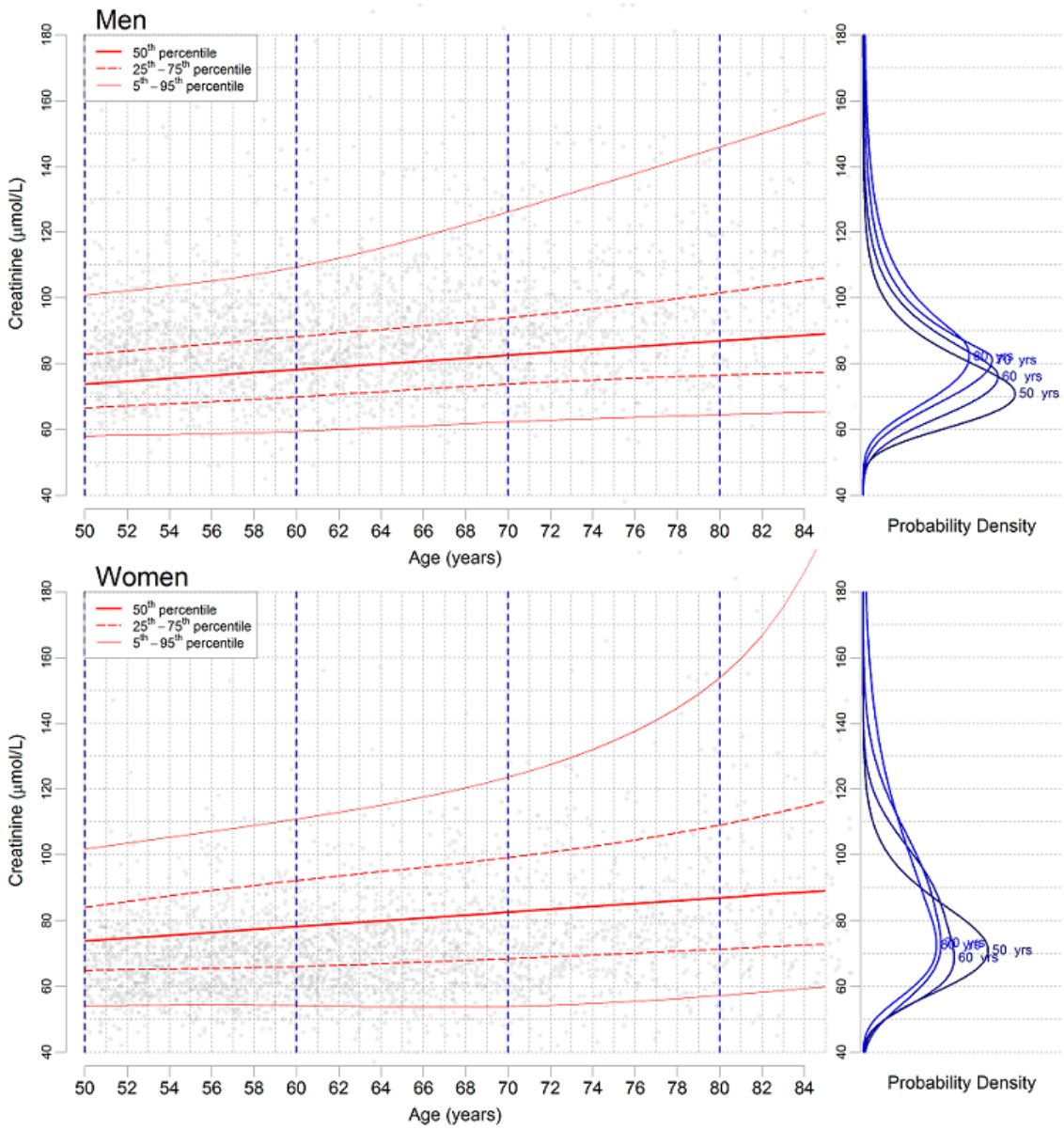


Figure 4.2: Predicted population limits (5th, 25th, 50th, 75th and 95th centiles) for creatinine (µmol/L) per year of age between 50 and 85 years in men (top panel) and women (bottom panel) superimposed on scatter plots (grey dots) of the observed relationship between creatinine and age. The side panels illustrate the modelled distribution of creatinine at specific ages (50, 60, 70 and 80 years).

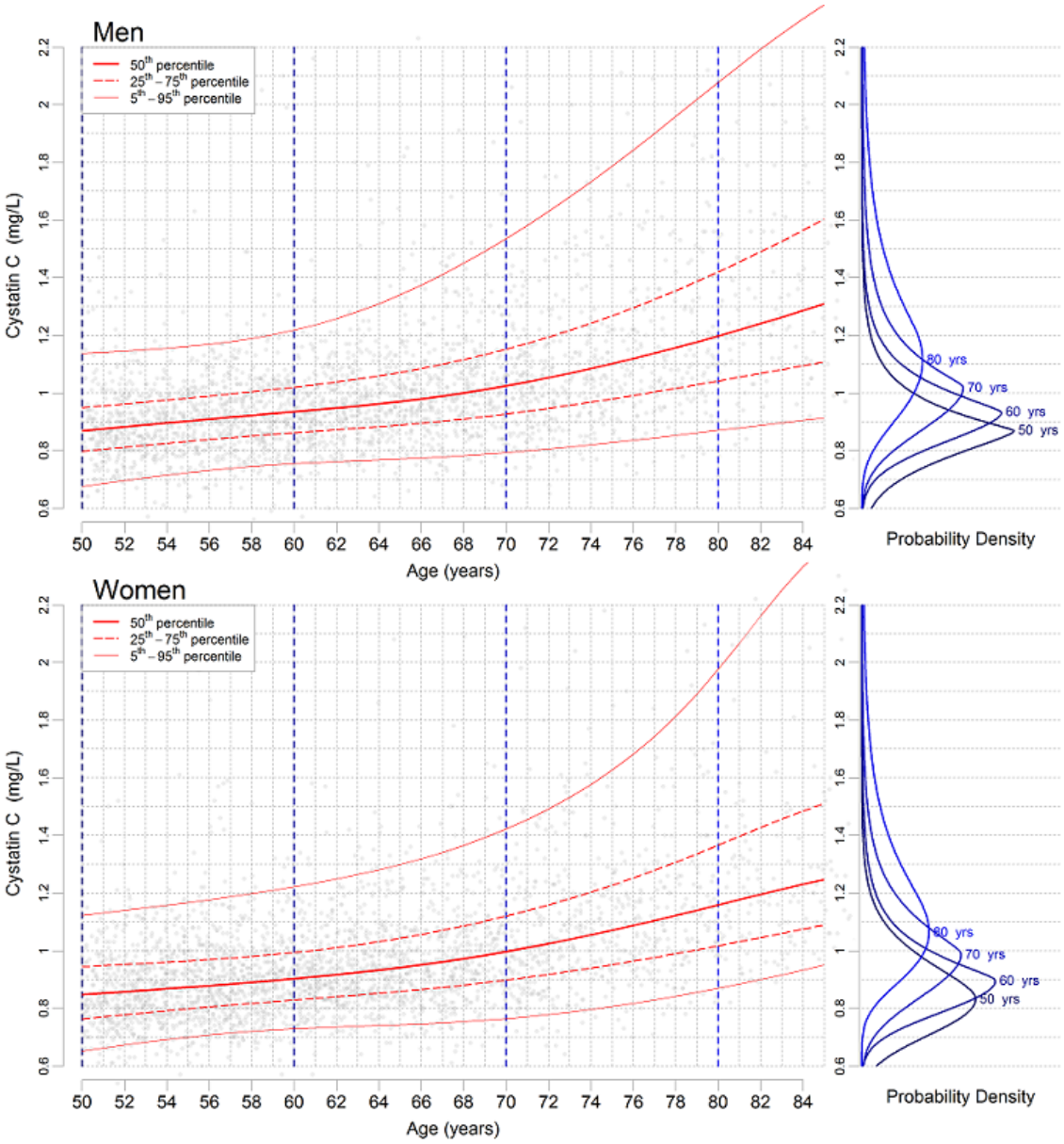


Figure 4.3: Predicted population limits (5th, 25th, 50th, 75th and 95th centiles) for cystatin C (mg/L) per year of age between 50 and 85 years in men (top panel) and women (bottom panel) superimposed on scatter plots (grey dots) of the observed relationship between cystatin C and age. The side panels illustrate the modelled distribution of cystatin C at specific ages (50, 60, 70 and 80 years).

4.3.3 Cystatin C as a confirmatory test of Stage 3a chronic kidney disease

A total of 463 participants had CKD Stage 3a defined by GFRcr 45-59 mL/min per 1.73m^2. The predicted probability of GFRcys <60 mL/min per 1.73m^2 in this subgroup of participants increased with age (Figure 4.4). For example the probability (95% confidence interval) of GFRcys <60 mL/min per 1.73m^2 for an individual aged 50, 60, 70 and 80 years was 0.15 (0.08 to 0.22), 0.34 (0.27 to 0.41), 0.60 (0.55 to 0.65) and 0.81 (0.76 to 0.86) respectively. This pattern of increasing probability with age was consistent in men and women.

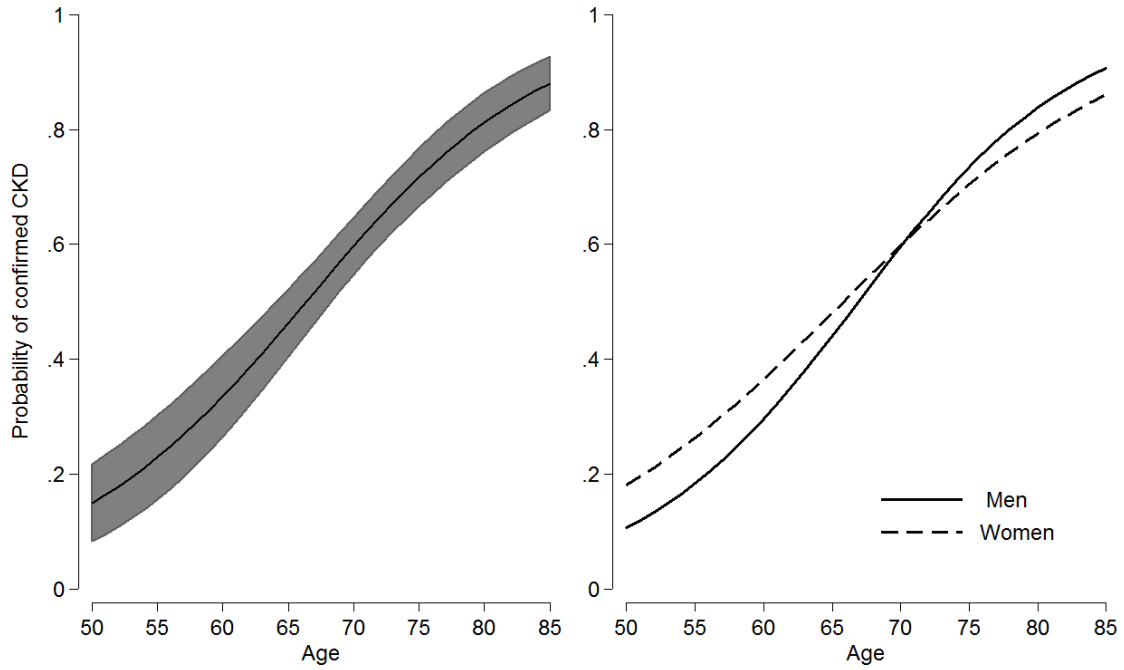


Figure 4.4: Predicted probability of GFRcys <60 mL/min per 1.73m^2 per year of age (left panel), and stratified by gender (right panel), among participants with CKD stage 3a

Table 4.3 compares the clinical characteristics of participants (all with CKD Stage 3a) with confirmed and unconfirmed CKD, overall and within age categories (50-64, 65-74 and ≥75 years). Overall, participants with confirmed CKD (N=278, 60%) had a higher prevalence of diabetes (17 versus 8%), cardiovascular disease (27 versus 17%), and hypertension (76 versus 52%). Differences in mean waist circumference between confirmed and unconfirmed CKD were most marked in the oldest age category (99 cm versus 89 cm), whereas differences in mean blood pressure between the groups were most marked in the youngest age category (137/87 mmHg versus 132/82 mmHg in confirmed versus unconfirmed CKD). Among 173 participants aged ≥75 years with CKD Stage 3a, only 25 (14%) were reclassified as not having CKD after testing with cystatin C. In contrast, among 113 participants aged 50-64 years, a higher proportion (N=74, 65%) were reclassified as not having CKD, in keeping with a lower burden of cardiovascular risk factors in this group.

Table 4.3: Characteristics of participants with chronic kidney disease Stage 3a, confirmed or unconfirmed by cystatin C

Variable	All (N=463)		50-64 years (N=113)		65-74 years (N=177)		≥75 years (N=173)	
	Confirmed (278, 60%)	Unconfirmed (185, 40%)	Confirmed (39, 35%)	Unconfirmed (74, 65%)	Confirmed (91, 51%)	Unconfirmed (86, 49%)	Confirmed (148, 86%)	Unconfirmed (25, 14%)
Male, N (%)	121 (43.5)	76 (41.1)	12 (30.8)	28 (37.8)	41 (45.1)	38 (44.2)	68 (46.0)	10 (40)
Waist (cm)	99.7 (13.9)	96.2 (12.8)	98.5 (14.4)	96.9 (11.4)	101.6 (13.8)	97.5 (12.9)	98.7 (13.8)	89.4 (14.6)
Diabetes, N (%)	47 (17.0)	14 (7.7)	7 (18.0)	2 (2.7)	19 (20.9)	10 (11.8)	21 (14.3)	2 (8.0)
CVD, N (%)	76 (27.3)	31 (16.8)	5 (12.8)	8 (10.8)	24 (26.4)	16 (18.6)	47 (31.8)	7 (28.0)
HTN, N (%)	212 (76.3)	96 (51.9)	30 (76.9)	31 (41.9)	69 (75.8)	52 (60.5)	113 (76.4)	13 (52.0)
SBP (mmHg)	140.0 (21.4)	135.2 (20.9)	136.6 (21.6)	131.9 (20.3)	133.9 (22.0)	134.9 (21.2)	144.7 (19.9)	145.9 (19.1)
DBP (mmHg)	80.7 (11.9)	80.0 (11.1)	87.4 (11.3)	81.6 (12.0)	79.0 (11.0)	78.9 (10.9)	79.9 (12.0)	78.7 (8.4)

CVD, cardiovascular disease (yes/no); DBP, diastolic blood pressure; HTN, hypertension; SBP, systolic blood pressure
Numbers expressed as mean (standard deviation) unless otherwise stated

4.3.4 Prevalence of reduced kidney function

The prevalence of CKD, as defined by GFR <60 mL/min per 1.73m^2, is reported in Table 4.4 for the entire sample, by gender and by age category. Prevalence estimates are weighted to be representative of the Irish community-dwelling population aged 50 years and over. The overall prevalence of CKD varied between 14.3% and 19.1% depending on the estimating equation used and the choice of filtration marker. The highest prevalence estimates were observed with the cystatin C-only equation. The prevalence of CKD was consistently greater among female participants across all age categories. We observed a steep age gradient in the prevalence of CKD in both sexes (Figure 4.5). The prevalence of CKD exceeded 70% in participants aged 80 years and over using the cystatin C-only equation.

4.3.5 Expected values of GFR per year of age

The expected values of GFRcr for men and women are illustrated in Figure 4.6. The distribution of GFRcr demonstrated a gradual linear decrease in GFRcr with increasing age in both sexes. The distribution of GFRcys in men and women is illustrated in Figure 4.7. The slope of age-related decline in GFRcys was steeper than that for GFRcr, particularly in women. For example, a GFRcr of 60 mL/min per 1.73m^2 for an 80 year-old woman lies between the 25th and 50th centiles, whereas a GFRcys of 60 mL/min per 1.73m^2 lies between the 50th and 75th centiles.

Table 4.4: Prevalence of chronic kidney disease (95% confidence interval) by age category, gender and GFR estimating equation

Sample	N	CKD-EPI (cr)	MDRD	CKD-EPI (cys)	CKD-EPI (cr-cys)
All ages					
Total	5386	14.3 (13.1-15.5)	16.0 (14.8-17.3)	19.1 (17.8-20.6)	15.4 (14.1-16.7)
Male	2505	11.9 (10.6-13.4)	12.8 (11.4-14.3)	15.5 (13.9-17.3)	12.1 (10.7-13.6)
Female	2881	16.5 (14.7-18.3)	19.0 (17.2-20.9)	22.5 (20.6-24.6)	18.5 (16.7-20.5)
50 to 59 years					
Total	2274	3.0 (2.4-3.9)	5.0 (4.1-6.1)	3.2 (2.5-4.1)	2.2 (1.6-2.9)
Male	1032	2.6 (1.7-4.0)	4.3 (3.1-6.0)	2.4 (1.6-3.8)	1.6 (0.9-2.8)
Female	1242	3.5 (2.6-4.7)	5.7 (4.5-7.1)	3.9 (2.9-5.2)	2.7 (1.9-3.8)
60 to 69 years					
Total	1821	9.9 (8.4-11.5)	13.4 (11.8-15.2)	11.4 (9.8-13.2)	9.1 (7.7-10.7)
Male	849	8.9 (7.0-11.2)	11.0 (9.0-13.4)	9.6 (7.6-12.1)	7.3 (5.5-9.5)
Female	972	10.8 (8.8-13.2)	15.8 (13.4-18.5)	13.3 (11.0-15.9)	10.9 (8.8-13.4)
70 to 79 years					
Total	997	27.8 (24.8-31.1)	28.6 (25.5-31.9)	39.8 (36.4-43.2)	32.0 (28.8-35.4)
Male	497	24.9 (21.2-29.1)	23.9 (20.3-27.9)	34.6 (30.0-39.4)	27.3 (23.4-31.5)
Female	500	30.5 (26.0-35.4)	32.9 (28.1-38.0)	44.5 (39.6-49.6)	36.4 (31.6-41.4)
80 years and over					
Total	294	52.4 (46.1-58.5)	48.7 (42.4-55.1)	75.4 (69.8-80.3)	62.6 (56.2-68.6)
Male	127	49.6 (40.2-59.1)	44.1 (34.9-53.7)	73.2 (63.6-81.0)	58.8 (49.2-67.8)
Female	167	53.9 (45.6-61.9)	51.3 (43.1-59.5)	76.7 (69.5-82.6)	64.7 (56.5-72.2)

CKD-EPI, Chronic Kidney Disease Epidemiology; cr, creatinine; cys, cystatin C; MDRD, Modification of Diet in Renal Disease

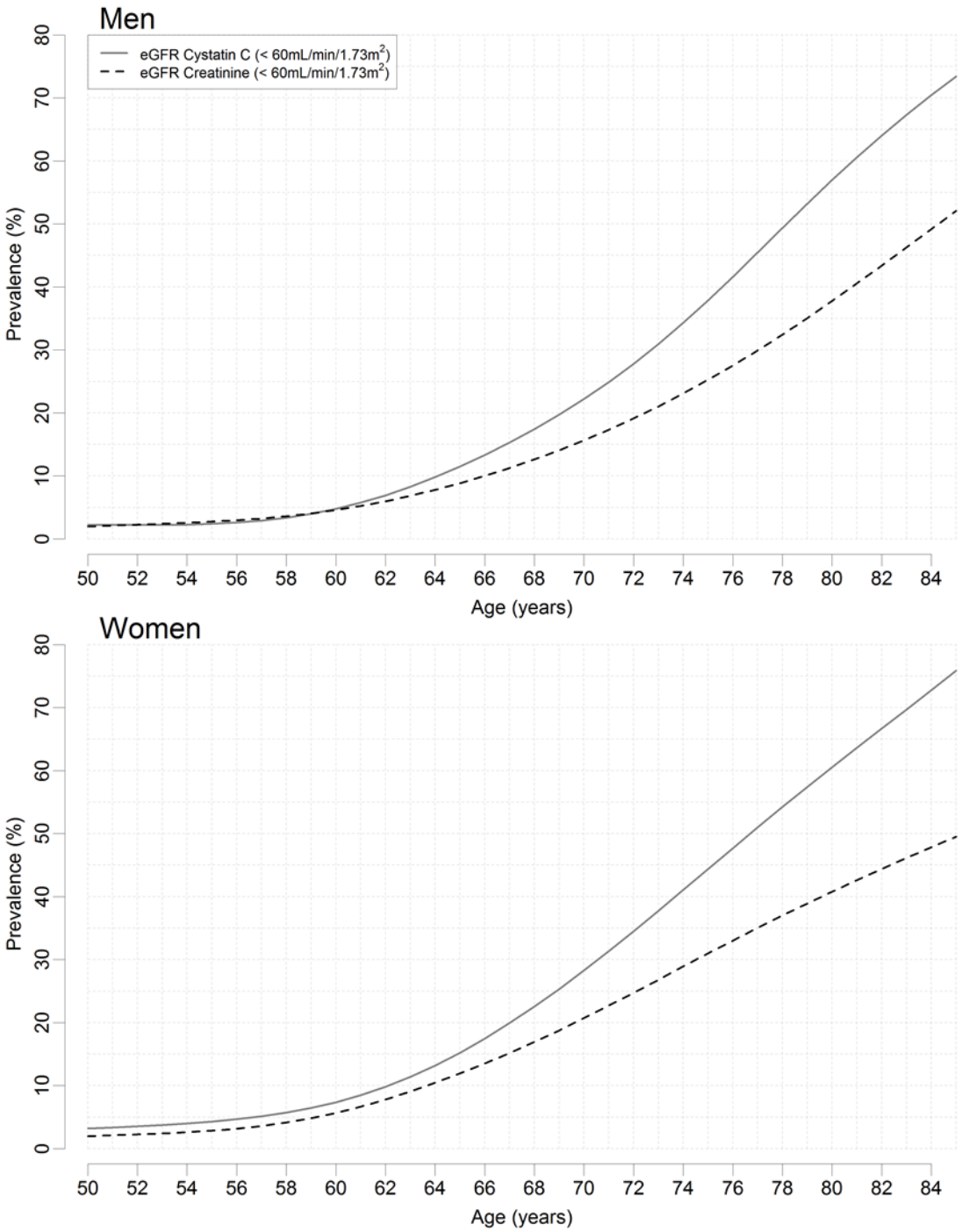


Figure 4.5: Prevalence of GFR <60 mL/min per 1.73m^2 per year of age in men (top panel) and women (bottom panel) calculated from creatinine (dotted line) or cystatin C (solid line)

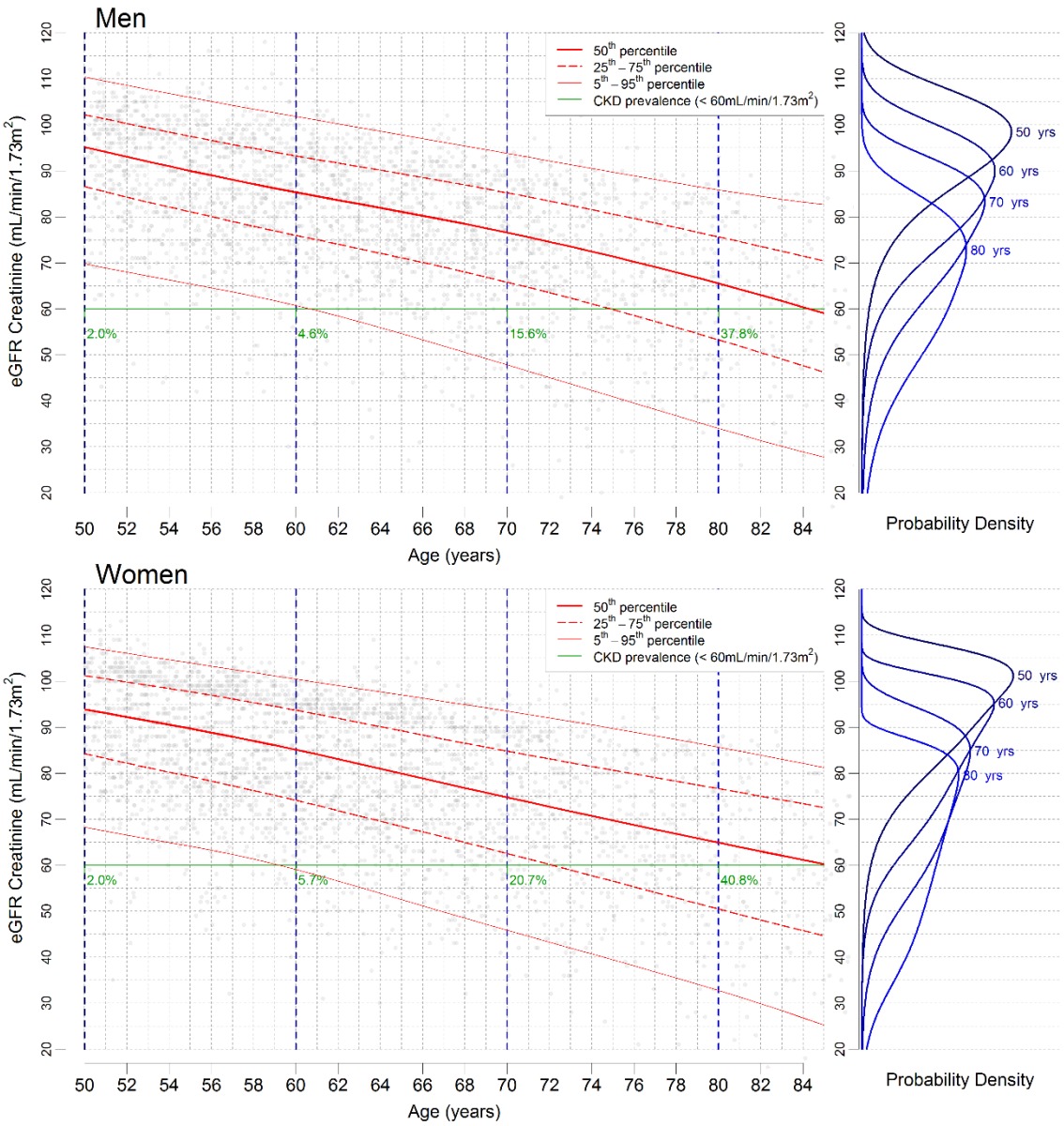


Figure 4.6: Predicted population limits (5th, 25th, 50th, 75th and 95th centiles) for GFR estimated from creatinine per year of age between 50 and 85 years in men (top panel) and women (bottom panel) superimposed on scatter plots (grey dots) of the observed relationship between GFRcr and age. The side panels illustrate the modelled distribution of GFRcr at specific ages (50, 60, 70 and 80 years) for men and women respectively.

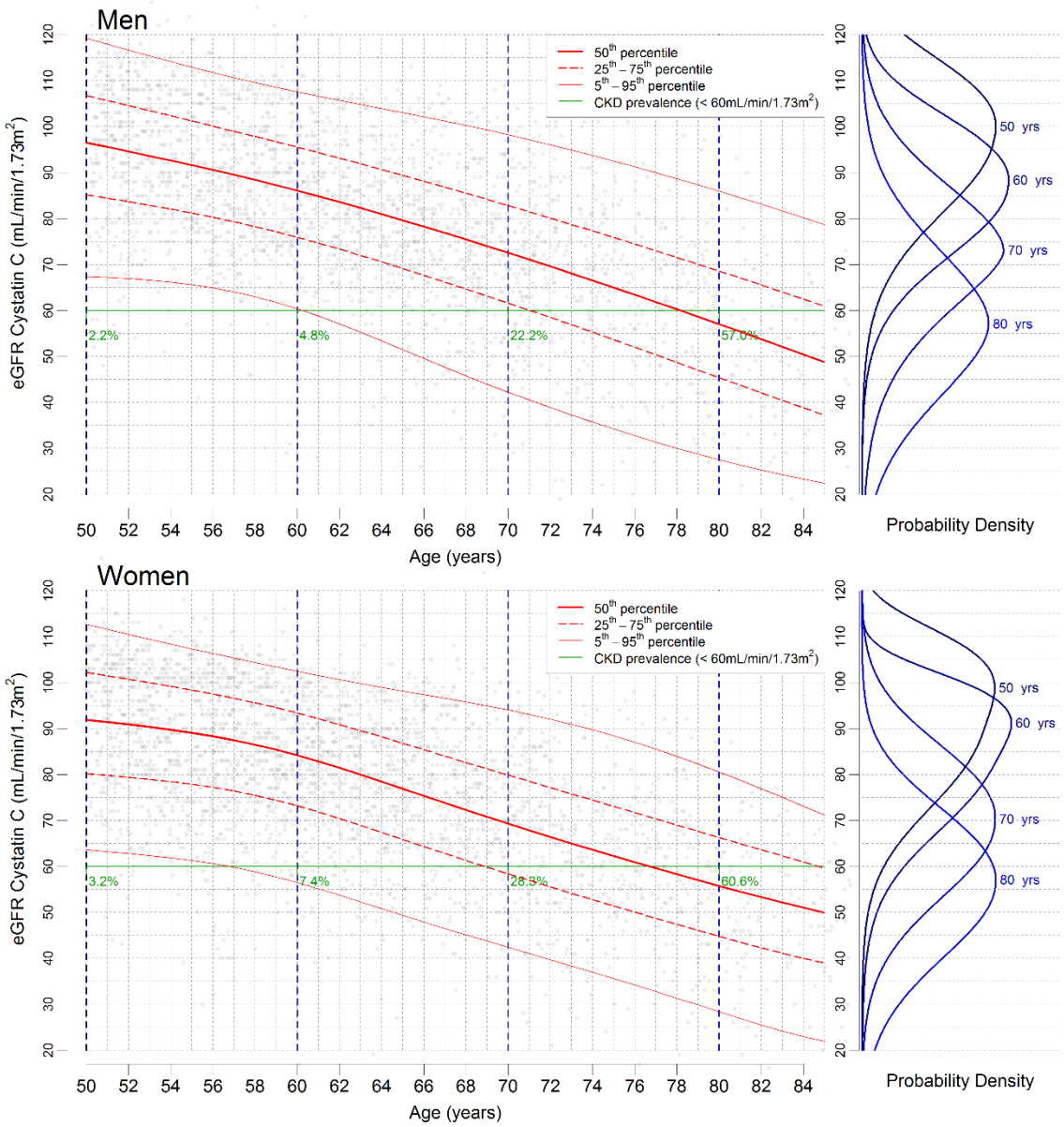


Figure 4.7: Predicted population limits (5th, 25th, 50th, 75th and 95th centiles) for GFR estimated from cystatin C per year of age between 50 and 85 years in men (top panel) and women (bottom panel) superimposed on scatter plots (grey dots) of the observed relationship between GFRcys and age. The side panels illustrate the modelled distribution of GFRcys at specific ages (50, 60, 70 and 80 years) for men and women respectively.

4.4 Discussion

The primary findings of this study were three-fold: (1) we observed progressive variability in the distribution of filtration markers with increasing age, which was much more pronounced for cystatin C than creatinine; (2) beyond the age of approximately 65 years there was a sharp curvilinear increase in cystatin C levels with age in both men and women, which was not observed with creatinine; (3) in the subgroup with CKD stage 3a, the predicted probability of GFRcys <60 mL/min per 1.73m^2 ("confirmed CKD") increased steadily with age. Taken together, these findings suggest that cystatin C performs better as a confirmatory test of CKD in middle-aged adults, while providing little additional diagnostic information in those over 75 years of age.

Cystatin C has consistently been shown to be a stronger predictor of hard adverse outcomes than creatinine, including in an older adult population (5, 6, 57). Conversely, a "normal" cystatin C level predicts a favourable outcome (113). The potential for cystatin C to stratify risk in this way was demonstrated in a large meta-analyses of both general population and CKD cohorts (59). Individuals whose CKD was not confirmed by cystatin C had a substantially lower risk profile for end stage kidney disease, cardiovascular and all-cause mortality. Given that the majority of older adults with CKD fall into the G3a category (GFR 45 to 59 mL/min per 1.73m^2), and their absolute risk of ESKD is low (11), it was hoped that additional testing with cystatin C could remove a large proportion of low-risk older adults from that category and reclassify them as not having CKD. It is evident from our findings, however, that such reclassification is not uniform across age. In the subpopulation of adults aged 75 years and over, we estimate that for every 7 adults tested, only 1 will be reclassified as not having CKD. This testing comes at a cost, both to the health care provider in terms of time and the expense of the additional assay, and to the individual patients who must undergo extra blood draws. Examining the distribution of cardiovascular risk factors in confirmed versus unconfirmed CKD suggests that the pre-test probability of confirming CKD in those over 75 years could be further refined by consideration of these risk factors, for example waist circumference.

Our findings are in keeping with an analysis from the REasons for Geographical And Racial Differences in Stroke (REGARDS) study (116). The authors examined the reclassification of CKD using cystatin C within three age categories (<65, 65-79, ≥80 years) and found that CKD was confirmed in almost all participants aged 80 years and over. The REGARDS cohort is a United States population sample with over-representation of black participants, and the authors did

not stratify their results by race. The present analysis provides a more granular description of the relationship between cystatin C and age, including the probability of CKD reclassification by continuous age, in a homogeneous and population-representative European Caucasian sample. Our data suggest that the clinical utility and cost-effectiveness of measuring cystatin C may be maximised in middle-aged adults, in whom the distribution of cystatin C is less variable, and the predicted probability of GFRcys <60 mL/min per 1.73m^2 is lower. For example, two-thirds of community-dwelling adults aged 50 to 64 years would be reclassified as not having CKD after cystatin C testing, potentially resulting in fewer investigations and fewer referrals to nephrology services.

The differences we observed in the relative distributions of cystatin C and creatinine with age were striking. Few studies have interrogated the relationship between cystatin C and age. A pooled analysis of individual-level data from four different cohorts demonstrated a non-linear relationship between cystatin C and age using a locally weighted smoothed regression plot, even in the absence of traditional risk factors for kidney disease (117). The authors compared the distribution of cystatin C (untransformed) by decade of age using kernel density estimates and showed increasing mean and variance with each ascending decade in this clinically heterogeneous sample. Data from a sub-sample of NHANES III, which encompassed a broader age range, showed that median cystatin C levels began to rise beyond the age of 40 years in both sexes (118). The distribution of the inverse of cystatin C was modelled across the age range, which did not facilitate interpretation of variability with age. These two studies pre-dated both the standardisation of cystatin C assays and the development of a well-validated GFR estimating equation using cystatin C (53, 119). In the present analysis we employed a novel and flexible modelling approach to describe and compare the distributions of cystatin C and creatinine across age in a well-characterised national cohort of older community-dwelling adults.

When discussing the clinical implications of kidney disease, clinicians tend to be focused on outcomes, principally cardiovascular disease, ESKD and mortality. The risk of these outcomes has underpinned the diagnostic thresholds for CKD (7). The same outcomes may not be the primary concern of patients, who may wish to know how their GFR compares to others of the same age in the population. This may be particularly pertinent for older individuals, in whom the risk of hard outcomes related to their kidney function is low. Our modelling approach facilitated the generation of population-level data for GFR across a continuous age range, and stratified by gender. We suggest that this data could inform discussions with patients when explaining the significance of their GFR result. Take for example two men with the same GFR value but different

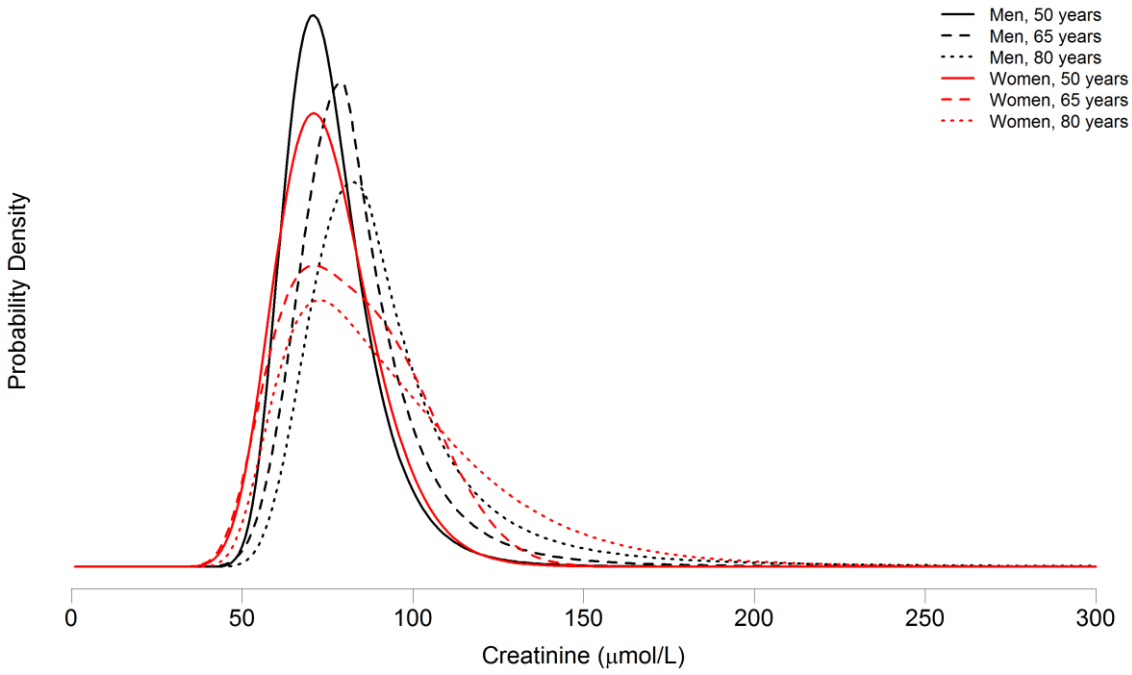
ages – one is 60 years old and the other is 80 years old. It is evident from Figure 4.6 that a GFR of 60 mL/min per 1.73m^2 has very different implications at a population level for each of them. Less than 5% of the male general population aged 60 would be expected to have a GFR of 60 mL/min per 1.73m^2, whereas the same GFR would be expected in approximately 40% of 80 year olds. Both individuals need to be counselled about their risks, however the nature of these risks is not necessarily the same. The discussion with the 60 year-old may be centred on cardiovascular risk reduction or blood pressure control, whereas the emphasis for the 80 year-old may be the avoidance of preventable acute kidney injury or exercising caution with certain medications such as non-steroidal anti-inflammatory drugs. In either case, framing the level of GFR in the context of expected levels for the background population, rather than a dichotomous definition of disease versus no disease, is likely to prove useful in these clinical encounters.

Our study has a number of limitations. Creatinine and cystatin C were measured at a single time point. The cystatin C guideline is suggested for individuals without evidence of kidney damage such as albuminuria, however we did not measure urinary albumin in tandem with the plasma biomarkers. For the same reason, estimates of CKD prevalence are under-estimated. Some of our health variables were self-reported physician-diagnosed conditions, which are subject to measurement error. These limitations are balanced by several strengths. The TILDA sample is large and enriched for the at-risk population. Our study population included 1291 participants (24% of the cohort) who were aged 70 years or over. Health assessments were performed in the home for older and frailer participants who could not attend the research centre. Both creatinine and cystatin C were measured simultaneously in a central laboratory using standardised assays for both filtration markers. A key strength of our study is the household-level sampling of participants which, along with application of an inverse probability weight, facilitated the generation of robust population-level data for kidney biomarkers.

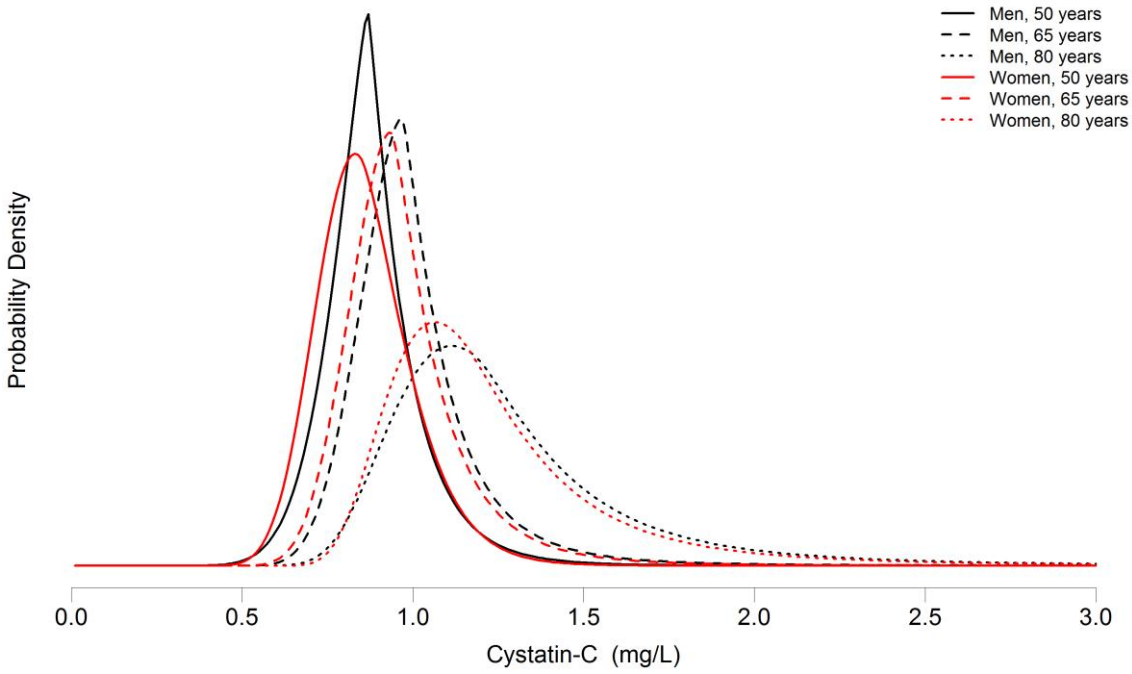
In conclusion, we observed substantial non-linearity in cystatin C distribution as a function of age in a large cohort of community-dwelling older adults. The predicted probability of "confirmed CKD" using cystatin C increased steadily with age, approaching 80% at age 80 years. Our findings suggest that the usefulness of cystatin C as a confirmatory test of CKD may not be uniform across age. Among community-dwelling adults over 75 years, the diagnostic yield of additional testing with cystatin C may be small relative to the extra cost and burden involved. While cystatin C clearly has a role in clinical risk-stratification of CKD, more work is needed to further our understanding of this biomarker and its clinical utility in the general population of

older adults. Specifically, future studies should investigate the cost-effectiveness and acceptability of using cystatin C as a confirmatory test of CKD irrespective of age.

4.5 Appendix



Appendix Figure 4.1: Distribution of creatinine at ages 50, 65 and 80 years



Appendix Figure 4.2: Distribution of cystatin C at ages 50, 65 and 80 years

5 Cross-sectional association between kidney function and objective tests of physical performance

5.1 Introduction

Chronic kidney disease increases the risk of cardiovascular and all-cause mortality independent of traditional risk factors such as hypertension (82) and diabetes (81). The risk-based paradigm of CKD classification (4) has come under scrutiny due to a high burden of CKD among older individuals despite a comparatively low incidence of end stage kidney disease (11). The majority of older adults with CKD have relatively modest reductions in GFR, and would not be expected to experience symptoms attributable solely to kidney disease. It is in this heterogeneous population that there is a pressing need to better understand the clinical phenotype of CKD. Changing the outcome measure in the older CKD population from a "hard" outcome such as mortality to a more proximal, person-centred outcome such as frailty could improve our understanding of CKD as a disease entity.

Studies of frailty in kidney disease to date have tended to adopt a phenotypic definition of frailty to identify robust, pre-frail and frail individuals (83). The frailty phenotype, a combination of self-reported and objectively measured variables, has demonstrated an independent and graded association with CKD and has been shown to predict all-cause mortality in the CKD population (87, 120). There has, however, been considerable heterogeneity among prior studies with respect to the definition of frailty (121). The original frailty criteria have not been consistently applied across different cohorts (122). There are potential limitations associated with the use of self-reported variables in the context of perceived physical ability (123). Recent studies have instead focused their attention on objective measures of physical performance in specific populations such as older hospitalised patients (124), individuals with coronary artery disease (123), and CKD patients recruited from out-patient clinics (91). There is a paucity of data regarding the relationship between objective tests of physical performance and kidney function in the general population of older adults. Most studies to date have used creatinine to estimate glomerular filtration rate. Creatinine is known to display U-shaped relationships with clinical outcomes due to confounding by muscle mass, an issue that is particularly relevant in the context of ageing and frailty. Cystatin C has emerged as a potentially preferable filtration marker in older people as it appears to be less influenced by muscle mass (125) or dietary protein intake (126).

The aims of this study were to examine the association between GFR and objective physical outcomes across the GFR range in community-dwelling older adults, investigate whether this relationship varies by age, and compare the relative ability of cystatin C or creatinine to predict physical performance.

5.2 Methods

5.2.1 Participants

This was a cross-sectional analysis from Wave 1 of The Irish Longitudinal Study on Ageing. In the primary analysis, we included participants who completed a health centre assessment with complete data for kidney function and all three outcomes (N=4562, Figure 5.1). In a secondary analysis, we included participants who performed the TUG and grip strength tests during either a centre- or home-based assessment (N=5206). In keeping with the original frailty construct from the Cardiovascular Health Study, we excluded participants with Parkinson Disease (PD) or stroke, or a MMSE score less than 18 out of 30 (83).

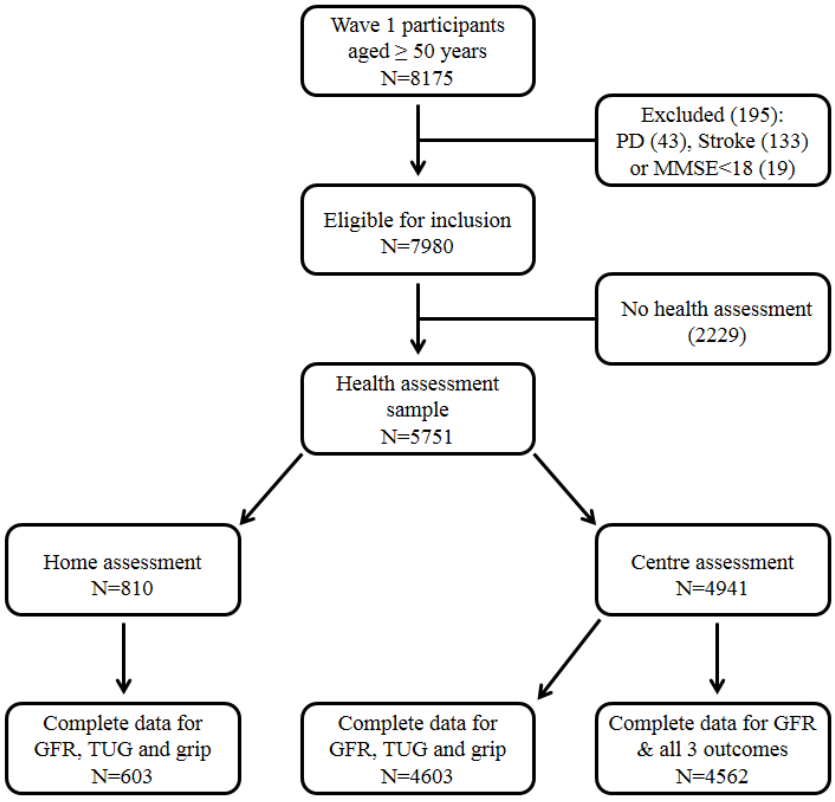


Figure 5.1: Flowchart of case ascertainment

5.2.2 Outcomes

Gait speed was measured using the GAITRite portable electronic walkway system (CIR Systems Inc, Havertown, PA). Participants were instructed to walk at their usual pace along the 4.88 metre walkway. They started walking 2.5 metres before the walkway and finished walking 2 metres after the walkway to allow for acceleration and deceleration respectively. The average gait speed from two walks was recorded in centimetres per second (cm/s). For the TUG test participants were asked to stand from a seated position, walk 3 metres at their usual pace, turn around, walk back to the chair and sit down. The time taken from the command "Go" to when the participant was sitting with their back resting against the chair was recorded in seconds. In the health centre the chair had armrests and was 46cm high. Walking aids were permitted and the test was performed once. Grip strength was measured twice from the dominant hand using a hydraulic hand dynamometer (Baseline, Fabrication Enterprises Inc., White Plains, NY). The maximum reading of force was recorded in kilograms (kg).

5.2.3 Predictor

The CKD-EPI equations were used to estimate GFR from either cystatin C alone (53) or creatinine alone (25). Both GFRcys and GFRcr were categorised as follows: ≥90 mL/min per 1.73m^2 (reference); 75-89 mL/min per 1.73m^2; 60-74 mL/min per 1.73m^2; 45-59 mL/min per 1.73m^2; <45 mL/min per 1.73m^2. These categories are in keeping with KDIGO guidelines for staging of GFR. Due to small numbers of participants with GFR values below 30 mL/min per 1.73m^2, we created a single category for all participants with GFR less than 45 mL/min per 1.73m^2. Cystatin C and creatinine were measured simultaneously from frozen plasma using standardised assays as described previously.

5.2.4 Covariates

Participant characteristics included age, sex, smoking history (current/former/never) and self-reported physician-diagnosed conditions. Medication use was recorded during the interview and cross-checked with medication labels. All medications were coded according to the World Health Organisation Anatomical Therapeutic Chemical Classification (104). Low (LDL) and high density lipoprotein (HDL) were measured from participants' blood prior to freezing of the samples. We defined the presence of diabetes as a self-reported physician's diagnosis and/or receiving insulin or oral hypoglycaemic medication. We defined the presence of hypertension as a self-reported physician's diagnosis and/or receiving antihypertensive medications. The

presence of cardiovascular disease was defined as the number (0, 1, 2 or more) of the following self-reported physician-diagnosed conditions: angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, heart failure, or transient ischaemic attack. Height and waist circumference were measured at the health assessment. Comorbidity variables included polypharmacy (regular use of ≥5 medications excluding supplements) and number (0, 1, 2 or more) of the following self-reported physician-diagnosed chronic health conditions: chronic lung disease, asthma, arthritis, osteoporosis, malignancy, stomach ulcers, varicose ulcers, cirrhosis or severe liver damage.

5.2.5 Statistical analysis

Analyses were performed using Stata version 14 (StataCorp, College Station, TX). Continuous variables are presented as mean (SD) and median (IQR) for normal and non-normal distributions respectively. Categorical variables are presented as count (percentage). The relationships between GFR categories and the outcomes gait speed and grip strength were assessed by multivariable linear regression. As TUG demonstrated a prominent right skew, we used quantile regression to investigate the relationship between GFR categories and TUG time. Model 1 was adjusted for age (uncentred), age-squared, sex, height and waist circumference. Model 2 was adjusted for model 1 covariates plus cardiovascular disease, diabetes, hypertension, smoking, LDL, HDL, polypharmacy and chronic health conditions.

To further examine the relationship between GFR and each outcome in the health centre cohort, we modelled natural splines of GFR in the multivariable adjusted models. We generated restricted cubic splines of continuous GFR by placing five knots at equally spaced intervals (5th, 27.5th, 50th, 72.5th and 95th centiles) along the distribution of GFR. In an exploratory analysis, we investigated whether the relationship between GFR and gait speed varied by age, by interacting continuous age with continuous GFR, both expressed as quadratic terms. Interactions are presented graphically using the *marginsplot* command in Stata. We modelled the associations between GFRcys and each outcome within age strata (50-64, 65-74, ≥75 years). Stratum-specific models were adjusted for age, sex, height and waist circumference.

Missing data were assumed to be missing at random, and only complete cases were analysed.

5.3 Results

5.3.1 Characteristics of the health centre sample

A total of 4562 participants had complete data for kidney function and all outcomes, and were included in the primary analysis. Participant characteristics are detailed in Table 5.1. Mean (SD) age of the cohort was 61.8 (8.3) years, 53.6% were female and median (IQR) GFRcys was 82 (70-94) mL/min per 1.73m^2. Compared to participants with preserved kidney function (GFRcys≥90 mL/min per 1.73m^2), participants in the lowest GFRcys category (<45 mL/min per 1.73m^2) were older (73.7 vs 57.2 years) and tended to have a greater burden of cardiovascular and non-cardiovascular conditions. Compared to the final study population, participants excluded because of missing data for either a physical performance outcome (N=97) or GFRcys (N=282) tended to be slightly older, were more likely female and had a higher prevalence of diabetes and non-cardiovascular comorbidity (Appendix Table 5.1).

5.3.2 Association between cystatin C estimated GFR and physical outcomes

The association between categories of GFRcys and each outcome is provided in Table 5.2. There was a trend for poorer performance across each test with decreasing GFRcys. In multivariable-adjusted models (Model 2), participants in the lowest GFRcys category had, on average, 3.32cm/s (95% confidence interval [95%CI] 0.02 to 6.62) slower gait speed compared to the reference group. They also demonstrated longer median TUG time (0.31 seconds [95% CI -0.04 to 0.65]) and lower mean grip strength (-1.32kg [95% CI -0.20 to -2.44]). The relationship between restricted cubic splines of GFRcys and each outcome is illustrated in Figure 5.2. For gait speed and TUG time, the threshold for poorer performance was below a GFRcys of approximately 80 mL/min per 1.73m^2, beyond which the relationship was linear. The relationship between GFRcys and grip strength was broadly linear across the GFRcys range.

Table 5.1: Characteristics of the health centre assessment sample

Variable	Cystatin C estimated GFR category				
	≥ 90 (N=1524)	75-89 (N=1486)	60-74 (N=1027)	45-59 (N=379)	< 45 (N=146)
Age	57.2 (6.1)	60.9 (6.7)	65.0 (8.2)	69.9 (8.2)	73.7 (8.2)
Female sex	790 (51.8)	792 (53.3)	555 (54.0)	235 (62.0)	75 (51.4)
Height (cm)	167.2 (8.9)	166.6 (9.2)	165.9 (9.2)	163.7 (9.0)	163.6 (8.6)
Smoking					
Current	167 (11.0)	224 (15.1)	198 (19.3)	71 (18.7)	13 (8.9)
Former	618 (40.6)	578 (38.9)	382 (37.2)	153 (40.4)	70 (48.0)
Never	739 (48.5)	684 (46.0)	447 (43.5)	155 (40.9)	63 (43.2)
Waist (cm)	91.9 (13.0)	94.0 (12.9)	97.5 (13.9)	99.2 (14.2)	101.0 (15.8)
Hypertension	433 (28.4)	488 (32.8)	495 (48.2)	246 (64.9)	119 (81.5)
Diabetes	72 (4.7)	73 (4.9)	70 (6.8)	44 (11.6)	27 (18.5)
CV conditions					
0	1458 (95.7)	1386 (93.3)	908 (88.4)	317 (83.6)	100 (68.5)
1	53 (3.5)	78 (5.3)	86 (8.4)	49 (12.9)	27 (18.5)
2 or more	13 (0.9)	22 (1.5)	33 (3.2)	13 (3.4)	19 (13.0)
LDL (mmol/L)	3.02 (0.92)	3.03 (0.92)	2.87 (0.96)	2.68 (0.95)	2.49 (0.89)
HDL (mmol/L)	1.62 (0.45)	1.57 (0.42)	1.51 (0.43)	1.45 (0.41)	1.39 (0.44)
Comorbidities					
0	921 (60.4)	791 (53.2)	496 (48.3)	143 (37.7)	50 (34.3)
1	447 (29.3)	513 (34.5)	356 (34.7)	156 (41.2)	59 (40.4)
2 or more	156 (10.2)	182 (12.3)	175 (17.0)	80 (21.1)	37 (25.3)
Polypharmacy	97 (6.4)	146 (9.9)	187 (18.3)	115 (30.8)	73 (50.7)

Numbers expressed as mean (SD) or count (percent)
CV, cardiovascular; HDL, high density lipoprotein; LDL, low density lipoprotein; TUG, timed up and go
Data missing for height (N=1), waist circumference (N=6), LDL/HDL (N=9), polypharmacy (N=21)

Table 5.2: Relationship between categories of cystatin C estimated GFR and physical performance tests

GFRcys	Model 1	P	Model 2	P
Gait Speed (cm/s)				
≥ 90	137.37 *(Reference)*		136.66 *(Reference)*	
75-89	0.14 (-1.15 to 1.44)	0.83	0.63 (-0.65 to 1.90)	0.34
60-74	-1.76 (-3.28 to -0.23)	0.02	-0.48 (-2.0 to 1.04)	0.54
45-59	-6.40 (-8.62 to -4.17)	<0.001	-3.83 (-6.06 to -1.59)	0.001
< 45	-7.21 (-10.49 to -3.93)	<0.001	-3.32 (-6.62 to -0.02)	0.05
P trend[a]	<0.001		0.006	
Timed Up and Go (seconds)				
≥ 90	8.30 *(Reference)*		8.35 *(Reference)*	
75-89	-0.02 (-0.15 to 0.11)	0.74	-0.07 (-0.20 to 0.06)	0.30
60-74	0.12 (-0.04 to 0.27)	0.13	0.07 (-0.09 to 0.23)	0.38
45-59	0.56 (0.34 to 0.77)	<0.001	0.26 (0.03 to 0.49)	0.03
< 45	0.61 (0.29 to 0.94)	<0.001	0.31 (-0.04 to 0.65)	0.08
P trend[a]	<0.001		0.02	
Grip Strength (kg)				
≥ 90	27.87 *(Reference)*		27.86 *(Reference)*	
75-89	-0.31 (-0.74 to 0.12)	0.16	-0.28 (-0.72 to 0.15)	0.20
60-74	-0.40 (-0.91 to 0.10)	0.12	-0.38 (-0.89 to 0.14)	0.15
45-59	-0.62 (-1.36 to 0.12)	0.10	-0.53 (-1.29 to 0.23)	0.17
< 45	-1.44 (-2.53 to -0.35)	0.01	-1.32 (-2.44 to -0.20)	0.02
P trend[a]	0.01		0.03	

Model 1 (N=4555) adjusted for age, age-squared, sex, height and waist circumference

Model 2 (N=4525) adjusted for model 1 covariates plus cardiovascular disease, diabetes, hypertension, smoking, low and high density lipoprotein, polypharmacy, chronic health conditions

[a] p value for linear trend across ordered categorical variable

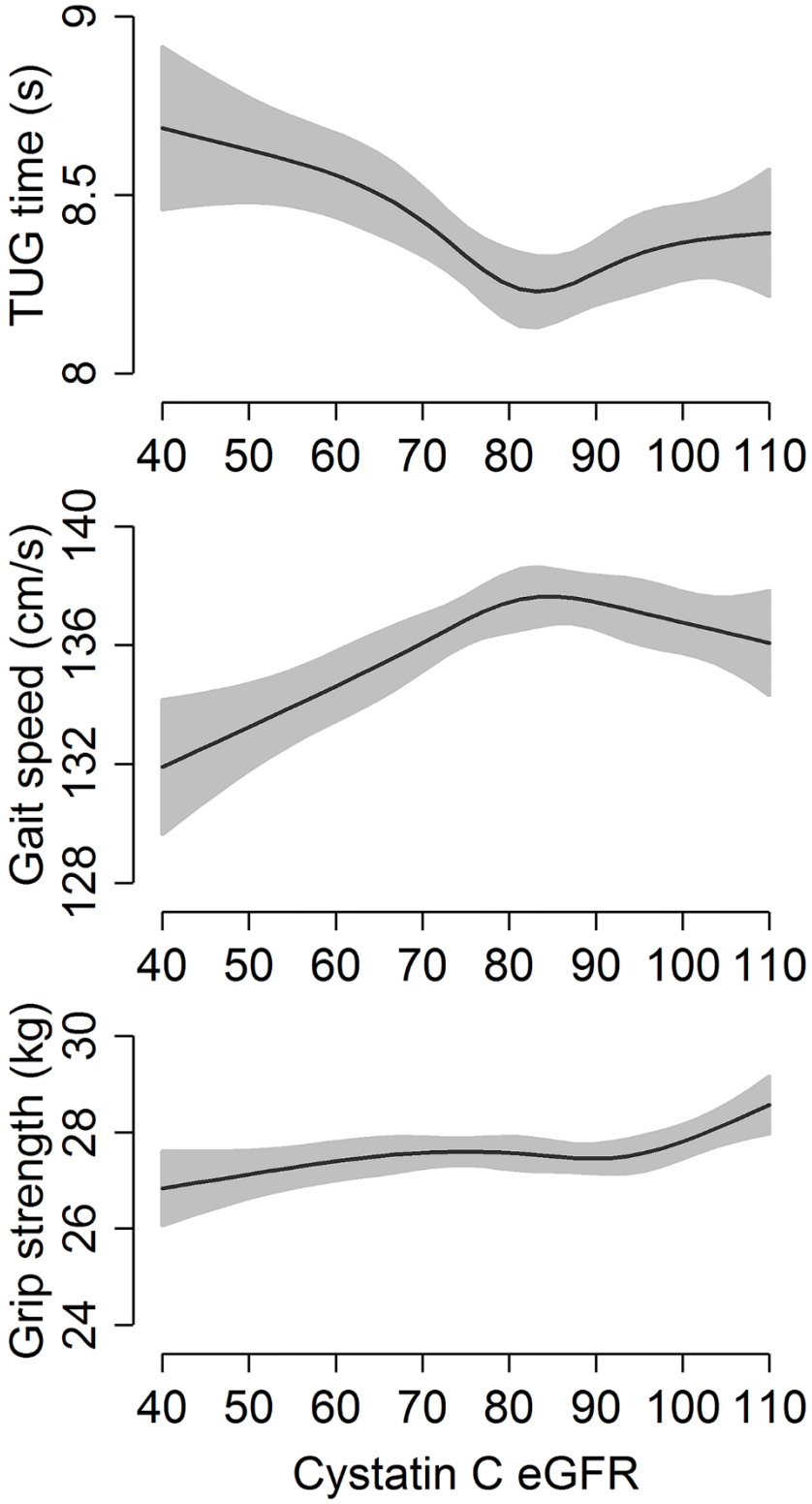


Figure 5.2: Multivariable adjusted relationship between restricted cubic splines of cystatin C estimated GFR and physical performance tests

5.3.3 Association between creatinine estimated GFR and physical outcomes

The associations between GFRcr categories and each outcome are described in Table 5.3. In multivariable-adjusted models (Model 2), GFRcr was not associated with poorer performance in any test. For some outcomes, the direction of the relationship was opposite to that of GFRcys. For example, participants with GFRcr of 45-59 mL/min per 1.73m^2 had, on average, 1.36 (95% CI 0.62 to 2.11) kg *higher* grip strength than those with GFRcr ≥90 mL/min per 1.73m^2. The relationships between cubic splines of GFRcr and the outcomes gait speed and TUG tended towards a U-shape or inverse U-shape (Figure 5.3).

Table 5.3: Relationship between categories of creatinine estimated GFR and physical performance tests

GFRcr	Model 1	P	Model 2	P
Gait Speed (cm/s)				
≥ 90	135.07 *(Reference)*		135.14 *(Reference)*	
75-89	1.86 (0.58 to 3.14)	0.004	1.68 (0.42 to 2.94)	0.009
60-74	2.69 (1.18 to 4.21)	<0.001	2.53 (1.04 to 4.02)	0.001
45-59	0.86 (-1.36 to 3.08)	0.45	1.55 (-0.65 to 3.75)	0.17
< 45	-4.87 (-8.60 to -1.14)	0.01	-2.26 (-5.98 to 1.46)	0.23
P trend[a]	0.37		0.08	
Timed Up and Go (seconds)				
≥ 90	8.40 *(Reference)*		8.40 *(Reference)*	
75-89	-0.03 (-0.16 to 0.09)	0.63	-0.02 (-0.15 to 0.11)	0.78
60-74	-0.10 (-0.25 to 0.05)	0.18	-0.13 (-0.28 to 0.03)	0.11
45-59	-0.004 (-0.22 to 0.21)	0.97	-0.11 (-0.34 to 0.12)	0.36
< 45	0.51 (0.15 to 0.88)	0.006	0.32 (-0.07 to 0.71)	0.11
P trend[a]	0.85		0.28	
Grip Strength (kg)				
≥ 90	26.99 *(Reference)*		27.04 *(Reference)*	
75-89	0.78 (0.36 to 1.21)	<0.001	0.73 (0.31 to 1.16)	0.001
60-74	0.91 (0.41 to 1.41)	<0.001	0.85 (0.34 to 1.35)	0.001
45-59	1.35 (0.62 to 2.09)	<0.001	1.36 (0.62 to 2.11)	<0.001
< 45	0.98 (-0.26 to 2.21)	0.12	1.03 (-0.23 to 2.29)	0.11
P trend[a]	<0.001		<0.001	

[a] p value for linear trend across ordered categorical variable

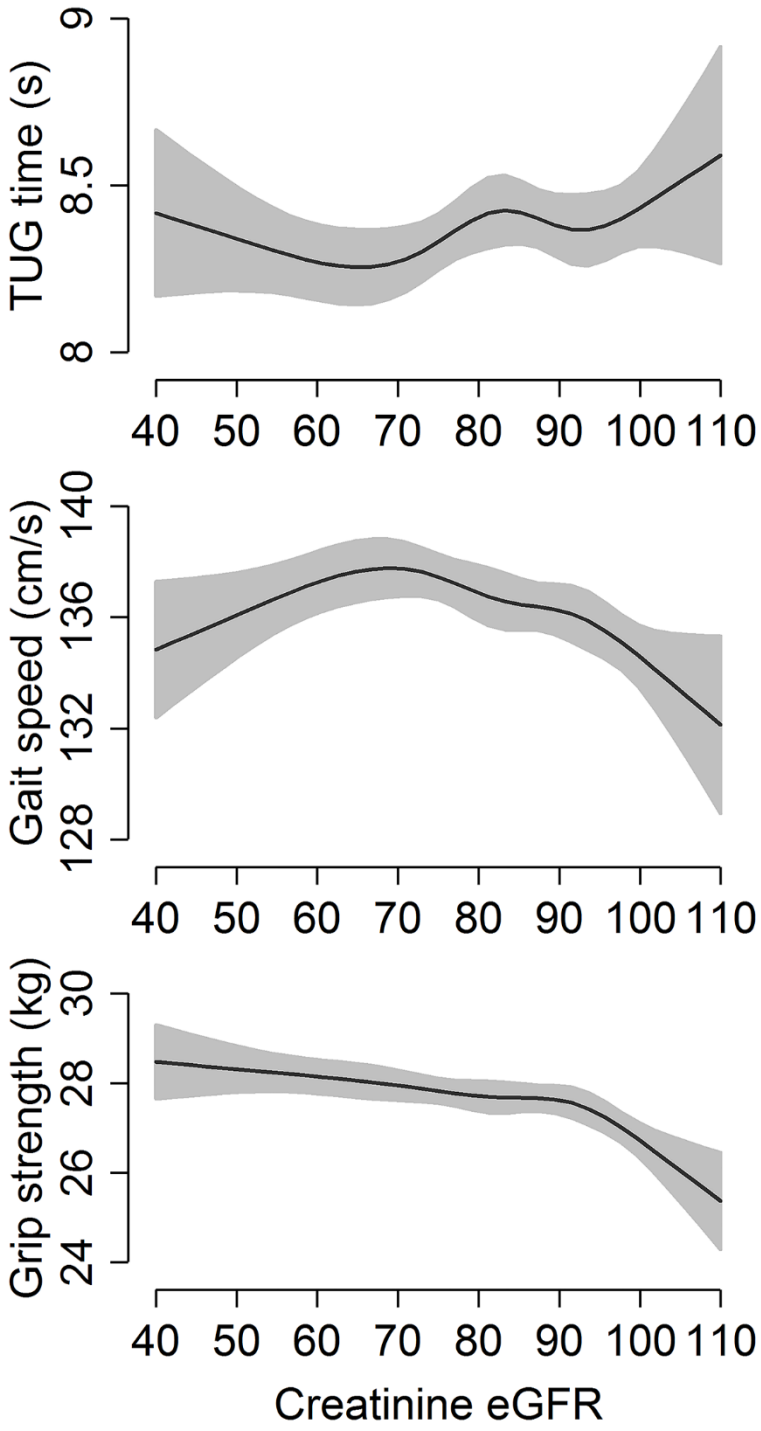


Figure 5.3: Multivariable adjusted relationship between restricted cubic splines of creatinine estimated GFR and physical performance tests

5.3.4 Age interaction

Figure 5.4 provides a graphical illustration of the differential relationship between GFR and gait speed for a participant aged 55, 65 or 75 years. There was little evidence of an association between GFRcys and gait speed at age 55 years. The linear relationship between GFRcys and gait speed became evident at the latter two ages. The relationship between GFRcr and gait speed became progressively inverse U-shaped with age. Table 5.4 reports age stratum-specific estimates for the association between continuous GFRcys (per 10 mL/min per 1.73m^2 decrease) and each outcome. These slope estimates indicate comparatively worse performance in gait speed and TUG with advancing age per unit decrease in GFRcys. The relationship between GFRcys and grip strength did not vary as much by age. Box plots illustrating the distribution of GFRcys across age categories are provided in Appendix Figure 5.1. It should be acknowledged that the interaction between age and GFR may have been limited by reduced sample sizes at the extremes of age and GFR i.e. low numbers of older participants with preserved GFR, and low numbers of younger participants with severe reductions in GFR.

Table 5.4: Age stratum-specific estimates of association between cystatin C estimated GFR and physical performance tests

Age (Years)	Gait speed (cm/s)	P	TUG (seconds)	P	Grip strength (kilograms)	P
50 - 64	-0.60	0.01	0.03	0.16	-0.19	0.02
N=2968	(-1.06, -0.14)		(-0.01, 0.07)		(-0.34, -0.03)	
65 - 74	-1.50	<0.001	0.17	<0.001	-0.12	0.25
N=1200	(-2.13, -0.87)		(0.10, 0.24)		(-0.32, 0.08)	
≥ 75	-2.49	<0.001	0.15	0.13	-0.26	0.12
N=394	(-3.74, -1.23)		(-0.05, 0.34)		(-0.58, 0.07)	
Interaction†		<0.001		<0.001		0.46

GFR modelled per 10 mL/min per 1.73m^2 decrease
Models adjusted for age, sex, height, and waist circumference
†Test for age*GFR interaction using the likelihood ratio test

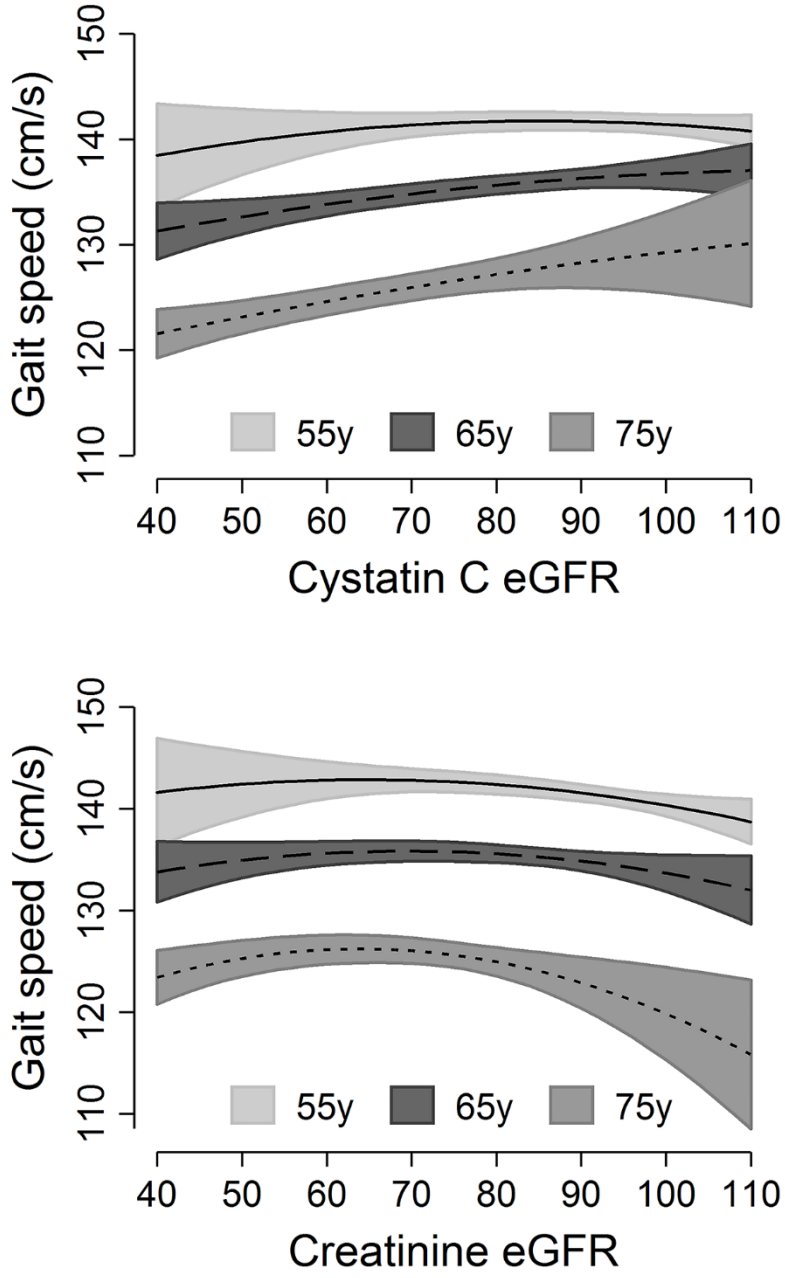


Figure 5.4: Predicted marginal gait speed for a participant aged 55 (solid line), 65 (dashed line) and 75 (dotted line) across the range of GFR estimated from cystatin C (top) or creatinine (bottom)

5.3.5 Secondary analysis

A total of 5206 participants completed the TUG and grip strength tests at either a centre- (N=4603) or home-based (N=603) assessment (Figure 5.1). Appendix Table 5.2 compares their characteristics to those who did not partake in any form of health assessment (N=2229). Compared to those with no assessment, the centre assessment cohort tended to be younger with less cardiovascular risk factors and polypharmacy. In contrast, the home assessment sample tended to be older with a greater degree of cardiovascular and non-cardiovascular comorbidity. The pattern of association between GFRcys categories and physical performance was similar to that in the primary analysis (Table 5.5). In fully adjusted models, participants with GFRcys <45 mL/min per 1.73m^2 had evidence of longer median TUG time (0.73s [95% CI 0.42 to 1.03]) and lower mean grip strength (-1.21kg [95% CI -0.29 to -2.14]) compared to the reference group.

Table 5.5: Association between cystatin C estimated GFR and physical performance tests among participants with either a centre- or home-based health assessment

GFRcys	Model 1	P	Model 2	P
Timed Up and Go (seconds)				
≥ 90	8.56 *(Reference)*		8.61 *(Reference)*	
75-89	-0.03 (-0.16 to 0.11)	0.71	-0.06 (-0.19 to 0.08)	0.43
60-74	0.06 (-0.09 to 0.22)	0.42	0.04 (-0.12 to 0.21)	0.60
45-59	0.49 (0.27 to 0.71)	<0.001	0.29 (0.06 to 0.52)	0.01
< 45	0.91 (0.61 to 1.20)	<0.001	0.73 (0.42 to 1.03)	<0.001
P trend[a]	<0.001		0.01	
Grip Strength (kilograms)				
≥ 90	27.67 *(Reference)*		27.65 *(Reference)*	
75-89	-0.33 (-0.75 to 0.09)	0.12	-0.27 (-0.69 to 0.14)	0.20
60-74	-0.47 (-0.95 to 0.02)	0.06	-0.41 (-0.91 to 0.08)	0.10
45-59	-0.53 (-1.20 to 0.15)	0.13	-0.40 (-1.10 to 0.29)	0.25
< 45	-1.36 (-2.26 to -0.47)	0.003	-1.21 (-2.14 to -0.29)	0.01
P trend[a]	0.006		0.02	

A total of 5206 participants had either a centre- or home-based health assessment

[a] p value for linear trend across ordered categorical variable

5.4 Discussion

In this large cohort of community-dwelling older adults, reductions in kidney function were associated with poorer performance in objective tests of physical function. This relationship was stronger when GFR was estimated from cystatin C compared to creatinine, the latter tending towards a U- or inverse U-shape. GFRcys was linearly related to slower gait speed and longer TUG below a GFRcys of approximately 80 mL/min per 1.73m^2. The association between GFRcys and gait speed varied by age. Our findings suggest that GFRcys is a predictor of poorer physical performance in older adults, but the potential contribution of a diminished level of kidney function to poorer physical outcomes may only be encountered in the oldest old.

Frailty has been shown to predict adverse outcomes among patients receiving dialysis (127). This unique population has a complex set of comorbidities and exhibits a markedly higher prevalence of frailty compared to age-matched peers in the general population (84). Similarly, individuals with referred CKD tend to have substantial reductions in GFR and, as such, might be expected to have complications from their CKD. For example, in a study of 385 patients referred to a CKD clinic, the mean GFR of the sample was 41 mL/min per 1.73m^2 (91). Performance in tests of lower extremity function was reduced in these patients compared to healthy controls, and poor physical performance was an independent predictor of mortality. Given the steep age gradient in CKD prevalence in the general population (29), along with anticipated rapid growth in the older population, the bulk of CKD will be encountered in the community rather than the minority referred to a nephrology clinic. Our study expands existing knowledge by demonstrating declines in standardised tests of physical performance with diminishing GFR in a large sample of older community-dwelling adults across a broad range of GFR.

Similar to other studies, we found that cystatin C out-performed creatinine as a predictor of physical function or frailty. In a sub-sample of 1226 participants aged over 60 years from the Framingham Offspring Study, CKD defined by GFRcys <60 mL/min per 1.73m^2 (but not GFRcr <60 mL/min per 1.73m^2) was associated with higher odds of self-reported incident mobility disability (128). An analysis of Cardiovascular Health Study participants demonstrated a graded association between GFRcys and prevalent and incident frailty which, like our study, became evident below a GFRcys of 75 mL/min per 1.73m^2 (129). A study from the Health, Aging and Body Composition (Health ABC) cohort documented U-shaped relationships between GFRcr and a number of objective tests of physical function (130). Compared to the Health ABC cohort, our study population was more population-representative and had a broader range of age. In

addition, we have provided a more granular comparison of creatinine and cystatin C, with both biomarkers expressed as GFR using standardised equations.

We found that the relationship between GFRcr and gait speed became progressively U-shaped with age. Creatinine GFR was linearly related to grip strength but in the opposite direction to GFRcys. These findings mirror the risk relationships of creatinine with mortality, and emphasise the limitations of using creatinine as a predictor of outcomes in older individuals. For outcomes such as frailty, which are linked to muscle quality and function, cystatin C is likely to be a superior biomarker to creatinine. It must also be acknowledged that cystatin C has been shown to have "non-GFR" determinants such as inflammation, smoking and obesity, which could also contribute to frailty and poorer physical performance (64, 68, 69). There is emerging evidence that cystatin C may be a biomarker of unsuccessful ageing. For example, in a study of older men, cystatin C was associated in a graded fashion with increased risks of frailty and mortality (131). Conversely, in a study of older women, the lowest quartile of cystatin C was an independent predictor of preserved mobility 10 years later (132).

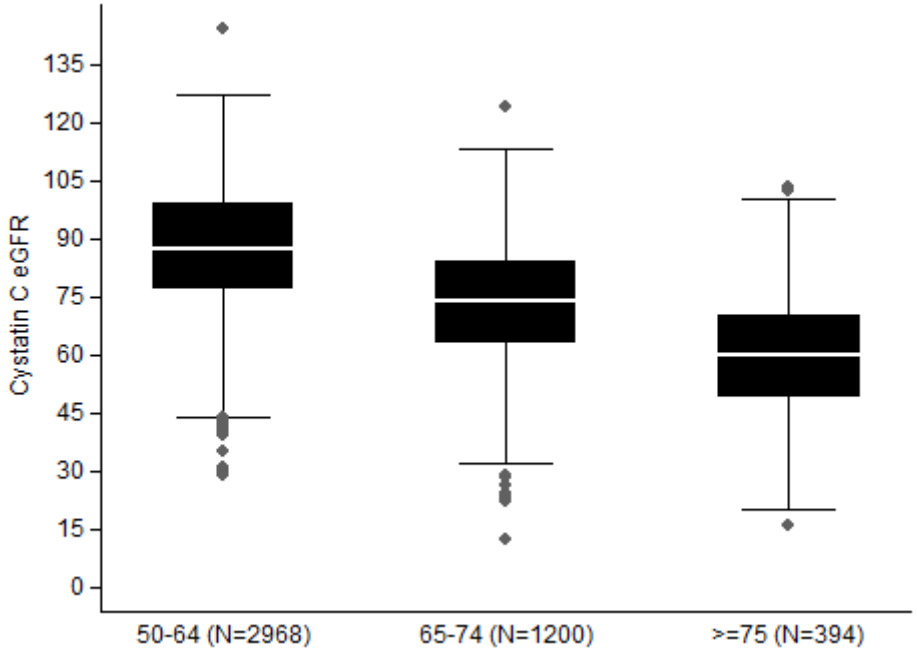
The linear relationship we observed between GFRcys and gait speed only became evident after middle-age. Older adults have by far the highest prevalence of undifferentiated CKD. The development of frailty in this age demographic is of paramount concern as it can lead to loss of independence and an increased rate of complications such as falls and disability. The independent association between GFR and physical performance suggests that a reduction in GFRcys is not a benign entity in this sub-population of older individuals. The threshold for poorer performance was consistent with studies of endpoints such as cardiovascular events and mortality (7). Future studies should examine whether physical performance tests could provide a means of better risk-stratifying the heterogeneous population of older adults with diminished GFR. In the clinical setting, objective and easily standardised tests of frailty could offer a practical advantage over frailty constructs, the latter more time-consuming to obtain and variably applied across studies, thereby limiting comparability of findings in the literature.

Our findings should be interpreted in the context of potential limitations. The cross-sectional design limits our ability to infer causality in the relationship between kidney function and physical outcomes. There may have been residual measured or unmeasured confounding in this relationship. The observations regarding a modifying effect of age should be interpreted in the context of their exploratory nature. Kidney function was measured at a single time point and urinary protein was not measured in the participants. The TILDA sample is virtually all Caucasians

and excluded individuals in institutionalised care, limiting the generalisability of our findings. These limitations are balanced by several strengths. We measured physical performance using objective standardised tests in a large sample of community-dwelling older adults encompassing a broad range of age and GFR. The TILDA dataset is comprehensive, facilitating a robust appraisal of potential confounders. Creatinine and cystatin C were measured simultaneously using standardised assays, and the participants' blood samples were taken on the same day as their health assessment.

In conclusion, we report a relationship between reductions in kidney function defined by cystatin C and objective markers of physical performance in a large national cohort of community-dwelling older adults. The association between creatinine GFR and physical performance was non-linear, underscoring the limitations of creatinine as a predictor of clinical outcomes in this population. Further studies in similarly representative populations are warranted to ascertain the potential value of incorporating physical performance tests into the clinical and risk assessment of CKD in an ageing population.

5.5 Appendix



Appendix Figure 5.1: Box plots illustrating the distribution of GFR estimated from cystatin C (Y-axis) according to age category (X-axis)

Appendix Table 5.1: Characteristics of participants excluded due to incomplete data for either a test of physical performance (N=97) or kidney function (N=282) compared to included participants

Variable	Excluded participants (N=379)	Included participants (N=4562)	P
Age in years	63.0 (9.6)	61.8 (8.3)	0.007
Female sex	237 (62.5)	2447 (53.6)	0.001
Smoking			
Never	177 (46.7)	2088 (45.8)	
Former	133 (35.1)	1801 (39.5)	0.1
Current	69 (18.2)	673 (14.8)	
Waist (cm)	94.2 (14.7)	94.8 (13.6)	0.43
Cardiovascular conditions			
None	336 (88.6)	4169 (91.4)	
One	29 (7.7)	293 (6.4)	0.1
Two or more	14 (3.7)	100 (2.2)	
Diabetes	37 (9.8)	286 (6.3)	0.008
Hypertension	165 (43.5)	1781 (39.0)	0.09
Comorbidities			
None	175 (46.2)	2401 (52.6)	
One	132 (34.8)	1531 (33.6)	0.008
Two or more	72 (19.0)	630 (13.8)	
Polypharmacy	92 (24.4)	618 (13.6)	<0.001

Numbers expressed as mean (SD) or count (percent) and compared using independent samples t-test and the chi-squared test, respectively

Appendix Table 5.2: Characteristics of participants who did not complete a health assessment (N=2229), and of those with complete data for kidney function, timed-up-and-go and grip strength tests from either a home-based (N=603) or centre-based assessment (N=4603)

Variable	No assessment (N=2229)	Home assessment (N=603)	Centre assessment (N=4603)
Age	65.5 (10.6)	70 (11.2)	61.8 (8.3)
Female Sex	1216 (54.6)	316 (52.4)	2472 (53.7)
Height (cm)	NA	163.8 (9.9)	166.3 (9.2)
Smoking status			
Never	914 (41.0)	258 (42.8)	2104 (45.7)
Former	778 (34.9)	218 (36.2)	1816 (39.5)
Current	536 (24.1)	127 (21.1)	683 (14.8)
Waist (cm)	NA	99.1 (13.7)	94.8 (13.7)
HDL (mmol/L)	NA	1.48 (0.40)	1.55 (0.44)
LDL (mmol/L)	NA	2.77 (0.98)	2.94 (0.94)
GFR (mL/min/1.73m^2)	NA	67 (50-83)	81 (69-94)
Diabetes	218 (9.8)	77 (12.8)	293 (6.4)
Hypertension	1071 (48.1)	375 (62.2)	1808 (39.3)
CV conditions			
None	1987 (89.1)	507 (84.1)	4205 (91.3)
One	189 (8.5)	66 (10.9)	297 (6.5)
Two or more	53 (2.4)	30 (5.0)	101 (2.2)
Polypharmacy	399 (18.3)	181 (30.5)	633 (13.8)
Comorbidities			
None	1246 (55.9)	241 (40.0)	2420 (52.6)
One	679 (30.5)	253 (42.0)	1545 (33.6)
Two or more	304 (13.6)	109 (18.1)	638 (13.9)

CV, cardiovascular; GFR, glomerular filtration rate (estimated from cystatin C); HDL, high density lipoprotein; LDL, low density lipoprotein; NA, not available

Data missing for age (N=1), waist circumference (N=7), LDL/HDL (N=11) and polypharmacy (N=74)

6 Longitudinal association between kidney function and lower extremity physical performance

6.1 Introduction

Chronic kidney disease has been proposed as a model of accelerated or unsuccessful ageing based on the observation that individuals with CKD exhibit a clinical phenotype that is similar to that of much older segments of the general population. This phenotype includes higher than anticipated rates of frailty (84, 87, 120), and lower scores in tests of physical performance compared to population normative values (91). Declines in mobility can herald downstream problems such as falls, reduced confidence and, ultimately, loss of functional independence. Early detection of changes in mobility could provide opportunities to intervene before the onset or at the early stages of functional decline. Structured exercise programs have been shown to reduce the risk of persistent mobility disability in older people with physical limitations (133). Small studies in CKD and dialysis patients have also suggested beneficial effects of exercise (134). Therefore there is emerging interest in screening patients with advanced CKD for increased risk of functional impairment. Tests of mobility such as such as gait speed and TUG are useful for this purpose because they are objective, simple to administer, and powerful predictors of outcomes (88).

The highest burden of CKD is encountered in the general population of older adults (2, 29), the majority of whom will not progress to an advanced stage of the disease (11). Whether declines in mobility can be detected at earlier stages of CKD among older individuals is largely unknown. The majority of studies examining the relationship between CKD and physical performance in general population samples have been cross-sectional, making it difficult to disentangle this relationship from confounding due to shared risk factors such as cardiovascular disease and other comorbidities. A key unanswered question is whether reduced kidney function is an important driver of physical performance outcomes. Longitudinal studies could inform this question by examining the relationship between kidney function and repeated measures of physical performance over time.

We hypothesised that a reduced GFR would be associated with an accelerated decline in physical function among the general population of older adults. We tested this by examining the

relationship between GFR and repeated measures of gait speed and TUG in a large population-based sample of older community-dwelling adults.

6.2 Methods

6.2.1 Participants

This was a prospective observational study of participants from the first three waves of TILDA. Gait speed was measured during a centre-based health assessment at Wave 1 and Wave 3. The TUG test was performed either in the research centre or in the respondent's home at Wave 1 and Wave 3, and in the respondent's home at Wave 2. In order to be consistent with the previous cross-sectional analysis (Chapter 5), and the frailty construct developed by the Cardiovascular Health Study (83), participants were excluded from the analysis if they had a history of Parkinson Disease or stroke, or a MMSE score <18 (N=195). Of 7980 eligible participants, 5227 performed a TUG test and had cystatin C measured at Wave 1 (Figure 6.1). A total of 388 participants did not have a TUG test repeated at Wave 2 or Wave 3 and were excluded from the analysis. The final study population consisted of 4839 participants who had a TUG test at Wave 1 and at least one repeat measure. The majority (N=3764, 78%) performed a TUG test at both Wave 2 and Wave 3. A more detailed flow diagram is provided in Appendix Figure 6.1, illustrating the numbers of participants who had a centre- or home-based assessment of TUG at each wave.

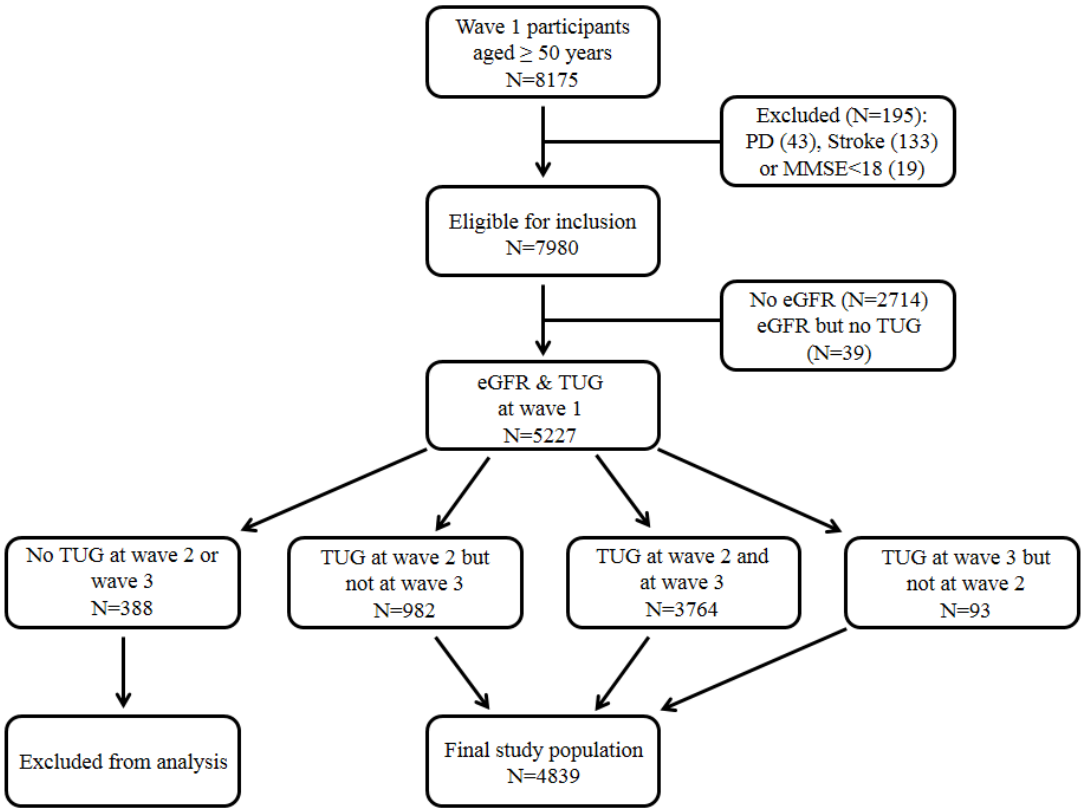


Figure 6.1: Flowchart of case ascertainment for TUG study population

A total of 4583 participants had a measurement of both cystatin C and gait speed at the Wave 1 centre-based health assessment (Figure 6.2). The final study population consisted of 3107 participants who had a repeat measure of gait speed at the Wave 3 centre-based health assessment.

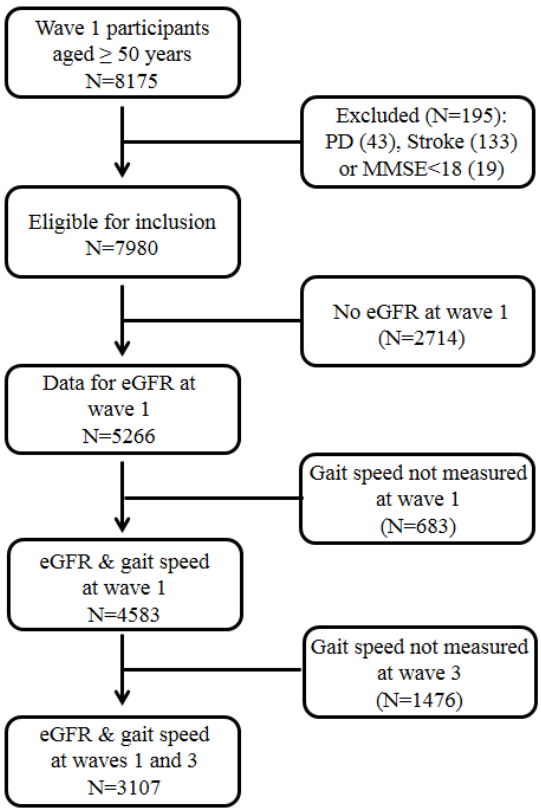


Figure 6.2: Flowchart of case ascertainment for gait speed population

6.2.2 Outcomes

For the TUG test, participants were asked to stand unaided from a seated position, walk 3 metres at their usual pace, turn around, walk back to the chair and sit down. The 3 metre distance was fixed by a marked point on the floor. The time taken from the command "Go" to when the participant was sitting with their back resting against the chair was recorded in seconds. Walking aids were permitted and the test was performed once. In the research centre, a chair with armrests and seat height of 46cm was used. In the participant's home, the research nurse selected a chair that matched these dimensions as closely as possible (a chair with arm rests and seat height of between 40 and 50cm). Similar to the health centre, a measuring tape was used to mark the 3 metre distance on the floor (106). Gait speed was measured using the GAITRite portable electronic walkway system (CIR Systems Inc, Havertown, PA). Participants were instructed to walk at their usual pace along the 4.88 metre walkway. They started walking 2.5 metres before the walkway and finished walking 2 metres after the walkway, to allow for acceleration and deceleration respectively. The test was repeated once and the average gait speed from the two walks was recorded in cm/s.

6.2.3 Predictor

The predictor of interest was glomerular filtration rate categorised as follows: ≥90mL/min per 1.73m^2 (reference group), 60 to 89mL/min per 1.73m^2, <60mL/min per 1.73m^2. Based on the previous cross-sectional analysis in Chapter 5, which showed substantial non-linearity in the relationship between GFRcr and tests of lower extremity physical performance, cystatin C was used to estimate GFR for the present analysis. The CKD-EPI equation was used to estimate GFR from cystatin C (53).

6.2.4 Covariates

Covariates were chosen based on biological plausibility, prior literature, and their association with both exposure (GFR) and outcome (gait speed and TUG). All covariates were derived from the Wave 1 interview and health assessment data. Demographic variables included age and gender. Lifestyle risk factors included smoking history (current, former or never) and objectively measured waist circumference. The presence of diabetes mellitus was defined as a self-reported physician's diagnosis and/or regular use of insulin or hypoglycaemic medications. Medication use was recorded during the interview and cross-checked with medication labels. All medications were coded according to the World Health Organisation Anatomical Therapeutic

Chemical Classification (104). Cardiovascular disease was defined by the presence of at least one of the following self-reported physician-diagnosed conditions: angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, heart failure, or transient ischaemic attack. Comorbidity variables included polypharmacy (regular use of ≥5 medications excluding supplements) and number (0, 1, 2 or more) of the following self-reported physician-diagnosed chronic health conditions: chronic lung disease, asthma, arthritis, osteoporosis, malignancy, stomach ulcers, varicose ulcers, cirrhosis or severe liver damage. Participant height, a predictor of stride length and walking speed, was objectively measured at the health assessment. Pulse pressure (the difference between systolic and diastolic blood pressure readings) was included in the models as a marker of vascular fitness. Blood pressure was measured by a research nurse according to a standard protocol using a digital automated BP monitor (Omron M10-IT, Omron Inc. Kyoto, Japan). Two measurements were recorded with the participant seated, one minute apart, and the average of these measurements was calculated.

6.2.5 Statistical analysis

All analyses were performed using Stata version 14 (StataCorp, College Station, TX). For descriptive analyses, data are presented as mean (SD) or median (IQR) for normally distributed and non-normally distributed continuous variables, respectively. Categorical variables are presented as count (percentage). The time taken to complete the TUG test at all waves exhibited a highly skewed distribution with a long right hand tail. The inverse of TUG time was chosen as an appropriate transformation (see Appendix Figure 6.2). A lower value for inverse TUG indicates a longer time to complete the test. A small number of participants at Wave 3 had implausibly short or long values for TUG time. These outliers were excluded (N=46) by trimming the Wave 3 TUG distribution at the 0.5^{th} and 99.5^{th} centiles before transforming the variable. Gait speed at Wave 1 and Wave 3 was normally distributed (Appendix Figure 6.2).

Repeated measures of TUG and gait speed were nested within the individual. Measurements made on the same individual are likely to be more similar than measurements made on different individuals. Ignoring the correlation in residuals can result in an incorrect lowering of the standard error of the estimate, increasing the risk of type 1 error. We used mixed effects linear regression to examine the relationship between GFR and repeated TUG or gait speed values. The total unexplained variance in each outcome, conditional on the fixed effects, was broken down into two components: (i) between-subject variance (BSV), represented by the variance in subject-specific intercepts (the random effect) (ii) within-subject variance (WSV), represented

by the variance of the residuals (residual error). The degree of correlation between the repeated outcome measures was estimated by the intra-class correlation coefficient, calculated as BSV / (WSV + BSV). In the present analysis, the intra-class correlation coefficients for TUG and gait speed were 67% and 73% respectively.

Three models were constructed for each outcome: (1) unadjusted (2) adjusted for age (uncentred), age-squared, height and sex (3) further adjusted for cardiovascular risk factors and chronic health conditions. In each case, the parameter of interest was the time*GFR interaction term. Values for covariates were taken from data at Wave 1. All covariates of interest were included in the fixed statement of the model. Each covariate was modelled as a main effect and as a time*covariate interaction, to allow the covariate effects to vary over time. The predicted values for TUG and gait speed for each level of the GFR variable at each wave were obtained using the *margins* command in Stata. These marginal estimates were conditional on the means of all other covariates in the model i.e. each covariate was fixed at its mean value for the sample when estimating the association between GFR and each outcome. Standard errors accounted for the household level clustering of participants. A Wald p value of less than 0.05 was considered to be statistically significant. All models incorporated an inverse probability weight to counteract bias from differential non-participation in the components of the study that were required for inclusion in the TUG or gait speed samples (see Chapter 3 Section 3.5.2 “Description of inverse probability weight for longitudinal data”).

6.3 Results

6.3.1 Timed-up-and-go

6.3.1.1 Participant characteristics

A description of the demographic and clinical characteristics of the TUG study population (based on their Wave 1 data) is provided in Table 6.1. Median (IQR) age of the sample was 61 (55-68) years, 53.8% were female, and median (IQR) GFR was 81 (68-93) mL/min per 1.73m^2. Compared to participants with preserved kidney function (GFR ≥90mL/min per 1.73m^2), those with GFR <60mL/min per 1.73m^2 tended to be older (median age 73 versus 56 years), more likely female (58.6% versus 51.3%) and have a higher prevalence of diabetes (13.2% versus 6.8%) and cardiovascular disease (21.1% versus 4.1%). Participants with reduced GFR also had higher waist circumference, higher pulse pressure and a greater number of chronic conditions.

6.3.1.2 Longitudinal analysis

The predicted estimates for (inverse) TUG time for each category of GFR, at each wave, are illustrated in Figure 6.3 and compared in Table 6.2. In the unadjusted analysis (Figure 6.3A), the time*GFR interaction was strongly statistically significant (p<0.001), suggesting that participants with lower GFR had greater declines in TUG performance over time. After adjusting for age, age^2, sex and height, the time*GFR interaction parameter was no longer statistically significant (p=0.54). This is demonstrated in Figure 6.3B, showing parallel trajectories for TUG across categories of GFR. A similar pattern was observed in the extended model (p=0.44, Figure 6.3C).

Table 6.1: Characteristics of TUG study population overall and by category of GFR estimated from cystatin C

Characteristic	Total N=4839	GFR ≥90 N=1555	GFR 60-89 N=2615	GFR <60 N=669
Female sex, N (%)	2603 (53.8)	798 (51.3)	1413 (54.0)	392 (58.6)
Age (years), median (IQR)	61 (55-68)	56 (52-61)	62 (57-68)	73 (67-79)
Height (cm), mean (SD)	166.1 (9.3)	167.2 (9.0)	166.0 (9.3)	163.4 (9.0)
Waist (cm), mean (SD)	95.1 (13.7)	92.2 (13.1)	95.7 (13.4)	99.9 (14.7)
Pulse pressure (mmHg), mean (SD)	53.0 (13.7)	49.9 (11.7)	53.1 (13.7)	59.8 (15.5)
Diabetes, N (%)	331 (6.8)	77 (5.0)	166 (6.4)	88 (13.2)
Cardiovascular disease, N (%)	441 (9.1)	64 (4.1)	236 (9.0)	141 (21.1)
Smoking status, N (%)				
Never	2215 (45.8)	756 (48.6)	1181 (45.2)	278 (41.6)
Former	1904 (39.3)	626 (40.3)	995 (38.0)	283 (42.3)
Current	720 (14.9)	173 (11.1)	439 (16.8)	108 (16.1)
Polypharmacy, N (%)	719 (14.9)	101 (6.5)	369 (14.2)	249 (37.7)
Chronic conditions, N (%)				
None	2494 (51.5)	930 (59.8)	1322 (50.6)	242 (36.2)
One	1660 (34.3)	464 (29.8)	919 (35.1)	277 (41.4)
Two or more	685 (14.2)	161 (10.4)	374 (14.3)	150 (22.4)
GFR (mL/min per 1.73m^2), median (IQR)	81 (68-93)	99 (94-104)	77 (69-83)	50 (42-55)

Missing data for height (N=2), waist circumference (N=8), pulse pressure (N=21)

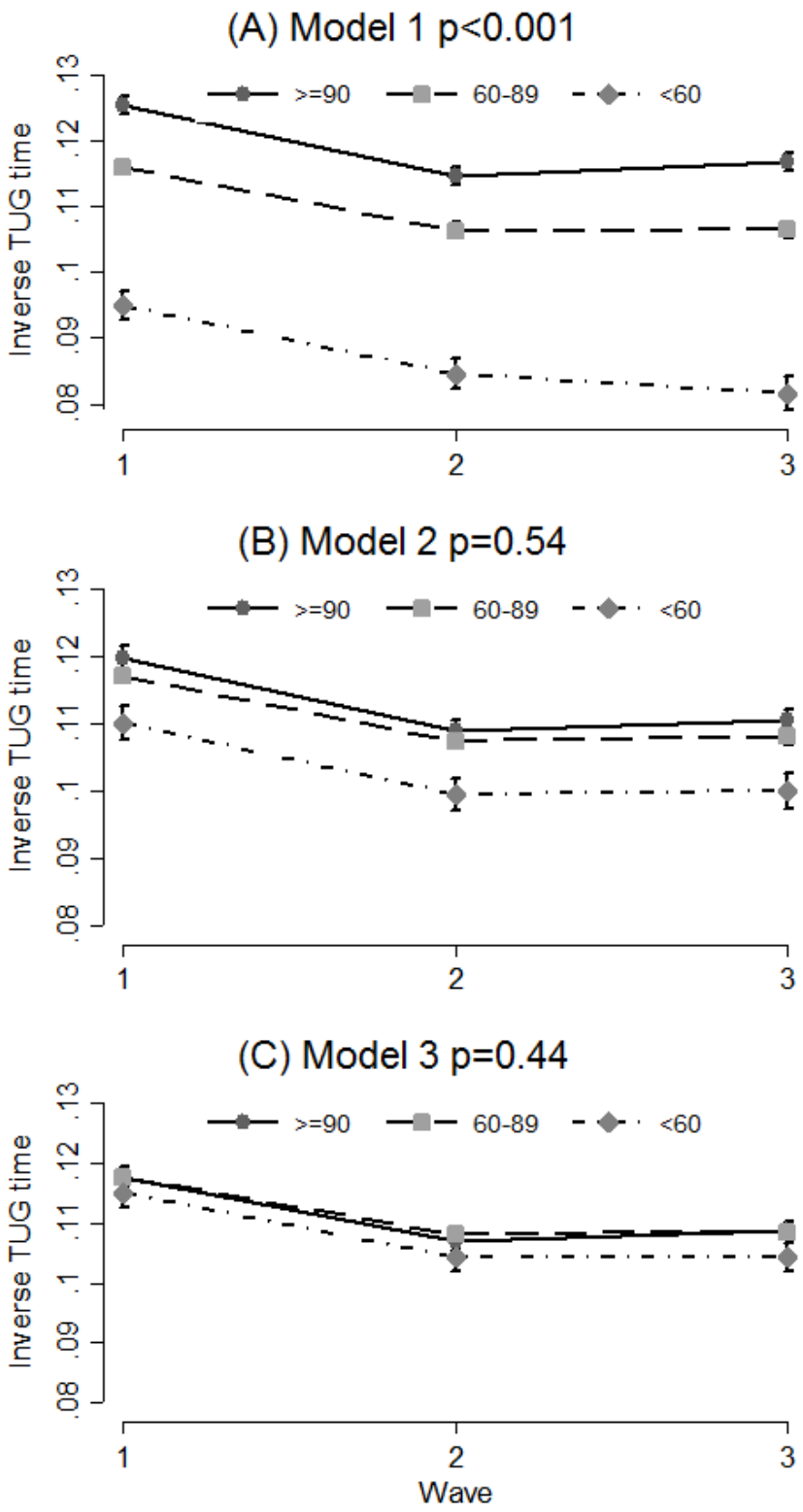


Figure 6.3: Predicted (inverse) TUG time for each category of GFR in primary analysis
The p values indicate the strength of the time*GFR interaction
Model 1 – unadjusted; Model 2 – adjusted for age, age^2, sex and height; Model 3 – further adjusted for smoking, waist circumference, diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions
GFR, glomerular filtration rate (estimated from cystatin C)

Table 6.2: Predicted TUG time (seconds) for each category of GFR (estimated from cystatin C) across the three waves

GFR	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Wave 1						
≥ 90	7.99 (7.90, 8.07)	Ref	8.35 (8.24, 8.46)	Ref	8.50 (8.39, 8.62)	Ref
60-89	8.63 (8.54, 8.72)	<0.001	8.54 (8.46, 8.63)	0.002	8.49 (8.41, 8.57)	0.9
< 60	10.53 (10.30, 10.78)	<0.001	9.09 (8.89, 9.29)	<0.001	8.69 (8.51, 8.88)	0.07
Wave 2						
≥ 90	8.74 (8.64, 8.84)	Ref	9.19 (9.05, 9.33)	Ref	9.35 (9.21, 9.49)	Ref
60-89	9.41 (9.30, 9.51)	<0.001	9.31 (9.21, 9.42)	0.08	9.25 (9.16, 9.35)	0.2
< 60	11.82 (11.52, 12.13)	<0.001	10.06 (9.82, 10.31)	<0.001	9.58 (9.37, 9.81)	0.06
Wave 3						
≥ 90	8.57 (8.48, 8.67)	Ref	9.05 (8.92, 9.19)	Ref	9.20 (9.06, 9.33)	Ref
60-89	9.40 (9.29, 9.51)	<0.001	9.26 (9.16, 9.37)	0.004	9.21 (9.11, 9.31)	0.88
< 60	12.25 (11.88, 12.65)	<0.001	10.01 (9.76, 10.27)	<0.001	9.59 (9.36, 9.82)	0.002

Model 1 – unadjusted

Model 2 – adjusted for age, age^2, sex and height

Model 3 – further adjusted for smoking, waist circumference, diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions

6.3.1.3 Secondary analysis

Anticipating that participants with CKD (GFR <60mL/min per 1.73m^2) at Wave 1 would be likely to manifest the clearest decrements in TUG performance over time, we sought to better characterise the TUG findings within the CKD group, as compared to participants without CKD (GFR ≥60 mL/min per 1.73m^2). In a secondary analysis, all participants with GFR ≥60 mL/min per 1.73m^2 were pooled into a single category. Participants with CKD were subdivided into two groups stratified by the median GFR in the CKD subpopulation (50 mL/min per 1.73m^2). This resulted in the following exposure groups for GFR: ≥60 mL/min per 1.73m^2 (N=4170, reference), 50-59 mL/min per 1.73m^2 (N=354), <50 mL/min per 1.73m^2 (N=315).

The predicted values for TUG time for each category of the new GFR variable across the three waves are illustrated in Figure 6.4, and their comparisons detailed in Appendix Table 6.1. After multivariable adjustment (Figure 6.4C), individuals with GFR <50 mL/min per 1.73m^2 appeared to have a more consistent decline in TUG performance over time compared to the other two GFR categories (p=0.01 for time*GFR interaction).

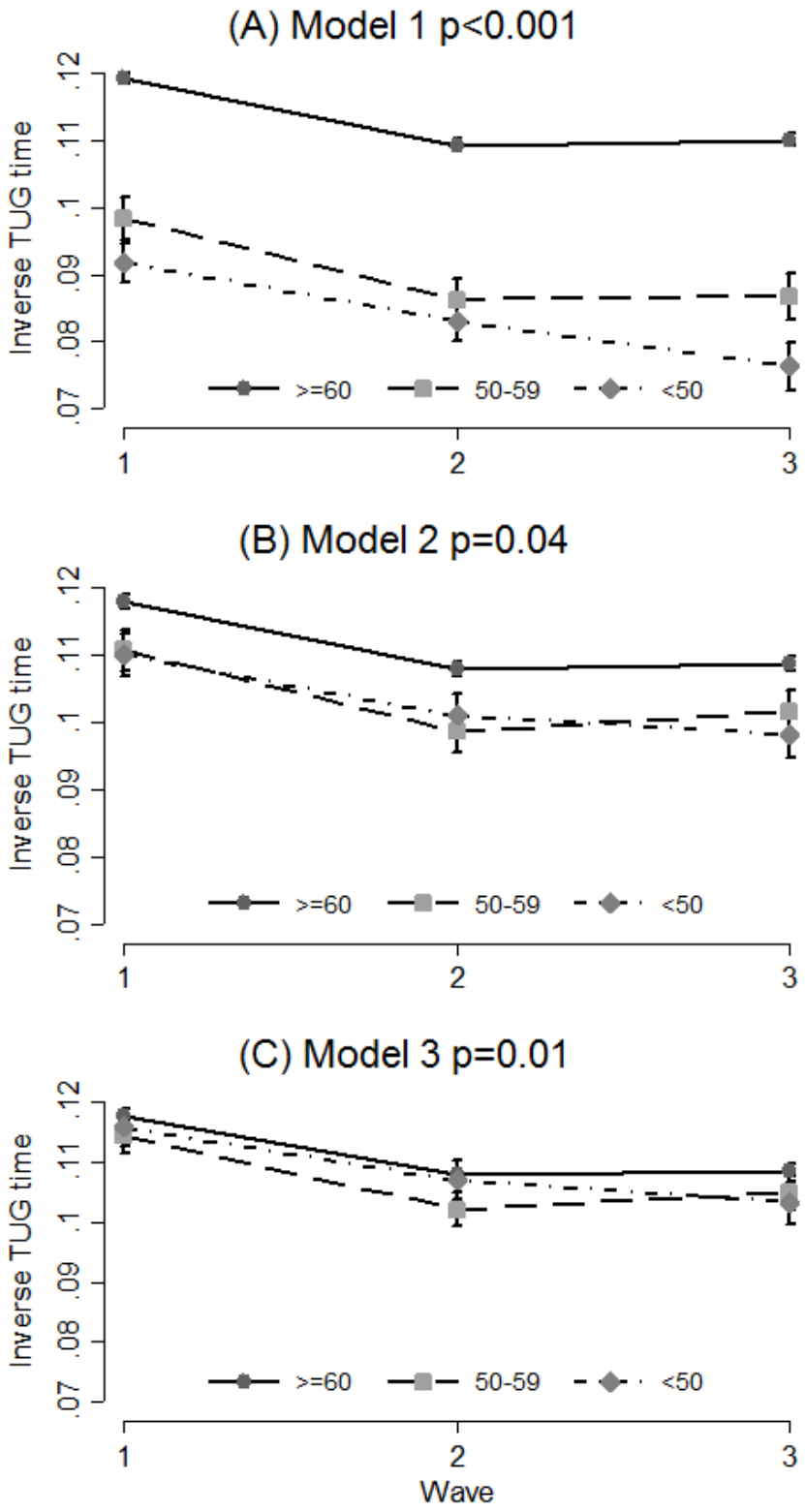


Figure 6.4: Predicted (inverse) TUG time for each category of GFR in secondary analysis
The p values indicate the strength of the time*GFR interaction
Model 1 – unadjusted; Model 2 – adjusted for age, age^2, sex and height; Model 3 – further adjusted for smoking, waist circumference, diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions
GFR, glomerular filtration rate (estimated from cystatin C)

6.3.2 Gait speed

6.3.2.1 Participant characteristics

The baseline (Wave 1) characteristics of the gait speed study population are detailed in Table 6.3. A slight majority of participants were female (53.8%), median (IQR) age was 60 (55-66) years, and median (IQR) GFR was 83 (72-95) mL/min per 1.73m^2. Compared to individuals with preserved kidney function (GFR ≥90 mL/min per 1.73m^2), those with diminished GFR tended to be older, more likely female, and have a greater degree of cardiovascular and non-cardiovascular conditions. They also tended to have higher waist circumference and higher pulse pressure.

Table 6.3: Characteristics of gait speed study population overall and by category of GFR estimated from cystatin C

Characteristic	Total N=3107	GFR ≥90 N=1128	GFR 60-89 N=1710	GFR <60 N=269
Female sex	1670 (53.8)	599 (53.1)	911 (53.3)	160 (59.5)
Age (years), median (IQR)	60 (55-66)	56 (52-60)	62 (56-67)	69 (64-75)
Height (cm)	166.7 (9.1)	167.1 (8.9)	166.7 (9.2)	164.9 (8.9)
Waist (cm)	94.3 (13.4)	91.6 (12.8)	95.4 (13.2)	98.8 (14.6)
Pulse pressure (mmHg)	51.4 (12.9)	49.2 (11.8)	52.0 (13.2)	56.3 (14.1)
Diabetes	165 (5.3)	49 (4.3)	87 (5.1)	29 (10.8)
Cardiovascular disease	232 (7.5)	45 (4.0)	134 (7.8)	53 (19.7)
Smoking status				
Never	1477 (47.5)	562 (49.8)	793 (46.4)	122 (45.4)
Former	1225 (39.4)	454 (40.3)	661 (38.7)	110 (40.9)
Current	405 (13.0)	112 (9.9)	256 (15.0)	37 (13.8)
Polypharmacy	344 (11.1)	59 (5.2)	206 (12.1)	79 (29.8)
Chronic conditions				
None	1660 (53.4)	667 (59.1)	890 (52.1)	103 (38.3)
One	1064 (34.3)	345 (30.6)	600 (35.1)	119 (44.2)
Two or more	383 (12.3)	116 (10.3)	220 (12.9)	47 (17.5)
GFR (mL/min/1.73m^2), median (IQR)	83 (72-95)	99 (94-104)	77 (70-83)	52 (46-56)

Data reported as count (%) or mean (standard deviation) unless otherwise stated
Missing data for height (N=1), waist circumference (N=3), pulse pressure (N=11)

6.3.2.2 Longitudinal analysis

The predicted values for gait speed for each category of GFR at Wave 1 and Wave 3 are illustrated in Figure 6.5, and their contrasts provided in Table 6.4. In the unadjusted analysis (Figure 6.5A), the time*GFR interaction was strongly statistically significant ($p<0.001$), indicating greater declines in gait speed over time among participants with lower baseline GFR. After adjusting for demographics (model 2, Figure 6.5B), the interaction parameter was no longer statistically significant ($p=0.16$). A similar pattern was observed in the extended model (model 3, Figure 6.5C).

6.3.2.3 Secondary analysis

Similar to the findings for TUG, participants with GFR <60 mL/min per 1.73m^2 demonstrated lower gait speed at each wave than the other two GFR categories, whose mean values for gait speed were similar in the multivariable-adjusted analysis. The secondary analysis described for TUG was repeated for gait speed. In the case of gait speed, the median GFR in the CKD subpopulation was 52 mL/min per 1.73m^2, resulting in the following GFR categorical variable for the secondary analysis: ≥60 mL/min per 1.73m^2 (N=2838, reference), 52-59 mL/min per 1.73m^2 (N=143), <52 mL/min per 1.73m^2 (N=126).

The predicted values for gait speed at each wave for each category of this GFR variable are illustrated in Appendix Figure 6.3 and their comparisons detailed in Appendix Table 6.2. The time*GFR interaction parameter was not statistically significant after adjustment for demographic variables (model 2, $p=0.22$), or in the extended model (model 3, $p=0.46$).

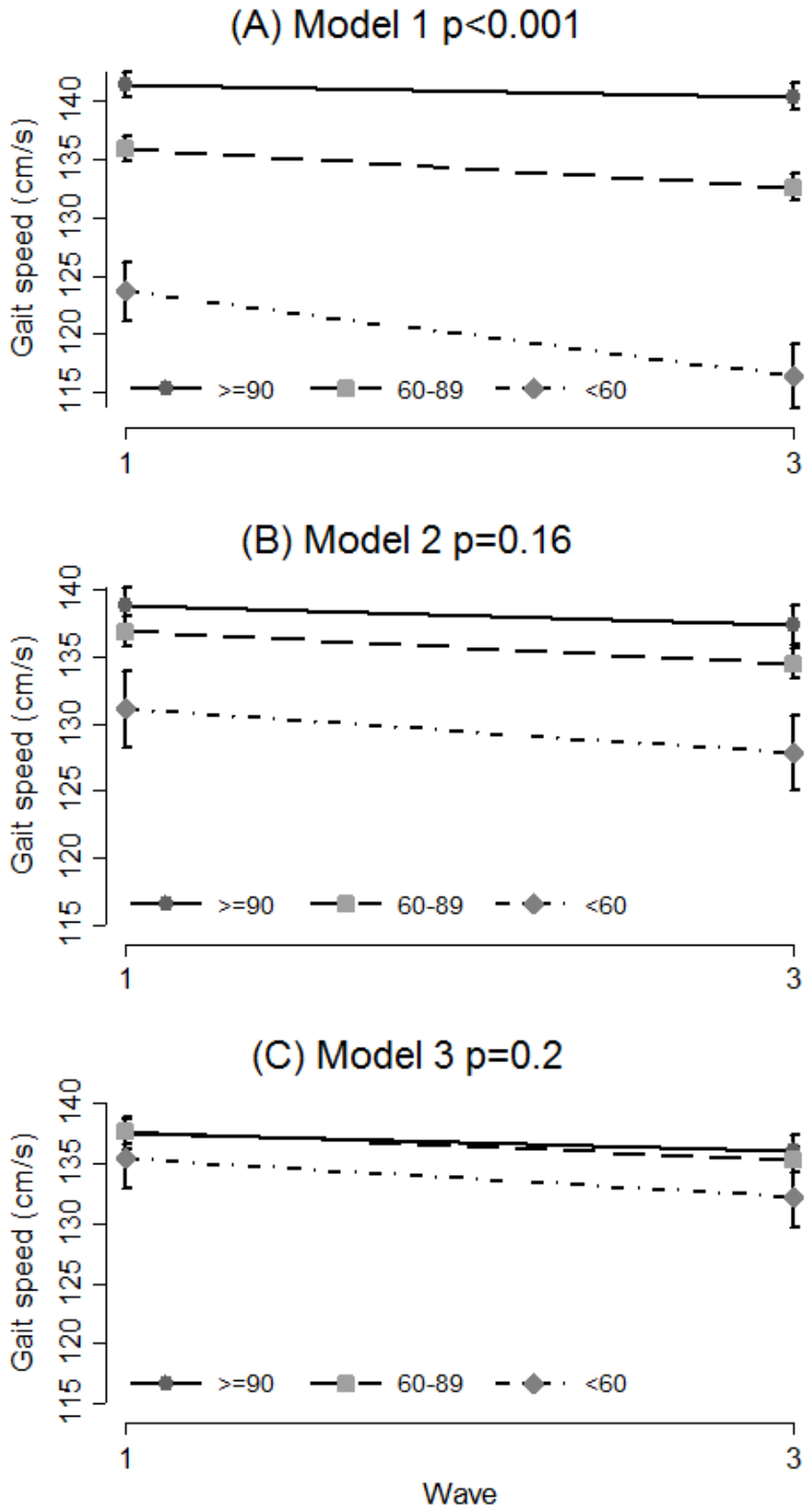


Figure 6.5: Predicted gait speed for each category of GFR in primary analysis

The p values indicate the strength of the time*GFR interaction

Model 1 – unadjusted; Model 2 – adjusted for age, age^2, sex and height; Model 3 – further adjusted for smoking, waist circumference, diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions

GFR, glomerular filtration rate (estimated from cystatin C)

Table 6.4: Predicted gait speed (cm/s) at each wave for each category of GFR estimated from cystatin C

GFR	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Wave 1						
≥ 90	141.4 (140.3, 142.5)	Ref	138.8 (137.4, 140.2)	Ref	137.5 (136.7, 138.7)	Ref
60-89	135.9 (134.9, 136.9)	<0.001	136.9 (135.8, 138.0)	0.02	137.7 (136.7, 138.7)	0.78
< 60	123.7 (121.1, 126.2)	<0.001	131.1 (128.3, 133.9)	<0.001	135.4 (132.9, 137.4)	0.13
Wave 3						
≥ 90	140.4 (139.1, 141.5)	Ref	137.4 (135.9, 138.9)	Ref	136.1 (134.7, 137.4)	Ref
60-89	132.6 (131.4, 133.8)	<0.001	134.5 (133.3, 135.6)	<0.001	135.3 (134.2, 136.4)	0.31
< 60	116.4 (113.6, 119.2)	<0.001	127.8 (125.0, 130.6)	<0.001	132.2 (129.6, 134.7)	0.007

Model 1 – unadjusted
Model 2 – adjusted for age, age^2, sex and height
Model 3 – further adjusted for smoking, waist circumference, diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions

6.4 Discussion

In this large cohort of community-dwelling older adults, lower baseline kidney function was not associated with greater declines in either gait speed or TUG over two and three waves of follow-up, respectively. After subdividing participants with CKD in a secondary analysis, those with greater reductions in GFR (GFR <50 mL/min per 1.73m^2) appeared to have a more persistent decline in TUG performance, suggesting a possible threshold effect for lower physical performance in CKD. This was not observed for declines in gait speed. At each wave of data collection, a reduced GFR was associated with poorer physical performance, particularly in the TUG test.

Few studies have investigated the longitudinal association between kidney function and objective measures of physical performance. A study from the Invecchiare in Chianti (InCHIANTI) cohort, using data from 826 community-dwelling participants who were free of stroke or activities of daily living disability at baseline, examined the longitudinal relationship between creatinine clearance and three objective tests of physical performance: 7-metre usual walking speed, 400-metre fast walking speed and knee extension strength (135). The authors used a mixed effects model with participant age at each examination as the time variable. Similar to the present analysis, creatinine clearance was categorised as ≥90 mL/min per 1.73m^2, 60-89 mL/min per 1.73m^2, <60 mL/min per 1.73m^2. The interaction between time (age) and category of creatinine clearance provided estimates of mean annual change in each physical performance outcome. After multivariable adjustment, the interaction was statistically significant for knee extension strength only. The authors proposed that changes in knee extension strength may precede declines in walking speed. In a secondary analysis, GFR (estimated from cystatin C) was modelled as the primary exposure variable. There was no substantive association between GFR and longitudinal change in any outcome. The InCHIANTI participants were older than TILDA participants (mean age 74 years) and the sample size for CKD (creatinine clearance <60mL/min per 1.73m^2) was small at baseline (N=183). Attrition was higher among individuals with lower kidney function, such that only 112 participants with CKD had a repeated measure of physical performance. Compared to the InCHIANTI cohort, the TILDA sample is a larger and more representative study population. The present analysis also incorporated an inverse probability weight to account for differential non-response and attrition across waves of data collection. Despite these differences in study design, our findings were quite similar to those from the InCHIANTI cohort.

A prospective analysis from the Framingham Offspring Study suggested greater declines in gait speed among older individuals with CKD (128). Participants with GFR <60 mL/min per 1.73m^2 (estimated from cystatin C) had greater declines in gait speed between examination 7 and examination 8 (mean follow-up of 6.6 years) of the study compared to those with GFR ≥60 mL/min per 1.73m^2. The authors selected a subset of the parent cohort which was free of mobility disability at baseline, resulting in a sample size of 892 participants. The present analysis is also limited by the availability of just one repeated gait speed measure, however there are important methodological differences between the two studies. First, The Framingham Offspring Study cohort were older (mean age 68 years versus 61 years in TILDA) and had a higher prevalence of diabetes (12% versus 5%) and cardiovascular disease (16% versus 8%). The mean GFRcys in the Framingham cohort was 10 mL/min per 1.73m^2 lower than the mean GFRcys of TILDA participants (72.8 versus 82.7). The investigators included baseline gait speed as a predictor in the multivariable linear regression model, and did not report the correlation between the two gait speed results. The present analysis used a mixed effects regression model due to the high degree of correlation between repeated measures.

The lack of a strong longitudinal association between GFR and physical performance tests in the present analysis could be explained by aspects of the study design. The secondary analysis for TUG suggested that participants with the most severe reductions in GFR had a more persistent decline in physical function. Previous studies have demonstrated that, at the extreme end of the GFR spectrum, advanced CKD is associated with rapid declines in physical function in older people (136). The TILDA cohort represents community-dwelling adults who were fit enough to take part in a health assessment (106). As such, there may not have been sufficient numbers of participants with severely reduced kidney function to adequately power tests of interaction between time and GFR. After three waves of data collection over a period of 5-6 years in a predominantly middle-aged sample, it may be too early in the course of the study to observe clinically meaningful changes in physical function in this population. The health assessment component of the study will be repeated in future waves, which will facilitate a more in-depth analysis.

Despite the lack of evidence for a time*GFR interaction in the primary analysis, values for both gait speed and TUG were lower at each wave for participants with GFR <60 mL/min per 1.73m^2 compared to those with higher levels of GFR. The contrasts were robust to adjustment for age, cardiovascular risk factors and other comorbidities. These findings are consistent with other studies that have evaluated the relationship between kidney function and either frailty or

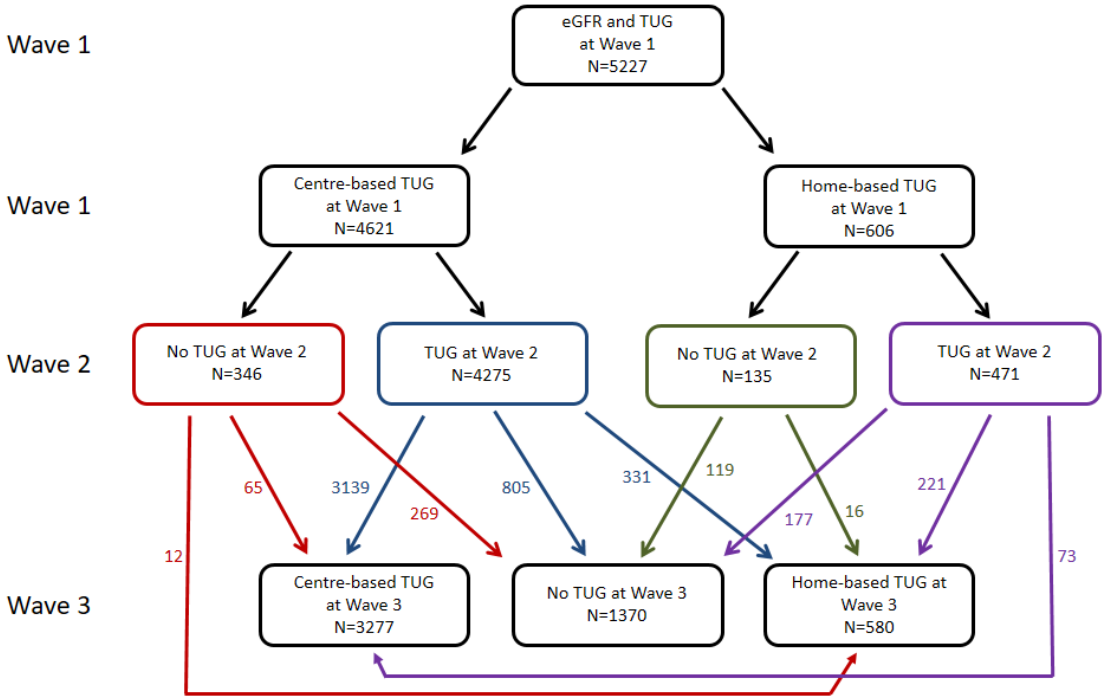
physical performance (86, 87, 91, 130). The potential mechanisms underlying this relationship are not well understood. Reductions in GFR correlate with lower muscle cross-sectional area (135), lower muscle density (135) and longitudinal declines in lean body mass (137), suggesting that CKD could have detrimental effects on skeletal muscle quality and function. Preliminary data from animal studies and small studies in humans point to disruption in mitochondrial metabolism in muscle cells as a possible mediator in the association between CKD, skeletal muscle dysfunction and consequent physical or mobility impairment (138, 139). CKD is also associated with a pro-inflammatory environment, which could negatively affect muscle quality and function. A prospective analysis from the Health ABC study found that the association between cystatin C and self-reported incident functional limitation was attenuated after adjustment for inflammatory markers including C-reactive protein, interleukin-6 and tumour necrosis factor-alpha (140). This suggested that inflammation could be mediating the relationship between deteriorating kidney function and new-onset functional limitation. Poorer physical function could be explained by a higher burden of vascular disease in CKD. This could be more pertinent for the TUG test, which is more than a test of muscular strength. When performing the test, participants must follow instructions (requiring intact cognitive function), undergo a postural change (requiring robust haemodynamics), and complete a turn at the 3-metre marker (requiring adequate balance and co-ordination).

The findings should be interpreted in the context of the study's limitations. Kidney function was estimated rather than measured, which could have led to misclassification of participants in the categorisation of GFR. Additionally, it is possible that the pattern of change in GFR over time, rather than a baseline value, could have explained more of the variability in the outcome measures. Some of the covariates were self-reported, such as chronic health conditions, which could have contributed to measurement error in these predictor variables. Participants who attend follow-up waves of the study tend to be younger and healthier than those who leave the study, which can be a source of bias. This may have led to under-representation of participants with diminished kidney function at later waves. The analyses incorporated an inverse probability weight in an attempt to overcome bias due to differential non-response at Wave 1, and differential attrition over follow-up waves of the study. Finally, CKD is associated with complications such as anaemia, metabolic acidosis and mineral bone disease, all of which could conceivably hinder physical performance. Although these factors were not measured in TILDA, such complications are not usually encountered until quite advanced stages of CKD (GFR <30 mL/min per 1.73m^2). As such, they are unlikely to contribute to physical performance in a general population sample with median GFR of approximately 80 mL/min per 1.73m^2.

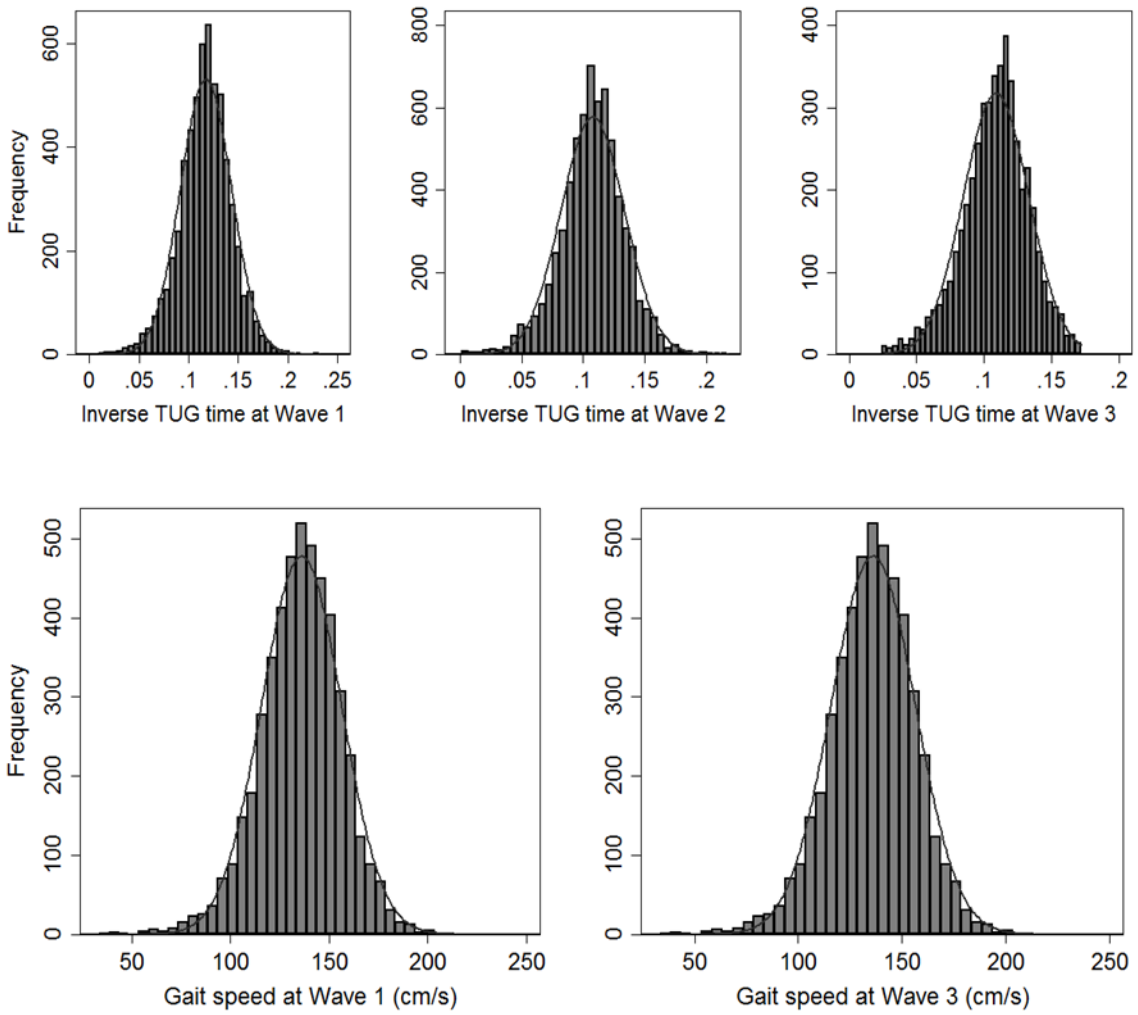
The study also has several strengths, most notably the availability of repeated standardised measures of gait speed and TUG in a representative sample of older adults. The sample size was large and included a broad range of kidney function. The dataset is comprehensive and complete with respect to relevant covariates.

In conclusion, community-dwelling older adults with diminished kidney function at baseline did not consistently demonstrate an accelerated decline in objective measures of lower extremity physical performance over time, compared to those with preserved kidney function. This suggests that, although a marker of poorer physical performance, reduced kidney function is not a major driver of physical function decline in the general population of middle aged and older adults.

6.5 Appendix



Appendix Figure 6.1: Participants who performed a timed-up-and-go (TUG) test at each wave
eGFR, estimated glomerular filtration rate



Appendix Figure 6.2: Distribution of inverse timed-up-and-go (TUG, top panels) and gait speed (bottom panels)

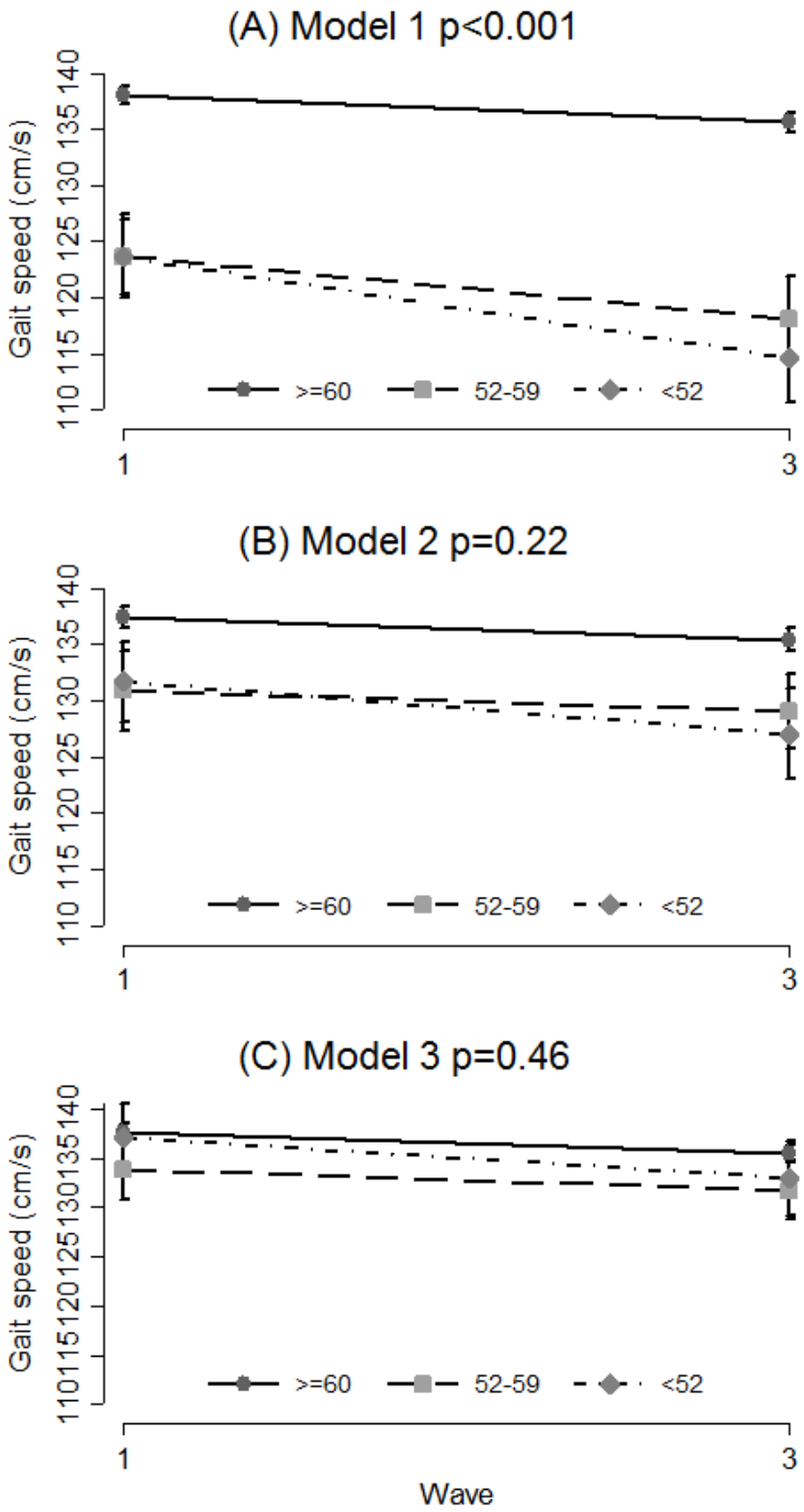
Appendix Table 6.1: Predicted TUG time (seconds) for each GFR category (estimated from cystatin C) across the three waves in secondary analysis

GFR	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Wave 1						
≥ 60	8.39 (8.33, 8.45)	Ref	8.49 (8.42, 8.57)	Ref	8.49 (8.42, 8.56)	Ref
50-59	10.17 (9.86, 10.50)	<0.001	9.04 (8.80, 9.29)	<0.001	8.74 (8.51, 8.97)	0.03
< 50	10.90 (10.56, 11.27)	<0.001	9.10 (8.84, 9.37)	<0.001	8.64 (8.41, 8.88)	0.22
Wave 2						
≥ 60	9.16 (9.08, 9.24)	Ref	9.28 (9.18, 9.37)	Ref	9.27 (9.18, 9.35)	Ref
50-59	11.59 (11.20, 12.01)	<0.001	10.15 (9.85, 10.47)	<0.001	9.79 (9.52, 10.07)	<0.001
< 50	12.03 (11.60, 12.50)	<0.001	9.91 (9.60, 10.24)	<0.001	9.35 (9.08, 9.64)	0.55
Wave 3						
≥ 60	9.09 (9.01, 9.16)	Ref	9.21 (9.12, 9.31)	Ref	9.21 (9.12, 9.30)	Ref
50-59	11.53 (11.08, 12.01)	<0.001	9.84 (9.55, 10.15)	<0.001	9.53 (9.27, 9.80)	0.01
< 50	13.11 (12.52, 13.75)	<0.001	10.19 (9.85, 10.56)	<0.001	9.68 (9.36, 10.03)	0.004

Model 1 – unadjusted

Model 2 – adjusted for age, age^2, sex and height

Model 3 – further adjusted for smoking, waist circumference, diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions



Appendix Figure 6.3: Predicted gait speed for each category of GFR in secondary analysis
The p values indicate the strength of the time*GFR interaction
Model 1 – unadjusted; Model 2 – adjusted for age, age^2, sex and height; Model 3 – further adjusted for smoking, waist circumference, diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions
GFR, glomerular filtration rate (estimated from cystatin C)

Appendix Table 6.2: Predicted gait speed (cm/s) at each wave for each GFR category (estimated from cystatin C) in secondary analysis

GFR	Model 1		Model 2		Model 3	
	Estimate (95% CI)	P	Estimate (95% CI)	P	Estimate (95% CI)	P
Wave 1						
≥ 60	138.0 (137.3, 138.8)	Ref	137.5 (136.6, 138.5)	Ref	137.6 (136.8, 138.5)	Ref
52-59	123.7 (120.0, 127.4)	<0.001	130.9 (127.3, 134.5)	<0.001	133.9 (130.8, 136.9)	0.01
< 52	123.6 (120.3, 126.9)	<0.001	131.7 (128.1, 135.3)	0.001	137.1 (133.6, 140.5)	0.75
Wave 3						
≥ 60	135.6 (134.7, 136.5)	Ref	135.4 (134.4, 136.4)	Ref	135.5 (134.6, 136.5)	Ref
52-59	118.1 (114.3, 121.9)	<0.001	129.1 (125.8, 132.4)	<0.001	131.7 (128.7, 134.7)	0.01
< 52	114.6 (110.6, 118.7)	<0.001	127.0 (123.0, 131.1)	<0.001	133.0 (129.2, 136.8)	0.19

Model 1 – unadjusted
Model 2 – adjusted for age, age^2, sex and height
Model 3 – further adjusted for smoking, waist circumference, diabetes, cardiovascular disease, pulse pressure, polypharmacy and chronic health conditions

7 The association between kidney function and quality of life

7.1 Introduction

To date, studies examining the relationship between kidney disease and quality of life have mainly been restricted to the end stage kidney disease and referred CKD populations. Individuals with advanced CKD have markedly lower QoL scores than the general population, and poorer QoL is a predictor of mortality in this group (141, 142). The prevalence of CKD is highest among the general population of older adults (29), yet few population studies have assessed the potential impact of a reduced level of kidney function on the QoL of an older person, or where along the range of kidney function one might expect to see changes in QoL. Prior studies (143-145) have defined CKD using creatinine, the generation of which can be unstable with increasing age due to changing muscle mass. Cystatin C, produced by all nucleated cells in the body, has been proposed as an alternative filtration marker in this population, as it is less influenced by muscle mass (125), and is a stronger predictor of clinical outcomes (5).

Many of the instruments used to quantify health-related QoL tend to emphasise physical determinants, such that a high QoL is characterised by the lack of functional impairments to fulfilling a "normal" life (146). This represents a somewhat narrow view of QoL, especially among older individuals who may have excellent QoL despite the presence of physical limitations. The Control Autonomy Self-realisation and Pleasure (CASP-19) scale was developed in a general population sample aged 65 to 75 years with the aim of providing a broader conceptualisation of QoL, encompassing both positive and negative influences of QoL in early old age (92). By focusing on a "needs satisfaction" approach, the CASP-19 can distinguish between physical limitations or perceived health status, and overall QoL. It has been argued that a QoL instrument that measures overall satisfaction with life is superior to those that conflate health status and QoL (146). The CASP-19 instrument has been validated across several different cohorts around the world, including longitudinal ageing studies (147). A number of health conditions have been associated with reductions in CASP-19, including decreased lung function (148) and central obesity (149). Data from older Irish adults have demonstrated that the mean CASP-19 score is curvilinear with age, increasing from age 50 to a peak at age 67, before falling gradually thereafter (150).

We sought to examine the relationship between kidney function and CASP-19 in community-dwelling older adults, compare cystatin C and creatinine as predictors of CASP-19, and explore whether the association between kidney function and CASP-19 varies by age.

7.2 Methods

7.2.1 Participants

This was a cross-sectional analysis from Wave 1 (June 2009-June 2011) of The Irish Longitudinal Study on Ageing. Participants were interviewed in their homes by way of a computer-assisted personal interview. Separately, they were asked to fill out and return a self-completion questionnaire, which included the CASP-19. All participants were subsequently invited to take part in a health assessment, either in their home or at a dedicated health centre. The present study includes 4293 participants who completed the CASP-19 and had a blood sample taken for estimation of glomerular filtration rate at the health assessment (Figure 7.1).

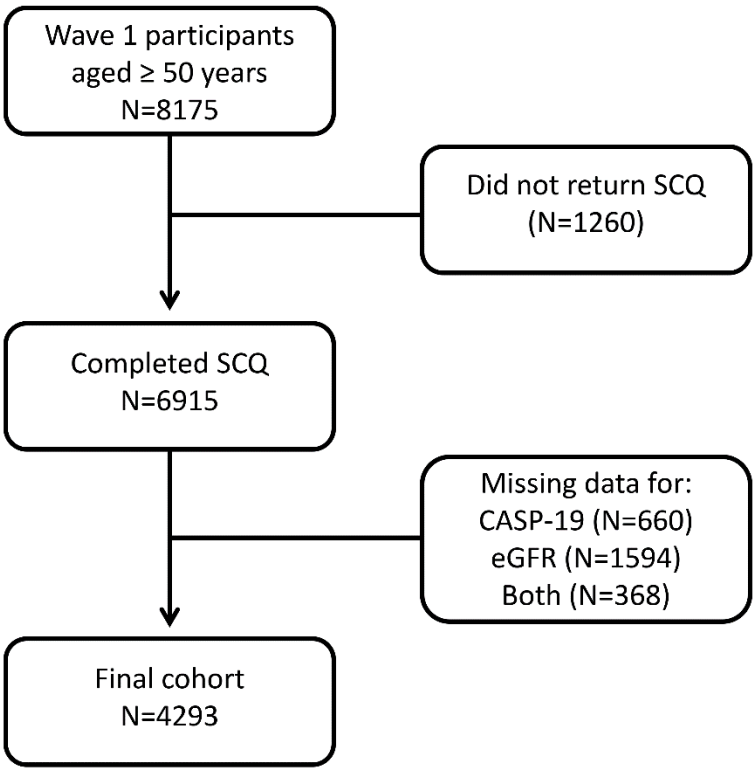


Figure 7.1: Flowchart of case ascertainment
CASP-19, Control Autonomy Self-realisation and Pleasure scale; eGFR, estimated glomerular filtration rate, SCQ, self-completion questionnaire

7.2.2 Outcome

The CASP-19 consists of 19 Likert scale items capturing four domains of QoL: control, autonomy, self-realisation and pleasure (92). A full description is provided in the Appendix. Respondents are shown a statement and are asked to rate how often they feel a particular way about that aspect of their life (coded Often 3, Not Often 2, Sometimes 1, Never 0). An example of a positive statement is "I can do the things that I want to do." Negative items (e.g. "I feel that what happens to me is out of my control") are reverse coded, such that higher scores represent higher QoL. The total score can range from 0 to 57.

7.2.3 Predictor

We categorised glomerular filtration rate estimated from either cystatin C or creatinine as follows: ≥90 mL/min per 1.73m^2 (reference); 75-89 mL/min per 1.73m^2; 60-74 mL/min per 1.73m^2; 45-59 mL/min per 1.73m^2; <45 mL/min per 1.73m^2. Due to relatively small numbers of participants with GFR values less than 30 mL/min per 1.73m^2 we created a single category for participants with GFR below 45 mL/min per 1.73m^2. Cystatin C and creatinine were measured simultaneously from frozen plasma as previously described. GFR was estimated using the CKD-EPI equations for cystatin C (53) or creatinine (25).

7.2.4 Covariates

Covariates were chosen based on their association with both exposure of interest (GFR) and outcome (CASP-19). Demographic variables included age, sex and educational attainment (primary/none, secondary, tertiary/higher). We included a quadratic age term to account for non-linear relationships between age and both CASP-19 (150) and GFR (29). Medication use was recorded during the interview and cross-checked with medication labels. All medications were coded according to the World Health Organisation Anatomical Therapeutic Chemical Classification (104). We defined the presence of diabetes as a self-reported physician's diagnosis and/or receiving insulin or oral hypoglycaemics. We defined the presence of hypertension as a self-reported physician's diagnosis and/or receiving antihypertensives. We defined the presence of cardiovascular disease as the number (0, 1, 2 or more) of the following self-reported physician-diagnosed conditions: angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, heart failure, stroke, transient ischaemic attack. Smoking status was coded as current, former or never. Waist circumference was measured at the health assessment. Comorbidity variables included polypharmacy (use of ≥5 medications

excluding supplements) and the number (0, 1, 2 or more) of the following self-reported physician-diagnosed conditions: chronic lung disease, asthma, arthritis, osteoporosis, malignancy, stomach ulcers, varicose ulcers, cirrhosis/severe liver damage.

7.2.5 Statistical analysis

All analyses were performed using Stata version 14 (StataCorp, College Station, TX). Continuous variables are reported as mean (SD) or median (IQR) as appropriate. Categorical variables are reported as count (percentage). As CASP-19 demonstrated a ceiling effect, we created a "QoL deficits" count variable by subtracting each participant's score from 57, the maximum score obtainable. This QoL deficits variable is therefore a count of impairments in the CASP-19 score. Due to evidence of over-dispersion in the QoL deficits variable, we used negative binomial regression (rather than a Poisson model) to quantify the relationship between GFR categories and QoL deficits. Model coefficients are expressed as incident rate ratios (IRR). For example, an IRR of 1.20 represents a 20% increase in the severity of the outcome for a given factor relative to the reference group. Analyses incorporated a survey weight to account for cluster sampling at the household level (102). Two models were generated: model 1 - adjusted for age (uncentred), age^2, sex and educational attainment; model 2 - further adjusted for smoking status, waist circumference, diabetes, hypertension, number of cardiovascular conditions, polypharmacy and number of chronic health conditions. We explored the association between GFRcys categories and QoL deficits within age strata (50-64, 65-74, ≥75 years) in a secondary analysis.

7.3 Results

7.3.1 Participant characteristics

A description of the characteristics of the cohort, stratified by GFRcys categories, is provided in Table 7.1. Median (IQR) age was 61 (55-68) years, 52.5% were female, median (IQR) GFRcys was 81 (68-93) mL/min per 1.73m^2, and mean (SD) CASP-19 score was 44.8 (7.4). Individuals with diminished GFRcys (<45 mL/min per 1.73m^2) tended to be older, have less educational attainment, and have a higher prevalence of cardiovascular and non-cardiovascular conditions. A description of participants who did not complete the SCQ, and participants who completed the SCQ but had missing data for CASP-19 or GFR, is provided in Appendix Table 7.1. Compared to the final study population, participants with missing data tended to be older, female and have less educational attainment. They also tended to have a higher burden of diabetes, hypertension, cardiovascular disease and polypharmacy.

7.3.2 Association between GFR and quality of life

GFR estimated from cystatin C

After adjusting for age, age^2, sex and educational attainment, participants with GFRcys<45 mL/min per 1.73m^2 had 28% greater QoL deficits (IRR 1.28, 95% CI 1.16, 1.40) relative to the reference group (Table 7.2). This corresponds to an absolute increase (95% CI) in QoL deficit count of 3.2 (1.8, 4.5). The relationship appeared linear across GFRcys categories (Figure 7.2). After further adjustment for cardiovascular risk factors and comorbidities, participants with GFRcys<45 mL/min per 1.73m^2 had 14% greater QoL deficits (IRR 1.14 [1.03, 1.25]) versus the reference group. This corresponds to an absolute increase in QoL deficit count of 1.6 (0.4, 2.8). The full output from the extended model (model 2) is provided in Appendix Table 7.2. Younger age, male sex, less educational attainment, current smoking and higher burden of comorbidities were all strong predictors of lower CASP-19 scores.

GFR estimated from creatinine

In the base model, only individuals with GFRcr <45 mL/min per 1.73m^2 had any evidence of an increase in QoL deficit count compared to the reference group (IRR 1.12 [95% CI 1.00, 1.24]). We found no statistically significant association between GFRcr categories and QoL deficits in the extended model (Table 7.2).

Table 7.1: Participant characteristics according to level of glomerular filtration rate estimated from cystatin C

Variable	GFR ≥90 N=1380	GFR 75-89 N=1328	GFR 60-74 N=976	GFR 45-59 N=418	GFR <45 N=191
Age in years					
Median (IQR)	56 (52-61)	60 (55-65)	66 (59-71)	72 (66-78)	77 (71-83)
50 to 64	1194 (86.5)	935 (70.4)	443 (45.4)	89 (21.3)	22 (11.5)
65 to 74	169 (12.3)	348 (26.2)	383 (39.2)	165 (39.5)	57 (29.8)
75 and over	17 (1.2)	45 (3.4)	150 (15.4)	164 (39.2)	112 (58.6)
Female sex	698 (50.6)	687 (51.7)	526 (53.9)	243 (58.1)	98 (51.3)
Education					
Primary/none	185 (13.4)	260 (19.6)	263 (27.0)	151 (36.1)	83 (43.7)
Secondary	634 (45.9)	527 (39.7)	388 (39.8)	157 (37.6)	75 (39.5)
Tertiary/higher	561 (40.7)	541 (40.7)	324 (33.2)	110 (26.3)	32 (16.8)
Smoking					
Never	678 (49.1)	622 (46.8)	424 (43.4)	166 (39.7)	85 (44.5)
Former	556 (40.3)	506 (38.1)	367 (37.6)	173 (41.4)	90 (47.1)
Current	146 (10.6)	200 (15.1)	185 (19.0)	79 (18.9)	16 (8.4)
Waist (cm)	92.1 (13.0)	94.3 (12.8)	97.6 (13.8)	99.1 (14.6)	102.1 (15.8)
Diabetes	70 (5.1)	73 (5.5)	78 (8.0)	54 (12.9)	32 (16.8)
Hypertension	392 (28.4)	443 (33.4)	472 (48.4)	287 (68.7)	158 (82.7)
CV conditions					
None	1308 (94.8)	1228 (92.5)	859 (88.0)	336 (80.4)	133 (69.6)
One	58 (4.2)	76 (5.7)	80 (8.2)	63 (15.1)	32 (16.8)
2 or more	14 (1.0)	24 (1.8)	37 (3.8)	19 (4.6)	26 (13.6)
Polypharmacy	96 (7.0)	137 (10.4)	191 (19.6)	140 (33.9)	103 (54.8)
Comorbidities					
None	829 (60.1)	706 (53.2)	465 (47.6)	151 (36.1)	72 (37.7)
One	418 (30.3)	452 (34.0)	352 (36.1)	180 (43.1)	67 (35.1)
2 or more	133 (9.6)	170 (12.8)	159 (16.3)	87 (20.8)	52 (27.2)
CASP-19	45.1 (7.2)	45.2 (7.3)	44.7 (7.4)	43.7 (7.6)	42.6 (7.6)

Numbers expressed as count (percentage) or mean (SD) unless otherwise stated.
Data missing for education (N=2), waist circumference (N=15) and polypharmacy (N=23).
CV, cardiovascular

Table 7.2: Association between categories of GFR and quality of life deficits

GFR category	Model 1	P value	Model 2	P value
GFR estimated from cystatin C				
≥ 90	*reference*		*reference*	
75-89	1.04 (1.00, 1.09)	0.08	1.03 (0.98, 1.08)	0.21
60-74	1.11 (1.05, 1.17)	<0.001	1.07 (1.01, 1.12)	0.02
45-59	1.21 (1.13, 1.31)	<0.001	1.11 (1.03, 1.20)	0.004
< 45	1.28 (1.16, 1.40)	<0.001	1.14 (1.03, 1.25)	0.008
GFR estimated from creatinine				
≥ 90	*reference*		*reference*	
75-89	0.98 (0.94, 1.03)	0.42	1.00 (0.95, 1.04)	0.86
60-74	1.00 (0.94, 1.05)	0.89	1.00 (0.95, 1.06)	0.99
45-59	0.99 (0.91, 1.07)	0.80	0.98 (0.91, 1.06)	0.66
< 45	1.12 (1.00, 1.24)	0.04	1.04 (0.94, 1.16)	0.42

Estimates are expressed as incident rate ratio (95% confidence interval)
Model 1 adjusted for age, age^2, sex and educational attainment
Model 2 further adjusted for smoking status, waist circumference, diabetes, hypertension, number of cardiovascular conditions, polypharmacy and number of chronic health conditions

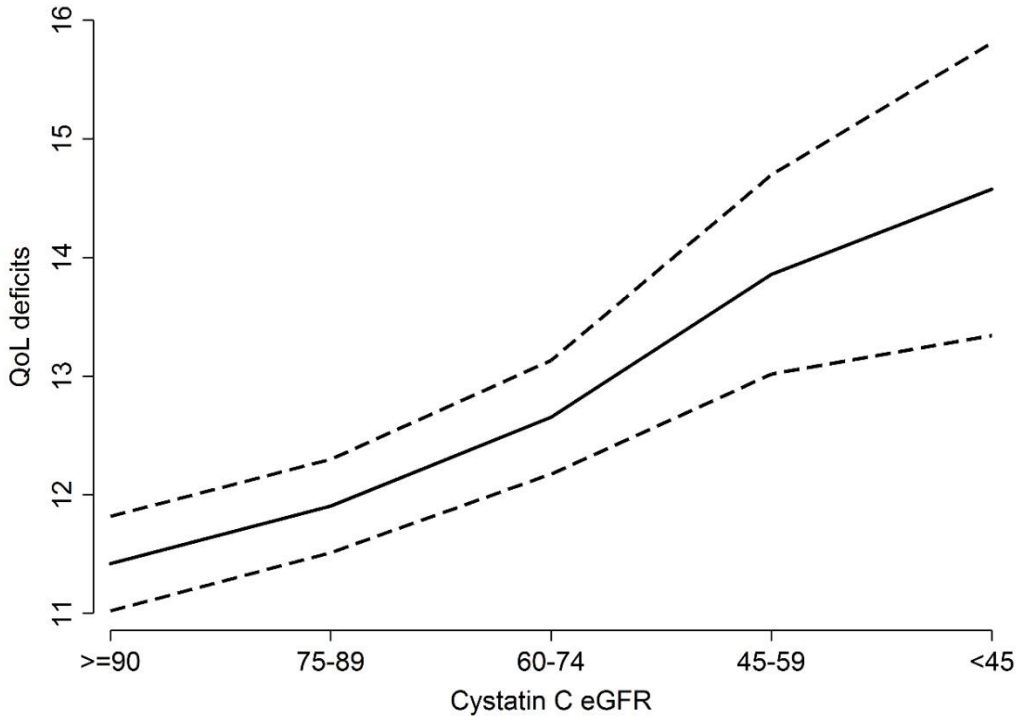


Figure 7.2: Predicted quality of life deficits by category of GFR estimated from cystatin C
Model adjusted for age, age^2, sex and education

7.3.3 Age strata

The relationship between GFRcys and QoL deficits was strongest among participants aged 50-64 years (Table 7.3). We did not observe any substantive associations between GFRcys and CASP-19 among participants aged 65-74 or among participants aged ≥75 years. It should be acknowledged that this analysis was exploratory and these estimates may have been under-powered by comparatively reduced sample sizes at the extremes of age and GFR i.e. younger participants with severe reductions in GFR and older participants with preserved GFR (Table 7.1). This is reflected in the weak evidence we observed for the full 3 x 5 interaction between age strata and GFR categories in Model 1 (p=0.15) and Model 2 (p=0.23).

Table 7.3: Age stratum-specific estimates of the association between categories of GFR estimated from cystatin C and quality of life deficits

GFR category	Model 1	P value	Model 2	P value
50 to 64 years (N=2683)				
≥ 90	*reference*		*reference*	
75-89	1.06 (1.00, 1.11)	0.04	1.04 (0.99, 1.10)	0.10
60-74	1.17 (1.09, 1.25)	<0.001	1.11 (1.04, 1.19)	0.002
45-59	1.29 (1.14, 1.46)	<0.001	1.16 (1.02, 1.32)	0.02
< 45	1.51 (1.26, 1.81)	<0.001	1.39 (1.16, 1.67)	<0.001
65 to 74 years (N=1122)				
≥ 90	*reference*		*reference*	
75-89	0.93 (0.84, 1.04)	0.19	0.92 (0.83, 1.02)	0.13
60-74	0.94 (0.85, 1.05)	0.28	0.92 (0.83, 1.02)	0.10
45-59	1.09 (0.96, 1.25)	0.17	1.02 (0.90, 1.15)	0.79
< 45	1.21 (1.03, 1.42)	0.02	1.07 (0.92, 1.24)	0.39
75 years and over (N=488)				
≥ 90	*reference*		*reference*	
75-89	1.22 (0.97, 1.55)	0.09	1.19 (0.94, 1.51)	0.15
60-74	1.17 (0.93, 1.48)	0.18	1.13 (0.91, 1.42)	0.27
45-59	1.20 (0.96, 1.50)	0.10	1.10 (0.88, 1.38)	0.38
< 45	1.21 (0.96, 1.53)	0.11	1.10 (0.87, 1.40)	0.42

Estimates are expressed as incident rate ratio (95% confidence interval)
Model 1 adjusted for age, sex and educational attainment
Model 2 further adjusted for smoking status, waist circumference, diabetes, hypertension, number of cardiovascular conditions, polypharmacy and number of chronic health conditions

7.4 Discussion

In this study of community-dwelling older adults, we observed a relationship between declines in kidney function and poorer QoL using the CASP-19 score, a holistic measure of QoL in older individuals. GFR estimated from cystatin C was linearly related to QoL after adjustment for demographics, cardiovascular risk factors and comorbidities. The relationship between GFRcys and QoL was strongest in middle-aged participants, whereas there was little evidence of an association among older participants. We found no substantive association between GFR estimated from creatinine and QoL.

Although we detected a statistically significant signal for GFRcys, this should be interpreted in the context of what constitutes a clinically meaningful difference in QoL score. Two approaches have been advocated in the literature: distribution-based and anchor-based (151). As neither strategy is unequivocally superior to the other (152), we discuss both approaches in an effort to enhance interpretation of our findings. The distribution-based approach expresses a change relative to the within-population standard deviation. An effect size of 0.2 standard deviations is considered "small", 0.5 is considered "moderate" and 0.8 or above is considered "large" (153). For example, in our base model adjusting for age, sex and educational attainment, participants with GFRcys <45 mL/min per 1.73m^2 had 3.2 more QoL deficits compared to the reference group. This represents an effect size of 0.43 (3.2/7.4), between small and moderate on the suggested scale. The corresponding score in the extended model was 0.22 (1.6/7.4), a small effect size. The distribution approach is based on statistical criteria which are dependent on the magnitude of variability in the particular sample studied, potentially limiting generalisability of results (151). The alternative anchor-based approach provides a context in which to interpret a difference in QoL score, by examining the association between the QoL instrument and an independent measure. An analysis from the English Longitudinal Study of Ageing, a similar cohort to TILDA, examined the cross-sectional and longitudinal relationships between CASP-19 and eight readily-interpretable independent variables that one would expect to correlate with QoL, such as health status and socio-economic position (154). The CASP-19 discriminated well between these anchor variables and was shown to be responsive to change in most variables over time. These models were adjusted for age, age^2, sex and education, thus facilitating a comparison with our model 1 estimates. The effect size for GFRcys <45 mL/min per 1.73m^2 in our analysis would correspond to less than half the effect size for CASP-19 and any of the following anchor variables in ELSA: having difficulty walking a quarter mile, having a limiting chronic illness, or the presence of depression.

Previous studies in CKD patients have observed an association between CKD severity and diminished QoL (155-157). Referred CKD populations are likely to have a different perception of their QoL to the general population. The mean GFR in these studies was generally below 30 mL/min per 1.73m^2, a level of kidney function at which complications such as anaemia and mineral bone disease are encountered. The prospect of the future need for renal replacement therapy could also contribute to an individual's QoL. Population studies offer key advantages over referred CKD samples, including a broader range of kidney function and the availability of an internal comparator group. The link between kidney function and QoL in population studies has not been consistent however. A study of older diabetic individuals found no association between kidney function, measured by 24-hour creatinine clearance, and QoL after adjustment for cardiovascular disease (158). A regional cohort of older Korean adults observed trends for poorer physical components of QoL with diminishing GFR, but these were only statistically significant below a GFR of 45 mL/min per 1.73m^2 (145). A similar trend for worsening physical, but not mental, components of QoL was found among a large US population sample (143). A population study of Australian adults demonstrated clear reductions in both physical and mental components of QoL among those with CKD (GFRcr <60mL/min per 1.73m^2) compared to those without CKD (144). In contrast to most of these studies, we examined QoL across the spectrum of GFR estimated from creatinine and cystatin C in a national cohort of community-dwelling older adults. We measured overall QoL using an instrument that does not emphasise physical ailments, but rather encompasses both positive and negative aspects of life in older adults.

The incongruous findings for cystatin C and creatinine raise important questions about these biomarkers. Cystatin C has a stronger correlation with directly measured GFR than creatinine (48), and it is generally assumed that the stronger associations with clinical outcomes observed for cystatin C (59) reflect more accurate estimation of GFR. The differential profile for cystatin C and creatinine in our study may well be explained by more accurate estimation of GFR by cystatin C compared to creatinine. However, the median GFRcys in our cohort was 81 mL/min per 1.73m^2, whereas symptoms of kidney disease are classically reported at very low levels of GFR. The differences between the biomarkers were so marked that other explanations should be considered. An increasing body of literature has identified correlations between cystatin C and non-GFR determinants such as obesity and inflammation (64, 68, 69). Rather than solely measuring kidney function, cystatin C may be a surrogate marker of other biological determinants of ill-health, which culminate in a phenotype of accelerated ageing (159) and contribute to lower QoL.

Analysis of the relationship between GFRcys and CASP-19 within age strata suggested greater differences among middle-aged compared to older participants. Among the Australian cohort, the effect of CKD was greater among younger individuals for mental components of QoL, and greater among older individuals for physical components (144). This is consistent with our findings, in that CASP-19 places less emphasis on physical determinants of QoL compared to instruments such as the Short Form-36 questionnaire. Given the relatively smaller sample size for TILDA participants in the oldest age category (≥75 years), estimates of association in this subgroup may have been underpowered. For example, in a large cohort of adults aged ≥75 years attending primary care services, a GFR <45 mL/min per 1.73m^2 was associated with poorer scores in QoL domains such as social interaction and home management (160). Given the high prevalence of "mild" CKD (GFR 45-59 mL/min per 1.73m^2) in the general population of older adults, the identification of meaningful connected outcomes such as reduced QoL would strengthen the case for detecting modest reductions in kidney function in this demographic.

Our findings should be interpreted in the context of the study's potential limitations. We measured kidney biomarkers at a single time point and urinary protein was not measured. The cross-sectional design of the study limits our ability to infer causality in the relationship between kidney function and QoL. There may have been residual observed or unobserved confounding in this relationship. There were missing data for both GFR and CASP-19, which may have introduced a selection bias into our results. The TILDA sample is a relatively robust cohort of middle-aged and older community-dwelling Caucasian adults, thus limiting the generalisability of our results. Although CASP-19 has been shown to be a valid and reliable tool, relatively few studies have investigated objective health measures as predictors of CASP-19 (147). These limitations are balanced by several strengths. The sample size is large with a broad range of age and GFR. The TILDA dataset is rich with respect to relevant covariates, including comorbidities and medications. Both cystatin C and creatinine were measured simultaneously using standardised assays, facilitating a comparison of both biomarkers as predictors of QoL.

In conclusion, we have demonstrated a statistically significant, but clinically modest, relationship between reduced GFR and lower QoL scores among community-dwelling older adults. This association was only evident using cystatin C to estimate GFR, and was more pronounced in participants under the age of 65 years. Our findings suggest that GFR is not a clinically significant predictor of overall QoL in the general population of older adults. In this population, a reduced GFR could be one of a number of chronic health conditions that accumulate with age and contribute to QoL.

7.5 Appendix

Appendix Table 7.1: Characteristics of participants who did not return a self-completion questionnaire (SCQ), and those with missing data for CASP-19 or GFR, compared to the final study population

Variable	No SCQ (N=1260)	Missing CASP-19/GFR (N=2622)	Final cohort (N=4293)
Age in years	62 (56 – 73)	65 (57 – 74)	61 (55 – 68)
Female sex	665 (52.8)	1514 (57.7)	2252 (52.5)
Education			
Primary/none	561 (44.6)	1001 (38.2)	942 (22.0)
Secondary	444 (35.3)	1038 (39.6)	1781 (41.5)
Tertiary/higher	253 (20.1)	583 (22.2)	1568 (36.5)
Smoking			
Current	319 (25.3)	546 (20.8)	626 (14.6)
Former	447 (35.5)	978 (37.3)	1692 (39.4)
Never	493 (39.2)	1098 (41.9)	1975 (46.0)
Diabetes	116 (9.2)	249 (9.5)	307 (7.2)
Hypertension	617 (49.0)	1301 (49.6)	1752 (40.8)
CV conditions			
None	1086 (86.2)	2269 (86.5)	3864 (90.0)
One	132 (10.5)	256 (9.8)	309 (7.2)
Two or more	42 (3.3)	97 (3.7)	120 (2.8)
Polypharmacy	233 (19.0)	561 (21.6)	667 (15.6)
Comorbidities			
None	684 (54.3)	1331 (50.8)	2223 (51.8)
One	391 (31.0)	873 (33.3)	1469 (34.2)
Two or more	185 (14.7)	418 (15.9)	601 (14.0)

Numbers expressed as median (interquartile range) or count (percent)
CV, cardiovascular
Missing data for age (N=1), education (N=4), smoking (N=1) and polypharmacy (N=82)

Appendix Table 7.2: Output from multivariable model (Model 2)

Variable	IRR	95% CI	P-value
GFRcys			
• *≥ 90*	*Reference*	*Reference*	
• *75-89*	1.03	0.98, 1.08	0.21
• *60-74*	1.07	1.01, 1.12	0.02
• *45-59*	1.11	1.03, 1.20	0.004
• *< 45*	1.14	1.03, 1.25	0.008
Age (per year)	0.89	0.87, 0.92	<0.001
Age^2	1.0008	1.0006, 1.001	<0.001
Female sex	0.95	0.92, 0.99	0.007
Education			
• *Tertiary/higher*	*Reference*	*Reference*	
• *Secondary*	1.06	1.02, 1.11	0.002
• *Primary/none*	1.14	1.08, 1.20	<0.001
CVD burden			
• *None*	*Reference*	*Reference*	
• *One*	1.07	1.00, 1.15	0.05
• *Two or more*	1.10	1.01, 1.21	0.03
Diabetes	1.02	0.95, 1.10	0.53
Hypertension	1.05	1.01, 1.10	0.01
Smoking			
• *Never*	*Reference*	*Reference*	
• *Former*	1.03	0.99, 1.07	0.13
• *Current*	1.14	1.08, 1.20	<0.001
Waist (per 10cm)	1.004	0.99, 1.02	0.61
Polypharmacy	1.14	1.08, 1.20	<0.001
Chronic conditions			
• *None*	*Reference*	*Reference*	
• *One*	1.12	1.08, 1.17	<0.001
• *Two or more*	1.27	1.20, 1.34	<0.001

Estimates expressed as incident rate ratio (IRR) with 95% confidence interval (95% CI)
CVD, cardiovascular disease; GFRcys, glomerular filtration rate estimated from cystatin C

The Control, Autonomy, Self-realisation and Pleasure (CASP-19) Scale. Respondents are shown the following list of statements and are asked "How often do you feel like this?"

PLEASE TICK ONE BOX PER LINE.	OFTEN	SOMETIMES	RARELY	NEVER
My age prevents me from doing the things I would like to.	☐	☐	☐	☐
I feel that what happens to me is out of my control.	☐	☐	☐	☐
I feel free to plan for the future.	☐	☐	☐	☐
I feel left out of things.	☐	☐	☐	☐
I can do the things that I want to do.	☐	☐	☐	☐
Family responsibilities prevent me from doing what I want to do.	☐	☐	☐	☐
I feel that I can please myself in what I can do.	☐	☐	☐	☐
My health stops me from doing the things I want to do.	☐	☐	☐	☐
Shortage of money stops me from doing the things that I want to do.	☐	☐	☐	☐
I look forward to each day.	☐	☐	☐	☐
I feel that my life has meaning.	☐	☐	☐	☐
I enjoy the things that I do.	☐	☐	☐	☐
I enjoy being in the company of others.	☐	☐	☐	☐
On balance, I look back on my life with a sense of happiness.	☐	☐	☐	☐
I feel full of energy these days.	☐	☐	☐	☐
I choose to do things that I have never done before.	☐	☐	☐	☐
I feel satisfied with the way my life has turned out.	☐	☐	☐	☐
I feel that life is full of opportunities.	☐	☐	☐	☐
I feel that the future looks good for me.	☐	☐	☐	☐

8 Novel association between kidney function and postural blood pressure responses

8.1 Introduction

Recent large-scale observational studies have demonstrated a J-shaped relationship between blood pressure and all-cause mortality in individuals with CKD (161, 162), raising concern about the potential harms associated with hypotension in this population. In the general population, orthostatic hypotension has been shown to be an independent predictor of cardiovascular outcomes including coronary artery disease, heart failure and stroke (93, 94, 163). Older individuals have the highest burden of both OH and CKD, yet the relationship between postural BP responses and kidney function has rarely been examined in this demographic. Furthermore, our tools for detecting OH are insensitive in clinical practice. OH is conventionally defined as a sustained drop in BP that exceeds consensus thresholds within three minutes of standing (97). However, what constitutes a sustained change in postural BP is not clearly defined. The current classification of OH is based on a small number of data points, which do not capture the full dynamic BP response to standing.

Beat-to-beat BP measurements offer the potential to refine our understanding of the relationship between postural BP behaviour and the kidney by mapping the postural BP response, including the initial drop in BP and the slope of BP recovery, or stabilization, towards baseline values. Older adults demonstrate progressively delayed BP recovery (hereafter referred to as impaired BP stabilization) (14), and this has important consequences such as an increased risk of falls (164) and all-cause mortality (98). Impaired BP stabilization is associated with end-organ dysfunction in areas of the body with high perfusion demand such as the eye (165) and the brain (16). A consistent finding among these studies is that the degree of BP stabilization, rather than the absolute initial fall in BP, appears to be the main predictor of outcome, suggesting that sustained reductions in BP result in relative hypo-perfusion to vital organs. As a highly vascular organ that relies on precise auto-regulation of blood flow to maintain function, the kidney may be susceptible to injury following repeated episodes of sustained hypotension. Kidney disease is also associated with the development of autonomic dysfunction, which itself could contribute to a greater likelihood of OH.

A more granular assessment of the postural BP response could inform clinicians attempting to balance the benefits of treating hypertension with attendant risks of hypotension in the clinically heterogeneous population of older adults with diminished kidney function. We sought to characterise the postural BP response, in particular sustained reductions in BP, among a large sample of older community-dwelling individuals across the spectrum of GFR.

8.2 Methods

8.2.1 Participants

Data from the first wave of The Irish Longitudinal Study on Ageing were analysed. A total of 5035 participants attended the Wave 1 health assessment. The majority (94.1%) of these participants had a venous blood sample taken for measurement of cystatin C and creatinine. Of these, 533 participants had incomplete active stand data, resulting in a study population of 4204 participants with complete data for kidney biomarkers and the active stand test (Figure 8.1).

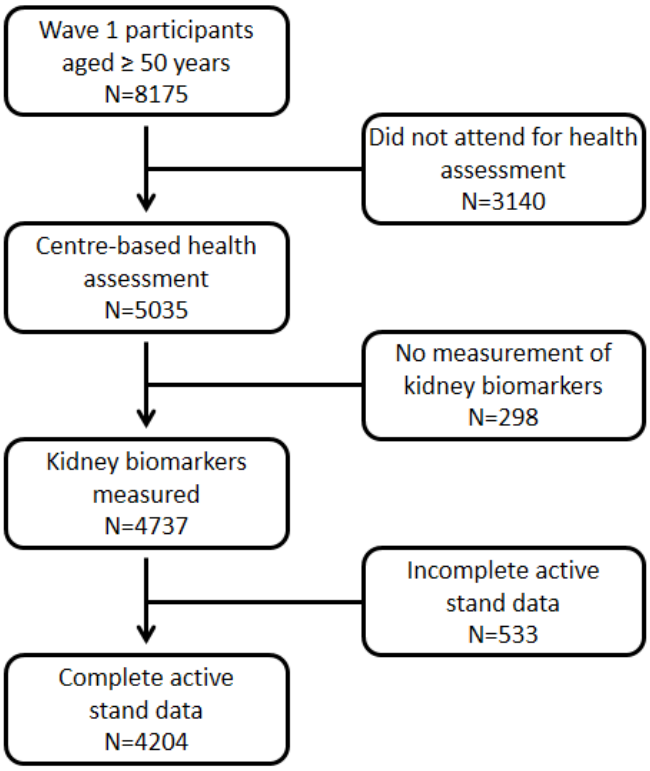


Figure 8.1: Flowchart of case ascertainment

8.2.2 Measurement of orthostatic blood pressure

The continuous BP response to postural change was recorded using the volume-clamp method combined with Physiocal and brachial artery waveform reconstruction (Finometer, Finapres Medical Systems, Amsterdam, Netherlands). Recordings were obtained in a comfortably lit quiet room at an ambient temperature of 21 to 23^{o}C. Participants were asked to rest in the supine position for ten minutes. Throughout this time the Physiocal (recalibration) function was enabled. The variables "baseline SBP" and "baseline DBP" were calculated as the mean systolic (SBP) and diastolic BP (DBP) values recorded between 60 and 30 seconds prior to the participant standing. Physiocal was switched off immediately prior to standing and remained off until completion of the test, to ensure that no data were lost during this time period due to the recalibration process. Participants were asked to stand in a timely manner (<5 seconds) with or without assistance from the research nurse. The participant's arm was resting by their side during the period of supine rest and during standing. Upon standing SBP and DBP were recorded for 2 minutes, during which time the participants stood quietly. The participants' BP was estimated at 10 second intervals using 5 second moving averages around each time point. The steps involved in data processing have been described in detail elsewhere (166).

8.2.3 Predictor

For all analyses GFR was estimated from cystatin C, and in secondary analyses from creatinine, according to the CKD-EPI equations (25, 53) and categorised as follows: ≥90 mL/min per 1.73m^2 (reference); 75-89 mL/min per 1.73m^2; 60-74 mL/min per 1.73m^2; 45-59 mL/min per 1.73m^2; <45 mL/min per 1.73m^2. These categories are consistent with KDIGO guidelines for staging of GFR. Due to relatively small numbers of participants with GFR <30 mL/min per 1.73m^2 we created a single category for participants with GFR <45 mL/min per 1.73m^2. Creatinine and cystatin C were simultaneously measured from frozen plasma as described previously.

8.2.4 Outcome

The primary outcome was "sustained OH", which we defined as a postural drop in BP that exceeded consensus BP thresholds for OH (SBP drop ≥20mmHg and/or DBP drop ≥10mmHg) (97) at each 10-second interval from 60 to 110 seconds inclusive (14). Only participants who met consensus OH criteria at all of these time points were considered to have sustained OH. In an exploratory analysis we examined the pattern of postural BP responses during the active stand test, characterized as the difference in mean SBP and DBP values from baseline (resting supine)

at each 10-second interval after standing, up to and including 110 seconds. The presence of "impaired BP stabilization" was inferred when the mean deficit in SBP or DBP for a given GFR category was statistically significantly greater than that of the reference group.

8.2.5 Covariates

Participant characteristics included age, gender, smoking history, and self-reported physician-diagnosed conditions. Medication use was recorded during the interview, cross-checked with medication labels and coded according to the World Health Organization Anatomical Therapeutic Chemical Classification (104). LDL and HDL cholesterol were measured from each of the blood samples prior to freezing. We defined the presence of diabetes as a self-reported physician's diagnosis, or receiving insulin or oral hypoglycemic medications. We defined the presence of cardiovascular disease as any one of the following self-reported physician-diagnosed conditions: angina, heart failure, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischemic attack or stroke. Height and waist circumference were measured at the health assessment.

8.2.6 Statistical analysis

Continuous variables are described as mean (SD) or median (IQR) as appropriate. Categorical variables are described as count (percentage). We examined the relationship between GFRcys categories and sustained OH using logistic regression, with estimates reported as odds ratios (OR) and 95% confidence intervals. These models were adjusted for the following covariates: age, sex, height, baseline SBP, number of antihypertensive medications (0, 1, 2, 3 or more), cardiovascular disease, diabetes, smoking (current/former/never), waist circumference, HDL and LDL cholesterol. The models included a quadratic term for age to account for non-linearity in the relationships between age and both postural BP responses (14) and prevalence of reduced GFR (29). Age was not centred in the creation of the quadratic term. In a stratified analysis, we examined the differential associations between GFRcys categories and sustained OH under antihypertensive therapy, using the likelihood ratio (LR) test.

For the exploratory analysis, we estimated the mean differences in SBP and DBP from baseline, at each 10-second interval after standing, for each category of GFRcys versus the reference group (GFRcys ≥90 mL/min per 1.73m^2). To account for the fact that the repeated BP measurements are nested within the individual, and therefore correlated with each other, we

ran mixed effects linear regression models. We re-parameterized the “time” variables from 11 discrete time variables (10 to 110 seconds inclusive) to a set of linear spline variables with 3 knots as follows: 10 to 20 seconds; 20 to 30 seconds; 30 to 110 seconds. We chose these knots because, at a population level, most of the absolute mean change in BP from baseline occurs within the first 30 seconds of standing, beyond which time the mean BP change from baseline is uniform. These re-parameterized time variables were included in the models as fixed effects and as random effects. As BP measurements closer together had stronger correlations than those further apart, conditional (residual) variance was modelled using an autoregressive variance-covariance matrix across all 11 time points per individual. Each independent variable was included in the fixed part of the model, both as a main effect and as an interaction term with the time variables. Based on the fitted models, for each GFR category, we estimated the conditional mean differences in SBP and DBP from baseline for each 10-second interval of the active stand test, and plotted these. These conditional mean estimates are conditional at the means of other covariates in the model.

In a secondary analysis we estimated and plotted the conditional mean differences in SBP and DBP from baseline at each 10 second interval after standing for each category of GFRcr, using the same mixed effects linear regression model as that described for GFRcys above.

Only complete cases were analysed. All analyses were performed using Stata version 14.1 (StataCorp, College Station, TX).

8.3 Results

8.3.1 Participant characteristics

Participant characteristics, by GFRcys category, are displayed in Table 8.1. Mean (SD) age of participants was 61.6 (8.2) years, 46.8% were male and median (IQR) GFRcys was 82 (70-94) mL/min per 1.73m^2. Participants with diminishing GFR tended to be older and to have a higher prevalence of diabetes and cardiovascular disease, higher baseline SBP and waist circumference, and a greater burden of antihypertensive therapy. Appendix Table 8.1 provides a description of study participants who did not attend for a health assessment, and participants who attended a health assessment but who were missing data for either GFR or the active stand test. Compared to the final study population, those who did not attend a health assessment were older (66.8 versus 61.6 years) and had a higher prevalence of diabetes (10.7% versus 6.6%), hypertension (52.9% versus 38.6%) and cardiovascular disease (14.3% versus 9.4%).

8.3.2 Sustained orthostatic hypotension

The results of logistic regression models for the outcome sustained OH are provided in Table 8.2. The overall frequency of sustained OH was 6.0% (N=252). In unadjusted analyses, the likelihood of sustained OH increased steadily with diminishing GFRcys (p for trend <0.001). A similar pattern was observed after multivariable adjustment; however the relatively low number of events contributed to wide error bounds for these estimates. In adjusted analyses, participants with GFRcys <60 mL/min per 1.73m^2 were approximately twice as likely to have sustained OH compared to those with preserved kidney function: OR 2.25 (95% CI 1.34 to 3.78) for GFRcys 45-59 mL/min per 1.73m^2; OR 1.77 (95% CI 0.85 to 3.72] for GFRcys <45 mL/min per 1.73m^2. We stratified the sample by the presence or absence of CKD (GFRcys <60 mL/min per 1.73m^2). After multivariable adjustment, participants with CKD had a 67% increased likelihood of having sustained OH compared to those without CKD (OR 1.67 [95% CI 1.13 to 2.47]). The association between GFRcys categories and sustained OH did not vary significantly by the presence or absence of antihypertensive therapy (LR p=0.42).

Table 8.1: Participant characteristics by category of glomerular filtration rate

Variable	GFR > 90 (N=1414)	GFR 75 - 89 (N=1379)	GFR 60 - 74 (N=942)	GFR 45 - 59 (N=337)	GFR < 45 (N=132)
Age in years	57.1 (6.0)	60.8 (6.6)	64.9 (8.1)	69.8 (7.8)	73.4 (8.6)
Male sex	692 (48.9)	640 (46.4)	436 (46.3)	134 (39.8)	64 (48.5)
Height (cm)	167.3 (9.0)	166.5 (9.3)	166.1 (9.3)	163.9 (9.0)	164.0 (8.4)
Diabetes	74 (5.2)	69 (5.0)	67 (7.1)	43 (12.8)	26 (19.7)
CV disease	74 (5.2)	99 (7.2)	118 (12.5)	63 (18.7)	42 (31.8)
Waist (cm)	91.9 (13.0)	93.8 (12.8)	97.6 (13.8)	99.8 (13.9)	101.3 (15.6)
LDL (mmol/L)	3.01 (0.93)	3.02 (0.92)	2.89 (0.97)	2.65 (0.95)	2.55 (0.91)
HDL (mmol/L)	1.61 (0.45)	1.57 (0.43)	1.50 (0.42)	1.42 (0.41)	1.38 (0.42)
Smoking status					
Current	159 (11.2)	209 (15.2)	181 (19.2)	63 (18.7)	11 (8.3)
Former	571 (40.4)	532 (38.6)	350 (37.2)	145 (43.0)	67 (50.8)
Never	684 (48.4)	638 (46.3)	411 (43.6)	129 (38.3)	54 (40.9)
SBP (mmHg)	133.7 (21.3)	136.3 (22.1)	138.3 (22.8)	140.3 (22.6)	138.8 (28.8)
DBP (mmHg)	73.5 (11.2)	73.8 (10.9)	73.3 (11.1)	71.6 (10.8)	69.9 (13.9)
Antihypertensives					
None	1109 (78.4)	1022 (74.1)	555 (58.9)	132 (39.2)	30 (22.7)
1 agent	186 (13.2)	183 (13.3)	182 (19.3)	81 (24.0)	31 (23.5)
2 agents	86 (6.1)	124 (9.0)	142 (15.1)	79 (23.4)	40 (30.3)
3 or more agents	33 (2.3)	50 (3.6)	63 (6.7)	45 (13.4)	31 (23.5)
Beta-blocker	94 (6.7)	131 (9.5)	133 (14.1)	93 (27.6)	44 (33.3)
RAAS blocker	197 (13.9)	232 (16.8)	274 (29.1)	138 (41.0)	75 (56.8)
CCB	79 (5.6)	94 (6.8)	94 (10.0)	53 (15.7)	35 (26.5)
Diuretic	31 (2.2)	61 (4.4)	65 (6.9)	51 (15.1)	32 (24.2)

Numbers are expressed as count (%) or mean (SD)
CCB, calcium channel blocker; CV, cardiovascular; DBP, diastolic blood pressure; HDL, high density lipoprotein; LDL, low density lipoprotein; RAAS, renin angiotensin aldosterone system; SBP, systolic blood pressure
Data missing for height (N=2), waist circumference (N=11) and lipids (N=7)

Table 8.2: Association between GFR categories and sustained orthostatic hypotension

GFR stage	Count (%)	Model 1	Model 2
≥ 90	58 (4.1)	*reference*	*reference*
75 - 89	76 (5.5)	1.36 (0.96 – 1.94)	1.23 (0.85 – 1.78)
60 - 74	64 (6.8)	1.70 (1.18 – 2.46)**	1.38 (0.91 – 2.09)
45 - 59	39 (11.6)	3.06 (2.00 – 4.68)***	2.25 (1.34 – 3.78)**
< 45	15 (11.4)	3.00 (1.65 – 5.45)***	1.77 (0.85 – 3.72)
P trend		<0.001	0.008

Estimates expressed as odds ratios (95% confidence interval)
Model 1 (n=4204) - unadjusted
Model 2 (n=4185) - adjusted for age, age^2, sex, height, baseline systolic blood pressure, cardiovascular disease, diabetes, smoking, waist circumference, LDL/HDL cholesterol, number of antihypertensive medications
**p<0.01
***p<0.001

8.3.3 Pattern of postural blood pressure change

The unadjusted and multivariable adjusted relationships between GFRcys and postural SBP responses during the active stand test are illustrated graphically in Figure 8.2. The pattern of SBP responses differed by GFRcys category. In unadjusted analyses, there was a graded association between lower GFRcys categories and impaired SBP stabilization, which was particularly marked below a GFRcys of 45 mL/min per 1.73m^2. This pattern was evident from 20 seconds after standing and was most pronounced within the first minute. The graded nature of the association was consistent in the multivariable adjusted models. The relationship between GFRcys categories and postural DBP responses during the active stand test is illustrated in Figure 8.3. While acknowledging the difference in BP scale, the adjusted association between GFRcys categories and the DBP response was overall less pronounced than the adjusted association between GFRcys categories and the SBP response.

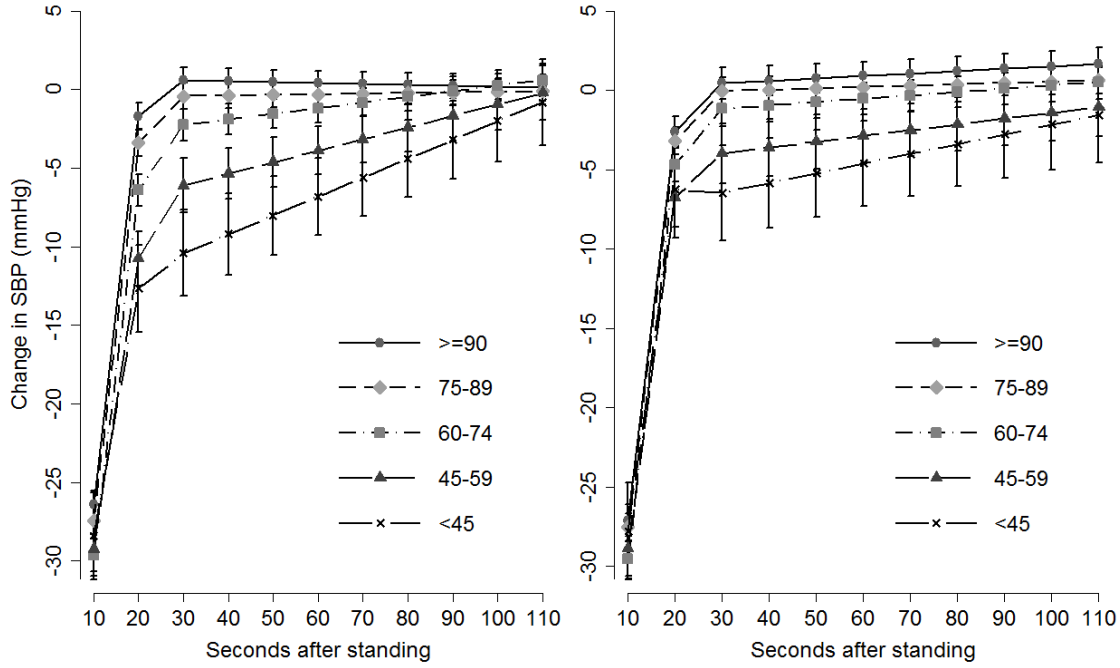


Figure 8.2: Unadjusted (left panel) and multivariable adjusted (right panel) estimate of the conditional mean difference in systolic blood pressure (SBP) from baseline (y-axis) at each 10-second interval after standing among categories of GFR estimated from cystatin C

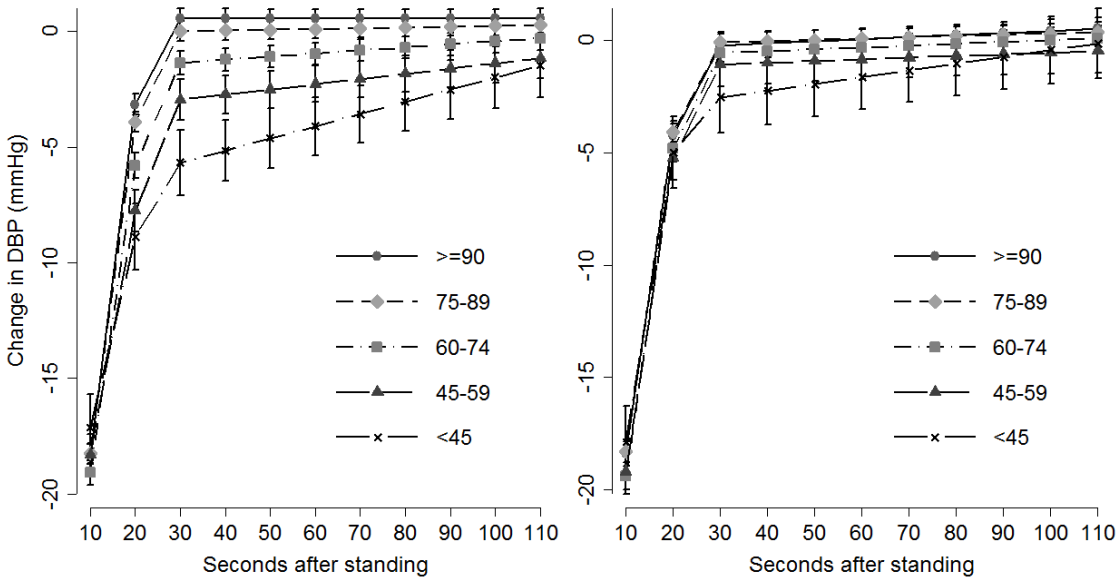


Figure 8.3: Unadjusted (left panel) and multivariable adjusted (right panel) estimate of the conditional mean difference in diastolic blood pressure (DBP) from baseline (y-axis) at each 10-second interval after standing among categories of GFR estimated from cystatin C

The results of the multivariable-adjusted regression model for the systolic blood pressure response at each 10-second interval during the active stand test are summarized graphically in Figure 8.4. Each GFRcys category is compared to the reference group (GFRcys ≥90 mL/min per 1.73m^2, represented by a horizontal line extending from the Y-axis). Differences in the SBP response were most marked below a GFRcys of 60 mL/min per 1.73m^2.

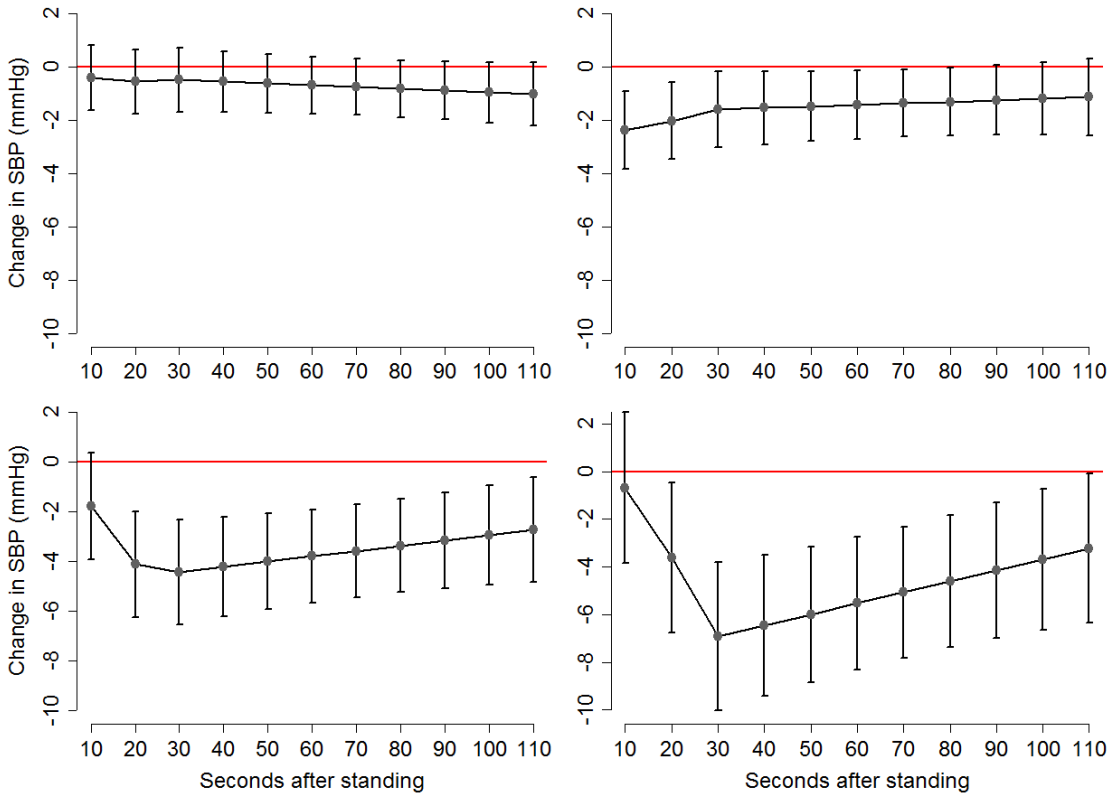


Figure 8.4: Multivariable adjusted differences across GFR categories in the change from baseline in systolic blood pressure (y-axis) at each 10-second interval after standing (x-axis)
Each GFR category is compared to the reference group (GFR >90, red line): GFR 75-89 (top left), GFR 60-74 (top right), GFR 45-59 (bottom left), GFR <45 (bottom right)

8.3.4 Secondary analysis

The unadjusted relationship between GFR estimated from creatinine and the SBP response was similar to the unadjusted association between GFRcys categories and the SBP response (Appendix Figure 8.1). After multivariable adjustment, the differences between GFRcr groups in mean postural SBP were consistently smaller than those for GFRcys groups. A similar pattern was observed for the association between GFRcr and the postural DBP response (Appendix Figure 8.2).

8.4 Discussion

In this study of postural blood pressure responses among older community-dwelling adults, we observed an increased likelihood of sustained OH with greater reductions in kidney function. This relationship was evident in individuals with relatively modest declines in GFRcys and was independent of age, cardiovascular risk factors, resting mean BP and anti-hypertensive therapy. By mapping the postural BP response across the range of GFRcys, we observed a graded association between GFRcys and impaired BP stabilization. This pattern was particularly marked within the first minute of standing, a time window not routinely captured in clinical practice.

There is a paucity of data describing the relationship between the postural BP response and the kidney. A study examining determinants of OH in middle-aged men found a cross-sectional association between postural SBP impairment and lower GFR (167). A longitudinal study of middle-aged community-dwelling adults demonstrated an increased risk of incident kidney dysfunction with OH, defined by consensus criteria using oscillometric measurements (99). The magnitude of this risk was modest in Caucasians using a creatinine-based GFR threshold (<60 mL/min per 1.73m^2) to define CKD. Creatinine generation tends to be unstable in older individuals due to changes in muscle mass, often resulting in non-linear relationships with clinical outcomes. Cystatin C has gained traction as an alternative filtration marker in older individuals as, unlike creatinine, it is not influenced by dietary protein intake (126) or muscle mass (125). Cystatin C has demonstrated stronger and more linear risk relationships with clinical outcomes than creatinine (59). Our study advances the literature by providing a granular description of the postural BP response in a large sample of older community-dwelling adults using novel beat-to-beat measurements across the spectrum of GFR estimated from cystatin C.

The cross-sectional design of our study limits a discussion regarding a causal relationship between kidney function and postural BP responses. Nevertheless, the association was strong and should generate some hypotheses regarding this relationship. The differential postural BP response across GFR categories occurred early, and was pronounced within the first 40 seconds of standing. Short-term regulation of BP is governed principally by the baroreceptor reflex arc. CKD has been shown to be associated with reduced baroreflex sensitivity (168), which could explain wider fluctuations in early postural BP responses with diminished GFR. Reductions in baroreflex sensitivity have been linked to stiffness or lower compliance of large arteries (169). Vascular stiffness is predominantly a complication of advanced CKD, but has also been demonstrated in earlier stages of CKD (170). We also observed an increased likelihood of

sustained OH in individuals with GFRcys <60 mL/min per 1.73m^2. This suggests a greater degree of autonomic dysfunction in this population, which in theory could affect several components of the circulatory reflex including reduced vasomotor responsiveness or impaired central control of BP. Studies in patients with advanced CKD and those receiving dialysis have proposed that autonomic dysfunction is an important factor in the progression of kidney disease and its cardiovascular complications (171). Our findings suggest that autonomic dysfunction may be occurring at much earlier stages of kidney disease, contributing to a greater likelihood of OH.

The presence of impaired orthostatic BP stabilization may be a surrogate marker for vascular disease. Although GFR is known to decrease with age, the underlying mechanisms and natural history of this process are poorly understood. Ageing is associated with a number of structural and functional changes in the kidney that might predispose to an increased susceptibility to injury from a vascular insult. Renal blood flow declines with age, particularly in the cortex, and the kidney's ability to preserve glomerular hydrostatic pressure via autoregulation also diminishes (172). The number of functioning glomeruli reduces with advancing age (77), further hindering the compensatory response. Glomerulosclerosis increases in a linear fashion across the age spectrum in healthy kidney donors (78), and the ischemic pattern of this age-related glomerulosclerosis suggests an underlying vascular etiology (79). It is thus plausible that repeated episodes of sustained hypotension, as a consequence of impaired orthostatic BP stabilization, could overwhelm the already diminished autoregulatory capacity of the ageing kidney.

The association between GFR and postural BP responses could also be explained by a greater level of cardiovascular comorbidity among participants with diminished kidney function. Individuals with lower GFR tend to have a greater burden of cardiovascular disease which could also account for an exaggerated orthostatic fall in BP due to reduced stroke volume. The prevalence of self-reported physician-diagnosed cardiovascular disease was low (<10%) in our study population. We adjusted for cardiovascular disease in our analysis, as well as for cardiovascular risk factors including diabetes, central adiposity, smoking and dyslipidemia, although it remains possible that unidentified cardiovascular disease may have contributed to our findings. Participants with lower GFR also tended to have higher baseline SBP and proportionately greater use of antihypertensive medications. Adjusting for baseline SBP or the burden of antihypertensive therapy did not attenuate the strength of the association between GFR and postural BP responses. Furthermore, the estimates of association in multivariable adjusted models did not vary by the presence or absence of antihypertensive therapy.

Our study has several strengths. We measured beat-to-beat BP during an active stand test in a large sample of older individuals. The Finapres® device has been used extensively as both a clinical and research tool, and its methodology is well-validated (173, 174). We estimated kidney function from a standardized measurement of cystatin C, a potentially preferable filtration marker to creatinine in older adults. The TILDA dataset is comprehensive, facilitating a robust appraisal of potential confounders including medications. The findings should be interpreted in the context of the study's exploratory nature and potential limitations. Our ability to infer any causal relationship between BP instability and GFR is limited by the study's cross-sectional design. There remains the possibility of residual measured or unmeasured confounding. We included self-reported physician-diagnosed conditions as covariates, which are subject to measurement error. No explicit adjustment for multiple testing was performed, although the actual confidence intervals are provided to allow interpretation of the results. Cystatin C and creatinine were measured at a single time point and we did not measure urinary albumin excretion. Data were missing for both kidney function and the active stand test, which may have introduced a selection bias. The degree of this bias is likely to be smaller in the estimates from the multivariable adjusted models, as the covariates in these models are predictive of missingness, as well as predictive of exposure and outcome. Nevertheless, the potential for bias remains, and our findings are only generalizable to older community-dwelling Caucasian adults who would have been healthy enough to attend our health centre assessment (106).

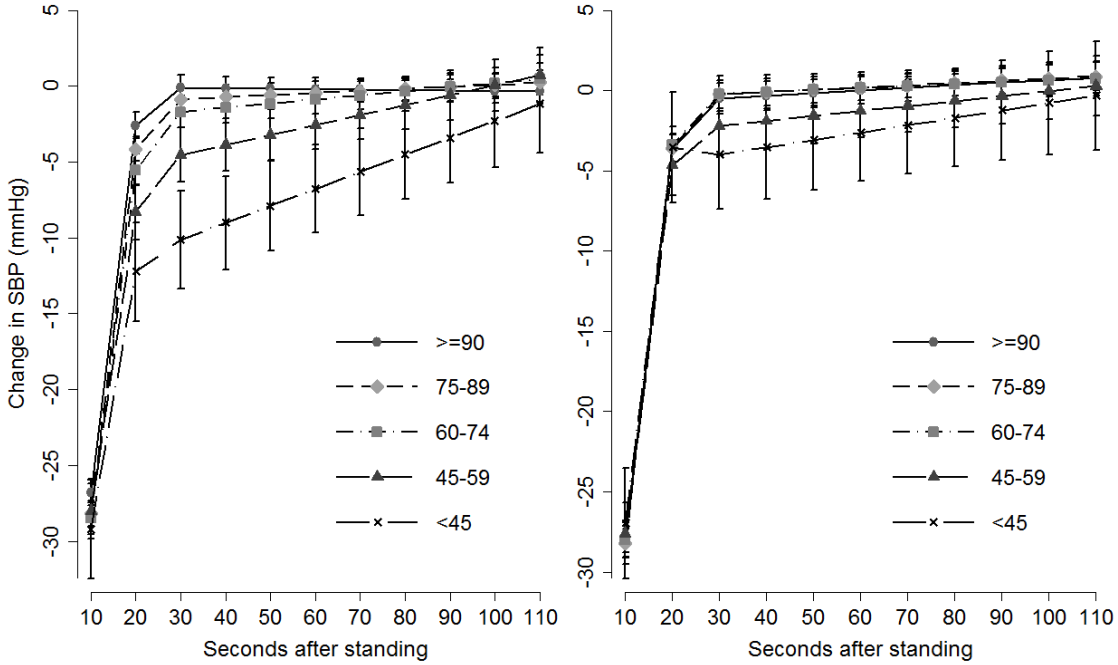
In conclusion, we report a novel association between postural BP responses and kidney function in community-dwelling older adults using beat-to-beat BP measurements. We identified an independent and graded association between impaired orthostatic BP stabilization and reductions in GFR, which was stronger for GFR estimated from cystatin C compared to GFR estimated from creatinine. This pattern of impaired BP stabilization was evident at early stages of kidney disease and was particularly marked within the first minute of standing, a time window not usually captured by conventional oscillometric BP measurements. While further studies are warranted to determine the clinical implications of these findings, our data suggest that there is a need for heightened awareness of postural BP behavior in those with diminished kidney function. Assessment of the postural BP response merits further study in the CKD population as a potential means of identifying individuals at higher risk of developing hypotension-related events.

8.5 Appendix

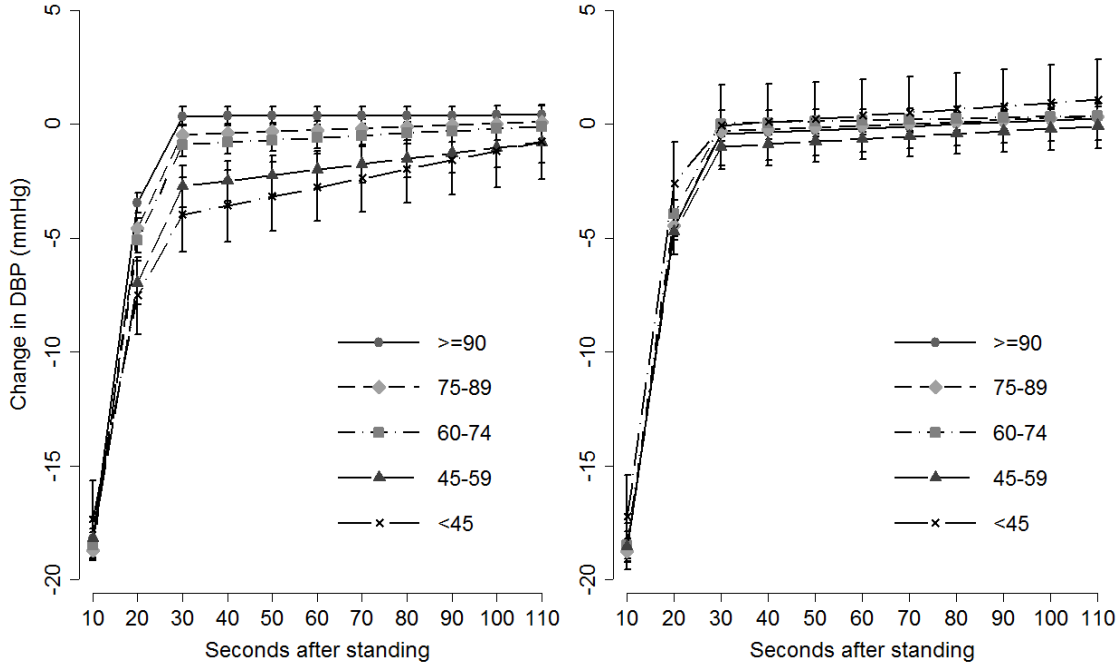
Appendix Table 8.1: Characteristics of participants who did not attend for a health assessment, and participants with missing data for either kidney function or the active stand test, compared to the final study population

Variable	No assessment (N=3140)	Missing data (N=831)	Final cohort (N=4204)
Age	66.8 (10.9)	63.8 (9.4)	61.6 (8.2)
Female sex	1702 (54.2)	491 (59.1)	2238 (53.2)
Smoking			
Current	735 (23.4)	133 (16.0)	623 (14.8)
Former	1137 (36.2)	315 (37.9)	1665 (39.6)
Never	1267 (40.4)	383 (46.1)	1916 (45.6)
Diabetes	335 (10.7)	58 (7.0)	279 (6.6)
Hypertension	1660 (52.9)	389 (46.8)	1621 (38.6)
Cardiovascular disease	450 (14.3)	110 (13.2)	396 (9.4)
Antihypertensives			
None	1738 (55.4)	503 (60.5)	2848 (67.8)
1 agent	646 (20.6)	165 (19.9)	663 (15.8)
2 agents	457 (14.6)	107 (12.9)	471 (11.2)
3 or more agents	297 (9.5)	56 (6.7)	222 (5.3)

Numbers are expressed as count (percent) or mean (standard deviation)



Appendix Figure 8.1: Unadjusted (left panel) and multivariable adjusted (right panel) estimate of the conditional mean difference in systolic blood pressure (SBP) from baseline (y-axis) at each 10-second interval after standing among categories of GFR estimated from creatinine



Appendix Figure 8.2: Unadjusted (left panel) and multivariable adjusted (right panel) estimate of the conditional mean difference in diastolic blood pressure (DBP) from baseline (y-axis) at each 10-second interval after standing among categories of GFR estimated from creatinine

9 Summary

The overarching aim of this thesis was to investigate the health burden of reduced kidney function in older people by examining the relationship between glomerular filtration rate and proximal, person-centred outcomes. The study population was a large and representative national cohort of community-dwelling Irish adults aged 50 years and over with a broad range of age and GFR. The depth and quality of the data collected in TILDA facilitated the exploration of outcomes pertinent to older individuals.

9.1 Key findings and their clinical implications

9.1.1 The distribution of cystatin C changes markedly with advancing age

The primary aim of Chapter 4 was to assess the clinical utility of cystatin C as a confirmatory test of CKD. Secondary aims were to define the prevalence of CKD (GFR <60 mL/min per 1.73m^2) among community-dwelling middle-aged and older adults, and generate plots of predicted values of GFR for the target population per year of age in both sexes. Using a flexible approach, we modelled the distributions of creatinine, cystatin C and GFR estimated from either marker as functions of age and sex. We observed a clear separation in the relative trajectories of creatinine and cystatin C after the age of approximately 65 years in both sexes. Beyond this age, cystatin C levels rose sharply with evidence of progressively greater variability. Without measuring GFR in the participants, one can only speculate if this change in the distribution of cystatin C represents an accelerated loss of kidney function in older age, or the accumulation of non-GFR determinants with age, or both. It does, however, have important implications for the suggested use of cystatin C in the clinical arena, that of a confirmatory test of CKD. The predicted probability of confirming CKD with cystatin C increases steadily with age, reaching 80% at the age of 80 years. Given this high pre-test probability, in tandem with the extra cost and burden associated with additional testing, these findings question the appropriateness of using cystatin C as a confirmatory test of CKD irrespective of age. The clinical utility of cystatin C could perhaps be maximised in middle-aged individuals. We estimate that two-thirds of people aged 50-64 years would be reclassified as not having CKD using cystatin C, as opposed to just one out of seven people aged ≥75 years.

We observed substantial variability in prevalence estimates for CKD depending on the GFR estimating equation used, highlighting the need for clinicians to be cognisant of the relative

merits and limitations of these equations. This variability was more pronounced in older age categories. Similar to other cohorts, we observed a steep age gradient in the prevalence of CKD in both men and women, in particular for estimates using cystatin C. Prevalence of CKD was remarkably high, exceeding 70%, in participants aged 80 years and over using cystatin C. Finally, we have provided expected values of GFR, from either creatinine or cystatin C, per year of age in men and women. These data incorporated an inverse probability weight to be representative of community-dwelling Irish adults aged 50 years and over. We suggest that this data may be helpful on a practical level when discussing the implications of a reduced GFR with an older individual, by framing their GFR result in the context of what would be expected for their age and sex in the general population.

9.1.2 GFR estimated from cystatin C, but not creatinine, is related to objective tests of physical performance in older adults

The remaining studies sought to provide an in-depth assessment of the potential impact of a reduced level of kidney function on the health and well-being of an older individual. Chapter 5 examined the cross-sectional relationship between GFR and three objective tests of physical performance – grip strength, gait speed and TUG. The illustration of this relationship using restricted cubic splines of GFR highlighted the limitations of creatinine in this context due to declining muscle mass. The association between GFRcr and lower extremity function was U- or inverse U-shaped, and grip strength appeared to improve slightly with lower GFRcr. In contrast, the association between GFRcys and each outcome was more linear, with steady declines in physical performance observed below a GFRcys of approximately 80 mL/min per 1.73m^2. There was some evidence of heterogeneity by age in this relationship, suggesting that the observed declines in physical performance associated with GFR may be more pronounced beyond middle age.

9.1.3 GFR does not appear to predict an accelerated decline in lower extremity physical performance

Building on these cross-sectional observations, Chapter 6 investigated the longitudinal relationship between GFR and lower extremity physical performance, assessed by repeated measures of gait speed and TUG. Due to the limitations of creatinine as a predictor of physical function tests, GFR was estimated from cystatin C in the longitudinal analysis. This study sought to answer an important research question: do reductions in GFR predict an accelerated decline

in physical performance? This would strengthen the hypothesis that decreased kidney function contributes directly to declines in functional capacity. The predictor of interest therefore was the interaction between time (wave) and GFR. For both TUG and gait speed, this interaction was not statistically significant after adjusting for the demographic variables age, age^2, sex and height. Only in a secondary analysis was there a signal for more consistent declines in the TUG test among participants with the most severe reductions in GFR (<50 mL/min per 1.73m^2). Overall, the findings argue against a reduced GFR being a major driver of declines in physical function in the general population of older adults.

9.1.4 Diminished levels of GFR are associated with clinically modest reductions in quality of life

When determining the impact of a disease on an individual level, an important question to ask is whether that condition is associated with clinically significant reductions in a person's well-being or quality of life. Chapter 7 assessed the relationship between GFR and quality of life using the CASP-19 score, a holistic QoL measurement tool that assesses positive and negative aspects of life across four dimensions: control, autonomy, self-realisation and pleasure. Similar to the findings for physical performance, there were marked differences between creatinine and cystatin C as predictors of QoL score. There was essentially a null association between GFRcr and QoL score, whereas the relationship between GFRcys and QoL score was broadly linear. These discordant findings for creatinine and cystatin C could be explained by non-GFR determinants of either filtration marker. Despite a statistically significant association between reductions in GFRcys and QoL, the magnitude of these differences in QoL score was clinically modest. Taking a distribution-based approach, participants in the lowest GFRcys category (<45 mL/min per 1.73m^2) had a 0.2 standard deviation difference in QoL score compared to the reference group (GFR ≥90 mL/min per 1.73m^2). Taking an anchor-based approach, this effect size would amount to less than half the effect size attributed to having difficulty walking a quarter-mile. Interestingly, the association between GFRcys and QoL appeared to be stronger in participants aged 50 to 64 years, compared to older participants.

9.1.5 Novel association between GFR and postural blood pressure responses

Similar to CKD, orthostatic hypotension is associated with an increased risk of cardiovascular endpoints and all-cause mortality in older people (163). Prior research from TILDA identified a high prevalence of impaired BP stabilisation in participants, particularly among older age groups

(14). Impaired stabilisation of BP after standing is associated with important outcomes in this population, including falls (15). Chapter 8 tested the hypothesis that reductions in GFR would be associated with a greater degree of impaired orthostatic BP stabilisation. The results demonstrated a correlation between reductions in GFR (estimated from either cystatin C or creatinine) and more profound BP changes after standing. Participants with CKD had a 67% increased likelihood of sustained orthostatic hypotension compared to those without CKD. This study was the first to investigate the relationship between GFR and postural BP responses using beat-to-beat data. The observations generate some interesting hypotheses. For example, the kidney may be a vulnerable organ in the setting of repeated and sustained postural drops in BP due to the dependence of the glomerulus on tight regulation of blood flow to maintain GFR. Alternatively, even early stages of CKD may be associated with evidence of autonomic dysfunction, manifesting as orthostatic hypotension.

9.2 Methodological considerations

Relative strengths and limitations of the studies in this thesis were addressed in the discussion sections of each chapter. However, a number of important methodological issues warrant further discussion here.

9.2.1 Secondary data analysis

The type and quantity of data to be collected in TILDA was chosen on the basis of several factors, including the burden on the respondent in terms of time and fatigue, acceptability of tests in the health assessment, constraints due to costs, and resources such as staffing and equipment that were available at each wave of data collection. As a result, some aspects of health have been examined to a greater or lesser degree than others. In the case of kidney disease, it is a strength that both creatinine and cystatin C were measured simultaneously in over 5000 participants. However, they were only measured once and this could have led to misclassification of CKD stage for the participants. KDIGO recommends that GFR be estimated twice, at least three months apart, before classifying CKD stage. This is often not feasible in population studies, especially in large studies with structured data collection such as TILDA. Along similar lines, urinary protein excretion was not measured in TILDA participants at Wave 1. On a practical level, this means that prevalence estimates for CKD are under-estimated. The absence of proteinuria data also has theoretical implications. While the association between GFR and outcomes such as quality of life or repeated measures of physical performance was

fairly modest, there may have been a stronger relationship between these outcomes and urinary protein excretion. For example, compared to GFR, urinary ACR has been found to be a stronger predictor of falls (175), perhaps reflecting the role of ACR as a marker of microvascular disease.

9.2.2 Cross-sectional study design

The majority of the studies in this thesis were cross-sectional, which carries several limitations. In this situation, all variables including GFR and outcomes were captured simultaneously. We do not know the exact timing of these variables, for example when a participant developed kidney disease or an important confounding condition such as diabetes mellitus or cardiovascular disease. The results need to be interpreted in the context of residual confounding, which could be measured or unmeasured. In the former case, the confounding variable is included in the regression model but in the presence of measurement error. This is a concern for self-reported variables such as physician-diagnosed cardiovascular disease. In the latter case, there may have been other variables that could have explained the association between GFR and a particular outcome, but those variables were not included in the models. In the case of kidney disease, one might hypothesise that the inclusion of variables such as inflammatory mediators may have explained more of the variability in physical performance outcomes. The potential for residual confounding is balanced by the need for parsimony in the selection of model covariates, to avoid problems such as multicollinearity and over-fitting. For example, even if a panel of inflammatory markers was available, it is likely that many of them would have been highly correlated with cystatin C (69, 176).

9.2.3 Small number of data points for longitudinal analysis

Chapter 6 examined the longitudinal relationship between GFR and repeated measures of lower extremity physical function. The mixed effects regression model in this analysis was demonstrated to be superior to a standard linear regression model (evidenced by high intra-class correlation for both gait speed and TUG values). However, only two data points were available for gait speed and just three for the TUG test. The analysis was restricted to a random intercept model, which provides subject-specific intercepts for participants but assumes that these trajectories are parallel to the overall mean. A more elaborate analysis allowing for each participant's intercept and slope to vary (random slope model) would likely result in a better fit to the data, but would require multiple data points for the outcome variable. The relatively young mean age of the cohort is a factor here too. A recent study from the Cardiovascular Health

Study, which has followed its participants since 1990, demonstrated that gait speed did not decline in this study population until after the age of 70 years (177).

9.3 Future directions

Compared to other longitudinal studies of ageing, such as the HRS which began in the 1990s, TILDA is at an early stage of data collection. The research questions in this thesis examined data from the first three waves of TILDA, encompassing two centre-based health assessments. As the study matures, and the cohort gets older, there will be opportunities to examine these research questions in more detail by including multiple data points for outcomes such as physical performance and phasic blood pressure. The kidney biomarkers will be measured again from plasma stored at Wave 3, which will help to reduce the potential for misclassification of GFR stage. The availability of repeated GFR will also facilitate modelling the exposure as a change in GFR over time, as opposed to a single GFR value. It is possible that urinary protein excretion may be incorporated into the next health assessment wave, which would allow a more robust assessment of CKD prevalence. Given the potentially large at-risk population with Stage 3a CKD, the cost-effectiveness of measuring cystatin C to confirm CKD across the age spectrum warrants further study.

The relationship between GFR and postural blood pressure responses was particularly novel and the association was robust. The connection between the kidney and the autonomic nervous system, and particularly neurocardiovascular instability, merits further study. TILDA has collected data on other aspects of autonomic function such as heart rate variability, which has been linked to cognitive function (178), and speed of heart rate recovery after standing, a novel predictor of mortality in older adults (179). Finally, the findings from this thesis will stimulate further research into organ-specific associations with kidney disease using the wide-ranging objective health data collected in TILDA. For example, cognitive health has been extensively quantified in participants using both traditional metrics such as paper-and-pencil tests, innovative technologies such as choice reaction time, and imaging modalities such as magnetic resonance imaging of the brain.

9.4 Conclusion

This thesis began by providing a rationale for exploring more proximal or person-centred outcomes in kidney disease, making the case that an older individual may wish to know what implications a reduced level of kidney function might have for their day-today health and well-being. The purpose of this was not to supplant the CKD classification system or dispute the importance of the hard outcomes that underpin that system. Rather, this thesis sought to advance the literature by moving beyond a dichotomous definition of CKD to describe the associations between kidney function and alternative outcomes in an older population across the range of GFR. We envisage that this data could inform discussions with older patients with respect to the clinical implications of CKD or a reduced GFR.

So what are these implications? One might start by framing that person's GFR result in the context of what would be expected for their age and gender in the population. Depending on their age, and perhaps other factors such as central adiposity, additional testing with cystatin C may not provide additional diagnostic information. There may be opportunities during the clinical encounter to identify health problems not usually considered in CKD. For example, asking about postural symptoms and measuring orthostatic blood pressure, or performing a simple test such as the timed-up-and-go which does not require any specialised equipment. Future work will leverage the rich longitudinal data from TILDA to build on these observations and create a clearer and more holistic picture of the manifestations of reduced kidney function in older people.

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