RE-EXAMINING ADVERSE OUTCOMES OF CHRONIC KIDNEY DISEASE IN ONTARIO ADULTS: A RETROSPECTIVE COHORT STUDY

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Preface

Author Contributions

The research question and topic were developed through discussion between my primary supervisor, Dr. Manish Sood, and me. Dr. Sood provided supervision for all aspects of the thesis, including the selection of the Thesis Advisory Committee (TAC): Dr. Greg Knoll (co-supervisor), Dr. Greg Hundemer, and Dr. Pietro Ravani. This thesis initially sought to examine adverse cardiac outcomes in older adults with chronic kidney disease. We then expanded the scope of the thesis to explore risks for all adults in Ontario, based on earlier work by an MSc Clinical Epidemiology graduate supervised by Dr. Sood, Junayd Hussain, on young individuals in Ontario. I conducted the statistical analysis, which Dr. Sood and Ed Yu reviewed. The Institute for Clinical Evaluative Sciences (ICES) Analysts Robert Talarico and Samatha Yoo created the project dataset using linked ICES Ontario health administrative databases. ICES Analyst Dr. Ed Yu developed the regression discontinuity model with input from Drs. Ariana Noel and Manish Sood. The model was developed based on the data and analysis completed by Dr. Noel. Dr. Noel was involved in and is responsible for every aspect of this thesis, including data analysis, literature review, statistical code and analysis, table and figure generation, thesis preparation, and submission. Dr. Sood and all TAC members assisted in developing the study design through discussions and official TAC meetings.

Ethics review and approval

Data used in this project is deidentified and authorized under section 45 of Ontario's Personal Health Information Protection Act. It does not require review by a Research Ethics Board. ICES Central provided privacy and data management training to Ariana Noel as part of the project approval process (1). ICES is authorized to collect Ontario healthcare data for health system evaluation and analysis, and secure access to these data is approved by the Information and Privacy Commissioner of Ontario. Recommendations from Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD) were followed (2). To further facilitate research ethics, Ariana Noel completed CIHR Sex and Gender training in the fall of 2022 and TCPS2 before starting the thesis research.

Acknowledgements

I am grateful for the teaching and guidance provided by my supervisors, Drs. Manish Sood and Greg Knoll. I am grateful to each member of the Thesis Advisory Committee for their time and expertise, which significantly contributed to the preparation of this project. I also appreciate the feedback provided by Drs. Ayub Akbari, Mark Canney, and Steve Hawken during the initial stages of the project. I want to extend a special thanks to ICES Analysts Robert Talarico and Samantha Yoo for creating the dataset, without which this project would not have been possible. The addition of Dr. Ed Yu strengthened our team. The regression discontinuity expertise provided by Ed Yu was instrumental in developing the model for the thesis, and I am incredibly grateful for Ed's collaboration on this work. Next, I would like to thank the Clinician Investigator Program, University of Ottawa Post-Graduate Medical Education, and the Ottawa Hospital Department of Medicine Academic Scholar Program for funding the MSc in Clinical Epidemiology during my Nephrology residency. I want to extend my heartfelt thanks to Dr. Paul Macpherson. Thank you for inspiring trainees to embrace their authentic selves in their work and share their academic passion through their research. I want to thank my mom for their active listening and support. Special thanks are reserved for Nutmeg (October 3, 2011 – January 13, 2025), who sat by my side as I worked for the last thirteen years of post-graduate education and medical training. I know you kept an eye on me while I finished this thesis and made some Pomeranian spins when I submitted.

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1) Clinician Investigator Program – program director: Dr. Paul Macpherson. The CIP program provided me with protected time and 0.5 salary support to complete the MSc Clinical Epidemiology

2) The Department of Medicine Academic Scholar program provided 0.5 salary support to complete the two years of the Clinician Investigator Program

Abstract

Background and rationale: Chronic kidney disease (CKD) has increased in prevalence over the last twenty years in Canada, now affecting up to one in ten Canadians (3). CKD is associated with adverse cardiovascular outcomes, end-stage kidney disease (ESKD) and all-cause mortality. CKD is diagnosed through blood and urine testing and is defined as a reduced estimated glomerular filtration rate (eGFR) of <= 60 ml/min/1.73 m^2 for three months or more and albuminuria > 3 mg/mmol (4,5). The discrete eGFR cut-off for diagnosing CKD has been questioned due to physiologic changes in kidney function. Recent evidence suggests the CKD eGFR diagnostic threshold should be much higher in young adults (above 60 ml/min/1.7 3m^2, e.g., 75 ml/min/1.73 m^2), regardless of albuminuria and lower (< 60 ml/min/1.73 m^2, e.g., < 45 ml/min/1.73 m^2 in the absence of albuminuria) in older adults with CKD. Identifying age-specific, outcome-based threshold levels of eGFR would improve early CKD identification and treatment in the young, reduce overdiagnosis and overtreatment, and reduce inappropriate utilization of healthcare resources (6).

Objectives: To examine the association of age-specific eGFR thresholds with mortality, major adverse cardiac events (MACE), and ESKD using population-based data from Ontario, Canada.

Methods: Using linked, de-identified administrative datasets housed at ICES, we created a cohort of all adults (18-105) with at least two available eGFR measures between 90 and 730 days apart in Ontario, Canada, from January 2008 to December 2021, with a minimum follow-up of one year. We examined the associations of eGFR and age with adverse outcomes (all-cause mortality, MACE, MACE+, and ESKD) using Cox proportional hazards models and a regression

discontinuity design (RDD) to identify specific risk-based eGFR thresholds in adults by age. Reclassification was used to examine event frequencies by eGFR in younger adults to determine an optimal eGFR cutoff for screening for adverse events associated with eGFR reduction.

Results: The cohort included 8,388,340 individuals (mean age 51.27, SD 17.37, 62.3% female, mean baseline eGFR 92.59 +/- 20.17) with a median follow-up time of approximately 1 year. The age distribution was as follows: 27.28% from 18-39, 50.94% from 40-65, 16.68% from 66-80, and 5.11% 80 or older. In adjusted models, the risk of all-cause mortality, MACE, MACE+ and ESKD was higher in 18- to 30-year-olds at a threshold of eGFR 80-90, with a stepwise decline in risk with age. Among those aged 80 or older, the risk of adverse events was higher only when eGFR was 50 or lower. Cox proportional hazard analysis demonstrated that younger individuals had a discrete increase in all-cause mortality and adverse cardiac events at eGFR < 90 ml/min/1.73 m^2. Adults over age 50 and older adults up to age 80 experienced adverse events at eGFR < 60 ml/min/1.73 m^2 and at eGFR > 110 ml/min/1.73 m^2. Sub-analyses for albuminuria and diabetes demonstrated similar results to the total population with modest reductions in risk; however, risk for younger individuals eGFR <90 ml/min were still present with albuminuria and diabetes. Regression discontinuity modelling did not identify a granular threshold by age for adverse outcomes; however, analyzing 3-, 5-, and 10-year risk for adverse outcomes in younger adults suggested that those with reductions in eGFR < 75 ml/min/1.73 m^2 would benefit from closer monitoring.

Conclusions: This retrospective cohort study of 8.3 million Ontario individuals has provided a novel and robust assessment of optimal risk-based eGFR cut-offs for CKD diagnosis and related

adverse events. However, a definitive cut-off for the eGFR threshold by age could not be identified through Cox proportional hazards and RDD. In younger adults, an eGFR below 90 ml/min/1.73m^2 consistently showed a significant association with adverse events at 3, 5, and 10 years. A U-shaped pattern for adverse cardiovascular events was observed in middle-aged to older adults, where hyperfiltration was linked to negative outcomes. Examining adverse event frequency by eGFR in younger adults suggests that screening individuals with eGFR 75 ml/min/1.73 m^2 or lower would be optimal. Improved risk-based determination of eGFR thresholds for adverse events associated with CKD will guide primary care providers, specialists, and policymakers and may influence clinical practice.

Acronyms

ACR – Albumin-to-creatinine ratio

ACS - Acute coronary syndrome

Afib – Atrial fibrillation

AKI – Acute kidney injury

CARDIA – Coronary Artery Risk Development in Young Adults

CHF – Congestive heart failure

CI – Confidence interval

CKD – Chronic kidney disease

eGFR – Estimated glomerular filtration rate

ESKD – End-stage kidney disease

ICD-10 – International Classification of Diseases 10

ICES – Institute of Clinical Evaluative Sciences

KDIGO – Kidney Disease: Improving Global Outcomes

KTx – Kidney transplant

MACE – Major adverse cardiac events

MACE-plus – Major adverse cardiac events plus hospitalization for heart failure

RDD – Regression discontinuity design

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Chapter 1: Overview and Objectives

Chronic kidney disease (CKD) is a common chronic disease with increasing prevalence in Canada and globally (7–9). For this reason, we are seeing a higher prevalence of CKD and end-stage kidney disease (ESKD) now than in the past. Once nephron damage has occurred, CKD is irreversible and progresses over time in those with proteinuric CKD. CKD is often asymptomatic in its early stages (10–12). The aging Canadian population is growing, with more adults aged 65 and older. To that end, CKD affects up to 1 in 10 Canadians, and this prevalence increases as patients age due to comorbidities related to aging and lifestyle (3,13,14).

The guidelines for diagnosing CKD in adults include a diagnostic threshold of < 60 ml/min/1.73 m^2 for all adult patients over age 18, and there are no evidence-based age or eGFR-associated thresholds to determine who needs closer monitoring if they demonstrate a reduction in their eGFR at a younger age (5). The current CKD diagnostic criteria are outlined in the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, published in 2013 and updated in 2024 (4,5). CKD is diagnosed by nephron loss, as evidenced by a decline in eGFR for more than 3 consecutive months (15–17). CKD diagnosis relies on eGFR measurement; however, eGFR measurement methods are imperfect. Measurement of serum creatinine using this method is indirect and can be influenced by various factors. For example, sex and age are factors that influence nephron mass. Sex is associated with differences in nephron mass; Women are more likely to be born with lower nephron mass than men (18–20). Age is another significant factor skewing accurate eGFR measurement. As individuals age, it is well known that nephron mass is gradually lost over time through the aging process at an estimated rate of 1 ml/min/year beginning at age 45 (21,22).

Why is the determination of an optimal eGFR cut-off for CKD important? The cut-off for diagnosis of CKD is set at a discrete 60 ml/min/1.73 m² for more than 3 months, which is the renal function threshold at which significant adverse cardiac events begin to be observed (4). The CKD cut-off is a topic of controversy in the nephrology community. Over the last decade, database retrospective cohort studies have made large datasets more accessible for studying trends in kidney function across millions of individuals. Access to population data, including hundreds of thousands of individuals, has enabled the examination of the nuances of these cut-offs (6,23). There is emerging evidence that using a 60ml/min/1.73m^2 cut-off may lead to underdiagnosis of CKD in young adults and overdiagnosis in older individuals (23–25). Some researchers suggest that mortality risk in older adults may not be affected until eGFR falls to < 45ml/min/1.73 m^2, when cardiac events are more likely to occur (16,26–28). Past population-level research by Canadian colleagues in Alberta has shown similar results, indicating that an age-adapted cut-off for CKD diagnosis may be more appropriate for the elderly (6,29,30).

Purpose and Rationale

In this thesis, we aim to determine a more granular eGFR range or threshold to diagnose CKD in younger and older adults. Large health administrative databases enable improved analysis of adverse events across different eGFR thresholds (15,31,32). We analyzed the association between age and eGFR with mortality and adverse cardiac events in a population dataset comprising over 8 million individuals, using Ontario health-linked administrative databases. The goal is to determine whether the frequency and type of adverse events vary by eGFR and differ across age groups. Is an eGFR cut-off of 60 ml/min/1.73 m^2 appropriate across ages 18 to individuals over

80? Determining specific eGFR cut-offs by age group for CKD would enable more accurate prevention, diagnosis, and treatment of CKD in Canadian adults.

Objectives

1) To describe the adult Ontario population across different levels of eGFR, including the prevalence of various comorbidities linked to CKD, as well as their all-cause mortality prevalence, major adverse cardiac events (MACE), renal failure, and healthcare utilization in the population.

2) To examine the associations of mortality, MACE, MACE plus and ESKD with eGFR in categories using Cox proportional hazards to identify significant eGFR and age cut-offs for each outcome.

3) To assess granular eGFR cut-offs using a regression discontinuity design to determine an optimal cut-off for eGFR by age for mortality, MACE, MACE-plus, and ESKD.

4) To examine practical eGFR cut-offs for young adults based on the frequency of adverse outcomes associated with CKD when followed for 3-, 5-, and 10-years to determine an eGFR to screen vulnerable young adults' serum creatinine using reclassification.

Thesis Outline

This thesis begins with a narrative review of relevant background literature examining CKD diagnosis thresholds; population-based retrospective cohort studies of CKD diagnostic cut-offs and adverse outcomes; a summary of the scholarly debate regarding age-adjusted CKD diagnosis; and an introduction to regression discontinuity design in health research. Next, we discuss the descriptive statistics of the Ontario population cohort, comprising over 8.3 million individuals, focusing on renal function, demographics, comorbidities, healthcare utilization, and the associations between age, eGFR, and adverse cardiac outcomes in CKD. Using several methods to investigate the risk of adverse events associated with reductions in eGFR, including Cox proportional hazards, regression discontinuity, and reclassification, we suggest optimal cut-offs based on age. Finally, we compare the results with existing literature, discuss the limitations of the design and methods used, and draw significant conclusions.

Chapter 2: Background – The increasing prevalence of CKD in Ontario adults and the importance of examining CKD diagnostic cut-offs

Literature for this thesis was obtained through PubMed search, thesis databases, and the University of Ottawa for online textbook resources.

The prevalence of CKD in Canada is considerable, impacting about 10 percent of all adults (33). The prevalence of CKD is expected to increase to 20% among those aged 65 years or older in the coming years (8,14,34,33). Symptoms related to the metabolic complications of chronic kidney disease and proteinuria typically do not appear until advanced stages, usually near an eGFR of 30 ml/min/1.73 m^2, with signs like anemia or volume overload (10,12). Damage to nephrons and the loss of nephron mass are irreversible, highlighting the importance of early intervention (26,35). CKD is the result of irreversible damage to nephrons. Once diagnosed, its progression can be managed by prompt recognition and management by clinicians. Individuals are often referred to nephrologists only after the disease has already advanced and is symptomatic (36,37). There are limited screening guidelines for the early detection of CKD. Individuals with hypertension or diabetes are recommended to undergo monitoring; however, the general population may never have their serum creatinine measured (38,39). There are no screening guidelines for an individual who has a reduction in eGFR from 90 to 60 ml/min/1.73 m^2 to monitor kidney function. Consequently, public awareness of CKD remains low at around 10% (40–42). Due to the increasing prevalence of multiple chronic conditions, lack of screening, and an aging population, the number of people with CKD progressing to end-stage kidney disease (ESKD) requiring life-sustaining dialysis has doubled over the past 20 years (43). The average annual cost of hemodialysis per patient per year in Canada is $88,000 (44–46). Hemodialysis is associated with higher patient mortality and reduced quality of life (47–49). Preventive measures and early

detection could reduce the number of patients progressing to dialysis. Avoiding ESKD is preferable from both health-economic and quality-of-life perspectives.

Currently, the CKD diagnosis guidelines are based on kidney function of eGFR < 60 ml/min/1.73 m^2 where adverse cardiovascular events have increased in frequency (4,5,16). The Kidney Disease Improving Global Outcomes (KDIGO) guidelines for CKD suggest that adults of all ages with an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2 or albuminuria >30 mg/mmol have CKD (5). The KDIGO cutoff is strict; the internationally accepted definition of CKD in adults is an eGFR of less than 60 ml/min/1.73 m^2 persisting for more than three consecutive months (10, 11). eGFR (ml/min/1.73 m^2) is the standard measure of renal function based on serum creatinine. Since serum creatinine is a by-product of muscle breakdown, eGFR may vary with sex and age using the CKD-EPI equation (50–52). Due to body size and genetic factors, women are generally born with lower nephron mass than their age-matched male counterparts but have the same CKD diagnosis criteria (22). All individuals are born with their peak nephron number and nephron mass, which decline steadily at about 1ml/min/1.73 m^2 per year after approximately age 45 (53–56). The current measures of eGFR do not include precise assessments of an individual's muscle mass versus overall body mass (50–52). Serum creatinine for eGFR measurement using the CKD-EPI equation is the most convenient and accessible way to assess eGFR. Other options include a 24-hour urine collection for creatinine clearance, which can serve as an alternative evaluation method at extremes of body mass (obesity, cachexia, or a very muscular individual). Alternatively, cystatin C is available as a renal function test at some academic centres; however, it is not widely available in the community (53–56). Regardless of the measurement method, the current definition of CKD assumes that nephron mass loss at an eGFR threshold of 60 ml/min/1.73 m^2 is pathological

Figure 1. Summary of KDIGO 2012 CKD Diagnosis eGFR thresholds. CKD is defined by an eGFR cut-off of 60 ml/min/1.73m^2 and elevated albuminuria for more than 90 days (57–60)

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m^2) 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			

Figure 2. KDIGO CKD Management Guidelines 2024 now include recommendations for screening individuals with eGFR >90 and 60– in the G1 and G2 categories, and treatment recommendations for individuals with proteinuria (4).

				Albuminuria categories Description and range		
				A1	**A2**	**A3**
CKD is classified based on: • **Cause (C)** • **GFR (G)** • **Albuminuria (A)**				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–299 mg/g 3–29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73 m²) Description and range	**G1**	Normal or high	≥90	Screen 1	Treat 1	Treat 3
	G2	Mildly decreased	60–89	Screen 1	Treat 1	Treat 3
	G3a	Mildly to moderately decreased	45–59	Treat 1	Treat 2	Treat 3
	G3b	Moderately to severely decreased	30–44	Treat 2	Treat 3	Treat 3
	G4	Severely decreased	15–29	Treat* 3	Treat* 3	Treat 4+
	G5	Kidney failure	<15	Treat 4+	Treat 4+	Treat 4+

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Adverse cardiac outcomes associated with CKD are the basis for current diagnosis thresholds

CKD is strongly linked to serious adverse cardiac outcomes, including mortality, coronary artery disease, and ischemic cardiomyopathy (16,17,29). Decline in eGFR and proteinuria can be asymptomatic in adults, which can lead to missed opportunities for early diagnosis of cardiovascular disease and related conditions (16,27). Large-scale retrospective cohort studies have shown a connection between reduced GFR and adverse cardiac outcomes (32,57,58). Higher levels of proteinuria, even with preserved GFR, are also associated with increased all-cause mortality and adverse cardiac outcomes (15–17). Individuals with reduced GFR and proteinuric CKD face a higher risk of major adverse cardiovascular events (MACE) compared to those with non-proteinuric CKD (16,17,59–61).

Retrospective cohort studies have been instrumental in examining the links between different levels of renal dysfunction and CKD-related adverse events and risk factors. One of the most detailed longitudinal, retrospective cohort studies, the Chronic Renal Insufficiency Cohort Study (CRIC), collected data from healthcare databases on over 5000 individuals at seven US centres between 2003 and 2008 (60–69). The study aimed to identify risk factors for the progression of CKD and cardiovascular disease. Participants ranged in age from 21 to 74 years, and all had an eGFR between 20 and 60 ml/min/1.73 m^2. Those with previous cardiovascular events were excluded. The participants had multiple GFR readings, typically including more than four serum creatinine repeats per age group. Serum creatinine measurements helped estimate the rate of GFR decline in relation to adverse cardiac events. It has been well established from previous literature that proteinuria is a risk factor for CKD progression and adverse cardiac outcomes. Emerging data

from the CRIC Study Investigators in 2024 examined 1463 adults with normal, moderate, or severe proteinuria over a 10-year follow-up period. After adjustment in their Cox analysis, there was no significant difference between proteinuric and non-proteinuric CKD, suggesting that all individuals with CKD are at increased risk of mortality (60).

Retrospective cohort studies allow researchers to observe large groups of individuals over long periods of time to identify outcomes that may happen many years after disease onset. Other CRIC data evaluate cardiovascular risk in stages II-IV CKD to predict the 10-year risk of cardiovascular disease. Bundy et al. developed a validated 10-year risk prediction model for atherosclerosis in individuals with CKD (64). The study involved 2,604 participants, who experienced 252 adverse cardiac events over a ten-year period. Their model included age, sex, race, BMI, HbA1c, smoking history, urine ACR, and cholesterol, among other factors. Age, sex, smoking, and HbA1c were most strongly linked with CKD progression. In another CRIC Investigators study by Cao et al., better cardiovascular health was associated with improved 5-year outcomes in CKD (68). In this study, self-reported baseline characteristics of 3939 individuals with cardiovascular risk factors were used to assess their 5-year risk of ESKD. Participants with higher scores or fewer risk factors had a significantly lower 5-year risk of ESKD (HR 0.62 [0.44–0.86]) and incident cardiovascular events (HR 0.44 [0.31–0.62]), but not all-cause mortality, after adjustment (68). Therefore, there is a notable risk for adverse cardiac events associated with CKD that can be identified and examined through a retrospective cohort approach.

Another benefit of retrospective cohort studies is the ability to examine rare events, such as cardiovascular or kidney disease, within a specific population, given the large number of

individuals included. The CARDIA (Coronary Artery Risk Development in Young Adults) study was initiated in 1984 to investigate risk factors for the development of cardiovascular disease and lifestyle factors associated with cardiac disease (70). The study recruited 5116 individuals ages 18–30 from urban areas of the United States and followed them over several decades to examine cardiovascular disease risk (70). The investigators identified that young adults could have risk factors for cardiovascular disease that predicted onset later in life. Individuals were followed into their mid-life from recruitment. Results demonstrated that early life health behaviours predicted later life risk of cardiovascular disease, including body mass index and smoking. Analyses of later life data have revealed that individuals with risk factors such as higher cholesterol, smoking, chronic stress, and lower fitness were associated with mid-life cardiovascular disease when followed from young adulthood, ages 18 – 30 (71–74). The original CARDIA study and associated studies demonstrate that the risk of chronic disease starts early in adulthood and can predict disease outcomes later in life.

Retrospective cohort studies allow for the examination of the frequency of outcomes in large populations, which is useful for reassessing CKD diagnosis thresholds. One potential emerging method for examining eGFR thresholds is the regression discontinuity design (RDD). Initially, the RDD was used for economic data analysis because it is well-suited to large databases and continuous variables, it may apply to the examination of the eGFR threshold for CKD diagnosis. Developed in the 1960s, its use has grown rapidly over the past four decades, initially mainly in economic analysis but increasingly in clinical data (69–75). The RDD is a method for analyzing healthcare database data that can supplement insights from survival analysis in retrospective cohort studies. RDD is a non-randomized modelling approach that examines continuous variables directly

above and below a specified value or threshold. For example, RDD has been applied to eGFR as a continuous variable. Researchers at McGill investigated long-term renal outcomes after dye administration for CT scans in the emergency department in a retrospective cohort study involving over 150,000 individuals from Alberta databases (82). Goulden et al. employed an RDD approach to examine eGFR in 84,000 patients, using eGFR as the outcome variable and D-dimer as the covariate. Through this method, they found no association between radiocontrast dye and a 6-month decline in eGFR (mean eGFR, 86 ml/min/1.73 m^2) (82). Researchers in South Africa have used the RDD to evaluate the threshold CD4 count and retention in HIV-positive patients starting early versus deferred antiretroviral treatment (83). Since they met the CD4 count cut-off, patients eligible for early antiretroviral treatment showed higher HIV clinic retention than those just below the cut-off, indicating an added benefit of early treatment (83). Incorporating RDD analysis could offer insights into granular age-related eGFR thresholds for CKD diagnosis, based on higher rates of adverse cardiac events observed in population studies. There may be a cut-off in eGFR values by age in a retrospective cohort of 8 million patients. To date, the RDD has not been applied to the study of eGFR diagnostic thresholds or adverse events associated with CKD. In this study, we will use the RDD to determine if there is a significant eGFR cut point by age that may improve CKD diagnostic clarity.

An age-adjusted threshold for CKD diagnosis may differ for younger and older adults

The 60 ml/min/1.73 m^2 threshold for CKD diagnosis was established in population-based cohort studies, notably by the CKD Prognosis Consortium, which showed an increased risk of adverse events for eGFR < 70 ml/min/1.73 m^2 and eGFR > 120 ml/min/1.73 m^2 (84). According to this

research, a range of 60–74 ml/min/1.73 m^2 was considered accurate for individuals of all ages, including those aged 65 years or older (84). The influence of age on CKD diagnosis is a frequently debated topic in nephrology (6,21,85,29,86,87). It has been suggested that using a fixed eGFR across different ages may lead to misdiagnosis or overlook younger individuals at risk of disease progression. Equations for estimating creatinine clearance depend on age, sex, and serum creatinine. However, these variables can give the impression of declining kidney function as people age, without accounting for the known physiological decline in nephron mass. It is generally accepted that kidney function declines by approximately 1 ml/min/1.73 m^2 per year after age 45 (88). Physiological differences in nephron mass exist between sexes, and muscle mass varies between individuals of different ages and sexes. Since muscle mass and nephron mass change with age, emerging evidence over the past decade suggests that a fixed eGFR cut-off like 60 ml/min/1.73 m^2 is less suitable for both older and younger populations (21,24).

The occurrence of adverse cardiovascular outcomes increases with age (29,89,90). Establishing a CKD diagnosis threshold based on the occurrence of adverse cardiac events may exclude younger adults, who physiologically are less likely to experience such events. Most of the literature on age and CKD has concentrated on older adults, due to higher diagnosis rates and the development of related conditions like coronary artery disease and type 2 diabetes with age. Research from the CKD Prognosis Consortium, a meta-analysis of over 2,000,000 participants, including older adults, shows that hazard ratios (HRs) for mortality and decreasing eGFR did not rise as sharply as the absolute mortality rate associated with lower eGFR. Their study found that age and ESKD were not significantly associated (84,91–93).

Population-based healthcare databases have been crucial for understanding age-adjusted CKD cutoffs, as they include a larger number of younger individuals (23,24). Recently, larger and more robust retrospective studies using Canadian data have focused on an age-adjusted definition of CKD. In a study from Alberta involving over 4 million adults, over 30,000 individuals aged 18 and above with CKD IV were examined to explore the relationship between age, ESKD, and death (3). The incidence of CKD IV increased with age, from 20 per 100,000 in younger individuals to 250 per 100,000 in older adults, after adjusting for age (58). For older adults, their risk of all-cause mortality rose over time, but among younger adults, the risk of progression to ESKD was higher (3). Although the prevalence of CKD is expected to increase with an aging population, those who are older with CKD are more likely to die from other causes, such as cardiovascular disease. Younger adults with CKD are more likely to progress to ESKD over time.

There has been emerging information on the risk of younger adults progressing to ESKD or experiencing adverse cardiovascular events. It has been shown that young adults with eGFR 60 – 75 ml/min/1.73 m^2 have an increased risk of coronary artery disease (94). It has been recommended that children with low birth weight be screened for CKD due to the potential for low nephron mass with long-term risk for adverse cardiac events (95). Additionally, it has been suggested that children with low birth weight have a mean difference of 5.5 mL/min/1. 73 m^2 ($p < 0.01$) compared to children with normal birth weight, and should begin screening at 9 years of age (95). In earlier research by Hussain et al., a retrospective cohort study of over 8 million individuals in Ontario spanning 2008 to 2021 aimed to better understand the association between declining eGFR and adverse outcomes in adults aged 18–65 (23). Modest reductions in eGFR were common among the youngest group aged 18–39, with 18.9% having an eGFR between 70 – 80 ml/min/1.73 m^2.

Even these small reductions in eGFR were significantly associated with adverse outcomes, with a hazard ratio of 1.42 [1.35 – 1. 49] and 4.39 per 1,000 person-years (23). Another analysis showed between 2.37 and 14.9 events per 1,000 person-years among individuals aged 18–65, with the highest risk observed in younger persons (24). These studies indicate that even a single serum creatinine measurement can help predict long-term risk for adverse events. Research by the same group also revealed that younger individuals are less likely to be referred to nephrologists, undergo a urine ACR test, or receive follow-up testing (96). Those with a reduction in eGFR below the 10th percentile were more prone to progress to ESKD, with a hazard ratio of 5.57 [3.79-8.19] (96). Similar findings were reported by Liu et al. using Alberta data, where individuals under 40 had an 85% lower incidence rate when applying a fixed eGFR cut-off compared to an age-adjusted cut (58). When age-adapted eGFR thresholds were used, 9,297 incident CKD diagnoses occurred in the 18-39 age group, compared to only 1,518 with a fixed threshold (58). Comparing fixed versus age-adapted diagnoses, 57.2% of fixed-threshold diagnoses did not align with age-specific criteria, suggesting that young patients are underdiagnosed, while older patients may be diagnosed more often than necessary (58). The evidence on eGFR reductions in younger individuals supports early screening by physicians to help prevent progression to CKD.

Predicting the risk of progression or development of CKD would assist clinicians in early identification of young adults at risk of adverse events associated with CKD. Risk prediction models have been developed by Sood et al.; however, currently available prediction tools are for the general population or those with pre-existing CKD (42,51,97–99). Another method to investigate age-adjusted thresholds is reclassification. By examining retrospective cohort event frequency trends in outcomes can be examined by age and/or eGFR. Reclassification is the method

by which a new diagnostic threshold is determined by examining thresholds at which adverse events increase. Reclassification allows for practical clinical targets based on an individual's risk. In a study by Tangri et al., progression to ESKD was investigated by developing risk prediction models from two Canadian populations of 3449 individuals with CKD 3 to 5 referred to nephrologists from 2001 to 2008 (100). By including a reclassification analysis, a superior Cox model was selected compared with their other models (100). Ultimately, reclassification enhances the selection of a diagnostic threshold when paired with other analyses.

In summary, CKD is a common disease that often takes many years to develop and is associated with all-cause mortality and cardiovascular disease. Retrospective cohort studies allow large-scale examination of adverse events to determine optimal diagnostic thresholds, thereby clarifying age-specific CKD diagnostic cut-offs.

Figure 3. The incidence of CKD increases with age; however, when an age-adapted cohort is examined, the number of incident CKD cases decreases (6).

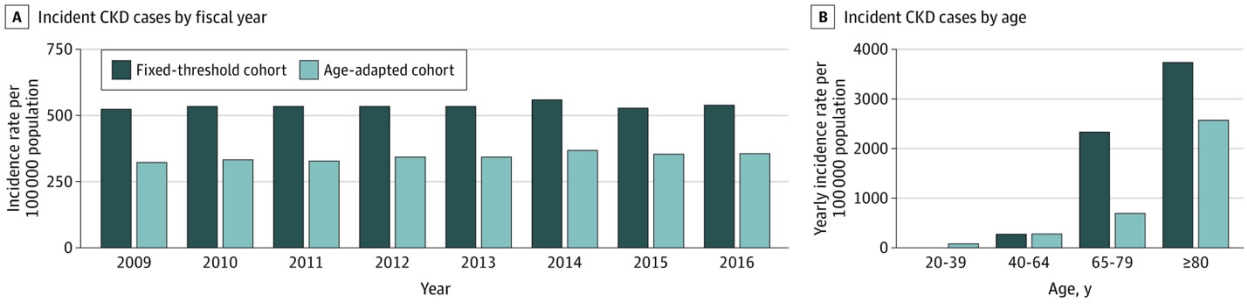


Figure 4. Increase in all-cause mortality, adverse cardiovascular events, and progression to ESKD occur in younger adults beginning at eGFR < 90 ml/min/1.73m^2 (23)

	18-39 years			40-49 years			50-65 years		
ACR	<3	3 to <30	≥30	<3	3 to <30	≥30	<3	3 to <30	≥30
Any adverse outcome									
eGFR									
50-60	2.27	3.60	7.90	1.63	2.46	3.98	1.37	1.81	2.68
60-70	1.72	3.15	6.24	1.16	1.92	3.52	1.19	1.82	2.37
70-80	1.53	2.38	4.07	1.01*	1.68	2.96	1.07	1.61	2.39
80-90	1.13*	1.96	3.73	1.00*	1.60	2.69	1.00	1.53	2.30
90-100	1.03*	1.47	3.75	1.00	1.48	2.39	1.05	1.51	2.22
100-110	1.00	1.51	2.59	1.09	1.54	2.53	0.96	1.41	2.03
110-120	1.12	1.70	2.88	1.04*	1.58	2.13	1.06	1.47	2.10
>120	0.80	1.43	2.02	1.21	2.03	2.43	1.70	1.92	2.93
All cause mortality									
eGFR									
50-60	1.69*	3.50	6.76	2.35	2.66	4.84	1.67	2.76	4.20
60-70	1.24*	2.18	4.83	1.49	2.81	5.58	1.36	2.51	3.72
70-80	1.51	2.22	2.50	1.22	2.17	4.27	1.12	2.03	3.53
80-90	1.17*	2.17	4.12	1.18	1.85	4.08	1.00	1.85	3.44
90-100	0.99*	1.49	4.34	1.00	2.16	3.71	1.10	1.86	3.25
100-110	1.00	1.39	2.99	1.15	1.94	3.93	1.02*	1.73	3.04
110-120	1.02*	1.80	2.59	1.24	2.18	3.32	1.33	1.93	3.17
>120	1.08*	1.87	2.53	1.95	3.88	3.91	2.35	3.59	4.61
Cardiovascular composite outcome									
eGFR									
50-60	1.36*	2.24	3.32	1.31	2.04	2.25	1.31	1.60	2.10
60-70	1.53	2.13	2.65	1.10	1.70	2.18	1.17	1.69	2.10
70-80	1.48	1.93	2.41	0.94*	1.51	2.37	1.06	1.56	2.19
80-90	1.10*	1.84	2.73	0.96*	1.53	2.32	1.00	1.49	2.05
90-100	1.01*	1.33	2.74	1.00	1.38	2.16	1.03	1.46	2.07
100-110	1.00	1.50	1.91	1.08	1.47	2.33	0.93*	1.35	1.86
110-120	1.13	1.64	2.48	1.00*	1.47	1.86	0.95*	1.37	1.92
>120	0.69	1.27	1.40	1.07*	1.72	2.05	1.44	1.47	2.85
Kidney failure									
eGFR									
50-60	55.4	118	424	20.7	42.60	265.0	5.07	21.4	106
60-70	20.0	66.4	325	5.70	21.20	198.0	2.28	14.7	73.3
70-80	2.79*	37.8	182	3.48	14.20	121.0	1.24*	9.05	53.9
80-90	1.34*	11.2	124	1.00*	15.40	85.70	1.00	5.36	45.3
90-100	1.28*	9.19	137	1.00	9.94	63.80	0.96*	3.87	33.3
100-110	1.00	10.7	64.6	1.13*	7.65	50.70	0.87*	3.60	24.9
110-120	0.89*	6.41	61.0	1.80	7.24	36.60	0.80*	4.38	18.5
>120	1.02*	7.96	47.6	1.91*	10.50	50.40	2.01*	5.96	23.2

Rationale and Impact

The development and adoption of an age-specific definition of CKD have been proposed, but the eGFR cutoff for such a definition needs clarification. Recent studies show that an age-adjusted definition of CKD applies to both younger and older adults. Adverse events linked to CKD in older individuals may occur at lower eGFRs than currently accepted, while a slightly lower eGFR (< 90 ml/min/1.73 m^2) in younger adults might indicate a poorer prognosis for adverse events over 5- and 10-year periods. Ideally, a large population should be used to capture adverse events in individuals aged 18 and above. Application of a novel method for examining cut points, the regression discontinuity design, may provide greater clarity into a CKD cut-off by age using population data. To our knowledge, the number of participants in this thesis represents one of the largest population sizes for a retrospective cohort study to date on eGFR. The use of Cox proportional hazards, RDD, and reclassification will enhance the understanding of adverse outcomes in younger adults, an emerging area of CKD research. We will examine adverse events over 10 years in both young and older adults to determine whether the risk of all-cause mortality, cardiac events, and ESKD increases over time. This thesis will offer new insights into the risk and frequency of cardiovascular outcomes related to decreased kidney function. We aim to better determine whether mortality, MACE, MACE-plus, and ESKD occur at an eGFR of 60 ml/min/1.73 m^2 or at another threshold by age group.

Chapter 3: Adverse outcomes associated with CKD in Ontario adults: a retrospective cohort study

Chronic kidney disease (CKD) is a common condition caused by irreversible structural damage to the kidneys. The prevalence of CKD is increasing in the Canadian population, affecting about 10% (33). CKD is diagnosed through a sustained reduction in eGFR of eGFR <60 ml/min/1.73 m^2 for longer than three months (4,101). Currently, the universal diagnostic threshold for CKD is set at 60 ml/min/1.73 m^2 due to the association of adverse cardiac events with this eGFR threshold; however, adverse events may occur at eGFRs below or above 60 ml/min/1.73 m^2, depending on an individual's age (4,101). An age-adapted definition of CKD might better identify the condition in younger and older individuals (6,8,23). Clarifying specific age and eGFR thresholds for CKD diagnosis allows us to identify at-risk individuals earlier, potentially preventing CKD progression or adverse events, including mortality. Previous research by Hussein et al. and the Chronic Kidney Disease Consortium indicates that a significant number of adverse cardiac events occur at higher GFR levels than previously thought, with individuals aged 18–39 experiencing increased adverse events at an eGFR < 90 ml/min/1.73 m^2 (23,84). An optimal eGFR threshold for diagnosing and monitoring individuals at risk of CKD has not been established previously. In this thesis, we explore the relationship between eGFR and adverse outcomes, including all-cause mortality, major cardiac adverse events, and ESKD, among Ontario adults aged 18 and older.

Methods

Study design and setting

We conducted a retrospective population-based cohort study using Ontario data from the Institute for Clinical Evaluative Sciences (ICES). All ICES data is de-identified and does not require research ethics board approval (1). Additional methodological documentation is available in the

appendices, including the Reporting of Studies Conducted using Observational Routinely Collected Data (RECORD) statement (Appendix X).

Data sources

We obtained data, including International Classification of Diseases (ICD-10) codes, for individual demographics such as age, sex, urban or rural residence, income quintile, comorbidities, serum creatinine, and healthcare utilization from eight linked databases listed in Appendix I and Appendix II. Unique, de-identified codes were used for all participants. Demographics and results with fewer than five individuals were either removed or combined with another age group or eGFR to prevent the identification of individuals.

Study cohort

There were initially 12,548,548 Ontario adults in the dataset. The data was cleaned to remove patients with missing age and demographic data. Individuals who were missing a second serum creatinine, had prior CKD, were kidney transplant recipients, ESKD, or had follow-up for less than one year were also excluded from the dataset (N = 4,160,208). The final population cohort of 8,388,340 Ontario adults was used for analysis. We included all adults aged 18–105 living in Ontario with more than one serum creatinine measurement available within 90-730 days. The study period included data from January 1, 2008, to December 31, 2021, with a follow-up period ending on December 31, 2022. The study start date of January 1, 2008, was used because this was when serum creatinine data first became available for cohort studies through ICES. The index date was each individual's second serum creatinine measurement, with follow-up continuing until death, emigration from Ontario, or the end of the study period. Each individual's serum creatinine

was the average of their two serum creatinine values. The cohort was divided into age groups: 18–30, 31–40, 41 – 50, 51–60, 61–70, 71–80, and over 80, for both the crude and adjusted Cox proportional hazards models.

Figure 5. Study design included index event date with a five-year lookback window and one-year follow-up between 2008 – 2022

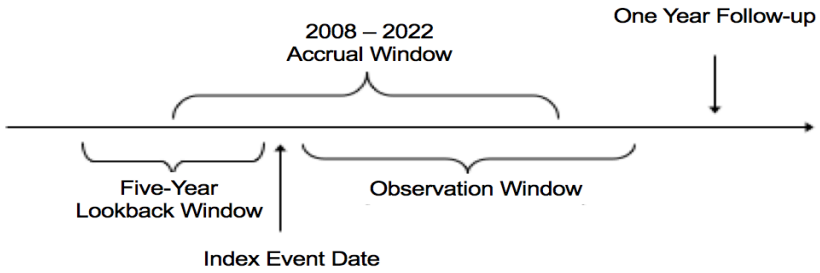
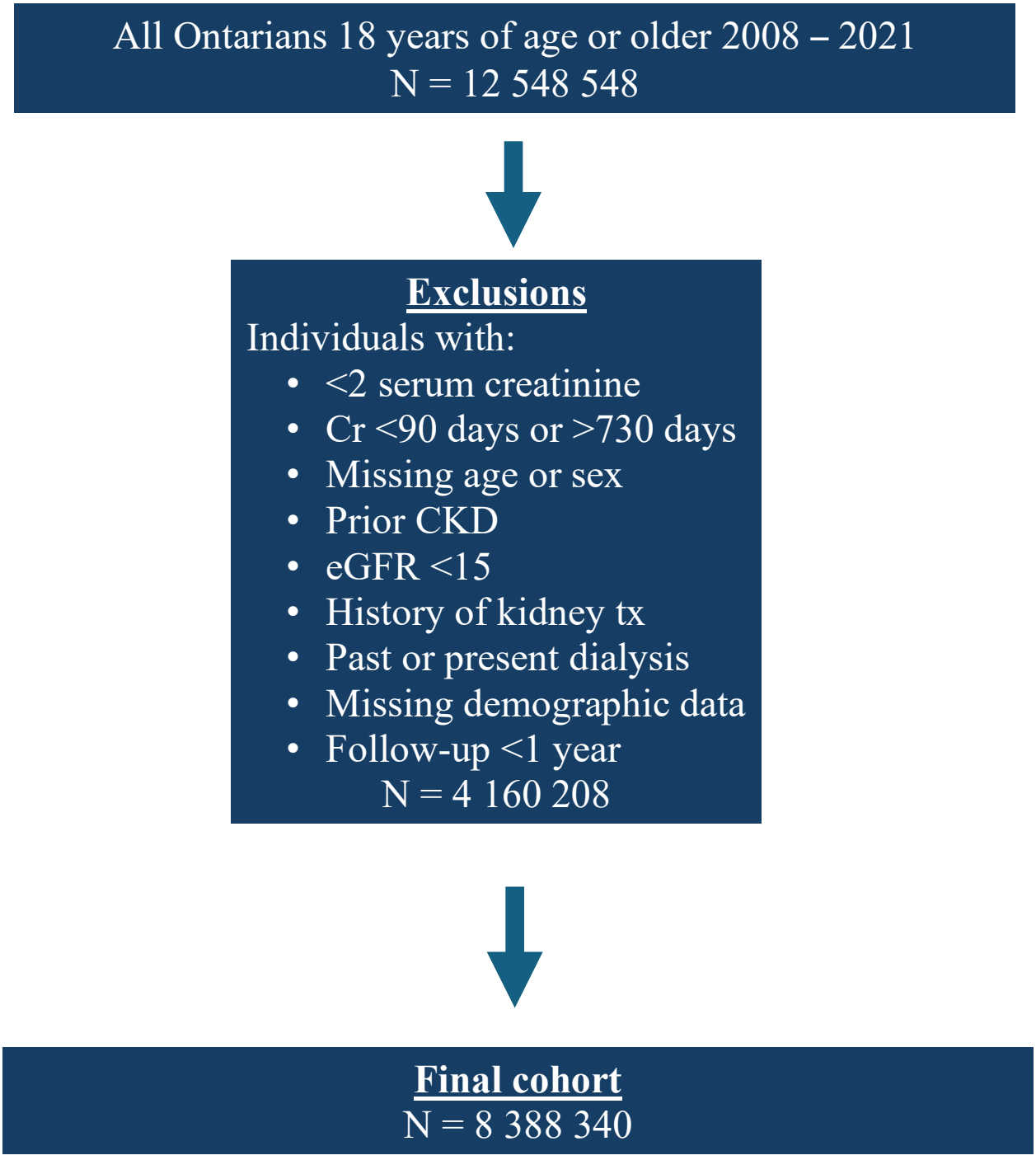


Figure 6. Participant flow diagram



Exposures

Age and eGFR were the two exposures included in this study, with age being the primary exposure. Everyone's study eGFR was calculated as the average of the participants' first two serum creatinine measurements obtained at outpatient Ontario labs. The index date was set at the time of the second creatinine measurement. eGFR was calculated using the race-free CKD-EPI equation that incorporates sex, age, and serum creatinine to estimate eGFR (102). Individuals' serum creatinine values were categorized into groups by 10 ml/min/1.73 m^2 intervals: eGFR >110, 100–110, 90–100, 80–90, 70–80, 60–70, 50–60, and eGFR < 50 ml/min/1.73 $m^{2.}$ Some analyses required increasing the size of the age- or eGFR-cohort to comply with ICES confidentiality requirements, as small cell sizes are not permitted. Reference values were established by age group based on current literature, measured using nuclear imaging in healthy living kidney donors (103–105). Age-specific reference values for this study were > 110ml/min/1.7 $3m^2$ for ages 18–30, 100–110 ml/min/1.$73m^2$ for ages 31–50, 80–90 ml/min/1.73 m^2 for ages 51–60, 70–80ml/min/1.73 m^2 for ages 61–70, 60-70ml/min/1.$73m^2$ for ages 71–80, and 50–60 ml/min for individuals over 80.

Outcomes

The primary outcomes included all-cause mortality, MACE, MACE-plus and ESKD. We used the first event for each adverse event that occurred, with a 5-year lookback period and a 1-year follow-up, to evaluate these outcomes.

Covariates

For the Cox proportional hazards model, covariates included sex, living status, income quintile, healthcare utilisation, comorbidities (such as diabetes, hypertension, congestive heart failure, atrial fibrillation, acute coronary syndrome, ischemic stroke, obesity, hypercholesterolemia, smoking, alcoholism, and cancer), and healthcare utilisation (primary care visits, emergency department visits, referrals, and visits to nephrologists, endocrinologists, and cardiologists). Living status was defined using postal codes available through ICES data. Covariates were selected based on the existing literature, with well-established associations with CKD adverse outcomes or disease progression (16,27,59,68,92,106,107). Models were adjusted for sex, income quintile, comorbidities and healthcare utilization.

Statistical analysis

Cox proportional hazards

Descriptive statistics for the total study population are provided for the study cohort and each study group using means and standard deviations (SD) for normally distributed variables. The median is used to describe non-normally distributed variables, along with the interquartile range (IQR). Crude proportions and frequencies are utilized to describe categorical variables for descriptive purposes. Associations between age, eGFR, and outcome variables are analyzed using Cox regression models with follow-up from the index date to the first event of interest or individual censoring (emigration or study completion) (108–110). Models are created for each age group to estimate hazard ratios (HRs) relative to the age-specific reference groups based on values from healthy living donor candidates for kidney transplantation (104,111). Models are adjusted for sex,

urban or rural residence, income quintile, interactions with the healthcare system, and comorbidities. All analyses are performed using SAS Enterprise Guide version 7.15 (SAS Institute Inc., Cary, NC, USA).

We conducted sub-analyses of the effect of urine ACR and diabetes on the frequency and risk of adverse events in the analytic cohort. There were N = 1,120,594 individuals included with valid urine ACR values. Three groups of urine albuminuria were created: 0 – 3 mg/mmol, 3.01 – 30 mg/mmol, and >30 mg/mmol. Using Cox regression models, a stratified analysis was completed to assess the effect of increased urine albumin on HR for all-cause mortality, MACE, MACE-plus, and ESKD outcomes.

Regression discontinuity design

A regression discontinuity model was created in RStudio to verify the results from the Cox proportional hazards analysis. Methodology for developing the RDD from Calonico et al. was used (81). The purpose of this analysis was to estimate the impact of eGFR and age on adverse outcomes associated with CKD at a more granular level than in the Cox analysis. The running variable for the model was eGFR divided by age, as shown on the X-axis of the cubic spline (Appendices V and VI). The cut-off values used for modelling were determined by the eGFR identified in the previous Cox analysis as the point at which the HR for adverse outcomes increased. We then used increments of 3, 5, and 10 ml/min/1.73 m^2 above and below cut-offs of 75 ml/min/1.73 m^2 and 85 ml/min/1.73 m^2 to assess whether there was a significant unadjusted risk difference. Risk difference compares outcomes above and below the cut-off to estimate the probability that the

event occurs at that point, much as the average treatment effect does at the cut-off point (75,80,81). A significant risk difference suggests an increase in adverse outcomes at that eGFR.

Reclassification

Reclassification is the examination of disease risk categories or outcomes to improve the identification of individuals at risk (100,112,113). Adverse outcomes in younger adults have been reported to increase at eGFR < 90 ml/min/1.73 m^2 rather than at eGFR <60 ml/min/1.73 m^2. We analyzed individuals ages 18 – 39 over 3, 5, and 10 years to assess the frequency of all-cause mortality, MACE, MACE-plus and ESKD in eGFR groups < 95ml/min/1.73 m^2, < 85 ml/min/1.73 m^2, <75 ml/min/1.73 m^2 and <60 ml/min/1.73 m^2 (referent) to examine the frequency of adverse events at different levels of reduction in eGFR. We aimed to determine whether there is an optimal practical eGFR cut-off for younger adults, based on the number of individuals with outcomes of interest per group. We examined differences in the number of individuals per group to determine whether there is an optimal level of reduced eGFR at which physicians may monitor younger adults more closely for adverse events.

Results

Objective I: Descriptive statistics

The study includes 8,388,340 individuals aged 18 to 105 in Ontario from January 1, 2008, to December 1, 2021, with a one-year follow-up period ending on December 31, 2022. The mean follow-up time was 361.63 ± 177.15 days. The 18–39 age group consisted of 2,287,969 individuals. The 40–65 age group included 4,272,634 individuals. In the 66–80 age group, there were 1,398,758 individuals: in the 80+ age group, 428,979. The overall mean age of participants was 51.27 ± 17.37 years. The mean age in the 18–39 group was 29.65 ± 6.22 years, in the 40–65 group it was 52.61 ± 7.22 years, in the 66-80 group it was 71.95 ± 4.25 years, and for those over 80, the average age was 85.80 ± 4.10 years. The dataset consisted of 62.3% female and 37.7% male participants. Approximately 6.8% of Ontario's population resided in rural areas.

The median number of eGFR measures for all individuals in the dataset was 8 (IQR 4–17). The overall mean eGFR in the study population was 92.59 ± 20.17 ml/min/1.73 m^2. The mean eGFR by age group was 110.91 ± 14.43 ml/min/1.73 m^2 for individuals aged 18–39, 91.88 ± 14.04 for ages 40–65, 74.46 ± 15.20 for those aged 66–80, and 61.06 ± 16.37 for individuals over 80. The mean number of serum creatinine measurements was a median of 4 (IQR 2–9) for ages 18–39, 8 (IQR 4–16) for ages 40–65, 15 (IQR 7–30) for ages 66–80, and 13 (IQR 6–27) for those over 80.

In the study population of 8.3 million Ontario adults, very few patients aged 18–39 years had comorbidities associated with CKD. Diabetes (6.2%), hypertension (5.1%), and alcoholism (2.3%) were most common in the youngest group. The proportion of individuals with diabetes,

hypertension, ischemic stroke, atrial fibrillation, obesity, and cancer increased with age. The most prevalent comorbidities included hypertension (28.3%), diabetes (18.0%), congestive heart failure (11.5%), ischemic stroke (3.6%), acute coronary syndrome (2.9%), cancer (2.3%), atrial fibrillation (1.7%), and alcohol use disorder (1.5%). All other comorbidities were observed at a population proportion of less than 1%. There were virtually no emergency department visits recorded among patients in the dataset; however, patients visited their family physicians a median of 20 times (IQR 12–34) during the study period.

Table 1. Baseline study population characteristics, including the total cohort and age groups

		18 - 39	40 - 65	66 - 80	80 +	TOTAL
		N=2,287,969	N=4,272,634	N=1,398,758	N=428,979	N=8,388,340
Age	Mean ± SD	29.65 ± 6.22	52.61 ± 7.22	71.95 ± 4.25	85.80 ± 4.10	51.27 ± 17.37
	Median (IQR)	30 (25-35)	53 (47-59)	71 (68-75)	85 (83-88)	51 (38-64)
Sex	F	1,424,703 (62.3%)	2,240,375 (52.4%)	740,283 (52.9%)	273,094 (63.7%)	4,678,455 (55.8%)
	M	863,266 (37.7%)	2,032,259 (47.6%)	658,475 (47.1%)	155,885 (36.3%)	3,709,885 (44.2%)
Rural	N	2,132,710 (93.2%)	3,813,077 (89.2%)	1,203,149 (86.0%)	374,873 (87.4%)	7,523,809 (89.7%)
	Y	155,259 (6.8%)	459,557 (10.8%)	195,609 (14.0%)	54,106 (12.6%)	864,531 (10.3%)
Income Quintile	1	511,421 (22.4%)	779,529 (18.2%)	256,048 (18.3%)	90,028 (21.0%)	1,637,026 (19.5%)
	2	478,883 (20.9%)	827,235 (19.4%)	283,478 (20.3%)	91,076 (21.2%)	1,680,672 (20.0%)
	3	468,607 (20.5%)	860,136 (20.1%)	279,436 (20.0%)	84,227 (19.6%)	1,692,406 (20.2%)
	4	451,233 (19.7%)	903,296 (21.1%)	284,976 (20.4%)	80,897 (18.9%)	1,720,402 (20.5%)
	5	377,825 (16.5%)	902,438 (21.1%)	294,820 (21.1%)	82,751 (19.3%)	1,657,834 (19.8%)
eGFR	Mean ± SD	110.91 ± 14.43	91.88 ± 14.04	74.46 ± 15.20	61.06 ± 16.37	92.59 ± 20.17
	Median (IQR)	113 (102-121)	94 (83-102)	77 (65-87)	62 (49-75)	94 (80-107)
Number of serum creatinine measures	Mean ± SD	7.63 ± 13.55	14.16 ± 20.34	23.24 ± 26.13	20.14 ± 22.15	14.46 ± 20.86
	Median (IQR)	4 (2-9)	8 (4-16)	15 (7-30)	13 (6-27)	8 (4-17)
Time in study	Mean ± SD	375.12 ± 180.05	371.32 ± 176.60	328.31 ± 169.59	301.74 ± 165.08	361.63 ± 177.15
	Median (IQR)	369 (217-517)	370 (217-503)	321 (180-436)	271 (161-402)	360 (204-492)
Hypertension		117,718 (5.1%)	1,180,228 (27.6%)	785,689 (56.2%)	288,821 (67.3%)	2,372,456 (28.3%)
Diabetes		140,817 (6.2%)	841,313 (19.7%)	421,719 (30.1%)	104,806 (24.4%)	1,508,655 (18.0%)

Congestive heart failure		41,969 (1.8%)	420,459 (9.8%)	349,499 (25.0%)	154,353 (36.0%)	966,280 (11.5%)
Acute coronary syndrome		2,880 (0.1%)	103,557 (2.4%)	92,965 (6.6%)	44,473 (10.4%)	243,875 (2.9%)
Atrial fibrillation		3,075 (0.1%)	36,601 (0.9%)	57,184 (4.1%)	44,254 (10.3%)	141,114 (1.7%)
Ischemic stroke		15,310 (0.7%)	107,102 (2.5%)	107,080 (7.7%)	68,693 (16.0%)	298,185 (3.6%)
Obesity		9,738 (0.4%)	22,725 (0.5%)	8,850 (0.6%)	1,433 (0.3%)	42,746 (0.5%)
Hypercholesterolemia		368 (0.0%)	9,787 (0.2%)	10,768 (0.8%)	4,767 (1.1%)	25,690 (0.3%)
Hyperkalemia		668 (0.0%)	2,984 (0.1%)	3,392 (0.2%)	2,458 (0.6%)	9,502 (0.1%)
Cancer		12,522 (0.5%)	86,784 (2.0%)	66,754 (4.8%)	24,393 (5.7%)	190,453 (2.3%)
Alcoholism		52,024 (2.3%)	57,610 (1.3%)	13,425 (1.0%)	2,651 (0.6%)	125,710 (1.5%)
Smoking		1,422 (0.1%)	4,587 (0.1%)	1,625 (0.1%)	232 (0.1%)	7,866 (0.1%)
Emergency medicine visit	Mean ± SD	0.39 ± 3.00	0.25 ± 2.15	0.23 ± 1.35	0.36 ± 1.64	0.29 ± 2.29
	Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Family medicine visit	Mean ± SD	22.87 ± 25.61	25.30 ± 25.86	34.16 ± 28.55	49.00 ± 38.78	27.32 ± 27.78
	Median (IQR)	17 (10-28)	19 (11-31)	27 (16-43)	39 (23-64)	20 (12-34)

Objective 2: Cox proportional hazard analysis demonstrates increased risk of adverse events at eGFR <90 ml/min/1.73 m^2 for younger individuals

The primary outcomes included analyses of all-cause mortality, MACE, MACE-plus, and ESKD in the study population, stratified by age and eGFR. In the 18–30 age group, individuals with eGFR less than 80 ml/min/1.73 m^2 experienced a significant 50% increase in mortality (HR 1.51 [1.31–1.75]). The same trend was observed in the 31-40 group, with HR 1.32 [1.20–1.44]. Interestingly, a bimodal distribution emerged in the 31-40 group, with individuals with eGFR > 110 ml/min/1.73 m^2 experiencing higher mortality (HR 1.27 [1.21–1.33]). For those aged 41-60, the increased risk started at an eGFR of 70 ml/min/1.73 m^2 (HR 1.47 [1.39–1.56]) and was also observed at eGFR greater than 110 ml/min/1.73 m^2 (HR 1.71 [1.66–1.76] and 3.03 [2.94-3.13). For adults over 61 years, higher mortality was observed at eGFR < 50 ml/min/1.73 m^2 , but increased risk was noted at levels above 90 ml/min/1.73 m^2.

For MACE, a total of 840,130 events were recorded from the study population. Among individuals aged 18 – 30, the hazard ratio (HR) increased to suggest a 20% rise in MACE with eGFR below 90 ml/min/1.73 m^2 (1.20 [1.02-1.41]). For ages 31 – 40, HR increased by 28% in individuals with eGFR below 80 ml/min/1.73 m^2 (1.28 [1.18-1.40]), and by 16% in individuals with eGFR below 80 ml/min/1.73 m^2 (1.16 [1.13-1.20]). MACE risk increased by 26% at eGFR less than 60 in the 61 – 70 age group. Adults over 70 had an increased risk with eGFR below 50 ml/min/1.73 m^2 (1.39 [1.37-1.41], 1.26 [1.25-1.28]). We observed a bimodal distribution of increased MACE risk at higher eGFR levels, with peaks at ages 51 to 80, and risk increases ranging from 28% to 89%. For MACE-plus (which includes hospitalization for heart failure), there were 808441 total events. The same trend was seen, with events increasing by 28% at eGFR below 90 ml/min/1.73 m^2 in ages

18 – 30 (1.28 [1.13-1.45]), at eGFR below 70 ml/min/1.73 m^2 in adults over 31 by 39% (1.39 [1.28-1.50]), 20% for eGFR below 70 ml/min/1.73 m^2 in adults over 41 (1.20 [1.17-1.24]), and 19% for adults over 61 at eGFR below 60 ml/min/1.73 m^2 (1.19 [1.17-1.22]). Adults over 60 had a 28% to 68% increased risk of MACE-plus events at eGFR below 50 ml/min/1.73 m^2. Once again, a bimodal distribution was observed, where individuals aged 51 to 80 faced increased risks of adverse cardiovascular events at eGFR above 110 ml/min/1.73 m^2, with increases ranging from 39% to 109%. Adults aged 71 – 80 faced the highest risk of both MACE and MACE-plus when eGFR exceeded 110 ml/min/1.73 m^2 (2.09 [1.67-2.62]). In the study population, there were 27,676 ESKD events. For individuals under 30, there were 988 events of ESKD; between 30 and 40, 1,569; between 40 and 50, 3,735; between 50 and 60, 6,536; and between 60 and 70, 5,515. Upon reviewing HRs for ESKD across all age groups, an increased risk of progression to ESKD is observed with an eGFR of < 60 ml/min/1.73 m^2. Among individuals aged 18-50, ESKD was more common in those with an eGFR of 80-90 ml/min/1.73 m^2. Adults ages 18 – 30 were 29% more likely to progress to ESKD with eGFR < 90 ml/min/1.73 m^2 (1.29 [0.97-1.70]). Their risk of progression to ESKD increases by over 200% at eGFR < 80 ml/min/1.73 m^2. This was true even when the age-based reference values ranged from 80 to 90 ml/min/1.73 m^2. The results demonstrate that higher eGFR at younger age groups is less likely to be associated with ESKD. However, in the 40-70 years age group, individuals with an eGFR greater than 110 ml/min/1.73 m^2 were significantly more likely to progress to ESKD in the study. No events were captured for individuals with eGFR in the 71+ age group. Crude incidence rates are available in Appendix IV.

Table 2. Association of adverse outcomes by age with various thresholds of eGFR

2A. Mortality

	18 - 30	31 - 40	41 - 50	51 - 60	61 - 70	71 - 80	> 80
Total patients	1175062	1253091	1612683	1751954	1371951	794620	428979
Total events	11093	17450	50669	128665	230372	336888	341658
eGFR							
0-50	**2.74[2.05-3.66]**	**3.40[2.85-4.05]**	**2.69[2.47-2.92]**	**2.97[2.86-3.09]**	**2.26[2.22-2.31]**	**1.62[1.60-1.64]**	**1.27[1.26-1.29]**
50-60	**5.42[4.12-7.12]**	**2.98[2.47-3.60]**	**2.10[1.93-2.27]**	**1.88[1.81-1.94]**	**1.50[1.47-1.52]**	1.17[1.15-1.18]	Ref
60-70	**1.52[1.19-1.95]**	**1.91[1.68-2.17]**	**1.47[1.39-1.56]**	**1.30[1.27-1.34]**	1.17[1.15-1.18]	Ref	0.92[0.91-0.93]
70-80	**1.51[1.31-1.75]**	**1.32[1.20-1.44]**	1.10[1.06-1.15]	1.06[1.04-1.09]	Ref	0.92[0.91-0.93]	0.97[0.96-0.98]
80-90	1.04[0.95-1.15]	1.07[1.00-1.14]	1.01[0.98-1.04]	Ref	1.03[1.02-1.05]	0.97[0.96-0.98]	0.89[0.88-0.90]
90-100	0.87[0.81-0.94]	Ref	Ref	1.14[1.12-1.16]	1.11[1.10-1.12]	1.12[1.11-1.14]	**1.40[1.34-1.45]**
100-10	0.86[0.82-0.91]	1.03[0.98-1.09]	1.16[1.13-1.19]	**1.40[1.37-1.42]**	**1.86[1.82-1.90]**	**2.66[2.52-2.81]**	**2.13[1.82-2.49]**
110+	Ref	**1.27[1.21-1.33]**	**1.71[1.66-1.76]**	**3.03[2.94-3.13]**	**4.42[4.18-4.68]**	**4.35[3.80-4.99]**	**1.57[1.08-2.29]**

*adjusted for sex, hypertension, diabetes, cardiovascular disease, obesity, smoking, alcoholism, 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 >110 for 18-30 years, 90-100 for 31-50 years, 70 – 80 for 61-70 years, 60 – 70 for 71- 80 years, and 50 – 60 for >80 years of age.

*** bolded HR suggest a significant risk for adverse event

2B. MACE

	18 - 30	31 - 40	41 - 50	51 - 60	61 - 70	71 - 80	> 80
Total patients	1175062	1253091	1612683	1751954	1371951	794620	428979
Total events	3456	16216	71627	165449	226381	208140	148861
eGFR							
0-50	**2.38 [1.49-3.81]**	**3.56[2.99-4.23]**	**2.52[2.34-2.72]**	**1.72[1.66-1.79]**	**1.52[1.49-1.55]**	**1.39[1.37-1.41]**	**1.26[1.25-1.28]**
50-60	**4.36[2.69-7.08]**	**2.21[1.83-2.68]**	**1.62[1.50-1.75]**	**1.39[1.34-1.43]**	**1.26[1.23-1.28]**	1.12[1.11-1.14]	
60-70	**2.24[1.54-3.26]**	**1.31[1.14-1.51]**	**1.34[1.28-1.41]**	**1.16[1.14-1.19]**	1.06[1.04-1.08]		0.91[0.89-0.92]
70-80	**1.81[1.42-2.29]**	**1.28[1.18-1.40]**	**1.16[1.13-1.20]**	1.06[1.04-1.08]		0.92[0.91-0.93]	0.90[0.89-0.92]
80-90	**1.20[1.02-1.41]**	1.05[0.98-1.12]	1.05[1.03-1.08]		0.98[0.97-1.00]	0.90[0.89-0.92]	0.82[0.81-0.84]
90-100	1.03[0.92-1.16]			1.01[1.00-1.03]	0.95[0.94-0.96]	0.94[0.92-0.96]	1.03[0.96-1.10]
100-10	0.96[0.87-1.06]	1.06[1.00-1.11]	1.06[1.04-1.08]	0.99[0.97-1.00]	1.08[1.05-1.11]	**1.36[1.24-1.50]**	1.15[0.84-1.59]
110+		0.98[0.94-1.03]	1.09[1.06-1.11]	**1.28[1.23-1.33]**	**1.61[1.47-1.77]**	**1.89[1.45-2.45]**	0.33[0.11-1.01]

2C. MACE-plus

	18 - 30	31 - 40	41 - 50	51 - 60	61 - 70	71 - 80	> 80
Total patients	1175062	1253091	1612683	1751954	1371951	794620	428979
Total events	5432	19308	79073	183262	258527	256181	189920
eGFR							
0-50	**3.00[2.17-4.13]**	**3.97[3.41-4.62]**	**2.81[2.61-3.01]**	**1.91[1.84-1.98]**	**1.68[1.65-1.72]**	**1.47[1.45-1.49]**	**1.28[1.27-1.30]**
50-60	**4.65[3.19-6.78]**	**2.84[2.41-3.36]**	**1.67[1.55-1.80]**	**1.49[1.44-1.53]**	**1.32[1.30-1.34]**	1.14[1.13-1.16]	
60-70	**3.10[2.36-4.06]**	**1.70[1.51-1.92]**	**1.43[1.36-1.49]**	**1.19[1.17-1.22]**	1.07[1.06-1.09]		0.90[0.89-0.91]
70-80	**1.96[1.63-2.36]**	**1.39[1.28-1.50]**	**1.20[1.17-1.24]**	1.05[1.03-1.07]		0.91[0.90-0.92]	0.90[0.89-0.91]
80-90	1.28[1.13-1.45]	1.13[1.06-1.20]	1.08[1.05-1.10]		0.99[0.98-1.00]	0.91[0.90-0.92]	0.83[0.81-0.84]
90-100	0.94[0.85-1.04]			1.01[1.00-1.02]	0.96[0.95-0.97]	0.96[0.94-0.98]	1.03[0.97-1.09]
100-10	0.87[0.81-0.95]	1.10[1.05-1.15]	1.08[1.06-1.10]	1.00[0.99-1.01]	1.16[1.13-1.19]	**1.51[1.39-1.64]**	1.19[0.90-1.58]
110+		1.06[1.01-1.11]	1.15[1.12-1.18]	**1.39[1.35-1.44]**	**1.80[1.66-1.96]**	**2.09[1.67-2.62]**	0.51[0.21-1.22]

3D. ESKD

	18 - 30	31 - 40	41 - 50	51 - 60	61 - 70	71 - 80	> 80
Total patients	1175062	1253091	1612683	1751954	1371951	794620	428979
Total events	988	1569	3735	6536	8051	5515	1282
eGFR							
0-50	**253.83 [210.19-306.54]**	**134.45 [106.72-169.38]**	**55.39 [48.11-63.78]**	**27.00 [24.47-29.79]**	**12.35 [11.37-13.41]**	**7.56 [6.88-8.31]**	**4.84 [4.04-5.79]**
50-60	**98.11 [73.84-130.34]**	**42.30 [32.34-55.34]**	**19.07 [16.23-22.41]**	**9.00 [8.05-10.06]**	**4.00 [3.65-4.39]**	**1.96 [1.75-2.19]**	
60-70	**30.58 [22.76-41.10]**	**19.68 [15.18-25.50]**	**7.91 [6.74-9.28]**	**3.60 [3.23-4.01]**	**1.80 [1.64-1.97]**		0.48 [0.37-0.63]
70-80	**4.49 [3.20-6.32]**	**5.24 [4.03-6.82]**	**2.76 [2.36-3.21]**	**1.55 [1.39-1.73]**		0.70 [0.62-0.80]	0.63 [0.48-0.83]
80-90	**2.98 [2.23-3.99]**	**1.49 [1.13-1.97]**	**1.39 [1.19-1.62]**		0.71 [0.65-0.79]	0.54 [0.47-0.61]	0.37 [0.25-0.54]
90-100	**1.29 [0.97-1.70]**			0.78 [0.70-0.86]	0.67 [0.60-0.73]	0.42 [0.32-0.54]	0.89 [0.28-2.79]
100-10	1.03 [0.80-1.32]	0.83 [0.64-1.07]	0.95 [0.83-1.09]	0.93 [0.84-1.04]	0.72 [0.57-0.91]	0.55 [0.14-2.21]	0.00 [0.00-3.31E162]
110+		0.91 [0.74-1.14]	**1.41 [1.21-1.64]**	**1.81 [1.46-2.24]**	**1.57 [0.75-3.31]**	0.00 [0.00-3.57E107]	0.00[0.00-.]

Objective 3. Regression discontinuity design demonstrates that there is no significant eGFR cut-off by age

A regression discontinuity model was used to assess the granularity of age-by-eGFR cut-offs in relation to adverse outcomes. Cut points were examined around a hypothesized eGFR threshold for an adverse CKD event by age, identified using Cox analysis. Cut points at 85 ml/min/1.73 m^2 and 75 ml/min/1.73 m^2 were examined based on increased adverse events below 90 ml/min/1.73 m^2. We first plotted the probabilities of outcomes across eGFR, divided by age group, and formally tested these relationships using regression discontinuity models developed in RStudio based on the methodology outlined in Calonico et al. (81). No significant cut-off for adverse events by age was identified using a regression discontinuity model for younger and older individuals across age groups and outcomes (mortality, MACE, MACE-plus, and ESKD). Distribution of risk differences through spline figures did not indicate any sharp or fuzzy cut points suggestive of a significant difference (114). The risk differences around the cut point mostly crossed one for all outcomes, ages, and ml/min from 75 to 85ml/min/1.73 m^2 (Table 3, Appendices V and VI).

Table 3. Regression-discontinuity design results. Results were not significant across all tested eGFR groups and age groups. Additional spline figures are available in Appendix VI.

3A. Mortality, 85 ml/min/1.73 m^2

Age group	*ml/min +/- 85 ml/min*	*RD*	*CI*
18-39	3	0.000835347	[-0.0021, 0.0037]
	5	0.000315621	[-0.002, 0.0026]
	10	0.000741891	[-0.00092, 0.002]
40 - 64			
	3	0.002440678	[-0.00029, 0.0052]
	5	0.000969256	[-0.0011, 0.0031]
	10	-0.003414685	[-0.0049, 0.0019]
65 - 80			
	3	0.005714948	[-0.0057, 0.0016]
	5	-0.001412912	[-0.0071, 0.004]
	10	-0.004276673	[-0.008, -0.0002]
80 - 105			
	3	-0.001777012	[-0.022, 0.019]
	5	0.003631906	[-0.013, 0.020]
	10	0.024593261	[0.0122, 0.037]

3B. MACE, 85 ml/min/1.73 m^2

Age group	*ml/min +/- 85 ml/min*	*RD*	*CI*
18-39	3	-0.001014092	[-0.001, 0.0037]
	5	9.25407E-05	[0.00009, 0.0039]
	10	0.000175344	[0.0002, 0.0029]
40 - 64			
	3	-0.004956167	[-0.005, 0.001]
	5	-0.003568435	[-0.0036, 0.001]
	10	-0.005800987	[-0.0058, -0.0025]
65 - 80			
	3	-0.003855083	[-0.0039, 0.0088]
	5	-0.005230863	[-0.005, 0.0043]
	10	-0.005202531	[-0.0052, 0.0019]
80 - 105			
	3	-0.016459648	[-0.016, 0.029]
	5	-0.008368317	[-0.0084, 0.027]
	10	-0.001767502	[-0.0018, 0.025]

3C. MACE-Plus, 85 ml/min/1.73 m^2

Age group	*ml/min +/- 85 ml/min*	*RD*	*CI*
18-39	3	7.88794E-05	[-0.0027, 0.0028]
	5	0.001069879	[-0.0011, 0.0032]
	10	0.000831865	[-0.00074, 0.0024]
40 - 64			
	3	-0.002355912	[-0.0055, 0.00075]
	5	-0.001486008	[-0.0039, 0.00092]
	10	-0.004854618	[-0.0067, 0.0031]
65 - 80			
	3	0.001478586	[-0.0052, 0.0082]
	5	-0.002135573	[-0.0073, 0.0031]
	10	-0.003776285	[-0.0075, 0.00003]
80 - 105			
	3	0.010733857	[-0.013, 0.035]
	5	0.010779238	[-0.0083, 0.030]
	10	0.010525072	[-0.0039, 0.025]

3D. ESKD, 85 ml/min/1.73 m^2

Age group	*ml/min +/- 85 ml/min*	*RD*	*CI*
18 - 39	3	0.00023121	[-0.0005, 0.000959]
	5	4.2492E-05	[-0.000533, 0.000618]
	10	-0.000151855	[-0.000582, 0.00028]
40 - 64			
	3	0.000170289	[-0.00026, 0.00061]
	5	0.000146901	[-0.00019, 0.00048]
	10	6.44823E-05	[-0.00018, 0.00030]
65 - 80			
	3	0.000104715	[-0.00054, 0.00075]
	5	-0.000109186	[-0.000621, 0.00040]
	10	1.06645E-06	[-0.00037, 0.00038]
>80			
	3	1.03841E-05	[-0.0010, 0.0011]
	5	-0.000176536	[-0.00099, 0.00064]
	10	3.21635E-05	[-0.00059, 0.00065]

3E. Mortality, 75 ml/min/1.73 m^2

Age group	*ml/min +/- 75 ml/min*	*RD*	*CI*
18 - 39			
	3	0.0011496	[-0.0055, 0.0078]
	5	0.001315727	[-0.0037, 0.006]
	7	0.000170252	[-0.0041, 0.0044]
	10	-0.00018648	[-0.004, 0.0025]
40 - 64			
	3	-0.00123925	[-0.0049, 0.0025]
	5	-0.00306963	[-0.0060, -0.0002]
	7	-0.00348471	[-0.0052, -0.001]
	10	-0.00309888	[-0.0052, -0.001]
65 - 80			
	3	-0.00262582	[-0.011, 0.021]
	5	-0.00046715	[-0.007, 0.006]
	7	-0.00076719	[-0.006, 0.004]
	10	-0.00789086	[-0.012, -0.0035]
>80			
	3	0.004920803	[-0.011, 0.020]
	5	0.0138081	[0.0018, 0.026]
	7	0.029473889	[0.019, 0.040]
	10	0.0400031	[-0.0006, 0.0003]

3F. MACE, 75 ml/min/1.73 m^2

Age group	*ml/min +/- 75 ml/min*	*RD*	*CI*
18 - 39	3	-0.00293701	[-0.0081, 0.0022]
	5	-0.00306156	[-0.0070,0.00091]
	7	-0.00230101	[-0.0057, 0.0011]
	10	-0.00141157	[-0.0043, 0.0014]
40 - 64			
	3	0.003407902	[-0.0006, 0.0075]
	5	0.001842975	[-00.13,0050]
	7	0.000568142	[-0.0021,0.0032]
	10	0.000209226	[-0.002-0.0025]
65 - 80			
	3	-0.00436382	[-0.011,0.0025]
	5	-0.00375359	[-0.0093, 0.0018]
	7	-0.0033214	[-0.0081, 0.0014]
	10	-0.00567491	[-0.0096, -0.0018]
>80			
	3	0.001614008	[-0.017, 0.020]
	5	0.000412995	[-0.014, 0.014]
	7	0.006754438	[-0.005, 0.018]
	10	0.012009926	[0.0022, 0.022]

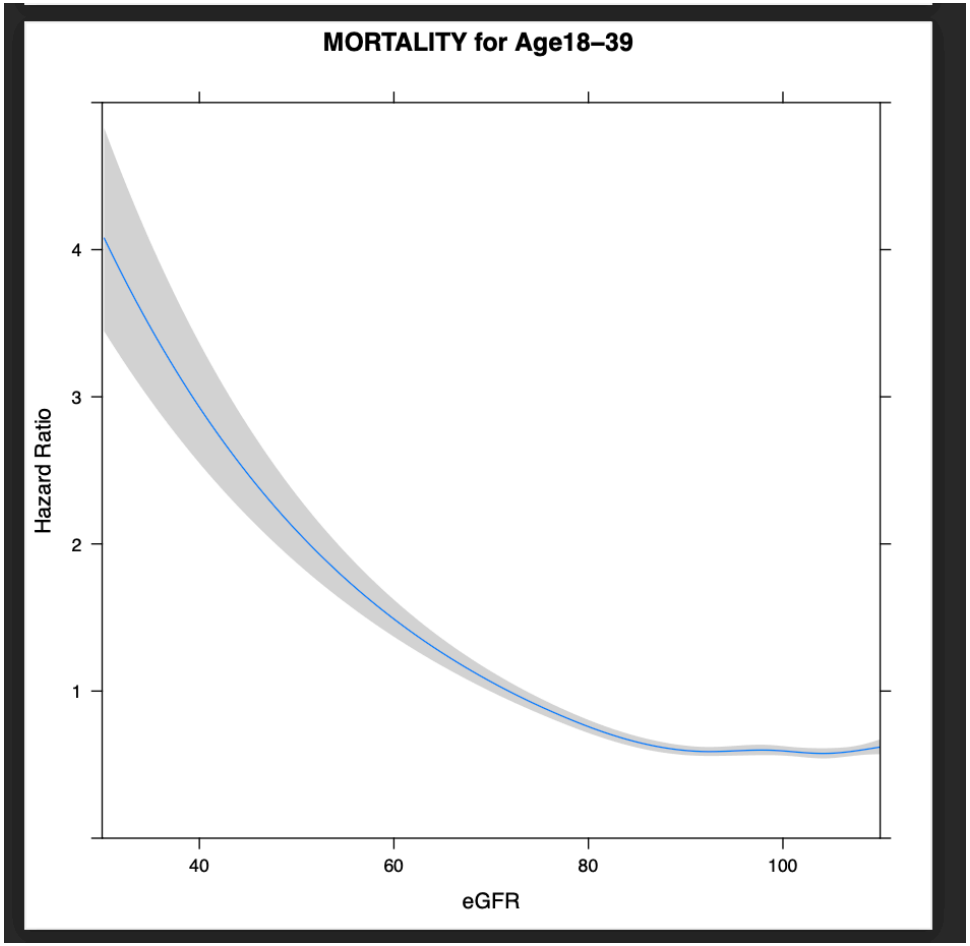
3G. MACE-plus, 75 ml/min/1.73 m^2

Age group	*ml/min +/- 75 ml/min*	*RD*	*CI*
18 - 39	3	-0.00262093	[-0.0082, 0.0030]
	5	-0.00260305	[-0.007, 0.0018]
	7	-0.00197958	[-0.0057, 0.0018]
	10	-0.0010368	[-0.0010, 0.0042]
40 - 64			
	3	0.004658097	[0.0005, 0.0089]
	5	0.002786917	[-0.0057, 0.0018]
	7	0.001178567	[-0.0016, 0.0039]
	10	0.000711187	[-0.0005, 0.0060]
65 - 80			
	3	-0.00490138	[-0.012, 0.0026]
	5	-0.00458869	[-0.0104, 0.0013]
	7	-0.00419595	[-0.0028, 0.0219]
	10	-0.00730505	[-0.011, -0.0032]
>80			
	3	0.006882186	[-0.012, 0.026]
	5	0.004445971	[-0.0103, 0.019]
	7	0.009469907	[-0.0028, 0.022]
	10	0.01383443	[0.0035, 0.024]

3H. ESKD, 75 ml/min/1.73 m^2

Age group	*ml/min +/- 75 ml/min*	*RD*	*CI*
18 - 39	3	-2.3792E-05	[-0.0027, 0.0026]
	5	-0.00047931	[-0.0026, 0.0001]
	7	-0.00048871	[-0.002, 0.001]
	10	-0.00024199	[-0.0018, 0.001]
40 - 64			
	3	4.27951E-05	[-0.0007, 0.0008]
	5	-0.00014293	[-0.0007, 0.0004]
	7	-0.0001523	[-0.0007, 0.0004]
	10	-0.00010783	[-0.0005, 0.0003]
65 - 80			
	3	-0.00015661	[-0.0011, 0.00075]
	5	-0.00018719	[-0.0009, 0.0005]
	7	-0.00017619	[-0.0008, 0.0004]
	10	-0.00021817	[-0.0007, 0.0003]
>80			
	3	0.000696444	[-0.0003, 0.0017]
	5	0.000569086	[-0.0002, 0.0013]
	7	0.000386079	[-0.0003, 0.0011]
	10	0.000251531	[-0.0003, 0.0008]

Figure 6. Cubic spline representation of RDD. No significant fuzzy cut-point was identified in analysis (Appendix VI)



Objective 4. Reclassification suggests that eGFR <75 ml/min/1.73 m^2 is an optimal kidney function to monitor younger adults for adverse events associated with CKD

We examined young adult (18–30) outcomes at 3-, 5-, and 10-year observation points with eGFR 60, 75, 85, and 95 ml/min/1.73 m^2 to determine the risk of adverse events over time at modest reductions in eGFR. Outcomes of all-cause mortality, MACE, MACE-plus and ESKD were included (Table 4). The number of individuals included over the three years was N = 2,428,153. After three years of follow-up, young adults with modest reductions in eGFR had an increased risk of MACE of HR 1.79 [1.86 – 1.91], with 11% increased risk of all-cause mortality (HR 1.11 [1.05-1.17]) and a risk of progression to ESKD increased by 1600% (HR 16.33 [13.75-19.39]). Risk increases with a decrease in eGFR to an over 800% increased risk of MACE, 970% increase in MACE-plus (9.74 [8.25-11.51]) and HR of 650 for individuals 18 – 30 with eGFR less than 60 ml/min/1.73 m^2 (650.31 [561.24-753.53]). At five years, risk for the eGFR group of 95ml/min increases by 68% for MACE (1.68 (1.6-1.76)), and by 1200% for ESKD (12.18 [10.77-13.78]) versus 850% increase for eGFR 60 (8.49 [7.19-10.01]) and HR 497 for ESKD (498.07 [446.03-556.19]) (46).

Table 4. Longitudinal follow-up of adults 18 – 30 with reduced eGFR association with adverse outcomes

4A. Three years

	EGFR 60	EGFR 75	EGFR 80	EGFR 95
MACE	**8.49 (7.19-10.01)**	**3.37 (3.05-3.72)**	**2.15 (2.01-2.3)**	**1.68 (1.6-1.76)**
MACE-plus	**10.06 (8.82-11.46)**	**3.64 (3.35-3.96)**	**2.2 (2.08-2.33)**	**1.62 (1.55-1.7)**
Mortality	**6.36 (5.54-7.31)**	**2.50 (2.3-2.72)**	**1.44 (1.36-1.53)**	1.06 (1.02-1.11)
ESKD	**498.07 (446.03-556.19)**	**96.43 (85.91-108.25)**	**30.86 (27.39-34.76)**	**12.18 (10.77-13.78)**

4B. Five years

	EGFR 60	EGFR 75	EGFR 80	EGFR 95
MACE	**8.19 (6.61-10.14)**	**3.47 (3.06-3.92)**	**2.25 (2.07-2.45)**	**1.79 (1.68-1.91)**
MACE-plus	**9.74 (8.25-11.51)**	**3.70 (3.34-4.1)**	**2.28 (2.12-2.45)**	**1.70 (1.61-1.8)**
Mortality	**7.02 (5.96-8.27)**	**2.68 (2.43-2.96)**	**1.55 (1.45-1.66)**	**1.11 (1.05-1.17)**
ESKD	**650.31 (561.24-753.53)**	**128.35 (109.73-150.13)**	**40.26 (34.2-47.39)**	**16.33 (13.75-19.39)**

4C. Ten years

	EGFR 60	EGFR 75	EGFR 80	EGFR 95
MACE	**7.66 (6.73-8.71)**	**3.06 (2.83-3.31)**	**1.99 (1.89-2.09)**	**1.56 (1.5-1.62)**
MACE-plus	**8.81 (7.93-9.79)**	**3.29 (3.07-3.51)**	**2.04 (1.95-2.13)**	**1.52 (1.47-1.57)**
Mortality	**6.36 (5.72-7.08)**	**2.42 (2.27-2.59)**	**1.40 (1.34-1.47)**	1.06 (1.02-1.1)
ESKD	**337.01 (311.08-365.09)**	**69.07 (63.59-75.02)**	**22.49 (20.68-24.46)**	**9.23 (8.47-10.06)**

There was a significantly increased risk among young adults across all outcomes at 3, 5, and 10 years, so we examined the frequency of adverse events within eGFR groups to better classify young adults with increased long-term cardiovascular risk associated with CKD. There were N= 2,425,183 individuals included in the analysis. We hypothesized that we could capture many individuals at risk by raising the eGFR threshold for CKD, enabling long-term monitoring for adverse events by examining event frequencies by eGFR. For the number of individuals monitored in each eGFR group, the eGFR with the most events and the fewest individuals monitored was 75 ml/min/1.73 m^2 across all outcomes—mortality, MACE, MACE-plus, and ESKD. In the eGFR < 60 ml/min/1.73 m^2 at 10 years of follow-up, there were 317 events of mortality, 225 events of MACE, 328 events of MACE-plus, and 897 events of ESKD. For individuals with < 75 ml/min/1.73 m^2, there were 892 mortality events, 661 MACE events, 898 MACE-plus events, and 1138 ESKD events. Increasing the eGFR threshold to < 75 ml/min/1.73 m^2 captured approximately 3 times as many events as < 60 ml/min/1.73 m^2 for mortality, MACE, and MACE-plus. In ESKD, more than half of the at-risk population is captured at eGFR < 75 ml/min/1.73 m^2, with a 30,000-person increase in monitoring. If the threshold were set at <85 ml/min/1.73 $m^{2,}$ over 100,000 individuals would need to be monitored to identify an additional 10% of individuals at risk. If the eGFR threshold for younger adults were lowered to < 75 ml/min/1.73 m^2, more than 50% of individuals at risk could be identified and monitored over time to prevent adverse events associated with CKD (Table 5).

Table 5. Reclassification of adverse outcomes based on eGFR categories for ages 18 – 30

5A. Mortality

5 YEARS	eGFR 60	eGFR 75	eGFR 85	eGFR 95
Total events (%)	4890 (0.20)	36554 (1.51)	137240 (5.66)	379311 (15.64)
Number of patients with an eGFR below threshold	195	566	1222	2529
Difference in events between lower eGFR group	NA	371	656	1307
Difference in number monitored between lower eGFR group	NA	31664	100686	242071
Proportion of patients with Mortality and eGFR below threshold (%)	195/15384 (1.28)	566/15384 (3.68)	1222/15384 (7.94)	2529/15384 (16.44)

10 YEARS	eGFR 60	eGFR 75	eGFR 85	eGFR 95
Total events (%)	4890 (0.20)	36554 (1.51)	137240 (5.66)	379311 (15.64)
Number of patients with an eGFR below threshold	317	892	1938	4100
Difference in events between lower eGFR group	NA	575	1046	2162
Difference in number monitored between lower eGFR group	NA	31664	100686	242071
Proportion of patients with Mortality and eGFR below threshold (%)	317/25008 (1.27)	892/25008 (3.57)	1938/25008 (7.50)	4100/25008 (16.39)

5B. MACE

5 YEARS	eGFR 60	eGFR 75	eGFR 85	eGFR 95
Total events (%)	4890 (0.20)	36554 (1.51)	137240 (5.66)	379311 (15.64)
Number of patients with an eGFR below threshold	139	404	941	1957
Difference in events	N/A	265	537	1016
Difference in number monitored	N/A	31664	100686	242071
Proportion of patients with MACE and eGFR below threshold (%)	139/8257 (1.68)	404/8257 (4.89)	941/8257 (11.39)	1957/8257 (23.70)

10 YEARS	eGFR 60	eGFR 75	eGFR 85	eGFR 95
Total events (%)	4890 (0.20)	36554 (1.51)	137240 (5.66)	379311 (15.64)
Number of patients with an eGFR below threshold	225	661	1572	3308
Difference in events	NA	440	911	1736
Difference in number monitored	NA	31228	99775	240335
Proportion of patients with MACE and eGFR below threshold (%)	225/14782 (1.52)	661/14782 (4.47)	1572/14782 (10.63)	3308/14782 (22.38)

5C. MACE PLUS

5 YEARS	eGFR 60	eGFR 75	eGFR 85	eGFR 95
Total events (%)	4890 (0.20)	36554 (1.51)	137240 (5.66)	379311 (15.64)
Number of patients with an eGFR below threshold	218	578	1276	2532
Difference in events between lower eGFR group	NA	360	698	1256
Difference in number monitored between lower eGFR group	NA	31664	100686	242071
Proportion of patients with MACE-plus and eGFR below threshold (%)	218/10961 (1.98)	578/10961 (5.27)	1276/10961 (11.64)	2532/10961 (23.10)

10 YEARS	eGFR 60	eGFR 75	eGFR 85	eGFR 95
Total events (%)	4890 (0.20)	36554 (1.51)	137240 (5.66)	379311 (15.64)
Number of patients with an eGFR below threshold	328	898	2043	4121
Difference in events between lower eGFR group	NA	570	1145	2078
Difference in number monitored between lower eGFR group	NA	31664	100686	242071
Proportion of patients with MACE-plus and eGFR below threshold (%)	328/18781 (1.75)	898/18781 (4.78)	2043/18781 (10.79)	4121/18781 (21.94)

5D. ESKD

5 YEARS	eGFR 60	eGFR 75	eGFR 85	eGFR 95
Events (%)	4890 (2.00)	36554 (1.51)	137240 (5.65)	379311 (15.62)
eGFR below threshold with ESKD	594	706	769	821
Difference in events between lower eGFR group	NA	112	63	52
Difference in number monitored between lower eGFR group	NA	31664	100686	242071
Proportion of patients with MACE and eGFR below threshold (%)	594/1185 (50.12)	706/1185 (59.58)	769/1185 (64.89)	821/1185 (69.28)

10 YEARS	eGFR 60	eGFR 75	eGFR 85	eGFR 95
Events (%)	4890 (0.02)	36554 (1.42)	137240 (5.60)	379311 (15.56)
Number of patients with an eGFR below threshold	897	1138	1272	1398
Difference in events between lower eGFR group	NA	241	134	126
Difference in number monitored between lower eGFR group	NA	31664	100686	242071
Proportion of patients with MACE and eGFR below threshold (%)	897/2216 (40.50)	1138/2216 (51.35)	1272/2216 (57.40)	1398/2216 (63.06)

Sub-analysis of individuals for urine ACR and diabetes

Since elevated urine protein is associated with chronic kidney disease and reduced eGFR, a sub-analysis of urine ACR was done. In the study population of 8.3 million individuals, 1,120,594 had valid, available urine ACR measures. Data were cleaned to remove individuals without ACR measures, negative values, or values that were inappropriately high. Individuals with one valid ACR were included. The median number of urine ACR measures was 1.0 (IQR 0), and the mean was 1.27 (+/- 0.53). Due to small cell sizes, descriptive statistics were assessed with age groups 18 - 50, 50 - 80, and >80. Urine ACR groups were organized into three groups: 0 - 3 mg/mmol, 3.01 - 30 mg/mmol, and >30 mg/mmol. 450, 870 individuals had urine ACR <3 mg/mmol, 93,978 with 3.01 - 30 mg/mmol and >30 mg/mmol, and 15,021 individuals with urine ACR >30mg/mmol. Descriptive statistics for urine ACR by associated comorbidity were also assessed. Individuals with ACR over 30 mg/mmol were consistently more likely to have adverse events of all-cause mortality, MACE, MACE-plus, and ESKD in adults 18 – 80. Under 30% of individuals with urine ACR >3mg/mmol were seen by nephrologists (Appendix VIII). A Cox proportional hazards analysis of urine ACR showed that risk of all-cause mortality increases below 80 ml/min for individuals under 50, below 90 ml/min for individuals 50–80, and not until eGFR <50 ml/min for individuals over 80 (Table 7). A sub-analysis of individuals with diabetes was conducted, as it is common in younger adults and has screening guidelines for serum creatinine and urine ACR. Of the study cohort, 44.95% of patients had diabetes across all age groups (N = 1,614,840). Adverse outcome event frequencies are listed in Table 8. A Cox analysis was performed for the diabetes sub-analysis, which showed results similar to the ACR analysis: younger individuals had increased risk at eGFR less than 80 for adults under age 50, and increased risk at eGFR under 50 ml/min for those over 80 years of age (Table 9).

Table 6. Outcome frequencies for ACR sub-analysis

	18 - 50	*50 - 80*	*80 - 105*	*Total*
ESRD				
0 - 3	346	1603	87	2036/855107
3.01 - 30	663	2611	177	3451/218388
>30	1613	4317	234	6164/47099
Mortality				
0 - 3	6335	84863	24838	116036/855107
3.01 - 30	2566	43161	18403	64130/218388
>30	1234	13825	3848	18907/47099
MACE				
0 - 3	12167	88171	11763	112101/855107
3.01 - 30	463	37941	9148	51452/218388
>30	1805	11496	2022	15323/47099
MACE plus				
0 - 3	13361	100954	15316	34825/855107
3.01 - 30	5017	45192	11936	62145/218388
>30	2173	13994	2665	18832/47099

Table 7. Association of all-cause mortality by age with various thresholds of eGFR, ACR sub-analysis

		18 - 50	*51 - 80*	*>80*
0-50 ml/min	0 – 3 mg/mmol	**2.42 [1.78, 3.30]**	**3.33 [3.24, 3.42]**	**1.04 [0.86, 1.25]**
	3 – 30 mg/mmol	**1.60 [1.28, 2.01]**	**2.94 [2.85, 3.03]**	**1.29 [1.03, 1.62]**
	>30 mg/mmol	**2.44 [2.16, 2.75]**	**3.62 [3.50, 3.68]**	**1.21 [1.06, 1.39]**
51-60 ml/min	0 – 3 mg/mmol	**2.02 [1.58, 2.58]**	**2.35 [2.29, 2.41]**	0.84 [0.70, 1.00]
	3 – 30 mg/mmol	**1.80 [1.41, 2.29]**	**2.16 [2.09, 2.24]**	1.04 [0.82, 1.30]
	>30 mg/mmol	**2.02 [1.76, 2.34]**	**2.43 [2.38, 2.47]**	0.93 [0.81, 1.07]
61-70 ml/min	0 – 3 mg/mmol	**1.41 [1.20, 1.66]**	**1.91 [1.87, 1.95]**	0.78 [0.65, 0.94]
	3 – 30 mg/mmol	**1.29 [1.04, 1.61]**	**1.81 [1.75, 1.87]**	1.00 [0.79, 1.25]
	>30 mg/mmol	**1.58 [1.42, 1.77]**	**1.92 [1.89, 1.96]**	0.87 [0.75, 0.99]
71-80 ml/min	0 – 3 mg/mmol	**1.11 [0.99, 1.24]**	**1.52 [1.49, 1.56]**	0.80 [0.67, 0.96]
	3 – 30 mg/mmol	**1.18 [0.99, 1.41]**	**1.58 [1.53, 1.63]**	0.99 [0.79, 1.24]
	>30 mg/mmol	**1.16 [1.07, 1.27]**	**1.54 [1.51, 1.57]**	0.80 [0.70, 0.92]
81-90 ml/min	0 – 3 mg/mmol	**1.00 [0.92, 1.08]**	**1.47 [1.44, 1.50]**	0.72 [0.61, 0.88]

	3 – 30 mg/mmol	**1.10 [0.95, 1.26]**	**1.50 [1.45, 1.54]**	0.91 [0.72, 1.14]
	>30 mg/mmol	1.04 [0.97, 1.11]	**1.46 [1.44, 1.48]**	0.77 [0.75,0.78]

*adjusted for sex, hypertension, diabetes, cardiovascular disease, obesity, smoking, alcoholism, 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 >90, diabetes present, ACR <3 mg/mmol
*** bolded HR suggest a significant risk for adverse event

Table 8. Outcome frequencies for diabetes sub-analysis

		18 - 50	*50 - 80*	*80 - 105*	*Total*
Diabetic	**Mortality (N, %)**	775 (1.02)	119491 (16.46)	30995 (4.27)	157861 (21.75)
Non-diabetic		6250 (0.70)	60414 (6.80)	26708 (3.00)	93372 (10.50)
Diabetic	**MACE**	14959 (2.06)	120058 (16.54)	15583 (2.15)	150600 (20.75)
Non-diabetic		8962 (1.01)	57387 (6.46)	12314 (1.39)	78663 (8.85)
Diabetic	**MACE-Plus**	16501 (2.27)	139206 (19.18)	20041 (2.76)	175748 (24.21)
Non-diabetic		10209 (1.15)	66758 (7.51)	16444 (1.85)	93411 (10.51)
Diabetic	**ESKD**	1821 (0.25)	7386 (1.02)	289 (0.04)	9496 (1.31)
Non-diabetic		1178 (0.13)	2319 (0.26)	267 (0.03)	3764 (0.42)

Table 9. Association of all-cause mortality by age with various thresholds of eGFR, Diabetes sub-analysis

	18 – 50	*51 – 80*	*>80*
0-50 ml/min DM No DM	**2.57 [2.22, 2.98]** **2.84 [2.39, 3.38]**	**3.61 [3.42, 3.69]** **3.58 [3.47, 3.68]**	**1.10 [0.94, 1.29]** **1.24 [1.02, 1.47]**
51-60 ml/min	**2.24 [1.90, 2.63]** **2.03 [1.69, 2.48]**	**2.46 [2.41, 2.51]** **2.34 [2.27, 2.42]**	0.85 [0.73, 1.00] 0.94 [0.78, 1.14]
61-70 ml/min DM	**1.98 [1.74, 2.25]** **1.26 [1.09, 1.47]**	**1.96 [1.93, 2.00]** **1.82 [1.77, 1.87]**	0.79 [0.67, 0.92] 0.87 [0.72, 1.05]
71-80 ml/min DM	**1.18 [1.06, 1.32]** **1.14 [1.03, 1.27]**	**1.56 [1.53, 1.59]** **1.47 [1.43, 1.51]**	0.80 [0.68,0.94] 0.89 [0.73,1.08]
81-90 ml/min DM	**1.04 [0.96,1.13]** **1.06 [0.98, 1.15]**	**1.47 [1.44, 1.49]** **1.42 [1.39, 1.45]**	0.75 [0.64, 0.87] 0.78 [0.64, 0.94]
>90 ml/min DM	Ref	Ref	Ref

Chapter 4: Discussion and Conclusions

CKD affects about 10% of the population and is becoming more common, yet public awareness remains limited (9,33,40,41). Currently, CKD is diagnosed when eGFR is less than 60 ml/min/1.73 m^2 for adults of all ages. Research has shown that early detection and management of CKD can prevent mortality and adverse cardiac events (17,23). These adverse events are usually thought to affect only older adults; however, recent research and findings from this thesis indicate that mortality and adverse events can also impact younger adults, with a modest decline in eGFR (23,96). An age-adjusted diagnostic threshold for CKD has been proposed based on prior population studies that account for the physiological decrease in nephron mass with age. Still, a concrete cut-off eGFR has not been established (29,52,58,90,115).

The aim of this thesis research was to provide greater clarity into an age-related CKD cut-off using the largest retrospective cohort to our knowledge. This study is the first of our knowledge to use two serum creatinine levels as previous, similar studies used one serum creatinine to study adverse events, In this thesis, we examined over 8.3 million Ontario adults and found that younger adults have a higher risk of experiencing an adverse event associated with CKD at an eGFR threshold of < 90 ml/min/1.73 m^2 than older adults. Younger adults aged 18–30 face a significantly higher risk of all-cause mortality, adverse cardiac events, and ESKD when followed for three, five, and ten years, even at a modest reduction of eGFR < 85 ml/min/1.73 m^2. There was no specific eGFR cutoff for older adults regarding CKD adverse events, which generally occurred at an eGFR of about 60 ml/min/1.73 m^2 in adults aged 40 and older. This was first assessed with Cox analysis and confirmed with a regression discontinuity design, the first of its kind used to assess eGFR and adverse events. The RDD examined potential cut-offs for all outcomes at 3-, 5-, and 10

ml/min/1.73 m^2 above and below eGFRs of interest, allowing for examination at different degrees of granularity and concluding that there was no exact cut-off by age. In addition to using different methods to assess potential cut-offs, we examined adverse events related to CKD using two serum creatinine levels to improve accuracy across everyone's baseline creatinine. The study also included adults ages 18 to 105, expanding the analysis of the over-80-year-old group to better understand thresholds for adverse events associated with CKD in older adults, especially as the patient population ages and longevity improves.

Additionally, we examined adverse events associated with CKD over time and identified events up to 10 years after inclusion. The frequency of adverse events in younger adults showed that individuals with eGFR < 90 ml/min/1.73 m^2 had a significantly greater risk of adverse events; however, an optimal eGFR for monitoring younger adults was < 75 ml/min/1.73 m^2. Event frequency for mortality, MACE, MACE-plus, and ESKD increases below 90 ml/min/1.73 m^2, but over 130,000 individuals would need to be monitored for adverse events at eGFR < 85ml/min/1.73 m^2. Using a cut-off of < 75ml/min/1.73 m^2 would include approximately 51% of young adults with ESKD, at the cost of about 70,000 fewer individuals being monitored. An eGFR of 95 ml/min/1.73 m^2 included just 13% more of the ESKD population, among over 350,000 individuals monitored. Monitoring 350,000 additional individuals would not be feasible from a health system perspective: the cost of screening would be high, and there would likely be constraints within our current healthcare system. Therefore, a practical eGFR cut-off for monitoring younger individuals with reductions in eGFR, beginning at eGFR < 75ml/min/1.73 $m^{2,}$ may be appropriate.

The results of this study provided insight into the U-shaped distribution of adverse cardiovascular events at both low and high eGFR levels. While we did not observe a consistent diagnostic

threshold for adults aged 40 and older, several trends emerged. One, adults tend to experience adverse events associated with CKD at eGFR < 60ml/min/1.73 m^2 and two, adults over age 50 experienced adverse events once eGFR was >110ml/min/1.73 m^2. A U-shaped distribution was not present in younger adults. The U-shaped distribution of adverse events has been demonstrated in previous retrospective cohort studies. Previous research by Tonelli et al. used Alberta retrospective cohort data to demonstrate a similar trend in older adults (116). The risk of all-cause mortality was similar to that reported in this thesis; individuals with an eGFR above 105 ml/min/1.73 m^2 had a higher risk of all-cause mortality (HR 3.0 [2.8–3.3]) (116). These findings were more pronounced in older adults than in younger adults. In a Quebec retrospective cohort study, individuals with hyperfiltration were more likely to experience adverse cardiovascular events (117). Dupuis et al. examined 9,500 healthy individuals to explore the link between glomerular hyperfiltration and adverse cardiovascular outcomes (117). They found that many individuals with hyperfiltration faced an increased risk of adverse events (unadjusted HR, 1.71 [1.20-2.44]; adjusted HR, 1.88 [1.30-2.74]) (117). This thesis is the first Ontario study to show a similar U-shaped pattern in cardiovascular risk associated with decreased eGFR and hyperfiltration (118). Higher GFR may be related to lower muscle mass, resulting in lower serum creatinine. These results would be found in frail individuals with cachexia and sarcopenia. Higher eGFR in older adults may be related to cachexia, which is associated with chronic disease and, therefore, closely linked to mortality risk. It may also be associated with individuals with hyperfiltration caused by diabetes or obesity, which are risk factors for adverse events. These findings suggest that adults at both ends of the eGFR spectrum may benefit from closer monitoring of kidney function, cardiovascular risk factors, and comorbidities. Further work is required to investigate

adults at risk of adverse outcomes associated with hyperfiltration or elevated eGFR to determine an optimal monitoring strategy.

So why might there be a more defined CKD diagnostic threshold in younger adults than in older adults? One possible explanation for these findings is that individuals under 40 are not expected to experience physiologic changes in nephron mass (21,86,87,119). In contrast, older adults, especially those over 65, undergo physiologic changes associated with aging. These individuals may have had kidney physiologic alterations for more than 25 years. Additionally, there is a sex-based difference in nephron mass between the older male and female patients, which can obscure a more precise eGFR cut-off (18–20,120). Currently, we lack an optimal method to distinguish between physiologic and pathologic changes contributing to CKD. The reduced granularity in adverse events, age, and eGFR cutoffs may reflect physiological changes rather than pathologic changes over time. Before age 40, a reduction in eGFR could be considered pathological, particularly in the absence of the natural decline associated with aging. Identifying individuals with low nephron mass at baseline may help prevent future adverse events.

Research from the CRIC study, the CKD Prognosis Consortium, and other international retrospective cohort studies has shown that CKD is associated with adverse events; however, the best way to identify individuals at risk and monitor them remains unclear despite many cohort studies attempting to clarify a diagnostic threshold over recent years (59,65,67,121–123). Past research, including the CARDIA studies, has demonstrated that risk for chronic disease can be predicted from early adulthood (70,124,73). This research underscores the importance of monitoring younger adults with reduced eGFR, as there appears to be a more defined cut point for this population. It also confirms that significant adverse events are associated with reduced eGFR

across the adult age range, particularly in those with eGFR levels below the age-specific reference. Currently, there are no guidelines advising physicians on when to refer patients with reduced GFR to a nephrologist or on how to monitor individuals with GFR above 60 ml/min/1.73 m^2 in a primary care setting with a reduction in eGFR that may not meet KDIGO CKD diagnostic criteria. It is well established that patients with CKD benefit from specialist care. Studies have shown that patients with CKD have better survival when referred to a nephrologist for ongoing care. For example, a 2019 retrospective population cohort study published in CMAJ found that individuals with CKD stage IV experienced a 40% improvement in all-cause mortality when followed by a nephrologist (57). Nephrology consultation was associated with lower mortality (HR 0.88, [0.82-0.93]). The strongest association was observed in people under 70 years old (HR 0.78, [0.65-0.92]), with the benefit decreasing with age and disappearing in those 90 years and older (HR 1.05, [0.88-1.25]) (57). These findings support revisiting nephrology referral guidelines and considering age-adjusted eGFR thresholds to improve accuracy.

Several research design considerations for retrospective cohort studies have been addressed in the study design. One challenge of retrospective cohort studies is their generalizability to the chronic kidney disease population. This study included 8.3 million Ontario adults from 2008 to 2021, including individuals aged 18 to 105, many of whom were followed for the whole 10-year study period. One strength of this thesis is its generalizability to the Ontario population. This is supported by previous research by Hussain et al., who studied the same Ontario population using a single serum creatinine measurement (23,96). Their research yielded similar results, as presented in this thesis, showing that adverse events occur at eGFR < 90 ml/min/1.73 m^2 in adults 18 – 30 (23,96). This thesis has several strengths in terms of design and analysis. The studies considered several factors for managing bias. To reduce immortal time bias, we used the second serum creatinine

measurement as the index date for participants. Using the second creatinine to establish an index date prevents the inclusion of patients with acute kidney injury.

In retrospective cohort studies, we must be aware of potential recall and misclassification bias that could influence the underreporting or overreporting of information used for the covariates. The use of multiple linked population databases reduces the risk of recall bias. For the study, we included multiple ICD codes for most comorbidities, thereby lowering the chance of misclassification or missing data (Appendix II). These ICD codes have been previously utilized in ICES retrospective cohort studies. The ICD codes used for primary outcomes of MACE and MACE-plus have been validated through their use in earlier retrospective cohort studies (23,125,126).

To prevent confounding and selection bias, a range of covariates was included, including individuals' demographics, comorbidities, and healthcare access. These covariates have been used in similar research studies and are well known to be associated with CKD (ex., hypertension, diabetes) (57,127,128). We also examined interaction terms to formally test whether changes in eGFR and age are associated with adverse outcomes. The population consisted of all adult individuals in Ontario aged 18 and above, with individuals with missing data excluded from the dataset. An improvement in this study over previous research was the use of two serum creatinine levels to determine a reduction in eGFR, which reduced the likelihood of falsely including individuals with AKI. Of course, since we did not track creatinine over time for everyone, there is a possibility that eGFR was not estimated accurately; however, the population data on mean and median eGFR are supported by previous research and by established reference values for different ages in the population (23,111).

Our retrospective cohort included population-level data from individuals with two serum creatinine measurements obtained between 90 and 730 days. This approach allowed us to have a large dataset while attempting to remove individuals with acute kidney injuries to include only those with CKD. Inclusion of a large number of patients for population study can introduce bias by indication. Individuals in the dataset had to have at least 2 serum creatinine measurements. Often, healthy individuals will not have their serum creatinine measured by family physicians. Our approach of including individuals with two or more serum creatinine levels may have led to the inclusion of individuals who had co-morbidities and were having their kidney function assessed as part of their chronic disease monitoring. Bias by indication is more likely in younger individuals, as they are less likely to have serum creatinine monitored without other health issues or repeated emergency visits or hospitalizations. Sub-analyses for diabetes and ACR were conducted to investigate possible bias by indication on these results. The results of the sub-analysis suggested that younger individuals with diabetes and elevated ACR are more likely to have eGFR <80 ml/min than those with eGFR 90 ml/min. These results were supported by reclassification results suggesting that the optimal timing for monitoring individuals with reductions in eGFR is eGFR <75 ml/min. An additional method that could be used in future studies to reduce bias by indication would be the use of a dataset with matched individuals and analysis done with propensity score matching. The dataset for this thesis did not include matched individuals; therefore, this analysis could not be completed. Future studies could request matched individuals from ICES.

Despite the study's methodological strengths, several limitations are associated with the study design. One is that the serum creatinine on the index date is an average of two values. While this improves upon previous studies by using two serum creatinine measures, there is a risk that relying on two creatinine measures rather than a trend over time may lead to inaccurate eGFR estimates.

However, given that the data includes 8.3 million individuals, this risk is less likely to occur. We did not screen for the cause of chronic kidney disease to include in the data. The dataset may have included individuals with glomerulonephritis, polycystic kidney disease, or other chronic kidney disease conditions with eGFRs > 60 ml/min/1.73 $m^{2.}$ Individuals who had previously undergone dialysis, ESKD, or kidney transplantation were excluded from the dataset. Similarly, pregnant individuals were not excluded. Pregnancy can cause hyperfiltration, or a lower-than-normal eGFR, which may obscure the eGFR and result in lower serum creatinine (129). The number of ACR measures in the patient population was limited and required significant cleaning due to increased variability in the ACR readings. Including more ACR measures over time could offer further insights into cardiovascular risk and is a focus of future research.

Consequently, we have identified that younger adults with reduced GFR experience more adverse cardiac outcomes and a higher risk of ESKD over time. Future research on eGFR monitoring frequency could help determine how to detect and prevent the progression of renal dysfunction in younger adults. Future studies may include more serum creatinine values or longer follow-up. This could be achieved in future studies by analyzing creatinine or eGFR trends over time within a retrospective population cohort. In addition to an increased serum creatinine value, the presence of albuminuria, combined with a reduced or declining eGFR, would improve understanding of eGFR decline in at-risk younger adults. Moreover, adding a survival analysis that accounts for the normal physiologic decline of eGFR in older adults may enable researchers to examine reduced eGFR in older populations with greater detail.

In conclusion, CKD adverse events affect all adults across the age spectrum, even with modest reductions in eGFR. Diagnostic thresholds for CKD were set over ten years ago based on population data showing adverse cardiac events at eGFR levels below 60 ml/min/1.73 m^2 for all adults. However, emerging evidence, supported by this thesis, suggests that younger adults are at risk of adverse events at eGFR levels under 90 ml/min/1.73 m^2. In this retrospective, population-based cohort study of over 8.3 million adults in Ontario, we demonstrated that an age-specific CKD diagnostic cut-off of 90 ml/min/1.73 m^2 may be more suitable for those under 40, as adverse events tend to occur more frequently at lower eGFRs. These findings imply that younger adults with modestly decreased GFR are at risk of developing CKD and related complications later in life. Increased monitoring could help prevent these issues in younger adults. Based on this research, the optimal threshold for enhanced monitoring of adverse events occurs when eGFR falls below 90 ml/min/1.73 m^2 in young adults. Further studies are needed to determine the best frequency of kidney function monitoring for younger adults with reduced eGFR. This evidence could lead to better care for younger adults with reduced kidney function, ultimately decreasing their cardiovascular and CKD risk.

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Appendix I: ICES databases used for the population cohort

ICES Database		Description
OHIP	Ontario Health Insurance Policy Claims	Information on publicly funded inpatient and outpatient Ontario residents' encrypted identification, dates, services, fees, and diagnoses
ODB	Ontario Drug Benefit	Information on Ontario publicly funded medications for individuals >=65 including encrypted identification medication, date, fees
ORRS	Ontario Renal Reporting System	Information on individuals' inpatient and outpatient encounters with nephrologists and diagnosis
ORGD	Vital Statistics – Death	Information on Ontario death certificate individuals' cause of death and interval between illness and death
ONMARG	Ontario Marginalization Index	Information on individuals' deidentified Ontario health region, ethnicity,
RPDB	Registered Persons Database	Information on individuals' deidentified age, sex, and date of death
CHF	Congestive heart failure	Information on individuals' age and CHF diagnosis
HYPER	Ontario Hypertension	Information on individuals' age, incidence and prevalence of hypertension

Appendix II: ICD-10 Codes for cohort creation

Variables	**Possible values**	**Dataset**	**Categories**	**Codes**
Baseline/index eGFR	Any value (include 0, except missing)	OLIS	Determined from first available SCr measurement for each individual, categorized into >120, 110-120, 100-110, 90-100, 80-90, 70-80, 60-70, 55-60, 50 – 55, 45 – 50, 40 – 45, 35 – 40, 30 – 35, 25 – 29, 20 – 25, 15 – 20	OBSERVATIONCODE = 14682-9 VALUE_RECOMMENDED_D SUBVALUE2_D OBSERVATIONDATETIME
Age at baseline	>18, inclusive, at time of index eGFR	RPDB	Categorized into age group increments (ie. 18 – 23…)	BDATE
Sex	Male, female	RPDB	Male assigned value of 1, female as reference group	SEX
Albumin-creatinine ratio (ACR)	Lab measurement within 12 months of the first available eGFR measure	OLIS	Categorized according to KDIGO guidelines: <3, 3-30, >30 mg/mmol	OBSERVATIONCODE = 32294-1, 14959-1, 30000-4 VALUE_RECOMMENDED_D SUBVALUE2_D OBSERVATIONDATETIME
Socioeconomic status	At index date	RPDB		PSTLYEAR
Hypertension	5-year look back from index eGFR measurement for history of 1 hospitalization/2 physician billings for hypertension	CIHI-DAD, OHIP, HYPER		ICD-9: 401, 402, 403, 404, 405 ICD-10: I10, I11, I12, I13, I15 OHIPdx: 401, 402, 403
Diabetes mellitus	5-year look back from index eGFR measurement for history of 1 hospitalization/2 physician billings for diabetes	CIHI-DAD, OHIP, ODD		ICD-9: 250 ICD 10: “E10” “E11” “E12” “E13” “E14” OHIP fee code: “Q040” “K029” “K030” “K045” “K046” OHIP diagnosis code: “250”
Obesity	5 year look back for individuals	CIHI-DAD, OHIP		ICD-9: 278, 649, V45.86 ICD-10: E23.6, E88.2, E66.0, E66.8, E66.9
Hyperkalemia	5 year look back for individuals	CIHI-DAD, OHIP		ICD-10: E875
Hypercholesterolemia	5 year look back for individuals	CIHI-DAD, OHIP		ICD-10: E78.00
Chronic dialysis	Exclude those with evidence of chronic dialysis on or prior	CORR		RECIPIENT_TREATMENT database

	to index eGFR measurement – include any after index eGFR measurement			Treatment_Code ≠ 171, 181
Kidney transplant	Exclude those with evidence of kidney transplant on or prior to index date – include after index eGFR measurement	CORR		RECIPIENT_TREATMENT database Treatment_Code ≠ 171, 181 Treatment_Date *Chronic dialysis:* all codes except 171, 181 *Kidney transplant:* 171, 181
Death	All-cause mortality, following first eGFR measurement	RPDB		DTH
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		
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	Five year lookback from index date for diagnoses of cigarette smoking, nicotine dependence	CIHI-DAD, NACRS		ICD-10 code: F17
MACE	MACE – CV death, ischemic stroke, or ACS	CIHI-DAD, NACRS, OHIP, ORGD		

	MACE-plus – MACE plus hospitalization for HF			
Cardiovascular events		CIHI-DAD, NACRS, OHIP		<u>Heart failure:</u> ICD-9: 425, 5184, 428 ICD 10: “I20” “I21” “I22” “I23” “I24” “I25” “Z955” “Z958” “Z959” “R931” “T822” ICD 10 intervention code: “1IJ26” “1IJ27” “1IJ54” “1IJ57” “1IJ50” “1IJ76” “I20” “I21” “I22” “I23” “I24” “I25” “Z955” “Z958” “Z959” “R931” “T822” OHIP fee code: “R741” “R742” “R743” “G298” “E646” “E651” “E652” “E654” “E655” “G262” “Z434” “Z448” OHIP diagnosis code: “410” “412” “413” <u>Acute coronary syndrome:</u> ICD-9: 411, 412, 413, 414 ICD-10: I20, I22-I25 <u>Stroke:</u> ICD-9: 430, 431, 432, 434, 435, 436, 3623 ICD 10: “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” <u>MI:</u> ICD-9: 410 ICD 10: “I21” “I22” ICD 10 intervention code: “1HP53” “1HP55” “1HZ53GRFR” “1HZ53LAFR” “1HZ53SYFR”

				CABG: ICD 10 intervention code: "1IJ76" OHIP fee code: "R742" "R743" "E654" "E645" "E652" "E646" Atrial fibrillation: ICD-10: I48
Primary care codes	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 00 = FAMILY PRACTICE AND GENERAL PRACTICE
ED visits	OHIP Indicator for presence of at least one NACRS record in 5 years prior to index			12 = EMERGENCY MEDICINE
Cardiologist visits	OHIP Frequency of cardiologist service claims in 5 years prior to index			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 60 = CARDIOLOGY
Endocrinology visits	OHIP Frequency of endocrinologist service claims in 5 years prior to index			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 15 = ENDOCRINOLOGY
Nephrologist visits	OHIP Frequency of nephrologist service claims in 5 years prior to index			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 16 = NEPHROLOGY

Appendix III. Frequency of individuals with primary outcomes and percent of the total population with the primary outcome

MORTALITY (N = 251233)

	18 – 50	50 – 80	Over 80
EGFR <50 ML/MIN	432 (0.07)	25141 (2.64)	20035 (25.83)
50 – 60 ML/MIN	273 (0.05)	19266 (2.02)	1101 (14.20)
60.01 – 70 ML/MIN	426 (0.07)	25581 (2.68)	10361 (13.36)
70.01 – 80 ML/MIN	754 (0.13)	29384 (3.08)	9584 (12.36)
80.01 – 90 ML/MIN	1419 (0.24)	38365 (4.02)	6438 (8.30)
90.01 ML/MIN	10321 (1.77)	42168 (4.42)	274 (0.35)
TOTAL	13625	179905	57703

*percent of total population represented in brackets

CV DEATH (N = 36297)

	18 – 50	50 – 80	Over 80
EGFR <50 ML/MIN	50 (0.01)	4662 (0.49)	4792 (6.18)
50 – 60 ML/MIN	45 (0.01)	2912 (0.31)	2274 (2.93)
60.01 – 70 ML/MIN	57 (0.01)	3468 (0.36)	1985 (2.56)
70.01 – 80 ML/MIN	90 (0.02)	3551 (0.37)	1735 (2.24)
80.01 – 90 ML/MIN	158 (0.03)	4302 (0.45)	1097 (1.41)
>90.01 ML/MIN	818 (0.14)	4251 (0.45)	50 (0.06)
TOTAL	1218	23146	11933

ACS (N = 180699)

	18 – 50	50 – 80	Over 80
<50 ML/MIN	413 (0.07)	13608 (1.43)	5943 (7.66)
50 – 60 ML/MIN	269 (0.05)	12495 (1.31)	3211 (4.14)
60.01 – 70 ML/MIN	566 (0.10)	18487 (1.94)	2986 (3.85)
70.01 – 80 ML/MIN	1245 (0.21)	24150 (2.53)	2581 (3.33)
80.01 – 90 ML/MIN	2342 (0.40)	31305 (3.28)	1735 (2.24)
>90.01 ML/MIN	15474 (2.65)	43816 (4.60)	73 (0.09)
TOTAL	20309	143861	16529

MACE
(N = 226694)

	18 – 50	50 – 80	Over 80
EGFR <50 ML/MIN	480 (0.08)	17697 (1.86)	10036 (12.94)
50 – 60 ML/MIN	342 (0.06)	15766 (1.65)	5366 (6.92)
60.01 – 70 ML/MIN	705 (0.12)	23108 (2.42)	4919 (6.34)
70.01 – 80 ML/MIN	1438 (0.25)	29314 (3.07)	4384 (5.65)
80.01 – 90 ML/MIN	2723 (0.47)	38041 (3.99)	2876 (3.71)
>90.01 ML/MIN	17806 (3.05)	51573 (5.41)	120 (0.15)
TOTAL	23494	175499	27701

ISCHEMIC STROKE
(N = 42320)

	18 – 50	50 – 80	Over 80
EGFR <50 ML/MIN	84 (0.01)	3500 (0.37)	2007 (2.59)
50 – 60 ML/MIN	72 (0.01)	3181 (0.33)	1272 (1.64)
60.01 – 70 ML/MIN	151 (0.03)	4744 (0.50)	1175 (1.52)
70.01 – 80 ML/MIN	230 (0.04)	5558 (0.58)	1089 (1.40)
80.01 – 90 ML/MIN	401 (0.07)	6976 (0.73)	684 (0.88)
>90.01 ML/MIN	2653 (0.45)	8524 (0.89)	19 (0.02)
TOTAL	3591	32483	6246

MACE PLUS
(N = 269159)

	18 – 50	50 – 80	Over 80
EGFR <50 ML/MIN	601 (0.10)	22232 (2.33)	13210 (17.03)
50 – 60 ML/MIN	411 (0.07)	19183 (2.01)	70 25 (9.06)
60.01 – 70 ML/MIN	823 (0.14)	27337 (2.87)	6492 (8.37)
70.01 – 80 ML/MIN	1641 (0.28)	34185 (3.59)	5743 (7.41)
80.01 – 90 ML/MIN	3049 (0.51)	44335 (4.65)	3858 (4.97)
>90.01 ML/MIN	20185 (3.46)	58692 (6.16)	157 (0.20)
TOTAL	26710	205964	36485

ESKD (N = 13260)

	18 – 50	50 – 80	Over 80
EGFR <50 ML/MIN	1071 (0.18)	4905 (0.51)	443 (0.57)
50.01 – 60 ML/MIN	286 (0.05)	1157 (0.12)	49 (0.06)
60.01 – 70 ML/MIN	256 (0.04)	970 (0.10)	26 (0.03)
70.01 – 80 ML/MIN	212 (0.04)	837 (0.09)	29 (0.04)
>80.01 ML/MIN	1174 (0.20)	1836 (0.19)	9 (0.01)
TOTAL	2999	9705	556

Appendix IV: Crude incidence rates per 1000 person-years for outcomes

A. All-cause mortality

Age Group	eGFR	Incidence rate per 1000 person years	Lower 95% CI	Upper 95% CI
18 - 30	<50 ml/ min	6.0891	3.6063	10.2812
	50 - 60 ml/min	5.0451	2.4052	10.5826
	60 - 70 ml/min	3.8871	2.3434	6.4478
	70 - 80 ml/ min	2.4273	1.6130	3.6526
	80 - 90 ml/min	1.7865	1.3463	2.3707
	90 - 100 ml/min	1.2248	0.9767	1.5359
	100 - 110 ml/min	1.3021	1.0972	1.5453
	>110 ml/min	1.3953	1.2964	1.5017
31 - 40	<50 ml/ min	11.3119	8.8539	14.4523
	50 - 60 ml/min	6.9235	4.9710	9.6429
	60 - 70 ml/min	4.3049	3.3206	5.5810
	70 - 80 ml/ min	2.6151	2.1475	3.1844
	80 - 90 ml/min	2.2085	1.9266	2.5317
	90 - 100 ml/min	1.7710	1.5800	1.9851
	100 - 110 ml/min	1.7840	1.6253	1.9581
	>110 ml/min	2.1016	1.9904	2.2190
41 - 50	<50 ml/ min	22.1143	19.9265	24.5422
	50 - 60 ml/min	12.3987	10.8987	14.1053
	60 - 70 ml/min	6.1588	5.5495	6.8349
	70 - 80 ml/ min	4.1551	3.8435	4.4920
	80 - 90 ml/min	3.6631	3.4587	3.8796

	90 - 100 ml/min	3.3817	3.2152	3.5569
	100 - 110 ml/min	3.9717	3.8468	4.1008
	>110 ml/min	5.6880	5.4497	5.9368
51 - 60	<50 ml/ min	36.5507	34.8104	38.3781
	50 - 60 ml/min	18.2744	17.2643	19.3437
	60 - 70 ml/min	11.4703	10.9799	11.9826
	70 - 80 ml/ min	8.9281	8.6364	9.2297
	80 - 90 ml/min	7.6679	7.4524	7.8896
	90 - 100 ml/min	8.6639	8.4915	8.8398
	100 - 110 ml/min	9.6695	9.4489	9.8954
	>110 ml/min	19.9737	18.8718	21.1398
61 - 70	<50 ml/ min	48.8401	47.6419	50.0683
	50 - 60 ml/min	28.8012	28.0266	29.5971
	60 - 70 ml/min	22.0141	21.5343	22.5047
	70 - 80 ml/ min	18.6892	18.3379	19.0472
	80 - 90 ml/min	18.3228	18.0126	18.6383
	90 - 100 ml/min	18.4921	18.2165	18.7718
	100 - 110 ml/min	26.0668	25.0352	27.1409
	>110 ml/min	60.0417	51.7294	69.6897
71 - 80	<50 ml/ min	78.9140	77.7468	80.0987
	50 - 60 ml/min	55.8781	54.9224	56.8504
	60 - 70 ml/min	47.9081	47.1636	48.6643
	70 - 80 ml/ min	44.2813	43.5837	44.9901
	80 - 90 ml/min	43.6823	43.0878	44.2850
	90 - 100 ml/min	44.7151	43.4241	46.0444
	100 - 110 ml/min	79.2148	68.2482	91.9437

	>110 ml/min	199.27	132.42	299.87
> 80	<50 ml/ min	138.19	136.29	140.12
	50 - 60 ml/min	111.37	109.31	113.47
	60 - 70 ml/min	103.87	101.89	105.89
	70 - 80 ml/ min	106.26	104.16	108.41
	80 - 90 ml/min	97.1322	94.7883	99.5341
	90 - 100 ml/min	126.90	112.51	143.14
	100 - 110 ml/min	183.46	82.4228	408.37
	>110 ml/min	218.04	70.3228	676.05

B. MACE

Age Group	eGFR	Incidence rate per 1000 person years	Lower 95% CI	Upper 95% CI
18 - 30	<50 ml/ min	2.1858	0.9098	5.2515
	50 - 60 ml/min	3.6165	1.5053	8.6888
	60 - 70 ml/min	3.6831	2.1814	6.2189
	70 - 80 ml/ min	1.0585	0.5695	1.9673
	80 - 90 ml/min	1.0451	0.7216	1.5137
	90 - 100 ml/min	0.9666	0.7489	1.2476
	100 - 110 ml/min	0.5477	0.4205	0.7134
	>110 ml/min	0.8104	0.7358	0.8926
31 - 40	<50 ml/ min	11.6247	9.0811	14.8806
	50 - 60 ml/min	10.0368	7.5857	13.2800
	60 - 70 ml/min	5.9167	4.7323	7.3975
	70 - 80 ml/ min	4.4539	3.8254	5.1857
	80 - 90 ml/min	3.3200	2.9681	3.7137
	90 - 100 ml/min	2.9024	2.6538	3.1744
	100 - 110 ml/min	3.1369	2.9231	3.3664
	>110 ml/min	3.1284	2.9914	3.2717

41 - 50	<50 ml/ min	28.5162	25.8945	31.4034
	50 - 60 ml/min	16.4934	14.6944	18.5126
	60 - 70 ml/min	11.1361	10.2892	12.0528
	70 - 80 ml/ min	8.6037	8.1426	9.0910
	80 - 90 ml/min	7.7414	7.4373	8.0580
	90 - 100 ml/min	7.8688	7.6085	8.1379
	100 - 110 ml/min	8.2055	8.0221	8.3931
	>110 ml/min	8.9404	8.6352	9.2563
51 - 60	<50 ml/ min	41.1465	39.1589	43.2350
	50 - 60 ml/min	24.3052	23.0792	25.5963
	60 - 70 ml/min	18.5350	17.8846	19.2091
	70 - 80 ml/ min	16.2725	15.8639	16.6916
	80 - 90 ml/min	14.7941	14.4843	15.1106
	90 - 100 ml/min	15.3468	15.1093	15.5880
	100 - 110 ml/min	14.6581	14.3778	14.9438
	>110 ml/min	20.6403	19.4797	21.8700
61 - 70	<50 ml/ min	48.2656	46.9729	49.5939
	50 - 60 ml/min	34.6735	33.7642	35.6072
	60 - 70 ml/min	28.0652	27.4908	28.6515
	70 - 80 ml/ min	24.7176	24.2921	25.1506
	80 - 90 ml/min	23.8169	23.4452	24.1944
	90 - 100 ml/min	22.8054	22.4845	23.1308
	100 - 110 ml/min	25.3195	24.2545	26.4314
	>110 ml/min	41.8524	34.6588	50.5390
71 - 80	<50 ml/ min	59.4507	58.3472	60.5751
	50 - 60 ml/min	45.0415	44.1154	45.9870
	60 - 70 ml/min	39.2341	38.5119	39.9699
	70 - 80 ml/ min	35.3015	34.6374	35.9783
	80 - 90 ml/min	33.7650	33.2094	34.3300
	90 - 100 ml/min	32.7280	31.5609	33.9384
	100 - 110 ml/min	45.3618	36.7200	56.0374
	>110 ml/min	117.63	61.2058	226.08
> 80	<50 ml/ min	81.0984	79.5281	82.6996

50 - 60 ml/min	62.9366	61.2757	64.6424
60 - 70 ml/min	56.7369	55.1744	58.3436
70 - 80 ml/ min	55.4610	53.8441	57.1265
80 - 90 ml/min	49.1649	47.4011	50.9943
90 - 100 ml/min	65.0113	54.2787	77.8661
100 - 110 ml/min	30.5772	4.3072	217.07
>110 ml/min	84.6083	11.9182	600.64

C. MACE plus

Age Group	eGFR	Incidence rate per 1000 person years	Lower 95% CI	Upper 95% CI
18 - 30	<50 ml/ min	6.6413	4.0038	11.0163
	50 - 60 ml/min	5.1056	2.4340	10.7095
	60 - 70 ml/min	4.7562	2.9966	7.5490
	70 - 80 ml/ min	2.4413	1.6223	3.6738
	80 - 90 ml/min	1.5701	1.1603	2.1245
	90 - 100 ml/min	1.2301	0.9809	1.5425
	100 - 110 ml/min	0.8572	0.6939	1.0589
	>110 ml/min	1.2213	1.1288	1.3213
31 - 40	<50 ml/ min	15.6473	12.6185	19.4031
	50 - 60 ml/min	12.5102	9.7135	16.1122
	60 - 70 ml/min	7.1755	5.8558	8.7926
	70 - 80 ml/ min	5.2809	4.5910	6.0744
	80 - 90 ml/min	3.7490	3.3736	4.1662
	90 - 100 ml/min	3.2651	3.0005	3.5530
	100 - 110 ml/min	3.5954	3.3658	3.8407
	>110 ml/min	3.6394	3.4913	3.7938
41 - 50	<50 ml/ min	34.3647	31.4356	37.5668
	50 - 60 ml/min	19.4084	17.4374	21.6021
	60 - 70 ml/min	12.6298	11.7230	13.6067

	70 - 80 ml/ min	9.3874	8.9042	9.8967
	80 - 90 ml/min	8.4670	8.1481	8.7983
	90 - 100 ml/min	8.4872	8.2164	8.7669
	100 - 110 ml/min	8.9923	8.7999	9.1889
	>110 ml/min	9.9804	9.6571	10.3145
51 - 60	<50 ml/ min	50.4716	48.2269	52.8208
	50 - 60 ml/min	28.8703	27.5207	30.2861
	60 - 70 ml/min	20.8670	20.1730	21.5850
	70 - 80 ml/ min	17.8608	17.4312	18.3010
	80 - 90 ml/min	16.2468	15.9210	16.5792
	90 - 100 ml/min	16.8319	16.5825	17.0852
	100 - 110 ml/min	16.3277	16.0309	16.6300
	>110 ml/min	24.1139	22.8494	25.4484
61 - 70	<50 ml/ min	60.9043	59.4214	62.4243
	50 - 60 ml/min	41.2591	40.2562	42.2870
	60 - 70 ml/min	32.3547	31.7333	32.9883
	70 - 80 ml/ min	28.2420	27.7846	28.7070
	80 - 90 ml/min	26.9620	26.5646	27.3653
	90 - 100 ml/min	26.0523	25.7075	26.4017
	100 - 110 ml/min	30.1594	28.9869	31.3794
	>110 ml/min	49.1335	41.2038	58.5892
71 - 80	<50 ml/ min	78.9129	77.6105	80.2371
	50 - 60 ml/min	57.3794	56.3173	58.4614
	60 - 70 ml/min	48.7636	47.9484	49.5926
	70 - 80 ml/ min	43.8554	43.1068	44.6171
	80 - 90 ml/min	42.2514	41.6230	42.8894
	90 - 100 ml/min	41.9278	40.5892	43.3105
	100 - 110 ml/min	63.5090	52.9424	76.1846
	>110 ml/min	133.78	71.9799	248.63
> 80	<50 ml/ min	112.65	110.73	114.59
	50 - 60 ml/min	85.9578	83.9647	87.9982

	60 - 70 ml/min	77.8607	75.9826	79.7851
	70 - 80 ml/ min	75.4502	73.5192	77.4319
	80 - 90 ml/min	68.4898	66.3574	70.6906
	90 - 100 ml/min	88.2470	75.3155	103.40
	100 - 110 ml/min	66.1292	16.5388	264.41
	>110 ml/min	84.6083	11.9182	600.64

D. ESKD

Age Group	eGFR	Incidence rate per 1000 person years	Lower 95% CI	Upper 95% CI
18 - 30	<50 ml/ min	88.2622	74.8326	104.10
	50 - 60 ml/min	21.7798	15.0380	31.5439
	60 - 70 ml/min	8.5934	6.0770	12.1517
	70 - 80 ml/ min	2.6616	1.7985	3.9390
	80 - 90 ml/min	0.6717	0.4232	1.0661
	90 - 100 ml/min	0.3271	0.2110	0.5070
	100 - 110 ml/min	0.2687	0.1843	0.3919
	>110 ml/min	0.2377	0.1989	0.2841
31 - 40	<50 ml/ min	64.1309	57.0185	72.1305
	50 - 60 ml/min	18.3376	14.8257	22.6813
	60 - 70 ml/min	5.3938	4.2673	6.8176
	70 - 80 ml/ min	1.4340	1.0983	1.8724
	80 - 90 ml/min	0.4080	0.2969	0.5608
	90 - 100 ml/min	0.2705	0.2019	0.3622
	100 - 110 ml/min	0.2096	0.1597	0.2751
	>110 ml/min	0.2266	0.1920	0.2674
41 - 50	<50 ml/ min	50.8497	47.0926	54.9065

	50 - 60 ml/min	9.6331	8.2995	11.1811
	60 - 70 ml/min	2.7038	2.3088	3.1664
	70 - 80 ml/ min	0.8774	0.7402	1.0399
	80 - 90 ml/min	0.4631	0.3940	0.5444
	90 - 100 ml/min	0.2856	0.2400	0.3398
	100 - 110 ml/min	0.2847	0.2526	0.3209
	>110 ml/min	0.4594	0.3951	0.5341
51 - 60	<50 ml/ min	32.2708	30.5319	34.1087
	50 - 60 ml/min	5.1167	4.5911	5.7025
	60 - 70 ml/min	1.9124	1.7176	2.1292
	70 - 80 ml/ min	0.8137	0.7287	0.9085
	80 - 90 ml/min	0.4341	0.3850	0.4894
	90 - 100 ml/min	0.3589	0.3251	0.3962
	100 - 110 ml/min	0.3901	0.3477	0.4377
	>110 ml/min	0.8748	0.6666	1.1481
61 - 70	<50 ml/ min	16.3020	15.5960	17.0398
	50 - 60 ml/min	3.0594	2.8124	3.3281
	60 - 70 ml/min	1.2530	1.1421	1.3747
	70 - 80 ml/ min	0.6287	0.5667	0.6974
	80 - 90 ml/min	0.4107	0.3663	0.4604
	90 - 100 ml/min	0.3673	0.3301	0.4087
	100 - 110 ml/min	0.4229	0.3077	0.5812
	>110 ml/min	1.4051	0.5273	3.7437
71 - 80	<50 ml/ min	7.9681	7.5974	8.3568
	50 - 60 ml/min	1.2610	1.1235	1.4154
	60 - 70 ml/min	0.5866	0.5088	0.6762
	70 - 80 ml/ min	0.4808	0.4125	0.5603
	80 - 90 ml/min	0.2993	0.2534	0.3534
	90 - 100 ml/min	0.2014	0.1299	0.3121
	100 - 110 ml/min	0.4614	0.06499	3.2755
	>110 ml/min	0	0	I

> 80	<50 ml/ min	3.1106	2.8340	3.4142
	50 - 60 ml/min	0.5018	0.3792	0.6639
	60 - 70 ml/min	0.2637	0.1795	0.3872
	70 - 80 ml/ min	0.3255	0.2262	0.4684
	80 - 90 ml/min	0.1221	0.06108	0.2442
	90 - 100 ml/min	0.4847	0.06827	3.4408
	100 - 110 ml/min	0	0	I
	>110 ml/min	0	0	I

Appendix V: Specialists' visit frequency tables

18-50	CARDIOLOGY REFERRAL		
	0 – 3	**4 to 6**	**7 or more**
EGFR <50 ML/MIN	1775 (0.30)	416 (0.07)	994 (0.17)
50.01 – 60 ML/MIN	2667 (0.46)	362 (0.06)	655 (0.11)
60.01 – 70 ML/MIN	8690 (1.49)	1093 (0.19)	1388 (0.24)
70.01 – 80 ML/MIN	23404 (4.01)	2768 (0.47)	3276 (0.56)
80.01 ML/MIN	438756 (75.14)	48855 (8.37)	48803 (8.36)
TOTAL	475292	53494	55116
50 – 80			
EGFR <50 ML/MIN	23896 (2.51)	6865 (0.72)	20432 (2.14)
50.01 – 60 ML/MIN	31159 (3.27)	7780 (0.82)	20385 (2.14)
60.01 – 70 ML/MIN	59611 (6.25)	13901 (1.46)	32479 (3.41)
70.01 – 80 ML/MIN	95269 (9.99)	20753 (2.18)	43614 (4.57)
80.01 ML/MIN	361498 (37.92)	76052 (7.98)	139690 (14.65)
TOTAL	571433	125351	256600

>80			
EGFR <50 ML/MIN	13631 (17.58)	3425 (4.42)	7668 (9.89)
50.01 – 60 ML/MIN	8136 (10.49)	2128 (2.74)	4743 (6.12)
60.01 – 70 ML/MIN	7981 (10.29)	2087 (2.69)	4608 (5.94)
70.01 – 80 ML/MIN	7492 (9.66)	1877 (2.42)	4020 (5.18)
80.01 ML/MIN	5353 (6.90)	1388 (1.79)	3017 (3.89)
TOTAL	42593	10905	24056

CARDIOLOGY HISTORY

18-50	**0 – 3**	**4 to 6**	**7 or more**
EGFR <50 ML/MIN	2910 (0.5)	154 (0.03)	121 (0.02)
50.01 – 60 ML/MIN	3400 (0.58)	144 (0.02)	140 (0.02)
60.01 – 70 ML/MIN	10516 (1.80)	392 (0.07)	263 (0.05)
70.01 – 80 ML/MIN	27835 (4.77)	1032 (0.18)	581 (0.10)
80.01 ML/MIN	514982 (4.77)	13910 (0.18)	7522 (1.29)
TOTAL	559643	15632	8627
50 – 80			
EGFR <50 ML/MIN	39300 (4.12)	4767 (0.50)	7126 (0.75)
50.01 – 60 ML/MIN	47584 (4.99)	5072 (0.53)	6668 (0.70)
60.01 – 70 ML/MIN	88146 (9.25)	8296 (0.87)	9549 (1.00)
70.01 – 80 ML/MIN	136632 (14.33)	11417 (1.20)	11587 (1.22)
80.01 ML/MIN	508910 (53.38)	36177 (3.79)	321523 (3.37)
TOTAL	820572	65729	67083
> 80			
EGFR <50 ML/MIN	18369 (23.69)	2501 (3.22)	3854 (4.97)

50.01 – 60 ML/MIN	11442 (14.75)	1401 (1.81)	2164 (2.79)
60.01 – 70 ML/MIN	11261 (14.75)	1478 (1.91)	1937 (2.50)
70.01 – 80 ML/MIN	10462 (13.49)	1283 (1.65)	1644 (2.12)
80.01 ML/MIN	7720 (9.95)	946 (1.22)	1092 (1.41)
TOTAL	59254	7609	10691

	ENDOCRINOLOGY REFERRAL		
18-50	**0 – 3**	**4 to 6**	**7 or more**
EGFR <50 ML/MIN	2514 (0.43)	175 (0.03)	496 (0.08)
50.01 – 60 ML/MIN	3107 (0.53)	169 (0.03)	408 (0.03)
60.01 – 70 ML/MIN	10005 (1.71)	372 (0.06)	794 (0.14)
70.01 – 80 ML/MIN	26 707 (4.57)	935 (0.16)	1806 (0.31)
80.01 ML/MIN	463665 (79.41)	23333 (4.00)	49416 (8.46)
TOTAL	595998	24984	52920
50 – 80			
EGFR <50 ML/MIN	42048 (4.41)	2661 (0.28)	6484 (0.68)
50.01 – 60 ML/MIN	51049 (5.35)	2432 (0.26)	5843 (0.61)
60.01 – 70 ML/MIN	93093 (9.76)	3943 (0.41)	8955 (0.94)
70.01 – 80 ML/MIN	141799 (14.87)	5725 (0.60)	12112 (1.27)
80.01 ML/MIN	503989 (52.86)	22341 (2.34)	50910 (5.34)
TOTAL	831978	37102	84304
>80			
EGFR <50 ML/MIN	22985 (29.64)	703 (0.91)	1036 (1.34)
50.01 – 60 ML/MIN	14023 (18.08)	450 (0.58)	534 (0.69)
60.01 – 70 ML/MIN	13746 (17.72)	377 (0.49)	553 (0.71)

70.01 – 80 ML/MIN	12622 (16.28)	360 (0.46)	407 (0.52)
80.01 ML/MIN	9191 (11.85)	251 (0.32)	316 (0.41)
TOTAL	72567	2141	2846

ENDO HISTORY **18 – 50**	**0 – 2**	**3 OR MORE**
EGFR <50 ML/MIN	3113 (0.53)	72 (0.01)
50.01 – 60 ML/MIN	3595 (0.62)	89 (0.02)
60.01 – 70 ML/MIN	10996 (1.88)	175 (0.03)
70.01 – 80 ML/MIN	29031 (4.97)	417 (0.07)
80.01 ML/MIN	523157 (89.60)	13257 (2.27)
TOTAL	569892	14010
50 – 80		
EGFR <50 ML/MIN	50204 (5.27)	989 (0.10)
50.01 – 60 ML/MIN	58438 (6.13)	886 (0.09)
60.01 – 70 ML/MIN	104667 (10.98)	1324 (0.14)
70.01 – 80 ML/MIN	157730 (16.34)	1906 (0.20)
80.01 ML/MIN	569829 (59.77)	7411 (0.78)
TOTAL	940868	12516
> 80		
EGFR <50 ML/MIN	24482 (31.57)	242 (0.31)
50.01 – 60 ML/MIN	14886 (19.19)	121 (0.16)
60.01 – 70 ML/MIN	14549 (18.76)	127 (0.16)
70.01 – 80 ML/MIN	13297 (17.15)	92 (0.12)
80.01 ML/MIN	9683 (12.49)	75 (0.10)
TOTAL	76897	657

	NEPHROLOGY REFERRAL		
18 – 50	**0 – 3**	**4 to 6**	**7 or more**
EGFR <50 ML/MIN	948 (0.16)	288 (0.05)	1949 (0.33)
50.01 – 60 ML/MIN	2448 (0.42)	295 (0.05)	941 (0.16)
60.01 – 70 ML/MIN	9610 (1.65)	456 (0.08)	1105 (0.19)
70.01 – 80 ML/MIN	27831 (4.77)	524 (0.09)	1093 (0.19)
80.01 ML/MIN	523539 (89.66)	4682 (0.80)	8193 (1.40)
TOTAL	564396	6245	13281
50 – 80			
EGFR <50 ML/MIN	29041 (3.05)	4777 (0.50)	17375 (1.82)
50.01 – 60 ML/MIN	48263 (5.06)	3440 (0.36)	7621 (0.80)
60.01 – 70 ML/MIN	95990 (10.07	3521 (0.37)	6480 (0.68)
70.01 – 80 ML/MIN	151138 (15.85)	3175 (0.33)	5323 (0.56)
80.01 ML/MIN	558750 (58.61)	6926 (0.73)	11564 (1.21)
TOTAL	883182	21839	48363
>80			
EGFR <50 ML/MIN	19177 (24.73)	1883 (2.43)	3664 (4.72)
50.01 – 60 ML/MIN	13976 (18.02)	445 (0.57)	586 (0.76)
60.01 – 70 ML/MIN	14057 (18.13)	300 (0.39)	319 (0.41)
70.01 – 80 ML/MIN	12969 (16.72)	199 (0.26)	221 (0.28)
80.01 ML/MIN	9516 (12.27)	118 (0.15)	124 (0.16)
TOTAL	69695	2945	4914

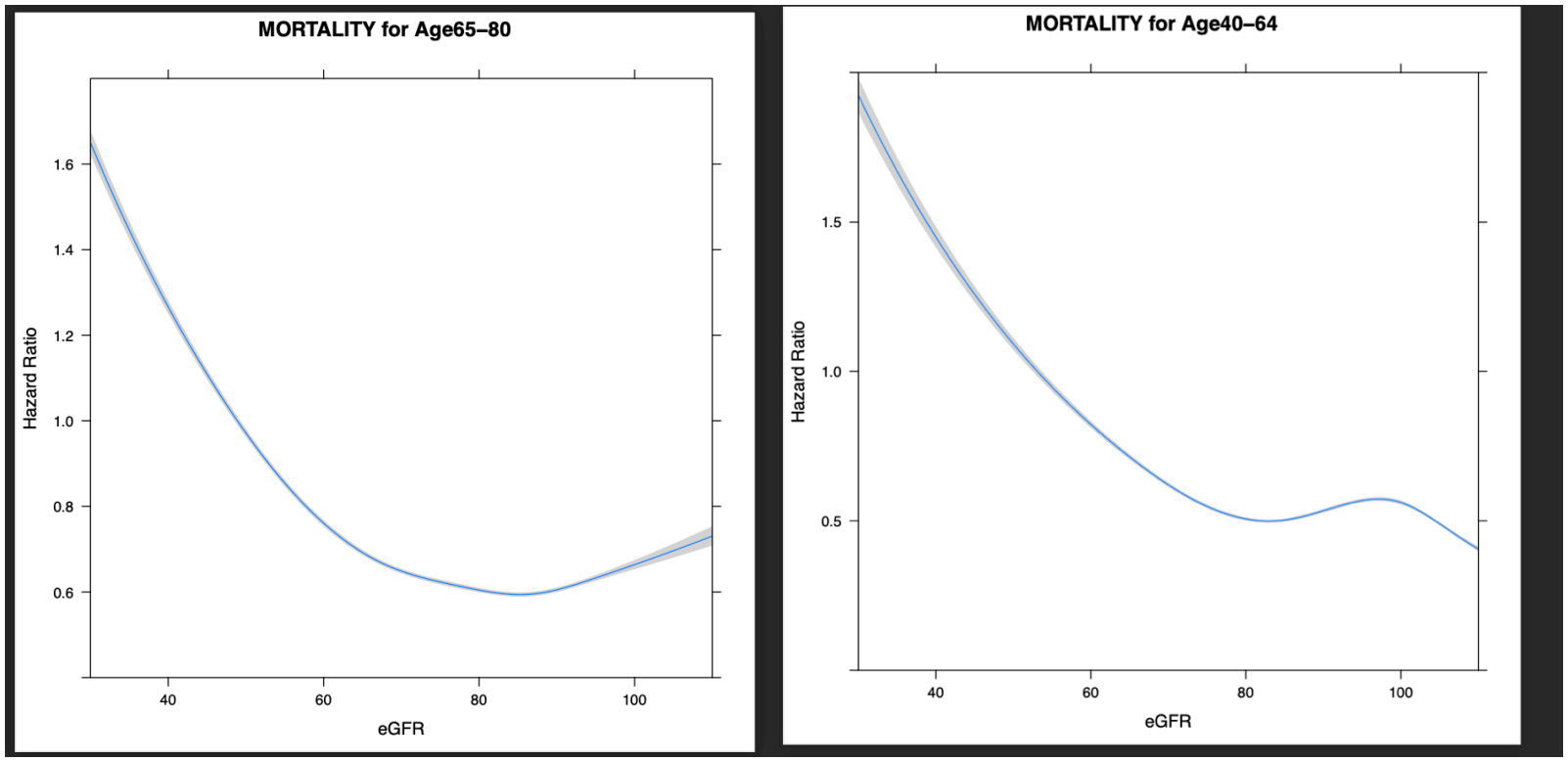
NEPHROLOGY HISTORY

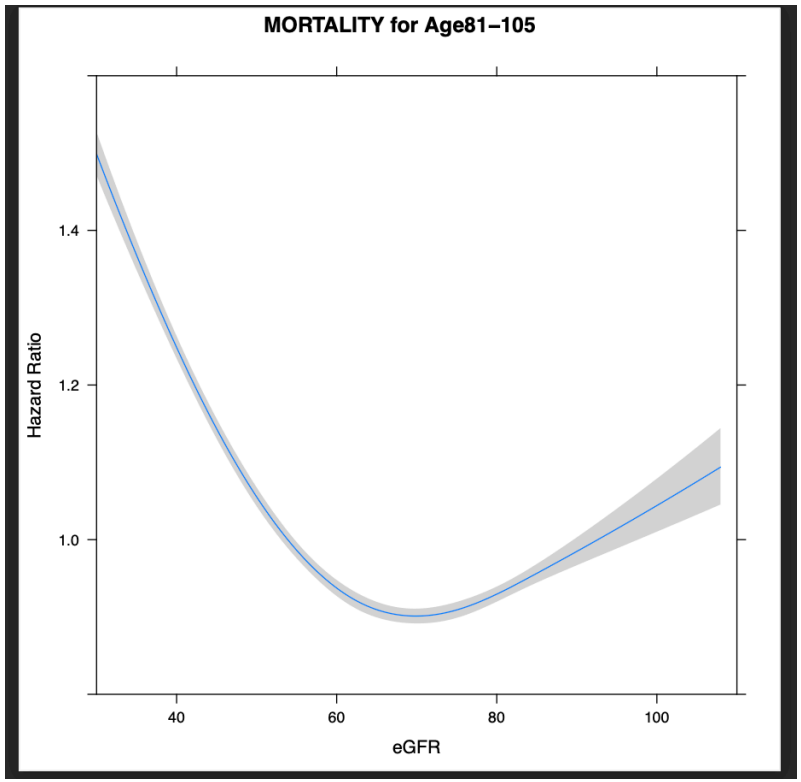
18-50	**0 – 3**	**4 to 6**	**7 or more**
EGFR <50 ML/MIN	2529 (0.43)	405 (0.07)	251 (0.04)
50.01 – 60 ML/MIN	3398 (0.58)	200 (0.03)	86 (0.01)
60.01 – 70 ML/MIN	10831 (1.85)	236 (0.04)	104 (0.02)
70.01 – 80 ML/MIN	29085 (4.98)	250 (0.04)	113 (0.02)
80.01 ML/MIN	533503 (91.37)	1977 (0.34)	934 (0.016)
TOTAL	579346	3068	1488
50 – 80			
EGFR <50 ML/MIN	48268 (5.06)	1813 (0.19)	1112 (0.12)
50.01 – 60 ML/MIN	58440 (6.13)	597 (0.06)	287 (0.03)
60.01 – 70 ML/MIN	105367 (11.05)	428 (0.04)	196 (0.02)
70.01 – 80 ML/MIN	159113 (16.69)	345 (0.04)	178 (0.02)
80.01 ML/MIN	575785 (60.39)	990 (0.10)	465 (0.05)
TOTAL	946973	4173	2238
> 80			
EGFR <50 ML/MIN	23913 (30.83)	458 (0.59)	353 (0.46)
50.01 – 60 ML/MIN	14915 (19.23)	63 (0.08)	29 (0.04)
60.01 – 70 ML/MIN	14633 (18.87)	27 (0.03)	16 (0.02)
70.01 – 80 ML/MIN	13353 (17.22)	21 (0.03)	15 (0.02)
80.01 ML/MIN	9732 (12.55)	16 (0.02)	10 (0.01)
TOTAL	76546	585	423

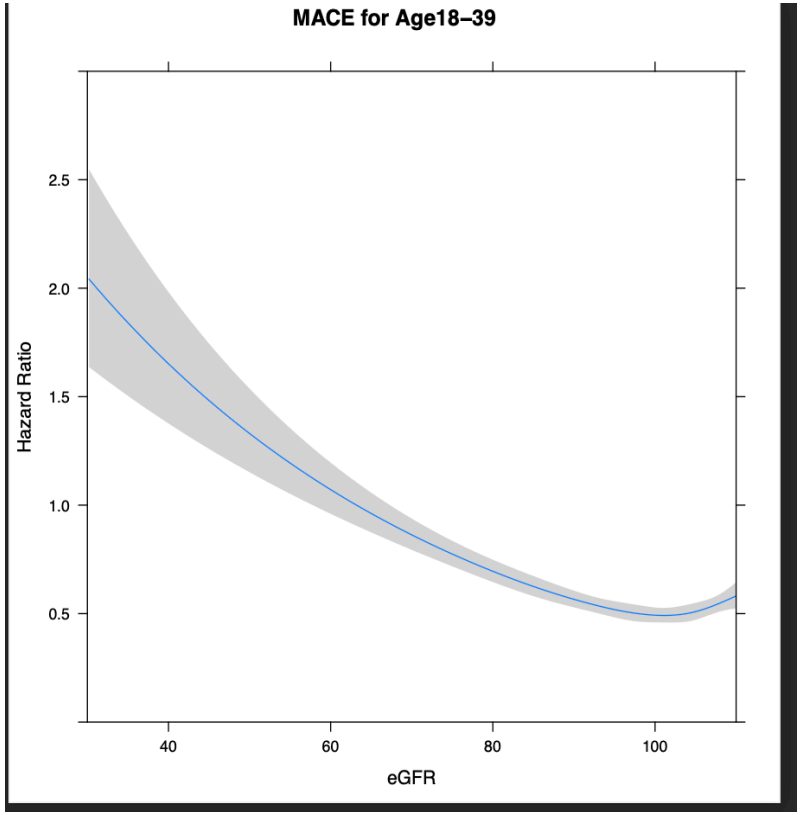
EMERGENCY DEPARTMENT HISTORY		
18-50	**0**	**1.00**
EGFR <50 ML/MIN	3142 (0.54)	43 (0.01)
50.01 – 60 ML/MIN	3623 (0.62)	61 (0.01)
60.01 – 70 ML/MIN	111064 (1.89)	107 (0.02)
70.01 – 80 ML/MIN	29164 (4.99)	284 (0.05)
80.01 ML/MIN	530720 (90.89)	5694 (0.98)
TOTAL	577713	6189
50 – 80		
EGFR <50 ML/MIN	50679 (5.32)	514 (0.05)
50.01 – 60 ML/MIN	58816 (6.17)	508 (0.05)
60.01 – 70 ML/MIN	105622 (11.04)	769 (0.08)
70.01 – 80 ML/MIN	158542 (16.76)	1094 (0.11)
80.01 ML/MIN	572857 (60.09)	4383 (0.46)
TOTAL	946116	7268
>80		
EGFR <50 ML/MIN	24428 (31.50)	296 (0.38)
50.01 – 60 ML/MIN	14846 (19.14)	161 (0.21)
60.01 – 70 ML/MIN	14499 (18.70)	177 (0.23)
70.01 – 80 ML/MIN	13220 (17.05)	169 (0.22)
80.01 ML/MIN	9641 (12.43)	117 (0.15)
TOTAL	76634	920

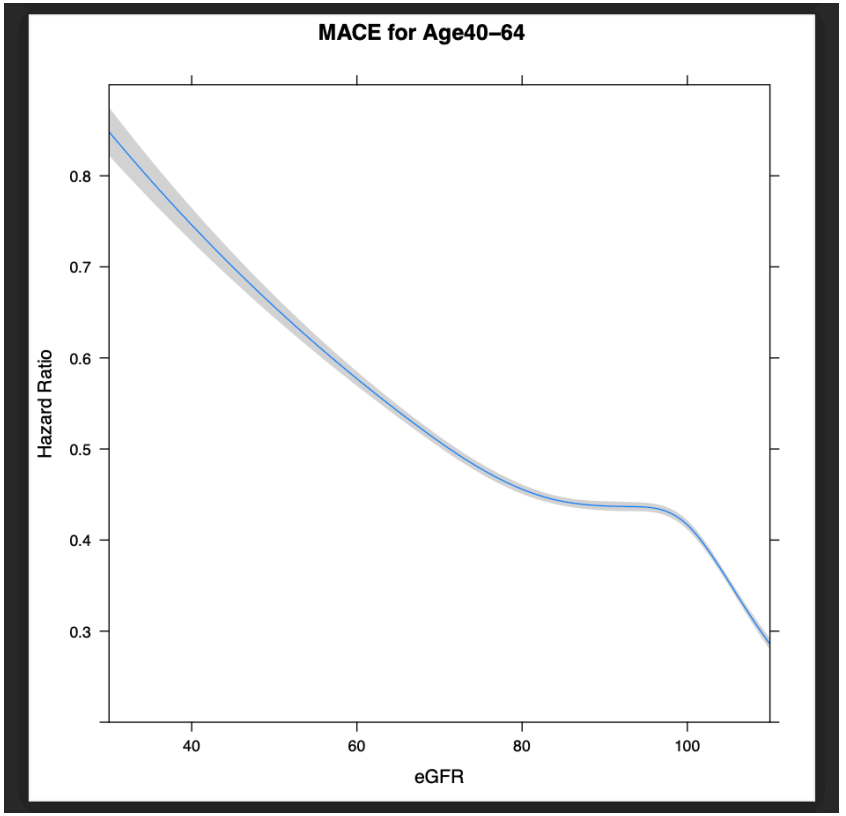
	FAMILY MED HISTORY		
18 – 50	**0 – 3**	**4 to 6**	**7 or more**
EGFR <50 ML/MIN	402 (0.52)	589 (0.76)	23733 (30.60)
50.01 – 60 ML/MIN	187 (0.24)	365 (0.47)	14455 (18.64)
60.01 – 70 ML/MIN	218 (0.28)	371 (0.48)	14087 (18.16)
70.01 – 80 ML/MIN	193 (0.25)	313 (0.40)	12883 (16.61)
80.01 ML/MIN	125 (0.16)	229 (0.30)	9404 (12.13)
TOTAL	1125	1867	74562
50 – 80	1308 (0.14)	2374 (0.25)	47511 (4.98)
50.01 – 60 ML/MIN	1465 (0.15)	2892 (0.30)	54967 (5.77)
60.01 – 70 ML/MIN	2484 (0.26)	5293 (0.56)	98214 (10.30)
70.01 – 80 ML/MIN	3763 (0.39)	8937 (0.94)	146936 (15.41)
80.01 ML/MIN	14665 (1.54)	34267 (3.59)	528308 (55.41)
TOTAL	23685	53763	875936
>80			
EGFR <50 ML/MIN	402 (0.52)	589 (0.76)	23733 (30.60)
50.01 – 60 ML/MIN	187 (0.24)	365 (0.47)	14455 (18.64)
60.01 – 70 ML/MIN	218 (0.28)	371 (0.48)	14087 (18.16)
70.01 – 80 ML/MIN	193 (0.25)	313 (0.40)	12883 (16.61)
80.01 ML/MIN	125 (0.16)	229 (0.30)	9404 (12.13)
TOTAL	1125	1867	74562

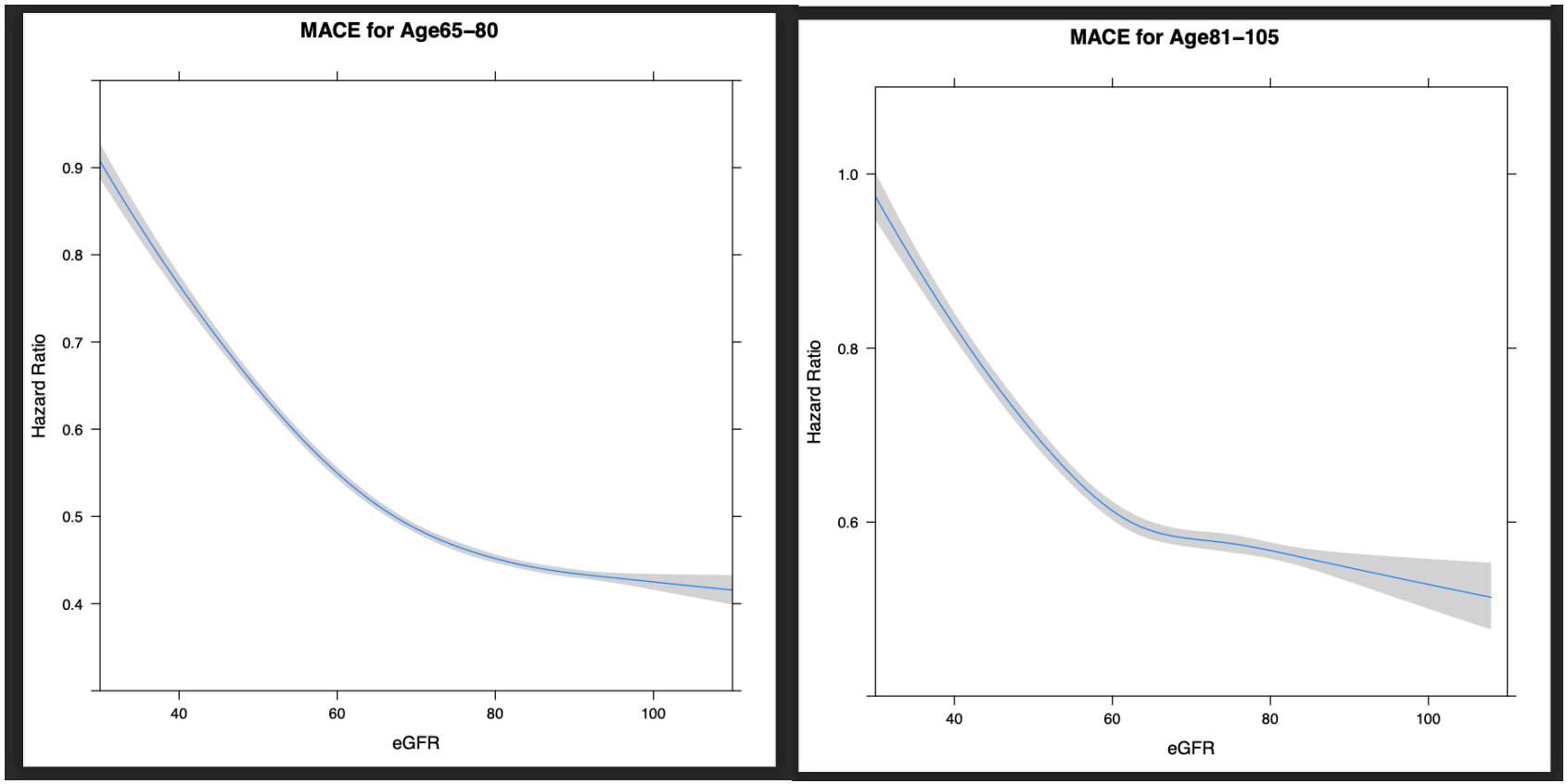
Appendix VI: RDD cubic spline plots for adverse outcomes, eGFR 85 ml/min/1.73 m^2

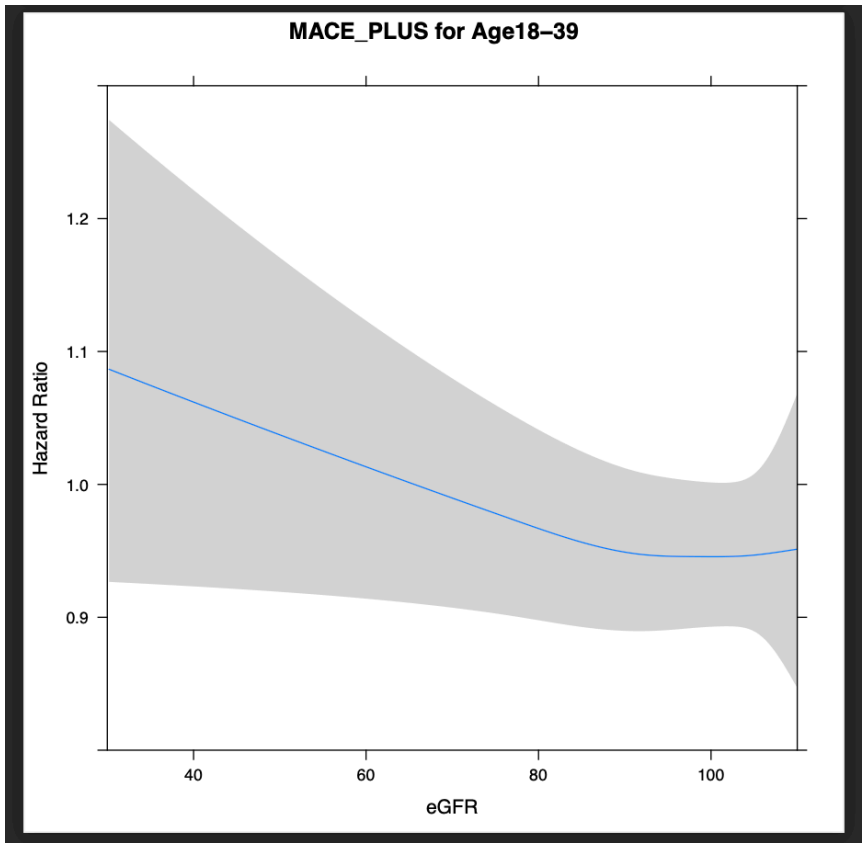


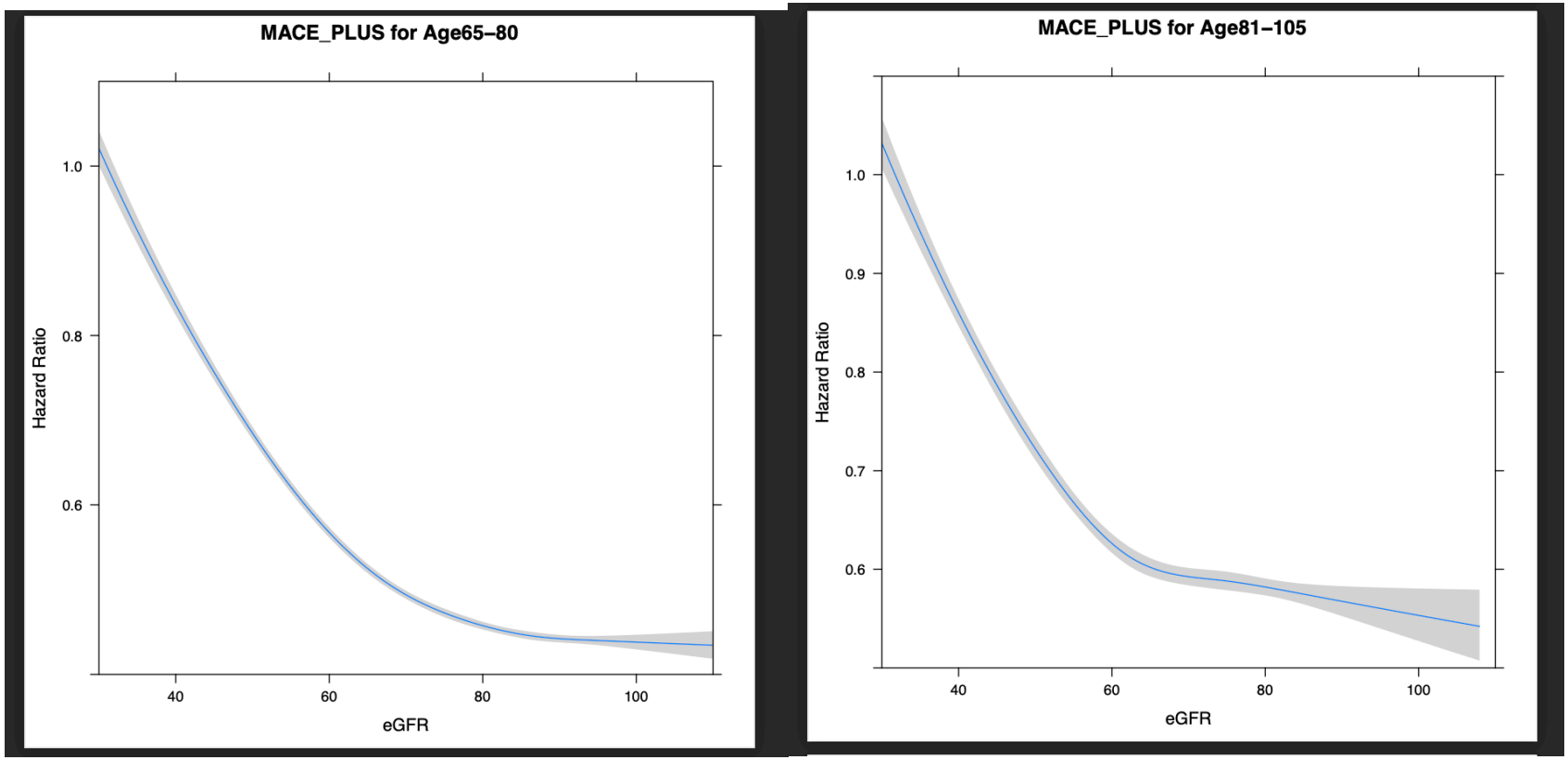

MORTALITY for Age81–105
Hazard Ratio
1.4
1.2
1.0
40
60
80
100
eGFR

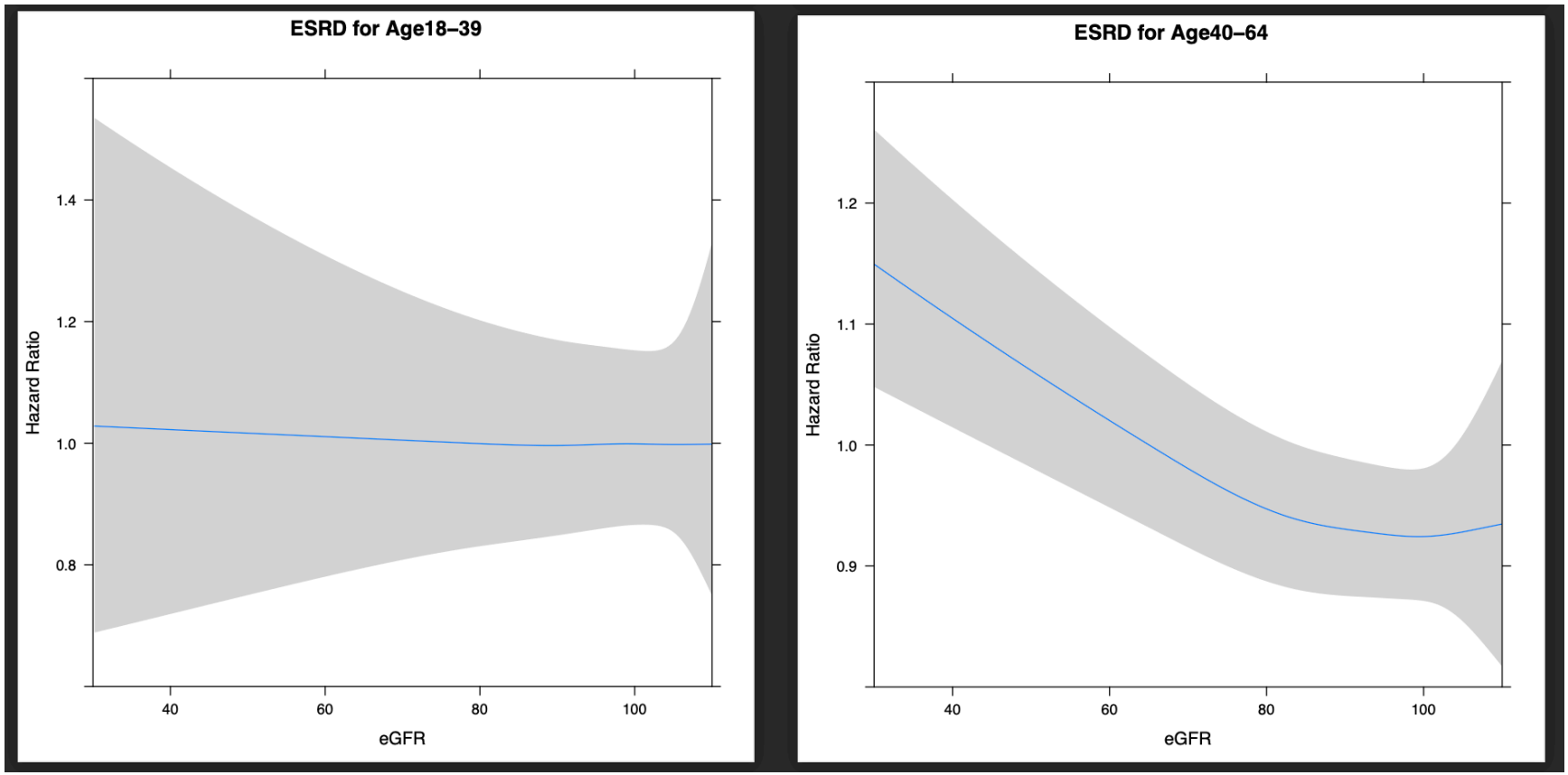

MACE for Age18–39
Hazard Ratio
2.5
2.0
1.5
1.0
0.5
40
60
80
100
eGFR

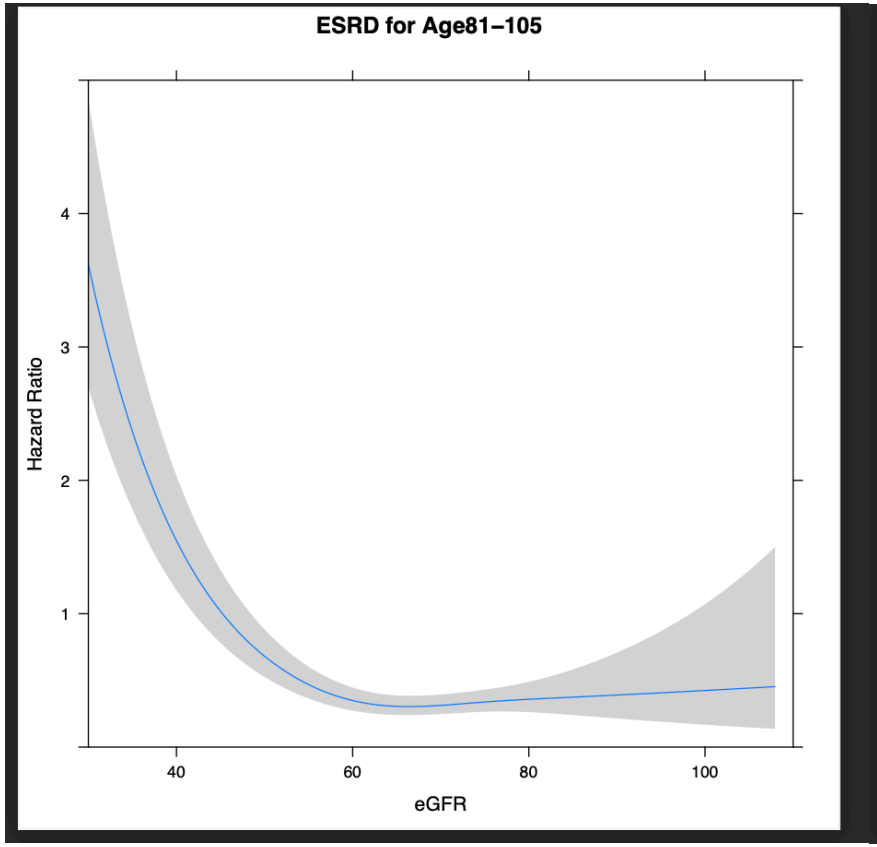

MACE for Age40–64
Hazard Ratio
0.8
0.7
0.6
0.5
0.4
0.3
40
60
80
100
eGFR

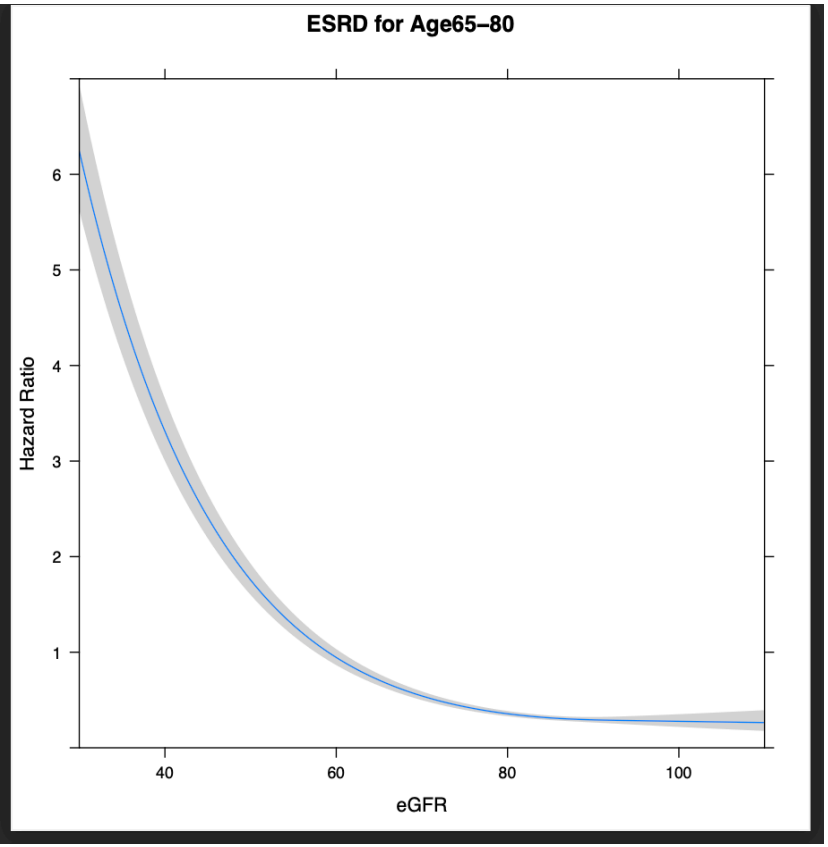

MACE for Age65–80
Hazard Ratio
0.9
0.8
0.7
0.6
0.5
0.4
40
60
80
100
eGFR
MACE for Age81–105
Hazard Ratio
1.0
0.8
0.6
40
60
80
100
eGFR


MACE_PLUS for Age18–39
Hazard Ratio
1.2
1.1
1.0
0.9
40
60
80
100
eGFR

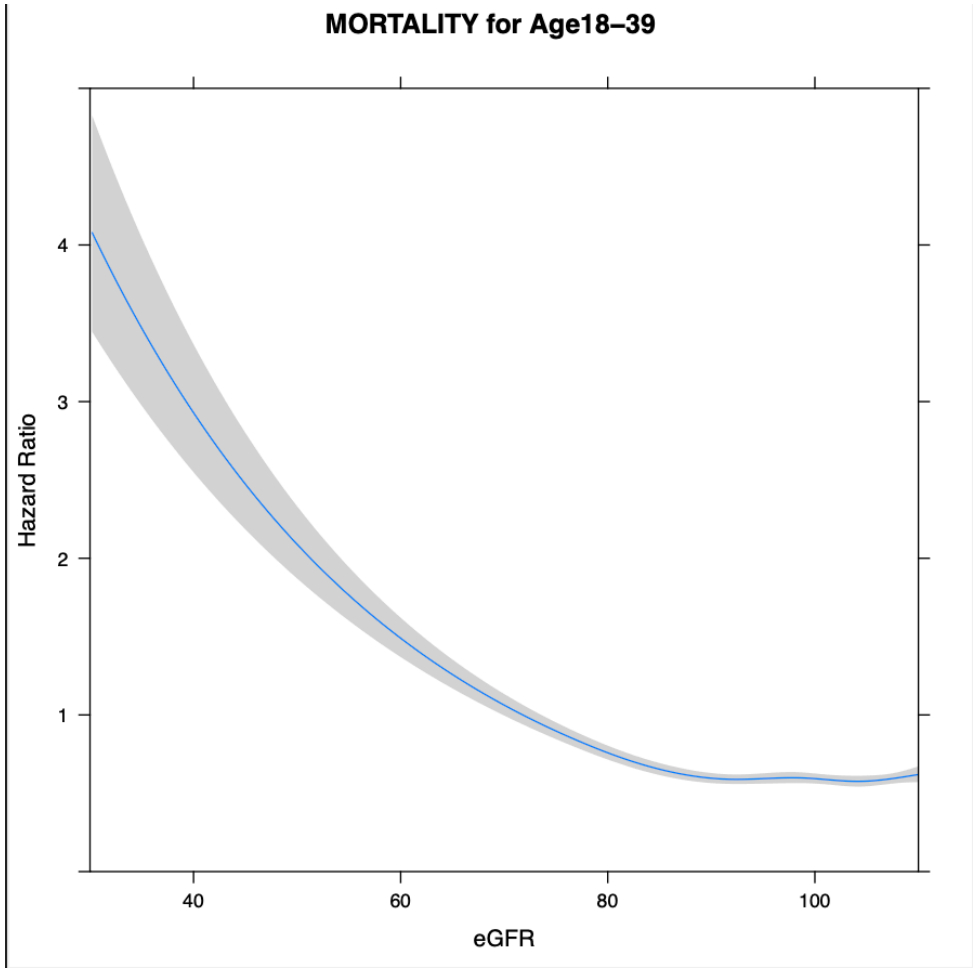

MACE_PLUS for Age65–80
Hazard Ratio
1.0
0.8
0.6
40
60
80
100
eGFR
MACE_PLUS for Age81–105
Hazard Ratio
1.0
0.9
0.8
0.7
0.6
40
60
80
100
eGFR

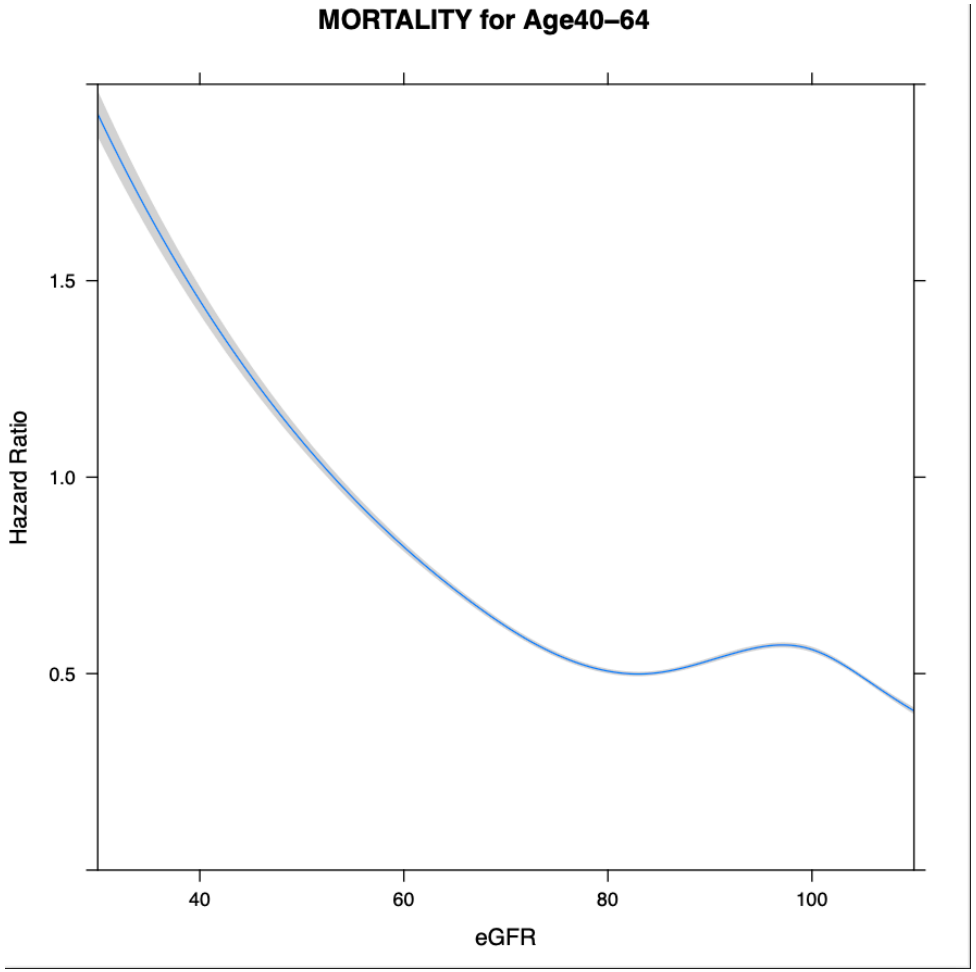

ESRD for Age18–39
Hazard Ratio
1.4
1.2
1.0
0.8
40
60
80
100
eGFR
ESRD for Age40–64
Hazard Ratio
1.2
1.1
1.0
0.9
40
60
80
100
eGFR

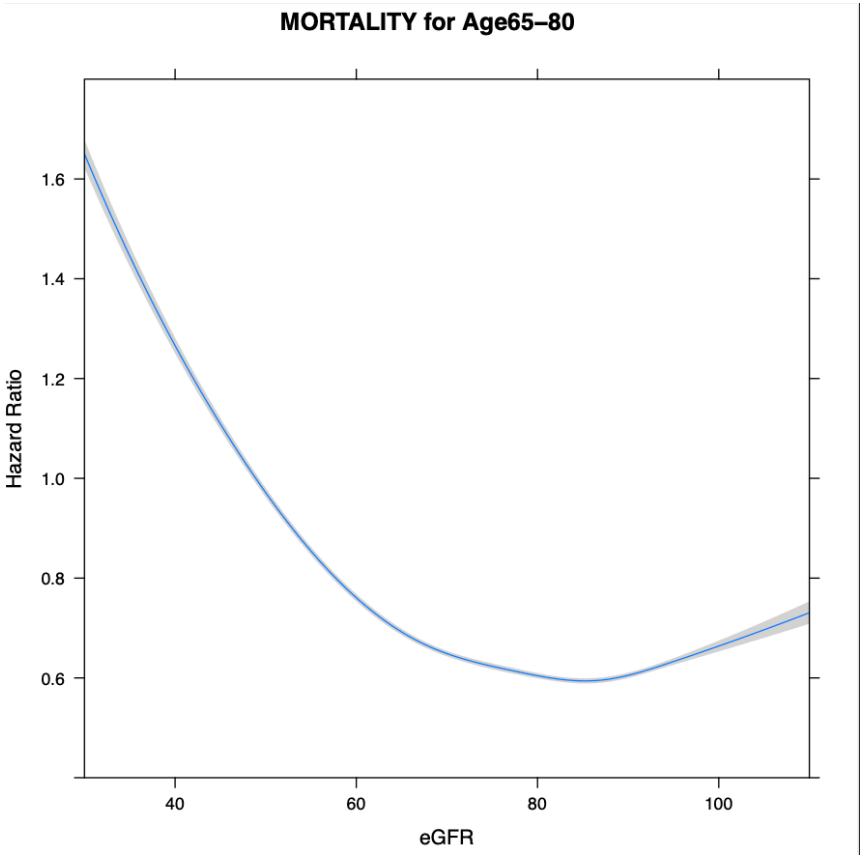

ESRD for Age81–105
Hazard Ratio
1
2
3
4
40
60
80
100
eGFR

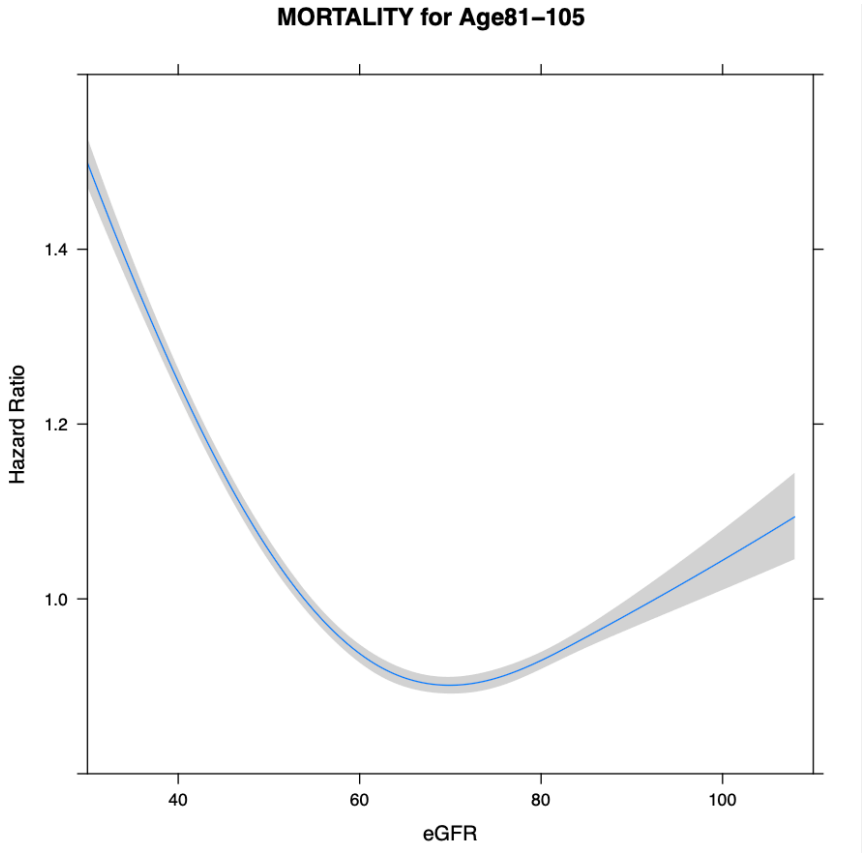

ESRD for Age65–80
Hazard Ratio
1
2
3
4
5
6
40
60
80
100
eGFR

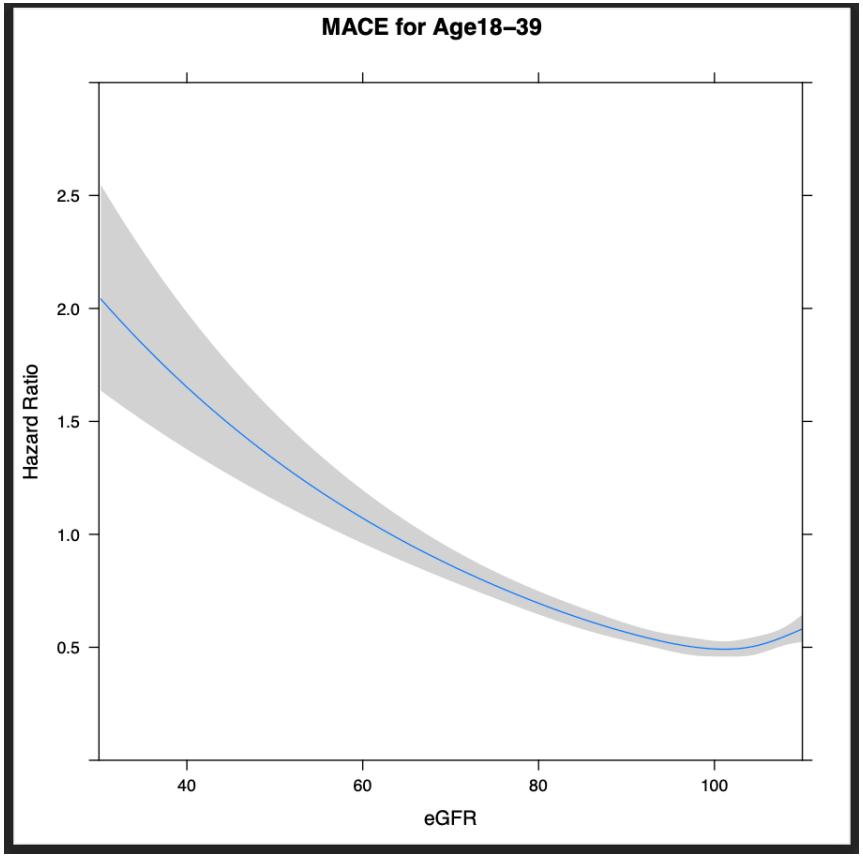
Appendix VII: RDD cubic spline plots for adverse outcomes, eGFR 75 ml/min/1.73 m^2

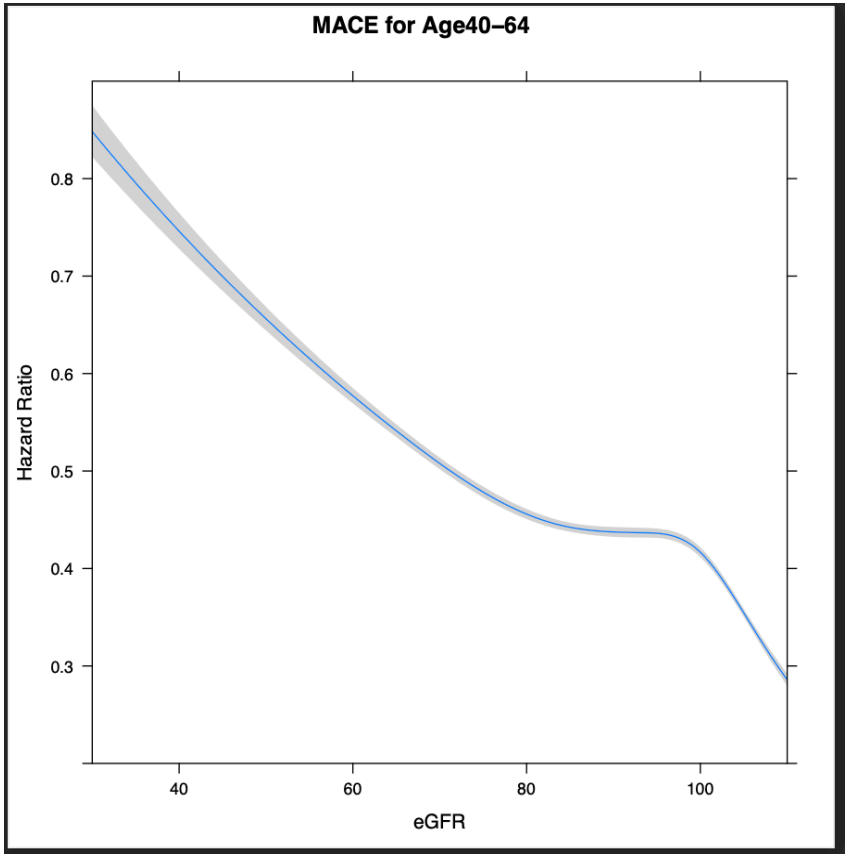


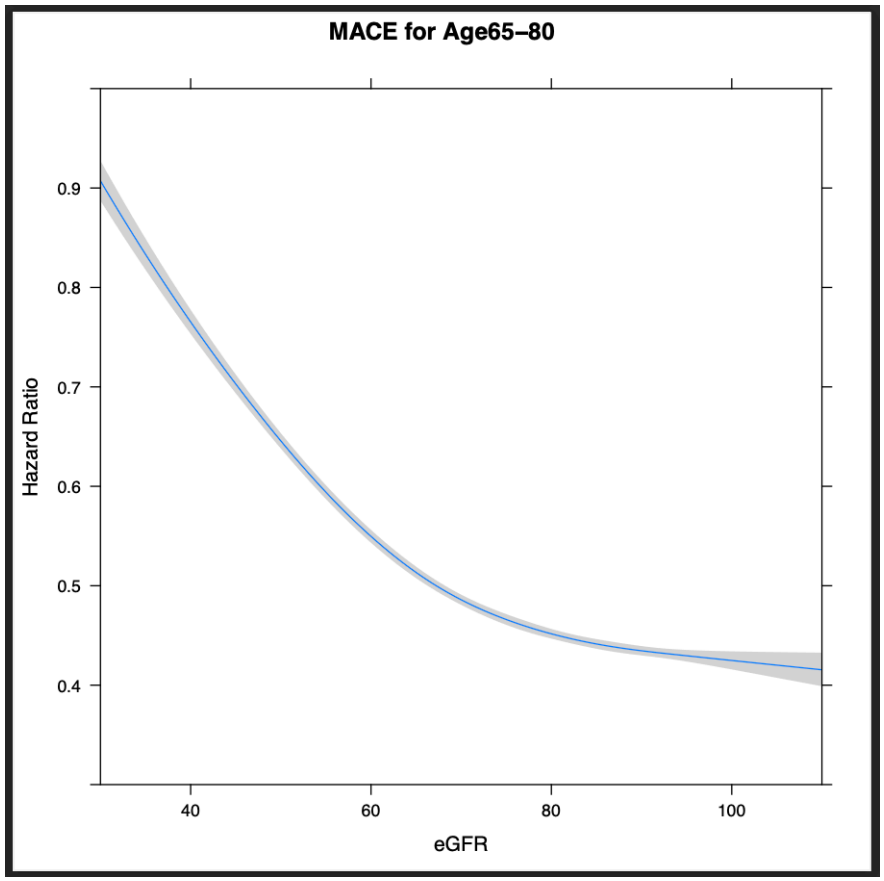


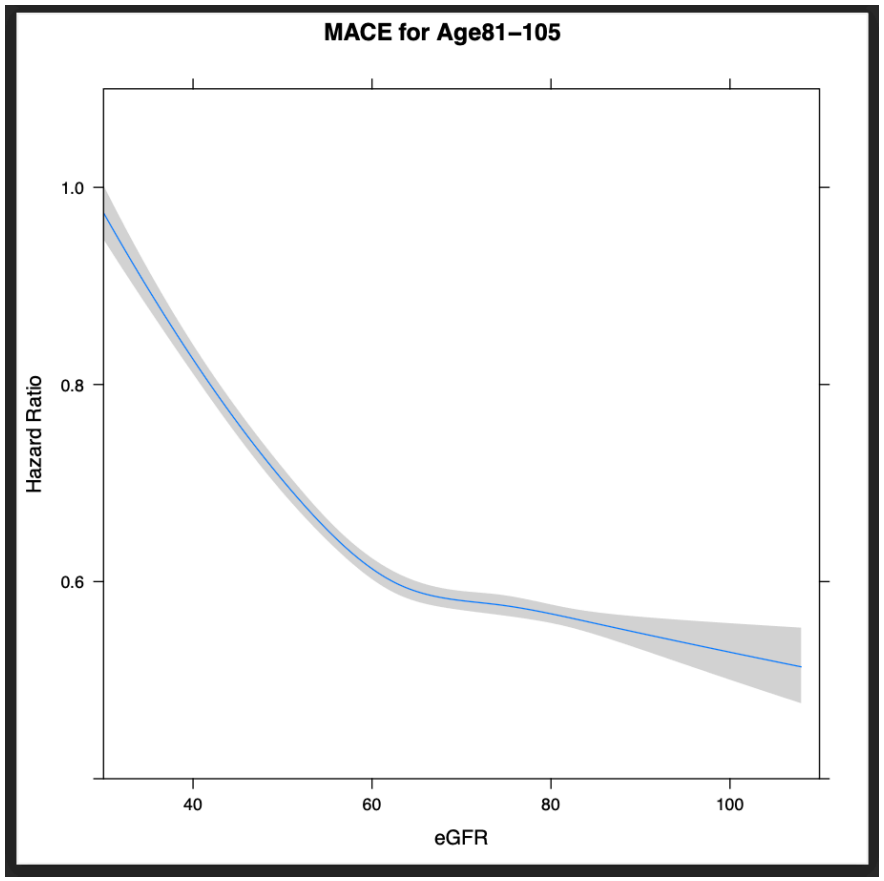

MORTALITY for Age65–80
Hazard Ratio
1.6
1.4
1.2
1.0
0.8
0.6
40
60
80
100
eGFR

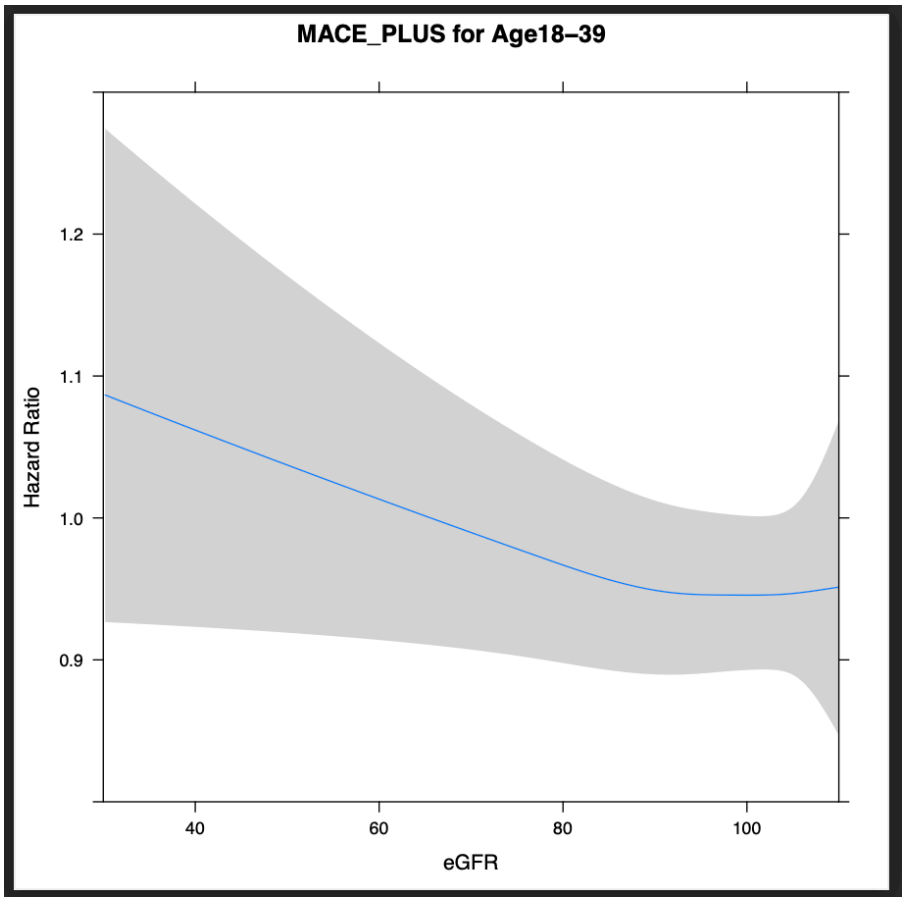

MORTALITY for Age81–105
Hazard Ratio
1.4
1.2
1.0
40
60
80
100
eGFR

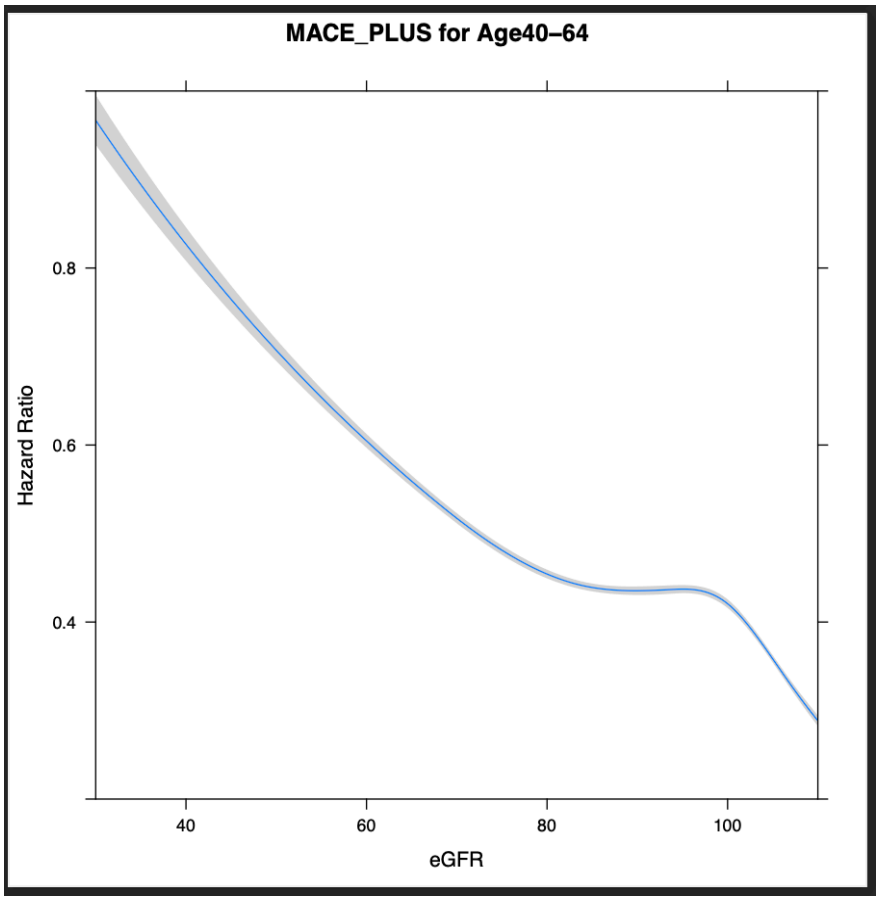

MACE for Age18–39
Hazard Ratio
2.5
2.0
1.5
1.0
0.5
40
60
80
100
eGFR

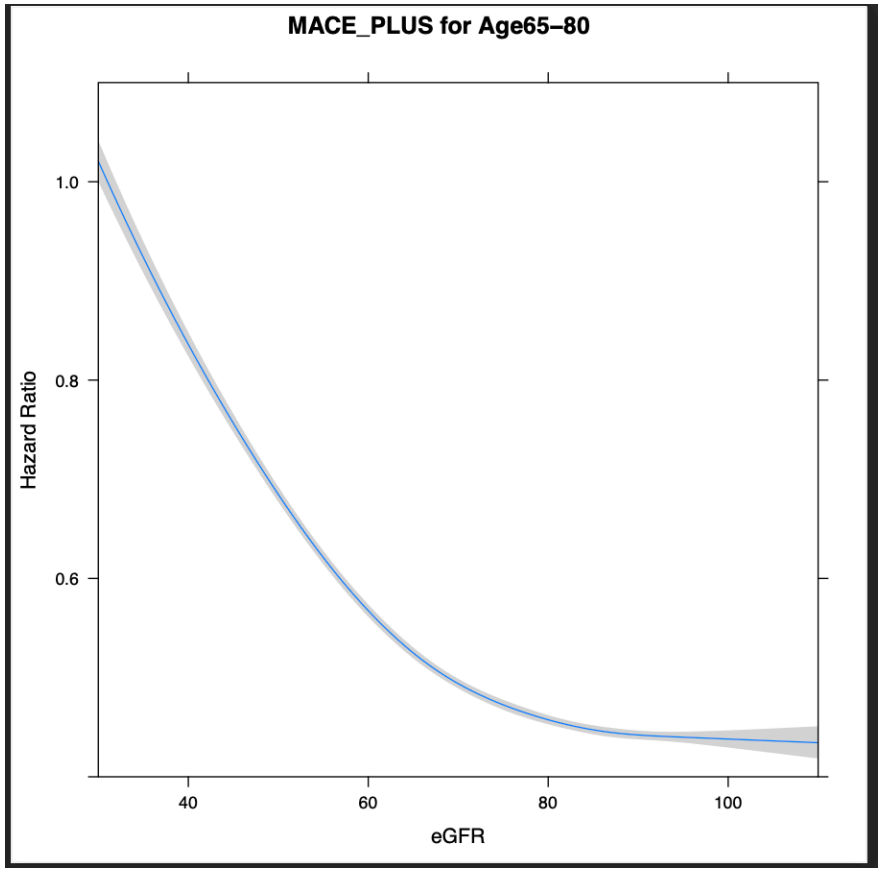

MACE for Age40–64
Hazard Ratio
0.8
0.7
0.6
0.5
0.4
0.3
40
60
80
100
eGFR

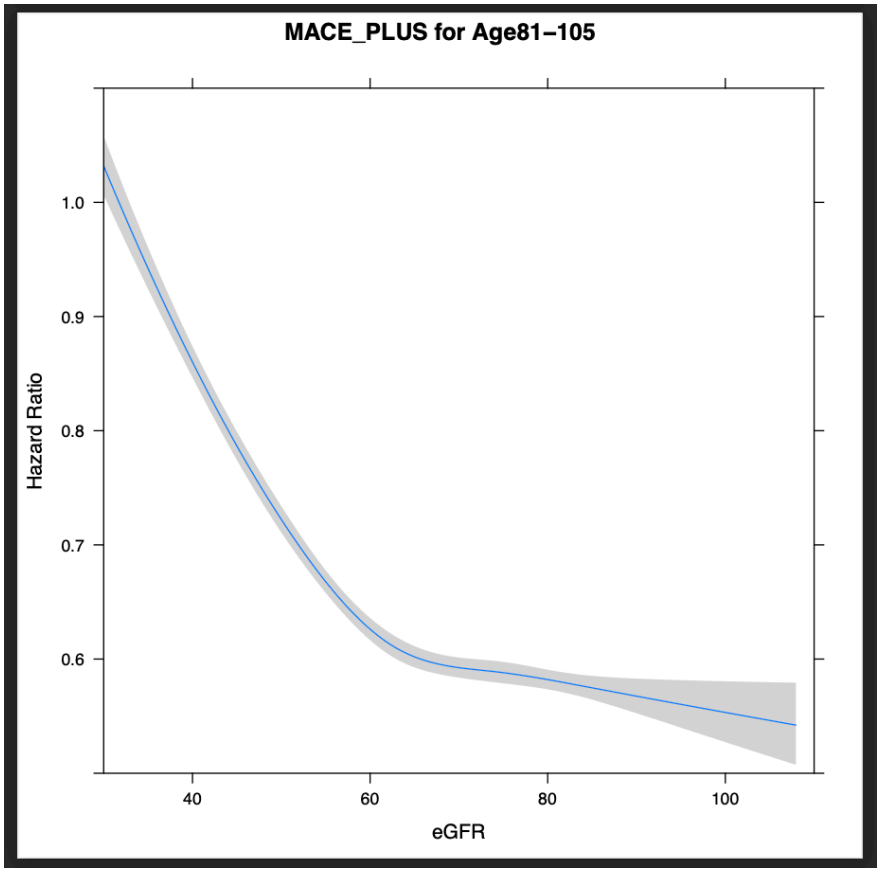

MACE for Age65–80
Hazard Ratio
0.9
0.8
0.7
0.6
0.5
0.4
40
60
80
100
eGFR

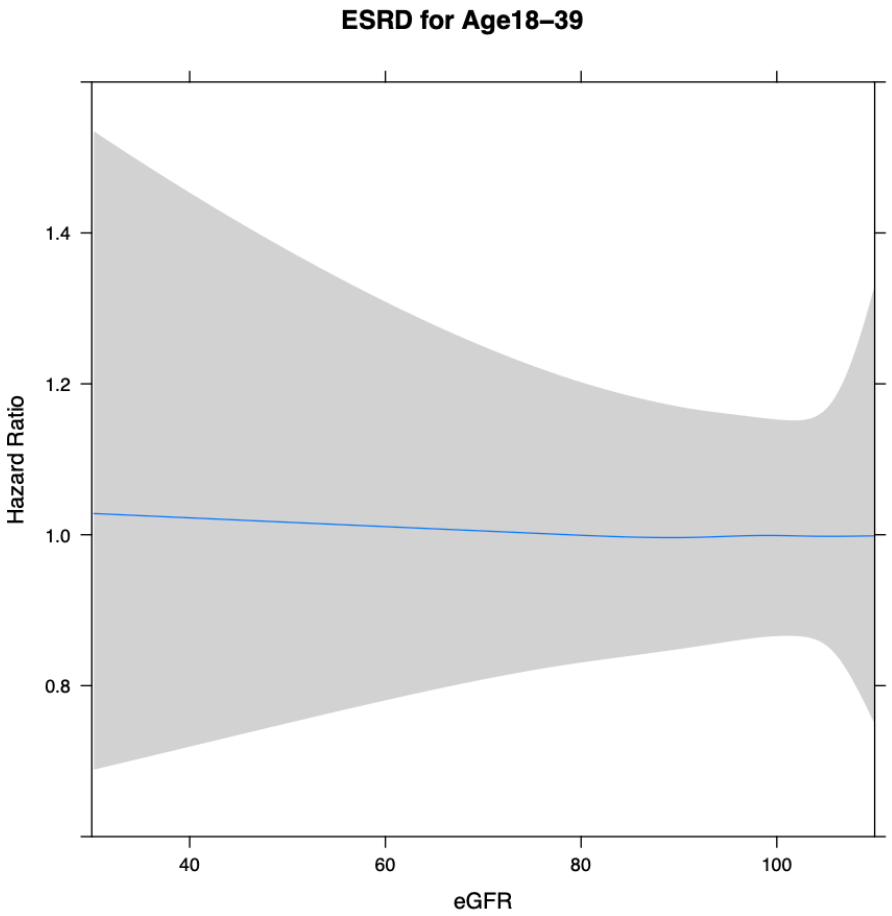

MACE for Age81–105
Hazard Ratio
1.0
0.8
0.6
40
60
80
100
eGFR

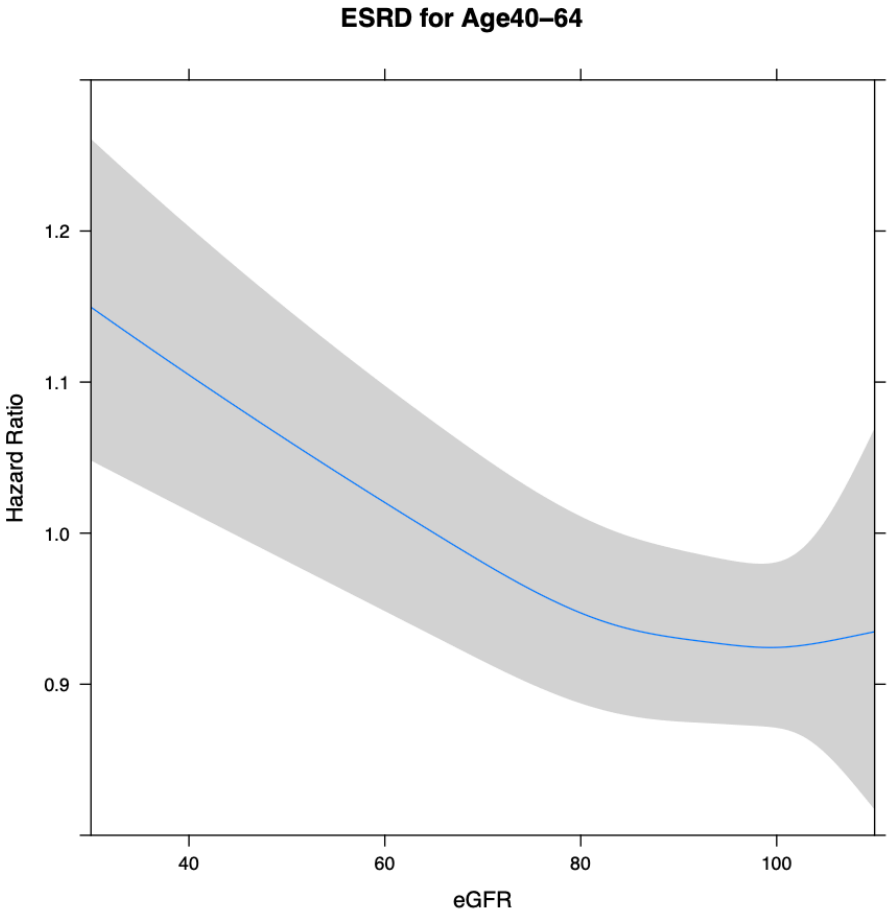

MACE_PLUS for Age18–39
Hazard Ratio
1.2
1.1
1.0
0.9
40
60
80
100
eGFR

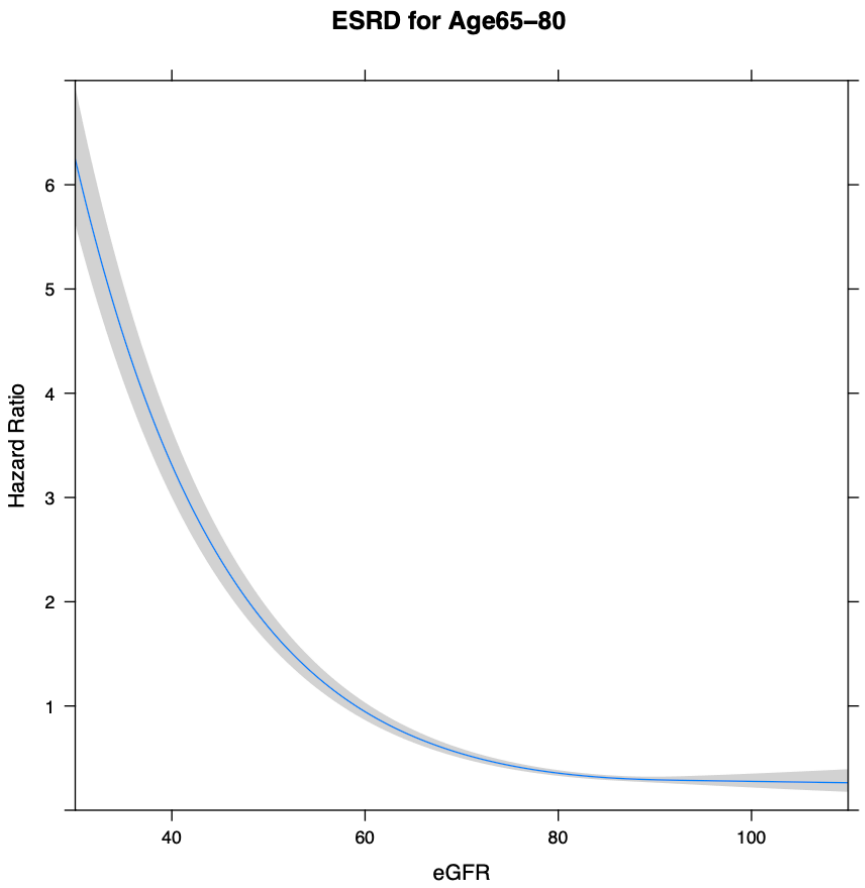

MACE_PLUS for Age40–64
Hazard Ratio
0.8
0.6
0.4
40
60
80
100
eGFR

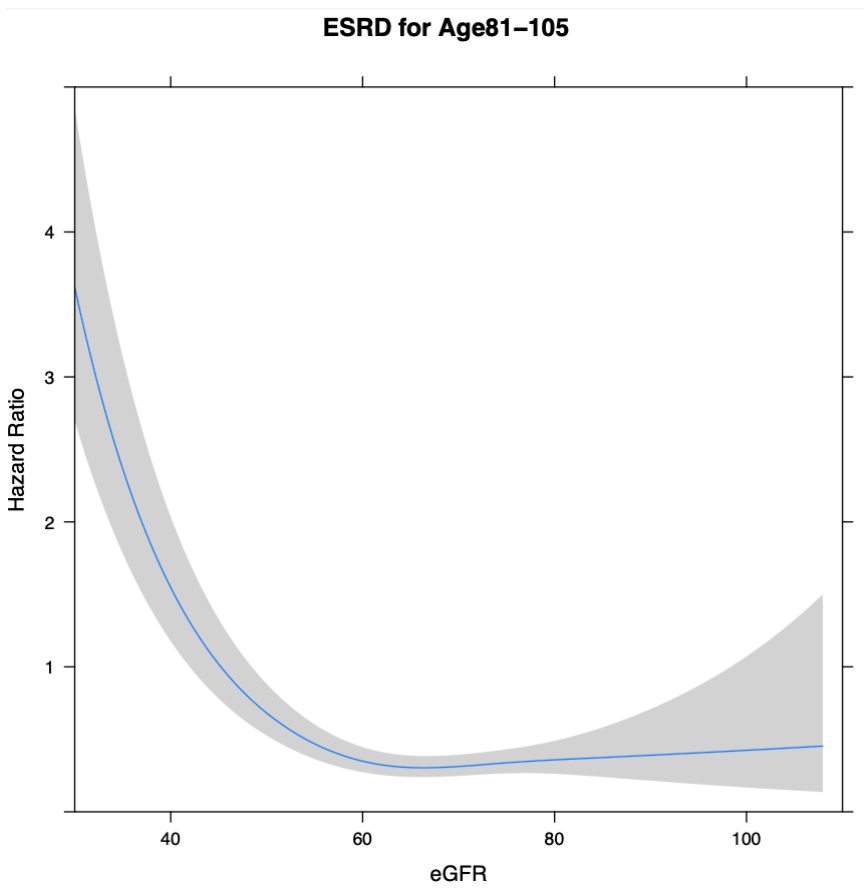

MACE_PLUS for Age65–80
Hazard Ratio
1.0
0.8
0.6
40
60
80
100
eGFR


MACE_PLUS for Age81–105
Hazard Ratio
1.0
0.9
0.8
0.7
0.6
40
60
80
100
eGFR


ESRD for Age18–39
Hazard Ratio
1.4
1.2
1.0
0.8
40
60
80
100
eGFR


ESRD for Age40–64
Hazard Ratio
1.2
1.1
1.0
0.9
40
60
80
100
eGFR


ESRD for Age65–80
Hazard Ratio
1
2
3
4
5
6
40
60
80
100
eGFR


ESRD for Age81–105
Hazard Ratio
1
2
3
4
40
60
80
100
eGFR

Appendix VIII: STROBE Checklist

	Item No.	STROBE items	RECORD items	Location in manuscript where items are reported
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	RECORD 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. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	Title and abstract. Pages 1 and 5
Background rationale	2	Explain the scientific background and rationale for the investigation being reported		Background and rationale. Pages 12, 15
Objectives	3	State specific objectives, including any prespecified hypotheses		Objectives – page 13
Study Design	4	Present key elements of study design early in the paper		Study design – page 32
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection		Study design – page 32
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and	RECORD 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.	Study design – page 32

		control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	RECORD 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. RECORD 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.	References are provided for the ICD codes used – appendix II
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	RECORD 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 II
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		Study design – page 36
Bias	9	Describe any efforts to address potential sources of bias		Discussion
Study size	10	Explain how the study size was arrived at		Figure 6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why		Study design – page 36
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		Study design – page 36

		(c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses		
Data access and cleaning methods		..	RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	Study design – page 32
Linkage		..	RECORD 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.	Study design – page 32
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	RECORD 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.	Study design – page 32, figure 6
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic,		Table 1

		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* - summarise follow-up time (*e.g.*, average and total amount)		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures		Table 2 Appendix III and IV
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		Tables 3, 4, appendix III and IV
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses		Objective 2, appendix
Key results	18	Summarise key results with reference to study objectives		Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include	Discussion

		or imprecision. Discuss both direction and magnitude of any potential bias	discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence		Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results		Discussion
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		Funding, page 4
Accessibility of protocol, raw data, and programming code		..	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Methods, Appendices