MODEST REDUCTIONS IN KIDNEY FUNCTION AND ADVERSE OUTCOMES IN YOUNGER ADULTS

Junayd Hussain[1]

Thesis Primary Supervisor

Manish Sood, MD MSc FRCPC[2,3]

Thesis Co-Supervisor

Greg Knoll, MD MSc FRCPC[2,4]

Thesis Advisory Committee

Edward Clark, MD MSc FRCPC[2,4]

Tim Ramsay, PhD[1,4]

Navdeep Tangri, MD PhD FRCPC[5]

Gregory Hundemer, MD MPH[2,4]

[1]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario

[2]Division of Nephrology, Department of Medicine, University of Ottawa, Ottawa, Ontario

[3]Institute for Clinical Evaluative Sciences (ICES), Ottawa, Ontario

[4]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario

[5]Division of Nephrology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba

Thesis submitted to the University of Ottawa in fulfillment of the requirements for the Master of Science in Epidemiology

School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa

PREFACE

Author Contributions

The topic of the present thesis stemmed from discussions between Junayd Hussain, Dr. Manish Sood, and Dr. Greg Knoll.

Junayd Hussain was involved in and is responsible for every aspect of this thesis: literature review, obtaining health administrative data from ICES with appropriate privacy training, statistical analyses, creation of tables and figures, drafting of the thesis, final proof-reading, and submission.

For both manuscripts within this thesis, Junayd Hussain is the first author and Dr. Sood is the senior author. Dr. Sood, Dr. Knoll, and members of the Thesis Advisory Committee (TAC) assisted in analysis of data through both informal email discussions and official TAC meetings, as well as in drafting of final versions.

Dr. Sood provided supervision on all aspects of the thesis, including the overarching study design for this project. Dr. Sood and Dr. Tim Ramsay also provided valuable insights on statistical methods for both manuscripts. Drs. Edward Clark, Navdeep Tangri, and Gregory Hundemer also provided clinical background expertise and further advice on details of the study design.

Ethics review and approval

Analyses in both manuscripts presented in this thesis use de-identified data from the Institute of Clinical Evaluative Sciences (ICES) accessed remotely over a secure intranet platform. ICES is an independent, non-profit research institute funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). As a prescribed entity under Ontario's privacy legislation (section 45 of Ontario's Personal Health Information Protection Act, PHIPA), ICES is authorized to collect and use healthcare data for the purposes of health system analysis, evaluation, and decision support. Secure access to these data is governed by policies and procedures that are approved by the Information and Privacy Commissioner of Ontario. As such, the analyses presented in this thesis do not require review by a research ethics board. Necessary training was completed on maintaining data privacy, the use of the remote analytic environment, and the concealment of small cells when disseminating results.

Acknowledgements

Firstly, I would sincerely like to thank my MSc thesis supervisor, Dr. Manish Sood, for his undying support and enthusiasm throughout the conception of the thesis, from the initial analyses to the final writing stages. More importantly, he instilled in me a passion to wholeheartedly pursue interesting questions in clinical research and was always approachable to my endless questions and concerns.

Next, I would also like to acknowledge the invaluable advice provided by my thesis co-supervisor, Dr. Greg Knoll, and the members of the Thesis Advisory Committee (Dr. Edward Clark, Dr. Tim Ramsay, Dr. Navdeep Tangri, and Dr. Gregory Hundemer). Their time, assistance, and guidance through the clinical and statistical aspects of this work were instrumental to the sound preparation of the manuscripts presented in this thesis.

I would especially like to thank the staff at ICES: Nicholas Grubic, Haris Imsirovic, and Meltem Tuna for their care and competence in pulling and cleaning data from ICES data holdings, and patiently navigating me through the world of administrative healthcare datasets and big data analytics.

Throughout my MSc thesis journey, I was fortunate to have found great friends amongst my classmates. In particular, I would like to thank Gamal, Robert, Carolina, Haben, Mia, and Lama for their support and good laughs as we struggled virtually and in-person through endless SAS coding assignments, projects, paperwork – and life – together. I hope our paths cross again in the future.

Finally, I attribute much of my personal and professional progress to my family's unwavering support from near and far. Thanks Mom, Baba, and Zayd for teaching me to act with greater integrity and sense of responsibility to those around me.

Funding

I would like to acknowledge the following organizations for the funding I have received for the execution of the MSc thesis:

1) Canadian Institutes of Health Research for conferring the Canada Graduate Scholarship – Master's (CGS-M) for a 12-month term (17,500 CAD)
2) University of Ottawa for conferring the uOttawa Graduate Admission Scholarship for the first three terms of my MSc thesis stream (12 months; 7,500 CAD)

In addition, Dr. Manish Sood and Dr. Greg Knoll would like to acknowledge supervisor funding from the TOHAMO Innovation Fund (grant number TOH-23-012).

THESIS SYNOPSIS

Chronic kidney disease (CKD) is a complex and progressive condition with limited curative therapies and is associated with both physical comorbidity, impaired health-related quality of life, and financial strain on the healthcare system. Currently, CKD is defined by a fixed threshold of an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2, which coincides with approximately 60% of healthy kidney function, for ≥3 months regardless of age. However, this definition does not account for natural declines in kidney function with advanced age, leaving older individuals (ages >65 years) with naturally lower eGFR and without significant kidney damage being over-diagnosed with CKD. Conversely, there is also concern of underdiagnosis of CKD in younger adults (ages <40 years) with "modest" eGFR reductions (eGFR levels well above 60, but below age-expected values). Indeed, severe impairment is not detected in younger adults until they lose close to 50% of their healthy kidney function, precluding timely prevention of CKD progression and its associated complications (premature mortality, cardiovascular events, etc.). However, whether these "modest" eGFR reductions are associated with elevated clinical risk in younger adults is unknown. This thesis is based on a retrospective cohort study using linked healthcare administrative databases to examine the association of index eGFR categories with time to adverse outcomes, relative to age-specific referents. In the first manuscript, we compared associations with key adverse outcomes (all-cause mortality, cardiovascular events, and kidney failure) and patterns of healthcare utilization between younger (ages 18-39), middle-aged (40-49), and older adults (50-65 years). In the second manuscript, we examined associations with major cardiovascular events (cardiovascular mortality, acute coronary syndrome, ischemic stroke, heart failure) by age group. In both manuscripts, we noted significant elevations in risk of adverse outcomes at higher eGFR levels relative to age-specific referents in younger, compared to middle-aged and older adults. Despite this age-related

disparity in clinical risk with modestly reduced eGFR, younger adults were least likely to obtain a repeated eGFR measure or be referred to a specialist during follow-up. Notably, these findings persisted for individual adverse events and in clinically important subgroups, as well as after various sensitivity analyses (adjusting for additional comorbidities, defining index eGFR using repeated measures, using common referents, and excluding individuals with different underlying mechanisms for reduced eGFR (pregnancy, acute kidney injury, etc.)). The current thesis presents evidence of elevated clinical risk with modest reductions in kidney function in younger adults, emphasizing the importance of risk-based eGFR thresholds that vary with age and considering modestly reduced eGFR as important cardiovascular risk factors worth monitoring in routine clinical practice.

TABLE OF CONTENTS

CHAPTER 1: OVERVIEW AND OBJECTIVES

Problem

Chronic kidney disease (CKD) is a complex, progressive condition characterized by persistent kidney dysfunction and is often described as a "silent killer" as symptoms are not apparent until kidney function has severely deteriorated.[1] CKD affects between 10% to 13% of adults globally (including 4 million adults in Canada), with a greater reported burden among adults aged 65 years and older[2,3] and those suffering from obesity, diabetes, and hypertension.[4–7] Current internationally recognized diagnostic criteria[8] for CKD in adults include: (i) signs of kidney damage, or (ii) reduced kidney function, indicated by estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2 (units henceforth omitted), for more than 3 months, regardless of age. However, the validity of this "one-size-fits-all" threshold has been debated, as it does not account for natural age-related declines in kidney function, running the risk of overdiagnosis in older adults and underdiagnosis in younger adults.[1,9–14]

While re-analyses of population-level data from the CKD Prognosis Consortium[7,10] and other cohorts[12,15,16] show that mortality risk among older adults did not until increase until eGFR<45, there is little evidence on the impact of modestly reduced eGFR (eGFR>60 but below age-expected levels) on clinical risk in younger adults (aged <40 years). Such individuals may have already lost over half their kidney function before reaching the eGFR<60 threshold, representing a missed opportunity for mortality and cardiovascular disease prevention from eGFR decline.[9,15] Early evidence has shown that such early reductions in younger adults can contribute to premature cardiovascular disease.[17,18] However, such studies have relied on broad age and eGFR categories and surrogate outcomes, while true endpoints of mortality, cardiovascular events, and kidney failure occur over longer time horizons. Given these methodological gaps and rare outcome occurrence in younger age groups, real-world healthcare data and longer follow-up windows can more precisely characterize the clinical risk of modestly reduced eGFR in younger adults.

Purpose and Rationale

Accurate determination of age-specific, prognosis-based thresholds of eGFR associated with mortality and adverse event risk would aid timely prevention and management of CKD and its

complications in this under-recognized group. Such thresholds can also aid age-specific assessment of impacts of interventions on kidney function and future adverse events. The purpose of this thesis is to examine and compare associations between baseline kidney function (index eGFR) and adverse outcomes in different age groups using age-specific reference ranges in a population-based retrospective cohort derived from Ontario's linked health administrative databases.

Objectives

The two specific objectives of the thesis are:

1) To examine the extent of modest reductions in index eGFR and compare their associations with time to adverse outcomes (all-cause mortality, composite of cardiovascular events, kidney failure) and patterns of healthcare utilization between younger (18-39 years), middle-aged (40-49), and older adults (50-65).
2) To examine associations of index eGFR with time to major cardiovascular events (MACE: cardiovascular mortality, acute coronary syndrome, ischemic stroke) and MACE plus heart failure (MACE+), by age group.

Thesis Outline

The thesis begins with a background of the literature (**Chapter 2**) on the population-level burden of CKD and its complications, as well as the ongoing age controversy of defining CKD in the population and its impacts on clinical identification and management in younger adults. **Chapter 3** presents associations between index eGFR and adverse outcomes in a large population-based cohort of Ontario adults, using separate GFR reference categories for each age group, in a manuscript titled "Associations between modest reductions in kidney function and adverse outcomes in young adults: retrospective, population based cohort study" (accepted for publication in the *BMJ*). **Chapter 4** addresses the second thesis objective, restricting focus on specific cardiovascular outcomes separately in addition to *de novo* hypertension in the same cohort in a manuscript titled "The association between subclinical reductions in kidney function and major adverse cardiovascular events in young adults: a population-based retrospective cohort study" (submitted for publication in the *Journal of the American College of Cardiology, JACC*).

Finally, **Chapter 5** presents a summary of the findings of the thesis, alongside a discussion on its strengths, limitations, and avenues of future research.

CHAPTER 2: BACKGROUND

Burden of chronic kidney disease

Chronic kidney disease (CKD) is a complex, progressive condition characterized by persistent kidney dysfunction, often sub-categorized by cause, severity of dysfunction, and rate of progression.[8,19] CKD is often described as a "silent killer" as signs of overt damage or symptoms are not apparent in patients until kidney function has severely deteriorated, and can only be treated by dialysis or transplantation.[1,8,9] Prognosis is noted to vary between cases of CKD: for some, rapidly progressive disease can lead to kidney failure within months, while for others, CKD many not progress over many years of follow-up.[9,20] A published conceptual model for CKD[21] categorized risk factors into sociodemographic or genetic factors that increase susceptibility to CKD, as well as factors that initiate kidney disease. CKD's complications can affect multiple organ systems, placing individuals with CKD at risk of uremia, kidney failure, cardiovascular disease, impaired physical function, and adverse effects of drugs and invasive procedures.[8,9,19,22] Indeed, diabetes, hypertension, and other conditions related to a sedentary lifestyle were cited as leading causes of CKD in both developed and developing countries.[2]

In addition to its clinical impact, CKD's increasing population health burden is worth noting. The prevalence of CKD is estimated to be between 10% to 13% of adults globally, with a greater reported burden among those aged 65 years and older, as well as in low-middle-income countries.[2,3,19] Over the past two decades, the global presence and burden of CKD has been rising steadily, experiencing an 82% increase in overall years of life lost due to premature mortality, second only to HIV and diabetes.[2,23] This increase in years of life lost, incidence, and prevalence of CKD is paralleled by increasing rates of obesity, diabetes, hypertension, and bone and mineral disorders.[4–6,24]

In Canada, CKD affects over 4 million adults (of whom 43,000 are diagnosed from end-stage kidney disease (ESKD), i.e., irrecoverable loss of kidney function). Moreover, CKD has considerable financial impacts on the healthcare system, as dialysis and transplantation for CKD take up a large proportion of healthcare budgets in multiple countries.[8,25–27] In Canada, annual healthcare costs range from 71,000 to 107,000 CAD per patient per years among those requiring hemodialysis.[25] Thus, given its diversity of risk factors, lack of curative therapies, and increasing

healthcare costs, early and regular testing of kidney function has received greater attention to foster timely recognition and intervention on CKD and its complications.[1,8,9,28]

Measuring kidney function and the current definition of CKD

The most commonly used index of kidney function is the glomerular filtration rate (GFR), as it is generally reduced after widespread structural kidney damage. GFR is usually measured directly from plasma samples of an exogenous, radionuclide-labelled filtration marker (such as inulin and iohexol).[15,29] GFR determined directly from the clearance of such markers is often considered a "gold standard"[15]. However, these direct methods are not routinely employed, as they are considered expensive, invasive, and time-consuming.[30–32] As such, in clinical practice and research, kidney function is more commonly estimated from endogenous, renally filtered markers such as serum creatinine (SCr) or cystatin-C (cys-C) levels from outpatient blood tests.[9] In particular, SCr is often dependent on underlying kidney function as well as muscle mass and other comorbidities, and estimated GFR (eGFR) is estimated from SCr, gender, race (in some equations) and age.[1,8,21] Multiple eGFR equations have been developed[33–36], with the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines[8] recommending the use of the Chronic Kidney Disease Epidemiology (CKD-EPI) race-free equation for eGFR[33] and the urinary albumin/protein-creatinine ratio (ACR/PCR) from a random spot urine sample.

According to current internationally-recognized KDIGO 2012 guidelines[8], diagnostic criteria for CKD in adults include: (i) signs of structural kidney damage (elevated ACR or pathologic abnormalities noted in medical imaging), and/or (ii) reduced kidney function, indicated by eGFR < 60 mL/min/1.73m^2 (units henceforth omitted), for more than three months. CKD severity is further graded based on six categories of eGFR (G1, G2, G3a, G3b, G4, G5) and three ACR categories (A1, A2, A3) (**Figure 1**). Structural abnormalities have different clinical implications and are thus not the focus of this thesis. The criterion for functional abnormalities (eGFR < 60, with a second confirmatory value after 90 days), on the other hand, is used to diagnose new-onset CKD regardless of age and even in the absence of albuminuria.[9,13]

Delanaye and colleagues[1,9] describe two methods for using eGFR to define CKD in the population: (i) based on thresholds of extreme values of eGFR in a representative population distribution (for example, using 2.5th or 5th percentile of eGFR to define CKD), and (ii) using thresholds associated with adverse outcomes (i.e., a "prognostic" approach). Indeed, the current

eGFR criterion of eGFR<60 was developed based on the latter method. This fixed threshold was selected as it is believed to correspond to <60% of healthy kidney function in young adults. In addition to its simplicity in clinical practice and public health messaging, eGFR<60 was associated with elevated risks of kidney failure, cardiovascular events, and mortality in most age-groups in both general and high-risk cohorts (such as the CKD Prognosis Consortium, CKD-PC) (**Figure 2**).[9,10,12,37] However, while it is broadly agreed that severe albuminuria is indicative of CKD, setting the most appropriate eGFR criteria is debated.[1,9,13,14,38,39]

Age controversy in CKD

The fixed, "one-size-fits-all" threshold of eGFR<60 was selected for its increased clinical risk in most age groups, making it easier for widespread adoption in clinical practice and public health. However, kidney function has clearly and ubiquitously been shown to decline with age (**Figure 3**) due to natural, age-related "kidney senescence".[9,20,40] Thus, the use of a fixed threshold conflates structural differences due to an aging kidney (characterized by nephron loss and atrophy without notable changes in single-nephron GFR and filtration capacity) with those associated with CKD (characterized by progressive nephrosclerosis).[11,40,41] Indeed, based on eGFR criteria alone, around 70% of incident CKD occurs in individuals aged 70 years and older, resulting in unnecessary specialist referrals, clinical testing, polypharmacy, and subsequent anxiety due to potential overdiagnosis.[42,43] Indeed, recent re-analyses of data from CKD-PC[10,37] – the largest global consortium of general and high-risk population cohorts (n = 2.0 million) – as well as other cohorts[14–16,38,42–45] show the risk of progression to ESKD was rare in older individuals (<1% risk in 5 years). Moreover, mortality risk for those aged >65 years did not increase until eGFR<45, much lower than the current diagnostic threshold for CKD (**Figure 4**).[1,11]

On the other hand, similar re-analyses of CKD-PC data suggest that clinical risk is not significantly elevated until eGFR<75 for younger individuals (i.e., those aged 18-54 years), suggestive of kidney dysfunction above the current eGFR<60 threshold, but below what is expected for age.[1,9,11] Indeed, in a study using CKD-PC data,[10] a sharp increase in adjusted relative risk was found for all-cause and cardiovascular mortality among those aged 18-54 years, comparing eGFR 75-89 to the reference category of 90-104. Despite this, there is a paucity of evidence for the validity and acceptability of an age-adapted CKD definition among younger

adults (those aged <40 years in our cohort). While the current fixed eGFR threshold may overdiagnose CKD in the elderly, younger individuals may need to incur a large drop in their eGFR (by as much as >50%) to meet this threshold and be seen clinically.[9,10,38] This lack of recognition of subclinical or "modest" eGFR declines in younger adults place them at risk for developing progressive CKD and associated comorbidities which would be under-detected over their lifetime.[9,46–48]

Early evidence exists of early sustained reductions in eGFR in younger adults (relative to the mean measured GFR of 100) contributing to increases in left ventricular mass (surrogate for heart failure)[17], coronary artery calcification[18], and cardiovascular mortality.[49] This, combined with the lack of routine monitoring of kidney function and CKD in younger adults, represents a missed opportunity for prevention of CKD-related complications in this age group, highlighting the importance of age-specific prognostic criteria for eGFR.[9,19,47] However, past studies have mainly relied using common referents (regardless of age), surrogate outcomes, attrition, and less granular age and eGFR categories, clouding the full extent of associations of eGFR with adverse outcomes in younger adults.[47] (Please consult Delanaye and colleagues[9] for a detailed overview of age-eGFR disparities in past general-population and CKD cohorts.) As adverse endpoints can take many years to manifest in younger individuals, following larger population cohorts over longer time horizons can inform monitoring and management of adverse outcomes from modest eGFR declines.

Mechanisms of modest eGFR reductions in younger adults

As mentioned previously, studies in both general and high-risk population cohorts have cited age disparities in eGFR decline and associated clinical risk. However, the physiological mechanisms underlying these observed associations are unknown, and likely to be multifactorial, especially as premature death and cardiovascular events tend to be rare in younger adults.[9,13] Many studies have shown micro- and macrostructural kidney changes associated with aging, ranging from glomerulosclerosis to tubular atrophy and vascular sclerosis.[11,20] These changes are often associated with the age-related decrease in kidney function observed in numerous cohorts[15,39,50] In particular, directly measured GFR from population cohorts (most notably from the Renal Iohexol Clearance Survey (RENIS)[15,51]) has been noted to decline significantly starting from 40 years of age in both men and women.

While mGFR and eGFR declines are ubiquitous with age, past studies on kidney function decline tend to focus on middle-aged and older groups, precluding meaningful inference in younger adults (aged <40 years). Indeed, younger individuals diagnosed with kidney disease often have severe albuminuria (high ACR) yet have eGFR well above the current threshold of 60. Indeed, it is estimated that as much as 75% of CKD diagnoses can be attributed to elevated ACR in younger adults, compared to 25% to eGFR<60[11]. Moreover, according to the Kidney Failure Risk Equation and other models[52], older patients have a much lower risk of progression to ESKD compared to younger adults at the same eGFR, further highlighting a missed disparity in preventing CKD progression in younger adults. However, another complicating factor to consider is the increased absolute risk of mortality and adverse events in older adults, yet increased risk on the relative scale in younger adults.[10,37,53] While the higher absolute risk in the elderly has been attributed to their limited lifespan[9], possible reasons behind the relative risk elevations in younger individuals are not well understood.

The current threshold may result in missed CKD diagnoses in younger individuals without overt signs of kidney damage and who have an eGFR above the current threshold (eGFR>60), yet below what is expected for their age (i.e., subclinical or "modest" eGFR declines). Some physiological underpinnings to modest eGFR declines and subsequent progressive CKD can include individuals with low nephron endowment, such as those born with a single kidney, those born pre-term and/or with low birth weight, as well as patients with Down syndrome.[1,9,11,54–56] In fact, one study found that patients aged 35-59 years with history of hypertension had significantly fewer glomeruli per kidney compared to matched normotensive controls.[57] While this finding was derived from a relatively small clinical sample, similar nephron loss was noted in a large cohort of healthy living donors beginning as early as age 18-29, losing as much as half of their nephron reserves over their lifetime.[20,40,58] Despite these findings and previous evidence of possible cellular mechanisms in animal models[59], how nephron endowment varies in humans warrants further investigation.

Extrinsic factors behind modestly reduced eGFR and subsequent CKD progression include exposure to nephrotoxic agents (such as lithium, calcineurin, vancomycin, etc.)[8,60], perinatal oxidative stress[58,59], history of conventional cardiovascular risk factors (such as obesity, hypertension)[61], and changes in key biomarkers (hemoglobin, ACR, etc.).[9,38] While each of these

play a role in CKD progression during the life course, their relative contributions alongside intrinsic physiological factors are unknown. Indeed, it has been noted that individuals with cardiovascular events secondary or concurrent to CKD have worse prognoses, warranting further attention, especially in younger adults.[17,43,49] Elevations in premature cardiovascular risk and related mortality, especially when they are foreseeable with early eGFR declines in otherwise healthy younger adults, can prompt screening and monitoring for other risk factors.[22,28,61] Flagging decreased eGFR can also alert clinicians to adjust ongoing treatments (such as modifying doses of drugs excreted by the kidney) and engage in preventive measures earlier in the CKD course.[62,63] Thus, it is important to appreciate that eGFR values slightly above the current definition of 60 mL/min/1.73m^2 are not necessarily normal.[8,38] Considering both physiological and extrinsic mechanisms behind modest eGFR declines can aid proactive prevention of CKD and its complications, especially in younger adults where it can negatively impact healthy life expectancy.[9,19,47]

Implications of early eGFR monitoring in younger adults

As existing therapies for CKD (dialysis and kidney transplantation) are hardly curative and better suited for slowing than preventing CKD progression[9], timely identification and prevention of progressive CKD and related complications earlier in life are paramount. Not only would this aid in implementation of age-specific eGFR threshold and individualization of care, it would facilitate earlier preventive measures at an earlier stage of CKD when outcomes would be more favorable.[9,19] Such measures can include lifestyle changes (such as dietary modifications, exercise) as well as timely initiation of pharmacological interventions (such as early initiation of statins and anti-hypertensives for anyone with significant cardiovascular risk in five years[28,62]). Furthermore, this can facilitate further investigations into whether established interventions are similarly efficacious or effective against adverse outcomes across age groups with eGFR values too low for their age.[9] An added benefit of using age-specific thresholds would be that it maintains consistency with past observed associations between low eGFR and adverse outcomes, reconciling the "distribution-based" and "prognostic" approaches to defining CKD.[1,13,56] Re-orienting the focus of CKD prevention on younger adults not only presents an opportunity for younger individuals to engage with the healthcare system, but it would also prevent excessive misdiagnosis and intervention in older groups.

From the perspective of population health, adopting an age-specific eGFR threshold for defining and managing CKD and its complications can impact how CKD burden is estimated in certain population groups.[9,47] Accounting for natural age-related declines in kidney function can reclassify older individuals previously believed to have disease as now not having CKD (as nearly 4 in 5 individuals aged >50 years have been misdiagnosed with CKD despite normal urinalysis).[9,16,19] On the other hand, around 70-80% of individuals aged 18-39 years are diagnosed with CKD due to abnormal urinalysis despite eGFR values well above the current definition of eGFR<60.[9,46–48] Using age-specific thresholds in younger individuals would reclassify a considerable fraction as having disease, raising concerns of how to best prevent CKD and its complications in this under-appreciated group. The sooner significant eGFR decline is identified in younger adults, the more likely that adverse outcomes from CKD can be anticipated and prevented. Thus, monitoring for early subclinical, "modest" declines in eGFR in younger adults while acknowledging the importance of age-specific risk thresholds can orient attention and resources towards individuals at higher risk of progressive CKD and its adverse complications.

FIGURES (Chapter 2)

Figure 1: Current KDIGO 2012 definition of CKD based on eGFR and ACR/PCR stages

(Adapted from Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[8])

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

Figure 2: Hazard ratios for all-cause and cardiovascular mortality according to splines of eGFR in a collaborative individual meta-analysis of 21 different cohorts. Evidence from this and other studies using Chronic Kidney Disease Prognosis Consortium Data have motivated the current definition of CKD as eGFR<60 regardless of age. Shaded areas indicate 95% CI of the hazard ratios.

(Adapted from Matsushita et al, 2010[37])

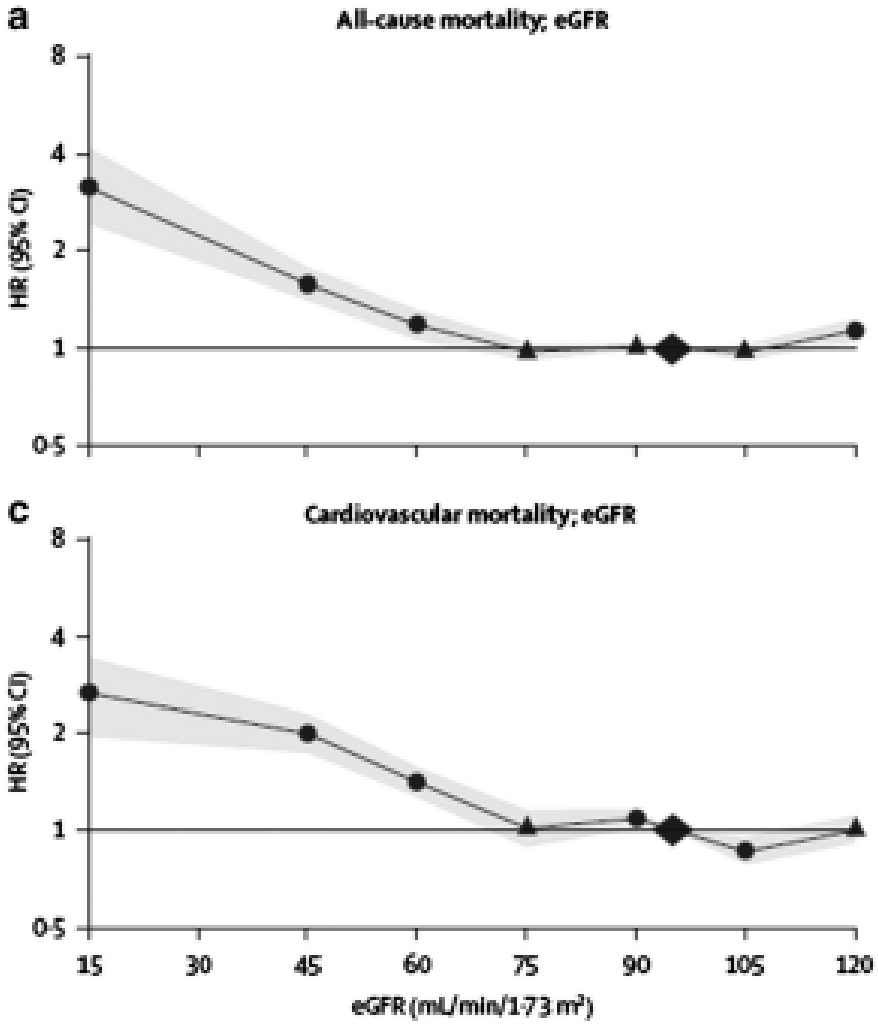


Figure 3: Distribution of mean glomerular filtration rate (GFR) values derived directly from urinary clearance of inulin, by age and sex, compared to eGFR<60 (horizontal line). Dotted lines represent 95% CI of eGFR estimated by inulin clearance.

(Adapted from Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease[8])

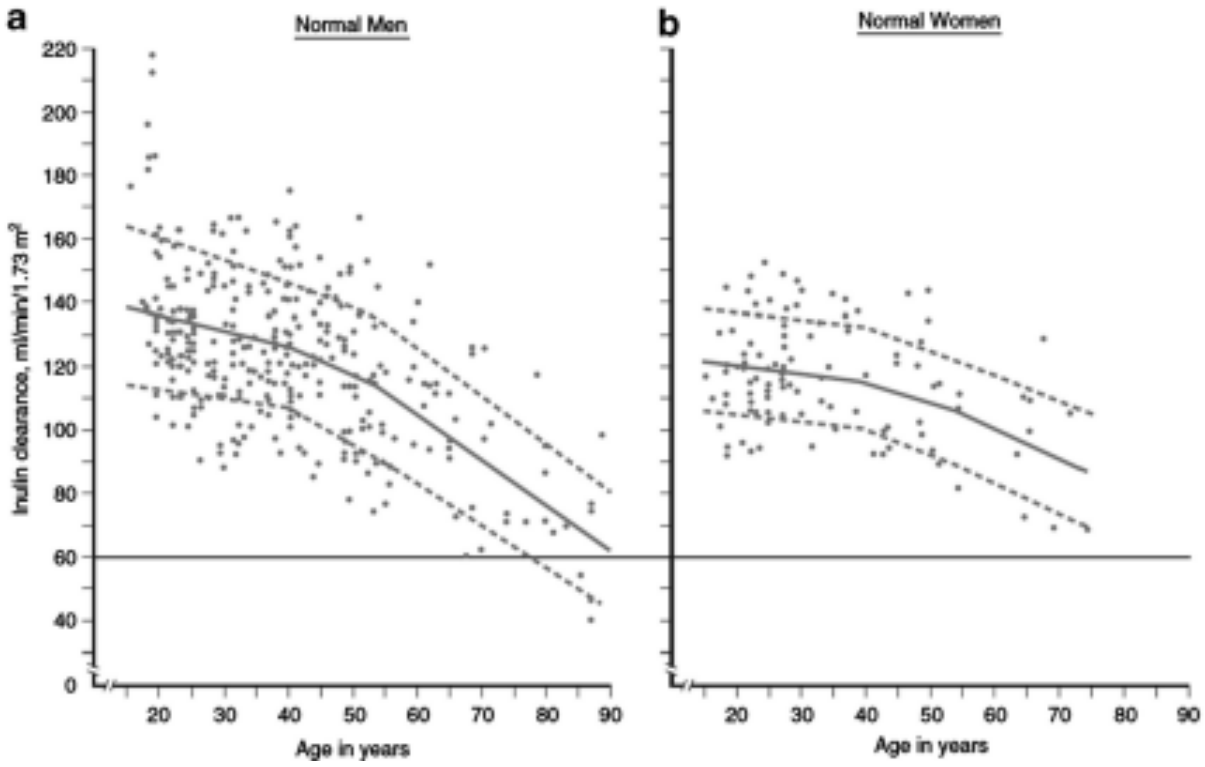
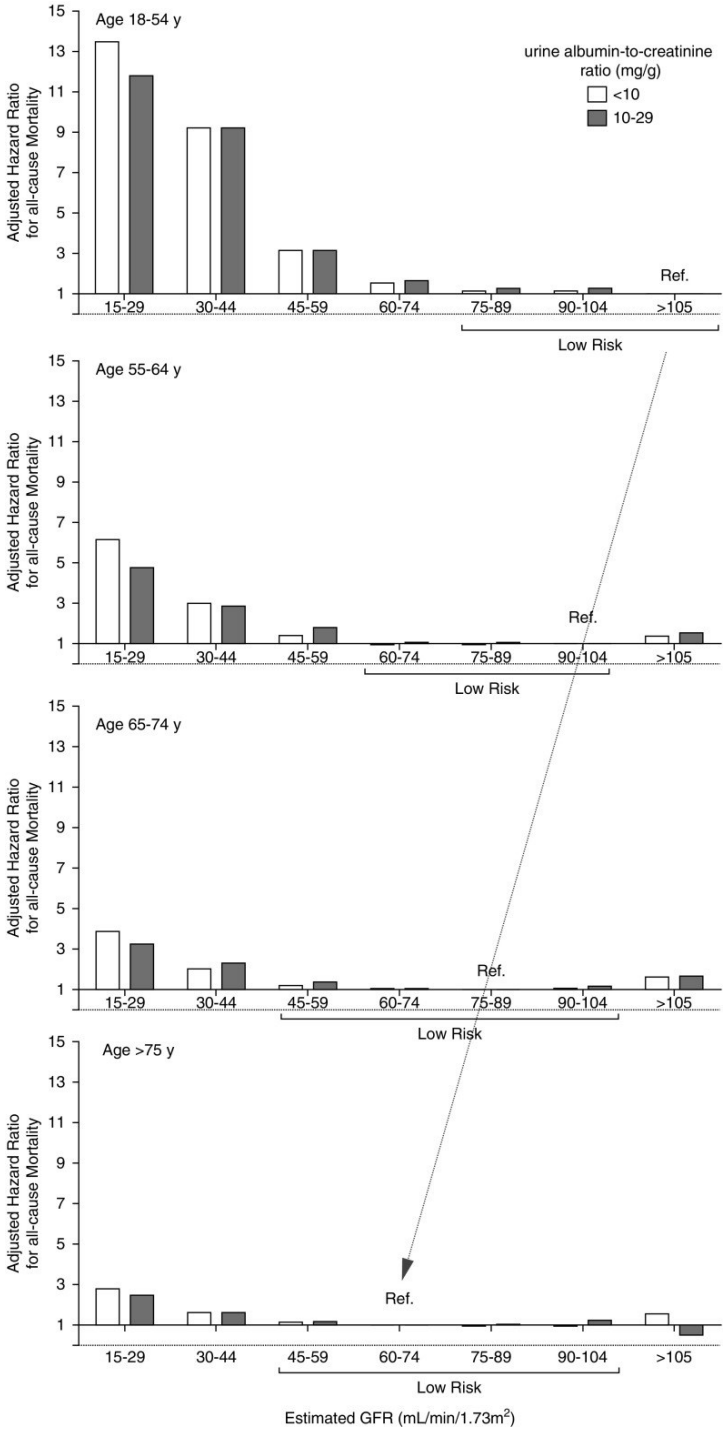


Figure 4: Association between eGFR and all-cause mortality, dependent on age group. Hazard ratio for mortality determined with reference group being one with lowest risk. eGFR ranges within "Low risk" brackets are not significantly different from reference group.

(Adapted from Denic et al[11] and Delanaye et al[9])



CHAPTER 3: MANUSCRIPT I: ASSOCIATIONS BETWEEN MODEST REDUCTIONS IN KIDNEY FUNCTION AND ADVERSE OUTCOMES IN YOUNG ADULTS: retrospective, population-based cohort study

Junayd Hussain BSc[1,2], Nicholas Grubic MSc[2], Ayub Akbari MD MSc[3], Mark Canney MD PhD[3,4], Meghan J. Elliott MD MSc[5,6], Pietro Ravani MD PhD[5,6], Peter Tanuseputro MD MSc[1,2,4], Edward G. Clark MD MSc[3,4], Gregory L. Hundemer MD MPH[2,3,4], Tim Ramsay PhD[1,4], Navdeep Tangri MD PhD[7], Greg A. Knoll MD MSc*[3,4], Manish M. Sood MD MSc*[2,3,4]

*Denotes equal contribution

[1]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, K1H 8M5, CANADA

[2]Institute of Clinical Evaluative Sciences (ICES), Ottawa, Ontario, K1Y 4E9 CANADA

[3]Division of Nephrology, Department of Medicine, The Ottawa Hospital, Ottawa, Ontario, K1Y 4E9, CANADA

[4]Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, K1Y 4E9, CANADA

[5]Department of Medicine, University of Calgary, Calgary, Alberta, T2N 4N1, CANADA

[6]Department of Community Health Sciences, University of Calgary, Calgary, Alberta, T2N 1N4, CANADA

[7]Division of Nephrology, Max Rady College of Medicine, University of Manitoba, Winnipeg, R3E 0W2 Manitoba, CANADA

Accepted for publication in the BMJ on May 10, 2023

SUMMARY

What is already known about the topic

- The current kidney function threshold for defining chronic kidney disease is fixed and thus does not discern between age related kidney senescence and possible kidney disease.

- Young According to the age independent threshold, young adults (aged <40 years) may be diagnosed with chronic kidney disease only after their kidney function has halved.

- Evidence from small cohorts suggests that kidney function level above the threshold, but below age expected values, is associated with risk of adverse outcomes (death, cardiovascular events, kidney failure) in younger adults.

What this study adds

- In this large population based cohort of 8.7 million adults, modest kidney function reductions were associated with elevated clinical risk relative to age specific referents.

- Increases in risk were most prominent in younger adults (18-39 years), compared with middle and older age groups (40-65 years).

- More frequent measurement and monitoring of kidney function in younger adults might be needed to identify individuals at risk and to prevent chronic kidney disease and its complications.

ABSTRACT

Objectives

To study age specific associations of modest reductions in estimated glomerular filtration rate (eGFR) with adverse outcomes.

Design

Retrospective, population based cohort study.

Setting

Linked healthcare administrative datasets in Ontario, Canada.

Participants

Adult residents (18-65 years) with at least one outpatient eGFR value (categorized in 10 unit increments from 50 mL/min/1.73m2 to >120 mL/min/1.73m2), with no history of kidney disease.

Main Outcomes Measures

eGFRs and hazard ratios of composite adverse outcome (all cause mortality, any cardiovascular event, and kidney failure) stratified by age (18-39 years, 40-49 years, and 50-65 years), and relative to age specific eGFR referents (100-110 mL/min/1.73m2) for ages 18-39 years, 90-100 for 40-49 years, 80-90 for 50-65 years).

Results

From 1 January 2008 to 31 March 2021, among 8 703 871 adults (mean age 41.3 (standard deviation ±13.6) years; mean index eGFR 104.2 mL/min/1.73m2 (standard deviation 16.1); median follow-up 9.2 years (interquartile range 5.7-11.4)), modestly reduced eGFR measurements specific to age were recorded in 18.0% of those aged 18-39, 18.8% in those aged 40-49, and 17.0% in those aged 50-65. In comparison with age specific referents, adverse outcomes were consistently higher by hazard ratio and incidence for ages 18-39 compared with older groups across all eGFR categories. For modest reductions (eGFR 70-80 mL/min/1.73m2), the hazard ratio for ages 18-39 years was 1.42 (95% confidence interval 1.35 to 1.49), 4.39 per 1000 person years; for ages 40-49 years was 1.13 (1.10 to 1.16), 9.61 per 1000 person years; and for ages 50-65 years was 1.08 (1.07 to 1.09), 23.4 per 1000 person years. Results persisted for each individual outcome and in many sensitivity analyses.

Conclusions

Modest eGFR reductions were consistently associated with higher rates of adverse outcomes. Higher relative hazards were most prominent and occurred as early as eGFR <80 in younger adults, compared with older groups. These findings suggest a role for more frequent monitoring

of kidney function in younger adults to identify individuals at risk to prevent chronic kidney disease and its complications.

INTRODUCTION

Chronic kidney disease (CKD) is characterized by structural damage in the kidneys (detected by albuminuria), or in its absence, by a reduced estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m^2 for at least 90 days regardless of age.[8] CKD is a progressive yet modifiable condition associated with adverse outcomes such as mortality and cardiovascular disease[10,12,22] and affects 8% to 16% of adults globally.[2,64–66]

The current, "one-size-fits-all" criterion for incident CKD was determined based on an elevated risk of adverse events across all age groups in large epidemiological studies.[9] However, younger individuals (aged <40 years) tend to have mean eGFRs above 100 mL/min/1.73m^2, and would face a large loss of kidney function prior to recognition.[9,15] Uncertainty exists regarding age's influence on the association between eGFR and clinical risk, specifically at higher levels of eGFR (60 to 100 ml/min/1.73m^2).[1,9,10,14,20,39,47,67] This has resulted in limited guidance on how best to manage and potentially mitigate risk in younger adults with early eGFR declines.

Previous studies[68–71] suggest early sustained eGFR declines in younger adults are associated with premature cardiovascular disease. In the Coronary Artery Risk Development in Young Adults (CARDIA) study, eGFRs from 60-75 were independently associated with increased left ventricular mass index and coronary artery calcification up to 10 years later.[17,18] Non-surrogate, clinical outcomes are often difficult to study in young adults due to low event rates and as such, there is a lack of direct, real-world evidence characterizing the risk of a modest eGFR reduction and adverse events. The Chronic Kidney Disease Prognosis Consortium (CKD-PC; n = 2.0 million)[7,10,12], reported higher all-cause mortality, cardiovascular risk, and end-stage kidney disease across a range of eGFR and age groups. However, risks were characterized using a low common referent (eGFR 80 mL/min/1.73m^2) and less granular age categories (18-54 years), clouding the full extent of associations of eGFR with adverse outcomes in younger adults.

The detection of higher clinical risks with a modest, early eGFR decline in young adults, using larger population-based cohorts and longer time horizons, could lead to changes in monitoring,

referral criteria and the pursuit of interventions. Thus, we determined the extent of modest eGFR declines in the cohort, and their associations with adverse outcomes (all-cause mortality, cardiovascular events, kidney failure) in a population-based cohort of young (18-39 years), middle-aged (40-49), and older adults (50-65).

METHODS

Study Design and Setting

We conducted a population-based, retrospective cohort study using healthcare administrative databases at the Institute for Clinical and Evaluative Sciences (ICES) in Ontario, Canada. Additional methodological details are presented in the Supplementary Material (see **Additional Methodological Details**). All data were collected and de-identified by ICES to ensure patient confidentiality, and thus did not require informed consent. The reporting of this study followed the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement (**Appendix A**).[72]

Data Sources

We obtained data on demographics, vital statistics, healthcare encounters, and laboratory tests for all participants from seven databases linked that included International Classification of Diseases (ICD)-10 codes and physician billing data by unique encoded identifiers for each patient at ICES. Serum creatinine (SCr) and urine albumin measurements from outpatient urine and blood testing at the time of study entry and during follow-up were obtained from the Ontario Laboratory Information System (OLIS). Detailed descriptions of linked databases are provided in **Appendix B**.

Study Cohort

We included all Ontario adult residents (aged 18-65 years, inclusive) with at least one outpatient SCr measurement in the cohort accrual period (January 1, 2008, to March 31, 2020, inclusive). Follow-up started from index date (date of first available SCr measurement within the accrual period) until the first of either death, emigration, or end of study on March 31, 2021. We excluded non-Ontario residents, those with history of kidney disease (diagnosis of CKD, or CKD treated with initiation of dialysis or receipt of kidney transplant within 5 years prior to index

date), short follow-up (<1 year), acute kidney injury, kidney stones, who visited a nephrologist or urologist, who had donated a kidney (all within 5 years pre-index), and pregnant women at index (as pregnancy-adapted eGFR may increase by up to 50%).[73]

Index Kidney Function Measurement

An eGFR measure, derived from the index outpatient SCr measurement (in μmol/L) for each patient using the race-free Chronic Kidney Disease-Epidemiology (CKD-EPI) equation, was the exposure.[33] A single outpatient eGFR has been previously demonstrated to provide an accurate estimate of baseline kidney function in a similar ICES-based cohort (83% of participants were within +/- 5 mL/min/1.73m^2[74]) and external cohorts.[56,75] If multiple SCr measurements were present on the same index date, the lowest value was selected. Index eGFR values were categorized into 10-unit increments from 50-60 to >120 ml/min/1.73m^2. Reference categories set for each age group in our cohort were based on age-normalized mean values of directly measured GFR using radionucleotide methods, adapted from over 1000 healthy living donors across four population cohorts[76–79], following methods presented by Hallan et al.[80] Age-specific referents in our analyses were thus set as follows: eGFR 100-110 mL/min/1.73m^2 for ages 18-39, 90-100 mL/min/1.73m^2 for ages 40-49, and 80-90 mL/min/1.73m^2 for ages 50-65, respectively.

Outcomes

We examined a composite adverse outcome, defined as the first occurrence of: all-cause mortality, any cardiovascular (CV) outcome, or kidney failure defined as initiation of dialysis or kidney transplant receipt.[81] Any CV outcome was defined as time to heart failure, acute coronary syndrome (ACS), stroke, or atrial fibrillation (AF), whichever occurred first.[82,83] We further examined each aforementioned adverse outcome (death, CV, kidney failure) separately.

Covariates

Information on sex, income quintile, and urban/rural living status (derived using postal codes by ICES as described previously[84–87]), as well as hypertension[88], diabetes[89,90], and past cardiovascular disease (including heart failure, ACS, stroke, AF) were included. All comorbidities were identified within 5 years pre-index. We also obtained urine albumin-creatinine ratios (ACR), derived from spot samples, for a subset of individuals in the cohort within 1 year before and after index as a measure of albuminuria. ACR values were categorized

into normal-to-mild (<3 mg/mmol), moderate (3-30), and severe albuminuria (>30), according to KDIGO 2012 criteria.[8] All defining codes are presented in **Appendix C**.

Statistical Analysis

Descriptive statistics for the total analytic cohort and for each age group (18-39, 40-49, and 50-65 years) are presented using mean and standard deviation (SD) for normally distributed continuous variables, median and interquartile range (IQR) for non-normally distributed continuous variables, and frequency and proportion for categorical variables. Crude measures of event occurrence for each outcome were presented as frequency and incidence rates per 1000 person-years for each index eGFR category and age group.

Associations between eGFR categories and outcomes were examined using Cox regression models, with follow-up from index date until the first of outcome of interest or censoring (emigration or end of study). Models were constructed for each age group to estimate hazard ratios (HRs) relative to age-specific reference eGFR categories. Models were adjusted for sex, income quintile, hypertension, diabetes, and past cardiovascular disease. Models were also adjusted for other covariates (obesity[91], alcoholism, smoking, hypercholesterolemia, hyperkalemia[92], cancer, chronic liver disease[93], chronic lung disease[94]), urban/rural living status, and healthcare utilization variables (specialist visit or emergency department visit within 5 years pre-index). The proportional hazards assumption was assessed graphically for index eGFR categories and covariates in all models using Kaplan-Meier curves and Schoenfeld residuals.[95,96] We also repeated analyses for the kidney failure outcome to model the competing risk of all-cause mortality, as older participants may die of other causes before reaching end-stage kidney disease.[97]

Pre-defined stratified analyses were also conducted among those aged 18-39 by sex, history of hypertension, history of diabetes, and past cardiovascular disease, which have been identified as important risk factors for both CKD and adverse outcomes. Multiplicative interactions were evaluated in both the overall cohort using an interaction term of the stratifying variable and continuous index eGFR, and in the subgroups using an interaction term with categorized index eGFR. Among those with ACR measurements within a year of index date, we also examined associations of outcomes with interacting categories of index eGFR and ACR, stratified by age group, and relative to individuals in age-specific reference category with ACR values <3

mg/mmol. For those with ACR measures after index, follow-up started at the date of index ACR measurement to prevent potential immortal time bias. In addition, we repeated similar models as the main analyses among those aged 18-39 years without an eligible ACR measure to clarify the influence of ACR measurements on the results. Both stratified models and models of interacting index eGFR and ACR were adjusted for the same aforementioned covariates. All analyses were conducted using SAS Enterprise Guide version 7.15 (SAS Institute Inc., Cary, NC, USA).

Additional analyses

We conducted several additional analyses. First, we repeated our models using two eGFR measures (>90 days to 2 years post-index). The main exposure was the mean of index and second eGFR values while follow-up began from the date of the second eGFR measure. Second, we examined non-linear associations between continuous index eGFR and each adverse outcome using restricted cubic splines.[98] Knots were set at 10-unit increments from 60 to 120 mL/min/1.73m^2. These models were adjusted for the same covariates as the main analyses and stratified by age group, with HRs estimated relative to age-specific reference values (105 mL/min/1.73m^2 for ages 18-39, 95 for ages 40-49, 85 for ages 50-65). Third, models were reconstructed using a common eGFR reference range for all age groups (eGFR 90-110 mL/min/1.73m^2) to examine the impact of consistent comparisons across age strata.

Patient and public involvement

Although cohort members contributed to this research in important ways, we did not involve them in the design, conduct, reporting, or dissemination pans of our study due to time constraints. Similarly, we were unable to involve members of the public in this research.

RESULTS

Baseline characteristics of study participants are presented in **Table 1**. After exclusions, 8,703,871 out of 9,106,033 (96%) adults aged 18-65 years identified during the accrual period were included in our analytic cohort with 4,468,335 individuals (51%) having at least two repeated eGFR measures and 746,948 (9%) with an ACR measure within one year of index (**Figure 1**). Participants had a mean (SD) age of 41.3 (13.6) years and a median [IQR] follow-up of 9.2 [5.7-11.4] years. The mean (SD) index eGFR value was 104.2 (16.1) mL/min/1.73m^2 and participants had a median [IQR] of 4 [1-10] eGFR measures during follow-up.

The mean (SD) eGFR in ages 18-39, 40-49 and 50-65 were 113.6 (14.2), 101.8 (12.6) and 93.1 (12.8), respectively. Among those aged 50-65, 14.9% had hypertension and 8.5% had diabetes compared to 2.1% and 1.5% in the youngest group, respectively. Median ACR was 0.6 [0.4-1.6] mg/mmol for those aged 18-39, compared to 0.7 [0.4-1.9] and 0.9 [0.5-2.4] in those aged 40-49 and 50-65, respectively. Distribution of index eGFR categories by age group are presented in **Appendix D**. In general, the eGFR distribution was higher among those aged 18-39. When comparing index eGFR relative to age-specific reference categories (**Figure 2**), the prevalence of below-reference eGFR was 18.0% for ages 18-39, 18.8% for 40-49 and 17.0% for 50-65.

Associations of eGFR with outcomes

Adverse outcomes occurred in 2.0%, 7.6%, and 19.2% of participants aged 18-39, 40-49, and 50-65 years, respectively, with a graded increase in the crude incidence of any adverse outcome with a lower eGFR (see **Tables 2-5, Figure 3**). Adjusted HRs for any adverse outcome were highest (and crude incidence rates lowest) among those aged 18-39 compared to older groups at each eGFR level below age-specific referents (**Table 2**). For instance, at eGFR 60-70, ages 18-39 had higher HR [2.00 (95% CI 1.86 to 2.16)] and lower incidence (8.08 events per 1000 p-y) than ages 40-49 (HR 1.35 (1.30 to 1.40), incidence 13.6 per 1000 p-y) and 50-65 [HR 1.25 (1.24 to 1.27), incidence 30.5 per 1000 p-y]. Furthermore, **Figure 3a** shows a consistently higher relative hazard in 18-39-year-olds compared to older groups, with a widening gap between age groups, across eGFRs below age-specific referents, beginning as early as eGFR 80-90 and below.

Findings were similar when examining each adverse outcome individually (all-cause mortality, CV events, and kidney failure in **Tables 3-5**, respectively). For mortality, 0.8%, 2.5%, and 7.9% died among those aged 18-39, 40-49, and 50-65 years. Like the adverse outcome composite, HRs for mortality were highest (and mortality rates lowest) in the youngest age group (e.g. at eGFR 60-70, ages 18-39: HR 2.26 (2.00 to 2.55), incidence 2.89 deaths per 1000 p-y) compared to middle-aged (HR 1.61 (1.51 to 1.72), 4.35 deaths per 1000 p-y) and older adults (HR 1.43 (1.40 to 1.46), 11.9 deaths per 1000 p-y) when eGFRs were below age-specific referents (**Table 3**). This was paired with noticeably higher increases in the HRs and crude incidence rates in the youngest group as early as eGFR 80-90 and below (**Figure 3b**). Regarding CV outcomes, around 1.3%, 5.7%, and 14.3% experienced an incident CV event among those aged 18-39, 40-49, and

50-65, respectively, with higher HRs and lower incidence (**Table 4**) and similarly widening age gaps in HRs (**Figure 3c**) as all-cause mortality. Kidney failure was a relatively rare outcome in the cohort, as it occurred in 0.05%, 0.1%, and 0.3% of participants aged 18-39, 40-49, and 50-65, respectively. Sharp increases in both crude incidence and adjusted HRs for kidney failure were noted, particularly in the youngest group from eGFR 90-100 to 50-60 (e.g., a 117-fold increase in crude incidence from 0.0651 to 7.62 events per 1000 p-y, and a 32-fold increase in adjusted HR from 1.54 (1.26 to 1.89) to 48.7 (39.6 to 60.0)) (**Table 5** and **Figure 3d**). Patterns kidney failure risk persisted after accounting for competing risk of death (**Appendix E**).

Sex, diabetes, and hypertension-stratified models, as well as models stratified by past cardiovascular disease, are presented in **Appendices F, G, H, and I**, respectively. The crude incidence of any adverse outcome was mostly higher in males while adjusted HRs were higher among females across index eGFR levels [(overall p-value of interaction < 0.001; e.g., at eGFR 60-70 mL/min/1.73m^2: HR 1.86 (1.69 to 2.05), 9.05 per 1000 person years for males vs HR 2.21 (1.97 to 2.49), 6.92 per 1000 for females, p = 0.028]. Similar patterns were noted in other outcomes, with the greatest sex differences in risk estimates at eGFR 50-60 for most outcomes. The risk of any adverse outcome were generally higher among those with diabetes (overall p-value of interaction < 0.001), past cardiovascular disease (p = 0.007), and (to a lesser extent) hypertension (p = 0.068).

Association of eGFR and ACR with outcomes

The risk of adverse outcomes with index eGFR increment and ACR (<3, 3-30, >30 mg/mmol) by age group are illustrated in **Figure 4 and Appendix J**, among those with ACR measures within a year of index (n = 746,948). Generally, adjusted HRs for any adverse outcome were highest (and crude incidence rates lowest) in those aged 18-39 years, compared to ages 40-49 and 50-65, across all eGFR and ACR categories. In each eGFR category across all age groups, higher ACR categories were associated with higher incidence and HRs for each outcome. Moreover, within each ACR category, decreasing index eGFR was associated with higher incidence and HRs of adverse outcomes, most prominently in the top-right corner of the heatmaps for across all age groups (i.e., close to eGFR 50-60 and ACR≥30 mg/mmol)(**Figure 4**). This was prominent in young adults 18-39 regardless of outcome [e.g., for any adverse outcome: HR 7.90 (6.24 to 10.0) and incidence 65.3 per 1000 p-y for ages 18-39, HR 3.98 (3.34 to 4.74) and incidence 82.2 per

1000 p-y for ages 40-49, HR 2.68 (2.48 to 2.89) and incidence 114 per 1000 p-y for ages 50-65] (**Figure 4a, Table J1**). Similar elevations in clinical risk can be noted by strata of ACR for individual outcomes (**Figures 4b-d, Tables J2-J4**), as well as among those aged 18-39 without an eligible ACR measure (n = 7,956,923; **Table J5**).

Additional Analyses

Results conducted among individuals with at least two repeated eGFR measures (n = 4,468,335) are presented in **Appendix K**. **Appendix L** illustrates non-linear trends of HRs of adverse outcomes with continuous index eGFR by age group. **Appendix M** presents models with a common reference eGFR range for all age groups (eGFR 90-110 mL/min/1.73m^2). Across analyses, similar trends in both crude incidence rates and adjusted HRs for adverse outcomes were observed.

Repeated eGFR Measures and Healthcare Utilization

Among younger adults with index eGFR below age-specific referent (i.e., eGFR 100-110 or lower), 39.2% had a second eGFR measure and 5.2% had an ACR within one year of index eGFR measure, compared to 51.3% and 8.1% in adults aged 40-49 (reference eGFR 90-100) and 65.4% and 12.8% among those aged 50-65 (reference eGFR 80-90), respectively. Moreover, 3.7% of adults aged 18-39 with index eGFR below age-specific referent were referred to a specialist within a year of follow-up, compared to individuals aged 40-49 (5.3%) and 50-65 (9.4%), respectively. This difference persists in referrals within a year of index eGFR measurement to nephrologists among those below age-specific referent (0.3% for ages 18-39, 0.4% for ages 40-49, and 0.6% for ages 50-65), endocrinologists (1.3%, 1.2%, and 1.4%), and cardiologists (2.1%, 4.0%, and 7.9%, respectively).

DISCUSSION

Principal findings

Young adults require a large reduction in kidney function before meeting the current CKD threshold of 60 mL/min/1.73m^2, a level that prompts recognition, monitoring, and trial enrollment. In this population-based cohort of 8.7 million adults, we found 17% of younger adults had a modestly reduced eGFR, above the current CKD threshold, but below levels

expected for age (i.e., eGFR 60-100 mL/min/1.73m^2). Modestly reduced eGFR was associated with a higher adverse risk, relative to age-specific referents (eGFR 100-110 for ages 18-39, eGFR 90-100 for 40-49, eGFR 80-90 for 50-65 years, respectively). Importantly, these findings persist across strata of sex and comorbidities, when using two repeated measures to define index eGFR, after excluding pregnancies and other eGFR-altering conditions pre-index, and when examined against a common index eGFR referent for all ages. These findings suggest that even modest reductions in kidney function in younger adults (i.e., eGFR <100 mL/min/1.73m^2) are significantly associated with adverse outcomes.

Comparison with other studies

Our findings are consistent with and expand on previous studies. Analyses of CKD-PC data[10,12,37] reported elevations in all-cause mortality and kidney failure risk with eGFR levels below roughly 105 mL/min/1.73m^2 in adults aged 18-54. Interestingly, no significant increase in CV mortality risk was found across all ages when the eGFR was <60 mL/min/1.73m^2[2,1,9,47]. Our cohort expands on these findings with more granular age groups and eGFR increments and the addition of non-mortality CV outcomes in young adults. The CARDIA study[17,18] reported eGFR values <110 mL/min/1.73m^2 among those aged <40 years were associated with relative risk for detectable coronary artery calcification over 10 years of follow-up as a proxy of CV outcomes. Our findings are consistent with the CARDIA study and other population-based studies[68–71] in finding elevated CV risks occurring as early as eGFR 80-90 mL/min/1.73m^2 and below in younger adults. Whether these observations apply to CV disease broadly or is more specific to one type of event remains to be determined.

Although we reported elevated relative hazards in younger adults, the absolute risk (in terms of differences in crude incidence rates) remains modest. From a public health perspective, even if crude incidence rates are low in younger adults, the population at risk in our cohort is large, and with a longer life expectancy in this group, the burden of CKD and its complications can be considerable. For this reason, even modest increases in event rates in young adults are concerning and represent a potentially large number of years lost to illness and disability.[9,13,67] Cost-effective methods of risk reduction by lifestyle modification and possible emerging therapeutics (e.g. SGLTs) for certain high-risk individuals remain unexplored. The recognition of

an elevated risk in this population should prompt appropriate monitoring, referral, and future trial enrollment.

Our stratified analyses revealed important differences. Crude incidence rates of adverse outcomes were generally higher among males aged 18-39, while adjusted HRs for each outcome were generally higher among females. Indeed, previous epidemiologic studies, including analyses of data from the Chronic Renal Insufficiency Cohort in the US[99] and the Renal Iohexol Clearance Survey in northern Europe[51] reported higher baseline prevalence of CKD among women. However, men were more likely to progress to end-stage kidney disease (ESKD) or die from any cause, suggesting slower rate of eGFR decline in women than men. As expected, event rates and adjusted HRs for adverse outcomes were higher among those with diabetes and hypertension across eGFR levels.[40,41,46]

A low eGFR for one's age and albuminuria were associated with elevated risk of adverse outcomes on both absolute and relative scales across all age groups. With a lower eGFR relative to an age-specific referent and higher ACR, crude events rates for outcomes were higher in older participants, while relative risks were higher in young adults. These independent associations of eGFR and ACR were similarly reported in previous studies for mortality[10], ESKD[10,53], and CV outcomes.[37] However, the current study examined more granular eGFR increments relative to age-appropriate referent values. Of concern is how few individuals in our cohort had an ACR measure (roughly 4%) despite the rapid elevations in risk with increasing albuminuria severity with intact eGFR.

Policy implications

As existing therapies solely focus on slowing progression, it follows that the early recognition of progressive kidney damage earlier in life may be beneficial.[1] Our findings have important implications for population-level CKD monitoring, as well as accurate prognostication of adverse outcomes given baseline kidney function in younger adults. In our cohort, 17% of younger adults (18-39 years) had an index eGFR below referent. Despite this, young adults were the least likely to receive appropriate laboratory monitoring (serum creatinine and/or ACR measurement) or be referred to a specialist. As CKD is currently defined as an eGFR < 60 mL/min/1.73m^2[8], this may result in an under-appreciation of less severe kidney function loss in young adults. Such age-related disparities in CKD burden has been noted in other settings using

real-world healthcare data, such as one nationwide study in Iceland[100], two from Germany[64,101], and an analysis of NHANES data from the US.[102] Younger individuals, regardless of their nephron mass[20,40], albuminuria severity[53,67], or comorbidities[46], are at risk of developing progressive CKD over their lifetime, elevating their risk of CV and all-cause mortality. There can be benefit derived from more frequent, proactive screening of kidney function. More eGFR and ACR measurements could better inform next steps for prevention or treatment, such as deciding whether early intervention (lifestyle modification, initiation of therapeutics, or otherwise) is warranted. From the patients' perspective, while it can be distressing, raising awareness of such risks could facilitate engagement with healthcare services, as well as detect CKD progression at an earlier, more preventable stage, well before adverse outcomes occur.[9,103]

Strengths and limitations

Our study has some limitations. Firstly, there is a possibility of misclassification from ICD-10 codes for some comorbidities such as alcoholism and smoking, as these may have been evaluated based on self-report. Despite this, outcomes, and other comorbidities (such as diabetes, hypertension) were objectively identified using previously validated ICD-10 codes. Second, there is a possibility of unmeasured confounding and alternative explanations for observed associations, such as medication use (as this data was only available for those aged >65 years). However, our large cohort size, and consistency across additional analyses and with existing literature strengthen our findings, even after controlling for various underlying conditions. Third, eGFR and/or ACR measures were not randomly conducted with a potential for selection bias.[35] However, healthcare provision in Ontario is public and there is no cost barrier for obtaining a blood test or visiting a physician from the perspective of the patient. Moreover, due to the lack of population-level screening of kidney function, serum creatinine measurements may often be conducted at the physician's discretion. To account for potential heterogeneity in participants' health status pre-index, we adjusted for various underlying comorbidities and for physician visits within a 5-year lookback window. Fourth, we defined baseline kidney function using a single outpatient eGFR measure when constructing our cohort. While it does not account for the chronicity of kidney function or its stability over a period of time, it has been shown to be a reasonable estimate of baseline kidney function in past studies of ICES data and external cohorts.[56,74,75] Defining index eGFR with one measure is likely to result in a broader, more

generalizable cohort with average kidney function representative of the general population, while using two measures may bias the cohort to individuals who would require repeated testing (and are generally less healthy). Nevertheless, patterns in both crude incidence rates and adjusted HRs of adverse outcomes remained consistent after sensitivity analyses defining index eGFR with two measures at least 90 days apart. Fifth, we estimated index eGFR using the 2021 CKD-EPI race free equation based on outpatient serum creatinine markers.[33] Despite this being a widely adopted equation for estimating kidney function, concerns have been raised regarding its potentially biased estimation by race and differing accuracy with other clinical biomarkers (most notably cystatin C).[50] While serum creatinine is dependent on muscle mass and is more prevalent in older age, this is less common in younger adults and eGFR using both serum creatinine and cystatin C have been shown to be similar in this age group.[33,34] Finally, our findings did not provide insight into the mechanism of these modest eGFR reductions, nor did we examine the underlying mechanisms of how important comorbidities (such as hypertension) influenced the results. However, to account for this, we excluded individuals with past history of kidney disease (including AKI, kidney stones, and those who consulted nephrologists which would rely in inpatient eGFR) and stratified by various comorbidities within 5 years pre-index. All of these additional analyses have shown consistency with main analyses and findings from past studies, lending confidence to the importance of modest reductions in eGFR in this cohort.

Conclusions

In this population-based cohort of 8.7 million adults, we found consistent elevations in clinical risk (risk of all-cause mortality, cardiovascular events, and kidney failure) on a relative scale with modest eGFR reductions above the current threshold of 60 mL/min/1.73m^2, but below age-specific referents. These elevations were most prominent and started at higher index eGFR (as early as eGFR<80) in young adults (18-39 years) compared to middle-aged and older adults (40-65 years). This disparity between age groups persisted after accounting for various underlying differences in kidney function, albuminuria, and across sex- and comorbidity-based strata. The findings suggest there may be a role for more frequent measurement and monitoring of kidney function (through both eGFR and ACR) in younger adults to identify individuals at risk to prevent CKD and its complications.

FIGURES (Chapter 3)

FIGURE 1: Participant flow diagram

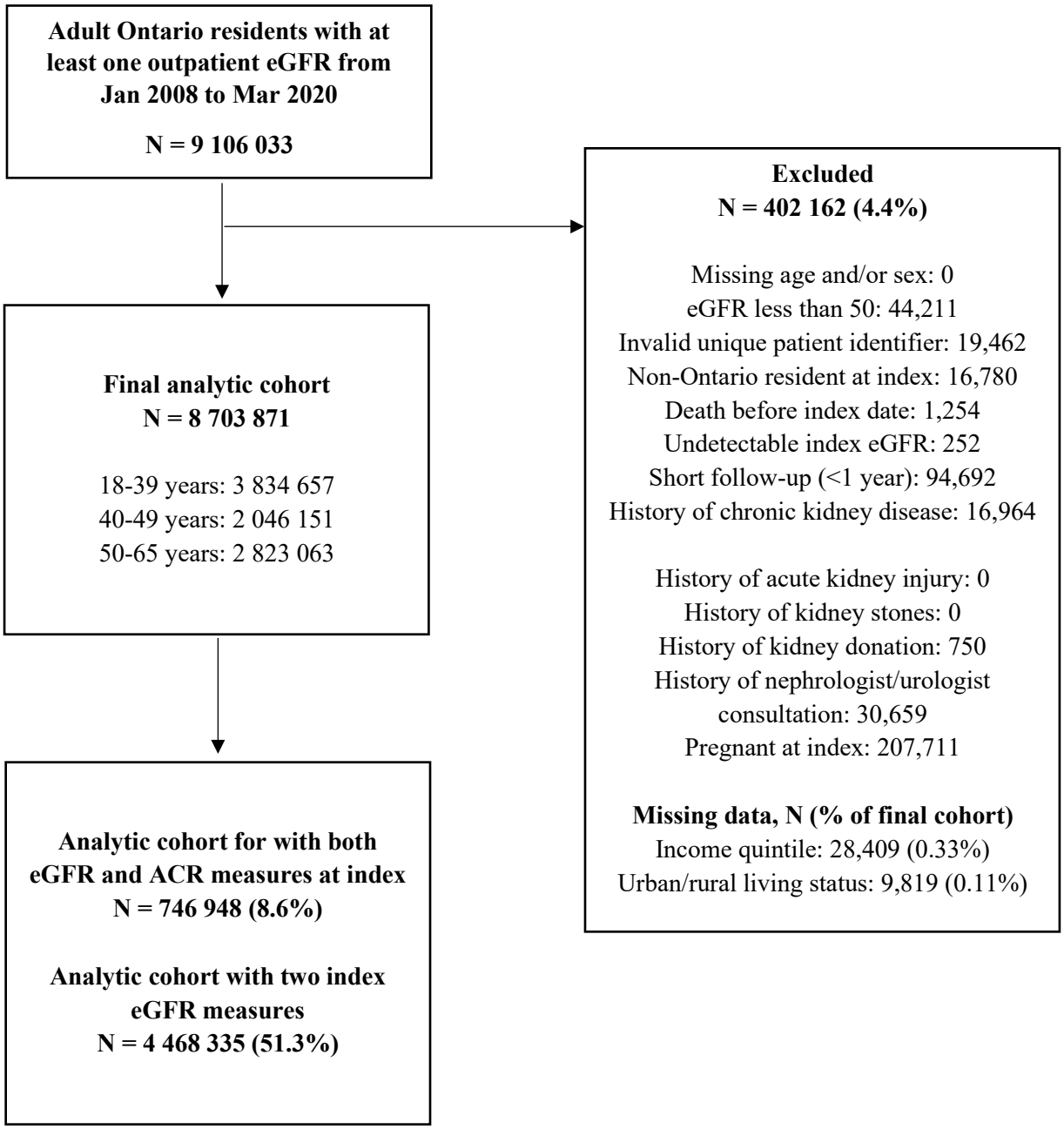
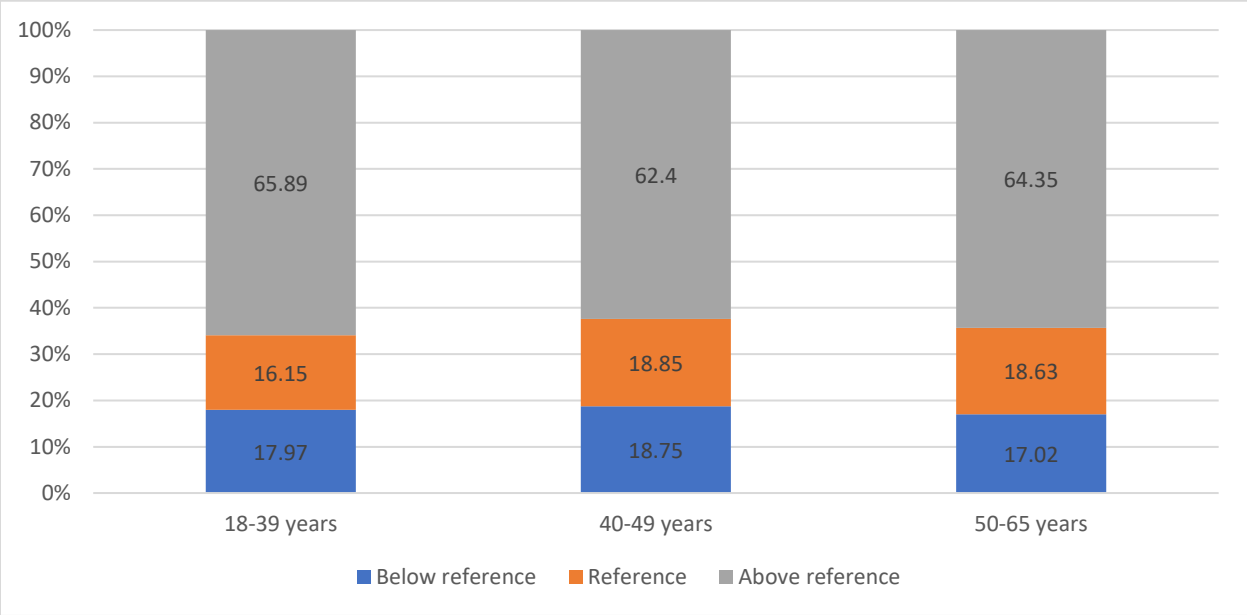
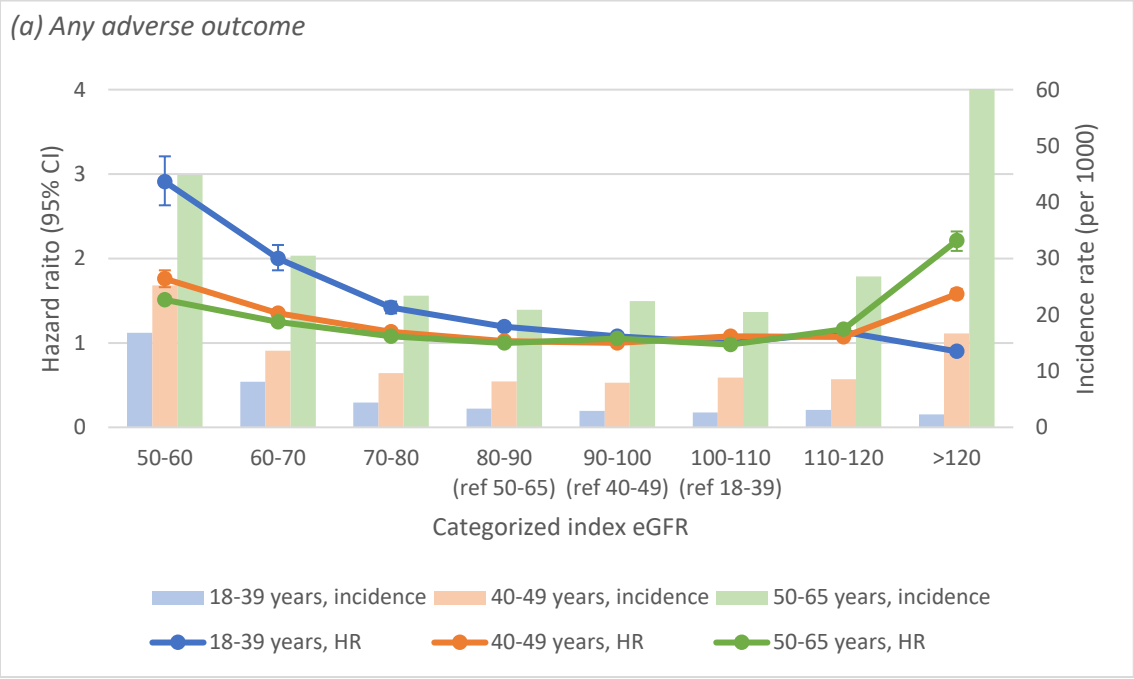


FIGURE 2: Proportion (%) of participants in index eGFR categories relative to age-specific reference categories*, by age group

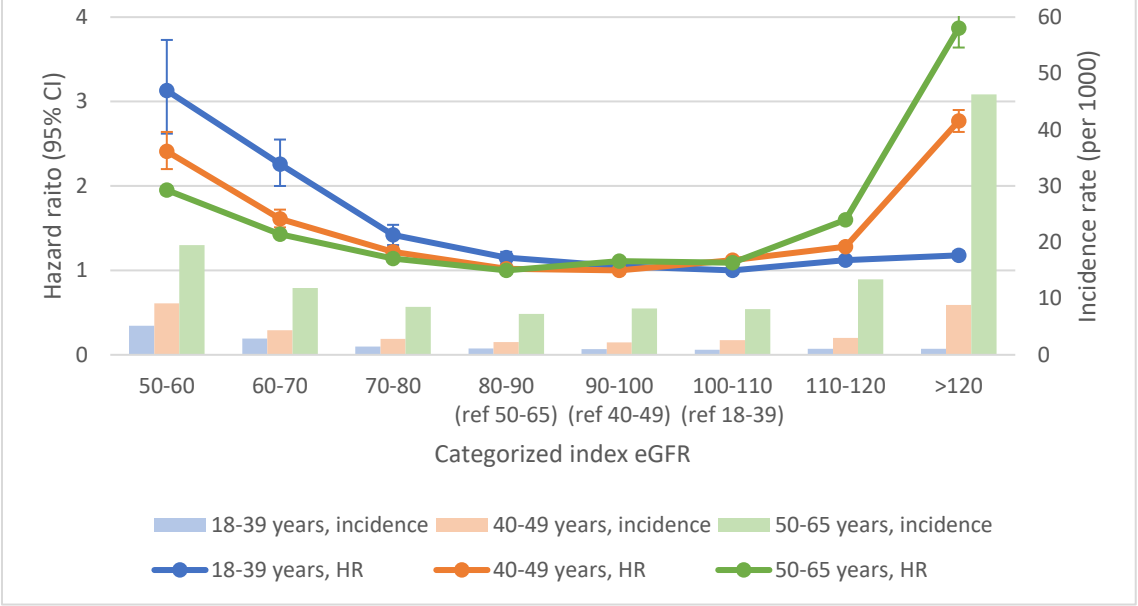


**reference categories by age: eGFR 100-110 for 18-39 years, 90-100 for 40-49 years, 80-90 for 50-65 years*

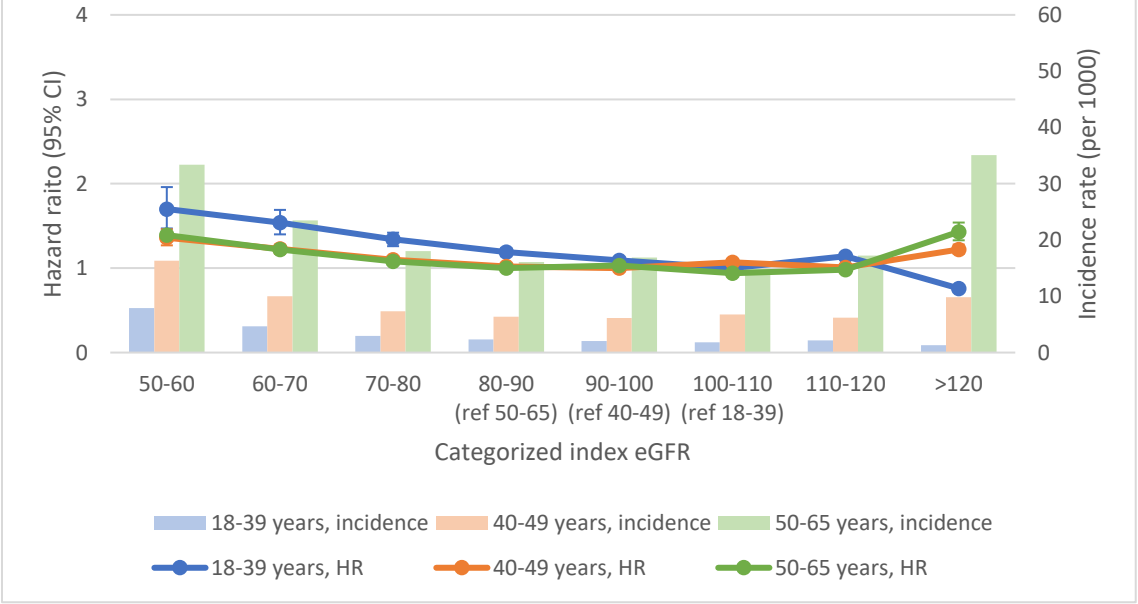
FIGURE 3: Incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) any adverse outcome (first of all-cause mortality, cardiovascular outcomes, kidney failure), (b) all-cause mortality, (c) cardiovascular composite outcome (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation), and (d) kidney failure (with a zoomed-in panel (e)), relative to age-specific eGFR reference ranges, by age-group

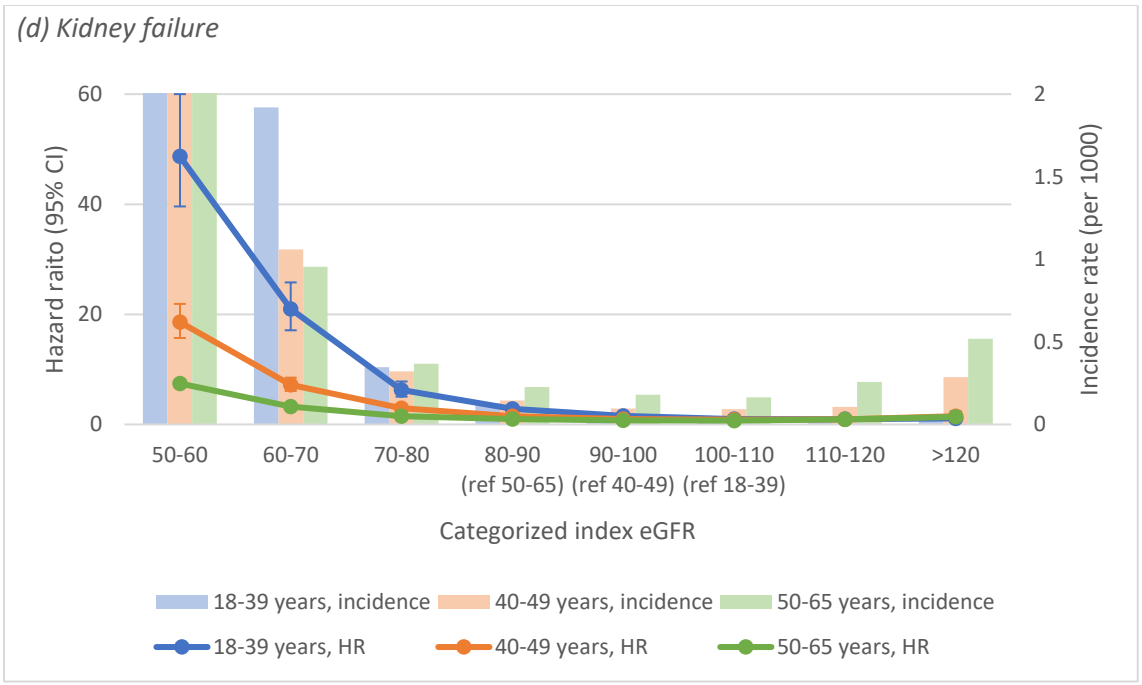


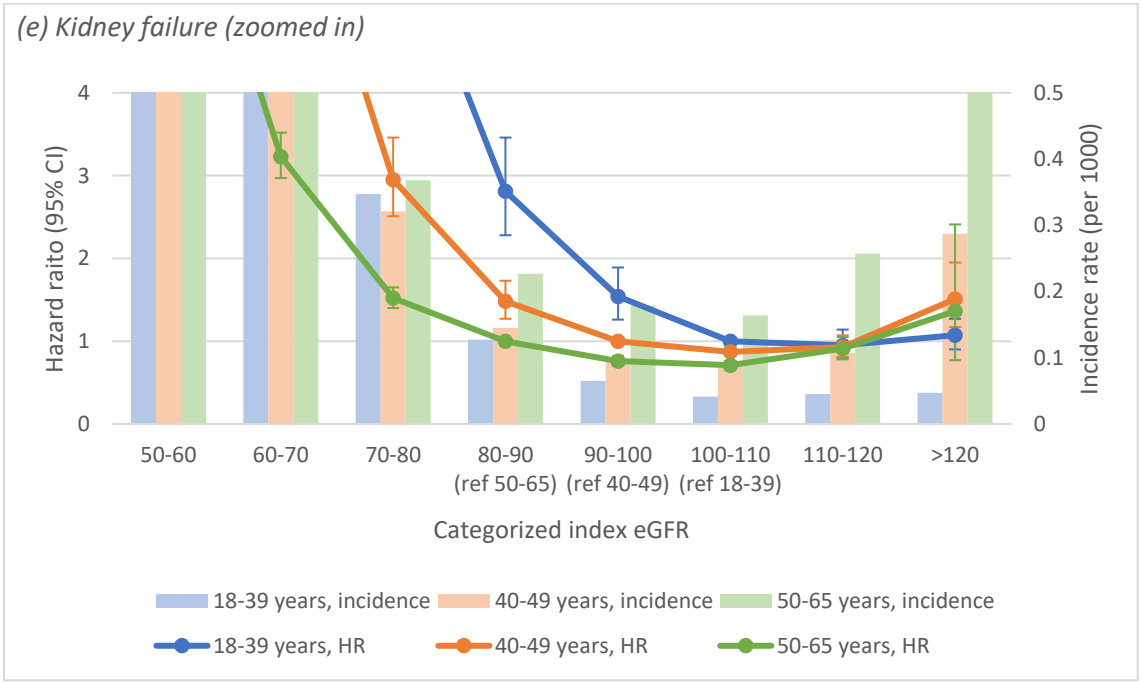
(b) All-cause mortality



(c) Cardiovascular composite outcome







**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Figure 4: Adjusted* hazard ratios (95% CI) of (a) ANY ADVERSE OUTCOME, (b) ALL-CAUSE MORTALITY, (c) CARDIOVASCULAR COMPOSITE OUTCOME, (d) KIDNEY FAILURE by interacting categories of index eGFR (mL/min/1.73m^2) and albumin-creatinine ratio (ACR, mg/mmol), stratified by age group (reference: age-specific reference category (underlined) and <3 mg/mmol)

(a) Any adverse outcome

18-39 years

eGFR/ACR	<3	3-<30	≥30
50-60	2.27	3.60	7.90
60-70	1.72	3.15	6.24
70-80	1.53	2.38	4.07
80-90	*1.13*	1.96	3.73
90-100	*1.03*	1.47	3.75
100-110	1.00	1.51	2.59
110-120	1.12	1.70	2.88
>120	0.80	1.43	2.02

40-49 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.63	2.46	3.98
60-70	1.16	1.92	3.52
70-80	*1.01*	1.68	2.96
80-90	*1.00*	1.60	2.69
90-100	1.00	1.48	2.39
100-110	1.09	1.54	2.53
110-120	*1.04*	1.58	2.13
>120	1.21	2.03	2.43

50-65 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.37	1.81	2.68
60-70	1.19	1.82	2.37
70-80	1.07	1.61	2.39
80-90	1.00	1.53	2.30
90-100	1.05	1.51	2.22
100-110	0.96	1.41	2.03
110-120	1.06	1.47	2.10
>120	1.70	1.92	2.93

(b) All-cause mortality

18-39 years

eGFR/ACR	<3	3-<30	≥30
50-60	*1.69*	3.50	6.76
60-70	*1.24*	2.18	4.83
70-80	1.51	2.22	2.50
80-90	*1.17*	2.17	4.12
90-100	*0.99*	1.49	4.34
100-110	1.00	1.39	2.99
110-120	*1.02*	1.80	2.59
>120	*1.08*	1.87	2.53

40-49 years

eGFR/ACR	<3	3-<30	≥30
50-60	2.35	2.66	4.84
60-70	1.49	2.81	5.58
70-80	1.22	2.17	4.27
80-90	1.18	1.85	4.08
90-100	1.00	2.16	3.71
100-110	1.15	1.94	3.93
110-120	1.24	2.18	3.32
>120	1.95	3.88	3.91

50-65 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.67	2.76	4.20
60-70	1.36	2.51	3.72
70-80	1.12	2.03	3.53
80-90	1.00	1.85	3.44
90-100	1.10	1.86	3.25
100-110	*1.02*	1.73	3.04
110-120	1.33	1.93	3.17
>120	2.35	3.59	4.61

(c) Cardiovascular composite outcome

18-39 years

eGFR/ACR	<3	3-<30	≥30
50-60	*1.36*	2.24	3.32
60-70	1.53	2.13	2.65
70-80	1.48	1.93	2.41
80-90	*1.10*	1.84	2.73
90-100	*1.01*	1.33	2.74
100-110	1.00	1.50	1.91
110-120	1.13	1.64	2.48
>120	0.69	1.27	1.40

40-49 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.31	2.04	2.25
60-70	*1.10*	1.70	2.18
70-80	*0.94*	1.51	2.37
80-90	*0.96*	1.53	2.32
90-100	1.00	1.38	2.16
100-110	1.08	1.47	2.33
110-120	*1.00*	1.47	1.86
>120	*1.07*	1.72	2.05

50-65 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.31	1.60	2.10
60-70	1.17	1.69	2.10
70-80	1.06	1.56	2.19
80-90	1.00	1.49	2.05
90-100	1.03	1.46	2.07
100-110	0.93	1.35	1.86
110-120	*0.95*	1.37	1.92
>120	1.44	1.47	2.85

(d) Kidney failure

18-39 years

eGFR/ACR	<3	3-<30	≥30
50-60	55.4	118	424
60-70	20.0	66.4	325
70-80	*2.79*	37.8	182
80-90	*1.34*	11.2	124
90-100	*1.28*	9.19	137
100-110	1.00	10.7	64.6
110-120	*0.89*	6.41	61.0
>120	*1.02*	7.96	47.6

40-49 years

eGFR/ACR	<3	3-<30	≥30
50-60	20.7	42.60	265.00
60-70	5.70	21.20	198.00
70-80	3.48	14.20	121.00
80-90	*1.00*	15.40	85.70
90-100	1.00	9.94	63.80
100-110	*1.13*	7.65	50.70
110-120	1.80	7.24	36.60
>120	*1.91*	10.50	50.40

50-65 years

eGFR/ACR	<3	3-<30	≥30
50-60	5.07	21.4	106
60-70	2.28	14.7	73.3
70-80	*1.24*	9.05	53.9
80-90	1.00	5.36	45.3
90-100	*0.96*	3.87	33.3
100-110	*0.87*	3.60	24.9
110-120	*0.80*	4.38	18.5
>120	*2.01*	5.96	23.2

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

***reference categories by age: eGFR 100-110 for 18-39 years, 90-100 for 40-49 years, 80-90 for 50-65 years*

****estimates that are not statistically significant are shown in italics; for each outcome, values closer to HR 1.00 are colored in yellow, while extremely high HRs (HR >>1) are colored in red, while extremely low HRs (HR << 1) are colored in green*

TABLES (Chapter 3)

TABLE 1: Baseline population characteristics (total cohort and by age group)

Characteristic	Complete cohort (n = 8,703,871)		Baseline age					
			18-39 (n = 3,834,657)		40-49 (n = 2,046,151)		50-65 (n = 2,823,063)	
	N	%	N	%	N	%	N	%
Age, mean (SD; standard deviation)	41.3 (13.6)		28.2 (6.7)		44.6 (2.9)		56.8 (4.6)	
Follow-up duration in years, median [interquartile range, IQR]	9.2 [5.7-11.4]		7.6 [4.3-10.6]		10.0 [6.9-11.6]		10.4 [7.3-11.8]	
Total number of person-years of follow-up	73,011,249		28,362,503		18,460,491		26,188,254	
Sex								
Male	4,153,412	47.7%	1,762,599	46.0%	992,667	48.5%	1,398,146	49.5%
Female	4,550,459	52.3%	2,072,058	54.0%	1,053,484	51.5%	1,424,917	50.5%
Living status								
Urban	7,850,229	90.3%	3,544,001	92.6%	1,851,362	90.5%	2,454,866	87.0%
Rural	843,851	9.7%	283,521	7.4%	193,676	9.5%	366,654	13.0%
Income quintile								
1	1,706,093	19.7%	830,423	21.7%	380,983	18.7%	494,687	17.6%
2	1,725,605	19.9%	790,257	20.7%	390,361	19.1%	544,987	19.4%
3	1,740,457	20.1%	769,353	20.1%	412,271	20.2%	558,833	19.9%
4	1,788,103	20.6%	757,067	19.8%	438,743	21.5%	592,293	21.0%
5	1,715,331	19.8%	672,751	17.6%	418,501	20.5%	624,079	22.2%
Measures of kidney function								
Index eGFR, mean (SD)	104.2 (16.1)		113.6 (14.2)		101.8 (12.6)		93.1 (12.8)	

Number of repeated eGFR measurements post-index, median [IQR]	4 [1-10]		2 [1-6]		5 [2-10]		9 [4-16]	
Time between index and first repeat eGFR measurement in days, median [IQR]	499 [257-966] (n = 4,468,335)		574 [283-1119] (n = 1,565,383)		533 [295-1002] (n = 1,084,951)		421 [212-780] (n = 1,818,001)	
First ACR from one year pre- to one year post-index, median [IQR]	0.8 [0.4-2.0] (n = 746,948)		0.6 [0.4-1.6] (n = 205,631)		0.7 [0.4-1.9] (n = 179,108)		0.9 [0.5-2.4] (n = 362,209)	
Comorbidities in the past 5 years								
Hypertension	667,523	7.7%	79,741	2.1%	167,419	8.2%	420,363	14.9%
Diabetes mellitus	385,141	4.4%	57,987	1.5%	87,067	4.3%	240,087	8.5%
Congestive heart failure	26,553	0.31%	833	0.02%	4,307	0.21%	21,413	0.76%
Acute coronary syndrome	95,054	1.1%	3,236	0.08%	16,204	0.79%	75,614	2.7%
Stroke	37,493	0.43%	3,976	0.10%	6,914	0.34%	26,603	0.94%
Atrial fibrillation	30,396	0.35%	2,583	0.07%	4,637	0.23%	23,176	0.82%
Obesity	30,711	0.35%	8,837	0.23%	6,837	0.33%	15,037	0.53%
Alcoholism	123,392	1.4%	68,622	1.8%	22,302	1.1%	32,468	1.2%
Smoking/nicotine dependence	5,500	0.06%	1,495	0.04%	1,221	0.06%	2,784	0.10%
Hypercholesterolemia	39,006	0.45%	1,364	0.04%	5,981	0.29%	31,661	1.1%
Hyperkalemia	2,794	0.03%	584	0.02%	484	0.02%	1,726	0.06%
Cancer	184,586	2.1%	24,706	0.64%	34,968	1.7%	124,912	4.4%
Chronic liver disease	40,221	0.46%	10,059	0.26%	10,198	0.50%	19,964	0.71%

Chronic lung disease	272,389	3.1%	108,915	2.8%	60,029	2.9%	103,445	3.7%
Healthcare utilization								
Primary care visit in 5 years pre-index, n (%)	5,869,045	67.4%	2,388,449	62.3%	1,444,732	70.6%	2,035,864	72.1%
Emergency department visit in 5 years pre-index, n (%)	4,574,033	52.6%	2,102,675	54.8%	1,021,136	49.9%	1,450,222	51.4%
Specialist visit in 5 years pre-index, n (%)	1,254,525	14.4%	358,824	9.4%	289,105	14.1%	606,596	21.5%
Nephrologists	101,631	1.2%	27,905	0.73%	22,218	1.1%	51,508	1.8%
Endocrinologists	408,905	4.7%	171,457	4.5%	89,823	4.4%	147,625	5.2%
Cardiologists	866,567	9.9%	183,440	4.8%	203,270	9.9%	479,857	17.0%
Specialist visit within 1 year post-index, n (%)	486,627	5.6%	141,708	3.7%	104,816	5.1%	240,103	8.5%
Nephrologists	24,137	0.28%	9,636	0.25%	5,327	0.26%	9,174	0.32%
Endocrinologists	132,752	1.5%	62,891	1.6%	27,844	1.4%	42,017	1.5%
Cardiologists	345,586	4.0%	72,793	1.9%	74,893	3.7%	197,900	7.0%

TABLE 2: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for ANY ADVERSE OUTCOME (first of all-cause mortality, cardiovascular outcomes, kidney failure) relative to age-specific eGFR reference ranges, by age-group

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	398/3528 16.8 2.91 (2.63, 3.21)	1212/6227 25.2 1.76 (1.66, 1.86)	13861/39979 44.8 1.51 (1.49, 1.54)
60-70	760/14221 8.08 2.00 (1.86, 2.16)	2987/27455 13.6 1.35 (1.30, 1.40)	31634/127001 30.5 1.25 (1.24, 1.27)
70-80	1847/61781 4.39 1.42 (1.35, 1.49)	8120/102090 9.61 1.13 (1.10, 1.16)	61896/313400 23.4 1.08 (1.07, 1.09)
80-90 (reference for 50-65)	4512/193072 3.34 1.19 (1.15, 1.23)	17219/247809 8.17 1.02 (0.99, 1.04)	94546/526010 20.9 1.00 (reference)
90-100 (reference for 40-49)	8734/416431 2.93 1.08 (1.05, 1.11)	26410/385729 7.91 1.00 (reference)	144772/750625 22.4 1.05 (1.04, 1.06)
100-110	11949/619115	48876/626279	173742/971402

(reference for 18-39)	2.66 1.00 (reference)	8.82 1.08 (1.06, 1.10)	20.5 0.98 (0.97, 0.99)
110-120	25065/1061965 3.08 1.13 (1.11, 1.16)	47467/621341 8.56 1.07 (1.06, 1.09)	20487/91549 26.8 1.16 (1.14, 1.18)
>120	24534/1464544 2.30 0.90 (0.88, 0.92)	4137/29221 16.7 1.58 (1.53, 1.64)	1458/3097 71.5 2.21 (2.09, 2.32)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

TABLE 3: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for ALL-CAUSE MORTALITY relative to age-specific eGFR reference ranges, by age-group

Event frequency **Crude incidence rate** **Adjusted HR (95% CI)**

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	130/3528 5.15 3.13 (2.62, 3.73)	484/6227 9.17 2.41 (2.20, 2.64)	7058/39979 19.5 1.95 (1.90, 2.00)
60-70	279/14221 2.89 2.26 (2.00, 2.55)	1002/27455 4.35 1.61 (1.51, 1.72)	13807/127001 11.9 1.43 (1.40, 1.46)
70-80	630/61781 1.47 1.42 (1.30, 1.54)	2476/102090 2.83 1.22 (1.17, 1.28)	24521/313400 8.51 1.14 (1.12, 1.15)
80-90 (reference for 50-65)	1523/193072 1.12 1.15 (1.08, 1.22)	4917/247809 2.26 1.02 (0.98, 1.05)	35463/526010 7.28 1.00 (reference)
90-100 (reference for 40-49)	2990/416431 0.993 1.05 (1.00, 1.10)	7595/385729 2.21 1.00 (reference)	57740/750625 8.24 1.11 (1.09, 1.12)
100-110 (reference for 18-39)	4199/619115 0.926	14851/626279 2.59	73379/971402 8.10

	1.00 (reference)	1.12 (1.09, 1.15)	1.09 (1.08, 1.11)
110-120	8697/1061965 1.06 1.12 (1.08, 1.16)	16991/621341 2.98 1.28 (1.25, 1.32)	11052/91549 13.4 1.60 (1.57, 1.63)
>120	11512/1464544 1.08 1.18 (1.14, 1.23)	2285/29221 8.86 2.77 (2.64, 2.90)	1075/3097 46.3 3.87 (3.64, 4.11)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

TABLE 4: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for CARDIOVASCULAR COMPOSITE OUTCOME (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation) relative to age-specific eGFR reference ranges, by age-group

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	193/3528 7.92 1.70 (1.47, 1.96)	796/6227 16.3 1.36 (1.27, 1.46)	10385/39979 33.4 1.39 (1.36, 1.42)
60-70	441/14221 4.66 1.54 (1.40, 1.69)	2202/27455 10.0 1.23 (1.17, 1.28)	24378/127001 23.5 1.22 (1.20, 1.24)
70-80	1239/61781 2.94 1.34 (1.26, 1.42)	6186/102090 7.32 1.10 (1.07, 1.13)	47608/313400 18.0 1.08 (1.06, 1.09)
80-90 (reference for 50-65)	3117/193072 2.31 1.19 (1.14, 1.24)	13401/247809 6.36 1.02 (0.99, 1.04)	72594/526010 16.1 1.00 (reference)
90-100 (reference for 40-49)	6035/416431 2.02 1.09 (1.05, 1.12)	20470/385729 6.13 1.00 (reference)	109223/750625 16.9 1.03 (1.02, 1.04)
100-110	8155/619115	37402/626279	126280/971402

(reference for 18-39)	1.81 1.00 (reference)	6.74 1.07 (1.05, 1.09)	14.9 0.94 (0.93, 0.95)
110-120	17360/1061965 2.14 1.14 (1.11, 1.17)	34311/621341 6.19 1.01 (0.99, 1.03)	13125/91549 17.2 0.98 (0.96, 1.00)
>120	14076/1464544 1.32 0.76 (0.74, 0.78)	2430/29221 9.83 1.22 (1.17, 1.28)	717/3097 35.1 1.43 (1.33, 1.54)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

TABLE 5: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for KIDNEY FAILURE (initiation of dialysis or receipt of kidney transplant) relative to age-specific eGFR reference ranges, by age-group

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	186/3528 7.62 48.7 (39.6, 60.0)	261/6227 5.05 18.6 (15.7, 21.9)	1067/39979 2.98 7.44 (6.83, 8.11)
60-70	184/14221 1.92 21.0 (17.1, 25.8)	244/27455 1.06 7.19 (6.09, 8.50)	1104/127001 0.954 3.23 (2.97, 3.52)
70-80	148/61781 0.347 6.27 (5.05, 7.80)	281/102090 0.321 2.95 (2.51, 3.46)	1058/313400 0.368 1.52 (1.40, 1.65)
80-90 (reference for 50-65)	173/193072 0.127 2.81 (2.28, 3.46)	316/247809 0.145 1.48 (1.27, 1.73)	1104/526010 0.227 1.00 (reference)
90-100 (reference for 40-49)	196/416431 0.0651 1.54 (1.26, 1.89)	330/385729 0.0960 1.00 (reference)	1252/750625 0.179 0.76 (0.70, 0.82)
100-110	187/619115	532/626279	1486/971402

(reference for 18-39)	0.0413 1.00 (reference)	0.0929 0.87 (0.76, 1.00)	0.164 0.71 (0.65, 0.76)
110-120	370/1061965 0.0451 0.95 (0.80, 1.14)	608/621341 0.107 0.93 (0.81, 1.07)	211/91549 0.257 0.91 (0.78, 1.05)
>120	502/1464544 0.0469 1.07 (0.90, 1.27)	74/29221 0.287 1.51 (1.17, 1.95)	12/3097 0.518 1.36 (0.77, 2.41)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

CHAPTER 4: MANUSCRIPT II: THE ASSOCIATION BETWEEN SUBCLINICAL REDUCTIONS IN KIDNEY FUNCTION AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN YOUNG ADULTS: A population-based retrospective cohort study

Junayd Hussain[1,2], Haris Imsirovic[2], Mark Canney[3,4], Edward G. Clark[3,4], Meghan J. Elliott[5,6], Pietro Ravani[5,6], Peter Tanuseputro[1,2,4,7,8], Ayub Akbari[3], Gregory L. Hundemer[2,3,4], Tim Ramsay[1,4], Navdeep Tangri[7], Greg A. Knoll*[3,4], Manish M. Sood*[2,3,4]

*denotes equal contribution

[1]School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, CANADA

[2]ICES, Ottawa, Ontario, CANADA

[3]Division of Nephrology, Department of Medicine, The Ottawa Hospital, Ottawa, Ontario, CANADA

[4]Ottawa Hospital Research Institute, The Ottawa Hospital, Ottawa, Ontario, CANADA

[5]Department of Medicine, University of Calgary, Calgary, Alberta, CANADA

[6]Division of Nephrology, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, CANADA

[7]Division of Palliative Care, Department of Medicine, University of Ottawa, Ottawa, Ontario, CANADA

[8]Bruyère Research Institute, Ottawa, Ontario, CANADA

ABSTRACT

Background

Cardiovascular risk factors and disease in young adults (18-39 years) are on the rise. Whether early reductions in kidney function (i.e., estimated glomerular filtration rate [eGFR] above the current accepted threshold for chronic kidney disease [>60 mL/min/1.73m^2], but below age-expected values) are associated with elevated risk is unknown.

Objectives

We aim to examine age-specific associations of subclinical eGFR reductions in young adults with major adverse cardiovascular events (MACE) and MACE-plus-heart failure.

Methods

We conducted a retrospective cohort study of 8.7 million individuals (3.6 million aged 18-39 years) using linked provincial healthcare datasets from Ontario, Canada from January 2008 to March 2021. Cox models examined the association of categorized eGFR (50-120 mL/min/1.73m^2) with MACE (first of cardiovascular mortality, acute coronary syndrome, ischemic stroke) and MACE-plus-heart failure (MACE+), stratified by age (18-39, 40-49, 50-65 years).

Results

Among our cohort (mean age 41.3, mean eGFR 104.2, median follow-up 9.2 years), a stepwise increase in the relative risk of MACE and MACE+ was observed as early as eGFR<90 in young adults (e.g., for MACE, at eGFR 70-80, ages 18-30: 2.37 events per 1000 person-years(p-y), HR 1.31(1.27-1.40); ages 40-49: 6.26/1000p-y, HR 1.09(1.06-1.12); ages 50-65: 14.9/1000p-y, HR 1.07(1.05-1.08)). Elevations in relative risk occurred for 18-39-year-olds at higher eGFR levels than ages 40-49 and 50-65. This persisted when examining each component individually and in additional analyses (stratifying by past CV disease, accounting for albuminuria at index, using repeated measures to define index eGFR).

Conclusions

In young adults, eGFR levels above the current threshold for chronic kidney disease associated with an elevated risk for MACE and MACE+, warranting age-appropriate risk stratification, proactive monitoring, and timely intervention.

Keywords

Kidney failure, cardiovascular disease, hypertension, chronic, epidemiology, prevention

CONDENSED ABSTRACT

Young adults (18-39 years) may lose half of their kidney function prior to recognition and diagnosis of chronic kidney disease (CKD), which is associated with cardiovascular risk. In a population-based cohort of 8.7 million adults, we found subclinical reductions in kidney function (above definition for CKD, but below age-expected values) were associated with higher risk of adverse events (cardiovascular mortality, ischemic stroke, acute coronary syndrome, heart failure) in younger adults compared to middle-aged and older adults (40-65 years). These findings support proactive monitoring of cardiovascular risk and progressive heart disease in young adults at higher thresholds of kidney function.

INTRODUCTION

Over the last 20 years, advances in early cardiovascular (CV) risk factor detection and therapeutic advances have led to declines in CV disease in the general population.[28] However, these benefits are not uniform, occurring primarily in middle-age and older adults with paradoxical increases in young adults.[28,61] Epidemiologic shifts in CV risk factors have paralleled increasing rates of obesity, sedentary lifestyle, diabetes, and hypertension noted in young adults.[61] Past studies[37,61,71] and guidelines[28,62] put forth by the American College of Cardiology and American Heart Association cite chronic kidney disease (CKD) as a notable yet silent "risk-enhancing" factor for CV disease and related mortality.

CKD is defined by structural damage to the kidneys or an estimated glomerular filtration rate (eGFR)<60 mL/min/1.73m^2 (estimated from serum creatinine; units henceforth omitted), with or without albuminuria, regardless of age. While the presence of albuminuria or overt kidney damage is indicative of CKD, whether age influences the risk between eGFR and premature CV

risk is debated.[1,9,10,14,20,39,47,67] The threshold for defining CKD at an eGFR<60 was selected based on elevations in clinical risk across all age groups, enabling a simple cutoff in both clinical monitoring, trial enrollment, and public health messaging.[9] However, the current definition conflates natural age-related decline in kidney function with true disease, over-diagnosing CKD among the elderly. For instance, the mean measured GFR for ages 18-39 is 100-110, compared to 60-65 among those aged 65 or older.[10,37] While this issue has been previously explored in the elderly[9,67], age-adapted eGFR thresholds for CKD (and premature CV risk) have not been consistently applied in younger adults (<40 years), even though many such individuals would need to lose >50% of their healthy kidney function before being clinically recognized based on serum creatinine testing.[9,15] These individuals can benefit from mitigation of CV risk factors through earlier lifestyle modifications (such as exercise, smoking, fluid intake) or administration and examination of age-specific effects of emerging drugs (such as SGLT-2 inhibitors).

Early evidence from small cohorts[17,18,44,49] and large-scale epidemiologic studies[10,37] suggest that early, sustained eGFR declines elevated risks of events such as congestive heart failure and premature CV-related mortality in adults aged <40 years. However, CV outcomes occur rarely in younger adults, and past studies have neither specifically focus on this group nor eGFR values above the CKD definition but below values expected for age using granular categories. As such, cohorts built from "real-world" healthcare data can be better suited to quantify CV risk distribution with subclinical eGFR declines. Indeed, early detection, monitoring, and management of pertinent CV risk factors alongside kidney function decline may further reduce the burden of CV disease in younger individuals.[61,104] Thus, we examined associations of subclinical reductions in kidney function (eGFR between 60-100) with major adverse cardiovascular events (MACE; including CV mortality, acute coronary syndrome, ischemic stroke, and heart failure) in a population-based cohort in younger adults (18-39 years), compared to middle-aged (40-49) and older adults (50-65).

METHODS

Study Design and Setting

We conducted a retrospective cohort study using deidentified, linked health administrative databases housed at ICES (formerly the Institute for Clinical Evaluative Sciences) in Ontario, Canada. ICES is an independent, non-profit research institute whose legal status under Ontario's

health information privacy law allows it to collect and analyze data for health system evaluation and improvement. Ontario has around 15 million residents with universal access to healthcare services through the Ontario Health Insurance Plan (OHIP). Ethics board review was not required as analysis of study data is authorized under section 45 of Ontario's Personal Health Information Protection Act. The design and reporting of this study followed the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement (**Appendix A**).[72]

Data Sources

Data on demographics, vital statistics, healthcare encounters, and laboratory tests for all OHIP-registered residents were obtained from seven databases linked by unique, ICES-generated encoded identifiers for each patient. We sourced outpatient serum creatinine (SCr) and urine albumin measurements at the time of study entry and during follow-up from the Ontario Laboratory Information System (OLIS). Diagnoses of outcomes and other comorbidities were classified using International Classification of Diseases (ICD)-10 codes and were obtained from the Discharge Abstract Database (CIHI-DAD) for hospital admissions and the National Ambulatory Care Reporting System (NACRS) for ambulatory care centre visits in Ontario. Primary care and specialist visits were obtained from an OHIP database of physician service claims. Patients undergoing renal replacement therapy (in-home/in-center hemodialysis and kidney transplant recipients) were identified from the Canadian Organ Replacement Registry (CORR). Demographic data and vital statistics were obtained from the Ontario Registered Persons Database (RPDB). Detailed descriptions of linked databases are provided in **Appendix B**.

Study Cohort

In our analytic cohort, we included all Ontario adult residents between ages 18 and 65 (inclusive) with one or more outpatient SCr measurement in the cohort accrual period (January 1, 2008, to March 31, 2020, inclusive). We defined the date of first available SCr measurement within the accrual period as the start of each individual's follow-up, which was censored at first of either death from non-CV causes, outcome of interest, loss of OHIP eligibility (as individuals move out of Ontario), or end of study on March 31, 2021. We excluded those with missing age and sex, those with invalid IKN, non-Ontario residents at index, those with death date incorrectly

recorded as prior to index date, those with history of kidney disease (initiation of dialysis, receipt of kidney transplant, or diagnosis of untreated CKD within 5 years pre-index), and those with short follow-up (<1 year). Individuals with acute kidney injury or kidney stones, who visited a nephrologist or urologist, or who had donated a kidney (all within 5 years pre-index), and pregnant women[105] at index were also excluded.

Index Kidney Function Measurement

The eGFR, derived from the index outpatient SCr measurement (in μmol/L) for each patient using the 2021 race-free Chronic Kidney Disease-Epidemiology (CKD-EPI) equation, was the exposure of interest.[33,74] A single outpatient eGFR has been previously demonstrated to provide an accurate estimate of baseline kidney function (83% of participants were within +/- 5 mL/min/1.73m^2 in previous studies).[33] Index eGFR values were categorized into 10-unit increments (50-60, 60-70, 70-80, 80-90, 90-100, 100-110, 110-120, >120). Reference categories were set for each age group based on age-normalized values reported from studies using measured GFR with radionucleotide methods, adapted from four cohorts[10,12,37,80]: eGFR 100-110 for ages 18-39, 90-100 for ages 40-49, and 80-90 for ages 50-65, respectively.

Outcomes

The main outcome of interest was time to major adverse cardiovascular events (MACE), a composite outcome defined by first of cardiovascular mortality (occurrence of death during hospitalization or emergency room visit with a cardiovascular diagnosis)[49], acute coronary syndrome (including myocardial infarction events)[106], and ischemic stroke.[107] Secondary outcomes included a composite of MACE and heart failure (HF)[108,109], as well as individual MACE components, all of which were defined using validated ICD-10 diagnostic codes.

Covariates

Demographic covariates included sex, income quintile, and urban/rural living status (derived from confidential postal code information by ICES as described previously[85,87]). Diagnoses of comorbidities within 5 years pre-index were also obtained and adjusted for in Cox regression models, including hypertension[88], past CV disease (occurrence of an aforementioned CV event within 5 years pre-index), diabetes[89,90], obesity[91], alcoholism, smoking/nicotine dependence, hypercholesterolemia, hyperkalemia[92], cancer, chronic liver disease[93], and chronic lung disease

(including asthma, chronic obstructive pulmonary disease (COPD), asbestosis, and interstitial lung disease).[94] Albumin-creatinine ratios (ACRs), derived from urine spot samples, were obtained for a subset of individuals in the cohort within 1 year of index as a measure of albuminuria. ACR values were categorized into normal-to-mild (<3 mg/mmol), moderate (3-30), and severe albuminuria (>30), according to KDIGO 2012 criteria.[8] For healthcare utilization, we obtained frequency of primary care and emergency department visits and specialist (nephrologist, endocrinologist, cardiologist, and urologist) consultations during follow-up. Detailed outcome and covariate definitions used in the analyses are presented in **Appendix C**.

Statistical Analysis

Summary statistics for the total cohort and age groups (18-39, 40-49, 50-65 years) were conducted. Event frequency and crude incidence rates of outcomes per 1000 person-years were determined by index eGFR category and age group. We used Cox regression models to examine the association between categorized index eGFR and time to each CV outcome, with follow-up beginning from date of index eGFR and censored at first of death, occurrence of the relevant outcome, loss of OHIP eligibility, or end of study. Separate models were constructed for each age group to estimate hazard ratios (HRs) relative to age-specific reference eGFR categories, adjusting for sex, income quintile, urban/rural living status, specialist and emergency department visits within 5 years pre-index, and aforementioned comorbidities. Assumption of proportional hazards was assessed for categorized index eGFR and covariates in all models using Schoenfeld residuals.[95,96]

Albuminuria (indicated by ACR) potentially augments CKD prognosis and future CV risk across the range of eGFR values, especially among older younger individuals and those with very low eGFR at index.[37,53] Thus, among those with ACR values within 1 year of index, we assessed associations of interacting index eGFR and ACR categories with MACE outcomes, stratified by age group. HRs were estimated relative to individuals with ACR<3 in their age-specific eGFR reference category. For those with their closest ACR measure occurring after index, follow-up started at the date of this index ACR measurement to prevent immortal time bias. Secondly, we stratified participants aged 18-39 by past history of CV disease (presence of a CV event in 5 years pre-index). HRs were estimated relative to eGFR 100-110. Finally, to account for possible acute changes in eGFR near index and during follow-up, analyses were repeated after including

only those with ≥2 eGFR values with the second value being 90 days-2 years post-index. Here, the main exposure was the mean of index and second eGFR values, grouped using the same categories, with the date of the second eGFR measure as start of follow-up. All additional models were adjusted for the same covariates as the main analyses.

Data were missing only for income quintile and urban/rural living status in a small subset of individuals (<1%) in the cohort. There were no systematic differences in missingness between groups based on index eGFR and age (data not shown). As such, missingness was assumed to occur at random and multiple imputation with chained equations was employed to account for this.[110] All analyses were conducted using SAS Enterprise Guide version 7.15 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Baseline characteristics of study participants are presented in **Table 1**. After exclusion, 8,703,871 out of 9,106,033 (95.6%) potentially eligible adults aged 18-65 were included in the cohort. Of these, 4,468,335 (51.3%) participants had two or more index eGFR measures and 746,948 (8.6%) had an ACR measure within 1 year of index (**Appendix D)**. Participants had a mean (SD) age of 41.3 (13.6) years and were followed up for a median [IQR] of 9.2 [5.7-11.4] years. The mean (SD) index eGFR value was 104.2 (16.1) mL/min/1.73m^2 (units henceforth omitted) for the whole cohort, with the youngest group (18-39) having the highest mean eGFR value (113.6 (14.2)) compared to middle-aged (40-49; 101.8 (12.6)) and older adults (50-65; 93.1 (12.8)). The prevalence of eGFR below age-specific referents at index was 17.3% for aged 18-39, 18.7% for 40-49, and 17.1% for 50-65. Among those aged 18-39, 0.3% had past CV disease, 2.1% had hypertension, and 1.5% had diabetes within 5 years pre-index, compared to 4.5%, 14.9%, and 8.5% in the oldest group, respectively. Of those with ACR measures within 1 year of index, the youngest group had a median [IQR] of 0.6 [0.4-1.6] mg/mmol, compared to 0.7 [0.4-1.9] and 0.9 [0.5-2.4] in those aged 40-49 and 50-65 years, respectively.

Associations of eGFR with outcomes

In total, there were a total of 42,372 MACE events in the youngest group, compared to 102,039 and 342,197 among middle-aged and older adults, respectively. Accounting for HF, the MACE+ outcome added a further 4,924 events among those aged 18-39, compared to 8,037 and 32,540

additional events in ages 40-49 and 50-65 years, respectively. A gradual increase in crude incidence rates and adjusted HRs was noted with decreasing eGFR. Moreover, the adjusted HR for MACE and MACE+ was elevated at higher eGFR levels for ages 18-39 years compared to older groups, relative to age-specific referents. For instance, at eGFR 70-80, the youngest group had higher HR despite lower event incidence rates for MACE (HR 1.31 (1.27-1.40), 1.89 events per 1000 person-years (p-y)), compared to middle-aged (HR 1.09 (1.06-1.12), 5.40/1000 p-y) and older adults (HR 1.07 (1.05-1.08), 14.9/1000 p-y) (**Table 2**). **Figure 1a** illustrates a consistently higher relative risk for MACE among 18-39-year-olds compared to older groups, which became more pronounced as eGFR declined below 80-90. Similar age-based disparities in crude incidence rates and adjusted HRs for MACE+ (**Table 3, Figure 1b**) and individual MACE components (**Appendix E**).

Association of eGFR and ACR with outcomes

Risk of MACE and MACE+ by interacting index eGFR and ACR increments (<3, 3-30, >30 mg/mmol; for n = 746,948) by age group are illustrated in **Figure 2** and **Appendix F**. In general, adjusted HRs for both MACE and MACE+ were highest, and crude incidences lowest, in those aged 18-39 years, compared to older groups. In each eGFR category across all age groups, higher ACR was associated with greater incidence and adjusted HRs, with much risk being concentrated in the top-right corner of heatmaps across all age groups (i.e. those with the lowest eGFR and most severe albuminuria) (**Figure 2**). Specifically, the youngest group had the highest HRs in this region for both MACE and MACE+ (e.g. for MACE: HR 2.94 (1.99-4.35) and 18.2 events per 1000p-y among ages 18-39, HR 2.12 (1.67-2.70) and 36.4 per 1000p-y in ages 40-49, HR 1.91 (1.73-2.11) and 62.1 per 1000p-y in ages 50-65; **Figure 2a** and **Table F1**).

Additional analyses

Analyses for subgroups defined by past CV disease are presented in **Appendix G**. Event frequencies and crude incidence of MACE and MACE+ were generally higher in participants with history of CV disease. While overall trends in HRs were similar to those noted in the youngest group in the main analyses (elevations in HRs occurring as early as eGFR 80-90 and below), adjusted HRs were comparable between the two strata across the eGFR range.

Moreover, analyses were repeated among individuals with two or more repeated eGFR measures between 90 days and 2 years apart (n = 4,468,335; **Appendix H**). Similar trends in both crude incidence and adjusted HRs for both MACE and MACE+ (with elevated risks starting at higher eGFR in younger adults) to the main analyses were noted. However, it is important to note that gaps between younger and older groups were less prominent and estimates were less precise (wider confidence intervals), likely to due to fewer events in this subpopulation.

DISCUSSION

In this population-based cohort of 8.7 million community-dwelling adults, we found subclinical eGFR declines (i.e., eGFR above the current CKD definition but below age-expected values were associated with higher risk of MACE and MACE+ relative to age-specific referents. Moreover, this risk elevation occurred at higher eGFR thresholds in adults aged 18-39 years compared to 40 or older. These findings persisted across strata of past CV disease in the youngest group, as well as in interactions with index ACR and when using two repeated index eGFR measures. These findings suggest even subclinical eGFR declines (i.e. eGFR<100) in younger adults are associated with significant CV risk.

We noted striking age differences in risk of MACE, MACE+, and component CV events in our cohort, with elevated risks among younger adults occurring as early as eGFR of 90 and below. In both CARDIA[17,18,49] and ARIC[44] studies, eGFRs between 60-75 were independently associated with increased left ventricular mass index (a marker of atherosclerotic HF risk) and greater risk of coronary artery calcification 10 years later, especially in younger adults aged <40 years. Similar findings were noted in the PREVEND study[45], with comparable survival from CV events between younger individuals with stage I CKD (eGFR>90 and mild albuminuria) and stages II and III (eGFR≤90 and mild-to-severe albuminuria). However, findings from these studies and ours contrast with CKD-PC data[10,12,37] – the largest collection of general and high-risk cohorts to date (n = 2.0 million) – which identified elevated risk of heart failure and other CV events only when eGFR<60. The underlying mechanisms behind the age discrepancies in CV risk need to be elucidated, as CKD is known to mimic "accelerated aging of the cardiovascular system" through systemic, chronic inflammatory responses in the body.[61] Moreover, left ventricular hypertrophy has been reported in around one-third of all patients with CKD, which is an independent predictor of survival even in early-stage CKD.[28,61,104,111]

The elevated risk of both composite MACE and MACE+ outcomes as well as individual CV outcomes in younger adults is an important finding in this cohort. This suggests eGFR values above the current CKD definition (eGFR<60) and below age-specific mean values are an important, underrecognized marker for future CV risk. Indeed, a recent ACC/AHA guideline on primary prevention of CV disease published in 2019[28] suggests monitoring traditional risk factors every 4-6 years among those aged <40 years. Younger adults with subclinical eGFR declines are at a greater risk of new-onset, progressive kidney disease – an important risk factor for CV disease[1,61] – over their lifetime, which necessitates earlier identification and monitoring of other CV risks. Findings of subclinical eGFR declines can also guide discussions with patients about strategies to manage downstream CV risk, especially those with prior history of CV disease or other comorbidities (such as diabetes[112], hypertension[113]). Such strategies can include assessing patients' readiness for lifestyle changes (diet modification, exercise), screening for established CV risk factors, and possible trial enrollment.[28,62] The absolute risk of CV outcomes, as expected, were low among those aged 18-39 years[9], yet would over the course of a lifetime significantly decrease overall life expectancy. It is also important to recognize that there is an ongoing debate on the value and frequency of screening for CKD with the presence of albuminuria.[53,67] The present findings would support more frequent measurement of ACR in younger individuals with subclinical eGFR declines, which are incidentally discovered in routine serum creatinine measurement.

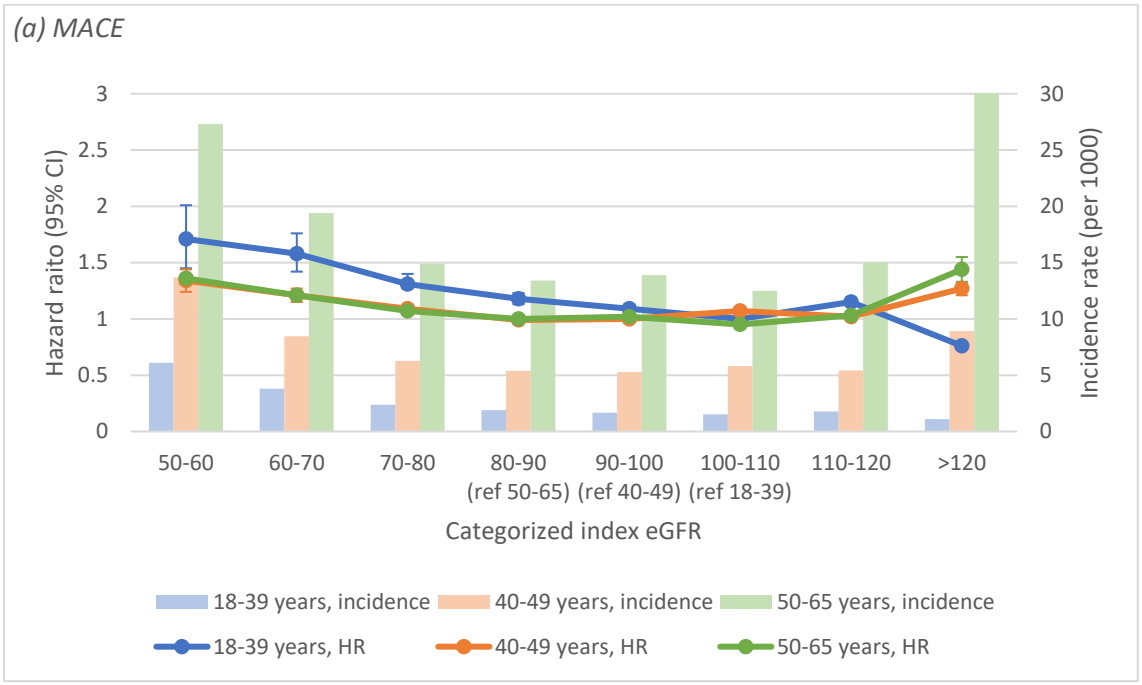
Another important consideration is our cohort's use of serum creatinine as a filtration marker and the use of the race-free CKD-EPI equation to estimate eGFR. In studies that focus on adults of all ages, creatinine and its relationship to muscle mass can lead to U-shaped associations at higher eGFR levels, potentially masking true risk relationships with eGFR. As sarcopenia and atrophy are less common in younger adults, creatinine may be a more reliable marker of kidney function, and therefore the risk relationships are more likely to be linear. However, the consistency of results between our cohort and other cohorts using serum creatinine and/or cystatin-C (an alternate biomarker with a stronger relationship to CV events[18,33,50]) to estimate kidney function is reassuring and illustrative of notable CV risk elevations in younger adults at higher eGFR values. Nonetheless, as the use of cystatin-C increases, it would be worthwhile to replicate these analyses using different eGFR-estimating equations and filtration markers, as well as biomedical cohorts such as the UK Biobank.[114–116]

Our study has some limitations. Firstly, misclassification from ICD-10 coding is possible. When possible, previously validated ICD-10 codes were used. Second, residual confounding and alternative explanations for observed associations are possible. However, our large cohort size, and consistency across additional analyses and pre-existing literature, strengthen our findings. Third, missing data was present for income and rurality, albeit in small proportions (<1%) and there was no missing exposure or outcome data. Fourth, only part of the cohort had repeated eGFR measures and/or an ACR measure. While these additional measures would have provided a more complete picture of kidney function, there is a potential for bias towards individuals who need to be repeatedly measured due to pre-existing conditions.[35] Moreover, single eGFR measures have been validated in outpatient populations as a reasonable estimate of stable kidney function.[33,74] It is important to note, however, that eGFR readings were not conducted randomly, and may be based on clinical indication. Finally, our findings did not provide insight into the mechanism of eGFR reduction, nor the risk of a particular etiology or subtype of CV outcomes (for instance, we could not differentiate between HF events with preserved and reduced ejection fraction[108]).

In this population-based cohort, an eGFR measure below a healthy age-specific mean was associated with elevated CV risk in younger adults (18-39 years), and this occurred at higher eGFR levels compared to middle-aged (40-49) and older adults (50-65). This age disparity persisted after accounting for repeated kidney function measures, interactions with albuminuria at index, and history of CV disease. We present evidence to illustrate the relevance of age-specific CV risk prognostication with subclinical declines in kidney function. This also motivates future initiatives for passive surveillance for CV and clinical risk, as well as assessment of age-specific assessments of therapeutic interventions, in younger adults with eGFR declines above the CKD threshold, but below age-expected values.

FIGURES (Chapter 4)

FIGURE 1: Incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) major cardiovascular adverse events (MACE; first of cardiovascular mortality, acute coronary syndrome, and ischemic stroke) and (b) MACE plus heart failure, relative to age-specific eGFR reference ranges, by age group



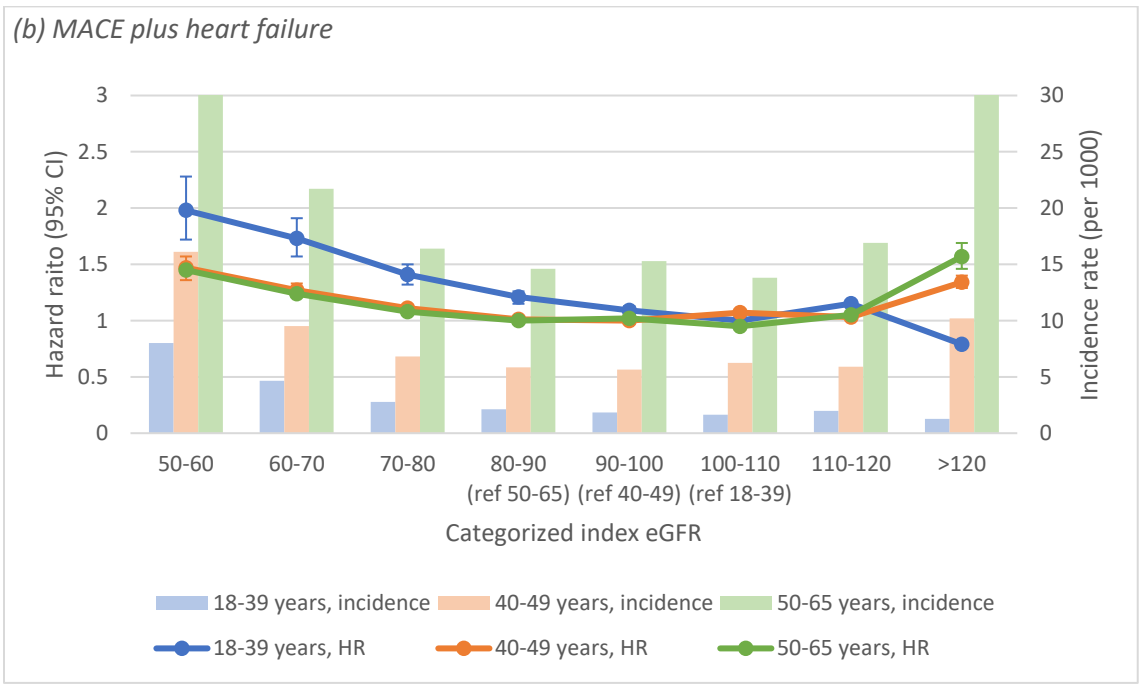


FIGURE 2: Adjusted* hazard ratios (95% CI) of (a) major cardiovascular adverse events (MACE; first of cardiovascular mortality, acute coronary syndrome, and ischemic stroke) and (b) MACE plus heart failure, by interacting categories of index eGFR (mL/min/1.73m^2) and albumin-creatinine ratio (ACR, mg/mmol), stratified by age group (reference: age-specific reference category and <3 mg/mmol)*****

(a) MACE

18-39 years

eGFR/ACR	<3	3-<30	≥30
50-60	*1.70*	1.83	2.94
60-70	1.77	2.00	2.54
70-80	1.56	2.01	2.36
80-90	*1.14*	1.89	2.63
90-100	1.06	1.41	2.62
100-110	**1.00**	1.47	2.11
110-120	1.18	1.67	2.22
>120	0.70	1.31	1.37

40-49 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.33	1.55	2.12
60-70	*1.09*	1.68	2.26
70-80	*0.93*	1.47	2.28
80-90	*0.96*	1.41	2.08
90-100	**1.00**	1.37	1.97
100-110	1.07	1.48	2.14
110-120	*1.00*	1.45	1.86
>120	*1.10*	1.68	1.8

50-65 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.30	1.52	1.91
60-70	1.14	1.67	2.02
70-80	1.04	1.49	2.05
80-90	**1.00**	1.44	2.02
90-100	*1.02*	1.42	1.93
100-110	0.93	1.32	1.74
110-120	*1.01*	1.32	1.65
>120	*1.22*	1.54	2.04

(b) MACE + heart failure

18-39 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.91	2.36	3.84
60-70	1.70	2.22	3.01
70-80	1.60	2.20	2.58
80-90	*1.16*	2.00	3.14
90-100	*1.04*	1.51	2.99
100-110	**1.00**	1.58	2.31
110-120	1.15	1.78	2.65
>120	0.72	1.38	1.59

40-49 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.33	1.89	2.40
60-70	*1.12*	1.86	2.52
70-80	*0.94*	1.55	2.62
80-90	*0.95*	1.54	2.47
90-100	**1.00**	1.44	2.20
100-110	1.07	1.53	2.40
110-120	*0.99*	1.51	2.00
>120	1.13	1.79	2.16

50-65 years

eGFR/ACR	<3	3-<30	≥30
50-60	1.32	1.67	2.29
60-70	1.17	1.78	2.24
70-80	1.05	1.61	2.3
80-90	**1.00**	1.54	2.21
90-100	*1.01*	1.49	2.18
100-110	0.93	1.39	1.98
110-120	*1.00*	1.43	1.95
>120	1.32	1.63	2.12

**adjusted for sex, hypertension (except for de novo hypertension outcome), diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

***reference categories by age: eGFR 100-<110 for 18-39 years, 90-<100 for 40-49 years, 100-<110 for 50-65 years*

****estimates that are not statistically significant are shown in italics*

TABLES (Chapter 4)

TABLE 1: Baseline population characteristics (total cohort and by age group)

Characteristic	Complete cohort (n = 8 703 871)		Baseline age					
			18-39 (n = 3 834 657)		40-49 (n = 2 046 151)		50-65 (n = 2 823 063)	
	N	%	N	%	N	%	N	%
Age, mean (SD; standard deviation)	41.3 (13.6)		28.2 (6.7)		44.6 (2.9)		56.8 (4.6)	
Follow-up duration in years, median [interquartile range, IQR]	9.2 [5.7-11.4]		7.6 [4.3-10.6]		10.0 [6.9-11.6]		10.4 [7.3-11.8]	
Total number of person-years of follow-up	73 011 249		28 362 503		18 460 491		26 188 254	
Sex								
Male	4 153 412	47.7%	1 762 599	46.0%	992 667	48.5%	1 398 146	49.5%
Female	4 550 459	52.3%	2 072 058	54.0%	1 053 484	51.5%	1 424 917	50.5%
Living status								
Urban	7 850 229	90.3%	3 544 001	92.6%	1 851 362	90.5%	2 454 866	87.0%
Rural	843 851	9.7%	283 521	7.4%	193 676	9.5%	366 654	13.0%
Income quintile								
1	1 706 093	19.7%	830 423	21.7%	380 983	18.7%	494 687	17.6%
2	1 725 605	19.9%	790 257	20.7%	390 361	19.1%	544 987	19.4%

3	1 740 457	20.1%	769 353	20.1%	412 271	20.2%	558 833	19.9%
4	1 788 103	20.6%	757 067	19.8%	438 743	21.5%	592 293	21.0%
5	1 715 331	19.8%	672 751	17.6%	418 501	20.5%	624 079	22.2%
Measures of kidney function								
Index eGFR in mL/min/1.73m^2, mean (SD)	104.2 (16.1)		113.6 (14.2)		101.8 (12.6)		93.1 (12.8)	
Number of repeated eGFR measurements beyond index, median [IQR]	4 [1-10]		2 [1-6]		5 [2-10]		9 [4-16]	
Time between index and first repeat eGFR measurement in days, median [IQR]	499 [257-966] (n = 7 499 611)		574 [283-1119] (n = 3 005 449)		533 [295-1002] (n = 1 841 692)		421 [212-780] (n = 2 652 470)	
First ACR from one year pre- to one year post-index in mg/mmol, median [IQR]	0.8 [0.4-2.0] (n = 746 948)		0.6 [0.4-1.6] (n = 205 631)		0.7 [0.4-1.9] (n = 179 108)		0.9 [0.5-2.4] (n = 362 209)	
Comorbidities in the past 5 years								
Hypertension	667 523	7.7%	79 741	2.1%	167 419	8.2%	420 363	14.9%
Diabetes mellitus	385 141	4.4%	57 987	1.5%	87 067	4.3%	240 087	8.5%
Heart failure	26 553	0.3%	833	0.02%	4 307	0.2%	21 413	0.8%
Acute coronary syndrome	95 054	1.1%	3 236	0.08%	16 204	0.8%	75 614	2.7%
Stroke	37 493	0.4%	3 976	0.1%	6 914	0.3%	26 603	0.9%

Atrial fibrillation	30 396	0.4%	2 583	0.07%	4 637	0.2%	23 176	0.8%
Obesity	30 711	0.4%	8 837	0.2%	6 837	0.3%	15 037	0.5%
Alcoholism	123 392	1.4%	68 622	1.8%	22 302	1.1%	32 468	1.2%
Smoking/nicotine dependence	5 500	0.06%	1 495	0.04%	1 221	0.06%	2 784	0.1%
Hypercholesterolemia	39 006	0.5%	1 364	0.04%	5 981	0.3%	31 661	1.1%
Hyperkalemia	2 794	0.03%	584	0.02%	484	0.02%	1 726	0.06%
Cancer	184 586	2.1%	24 706	0.7%	34 968	1.7%	124 912	4.4%
Chronic liver disease	40 221	0.5%	10 059	0.3%	10 198	0.5%	19 964	0.7%
Chronic lung disease	272 389	3.1%	108 915	2.8%	60 029	2.9%	103 445	3.7%
Healthcare utilization								
Primary care visit within 5 years of index, n (%)	5 869 045	67.4%	2 388 449	62.3%	1 444 732	70.6%	2 035 864	72.1%
Emergency department visit within 5 years of index, n (%)	4 574 033	52.6%	2 102 675	54.8%	1 021 136	49.9%	1 450 222	51.4%
Specialist visit within 5 years of index, n (%)	1 254 525	14.4%	358 824	9.4%	289 105	14.1%	606 596	21.5%
Nephrologists	101 631	1.2%	27 905	0.7%	22 218	1.1%	51 508	1.8%
Endocrinologists	408 905	4.7%	171 457	4.5%	89 823	4.4%	147 625	5.2%
Cardiologists	866 567	10.0%	183 440	4.8%	203 270	9.9%	479 857	17.0%
Specialist visit within 1 year post-index, n (%)	486 627	5.6%	141 708	3.7%	104 816	5.1%	240 103	8.5%
Nephrologists	24 137	0.3%	9 636	0.3%	5 327	0.3%	9 174	0.3%
Endocrinologists	132 752	1.5%	62 891	1.6%	27 844	1.4%	42 017	1.5%
Cardiologists	345 586	4.0%	72 793	1.9%	74 893	3.7%	197 900	7.0%

TABLE 2: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE; first of cardiovascular mortality, acute coronary syndrome, ischemic stroke) relative to age-specific eGFR reference ranges, by age-group

Index eGFR category	Age group		
	18-39	**40-49**	**50-65**
50-60	151/3528 6.11 1.71 (1.45, 2.01)	685/6227 13.7 1.34 (1.24, 1.44)	8834/39979 27.3 1.36 (1.33, 1.40)
60-70	361/14221 3.79 1.58 (1.42, 1.76)	1882/27455 8.47 1.21 (1.15, 1.27)	20670/127001 19.4 1.21 (1.19, 1.23)
70-80	1003/61781 2.37 1.31 (1.27, 1.40)	5328/102090 6.26 1.09 (1.06, 1.12)	40042/313400 14.9 1.07 (1.05, 1.08)
80-90 (reference for 50-65)	2560/193072 1.89 1.18 (1.13, 1.23)	11449/247809 5.40 0.99 (0.98, 1.02)	61359/526010 13.4 1.00 (reference)
90-100 (reference for 40-49)	5035/416431 1.68 1.09 (1.06, 1.13)	17740/385729 5.28 1.00 (reference)	91743/750625 13.9 1.02 (1.01, 1.03)
100-110 (reference for 18-39)	6788/619115 1.51 1.00 (reference)	32439/626279 5.82 1.07 (1.05, 1.08)	107231/971402 12.5 0.95 (0.94, 0.96)
110-120	14608/1061965	30290/621341	11677/91549

	1.79 1.15 (1.12, 1.19)	5.43 1.02 (1.00, 1.04)	15.0 1.03 (1.01, 1.05)
>120	11866/1464544 1.11 0.76 (0.74, 0.78)	2226/29221 8.92 1.27 (1.21, 1.32)	641/3097 30.1 1.44 (1.33, 1.55)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

TABLE 3: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for MAJOR ADVERSE CARDIOVASCULAR EVENTS PLUS HEART FAILURE (MACE+; first of cardiovascular mortality, acute coronary syndrome, ischemic stroke, and heart failure) relative to age-specific eGFR reference ranges, by age-group

Index eGFR category	Age group		
	18-39	**40-49**	**50-65**
50-60	196/3528 8.02 1.98 (1.72, 2.28)	791/6227 16.1 1.47 (1.36, 1.57)	10021/39979 31.6 1.45 (1.42, 1.48)
60-70	441/14221 4.65 1.73 (1.57, 1.91)	2104/27455 9.53 1.27 (1.22, 1.33)	22907/127001 21.7 1.24 (1.23, 1.26)
70-80	1170/61781 2.77 1.41 (1.32, 1.50)	5788/102090 6.82 1.11 (1.08, 1.14)	43822/313400 16.4 1.08 (1.06, 1.09)
80-90 (reference for 50-65)	2866/193072 2.12 1.21 (1.15, 1.26)	12365/247809 5.84 1.01 (0.99, 1.04)	66591/526010 14.6 1.00 (reference)
90-100 (reference for 40-49)	5522/416431 1.85 1.09 (1.06, 1.13)	18938/385729 5.65 1.00 (reference)	99928/750625 15.3 1.02 (1.01, 1.03)
100-110 (reference for 18-39)	7443/619115 1.65 1.00 (reference)	34721/626279 6.24 1.07 (1.05, 1.09)	117701/971402 13.8 0.95 (0.94, 0.96)
110-120	16014/1061965	32843/621341	13012/91549

	1.97 1.15 (1.12, 1.18)	5.90 1.03 (1.01, 1.05)	16.9 1.05 (1.03, 1.07)
>120	13644/1464544 1.28 0.79 (0.77, 0.82)	2526/29221 10.2 1.34 (1.29, 1.40)	755/3097 36.3 1.57 (1.46, 1.69)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

CHAPTER 5: DISCUSSION

Summary of thesis

In this population-based cohort of adults, the thesis examines the extent and clinical risk of modest declines in kidney function (eGFR) in younger adults (aged <40 years), using linked provincial health administrative datasets with age-specific eGFR referents. A brief background on the age controversy of measuring kidney function and detecting chronic kidney disease (CKD) in the population was presented in **Chapter 2**. Next, in **Chapter 3 (Manuscript I)**, we determined the extent of modest eGFR decline in the overall cohort and by age group. Moreover, age-specific associations of index eGFR with key adverse events (all-cause mortality, cardiovascular events, and kidney failure) were explored in both the overall cohort and important clinical subgroups based on prior comorbidities, kidney function patterns, and albuminuria. Finally, cardiovascular risk of modest eGFR declines were elucidated in **Chapter 4 (Manuscript II)**, using time to specific major cardiovascular outcomes (MACE: cardiovascular mortality, acute coronary syndrome, ischemic stroke) and heart failure. This discussion chapter will highlight the novel findings presented in the thesis, their implications for primary prevention and clinical management of CKD, and limitations of the two manuscripts. Future avenues of research are also described.

Novel findings

Generally, we found that risk of adverse outcomes was elevated in younger adults across the range of modest eGFR declines (eGFR values >60 but below age-expected values), compared to middle-aged and older adults. Moreover, age discrepancies in risk were prominent beginning at higher index eGFR categories, compared to older participants.

In **Manuscript I**, we found that modest eGFR declines was a common phenomenon in younger adults (17% with eGFR below age-specific referent of 100-110). Despite this, the youngest age group were least likely to receive repeated SCr measurements for further monitoring of kidney function, or referral to specialist, during follow-up. Modest eGFR declines were also associated with greater risk of key adverse events (composite of all-cause mortality, cardiovascular (CV) events, and kidney failure) relative to age-specific referents, with greater elevations in younger adults starting as early as eGFR<80 for most outcomes. Importantly, these findings persisted

after a series of sensitivity analyses, including: stratifying by important covariates (sex, diabetes, hypertension), examining interactions between index eGFR and ACR (a measure of albuminuria), comprehensively adjusting for additional comorbidities while excluding individuals with different underlying mechanisms of reduced eGFR (pregnancy, AKI, kidney stones, living kidney donation, past visits to nephrologist or urologist), and defining index eGFR using two repeated measures to account for acute changes. While there is still a possibility of misclassification and unmeasured confounding (such as from concurrent medication use not captured in our study), such risk elevations on the relative scale for mortality and CV events (and on both absolute and relative scales for kidney failure) illustrate the importance of accurate prognostication and discussions to initiate proactive prevention against CKD and its complications in younger adults.

Noting strong associations of index eGFR with CV outcomes in the first manuscript, **Manuscript II** sought to examine which specific CV events drive this association in younger adults. We compared associations between modest eGFR declines and major CV events (cardiovascular mortality, acute coronary syndrome, ischemic stroke, heart failure). Relative to age-specific referents, relative hazards were elevated in younger adults, with the most drastic age differences in risk elevation noted for stroke and heart failure. Despite various possible underlying mechanisms, these findings highlight modest eGFR decline as a potential CV risk factor worth frequent clinical monitoring in younger adults, similar to recent ACC/AHA recommendations.[28]

Implications for clinical practice

The current thesis presents evidence of elevated clinical risk with modest declines in kidney function in younger adults, emphasizing the importance of risk-based eGFR thresholds that vary with age in preventing CKD and its complications in the population. Previous evidence from smaller cohorts[17,39,44,45,49,53] has alluded to increased mortality and CV risk with eGFR declines earlier in life. Indeed, the largest collection of cohorts from CKD-PC (including 46 general and high-risk cohorts)[7,10,12] have indicated elevations in mortality risk beginning as early as eGFR<75 in younger adults (aged <40 years). However, these studies have used a high common eGFR referent for all ages, as well as less granular age and eGFR categories, clouding the validity of these conclusions. Moreover, these studies have focused on all-cause and CV

mortality to define clinical risk in clinically defined populations, rather than the occurrence of specific CV events and onset of kidney failure in the general population. Importantly, younger adults (aged <40 years) are least likely to either die or experience long-term comorbidities, compared to older adults. As such, larger, representative cohorts followed over longer time horizons are needed to adequately prognosticate clinical risk and aid population prevention in this under-appreciated age group.[1,9,20] With a retrospective cohort of over 8.9 million participants constructed from linked Ontario healthcare administrative datasets, we present the largest cohort to date examining kidney function decline and adverse outcomes by age.

The current definition[8] of new-onset CKD (eGFR<60 for atleast 3 months), as noted in this cohort, potentially ignores significant eGFR losses above this threshold in younger adults (while overestimating CKD burden in older individuals).[9] Indeed, reaching eGFR<60 could represent a loss of up to 50% of healthy kidney function before being recognized as abnormal. This translates to age-based disparities in routine monitoring and management of CKD and its complications in the population, including in our cohort and in other settings.[9,100–102] The lack of attention paid to such modest kidney function declines in adults aged <40 years, combined with the lack of guidance[9,13,20] regarding management of outcomes in this group, represents a missed opportunity for prevention of premature mortality and CV disease. Younger individuals, either due to low nephron endowment[40,117], albuminuria severity[53], or early exposure to nephrotoxic drugs or comorbidities[1,9,46], are at risk of developing progressive CKD over their lifetime. As existing therapies for CKD are hardly curative and better suited for slowing CKD progression[9], the results of this thesis can provide opportunities for preventing progressive kidney damage earlier in life.

Thus, adopting age-specific prognostic thresholds for CKD and related complications based on kidney function below age-expected values can help individualize care and adopt early interventions. Such interventions can include lifestyle changes (such as dietary modifications and exercise[118]) or timely initiation of therapeutics to address CKD and its complications.[28] In turn, this can substantiate future investigations into whether established interventions (such as early prescription of statins based on long-term CV risk[22]) are similarly efficacious or effective against adverse outcomes across age groups.[9,10] Finally, the evidence presented in the thesis can prompt discussions about such risks with patients presenting with modestly declined kidney function

(eGFR too low for their age) and/or early-stage kidney disease would be beneficial, especially when faced with additional comorbidities such as diabetes and hypertension. While it can be initially distressing, raising awareness of these risks can enable participation in screening for other risk factors of premature mortality and CV disease, foster further engagement in healthcare services, and initiate preventive measures well before the occurrence of adverse events.[9]

Limitations

The present thesis, across both manuscripts, has some limitations which warrant discussion. Firstly, there is a possibility of misclassification resulting from relying on ICD-10 diagnostic codes for some comorbidities, either because they had not been validated yet (such as hypercholesterolemia) or were evaluated based on self-report (such as alcoholism and nicotine dependence). Despite this, data on outcomes and other comorbidity data (such as diabetes and hypertension, which were important stratifiers) were objectively identified using previously validated ICD-10 codes. Secondly, unmeasured confounding and alternative explanations behind observed associations, most notably medication use (data only available for those aged >65 years), could be further explored. However, our large cohort size and consistency of results across various sensitivity analyses accounting for various underlying differences in index eGFR and with existing literature strengthen our results. Third, while there was missing data for income and rurality (both important determinants of health), this was negligible (<1%) and there was no missing exposure or outcome data. Any missingness was deemed to have occurred at random and these variables were multiply imputed using chained equations. Fourth, only part of the cohort had two or more repeated eGFR measures and/or an ACR measure close to index. While these additional measures would have provided a fuller picture of chronic kidney dysfunction, there is a potential for bias towards individuals who need to be repeatedly examined due to other comorbidities.[35] However, single outpatient eGFR measures have been previously validated as reasonable measures of stable kidney function in outpatient populations.[33,74] Fifth, our findings did not provide insight into the mechanism of reductions in eGFR, nor the cause of kidney decline and specific adverse outcomes (such as the cause of death, or differentiating between the subtypes of heart failure with preserved or reduced ejection fraction). However, we did conduct sensitivity analyses excluding individuals with non-progressive changes in kidney function prior to index, such as AKI, kidney donation, and pregnancy, while also adjusting for important

comorbidities which can influence kidney function. Finally, we estimated eGFR using the 2021 CKD-EPI race-free equation based on serum creatinine markers. Despite being the widely accepted equation for estimating kidney function[33], there have been concerns regarding its measurement properties, such as biased estimation in by race[119] and differing accuracy between clinical biomarkers (such as cystatin C).[34,50]

Future research avenues

The research presented as part of this thesis opens up several avenues of research within this cohort and for early prevention of CKD and its complications in general. Firstly, we used the prognostic approach in this thesis to examine associations of categorized eGFR below age-expected values with time to adverse outcomes. In a future study, we aim to examine differences in eGFR distributions, to determine which eGFR percentiles – and in turn, which eGFR values – are associated with significant elevations in clinical risk by continuous age. This is in line with recent calls for a distribution-based approach[9] to identifying risk-based eGFR thresholds, to corroborate the findings of this thesis using continuous age and eGFR values in non-linear models.

Secondly, concerns have been raised about the accuracy and measurement properties of the CKD-EPI race-free equation for estimating eGFR, as it has been shown to underestimate measured kidney function in Black individuals and overestimate it in non-Black individuals.[33] While the development of this race-free equation was done as a step in reducing implicit biases in diagnosing and managing CKD in racialized groups[119], its impacts on observed associations in our cohort – as well as how they differ between age groups – warrants further examination. Along this vein, there have been concerns about the measurement properties of using serum creatinine (SCr) over other biomarkers, such as cystatin C (cysC), in accurately estimating kidney function over the age spectrum. For instance, while SCr is dependent on an individual's muscle mass and can underestimate eGFR in older groups, cysC has been shown low variance and high consistency between similarly-aged individuals with different muscular compositions.[34] However, cysC has its own confounders, such as overestimating kidney function in those with chronic inflammation, making it a poorer prognostic marker in some cases.[50] While this thesis does not focus on comparing relative measurement properties of these biomarkers, comparing

the impact of different eGFR-estimating equations (by race and biomarker) on observed age-specific associations would be worthwhile.

While this thesis presents an epidemiological signal for baseline kidney function below age-expected values, we did not yet examine how changes in kidney function might influence clinical risk by age. Thus, a third major research avenue in this cohort would be finding a clinically meaningful percent change in kidney function between repeated eGFR measurements (i.e., associated with increased risk of patient-important outcomes), adjusting for age-specific baseline kidney function. Understanding decreases (and increases) in kidney function at various time points could aid in characterizing clinical risk in younger adults over meaningful timeframes, while also suggesting potential thresholds of change to trigger clinical monitoring for adverse outcomes.[10,12]

Finally, other areas of investigation include evaluating age-based differences in effectiveness of pharmacological and non-pharmacological therapies on CKD progression and time to adverse events (either prospectively or via post-hoc analyses of key trials), confirming of observed associations with modest eGFR declines in other population- and clinic-based cohorts, and potentially examining the impacts of kidney hyperfiltration (i.e., abnormally high eGFR) on adverse outcomes in younger adults.

Conclusions

In a population-based cohort of 8.9 million adults, we present evidence for a consistently elevated risk of adverse events (all-cause mortality, most cardiovascular events, and kidney failure) with modest declines in eGFR below age-expected values in younger adults (aged <40 years), compared to middle-aged and older adults (50-65 years). These elevations became prominent at eGFR levels as high as eGFR<80 for most outcomes. This age disparity in clinical risk persisted after accounting for various underlying differences in kidney function, incorporating albuminuria measures, and adjusting for various index comorbidities. These findings emphasize the need for age-specific, risk-based thresholds for identifying CKD in younger adults and highlights an opportunity for preventing premature mortality and CV risk due to modest kidney function declines in the population.

REFERENCES (Chapters 1-5)

1. Delanaye P, Glassock RJ, Pottel H, Rule AD. An Age-Calibrated Definition of Chronic Kidney Disease: Rationale and Benefits. *Clin Biochem Rev*. 2016;37(1):17-26.

2. Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. *The Lancet*. 2013;382(9888):260-272. doi:10.1016/S0140-6736(13)60687-X

3. Eckardt KU, Coresh J, Devuyst O, et al. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet Lond Engl*. 2013;382(9887):158-169. doi:10.1016/S0140-6736(13)60439-0

4. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care*. 2004;27(5):1047-1053. doi:10.2337/diacare.27.5.1047

5. Mills KT, Bundy JD, Kelly TN, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies From 90 Countries. *Circulation*. 2016;134(6):441-450. doi:10.1161/CIRCULATIONAHA.115.018912

6. Padwal RS, Bienek A, McAlister FA, Campbell NRC, Outcomes Research Task Force of the Canadian Hypertension Education Program. Epidemiology of Hypertension in Canada: An Update. *Can J Cardiol*. 2016;32(5):687-694. doi:10.1016/j.cjca.2015.07.734

7. Matsushita K, van der Velde M, Astor BC, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet Lond Engl*. 2010;375(9731):2073-2081. doi:10.1016/S0140-6736(10)60674-5

8. Levin A, Stevens PE, Bilous RW, et al. Kidney disease: Improving global outcomes (KDIGO) CKD work group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl*. 2013;3(1):1-150. doi:10.1038/kisup.2012.73

9. Delanaye P, Jager KJ, Bökenkamp A, et al. CKD: A Call for an Age-Adapted Definition. *J Am Soc Nephrol*. 2019;30(10):1785-1805. doi:10.1681/ASN.2019030238

10. Hallan SI, Matsushita K, Sang Y, et al. Age and Association of Kidney Measures With Mortality and End-stage Renal Disease. *JAMA*. 2012;308(22):2349. doi:10.1001/jama.2012.16817

11. Denic A, Glassock RJ, Rule AD. Structural and Functional Changes With the Aging Kidney. *Adv Chronic Kidney Dis*. 2016;23(1):19-28. doi:10.1053/j.ackd.2015.08.004

12. Coresh J, Turin TC, Matsushita K, et al. Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality. *JAMA*. 2014;311(24):2518. doi:10.1001/jama.2014.6634

13. Glassock RJ. Con: Thresholds to define chronic kidney disease should not be age dependent. *Nephrol Dial Transplant*. 2014;29(4):774-779. doi:10.1093/ndt/gft306

14. Coresh J, Gansevoort RT, Levin A, Jadoul M. Current CKD Definition Takes into Account Both Relative and Absolute Risk. *J Am Soc Nephrol*. 2020;31(2):447. doi:10.1681/ASN.2019101049

15. Eriksen BO, Palsson R, Ebert N, et al. GFR in Healthy Aging: an Individual Participant Data Meta-Analysis of Iohexol Clearance in European Population-Based Cohorts. *J Am Soc Nephrol*. 2020;31(7):1602-1615. doi:10.1681/ASN.2020020151

16. Pottel H, Hoste L, Yayo E, Delanaye P. Glomerular Filtration Rate in Healthy Living Potential Kidney Donors: A Meta-Analysis Supporting the Construction of the Full Age Spectrum Equation. *Nephron*. 2017;135(2):105-119. doi:10.1159/000450893

17. Bansal N, Lin F, Vittinghoff E, et al. Estimated GFR and Subsequent Higher Left Ventricular Mass in Young and Middle-Aged Adults With Normal Kidney Function: The Coronary Artery Risk Development in Young Adults (CARDIA) Study. *Am J Kidney Dis Off J Natl Kidney Found*. 2016;67(2):227-234. doi:10.1053/j.ajkd.2015.06.024

18. Bansal N, Vittinghoff E, Peralta CA, et al. Estimated Kidney Function Based on Serum Cystatin C and Risk of Subsequent Coronary Artery Calcium in Young and Middle-aged Adults With Preserved Kidney Function: Results From the CARDIA Study. *Am J Epidemiol*. 2013;178(3):410-417. doi:10.1093/aje/kws581

19. Glassock RJ, Warnock DG, Delanaye P. The global burden of chronic kidney disease: estimates, variability and pitfalls. *Nat Rev Nephrol*. 2017;13(2):104-114. doi:10.1038/nrneph.2016.163

20. Denic A, Glassock RJ, Rule AD. The Kidney in Normal Aging: A Comparison with Chronic Kidney Disease. *Clin J Am Soc Nephrol*. 2022;17(1):137-139. doi:10.2215/CJN.10580821

21. Levey AS, Stevens LA, Coresh J. Conceptual model of CKD: applications and implications. *Am J Kidney Dis Off J Natl Kidney Found*. 2009;53(3 Suppl 3):S4-16. doi:10.1053/j.ajkd.2008.07.048

22. Herzog CA, Asinger RW, Berger AK, et al. Cardiovascular disease in chronic kidney disease. A clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int*. 2011;80(6):572-586. doi:10.1038/ki.2011.223

23. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Lond Engl*. 2016;388(10053):1603-1658. doi:10.1016/S0140-6736(16)31460-X

24. Novak M, Mucsi I, Rhee CM, et al. Increased Risk of Incident Chronic Kidney Disease, Cardiovascular Disease, and Mortality in Patients With Diabetes With Comorbid Depression. *Diabetes Care*. 2016;39(11):1940-1947. doi:10.2337/dc16-0048

25. Manns B, Hemmelgarn B, Tonelli M, et al. The Cost of Care for People With Chronic Kidney Disease. *Can J Kidney Health Dis*. 2019;6:2054358119835521. doi:10.1177/2054358119835521

26. Sundström J, Bodegard J, Bollmann A, et al. Prevalence, outcomes, and cost of chronic kidney disease in a contemporary population of 2·4 million patients from 11 countries: The CaReMe CKD study. *Lancet Reg Health - Eur*. 2022;20:100438. doi:10.1016/j.lanepe.2022.100438

27. Nichols GA, Ustyugova A, Déruaz-Luyet A, O'Keeffe-Rosetti M, Brodovicz KG. Health Care Costs by Type of Expenditure across eGFR Stages among Patients with and without Diabetes, Cardiovascular Disease, and Heart Failure. *J Am Soc Nephrol*. 2020;31(7):1594. doi:10.1681/ASN.2019121308

28. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019;140(11):e596-e646. doi:10.1161/CIR.0000000000000678

29. Bjornstad P, Karger AB, Maahs DM. Measured GFR in Routine Clinical Practice – The Promise of Dried Blood Spots. *Adv Chronic Kidney Dis*. 2018;25(1):76-83. doi:10.1053/j.ackd.2017.09.003

30. Murray AW, Barnfield MC, Waller ML, Telford T, Peters AM. Assessment of Glomerular Filtration Rate Measurement with Plasma Sampling: A Technical Review. *J Nucl Med Technol*. 2013;41(2):67-75. doi:10.2967/jnmt.113.121004

31. Levey AS, Inker LA. GFR as the "Gold Standard": Estimated, Measured, and True. *Am J Kidney Dis Off J Natl Kidney Found*. 2016;67(1):9-12. doi:10.1053/j.ajkd.2015.09.014

32. Powers TA, Stone WJ, Grove RB, et al. Radionuclide measurement of differential glomerular filtration rate. *Invest Radiol*. 1981;16(1):59-64. doi:10.1097/00004424-198101000-00011

33. Inker LA, Eneanya ND, Coresh J, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *N Engl J Med*. 2021;385(19):1737-1749. doi:10.1056/NEJMoa2102953

34. Shlipak MG, Matsushita K, Ärnlöv J, et al. Cystatin C versus Creatinine in Determining Risk Based on Kidney Function. *N Engl J Med*. 2013;369(10):932-943. doi:10.1056/NEJMoa1214234

35. Shafi T, Zhu X, Lirette ST, et al. Quantifying Individual-Level Inaccuracy in Glomerular Filtration Rate Estimation. *Ann Intern Med*. 2022;175(8):1073-1082. doi:10.7326/M22-0610

36. Fu EL, Coresh J, Grams ME, et al. Removing race from the CKD-EPI equation and its impact on prognosis in a predominantly White European population. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2023;38(1):119-128. doi:10.1093/ndt/gfac197

37. Chronic Kidney Disease Prognosis Consortium. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet*. 2010;375:9. doi:10.1016/S0140-6736(10)60674-5

38. Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int*. 2011;80(1):17-28. doi:10.1038/ki.2010.483

39. Liu P, Ravani P. Age and the eGFR-dependent risk for adverse clinical outcomes. *Clin Kidney J*. Published online September 17, 2022:sfac213. doi:10.1093/ckj/sfac213

40. Denic A, Lieske JC, Chakkera HA, et al. The Substantial Loss of Nephrons in Healthy Human Kidneys with Aging. *J Am Soc Nephrol JASN*. 2017;28(1):313-320. doi:10.1681/ASN.2016020154

41. Hommos MS, Zeng C, Liu Z, et al. Global glomerulosclerosis with nephrotic syndrome; the clinical importance of age adjustment. *Kidney Int*. 2018;93(5):1175-1182. doi:10.1016/j.kint.2017.09.028

42. Al-Wahsh H, Tangri N, Quinn R, et al. Accounting for the Competing Risk of Death to Predict Kidney Failure in Adults With Stage 4 Chronic Kidney Disease. *JAMA Netw Open*. 2021;4(5):e219225-e219225. doi:10.1001/jamanetworkopen.2021.9225

43. O'Hare AM, Choi AI, Bertenthal D, et al. Age Affects Outcomes in Chronic Kidney Disease. *J Am Soc Nephrol*. 2007;18(10):2758-2765. doi:10.1681/ASN.2007040422

44. Manjunath G, Tighiouart H, Ibrahim H, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. *J Am Coll Cardiol*. 2003;41(1):47-55. doi:10.1016/S0735-1097(02)02663-3

45. Brantsma AH, Bakker SJL, Hillege HL, et al. Cardiovascular and renal outcome in subjects with K/DOQI stage 1-3 chronic kidney disease: the importance of urinary albumin excretion. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2008;23(12):3851-3858. doi:10.1093/ndt/gfn356

46. Benghanem Gharbi M, Elseviers M, Zamd M, et al. Chronic kidney disease, hypertension, diabetes, and obesity in the adult population of Morocco: how to avoid "over"- and

"under"-diagnosis of CKD. *Kidney Int*. 2016;89(6):1363-1371. doi:10.1016/j.kint.2016.02.019

47. Delanaye P, Glassock RJ, De Broe ME. Epidemiology of chronic kidney disease: think (at least) twice! *Clin Kidney J*. 2017;10(3):370-374. doi:10.1093/ckj/sfw154

48. De Broe ME, Gharbi MB, Zamd M, Elseviers M. Why overestimate or underestimate chronic kidney disease when correct estimation is possible? *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2017;32(suppl_2):ii136-ii141. doi:10.1093/ndt/gfw267

49. Choi Y, Jacobs DR, Shroff GR, Kramer H, Chang AR, Duprez DA. Progression of Chronic Kidney Disease Risk Categories and Risk of Cardiovascular Disease and Total Mortality: Coronary Artery Risk Development in Young Adults Cohort. *J Am Heart Assoc*. 2022;11(21):e026685. doi:10.1161/JAHA.122.026685

50. Meeusen JW, Rule AD, Voskoboev N, Baumann NA, Lieske JC. Cystatin C and Creatinine-based eGFR equation performance depends on patient characteristics. *Clin Chem*. 2015;61(10):1265-1272. doi:10.1373/clinchem.2015.243030

51. Melsom T, Norvik JV, Enoksen IT, et al. Sex Differences in Age-Related Loss of Kidney Function. *J Am Soc Nephrol*. 2022;33(10):1891. doi:10.1681/ASN.2022030323

52. Tangri N, Stevens LA, Griffith J, et al. A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure. *JAMA*. 2011;305(15):1553-1559. doi:10.1001/jama.2011.451

53. Gansevoort RT, Matsushita K, van der Velde M, et al. Lower estimated GFR and higher albuminuria are associated with adverse kidney outcomes. A collaborative meta-analysis of general and high-risk population cohorts. *Kidney Int*. 2011;80(1):93-104. doi:10.1038/ki.2010.531

54. Abitbol CL, DeFreitas MJ, Strauss J. Assessment of kidney function in preterm infants: lifelong implications. *Pediatr Nephrol Berl Ger*. 2016;31(12):2213-2222. doi:10.1007/s00467-016-3320-x

55. Pottel H, Hoste L, Delanaye P. Abnormal glomerular filtration rate in children, adolescents and young adults starts below 75 mL/min/1.73 m2. *Pediatr Nephrol*. 2015;30(5):821-828. doi:10.1007/s00467-014-3002-5

56. Denic A, Mathew J, Lerman LO, et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. *N Engl J Med*. 2017;376(24):2349-2357. doi:10.1056/NEJMoa1614329

57. Keller G, Zimmer G, Mall G, Ritz E, Amann K. Nephron Number in Patients with Primary Hypertension. *N Engl J Med*. 2003;348(2):101-108. doi:10.1056/NEJMoa020549

58. Ingelfinger JR. Disparities in renal endowment: causes and consequences. *Adv Chronic Kidney Dis*. 2008;15(2):107-114. doi:10.1053/j.ackd.2008.01.003

59. DeFreitas MJ, Katsoufis CP, Benny M, et al. Educational Review: The Impact of Perinatal Oxidative Stress on the Developing Kidney. *Front Pediatr*. 2022;10:853722. doi:10.3389/fped.2022.853722

60. Ellis MJ, Parikh CR, Inrig JK, Kambay M, Patel UD. Chronic Kidney Disease After Hematopoietic Cell Transplantation: a Systematic Review. *Am J Transplant Off J Am Soc Transplant Am Soc Transpl Surg*. 2008;8(11):2378-2390. doi:10.1111/j.1600-6143.2008.02408.x

61. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease. *Circulation*. 2021;143(11):1157-1172. doi:10.1161/CIRCULATIONAHA.120.050686

62. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):1269-1324. doi:10.1161/HYP.0000000000000066

63. Holden RM, Mustafa RA, Alexander RT, et al. Canadian Society of Nephrology Commentary on the Kidney Disease Improving Global Outcomes 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder. *Can J Kidney Health Dis*. 2020;7:205435812094427. doi:10.1177/2054358120944271

64. Adler J, Taneva E, Ansorge T, Mertens PR. CKD prevalence based on real-world data: continuous age-dependent lower reference limits of eGFR with CKD–EPI, FAS and EKFC algorithms. *Int Urol Nephrol*. 2022;54(11):2929-2937. doi:10.1007/s11255-022-03210-8

65. Bikbov B, Purcell CA, Levey AS, et al. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. *The lancet*. 2020;395(10225):709-733.

66. Xie Y, Bowe B, Mokdad AH, et al. Analysis of the Global Burden of Disease study highlights the global, regional, and national trends of chronic kidney disease epidemiology from 1990 to 2016. *Kidney Int*. 2018;94(3):567-581. doi:10.1016/j.kint.2018.04.011

67. Warnock DG, Delanaye P, Glassock RJ. Risks for All-Cause Mortality: Stratified by Age, Estimated Glomerular Filtration Rate and Albuminuria. *Nephron*. 2017;136(4):292-297. doi:10.1159/000455197

68. van der Burgh AC, Rizopoulos D, Ikram MA, Hoorn EJ, Chaker L. Determinants of the Evolution of Kidney Function With Age. *Kidney Int Rep*. 2021;6(12):3054-3063. doi:10.1016/j.ekir.2021.10.006

69. Astor BC, Hallan SI, Miller ER 3rd, Yeung E, Coresh J. Glomerular filtration rate, albuminuria, and risk of cardiovascular and all-cause mortality in the US population. *Am J Epidemiol*. 2008;167(10):1226-1234. doi:10.1093/aje/kwn033

70. Hallan S, Astor B, Romundstad S, Aasarød K, Kvenild K, Coresh J. Association of Kidney Function and Albuminuria With Cardiovascular Mortality in Older vs Younger Individuals: The HUNT II Study. *Arch Intern Med*. 2007;167(22):2490-2496. doi:10.1001/archinte.167.22.2490

71. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C yuan. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *N Engl J Med*. 2004;351(13):1296-1305. doi:10.1056/NEJMoa041031

72. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLOS Med*. 2015;12(10):e1001885. doi:10.1371/journal.pmed.1001885

73. Gao M, Vilayur E, Ferreira D, Nanra R, Hawkins J. Estimating the glomerular filtration rate in pregnancy: The evaluation of the Nanra and CKD-EPI serum creatinine-based equations. *Obstet Med*. 2021;14(1):31-34. doi:10.1177/1753495X20904177

74. Garg AX, Mamdani M, Juurlink DN, van Walraven C. Identifying Individuals with a Reduced GFR Using Ambulatory Laboratory Database Surveillance. *J Am Soc Nephrol*. 2005;16(5):1433. doi:10.1681/ASN.2004080697

75. Hirst JA, Montes MDV, Taylor CJ, et al. Impact of a single eGFR and eGFR-estimating equation on chronic kidney disease reclassification: a cohort study in primary care. *Br J Gen Pract J R Coll Gen Pract*. 2018;68(673):e524-e530. doi:10.3399/bjgp18X697937

76. Grewal GS, Blake GM. Reference data for 51Cr-EDTA measurements of the glomerular filtration rate derived from live kidney donors. *Nucl Med Commun*. 2005;26(1):61-65. doi:10.1097/00006231-200501000-00010

77. Rule AD, Gussak HM, Pond GR, et al. Measured and estimated GFR in healthy potential kidney donors. *Am J Kidney Dis Off J Natl Kidney Found*. 2004;43(1):112-119. doi:10.1053/j.ajkd.2003.09.026

78. Hamilton D, Riley P, Miola U, Mousa D, Popovich W, al Khader A. Total plasma clearance of 51Cr-EDTA: variation with age and sex in normal adults. *Nucl Med Commun*. 2000;21(2):187-192. doi:10.1097/00006231-200002000-00011

79. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J Clin Invest*. 1950;29(5):496-507. doi:10.1172/JCI102286

80. Hallan S, Astor B, Lydersen S. Estimating glomerular filtration rate in the general population: the second Health Survey of Nord-Trondelag (HUNT II). *Nephrol Dial Transplant*. 2006;21(6):1525-1533. doi:10.1093/ndt/gfl035

81. Fleet JL, Dixon SN, Shariff SZ, et al. Detecting chronic kidney disease in population-based administrative databases using an algorithm of hospital encounter and physician claim codes. *BMC Nephrol*. 2013;14(1):81. doi:10.1186/1471-2369-14-81

82. Liu L, Reeder B, Shuaib A, Mazagri R. Validity of Stroke Diagnosis on Hospital Discharge Records in Saskatchewan, Canada: Implications for Stroke Surveillance. *Cerebrovasc Dis*. 1999;9(4):224-230. doi:10.1159/000015960

83. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *Am Heart J*. 2002;144(2):290-296. doi:10.1067/mhj.2002.123839

84. Kapral MK, Wang H, Mamdani M, Tu JV. Effect of Socioeconomic Status on Treatment and Mortality After Stroke. *Stroke*. 2002;33(1):268-275. doi:10.1161/hs0102.101169

85. Alter DA, Iron K, Austin PC, Naylor CD, for the SESAMI Study Group. Socioeconomic Status, Service Patterns, and Perceptions of Care Among Survivors of Acute Myocardial Infarction in Canada. *JAMA*. 2004;291(9):1100-1107. doi:10.1001/jama.291.9.1100

86. Alter DA, Naylor CD, Austin P, Tu JV. Effects of Socioeconomic Status on Access to Invasive Cardiac Procedures and on Mortality after Acute Myocardial Infarction. *N Engl J Med*. 1999;341(18):1359-1367. doi:10.1056/NEJM199910283411806

87. Sholzberg M, Gomes T, Juurlink DN, Yao Z, Mamdani MM, Laupacis A. The Influence of Socioeconomic Status on Selection of Anticoagulation for Atrial Fibrillation. *PLOS ONE*. 2016;11(2):e0149142. doi:10.1371/journal.pone.0149142

88. Quan H, Khan N, Hemmelgarn BR, et al. Validation of a Case Definition to Define Hypertension Using Administrative Data. *Hypertension*. 2009;54(6):1423-1428. doi:10.1161/HYPERTENSIONAHA.109.139279

89. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25(3):512-516. doi:10.2337/diacare.25.3.512

90. Lipscombe LL, Hwee J, Webster L, Shah BR, Booth GL, Tu K. Identifying diabetes cases from administrative data: a population-based validation study. *BMC Health Serv Res*. 2018;18(1):316. doi:10.1186/s12913-018-3148-0

91. Clemens KK, Reid JN, Shariff SZ, Welk B. Validity of Hospital Codes for Obesity in Ontario, Canada. *Can J Diabetes*. 2021;45(3):243-248.e4. doi:10.1016/j.jcjd.2020.08.106

92. Sriperumbuduri S, McArthur E, Hundemer GL, et al. Initial and Recurrent Hyperkalemia Events in Patients With CKD in Older Adults: A Population-Based Cohort Study. *Can J Kidney Health Dis*. 2021;8:20543581211017410. doi:10.1177/20543581211017408

93. Philip G, Djerboua M, Carlone D, Flemming JA. Validation of a hierarchical algorithm to define chronic liver disease and cirrhosis etiology in administrative healthcare data. *PLOS ONE*. 2020;15(2):e0229218. doi:10.1371/journal.pone.0229218

94. Lee TM, Tu K, Ivers NM, Barnsley J, Gershon AS. Measuring chronic obstructive pulmonary disease (COPD) quality indicators using primary care electronic medical records (EMRs) in Ontario, Canada. *Can J Respir Crit Care Sleep Med*. 2022;6(3):169-183. doi:10.1080/24745332.2021.1913079

95. van Dijk PC, Jager KJ, Zwinderman AH, Zoccali C, Dekker FW. The analysis of survival data in nephrology: basic concepts and methods of Cox regression. *Kidney Int*. 2008;74(6):705-709. doi:10.1038/ki.2008.294

96. Kuitunen I, Ponkilainen VT, Uimonen MM, Eskelinen A, Reito A. Testing the proportional hazards assumption in cox regression and dealing with possible non-proportionality in total joint arthroplasty research: methodological perspectives and review. *BMC Musculoskelet Disord*. 2021;22(1):489. doi:10.1186/s12891-021-04379-2

97. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med*. 2017;36(27):4391-4400. doi:10.1002/sim.7501

98. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8(5):551-561. doi:10.1002/sim.4780080504

99. Ricardo AC, Yang W, Sha D, et al. Sex-Related Disparities in CKD Progression. *J Am Soc Nephrol*. 2019;30(1):137. doi:10.1681/ASN.2018030296

100. Jonsson AJ, Lund SH, Eriksen BO, Palsson R, Indridason OS. The prevalence of chronic kidney disease in Iceland according to KDIGO criteria and age-adapted estimated glomerular filtration rate thresholds. *Kidney Int*. 2020;98(5):1286-1295. doi:10.1016/j.kint.2020.06.017

101. Waas T, Schulz A, Lotz J, et al. Distribution of estimated glomerular filtration rate and determinants of its age dependent loss in a German population-based study. *Sci Rep*. 2021;11(1):10165. doi:10.1038/s41598-021-89442-7

102. Ren Q, Zhou Y, Chen G, Li X, Ye W. Age-adapted definition of chronic kidney disease based on Chronic Kidney Disease Epidemiology Collaboration and full age spectrum equation. *Kidney Int*. 2020;98(5):1350-1352. doi:10.1016/j.kint.2020.08.014

103. Hemmelgarn BR, Pannu N, Ahmed SB, et al. Determining the research priorities for patients with chronic kidney disease not on dialysis. *Nephrol Dial Transplant Off Publ Eur Dial Transpl Assoc - Eur Ren Assoc*. 2017;32(5):847-854. doi:10.1093/ndt/gfw065

104. Sarnak MJ, Amann K, Bangalore S, et al. Chronic Kidney Disease and Coronary Artery Disease: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2019;74(14):1823-1838. doi:https://doi.org/10.1016/j.jacc.2019.08.1017

105. Maynard SE, Thadhani R. Pregnancy and the Kidney. *J Am Soc Nephrol*. 2009;20(1):14-22. doi:10.1681/ASN.2008050493

106. Saunders-Hastings P, Heong SW, Srichaikul J, et al. Acute myocardial infarction: Development and application of an ICD-10-CM-based algorithm to a large U.S. healthcare claims-based database. *PLOS ONE*. 2021;16(7):e0253580. doi:10.1371/journal.pone.0253580

107. Davidson J, Banerjee A, Muzambi R, Smeeth L, Warren-Gash C. Validity of Acute Cardiovascular Outcome Diagnoses Recorded in European Electronic Health Records: A Systematic Review. *Clin Epidemiol*. 2020;12:1095-1111. doi:10.2147/CLEP.S265619

108. Pocobelli G, Ichikawa L, Yu O, et al. Validation of international classification of diseases, tenth revision, clinical modification diagnosis codes for heart failure subtypes. *Pharmacoepidemiol Drug Saf*. 2022;31(9):992-997. doi:10.1002/pds.5489

109. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of Heart Failure Diagnoses in Administrative Databases: A Systematic Review and Meta-Analysis. *PLoS ONE*. 2014;9(8):e104519. doi:10.1371/journal.pone.0104519

110. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med*. 2011;30(4):377-399. doi:10.1002/sim.4067

111. Glassock RJ, Pecoits-Filho R, Barberato SH. Left ventricular mass in chronic kidney disease and ESRD. *Clin J Am Soc Nephrol CJASN*. 2009;4 Suppl 1:S79-91. doi:10.2215/CJN.04860709

112. Griffin TP, O'Shea PM, Smyth A, et al. Burden of chronic kidney disease and rapid decline in renal function among adults attending a hospital-based diabetes center in Northern Europe. *BMJ Open Diabetes Res Care*. 2021;9(1):e002125. doi:10.1136/bmjdrc-2021-002125

113. Viazzi F, Leoncini G, Conti N, et al. Combined effect of albuminuria and estimated glomerular filtration rate on cardiovascular events and all-cause mortality in uncomplicated hypertensive patients. *J Hypertens*. 2010;28(4):848-855. doi:10.1097/HJH.0b013e328336ed09

114. Honigberg MC, Zekavat SM, Pirruccello JP, Natarajan P, Vaduganathan M. Cardiovascular and Kidney Outcomes Across the Glycemic Spectrum. *J Am Coll Cardiol*. 2021;78(5):453-464. doi:10.1016/j.jacc.2021.05.004

115. Wilkinson TJ, Miksza J, Yates T, et al. Association of sarcopenia with mortality and end-stage renal disease in those with chronic kidney disease: a UK Biobank study. *J Cachexia Sarcopenia Muscle*. 2021;12(3):586-598. doi:10.1002/jcsm.12705

116. Bullen AL, Katz R, Jotwani V, et al. Biomarkers of Kidney Tubule Health, CKD Progression, and Acute Kidney Injury in SPRINT (Systolic Blood Pressure Intervention

Trial) Participants. *Am J Kidney Dis*. 2021;78(3):361-368.e1. doi:10.1053/j.ajkd.2021.01.021

117. Denic A, Mathew J, Lerman LO, et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. *N Engl J Med*. 2017;376(24):2349-2357. doi:10.1056/NEJMoa1614329

118. Joshi S, Kalantar-Zadeh K, Chauveau P, Carrero JJ. Risks and Benefits of Different Dietary Patterns in CKD. *Am J Kidney Dis*. Published online January 20, 2023. doi:10.1053/j.ajkd.2022.08.013

119. Vyas DA, Eisenstein LG, Jones DS. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. *N Engl J Med*. 2020;383(9):874-882. doi:10.1056/NEJMms2004740

THESIS SUPPLEMENTARY MATERIAL

SUPPLEMENTARY MATERIAL FOR CHAPTER 3

ADDITIONAL METHODOLOGICAL DETAILS

Study Design and Setting

ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data for health system evaluation and improvement. Ontario is home to approximately 14 million residents with universal access to healthcare services through the Ontario Health Insurance Plan (OHIP). The use of the data in this project is authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a research ethics board.

Data Sources

Diagnoses of comorbidities and outcomes based on International Classification of Diseases (ICD)-10 codes were determined using the Discharge Abstract Database (CIHI-DAD) for hospital admissions and National Ambulatory Care Reporting System (NACRS) for patient visits to ambulatory care centers in Ontario. OHIP physician service claims were used to determine frequency of family physician and specialist visits. The Canadian Organ Replacement Registry (CORR) was used to identify patients on either in-home or in-center hemodialysis and kidney transplant recipients. Finally, demographic characteristics (age at index SCr measurement, sex, and vital statistics including all-cause mortality) were obtained from the Ontario Registered Persons Database (RPDB).

Statistical Analysis

Data were missing only for income quintile and urban/rural living status in a small subset of individuals in the cohort, and there were no systematic differences in missingness between index eGFR categories and age groups (data not shown). As such, missing data were assumed to be missing at random and were multiply imputed with chained equations based on Rubin's rules.[110] There were no missing index eGFR, outcome, or other covariate data.

Additional analyses

Additional covariates included in comprehensively adjusted model included obesity[91], alcoholism, smoking/nicotine dependence, hypercholesterolemia, hyperkalemia[92], cancer, chronic liver disease[93], and chronic lung disease (including asthma, chronic obstructive pulmonary disease [COPD], asbestosis, sleep apnea, and interstitial lung disease)[94], income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years. Specialist visits included nephrologist, endocrinologist, cardiologist, and urologist consultations.

APPENDIX A: RECORD STATEMENT

Section	Item Number	Recommendation	Reported
Title and abstract			
Title and abstract	1	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.	Title Page, 1-2
		1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	2
		1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.	5
		6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.	5-6
		6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Figure 1, Appendix B
Variables	7	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	5-6, Appendix C

Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	Appendix C
Bias	9	Describe any efforts to address potential sources of bias.	6-7
Study size	10	Explain how the study size was arrived at.	8, Figure 1
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	5-6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) Cohort study - If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	6-7, Additional Methodological Details
Data access and cleaning methods	12	12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	5-6
		12.2: Authors should provide information on the data cleaning methods used in the study.	5-6
Linkage	12	12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	5
Results			
Participants	13	13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	8, Figure 1
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) Cohort study – summarize follow-up time (e.g., average and total amount)	8, Table 1
Outcome data	15	Report numbers of outcome events or summary measures over time	8-9

Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8-10
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	10
Discussion			
Key results	18	Summarize key results with reference to study objectives	11
Limitations	19	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	11-12
Generalizability	21	Discuss the generalizability (external validity) of the study results.	13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Title Page, 15
Accessibility of protocol, raw data, and programming code		22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	15

APPENDIX B: ICES DATABASES USED IN THIS STUDY

Canadian Organ Replacement Registry (CORR)	CORR is the national information system that records and analyzes activity and outcome of vital organ transplantation and renal dialysis activities (ICES holding restricted to Ontario donors and recipients). CORR will be used to identify and exclude individuals with ongoing or past history of renal replacement therapy (either ongoing or past chronic dialysis, or past receipt of kidney transplant).
Canadian Institute of Health Information – Discharge Abstract Database (CIHI-DAD)	CIHI-DAD collects diagnostic and procedural variables for each hospital admission in Ontario. Coding of primary and secondary diagnoses and inpatient procedures was done using the 9th version of the Canadian Modified International Classification of Disease system (ICD-9-CA) before 2002, and the 10th version (ICD-10-CA) for diagnoses after 2002. CIHI-DAD will be used to obtain demographics, assess hospitalizations, and comorbid conditions for each patient. These characteristics will act as study inclusion/exclusion criteria, confounders in multivariable models, as well as exposure and outcomes for Objective II.
Ontario Health Insurance Plan (OHIP) Claims History Database	Physicians in Ontario submit billing claims using fee and diagnosis codes outlined in the OHIP Schedule of Benefits. These codes capture information on inpatient, outpatient, and laboratory services provided to the patient. OHIP also contains data on nature of the service and diagnostic information. OHIP will be used to examine specialist referrals and healthcare provision of patients. OHIP will also be used to exclude patients with history of previous dialysis and/or transplantation. Previous chart abstraction studies have noted considerable agreement between abstracted OHIP codes and physician-recorded codes on medical charts (>90% for diagnoses, >88% for procedural codes).
Registered Persons Database (RPDB)	The RPDB contains information regarding Ontario residents' gender, date of birth, postal code, and vital status.

Ontario Laboratory Information System (OLIS)	OLIS is an electronic system that contains laboratory tests conducted for patients in Ontario. Data is available from 2007-2016 with serum creatinine values cleaned and at ICES' Central branch. OLIS will be used to determine index eGFR and urine ACR measurements for patients, to inform calculations of relative eGFR reduction in Objective I and generate index eGFR categories in Objective II.
Ontario Marginalization Index (ONMARG)	ONMARG contains factor scores and factor quintiles of the Ontario Marginalization Index (OMI), a census-based index to measure social marginalization across Ontario regions.[36] Absolute and relative marginalization are estimated across 4 axes: residential instability, material deprivation, dependency, and ethnic concentration. ONMARG will be used to categorize patients by quintiles of overall marginalization, to illustrate patient's relative socioeconomic status in descriptive analyses, and as a potential confounder/stratifying variable in multivariable/subgroup analyses.
National Ambulatory Care Reporting System (NACRS)	The NACRS is compiled by the Canadian Institute of Health Information (CIHI) and contains administrative, clinical (diagnoses, procedures), demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centres (emergency departments, day surgery units, hemodialysis units, and cancer care clinics) in Ontario. At ICES, NACRS records are linked with CIHI-DAD and Ontario Mental Health Reporting System (OMHRS) to identify transitions to other care settings, such as inpatient acute care or psychiatric care. Prior to April 1, 2002, diagnoses (upto 6 per NACRS record) are captured using ICD-9 coding system and procedures (upto 10 per NACRS record) are captured using the CCP coding system. Following April 1, 2002, diagnoses (upto 10 per NACRS record) are captured using the ICD-10-CA coding system and interventions (upto 10 per NACRS record) are captured using the CCI coding system. NACRS emergency department diagnosis codes have been extensively validated previously.

APPENDIX C: COMMON DATA DEFINITIONS AND STUDY OUTCOMES ACROSS DATASETS

Variables	Description	Data Source	Codes or Possible Values
	Inclusion/exclusion criteria		
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)	At least one outpatient laboratory measures of serum creatinine for eGFR from January 1, 2008, to March 31, 2020 Sensitivity analysis: two or more outpatient laboratory measures, with at least one measure ≥90 days to ≤2 years post-index eGFR is based on serum creatinine measurements, converted using the 2021 Chronic Kidney Disease-Epidemiology (CKD-EPI) race-free equation	Ontario Laboratory Information System (OLIS)	Observation code = 14682-9
Albumin-to-creatinine ratio (ACR) (mg/mmol)	Laboratory measurement of urinary albumin within 1 year of index eGFR measure	OLIS	Observation code = 32294-1
Chronic dialysis	Evidence of chronic dialysis on or prior to index date, for exclusion	Canadian Organ Replacement Registry (CORR)	Treatment code ≠ 171, 181
Kidney transplant	Evidence of a kidney transplant on or prior to index date, either a single-kidney transplant or a multi-organ transplant including kidneys, for exclusion from cohort	CORR	Treatment code = 171, 181

Living kidney donation	Evidence of living kidney donation within 5 years prior to index date, for exclusion from strict comprehensive cohort	CORR, CIHI-DAD, NACRS	CORR donor type code: 02, 03, 04, 05, 06, 07, 10, 12, 15 ICD-10 code: Z524
Acute kidney injury	Evidence of diagnosis of acute kidney injury in the past 5 years prior to index, for exclusion from strict comprehensive cohort	CIHI-DAD, NACRS	ICD-10 code: N17
Kidney stone ("calculus of kidney and ureter")	Evidence of diagnosis of kidney stones in the past 5 years prior to index, for exclusion from strict comprehensive cohort	CIHI-DAD, NACRS	ICD-10 code: N20
Death	All-cause mortality prior to index date, for exclusion from cohort	Registered Persons Database (RPDB)	
Outcomes			
Death	All-cause mortality during follow-up, counted as outcome	RPDB	
Cardiovascular outcomes	Hospitalization or emergency room visit for heart failure, acute coronary syndrome, stroke, atrial fibrillation	Discharge Abstract Database (CIHI-DAD), National Ambulatory Care Reporting System (NACRS)	ICD-10 codes: *Heart failure:* I099, I420, I425, I426, I427, I428, I429, I43, I500, I501, I509, I255, J81 *Acute coronary syndrome:* I20, I22, I23, I24, I25 *Stroke*: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602,

			I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340 *Atrial fibrillation:* I48
Kidney failure	Evidence of initiating chronic dialysis after index date Evidence of receiving kidney transplant after index-date, either a single-kidney transplant or a multi-organ transplant including kidneys	CORR	Treatment codes *Chronic dialysis:* all codes except 171, 181 *Kidney transplant:* 171, 181
Key covariates			
Age	Age in years at index date	RPDB	
Sex	Biological sex at index date	RPDB	
Income quintile	Derived from postal codes and associated after-tax relative household income, within census areas	RPDB	
Rural living status	Derived from postal codes, Remoteness Index developed by Statistics Canada	RPDB	
Hypertension	Five year lookback from index date for history of hospitalizations for hypertension	ICES-generated cohort for hypertension (HYPERTENSION), derived from CIHI-DAD, NACRS	ICD-10 codes: I10, I11, I12, I13, I15

Diabetes mellitus	Five year lookback from index date for history of hospitalizations for diabetes	ICES-generated cohort for diabetes (ODD), derived from CIHI-DAD, NACRS	ICD-10 codes: E10, E11, E13, E14
Past cardiovascular outcomes	Five year lookback from index date for history of cardiovascular illness	CIHI-DAD, NACRS	ICD-10 codes: *Heart failure:* I099, I420, I425, I426, I427, I428, I429, I43, I500, I501, I509, I255, J81 *Acute coronary syndrome:* I20, I22, I23, I24, I25 *Stroke*: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340 *Atrial fibrillation:* I48
Obesity	Five year lookback from index date for diagnoses of obesity	CIHI-DAD, NACRS	ICD-10 code: E66
Alcoholism	Five year lookback from index date for diagnoses of alcoholism	CIHI-DAD, NACRS	ICD-10 code: E244, E512, F10, G312, G621, G721, I426, K292, K70, K860, T510,
Smoking/nicotine dependence	Five year lookback from index date for diagnoses of cigarette smoking, nicotine dependence	CIHI-DAD, NACRS	ICD-10 code: F17

Hypercholesterolemia	Five year lookback from index date for diagnoses of sustained high serum cholesterol or lipid levels	CIHI-DAD, NACRS	ICD-10 code: E78
Hyperkalemia	Five year lookback from index date for diagnoses of elevated serum potassium levels presented in acute care	CIHI-DAD, NACRS	ICD-10 code: E875
Cancer	Five year lookback from index date for diagnoses of cancer, including: skin, mouth (lip, tonsil, etc.), throat, stomach, small/large intestine, liver, gall bladder, pancreas, breast, male/female reproductive organs, heart, lung, bone, urinary system (kidney, bladder, etc.), endocrine glands, as well as leukemias and lymphomas	CIHI-DAD, NACRS	ICD-10 codes:  Cancer 20141031.txt
Chronic liver disease	Five year lookback from index for history of hospitalizations for chronic liver disease	CIHI-DAD, NACRS	ICD-10 codes: B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77
Chronic lung disease	Five year lookback from index for history of hospitalizations for chronic lung disease	CIHI-DAD, NACRS	ICD-10 codes: I272, I278, I279, J40, J41, J42, J43, J44, J45, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68, J701,

			J703, J704, J708, J709, J82, J84, J92, J941, J949, J953, J961, J969, J984, J988, J989, J99
Primary care visits	Frequency of physician billing claims for primary care visits during follow-up	Ontario Health Insurance Plan claims database (OHIP)	OHIP fee codes *Family medicine consultation:* A005, A911, A912, A905, A003, A900, A933 *Repeated consultation:* A006, A004 *Periodic health visit:* K131, K132 *Non-emergency inpatient services:* C005, C911, C912, C905, C006, C003, C004 *Subsequent visits:* C002, C007, C009
Emergency department visits	Frequency of emergency department visit/service claims in 5 years prior to index	NACRS	Indicator for presence of atleast one NACRS record in 5 years prior to index
Cardiologist visits	Frequency of cardiologist service claims in 5 years prior to index	OHIP	OHIP fee codes *Cardiology consultation:* A605, A765, A600, A675, A606, A603, A604, A601, A608 *Cardiology non-emergency visit:* C605, C765, C600,

			C675, C606, C603, C604, C601 *Cardiology subsequent visits:* C602, C607, C609
Endocrinologist visits	Frequency of endocrinologist service claims in 5 years prior to index	OHIP	OHIP fee codes *Endocrinology consultation:* A155, A765, A150, A255, A156, A153, A154, A151, A158 *Endocrinology non-emergency visit:* C155, C765, C150, C255, C156, C153, C154, C151 *Endocrinology subsequent visits:* C152, C157, C159
Nephrologist visits	Frequency of nephrologist service claims in 5 years prior to index	OHIP	OHIP fee codes *Nephrology consultation:* A165, A765, A160, A865, A166, A163, A164, A161, A168 *Non-emergency nephrology visit:* C165, C765, C160, C865, C166, C163, C164, C161 *Nephrology subsequent visits:* C162, C167, C169
Urologist visits	Frequency of urologist service claims in 5 years prior to index	OHIP	OHIP fee codes

			Urology consultation: A355, A935, A356, A353, A354 *Non-emergency urology visit:* C355, C935, C356, C353, C354 *Urology subsequent visits:* C352, C357, C359
Pregnancy at index	Exclude pregnant women at the time of index eGFR measurement (such as those resulting in single/multiple live births, induced abortion, spontaneous abortion, threatened abortion, non-spontaneous/spontaneous still birth, pre-term birth, ectopic pregnancies)	CIHI-DAD, NACRS, OHIP	ICD-10 codes: Z370-Z3791, O04, O08, O00, O021, O03, O04, O20, P072, P073, O30, O31, O60 OHIP fee codes: S785, A920, A921, P001, S752, A922, S756, S768, S784, S770

APPENDIX D: DISTRIBUTION OF INDEX EGFR CATEGORIES BY AGE

TABLE D1: Prevalence (n, %) of index eGFR categories relative to age-specific reference ranges, by age group and category of index year of cohort entry

Index eGFR category, mL/min/1.73m^2	18-39		40-49		50-65	
50-60	3,528	0.09%	6,227	0.30%	39,979	1.4%
60-70	14,221	0.37%	27,455	1.3%	127,001	4.5%
70-80	61,781	1.6%	102,090	5.0%	313,400	11.1%
80-90	193,072	5.0%	247,809	12.1%	526,010	18.6%
90-100	416,431	10.9%	385,729	18.9%	750,625	26.6%
100-110	619,115	16.2%	626,279	30.6%	971,402	34.4%
110-120	1,061,965	27.7%	621,341	30.4%	91,549	3.2%
>120	1,464,544	38.2%	29,221	1.4%	3,097	0.11%

APPENDIX E: ASSESSMENT OF RISK OF KIDNEY FAILURE WITH COMPETING RISK OF DEATH

TABLE E1: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for KIDNEY FAILURE (initiation of dialysis or receipt of kidney transplant) relative to age-specific eGFR reference ranges, accounting for all-cause mortality as a competing risk, by age-group

Event frequency **Crude incidence rate** **Adjusted HR (95% CI)**

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	186/3528 7.62 47.0 (37.4, 59.0)	261/6227 5.05 17.8 (14.9, 21.3)	1067/39979 2.98 5.84 (4.63, 7.12)
60-70	184/14221 1.92 20.6 (16.6, 25.7)	244/27455 1.06 7.01 (5.92, 8.30)	1104/127001 0.954 3.03 (2.73, 3.39)
70-80	148/61781 0.347 6.25 (5.02, 7.78)	281/102090 0.321 2.93 (2.50, 3.44)	1058/313400 0.368 1.49 (1.39, 1.63)
80-90 (reference for 50-65)	173/193072 0.127	316/247809 0.145 1.48 (1.27, 1.72)	1104/526010 0.227 1.00 (reference)

	2.80 (2.27, 3.45)		
90-100 (reference for 40-49)	196/416431 0.0651 1.55 (1.27, 1.89)	330/385729 0.0960 1.00 (reference)	1252/750625 0.179 0.75 (0.68, 0.82)
100-110 (reference for 18-39)	187/619115 0.0413 1.00 (reference)	532/626279 0.0929 0.87 (0.76, 1.00)	1486/971402 0.164 0.70 (0.65, 0.75)
110-120	370/1061965 0.0451 0.95 (0.80, 1.14)	608/621341 0.107 0.93 (0.81, 1.06)	211/91549 0.257 0.91 (0.77, 1.04)
>120	502/1464544 0.0469 1.07 (0.90, 1.27)	74/29221 0.287 1.41 (1.09, 1.83)	12/3097 0.518 1.28 (0.69, 2.44)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

APPENDIX F: SEX-STRATIFIED ANALYSES

Table F1. Sex-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for ANY ADVERSE OUTCOME (first of all-cause mortality, cardiovascular outcomes, kidney failure) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction < 0.0001

Index eGFR category	Sex	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Male**	228/2022	17.7	2.55 (2.23, 2.91)	0.0083
	Female	170/1506	15.6	3.41 (2.92, 3.98)	
60-70	**Male**	463/8226	9.05	1.86 (1.69, 2.05)	0.0278
	Female	297/5995	6.92	2.21 (1.97, 2.49)	
70-80	**Male**	1175/35304	5.18	1.38 (1.30, 1.47)	0.2970
	Female	672/26477	3.46	1.47 (1.35, 1.59)	
80-90	**Male**	2837/106875	3.99	1.17 (1.12, 1.22)	0.4272
	Female	1675/86197	2.62	1.21 (1.14, 1.28)	
90-100	**Male**	5481/223867	3.56	1.08 (1.04, 1.11)	0.8440
	Female	3253/192564	2.25	1.08 (1.03, 1.13)	
100-110	**Male**	7259/315758	3.29	(reference)	(reference)
	Female	4690/303357	2.05		
110-120	**Male**	14858/500528	4.07	1.16 (1.13, 1.20)	0.0053
	Female	10207/561439	2.28	1.09 (1.05, 1.13)	
>120	**Male**	13525/570021	3.42	0.98 (0.95, 1.01)	<0.0001
	Female	11009/894523	1.65	0.81 (0.78, 0.84)	

**adjusted for hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table F2. Sex-stratified event frequencies, incidence rates per one million person-years, and adjusted hazard ratios (95% CI) for ALL-CAUSE MORTALITY (first of all-cause mortality, cardiovascular outcomes, kidney failure) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction < 0.0001

Index eGFR category	Sex	Event frequency	Mortality rate (per 1000 p-y)	HR (95% CI) for all-cause mortality	P-value for interaction
50-60	**Male**	68/2022	4.94	2.71 (2.13, 3.45)	0.0243
	Female	62/1506	5.41	3.70 (2.86, 4.78)	
60-70	**Male**	167/8226	3.17	2.22 (1.90, 2.60)	0.3743
	Female	112/5995	2.55	2.26 (1.86, 2.74)	
70-80	**Male**	391/35304	1.70	1.40 (1.26, 1.56)	0.4076
	Female	239/26477	1.22	1.46 (1.28, 1.67)	
80-90	**Male**	926/106875	1.29	1.12 (1.04, 1.21)	0.1934
	Female	597/86197	0.927	1.20 (1.09, 1.32)	
90-100	**Male**	1837/223867	1.18	1.04 (0.98, 1.10)	0.3473
	Female	1153/192564	0.792	1.08 (1.00, 1.17)	
100-110	**Male**	2542/315758	1.14	(reference)	(reference)
	Female	1657/303357	0.718		
110-120	**Male**	5183/500526	1.40	1.15 (1.10, 1.21)	0.0504
	Female	3514/561439	0.779	1.06 (1.00, 1.12)	
>120	**Male**	7012/570021	1.76	1.39 (1.32, 1.45)	<0.0001
	Female	4500/894523	0.670	0.94 (0.89, 0.99)	

**adjusted for hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income*

quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years

Table F3. Sex-stratified event frequencies, incidence rates per one million person-years, and adjusted hazard ratios (95% CI) for CARDIOVASCULAR COMPOSITE OUTCOME (first of congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction < 0.0001

Index eGFR category	Sex	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Male**	117/2022	8.85	1.51 (1.25, 1.81)	0.2162
	Female	76/1506	6.82	1.94 (1.55, 2.44)	
60-70	**Male**	266/8226	5.17	1.37 (1.21, 1.55)	0.0168
	Female	175/5995	4.05	1.82 (1.56, 2.13)	
70-80	**Male**	799/35304	3.52	1.29 (1.20, 1.40)	0.4716
	Female	440/26477	2.26	1.38 (1.25, 1.53)	
80-90	**Male**	1989/106875	2.80	1.17 (1.12, 1.24)	0.8917
	Female	1128/86197	1.77	1.19 (1.11, 1.28)	
90-100	**Male**	3620/223867	2.48	1.09 (1.05, 1.14)	0.6626
	Female	2215/192564	1.53	1.08 (1.02, 1.14)	
100-110	**Male**	4949/315758	2.24	(reference)	(reference)
	Female	3206/303357	1.40		
110-120	**Male**	10261/500526	2.81	1.17 (1.13, 1.21)	0.0315
	Female	7099/561439	1.03	1.11 (1.06, 1.15)	
>120	**Male**	7162/570021	1.81	0.78 (0.75, 0.81)	0.1936
	Female	6914/894523	1.03	0.75 (0.72, 0.78)	

**adjusted for hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income*

quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years

Table F4. Sex-stratified event frequencies, incidence rates per one million person-years, and adjusted hazard ratios (95% CI) for KIDNEY FAILURE (first of initiation of dialysis or receipt of kidney transplant) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

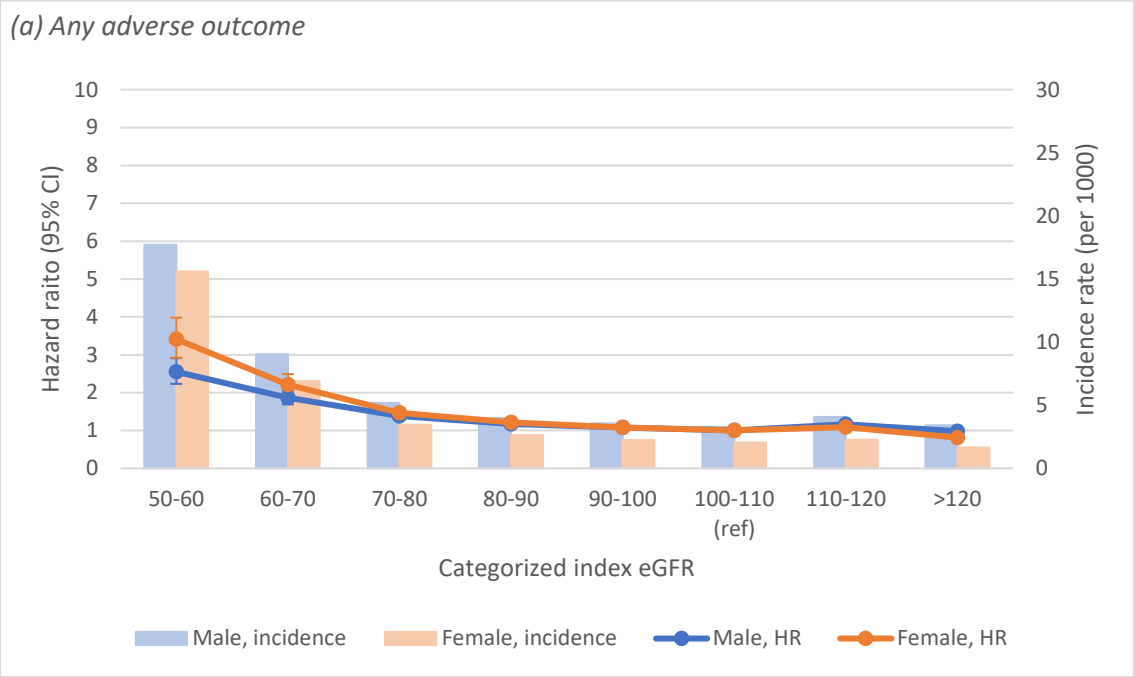
Overall P-value of interaction = 0.5577

Index eGFR category	Sex	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Male**	104/2022	7.82	49.5 (37.5, 65.4)	0.6754
	Female	82/1506	7.38	45.7 (33.3, 62.7)	
60-70	**Male**	116/8226	2.22	24.1 (18.4, 31.5)	0.3890
	Female	68/5995	1.56	17.1 (12.3, 23.8)	
70-80	**Male**	83/35304	0.360	6.08 (4.54, 8.14)	0.4742
	Female	65/26477	0.331	6.69 (4.83, 9.28)	
80-90	**Male**	106/106875	0.147	2.99 (2.27, 3.93)	0.5662
	Female	67/86197	0.104	2.57 (1.86, 3.55)	
90-100	**Male**	121/223867	0.0779	1.67 (1.28, 2.17)	0.4062
	Female	75/192564	0.0515	1.39 (1.02, 1.90)	
100-110	**Male**	105/315758	0.0472	(reference)	(reference)
	Female	82/303357	0.0356		
110-120	**Male**	222/500526	0.0601	1.09 (0.86, 1.38)	0.1025
	Female	148/561439	0.0328	0.80 (0.61, 1.05)	
>120	**Male**	261/570021	0.0654	1.21 (0.96, 1.52)	0.1554
	Female	241/894523	0.0359	0.93 (0.73, 1.20)	

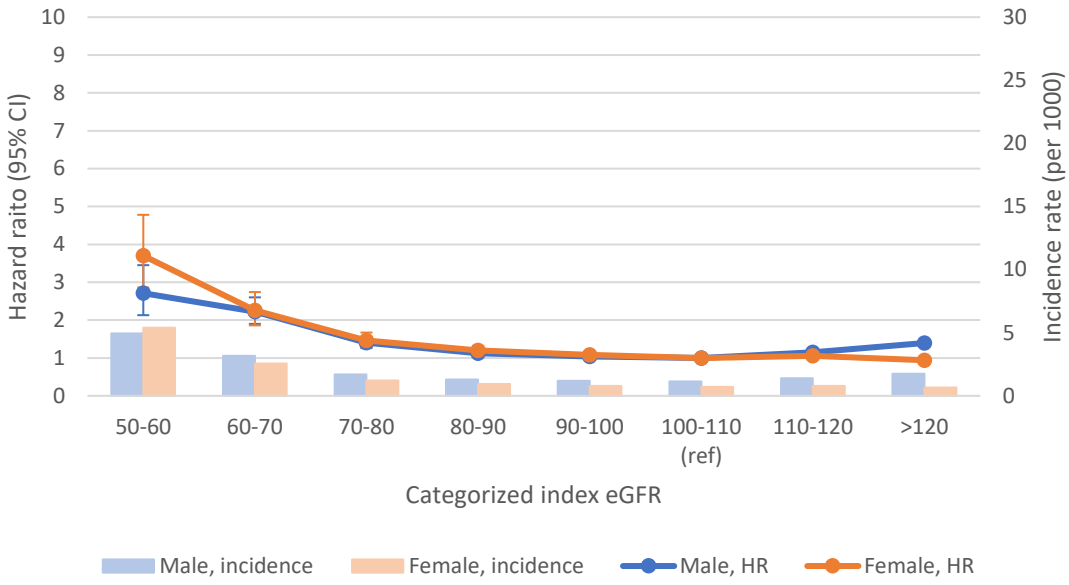
**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung*

disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years

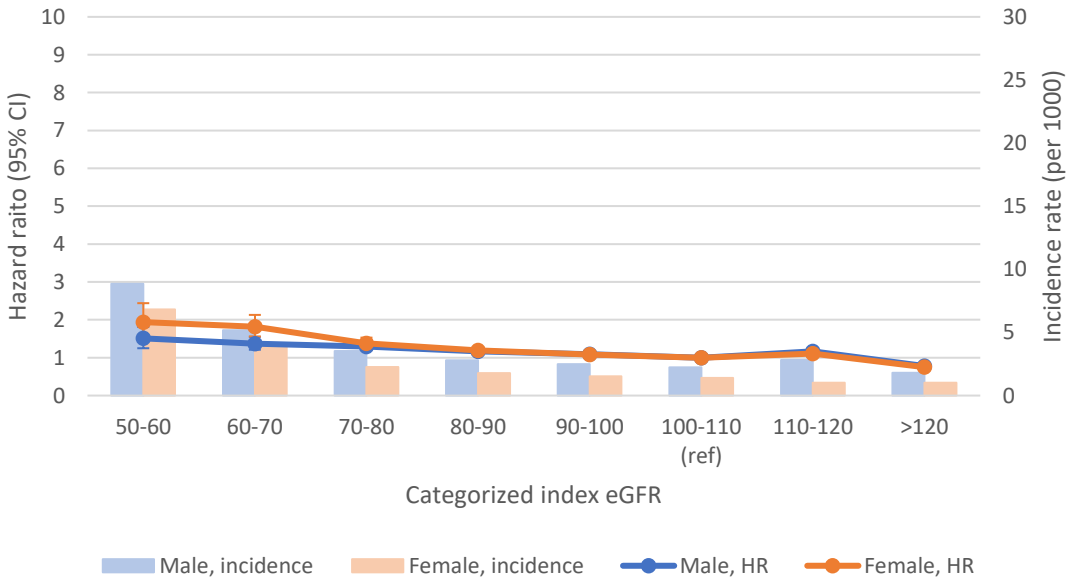
Figure F1: Sex-stratified incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) any adverse outcome (first of all-cause mortality, cardiovascular outcomes, kidney failure), (b) all-cause mortality, (c) cardiovascular composite outcome (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation), (d) kidney failure, among those aged 18-39 and relative to eGFR 100-110

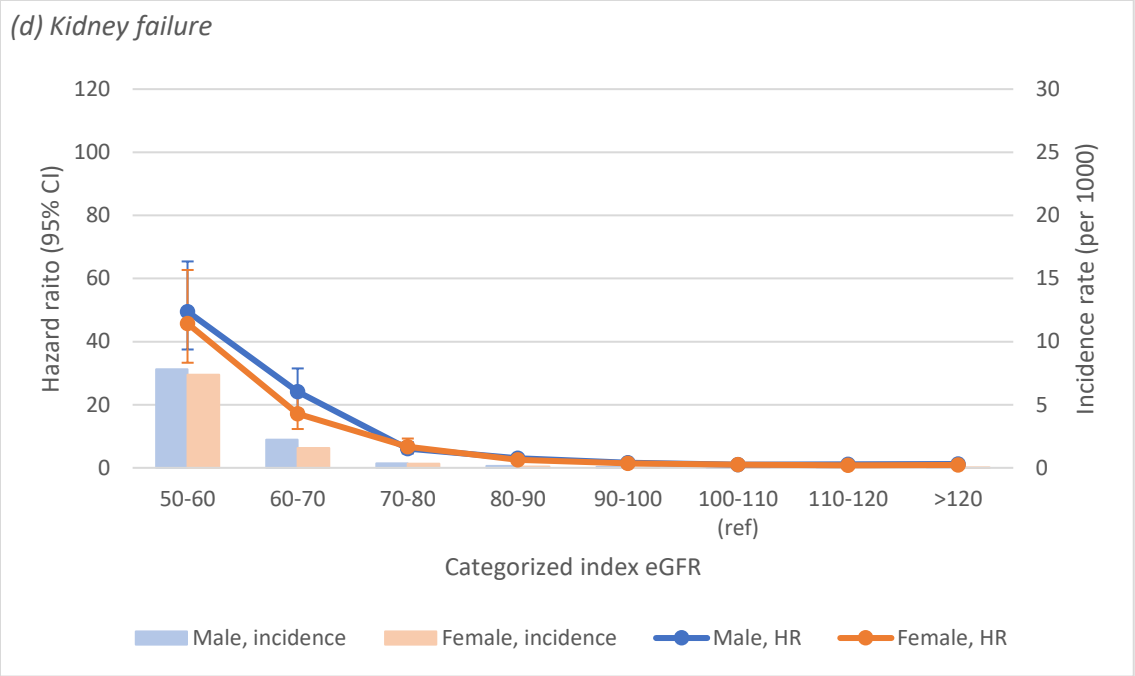


(b) All-cause mortality



(c) Cardiovascular composite outcome





**adjusted for hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

APPENDIX G: DIABETES-STRATIFIED ANALYSES

Table G1. Diabetes-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for ANY ADVERSE OUTCOME (first of all-cause mortality, cardiovascular outcomes, kidney failure) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction < 0.0001

Index eGFR category	Diabetes status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	78/170	66.8	4.30 (3.39, 5.46)	0.0676
	No	320/3358	14.2	2.70 (2.41, 3.02)	
60-70	**Yes**	101/337	38.7	2.33 (1.88, 2.88)	0.8493
	No	659/13884	7.20	1.97 (1.82, 2.13)	
70-80	**Yes**	147/867	20.0	1.68 (1.41, 2.02)	0.1908
	No	1700/60914	4.11	1.40 (1.33, 1.47)	
80-90	**Yes**	270/2159	14.6	1.40 (1.21, 1.62)	0.0628
	No	4242/190913	3.19	1.17 (1.13, 1.22)	
90-100	**Yes**	418/4454	10.6	1.02 (0.90, 1.16)	0.1364
	No	8316/411977	2.82	1.08 (1.05, 1.11)	
100-110	**Yes**	594/6896	9.88	(reference)	(reference)
	No	11355/612219	2.56		
110-120	**Yes**	1804/18193	11.0	1.10 (1.00, 1.21)	0.4317
	No	23261/1043772	2.92	1.13 (1.11, 1.16)	
>120	**Yes**	1805/24911	8.94	0.85 (0.77, 0.93)	0.0348
	No	22729/1439633	2.18	0.91 (0.89, 0.93)	

**adjusted for sex, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table G2. Diabetes-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for ALL-CAUSE MORTALITY by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction < 0.0001

Index eGFR category	Diabetes status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	39/170	25.9	5.05 (3.57, 7.16)	0.0070
	No	91/3358	3.84	2.65 (2.15, 3.26)	
60-70	**Yes**	38/337	12.7	2.22 (1.57, 3.15)	0.2914
	No	241/13884	2.57	2.28 (2.01, 2.60)	
70-80	**Yes**	61/867	7.75	1.80 (1.35, 2.40)	0.2209
	No	569/60914	1.36	1.39 (1.27, 1.51)	
80-90	**Yes**	109/2159	5.59	1.52 (1.20, 1.92)	0.0181
	No	1414/190913	1.05	1.13 (1.06, 1.20)	
90-100	**Yes**	153/4454	3.74	1.04 (0.85, 1.29)	0.7162
	No	2837/411977	0.956	1.05 (1.00, 1.11)	
100-110	**Yes**	211/6896	3.39	(reference)	(reference)
	No	3988/612219	0.892		
110-120	**Yes**	595/18193	3.50	1.02 (0.87, 1.19)	0.1901
	No	8102/1043772	1.01	1.12 (1.08, 1.17)	
>120	**Yes**	780/24911	3.76	1.06 (0.91, 1.24)	0.0431
	No	10732/1439633	1.02	1.19 (1.15, 1.24)	

**adjusted for sex, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income*

quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years

Table G3. Diabetes-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for CARDIOVASCULAR COMPOSITE OUTCOME (first of congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction = 0.0120

Index eGFR category	Diabetes status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	49/170	37.6	3.04 (2.26, 4.09)	0.0122
	No	144/3358	6.24	1.50 (1.27, 1.77)	
60-70	**Yes**	62/337	22.8	1.86 (1.42, 2.43)	0.6949
	No	379/13884	4.12	1.50 (1.35, 1.66)	
70-80	**Yes**	99/867	13.3	1.52 (1.22, 1.89)	0.3945
	No	1140/60914	2.75	1.31 (1.23, 1.40)	
80-90	**Yes**	183/2159	9.83	1.29 (1.08, 1.53)	0.6886
	No	2934/190913	2.20	1.18 (1.13, 1.23)	
90-100	**Yes**	296/4454	7.49	0.98 (0.85, 1.14)	0.0666
	No	5739/411977	1.95	1.09 (1.06, 1.13)	
100-110	**Yes**	433/6896	7.19	(reference)	(reference)
	No	7722/612219	1.74		
110-120	**Yes**	1336/18193	8.15	1.12 (1.00, 1.25)	0.6753
	No	16024/1043772	2.01	1.14 (1.11, 1.17)	
>120	**Yes**	1152/24911	5.70	0.75 (0.67, 0.83)	0.3660
	No	12924/1439633	1.24	0.77 (0.75, 0.79)	

**adjusted for sex, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income*

quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years

Table G4. Diabetes-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for KIDNEY FAILURE (first of initiation of dialysis or receipt of kidney transplant) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

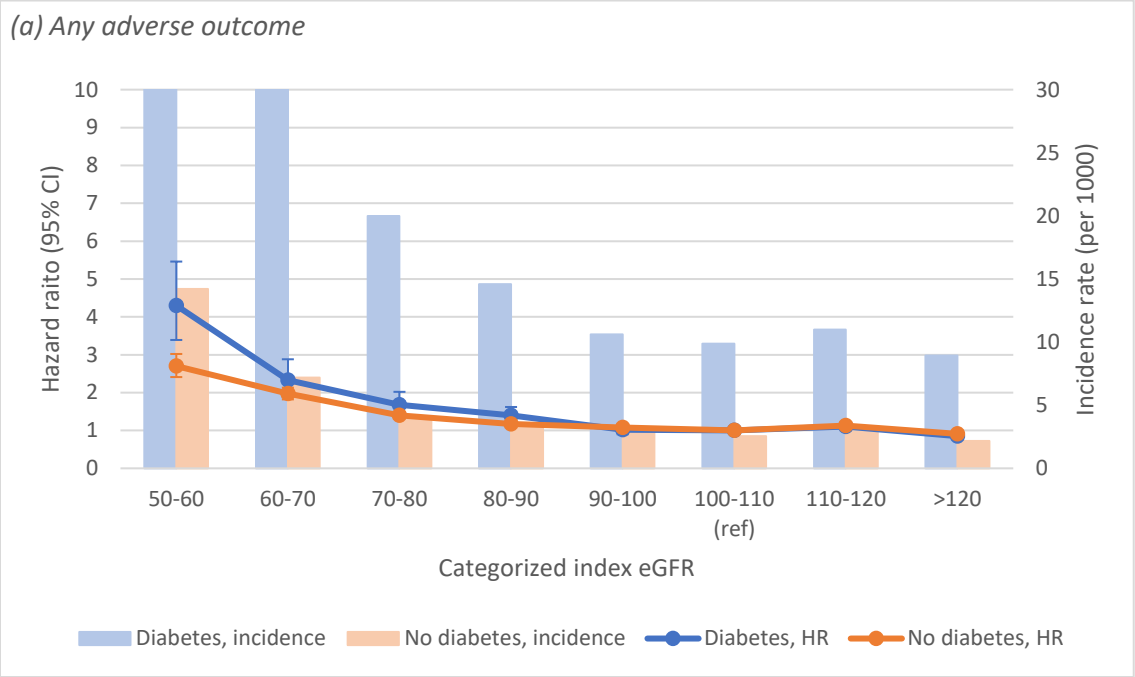
Overall P-value of interaction < 0.0001

Index eGFR category	Diabetes status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	43/170	33.3	21.4 (14.2, 32.4)	<0.0001
	No	143/3358	6.18	67.0 (52.6, 85.3)	
60-70	**Yes**	45/337	15.9	11.2 (7.46, 16.8)	<0.0001
	No	139/13884	1.49	27.1 (21.3, 34.4)	
70-80	**Yes**	42/867	5.47	5.31 (3.53, 7.98)	0.2628
	No	106/60914	0.253	6.49 (5.02, 8.38)	
80-90	**Yes**	48/2159	2.48	2.74 (1.85, 4.07)	0.8636
	No	125/190913	0.0931	2.80 (2.19, 3.58)	
90-100	**Yes**	61/4454	1.50	1.70 (1.17, 2.47)	0.6728
	No	135/411977	0.0455	1.49 (1.17, 1.89)	
100-110	**Yes**	53/6896	0.853	(reference)	(reference)
	No	134/612219	0.0300		
110-120	**Yes**	126/18193	0.742	0.86 (0.62, 1.19)	0.4758
	No	244/1043772	0.0304	0.97 (0.79, 1.20)	
>120	**Yes**	177/24911	0.856	0.93 (0.68, 1.27)	0.3444
	No	325/1439633	0.0310	1.11 (0.91, 1.37)	

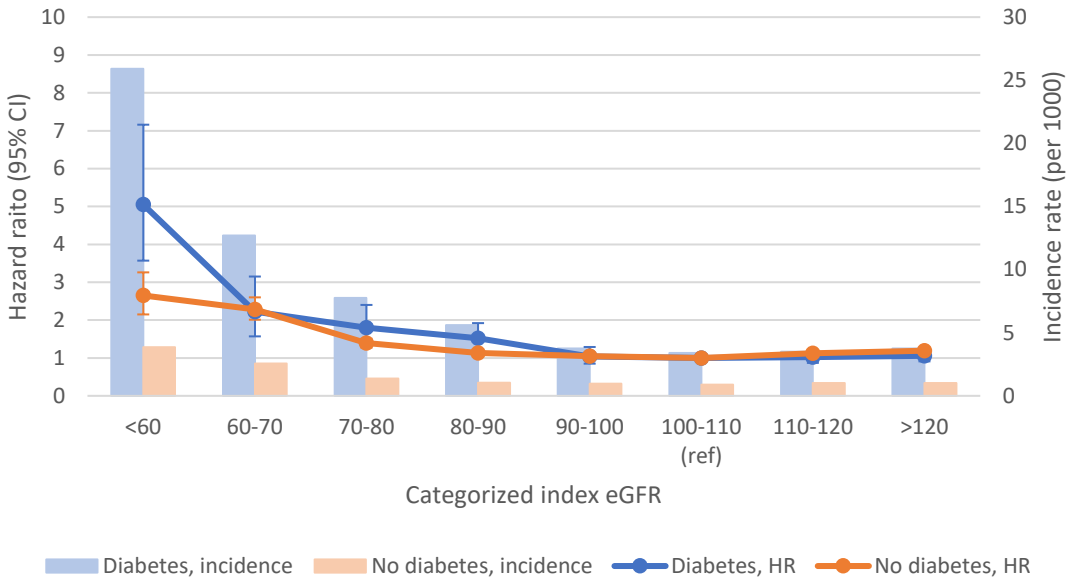
**adjusted for sex, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income*

quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years

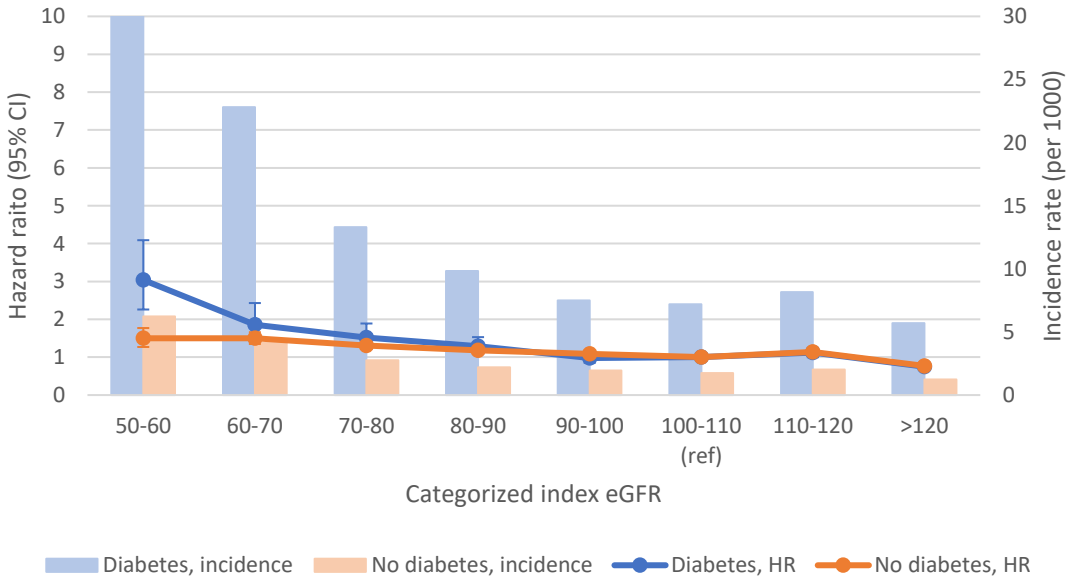
Figure G1: Diabetes-stratified, incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) any adverse outcome (first of all-cause mortality, cardiovascular outcomes, kidney failure), (b) all-cause mortality, (c) cardiovascular composite outcome (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation), (d) kidney failure, among those aged 18-39 and relative to eGFR 100-110

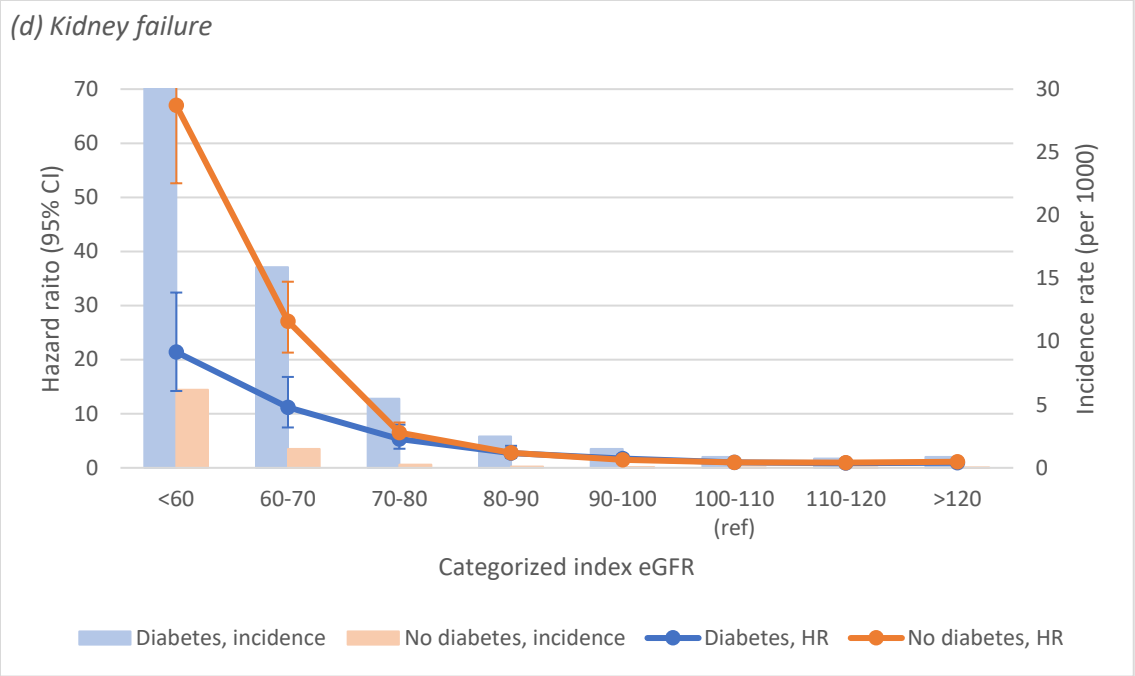


(b) All-cause mortality



(c) Cardiovascular composite outcome





**adjusted for sex, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

APPENDIX H: HYPERTENSION-STRATIFIED ANALYSES

Table H1. Hypertension-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for ANY ADVERSE OUTCOME (first of all-cause mortality, cardiovascular outcomes, kidney failure) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction = 0.0683

Index eGFR category	Hypertension status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	108/324	41.8	2.96 (2.42, 3.62)	0.0529
	No	290/3204	13.7	3.06 (2.72, 3.44)	
60-70	**Yes**	128/763	20.8	1.88 (1.56, 2.26)	0.0396
	No	632/13458	7.19	2.06 (1.90, 2.23)	
70-80	**Yes**	282/2230	15.5	1.70 (1.49, 1.95)	0.0385
	No	1565/59551	3.88	1.38 (1.31, 1.46)	
80-90	**Yes**	438/5549	9.34	1.21 (1.08, 1.36)	0.9008
	No	4074/187523	3.13	1.18 (1.14, 1.23)	
90-100	**Yes**	718/10473	8.02	1.08 (0.98, 1.19)	0.7171
	No	8016/405958	2.77	1.08 (1.05, 1.11)	
100-110	**Yes**	874/13532	7.39	(reference)	(reference)
	No	11075/605583	2.53		
110-120	**Yes**	2117/27848	8.50	1.11 (1.02, 1.20)	0.2871
	No	22948/1034117	2.91	1.13 (1.11, 1.16)	
>120	**Yes**	1279/19022	7.65	0.93 (0.85, 1.02)	0.7696
	No	23255/1445522	2.22	0.90 (0.88, 0.92)	

**adjusted for sex, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table H2. Hypertension-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for ALL-CAUSE MORTALITY by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction = 0.0237

Index eGFR category	Hypertension status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	31/324	10.0	3.02 (2.06, 4.40)	0.5574
	No	99/3204	4.47	3.18 (2.60, 3.89)	
60-70	**Yes**	33/763	4.92	1.71 (1.18, 2.47)	0.0621
	No	246/13458	2.74	2.35 (2.07, 2.68)	
70-80	**Yes**	56/2230	2.86	1.17 (0.87, 1.57)	0.0882
	No	574/59551	1.41	1.45 (1.33, 1.58)	
80-90	**Yes**	111/5549	2.28	1.15 (0.92, 1.44)	0.8955
	No	1412/187523	1.07	1.15 (1.08, 1.22)	
90-100	**Yes**	188/10473	2.03	1.05 (0.86, 1.27)	0.8664
	No	2802/405958	0.960	1.05 (1.00, 1.11)	
100-110	**Yes**	235/13532	1.93	(reference)	(reference)
	No	3964/605583	0.899		
110-120	**Yes**	541/27848	2.10	1.01 (0.87, 1.18)	0.1853
	No	8156/1034117	1.03	1.12 (1.08, 1.17)	
>120	**Yes**	465/19022	2.71	1.18 (1.01, 1.38)	0.8574
	No	11047/1445522	1.05	1.18	

				(1.14, 1.23)	

**adjusted for sex, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table H3. Hypertension-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for CARDIOVASCULAR COMPOSITE OUTCOME (first of congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction < 0.0001

Index eGFR category	Hypertension status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	54/324	19.3	1.63 (1.24, 2.16)	0.0325
	No	139/3204	6.44	1.87 (1.58, 2.21)	
60-70	**Yes**	80/763	12.7	1.38 (1.09, 1.74)	0.0159
	No	361/13458	4.09	1.62 (1.46, 1.80)	
70-80	**Yes**	229/2230	12.5	1.69 (1.45, 1.96)	0.0255
	No	1010/59551	2.50	1.29 (1.21, 1.38)	
80-90	**Yes**	339/5549	7.21	1.17 (1.03, 1.33)	0.6043
	No	2778/187523	2.13	1.19 (1.14, 1.24)	
90-100	**Yes**	567/10473	6.33	1.07 (0.96, 1.20)	0.5562
	No	5468/405958	1.89	1.09 (1.05, 1.13)	
100-110	**Yes**	692/13532	5.85	(reference)	(reference)
	No	7463/605583	1.70		
110-120	**Yes**	1711/27848	6.87	1.14 (1.04, 1.24)	0.5546
	No	15649/1034117	1.99	1.14 (1.11, 1.17)	
>120	**Yes**	911/19022	5.44	0.85 (0.77, 0.94)	0.0434
	No	13165/1445522	1.26	0.76 (0.74, 0.78)	

**adjusted for sex, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income*

quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years

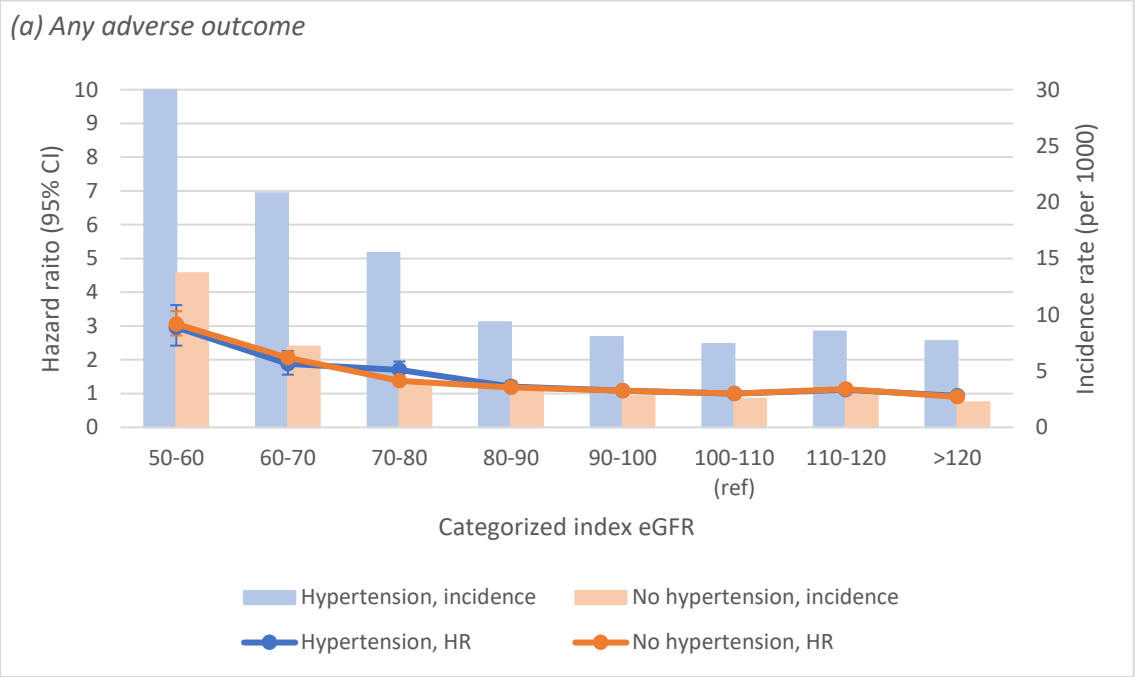
Table H4. Hypertension-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for KIDNEY FAILURE (first of initiation of dialysis or receipt of kidney transplant) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction < 0.0001

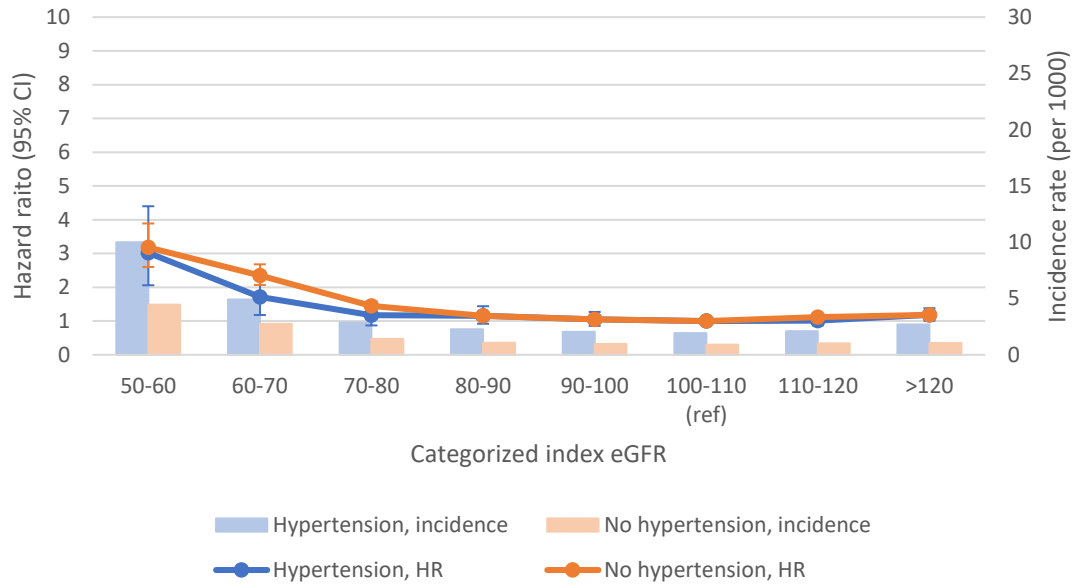
Index eGFR category	Hypertension status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	61/324	21.9	42.5 (27.0, 66.9)	0.1621
	No	125/3204	5.78	50.2 (39.6, 63.8)	
60-70	**Yes**	54/763	8.29	19.3 (12.2, 30.7)	0.2135
	No	130/13458	1.45	21.6 (17.0, 27.3)	
70-80	**Yes**	40/2230	2.06	6.66 (4.11, 10.8)	0.9605
	No	108/59551	0.265	6.05 (4.73, 7.74)	
80-90	**Yes**	35/5549	0.720	2.92 (1.77, 4.80)	0.8771
	No	138/187523	0.105	2.75 (2.18, 3.46)	
90-100	**Yes**	33/10473	0.358	1.52 (0.92, 2.52)	0.8675
	No	163/405958	0.0559	1.55 (1.24, 1.93)	
100-110	**Yes**	28/13532	0.230	(reference)	(reference)
	No	159/605583	0.0360		
110-120	**Yes**	44/27848	0.171	0.66 (0.41, 1.06)	0.0758
	No	326/1034117	0.0410	1.01 (0.83, 1.22)	
>120	**Yes**	47/19022	0.274	0.91 (0.57, 1.46)	0.3255
	No	455/1445522	0.0432	1.10 (0.92, 1.32)	

**adjusted for sex, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

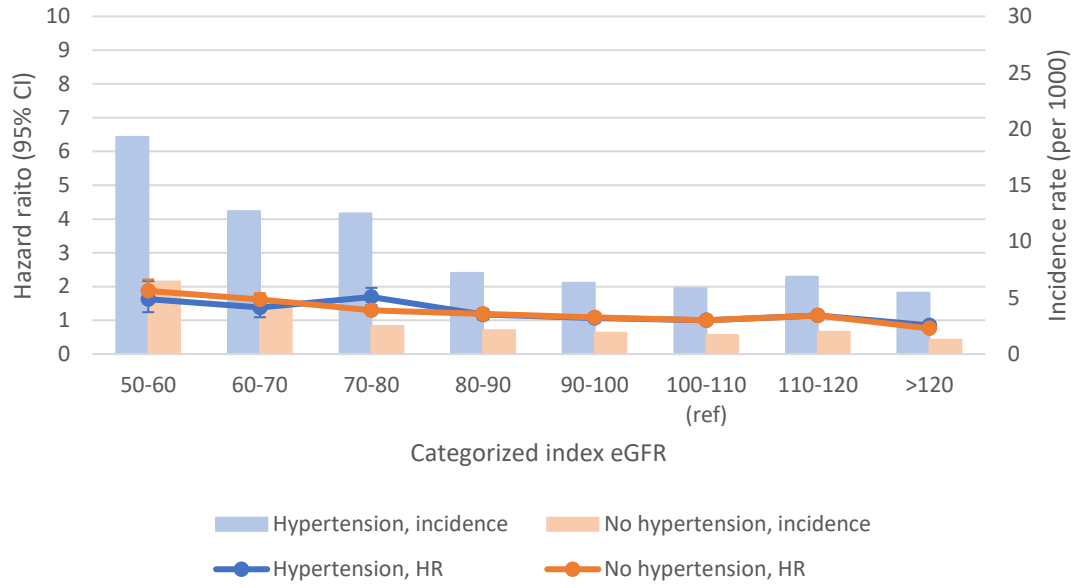
Figure H1: Hypertension-stratified, incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) any adverse outcome (first of all-cause mortality, cardiovascular outcomes, kidney failure), (b) all-cause mortality, (c) cardiovascular composite outcome (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation), (d) kidney failure, among those aged 18-39 and relative to eGFR 100-110

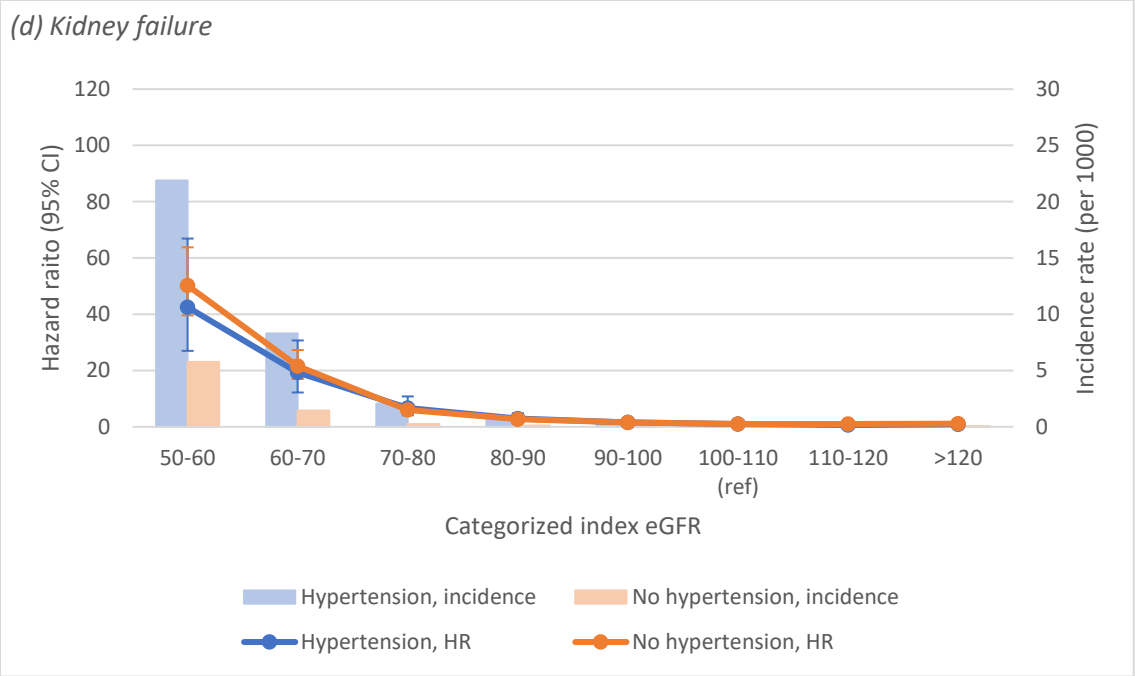


(b) All-cause mortality



(c) Cardiovascular composite outcome





**adjusted for sex, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

APPENDIX I: PAST CARDIOVASCULAR DISEASE-STRATIFIED ANALYSES

Table I1. Past cardiovascular disease-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for ANY ADVERSE OUTCOME (first of all-cause mortality, cardiovascular outcomes, kidney failure) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction = 0.0068

Index eGFR category	Past cardiovascular disease status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	22/39	92.3	1.58 (1.03, 2.43)	<0.0001
	No	376/3489	16.0	3.13 (2.82, 3.47)	
60-70	**Yes**	41/95	67.8	1.38 (1.00, 1.90)	0.0016
	No	719/14126	7.69	2.04 (1.89, 2.20)	
70-80	**Yes**	92/255	55.8	1.16 (0.93, 1.45)	0.0199
	No	1755/61526	4.18	1.43 (1.36, 1.51)	
80-90	**Yes**	217/669	50.6	1.12 (0.95, 1.31)	0.4352
	No	4295/192403	3.19	1.19 (1.15, 1.23)	
90-100	**Yes**	357/1164	46.1	1.04 (0.90, 1.19)	0.1651
	No	8377/415267	2.82	1.08 (1.05, 1.11)	
100-110	**Yes**	478/1665	41.4	(reference)	(reference)
	No	11471/617450	2.56		
110-120	**Yes**	1042/3432	43.4	1.01 (0.90, 1.12)	0.0011
	No	24023/1058533	2.96	1.14 (1.11, 1.16)	
>120	**Yes**	773/2870	39.5	0.96 (0.86, 1.08)	0.8824

	No	23761/1461674	2.24	0.90 (0.88, 0.92)	

**adjusted for sex, diabetes, hypertension, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table I2. Past cardiovascular disease-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for ALL-CAUSE MORTALITY by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction = 0.5039

Index eGFR category	Past cardiovascular disease status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	8/39	23.4	2.74 (1.31, 5.75)	0.5506
	No	122/3489	4.90	3.15 (2.63, 3.77)	
60-70	**Yes**	10/95	12.1	1.93 (0.99, 3.76)	0.6660
	No	269/14126	2.81	2.26 (2.00, 2.56)	
70-80	**Yes**	22/255	10.1	1.63 (1.00, 2.65)	0.8341
	No	608/61526	1.43	1.41 (1.30, 1.54)	
80-90	**Yes**	40/669	7.19	1.36 (0.92, 2.00)	0.4445
	No	1483/192403	1.09	1.14 (1.08, 1.21)	
90-100	**Yes**	53/1164	5.34	1.00 (0.70, 1.43)	0.7606
	No	2937/415267	0.979	1.05 (1.00, 1.10)	
100-110	**Yes**	72/1665	4.99	(reference)	(reference)
	No	4127/617450	0.913		
110-120	**Yes**	133/3432	4.42	0.80 (0.60, 1.07)	0.0116
	No	8564/1058533	1.05	1.12 (1.08, 1.17)	
>120	**Yes**	181/2870	7.66	1.31 (0.99, 1.73)	0.7550
	No	11331/1461674	1.06	1.18 (1.14, 1.23)	

**adjusted for sex, diabetes, hypertension, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table I3. Past cardiovascular disease-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for CARDIOVASCULAR COMPOSITE OUTCOME (first of congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Overall P-value of interaction < 0.0001

Index eGFR category	Past cardiovascular disease status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	22/39	91.4	1.76 (1.14, 2.71)	0.0997
	No	171/3489	7.09	1.72 (1.48, 2.01)	
60-70	**Yes**	36/95	58.1	1.30 (0.93, 1.83)	0.0310
	No	405/14126	4.31	1.57 (1.42, 1.73)	
70-80	**Yes**	82/255	49.5	1.11 (0.88, 1.41)	0.0126
	No	1157/61526	2.76	1.36 (1.28, 1.44)	
80-90	**Yes**	205/669	47.7	1.14 (0.96, 1.34)	0.5010
	No	2912/192403	2.16	1.19 (1.14, 1.24)	
90-100	**Yes**	336/1164	43.3	1.06 (0.92, 1.22)	0.3477
	No	5699/415267	1.91	1.09 (1.05, 1.13)	
100-110	**Yes**	441/1665	38.1	(reference)	(reference)
	No	7714/617450	1.72		
110-120	**Yes**	991/3432	41.3	1.04 (0.93, 1.17)	0.0130
	No	16369/1058533	2.02	1.15 (1.12, 1.18)	
>120	**Yes**	689/2870	35.2	0.95 (0.84, 1.07)	0.0010
	No	13387/1461674	1.26	0.76 (0.74, 0.78)	

**adjusted for sex, diabetes, hypertension, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table I4. Past cardiovascular disease-stratified event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) for KIDNEY FAILURE (first of initiation of dialysis or receipt of kidney transplant) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

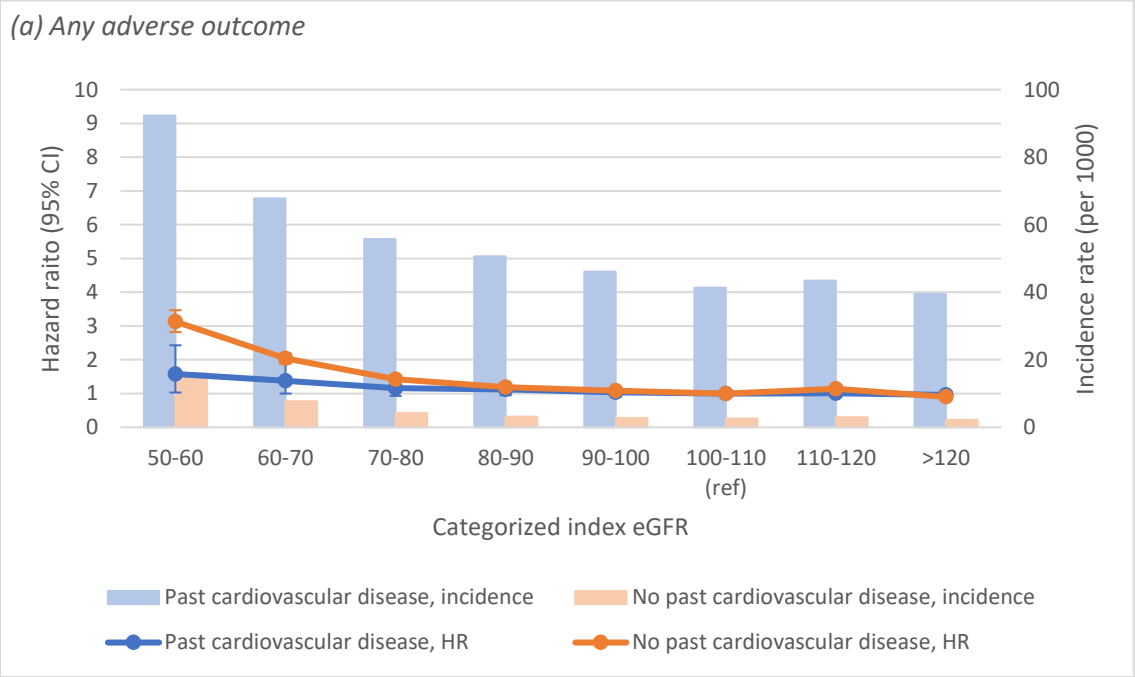
Overall P-value of interaction = 0.6636

Index eGFR category	Past cardiovascular disease status	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)	P-value for interaction
50-60	**Yes**	<6[a]/39	12.2	5.95 (1.69, 21.0)	0.0022
	No	182/3489	7.55	51.7 (41.8, 63.9)	
60-70	**Yes**	6/95	7.49	8.52 (2.88, 25.2)	0.0816
	No	178/14126	1.87	21.5 (17.4, 26.5)	
70-80	**Yes**	7/255	3.24	5.17 (1.84, 14.5)	0.3757
	No	141/61526	0.332	6.31 (5.05, 7.88)	
80-90	**Yes**	6/669	1.08	1.60 (0.55, 4.63)	0.2905
	No	167/192403	0.123	2.85 (2.31, 3.53)	
90-100	**Yes**	<6[a]/1164	0.403	0.65 (0.20, 2.17)	0.1286
	No	192/415267	0.0640	1.58 (1.29, 1.94)	
100-110	**Yes**	8/1665	0.556	(reference)	(reference)
	No	179/617450	0.0396		
110-120	**Yes**	8/3432	0.266	0.40 (0.15, 1.06)	0.0582
	No	362/1058533	0.0443	0.98 (0.82, 1.18)	
>120	**Yes**	7/2870	0.297	0.45 (0.16, 1.24)	0.1655
	No	495/1461674	0.0464	1.10 (0.93, 1.31)	

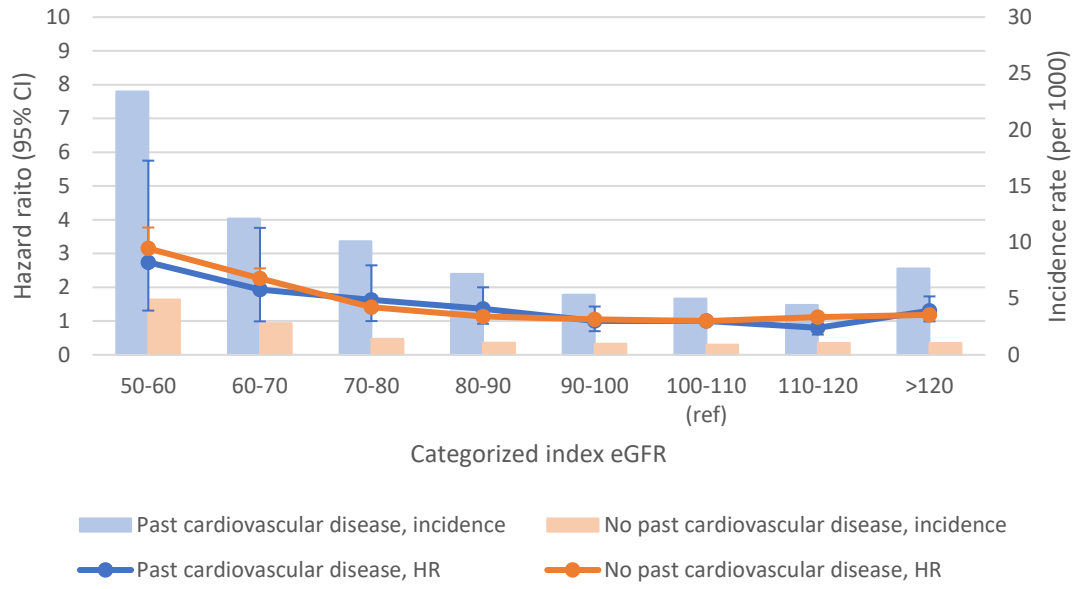
**adjusted for sex, diabetes, hypertension, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

[a]*Value suppressed per ICES privacy policies.*

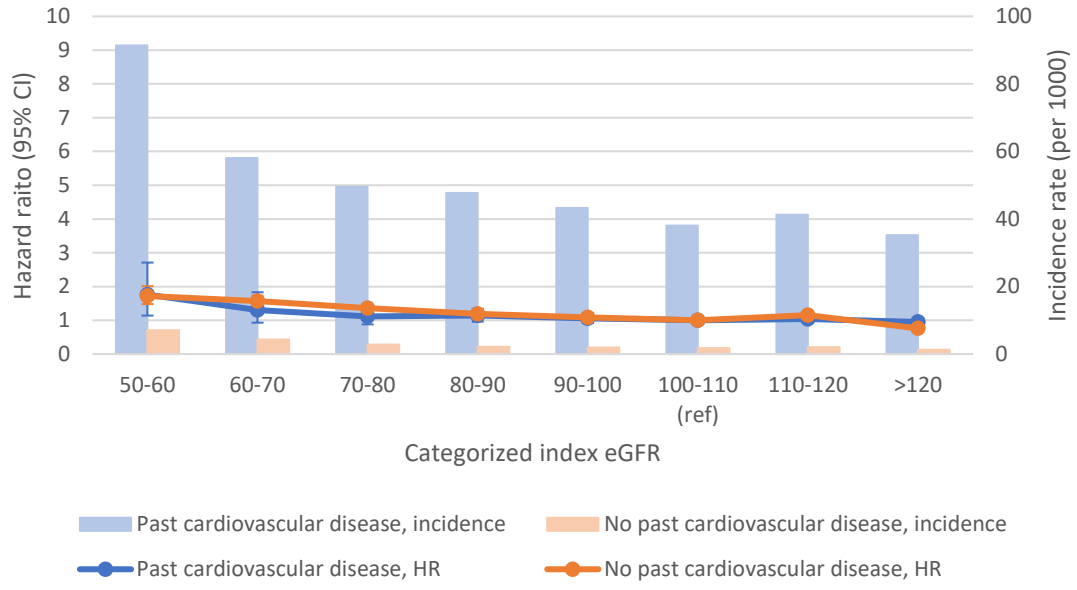
Figure I1: Past cardiovascular disease-stratified incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) any adverse outcome (first of all-cause mortality, cardiovascular outcomes, kidney failure), (b) all-cause mortality, (c) cardiovascular composite outcome (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation), (d) kidney failure, among those aged 18-39 and relative to eGFR 100-110

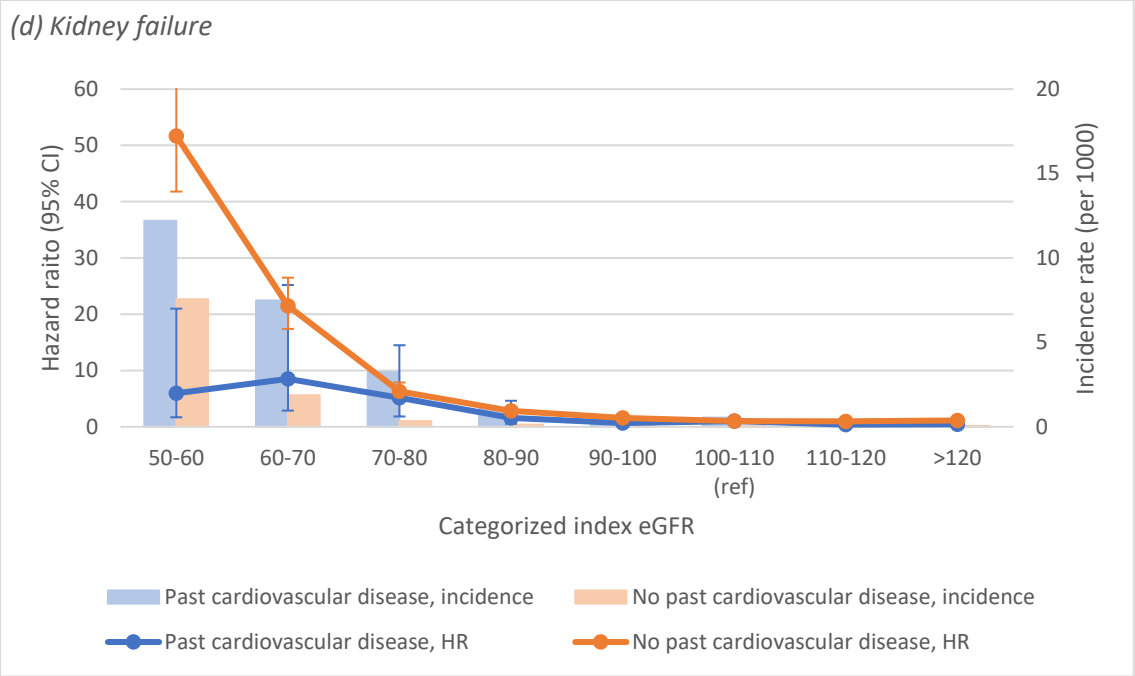


(b) All-cause mortality



(c) Cardiovascular composite outcome





**adjusted for sex, diabetes, hypertension, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

APPENDIX J: INTERACTIONS BETWEEN INDEX EGFR AND ACR (N = 773 615)

Table J1: Frequency, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) of ANY ADVERSE OUTCOME by interacting categories of index eGFR and albumin-creatinine ratio (ACR) measured within a year of index, in (a) ages 18-39, (b) ages 40-49, and (c) ages 50-65

Event frequency **Crude incidence rate** **Adjusted HR (95% CI)**

(a) 18-39 YEARS – ANY ADVERSE OUTCOME			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	16/247 10.2 2.27 (1.39, 3.74)	34/169 27.9 3.60 (2.55, 5.10)	79/203 65.3 7.90 (6.24, 10.0)
60-70	45/934 7.59 1.72 (1.27, 2.33)	45/306 22.4 3.15 (2.33, 4.27)	89/278 51.5 6.24 (4.99, 7.80)
70-80	121/3137 5.73 1.53 (1.26, 1.87)	51/542 13.7 2.38 (1.79, 3.17)	57/262 34.2 4.07 (3.10, 5.35)
80-90	254/8887 4.11 1.13 (0.98, 1.30)	73/1114 9.72 1.96 (1.54, 2.50)	72/370 29.6 3.73 (2.92, 4.77)
90-100	477/18521 3.62 1.03 (0.92, 1.16)	105/2196 6.89 1.47 (1.20, 1.81)	82/486 26.1 3.75 (2.97, 4.73)

100-110	666/26944 3.47 1.00 (reference)	170/3372 7.13 1.51 (1.27, 1.79)	62/554 16.1 2.59 (1.99, 3.37)
110-120	1561/50534 4.09 1.12 (1.02, 1.22)	433/7111 8.23 1.70 (1.50, 1.92)	152/1142 17.9 2.88 (2.41, 3.44)
>120	1315/64696 2.86 0.80 (0.73, 0.88)	551/11661 6.78 1.43 (1.28, 1.61)	183/1967 13.3 2.02 (1.71, 2.39)

(b) 40-49 YEARS – ANY ADVERSE OUTCOME			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	100/584 23.5 1.63 (1.33, 1.99)	111/347 44.2 2.46 (2.03, 2.98)	136/271 82.2 3.98 (3.34, 4.74)
60-70	250/2336 13.5 1.16 (1.02, 1.32)	148/628 32.3 1.92 (1.63, 2.27)	143/321 69.5 3.52 (2.97, 4.17)
70-80	611/7124 10.4 1.01 (0.92, 1.10)	224/1194 24.6 1.68 (1.46, 1.93)	149/396 53.7 2.96 (2.50, 3.49)
80-90	1368/16487 9.98 1.00 (0.93, 1.06)	369/2233 21.4 1.60 (1.43, 1.79)	189/551 50.3 2.69 (2.31, 3.12)

90-100	2201/25623 10.2 1.00 (reference)	539/3566 19.0 1.48 (1.35, 1.63)	195/609 43.0 2.39 (2.06, 2.77)
100-110	4428/44956 11.4 1.09 (1.04, 1.15)	1192/7338 20.0 1.54 (1.44, 1.66)	313/1064 40.0 2.53 (2.25, 2.85)
110-120	4430/46934 10.9 1.04 (0.99, 1.10)	1764/10600 20.5 1.58 (1.48, 1.68)	416/1502 36.9 2.13 (1.91, 2.37)
>120	365/2849 15.8 1.21 (1.08, 1.35)	279/1360 28.1 2.03 (1.79, 2.30)	63/233 39.6 2.43 (1.89, 3.12)

(c) 50-65 YEARS – ANY ADVERSE OUTCOME			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	1710/5317 41.2 1.37 (1.30, 1.44)	1104/2440 66.6 1.81 (1.70, 1.93)	693/1112 114 2.68 (2.48, 2.89)
60-70	3725/14457 31.9 1.19 (1.15, 1.24)	1768/4082 61.5 1.82 (1.73, 1.92)	809/1334 102 2.37 (2.20, 2.54)
70-80	6891/31210 26.8	2356/6443 50.3	827/1478 90.1

	1.07 (1.04, 1.10)	1.61 (1.54, 1.68)	2.39 (2.22, 2.56)
80-90	10309/50502 24.4 1.00 (reference)	3095/9153 45.3 1.53 (1.47, 1.59)	868/1640 83.7 2.30 (2.14, 2.46)
90-100	16474/75209 26.1 1.05 (1.02, 1.07)	5032/14942 44.8 1.51 (1.46, 1.56)	1134/2121 84.8 2.22 (2.08, 2.36)
100-110	19543/98418 23.4 0.96 (0.94, 0.98)	7195/23461 40.2 1.41 (1.37, 1.46)	1515/3182 71.4 2.03 (1.92, 2.14)
110-120	2242/10318 26.8 1.06 (1.01, 1.10)	1326/4167 43.4 1.47 (1.39, 1.56)	301/675 69.5 2.10 (1.87, 2.35)
>120	104/279 55.4 1.70 (1.40, 2.06)	85/211 61.4 1.92 (1.55, 2.38)	30/58 93.1 2.93 (2.05, 4.19)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table J2: Frequency, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) of ALL-CAUSE MORTALITY by interacting categories of index eGFR and albumin-creatinine ratio (ACR) measured within a year of index, in (a) ages 18-39, (b) ages 40-49, and (c) ages 50-65

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

(a) 18-39 YEARS – ALL-CAUSE MORTALITY			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	<6[a]/247 1.83 1.69 (0.54, 5.28)	6-10[a]/169 6.07 3.50 (1.72, 7.12)	20/203 12.6 6.76 (4.24, 10.8)
60-70	6-10[a]/934 1.47 1.24 (0.64, 2.42)	8/306 3.66 2.18 (1.07, 4.43)	21/276 10.1 4.83 (3.06, 7.63)
70-80	35/3137 1.62 1.51 (1.06, 2.16)	14/542 3.60 2.22 (1.29, 3.84)	9/262 4.68 2.50 (1.28, 4.90)
80-90	78/8887 1.25 1.17 (0.90, 1.52)	22/1114 2.84 2.17 (1.38, 3.40)	20/370 7.33 4.12 (2.59, 6.56)
90-100	135/18521 1.01 0.99 (0.80, 1.23)	30/2196 1.92 1.49 (1.01, 2.19)	26/486 7.58 4.34 (2.85, 6.63)

100-110	197/26944 1.01 1.00 (reference)	46/3372 1.88 1.39 (1.00, 1.93)	19/554 4.67 2.99 (1.84, 4.85)
110-120	432/50534 1.12 1.02 (0.86, 1.20)	135/7111 2.50 1.80 (1.44, 2.25)	44/1142 4.87 2.59 (1.86, 3.62)
>120	530/64696 1.14 1.08 (0.91, 1.26)	207/11661 2.50 1.87 (1.53, 2.28)	61/1967 4.26 2.53 (1.89, 3.40)

(b) 40-49 YEARS – ALL-CAUSE MORTALITY			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	35/584 7.54 2.35 (1.67, 3.31)	31/347 10.4 2.66 (1.85, 3.83)	44/271 19.9 4.84 (3.54, 6.61)
60-70	76/2336 3.89 1.49 (1.17, 1.89)	51/628 9.88 2.81 (2.10, 3.74)	58/321 22.4 5.58 (4.24, 7.35)
70-80	178/7124 2.92 1.22 (1.03, 1.45)	70/1194 7.01 2.17 (1.69, 2.80)	51/398 15.0 4.27 (3.20, 5.71)
80-90	392/16487 2.75 1.18 (1.03, 1.34)	106/2233 5.67 1.85 (1.50, 2.29)	75/551 16.4 4.08 (3.19, 5.21)

90-100	542/25623 2.41 1.00 (reference)	186/3566 6.11 2.16 (1.83, 2.55)	75/609 14.1 3.71 (2.91, 4.74)
100-110	1175/44956 2.91 1.15 (1.04, 1.28)	369/7338 5.73 1.94 (1.69, 2.21)	121/1064 13.3 3.93 (3.22, 4.80)
110-120	1337/46934 3.17 1.24 (1.12, 1.37)	601/10600 6.50 2.18 (1.94, 2.45)	158/1502 12.3 3.32 (2.77, 3.97)
>120	150/2849 6.20 1.95 (1.62, 2.34)	128/1360 11.8 3.88 (3.20, 4.72)	25/233 13.8 3.91 (2.61, 5.84)

(c) 50-65 YEARS – ALL-CAUSE MORTALITY			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	758/5317 15.7 1.67 (1.55, 1.81)	599/2440 29.1 2.76 (2.53, 3.01)	418/1112 47.8 4.20 (3.79, 4.65)
60-70	1527/14457 11.6 1.36 (1.28, 1.44)	897/4082 25.4 2.51 (2.33, 2.70)	464/1334 42.0 3.72 (3.38, 4.11)
70-80	2583/31210 9.07	1108/6443 19.9	470/1478 37.8

	1.12 (1.06, 1.18)	2.03 (1.90, 2.17)	3.53 (3.20, 3.89)
80-90	3701/50502 8.00 1.00 (reference)	1397/9153 17.4 1.85 (1.74, 1.97)	492/1640 35.8 3.44 (3.13, 3.79)
90-100	6276/75209 9.03 1.10 (1.06, 1.15)	2280/14942 17.4 1.86 (1.76, 1.96)	629/2121 35.5 3.25 (2.99, 3.54)
100-110	7547/98418 8.32 1.02 (0.98, 1.06)	3254/23461 15.9 1.73 (1.65, 1.82)	836/3182 31.5 3.04 (2.82, 3.28)
110-120	1035/10318 11.4 1.33 (1.24, 1.43)	621/4167 17.8 1.93 (1.77, 2.10)	160/675 30.4 3.17 (2.70, 3.71)
>120	56/279 25.7 2.35 (1.80, 3.06)	57/211 36.3 3.59 (2.76, 4.66)	17/58 40.9 4.61 (2.86, 7.43)

***adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

[a] Value suppressed per ICES privacy policies.

Table J3: Frequency, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) of CARDIOVASCULAR COMPOSITE OUTCOME by interacting categories of index eGFR and albumin-creatinine ratio (ACR) measured within a year of index, in (a) ages 18-39, (b) ages 40-49, and (c) ages 50-65

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

(a) 18-39 YEARS – CARDIOVASCULAR COMPOSITE OUTCOME			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	8/247 5.01 1.36 (0.68, 2.74)	18/169 14.4 2.24 (1.40, 3.60)	37/203 26.3 3.32 (2.37, 4.65)
60-70	32/934 5.38 1.53 (1.06, 2.20)	27/306 13.1 2.13 (1.44, 3.14)	40/276 20.6 2.65 (1.91, 3.66)
70-80	89/3137 4.21 1.48 (1.18, 1.85)	34/542 9.08 1.93 (1.36, 2.74)	33/262 18.6 2.41 (1.69, 3.43)
80-90	187/8887 3.03 1.10 (0.93, 1.30)	55/1114 7.31 1.84 (1.40, 2.44)	49/370 19.5 2.73 (2.03, 3.67)
90-100	353/18521 2.68 1.01 (0.88, 1.16)	76/2196 4.97 1.33 (1.05, 1.70)	54/486 16.7 2.74 (2.07, 3.64)

100-110	500/26944 2.60 1.00 (reference)	134/3372 5.61 1.50 (1.23, 1.81)	38/554 9.74 1.91 (1.36, 2.67)
110-120	1189/50534 3.12 1.13 (1.02, 1.26)	328/7111 6.23 1.64 (1.42, 1.89)	104/1142 12.1 2.48 (2.01, 3.08)
>120	846/64696 1.84 0.69 (0.62, 0.77)	381/11661 4.68 1.27 (1.11, 1.45)	107/1967 7.69 1.40 (1.13, 1.74)

(b) 40-49 YEARS – CARDIOVASCULAR COMPOSITE OUTCOME			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	70/584 16.4 1.31 (1.03, 1.67)	83/347 32.4 2.04 (1.63, 2.54)	82/271 44.2 2.25 (1.80, 2.81)
60-70	199/2336 10.7 1.10 (0.95, 1.27)	114/628 24.7 1.70 (1.41, 2.06)	92/321 40.9 2.18 (1.77, 2.70)
70-80	467/7124 7.97 0.94 (0.85, 1.04)	174/1194 19.1 1.51 (1.29, 1.76)	112/398 38.6 2.37 (1.95, 2.87)
80-90	1080/16487 7.88 0.96 (0.89, 1.04)	302/2233 17.5 1.53 (1.35, 1.73)	148/551 38.7 2.32 (1.96, 2.75)

90-100	1792/25623 8.28 1.00 (reference)	424/3566 14.9 1.38 (1.24, 1.53)	160/609 34.9 2.16 (1.83, 2.54)
100-110	3569/44956 9.22 1.08 (1.02, 1.14)	958/7338 16.0 1.47 (1.36, 1.60)	257/1064 32.6 2.33 (2.04, 2.66)
110-120	3465/46934 8.54 1.00 (0.95, 1.06)	1385/10600 16.1 1.47 (1.37, 1.57)	318/1502 28.0 1.86 (1.65, 2.10)
>120	261/2849 11.3 1.07 (0.94, 1.22)	201/1360 20.2 1.72 (1.48, 1.99)	48/233 30.0 2.05 (1.53, 2.73)

(c) 50-65 YEARS – CARDIOVASCULAR COMPOSITE OUTCOME			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	1342/5317 32.3 1.31 (1.23, 1.38)	842/2440 50.4 1.60 (1.49, 1.71)	512/1112 80.5 2.10 (1.92, 2.30)
60-70	2942/14457 25.1 1.17 (1.12, 1.22)	1384/4082 48.0 1.69 (1.60, 1.79)	655/1334 80.5 2.10 (193, 2.27)
70-80	5460/31210 21.2 1.06 (1.03, 1.10)	1898/6443 40.5 1.56 (1.49, 1.65)	667/1478 71.5 2.19 (2.02, 2.37)

80-90	8136/50502 19.3 1.00 (reference)	2481/9153 36.2 1.49 (1.42, 1.56)	684/1640 65.1 2.05 (1.89, 2.22)
90-100	12833/75209 20.3 1.03 (1.00, 1.06)	3990/14942 35.5 1.46 (1.41, 1.52)	925/2121 68.4 2.07 (1.94, 2.22)
100-110	14804/98418 17.7 0.93 (0.90, 0.95)	5581/23461 31.1 1.35 (1.30, 1.40)	1185/3182 55.6 1.86 (1.75, 1.98)
110-120	1587/10318 19.0 0.95 (0.90, 1.01)	1002/4167 32.8 1.37 (1.28, 1.46)	234/675 53.9 1.92 (1.69, 2.19)
>120	70/279 37.2 1.44 (1.14, 1.82)	54/211 39.0 1.47 (1.12, 1.93)	25/58 77.5 2.85 (1.93, 4.22)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table J4: Frequency, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) of KIDNEY FAILURE by interacting categories of index eGFR and albumin-creatinine ratio (ACR) measured within a year of index, in (a) ages 18-39, (b) ages 40-49, and (c) ages 50-65

Event frequency **Crude incidence rate** **Adjusted HR (95% CI)**

(a) 18-39 YEARS – KIDNEY FAILURE			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	6/247 3.75 55.4 (19.7, 156)	15/169 11.8 118 (51.2, 270)	64/203 48.9 424 (209, 859)
60-70	7/934 1.15 20.0 (7.43, 53.7)	14/306 6.57 66.4 (28.6, 154)	67/276 37.0 325 (161, 656)
70-80	<6[a]/3137 0.139 2.79 (0.75, 10.3)	11-15[a]/542 2.87 37.8 (15.6, 91.4)	37/262 20.9 182 (87.1, 379)
80-90	<6[a]/8887 0.0639 1.34 (0.41, 4.35)	6-10[a]/1114 0.777 11.2 (3.98, 31.5)	37/370 14.2 124 (59.8, 260)
90-100	8/18521 0.0600 1.28 (0.49, 3.31)	10/2196 0.642 9.19 (3.73, 22.7)	44/486 13.5 137 (66.7, 283)

100-110	9/26944 0.0463 1.00 (reference)	18/3372 0.737 10.7 (4.78, 23.8)	24/554 6.04 64.6 (29.9, 140)
110-120	18/50534 0.0465 0.89 (0.40, 1.97)	28/7111 0.520 6.41 (3.00, 13.7)	56/1142 6.31 61.0 (30.0, 124)
>120	25/64696 0.0540 1.02 (0.48, 2.19)	50/11661 0.604 7.96 (3.91, 16.2)	68/1967 4.83 47.6 (23.6, 96.0)

(b) 40-49 YEARS – KIDNEY FAILURE			
Index	**Index albumin-creatinine ratio (ACR), mg/mmol**		
eGFR	**<3**	**3-30**	**≥30**
50-60	11/584 2.38 20.7 (9.78, 43.9)	19/347 6.53 42.6 (22.3, 81.5)	83/271 43.9 265 (158, 445)
60-70	10/2336 0.513 5.70 (2.63, 12.4)	15/628 2.93 21.2 (10.7, 42.1)	68/321 29.4 198 (117, 334)
70-80	17/7124 0.279 3.48 (1.79, 6.76)	17/1194 1.71 14.2 (7.29, 27.5)	62/398 19.6 121 (71.1, 205)
80-90	11/16487 0.0773 1.00 (0.47, 2.12)	33/2233 1.77 15.4 (8.69, 27.5)	62/551 14.1 85.7 (50.4, 145)

90-100	19/25623 0.0845 1.00 (reference)	33/3566 1.09 9.94 (5.59, 17.7)	47/609 9.07 63.8 (36.9, 110)
100-110	39/44956 0.0965 1.13 (0.65, 1.98)	56/7338 0.871 7.65 (4.49, 13.0)	65/1064 7.33 50.7 (30.0, 85.8)
110-120	66-70[a]/46934 0.157 1.80 (1.07, 3.03)	78/10600 0.845 7.24 (4.32, 12.1)	73/1502 5.76 36.6 (21.8, 61.7)
>120	<6[a]/2849 0.207 1.91 (0.71, 5.15)	11-15[a]/1360 1.39 10.5 (5.20, 21.1)	13/233 7.25 50.4 (24.6, 103)

(c) 50-65 YEARS – KIDNEY FAILURE			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	57/5317 1.19 5.07 (3.63, 7.08)	119/2440 5.87 21.4 (16.2, 28.3)	251/1112 31.6 106 (82.9, 136)
60-70	62/14457 0.473 2.28 (1.64, 3.15)	132/4082 3.77 14.7 (11.2, 19.2)	226/1334 21.6 73.3 (57.0, 94.1)
70-80	69/31210 0.243	119/6443 2.14	188/1478 15.8

	1.24 (0.90, 1.70)	9.05 (6.86, 11.9)	53.9 (41.7, 69.7)
80-90	87/50502 0.188 1.00 (reference)	101/9153 1.26 5.36 (4.02, 7.16)	164/1640 12.3 45.3 (34.8, 58.8)
90-100	132/75209 0.190 0.96 (0.74, 1.27)	115/14942 0.878 3.87 (2.93, 5.11)	159/2121 9.21 33.3 (25.6, 43.3)
100-110	150/98418 0.166 0.87 (0.67, 1.13)	164/23461 0.802 3.60 (2.77, 4.67)	173/3182 6.63 24.9 (19.2, 32.3)
110-120	11-15[a]/10318 0.154 0.80 (0.45, 1.40)	31-35[a]/4167 1.01 4.38 (2.95, 6.52)	21-25[a]/675 4.80 18.5 (11.8, 29.2)
>120	<6[a]/279 0.461 2.01 (0.28, 14.4)	<6[a]/211 1.28 5.96 (1.47, 24.2)	<6[a]/58 4.86 23.2 (5.70, 94.2)

***adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

[a]*Value suppressed per ICES privacy policies.*

Table J5: Frequency, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) of adverse outcomes by index eGFR categories among those with no ACR testing within a year of index (n = 7,956,923) among those aged 18-39

Index eGFR	Any adverse outcome	All-cause mortality	Cardiovascular composite outcome	Kidney failure
50-60	269/2909 13.6 2.56 (2.27, 2.89)	99/2909 4.79 2.95 (2.41, 3.61)	130/2909 6.46 1.56 (1.31, 1.86)	101/2909 4.99 46.6 (35.8, 60.8)
60-70	581/12705 6.88 1.85 (1.70, 2.01)	241/12705 2.80 2.28 (2.00, 2.60)	342/12705 4.04 1.49 (1.34, 1.66)	96/12705 1.12 17.8 (13.6, 23.2)
70-80	1618/57840 4.10 1.38 (1.31, 1.46)	572/57840 1.43 1.41 (1.29, 1.54)	1083/57840 2.74 1.31 (1.23, 1.40)	97/57840 0.243 5.89 (4.52, 7.66)
80-90	4113/182701 3.22 1.18 (1.14, 1.22)	1403/182701 1.09 1.14 (1.07, 1.21)	2826/182701 2.21 1.19 (1.14, 1.24)	126/182701 0.0977 2.84 (2.22, 3.63)
90-100	8070/395228 2.85 1.08 (1.05, 1.11)	2799/395228 0.978 1.05 (1.00, 1.11)	5552/395228 1.96 1.09 (1.05, 1.13)	134/395228 0.0469 1.47 (1.15, 1.86)
100-110	11051/588245 2.58 1.00 (reference)	3937/588245 0.913 1.00 (reference)	7483/588245 1.75 1.00 (reference)	136/588245 0.0316 1.00 (reference)
110-120	22919/1003178 2.98	8088/1003178 1.04	15739/1003178 2.05	268/1003178 0.0346

	1.13 (1.11, 1.16)	1.12 (1.08, 1.16)	1.14 (1.11, 1.17)	1.00 (0.81, 1.23)
>120	22485/1386220 2.23 0.90 (0.88, 0.92)	10714/1386220 1.06 1.19 (1.14, 1.23)	12742/1386220 1.26 0.76 (0.74, 0.79)	359/1386220 0.0354 1.13 (0.92, 1.38)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

APPENDIX K: SENSITIVITY ANALYSES – INDIVIDUALS WITH TWO INDEX EGFR MEASURES 90 DAYS TO 2 YEARS APART (N = 4 615 582)

Table K1: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for ANY ADVERSE OUTCOME (first of all-cause mortality, cardiovascular outcomes, kidney failure) relative to age-specific eGFR reference ranges, by age-group among those with two repeated eGFR measures 90 days to 2 years apart

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

Averaged index eGFR category	Age group		
	18-39 years	**40-49 years**	**50-65 years**
50-60	364/1119 45.1 4.49 (4.03, 4.99)	869/2802 39.4 2.07 (1.93, 2.22)	10499/25431 53.0 1.54 (1.51, 1.57)
60-70	385/3774 13.8 2.07 (1.87, 2.29)	1783/11808 17.9 1.38 (1.31, 1.45)	23098/79142 34.7 1.27 (1.25, 1.29)
70-80	918/18570 6.56 1.46 (1.36, 1.56)	4856/47126 11.7 1.14 (1.10, 1.18)	46349/198990 26.7 1.09 (1.08, 1.11)
80-90 (reference for 50-65)	2328/65043 4.67 1.21 (1.15, 1.26)	10659/122408 9.70 1.02 (0.99, 1.04)	73185/350526 23.5 1.00 (reference)
90-100 (reference for 40-49)	4645/156397 3.81	18049/210882 9.39	116478/545562 23.9

	1.04 (1.01, 1.08)	1.00 (reference)	1.01 (1.00, 1.02)
100-110 (reference for 18-39)	7722/272631 3.58 1.00 (reference)	32727/365278 9.65 1.04 (1.02, 1.06)	112335/567403 21.9 0.95 (0.94, 0.96)
110-120	14063/482875 3.56 1.00 (0.97, 1.03)	28194/311128 9.70 1.55 (1.48, 1.62)	12202/49580 28.7 1.13 (1.11, 1.16)
>120	12397/564974 2.83 0.84 (0.82, 0.86)	2226/13519 18.8 1.55 (1.48, 1.62)	706/1367 76.3 2.29 (2.13, 2.47)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table K2: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for ALL-CAUSE MORTALITY relative to age-specific eGFR reference ranges, by age-group among those with two repeated eGFR measures 90 days to 2 years apart

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

Averaged index eGFR category	**Age group**		
	18-39 years	**40-49 years**	**50-65 years**
50-60	106/1119 11.0 4.30 (3.53, 5.23)	334/2802 12.9 2.91 (2.60, 3.26)	5423/25431 22.6 2.08 (2.02, 2.14)
60-70	118/3774 4.02 2.10 (1.74, 2.53)	641/11808 6.02 1.86 (1.71, 2.02)	10073/79142 13.3 1.48 (1.45, 1.52)
70-80	309/18570 2.16 1.59 (1.41, 1.79)	1423/47126 3.28 1.25 (1.18, 1.33)	17993/198990 9.34 1.16 (1.14, 1.18)
80-90 (reference for 50-65)	669/65043 1.32 1.08 (0.99, 1.17)	2944/122408 2.58 1.04 (0.99, 1.09)	26639/350526 7.81 1.00 (reference)
90-100 (reference for 40-49)	1394/156397 1.13 0.97 (0.90, 1.03)	4921/210882 2.47 1.00 (reference)	44114/545562 8.26 1.05 (1.03, 1.06)

100-110 (reference for 18-39)	2520/272631 1.16 1.00 (reference)	9322/365278 2.65 1.05 (1.01, 1.08)	45890/567403 8.27 1.05 (1.04, 1.07)
110-120	4662/482875 1.17 1.02 (0.98, 1.07)	9635/311128 3.20 1.25 (1.21, 1.29)	6517/49580 14.1 1.61 (1.56, 1.65)
>120	5487/564974 1.24 1.14 (1.09, 1.20)	1252/13519 10.1 2.94 (2.76, 3.13)	543/1367 51.5 4.60 (4.22, 5.01)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table K3: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for CARDIOVASCULAR COMPOSITE OUTCOME (first of congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation) relative to age-specific eGFR reference ranges, by age-group among those with two repeated eGFR measures 90 days to 2 years apart

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

Averaged index eGFR category	**Age group**		
	18-39 years	**40-49 years**	**50-65 years**
50-60	144/1119 16.0 1.83 (1.55, 2.16)	567/2802 24.8 1.48 (1.36, 1.61)	8126/25431 40.7 1.41 (1.38, 1.44)
60-70	228/3774 8.08 1.52 (1.33, 1.73)	1305/11808 13.1 1.22 (1.15, 1.29)	18119/79142 27.2 1.22 (1.20, 1.24)
70-80	629/18570 4.49 1.32 (1.22, 1.44)	3784/47126 9.12 1.10 (1.06, 1.14)	36491/198990 21.0 1.08 (1.07, 1.10)
80-90 (reference for 50-65)	1733/65043 3.48 1.24 (1.17, 1.31)	8498/122408 7.73 1.02 (0.99, 1.05)	57724/350526 18.5 1.00 (reference)
90-100 (reference for 40-49)	3406/156397 2.80	14322/210882 7.45	90365/545562 18.5

	1.07 (1.02, 1.11)	1.00 (reference)	0.99 (0.98, 1.00)
100-110 (reference for 18-39)	5505/272631 2.56 1.00 (reference)	25700/365278 7.58 1.01 (0.99, 1.03)	83771/567403 16.3 0.90 (0.89, 0.91)
110-120	10005/482875 2.53 1.00 (0.97, 1.03)	21020/311128 7.23 0.98 (0.96, 1.01)	7971/49580 18.8 0.95 (0.93, 0.98)
>120	7529/564974 1.72 0.72 (0.69, 0.75)	1290/13519 10.9 1.14 (1.08, 1.21)	353/1367 38.1 1.45 (1.31, 1.62)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table K4: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for KIDNEY FAILURE (first of initiation of dialysis or receipt of kidney transplant) relative to age-specific eGFR reference ranges, by age-group among those with two repeated eGFR measures 90 days to 2 years apart

Event frequency **Crude incidence rate** **Adjusted HR (95% CI)**

Averaged index eGFR category	**Age group**		
	18-39 years	**40-49 years**	**50-65 years**
50-60	235/1119 27.6 94.7 (76.5, 117)	309/2802 12.6 30.3 (25.6, 35.9)	1212/25431 5.13 11.4 (10.5, 12.5)
60-70	133/3774 4.62 25.7 (20.2, 32.6)	216/11808 2.05 9.24 (7.71, 11.1)	922/79142 1.22 3.70 (3.37, 4.06)
70-80	123/18570 0.862 9.15 (7.18, 11.6)	226/47126 0.522 3.32 (2.78, 3.96)	934/198990 0.486 1.77 (1.61, 1.94)
80-90 (reference for 50-65)	112/65043 0.221 2.96 (2.31, 3.79)	229/122408 0.201 1.49 (1.25, 1.78)	881/350526 0.258 1.00 (reference)
90-100 (reference for 40-49)	105/156397 0.0851 1.26 (0.98, 1.62)	267/210882 0.134 1.00 (reference)	995/545562 0.186 0.71 (0.65, 0.78)

100-110 (reference for 18-39)	149/272631 0.0684 1.00 (reference)	354/365278 0.100 0.70 (0.59, 0.82)	897/567403 0.162 0.61 (0.56, 0.67)
110-120	218/482875 0.0546 0.75 (0.61, 0.93)	365/311128 0.121 0.77 (0.66, 0.90)	125/49580 0.271 0.88 (0.72, 1.06)
>120	287/564974 0.0651 0.93 (0.76, 1.13)	37/13519 0.298 1.16 (0.82, 1.65)	7/1367 0.666 1.90 (0.90, 4.01)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table K5: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for ANY ADVERSE OUTCOME (first of all-cause mortality, cardiovascular outcomes, kidney failure) relative to age-specific eGFR reference ranges, by age group

Event frequency **Crude incidence rate** **Adjusted HR (95% CI)**

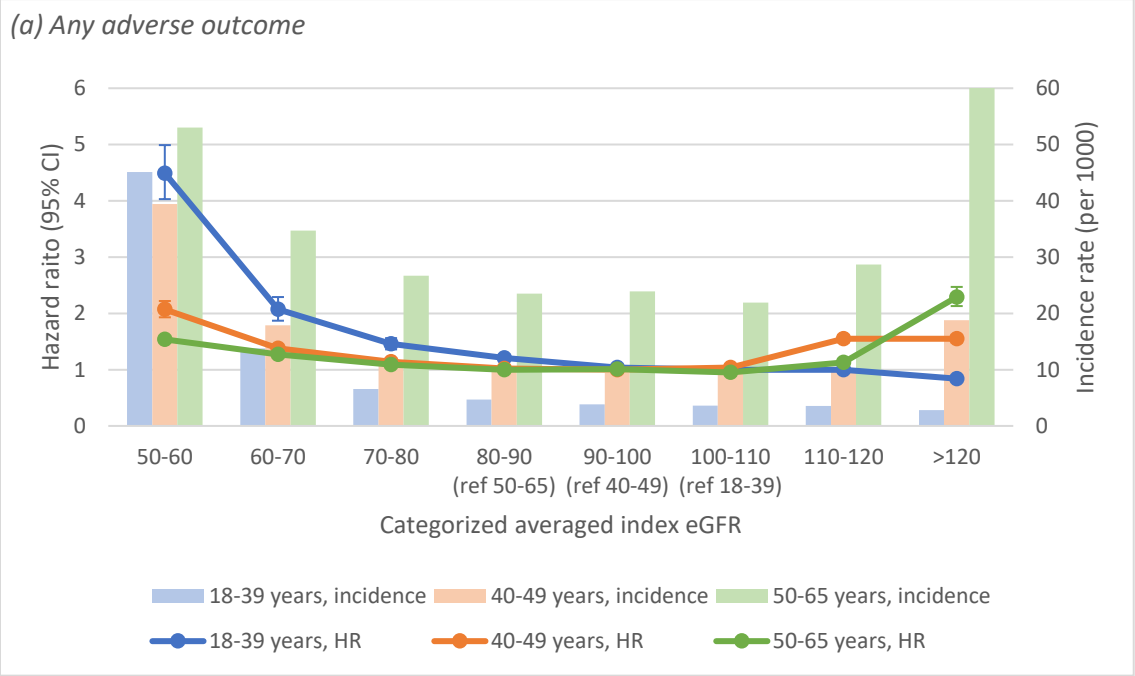
Index eGFR category	**Age group**					
	18-39		**40-49**		**50-65**	
	Main	**2 eGFR**	**Main**	**2 eGFR**	**Main**	**2 eGFR**
50-60	398/3528 16.8 2.91 (2.63, 3.21)	364/1119 45.1 4.49 (4.03, 4.99)	1212/6227 25.2 1.76 (1.66, 1.86)	869/2802 39.4 2.07 (1.93, 2.22)	13861/39979 44.8 1.51 (1.49, 1.54)	10499/25431 53.0 1.54 (1.51, 1.57)
60-70	760/14221 8.08 2.00 (1.86, 2.16)	385/3774 13.8 2.07 (1.87, 2.29)	2987/27455 13.6 1.35 (1.30, 1.40)	1783/11808 17.9 1.38 (1.31, 1.45)	31634/127001 30.5 1.25 (1.24, 1.27)	23098/79142 34.7 1.27 (1.25, 1.29)
70-80	1847/61781 4.39 1.42 (1.35, 1.49)	918/18570 6.56 1.46 (1.36, 1.56)	8120/102090 9.61 1.13 (1.10, 1.16)	4856/47126 11.7 1.14 (1.10, 1.18)	61896/313400 23.4 1.08 (1.07, 1.09)	46349/198990 26.7 1.09 (1.08, 1.11)

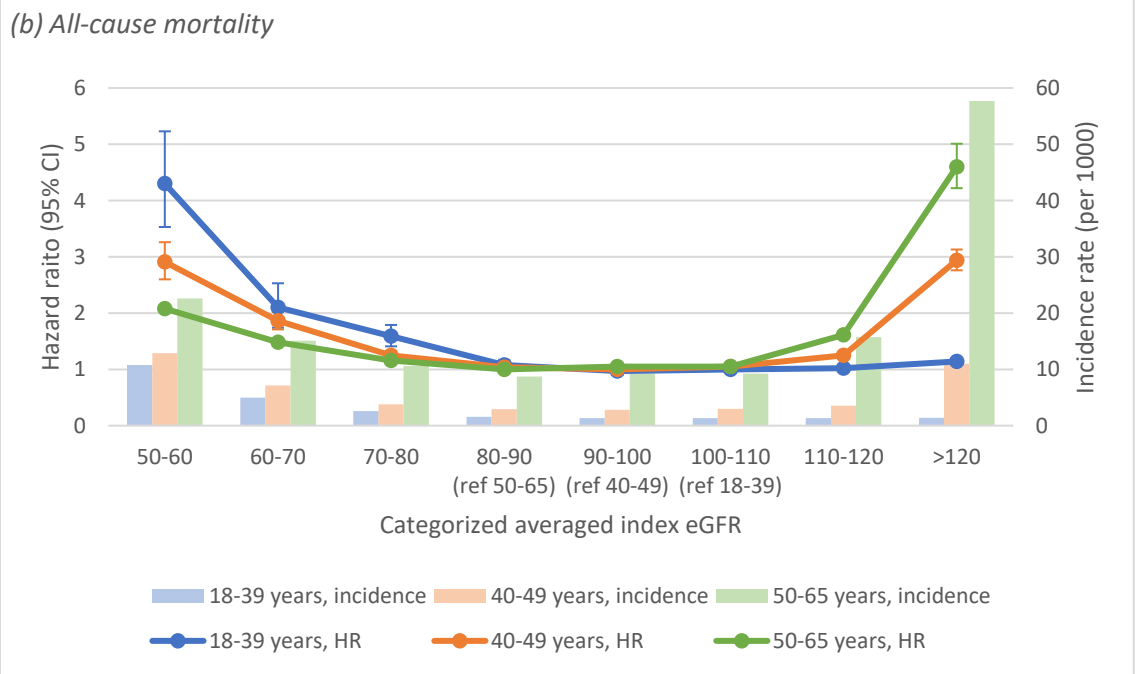
80-90 (reference for 50-65)	4512/193072 3.34 1.19 (1.15, 1.23)	2328/65043 4.67 1.21 (1.15, 1.26)	17219/247809 8.17 1.02 (0.99, 1.04)	10659/122408 9.70 1.02 (0.99, 1.04)	94546/526010 20.9 1.00 (reference)	73185/350526 23.5 1.00 (reference)
90-100 (reference for 40-49)	8734/416431 2.93 1.08 (1.05, 1.11)	4645/156397 3.81 1.04 (1.01, 1.08)	26410/385729 7.91 1.00 (reference)	18049/210882 9.39 1.00 (reference)	144772/750625 22.4 1.05 (1.04, 1.06)	116478/545562 23.9 1.01 (1.00, 1.02)
100-110 (reference for 18-39)	11949/619115 2.66 1.00 (reference)	7722/272631 3.58 1.00 (reference)	48876/626279 8.82 1.08 (1.06, 1.10)	32727/365278 9.65 1.04 (1.02, 1.06)	173742/971402 20.5 0.98 (0.97, 0.99)	112335/567403 21.9 0.95 (0.94, 0.96)
110-120	25065/1061965 3.08 1.13 (1.11, 1.16)	14063/482875 3.56 1.00 (0.97, 1.03)	47467/621341 8.56 1.07 (1.06, 1.09)	28194/311128 9.70 1.55 (1.48, 1.62)	20487/91549 26.8 1.16 (1.14, 1.18)	12202/49580 28.7 1.13 (1.11, 1.16)
>120	24534/1464544 2.30	12397/564974 2.83	4137/29221 16.7	2226/13519 18.8	1458/3097 71.5	706/1367 76.3

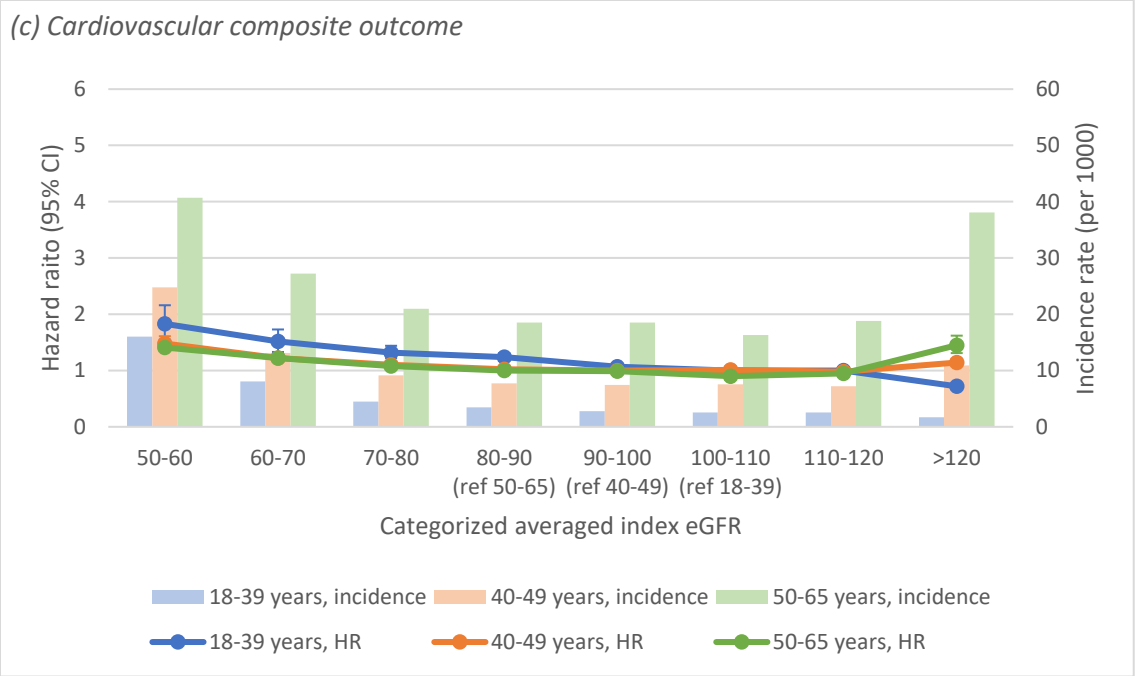
	0.90 (0.88, 0.92)	0.84 (0.82, 0.86)	1.58 (1.53, 1.64)	1.55 (1.48, 1.62)	2.21 (2.09, 2.32)	2.29 (2.13, 2.47)

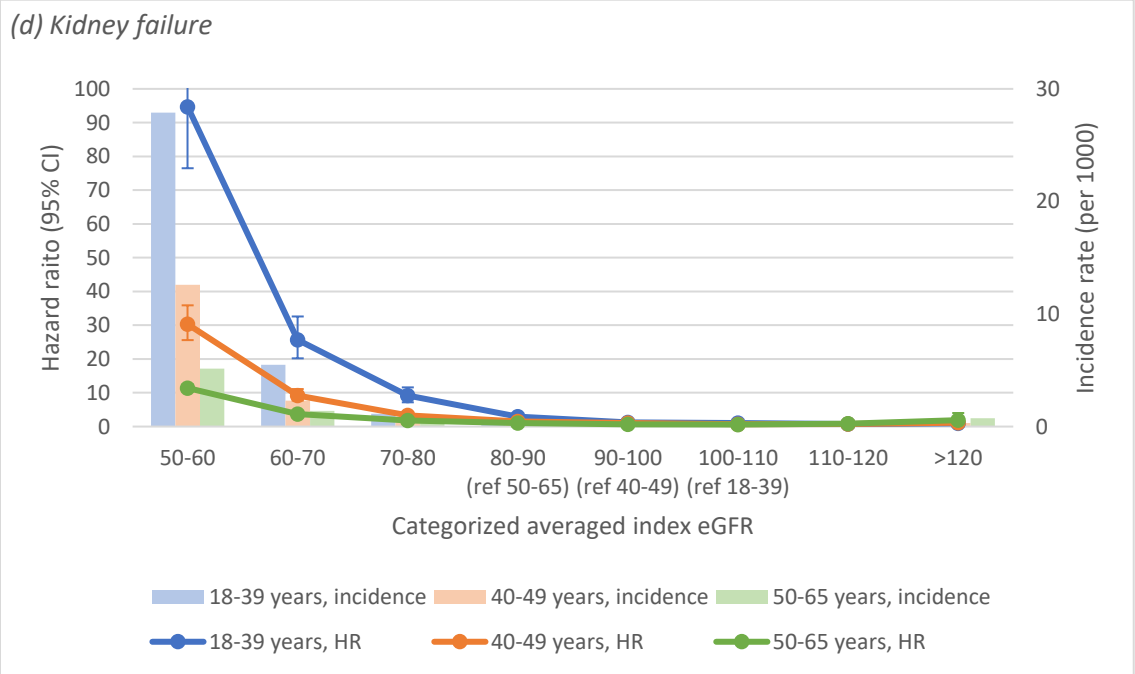
**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Figure K1: Incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) any adverse outcome, (b) all-cause mortality, (c) cardiovascular composite outcome, (d) kidney failure, by age-group among those with two repeated eGFR measures 90 days to 2 years apart







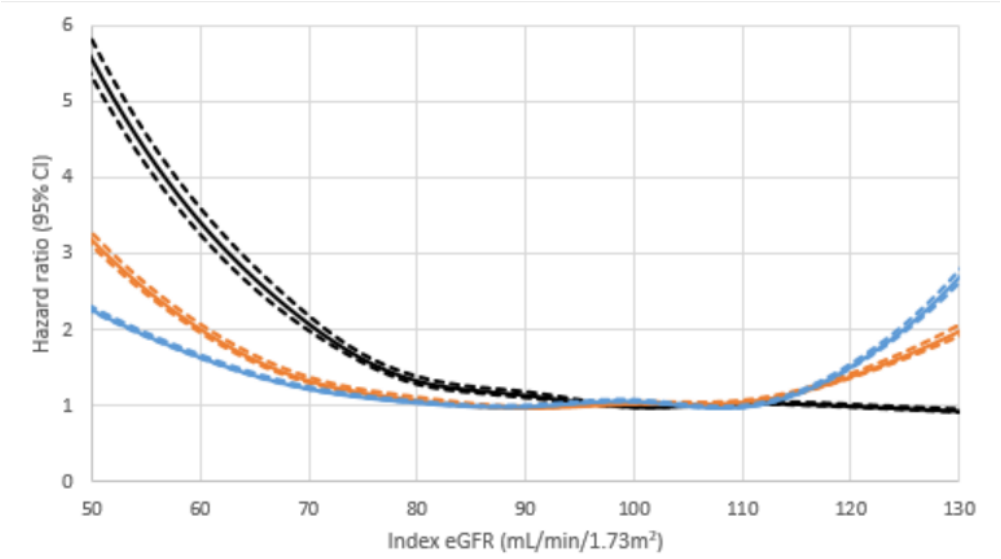


**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

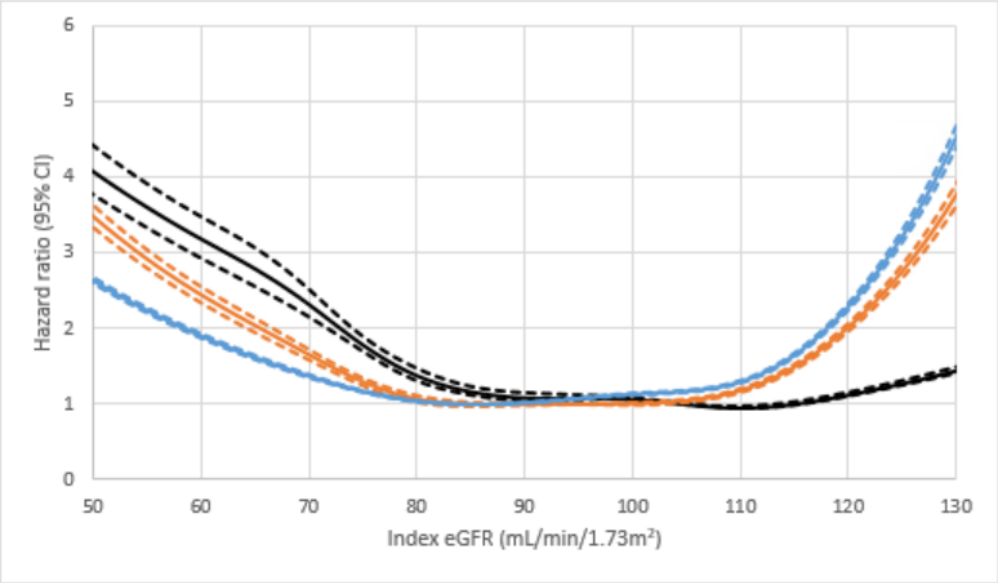
APPENDIX L: SENSITIVITY ANALYSES - RESTRICTED CUBIC SPLINES FOR HAZARD RATIOS OF ADVERSE OUTCOMES BY INDEX EGFR CATEGORIES

Figure L1: Restricted cubic splines of adjusted* hazard ratios of (a) any adverse outcome (first of all-cause mortality, cardiovascular outcomes, kidney failure), (b) all-cause mortality, (c) cardiovascular composite outcome (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation), and (d) kidney failure by age group**

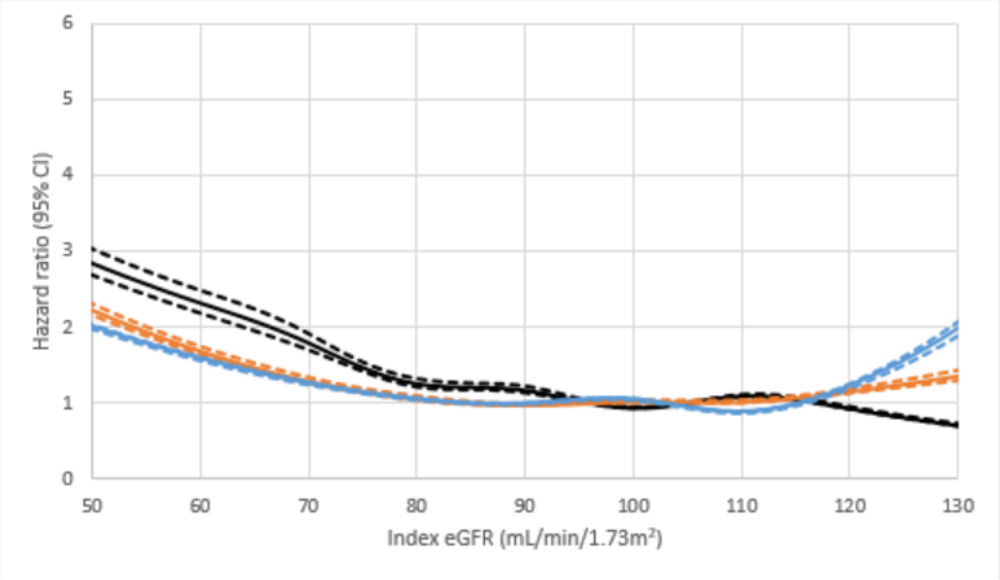
(a) Any adverse outcome



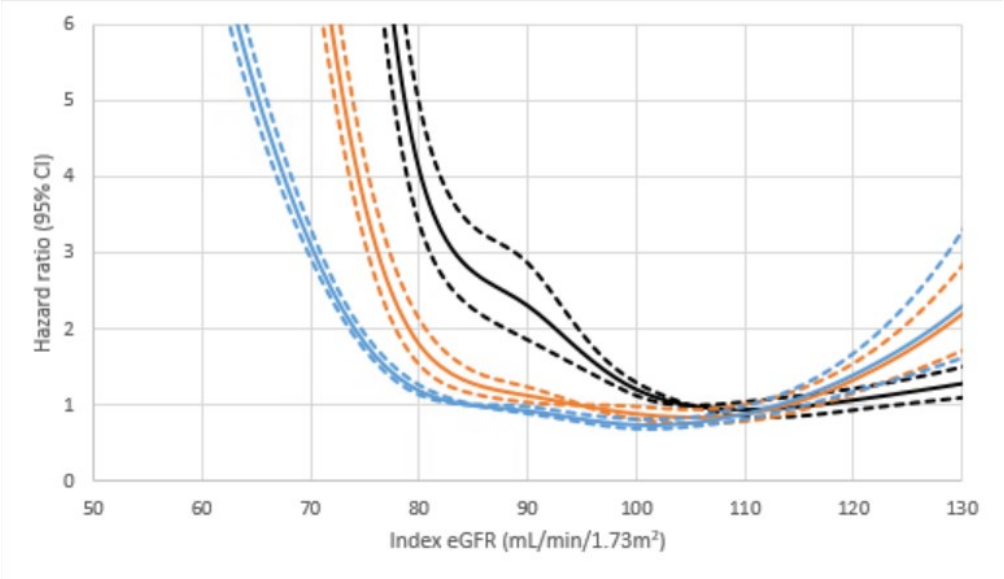
(b) All-cause mortality



(c) Cardiovascular composite outcome



(d) Kidney failure



**adjusted for sex, hypertension, diabetes, past cardiovascular disease, income quintile*

***18-39 years in black (reference eGFR 105), 40-49 years in orange (reference eGFR 95), 50-65 years in blue (reference eGFR 85), dashed lines represent 95% CI*

APPENDIX M: SENSITIVITY ANALYSES – INITIAL MODELS REPEATED USING A COMMON INDEX EGFR REFERENCE CATEGORY FOR ALL AGES (EGFR 90-110)

TABLE M1: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for ANY ADVERSE OUTCOME (first of all-cause mortality, cardiovascular outcomes, kidney failure) relative to eGFR 90-110, by age-group

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	398/3528 16.8 2.82 (2.55, 3.11)	1212/6227 25.2 1.67 (1.58, 1.77)	13861/39979 44.8 1.50 (1.47, 1.52)
60-70	760/14221 8.08 1.94 (1.81, 2.09)	2987/27455 13.6 1.28 (1.24, 1.33)	31634/127001 30.5 1.24 (1.22, 1.25)
70-80	1847/61781 4.39 1.38 (1.31, 1.44)	8120/102090 9.61 1.08 (1.05, 1.10)	61896/313400 23.4 1.07 (1.06, 1.08)
80-90	4512/193072 3.34 1.15 (1.12, 1.19)	17219/247809 8.17 0.97 (0.95, 0.98)	94546/526010 20.9 0.99 (0.98, 1.00)
90-110 (reference)	20683/1035546 2.76	75286/1012008 8.47	318514/1722027 21.3

	1.00 (reference)	1.00 (reference)	1.00 (reference)
110-120	25065/1061965 3.08 1.10 (1.08, 1.12)	47467/621341 8.56 1.02 (1.01, 1.03)	20487/91549 26.8 1.15 (1.13, 1.16)
>120	24534/1464544 2.30 0.87 (0.85, 0.89)	4137/29221 16.7 1.51 (1.46, 1.56)	1458/3097 71.5 2.18 (2.07, 2.30)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

TABLE M2: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for ALL-CAUSE MORTALITY relative to common eGFR 90-110, by age-group

Event frequency
Crude incidence rate
Adjusted HR (95% CI)

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	130/3528 5.15 3.06 (2.57, 3.65)	484/6227 9.17 2.24 (2.04, 2.45)	7058/39979 19.5 1.77 (1.73, 1.81)
60-70	279/14221 2.89 2.21 (1.96, 2.49)	1002/27455 4.35 1.50 (1.41, 1.60)	13807/127001 11.9 1.30 (1.28, 1.32)
70-80	630/61781 1.47 1.39 (1.28, 1.51)	2476/102090 2.83 1.13 (1.09, 1.18)	24521/313400 8.51 1.03 (1.02, 1.05)
80-90	1523/193072 1.12 1.12 (1.06, 1.19)	4917/247809 2.26 0.94 (0.91, 0.97)	35463/526010 7.28 0.91 (0.90, 0.92)
90-110 (reference)	7189/1035546 0.953 1.00 (reference)	22446/1012008 2.45 1.00 (reference)	131119/1722027 8.16 1.00 (reference)

110-120	8697/1061965 1.06 1.09 (1.06, 1.13)	16991/621341 2.98 1.19 (1.17, 1.21)	11052/91549 13.4 1.45 (1.43, 1.48)
>120	11512/1464544 1.08 1.16 (1.12, 1.19)	2285/29221 8.86 2.57 (2.46, 2.68)	1075/3097 46.3 3.52 (3.31, 3.74)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

TABLE M3: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for CARDIOVASCULAR COMPOSITE OUTCOME (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation) relative to common eGFR 90-110, by age group

Event frequency **Crude incidence rate** **Adjusted HR (95% CI)**

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	193/3528 7.92 1.64 (1.42, 1.89)	796/6227 16.3 1.30 (1.22, 1.40)	10385/39979 33.4 1.42 (1.39, 1.45)
60-70	441/14221 4.66 1.49 (1.35, 1.63)	2202/27455 10.0 1.18 (1.13, 1.23)	24378/127001 23.5 1.24 (1.23, 1.26)
70-80	1239/61781 2.94 1.29 (1.22, 1.37)	6186/102090 7.32 1.05 (1.02, 1.08)	47608/313400 18.0 1.10 (1.09, 1.11)
80-90	3117/193072 2.31 1.15 (1.10, 1.19)	13401/247809 6.36 0.97 (0.96, 0.99)	72594/526010 16.1 1.02 (1.01, 1.03)
90-110 (reference)	14190/1035546 1.90 1.00 (reference)	57872/1012008 6.51 1.00 (reference)	235503/1722027 15.8 1.00 (reference)

110-120	17360/1061965 2.14 1.10 (1.08, 1.13)	34311/621341 6.19 0.97 (0.96, 0.98)	13125/91549 17.2 1.00 (0.99, 1.02)
>120	14076/1464544 1.32 0.74 (0.72, 0.75)	2430/29221 9.83 1.17 (1.13, 1.22)	717/3097 35.1 1.46 (1.36, 1.57)

**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

TABLE M4: Event frequencies, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) for KIDNEY FAILURE (initiation of dialysis or receipt of kidney transplant) relative to common eGFR 90-110, by age group

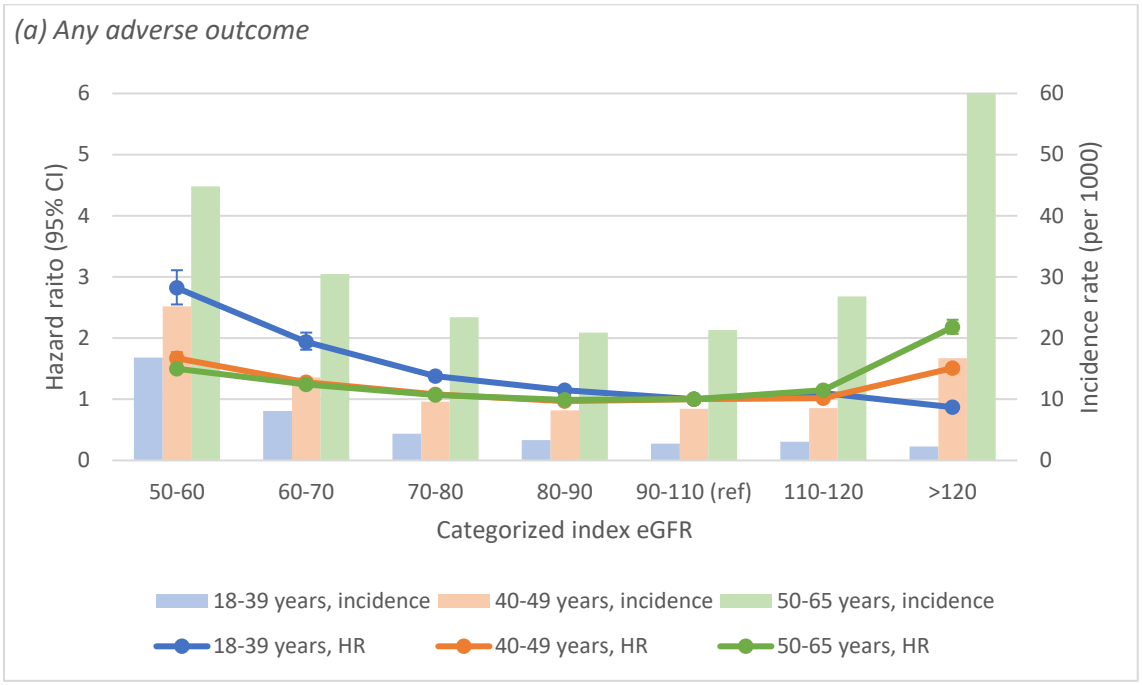
Event frequency
Crude incidence rate
Adjusted HR (95% CI)

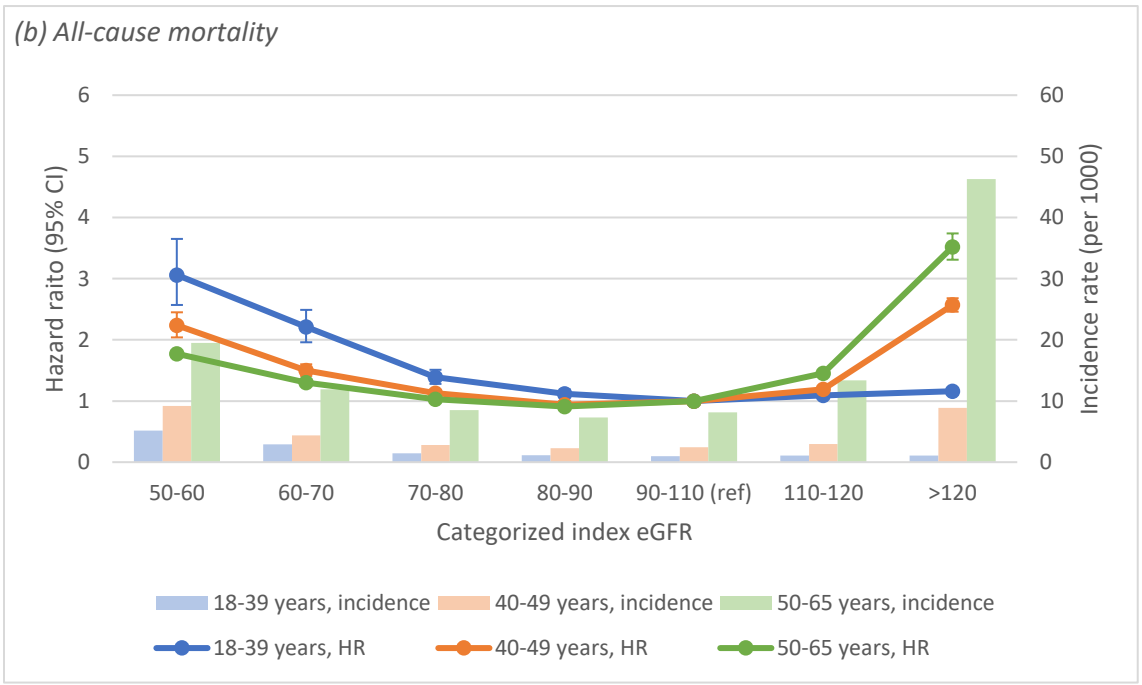
Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	186/3528 7.62 39.9 (33.3, 47.7)	261/6227 5.05 20.3 (17.6, 23.4)	1067/39979 2.98 10.2 (9.52, 11.0)
60-70	184/14221 1.92 17.2 (14.4, 20.6)	244/27455 1.06 7.86 (6.81, 9.08)	1104/127001 0.954 4.44 (4.14, 4.77)
70-80	148/61781 0.347 5.14 (4.24, 6.22)	281/102090 0.321 3.22 (2.82, 3.69)	1058/313400 0.368 2.09 (1.95, 2.24)
80-90	173/193072 0.127 2.30 (1.92, 2.76)	316/247809 0.145 1.62 (1.42, 1.84)	1104/526010 0.227 1.38 (1.28, 1.47)
90-110 (reference)	383/1035546 0.0508 1.00 (reference)	862/1012008 0.0941 1.00 (reference)	2738/1722027 0.170 1.00 (reference)

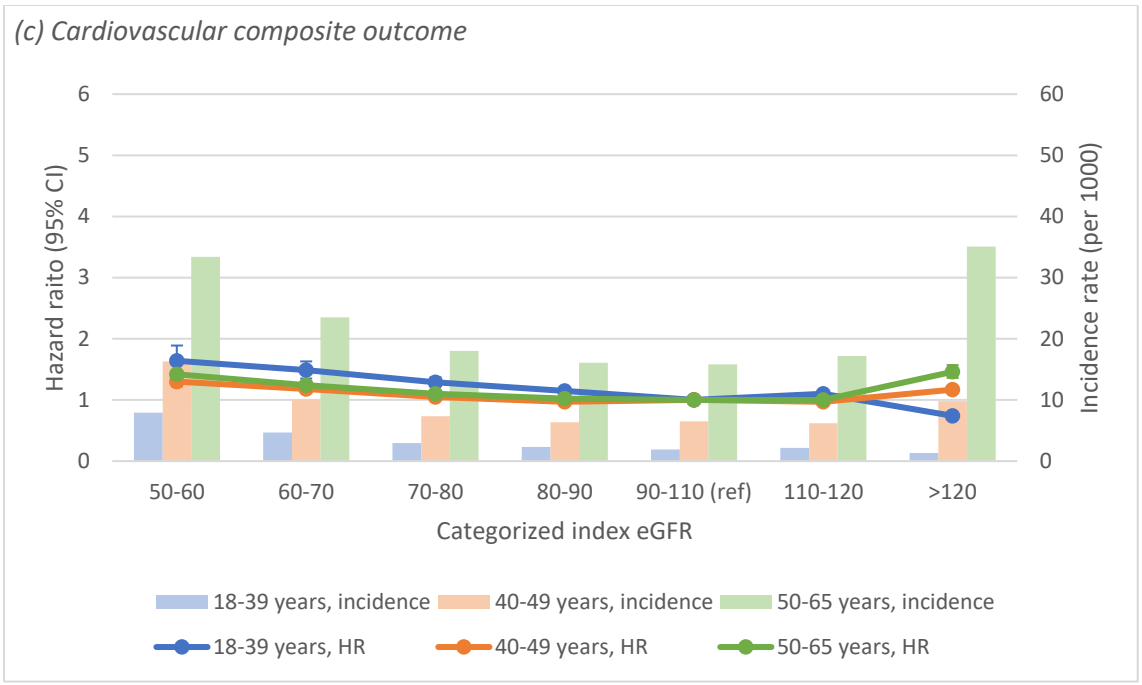
110-120	370/1061965 0.0451 0.78 (0.68, 0.90)	608/621341 0.107 1.02 (0.92, 1.13)	211/91549 0.257 1.25 (1.08, 1.44)
>120	502/1464544 0.0469 0.88 (0.77, 1.00)	74/29221 0.287 1.66 (1.30, 2.10)	12/3097 0.518 1.88 (1.06, 3.31)

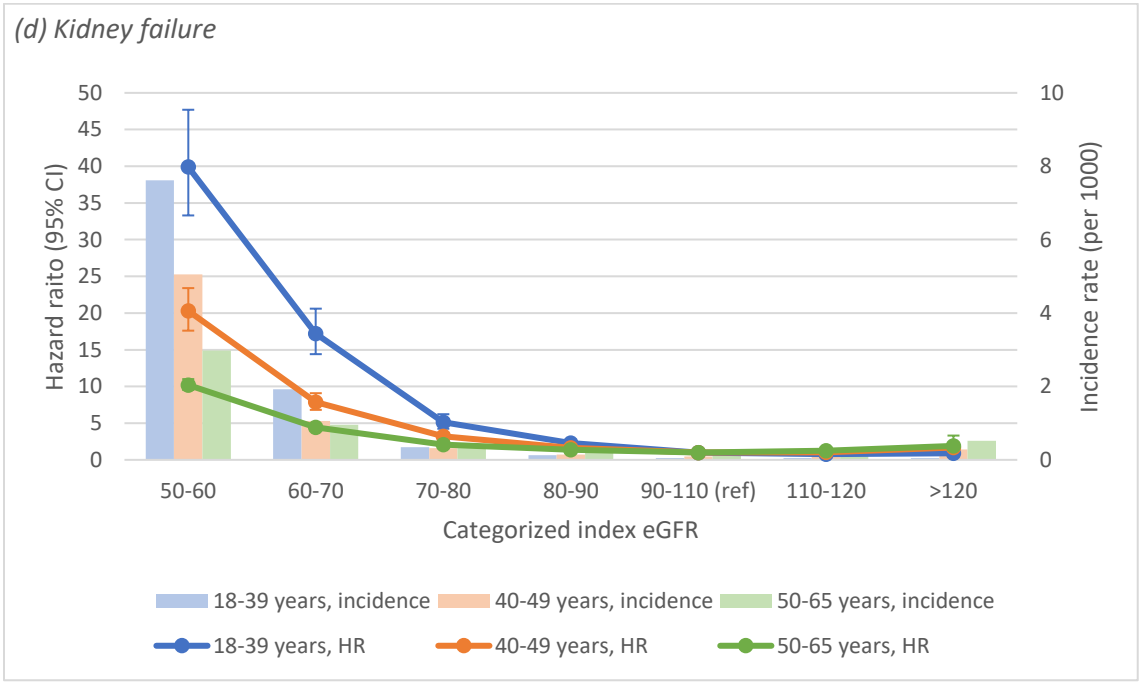
**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

FIGURE M1: Incidence rates (events per 1000 person-years) and adjusted* hazard ratios (HRs, 95% CI) for (a) any adverse outcome (first of all-cause mortality, cardiovascular outcomes, kidney failure), (b) all-cause mortality, (c) cardiovascular composite outcome (first of heart failure including congestive heart failure, acute coronary syndrome, stroke, atrial fibrillation), (d) kidney failure, relative to eGFR 90-110, by age-group









**adjusted for sex, diabetes, hypertension, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

SUPPLEMENTARY MATERIAL FOR CHAPTER 4

APPENDIX A: RECORD STATEMENT

Section	Item Number	Recommendation	Reported
Title and abstract			
Title and abstract	1	1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included.	Title page, page 1
		1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract.	Page 1
		1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Pages 1, 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Pages 4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 5
Methods			
Study design	4	Present key elements of study design early in the paper	Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 6

Participants	6	6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided.	Pages 6-7
		6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided.	Pages 7-8, Appendices B and C
		6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Appendix D
Variables	7	7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Appendix C
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	Appendix B
Bias	9	Describe any efforts to address potential sources of bias.	Page 8

Study size	10	Explain how the study size was arrived at.	Appendix D
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why.	Pages 7-8
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) Cohort study - If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	Pages 8-9
Data access and cleaning methods	12	12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	Pages 6-7
		12.2: Authors should provide information on the data cleaning methods used in the study.	Pages 6-7
Linkage	12	12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	Page 6
Results			

Participants	13	13.1: Describe in detail the selection of the persons included in the study (i.e., study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	Appendix D, page 10
Descriptive data	14	(a) Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) Cohort study – summarize follow-up time (e.g., average and total amount)	Page 10, Table 1
Outcome data	15	Report numbers of outcome events or summary measures over time	Tables 2, 3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Pages 10-11, Tables 2 and 3, Figures 1 and 2

Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Page 11, Appendices E-H
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 12
Limitations	19	19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Page 13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence.	Pages 12-13
Generalizability	21	Discuss the generalizability (external validity) of the study results.	Page 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Pages 15
Accessibility of protocol, raw data, and programming code		22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Page 15

APPENDIX B: ICES DATABASES USED IN THIS STUDY

Canadian Organ Replacement Registry (CORR)	CORR is the national information system that records and analyzes activity and outcome of vital organ transplantation and renal dialysis activities (ICES holding restricted to Ontario donors and recipients). CORR will be used to identify and exclude individuals with ongoing or past history of renal replacement therapy (either ongoing or past chronic dialysis, or past receipt of kidney transplant).
Canadian Institute of Health Information – Discharge Abstract Database (CIHI-DAD)	CIHI-DAD collects diagnostic and procedural variables for each hospital admission in Ontario. Coding of primary and secondary diagnoses and inpatient procedures was done using the 9th version of the Canadian Modified International Classification of Disease system (ICD-9-CA) before 2002, and the 10th version (ICD-10-CA) for diagnoses after 2002. CIHI-DAD will be used to obtain demographics, assess hospitalizations, and comorbid conditions for each patient. These characteristics will act as study inclusion/exclusion criteria, confounders in multivariable models, as well as exposure and outcomes for Objective II.
Ontario Health Insurance Plan (OHIP) Claims History Database	Physicians in Ontario submit billing claims using fee and diagnosis codes outlined in the OHIP Schedule of Benefits. These codes capture information on inpatient, outpatient, and laboratory services provided to the patient. OHIP also contains data on nature of the service and diagnostic information. OHIP will be used to examine specialist referrals and healthcare provision of patients. OHIP will also be used to exclude patients with history of previous dialysis and/or transplantation. Previous chart abstraction studies have noted considerable agreement between abstracted OHIP codes and physician-recorded codes on medical charts (>90% for diagnoses, >88% for procedural codes).
Registered Persons Database (RPDB)	The RPDB contains information regarding Ontario residents' gender, date of birth, postal code, and vital status.
Ontario Laboratory Information System (OLIS)	OLIS is an electronic system that contains laboratory tests conducted for patients in Ontario. Data is available from 2007-2016 with serum creatinine values

	cleaned and at ICES' Central branch. OLIS will be used to determine index eGFR and UACR measurements for patients, to inform calculations of relative eGFR reduction in Objective I and generate index eGFR categories in Objective II.
Ontario Marginalization Index (ONMARG)	ONMARG contains factor scores and factor quintiles of the Ontario Marginalization Index (OMI), a census-based index to measure social marginalization across Ontario regions.[36] Absolute and relative marginalization are estimated across 4 axes: residential instability, material deprivation, dependency, and ethnic concentration. ONMARG will be used to categorize patients by quintiles of overall marginalization, to illustrate patient's relative socioeconomic status in descriptive analyses, and as a potential confounder/stratifying variable in multivariable/subgroup analyses.
National Ambulatory Care Reporting System (NACRS)	The NACRS is compiled by the Canadian Institute of Health Information (CIHI) and contains administrative, clinical (diagnoses, procedures), demographic, and administrative information for all patient visits made to hospital- and community-based ambulatory care centres (emergency departments, day surgery units, hemodialysis units, and cancer care clinics) in Ontario. At ICES, NACRS records are linked with CIHI-DAD and Ontario Mental Health Reporting System (OMHRS) to identify transitions to other care settings, such as inpatient acute care or psychiatric care. Prior to April 1, 2002, diagnoses (upto 6 per NACRS record) are captured using ICD-9 coding system and procedures (upto 10 per NACRS record) are captured using the CCP coding system. Following April 1, 2002, diagnoses (upto 10 per NACRS record) are captured using the ICD-10-CA coding system and interventions (upto 10 per NACRS record) are captured using the CCI coding system. NACRS emergency department diagnosis codes have been extensively validated previously.

APPENDIX C: COMMON DATA DEFINITIONS AND STUDY OUTCOMES ACROSS DATASETS

Variables	Description	Data Source	Codes or Possible Values
	Inclusion/exclusion criteria		
Estimated glomerular filtration rate (eGFR) (mL/min/1.73m^2)	At least one outpatient laboratory measures of serum creatinine for eGFR from January 1, 2008, to March 31, 2020 Sensitivity analysis: two or more outpatient laboratory measures, with at least one measure ≥90 days to ≤2 years post-index eGFR is based on serum creatinine measurements, converted using the 2021 Chronic Kidney Disease-Epidemiology (CKD-EPI) race-free equation	Ontario Laboratory Information System (OLIS)	Observation code = 14682-9
Albumin-to-creatinine ratio (ACR) (mg/mmol)	Laboratory measurement of urinary albumin within 1 year of index eGFR measure	OLIS	Observation code = 32294-1
Chronic dialysis	Evidence of chronic dialysis on or prior to index date, for exclusion	Canadian Organ Replacement Registry (CORR)	Treatment code ≠ 171, 181
Kidney transplant	Evidence of a kidney transplant on or prior to index date, either a single-kidney transplant or a multi-organ transplant	CORR	Treatment code = 171, 181

	including kidneys, for exclusion		
Living kidney donation	Evidence of living kidney donation within 5 years prior to index date, for exclusion	CORR, CIHI-DAD, NACRS	CORR donor type code: 02, 03, 04, 05, 06, 07, 10, 12, 15 ICD-10 code: Z524
Acute kidney injury	Evidence of diagnosis of acute kidney injury in the past 5 years prior to index, for exclusion	CIHI-DAD, NACRS	ICD-10 code: N17
Kidney stone ("calculus of kidney and ureter")	Evidence of diagnosis of kidney stones in the past 5 years prior to index, for exclusion	CIHI-DAD, NACRS	ICD-10 code: N20
Death	All-cause mortality prior to index date, for exclusion from cohort if prior to index	Registered Persons Database (RPDB)	
Outcomes			
Major cardiovascular adverse events (MACE and MACE + heart failure)	Hospitalization or emergency room visit for acute coronary syndrome, ischemic stroke, and/or heart failure; and/or death associated with cardiovascular diagnoses during a hospitalization or emergency room visit	Discharge Abstract Database (CIHI-DAD), National Ambulatory Care Reporting System (NACRS), Registered Persons Database (RPDB)	ICD-10 codes: *Cardiovascular mortality:* death recorded within a hospitalization/emergency room visit with a cardiovascular diagnosis (I00-I99) *Acute coronary syndrome:* I20, I22, I23, I24, I25 *Ischemic stroke*: I630, I631, I632, I633, I634, I635, I638, I639 *Heart failure:* I099, I420, I425, I426, I427,

			I428, I429, I43, I500, I501, I509, I255, J81
Key covariates			
Age	Age in years at index date	RPDB	
Sex	Biological sex at index date	RPDB	
Income quintile	Derived from postal codes and associated after-tax relative household income, within census areas	RPDB	
Rural living status	Derived from postal codes, Remoteness Index developed by Statistics Canada	RPDB	
Hypertension	Five year lookback from index date for history of hospitalizations for hypertension	ICES-generated cohort for hypertension (HYPERTENSION), derived from CIHI-DAD, NACRS	ICD-10 codes: I10, I11, I12, I13, I15
Diabetes mellitus	Five year lookback from index date for history of hospitalizations for diabetes	ICES-generated cohort for diabetes (ODD), derived from CIHI-DAD, NACRS	ICD-10 codes: E10, E11, E13, E14
Past cardiovascular outcomes	Five year lookback from index date for history of cardiovascular illness	CIHI-DAD, NACRS	ICD-10 codes: *Heart failure:* I099, I420, I425, I426, I427, I428, I429, I43, I500, I501, I509, I255, J81 *Acute coronary syndrome:* I20, I22, I23, I24, I25

			Stroke: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340 *Atrial fibrillation:* I48
Obesity	Five year lookback from index date for diagnoses of obesity	CIHI-DAD, NACRS	ICD-10 code: E66
Alcoholism	Five year lookback from index date for diagnoses of alcoholism	CIHI-DAD, NACRS	ICD-10 code: E244, E512, F10, G312, G621, G721, I426, K292, K70, K860, T510,
Smoking/nicotine dependence	Five year lookback from index date for diagnoses of cigarette smoking, nicotine dependence	CIHI-DAD, NACRS	ICD-10 code: F17
Hypercholesterolemia	Five year lookback from index date for diagnoses of sustained high serum cholesterol or lipid levels	CIHI-DAD, NACRS	ICD-10 code: E78
Hyperkalemia	Five year lookback from index date for diagnoses of elevated serum potassium levels presented in acute care	CIHI-DAD, NACRS	ICD-10 code: E875
Cancer	Five year lookback from index date for diagnoses of cancer, including: skin, mouth (lip, tonsil, etc), throat, stomach, small/large intestine, liver, gall bladder, pancreas,	CIHI-DAD, NACRS	ICD-10 codes:  Cancer 20141031.txt

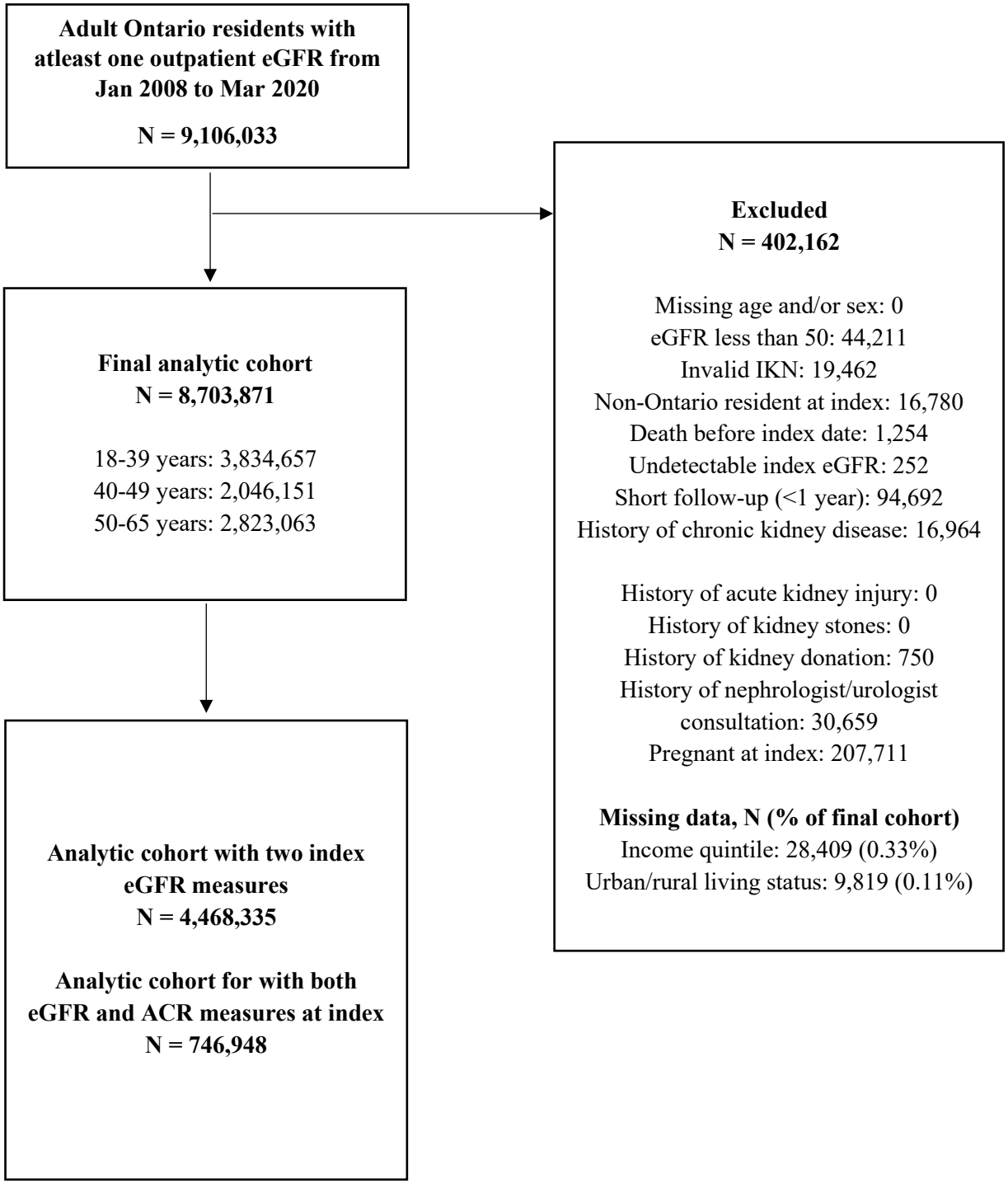
	breast, male/female reproductive organs, heart, lung, bone, urinary system (kidney, bladder, etc.), endocrine glands, as well as leukemias and lymphomas		
Chronic liver disease	Five year lookback from index for history of hospitalizations for chronic liver disease	CIHI-DAD, NACRS	ICD-10 codes: B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77
Chronic lung disease	Five year lookback from index for history of hospitalizations for chronic lung disease	CIHI-DAD, NACRS	ICD-10 codes: I272, I278, I279, J40, J41, J42, J43, J44, J45, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68, J701, J703, J704, J708, J709, J82, J84, J92, J941, J949, J953, J961, J969, J984, J988, J989, J99
Primary care visits	Frequency of physician billing claims for primary care visits during follow-up	Ontario Health Insurance Plan claims database (OHIP)	OHIP fee codes *Family medicine consultation:* A005, A911, A912, A905, A003, A900, A933 *Repeated consultation:* A006, A004 *Periodic health visit:* K131, K132 *Non-emergency inpatient services:* C005, C911, C912,

			C905, C006, C003, C004 *Subsequent visits:* C002, C007, C009
Emergency department visits	Frequency of emergency department visit/service claims in 5 years prior to index	NACRS	Indicator for presence of atleast one NACRS record in 5 years prior to index
Cardiologist visits	Frequency of cardiologist service claims in 5 years prior to index	OHIP	OHIP fee codes *Cardiology consultation:* A605, A765, A600, A675, A606, A603, A604, A601, A608 *Cardiology non-emergency visit:* C605, C765, C600, C675, C606, C603, C604, C601 *Cardiology subsequent visits:* C602, C607, C609
Endocrinologist visits	Frequency of endocrinologist service claims in 5 years prior to index	OHIP	OHIP fee codes *Endocrinology consultation:* A155, A765, A150, A255, A156, A153, A154, A151, A158 *Endocrinology non-emergency visit:* C155, C765, C150, C255, C156, C153, C154, C151 *Endocrinology subsequent visits:* C152, C157, C159

Nephrologist visits	Frequency of nephrologist service claims in 5 years prior to index	OHIP	OHIP fee codes *Nephrology consultation:* A165, A765, A160, A865, A166, A163, A164, A161, A168 *Non-emergency nephrology visit:* C165, C765, C160, C865, C166, C163, C164, C161 *Nephrology subsequent visits:* C162, C167, C169
Urologist visits	Frequency of urologist service claims in 5 years prior to index	OHIP	OHIP fee codes *Urology consultation:* A355, A935, A356, A353, A354 *Non-emergency urology visit:* C355, C935, C356, C353, C354 *Urology subsequent visits:* C352, C357, C359
Pregnancy at index	Exclude pregnant women at the time of index eGFR measurement (including those resulting in single/multiple live births, induced abortion, spontaneous abortion, threatened abortion, non-spontaneous/spontaneous still birth, pre-term	CIHI-DAD, NACRS, OHIP	ICD-10 codes: Z370-Z3791, O04, O08, O00, O021, O03, O04, O20, P072, P073, O30, O31, O60 OHIP fee codes: S785, A920, A921, P001, S752, A922, S756, S768, S784, S770

	birth, ectopic pregnancies)		

APPENDIX D: PATIENT FLOW DIAGRAM



APPENDIX E: RESULTS FROM INDIVIDUAL MACE COMPONENTS

Table E1: Event frequencies, crude incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) of CARDIOVASCULAR MORTALITY, relative to age-specific eGFR reference ranges, by age group

Index eGFR category	Age group		
	18-39	**40-49**	**50-65**
50-60	43/3528 1.70 3.80 (2.79, 5.17)	145/6227 2.75 2.64 (2.23, 3.14)	2379/39979 6.57 2.27 (2.17, 2.38)
60-70	83/14221 0.859 2.67 (2.13, 3.36)	277/27455 1.20 1.84 (1.62, 2.10)	4132/127001 3.56 1.58 (1.53, 1.64)
70-80	143/61781 0.335 1.48 (1.24, 1.77)	589/102090 0.673 1.28 (1.17, 1.41)	6654/313400 2.31 1.20 (1.16, 1.24)
80-90 (reference for 50-65)	316/193072 0.232 1.17 (1.03, 1.33)	1126/247809 0.518 1.05 (0.98, 1.14)	8953/526010 1.84 1.00 (reference)
90-100 (reference for 40-49)	615/416431 0.204 1.07 (0.96, 1.18)	1671/385729 0.486 1.00 (reference)	14339/750625 2.05 1.08 (1.05, 1.11)
100-110 (reference for 18-39)	845/619115 0.186 1.00 (reference)	3221/626279 0.562 1.09 (1.03, 1.16)	17864/971402 1.97 1.05 (1.03, 1.08)
110-120	1781/1061965	3972/621341	2831/91549

	0.217 1.10 (1.01, 1.19)	0.696 1.33 (1.25, 1.41)	3.44 1.57 (1.51, 1.64)
>120	2467/1464544 0.230 1.22 (1.13, 1.33)	581/29221 2.25 2.89 (2.63, 3.19)	283/3097 12.2 3.65 (3.24, 4.12)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table E2: Event frequencies, crude incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) of ACUTE CORONARY SYNDROME (including myocardial infarction events), relative to age-specific eGFR reference ranges, by age group

Index eGFR category	Age group		
	18-39	**40-49**	**50-65**
50-60	78/3528 3.13 1.41 (1.13, 1.77)	418/6227 8.26 1.17 (1.06, 1.29)	5692/39979 17.1 1.25 (1.21, 1.28)
60-70	169/14221 1.76 1.33 (1.14, 1.55)	1158/27455 5.16 1.12 (1.05, 1.19)	13266/127001 12.2 1.15 (1.13, 1.17)
70-80	491/61781 1.16 1.22 (1.11, 1.35)	3297/102090 3.84 1.06 (1.02, 1.10)	25598/313400 9.33 1.05 (1.03, 1.06)
80-90 (reference for 50-65)	1296/193072 0.955 1.19 (1.12, 1.27)	7154/247809 3.35 1.00 (0.97, 1.03)	39405/526010 8.44 1.00 (reference)
90-100 (reference for 40-49)	2489/416341 0.830 1.10 (1.04, 1.16)	10954/385729 3.24 1.00 (reference)	58395/750625 8.72 1.01 (0.99, 1.02)
100-110 (reference for 18-39)	3289/619115 0.728 1.00 (reference)	20621/626279 3.67 1.09 (1.07, 1.12)	66661/971402 7.64 0.93 (0.92, 0.94)
110-120	7222/1061965 0.884	17931/621341 3.19	6752/91549 8.56

	1.17 (1.12, 1.22)	1.00 (0.98, 1.03)	0.93 (0.91, 0.96)
>120	4295/1464544 0.402 0.60 (0.57, 0.62)	1190/29221 4.72 1.08 (1.01, 1.14)	291/3097 13.3 0.97 (0.86, 1.09)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table E3: Event frequencies, crude incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) of STROKE, relative to age-specific eGFR reference ranges, by age group

Index eGFR category	Age group		
	18-39	**40-49**	**50-65**
50-60	59/3528 2.36 1.88 (1.45, 2.43)	241/6227 4.67 1.55 (1.37, 1.77)	3095/39979 8.88 1.50 (1.45, 1.56)
60-70	155/14221 1.61 1.79 (1.53, 2.11)	670/27455 2.94 1.31 (1.20, 1.41)	7316/127001 6.48 1.29 (1.25, 1.32)
70-80	433/61781 1.02 1.38 (1.25, 1.53)	1905/102090 2.20 1.12 (1.07, 1.18)	14078/313400 5.00 1.09 (1.06, 1.11)
80-90 (reference for 50-65)	1088/193072 0.801 1.18 (1.10, 1.26)	4125/247809 1.91 1.02 (0.98, 1.06)	21357/526010 4.47 1.00 (reference)
90-100 (reference for 40-49)	2170/416431 0.723 1.10 (1.04, 1.16)	6329/385729 1.86 1.00 (reference)	31713/750625 4.62 1.02 (0.99, 1.04)
100-110 (reference for 18-39)	2970/619115 0.657 1.00 (reference)	11076/626279 1.95 1.00 (0.97, 1.04)	36946/971402 4.15 0.92 (0.91, 0.94)
110-120	6320/1061965 0.773	10991/621341 1.94	3897/91549 4.83

	1.14 (1.09, 1.19)	1.23 (1.14, 1.33)	0.99 (0.96, 1.02)
>120	5748/1464544 0.538 0.81 (0.78, 0.85)	739/29221 2.90 0.89 (0.87, 0.91)	208/3097 9.27 1.47 (1.28, 1.68)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

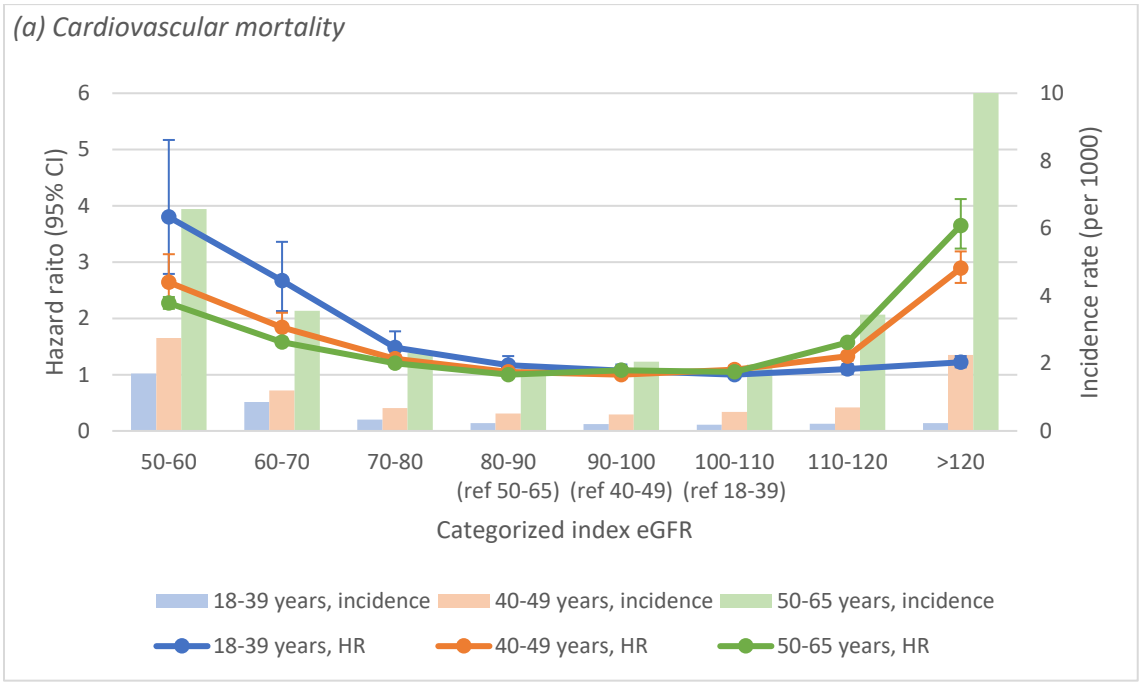
Table E4: Event frequencies, crude incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) of HEART FAILURE, relative to age-specific eGFR reference ranges, by age group

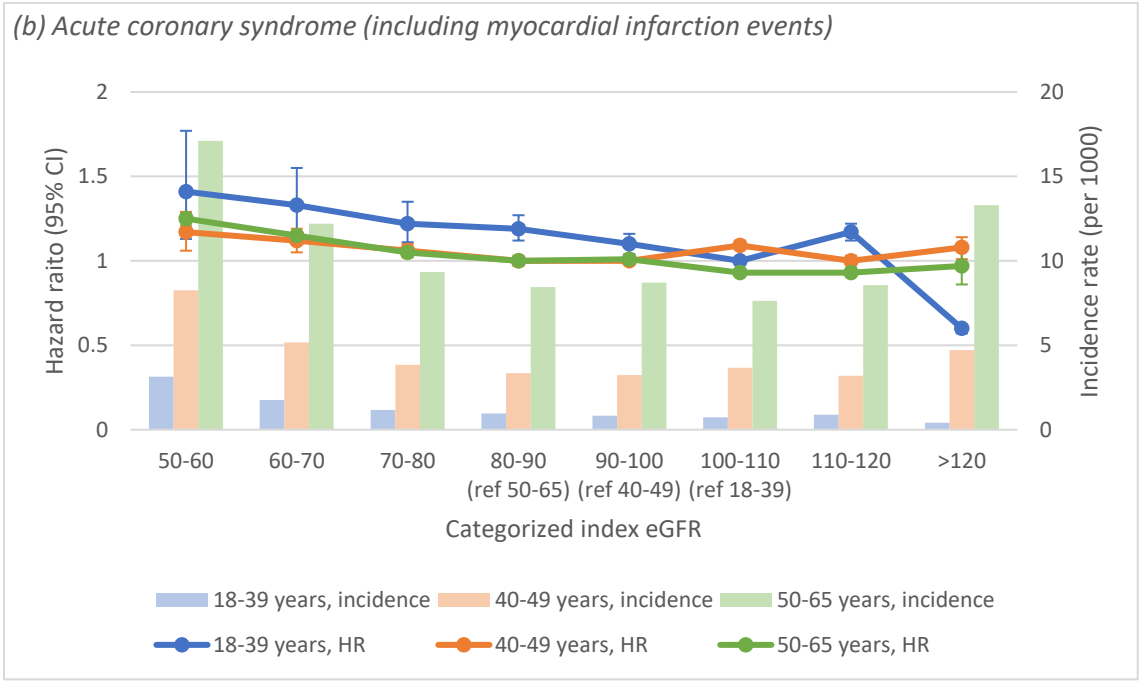
Index eGFR category	Age group		
	18-39	**40-49**	**50-65**
50-60	86/3528 3.46 4.25 (3.40, 5.30)	288/6227 5.60 2.89 (2.55, 3.27)	4017/39979 11.6 2.29 (2.21, 2.37)
60-70	148/14221 1.54 3.17 (2.66, 3.77)	517/27455 2.26 2.03 (1.85, 2.24)	6944/127001 6.12 1.64 (1.59, 1.69)
70-80	269/61781 0.632 2.09 (1.83, 2.39)	1025/102090 1.18 1.42 (1.32, 1.53)	10777/313400 3.79 1.22 (1.19, 1.25)
80-90 (reference for 50-65)	499/193072 0.367 1.45 (1.30, 1.61)	1823/247809 0.842 1.12 (1.05, 1.19)	14010/526010 2.91 1.00 (reference)
90-100 (reference for 40-49)	759/416431 0.252 1.05 (0.96, 1.15)	2526/385729 0.737 1.00 (reference)	22098/750625 3.19 1.07 (1.04, 1.09)
100-110 (reference for 18-39)	1042/619115 0.230 1.00 (reference)	4865/626279 0.852 1.09 (1.04, 1.14)	26285/971402 2.93 0.99 (0.98, 1.02)
110-120	2218/1061965 0.271	5348/621341 0.940	3457/91549 4.26

	1.08 (1.01, 1.17)	1.18 (1.12, 1.24)	1.26 (1.21, 1.31)
>120	2573/1464544 0.241 1.04 (0.97, 1.12)	622/29221 2.43 2.06 (1.88, 2.25)	257/3097 11.5 2.28 (2.01, 2.58)

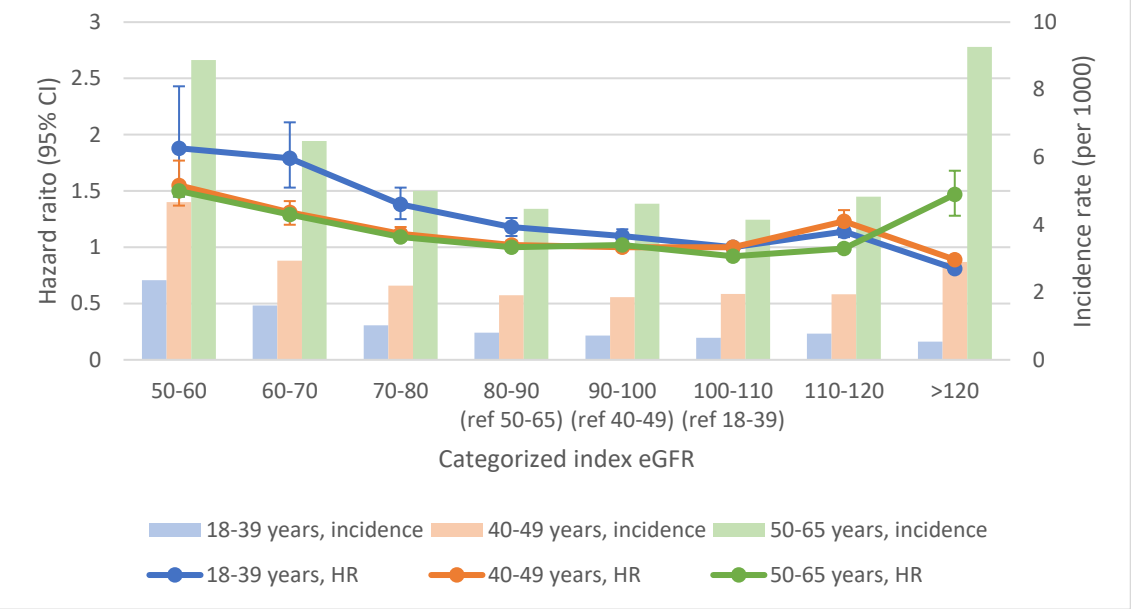
**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

FIGURE E1: Incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) cardiovascular mortality, (b) acute coronary syndrome (including myocardial infarction events), (c) stroke, and (d) heart failure (including congestive heart failure), relative to age-specific eGFR reference ranges, by age group

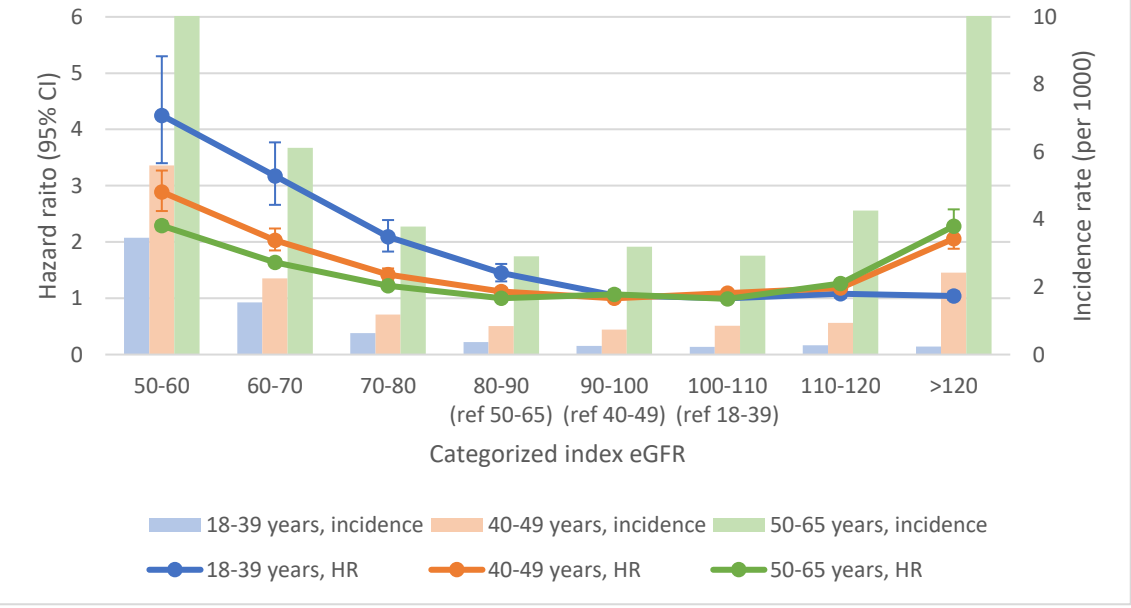




(c) Stroke



(d) Heart failure (including congestive heart failure)



APPENDIX F: INTERACTIONS BETWEEN INDEX EGFR AND ACR (N = 746 948)

Table F1: Frequency, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) of MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE; first of cardiovascular mortality, acute coronary syndrome, ischemic stroke) by interacting categories of index eGFR and albumin-creatinine ratio (ACR) measured within a year of index, in (a) ages 18-39, (b) ages 40-49, and (c) ages 50-65

(d) 18-39 YEARS – MACE			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	8/247 4.99 1.70 (0.85, 3.43)	12/169 9.41 1.83 (1.03, 3.26)	27/203 18.2 2.94 (1.99, 4.35)
60-70	29/934 4.85 1.77 (1.22, 2.59)	20/306 9.53 2.00 (1.28, 3.15)	31/276 15.6 2.54 (1.76, 3.67)
70-80	78/3137 3.68 1.56 (1.22, 1.98)	29/542 7.65 2.01 (1.37, 2.93)	26/262 14.3 2.36 (1.58, 3.51)
80-90	163/8887 2.63 1.14 (0.95, 1.37)	46/1114 6.06 1.89 (1.39, 2.57)	39/370 15.1 2.63 (1.89, 3.66)
90-100	306/18521 2.32 1.06 (0.91, 1.22)	66/2196 4.30 1.41 (1.09, 1.83)	42/486 12.7 2.62 (1.91, 3.61)
100-110	417/26944 2.16	109/3372 4.54	33/554 8.32

	1.00 (reference)	1.47 (1.19, 1.82)	2.11 (1.48, 3.01)
110-120	1044/50534 2.73 1.18 (1.06, 1.33)	282/7111 5.33 1.67 (1.44, 1.95)	80/1142 9.14 2.22 (1.74, 2.82)
>120	725/64696 1.57 0.70 (0.62, 0.79)	327/11661 4.00 1.31 (1.13, 1.51)	84/1967 5.97 1.37 (1.08, 1.74)

(e) 40-49 YEARS – MACE			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	63/584 14.6 1.33 (1.03, 1.71)	59/347 21.8 1.55 (1.19, 2.01)	71/271 36.4 2.12 (1.67, 2.70)
60-70	175/2336 9.36 1.09 (0.93, 1.27)	100/628 21.3 1.68 (1.37, 2.06)	85/321 36.5 2.26 (1.81, 2.81)
70-80	412/7124 6.98 0.93 (0.84, 1.04)	153/1194 16.5 1.47 (1.25, 1.74)	99/398 32.9 2.28 (1.86, 2.80)
80-90	951/16487 6.90 0.96 (0.89, 1.04)	254/2233 14.4 1.41 (1.23, 1.61)	124/551 31.2 2.08 (1.73, 2.50)
90-100	1588/25623	378/3566	136/609

	7.29 1.00 (reference)	13.1 1.37 (1.23, 1.54)	28.6 1.97 (1.65, 2.36)
100-110	3156/44956 8.10 1.07 (1.01, 1.14)	855/7338 14.1 1.48 (1.36, 1.61)	219/1064 26.7 2.14 (1.85, 2.47)
110-120	3058/46934 7.49 1.00 (0.94, 1.06)	1229/10600 14.1 1.45 (1.35, 1.57)	291/1502 24.9 1.86 (1.64, 2.11)
>120	240/2849 10.3 1.10 (0.96, 1.26)	178/1360 17.6 1.68 (1.44, 1.97)	39/233 23.6 1.80 (1.31, 2.48)

(f) 50-65 YEARS – MACE			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	1170/5317 27.3 1.30 (1.22, 1.38)	726/2440 41.1 1.52 (1.41, 1.64)	433/1112 62.1 1.91 (1.73, 2.11)
60-70	2507/14457 20.9 1.14 (1.09, 1.20)	1227/4082 40.6 1.67 (1.57, 1.77)	575/1334 65.5 2.02 (1.85, 2.20)
70-80	4628/31210 17.6 1.04 (1.00, 1.08)	1619/6443 33.1 1.49 (1.41, 1.58)	588/1478 58.5 2.05 (1.88, 2.23)
80-90	7065/50502	2157/9153	617/1640

	16.4 1.00 (reference)	30.4 1.44 (1.38, 1.52)	55.1 2.02 (1.86, 2.19)
90-100	11030/75209 17.1 1.02 (0.99, 1.05)	3452/14942 29.7 1.42 (1.37, 1.48)	800/2121 55.0 1.93 (1.79, 2.08)
100-110	12883/98418 15.2 0.93 (0.90, 0.96)	4841/23461 26.2 1.32 (1.27, 1.37)	999/3182 44.3 1.74 (1.63, 1.86)
110-120	1464/10318 17.3 1.01 (0.96, 1.07)	858/4167 27.3 1.32 (1.23, 1.42)	190/675 41.0 1.65 (1.43, 1.90)
>120	55/279 27.8 1.22 (0.93, 1.59)	50/211 35.3 1.54 (1.16, 2.03)	17/58 47.6 2.04 (1.27, 3.29)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table F2: Frequency, incidence rates per 1000 person-years, and adjusted* hazard ratios (95% CI) of MAJOR ADVERSE CARDIOVASCULAR EVENTS PLUS HEART FAILURE (MACE+; first of cardiovascular mortality, acute coronary syndrome, ischemic stroke, and heart failure) by interacting categories of index eGFR and albumin-creatinine ratio (ACR) measured within a year of index, in (a) ages 18-39, (b) ages 40-49, and (c) ages 50-65

(a) 18-39 YEARS – MACE+			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	10/247 6.26 1.91 (1.02, 3.57)	17/169 13.5 2.36 (1.45, 3.84)	37/203 26.1 3.84 (2.74, 5.38)
60-70	31/934 5.19 1.70 (1.18, 2.44)	25/306 12.1 2.22 (1.48, 3.33)	40/276 20.6 3.01 (2.17, 4.17)
70-80	88/3137 4.15 1.60 (1.27, 2.01)	35/542 9.32 2.20 (1.56, 3.10)	31/262 17.3 2.58 (1.79, 3.72)
80-90	183/8887 2.96 1.16 (0.98, 1.38)	54/1114 7.16 2.00 (1.51, 2.66)	50/370 19.8 3.14 (2.34, 4.22)
90-100	333/18521 2.52 1.04 (0.90, 1.20)	78/2196 5.10 1.51 (1.18, 1.91)	52/486 16.0 2.99 (2.24, 3.99)
100-110	461/26944 2.39	130/3372 5.43	40/554 10.2

	1.00 (reference)	1.58 (1.30, 1.92)	2.31 (1.67, 3.19)
110-120	1127/50534 2.95 1.15 (1.04, 1.29)	330/7111 6.25 1.78 (1.54, 2.06)	104/1142 12.0 2.65 (2.14, 3.29)
>120	822/64696 1.79 0.72 (0.64, 0.80)	387/11661 4.75 1.38 (1.21, 1.59)	109/1967 7.82 1.59 (1.29, 1.97)

(b) 40-49 YEARS – MACE+			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	68/584 15.8 1.33 (1.05, 1.70)	75/347 28.7 1.89 (1.50, 2.38)	83/271 44.0 2.40 (1.92, 2.99)
60-70	193/2336 10.4 1.12 (0.96, 1.30)	117/628 25.3 1.86 (1.54, 2.24)	99/321 43.9 2.52 (2.05, 3.09)
70-80	446/7124 7.58 0.94 (0.85, 1.05)	170/1194 18.5 1.55 (1.32, 1.81)	116/398 39.7 2.62 (2.17, 3.16)
80-90	1018/16487 7.40 0.95 (0.88, 1.03)	292/2233 16.8 1.54 (1.36, 1.74)	149/551 38.7 2.47 (2.08, 2.92)
90-100	1709/25623	422/3566	155/609

	7.87 1.00 (reference)	14.8 1.44 (1.29, 1.60)	33.5 2.20 (1.87, 2.60)
100-110	3388/44956 8.72 1.07 (1.01, 1.13)	948/7338 15.8 1.53 (1.41, 1.66)	254/1064 31.8 2.40 (2.10, 2.74)
110-120	3304/46934 8.11 0.99 (0.94, 1.05)	1372/10600 15.8 1.51 (1.40, 1.62)	329/1502 28.7 2.00 (1.77, 2.25)
>120	268/2849 11.6 1.13 (1.00, 1.29)	202/1360 20.1 1.79 (1.54, 2.07)	49/233 30.1 2.16 (1.63, 2.88)

(c) 50-65 YEARS – MACE+			
Index eGFR	**Index albumin-creatinine ratio (ACR), mg/mmol**		
	<3	**3-30**	**≥30**
50-60	1286/5317 30.4 1.32 (1.25, 1.41)	841/2440 49.0 1.67 (1.56, 1.80)	519/1112 80.1 2.29 (2.09, 2.50)
60-70	2785/14457 23.5 1.17 (1.12, 1.22)	1375/4082 46.8 1.78 (1.68, 1.89)	657/1334 78.9 2.24 (2.07, 2.43)
70-80	5078/31210 19.5 1.05 (1.01, 1.09)	1850/6443 38.7 1.61 (1.53, 1.70)	667/1478 69.8 2.30 (2.12, 2.49)
80-90	7667/50502	2429/9153	693/1640

	17.9 1.00 (reference)	34.9 1.54 (1.47, 1.61)	64.7 2.21 (2.04, 2.39)
90-100	11941/75209 18.7 1.01 (0.99, 1.04)	3852/14942 33.7 1.49 (1.43, 1.55)	926/2121 66.8 2.18 (2.04, 2.34)
100-110	14100/98418 16.7 0.93 (0.91, 0.96)	5443/23461 29.9 1.39 (1.34, 1.44)	1188/3182 54.9 1.98 (1.86, 2.11)
110-120	1580/10318 18.7 1.00 (0.95, 1.06)	991/4167 32.1 1.43 (1.34, 1.53)	229/675 51.7 1.95 (1.71, 2.22)
>120	65/279 33.6 1.32 (1.04, 1.69)	56/211 40.3 1.63 (1.25, 2.12)	19/58 54.7 2.12 (1.35, 3.33)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

APPENDIX G: PAST CARDIOVASCULAR DISEASE-STRATIFIED ANALYSES

Table G1. Event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) stratified by past cardiovascular disease for MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE; first of cardiovascular mortality, acute coronary syndrome, ischemic stroke) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

Index eGFR category	Cardiovascular disease history	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)
50-60	**Yes**	15/39	51.5	1.58 (0.93, 2.66)
	No	136/3489	5.57	1.72 (1.45, 2.04)
60-70	**Yes**	23/95	32.3	1.26 (0.82, 1.93)
	No	338/14126	3.57	1.60 (1.44, 1.79)
70-80	**Yes**	49/255	25.5	0.95 (0.70, 1.29)
	No	954/61526	2.26	1.34 (1.26, 1.44)
80-90	**Yes**	110/669	22.2	0.96 (0.77, 1.20)
	No	2450/192403	1.82	1.19 (1.14, 1.25)
90-100	**Yes**	205/1164	23.4	1.06 (0.88, 1.27)
	No	4830/415267	1.62	1.10 (1.06, 1.14)
100-110	**Yes**	271/1665	21.1	(reference)
	No	6517/617450	1.45	
110-120	**Yes**	639/3432	24.1	1.09 (0.95, 1.26)
	No	13969/1058533	1.72	1.15 (1.12, 1.19)
>120	**Yes**	406/2870	18.7	0.89 (0.76, 1.04)
	No	11460/1461674	1.08	0.76 (0.73, 0.78)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

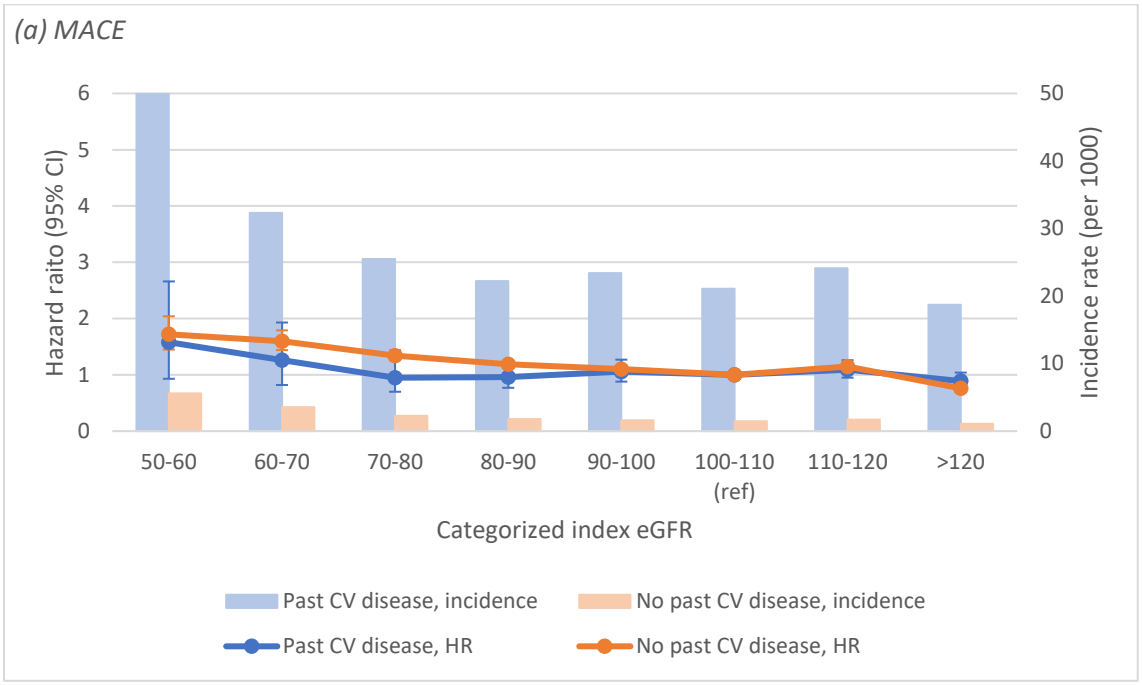
Table G2. Event frequencies, incidence rates per 1000 person-years, and adjusted hazard ratios (95% CI) stratified by past cardiovascular disease for MAJOR ADVERSE CARDIOVASCULAR EVENTS PLUS HEART FAILURE (MACE+; first of cardiovascular mortality, acute coronary syndrome, ischemic stroke, and heart failure) by index eGFR categories relative to eGFR 100-110 among those aged 18-39

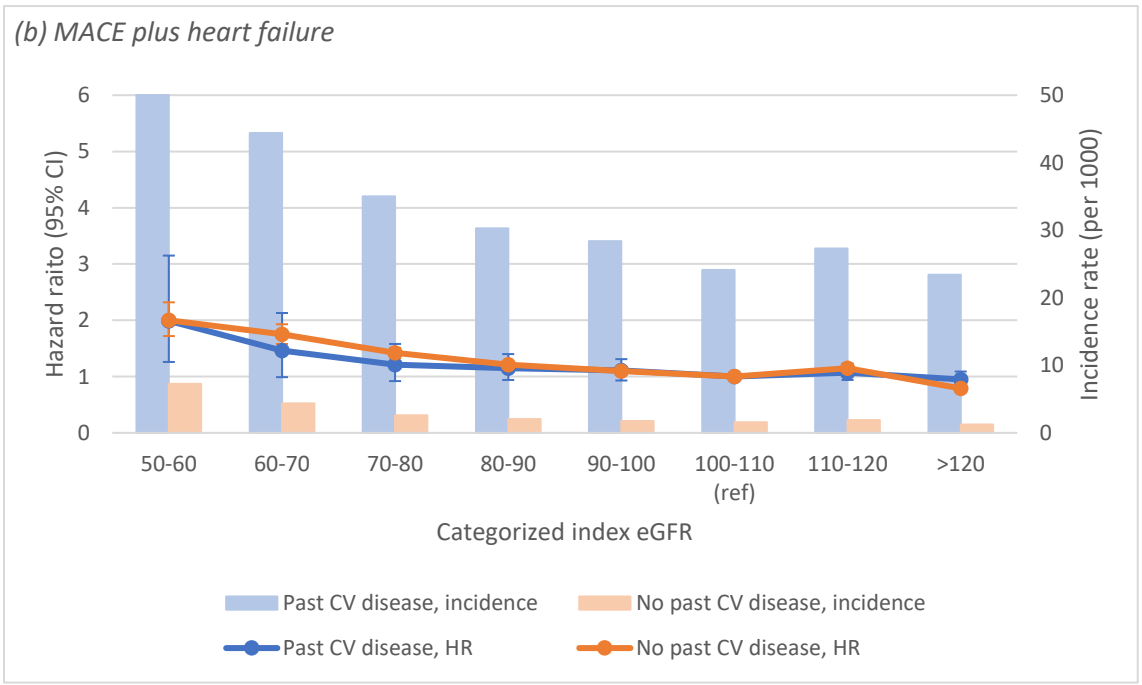
Index eGFR category	Cardiovascular disease history	Event frequency	Incidence rate (per 1000 p-y)	HR (95% CI)
50-60	**Yes**	20/39	77.9	1.99 (1.26, 3.15)
	No	176/3489	7.27	2.00 (1.72, 2.32)
60-70	**Yes**	30/95	44.4	1.46 (0.99, 2.13)
	No	411/14126	4.36	1.75 (1.58, 1.93)
70-80	**Yes**	63/255	35.0	1.21 (0.92, 1.58)
	No	1107/61526	2.63	1.42 (1.33, 1.51)
80-90	**Yes**	144/669	30.3	1.15 (0.94, 1.40)
	No	2722/192403	2.02	1.21 (1.16, 1.26)
90-100	**Yes**	241/1164	28.4	1.11 (0.93, 1.31)
	No	5281/415267	1.77	1.10 (1.06, 1.13)
100-110	**Yes**	305/1665	24.1	(reference)
	No	7138/617450	1.59	
110-120	**Yes**	709/3432	27.3	1.07 (0.94, 1.23)
	No	15305/1058533	1.89	1.15 (1.12, 1.18)
>120	**Yes**	493/2870	23.4	0.95 (0.82, 1.09)
	No	13151/1461674	1.24	0.79 (0.77, 0.81)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung*

disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years

Figure G1: Incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) stratified by past cardiovascular disease for (a) major cardiovascular adverse events (MACE; first of cardiovascular mortality, acute coronary syndrome, and ischemic stroke) and (b) MACE plus heart failure, among those aged 18-39 and relative to eGFR 100-110





APPENDIX H: SENSITIVITY ANALYSES – INDIVIDUALS WITH TWO INDEX EGFR MEASURES 90 DAYS TO 2 YEARS APART (N = 4 468 335)

Table H1: Event frequencies, incidence rates **per 1000 person-years, and adjusted* hazard ratios (95% CI) for MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE; first of cardiovascular mortality, acute coronary syndrome, ischemic stroke) relative to age-specific eGFR reference ranges, by age-group among those with two repeated eGFR measures 90 days to 2 years apart**

Index eGFR category	Age group		
	18-39	**40-49**	**50-65**
50-60	114/1119 12.3 1.86 (1.54, 2.24)	486/2802 20.5 1.45 (1.33, 1.59)	6887/25431 32.8 1.39 (1.35, 1.42)
60-70	190/3774 6.66 1.64 (1.42, 1.90)	1112/11808 11.0 1.20 (1.13, 1.28)	15237/79142 22.2 1.21 (1.19, 1.23)
70-80	500/18570 3.54 1.30 (1.19, 1.43)	3233/47126 7.72 1.09 (1.05, 1.14)	30573/198990 17.2 1.08 (1.06, 1.09)
80-90 (reference for 50-65)	1390/65043 2.77 1.21 (1.14, 1.28)	7215/122408 6.52 1.01 (0.98, 1.04)	48443/350526 15.3 1.00 (reference)
90-100 (reference for 40-49)	2765/156397 2.26 1.05 (1.01, 1.10)	12299/210882 6.35 1.00 (reference)	75705/545562 15.2 0.99 (0.98, 1.01)
100-110 (reference for 18-39)	4547/272631 2.10	22293/365278 6.53	70929/567403 13.6

	1.00 (reference)	1.02 (0.99, 1.04)	0.92 (0.90, 0.93)
110-120	8459/482875 2.14 1.02 (0.98, 1.05)	18428/311128 6.30 1.00 (0.98, 1.02)	7013/49580 16.2 0.99 (0.97, 1.02)
>120	6253/564974 1.43 0.72 (0.69, 0.74)	1179/13519 9.84 1.18 (1.11, 1.26)	329/1367 34.2 1.57 (1.41, 1.75)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Table H2: Event frequencies, incidence rates **per 1000 person-years, and adjusted* hazard ratios (95% CI) for MAJOR ADVERSE CARDIOVASCULAR EVENTS PLUS HEART FAILURE (MACE+; first of cardiovascular mortality, acute coronary syndrome, ischemic stroke, and heart failure) relative to age-specific eGFR reference ranges, by age-group among those with two repeated eGFR measures 90 days to 2 years apart**

Index eGFR category	**Age group**		
	18-39	**40-49**	**50-65**
50-60	153/1119 16.9 2.22 (1.90, 2.62)	573/2802 24.8 1.63 (1.50, 1.78)	7864/25431 38.5 1.48 (1.45, 1.52)
60-70	229/3774 8.09 1.74 (1.53, 1.99)	1263/11808 12.6 1.29 (1.21, 1.36)	17012/79142 25.1 1.25 (1.23, 1.27)
70-80	603/18570 4.29 1.42 (1.31, 1.55)	3553/47126 8.52 1.12 (1.08, 1.16)	33571/198990 19.0 1.09 (1.07, 1.10)
80-90 (reference for 50-65)	1601/65043 3.20 1.26 (1.20, 1.34)	7831/122408 7.09 1.02 (0.99, 1.05)	52766/350526 16.7 1.00 (reference)
90-100 (reference for 40-49)	3081/156397 2.52 1.06 (1.02, 1.11)	13207/210882 6.83 1.00 (reference)	82499/545562 16.7 0.99 (0.98, 1.00)
100-110 (reference for 18-39)	5031/272631 2.33 1.00 (reference)	23830/365278 6.99 1.01 (0.99, 1.03)	77972/567403 15.0 0.92 (0.91, 0.93)

110-120	9314/482875 2.35 1.01 (0.97, 1.04)	20072/311128 6.88 1.01 (0.99, 1.03)	7857/49580 18.3 1.02 (0.99, 1.04)
>120	7256/564974 1.66 0.74 (0.72, 0.77)	1356/13519 11.4 1.27 (1.20, 1.34)	381/1367 40.5 1.69 (1.52, 1.87)

**adjusted for sex, hypertension, diabetes, past cardiovascular disease, obesity, alcoholism, smoking, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, income quintile, urban/rural living status, specialist visit in past 5 years, emergency department visit in past 5 years*

Figure H1: Incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for (a) major cardiovascular adverse events (MACE; first of cardiovascular mortality, acute coronary syndrome, and ischemic stroke) and (b) MACE plus heart failure relative to age-specific eGFR reference ranges, by age-group among those with two repeated eGFR measures 90 days to 2 years apart