

**GFR estimating equations and their association with adverse clinical outcomes: A
population-based retrospective cohort study**

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PREFACE

Author Contributions

This thesis initiated from discussions between Sayem Chowdhury and his thesis supervisor Dr. Manish Sood. Dr. Sood helped in organising members of the Thesis Advisory Committee (TAC): himself, Dr. Gregory Hundemer (thesis co-supervisor), and Dr. David Massicotte-Azarniouch. Sayem is the primary author of all content within this thesis as part of his Master of Science (MSc) in Epidemiology. He is responsible for every aspect of the thesis including developing the project proposal, conducting the literature review, obtaining data from ICES, performing the statistical analysis, creating figures and tables, interpreting the results, writing the thesis manuscript, and final proofing. Dr. Sood provided supervision and guidance on all aspects of the thesis. All members of the TAC were also involved in providing insights into the statistical methods and analysis to be conducted. For all manuscripts within this thesis, Sayem is the first author and Dr. Sood is the senior author.

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Ethics review and approval

This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). This document used data adapted from the Statistics Canada Postal Code^{OM} Conversion File, which is based on data licensed from © Canada Post Corporation, and/or data adapted from the Ontario Ministry of Health Postal Code Conversion File, which contains data copied under license from © Canada Post Corporation and Statistics Canada. Parts of this material are based on data and/or information compiled and provided by CIHI and MOH. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

Usage of data for this study did not require ethics board approval as analysis of study data is authorised under section 45 of Ontario's Personal Health Information Protection Act. The project was submitted to and received approval from ICES Ottawa (TRIM: 2026 0901 467 000), with members of the project obtaining the necessary training set out by ICES.

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ABSTRACT

Chronic kidney disease (CKD) is a progressive condition characterised by abnormalities in kidney structure or function, and is classified by cause of injury, eGFR and albuminuria.¹ It carries an enormous global burden, affecting approximately 788 million adults worldwide, accounting for nearly 1.5 million deaths annually, and currently ranking as the ninth leading cause of death globally.^{1,2} In Canada alone, there are an estimated 4 million people who have CKD, costing Canadians approximately \$40 billion annually in both direct and indirect costs.^{1,2} Altogether, the irreversible nature of CKD, the absence of curative options, increasing risk beyond kidney outcomes, and the financial burden of CKD underscore the critical importance of accurate kidney function assessment to facilitate early recognition and intervention.

Glomerular filtration rate (GFR) is widely considered the best method in determining the kidney's health and function in both research and clinical settings.¹ It is also used in estimating the risk for kidney failure using tools such as the Kidney Failure Risk Equation.³ Multiple eGFR equations have been developed; however, serum creatinine (SCr) based equations are more utilised given that it is inexpensive, widely standardised, and routinely measured.^{1,4} In 2021, two new equations were developed, the 2021 Chronic Kidney Disease Epidemiology Collaboration (CK21) and the European Kidney Function Consortium Equation (EKFC), both of which were race-free equations. In North America, the CK21 has been widely adopted; however, the EKFC has been shown to have potential benefits in other populations.

Current evidence shows that EKFC shifts CKD prevalence but does not meaningfully improve prediction of outcome risk, with discrimination remaining the same across equations.^{5,6} Important methodological gaps remain, however. Prior analyses report only relative measures such as hazard ratios and reclassification metrics; none model the cumulative incidence function directly to estimate and assess the accuracy of a patient's absolute outcome risk. Calibration has

also not been formally assessed, a clinically relevant metric that provides insight as to whether predicted probabilities match reality. Furthermore, current studies are limited to two European populations or focus on a cardiovascular high-risk cohort, with no general North American population assessed. Lastly, there have been limited studies comparing the usage of eGFR in kidney failure risk tools using the EKFC. This thesis addresses these gaps by comparing CK21 and EKFC in a population-based Ontario cohort, evaluating discrimination, calibration, and reclassification for kidney and cardiovascular outcomes, and assessing their performance as inputs to the KFRE.

TABLE OF CONTENTS

PREFACE	ii
Author Contributions	ii
Ethics review and approval	iii
Acknowledgements	iv
ABSTRACT	v
TABLE OF CONTENTS	vii
LIST OF TABLES	xiii
LIST OF FIGURES	xiv
LIST OF ABBREVIATIONS	xvi
CHAPTER 1: INTRODUCTION	1
1.1 Problem	1
1.2 Purpose and Rationale	2
1.3 Objectives of the Study	2
1.4 Thesis Outline	3
CHAPTER 2: BACKGROUND	4
2.1 Importance of Assessing CKD	4
2.2 Measuring Kidney Health and Function	5
2.3 History of creatinine-based kidney function tests	5
2.4 Kidney Failure Risk Equation	7
2.5 Clinical Endpoints of Kidney Failure	7
2.5.1 Major Adverse Kidney Events	7
2.5.2 Major Adverse Cardiovascular Outcomes	8
2.6 Diagnostic Accuracy to Prognostic Utility	9
2.7 Current Literature on Recent Equations	9
2.8 Conclusion	10
CHAPTER 3: GFR ESTIMATING EQUATIONS AND THEIR ASSOCIATION WITH ADVERSE CLINICAL OUTCOMES: A POPULATION-BASED RETROSPECTIVE COHORT STUDY	11
3.1 Abstract	12

3.2 Introduction	14
3.3 Methods	14
3.3.1 Study Design and Setting	14
3.3.2 Data Sources	15
3.3.3 Study Cohort	16
3.3.4 Index Kidney Function Measurement	16
3.3.5 Outcomes	17
3.3.6 Covariates	17
3.3.7 Missing Data	17
3.3.8 Statistical Analysis	18
3.3.9 Additional Analysis	20
3.4 Results	20
3.4.1 Baseline Characteristics	20
3.4.2 Hazard Ratios	21
3.4.3 Discrimination	22
3.4.4 Calibration	22
3.4.5 Overall Accuracy	23
3.4.6 Reclassification	24
3.4.7 Decision Curve Analysis	25
3.5 Discussion	26
3.5.1 Population-Level Impact of EKFC Adoption on eGFR and CKD Prevalence	26
3.5.2 Equivalent Prognostic Performance for Kidney and Cardiovascular Outcomes	26
3.5.3 Reclassified Individuals Show Higher Risk Dependent on Baseline eGFR Category	27
3.5.4 Subgroup Analyses by Age, Sex, and Albuminuria Category	29
3.5.5 Policy Implications for EKFC Adoption	29
3.5.6 Strength and Limitations	30
3.6 Conclusion	31
Chapter 3: Figures	32
Figure 1. Patient flowchart diagram	32
Figure 2. eGFR Category Distribution Across Age Groups	33
Figure 3. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk	34

Figure 4. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk ..	35
Figure 5. Calibration scatter plot: observed versus predicted MAKE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.	36
Figure 6. Calibration scatter plot: observed versus predicted MACE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.	37
Figure 7. Decision Curve Analysis for MAKE using CKD-EPI 2021 and EKFC eGFR values for the overall cohort.	38
Figure 8. Decision Curve Analysis for MACE using CKD-EPI 2021 and EKFC eGFR values for the overall cohort.	39
Chapter 3: Tables	40
Table 1. Baseline Characteristics	40
Table 2. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MAKE & MACE by eGFR categories relative to G1 (≥ 90), accounting for all-cause/non-CVD mortality as a competing risk	43
Table 3. Cross-classification of eGFR categories between CK21 and EKFC equations (N = 5,507,066)	44
Table 4a. Risk of Major Adverse Kidney Events among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category	45
Table 4b. Risk of Major Adverse Cardiovascular Events among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category	45
CHAPTER 4: COMPARISON OF GFR ESTIMATING EQUATION INPUTS FOR THE KIDNEY FAILURE RISK EQUATION (KFRE): A POPULATION-BASED RETROSPECTIVE COHORT STUDY	46
4.1 Abstract	47
4.2 Introduction	49
4.3 Methods	50
4.3.1 Study Design and Setting	50
4.3.2 Data Sources	50
4.3.3 Study Cohort	51
4.3.4 Index Kidney Function Measurement	52
4.3.5 Outcomes	52
4.3.6 KFRE Risk Predictions	52
4.3.7 Statistical Analysis	52
4.3.8 Additional Analysis	53

4.4 Results	54
4.4.1 Cohort Characteristics	54
4.4.2 Discrimination.....	54
4.4.3 Calibration.....	54
4.4.4 Net Reclassification Improvement	55
4.4.5 Decision Curve Analysis.....	56
4.5 Discussion	56
Chapter 4: Figures.....	60
Figure 1. Patient flowchart diagram	60
Figure 2. Calibration plots for the 4-variable KFRE comparing CKD-EPI 2021 (CK21; blue circles) against EKFC (green squares) as eGFR inputs, shown at the 2-year (left) and 5-year (right) horizons	61
Figure 3. KFRE Risk Distribution by Equation and Calibration.	62
Figure 4. Scatterplot comparing 2-year kidney failure risk (threshold 10%) estimated by the 4-variable KFRE using uncalibrated CKD-EPI 2021 (CK21) versus calibrated EKFC eGFR inputs...	63
Figure 5. Scatterplot comparing 5-year kidney failure risk (threshold 5%) estimated by the 4-variable KFRE using uncalibrated CKD-EPI 2021 (CK21) versus calibrated EKFC eGFR inputs...	64
Figure 6. Decision curve analysis for the 4-variable KFRE at the 2-year horizon, with death treated as a competing event. CKD-EPI (blue) 2021 and EKFC (green) eGFR inputs, each uncalibrated (light) and recalibrated (dark). The "All" (treat everyone) and "None" (treat no one) reference strategies are shown for comparison	65
Figure 7. Decision curve analysis for the 4-variable KFRE at the 5-year horizon, with death treated as a competing event. CKD-EPI (blue) 2021 and EKFC (green) eGFR inputs, each uncalibrated (light) and recalibrated (dark). The "All" (treat everyone) and "None" (treat no one) reference strategies are shown for comparison	66
Chapter 4: Tables	67
Table 1. Baseline Characteristics	67
Table 2. Categorical NRI for CK21 versus EKFC at 2- and 5-year horizons.	69
Table 3. Categorical NRI for CK09 versus EKFC at 2- and 5-year horizons.	69
CHAPTER 5: DISCUSSION	70
5.1 Summary of Thesis.....	70
5.2 Novel Findings	70
5.3 Implications for Clinical Practice.....	71
5.4 Limitations.....	72
5.5 Future Research Avenues	73

5.6 Conclusions.....	74
References (Chapters 1-5).....	76
THESIS SUPPLEMENTARY MATERIAL	88
Chapter 3: Supplemental Material	88
Appendix A. Sensitivity and specificity of outcome definitions	88
Appendix B. Age-Stratified Analysis.....	89
Appendix C. Sex-Stratified Analysis	97
Appendix D. ACR-Stratified Analysis.....	103
Appendix E. Sensitivity Analysis for KRT, Overall Mortality, and no age/sex models	111
Appendix F. C-statistic, Calibration, and Brier Scores for CK21 and EKFC at 2- and 5-year timepoints.....	116
Appendix G. Calibration line plots for MAKE, MACE, KRT, and overall mortality	119
Appendix H. Calibration scatter plots for MAKE, MACE, KRT, and overall mortality	130
Appendix I. Decision Curve Analysis for MAKE, MACE, KRT, and overall mortality outcomes using CK21 and EKFC eGFR values for the overall cohort. MAKE and MACE models for female, male, age 18 to <40, 40 to ≤ 65, 66 to <80, ≥80, ACR categories A1 (<3 mg/mmol), A2 (3-30 mg/mmol), and A3 (>30 mg/mmol) strata.....	142
Chapter 4: Supplemental Material	164
Appendix J. Sensitivity and specificity of outcome definitions	164
Appendix K. Model discrimination, calibration and accuracy metrics.....	165
Appendix L1. Calibration line plots of observed versus predicted risk by deciles comparing uncalibrated CK21 to calibrated EKFC input to KRT at the 2- and 5-year horizons.	171
Appendix L2. Calibration line plots of observed versus predicted risk by deciles comparing uncalibrated CK21 to uncalibrated EKFC input to KRT at the 2- and 5-year horizons.....	181
Appendix L3. Calibration line plots of observed versus predicted risk by deciles comparing calibrated CK21 to calibrated EKFC input to KRT at the 2- and 5-year horizons.....	186
Appendix M1. Calibration line plots of observed versus predicted risk by deciles comparing uncalibrated CK09 to calibrated EKFC input to KRT at the 2- and 5-year horizons.	191
Appendix M2. Calibration line plots of observed versus predicted risk by deciles comparing uncalibrated CK09 to uncalibrated EKFC input to KRT at the 2- and 5-year horizons.	201
Appendix M3. Calibration line plots of observed versus predicted risk by deciles comparing calibrated CK09 to calibrated EKFC input to KRT at the 2- and 5-year horizons.....	206
Appendix N. Decision Curve Analysis for KRT outcomes comparing KFRC inputs using CK21, EKFC, CK21 (recalibrated), EKFC (recalibrated) for the overall cohort, and for age 18 to <40, 40 to ≤ 65, 66 to <80, ≥80, male, female, ACR categories A1 (<3 mg/mmol), A2 (3-30 mg/mmol), and A3 (>30 mg/mmol) strata.	211

Appendix O. Decision Curve Analysis for KRT outcomes comparing KFRE inputs using CK09, EKFC, CK09 (recalibrated), EKFC (recalibrated) for the overall cohort, and for age 18 to <40, 40 to ≤ 65, 66 to <80, ≥80, male, female, ACR categories A1 (<3 mg/mmol), A2 (3-30 mg/mmol), and A3 (>30 mg/mmol) strata. 221

Appendix P. Categorical NRI: Sensitivity analyses..... 231

Appendix Q. Density scatter plot comparing EKFC and CK21 233

LIST OF TABLES

Table 3-1. Baseline Characteristics

Table 3-2. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MAKE & MACE by eGFR categories relative to G1 (≥ 90), accounting for all-cause/non-CVD mortality as a competing risk

Table 3-3. Cross-classification of eGFR categories between CK21 and EKFC equations (N = 5,507,066)

Table 3-4a. Risk of Major Adverse Kidney Events among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category

Table 3-4b. Risk of Major Adverse Cardiovascular Events among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category

Table 4-1. Baseline Characteristics

Table 4-2. Categorical NRI for CK21 versus EKFC at 2- and 5-year horizons.

Table 4-3. Categorical NRI for CK09 versus EKFC at 2- and 5-year horizons.

LIST OF FIGURES

Figure 3-1. Patient flowchart diagram

Figure 3-2. eGFR Category Distribution Across Age Groups

Figure 3-3. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk

Figure 3-4. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk

Figure 3-5. Calibration scatter plot: observed versus predicted MAKE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

Figure 3-6. Calibration scatter plot: observed versus predicted MACE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

Figure 3-7. Decision Curve Analysis for MAKE using CKD-EPI 2021 and EKFC eGFR values for the overall cohort.

Figure 3-8. Decision Curve Analysis for MACE using CKD-EPI 2021 and EKFC eGFR values for the overall cohort.

Figure 4-1. Patient flowchart diagram

Figure 4-2. Calibration plots for the 4-variable KFRE comparing CKD-EPI 2021 (CK21; blue circles) against EKFC (green squares) as eGFR inputs, shown at the 2-year (left) and 5-year (right) horizons

Figure 4-3. KFRE Risk Distribution by Equation and Calibration

Figure 4-4. Scatterplot comparing 2-year kidney failure risk (threshold 10%) estimated by the 4-variable KFRE using uncalibrated CKD-EPI 2021 (CK21) versus calibrated EKFC eGFR inputs

Figure 4-5. Scatterplot comparing 5-year kidney failure risk (threshold 5%) estimated by the 4-variable KFRE using uncalibrated CKD-EPI 2021 (CK21) versus calibrated EKFC eGFR inputs

Figure 4-6. Decision curve analysis for the 4-variable KFRE at the 2-year horizon, with death treated as a competing event. CKD-EPI (blue) 2021 and EKFC (green) eGFR inputs, each uncalibrated (light) and recalibrated (dark). The "All" (treat everyone) and "None" (treat no one) reference strategies are shown for comparison.

Figure 4-7. Decision curve analysis for the 4-variable KFRE at the 5-year horizon, with death treated as a competing event. CKD-EPI (blue) 2021 and EKFC (green) eGFR inputs, each uncalibrated (light) and recalibrated (dark). The "All" (treat everyone) and "None" (treat no one) reference strategies are shown for comparison

LIST OF ABBREVIATIONS

ACR	Albumin-to-Creatinine Ratio
AUC	Area Under the Curve
CIF	Cumulative Incidence Function
CK09	Chronic Kidney Disease Epidemiology Collaboration 2009 equation
CK21	Chronic Kidney Disease Epidemiology Collaboration 2021 equation
CKD	Chronic Kidney Disease
CORR	Canadian Organ Replacement Registry
CSN	Canadian Society of Nephrology
CVD	Cardiovascular Disease
DCA	Decision Curve Analysis
eGFR	Estimated Glomerular Filtration Rate
EKFC	European Kidney Function Consortium
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
ICES	Institute for Clinical Evaluative Sciences
IPCW	Inverse Probability of Censoring Weighting
KDIGO	Kidney Disease: Improving Global Outcomes
KFRE	Kidney Failure Risk Equation
KRT	Kidney Replacement Therapy
MACE	Major Adverse Cardiovascular Events
MAKE	Major Adverse Kidney Events
MDRD	Modification of Diet in Renal Disease

mGFR	Measured Glomerular Filtration Rate
NRI	Net Reclassification Improvement
OE	Observed-to-expected
SCr	Serum Creatinine
SD	Standard Deviation

CHAPTER 1: INTRODUCTION

1.1 Problem

Chronic kidney disease (CKD) is a progressive condition characterised by persistent (≥ 3 months) abnormal kidney structure or function, most commonly classified using eGFR, and albuminuria.¹ In Canada alone, there are an estimated 4 million people who have CKD costing Canadians approximately \$40 billion annually.^{2,7,8} Beyond kidney specific outcomes, individuals with CKD have an increased risk of cardiovascular morbidity and overall mortality highlighting the interconnection of kidney health across different biological systems.^{2,9} It is considered to be irreversible, but the risks of progression and its associated complications can be minimised if detected and managed early which requires an accurate assessment of kidney function.¹

Measured GFR (mGFR) remains the gold standard for assessing kidney function, however, it is impractical on a large scale due to cost and time, leading clinicians to rely on estimated GFR (eGFR). Most commonly calculated using only serum creatinine (SCr) obtained from a routine blood test,^{10–12} eGFR has become the primary measure used globally to diagnose and stage CKD.^{13,14} These measures help inform decision making related to CKD from monitoring progression, predicting adverse clinical outcomes, and determining eligibility for treatments such as kidney replacement therapy (KRT).^{15,16}

Currently, there has been adoption of newer SCr-based eGFR equations – primarily the Chronic Kidney Disease Epidemiology Collaboration 2021 (CK21),^{1,10} and the European Kidney Function Consortium (EKFC).^{1,17} Health regions in Canada have been adopting the CK21 equation over its 2009 predecessor (CK09), with Ontario laboratories now using the equation.^{18–20} However, no studies have compared the prognostic utility of EKFC against CK21 in a general North American population. Furthermore, previous comparison studies have only assessed

metrics that focus on how risk is ranked and how patients are assigned to risk categories,^{5,6,21,22} leaving unanswered which eGFR equation produces more prognostically accurate estimates and greater net clinical benefit. Lastly, while other studies have compared the association of eGFR equations to clinical outcomes, these studies utilised a cause-specific approach, not a competing risk framework, which is more appropriate for prognostication.

1.2 Purpose and Rationale

Accurate prediction of patient outcomes is of greater clinical relevance for eGFR equations than accurate estimation of measured GFR. They aid in the timely prevention and management of CKD, and at a system level can guide health policy and inform clinical laboratories on the optimal eGFR equation for clinical prognostication. From a public health perspective, identifying and implementing the equation that best predicts outcomes could improve care at the population level in a cost-effective manner. The purpose of this study is to examine and compare the prognostic utility of eGFR equations, primarily the CKD-EPI and EKFC, to clinically relevant endpoints and kidney failure risk using population level data.

1.3 Objectives of the Study

The objectives of this study are the following:

- 1) to compare the association and prognostic performance of the EKFC and CK21 eGFR equations for Major Adverse Kidney Events (MAKE; need for dialysis, kidney transplantation, $\text{eGFR} < 15 \text{ mL/min/1.73m}^2$ or a GFR decline from baseline of 30% or more), and Major Adverse Cardiovascular Events (MACE; a composite of acute coronary syndrome, ischemic stroke, CV death) and MACE + (MACE plus hospitalization for heart failure).

- 2) to compare the 4-variable Kidney Failure Risk Equation (KFRE) using EKFC and CK21 eGFR inputs for predicting the need for kidney replacement therapy.

1.4 Thesis Outline

Following this introduction chapter, the thesis will begin with a background of the literature (**Chapter 2**) on the population-level burden of chronic kidney disease (CKD) and its kidney and cardiovascular complications, the role of the estimated glomerular filtration rate (eGFR) in CKD identification and risk prediction, and the history of competing creatinine-based eGFR equations, and the downstream consequences of equation choice for risk classification and clinical management. **Chapter 3** addresses the first thesis objective, comparing the CK21 and EKFC equations for the prediction of major adverse kidney events (MAKE) and major adverse cardiovascular events (MACE) in a population-based cohort of approximately 5.5 million Ontario adults, using Fine-Gray competing risks models, in a manuscript titled "GFR ESTIMATING EQUATIONS AND THEIR ASSOCIATION WITH ADVERSE CLINICAL OUTCOMES: A POPULATION-BASED RETROSPECTIVE COHORT STUDY " (intended for submission). **Chapter 4** addresses the second thesis objective, evaluating the impact of eGFR equation choice – CKD-EPI versus EKFC – as an input to the 4-variable Kidney Failure Risk Equation (KFRE) in a general population sub-cohort of those with CKD (eGFR < 60 mL/min/1.73m²) in a manuscript titled "COMPARISON OF GFR ESTIMATING EQUATION INPUTS FOR THE KIDNEY FAILURE RISK EQUATION (KFRE): A POPULATION-BASED RETROSPECTIVE COHORT STUDY" (intended for submission). Finally, **Chapter 5** presents a summary of the findings of the thesis, alongside a discussion of its strengths, limitations, and avenues for future research.

CHAPTER 2: BACKGROUND

2.1 Importance of Assessing CKD

Chronic kidney disease (CKD) is a progressive condition characterised by abnormalities in kidney structure or function, and is classified by cause of injury, eGFR and albuminuria.¹ It can arise from different aetiologies with diabetes and hypertension being the most common,² but the core mechanisms leading to CKD remain largely shared.²³ It begins with an initial injury to the nephrons, creating increased mechanical stress as remaining nephrons compensate via hyperfiltration.²³ This compensation is often why CKD goes undiagnosed until later stages as overall kidney function can initially remain preserved.^{23,24} However, sustained hyperfiltration eventually leads to progressive nephron loss, at which point the damage is generally irreversible,²³ with the cycle repeating if no intervention is taken. Should CKD progress to its end stages, kidney replacement therapy (KRT) – dialysis or kidney transplantation – becomes necessary as no curative therapies are available. Beyond kidney specific outcomes, individuals with CKD also face an elevated risk of a wide range of adverse health outcomes that can compete with kidney failure to cause death, underscoring that CKD carries a systemic burden extending well beyond the kidney.^{2,9}

CKD carries an enormous global burden – it affects approximately 788 million adults worldwide, accounts for nearly 1.5 million deaths annually, and is currently the ninth leading cause of death globally.^{1,2} Unlike many other leading causes of death, CKD mortality has continued to rise, with it estimated to become the fifth leading cause of years of life lost globally by 2040.²⁵ In Canada alone, there are an estimated 4 million people who have CKD, costing Canadians approximately \$40 billion annually in both direct and indirect costs.^{7,8} For those living with end-stage kidney disease, the cost per patient on dialysis is approximately \$100,000 which was estimated in 2017,

with current costs likely considerably higher.⁸ Altogether, the irreversible nature of CKD, the absence of curative options, increasing risk beyond kidney outcomes, and the financial burden of CKD underscore the critical importance of accurate kidney function assessment to facilitate early recognition and intervention.

2.2 Measuring Kidney Health and Function

Glomerular filtration rate (GFR) is widely considered the best method in determining the kidney's health and function in both research and clinical settings.¹ This can be assessed either using exogenous or endogenous markers, each offering their own set of benefits and drawbacks.⁴ Measured glomerular filtration rate (mGFR) is considered the gold standard and is preferred when accuracy and precision are needed.⁴ However, mGFR requires administration of an exogenous agent (e.g. iohexol, inulin and iothalamate) which takes time and can be costly on a large scale varying on the agent and procedure.⁴ Estimated glomerular filtration rate (eGFR) addresses the issue of time and cost as it depends on endogenous markers that can be collected during routine blood work.^{1,4} The most commonly used endogenous marker in clinical practice is serum creatinine, a byproduct of muscle metabolism.^{4,10} However, a drawback of using these markers is that age, sex, muscle mass, diet, and other factors impact the availability, factors which exogenous markers are specifically chosen to avoid.^{4,10} eGFR attempts to resolve this through mathematical prediction models derived from population data designed to closely correlate with mGFRs.^{1,10}

2.3 History of creatinine-based kidney function tests

Multiple eGFR equations have been developed over the years; however, serum creatinine (SCr) based equations are more utilised given that it is inexpensive, widely standardised, and routinely measured.^{1,10} The first widely utilised equation to measure kidney function was the Cockcroft-

Gault in 1976 which estimated creatinine clearance from age, sex, and body weight;²⁶ however, creatinine clearance overestimates true GFR because creatinine is not only filtered by the glomerulus but also secreted by the renal tubules. The Modification of Diet in Renal Disease (MDRD), published in 1999, was the first widespread equation that estimated GFR using SCr.²⁷ It introduced a race coefficient and utilised a more diverse demographic cohort;²⁷ however, it only included patients with CKD, resulting in underestimated eGFRs for healthier individuals.²⁸ The 2009 Chronic Kidney Disease Epidemiology Collaboration (CK09) equation was developed improving on these limitations with a larger sample and increased accuracy in healthier individuals, and, until recently, was the longstanding global standard.^{1,28,29} However, an issue which remained from both the MDRD and the CK09 was the race coefficient; race is a social construct rather than a biological one, and its inclusion in clinical tools brings up questions about equitability.^{10,30} In 2021, two new equations were developed, the 2021 Chronic Kidney Disease Epidemiology Collaboration CK21 and the European Kidney Function Consortium Equation (EKFC), both of which were race-free equations.^{10,17} CK21 remained largely the same as its predecessor CK09 being refitted without race,¹⁰ making it easier for laboratories to transition over. EKFC took a new approach by normalising SCr to age- and sex-specific medians, producing a race-free equation that also spans a wider age range (≥ 2 in EKFC vs ≥ 18 in CK21).¹⁷ These new equations are being adopted globally, with the latest publication of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, a leading international body on CKD, recommending both CK21 and EKFC for creatinine only GFR estimating equations alongside CK09, and other equations modified for their region;¹ a contrast with their 2012 guideline where only CK09 was recommended.²⁹

2.4 Kidney Failure Risk Equation

The Kidney Failure Risk Equation (KFRE) is a tool by Tangri et al developed in 2011 as a way for predicting future risk of kidney failure in CKD patients.³ It is currently validated in over 1 million individuals across 60 cohorts,⁹ with it garnering international support from organisations such as KDIGO,¹ and its current use globally. The equation has 2 main time horizons that it predicts at 2- and 5-years, with there being a 4- and 8-variable format.³ Age, sex, eGFR, and urine ACR are included in the 4-variable model, with serum bicarbonate, albumin, phosphorus and calcium included in an 8-variable model.³ Currently, both the 2009 and 2021 CKD-EPI equations have been validated as an eGFR input in the KFRE equation,^{31,32} with the KFRE initially developed and derived using the 2009 CKD-EPI equation,³ and the updated 2021 equation being for validated usage afterwards.³² However, there are currently no studies validating the usage of EKFC in the KFRE at this time, with no comparison studies existing to determine whether EKFC offers any benefit as an eGFR input.

2.5 Clinical Endpoints of Kidney Failure

2.5.1 Major Adverse Kidney Events

Major adverse kidney events (MAKE) is a composite kidney outcome that is used to capture the full spectrum of clinically meaningful kidney deterioration in clinical trials. While no universal consensus definition exists across the literature,³³ the International Society of Nephrology provided guidance on the topic during a meeting to formulate an international consensus regarding a composite outcome for clinical trials.³⁴ During the meeting, they defined MAKE as the composite of kidney transplantation, start of maintenance dialysis, and death from kidney failure, and also included outcomes based on eGFR alone including a sustained eGFR below 15 mL/min/1.73m², and a percent decline in eGFR (varies depending on context).³⁴ In the present

study, MAKE was defined as initiation of dialysis or transplantation, $\text{eGFR} < 15 \text{ mL/min/1.73m}^2$, or a sustained $\geq 30\%$ decline in eGFR from baseline.

A potential issue of eGFR-dependent MAKE components is that the equation used at baseline and follow-up directly determines which participants meet the criteria. This is concerning for studies comparing eGFR equations, as the structural properties of the equations could be attributed to outcome detection rather than true differences in prognostic performance between equations. Using hard clinical endpoints such as kidney replacement therapy (KRT) is therefore important in this context as they are objective and can corroborate findings for MAKE. KRT, defined as the initiation of maintenance dialysis or kidney transplantation,³⁴ has traditionally served as a clinical endpoint in nephrology studies. Unlike eGFR-based components of MAKE, it has no equation dependent criteria allowing it to help corroborate findings for MAKE.

2.5.2 Major Adverse Cardiovascular Outcomes

Individuals with CKD also carry increased risk of developing major cardiovascular events, with risk increasing as eGFR declines.³⁵ Most individuals with CKD either develop a disability or die from cardiovascular disease prior to progressing to kidney failure, making an eGFR equation's ability to stratify cardiovascular disease risk important.³⁶ Major adverse cardiovascular events (MACE) is a composite cardiac outcome that was developed to standardise cardiovascular outcomes across clinical trials.³⁷ Developed by the Standardised Data Collection for Cardiovascular Trials Initiative and the US Food and Drug Administration, MACE is defined as the first occurrence of acute coronary syndrome, ischemic stroke, or cardiovascular death, with MACE+ extending this definition to incorporate hospitalisation for heart failure.³⁷ In the present study, MACE/MACE+ is consistent with this definition using validated ICD-10 diagnostic

codes, with validation studies supporting the accuracy of these codes in administrative and electronic health record databases.^{38–43}

2.6 Diagnostic Accuracy to Prognostic Utility

Historically, the statistical accuracy of the relation of mGFR to eGFR has been the primary method of ascertaining an equation's clinical utility. This paradigm led to the development of the major eGFR equations including older equations such as MDRD and CK09,^{27,28} as well as newer equations such as CK21 and EKFC.^{10,17} While different methods were used in the development of these equations, mGFR served as the reference standard to develop and validate these equations. However, treating mGFR accuracy as the focal point of eGFR equations does not encapsulate its use case in the clinical setting, with values being used to help with prognostication, determine treatment eligibility, and estimate the likelihood of kidney failure among other outcomes.^{1,15,16} Consequently, this demonstrates the importance of eGFR's association to patient outcomes over its association with accurate mGFR estimates. In this context, an eGFR equation that demonstrates strong prognostic accuracy would therefore justify its use at a population level.

2.7 Current Literature on Recent Equations

There are a growing number of studies comparing the prognostic utility between equations, but currently the literature comparing EKFC against CKD-EPI equations remains limited. Current studies conducted in European populations have consistently demonstrated that EKFC adoption produces systematically lower eGFR values and higher CKD prevalence compared to CKD-EPI equations.^{5,6} Russel et al., in a cohort of 1.7 million Stockholm adults, reported a median eGFR reduction of 4.9 mL/min/1.73m² and a 38% relative increase in CKD G3–G5 prevalence,⁵ while Veltkamp et al. similarly observed a mean reduction of 6.3 mL/min/1.73m² and a 29% relative

increase in CKD prevalence in a Dutch cohort.⁶ Both studies found that reclassified individuals presented with more events, but this did not translate to higher risk as the hazard ratios did not reflect higher risk.^{5,6} Regarding prognostic performance, studies have largely looked at metrics regarding discrimination and reclassification. Emrich et al. found no improvement in cardiovascular risk prediction across CK09, CK21, and EKFC in a high-cardiovascular-risk cohort.²¹ Russel et al. reported that EKFC reclassification improved net reclassification for mortality and cardiovascular outcomes but was negative for kidney replacement therapy.⁵ Consistent with this, Veltkamp et al. found that EKFC reclassified predominantly older individuals to worse eGFR categories relative to CK09, and provided equal-to-improved risk stratification for all-cause mortality and acute kidney injury, though reclassification for kidney failure with replacement therapy was less consistent.⁶

2.8 Conclusion

Current evidence shows that EKFC shifts CKD prevalence but does not meaningfully improve prediction of outcome risk, with discrimination remaining the same across equations. Important methodological gaps remain, however. Prior analyses report only relative measures such as hazard ratios and reclassification indices; none model the cumulative incidence function directly to estimate and assess the accuracy of a patient's absolute outcome risk. Calibration has also not been formally assessed, a clinically relevant metric that provides insight as to whether predicted probabilities match reality. Furthermore, current studies are limited to two European populations or focus on a cardiovascular high-risk cohort, with no general North American population assessed.

CHAPTER 3: GFR ESTIMATING EQUATIONS AND THEIR ASSOCIATION WITH ADVERSE CLINICAL OUTCOMES: A POPULATION-BASED RETROSPECTIVE COHORT STUDY

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3.1 Abstract

Objectives

To compare the association and ability to predict clinical outcomes of the Chronic Kidney Disease Epidemiology Collaboration 2021 (CK21) and the European Kidney Function Consortium (EKFC) estimating equations for kidney and cardiac outcomes.

Design

Population-based retrospective cohort study.

Setting

Linked ICES healthcare administrative datasets in Ontario, Canada.

Participants

Adult Ontario residents (≥ 18) with two outpatient eGFR measurements (90 to 730 days apart).
(n=5,507,066)

Main Outcomes Measures

Fine-Gray subdistribution hazard ratios for composite kidney outcome (MAKE) and composite cardiac outcomes (MACE/MACE+) by EKFC and CK21, alongside metrics for discrimination (C-statistics/AUC), calibration (observed-to-expected ratios, and calibration plots), overall prediction accuracy (Brier scores), clinical utility (decision curve analysis), and reclassification table with hazard ratio analysis.

Results

From October 1, 2007, to December 31, 2021, among 5,507,066 adults [mean age 52.20 (SD ± 17.16); males 43.9%], the mean eGFR differed by 8.9 mL/min/1.73m² based on eGFR equation used (CK21 95.76 SD 19.49; EKFC 86.86 SD 18.87) with an increase in CKD (eGFR < 60) of 83% (506,838 / 276,588) using EKFC. MAKE occurred in 27.5% of patients defined with CK21

and 28.8% in EKFC, with combined MACE and MACE+ occurring in 15.2% of the cohort. Both equations demonstrated equivalent discrimination for MAKE and MACE outcomes at the 2- and 5-year timepoints. Calibration slopes exceeded 1.0 for both equations, with EKFC demonstrating slightly better calibration overall, but results varied by stratified analyses. Decision curve analyses (DCA) demonstrated a mild improvement in clinical utility for the CK21 equation at the 2-year threshold for MAKE, and no differences for MAKE at 5-year and MACE. EKFC reclassified 24% of participants to a more severe CKD stage with reclassified individuals showing a higher risk in all categories for MAKE and MACE.

Conclusions

Adoption of the EKFC would categorise more individuals with CKD and reclassify select individuals at higher risk with no substantive improvements in overall predictive performance for kidney and cardiac outcomes.

3.2 Introduction

The glomerular filtration rate (GFR) is the standard measure of kidney function, but measuring it directly is expensive and time-consuming.⁴ Estimating equations (eGFR), which combine serum creatinine with variables such as age and sex, offer a practical alternative and are widely used to assess kidney function, guide treatment, and inform prognosis. Beyond estimating GFR, these equations are strong predictors of kidney and cardiovascular outcomes.⁴⁴ In North America, the most frequently applied equation is the race-free CK21 equation as recommended by major Nephrology societies and guidelines.^{1,45,46} The European Kidney Function Consortium equation (EKFC) was developed in 2021 to be utilised across the age spectrum by rescaling serum creatinine to an age- and sex-specific median normal value (the Q-value), showing improved calibration in European populations.¹⁷ It is endorsed by the European Federation of Clinical Chemistry and Laboratory Medicine and is being considered for widespread adoption in Europe.⁴⁷ However, the implications of transitioning to the EKFC from CK21 in terms of CKD classification and prediction of kidney and cardiovascular clinical events in a North American population remain less clear. This study seeks to address this gap by assessing whether the two equations differ in their ability to predict clinically relevant kidney and cardiovascular endpoints.

3.3 Methods

3.3.1 Study Design and Setting

We conducted a retrospective cohort study in Ontario using deidentified, linked health administrative databases housed at the Institute for Clinical Evaluative Sciences. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. The use of the data in this project is authorised

under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board. Data was obtained from October 2002 to December 2023, accounting for the accrual window (October 2007 – December 2021), 5 years lookback window and a 2-year follow-up period. The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

3.3.2 Data Sources

All data used for baseline variables (sociodemographic, comorbidities, and healthcare utilisation), outcome development (kidney and cardiac composite), and lab measures [serum creatinine (SCr) and albumin-to-creatinine ratio (ACR)] were sourced from six ICES databases using unique, ICES-generated encoded identifiers for each patient to link the datasets together. These datasets were linked using unique encoded identifiers and analyzed at ICES. The Ontario Laboratory Information System (OLIS) was used to source outpatient SCr and ACR values at baseline with outpatient SCr during follow-up. Discharge Abstract Database (CIHI-DAD) was used to identify outcomes and comorbidities using International Classification of Diseases-10 (ICD-10) codes from hospital admissions in Ontario, with National Ambulatory Care Reporting System (NACRS) being used for similar purposes but for ambulatory care centre visits in Ontario. The Ontario Health Insurance Plan (OHIP) database was used to identify primary care,

emergency, and specialist visits through physician service claims; the Canadian Organ Replacement Registry (CORR) was used to identify patients undergoing renal replacement therapy (hemodialysis, and kidney transplant); lastly, the Ontario Registered Persons Database (RPDB) was used for demographic and vital statistics. Sensitivity, specificity and positive predictive values of ICD-10 codes used for defining primary outcomes are presented in **Appendix A**.

3.3.3 Study Cohort

We included Ontario adults aged 18 and greater with 2 outpatient SCr measurements (90 to 730 days apart) within the accrual period (October 1, 2007 to December 31, 2021) with an additional 2-year follow-up period (December 31, 2023); comorbidities were also collected with a 5-year lookback window. Follow-up started from index date, defined as the date of the second SCr measurement, until the participants met the following: outcome met, death, emigration, or end of study on December 31, 2023. Participants were excluded based on the following criteria as seen in **Figure 1**: missing identification data, <2 eGFR measurements or unidentifiable values, non-Ontario resident, death prior to index date, short follow-up (<90 days), patients who met the outcomes prior to index, pregnant within 10 months of index (pregnancy can increase eGFR by ~50%),⁴⁸ and <18 years of age at index (CK21 has been validated for those ≥ 18).¹⁰

3.3.4 Index Kidney Function Measurement

Baseline eGFR measurements were calculated as the mean from two index outpatient SCr measurements ($\mu\text{mol/L}$) between 90 to 730 days apart using both the CK21 and the EKFC equations. Index eGFR values were then placed in 5 eGFR categories as outlined in KDIGO 2024 Clinical Practice Guidelines for Chronic Kidney Disease.

3.3.5 Outcomes

Our main outcomes of interest were i) Major Adverse Kidney Event (MAKE) for our composite kidney endpoint, defined as the first occurrence of any of the following: initiation of chronic dialysis, kidney transplantation, a decline in eGFR of greater than 30% from baseline, or reaching an eGFR below 15 mL/min/1.73m²,³⁴ and ii) Major Adverse Cardiovascular Event (MACE) as our composite cardiac endpoint,³⁷ defined using validated ICD-10 codes, consists of the first occurrence of acute coronary syndrome,⁴⁰ ischemic stroke,⁴¹ or cardiovascular death,³⁹ as well as MACE+, defined as hospitalisation for heart failure.^{42,43} Our secondary outcomes of interest are i) kidney replacement therapy (KRT),³⁴ defined as the initiation of chronic dialysis and kidney transplantation; and ii) overall mortality.

MAKE outcomes that relied on eGFR were calculated by their own equation, CK21 or EKFC.

Cardiovascular death was defined as death within 1 week of a cardiovascular hospitalisation.

When possible, validated coding algorithms were employed with reported accuracy indicators.

3.3.6 Covariates

All models included the following covariates: eGFR category, age, sex, income quintile, rural living status (derived using postal codes by ICES), hypertension,⁴⁹ diabetes,^{50,51} past cardiovascular disease, obesity,⁵² alcohol use, hypercholesterolemia, hyperkalemia,⁵³ cancer, chronic liver disease,⁵⁴ chronic lung disease,⁵⁵ emergency room count, primary care count, and specialist care count.

3.3.7 Missing Data

A complete case analysis was conducted for this study. Of the initial 5,523,194 participants that met the inclusion and exclusion criteria, 16,128 (0.29%) had missing data resulting in cohort of 5,507,066. The variables that contained the missing data were income quintile (16,128) and rural

status (4,268). Given the marginal number of missing data, these participants were excluded from the analysis.

3.3.8 Statistical Analysis

Baseline characteristics of the total study cohort were summarised in **Table 1** using means and standard deviations for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and frequencies and percentages for categorical variables.

To assess whether the overall association between the eGFR categories and outcomes differs based on equation, we utilised an equation-stacking approach for effect modification testing. Each participant provided two observations with their corresponding eGFR categories (one per row; either CK21 or EKFC). An adjusted Fine-Gray model was then run to test for effect modification in all equation x eGFR category interaction terms with individuals in the G1 category serving as the reference population for each model.⁵⁶ For both outcomes, death was considered a competing risk; however, in the cardiac models, cardiovascular related deaths were removed as it is an outcome for MACE.

Afterwards, adjusted Fine-Gray subdistribution hazard regression models were fitted to obtain hazard ratios (HR) and 95% confidence intervals (CIs) for each equation, with eGFR category being the primary exposure. The eGFR category of G1 (≥ 90) was set as the reference group for all models in the primary analysis. For MAKE models, all-cause death was set as the competing risk variable with MACE including non-cardiovascular deaths only. Follow-up time was calculated from the index date to the earliest outcome, competing risk event, study end date, or loss to follow-up.

Patient-level cumulative incidence function (CIF) estimates were generated at the 2- and 5-year timepoints from the Fine-Gray model. These predicted CIFs were then used to assess model calibration, discrimination, overall accuracy, and clinical utility at both timepoints.

Discrimination was assessed using time-dependent AUC,⁵⁷ which measures how well the model assigns higher predicted risks to those who experienced the event than to those who did not.

Overall predictive accuracy was calculated via Brier scores, the mean squared difference between predicted risks and observed outcomes.^{58,59} Both discrimination and Brier scores were calculated using a marginal KM-based Inverse Probability of Censoring Weighting (IPCW) approach. Calibration was then assessed using calibration plots and slope capturing the agreement between predicted and observed risk. Decision curve analysis (DCA) was used to quantify clinical utility, with censored individuals treated as non-events. Kaplan-Meier curves and Schoenfeld residuals were used to assess the assumption of proportional hazards on cause-specific models as an approximation in index eGFR categories and covariates for all models. Reclassification was also assessed by cross-tabulating eGFR with CK21 and EKFC. Fine-Gray models on CK21 strata G1, G2, G3a, and G3b were then run comparing the hazard between those reclassified down by EKFC to those that were not. To ensure that outcomes were not frontloaded due to equation differences or impacted by boundary bias, cumulative incidence curves were plotted for concordant versus discordant to visually assess the separation of the curves.

All statistical analyses were performed using SAS Enterprise Guide version 8.3.7.202 (SAS Institute Inc., Cary, NC) and RStudio: Integrated Development for R version 1.1.456 (RStudio, Inc., Boston, MA). All models and interaction tests were run in SAS with hazard ratios and CIF

estimates being calculated. The remainder of the statistical analyses were then conducted in R. Packages used included riskRegression,⁶⁰ survival,⁶¹ cmprsk,⁶² rmda,⁶³ and prodlm.⁶⁴

3.3.9 Additional Analysis

Fine-Gray models were repeated using kidney replacement therapy (KRT) alone and all-cause mortality as equation-independent outcomes to assess whether associations were driven by equation-dependent (eGFR decline and eGFR < 15) MAKE components. All primary analyses were also reconducted with age and sex removed for the MAKE outcome to determine whether adjusting for age- and sex-specific functions within each eGFR equation influenced model performance. Prespecified stratified analyses were also conducted on age, sex, and ACR categories for main outcomes. DCA was repeated after excluding death.

3.4 Results

3.4.1 Baseline Characteristics

In **Figure 1**, 6,236,402 Ontario residents met the inclusion criteria of 2 eGFR values 90 to 730 days apart and 5,507,066 participants remained after exclusion, with 702,859 (12.8%) having an ACR value. The mean (SD) age of the cohort was 52.2 years (17.2, see **Table 1**), with a median [IQR] follow-up time of 10 years [6–13] for both CK21 and EKFC. Baseline eGFR mean (SD) for EKFC was 86.9 mL/min/1.73m² (18.9) and CK21 was 95.8 mL/min/1.73m² (19.5), with a median [IQR] of 12 (6-23) SCr measures. Overall, EKFC assigned more participants lower eGFR values compared to CK21 as seen in **Figure 2**, increasing the CKD (eGFR <60) population by 83% (CK21: 276,588 vs EKFC: 506,838), with similar increases at progressively lower eGFR thresholds: eGFR <45 by 78.3% (CK21: 87,925 vs EKFC: 156,746) and eGFR <30 by 68.1% (CK21: 18,021 vs EKFC: 30,298). Overall, there was a higher event count under

EKFC for MAKE outcomes (CK21: 1,515,233 vs EKFC: 1,584,836). With MACE, the event count was 835,915 (15.2%).

3.4.2 Hazard Ratios

A stepwise higher HR for MAKE was observed with lower eGFR for both equations, with the overall CK21 model having 1,515,233 (27.5%) MAKE outcomes and 387,423 (7.0%) deaths, and the overall EKFC model having 1,584,836 (28.8%) outcomes and 381,974 (6.9%) deaths (**Table 2, Figure 3**). In the overall model, CK21 produced higher hazard ratios than EKFC from G3a and below. This CK21–EKFC difference was further modified by age, sex, and ACR (all interaction $p < 0.0001$), motivating the stratified analyses. In age-stratified models, the HRs from EKFC and CK21 were divergent at the youngest age group, with HRs converging in the older age groups. In sex-stratified models, EKFC had similar risk at G2 compared to CK21, with CK21 demonstrating higher risk across the eGFR categories G3a onwards. In ACR-stratified models, both models demonstrated a graded increase in MAKE risk, with EKFC producing higher HRs than CK21 in A2 and A3, with HR in A1 being similar between the two.

Both models had 835,915 (15.2%) MACE outcomes with 428,169 (7.8%) deaths (**Table 2, Figure 4**). Age-stratified models displayed a similar trend in relative risk, however, EKFC consistently identified those aged 40-65 with a higher hazard compared to all other age categories, with CK21 only doing so for those in category G4. In sex-stratified models, the EKFC notably had a higher HR for females compared to CK21, with lower HR for males for most eGFR categories. ACR-stratified models showed higher HRs in Categories A2/A3 with EKFC.

In the overall mortality model, there were 821,126 events. EKFC had a HR less than 1 for categories G2 and G3a, with CK21 being slightly below 1 for only G2. For KRT models, there

were 27,667 (0.50%) events with 806,334 (14.64%) deaths. HRs presented a similar graded increase, but the differences between levels were much larger, with there being minimal incidence of KRT in higher eGFR strata. In the models without age and sex, HRs were more elevated with EKFC showing consistently higher HR compared to CK21.

See **Appendix B-D** for HR tables and figure on strata, and **Appendix E** for KRT, overall mortality, and no age/sex models.

3.4.3 Discrimination

The overall models demonstrated similar discrimination for MAKE outcomes [c-statistic 0.75 for both models at the 2-year mark; 0.73 and 0.74 for CK21 and EKFC at 5 years]. Discrimination was similar between the two equations across age, sex and ACR strata (**Appendix F**). For MACE, discrimination was higher overall, with the c-statistic being 0.82 for both models at the 2-year mark and 0.81 at 5 years and no substantive difference across strata. For overall mortality, KRT and no age/sex models, the c-statistic was nearly identical at both the 2- and 5-year mark.

3.4.4 Calibration

Calibration slopes exceeded 1.0 across all subgroups and both equations for MAKE, with slopes improving at the 5-year timepoint compared to the 2-year timepoint. EKFC produced calibration slopes closer to the ideal value of 1.0 than CK21 at both timepoints (2-year: CK21 1.52 vs EKFC 1.44; 5-year: CK21 1.35 vs EKFC 1.31). Visual inspection of calibration plots shows that both equations have some underprediction at higher risk deciles, with CK21 underpredicting more than EKFC (**Figure 5**).

In age-stratified groups, despite better overall calibration, EKFC performed worse in calibration slopes in 2 of the 4 age groups (66 to <80, and ≥ 80), performing equally in the 40 to ≤ 65 , and better in the youngest age group 18 to <40. In sex-stratified groups, calibration slopes were better

in males compared to females at both timepoints. EKFC had better calibrated slope values closer to 1, with calibration plots visually demonstrating smaller observed-vs-predicted gaps at both ends of the risk distribution. In ACR-stratified groups at 2 years, EKFC showed modest improvements in slope for ACR category 1 (CK21: 1.32 vs EKFC: 1.28), and CK21 had at ACR 3 (CK21: 1.49 vs EKFC: 1.52), with ACR 2 showing minimal change. At the 5-year time horizon, slopes were near identical.

For MACE, calibration slopes also slightly exceeded 1.0 across all subgroups, again improving at the 5-year timepoint (**Figure 6**). The two equations were nearly identical (change of slope <0.01) in terms of calibration slope with overlapping calibration plots. Findings were consistent in age- sex- and ACR stratified models, with marginal differences in slope at both timepoints.

For overall mortality, the calibration slope was 0.93 for CK21 and 0.92 for EKFC at the 2-year mark, and 1.02 and 1.01 at 5 years. For KRT, the calibration slope was 1.67 for CK21 and 1.64 for EKFC at the 2-year mark, and 1.43 and 1.41 at 5 years. For no age/sex models, the calibration slope was 1.90 for CK21 and 1.81 for EKFC at the 2-year mark, and 1.51 and 1.48 at 5 years. Calibration plots were near identical.

All plots are presented in **Appendix G & H**, with model metrics in **Appendix F**.

3.4.5 Overall Accuracy

Brier scores for MAKE were all marginally better for EKFC compared to CK21 across all models, with differences between scores ranging between <0.001 and 0.009 (**Appendix F**). This was consistent in age, sex, and ACR stratified models. For MACE, no substantive differences in Brier scores were noted. For overall mortality, the Brier score was 0.02 at the 2-year timepoint and 0.04 at 5 years for both equations. For KRT and no age/sex models, the Brier score was <0.01 at both timepoints for both equations.

3.4.6 Reclassification

EKFC reclassified 24% of participants to a different eGFR category, with nearly all reclassification by EKFC being to a lower eGFR category (**Table 3**). Reclassified individuals were 13 years older compared to those who remained in the same category (mean age 62.1 (SD 15.7) vs 49.1 (SD 16.4)). Death rates were increased, however, when stratified for age, death rates became similar between reclassified and non-reclassified groups. For MAKE, reclassified individuals had almost 1.5 times the proportion of events (concordant: 24.8% vs discordant: 36.1%; **Table 4a**). Fine-Gray models comparing reclassified to non-reclassified found a slight increase in MAKE risk across all eGFR categories for those reclassified downwards. For MACE, the pattern was similar, with reclassified individuals having near 1.5 times the proportion of events (concordant: 12.8% vs discordant: 22.8%; **Table 4b**). There was also a modest increase in MACE risk in most categories, except G1 where those reclassified downwards received lower risk. The same went for overall mortality, but with 2 times the proportion of outcomes for reclassified individuals, with similar increase in risk in all categories except G1, where risk was lower in those reclassified downward (**Table E4**). For KRT, outcomes were similar in proportion between reclassified vs non-reclassified, however, the risk in those moved downwards did show a substantial increase in risk in G2 [2.800 (2.622–2.990)], G3a [1.685 (1.566–1.814)], and G3b [1.394 (1.263–1.539)] categories (**Table E5**). When age and sex were removed from the MAKE models, the HRs did show an increase in risk for those discordantly classified in few categories (**Table E6**).

Cumulative incidence curves were also assessed between concordant and discordant groups. Individuals who were reclassified had a higher incidence of events for the MACE and overall mortality outcomes.

3.4.7 Decision Curve Analysis

For MAKE, across majority of models, the DCA demonstrated benefits over flagging all or flagging none of the patients, with the finding holding when deaths were excluded. Only in the ≥ 80 age group and ACR A3 category at 2 years did treating all patients provide benefit equal to either equation. The overall model shows a small net benefit from utilising the CK21 equation at the 2-year mark at lower risk thresholds, with the 5-year DCA looking identical (**Figure 7**). In sex-stratified DCA, findings were the same as the overall DCA. Across all age categories, the DCAs were identical between equations apart from the 66 to <80 and ≥ 80 age groups. At both the 2- and 5-year DCAs for the 66 to <80 age group, CK21 showed greater net benefits compared to EKFC, with the 2-year DCA showing a more pronounced separation; the same was for the ≥ 80 age group, but to a lesser extent. In ACR models, CK21 shows a slight benefit compared to EKFC in normal and moderate albuminuria levels, with severe levels showing equivalence.

For MACE, across all models including stratified models, both equations displayed no separation in their DCA curves (**Figure 8**). Both equations demonstrated benefits compared to flagging all or flagging none of the patients; this finding held when deaths were excluded. However, clinical utility was limited in age group 18–39 where the equations offered marginal benefits over flagging none, and ≥ 80 where both equations tracked closely the flagging-all line.

For overall mortality, results were similar to MACE with no differences in clinical utility, even after excluding for deaths. For KRT, at 2-years there was equivalent clinical utility, with CK21 performing better at 5-years at lower risk thresholds. All DCA plots are in **Appendix I**.

3.5 Discussion

3.5.1 Population-Level Impact of EKFC Adoption on eGFR and CKD Prevalence

In a large, population-based comparison of the EKFC and CK21, adopting the EKFC in a North American population would decrease the mean eGFR by 8.9 mL/min/1.73m² and increase the CKD (eGFR <60 mL/min/1.73m²) population by over 80%, while providing comparable prognostication for kidney and cardiovascular events. This was largely consistent across sex, age groups, and ACR categories. The EKFC would reclassify a select number of individuals who are at higher risk of adverse events but would not improve overall prediction of adverse clinical events.

Adoption of the EKFC would also significantly increase CKD prevalence. In a study conducted by Russel et al. on 1.7 million Stockholm adults, they reported a median eGFR reduction of 4.9 mL/min/1.73m² with CKD G3–G5 prevalence rising from 4.5% to 6.2% (a 38% relative increase);⁵ another study by Veltkamp et al. on 285,686 Utrecht adults reported a mean reduction of 6.3 mL/min/1.73m² with a 29% relative increase in CKD prevalence.⁶ Both studies used CK09 as the comparator rather than CK21, which explains their lower magnitude compared to our cohort, as CK21 produces higher eGFR measures in non-Black populations,¹⁰ further separating the eGFR values.

3.5.2 Equivalent Prognostic Performance for Kidney and Cardiovascular Outcomes

We found both equations were similar in predicting MAKE. Russel et al. and Veltkamp et al. examined KRT as an individual endpoint and reported equivalent discrimination between equations, consistent with our findings for both the MAKE composite and KRT outcome.^{5,6} Our analysis extends prior work by modelling absolute outcome risk through Fine-Gray subdistribution models, evaluating discrimination and calibration with censoring-adjusted C-

statistics and Brier scores, and adding decision curve analysis and ACR-stratified models.

Furthermore, with our sensitivity analysis of KRT, we found that CK21 had a modest overall benefit in the DCA at the 5-year timepoint in lower risk thresholds.

For MACE, no major differences between equations were observed across Fine-Gray subdistribution hazard ratios, discrimination, calibration, Brier scores, or DCA, indicating that both equations offer interchangeable population-level prediction of cardiovascular events. Those reclassified downwards did have increased risk but were modest in magnitude. Emrich et al., comparing CK09, CK21, and EKFC in a high-cardiovascular-risk cohort similarly found equivalent discrimination across all three equations, with offsetting NRI changes among event and non-event participants and no improvement in cardiovascular prediction.²¹ Our combined use of Fine-Gray competing-risks models, IPCW-corrected metrics, decision curve analysis, and ACR stratification extends prior work that largely reported discrimination only. It also generalises findings to a general cohort with 5.5 million adults and reinforces the conclusion that equation choice has minimal cardiovascular prognostic consequence at the population level.

3.5.3 Reclassified Individuals Show Higher Risk Dependent on Baseline eGFR Category

Majority of the reclassification by EKFC resulted in lower GFR categories, consistent with prior studies in Europe and in a high cardiac-risk cohort.^{5,6,21} While model metrics indicated that model prediction were equivalent between equations, reclassification revealed that those reclassified were, on aggregate, at a modestly higher risk for both MAKE and MACE, with the same findings in sensitivity outcomes KRT and overall mortality. The reclassified group had twice the proportion of deaths; however, age-stratified analysis showed similar death rates between both groups with an increased mean age of 13 years in reclassified group, indicating that mortality was driven primarily by age. Prior studies attributed the decreased risk observed in

reclassified groups primarily to EKFC's modeling of age-related physiological GFR decline.^{5,6} After adjusting for age and comorbidities, the subdistribution hazard was slightly elevated, suggesting that EKFC's downward reclassification captures higher-risk individuals, with results remaining consistent for overall mortality. KRT, however, showed a larger relative effect than the other outcomes. This was evident in the CIF curves which depicted a progressive separation that continue to widen across the 16 years of follow-up consistent with a biological signal, rather than an early front-loaded separation expected from a mathematical artefact. Furthermore, the reclassification signal was not uniform across the eGFR distribution as reclassified individuals with higher kidney function (G1-G2) had a higher cumulative incidence of all four outcomes, indicating that EKFC identified genuinely higher-risk individuals. In CKD categories (G3a–G3b), the reclassified group again had higher cumulative incidence of death and MACE, but similar or lower incidence of the kidney-specific outcomes KRT and MAKE. The excess risk in reclassified CKD patients therefore appears to reflect competing mortality and comorbidity burden rather than accelerated kidney progression. This finding provides a mechanism for the outcome-dependent reclassification reported by Russel et al., whose net reclassification improvement improved for mortality and MACE but was negative for kidney failure with replacement therapy.⁵ While our findings suggest that equation structure alone does not fully explain the reclassification pattern, they extend Russel et al.'s interpretation by demonstrating that the direction and clinical meaning of EKFC reclassification depend on where a patient lies on the CK21 eGFR distribution. Overall, although EKFC reclassifies a substantial proportion of patients downward, the associated prognostic signal is modest, location-dependent, and unaccompanied by any gain in clinical utility, which does not provide sufficient justification for adopting EKFC over CK21.

3.5.4 Subgroup Analyses by Age, Sex, and Albuminuria Category

EKFC's step-function age has a more aggressive correction compared to CK21's continuous function, placing more of the younger age category at G1, and fewer ≥ 80 individuals in higher GFR categories compared to CK21. While this did not impact the risk in older age groups as both HRs converged, HRs sharply rose at younger ages with there being greater separation between the two models. This stronger correction for age also resulted in a greater attenuation of EKFC HRs in the overall mortality outcome, where age is a strong confounder, making it difficult to fully ascertain EKFC's prognostic value in age-adjusted models. In sex-stratified models, there were no major differences with MAKE as EKFC provided lower HRs for most eGFR categories. However, with MACE, EKFC produced higher HRs in females, highlighting EKFC's higher weighting for female coefficient in the EKFC's sex-specific Q-values. This was not observed with MAKE as eGFR values from both equations similarly stratify kidney function categories, whereas MACE is a cardiovascular outcome, resulting in equation-specific differences to become more visible. Our study also included ACR stratified analysis, which found steeper HR gradients by EKFC, being more pronounced for MAKE than MACE. In our models where age and sex were removed, we found similar findings to Russel et al comparing models with and without age,⁵ where the strength of the association changed, but predictive performance did not.

3.5.5 Policy Implications for EKFC Adoption

Currently, laboratories in North America have been adopting CK21 creatinine equation, with 65.8% of laboratories in the United States and major laboratories in Canada adopting CK21 over CK09;^{65–67} Switching from CK21 to EKFC would see a decrease in the population's average eGFR if implemented as is, with potentially earlier treatment being made available due to this

shift. At the same time, it would also increase the burden on healthcare resources highlighted by the DCA. Our study indicates that adoption of EKFC would not improve prediction of adverse clinical outcomes compared with CK21; however, EKFC's eGFR categories appear more appropriate for risk stratification of those outcomes, which is an argument for adopting EKFC in Canada. Given the modest gains, the benefits may not justify the cost that would be incurred from such a shift as indicated by our DCA.

3.5.6 Strength and Limitations

A few limitations are present in our study. First, there are issues with misclassification for some comorbidities not being validated (hypercholesterolemia) or reliant on self-report (alcoholism). However, outcomes and key comorbidities were identified using previously validated case definitions, with consistency found across subgroups. Second, due to data unavailability, we were unable to assess variables such as medication use and muscle mass, potentially leading to unmeasured confounding. However, the size of our cohort, the consistency of our results across subgroups, consistency with previous studies, and the comprehensive framework utilised strengthens the results of our study. Third, we ran a complete case analysis removing any missing data. The number of datapoints removed was minuscule compared to our total representing less than 1 percent, which also highlights the completeness of data; furthermore, all missing data was deemed to be missing at random. Fourth, we could not assess cystatin C eGFRs as it was not widely adopted in North America. However, creatinine only equations are the most common eGFR equation worldwide reflecting real-world applications. Fifth, individuals with repeat creatinine testing may be a select group. In Canada, healthcare is publicly funded leading to no cost barriers which would improve generalizability. Sixth, cause of death in large health administrative databases are often inaccurate or untimely making it difficult to assess

cardiovascular deaths in retrospective studies.⁶⁸ However, we used a proxy with any recorded inpatient or emergency visits with ICD codes related to the circulatory system 1 week prior to death being classified as such. Lastly, population-specific Q values were not used in this study with default values being used which may not reflect the creatinine distribution accurately in our study population. However, this method is consistent with prior validation studies internationally,^{5,69–71} and a study that did use North American Q-values found modest impacts on eGFR values.⁷²

3.6 Conclusion

In this large population-based comparison, the EKFC and CK21 equations demonstrated equivalent prediction of kidney and cardiovascular outcomes. Though EKFC's downward reclassification identified individuals at modestly higher risk, these did not translate into improved discrimination. Calibration and decision curve analysis revealed small differences between the equations, but these were insufficient to favour EKFC over CK21. Therefore, adoption of EKFC in a North American population would not improve risk prediction at either the individual or population level, while its systematically lower eGFR values would shift more patients into worse eGFR categories.

Chapter 3: Figures

Figure 1. Patient flowchart diagram

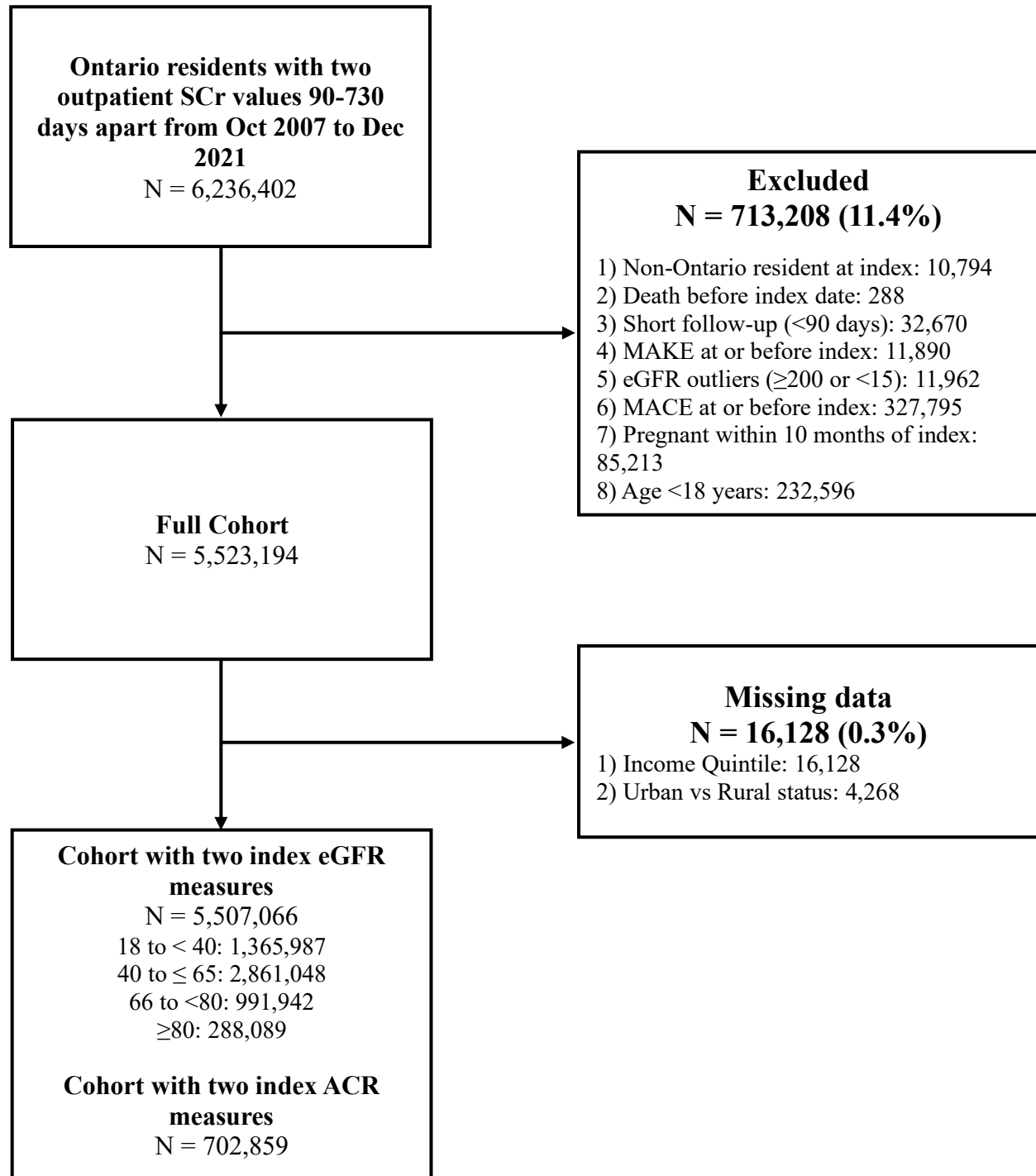


Figure 2. eGFR Category Distribution Across Age Groups

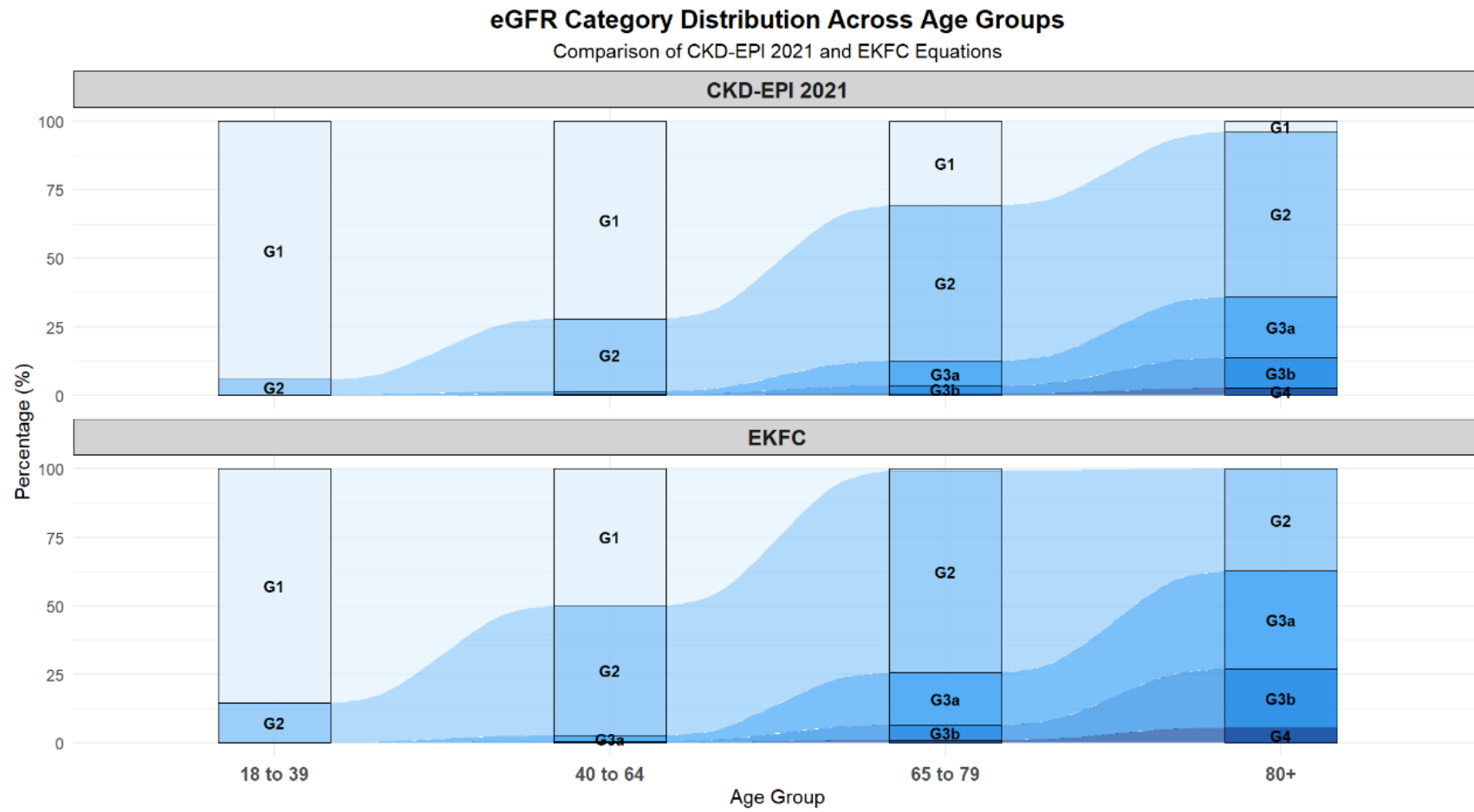


Figure 3. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk

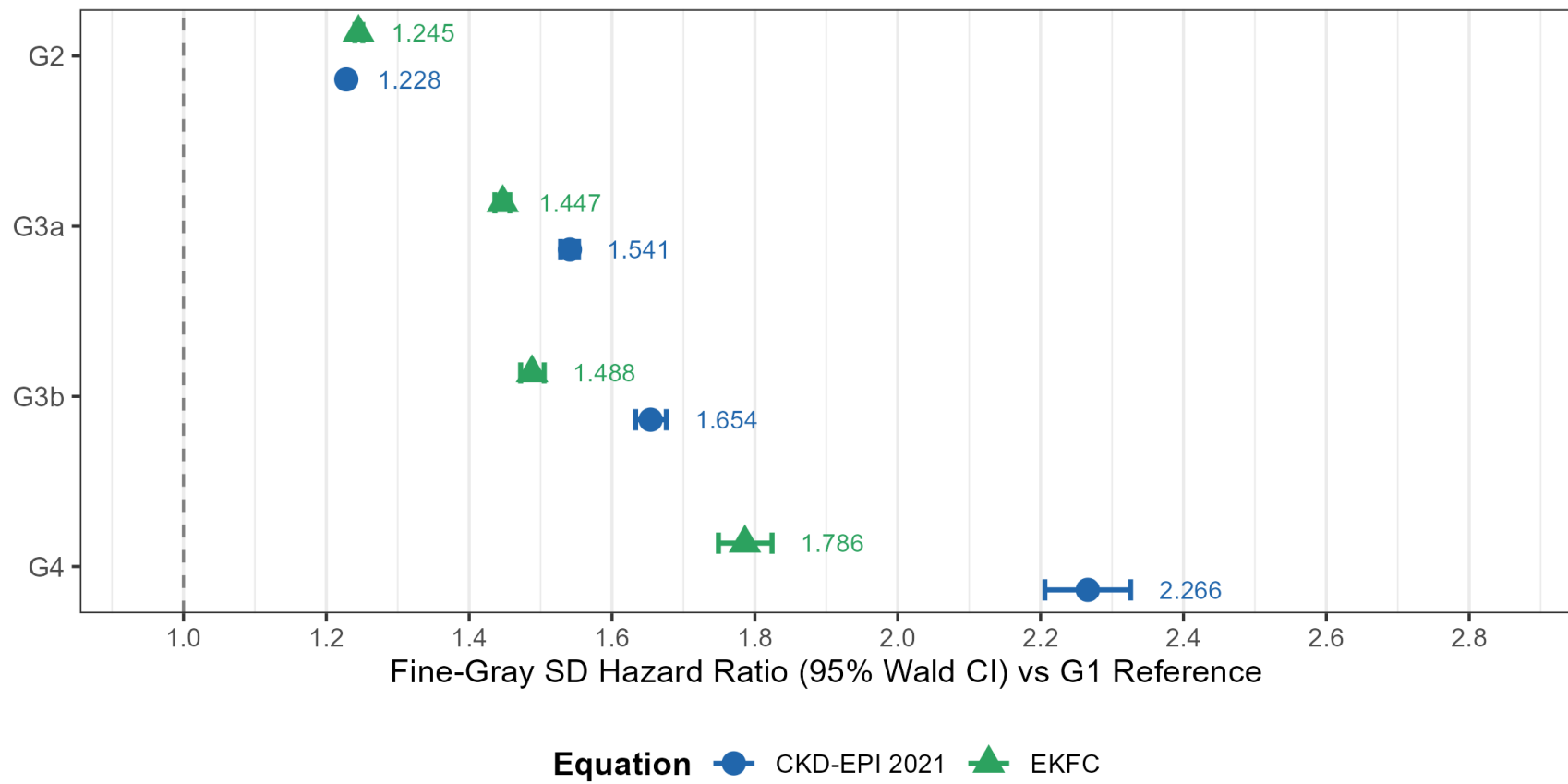


Figure 4. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk

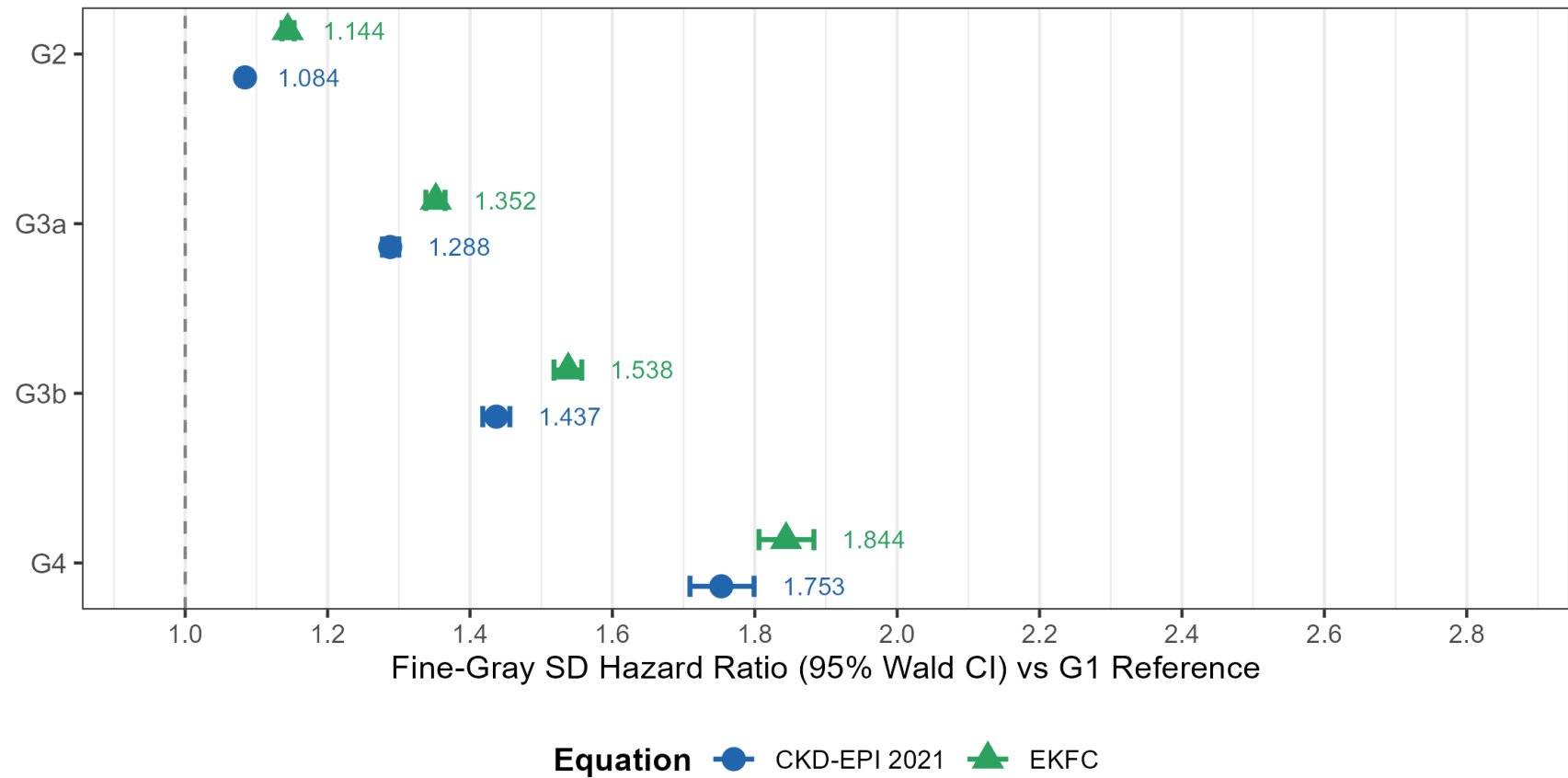


Figure 5. Calibration scatter plot: observed versus predicted MAKE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

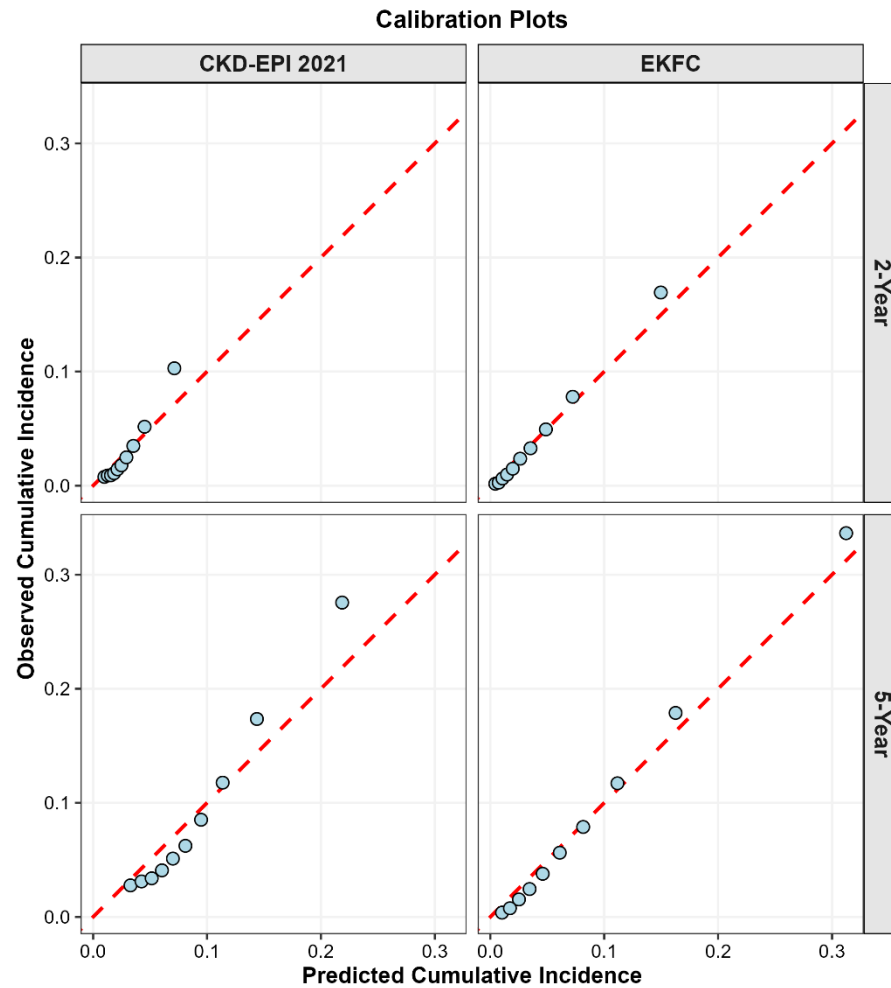


Figure 6. Calibration scatter plot: observed versus predicted MACE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

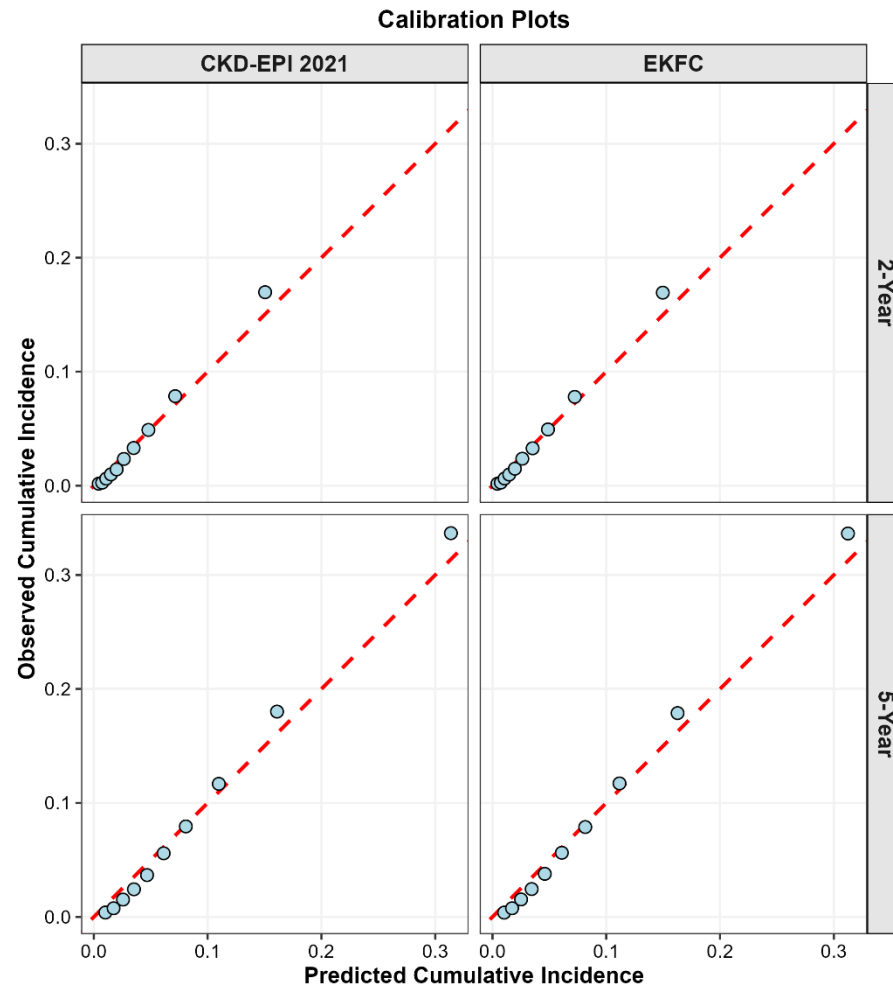


Figure 7. Decision Curve Analysis for MAKE using CKD-EPI 2021 and EKFC eGFR values for the overall cohort.

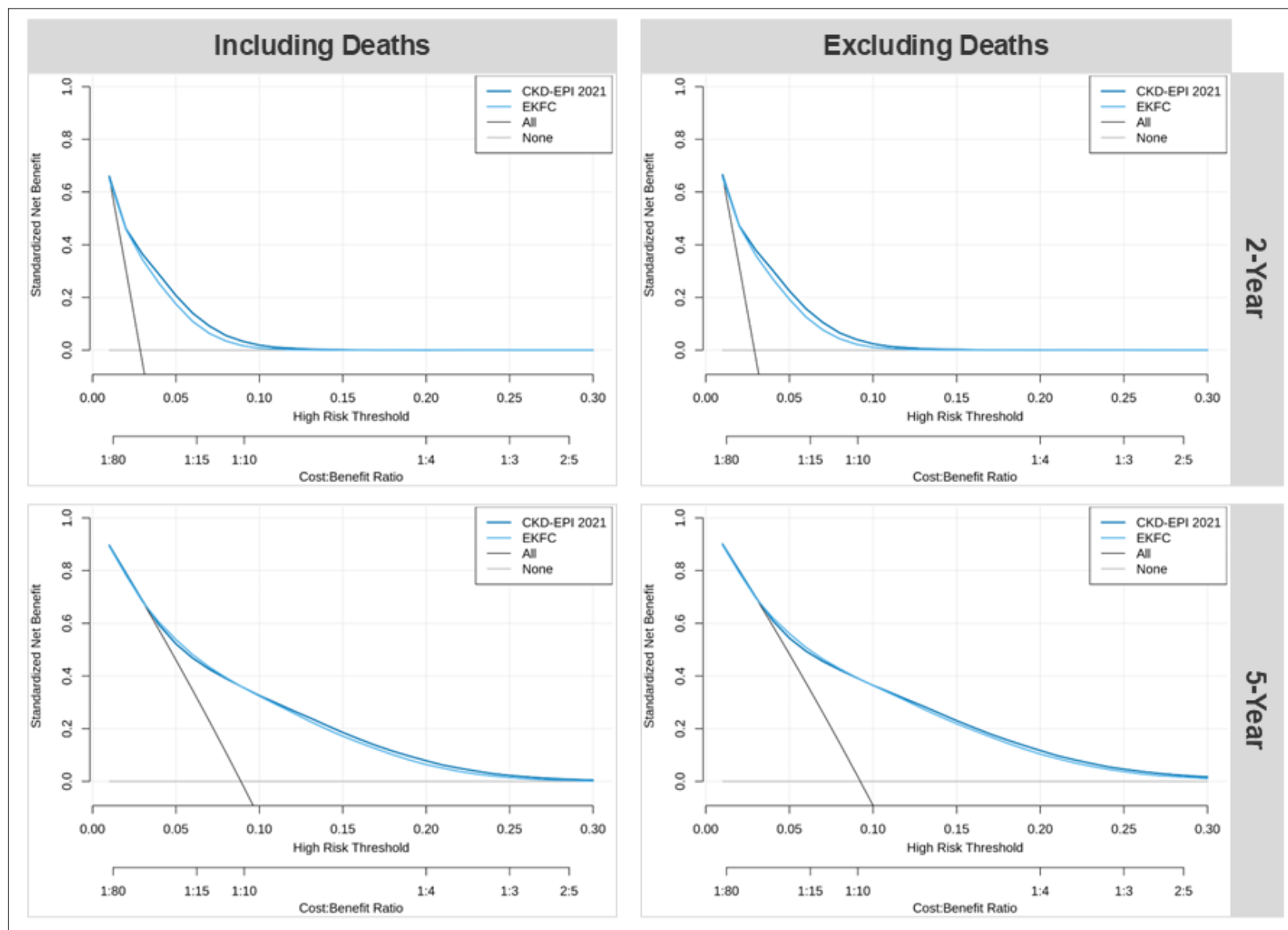
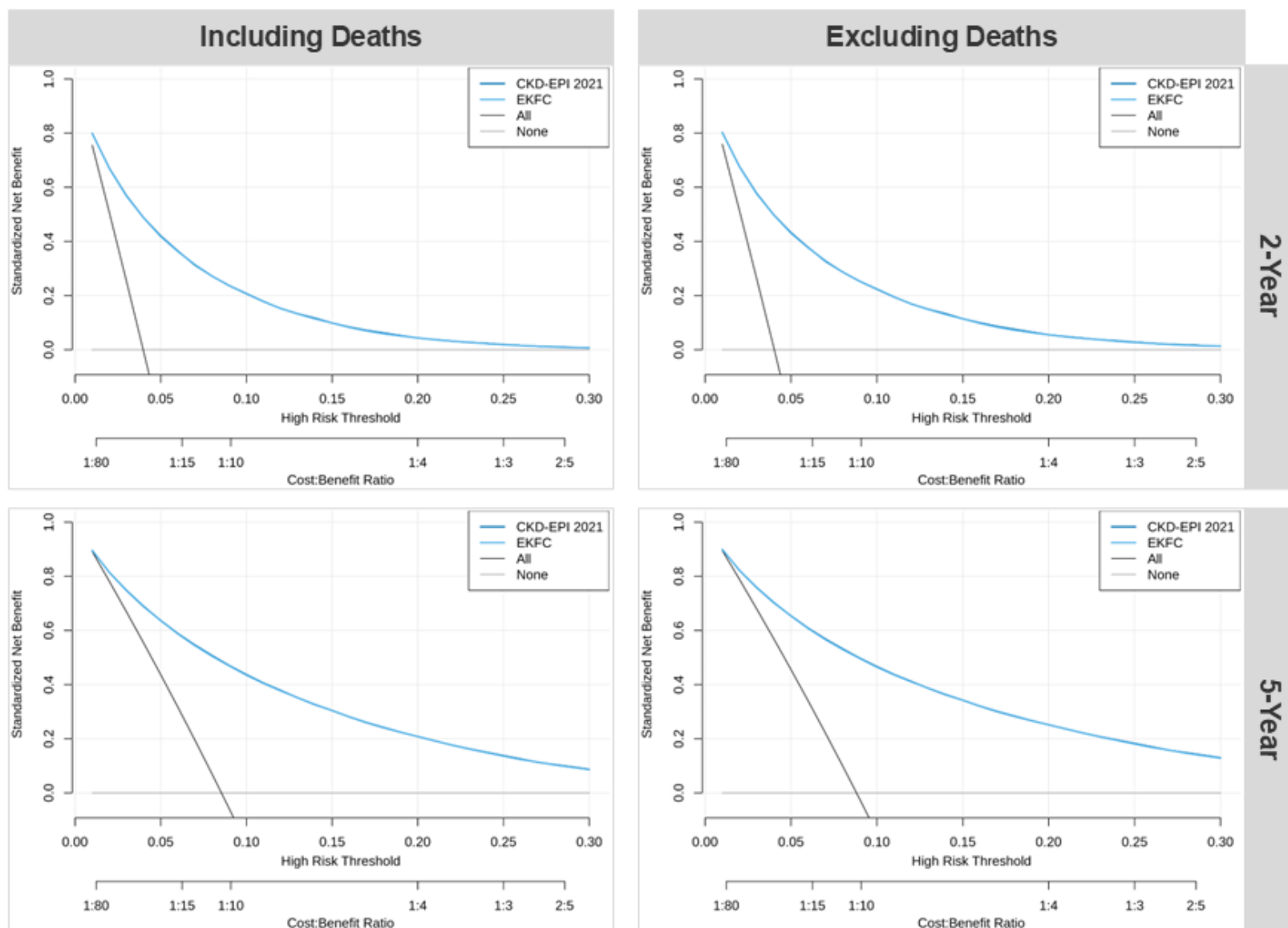


Figure 8. Decision Curve Analysis for MACE using CKD-EPI 2021 and EKFC eGFR values for the overall cohort.



Chapter 3: Tables

Table 1. Baseline Characteristics

<i>Characteristics</i>	<i>Complete Cohort</i>		<i>Baseline Age (in years)</i>		
	N=5,507,066	18 to <40 N=1,365,987	40 to ≤65 N=2,861,048	66 to <80 N=991,942	≥80 N=288,089
<i>Demographics</i>					
<i>Age; mean (SD)</i>	52.20 (17.16)	29.81 (6.28)	52.66 (7.23)	72.01 (4.25)	85.57 (3.97)
<i>Sex</i>					
<i>Male</i>	2,417,977 (43.9%)	536,732 (39.3%)	1,324,816 (46.3%)	454,314 (45.8%)	102,115 (35.4%)
<i>Female</i>	3,089,089 (56.1%)	829,255 (60.7%)	1,536,232 (53.7%)	537,628 (54.2%)	185,974 (64.6%)
<i>Living Status</i>					
<i>Urban</i>	4,955,861 (90.0%)	1,282,342 (93.9%)	2,562,610 (89.6%)	857,912 (86.5%)	252,997 (87.8%)
<i>Rural</i>	551,205 (10.0%)	83,645 (6.1%)	298,438 (10.4%)	134,030 (13.5%)	35,092 (12.2%)
<i>Income Quintile</i>					
1	1,074,287 (19.5%)	306,462 (22.4%)	528,608 (18.5%)	179,754 (18.1%)	59,463 (20.6%)
2	1,109,032 (20.1%)	287,252 (21.0%)	559,258 (19.5%)	201,701 (20.3%)	60,821 (21.1%)
3	1,109,185 (20.1%)	278,141 (20.4%)	576,086 (20.1%)	198,256 (20.0%)	56,702 (19.7%)
4	1,135,159 (20.6%)	270,224 (19.8%)	605,894 (21.2%)	204,144 (20.6%)	54,897 (19.1%)
5	1,079,403 (19.6%)	223,908 (16.4%)	591,202 (20.7%)	208,087 (21.0%)	56,206 (19.5%)
<i>Baseline data</i>					
<i>Follow-up in yrs (CK21); median [IQR]</i>	10 (6-13)	10 (6-12)	11 (7-13)	8 (5-12)	4 (2-7)

<i>Follow-up in yrs (EKFC); median [IQR]</i>	10 (6-13)	10 (6-12)	11 (7-13)	8 (5-12)	4 (2-7)
<i>Follow-up in yrs (MACE); median [IQR]</i>	11 [6-13]	10 [6-13]	12 [8-13]	10 [5-13]	5 [2-8]
<i>Follow-up in yrs (KRT); median [IQR]</i>	11 [8-13]	10 [6-13]	12 [9-14]	11 [7-14]	6 [3-10]
<i>Follow-up in yrs (Overall Mortality); median [IQR]</i>	12 (8-13)	10 (6-13)	12 (9-14)	12 (7-14)	6 (3-10)
Measure of kidney function					
<i>CK21 index eGFR (mean (SD))</i>	95.76 (19.49)	113.49 (13.47)	96.16 (13.79)	78.96 (15.68)	65.64 (17.20)
<i>EKFC index eGFR (Mean (SD))</i>	86.86 (18.87)	102.39 (11.56)	89.25 (13.71)	68.14 (13.43)	53.94 (13.79)
<i>eGFR measurements post-index [IQR]</i>	12 (6-23)	6 (3-12)	13 (7-23)	21 (11-37)	15 (6-29)
<i>Time between index and first repeat eGFR measurement (days) [IQR]</i>	365 (162-618)	435 (204-843)	372 (179-626)	266 (119-428)	203 (93-378)
Comorbidities in the past 5 years (n, %)					
<i>Hypertension</i>	631,514 (11.5%)	54,647 (4.0%)	388,778 (13.6%)	156,266 (15.8%)	31,823 (11.0%)
<i>Hypercholesterolemia</i>	29,158 (0.5%)	809 (0.1%)	10,974 (0.4%)	12,312 (1.2%)	5,063 (1.8%)
<i>Hyperkalemia</i>	7,434 (0.1%)	621 (0.0%)	2,536 (0.1%)	2,606 (0.3%)	1,671 (0.6%)
<i>Diabetes mellitus</i>	401,662 (7.3%)	40,733 (3.0%)	239,071 (8.4%)	101,313 (10.2%)	20,545 (7.1%)
<i>Obesity</i>	22,879 (0.4%)	4,771 (0.3%)	13,013 (0.5%)	4,441 (0.4%)	654 (0.2%)
<i>Alcoholism</i>	68,263 (1.2%)	24,395 (1.8%)	34,283 (1.2%)	7,942 (0.8%)	1,643 (0.6%)
<i>Past cardiovascular disease</i>	110,020 (2.0%)	3,448 (0.3%)	35,713 (1.2%)	42,861 (4.3%)	27,998 (9.7%)

<i>Chronic liver disease</i>	33,534 (0.6%)	6,677 (0.5%)	19,724 (0.7%)	5,681 (0.6%)	1,452 (0.5%)
<i>Chronic lung disease</i>	212,995 (3.9%)	42,865 (3.1%)	101,801 (3.6%)	49,286 (5.0%)	19,043 (6.6%)
<i>Cancer</i>	133,061 (2.4%)	9,226 (0.7%)	62,834 (2.2%)	46,204 (4.7%)	14,797 (5.1%)
<i>Healthcare Utilization</i>					
<i>Primary care</i>	2658532 (48.59)	648279 (45.69)	1387733 (48.56)	495284 (52.76)	127236 (49.75)
<i>Specialist Visit</i>	868030 (15.87)	123887 (8.73)	417432 (14.61)	254276 (27.09)	72435 (28.32)
<i>Emerge Depart Visits</i>	3092159 (56.52)	791800 (55.81)	1541221 (53.93)	558114 (59.45)	201024 (78.61)

Table 2. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MAKE & MACE by eGFR categories relative to G1 (≥ 90), accounting for all-cause/non-CVD mortality as a competing risk

<i>eGFR Category</i>	<i>CK21</i>		<i>EKFC</i>	
	MAKE	MACE	MAKE	MACE
<i>G1 (≥ 90)</i>	761,051/3,633,882 (20.94%) REF	333,697/3,633,882 (9.18%) REF	461,076/2,634,869 (17.50%) REF	163,897/2,634,869 (6.22%) REF
<i>G2 (60-89)</i>	598,534/1,596,596 (37.49%) 1.228 (1.223-1.232)	375,590/1,596,596 (23.52%) 1.084 (1.078-1.089)	845,917/2,365,359 (35.76%) 1.245 (1.240-1.251)	457,039/2,365,359 (19.32%) 1.144 (1.136-1.153)
<i>G3a (45-59)</i>	103,050/188,663 (54.62%) 1.541 (1.528-1.553)	80,884/188,663 (42.87%) 1.288 (1.277-1.300)	186,620/350,092 (53.31%) 1.447 (1.436-1.457)	135,947/350,092 (38.83%) 1.352 (1.338-1.365)
<i>G3b (30-44)</i>	40,845/69,904 (58.43%) 1.654 (1.633-1.676)	35,702/69,904 (51.07%) 1.437 (1.418-1.456)	72,606/126,448 (57.42%) 1.488 (1.472-1.505)	62,284/126,448 (49.26%) 1.538 (1.518-1.557)
<i>G4 (15-29)</i>	11,753/18,021 (65.22%) 2.266 (2.206-2.326)	10,042/18,021 (55.72%) 1.753 (1.709-1.799)	18,617/30,298 (61.45%) 1.786 (1.749-1.824)	16,748/30,298 (55.28%) 1.844 (1.806-1.883)

*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Table 3. Cross-classification of eGFR categories between CK21 and EKFC equations (N = 5,507,066)

CKD-EPI 2021					
EKFC	<i>G1 (≥ 90)</i>	<i>G2 (60-<90)</i>	<i>G3a (45-<60)</i>	<i>G3b (30-<45)</i>	<i>G4 (15-<30)</i>
<i>G1 (≥ 90)</i>	2,634,869 (72.5%)	0	0	0	0
<i>G2 (60-<90)</i>	999,013 (27.5%)	1,366,341-345* (85.6%)	1-5* (0.0%)	0	0
<i>G3a (45-<60)</i>	0	230,251-255* (14.4%)	119,821-825* (63.5%)	17 (0.0%)	0
<i>G3b (30-<45)</i>	0	0	68,838 (36.5%)	57,569 (82.4%)	41 (0.2%)
<i>G4 (15-<30)</i>	0	0	0	12,318 (17.6%)	17,980 (99.8%)

*Suppressed values according to ICES guidelines

Table 4a. Risk of Major Adverse Kidney Events among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category

MAKE Outcome	Concordant		Discordant		Fine-Gray SD HR (95% CI)
	Events	Total	Events	Total	
G1 (90+)	449,918 (17.1%)	2,634,869	311,133 (31.1%)	999,013	1.217 (1.210–1.224)
G2 (60–<90)	481,560 (35.2%)	1,366,345	116,974 (50.8%)	230,251	1.095 (1.087–1.103)
G3a (45–<60)	65,212 (54.4%)	119,824	37,838 (55.0%)	68,838	1.099 (1.084–1.114)
G3b (30–<45)	34,231 (59.5%)	57,569	6,604 (53.6%)	12,318	1.032 (1.004–1.061)
G4 (15–<30)	11,719 (65.2%)	17,980	0	0	—
Total	1,042,640 (24.8%)	4,196,587	472,549 (36.1%)	1,310,420	

Table 4b. Risk of Major Adverse Cardiovascular Events among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category

MACE/MACE+ Outcome	Concordant		Discordant		Fine-Gray SD HR (95% CI)
	Events	Total	Events	Total	
G1 (90+)	163,897 (6.2%)	2,634,869	169,800 (17.0%)	999,013	0.881 (0.872–0.889)
G2 (60–<90)	287,239 (21.0%)	1,366,345	88,351 (38.4%)	230,251	1.116 (1.107–1.126)
G3a (45–<60)	47,593 (39.7%)	119,824	33,291 (48.4%)	68,838	1.099 (1.082–1.116)
G3b (30–<45)	28,983 (50.3%)	57,569	6,716 (54.5%)	12,318	1.075 (1.045–1.106)
G4 (15–<30)	10,032 (55.8%)	17,980	0	0	—
Total	537,744 (12.8%)	4,196,587	298,158 (22.8%)	1,310,420	

CHAPTER 4: COMPARISON OF GFR ESTIMATING EQUATION INPUTS FOR THE KIDNEY FAILURE RISK EQUATION (KFRE): A POPULATION-BASED RETROSPECTIVE COHORT STUDY

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4.1 Abstract

Objectives

To evaluate the impact of estimated glomerular filtration rate (eGFR) equation choice on the performance of the 4-variable Kidney Failure Risk Equation (KFRE), comparing CKD-EPI 2021 (CK21) and the European Kidney Function Consortium (EKFC) equation in a population-based chronic kidney disease cohort.

Design

Population-based retrospective cohort study.

Setting

Linked ICES healthcare administrative datasets in Ontario, Canada.

Participants

Adult Ontario residents (≥ 18) with chronic kidney disease ($\text{eGFR} < 60$) defined by two outpatient eGFR measures 90 to 730 days apart and available albuminuria measurements ($n = 21,686$).

Main Outcomes Measures

Kidney replacement therapy within 2 and 5 years. KFRE performance was evaluated using the CK21 and EKFC eGFR inputs. Discrimination (AUC), calibration (observed-to-expected (OE) ratios, calibration plots), prediction accuracy (Brier scores), risk classification at clinically relevant KFRE thresholds, decision-curve analysis (DCA) and net reclassification improvement (NRI) were assessed before and after recalibration.

Results

Among 21,686 adults [mean age 70.6 (SD ± 13.5); males 51.9%], mean eGFR differed substantially between equations (46.5 mL/min/1.73m² using CK21 vs. 41.3 mL/min/1.73m²

using EKFC). During follow-up, 416 (1.9%) participants initiated KRT within 2 years and 1,139 (6.5%) within 5 years. Despite differences in eGFR estimates, KFRE discrimination was nearly identical using either equation (2-year AUC 0.929 versus 0.928; 5-year AUC 0.913 versus 0.910). Calibration was poorer with EKFC before recalibration (2-year O/E ratio 0.621 versus 0.751; 5-year O/E ratio 0.728 versus 0.894) but improved substantially after recalibration. Equation choice influenced classification around clinically relevant KFRE thresholds. At 2 years, the proportion of patients exceeding a 10% KFRE risk threshold was 6.4% using CK21 and 5.0% using recalibrated EKFC, whereas at 5 years the proportion exceeding a 5% threshold was 22.5% and 25.2%, respectively. NRI analyses demonstrated no improvement in risk prediction with EKFC compared with CK21.

Conclusions

Despite a reduction in eGFR estimates with the EKFC, discrimination and overall predictive performance were nearly identical compared to CK21. Noted differences in calibration and risk classification were observed at clinically relevant decision thresholds.

4.2 Introduction

Although differences among eGFR equations have been extensively evaluated against measured GFR, less is known about their impact on downstream risk prediction models, particularly on kidney failure. The KFRE is the most widely used tool for predicting risk of kidney failure at both 2- and 5-year timepoints, incorporating eGFR with additional variables such as age, sex and albumin-to-creatinine ratio (ACR). Because eGFR is a key component of the KFRE,³ systematic differences in eGFR estimates may alter predicted kidney failure risk even when the underlying risk of disease progression remains unchanged. Such differences may have important clinical implications as KFRE thresholds are increasingly used to guide nephrology referral and advanced CKD care. Importantly, changes in eGFR equations may influence not only discrimination but also calibration and risk classification around clinically relevant decision thresholds.

A recent study from Europe has suggested that the CKD-EPI and EKFC equations provide similar discrimination when incorporated into the KFRE.⁷³ However, formal calibration metrics and risk reclassification analyses have not been reported, and data from large North American populations remain limited. Furthermore, the extent to which recalibration may alter differences arising from equation choice remain unknown.

As such, we evaluated the impact of eGFR equation choice on the performance of the 4-variable KFRE in a large population-based cohort of adults with CKD in Ontario, Canada. Specifically, we compared CK21 and EKFC eGFR inputs with respect to discrimination, calibration, risk classification, net reclassification, and clinical utility at 2- and 5-year prediction horizons.

4.3 Methods

4.3.1 Study Design and Setting

We conducted a retrospective cohort study in Ontario using deidentified, linked health administrative databases housed at the Institute for Clinical Evaluative Sciences. ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze healthcare and demographic data, without consent, for health system evaluation and improvement. The use of the data in this project is authorised under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and does not require review by a Research Ethics Board. Data was obtained from October 2002 to December 2023, accounting for the accrual window (October 2007 – December 2021), 5 years lookback window and a 2-year follow-up period. The dataset from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the dataset publicly available, access may be granted to those who meet pre-specified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full dataset creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

4.3.2 Data Sources

All data used for baseline variables (sociodemographic, comorbidities, and healthcare utilisation), outcome development (KRT), and lab measures [serum creatinine (SCr) and albumin-to-creatinine ratio (ACR)] were sourced from six ICES databases using unique, ICES-generated encoded identifiers for each patient to link the datasets together. These datasets were

linked using unique encoded identifiers and analyzed at ICES. The Ontario Laboratory Information System (OLIS) was used to source outpatient SCr and ACR values at baseline with outpatient SCr during follow-up. Discharge Abstract Database (CIHI-DAD) was used to identify outcomes and comorbidities using International Classification of Diseases-10 (ICD-10) codes from hospital admissions in Ontario, with National Ambulatory Care Reporting System (NACRS) being used for similar purposes but for ambulatory care centre visits in Ontario. The Ontario Health Insurance Plan (OHIP) database was used to identify primary care, emergency, and specialist visits through physician service claims; the Canadian Organ Replacement Registry (CORR) was used to identify patients undergoing renal replacement therapy (hemodialysis, and kidney transplant); lastly, the Ontario Registered Persons Database (RPDB) was used for demographic and vital statistics. Sensitivity, specificity and positive predictive values of ICD-10 codes used for defining primary outcomes are presented in **Appendix J**.

4.3.3 Study Cohort

We included Ontario adults aged 18 and greater classified as having CKD (eGFR <60 mL/min/1.73m²) using 2 outpatient SCr measurements (90 to 730 days apart) within the accrual period (October 1, 2007, to December 31, 2021). There were an additional 2-year follow-up period (December 31, 2023) and a 5-year lookback window to collect data on comorbidities. Follow-up started from index date, defined as the date of the second SCr measurement, until the participants met the following: outcome met, death, administrative censoring, emigration, or end of study on December 31, 2023. Participants were excluded based on the following criteria as seen in **Figure 1**: missing identification data, <2 eGFR measurements or unidentifiable values, non-Ontario resident, death prior to index date, short follow-up (<90 days), patients who met the outcomes prior to index, pregnant within 10 months of index (pregnancy can increase eGFR by

~50%),⁴⁸ <18 years of age at index (CK21 has been validated for those ≥ 18),¹⁰ no ACR values available from index date to 1 year, and classified greater than eGFR category G3a (KFRE is validated for those lower than G3a).³ There were no missing data in the dataset.

4.3.4 Index Kidney Function Measurement

Baseline eGFR measurements were calculated as the mean from two index outpatient SCr measurements ($\mu\text{mol/L}$) between 90 to 730 days apart using both the CK21 and the EKFC equations. Baseline ACR values were taken from spot urine samples measured within 1 year of index.

4.3.5 Outcomes

The outcome of interest is initiation of kidney replacement therapy (KRT), defined as chronic dialysis or kidney transplantation.³⁴

4.3.6 KFRE Risk Predictions

The 4-variable KFRE equation (North American calibrated) was used for risk prediction calculated at both 2- and 5-year timepoints.³ These were generated separately using both EKFC and CK21 eGFR inputs. The EKFC-based KFRE risk predictions were recalibrated using KM O/E values, as the KFRE was developed using the CKD-EPI derived eGFR measurements.^{3,32}

4.3.7 Statistical Analysis

Baseline characteristics of the total study cohort were summarised in **Table 1** using means and standard deviations for normally distributed continuous variables, median and interquartile range for non-normally distributed continuous variables, and frequencies and percentages for categorical variables.

Discrimination was assessed using time-dependent AUC,⁵⁷ which measures how well the model assigns higher predicted risks to those who experienced the event than to those who did

not. Overall predictive accuracy was calculated via Brier scores, the mean squared difference between predicted risks and observed outcomes.^{58,59} Both discrimination and Brier scores were calculated using a marginal KM-based Inverse Probability of Censoring Weighting (IPCW) approach. Calibration was then assessed using calibration plots and slope capturing the agreement between predicted and observed risk. Decision curve analysis (DCA) was then used to assess clinical utility, and a categorical net reclassification improvement (NRI) was used to assess reclassification, with both censored observations and deaths treated as non-events. All analyses were conducted at the 2- and 5-year timepoints, with clinical thresholds used for reclassification being 10% at 2 years and 5% at 5 years.

All statistical analyses were performed using SAS Enterprise Guide version 8.3.7.202 (SAS Institute Inc., Cary, NC) and RStudio: Integrated Development for R version 1.1.456 (RStudio, Inc., Boston, MA). KFRE risk predictions were calculated in SAS, with the remainder of the statistical analyses then conducted in R. Packages used included riskRegression,⁶⁰ survival,⁶¹ rmda⁶³ and prodlm.⁶⁴

4.3.8 Additional Analysis

Prespecified stratified analyses were conducted on age, sex, and ACR categories. Statistical analyses conducted on the main models were replicated for each of the subgroups using the same methods. Sensitivity analyses were then run with both equations being compared with values calibrated and uncalibrated, and the DCA and NRI were repeated after excluding deaths before the time horizon. All analyses were also reconducted comparing EKFC to the CK09 equation.

4.4 Results

4.4.1 Cohort Characteristics

Among 702,859 Ontario residents with paired outpatient SCr and urine ACR measurements, 21,686 individuals met eligibility criteria and were included in the primary CK21 versus EKFC analysis (**Figure 1**). Mean (SD) age was 70.6 (13.5) years, 51.9% were male, and median (IQR) follow-up was 5.9 (3.7–9.4) years. Median (IQR) ACR was 4 (1–18) mg/mmol, while mean eGFR was lower using EKFC than CK21 (41.3 vs 46.5 mL/min/1.73m²). During follow-up, 416 (1.9%) individuals developed kidney failure within 2 years and 1,139 (6.5%) within 5 years, while 1,305 (6.0%) and 3,744 (21.2%) deaths occurred over the corresponding time horizons. Baseline characteristics are presented in **Table 1**.

4.4.2 Discrimination

Discrimination was excellent and nearly identical across eGFR equations. In the overall cohort, the 4-variable KFRE achieved AUCs of 0.929 and 0.928 at 2 years using CK21 and EKFC, respectively, and 0.913 and 0.910 at 5 years (**Supp. Table K1 & K2**). Similar findings were observed across age, sex, and ACR strata, with absolute differences in AUC generally <0.01 and no consistent difference for either equation. Brier scores were similarly comparable across all analyses.

4.4.3 Calibration

Before recalibration, both equations overpredicted kidney failure risk, although overprediction was greater when EKFC-derived eGFR values were used. At 2 years, O/E ratios were 0.75 for CK21 and 0.62 for EKFC; corresponding values at 5 years were 0.89 and 0.73, respectively (**Supp. Table K1**). Calibration slope intercepts demonstrated a similar pattern, indicating greater overestimation of risk with EKFC inputs. Following recalibration, calibration

improved substantially for both equations. Overall, O/E ratios approached one at both time horizons and were similar between equations (2-year O/E: 0.94 for CK21 vs 0.92 for EKFC; 5-year OE: 0.90 vs 0.86; **Supp. Table K2**). Calibration plots demonstrated close agreement between predicted and observed risk across deciles of risk for both equations (**Figure 2**). Calibration slopes and Brier scores remained highly similar, suggesting equivalent overall predictive performance after recalibration. With CK09 values, the same directional pattern was observed in comparison to EKFC, but the gap was more attenuated as CK09 itself overpredicted risk more than CK21 (**Supp. Table K3 & K4**). All plots are presented in **Appendix K, L & M**.

4.4.4 Net Reclassification Improvement

Equation choice resulted in modest differences in risk classification around clinically relevant KFRE thresholds (**Figure 3**). At the 2-year horizon, EKFC classified fewer individuals above the 10% kidney failure risk threshold than CK21, resulting in a significant negative net reclassification improvement (NRI) when calibrated EKFC was compared with uncalibrated CK21 (NRI -0.059 ; 95% CI -0.087 to -0.034 ; **Table 2**). This was driven primarily by EKFC's lower KFRE scores reclassifying individuals who developed kidney failure below the treatment threshold (**Figure 4**).

In contrast, reclassification differences at 5 years were small and not statistically significant, with KFRE scores being closer between equations (**Figure 5**). When both equations were recalibrated, reclassification effects were substantially attenuated, indicating that much of the observed difference was attributable to calibration rather than discrimination. Findings were similar in analyses comparing CK09 with EKFC. CK09 demonstrated a modest reclassification advantage at 2 years, which largely disappeared after recalibration (**Table 3**).

4.4.5 Decision Curve Analysis

DCA demonstrated nearly identical clinical utility for CK21- and EKFC-based KFRE models across a broad range of clinically relevant risk thresholds at both 2 and 5 years, with the uncalibrated EKFC performing worse compared to the other models (**Figures 6 & 7**). Overall, all models provided greater net benefit than treating all or treating no patients. After recalibration, decision curves for CK21 and EKFC were essentially superimposable, indicating no meaningful difference in clinical usefulness between equations. CK09 performed similarly to EKFC, with uncalibrated version underperforming. All plots are presented in **Appendix N and O**.

4.5 Discussion

In this population-based cohort of 21,686 adults with CKD, we evaluated the impact of replacing the CK21 with the EKFC equation as the eGFR input for the KFRE. We found that despite lower eGFR values with EKFC, predictive performance of the KFRE remained similar across equations. Discrimination, overall calibration (after recalibration), risk reclassification, and decision-curve analyses demonstrated minimal differences between CK21, CK09, and EKFC. These findings suggest that adoption of EKFC is unlikely to meaningfully alter kidney failure risk prediction at the population level. However, shifts in the proportion of patients exceeding referral and management thresholds were observed with the EKFC. This may lead to significant clinical implications on referral patterns, multidisciplinary CKD clinic enrollment, and kidney replacement therapy for regions considering implementation of the EKFC.

As reported in previous studies,^{5,6,74} there is a notable decrease in eGFR estimates with EKFC between both equations. EKFC produced eGFR values that were on average approximately 5 mL/min/1.73m² lower than CK21 and 2 mL/min/1.73m² lower than CK09. Despite these differences, discrimination remained virtually unchanged across equations, with

differences in AUC generally less than 0.01, and NRI showing modest or no change. These findings provide reassurance that implementation of alternative creatinine-based eGFR equations is unlikely to substantially alter the prognostic utility of the KFRE.

Our findings extend those of Lanot and colleagues, who evaluated CK09, CK21, and EKFC as KFRE inputs in the French CKD-REIN cohort ($n = 2,169$).⁷³ Similar to their study, we observed excellent discrimination across equations, only modest differences in performance, and found clinical utility to be grossly similar. However, several important distinctions exist. First, our cohort was approximately ten times larger and population-based rather than restricted to nephrology-referred patients. Second, we formally quantified calibration using multiple metrics rather than relying primarily on visual inspection. Third, we evaluated both recalibrated and uncalibrated models and examined clinical consequences using reclassification analyses and decision curve analyses. Fourth, we conducted a sensitivity analysis excluding deaths in both our NRI and decision-curve methodology. Together, these analyses provide a more comprehensive assessment of the practical impact of changing eGFR equations in routine clinical practice.

Although discrimination was nearly identical, we observed differences in calibration before recalibration. Both CK21 and EKFC tended to overpredict kidney failure risk, with overprediction greater when EKFC eGFR inputs were used. Following recalibration, calibration improved substantially and differences between equations narrowed considerably. These findings suggest that most apparent differences in prognostic performance are attributable to baseline risk calibration rather than intrinsic differences in discriminatory ability. Importantly, recalibration largely eliminated differences in calibration, risk classification and clinical utility.

The clinical implications of these findings are relevant given increasing international interest in adopting EKFC. Because KFRE thresholds are frequently used to guide nephrology

referral, multidisciplinary care, dialysis planning, and access to KRT education, systematic shifts in eGFR estimates could theoretically alter care pathways.¹ Our results suggest that such effects are likely modest. Although statistically significant reclassification was observed at the 2-year horizon before recalibration, the absolute number of reclassified individuals was small relative to the overall cohort and largely disappeared following recalibration. Decision-curve analyses further demonstrated nearly identical net benefit across clinically relevant thresholds, indicating little practical difference in patient management regardless of the eGFR equation used. However, the systematic reduction in eGFR with the EKFC shifted the proportion of individuals exceeding the 2-year 10% and 5-year 5% risk thresholds that would have clinical implications at a population-level.

Our findings highlight the importance of local validation when implementing new eGFR equations. EKFC was developed and validated primarily in European populations, whereas our study was conducted in a large North American healthcare system. The improved calibration of CK21 at the 2-year horizon and the attenuation of differences after recalibration illustrates the importance of local recalibration for maintaining accurate risk prediction.

There are a few limitations present in our study that warrant consideration. First, cystatin C measurements were unavailable, preventing the evaluation of combined creatinine-cystatin C equations. However, creatinine only equations are the most common eGFR equation worldwide reflecting real-world applications,¹² as well with the KFRE being developed without cystatin C.³ Second, factors such as muscle mass, nutritional status, and medication use could not be assessed due to data unavailability potentially leading to unmeasured confounding. However, the size of our cohort, the consistency of our results across subgroups, consistency with previous studies, and the comprehensive framework utilised strengthens the results of our study. Third, our

findings were derived from a Canadian healthcare system and may not fully generalise to other populations. However, the original KFRE was developed in Canadian populations, making Ontario an appropriate validation setting.³ Finally, the KFRE itself was originally developed using CKD-EPI-based eGFR estimates,³ which may inherently favour CKD-EPI-derived inputs. However, the consistency of findings across multiple analyses suggests that any such effect is unlikely to be clinically meaningful.

Chapter 4: Figures

Figure 1. Patient flowchart diagram

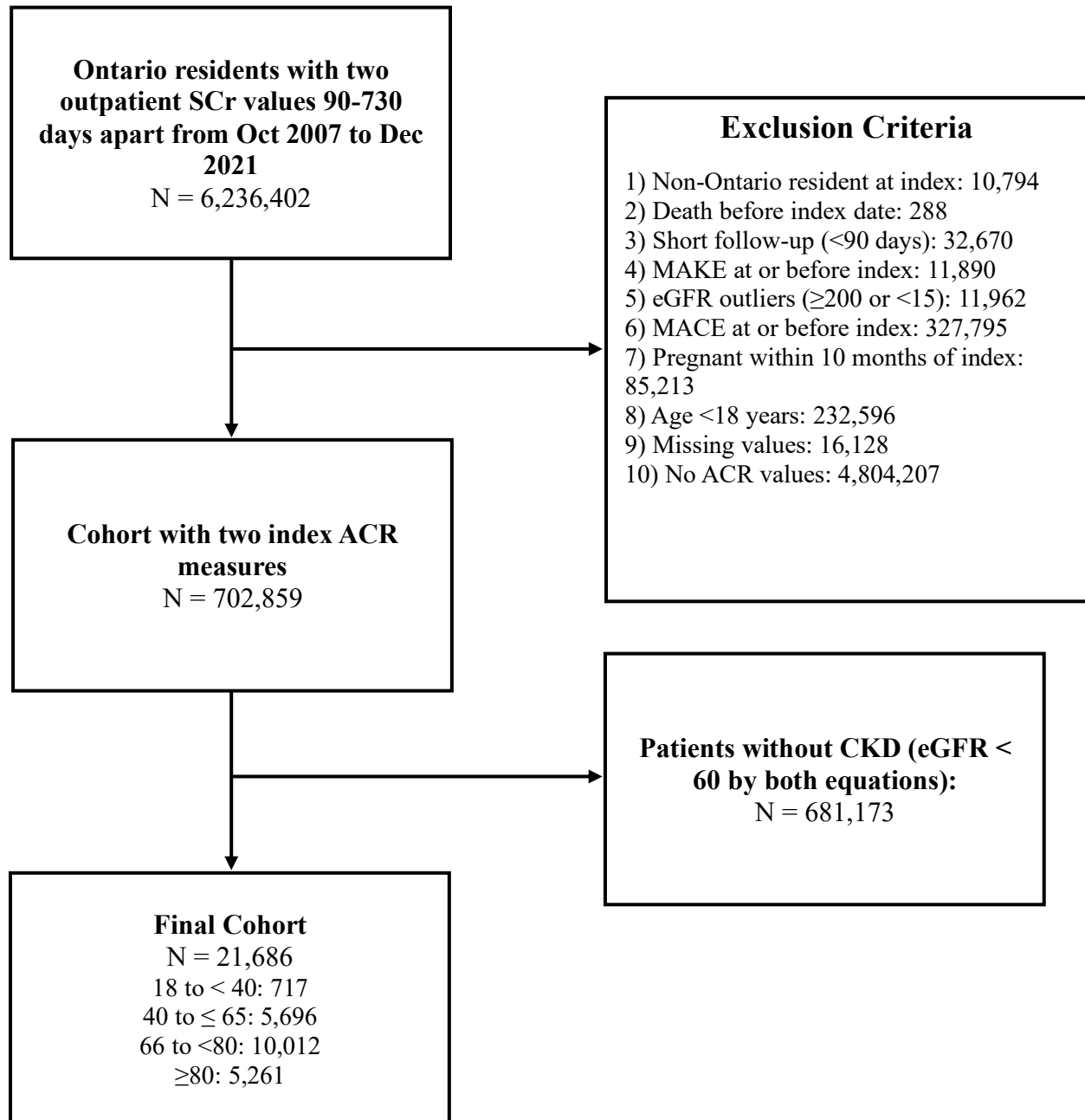


Figure 2. Calibration plots for the 4-variable KFRE comparing CKD-EPI 2021 (CK21; blue circles) against EKFC (green squares) as eGFR inputs, shown at the 2-year (left) and 5-year (right) horizons

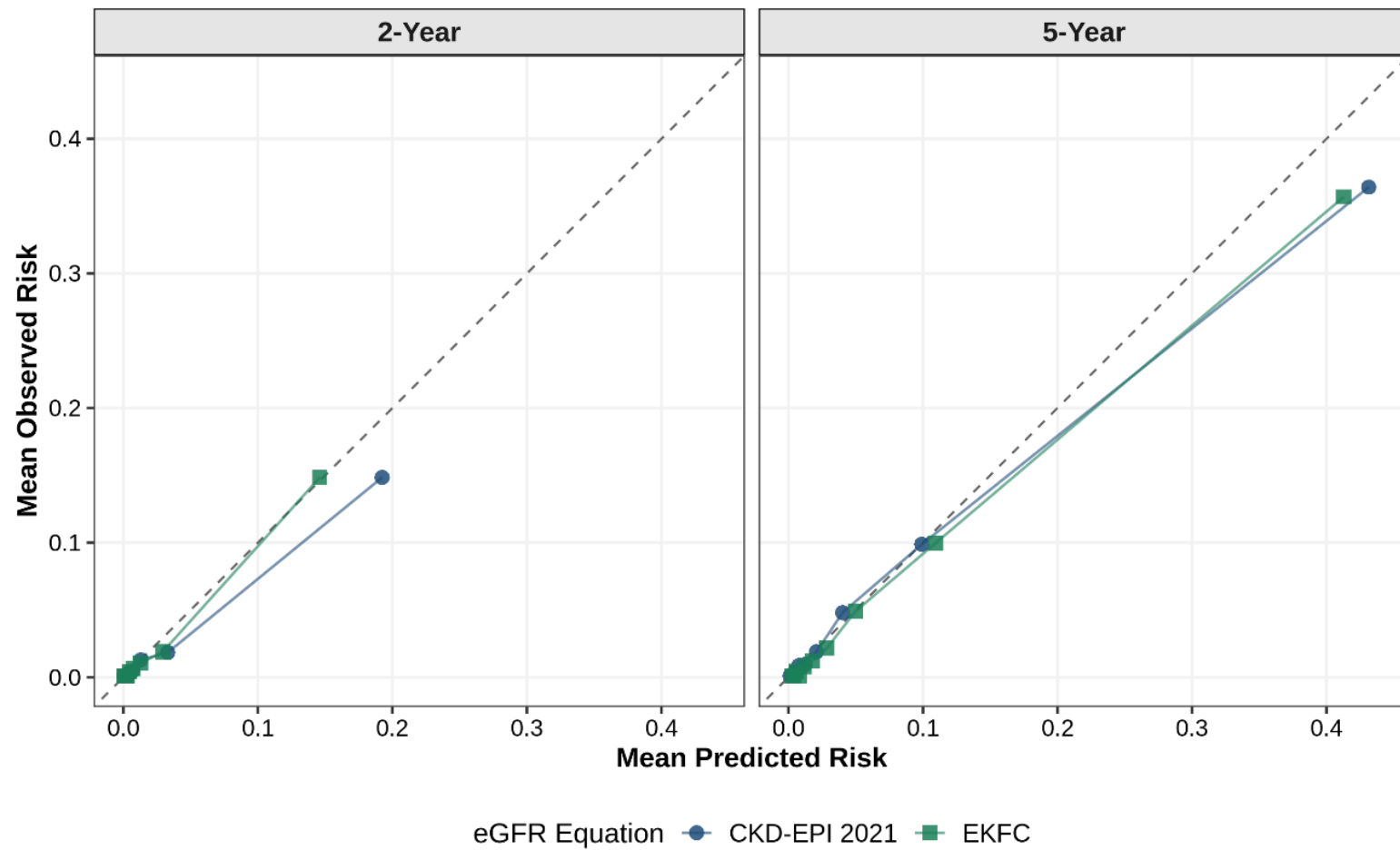


Figure 3. KFRE Risk Distribution by Equation and Calibration.

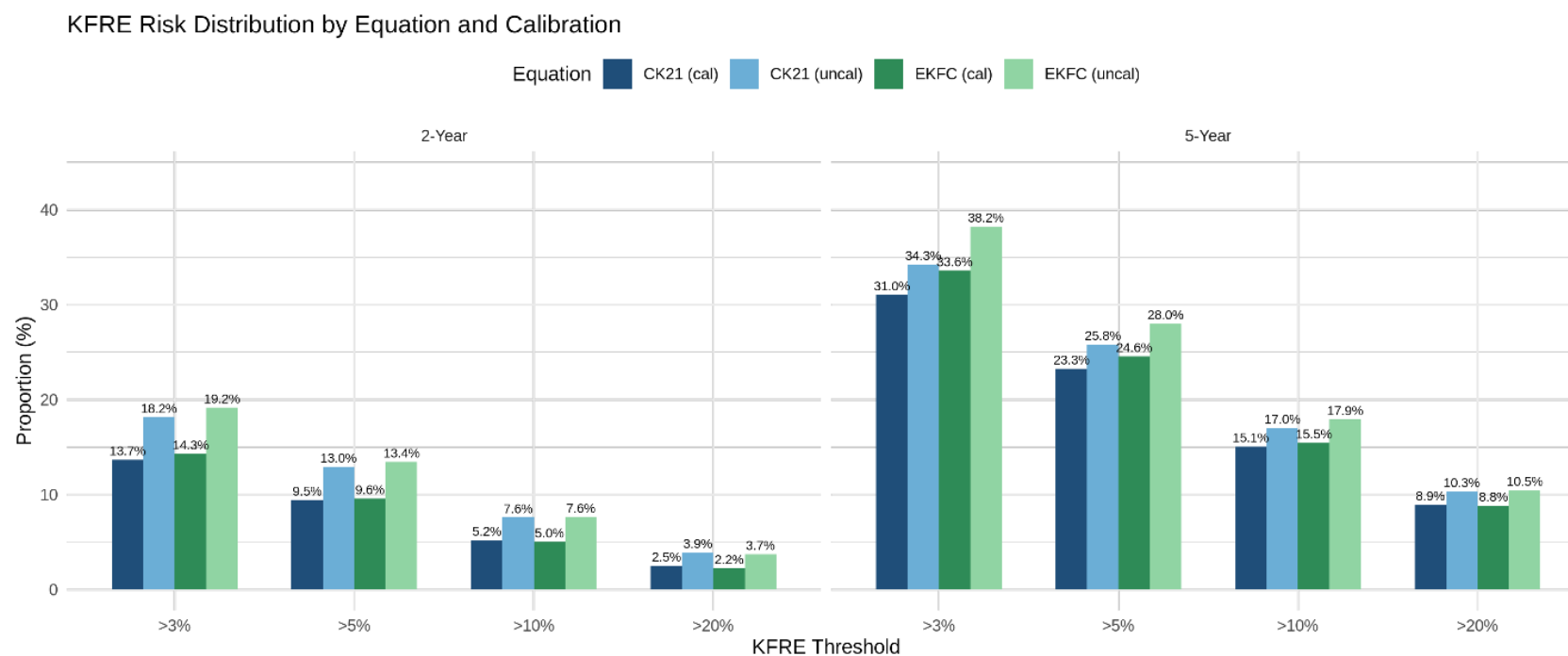


Figure 4. Scatterplot comparing 2-year kidney failure risk (threshold 10%) estimated by the 4-variable KFRE using uncalibrated CKD-EPI 2021 (CK21) versus calibrated EKFC eGFR inputs

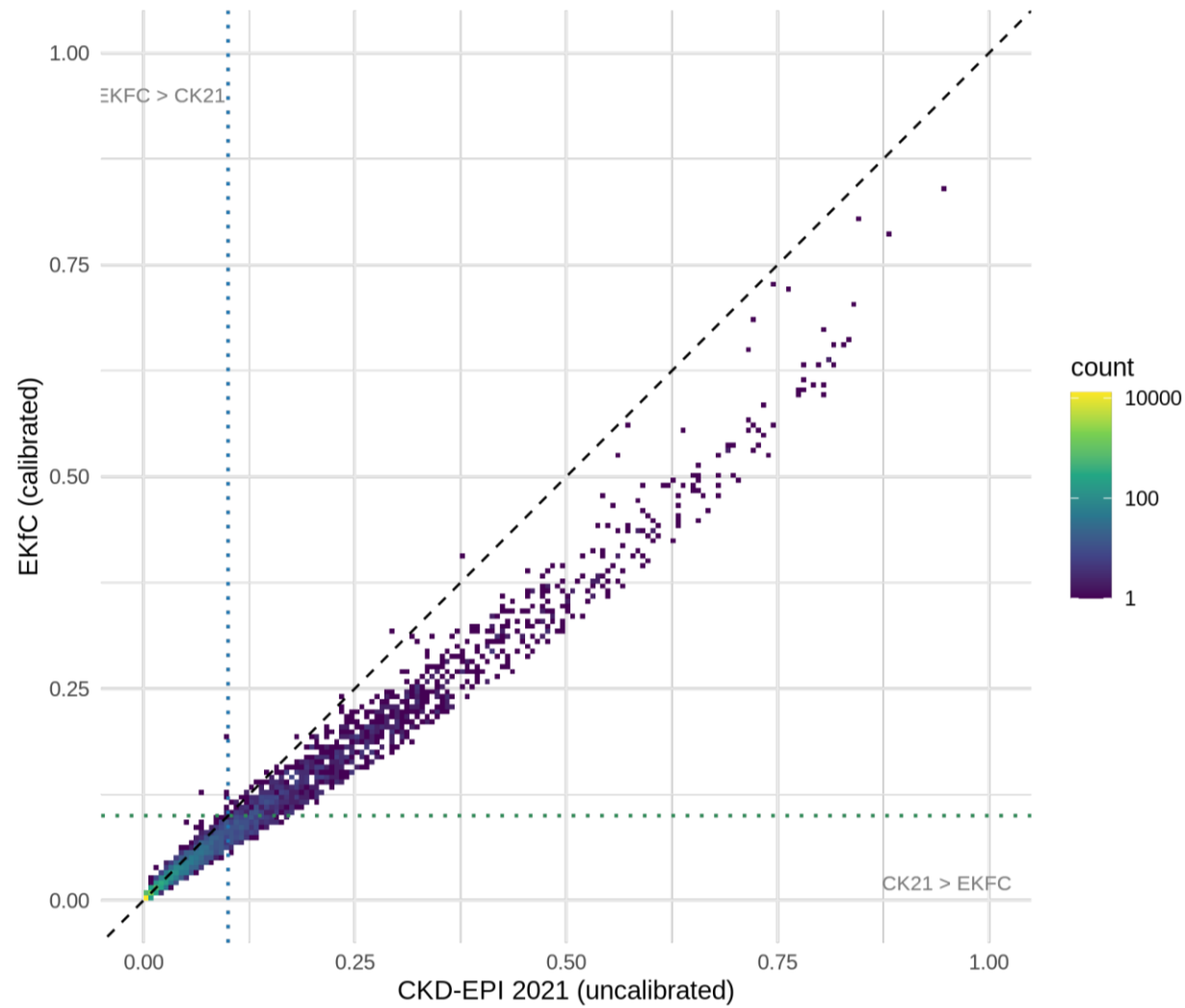


Figure 5. Scatterplot comparing 5-year kidney failure risk (threshold 5%) estimated by the 4-variable KFRE using uncalibrated CKD-EPI 2021 (CK21) versus calibrated EKfC eGFR inputs

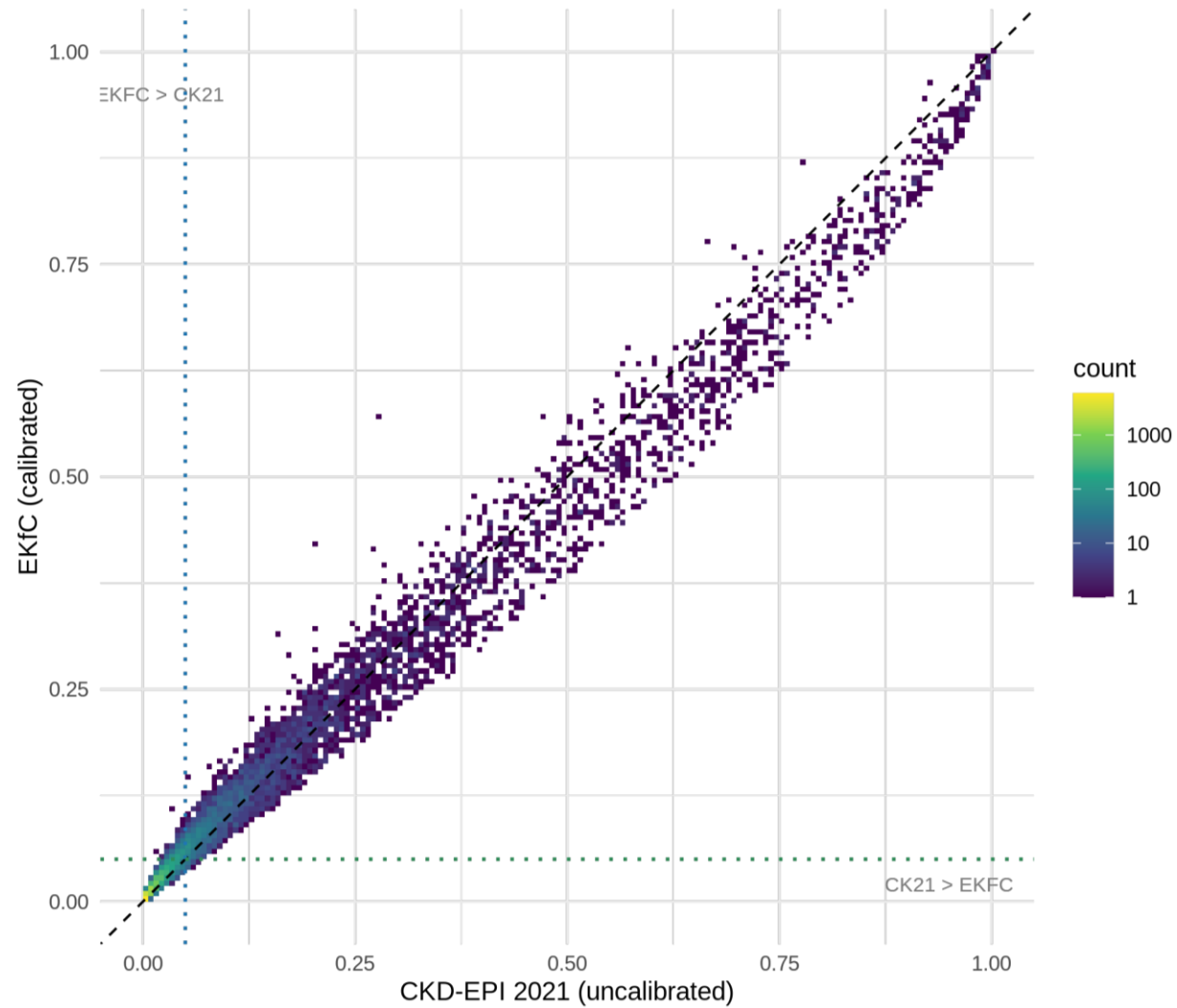


Figure 6. Decision curve analysis for the 4-variable KFRE at the 2-year horizon, with death treated as a competing event. CKD-EPI (blue) 2021 and EKFC (green) eGFR inputs, each uncalibrated (light) and recalibrated (dark). The "All" (treat everyone) and "None" (treat no one) reference strategies are shown for comparison

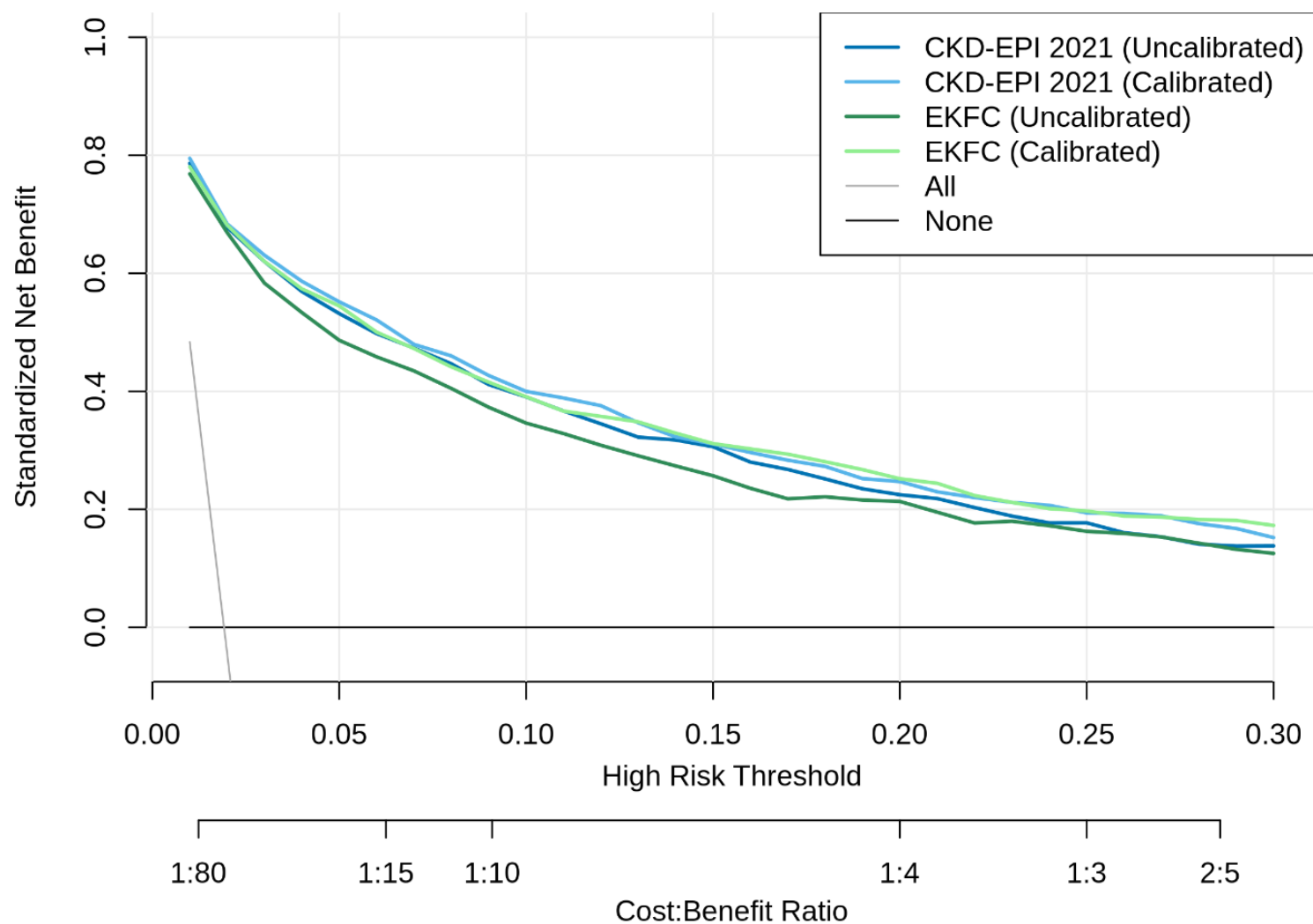
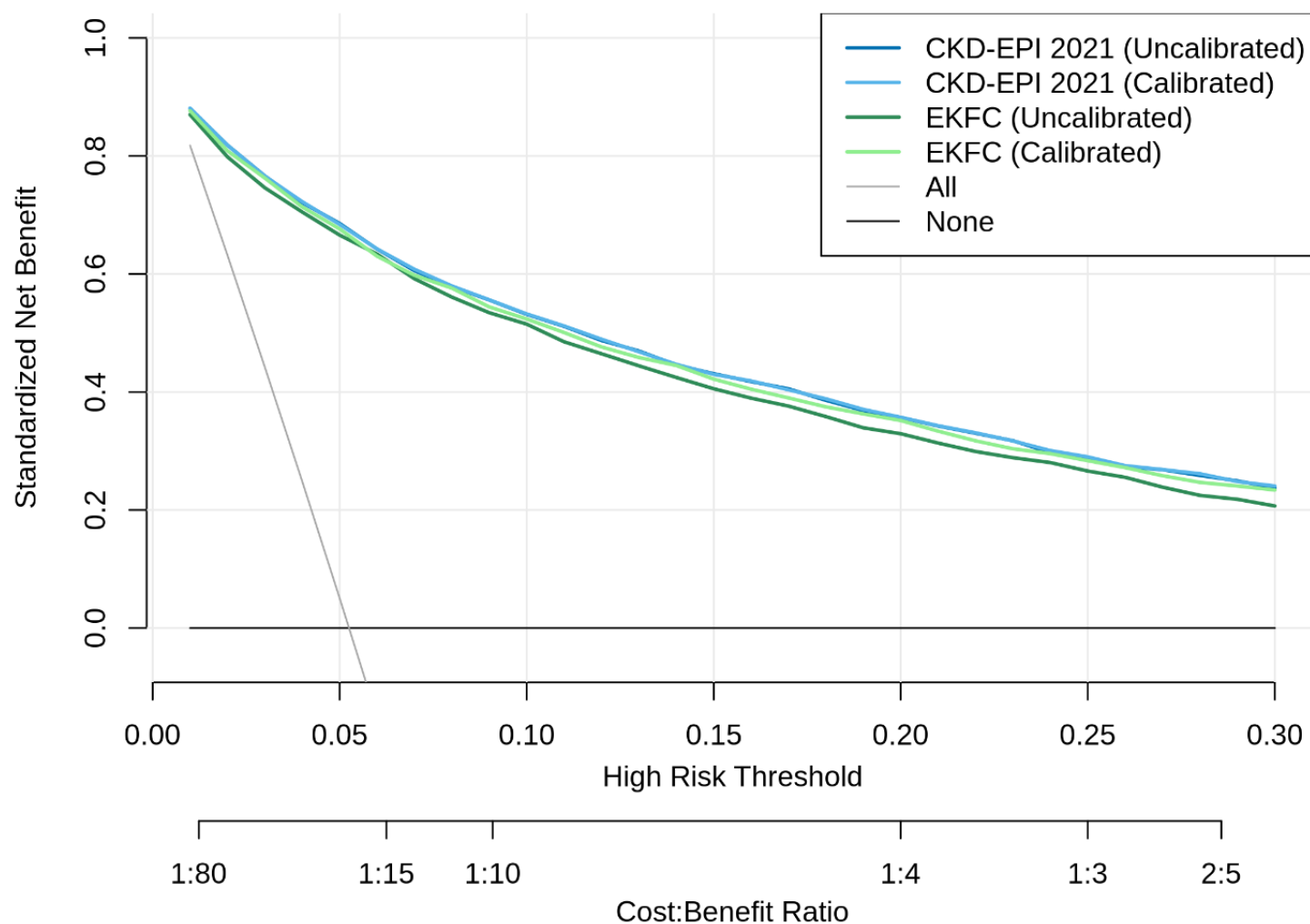


Figure 7. Decision curve analysis for the 4-variable KFRE at the 5-year horizon, with death treated as a competing event. CKD-EPI (blue) 2021 and EKFC (green) eGFR inputs, each uncalibrated (light) and recalibrated (dark). The "All" (treat everyone) and "None" (treat no one) reference strategies are shown for comparison



Chapter 4: Tables

Table 1. Baseline Characteristics

<i>Characteristics</i>	<i>Complete Cohort</i>		<i>Baseline Age (in years)</i>		
	N=21,686	18 to <40 N=717	40 to ≤65 N=5,696	66 to <80 N=10,012	≥80 N=5,261
<i>Demographics</i>					
<i>Age; mean (SD)</i>	70.60 (13.53)	31.73 (5.67)	56.84 (6.83)	73.32 (4.22)	85.62 (3.81)
<i>Sex</i>					
<i>Female</i>	10,426 (48.1%)	233 (32.5%)	2,375 (41.7%)	4,839 (48.3%)	2,979 (56.6%)
<i>Male</i>	11,260 (51.9%)	484 (67.5%)	3,321 (58.3%)	5,173 (51.7%)	2,282 (43.4%)
<i>Income Quintile</i>					
1	4,911 (22.6%)	203 (28.3%)	1,432 (25.1%)	2,145 (21.4%)	1,131 (21.5%)
2	4,597 (21.2%)	145 (20.2%)	1,190 (20.9%)	2,136 (21.3%)	1,126 (21.4%)
3	4,416 (20.4%)	140 (19.5%)	1,145 (20.1%)	2,038 (20.4%)	1,093 (20.8%)
4	4,101 (18.9%)	122 (17.0%)	1,041 (18.3%)	1,945 (19.4%)	993 (18.9%)
5	3,661 (16.9%)	107 (14.9%)	888 (15.6%)	1,748 (17.5%)	918 (17.4%)
<i>Measure of kidney function</i>					
<i>Follow-up in yrs; median [IQR]</i>	5.91 [3.67–9.40]	4.91 [2.76–7.51]	6.26 [4.01–9.92]	6.36 [4.13–9.92]	4.89 [2.95–7.73]
<i>CK21 index eGFR (mean (SD))</i>	46.47 (10.68)	42.19 (12.78)	46.40 (11.31)	47.49 (10.04)	45.18 (10.58)
<i>EKFC index eGFR (Mean (SD))</i>	41.30 (9.34)	40.70 (11.93)	43.76 (10.15)	41.77 (8.48)	37.83 (8.51)
<i>ACR (Median [IQR])</i>	4 (1-18)	45 (9-155)	7 (1-51)	3 (1-12)	3 (1-11)
<i>eGFR measurements post-index [IQR]</i>	20 (9-39)	26 (12-64)	23 (10-48)	20 (10-40)	15 (7-29)
<i>Time between index and first repeat eGFR measurement (days) [IQR]</i>	365 (162-618)	435 (204-843)	372 (179-626)	266 (119-428)	203 (93-378)
<i>Comorbidities</i>					
<i>Hypertension</i>	5,042 (23.3%)	245 (34.2%)	1,691 (29.7%)	2,325 (23.2%)	781 (14.8%)

<i>Diabetes mellitus</i>	4,012 (18.5%)	49-55* (7.5%)	1,156-1162* (20.3%)	2,152 (21.5%)	649 (12.3%)
<i>Healthcare Utilization Past 5 Years Median</i>					
<i>Primary care count</i>	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)
<i>Specialist Visit count</i>	0 (0-1)	1 (0-2)	0 (0-1)	0 (0-1)	0 (0-1)
<i>Emergent Depart Visits count</i>	1 (0-2)	1 (0-3)	1 (0-2)	1 (0-2)	1 (0-3)

Table 2. Categorical NRI for CK21 versus EKFC at 2- and 5-year horizons.

<i>Uncalibrated CK21 vs Calibrated EKFC</i>								
Timepoint	Death handling	N	Threshold	Reclassified	NRI Events	NRI Non-events	NRI Total	95% CI
2yr	Exclude	20,381	0.1	300	−0.072	0.013	−0.059	−0.087 to −0.034
2yr	Non-event	21,686	0.1	315	−0.072	0.013	−0.059	−0.086 to −0.033
5yr	Exclude	13,913	0.05	366	0.017	−0.020	−0.004	−0.015 to +0.007
5yr	Non-event	17,657	0.05	563	0.017	−0.028	−0.011	−0.021 to −0.001

Table 3. Categorical NRI for CK09 versus EKFC at 2- and 5-year horizons.

<i>Uncalibrated CK09 vs Calibrated EKFC</i>								
Timepoint	Death handling	N	Threshold	Reclassified	NRI Events	NRI Non-events	NRI Total	95% CI
2yr	Exclude	26,299	0.1	527	−0.111	0.019	−0.092	−0.124 to −0.063
2yr	Non-event	27,877	0.1	561	−0.111	0.019	−0.092	−0.122 to −0.063
5yr	Exclude	18,201	0.05	293	−0.016	0.011	−0.005	−0.014 to +0.003
5yr	Non-event	22,717	0.05	361	−0.016	0.009	−0.008	−0.016 to +0.000

CHAPTER 5: DISCUSSION

5.1 Summary of Thesis

In this population-based cohort of Ontario adults, the thesis examines how the choice of two contemporary creatinine-based estimated glomerular filtration rate (eGFR) equations affect the prediction of clinical outcomes, using linked provincial health administrative datasets. A background on the population-level burden of chronic kidney disease (CKD) and the ongoing discussion surrounding competing eGFR equations and their consequences for risk classification and clinical management was presented in **Chapter 2**. Next, in **Chapter 3 (Manuscript I)**, we compared the CKD-EPI 2021 (CK21) and EKFC equations for the prediction of two clinical outcomes, major adverse kidney events (MAKE) and major adverse cardiovascular events (MACE). Finally, the consequences of equation choice for individual-level kidney failure prediction were explained in **Chapter 4 (Manuscript II)**, in which the 4-variable Kidney Failure Risk Equation (KFRE) was compared for prediction of kidney failure using CK21 and EKFC eGFR values as inputs. Analyses also included both inputs left uncalibrated, and calibrated, as well as comparing CK09 and EKFC as an input. This discussion chapter will highlight the novel findings presented in the thesis, their implications for the risk-based identification and clinical management of CKD in North America, and the limitations of the two manuscripts. Future avenues of research are also described.

5.2 Novel Findings

Across both manuscripts, we found that the choice between the EKFC and CK21 creatinine-based equations carries prognostic consequences, but that these consequences depend on the outcome examined, timepoint of interest, and whether the equation is used directly to estimate eGFR or an input to a downstream risk model. In **Manuscript I**, we conducted the first

population-based comparison of the EKFC and CK21 equations in a North American population for MAKE, and the largest comparison to date for MACE. Using Fine-Gray subdistribution hazard models, we found that being reclassified into a worse GFR category by EKFC was associated with modestly higher subdistribution hazards for MAKE, MACE, kidney replacement therapy, and all-cause mortality, relative to individuals who were not reclassified. Importantly, this elevated risk among EKFC-reclassified individuals persisted after adjustment for age and comorbidities, indicating that EKFC's reclassification captures a modest but real prognostic signal, instead of one that is entirely age-driven, adding nuance to prior interpretations. However, despite these findings, the magnitude of this signal was small and did not translate into improved discrimination, calibration, or net benefit at the model level.

Building off the observation that equation choice influences kidney failure risk estimation, **Manuscript II** sought to examine whether EKFC offers any advantage when used as an input to the 4-variable Kidney Failure Risk Equation (KFRE). We found that EKFC was unlikely to substantially alter the prognostic utility of the KFRE in a North American population, a result that held for both the CKD-EPI 2009 (CK09) and CK21 equations. While EKFC did demonstrate substantial overprediction when left uncalibrated due to lower eGFR values, recalibrating the baseline risk improved calibration substantially with differences between equations narrowing. This systematic reduction in eGFR with EKFC shifted the proportion of patients exceeding clinical thresholds on the 2- and 5-year KFRE, a population-level effect with potential downstream implications for nephrology referral and multidisciplinary CKD care.

5.3 Implications for Clinical Practice

Our findings have direct implications for the choice of eGFR estimating equation in North American clinical practice. If the EKFC were to be applied, the lower eGFR values would cause

an increase in the CKD population, with patients potentially being referred earlier for treatment. However, when assessing eGFR's use case in our study for predicting clinical outcomes, or when used as an input in the KFRE, there was not enough evidence in our study to support a change in North America. CK21 is already being used in laboratory reporting, clinical decision support, and guideline-based CKD staging across Canada and the United States,^{1,9,19} and our data does not provide sufficient evidence that transitioning to EKFC will yield better prognostic performance. While there were instances of EKFC demonstrating benefits in certain metrics and strata, the systematic decrease of eGFR and the confusion associated with changing a population-wide reporting standard is not justifiable.

It should be noted that this recommendation is specific to the North American context and should not be read as a critique of the EKFC equation itself. EKFC was developed and validated in large European cohorts, where it has been shown to perform well. Comparator studies from the first manuscript largely agree on all results,^{5,6,73} with the comparator study from second manuscript indicating some differences. However, these should not be taken as a discouragement of the usage of EKFC abroad, rather that adoption of an equation should be based on evidence specific to one's population. Mirroring KDIGO's position, an eGFR equation should be adopted that has been validated for that population.¹

5.4 Limitations

There are few limitations that warrant mentioning found across both manuscripts. First, there are issues with misclassification for some comorbidities not being validated (hypercholesterolemia) or reliant on self-report (alcoholism). However, outcomes and key comorbidities were identified using previously validated case definitions, with consistency found across subgroups. Second, due to data unavailability, we were unable to assess variables such as medication use and muscle

mass, potentially leading to unmeasured confounding. However, the size of our cohort, the consistency of our results across subgroups, consistency with previous studies, and the comprehensive framework utilised strengthens the results of our study. Third, we ran a complete case analysis removing any missing data. The number of datapoints removed was minuscule compared to our total representing less than 1 percent, which also highlights the completeness of data. Fourth, we could not assess creatinine-cystatin C eGFRs as it was not available nor routinely reported in our cohort. However, creatinine is the most common eGFR equation worldwide reflecting real-world applications. Furthermore, specific to our second manuscript, the KFRE was developed without cystatin C, as well as prior studies finding minimal differences when assessing creatinine-cystatin based eGFRs as an input into the KFRE.⁷³ Fifth, individuals who get creatinine tested twice can be more likely to have CKD problems leading to a selection bias. In Ontario where we sourced our datasets from, healthcare is publicly funded leading to no cost barriers, as well with creatinine being routinely ordered in a standard metabolic assay not limiting our sample to measurements taken specifically for CKD concerns. Sixth, population-specific Q values were not used in this study with default values being used which may not reflect the creatinine distribution accurately in our study population. However, this method is consistent with prior validation studies internationally,^{5,69-71} and studies that did use North American Q-values found marginal difference in equation accuracy.⁷²

5.5 Future Research Avenues

Several avenues for future research follow from the limitations of this work. First, we did not have access to Q-values derived specifically for our Ontario population and relied on the European default values (0.90 mg/dL for males, 0.70 mg/dL for females) used throughout the EKFC literature. Because the Q-value anchors the EKFC equation to a population's normal

serum creatinine, the difference between European-derived values and the true Ontario distribution may have attenuated the benefits of EKFC over CK21 in our cohort. A population specific rederivation of EKFC's Q-values would represent the most direct extension of this thesis.

Second, given the slight increased risk observed in those reclassified downward when switching to EKFC, this group may warrant intensified surveillance and preventative therapies. Whether this benefit would be seen in clinical practice, and whether it would be an adequate use of limited health resources remains uncertain. Future work can model the projected changes in nephrology visits, lab testing, medication use, and healthcare costs that would follow EKFC adoption, and weigh these against the expected reduction in adverse outcomes.

Third, both manuscripts were limited to creatinine-based estimates. The EKFC cystatin-C and combined creatinine equations have not been assessed in North American compared to any of the corresponding CKD-EPI equations, potentially yielding different results. In a similar limitation, access to serum bicarbonate, albumin, phosphorus, and calcium measures will additionally enable us to conduct an assessment on the 8-variable KFRE equation as well.

Fourth, to increase generalisability, validation beyond Ontario will be essential. Expanding this study to other Canadian provinces as well as United States health systems or cohorts with differing demographics would confirm whether observed reclassification patterns and prognostic differences hold across regional populations.

5.6 Conclusions

In this large retrospective study cohort, we observed that EKFC would decrease the mean population eGFR, increase prevalence of CKD, and increase the proportion of CKD patients meeting clinical threshold for care. Though EKFC's downward reclassification identified

individuals at modestly higher risk, this did not translate into improved discrimination, with small differences in DCA and calibration. Similar findings were seen when used as an input for the KFRE equations, with uncalibrated inputs greatly overpredicting risk. However, this drawback can be addressed with recalibration, highlighting the importance of local validation when implementing new eGFR equations. Overall, in our study, adoption of EKFC in a North American population would not meaningfully improve risk prediction, while systematically lowering the eGFR values.

References (Chapters 1-5)

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, Stevens PE, Ahmed SB, et al. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International*. 2024;105(4):S117-S314. doi:10.1016/j.kint.2023.10.018
2. Mark PB, Stafford LK, Grams ME, et al. Global, regional, and national burden of chronic kidney disease in adults, 1990–2023, and its attributable risk factors: a systematic analysis for the Global Burden of Disease Study 2023. *The Lancet*. 2025;406(10518):2461-2482. doi:10.1016/S0140-6736(25)01853-7
3. Tangri N, Stevens LA, Griffith J, et al. A Predictive Model for Progression of Chronic Kidney Disease to Kidney Failure. *JAMA*. 2011;305(15):1553-1559. doi:10.1001/jama.2011.451
4. Seegmiller JC, Eckfeldt JH, Lieske JC. Challenges in Measuring Glomerular Filtration Rate: A Clinical Laboratory Perspective. *Advances in Chronic Kidney Disease*. 2018;25(1):84-92. doi:10.1053/j.ackd.2017.10.006
5. Russel WA, Fu EL, Creon A, et al. Changing from the CKD-EPI to the EKFC creatinine equation to estimate glomerular filtration rate in adults in a Northern European health system. *Nephrology Dialysis Transplantation*. 2026;41(2):275-285. doi:10.1093/ndt/gfaf148
6. Veltkamp DMJ, Rookmaaker MB, De Groot MCH, et al. Comparison of estimated glomerular filtration rate equations on prediction of mortality, kidney failure and acute kidney injury. *Nephrology Dialysis Transplantation*. 2025;40(10):1876-1886. doi:10.1093/ndt/gfaf054

7. Bello AK, Ronksley PE, Tangri N, et al. Prevalence and Demographics of CKD in Canadian Primary Care Practices: A Cross-sectional Study. *Kidney International Reports*. 2019;4(4):561-570. doi:10.1016/j.ekir.2019.01.005
8. Manns B, McKenzie SQ, Au F, Gignac PM, Geller LI. The Financial Impact of Advanced Kidney Disease on Canada Pension Plan and Private Disability Insurance Costs. *Can J Kidney Health Dis*. 2017;4:2054358117703986. doi:10.1177/2054358117703986
9. Navaneethan SD, Bansal N, Cavanaugh KL, et al. KDOQI US Commentary on the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD. *American Journal of Kidney Diseases*. 2025;85(2):135-176. doi:10.1053/j.ajkd.2024.08.003
10. Inker Lesley A., Eneanya Nwamaka D., Coresh Josef, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *New England Journal of Medicine*. 2021;385(19):1737-1749. doi:10.1056/NEJMoa2102953
11. Carrero JJ, Fu EL, Sang Y, et al. Discordances Between Creatinine- and Cystatin C–Based Estimated GFR and Adverse Clinical Outcomes in Routine Clinical Practice. *American Journal of Kidney Diseases*. 2023;82(5):534-542. doi:10.1053/j.ajkd.2023.04.002
12. Spencer S, Desborough R, Bhandari S. Should Cystatin C eGFR Become Routine Clinical Practice? *Biomolecules*. 2023;13(7):1075. doi:10.3390/biom13071075
13. Writing Group for the CKD Prognosis Consortium. Estimated Glomerular Filtration Rate, Albuminuria, and Adverse Outcomes: An Individual-Participant Data Meta-Analysis. *JAMA*. 2023;330(13):1266-1277. doi:10.1001/jama.2023.17002
14. Levey AS, Stevens LA, Coresh J. Conceptual Model of CKD: Applications and Implications. *American Journal of Kidney Diseases*. 2009;53(3):S4-S16. doi:10.1053/j.ajkd.2008.07.048

15. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C yuan. Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization. *N Engl J Med*. 2004;351(13):1296-1305. doi:10.1056/NEJMoa041031
16. Perkins RM, Bucaloiu ID, Kirchner HL, Ashouian N, Hartle JE, Yahya T. GFR Decline and Mortality Risk among Patients with Chronic Kidney Disease. *Clinical Journal of the American Society of Nephrology*. 2011;6(8).
https://journals.lww.com/cjasn/fulltext/2011/08000/gfr_decline_and_mortality_risk_among_patients_with.14.aspx
17. Pottel H, Björk J, Courbebaisse M, et al. Development and Validation of a Modified Full Age Spectrum Creatinine-Based Equation to Estimate Glomerular Filtration Rate. *Ann Intern Med*. 2021;174(2):183-191. doi:10.7326/M20-4366
18. McArthur E, Smith G, Sood MM, et al. Impact of the 2021 CKD-EPI eGFR Equation on Kidney Care Referral Criteria in Ontario, Canada: A Population-based Cross-sectional Study. *Can J Kidney Health Dis*. 2024;11:20543581241229258. doi:10.1177/20543581241229258
19. CHANGES TO KIDNEY FUNCTION TESTING – Supporting Clinicians in Improving Care for Patients with Chronic Kidney Disease – LifeLabs. Accessed February 24, 2026.
<https://www.lifelabs.com/notification/changes-to-kidney-function-testing-supporting-clinicians-in-improving-care-for-patients-with-chronic-kidney-disease/>
20. Ontario Renal Network, Ontario Health. *A New Race-Free Equation for Estimating Glomerular Filtration Rate (GFR)*. Ontario Health; 2024.
<https://www.ontariorenalnetwork.ca/sites/renalnetwork/files/assets/NewRaceFreeCalculationProviderDocument.pdf>

21. Emrich IE, Pickering JW, Götzinger F, et al. Comparison of three creatinine-based equations to predict adverse outcome in a cardiovascular high-risk cohort: an investigation using the SPRINT research materials. *Clinical Kidney Journal*. 2024;17(2):sfae011. doi:10.1093/ckj/sfae011
22. Lu S, Robyak K, Zhu Y. The CKD-EPI 2021 Equation and Other Creatinine-Based Race-Independent eGFR Equations in Chronic Kidney Disease Diagnosis and Staging. *The Journal of Applied Laboratory Medicine*. 2023;8(5):952-961. doi:10.1093/jalm/jfad047
23. Fogo AB. Mechanisms of progression of chronic kidney disease. *Pediatric Nephrology*. 2007;22(12):2011-2022. doi:10.1007/s00467-007-0524-0
24. The Lancet. Chronic kidney disease: breaking the silence. *The Lancet*. 2025;406(10518):2393. doi:10.1016/S0140-6736(25)02363-3
25. Foreman KJ, Marquez N, Dolgert A, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016–40 for 195 countries and territories. *The Lancet*. 2018;392(10159):2052-2090. doi:10.1016/S0140-6736(18)31694-5
26. Cockcroft DW, Gault H. Prediction of Creatinine Clearance from Serum Creatinine. *Nephron*. 1976;16(1):31-41. doi:10.1159/000180580
27. Levey AS, Bosch JP, Lewis JB, et al. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *Ann Intern Med*. 1999;130(6):461-470. doi:10.7326/0003-4819-130-6-199903160-00002
28. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006

29. Levin A, Stevens PE, Bilous RW, et al. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International Supplements*. 2013;3(1):1-150. doi:10.1038/kisup.2012.73
30. Vyas DA, Eisenstein LG, Jones DS. Hidden in Plain Sight — Reconsidering the Use of Race Correction in Clinical Algorithms. Malina D, ed. *N Engl J Med*. 2020;383(9):874-882. doi:10.1056/NEJMms2004740
31. Tangri N, Grams ME, Levey AS, et al. Multinational Assessment of Accuracy of Equations for Predicting Risk of Kidney Failure: A Meta-analysis. *JAMA*. 2016;315(2):164-174. doi:10.1001/jama.2015.18202
32. Grams ME, Brunskill NJ, Ballew SH, et al. The Kidney Failure Risk Equation: Evaluation of Novel Input Variables including eGFR Estimated Using the CKD-EPI 2021 Equation in 59 Cohorts. *Journal of the American Society of Nephrology*. 2023;34(3). https://journals.lww.com/jasn/fulltext/2023/03000/the_kidney_failure_risk_equation__evaluation_of.14.aspx
33. Maeda A, Inokuchi R, Bellomo R, Doi K. Heterogeneity in the definition of major adverse kidney events: a scoping review. *Intensive Care Medicine*. 2024;50(7):1049-1063. doi:10.1007/s00134-024-07480-x
34. Levin A, Herrington WG, Heerspink HL, et al. International consensus definitions of clinical trial outcomes for kidney failure: 2020. *Kidney International*. 2020;98(4):849-859. doi:10.1016/j.kint.2020.07.013
35. Matsushita K, Astor BC, Woodward M, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population

- cohorts: a collaborative meta-analysis. *Lancet*. 2010;375(9731):2073-2081.
doi:10.1016/s0140-6736(10)60674-5
36. Herrington WG, Judge PK, Grams ME, Wanner C. Chronic kidney disease. *The Lancet*. 2026;407(10523):90-104. doi:10.1016/S0140-6736(25)01942-7
37. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. *Circulation*. 2018;137(9):961-972.
doi:10.1161/CIRCULATIONAHA.117.033502
38. Liu L, Reeder B, Shuaib A, Mazagri R. Validity of Stroke Diagnosis on Hospital Discharge Records in Saskatchewan, Canada: Implications for Stroke Surveillance. *Cerebrovascular Diseases*. 1999;9(4):224-230. doi:10.1159/000015960
39. Austin PC, Daly PA, Tu JV. A multicenter study of the coding accuracy of hospital discharge administrative data for patients admitted to cardiac care units in Ontario. *American Heart Journal*. 2002;144(2):290-296. doi:10.1067/mhj.2002.123839
40. Saunders-Hastings P, Heong SW, Srichaikul J, et al. Acute myocardial infarction: Development and application of an ICD-10-CM-based algorithm to a large U.S. healthcare claims-based database. *PLOS ONE*. 2021;16(7):e0253580.
doi:10.1371/journal.pone.0253580
41. Davidson J, Banerjee A, Muzambi R, Smeeth L, Warren-Gash C. Validity of acute cardiovascular outcome diagnoses recorded in European electronic health records: a systematic review. *Clinical epidemiology*. Published online 2020:1095-1111.
42. Pocobelli G, Ichikawa L, Yu O, et al. Validation of international classification of diseases, tenth revision, clinical modification diagnosis codes for heart failure subtypes. *Pharmacoepidemiology and Drug Safety*. 2022;31(9):992-997.

43. McCormick N, Lacaille D, Bhole V, Avina-Zubieta JA. Validity of Heart Failure Diagnoses in Administrative Databases: A Systematic Review and Meta-Analysis. *PLOS ONE*. 2014;9(8):e104519. doi:10.1371/journal.pone.0104519
44. Ku E, Xie D, Shlipak M, et al. Change in Measured GFR Versus eGFR and CKD Outcomes. *Journal of the American Society of Nephrology*. 2016;27(7).
https://journals.lww.com/jasn/fulltext/2016/07000/change_in_measured_gfr_versus_egfr_and_ckd.34.aspx
45. Delgado C, Baweja M, Crews DC, et al. A Unifying Approach for GFR Estimation: Recommendations of the NKF-ASN Task Force on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *American Journal of Kidney Diseases*. 2022;79(2):268-288.e1. doi:10.1053/j.ajkd.2021.08.003
46. Auguste BL, Nadeau-Fredette AC, Parekh RS, et al. A Canadian Commentary on the NKF-ASN Task Force Recommendations on Reassessing the Inclusion of Race in Diagnosing Kidney Disease. *Kidney Medicine*. 2024;6(1). doi:10.1016/j.xkme.2023.100746
47. Cavalier E, Zima T, Datta P, et al. Recommendations for European laboratories based on the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Clinical Chemistry and Laboratory Medicine (CCLM)*. 2024;63(3):525-534. doi:10.1515/cclm-2024-1082
48. Gao M, Vilayur E, Ferreira D, Nanra R, Hawkins J. Estimating the glomerular filtration rate in pregnancy: The evaluation of the Nanra and CKD-EPI serum creatinine-based equations. *Obstet Med*. 2021;14(1):31-34. doi:10.1177/1753495X20904177

49. Quan H, Khan N, Hemmelgarn BR, et al. Validation of a Case Definition to Define Hypertension Using Administrative Data. *Hypertension*. 2009;54(6):1423-1428. doi:10.1161/HYPERTENSIONAHA.109.139279
50. Hux JE, Ivis F, Flintoft V, Bica A. Diabetes in Ontario: Determination of prevalence and incidence using a validated administrative data algorithm. *Diabetes Care*. 2002;25(3):512-516. doi:10.2337/diacare.25.3.512
51. Lipscombe LL, Hwee J, Webster L, Shah BR, Booth GL, Tu K. Identifying diabetes cases from administrative data: a population-based validation study. *BMC Health Services Research*. 2018;18(1):316. doi:10.1186/s12913-018-3148-0
52. Clemens KK, Reid JN, Shariff SZ, Welk B. Validity of Hospital Codes for Obesity in Ontario, Canada. *Canadian Journal of Diabetes*. 2021;45(3):243-248.e4. doi:10.1016/j.jcjd.2020.08.106
53. Sriperumbuduri S, McArthur E, Hundemer GL, et al. Initial and Recurrent Hyperkalemia Events in Patients With CKD in Older Adults: A Population-Based Cohort Study. *Can J Kidney Health Dis*. 2021;8:20543581211017408. doi:10.1177/20543581211017408
54. Philip G, Djerboua M, Carlone D, Flemming JA. Validation of a hierarchical algorithm to define chronic liver disease and cirrhosis etiology in administrative healthcare data. Lin W, ed. *PLoS ONE*. 2020;15(2):e0229218. doi:10.1371/journal.pone.0229218
55. Lee TM, Tu K, Ivers NM, Barnsley J, Gershon AS. Measuring chronic obstructive pulmonary disease (COPD) quality indicators using primary care electronic medical records (EMRs) in Ontario, Canada. *Canadian Journal of Respiratory, Critical Care, and Sleep Medicine*. 2022;6(3):169-183. doi:10.1080/24745332.2021.1913079

56. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94(446):496-509.
doi:10.2307/2670170
57. Blanche P, Dartigues JF, Jacqmin-Gadda H. Estimating and comparing time-dependent areas under receiver operating characteristic curves for censored event times with competing risks. *Statistics in Medicine*. 2013;32(30):5381-5397. doi:10.1002/sim.5958
58. Graf E, Schmoor C, Sauerbrei W, Schumacher M. Assessment and comparison of prognostic classification schemes for survival data. *Statistics in Medicine*. 1999;18(17-18):2529-2545.
doi:10.1002/(SICI)1097-0258(19990915/30)18:17/18<2529::AID-SIM274>3.0.CO;2-5
59. Schoop R, Beyersmann J, Schumacher M, Binder H. Quantifying the predictive accuracy of time-to-event models in the presence of competing risks. *Biometrical Journal*. 2011;53(1):88-112. doi:10.1002/bimj.201000073
60. Gerds TA, Ohlendorff JS, Ozenne B. riskRegression: Risk Regression Models and Prediction Scores for Survival Analysis with Competing Risks. Published online 2023. <https://CRAN.R-project.org/package=riskRegression>
61. Therneau TM. A Package for Survival Analysis in R. Published online 2023. <https://CRAN.R-project.org/package=survival>
62. Gray B. cmprsk: Subdistribution Analysis of Competing Risks. Published online 2022. <https://CRAN.R-project.org/package=cmprsk>
63. Brown M. rmda: Risk Model Decision Analysis. Published online 2018. <https://CRAN.R-project.org/package=rmda>
64. Gerds TA. prodlim: Product-Limit Estimation for Censored Event History Analysis. Published online 2023. <https://CRAN.R-project.org/package=prodlim>

65. Genzen JR, Souers RJ, Pearson LN, et al. An Update on Reported Adoption of 2021 CKD-EPI Estimated Glomerular Filtration Rate Equations. *Clinical Chemistry*. 2023;69(10):1197-1199. doi:10.1093/clinchem/hvad116
66. LifeLabs. Changes to Kidney Function Testing – Supporting Clinicians in Improving Care for Patients with Chronic Kidney Disease. April 22, 2024. Accessed April 5, 2026. <https://www.lifelabs.com/notification/changes-to-kidney-function-testing-supporting-clinicians-in-improving-care-for-patients-with-chronic-kidney-disease/>
67. White-Al Habeeb N, Catomeris P. *Kidney Function Laboratory Test Reporting Updates in Ontario*. Dynacare; 2024. Accessed April 5, 2026. <https://www.dynacare.ca>
68. Patel S, Thompson W, Sivaswamy A, et al. Development and validation of a model to categorize cardiovascular cause of death using health administrative data. *American Heart Journal Plus: Cardiology Research and Practice*. 2022;22:100207. doi:10.1016/j.ahjo.2022.100207
69. Napier K, Lim D, Thomas E, et al. Impact of routine reporting of estimated glomerular filtration rate using the European Kidney Function Consortium and Chronic Kidney Disease Epidemiology Collaboration equations in a Western Australian community population. *Nephrology*. 2022;27(10):823-833. doi:10.1111/nep.14083
70. Lee S, Lee GH, Kim H, Yang HS, Hur M. Application of the European Kidney Function Consortium Equation to Estimate Glomerular Filtration Rate: A Comparison Study of the CKiD and CKD-EPI Equations Using the Korea National Health and Nutrition Examination Survey (KNHANES 2008–2021). *Medicina*. 2024;60(4):612. doi:10.3390/medicina60040612

71. Zhao L, Li H li, Liu H jing, et al. Validation of the EKFC equation for glomerular filtration rate estimation and comparison with the Asian-modified CKD-EPI equation in Chinese chronic kidney disease patients in an external study. *Renal Failure*. 2023;45(1):2150217. doi:10.1080/0886022X.2022.2150217
72. Delanaye P, Rule AD, Schaeffner E, et al. Performance of the European Kidney Function Consortium (EKFC) creatinine-based equation in United States cohorts. *Kidney International*. 2024;105(3):629-637. doi:10.1016/j.kint.2023.11.024
73. Lanot A, Delanaye P, Metzger M, Hamroun A, Alencar de Pinho N, Mariat C. Which equation and which biomarker should be used in the Kidney Failure Risk Equation? A comparative analysis in the CKD-REIN cohort. *Clinical Kidney Journal*. 2026;19(4):sfag097. doi:10.1093/ckj/sfag097
74. Chowdhury S, Massicotte-Azarniouch D, Hundemer GL, Delanaye P, Akbari A, Sood MM. GFR ESTIMATING EQUATIONS AND THEIR ASSOCIATION WITH ADVERSE CLINICAL OUTCOMES: A POPULATION-BASED RETROSPECTIVE COHORT STUDY.
75. Lam NN, McArthur E, Kim SJ, Knoll GA. Validation of Kidney Transplantation Using Administrative Data. *Can J Kidney Health Dis*. 2015;2:54. doi:10.1186/s40697-015-0054-9
76. Coresh J, Turin TC, Matsushita K, et al. Decline in Estimated Glomerular Filtration Rate and Subsequent Risk of End-Stage Renal Disease and Mortality. *JAMA*. 2014;311(24):2518. doi:10.1001/jama.2014.6634
77. Kokotailo RA, Hill MD. Coding of Stroke and Stroke Risk Factors Using *International Classification of Diseases* , Revisions 9 and 10. *Stroke*. 2005;36(8):1776-1781. doi:10.1161/01.STR.0000174293.17959.a1

78. McCormick N, Bhole V, Lacaille D, Avina-Zubieta JA. Validity of Diagnostic Codes for Acute Stroke in Administrative Databases: A Systematic Review. Quinn TJ, ed. *PLoS ONE*. 2015;10(8):e0135834. doi:10.1371/journal.pone.0135834

THESIS SUPPLEMENTARY MATERIAL

Chapter 3: Supplemental Material

Appendix A. Sensitivity and specificity of outcome definitions

Outcome (component)	Data source & code / definition	Sens.	Spec.	PPV	Ref.
Composite Kidney Outcome: Major Adverse Kidney Events					
Need for dialysis	CORR; treatment code ≠ 171/181	Reference-standard registry (mandatory across Canadian); not ICD-coded			
Kidney transplant	CORR; treatment code = 171/181	96%	—	98%	75
eGFR <15 ml/min/1.73m ²	OLIS; serum creatinine (LOINC 14682-9)	Laboratory-defined			76
≥30% decline in eGFR from baseline	OLIS; serum creatinine (LOINC 14682-9)	Laboratory-defined			76
Composite Cardiac Outcome: Major Adverse Cardiovascular Events					
Acute coronary syndrome / acute MI	ICD-10 I21.x	88.8%	92.8%	88.5%	39
Ischemic stroke	ICD-10 I63.x	≥82%	≥95%	~82%	77,78
Heart-failure hospitalization	ICD-10 I50.x	75%	97%	≥87%	43
Cardiovascular death	RPDB death + circulatory cause (I00–I99)	Proxy definition, not validated			—

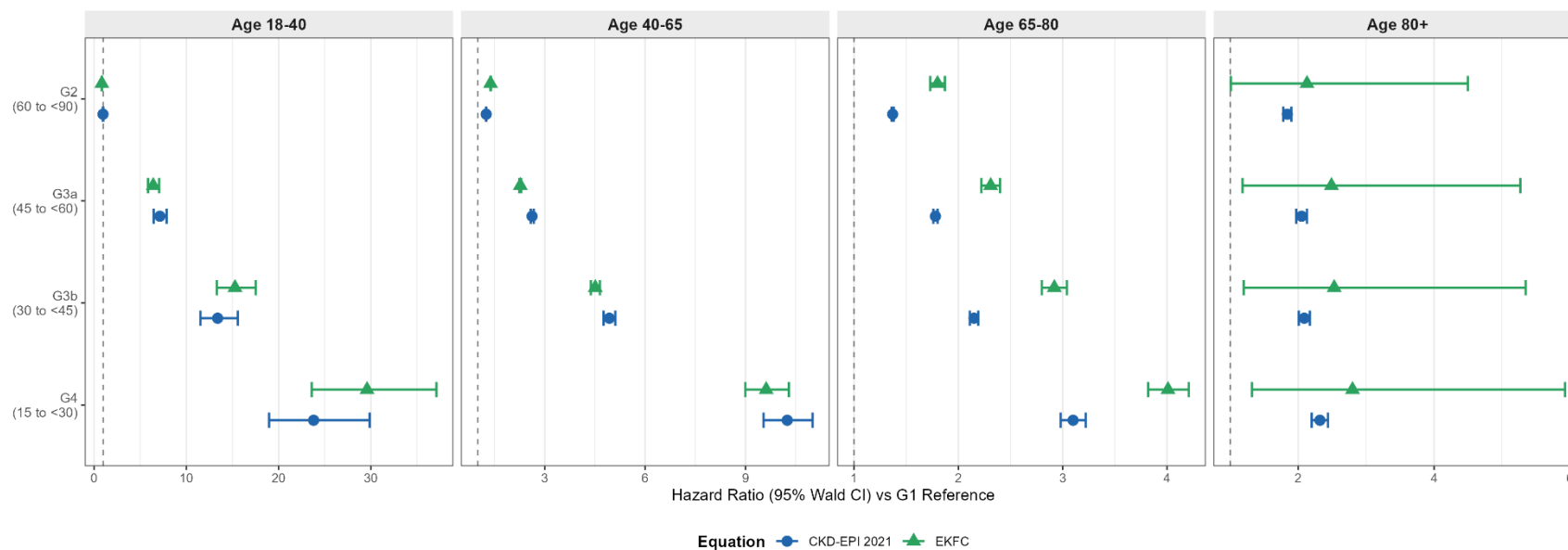
Appendix B. Age-Stratified Analysis

Table B1. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MAKE by eGFR categories relative to G1 (≥ 90)*, accounting for all-cause mortality as a competing risk, by age-group

eGFR	CKD-EPI 2021				EKFC			
Category	18 to <40	40 to ≤ 65	66 to <80	≥ 80	18 to <40	40 to ≤ 65	66 to <80	≥ 80
G1 (≥ 90)	142,500/1,283,690 11.10% REF	493,491/2,043,688 24.15% REF	122,045/296,390 41.18% REF	3,015/10,114 29.81% REF	96,804/1,157,992 8.36% REF	361,589/1,468,296 24.63% REF	2,676/8,550 31.30% REF	7/31 22.58% REF
G2 (60-89)	7,842/79,568 9.86% 0.98 (0.96 - 1.00)	219,037/773,477 28.32% 1.25 (1.24 - 1.25)	289,380/570,179 50.75% 1.37 (1.36 - 1.38)	82,275/173,372 47.46% 1.84 (1.78 - 1.90)	12,559/204,524 6.14% 0.85 (0.83 - 0.86)	421,651/1,317,312 32.01% 1.38 (1.38 - 1.39)	361,732/734,363 49.26% 1.80 (1.73 - 1.87)	49,975/109,160 45.78% 2.13 (1.01 - 4.50)
G3a (45-59)	870/1,498 58.08% 7.14 (6.47 - 7.88)	16,485/31,787 51.86% 2.62 (2.58 - 2.67)	53,474/90,590 59.03% 1.78 (1.76 - 1.80)	32,221/64,788 49.73% 2.05 (1.97 - 2.13)	933/2,090 44.64% 6.42 (5.86 - 7.05)	28,383/59,903 47.38% 2.27 (2.24 - 2.30)	106,213/186,160 57.05% 2.31 (2.22 - 2.40)	51,091/101,939 50.12% 2.49 (1.18 - 5.27)
G3b (30-44)	587/745 78.79% 13.40 (11.53 - 15.58)	6,377/8,803 72.44% 4.93 (4.76 - 5.11)	18,175/28,222 64.40% 2.15 (2.11 - 2.19)	15,706/32,134 48.88% 2.09 (2.01 - 2.17)	670/868 77.19% 15.28 (13.31 - 17.53)	8,326/11,848 70.27% 4.51 (4.38 - 4.65)	33,630/52,570 63.97% 2.92 (2.80 - 3.04)	29,980/61,162 49.02% 2.53 (1.20 - 5.35)
G4 (15-29)	428/486 88.07% 23.80 (18.97 - 29.86)	2,799/3,293 85.00% 10.25 (9.54 - 11.01)	4,701/6,561 71.65% 3.10 (2.98 - 3.22)	3,825/7,681 49.80% 2.32 (2.20 - 2.44)	450/513 87.72% 29.59 (23.60 - 37.11)	3,088/3,689 83.71% 9.62 (9.00 - 10.30)	7,232/10,299 70.22% 4.01 (3.82 - 4.21)	7,847/15,797 49.67% 2.80 (1.32 - 5.93)

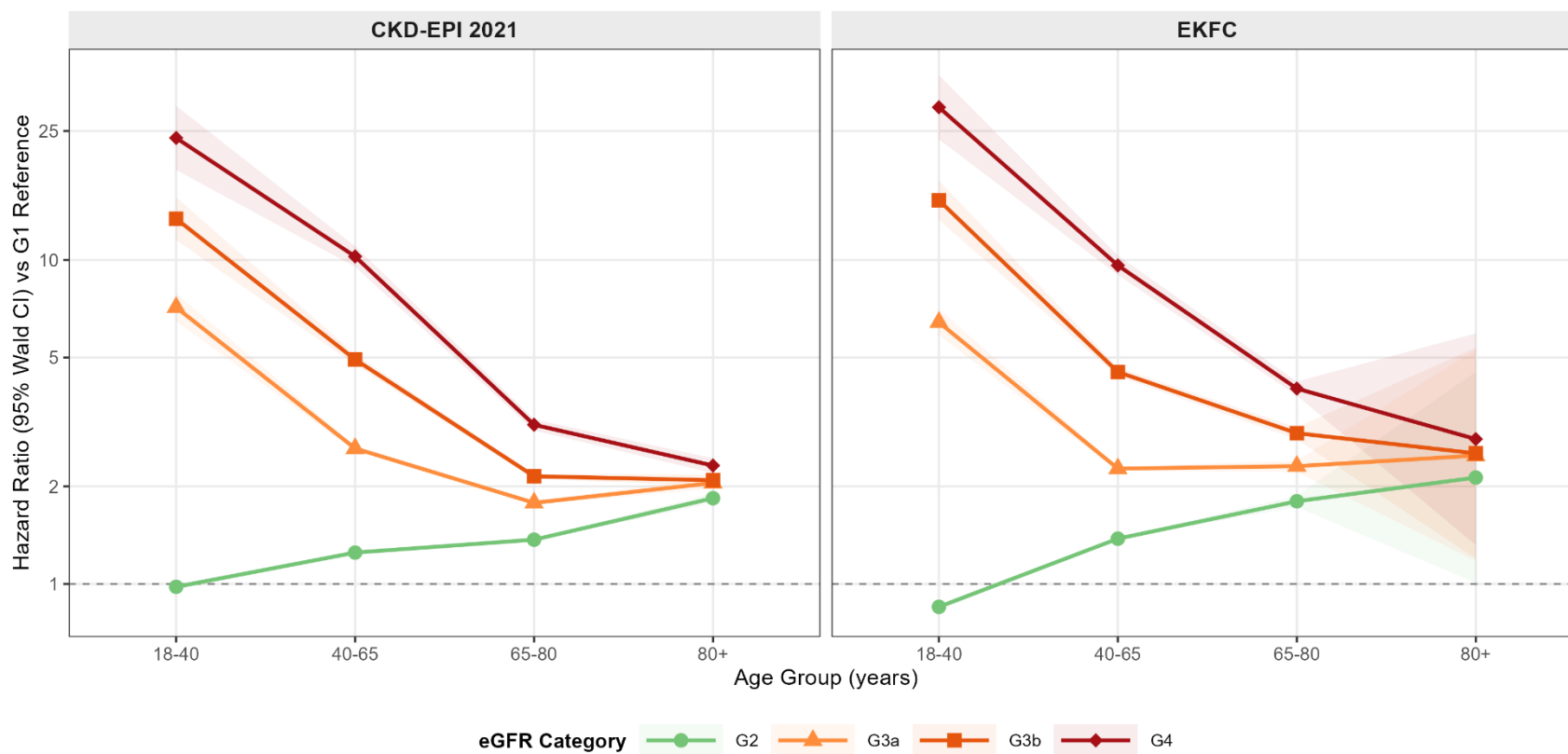
*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Figure B1. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MAKE by eGFR categories relative to G1 (≥ 90)*, accounting for all-cause mortality as a competing risk, by age-group



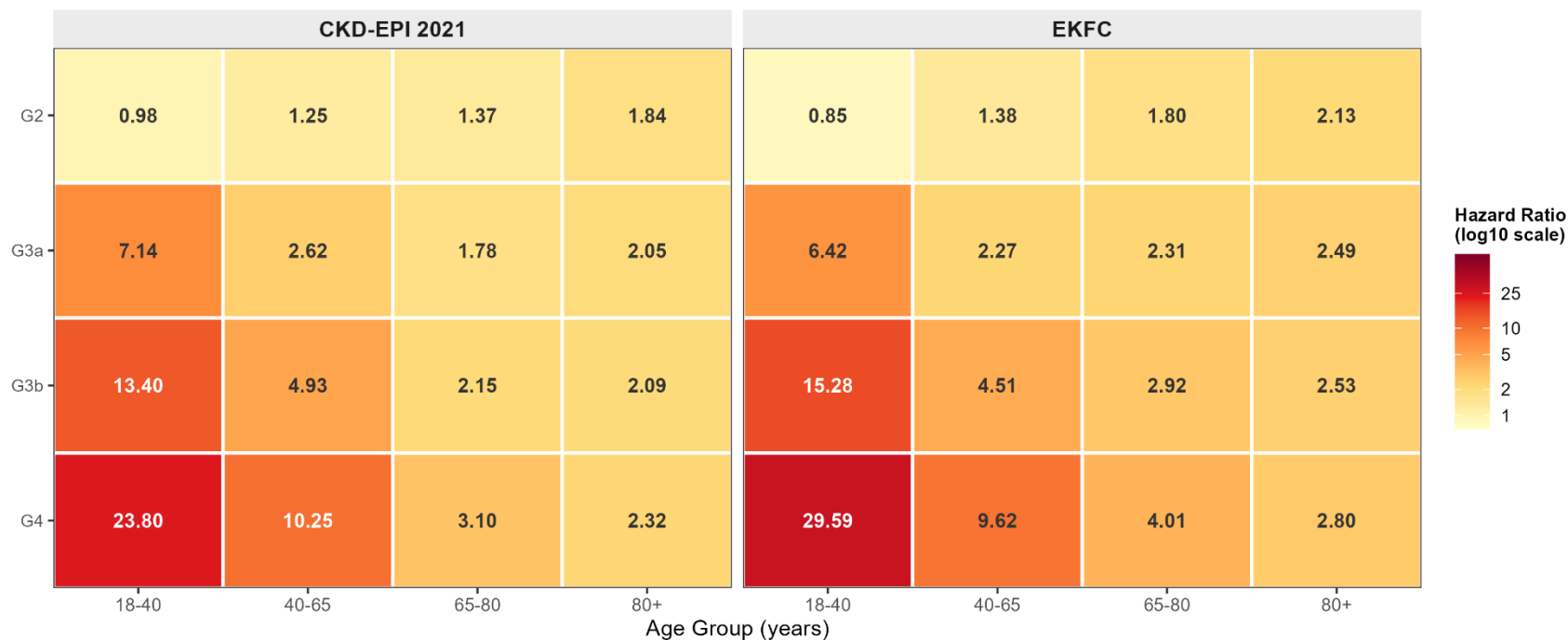
*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Figure B2. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MAKE by eGFR categories relative to G1 (≥ 90)*, accounting for all-cause mortality as a competing risk, by age-group; Y-axis is on log10 scale.



*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Figure B3. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) heat map for MAKE by eGFR categories relative to G1 (≥ 90)*, accounting for all-cause mortality as a competing risk, by age-group; colour is on log10 scale



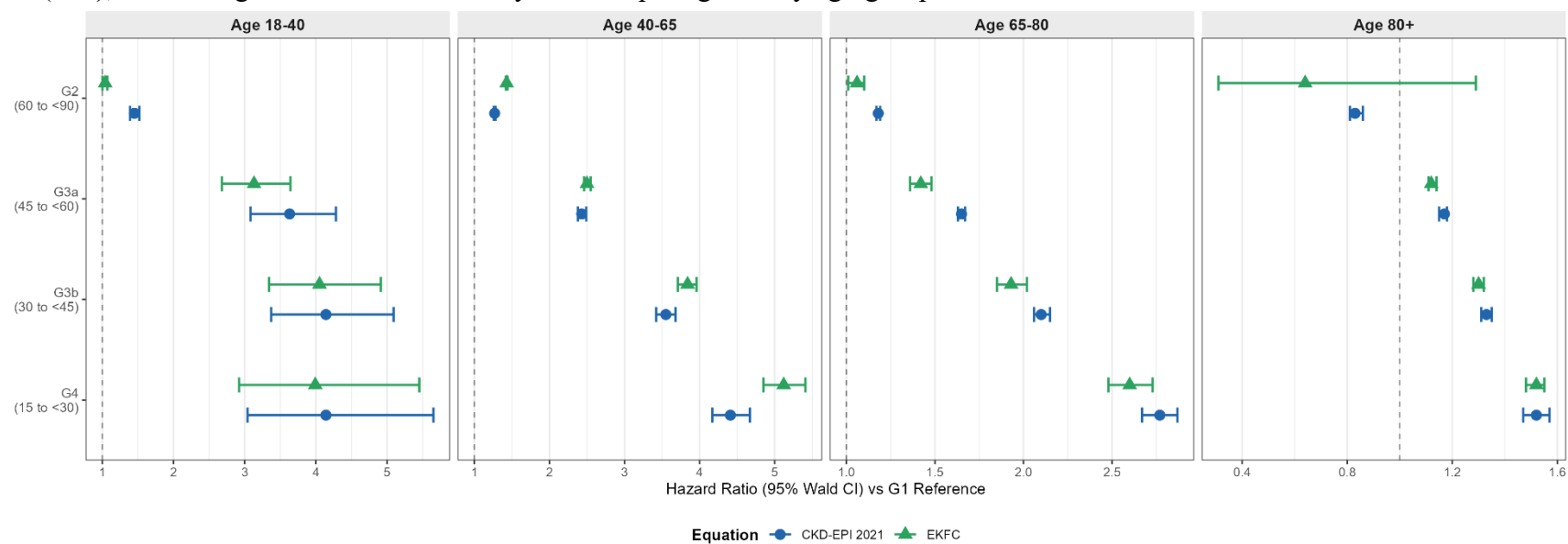
*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Table B2. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MACE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk, by age-group

eGFR Category	CKD-EPI 2021				EKFC			
	18 to <40	40 to ≤ 65	66 to <80	≥ 80	18 to <40	40 to ≤ 65	66 to <80	≥ 80
G1 (≥ 90)	22,976/1,283,690 (1.79%) REF	220,388/2,043,688 (10.78%) REF	86,335/296,390 (29.13%) REF	3,998/10,114 (39.53%) REF	21,420/1,157,992 (1.85%) REF	139,923/1,468,296 (9.53%) REF	2,545/8,550 (29.77%) REF	9/31 (29.03%) REF
G2 (60-89)	2,083/79,568 (2.62%) 1.45 (1.39-1.52)	104,743/773,477 (13.54%) 1.27 (1.26-1.28)	190,788/570,179 (33.46%) 1.18 (1.17-1.19)	77,976/173,372 (44.98%) 0.83 (0.81-0.86)	3,599/204,524 (1.76%) 1.04 (1.00-1.07)	178,287/1,317,312 (13.53%) 1.43 (1.42-1.44)	227,419/734,363 (30.97%) 1.06 (1.01-1.10)	47,734/109,160 (43.73%) 0.64 (0.31-1.29)
G3a (45-59)	176/1,498 (11.75%) 3.63 (3.08-4.28)	8,770/31,787 (27.59%) 2.43 (2.38-2.49)	39,831/90,590 (43.97%) 1.65 (1.63-1.67)	32,107/64,788 (49.56%) 1.17 (1.15-1.18)	199/2,090 (9.52%) 3.13 (2.68-3.64)	14,491/59,903 (24.19%) 2.50 (2.46-2.55)	73,332/186,160 (39.39%) 1.42 (1.36-1.48)	47,925/101,939 (47.01%) 1.12 (1.11-1.14)
G3b (30-44)	115/745 (15.44%) 4.14 (3.37-5.09)	3,523/8,803 (40.02%) 3.55 (3.42-3.68)	14,965/28,222 (53.03%) 2.10 (2.06-2.15)	17,099/32,134 (53.21%) 1.33 (1.31-1.35)	132/868 (15.21%) 4.05 (3.34-4.91)	4,522/11,848 (38.17%) 3.84 (3.71-3.96)	26,461/52,570 (50.33%) 1.93 (1.85-2.02)	31,169/61,162 (50.96%) 1.30 (1.28-1.32)
G4 (15-29)	85/486 (17.49%) 4.14 (3.04-5.65)	1,548/3,293 (47.01%) 4.41 (4.17-4.67)	4,079/6,561 (62.17%) 2.77 (2.67-2.87)	4,330/7,681 (56.37%) 1.52 (1.47-1.57)	85/513 (16.57%) 3.99 (2.92-5.45)	1,749/3,689 (47.41%) 5.12 (4.85-5.41)	6,241/10,299 (60.60%) 2.60 (2.48-2.73)	8,673/15,797 (54.90%) 1.52 (1.48-1.55)

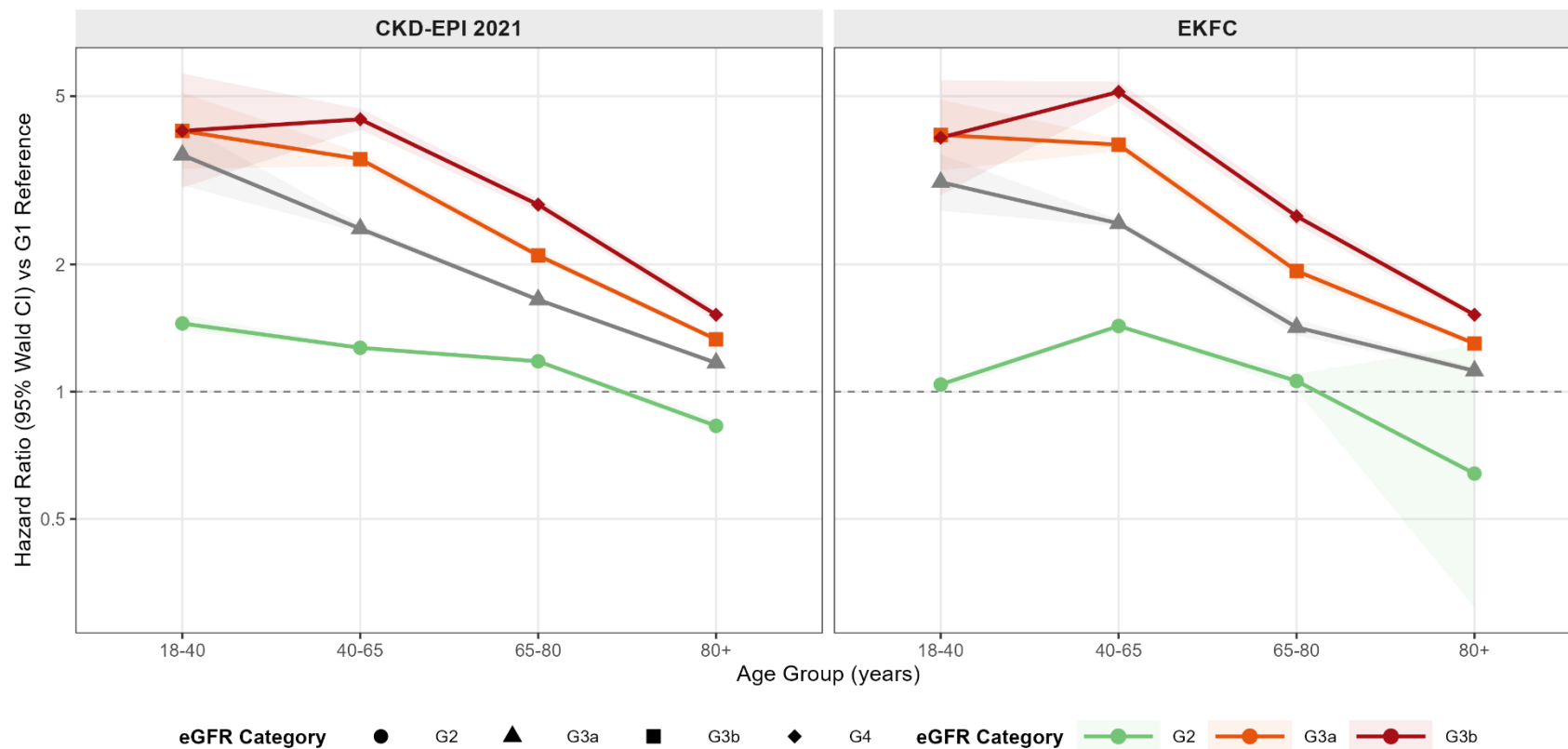
*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Figure B4. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by age-group



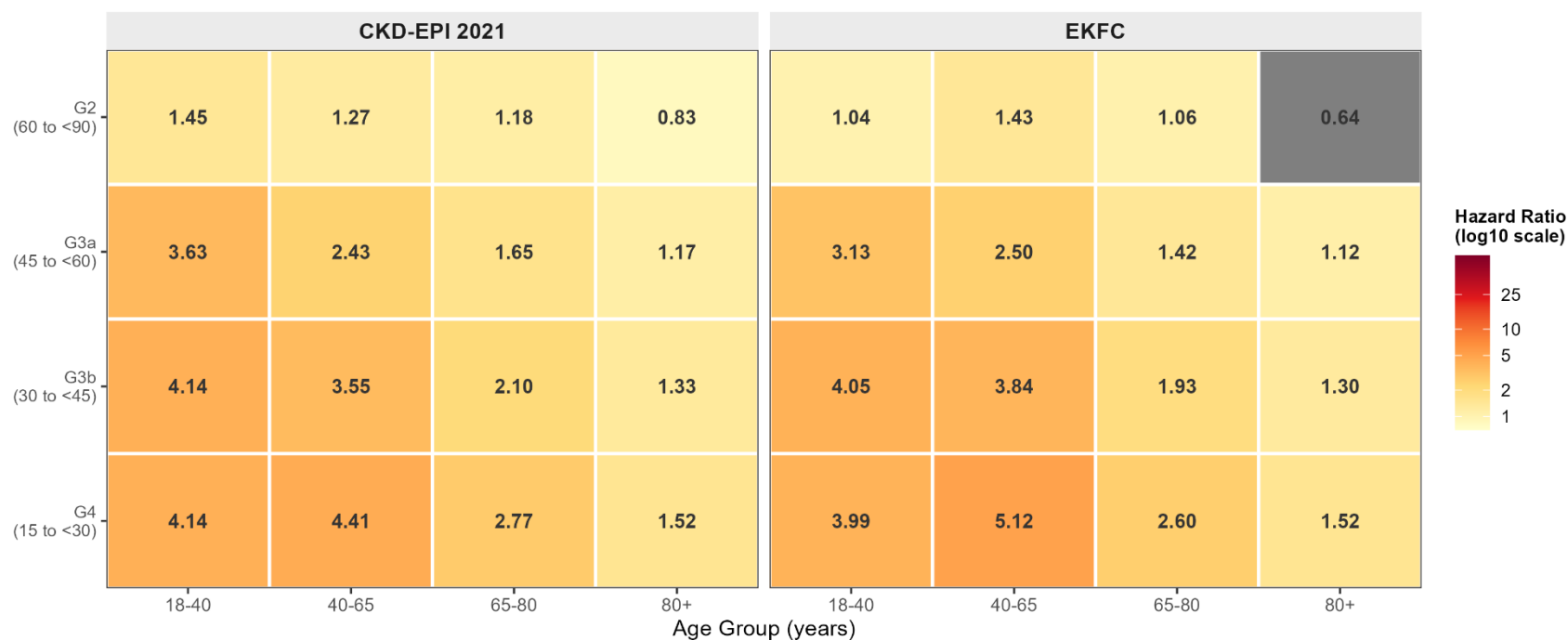
**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure B5. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) line plot for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by age-group; Y-axis is on log10 scale.



**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure B6. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) heat map for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by age-group; colour is on log10 scale



**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Appendix C. Sex-Stratified Analysis

Table C1. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk, by sex

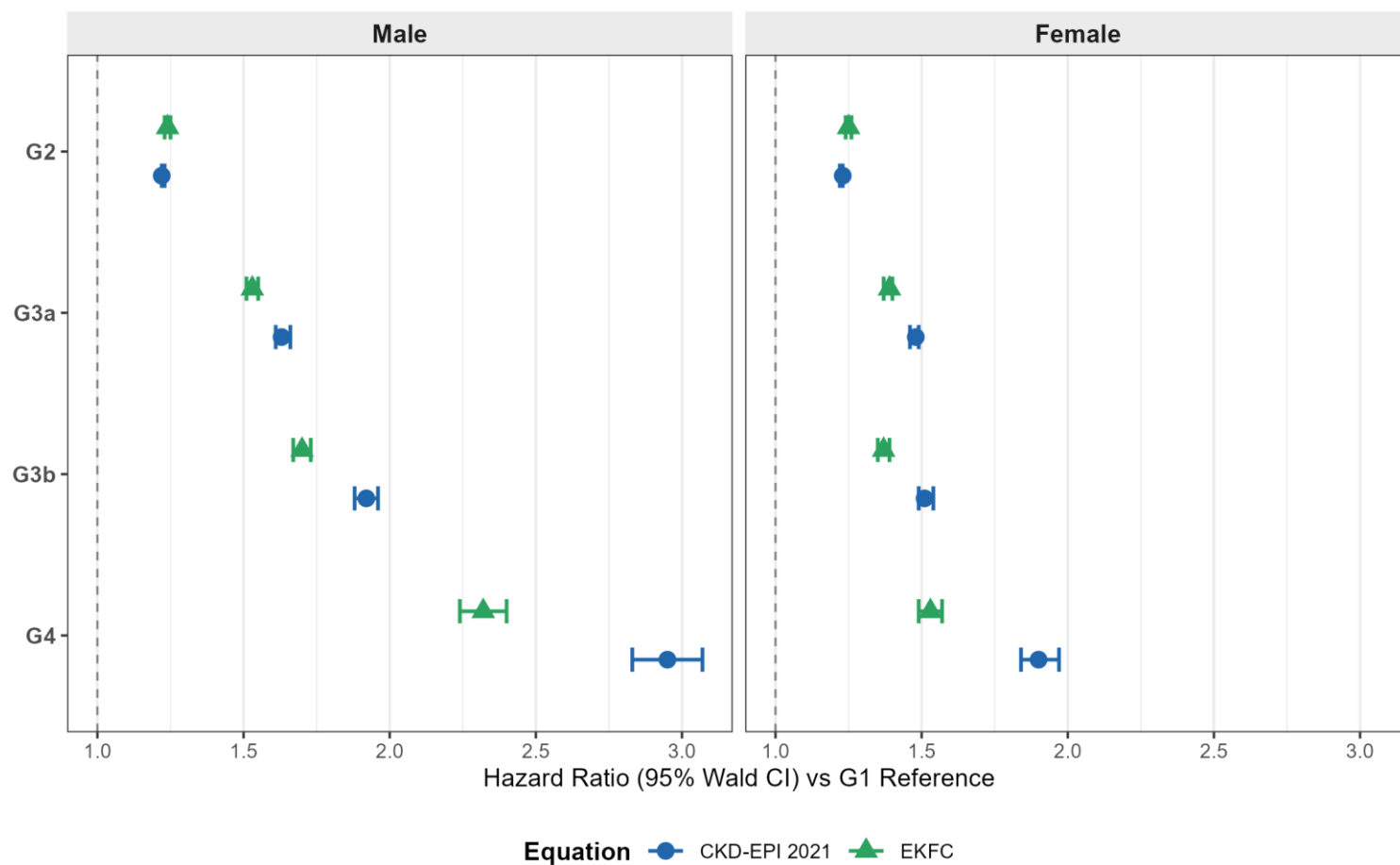
<i>eGFR</i>	<i>CK21</i>		<i>EKFC</i>	
<i>Category</i>	Male	Female	Male	Female
<i>G1 (≥ 90)</i>	320,206/1,566,393 (20.44%) REF	440,845/2,067,489 (21.32%) REF	186,121/1,105,273 (16.84%) REF	274,955/1,529,596 (17.98%) REF
<i>G2 (60-89)</i>	264,312/741,809 (35.63%) 1.22 (1.22 - 1.23)	334,222/854,787 (39.10%) 1.23 (1.22 - 1.23)	378,600/1,113,569 (34.00%) 1.24 (1.23 - 1.25)	467,317/1,251,790 (37.33%) 1.25 (1.24 - 1.26)
<i>G3a (45-59)</i>	41,620/75,464 (55.15%) 1.63 (1.61 - 1.66)	61,430/113,199 (54.27%) 1.48 (1.46 - 1.49)	75,328/140,992 (53.43%) 1.53 (1.51 - 1.55)	111,292/209,100 (53.22%) 1.39 (1.37 - 1.40)
<i>G3b (30-44)</i>	16,376/26,709 (61.31%) 1.92 (1.88 - 1.96)	24,469/43,195 (56.65%) 1.51 (1.49 - 1.54)	27,791/46,552 (59.70%) 1.70 (1.67 - 1.73)	44,815/79,896 (56.09%) 1.37 (1.35 - 1.39)
<i>G4 (15-29)</i>	5,311/7,602 (69.86%) 2.95 (2.83 - 3.07)	6,442/10,419 (61.83%) 1.90 (1.84 - 1.97)	7,635/11,591 (65.87%) 2.32 (2.24 - 2.40)	10,982/18,707 (58.71%) 1.53 (1.49 - 1.57)

*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Figure C1. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk, by sex

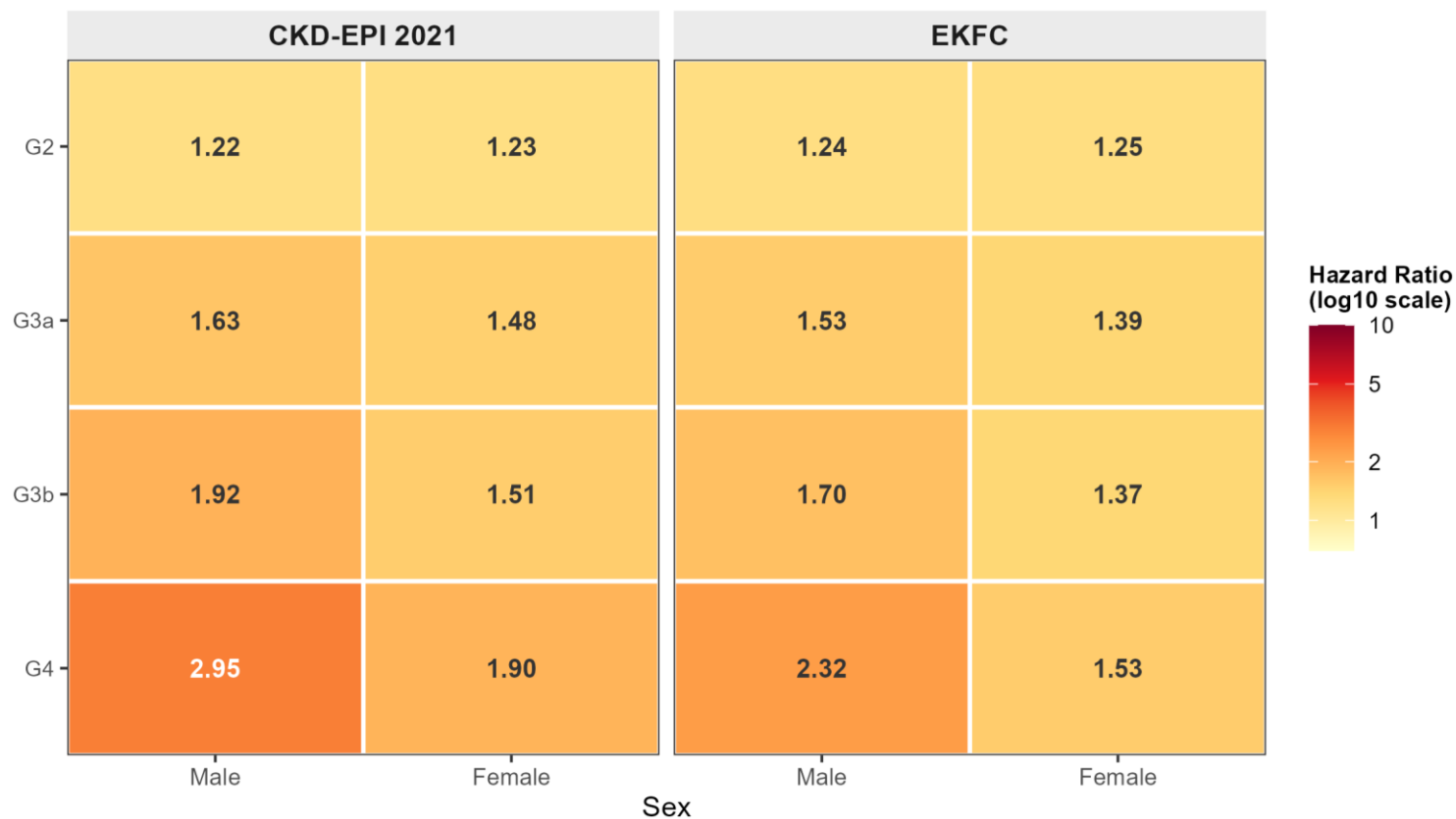
Sex-Stratified Hazard Ratios for Kidney Failure (MAKE) by eGFR Category

Reference: G1 Normal or high (eGFR ≥ 90)



**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure C2. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) heat map for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk, by sex; colour is on log10 scale



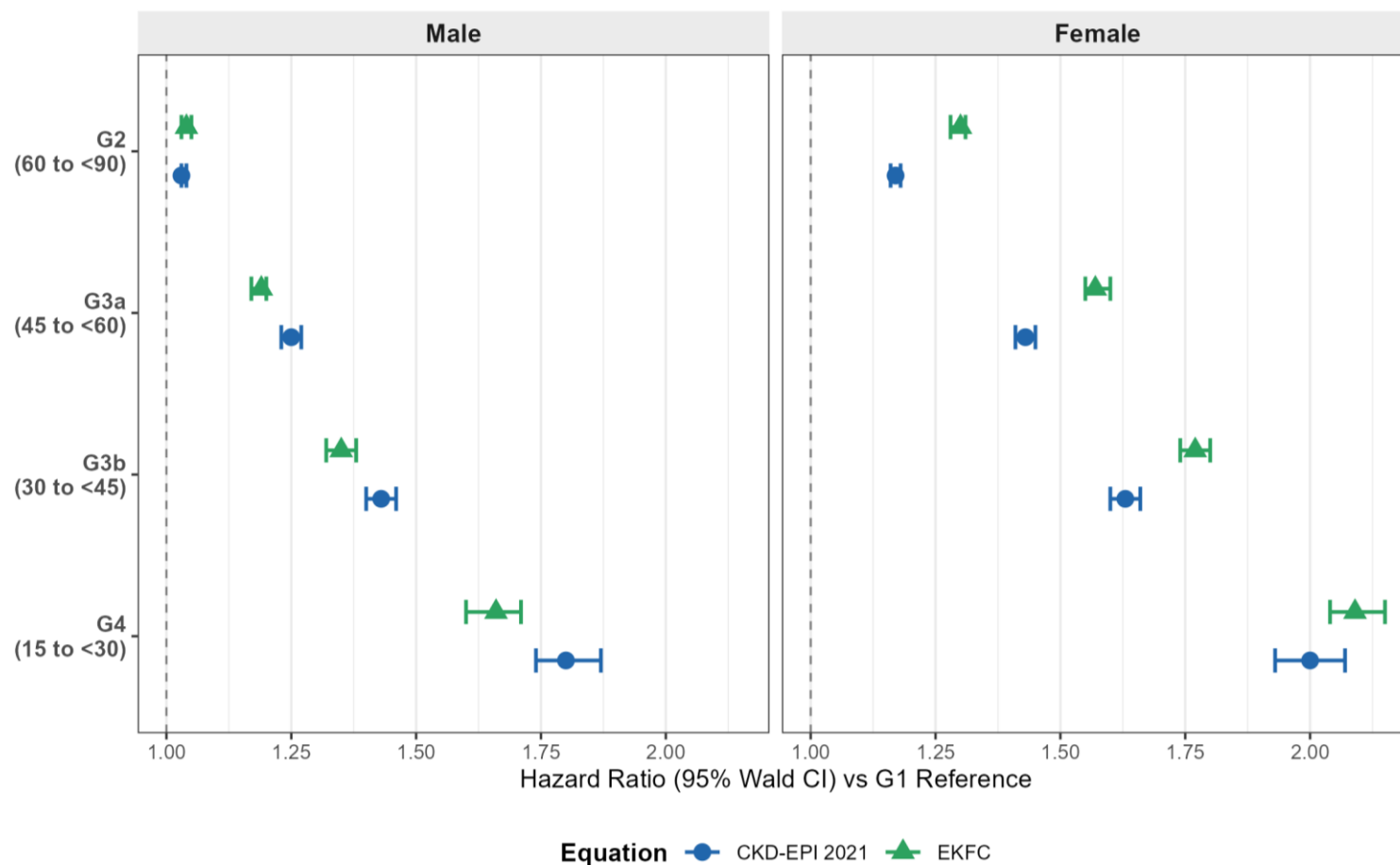
**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Table C2. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by sex

<i>eGFR</i> <i>Category</i>	<i>CK21</i>		<i>EKFC</i>	
	Male	Female	Male	Female
<i>G1 (≥ 90)</i>	188,533/1,566,393 (12.04%) REF	145,164/2,067,489 (7.02%) REF	95,115/1,105,273 (8.61%) REF	68,782/1,529,596 (4.50%) REF
<i>G2 (60-89)</i>	189,830/741,809 (25.59%) 1.03 (1.03-1.04)	185,760/854,787 (21.73%) 1.17 (1.16-1.18)	245,571/1,113,569 (22.05%) 1.04 (1.03-1.05)	211,468/1,251,790 (16.89%) 1.30 (1.28-1.31)
<i>G3a (45-59)</i>	34,470/75,464 (45.68%) 1.25 (1.23-1.27)	46,414/113,199 (41.00%) 1.43 (1.41-1.45)	59,618/140,992 (42.28%) 1.19 (1.17-1.20)	76,329/209,100 (36.50%) 1.57 (1.55-1.60)
<i>G3b (30-44)</i>	14,227/26,709 (53.27%) 1.43 (1.40-1.46)	21,475/43,195 (49.72%) 1.63 (1.60-1.66)	24,443/46,552 (52.51%) 1.35 (1.32-1.38)	37,841/79,896 (47.36%) 1.77 (1.74-1.80)
<i>G4 (15-29)</i>	4,302/7,602 (56.59%) 1.80 (1.74-1.87)	5,740/10,419 (55.09%) 2.00 (1.93-2.07)	6,615/11,591 (57.07%) 1.66 (1.60-1.71)	10,133/18,707 (54.17%) 2.09 (2.04-2.15)

*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Figure C3. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by sex



**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure C4. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) heat map for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by sex; colour is on log10 scale



**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

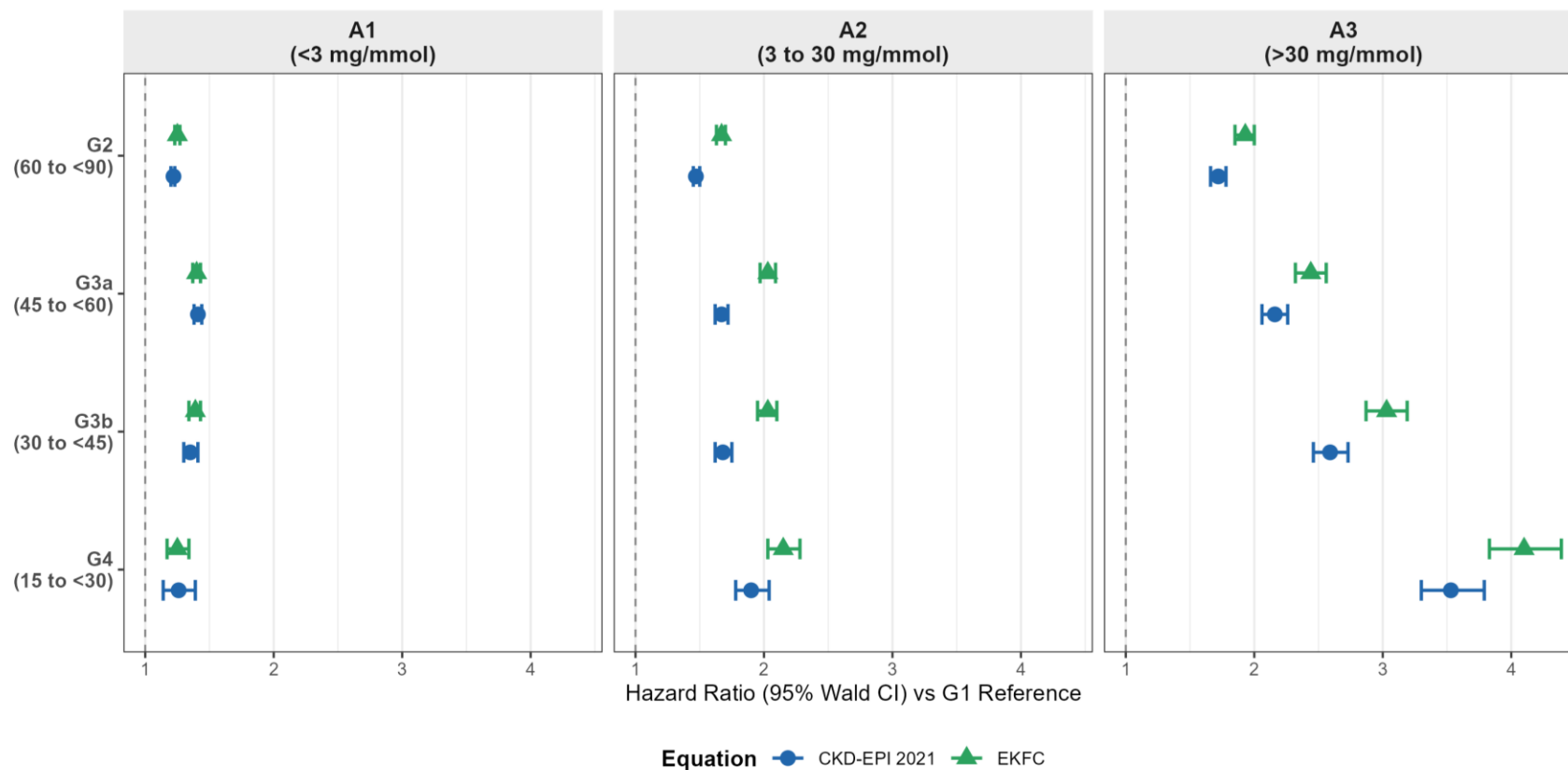
Appendix D. ACR-Stratified Analysis

Table D1. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk, by ACR category

<i>eGFR</i>	<i>CKD-EPI 2021</i>			<i>EKFC</i>		
<i>Category</i>	A1 (<3)	A2 (3-30)	A3 (>30)	A1 (<3)	A2 (3-30)	A3 (>30)
G1 (≥ 90)	83,377/329,635 (25.29%) REF	29,336/74,861 (39.19%) REF	6,347/11,093 (57.22%) REF	47,368/224,568 (21.09%) REF	16,776/49,801 (33.69%) REF	4,014/7,747 (51.81%) REF
G2 (60-89)	70,296/166,939 (42.11%) 1.22 (1.20 - 1.23)	28,538/48,097 (59.33%) 1.47 (1.45 - 1.50)	7,017/9,458 (74.19%) 1.72 (1.66 - 1.78)	100,937/246,745 (40.91%) 1.25 (1.23 - 1.27)	35,690/62,359 (57.23%) 1.67 (1.63 - 1.70)	7,733/10,629 (72.75%) 1.93 (1.85 - 2.00)
G3a (45-59)	12,070/21,722 (55.57%) 1.41 (1.38 - 1.44)	8,558/13,131 (65.17%) 1.67 (1.62 - 1.72)	3,359/4,281 (78.46%) 2.16 (2.06 - 2.26)	22,083/39,946 (55.28%) 1.40 (1.37 - 1.43)	12,471/18,983 (65.70%) 2.03 (1.97 - 2.09)	3,888/5,050 (76.99%) 2.44 (2.32 - 2.56)
G3b (30-44)	4,126/7,187 (57.41%) 1.35 (1.30 - 1.41)	4,638/7,131 (65.04%) 1.68 (1.62 - 1.75)	2,941/3,623 (81.18%) 2.59 (2.46 - 2.73)	7,677/13,096 (58.62%) 1.39 (1.34 - 1.43)	7,058/10,775 (65.50%) 2.03 (1.95 - 2.10)	3,614/4,476 (80.74%) 3.03 (2.87 - 3.19)
G4 (15-29)	649/1,170 (55.47%) 1.26 (1.14 - 1.39)	1,486/2,245 (66.19%) 1.90 (1.78 - 2.04)	1,923/2,286 (84.12%) 3.53 (3.30 - 3.79)	1,306/2,298 (56.83%) 1.25 (1.17 - 1.34)	2,296/3,547 (64.73%) 2.15 (2.03 - 2.28)	2,349/2,839 (82.74%) 4.10 (3.83 - 4.39)

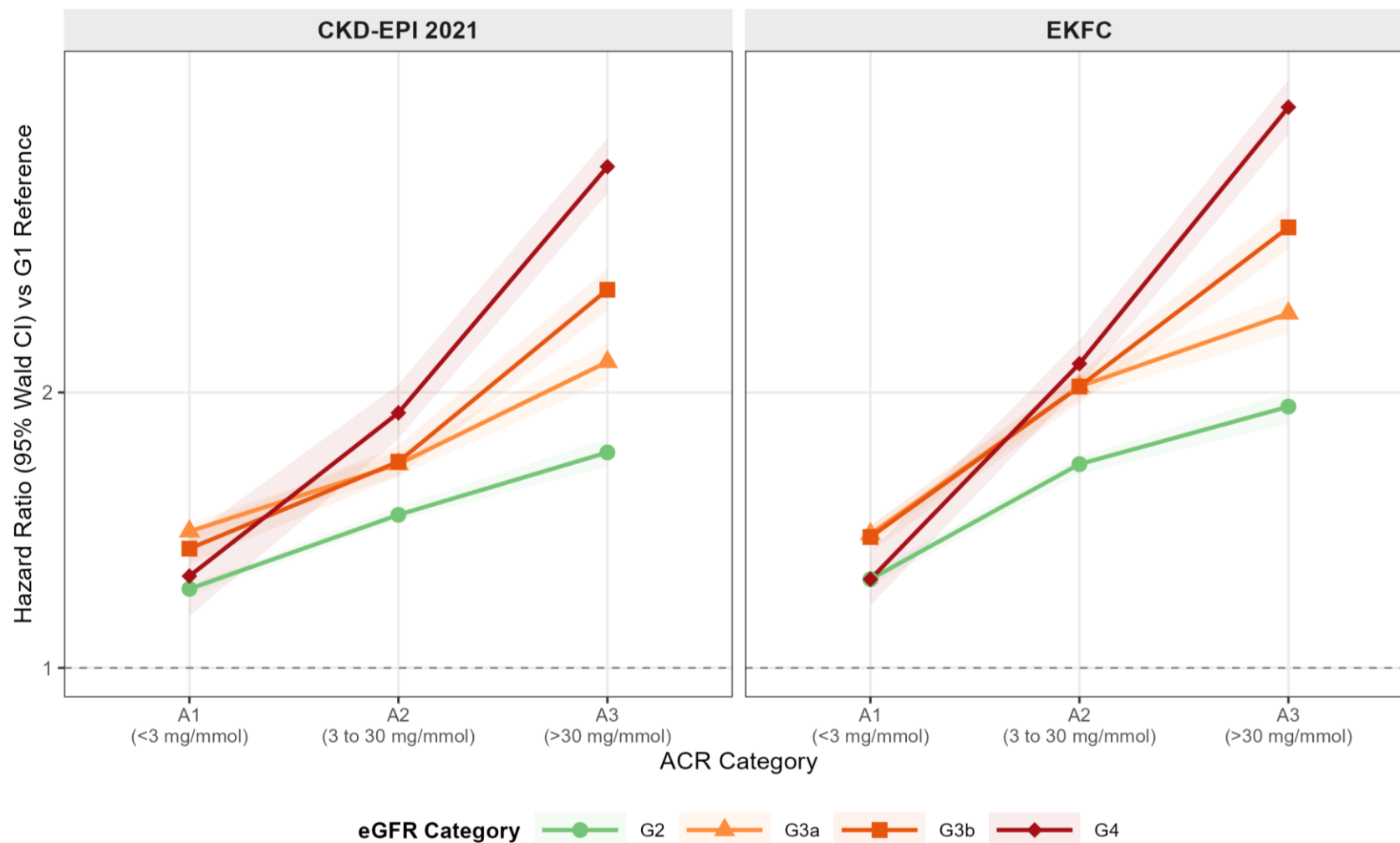
*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Figure D1. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk, by ACR category



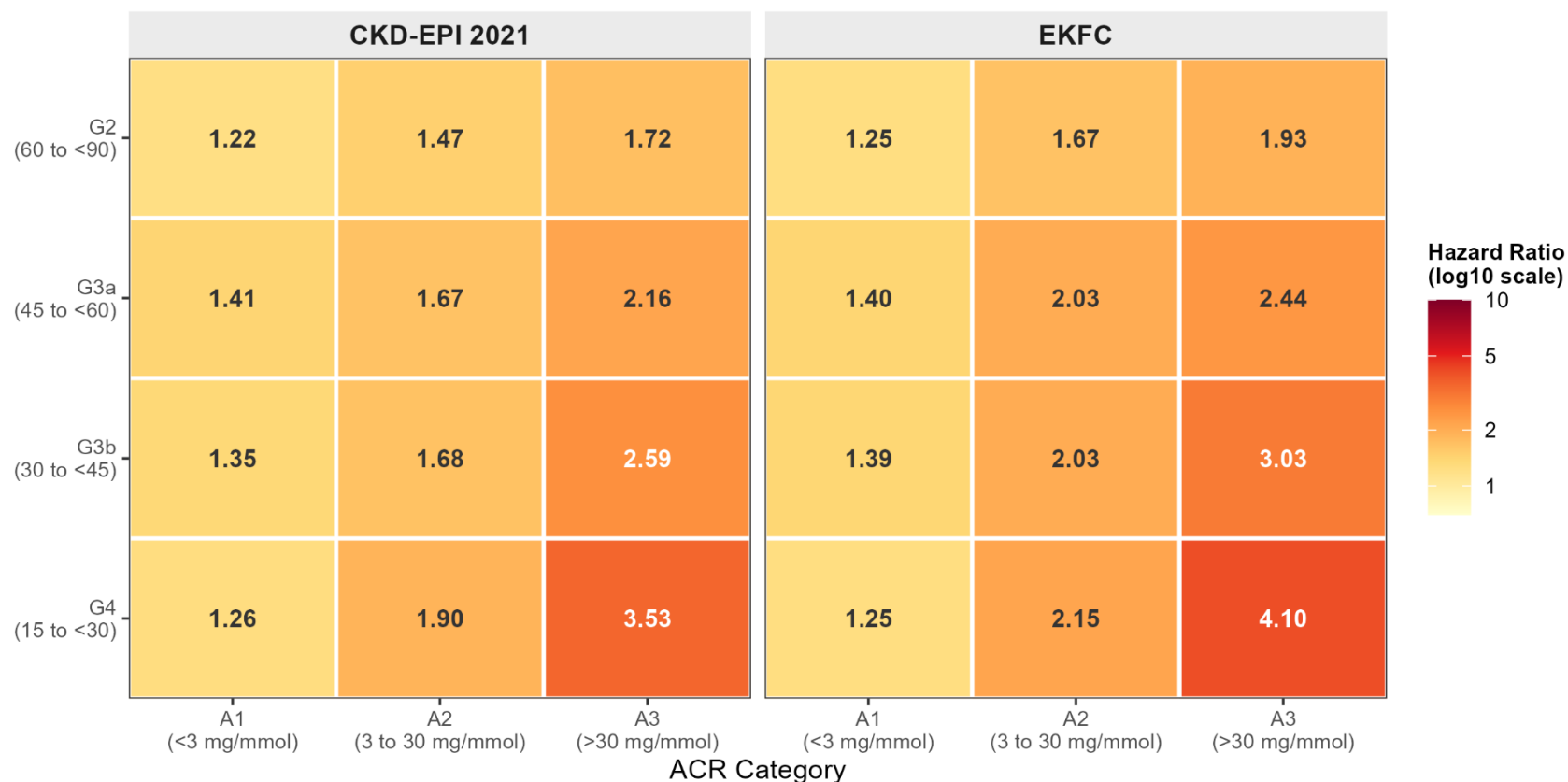
**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure D2. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk, by ACR category; Y-axis is on log10 scale.



***Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure D3. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) heat map for MAKE by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk, by ACR category; colour is on log10 scale



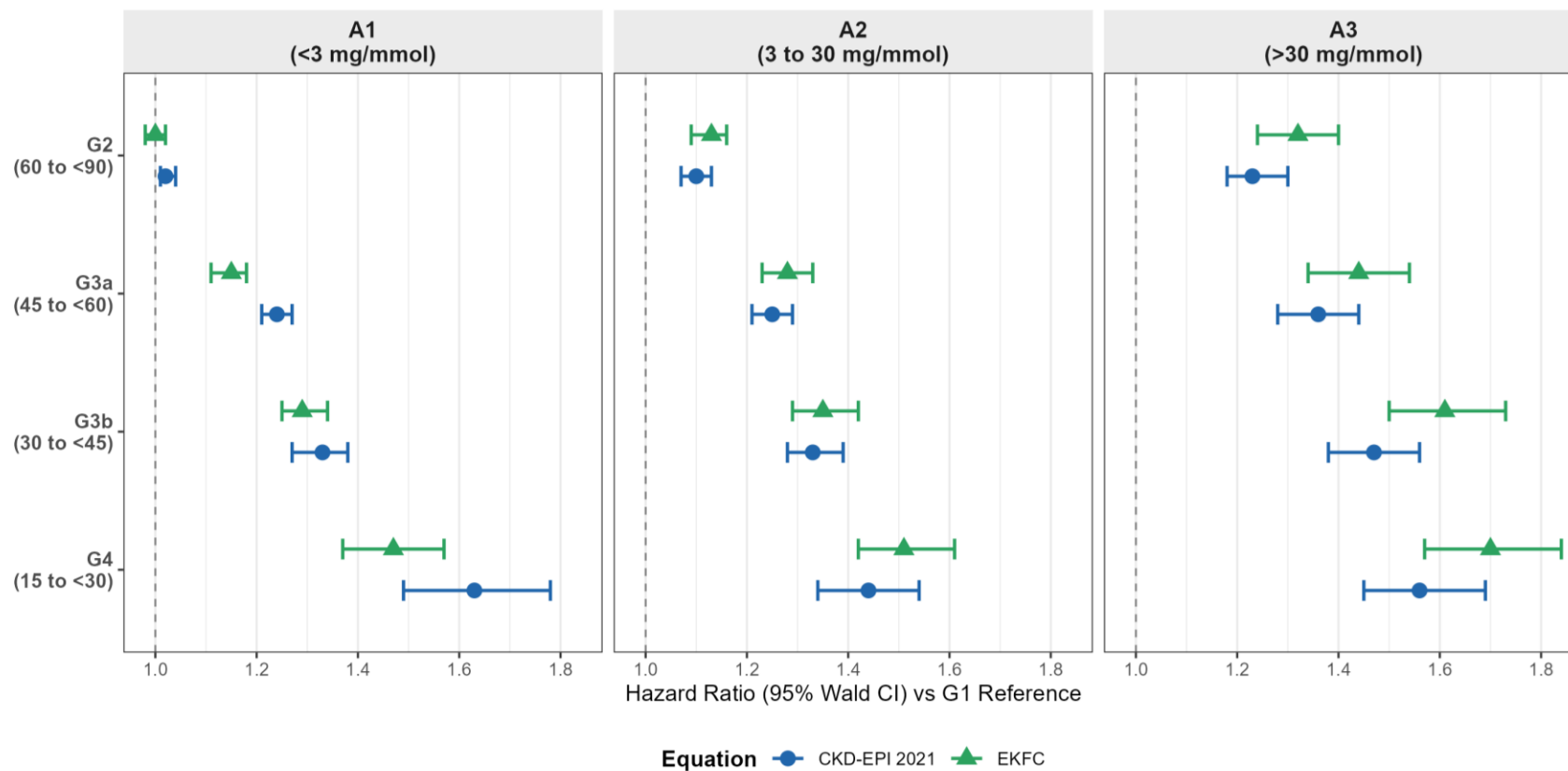
**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Table D2. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by ACR category

<i>eGFR</i>	<i>CKD-EPI 2021</i>			<i>EKFC</i>		
<i>Category</i>	A1 (<3)	A2 (3-30)	A3 (>30)	A1 (<3)	A2 (3-30)	A3 (>30)
<i>G1 (≥ 90)</i>	40,325/329,635 (12.23%) REF	15,471/74,861 (20.67%) REF	3,121/11,093 (28.13%) REF	19,469/224,568 (8.67%) REF	7,855/49,801 (15.77%) REF	1,774/7,747 (22.90%) REF
<i>G2 (60-89)</i>	41,349/166,939 (24.77%) 1.02 (1.01-1.04)	18,069/48,097 (37.57%) 1.10 (1.07-1.13)	4,289/9,458 (45.35%) 1.23 (1.18-1.30)	52,773/246,745 (21.39%) 1.00 (0.98-1.02)	20,675/62,359 (33.15%) 1.13 (1.09-1.16)	4,483/10,629 (42.18%) 1.32 (1.24-1.40)
<i>G3a (45-59)</i>	8,807/21,722 (40.54%) 1.24 (1.21-1.27)	6,242/13,131 (47.54%) 1.25 (1.21-1.29)	2,165/4,281 (50.57%) 1.36 (1.28-1.44)	14,886/39,946 (37.27%) 1.15 (1.11-1.18)	8,680/18,983 (45.73%) 1.28 (1.23-1.33)	2,504/5,050 (49.58%) 1.44 (1.34-1.54)
<i>G3b (30-44)</i>	3,409/7,187 (47.43%) 1.33 (1.27-1.38)	3,674/7,131 (51.52%) 1.33 (1.28-1.39)	1,928/3,623 (53.22%) 1.47 (1.38-1.56)	6,164/13,096 (47.07%) 1.29 (1.25-1.34)	5,486/10,775 (50.91%) 1.35 (1.29-1.42)	2,413/4,476 (53.91%) 1.61 (1.50-1.73)
<i>G4 (15-29)</i>	660/1,170 (56.41%) 1.63 (1.49-1.78)	1,185/2,245 (52.78%) 1.44 (1.34-1.54)	1,224/2,286 (53.54%) 1.56 (1.45-1.69)	1,258/2,298 (54.74%) 1.47 (1.37-1.57)	1,945/3,547 (54.84%) 1.51 (1.42-1.61)	1,553/2,839 (54.70%) 1.70 (1.57-1.84)

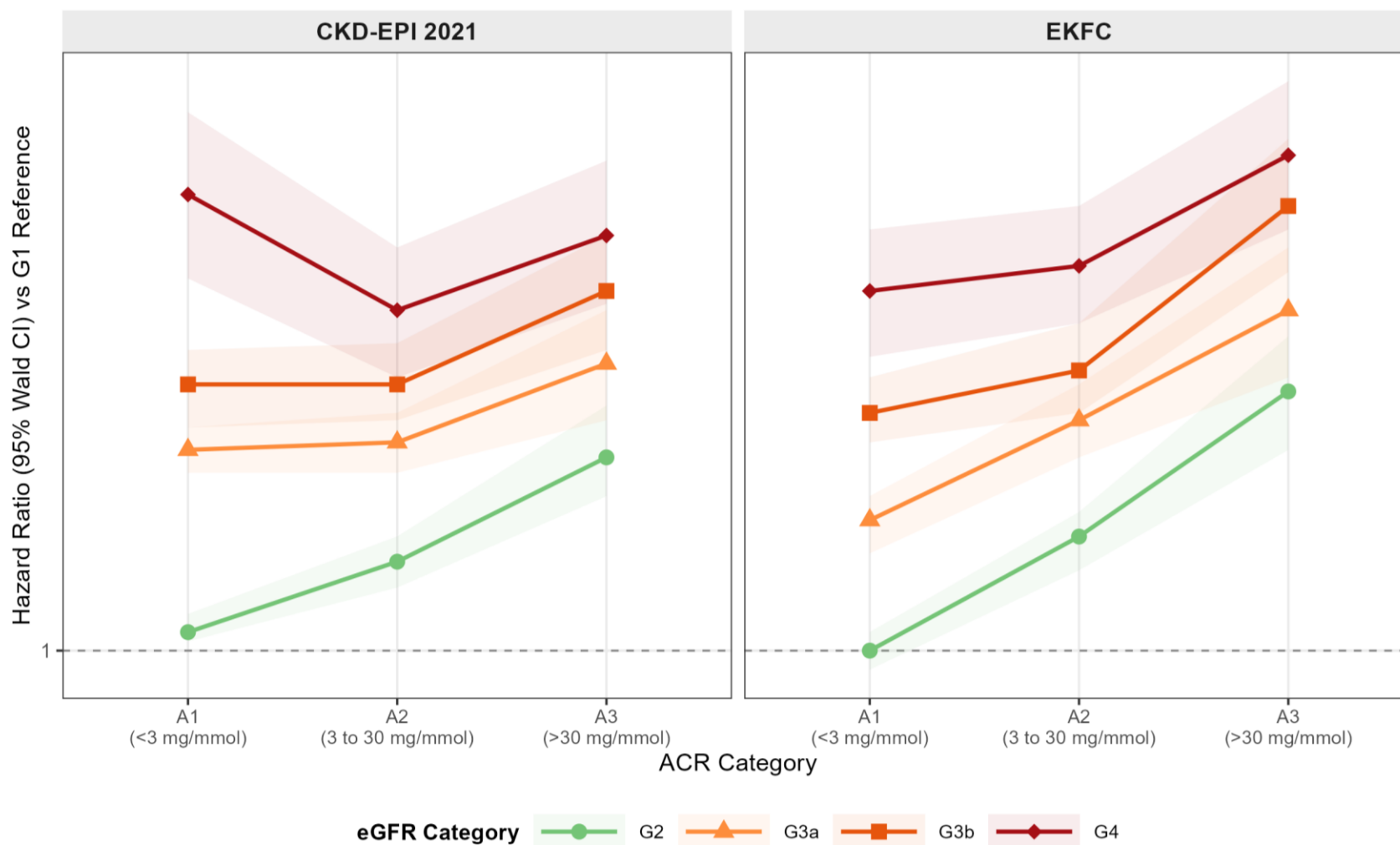
**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure D4. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by ACR category



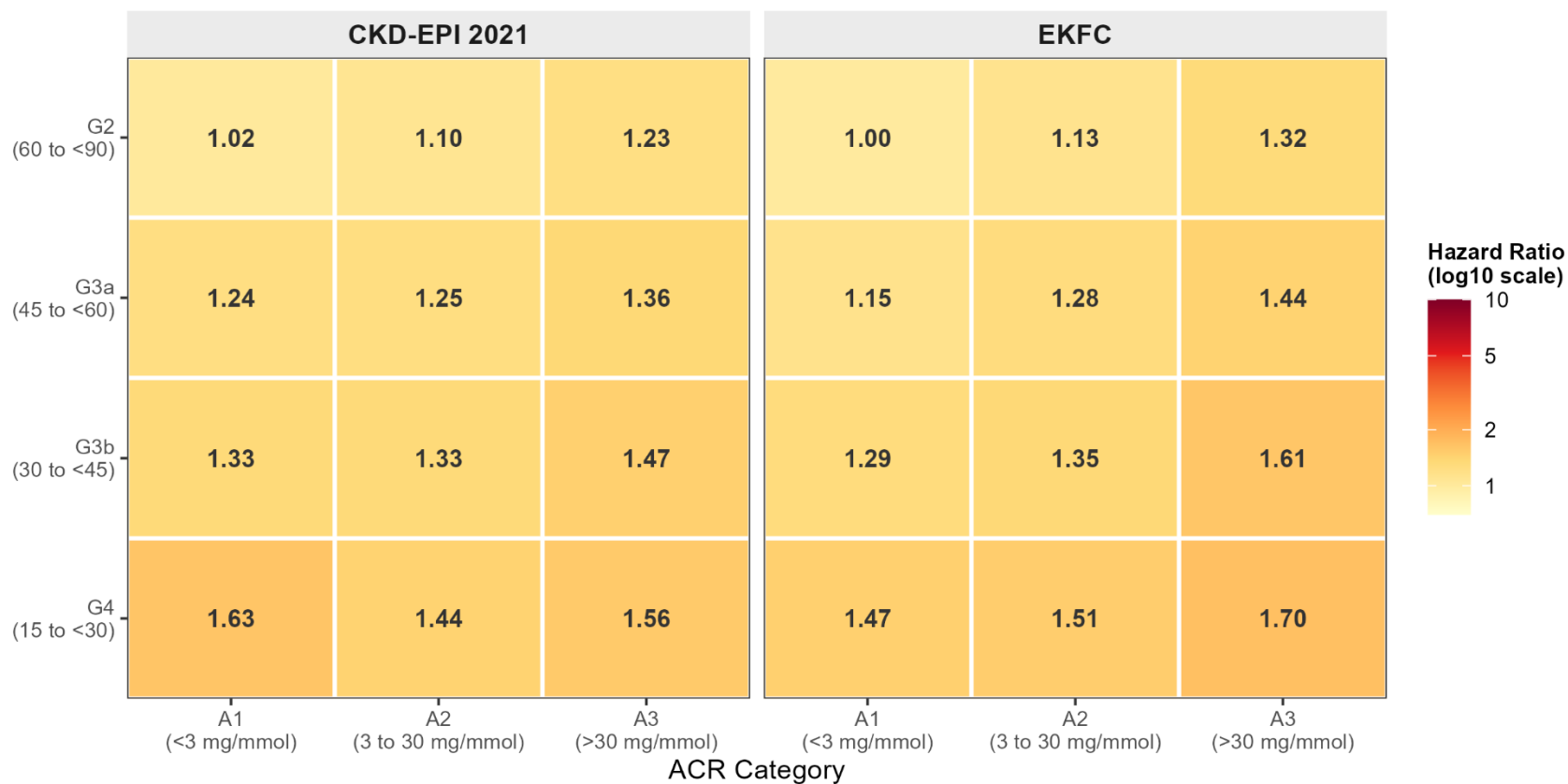
**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure D5. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) forest plot for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by ACR category; Y-axis is on log10 scale.



***Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Figure D6. CK21 and EKFC adjusted subdistribution hazard Ratios (95% CI) heat map for MACE by eGFR categories relative to G1 (≥ 90), accounting for non-CVD mortality as a competing risk, by ACR category; colour is on log10 scale



**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Appendix E. Sensitivity Analysis for KRT, Overall Mortality, and no age/sex models

Table E1. CK21 and EKFC event frequencies, and adjusted hazard Ratios (95% CI) for overall mortality by eGFR categories relative to G1 (≥ 90)

<i>eGFR Category</i>	<i>CKD21</i>	<i>EKFC</i>
<i>G1 (≥ 90)</i>	253,311/3,633,882 (6.97%) REF	106,387/2,634,869 (4.04%) REF
<i>G2 (60-89)</i>	397,259/1,596,596 (24.88%) 0.957 (0.951–0.962)	428,584/2,365,359 (18.12%) 0.732 (0.726–0.738)
<i>G3a (45-59)</i>	105,914/188,663 (56.14%) 1.228 (1.217–1.238)	172,724/350,092 (49.34%) 0.865 (0.855–0.874)
<i>G3b (30-44)</i>	50,589/69,904 (72.37%) 1.586 (1.568–1.605)	89,002/126,448 (70.39%) 1.092 (1.079–1.106)
<i>G4 (15-29)</i>	14,053/18,021 (77.98%) 2.245 (2.195–2.295)	24,429/30,298 (80.63%) 1.512 (1.485–1.541)

**Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Table E2. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for KRT by eGFR categories relative to G1 (≥ 90), accounting for all-cause mortality as a competing risk

<i>eGFR Category</i>	<i>CKD21</i>	<i>EKFC</i>
G1 (≥ 90)	6,158/3,633,882 (0.17%) REF	3,878/2,634,869 (0.15%) REF
G2 (60-89)	7,402/1,596,596 (0.46%) 4.757 (4.571–4.951)	7,978/2,365,359 (0.34%) 4.527 (4.344–4.717)
G3a (45-59)	4,434/188,663 (2.35%) 36.387 (34.475–38.405)	4,824/350,092 (1.38%) 36.709 (34.682–38.854)
G3b (30-44)	5,131/69,904 (7.34%) 129.923 (123.023–137.209)	5,760/126,448 (4.56%) 150.879 (142.292–159.984)
G4 (15-29)	4,542/18,021 (25.20%) 496.030 (468.678–524.978)	5,227/30,298 (17.25%) 639.212 (601.227–679.598)

*Adjusted for age, sex, income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count

Table E3. CK21 and EKFC event frequencies, and adjusted subdistribution hazard Ratios (95% CI) for MAKE (no age and sex adjustment) by eGFR categories relative to G1 (≥ 90), accounting for all-cause/non-CVD mortality as a competing risk

<i>eGFR Category</i>	<i>CK21</i>	<i>EKFC</i>
<i>G1 (≥ 90)</i>	761,051/3,633,882 (20.94%) REF	461,076/2,634,869 (17.50%) REF
<i>G2 (60-89)</i>	598,534/1,596,596 (37.49%) 1.861 (1.854-1.867)	845,917/2,365,359 (35.76%) 2.094 (2.086-2.102)
<i>G3a (45-59)</i>	103,050/188,663 (54.62%) 3.092 (3.069-3.116)	186,620/350,092 (53.31%) 3.538 (3.517-3.559)
<i>G3b (30-44)</i>	40,845/69,904 (58.43%) 3.618 (3.574-3.663)	72,606/126,448 (57.42%) 4.194 (4.155-4.234)
<i>G4 (15-29)</i>	11,753/18,021 (65.22%) 5.036 (4.909-5.166)	18,617/30,298 (61.45%) 5.313 (5.209-5.418)

**Adjusted for income quintile, rural living status, hypertension, diabetes, past cardiovascular disease, obesity, alcohol use, hypercholesterolemia, hyperkalemia, cancer, chronic liver disease, chronic lung disease, emergency room count, primary care count, and specialist care count*

Table E4. Risk of overall mortality among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category

Overall Mortality Outcome	Concordant		Discordant		Fine-Gray SD HR (95% CI)
	Events	Total	Events	Total	
G1 (90+)	106,387 (4.0%)	2,634,869	146,924 (14.7%)	999,013	0.768 (0.759–0.777)
G2 (60–<90)	281,660 (20.6%)	1,366,345	115,599 (50.2%)	230,251	1.074 (1.066–1.082)
G3a (45–<60)	57,121 (47.7%)	119,824	48,793 (70.9%)	68,838	1.146 (1.132–1.161)
G3b (30–<45)	40,198 (69.8%)	57,569	10,387 (84.3%)	12,318	1.155 (1.129–1.182)
G4 (15–<30)	14,042 (78.1%)	17,980	0	0	—
Total	499,408 (11.9%)	4,196,587	321,703 (24.6%)	1,310,420	

Table E5. Risk of kidney replacement therapy (KRT) among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category

KRT Outcome	Concordant		Discordant		Fine-Gray SD HR (95% CI)
	Events	Total	Events	Total	
G1 (90+)	3,878 (0.2%)	2,634,869	2,280 (0.2%)	999,013	1.082 (1.011–1.157)
G2 (60–<90)	5,698 (0.4%)	1,366,345	1,704 (0.7%)	230,251	2.800 (2.622–2.990)
G3a (45–<60)	3,115 (2.6%)	119,824	1,319 (1.9%)	68,838	1.685 (1.566–1.814)
G3b (30–<45)	4,419 (7.7%)	57,569	707 (5.7%)	12,318	1.394 (1.263–1.539)
G4 (15–<30)	4,520 (25.1%)	17,980	0	0	—
Total	21,630 (0.5%)	4,196,587	6,010 (0.5%)	1,310,420	

Table E6. Risk of Major Adverse Kidney Events (unadjusted for age and sex) among individuals with concordant vs. discordant eGFR category assignment between CK21 and EKFC, stratified by CK21 eGFR category

MAKE Outcome	Concordant		Discordant		Fine-Gray SD HR (95% CI)
	Events	Total	Events	Total	
G1 (90+)	449,918 (17.1%)	2,634,869	311,133 (31.1%)	999,013	1.785 (1.776–1.793)
G2 (60–<90)	481,560 (35.2%)	1,366,345	116,974 (50.8%)	230,251	1.566 (1.555–1.576)
G3a (45–<60)	65,212 (54.4%)	119,824	37,838 (55.0%)	68,838	1.038 (1.025–1.051)
G3b (30–<45)	34,231 (59.5%)	57,569	6,604 (53.6%)	12,318	0.891 (0.867–0.915)
G4 (15–<30)	11,719 (65.2%)	17,980	0	0	—
Total	1,042,640 (24.8%)	4,196,587	472,549 (36.1%)	1,310,420	

Appendix F. C-statistic, Calibration, and Brier Scores for CK21 and EKFC at 2- and 5-year timepoints

Table F1. C-statistic, Calibration, and Brier Scores for CK21 and EKFC at 2- and 5-year timepoints for MAKE Models

<i>Model</i>	Statistics	CKD-EPI 2021		EKFC	
		2 Year	5 Year	2 Year	5 Year
<i>Overall</i>	AUC	0.749	0.729	0.750	0.738
	Calibration Slope	1.521	1.348	1.442	1.313
	Brier	0.027	0.078	0.025	0.076
<i>18 to <40</i>	AUC	0.658	0.619	0.666	0.633
	Calibration Slope	1.747	1.341	1.559	1.303
	Brier	0.010	0.033	0.008	0.025
<i>40 to ≤65</i>	AUC	0.686	0.645	0.691	0.651
	Calibration Slope	2.131	1.502	2.295	1.579
	Brier	0.020	0.064	0.019	0.063
<i>66 to <80</i>	AUC	0.659	0.630	0.648	0.619
	Calibration Slope	2.462	1.722	2.835	1.895
	Brier	0.050	0.140	0.047	0.139
<i>≥80</i>	AUC	0.558	0.550	0.565	0.553
	Calibration Slope	1.622	1.269	1.901	1.352
	Brier	0.088	0.193	0.084	0.192
<i>Male</i>	AUC	0.734	0.721	0.735	0.730
	Calibration Slope	1.501	1.298	1.417	1.272
	Brier	0.028	0.079	0.026	0.076
<i>Female</i>	AUC	0.752	0.732	0.752	0.742
	Calibration Slope	1.619	1.399	1.502	1.354
	Brier	0.026	0.077	0.024	0.074
<i>< 3 mg/mmol</i>	AUC	0.700	0.698	0.700	0.702
	Calibration Slope	1.319	1.258	1.276	1.247
	Brier	0.028	0.091	0.025	0.089
<i>3 - 30 mg/mmol</i>	AUC	0.684	0.678	0.682	0.678
	Calibration Slope	1.497	1.329	1.493	1.328
	Brier	0.071	0.172	0.068	0.170
<i>> 30 mg/mmol</i>	AUC	0.699	0.694	0.702	0.696
	Calibration Slope	1.489	1.194	1.519	1.195
	Brier	0.169	0.222	0.165	0.221

Table F2. C-statistic, Calibration, and Brier Scores for CK21 and EKFC at 2- and 5-year timepoints for MACE Models

<i>Model</i>	Statistics	CKD-EPI 2021		EKFC	
		2 Year	5 Year	2 Year	5 Year
<i>Overall</i>	AUC	0.823	0.814	0.822	0.813
	Calibration Slope	1.111	1.084	1.117	1.087
	Brier	0.035	0.069	0.035	0.069
<i>18 to <40</i>	AUC	0.696	0.692	0.696	0.691
	Calibration Slope	1.152	1.071	1.166	1.079
	Brier	0.004	0.009	0.004	0.009
<i>40 to ≤65</i>	AUC	0.680	0.669	0.686	0.675
	Calibration Slope	1.229	1.135	1.206	1.120
	Brier	0.024	0.054	0.024	0.054
<i>66 to <80</i>	AUC	0.650	0.638	0.651	0.640
	Calibration Slope	1.370	1.242	1.363	1.238
	Brier	0.076	0.147	0.076	0.147
<i>≥80</i>	AUC	0.599	0.593	0.600	0.594
	Calibration Slope	1.530	1.299	1.552	1.322
	Brier	0.129	0.209	0.129	0.209
<i>Male</i>	AUC	0.789	0.780	0.788	0.780
	Calibration Slope	1.119	1.080	1.121	1.080
	Brier	0.042	0.083	0.042	0.083
<i>Female</i>	AUC	0.839	0.829	0.838	0.828
	Calibration Slope	1.146	1.089	1.158	1.095
	Brier	0.029	0.058	0.029	0.058
<i>< 3 mg/mmol</i>	AUC	0.770	0.760	0.770	0.760
	Calibration Slope	1.102	1.076	1.101	1.076
	Brier	0.038	0.080	0.038	0.080
<i>3 - 30 mg/mmol</i>	AUC	0.747	0.743	0.747	0.743
	Calibration Slope	1.172	1.120	1.176	1.121
	Brier	0.074	0.135	0.074	0.135
<i>> 30 mg/mmol</i>	AUC	0.719	0.723	0.718	0.722
	Calibration Slope	1.151	1.119	1.158	1.119
	Brier	0.110	0.177	0.110	0.177

Table F3. C-statistic, Calibration, and Brier Scores for CK21 and EKFC at 2- and 5-year timepoints for KRT and Overall Mortality Models

<i>Model</i>	Statistics	CKD-EPI 2021		EKFC	
		2 Year	5 Year	2 Year	5 Year
<i>Overall Mortality</i>	AUC	0.864	0.866	0.865	0.866
	Calibration Slope	0.934	1.020	0.920	1.010
	Brier	0.018	0.042	0.018	0.042
<i>KRT</i>	AUC	0.851	0.856	0.859	0.862
	Calibration Slope	1.669	1.428	1.644	1.409
	Brier	0.001	0.002	0.001	0.002
<i>MAKE (unadjusted for age and sex)</i>	AUC	0.734	0.703	0.743	0.719
	Calibration Slope	1.903	1.507	1.814	1.477
	Brier	0.027	0.079	0.025	0.076

Appendix G. Calibration line plots for MAKE, MACE, KRT, and overall mortality

Figure G1. Calibration line plot: observed versus predicted MAKE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

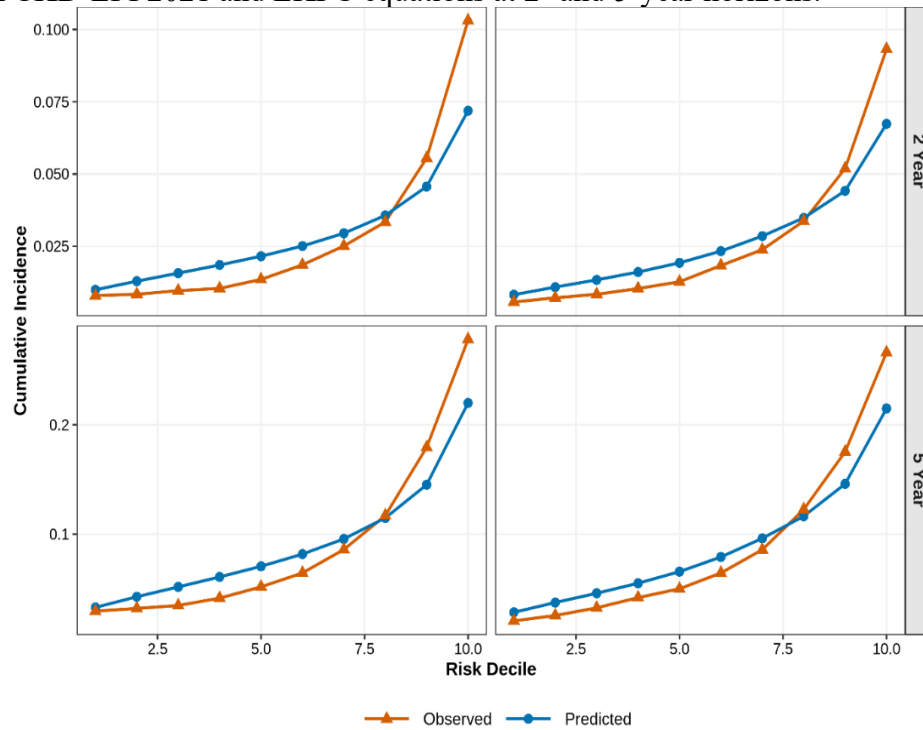


Figure G2. Calibration line plot: observed versus predicted MAKE risk by decile in the male subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

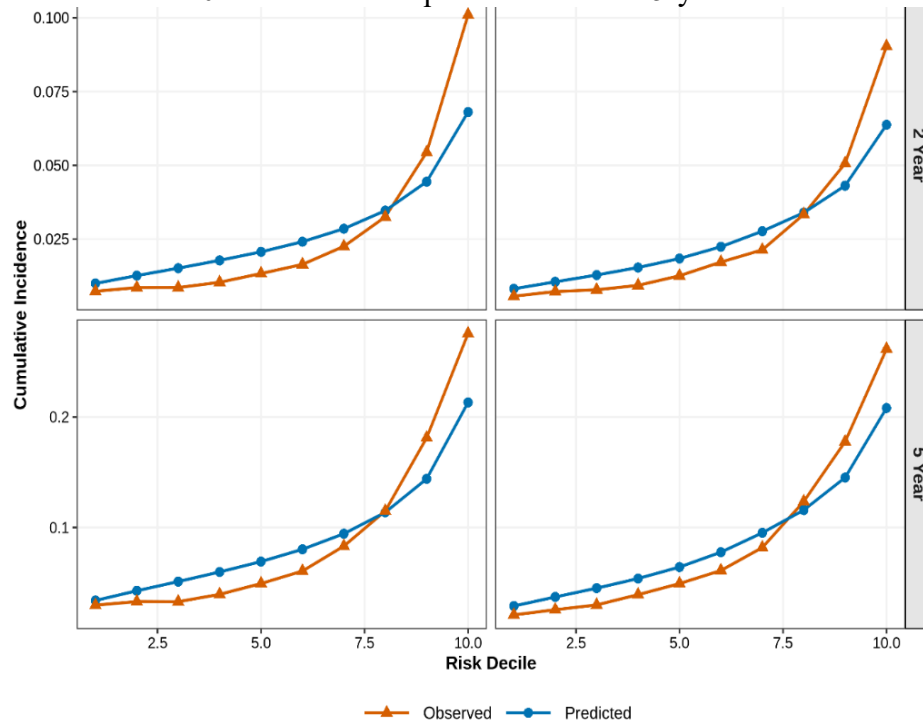


Figure G3. Calibration line plot: observed versus predicted MAKE risk by decile in the female subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

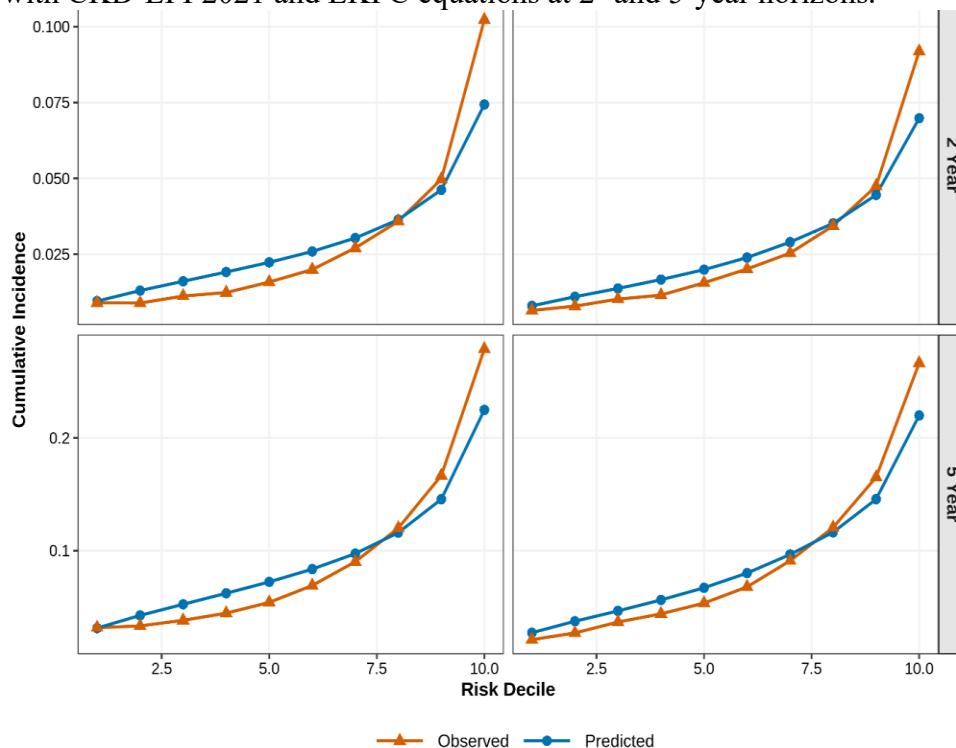


Figure G4. Calibration line plot: observed versus predicted MAKE risk by decile in the age 18 to <40 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

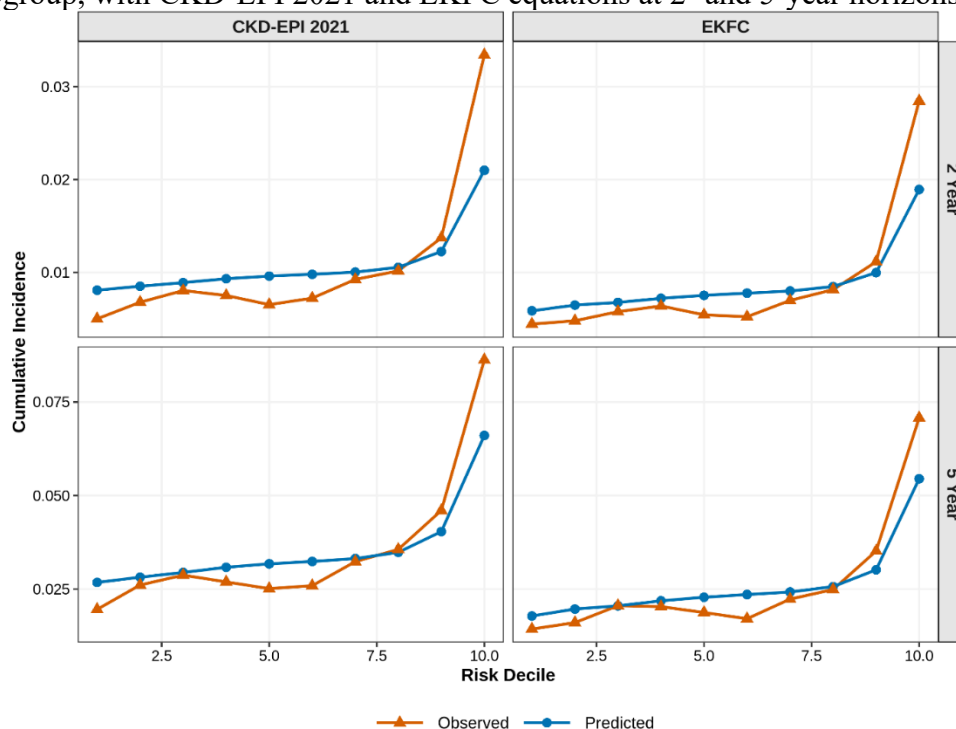


Figure G5. Calibration line plot: observed versus predicted MAKE risk by decile in the age 40 to ≤ 65 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

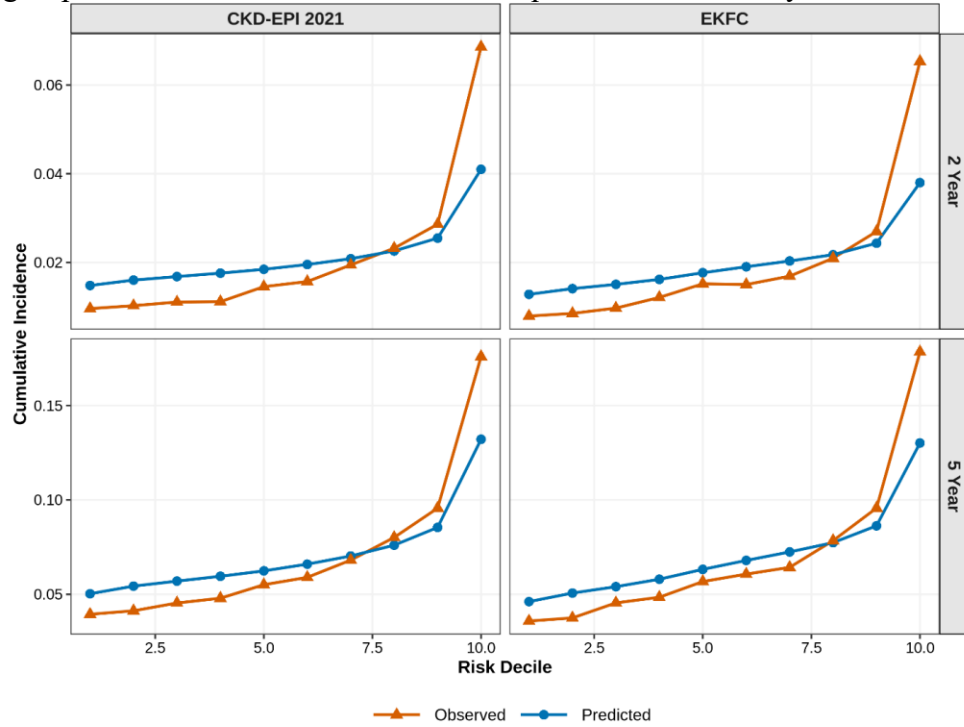


Figure G6. Calibration line plot: observed versus predicted MAKE risk by decile in the age 66 to < 80 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

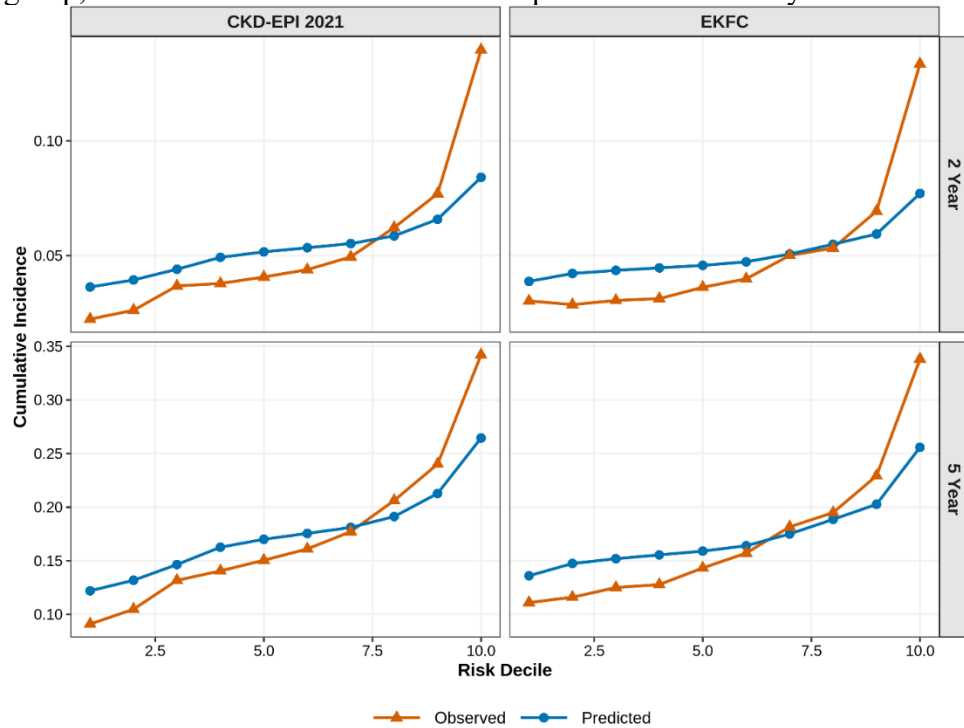


Figure G7. Calibration line plot: observed versus predicted MAKE risk by decile in the age ≥ 80 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

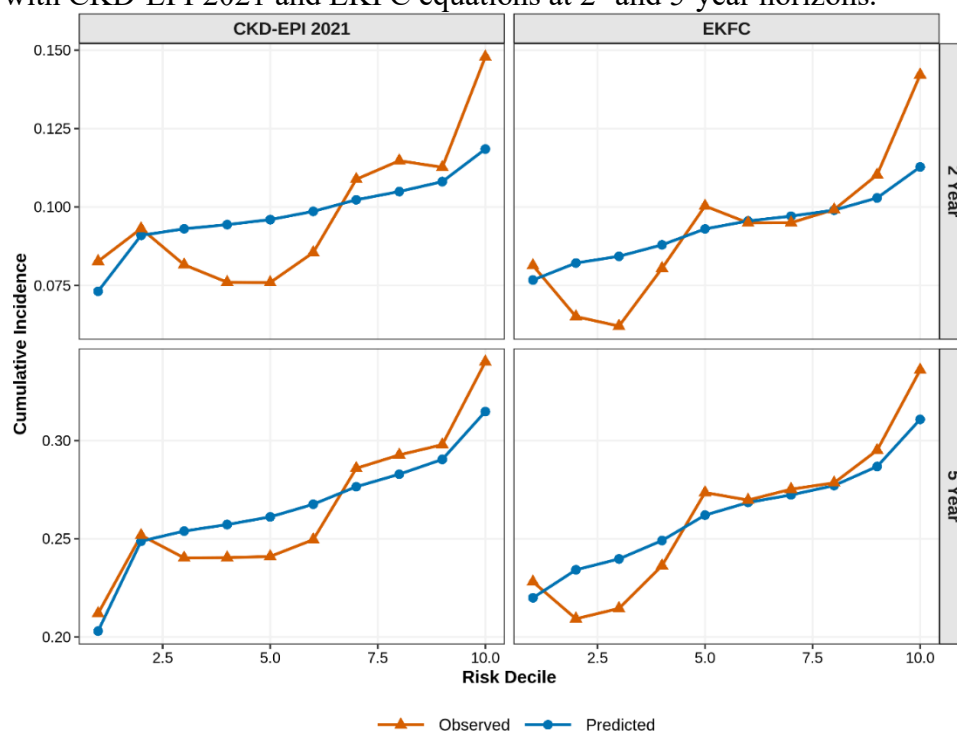


Figure G8. Calibration line plot: observed versus predicted MAKE risk by decile in the ACR category A1 (< 3 mg/dl) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

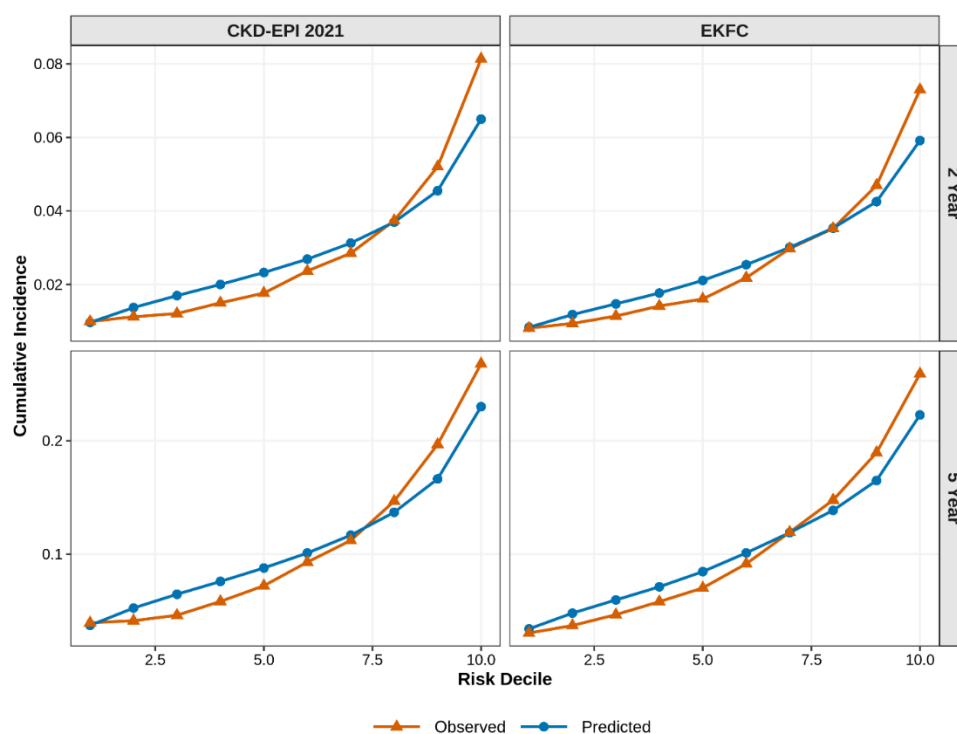


Figure G9. Calibration line plot: observed versus predicted MAKE risk by decile in the ACR category A2 (3–30 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

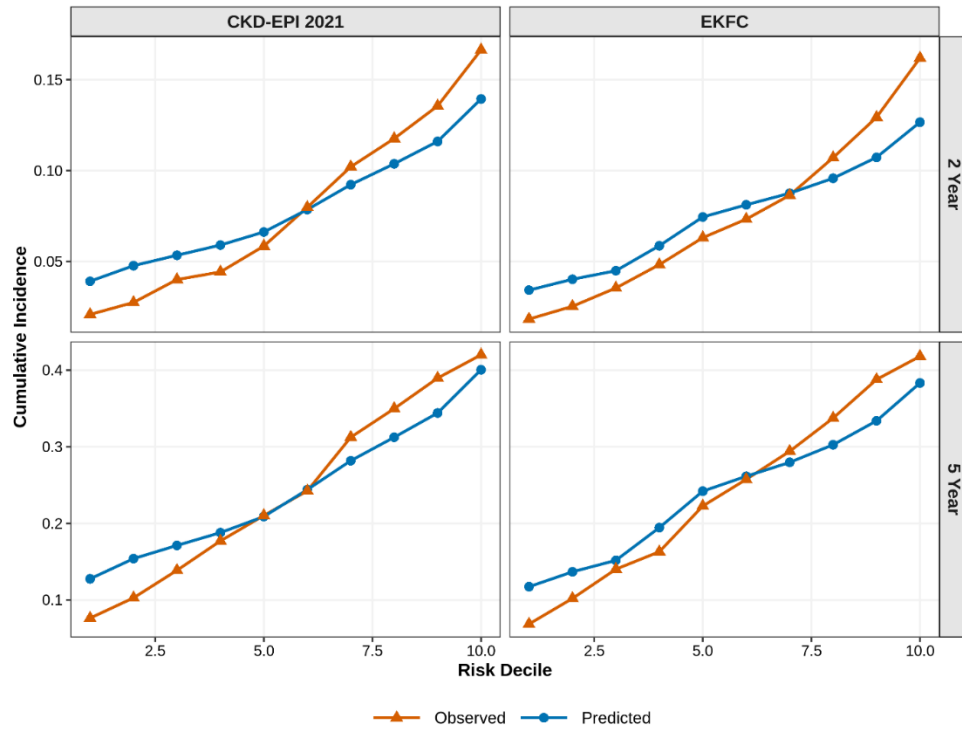


Figure G10. Calibration line plot: observed versus predicted MAKE risk by decile in the ACR category A3 (>30 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

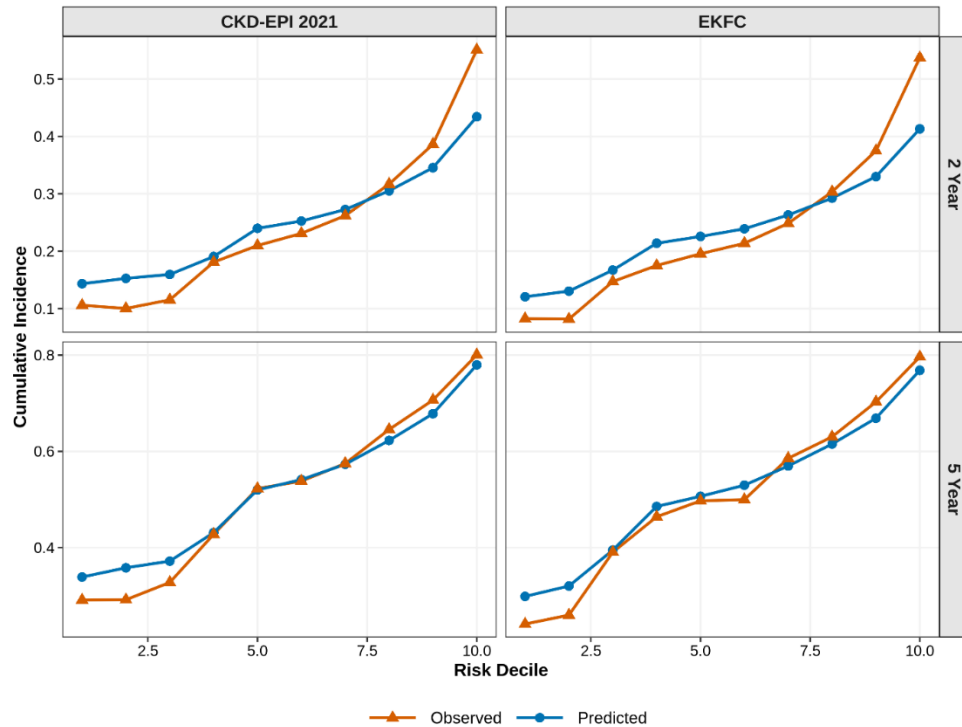


Figure G11. Calibration line plot: observed versus predicted MACE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

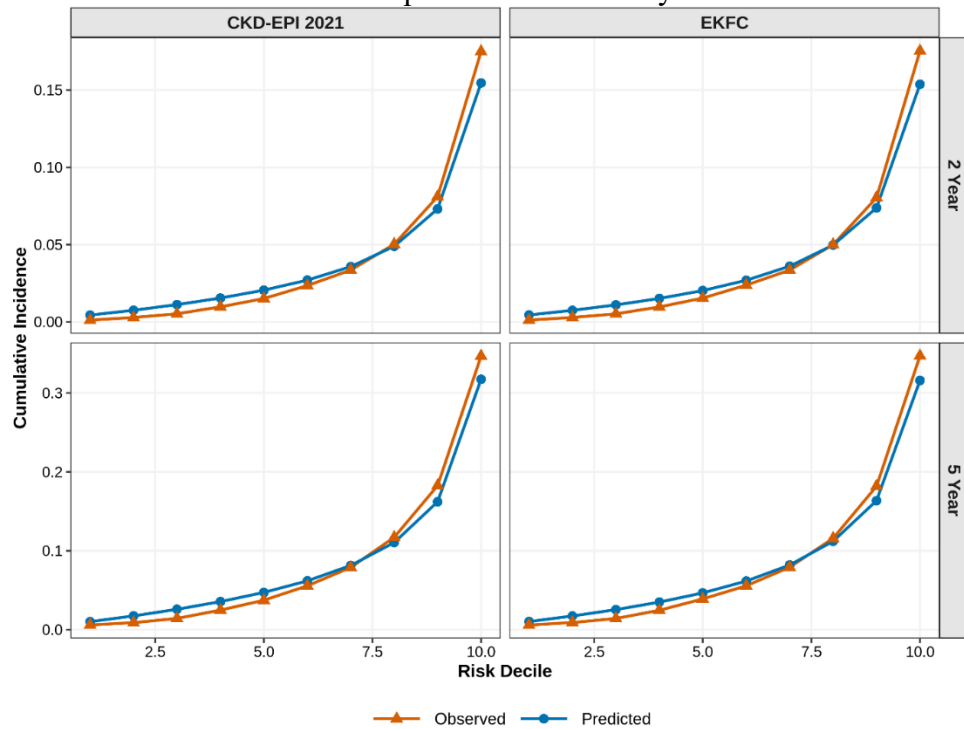


Figure G12. Calibration line plot: observed versus predicted MACE risk by decile in the male subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

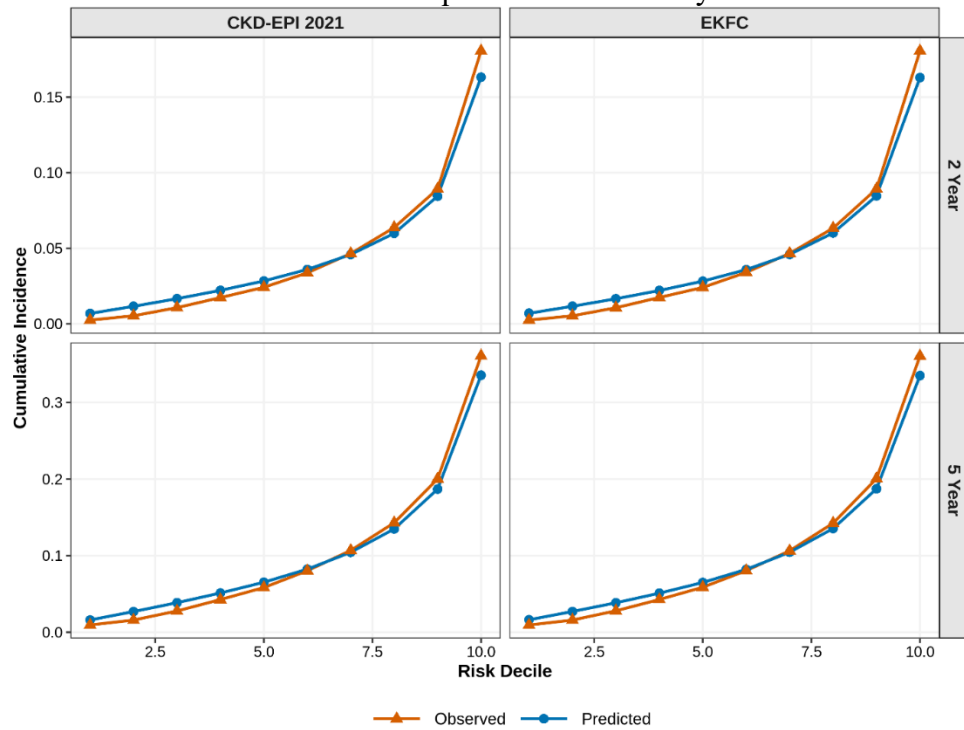


Figure G13. Calibration line plot: observed versus predicted MACE risk by decile in the female subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

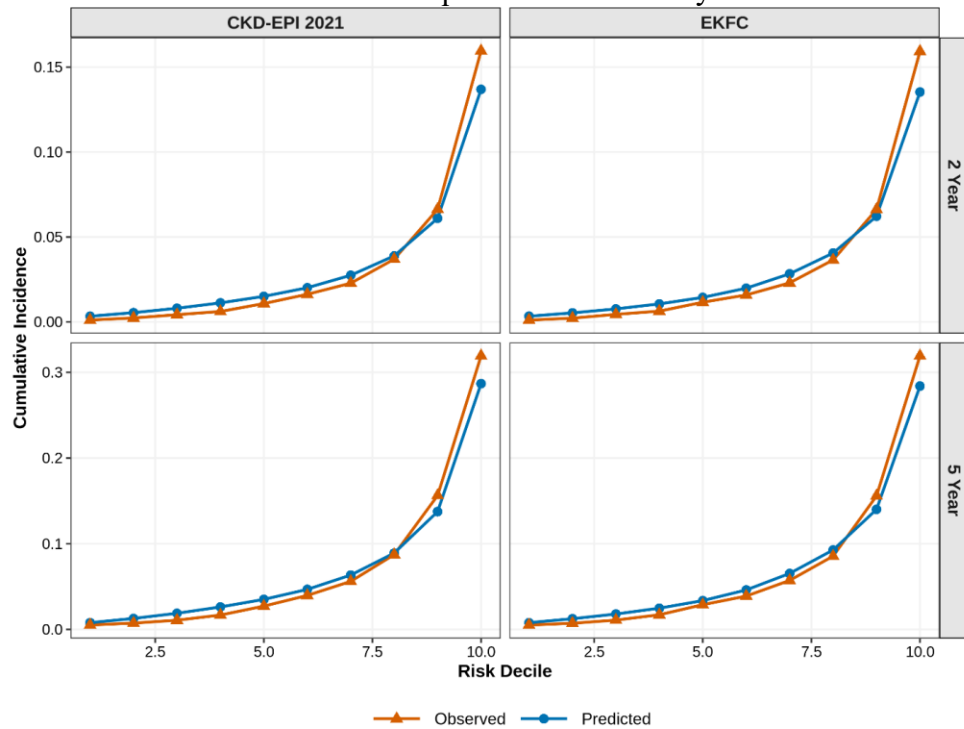


Figure G14. Calibration line plot: observed versus predicted MACE risk by decile in the age 18 to <40 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

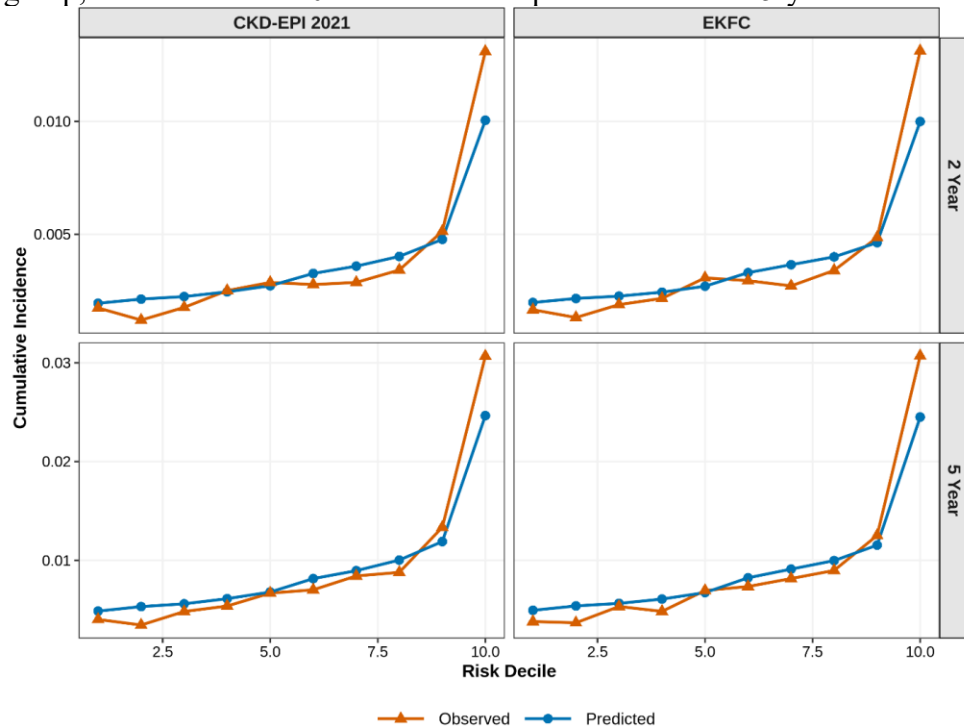


Figure G15. Calibration line plot: observed versus predicted MACE risk by decile in the age 40 to ≤ 65 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

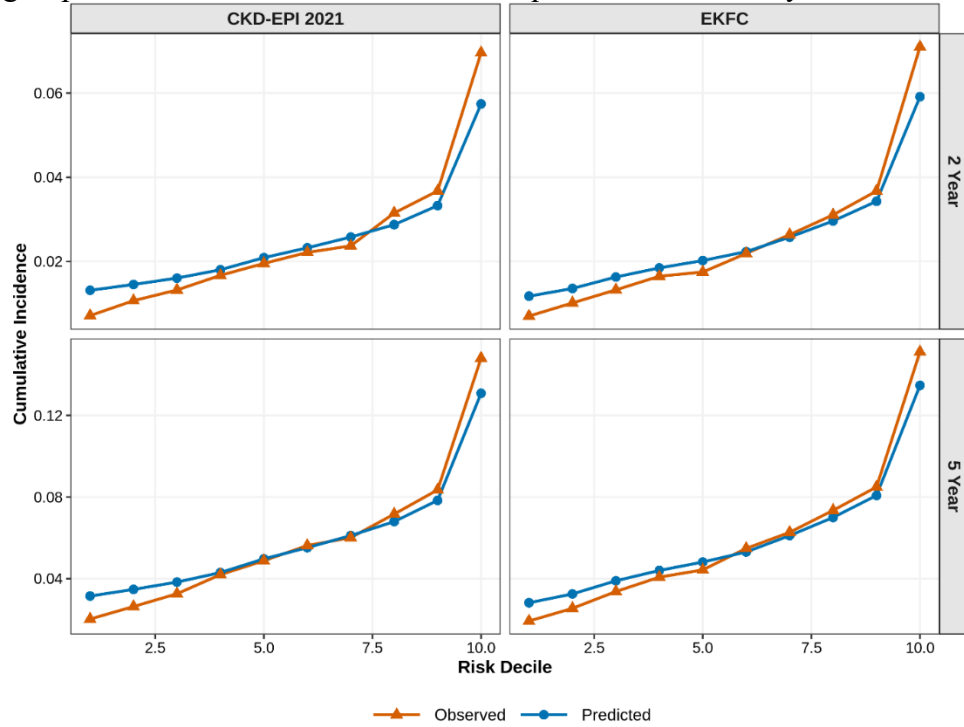


Figure G16. Calibration line plot: observed versus predicted MACE risk by decile in the age 66 to <80 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

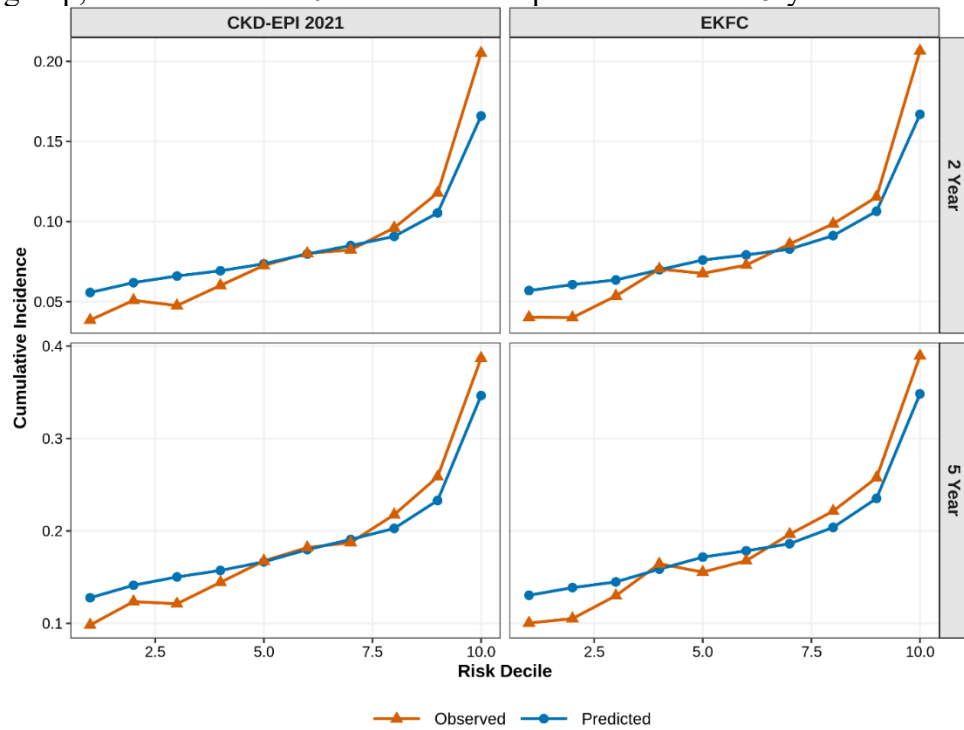


Figure G17. Calibration line plot: observed versus predicted MACE risk by decile in the age ≥ 80 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

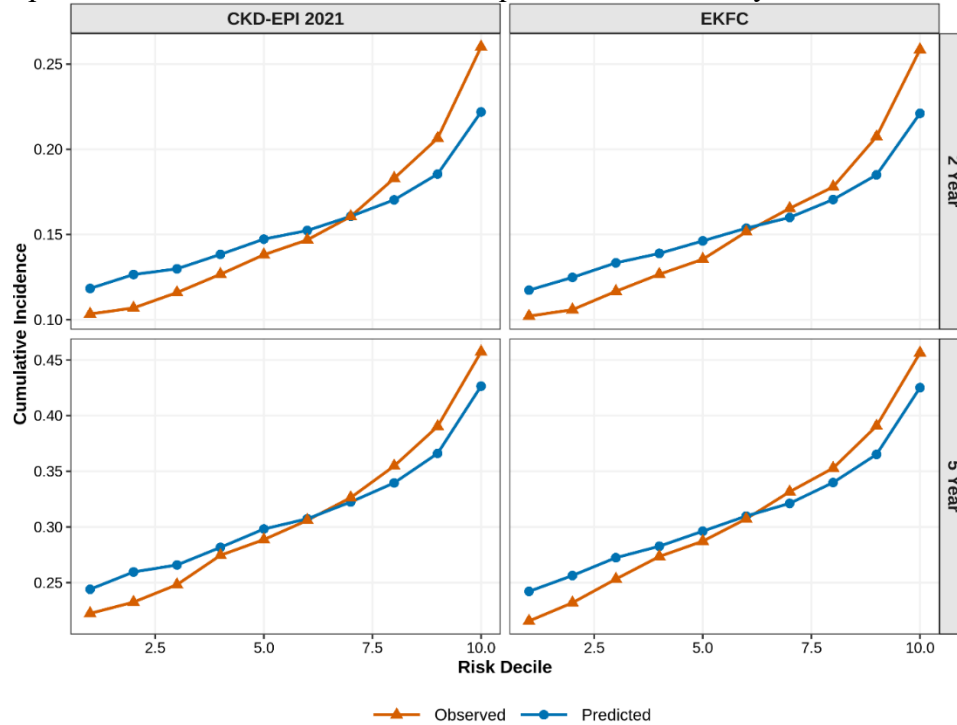


Figure G18. Calibration line plot: observed versus predicted MACE risk by decile in the ACR category A1 (< 3 mg/dl) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

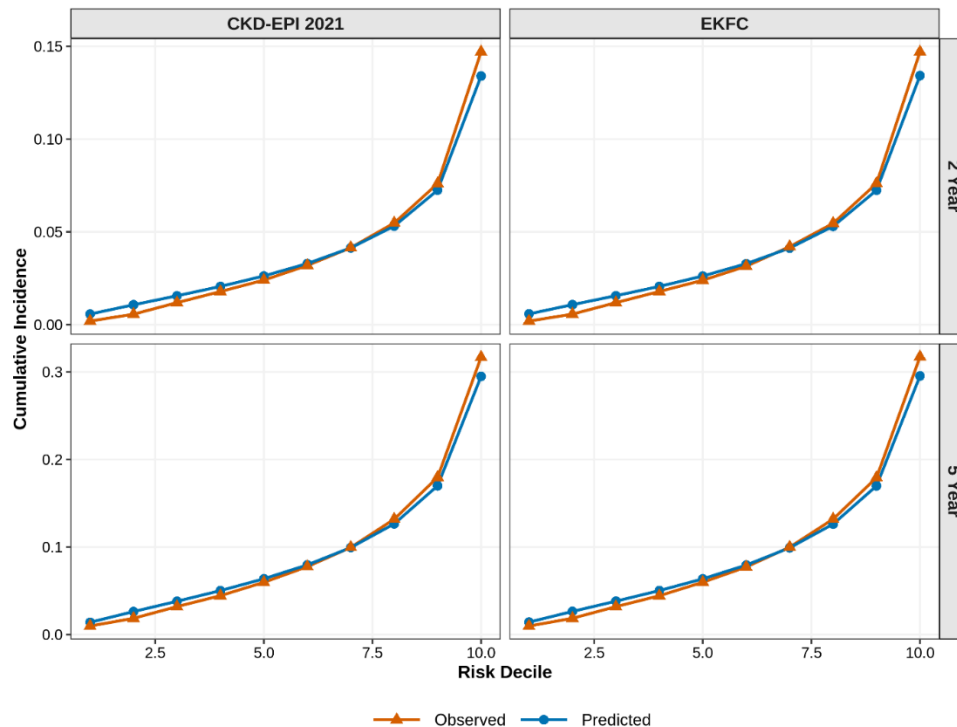


Figure G19. Calibration line plot: observed versus predicted MACE risk by decile in the ACR category A2 (3–30 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

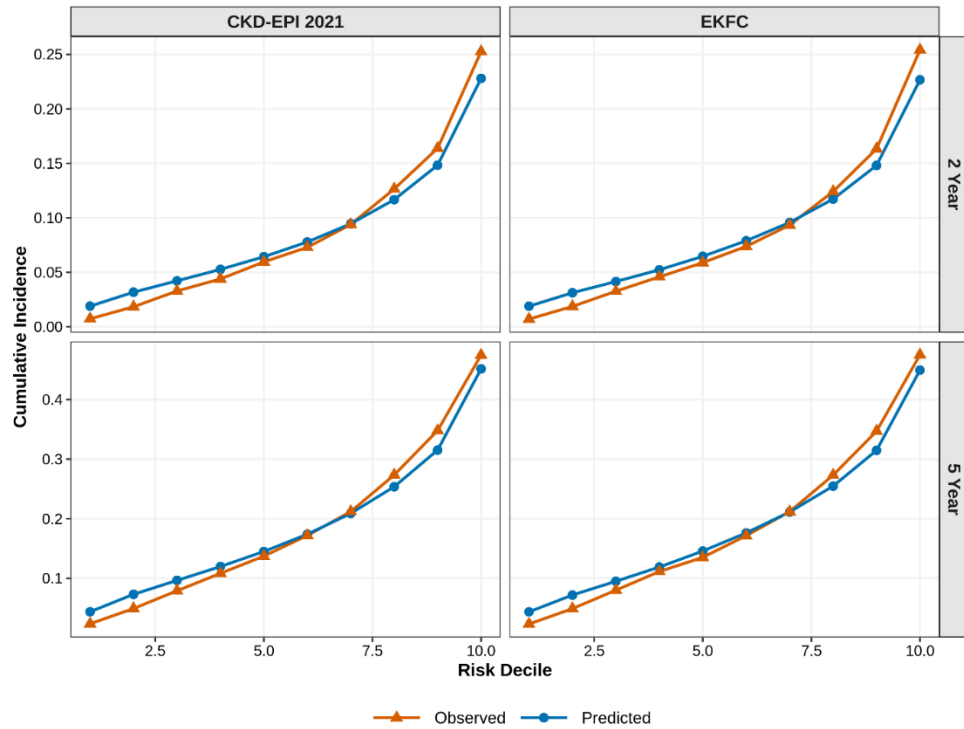


Figure G20. Calibration line plot: observed versus predicted MACE risk by decile in the ACR category A3 (>30 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

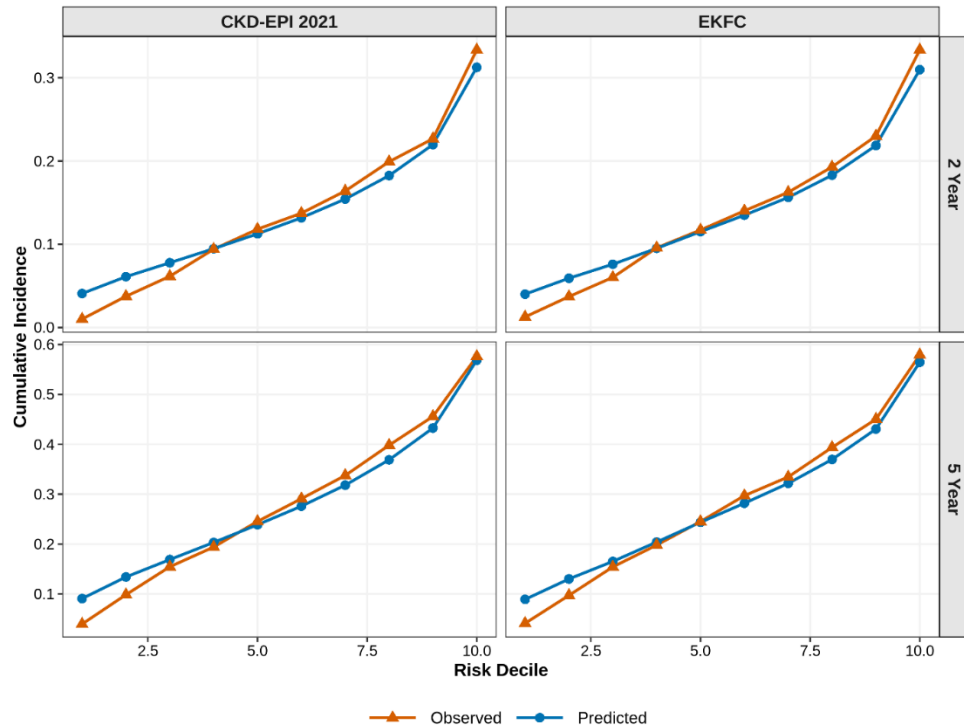


Figure G21. Calibration line plot: observed versus predicted KRT risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

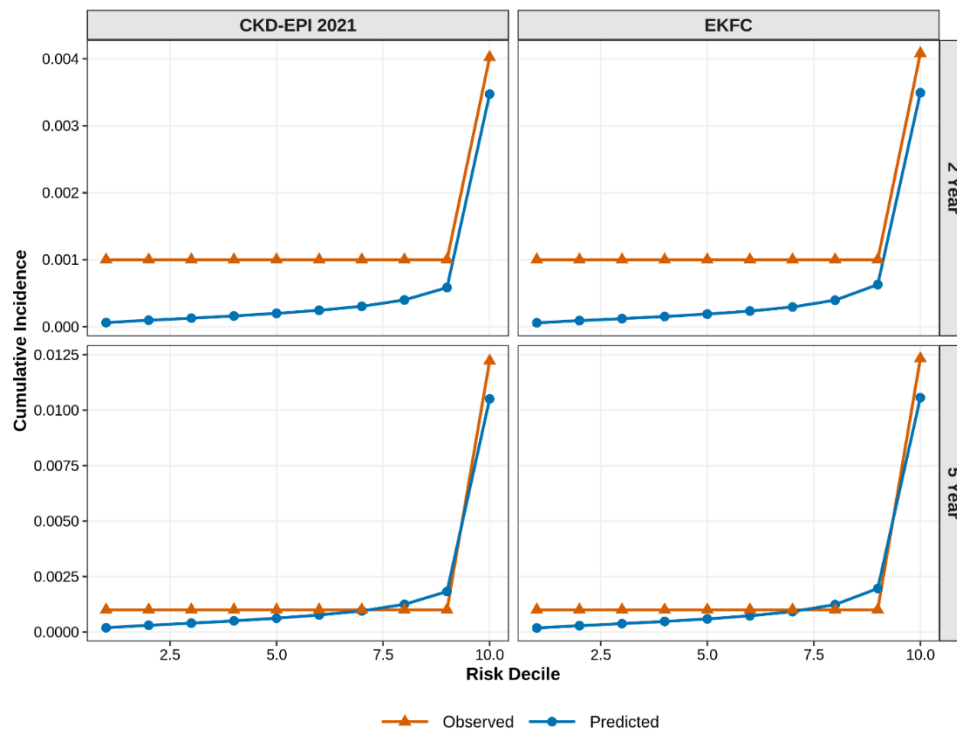
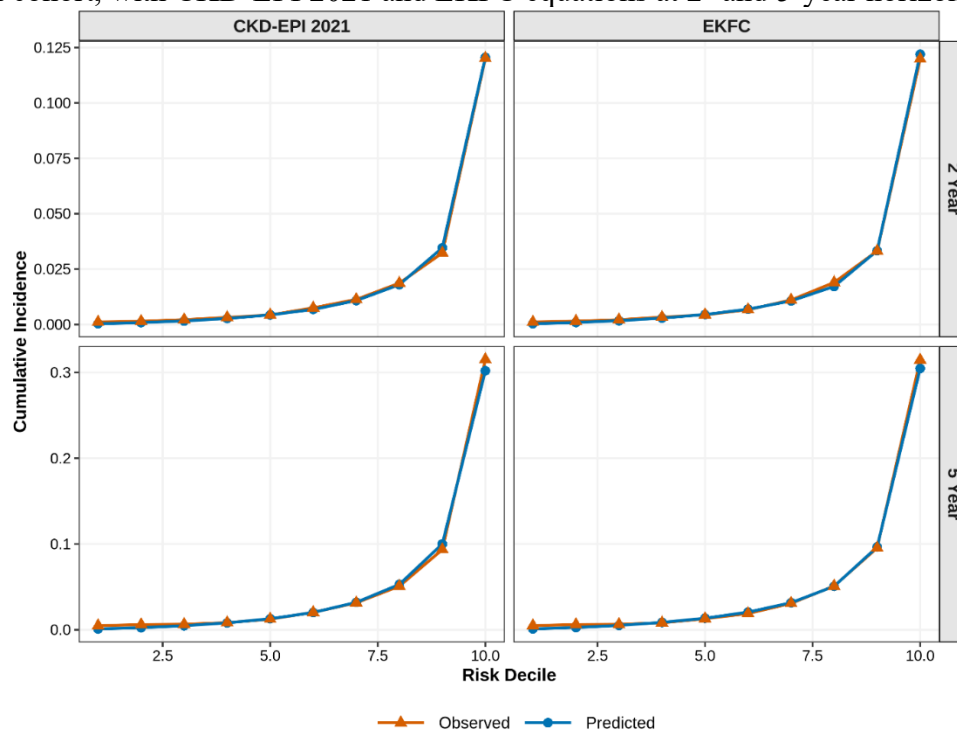


Figure G22. Calibration line plot: observed versus predicted overall mortality risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.



Appendix H. Calibration scatter plots for MAKE, MACE, KRT, and overall mortality

Figure H1. Calibration scatter plot: observed versus predicted MAKE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

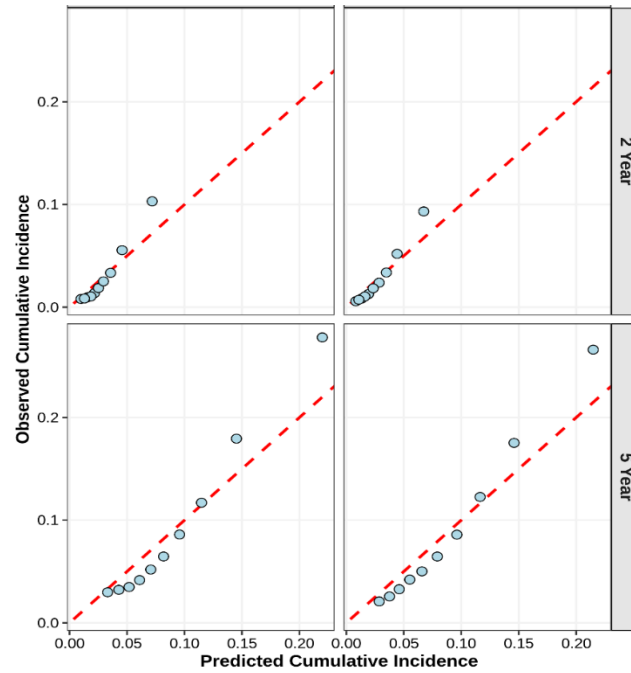


Figure H2. Calibration scatter plot: observed versus predicted MAKE risk by decile in the male subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

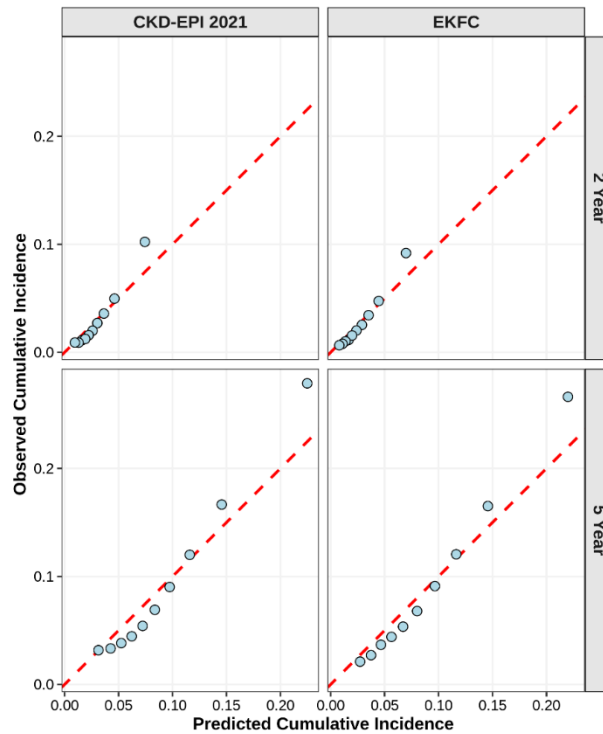


Figure H3. Calibration scatter plot: observed versus predicted MAKE risk by decile in the female subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

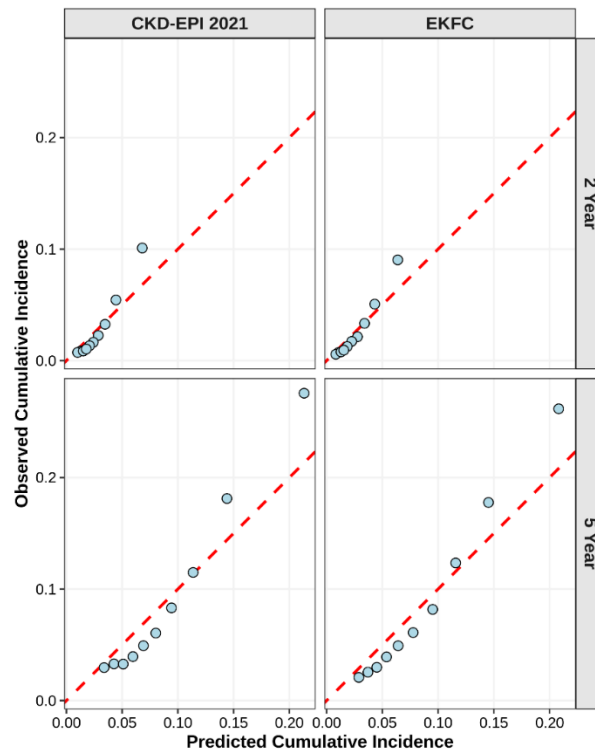


Figure H4. Calibration scatter plot: observed versus predicted MAKE risk by decile in the age 18 to <40 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

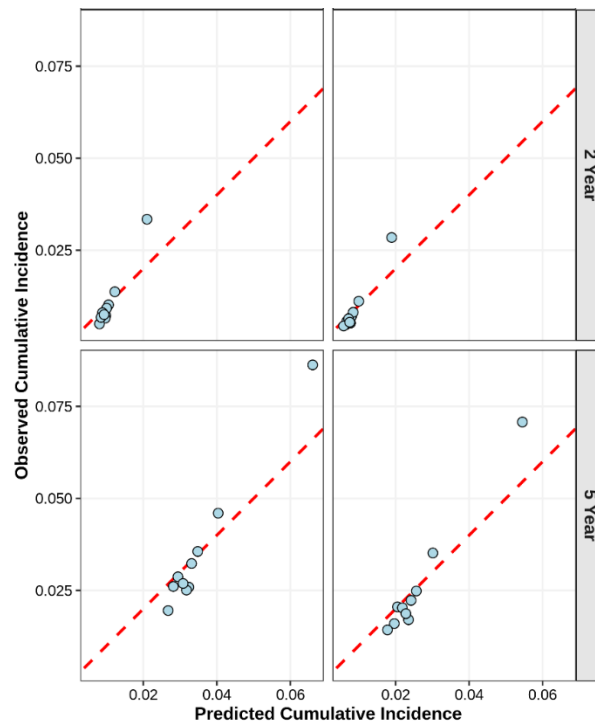


Figure H5. Calibration scatter plot: observed versus predicted MAKE risk by decile in the age 40 to ≤ 65 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

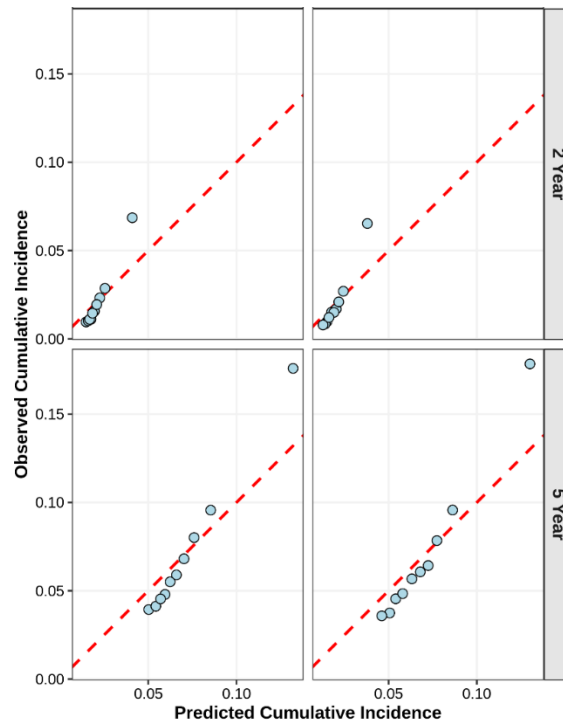


Figure H6. Calibration scatter plot: observed versus predicted MAKE risk by decile in the age 66 to <80 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

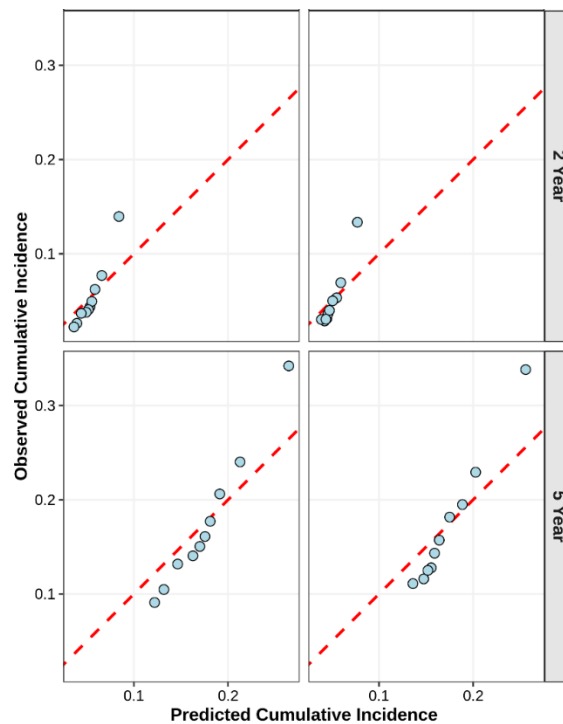


Figure H7. Calibration scatter plot: observed versus predicted MAKE risk by decile in the age ≥ 80 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

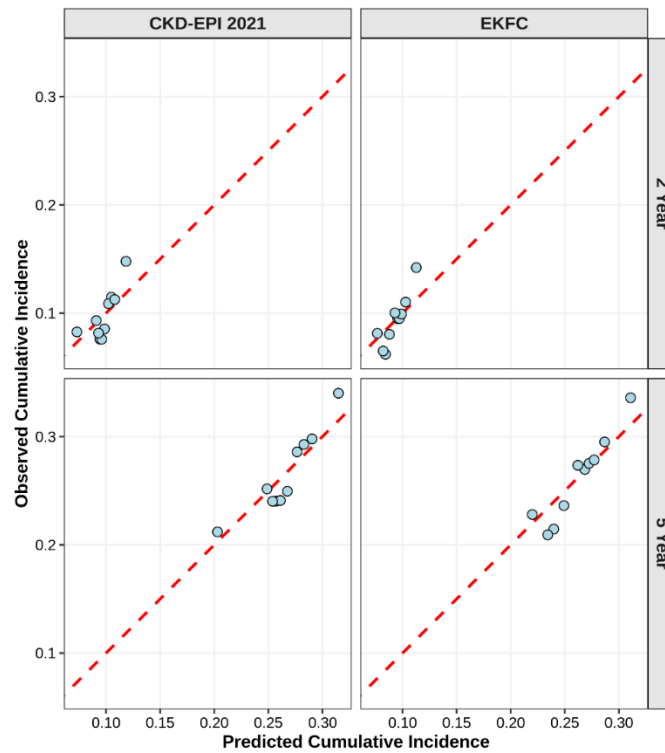


Figure H8. Calibration scatter plot: observed versus predicted MAKE risk by decile in the ACR category A1 (<3 mg/mm 3) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

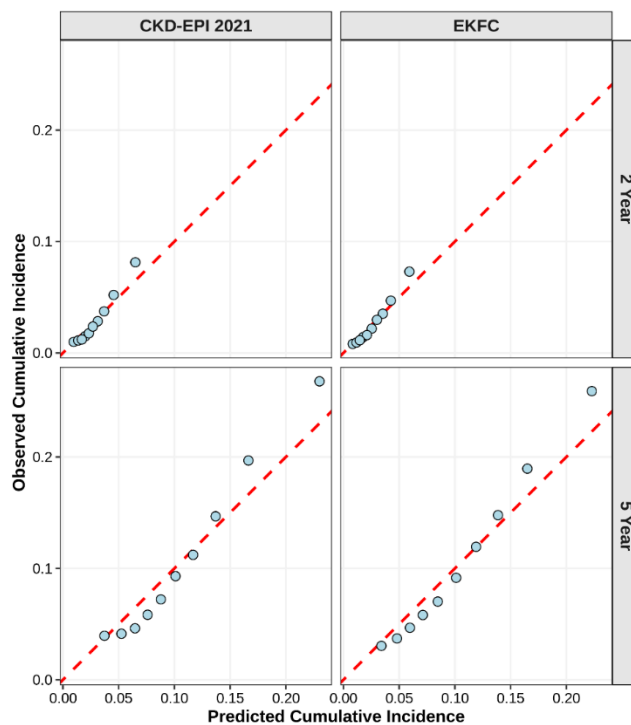


Figure H9. Calibration scatter plot: observed versus predicted MAKE risk by decile in the ACR category A2 (3–30 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

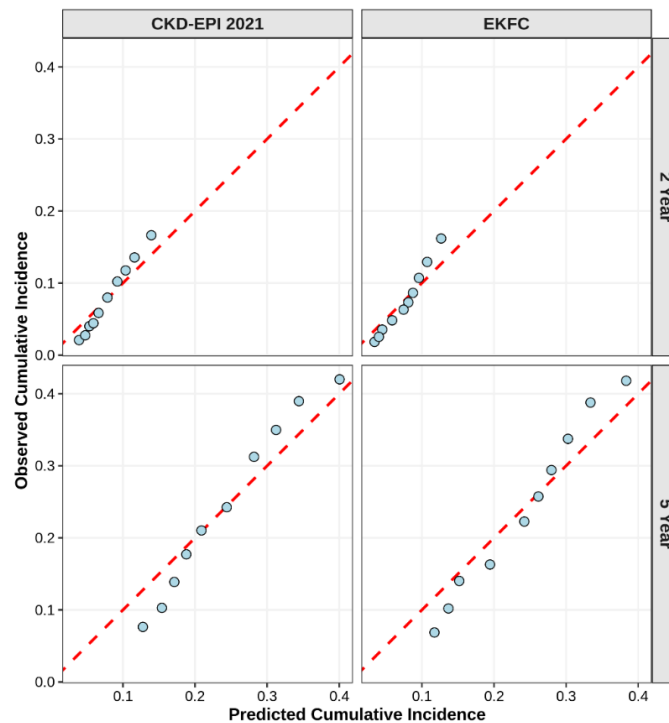


Figure H10. Calibration scatter plot: observed versus predicted MAKE risk by decile in the ACR category A3 (>30 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

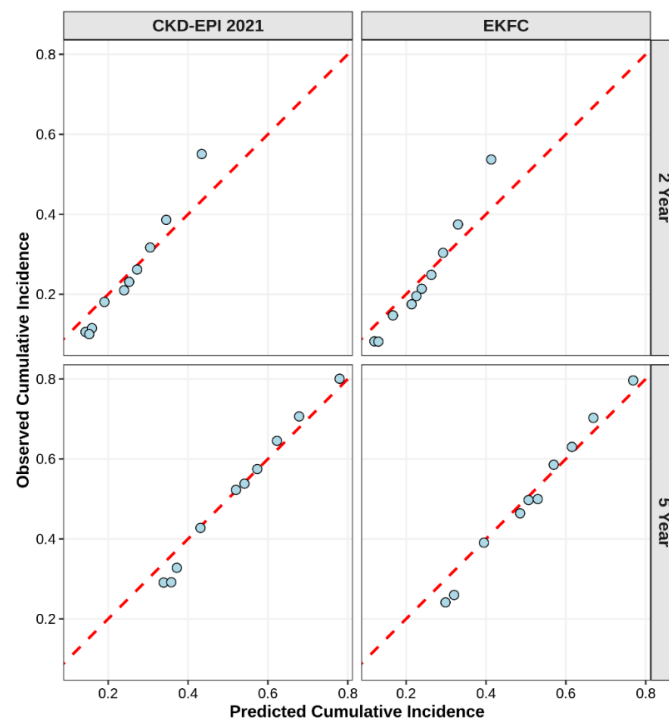


Figure H11. Calibration scatter plot: observed versus predicted MACE risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

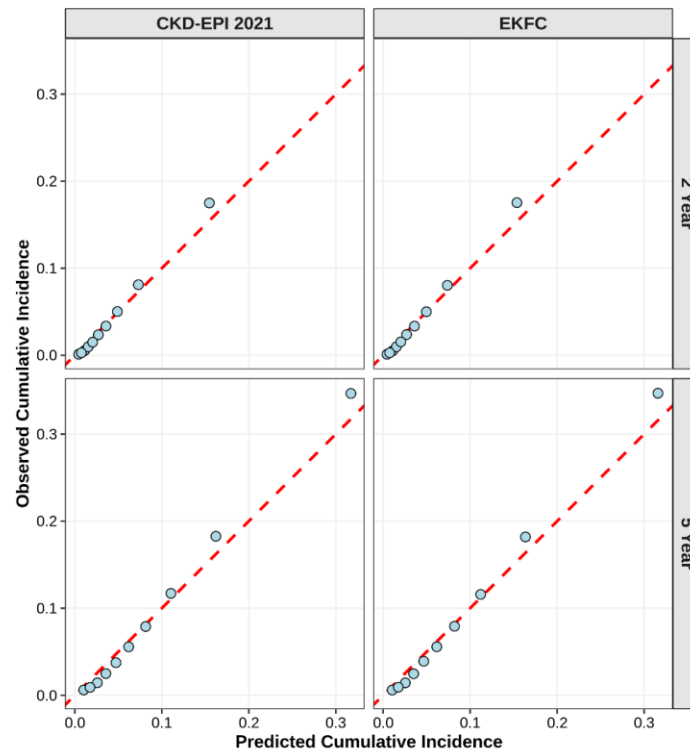


Figure H12. Calibration scatter plot: observed versus predicted MACE risk by decile in the male subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

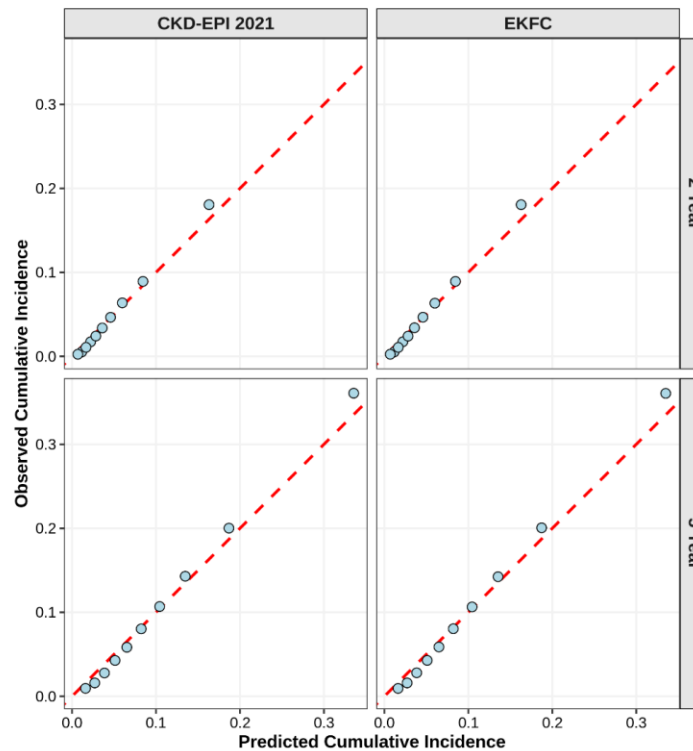


Figure H13. Calibration scatter plot: observed versus predicted MACE risk by decile in the female subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

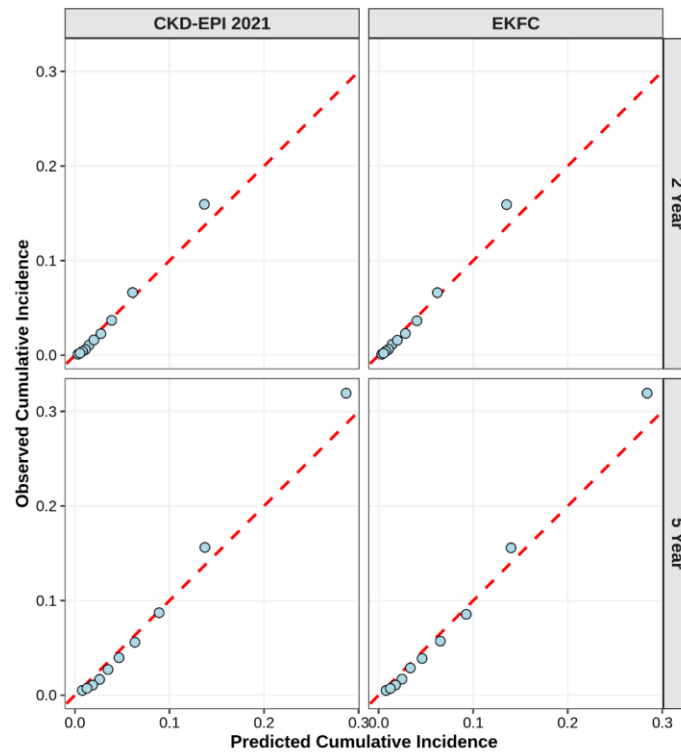


Figure H14. Calibration scatter plot: observed versus predicted MACE risk by decile in the age 18 to <40 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

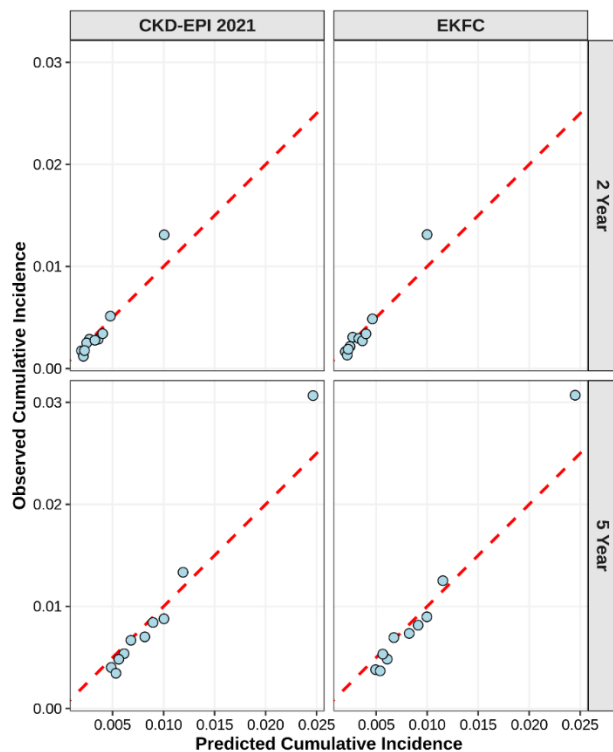


Figure H15. Calibration scatter plot: observed versus predicted MACE risk by decile in the age 40 to ≤ 65 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

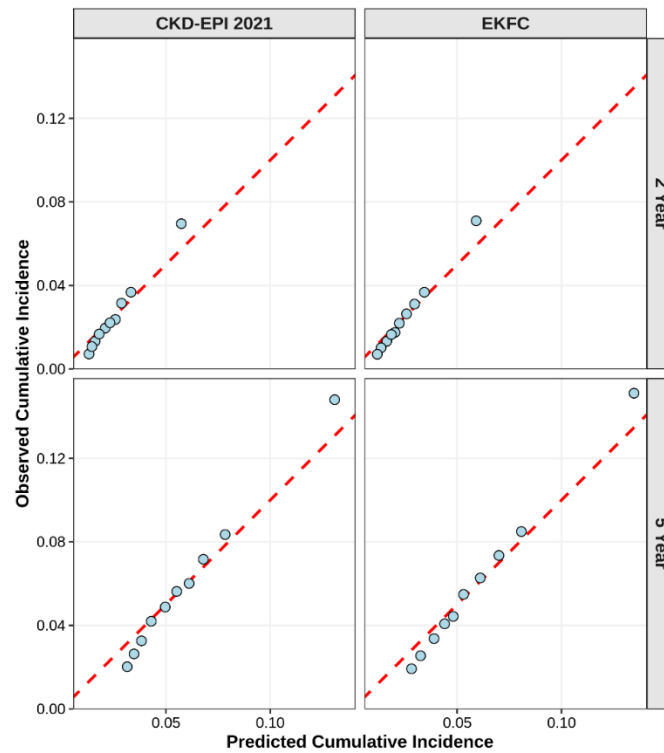


Figure H16. Calibration scatter plot: observed versus predicted MACE risk by decile in the age 66 to <80 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

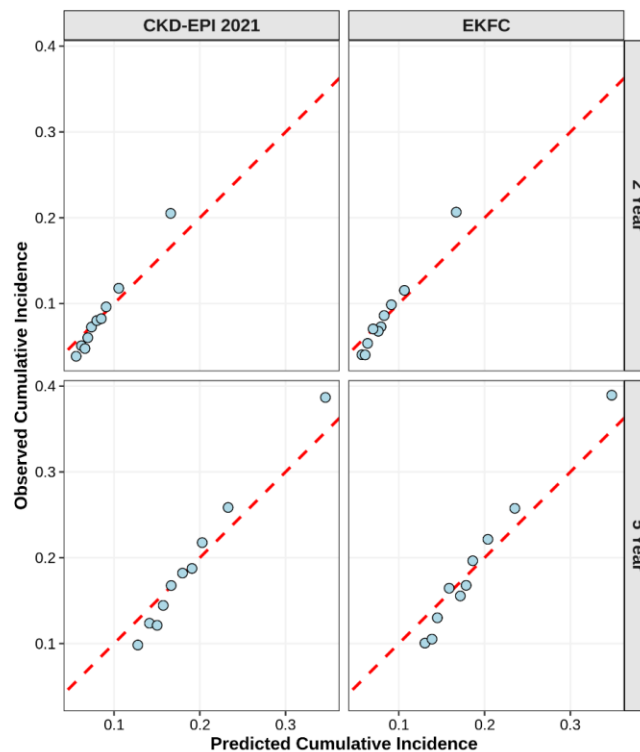


Figure H17. Calibration scatter plot: observed versus predicted MACE risk by decile in the age ≥ 80 subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

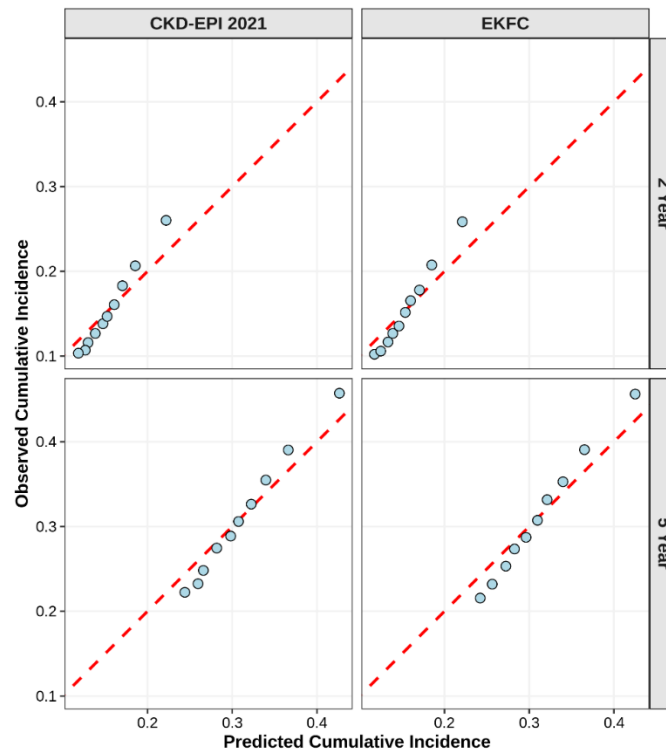


Figure H18. Calibration scatter plot: observed versus predicted MACE risk by decile in the ACR category A1 (<3 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

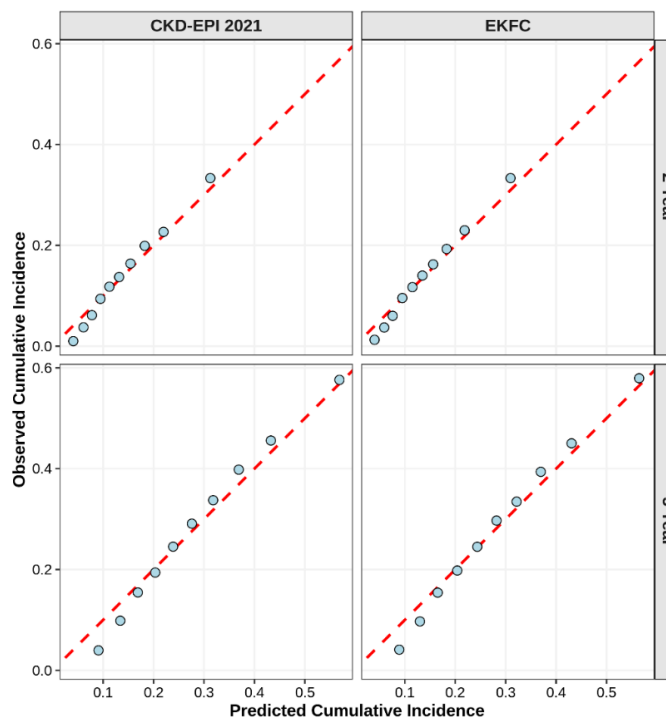


Figure H19. Calibration scatter plot: observed versus predicted MACE risk by decile in the ACR category A2 (3–30 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

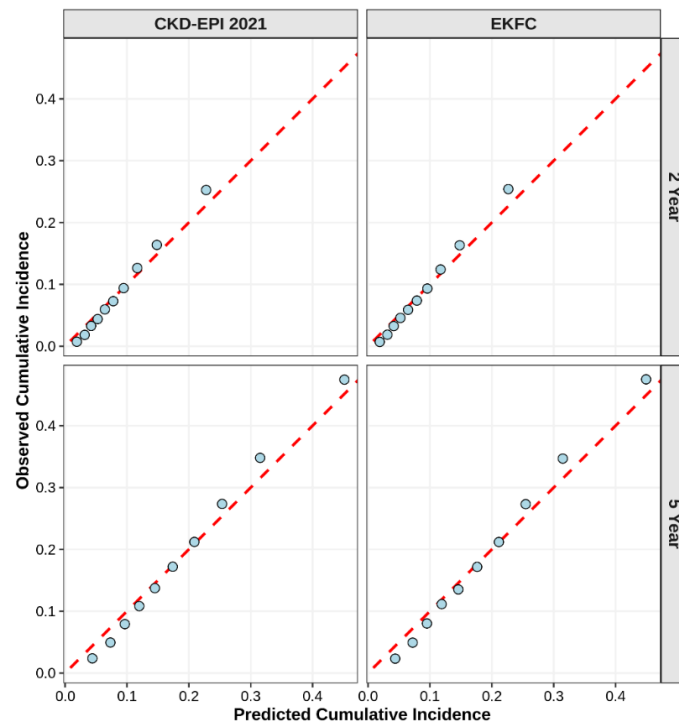


Figure H20. Calibration scatter plot: observed versus predicted MACE risk by decile in the ACR category A3 (>30 mg/mmol) subgroup, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

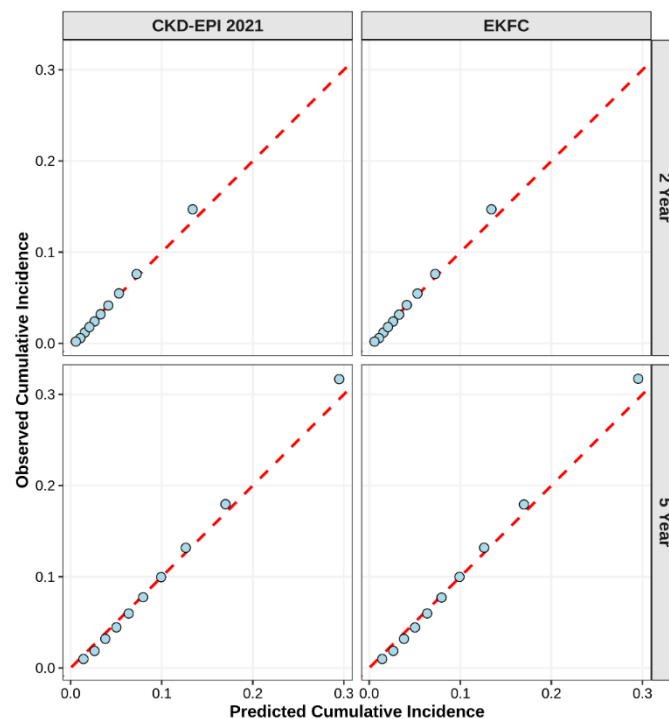


Figure H21. Calibration scatter plot: observed versus predicted KRT risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

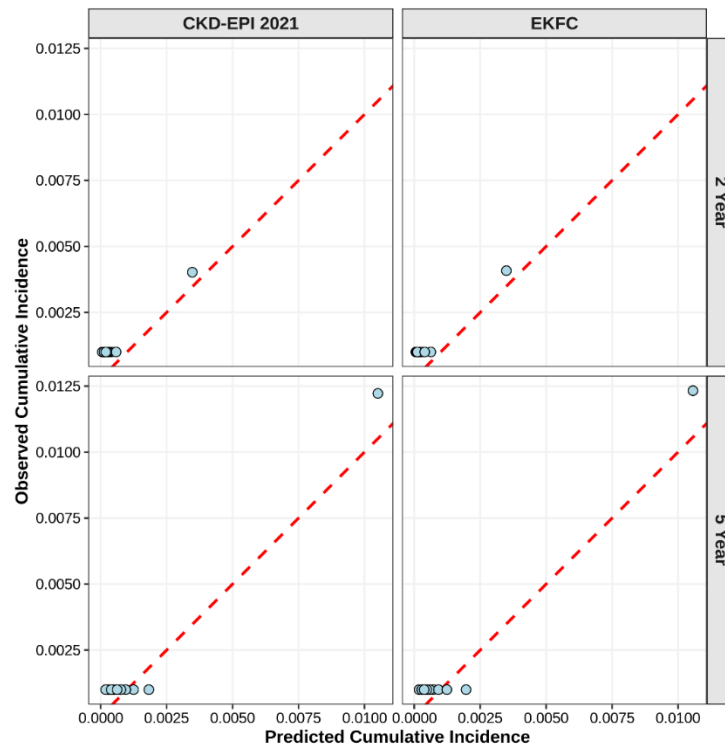


Figure H22. Calibration scatter plot: observed versus predicted overall mortality risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

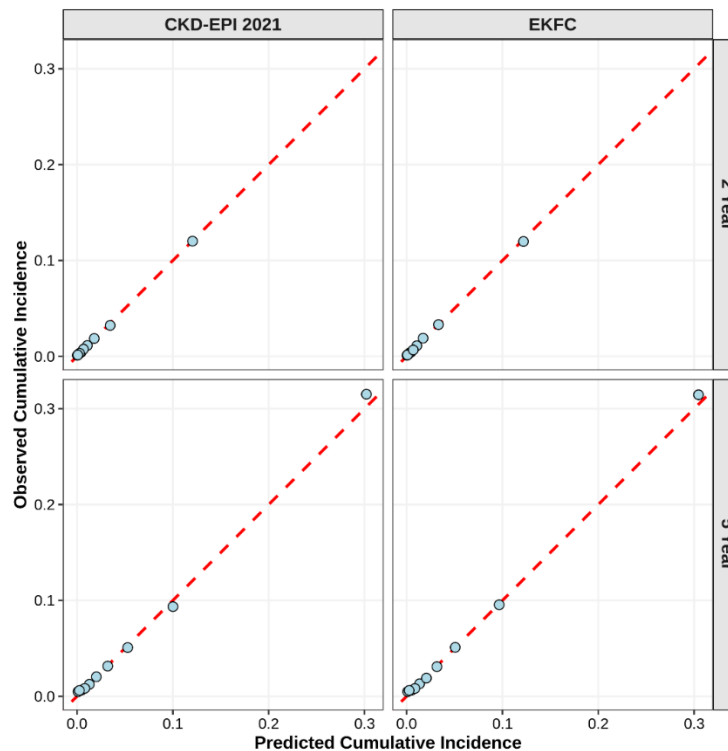
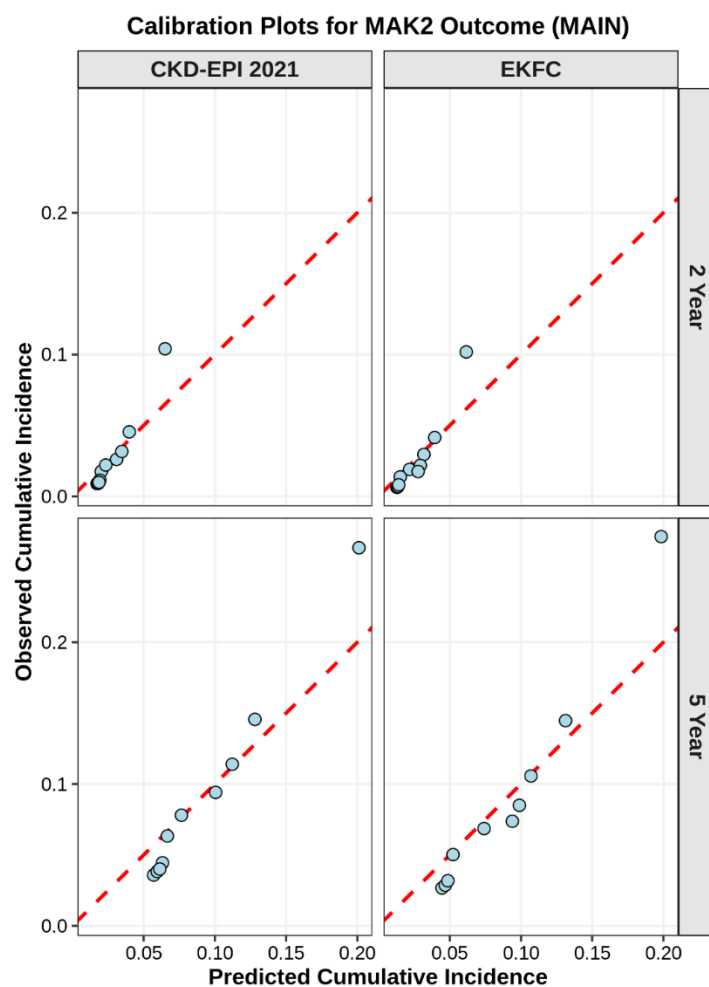
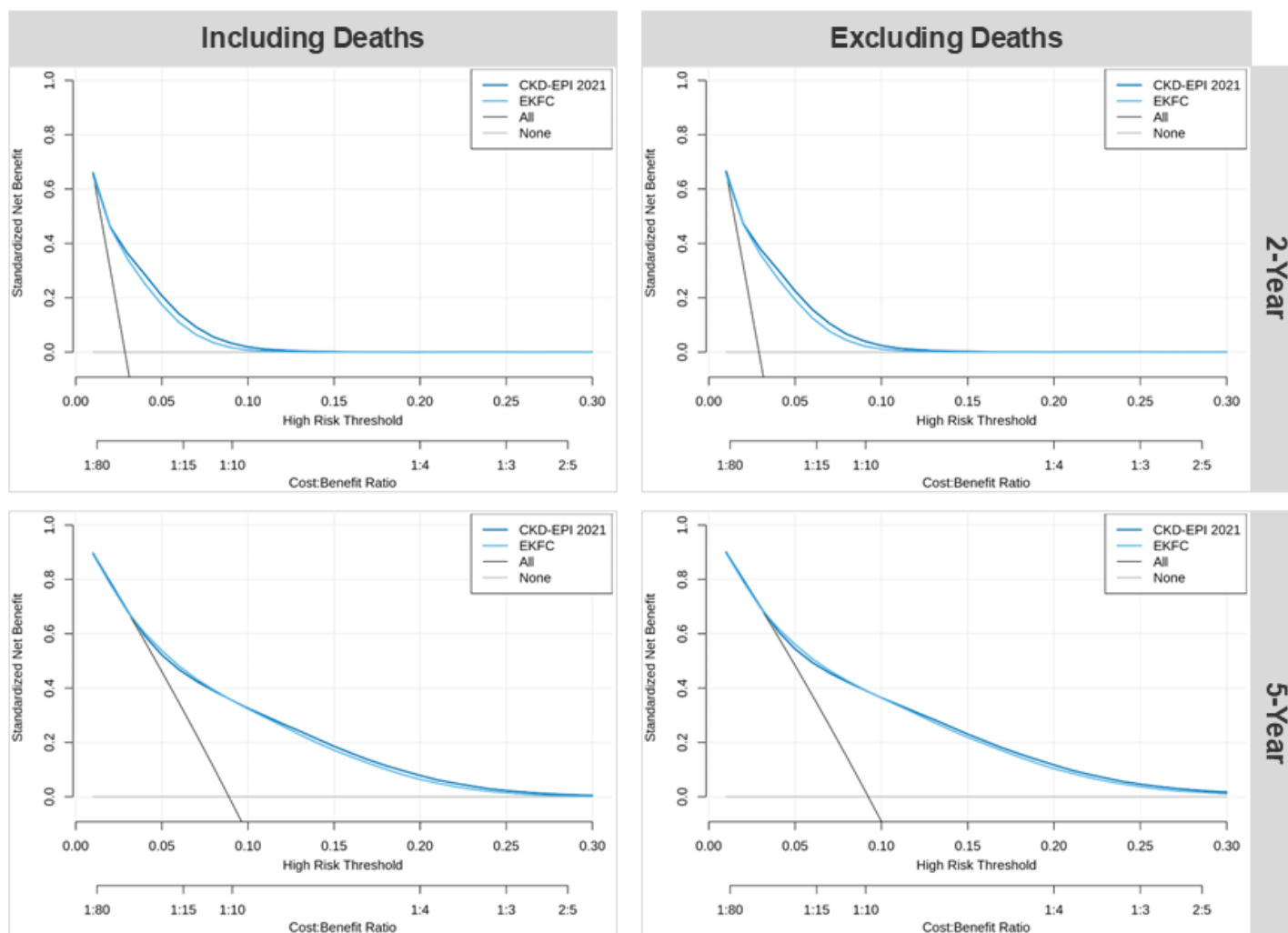


Figure H23. Calibration scatter plot: observed versus predicted MAKE (unadjusted for age and sex) risk by decile in the overall cohort, with CKD-EPI 2021 and EKFC equations at 2- and 5-year horizons.

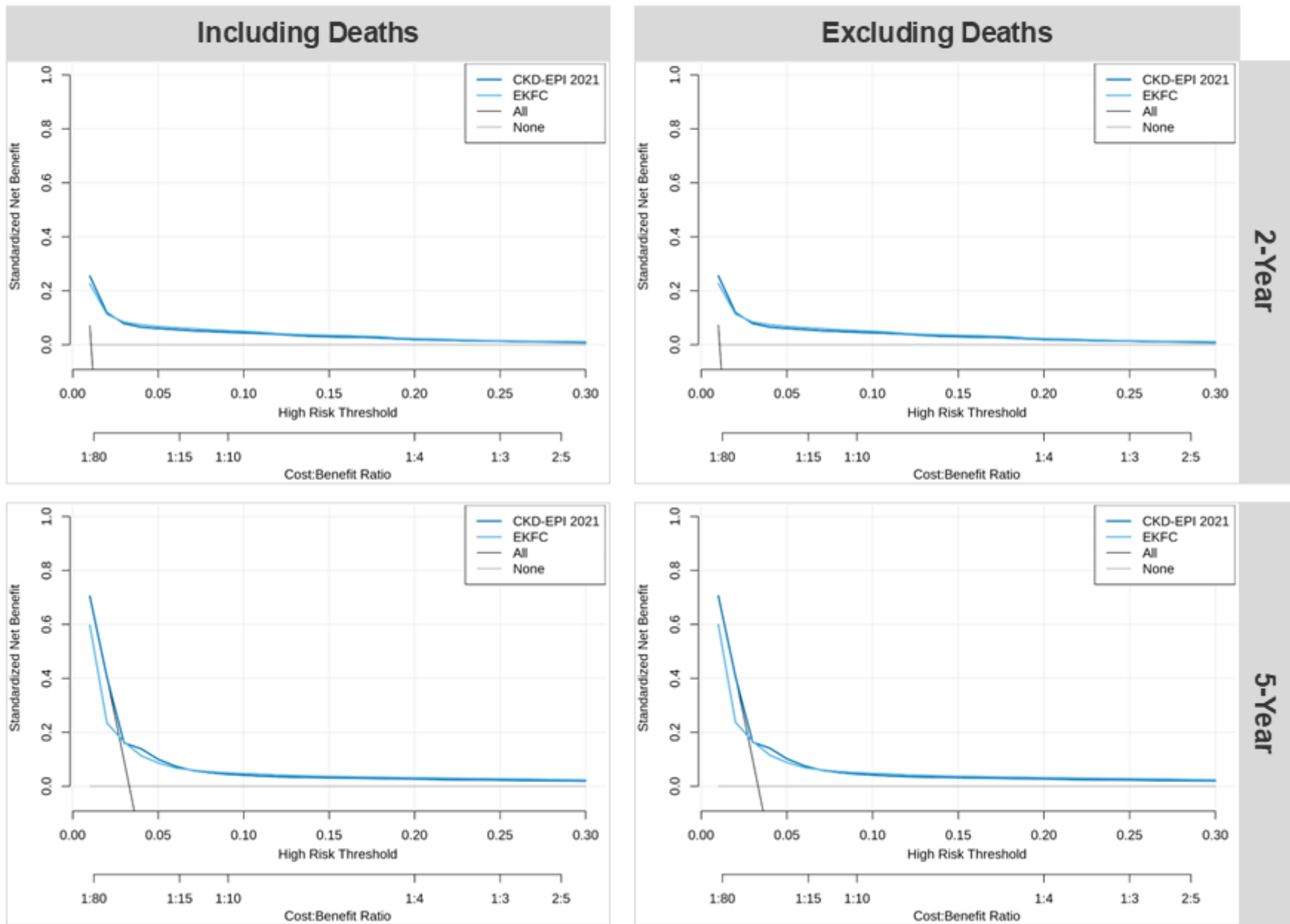


Appendix I. Decision Curve Analysis for MAKE, MACE, KRT, and overall mortality outcomes using CK21 and EKFC eGFR values for the overall cohort. MAKE and MACE models for female, male, age 18 to <40, 40 to ≤ 65, 66 to <80, ≥80, ACR categories A1 (<3 mg/mmol), A2 (3-30 mg/mmol), and A3 (>30 mg/mmol) strata.

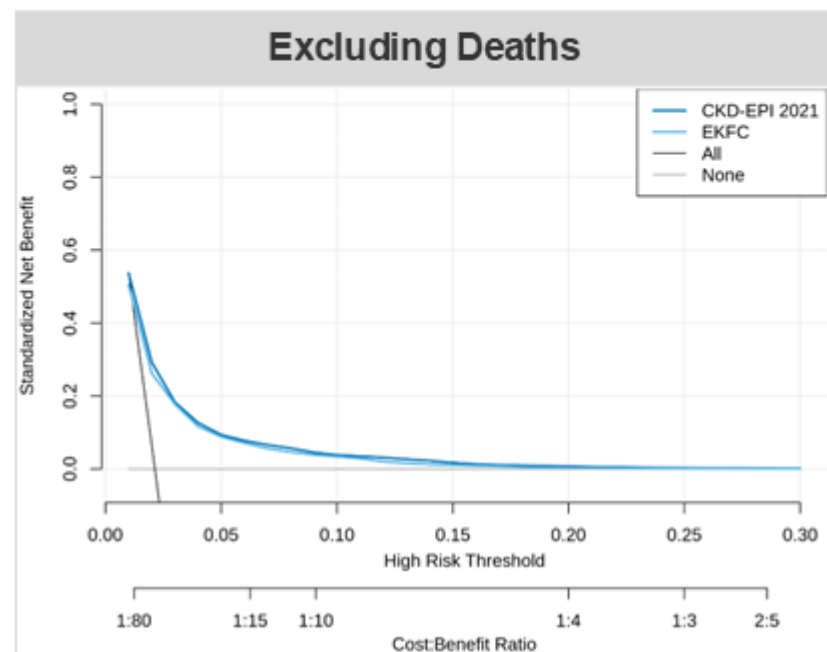
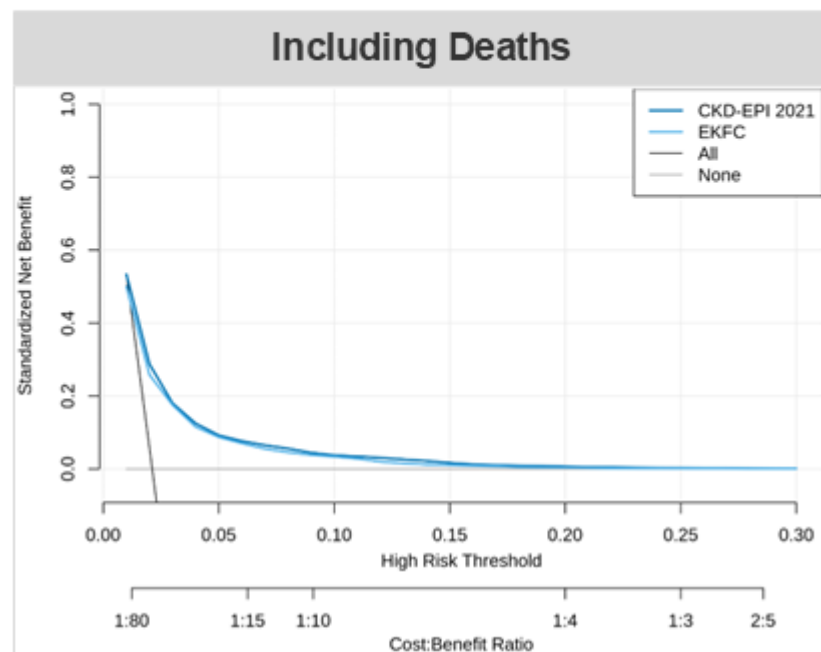
MAKE Decision Curve Analysis — Overall



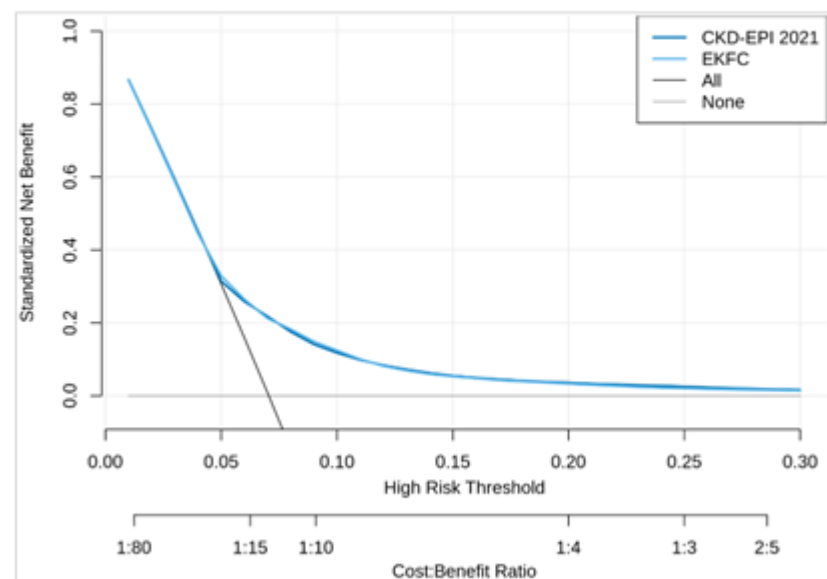
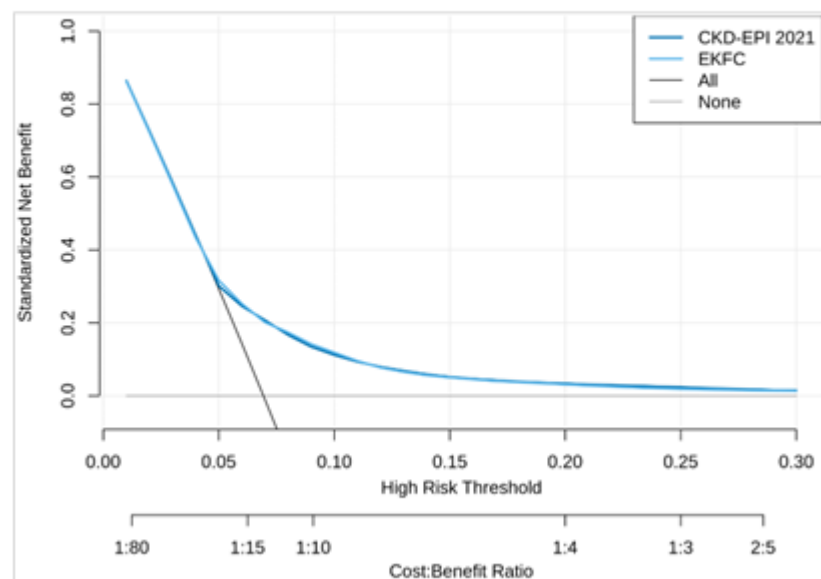
MAKE Decision Curve Analysis — Age 18 to <40



MAKE Decision Curve Analysis — Age 40 to ≤ 65

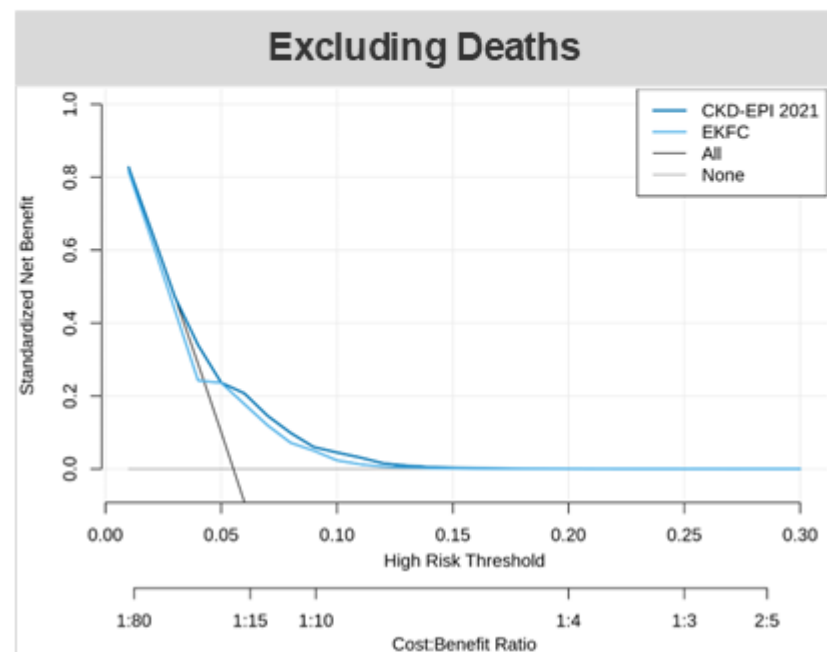
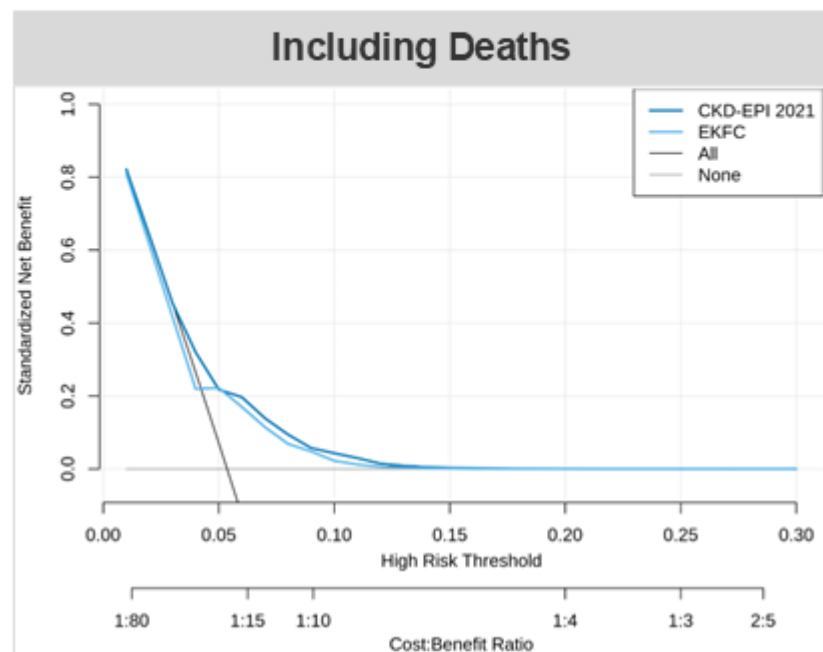


2-Year

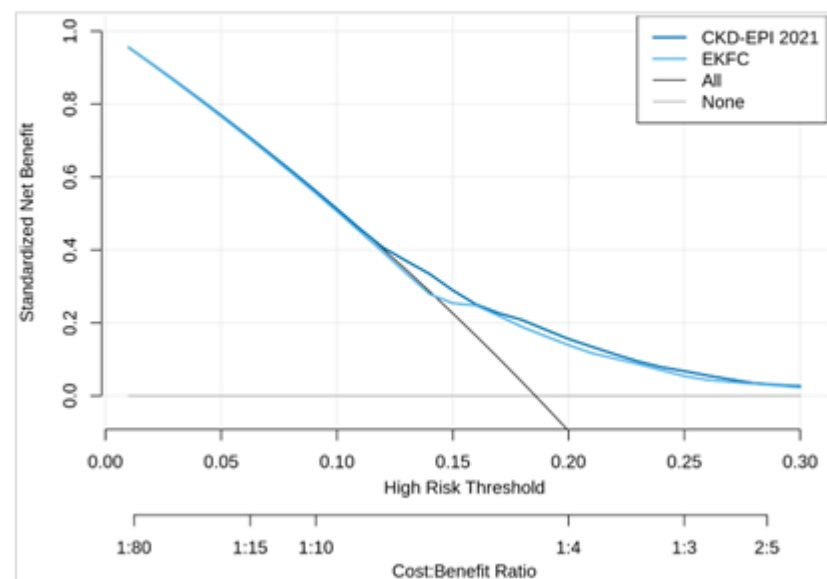
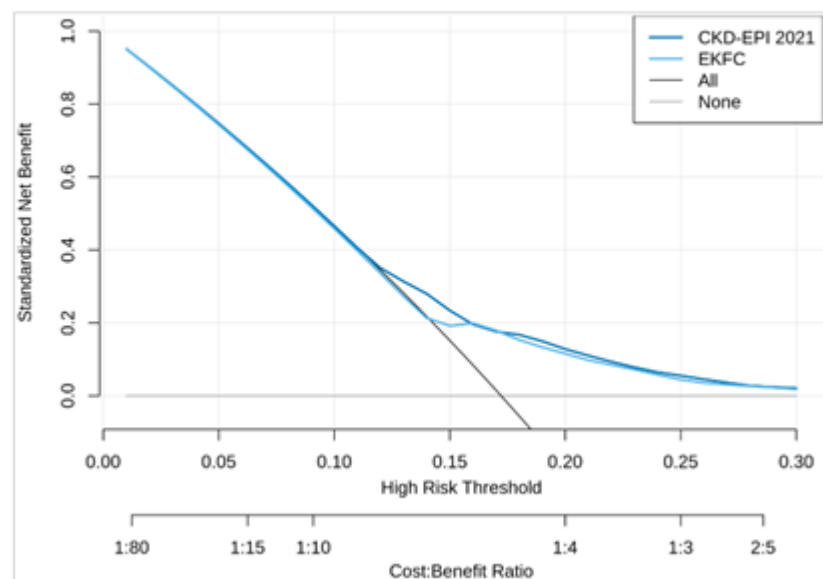


5-Year

MAKE Decision Curve Analysis — Age 65 to <80

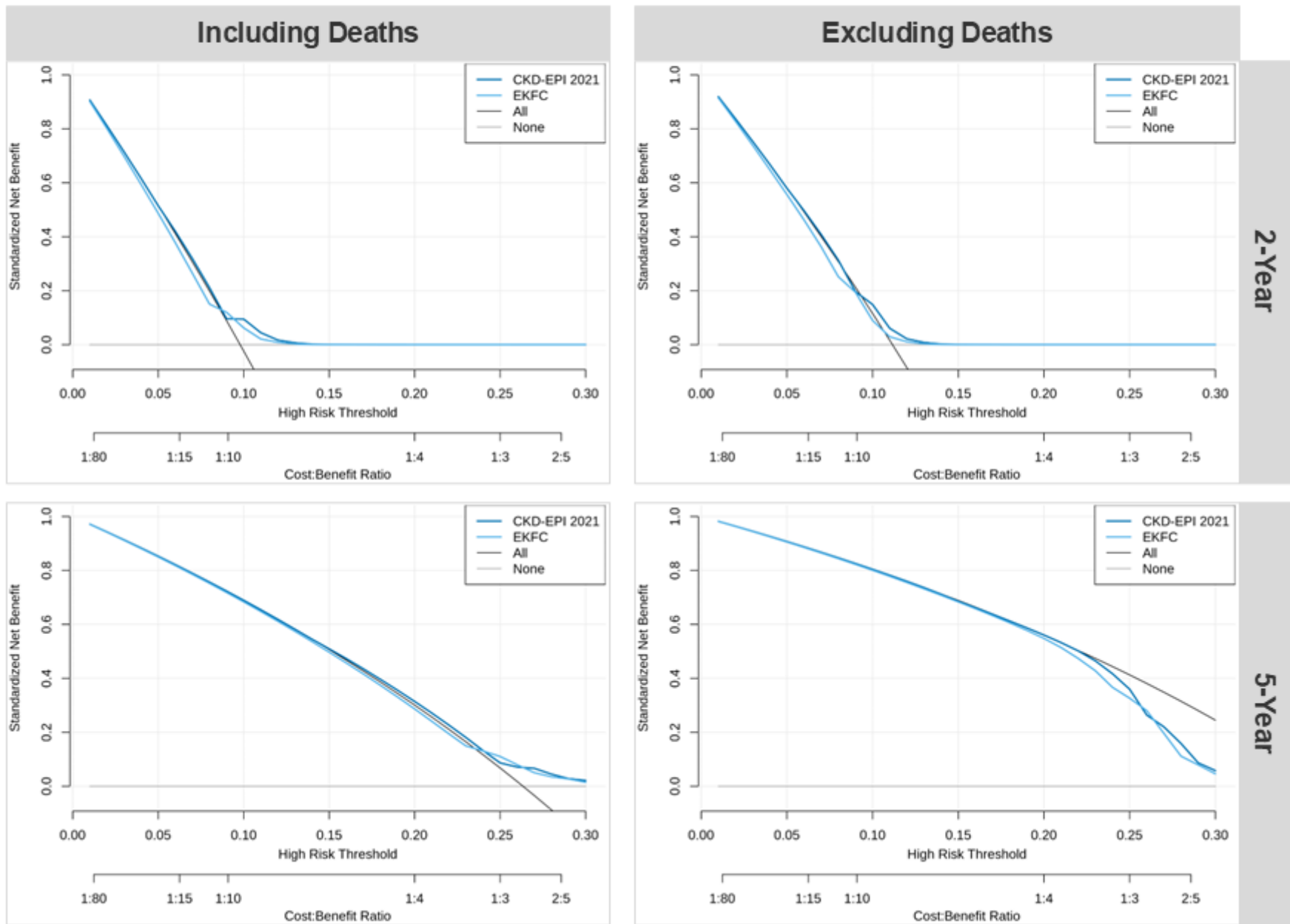


2-Year

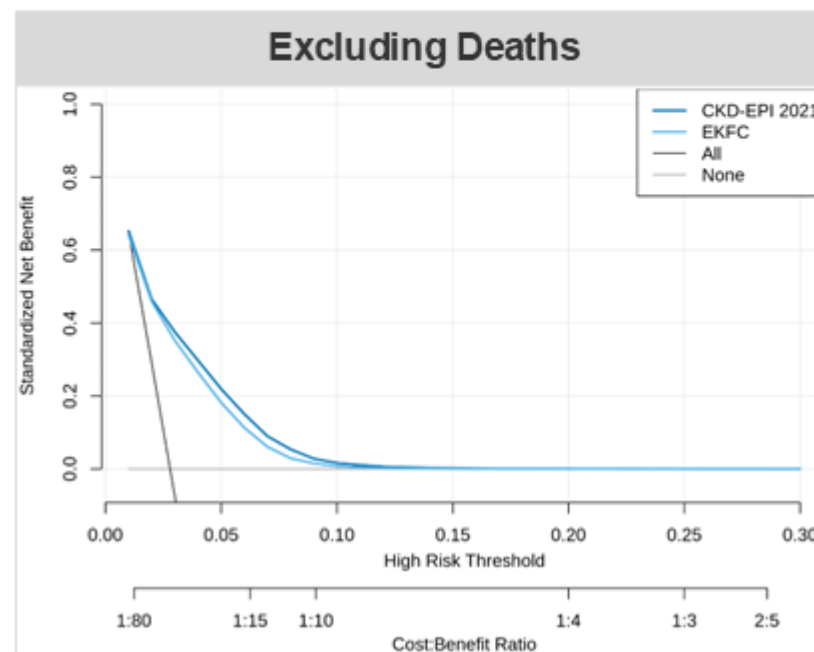
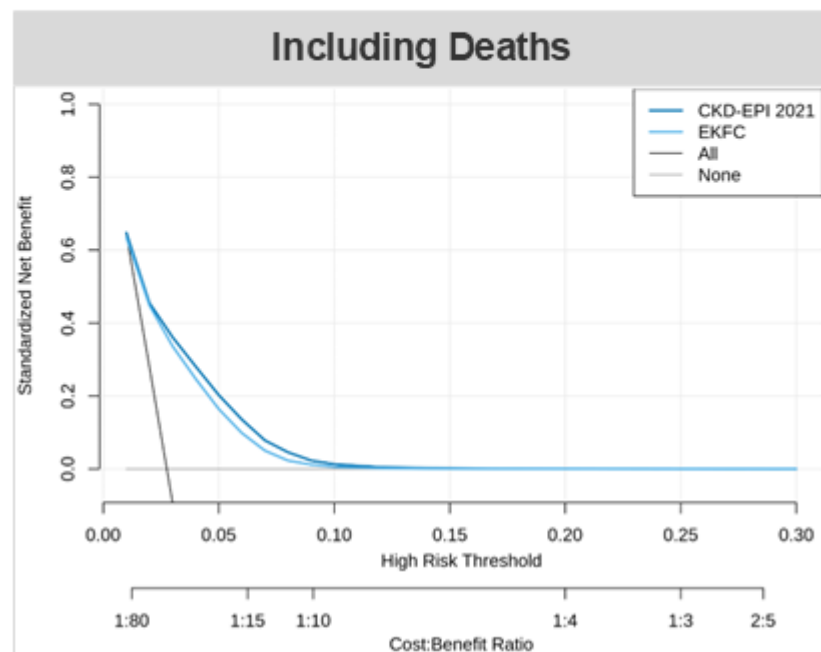


5-Year

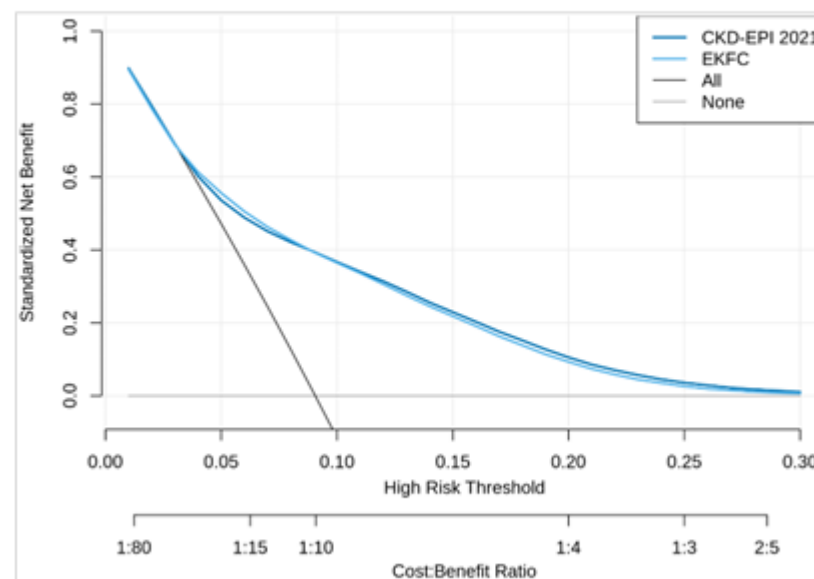
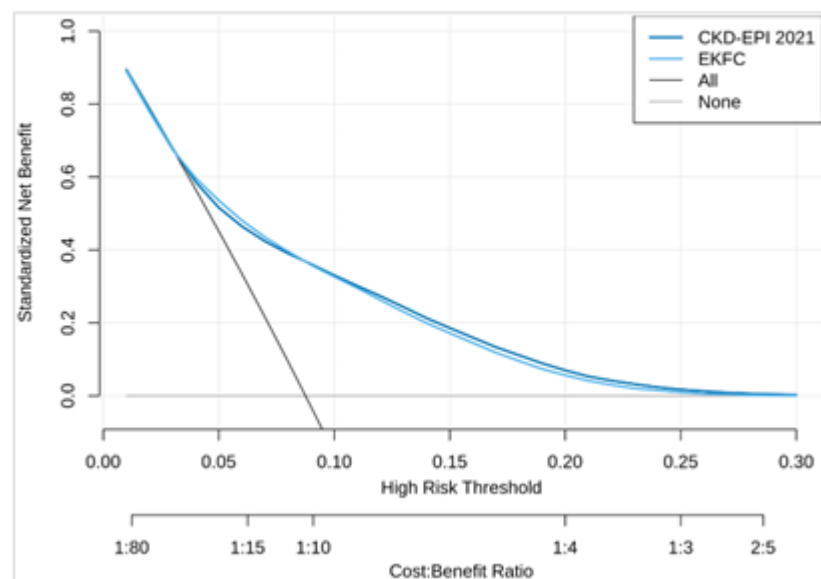
MAKE Decision Curve Analysis — Age 80+



MAKE Decision Curve Analysis — Female

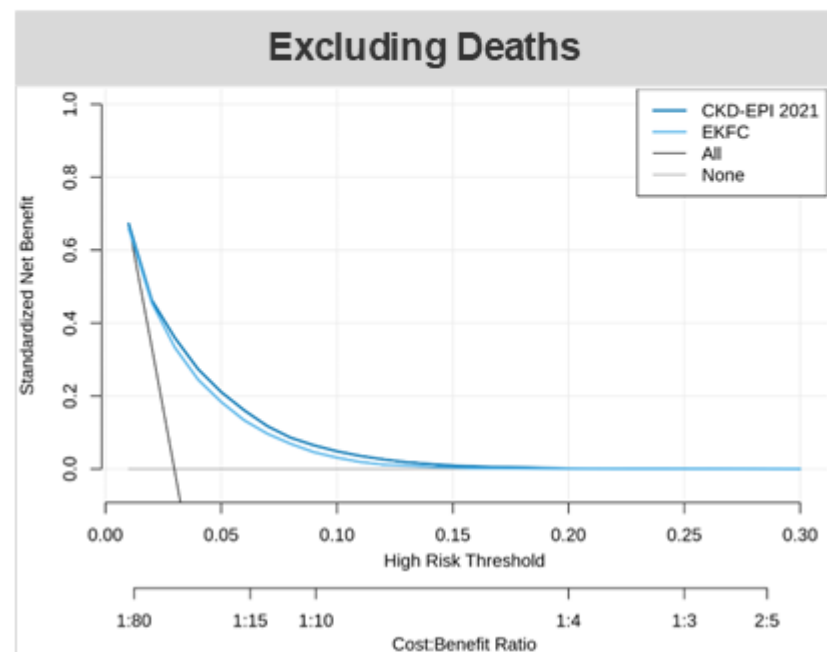
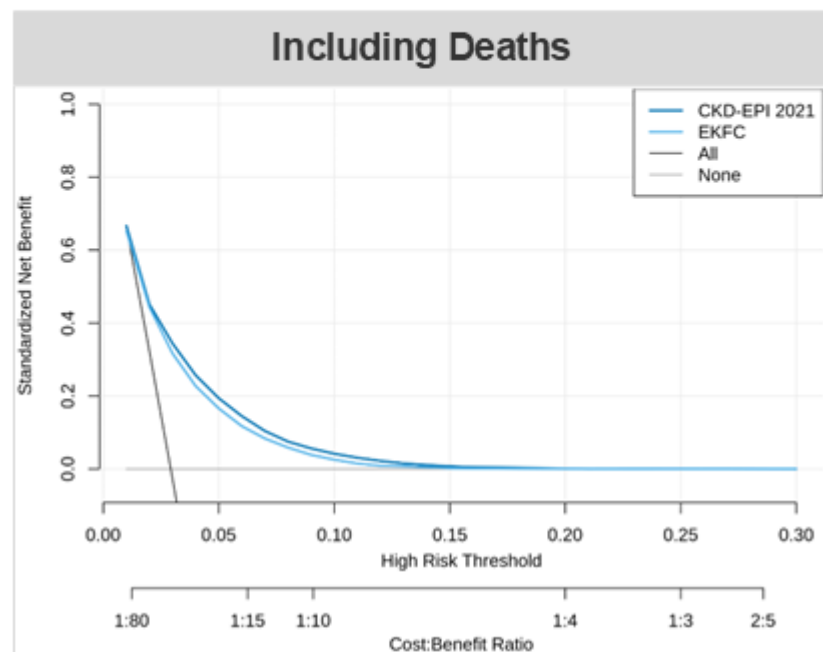


2-Year

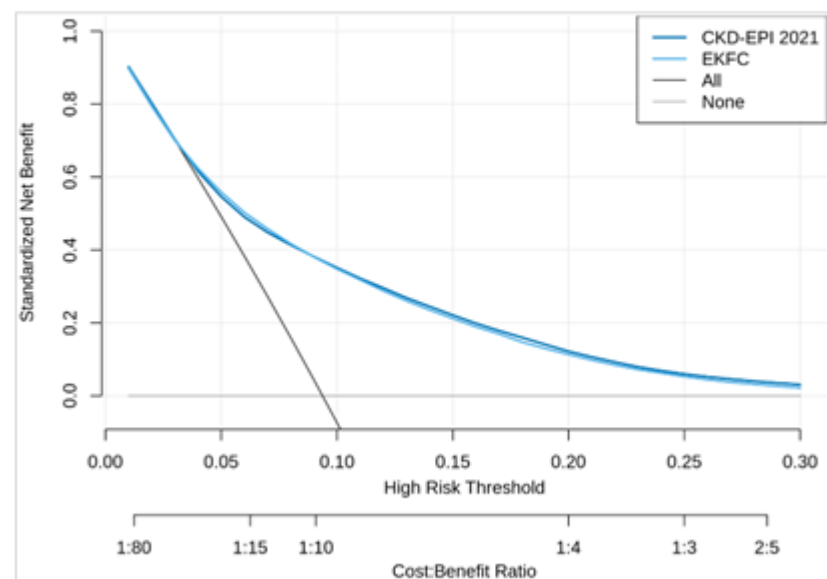
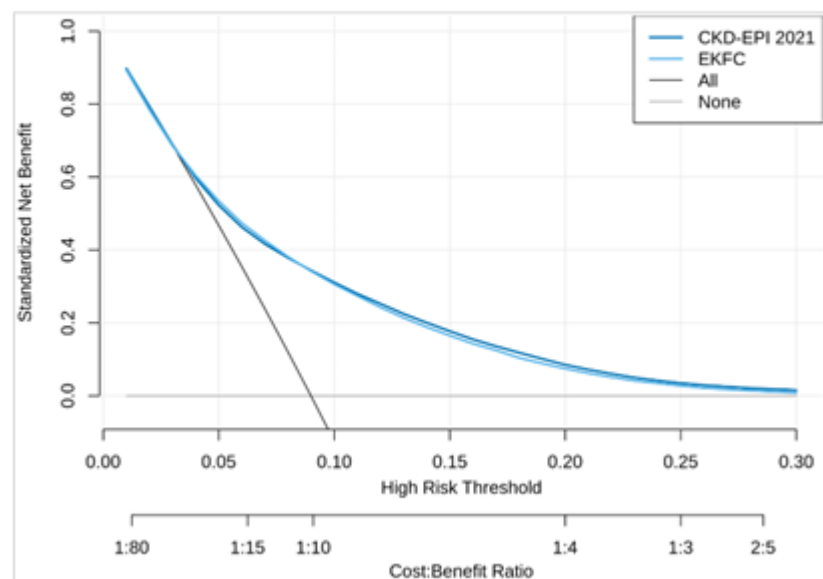


5-Year

MAKE Decision Curve Analysis — Male

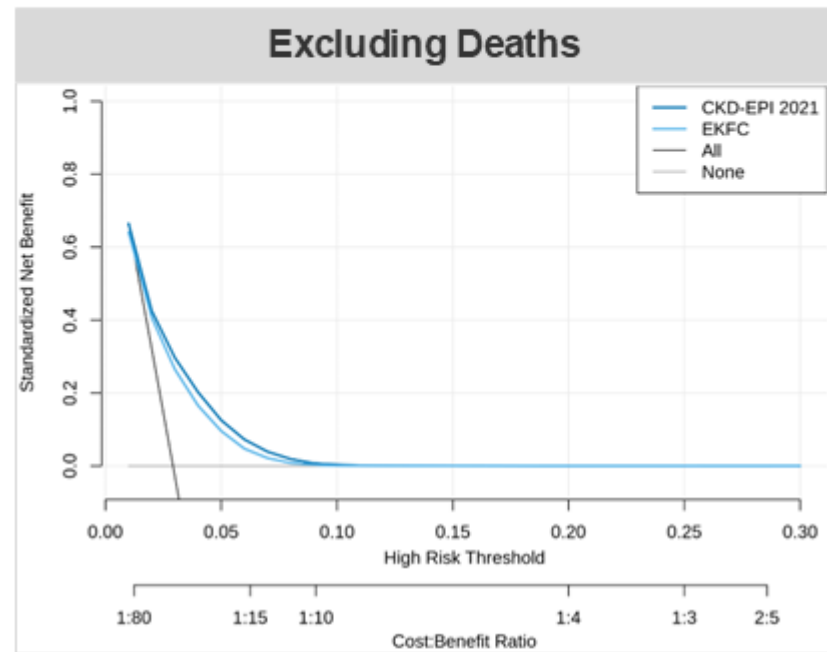
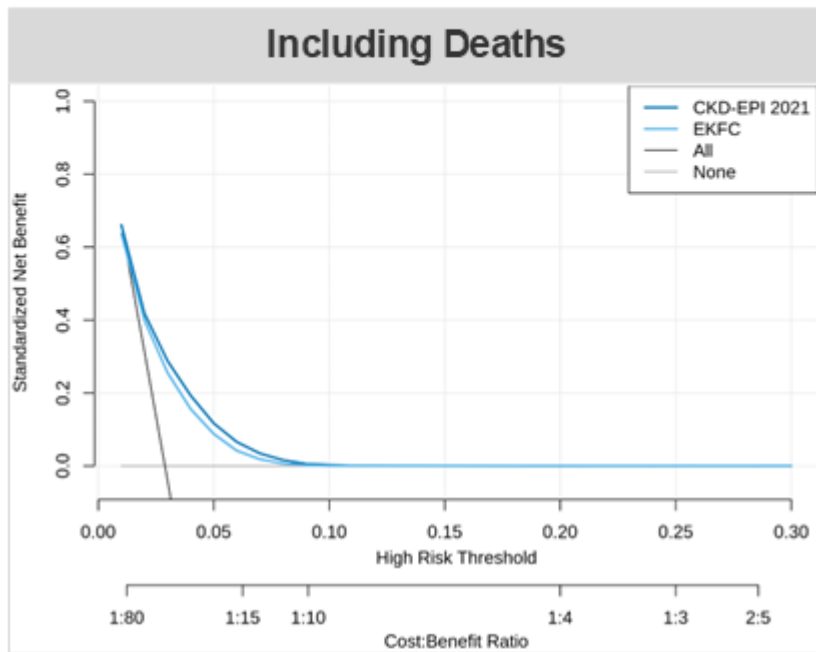


2-Year

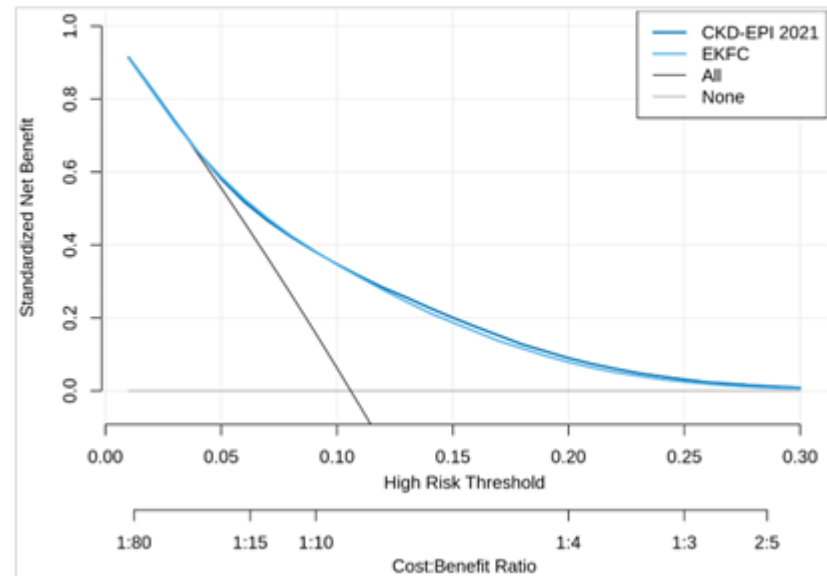
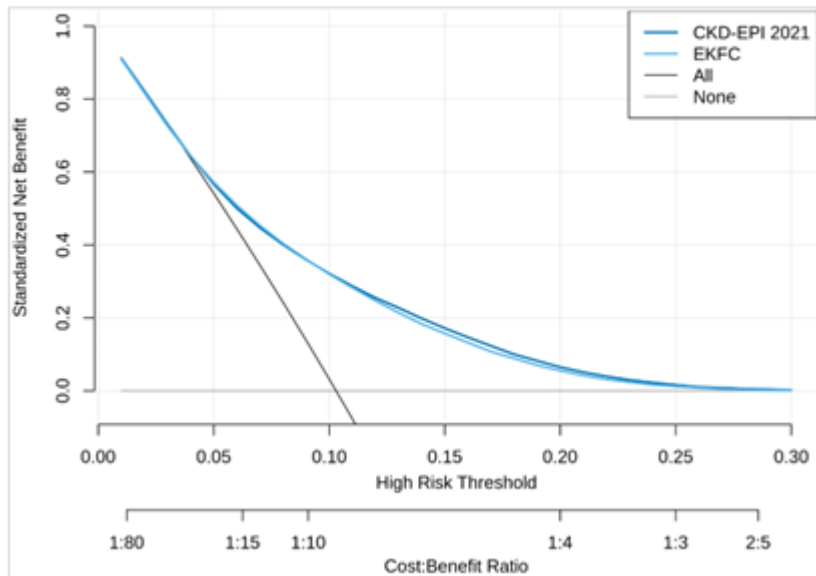


5-Year

MAKE Decision Curve Analysis — Albuminuria A1 (<3 mg/mmol)

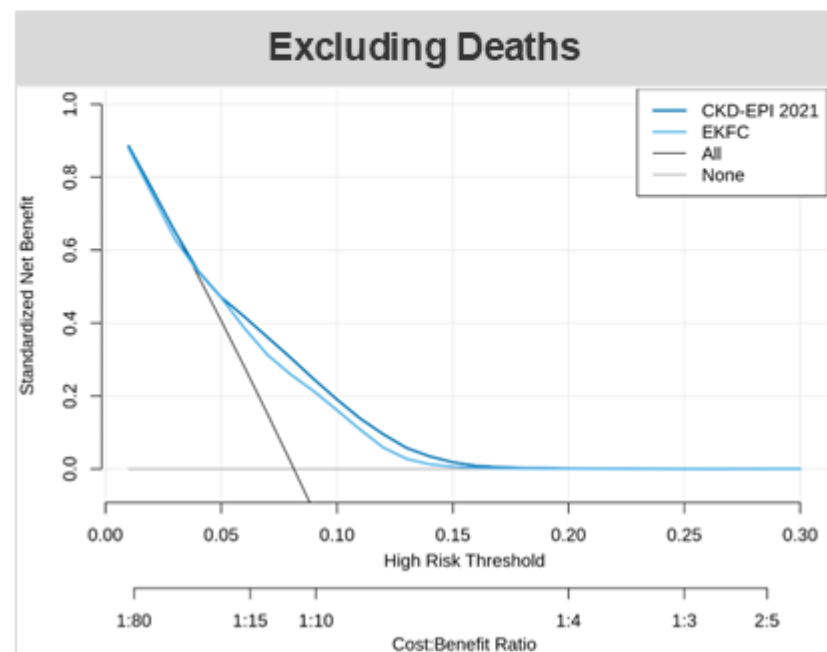
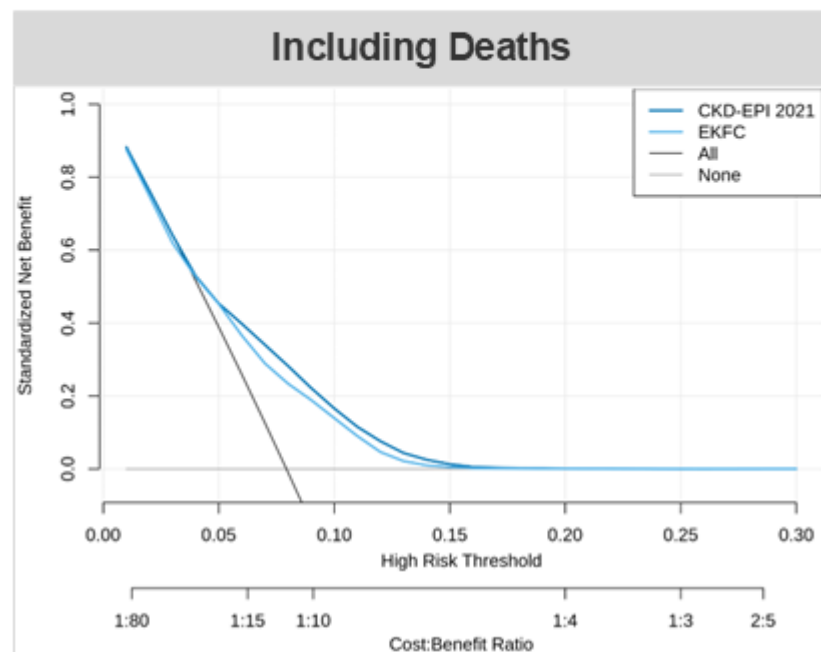


2-Year

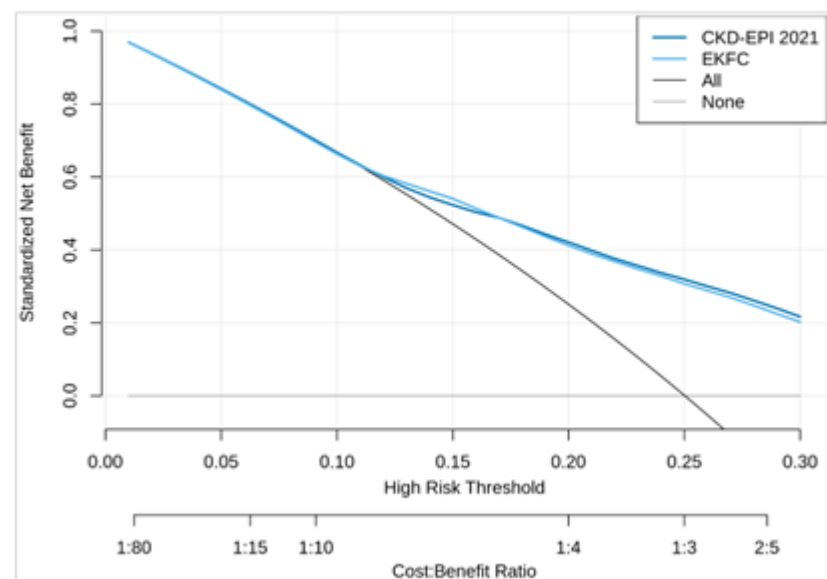
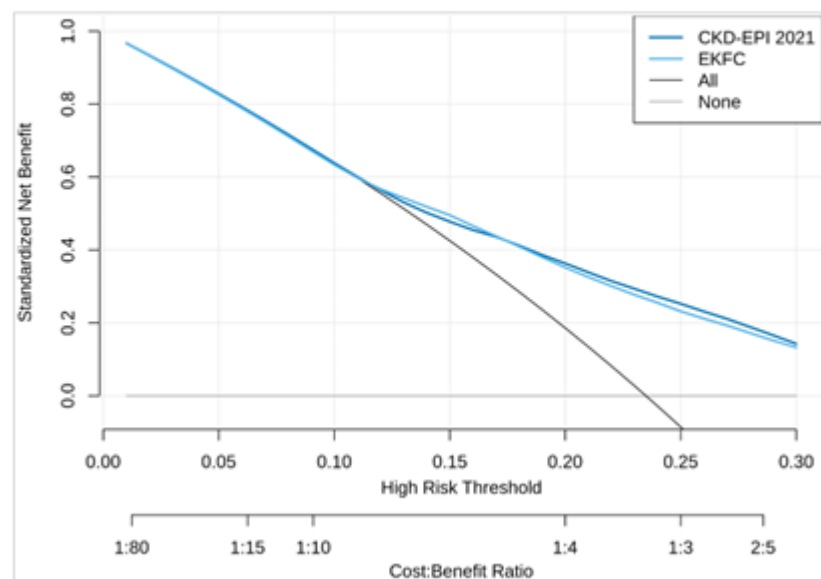


5-Year

MAKE Decision Curve Analysis — Albuminuria A2 (3–30 mg/mmol)

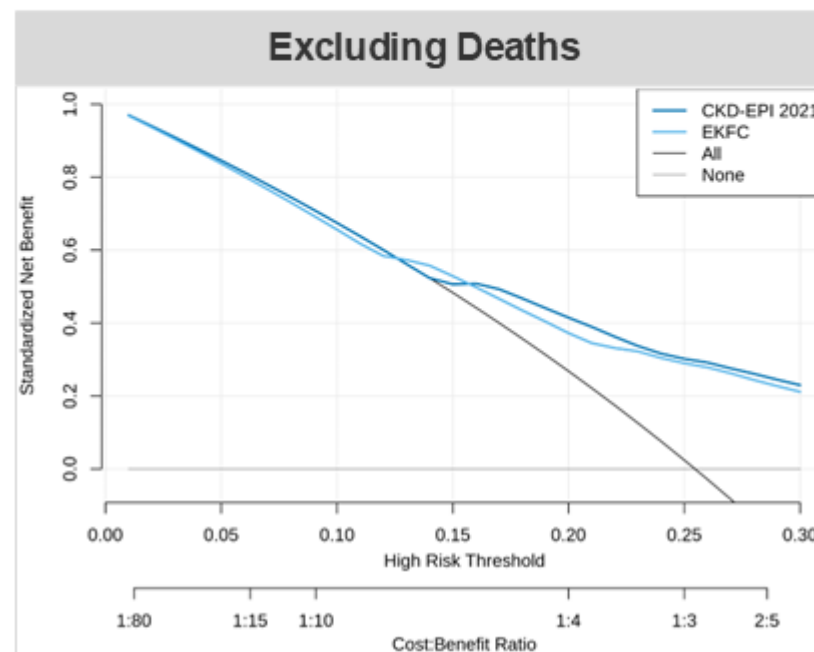
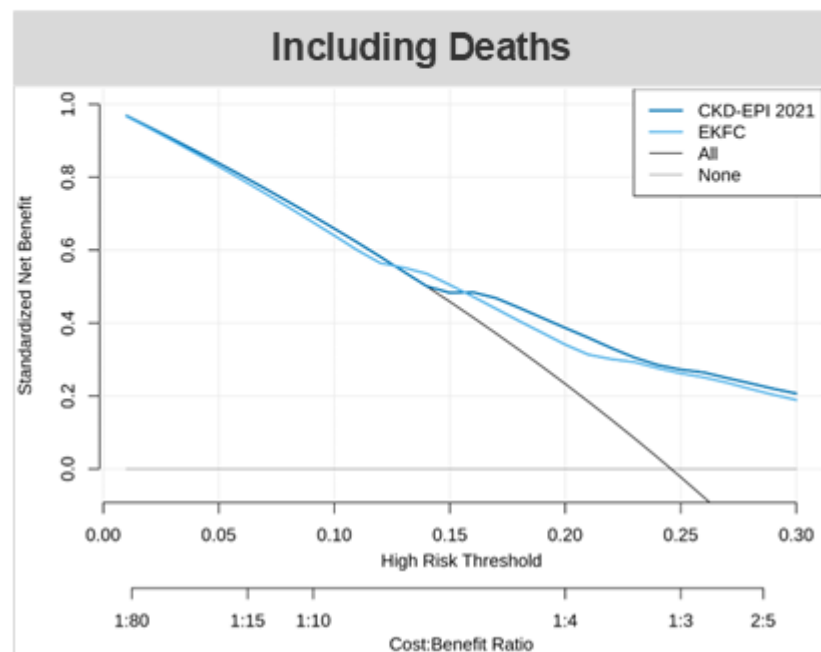


2-Year

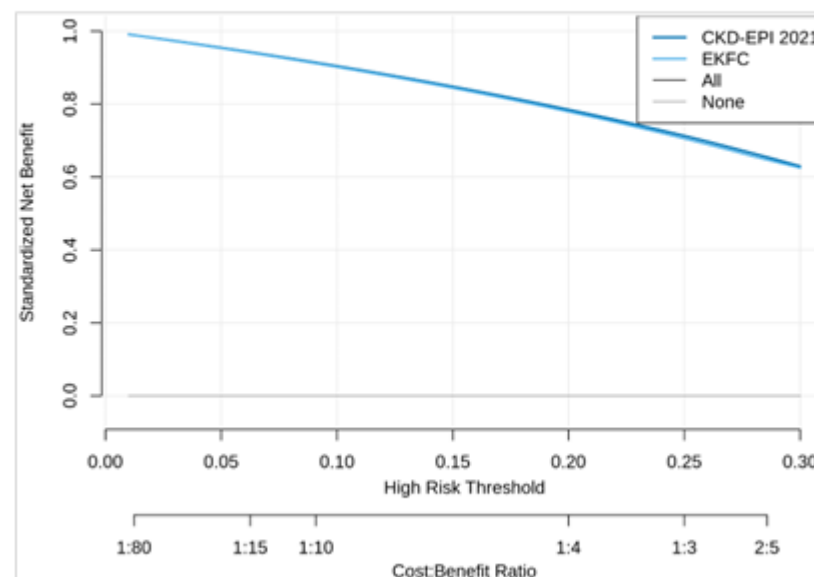
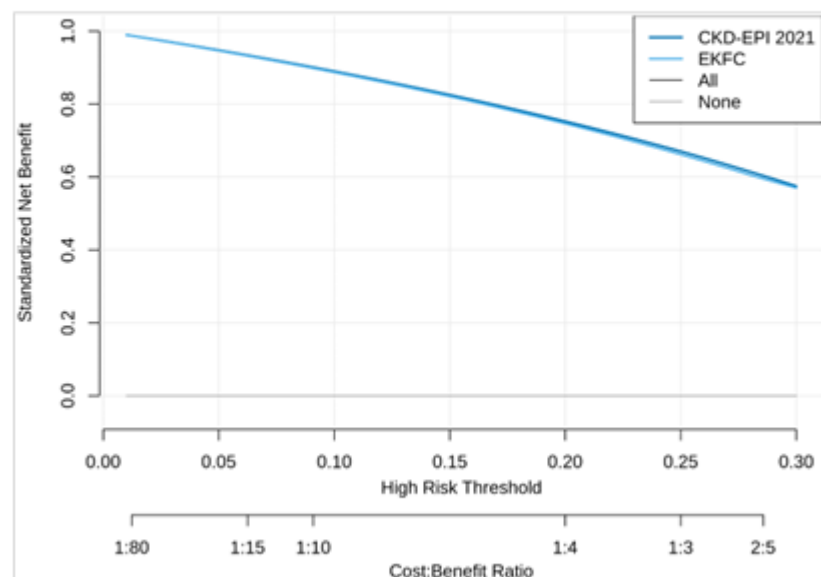


5-Year

MAKE Decision Curve Analysis — Albuminuria A3 (>30 mg/mmol)

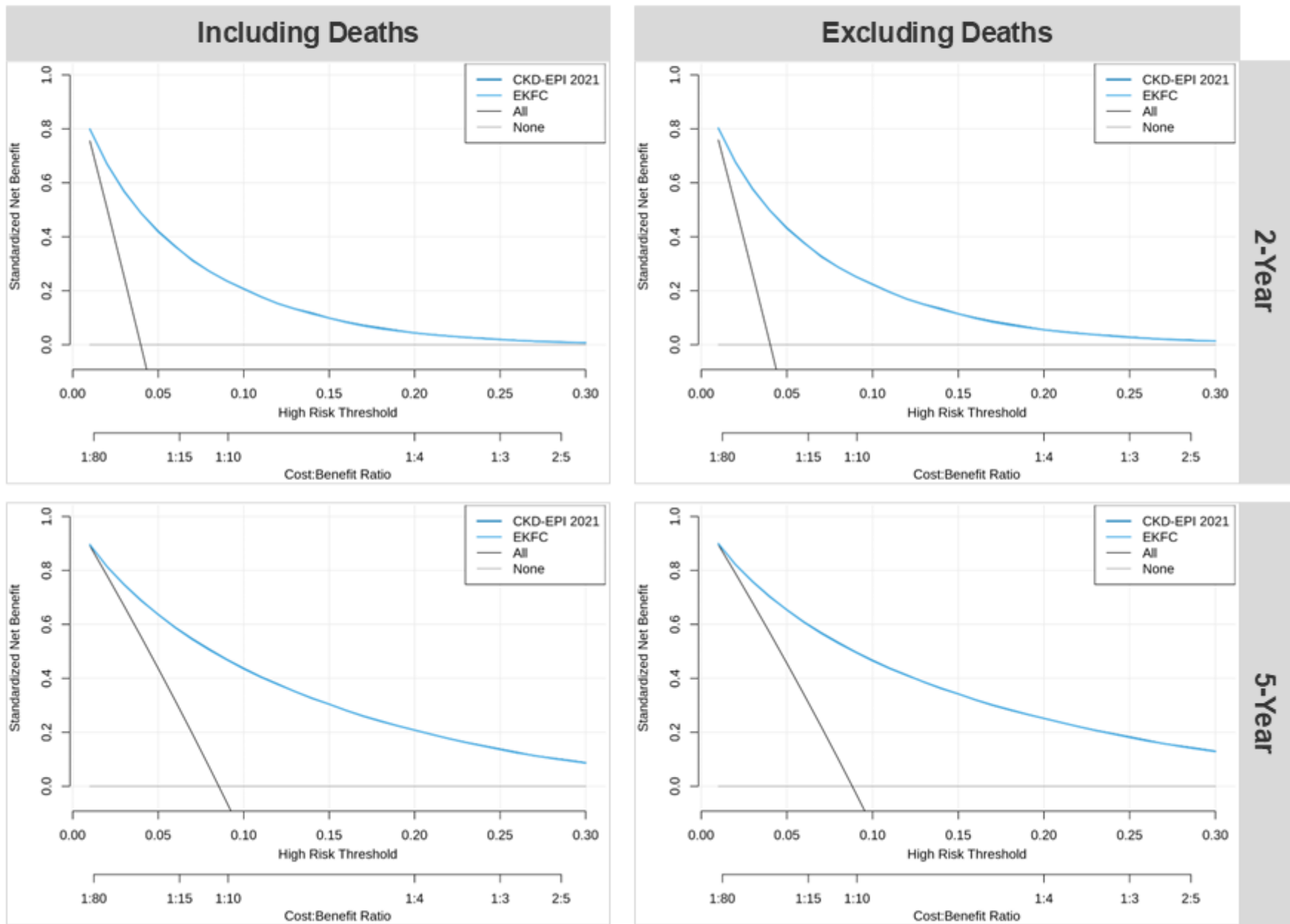


2-Year

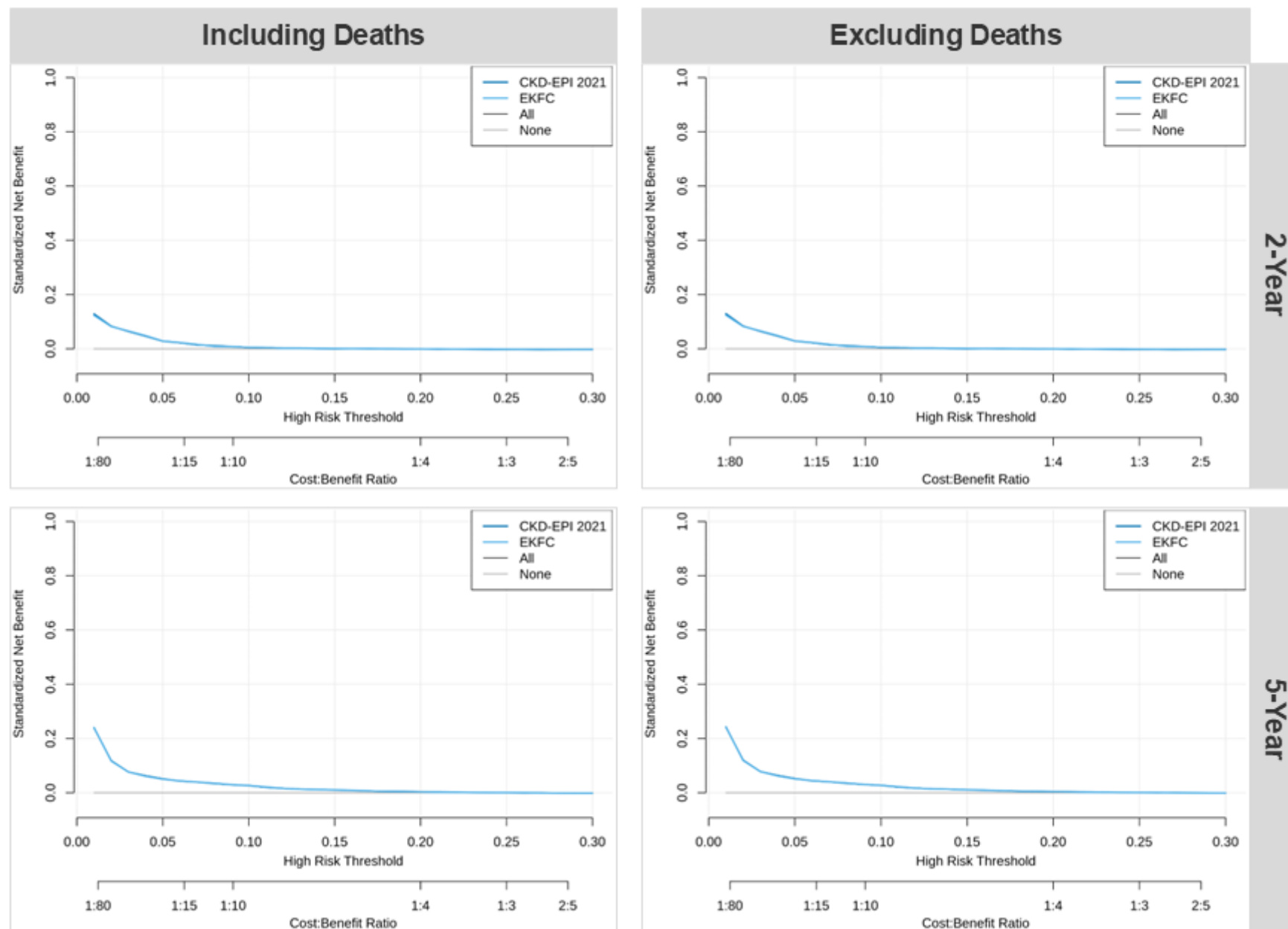


5-Year

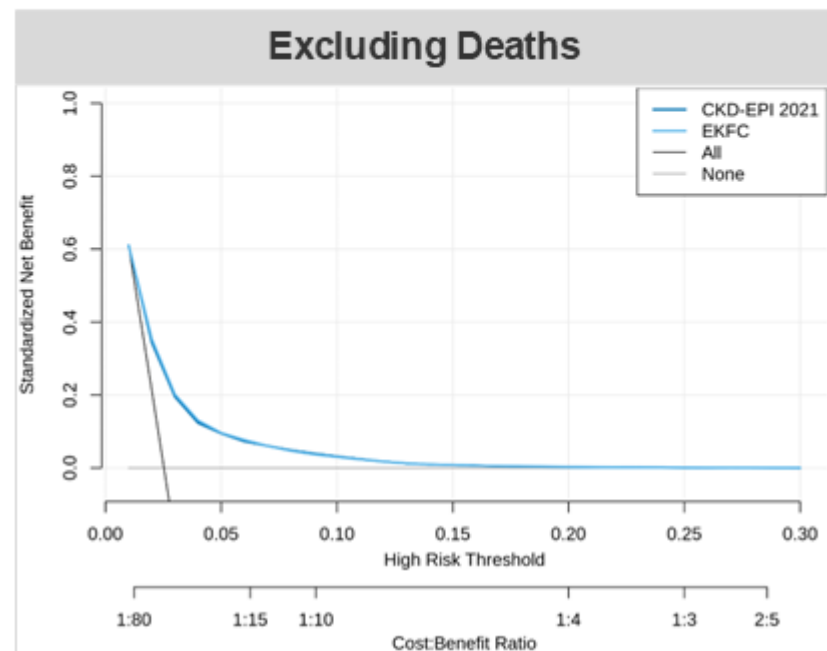
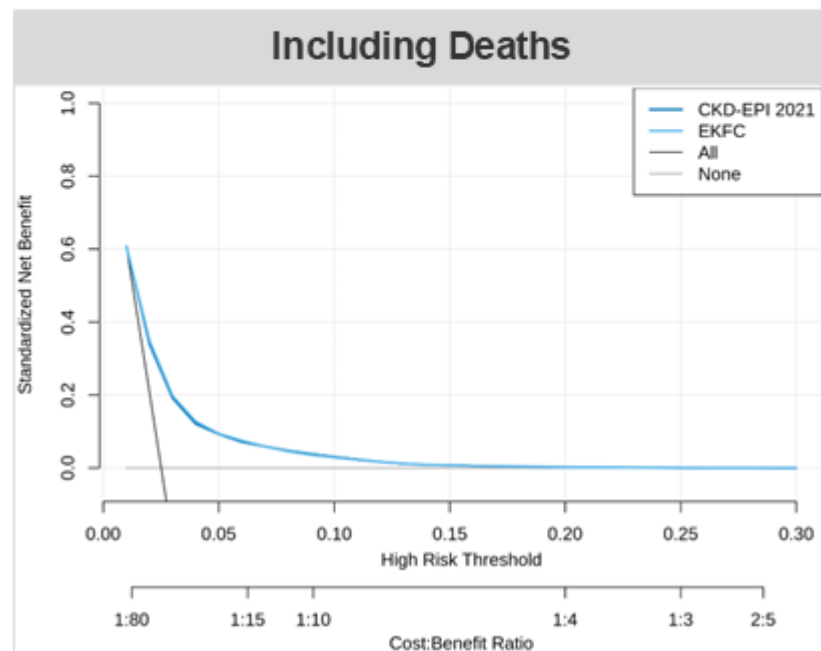
MACE Decision Curve Analysis — Overall



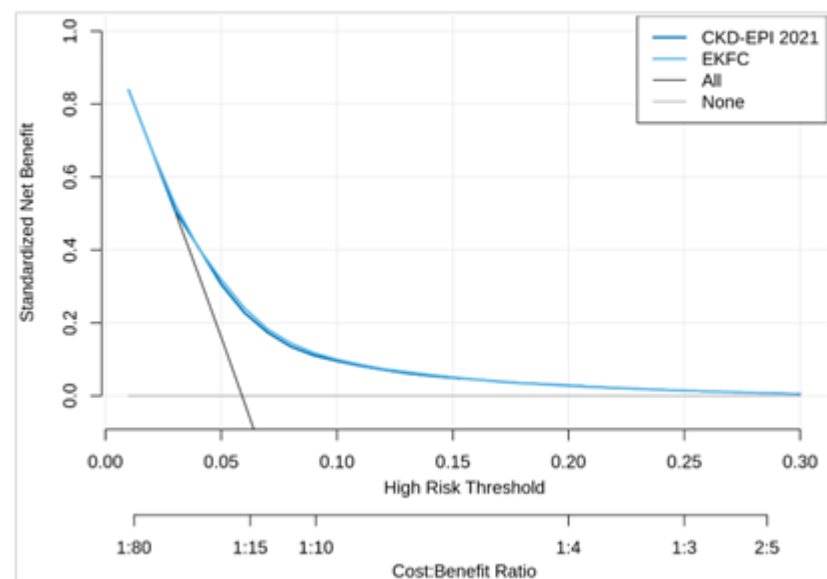
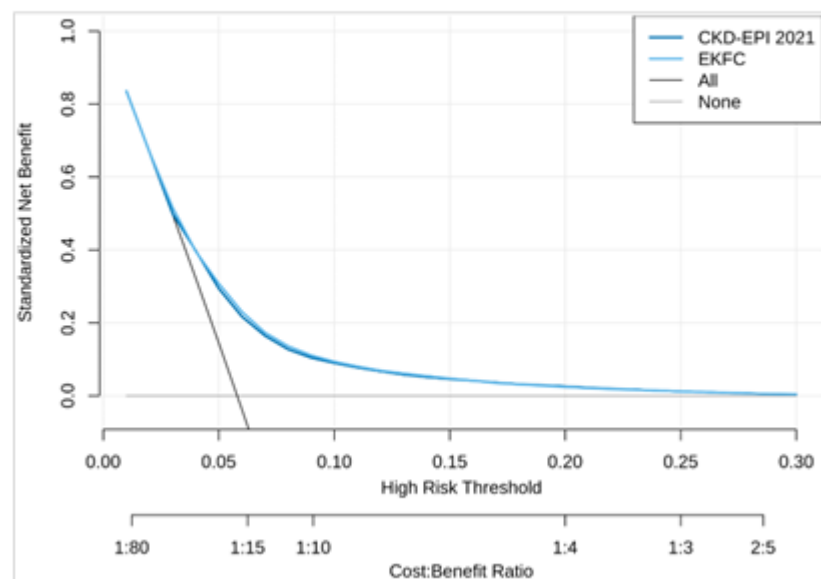
MACE Decision Curve Analysis — Age 18 to <40



MACE Decision Curve Analysis — Age 40 to ≤ 65

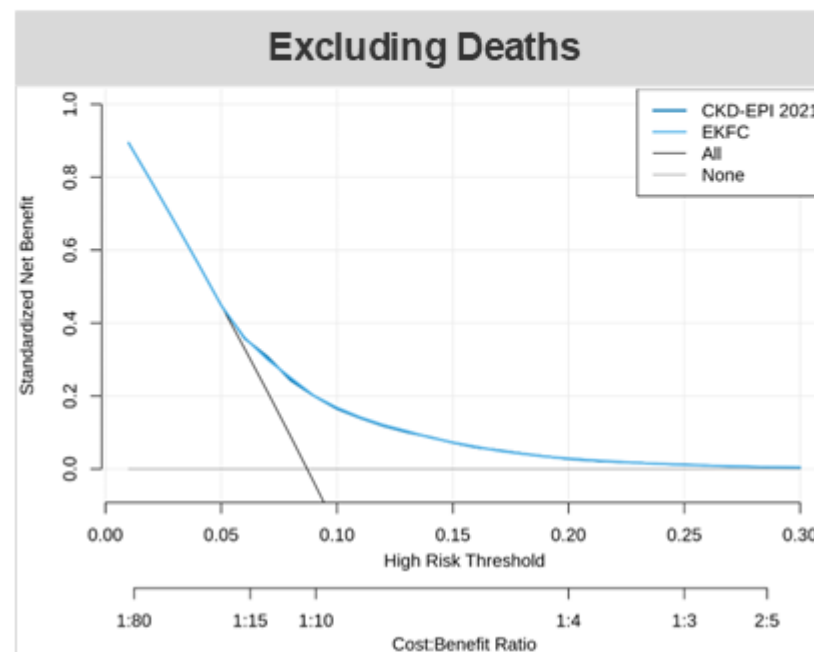
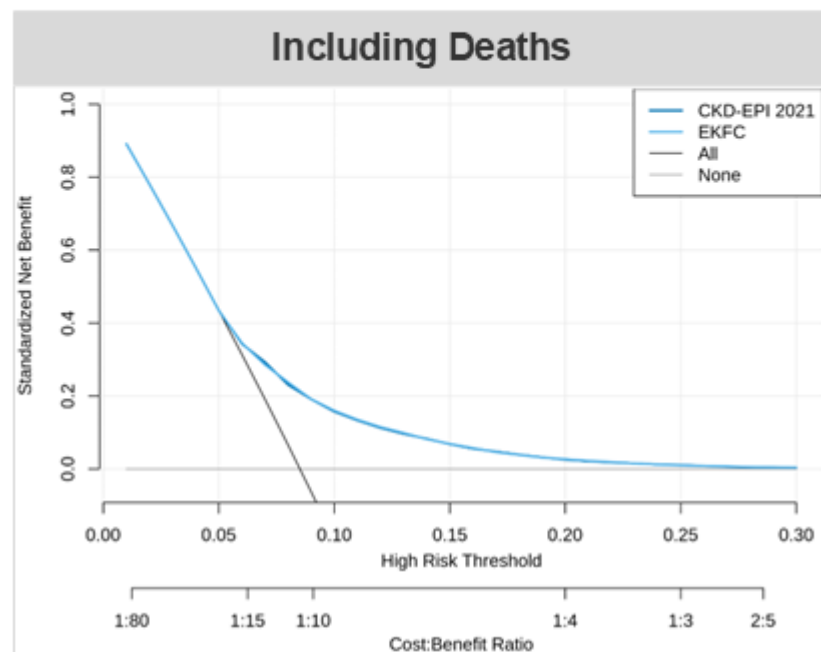


2-Year

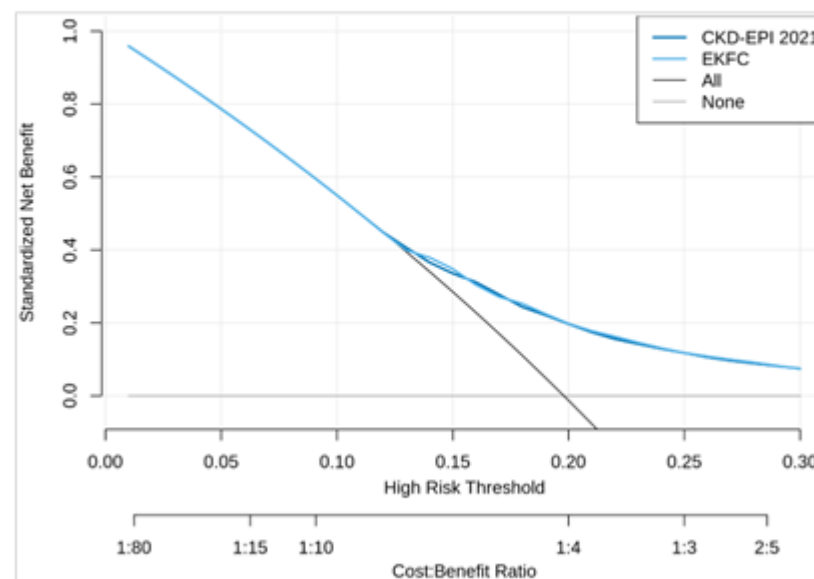
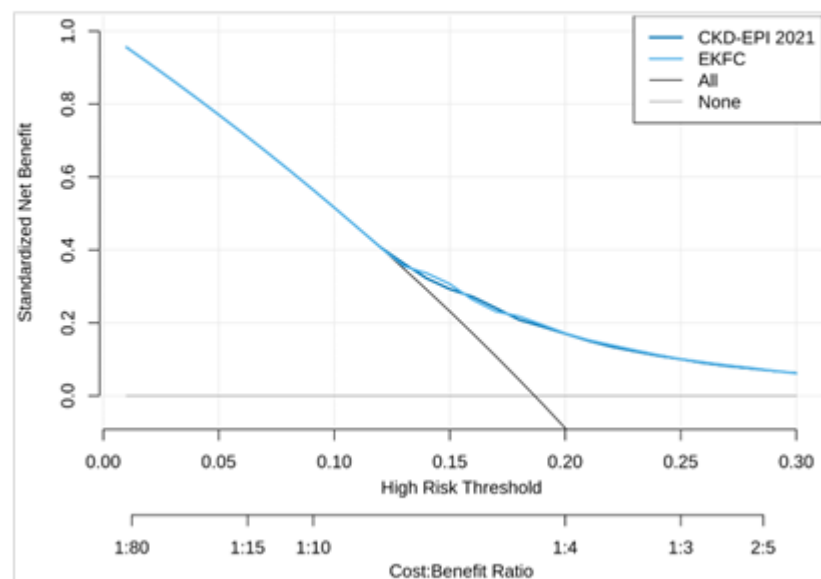


5-Year

MACE Decision Curve Analysis — Age 65 to <80

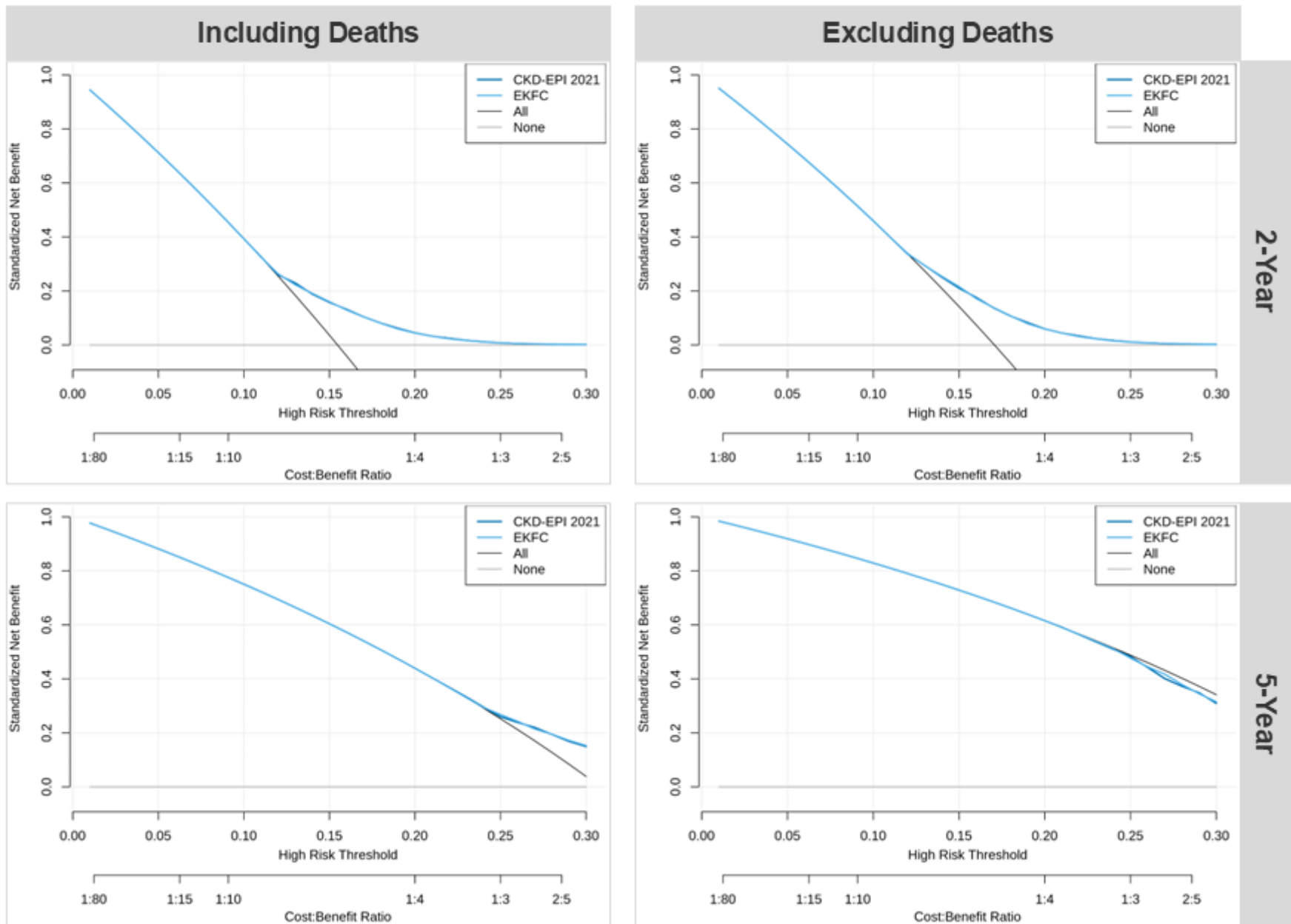


2-Year

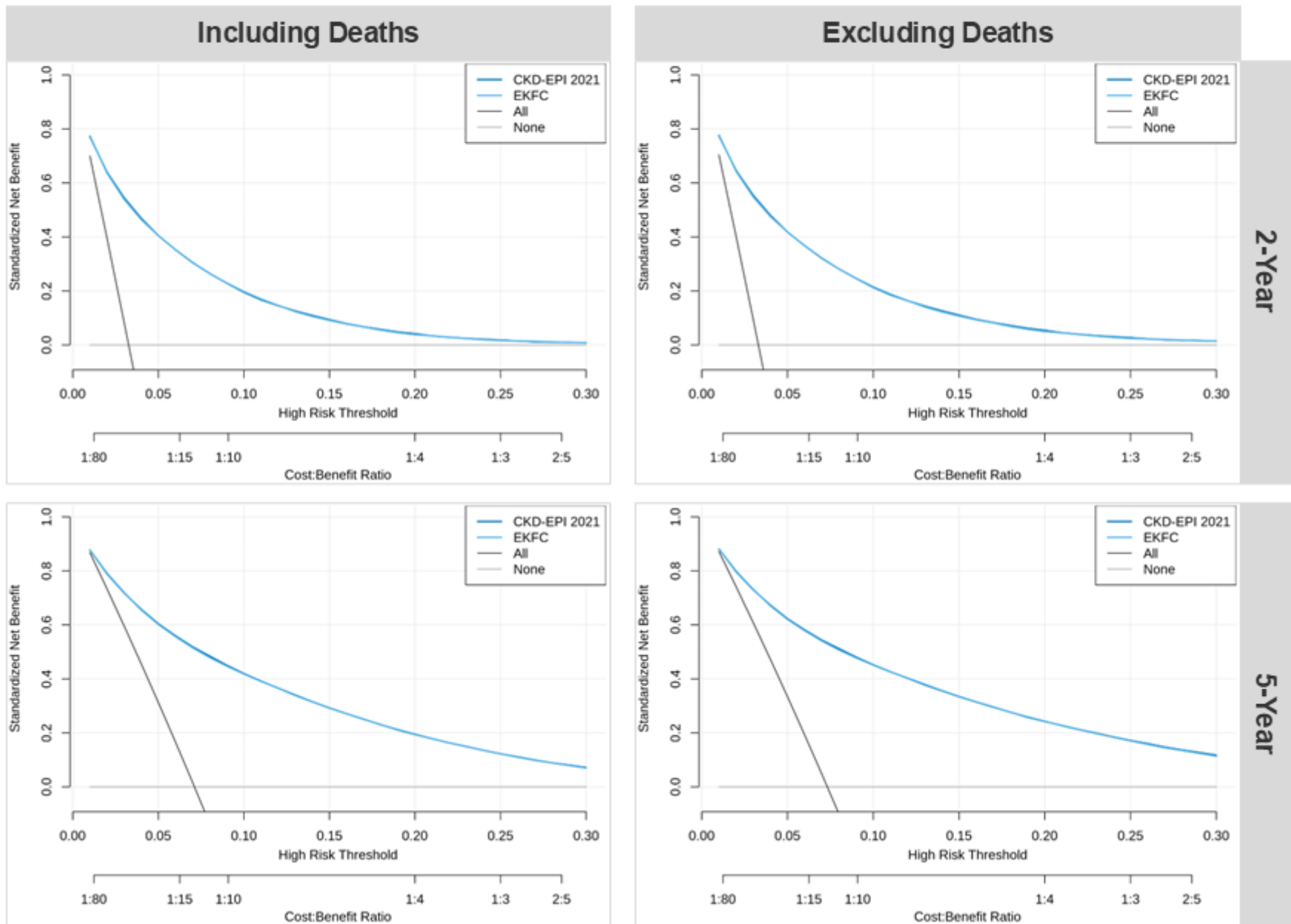


5-Year

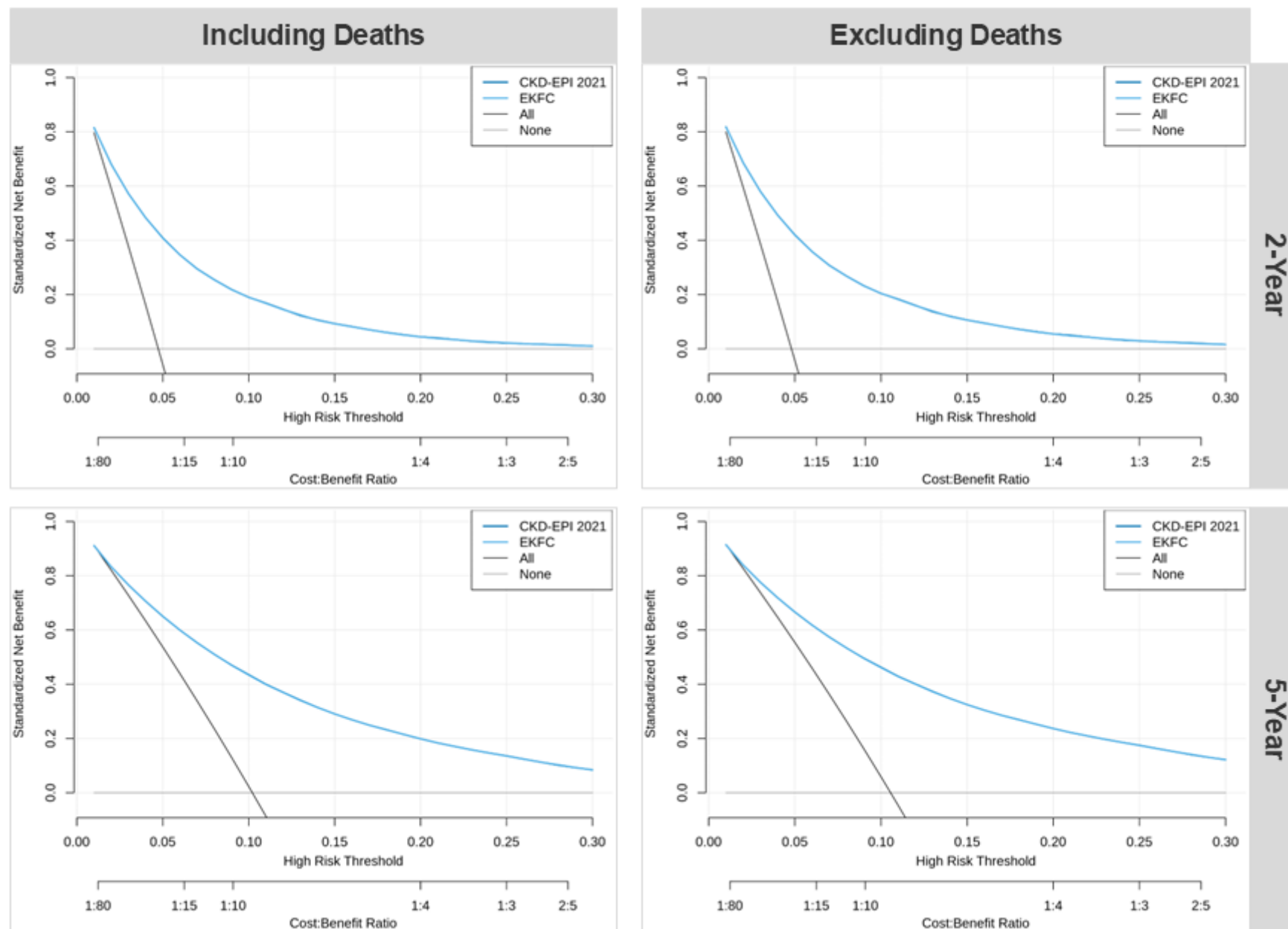
MACE Decision Curve Analysis — Age 80+



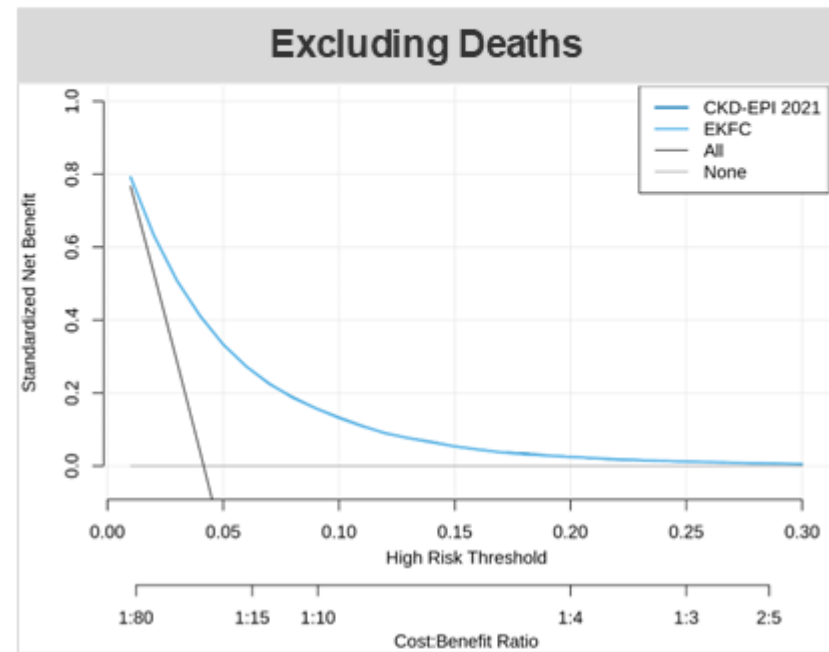
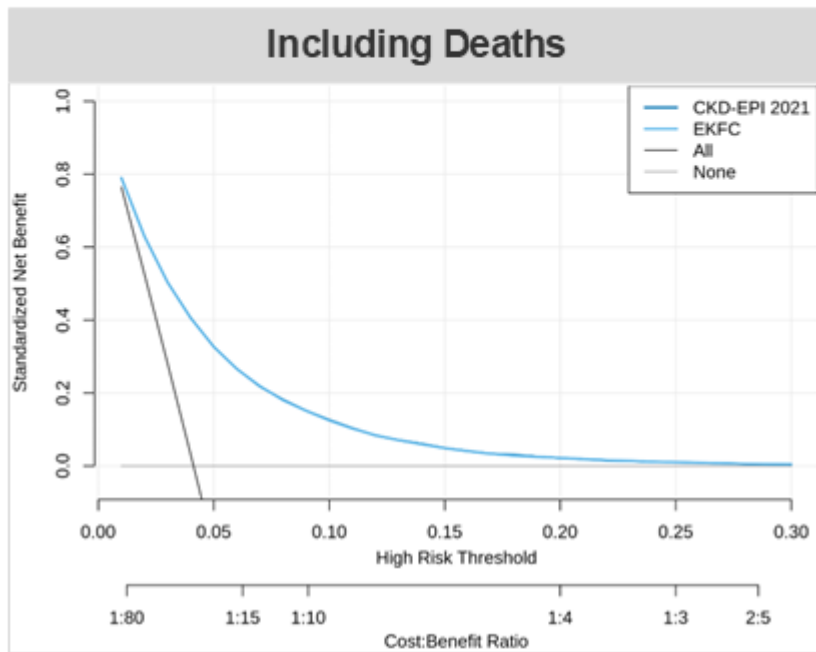
MACE Decision Curve Analysis — Female



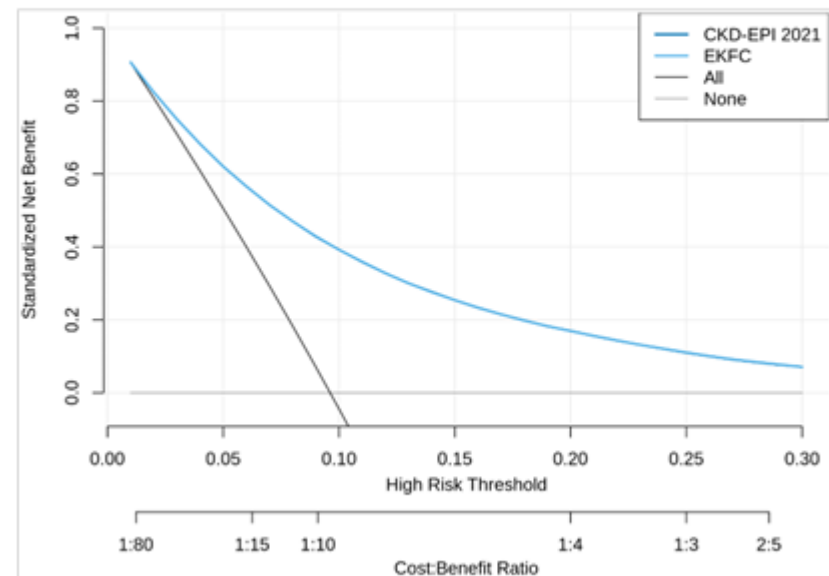
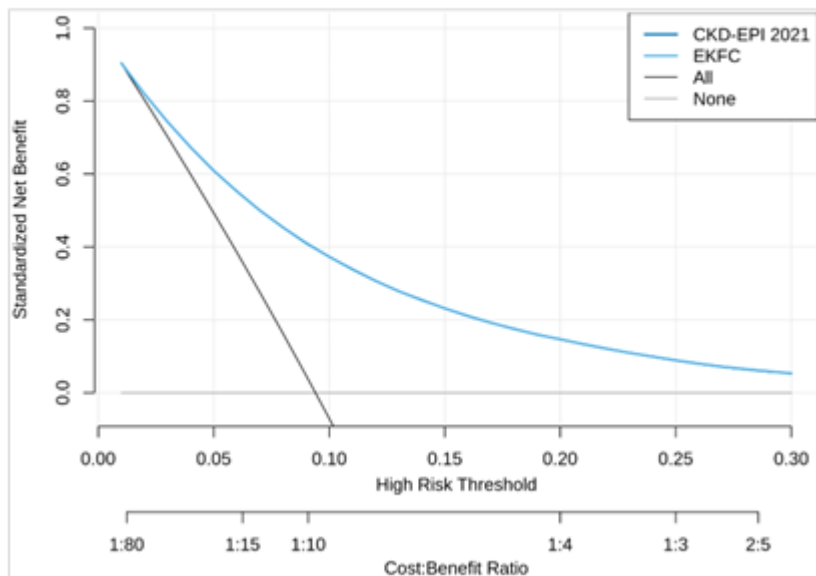
MACE Decision Curve Analysis — Male



MACE Decision Curve Analysis — Albuminuria A1 (<3 mg/mmol)

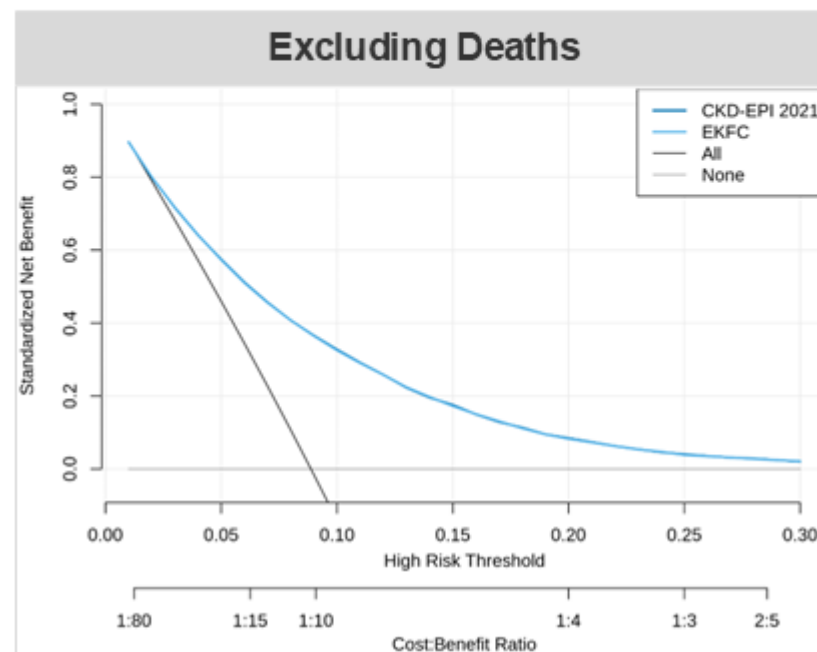
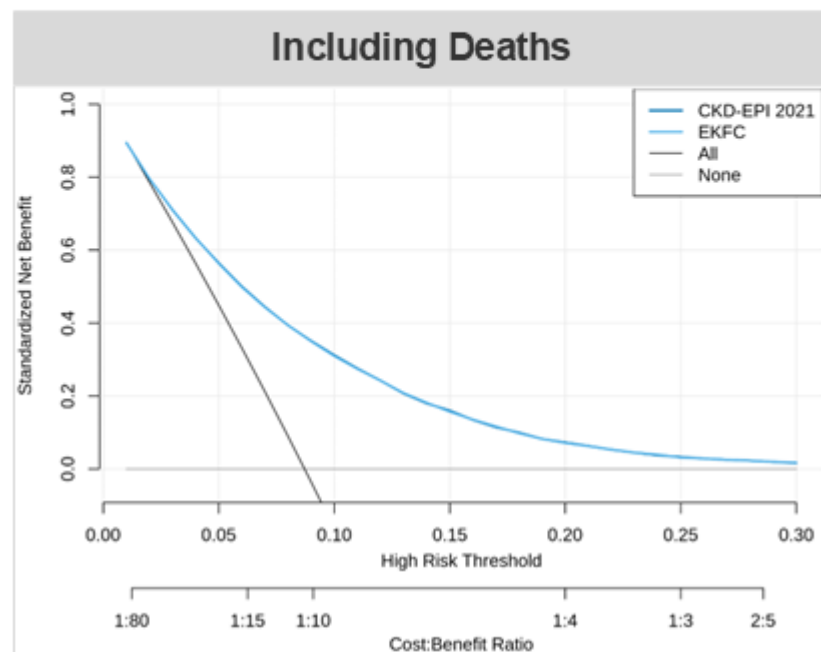


2-Year

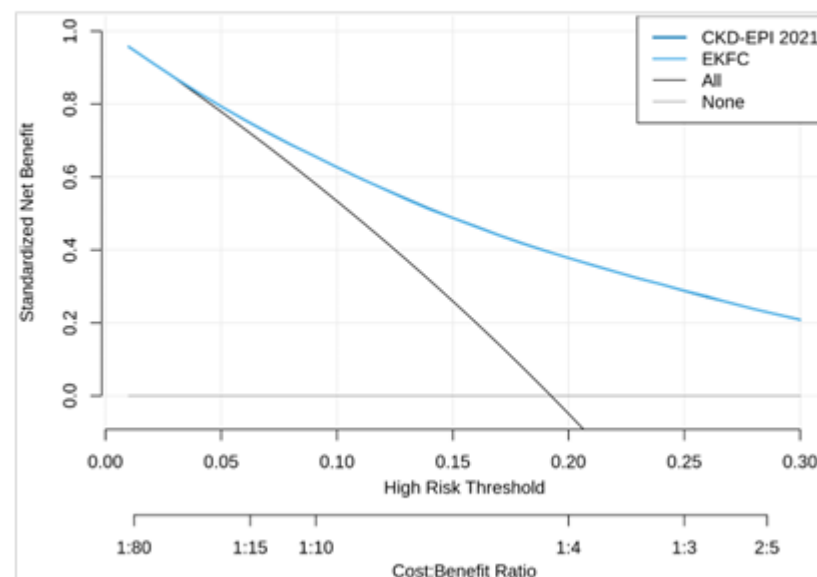
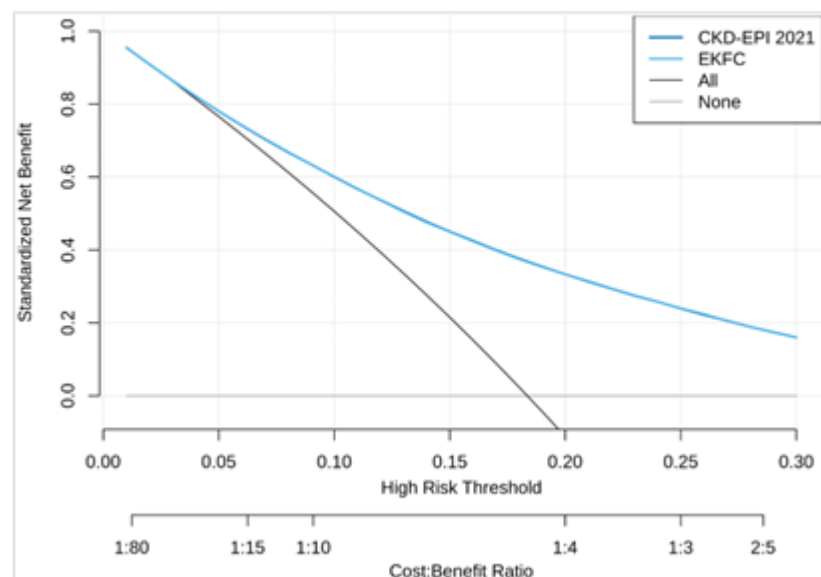


5-Year

MACE Decision Curve Analysis — Albuminuria A2 (3–30 mg/mmol)

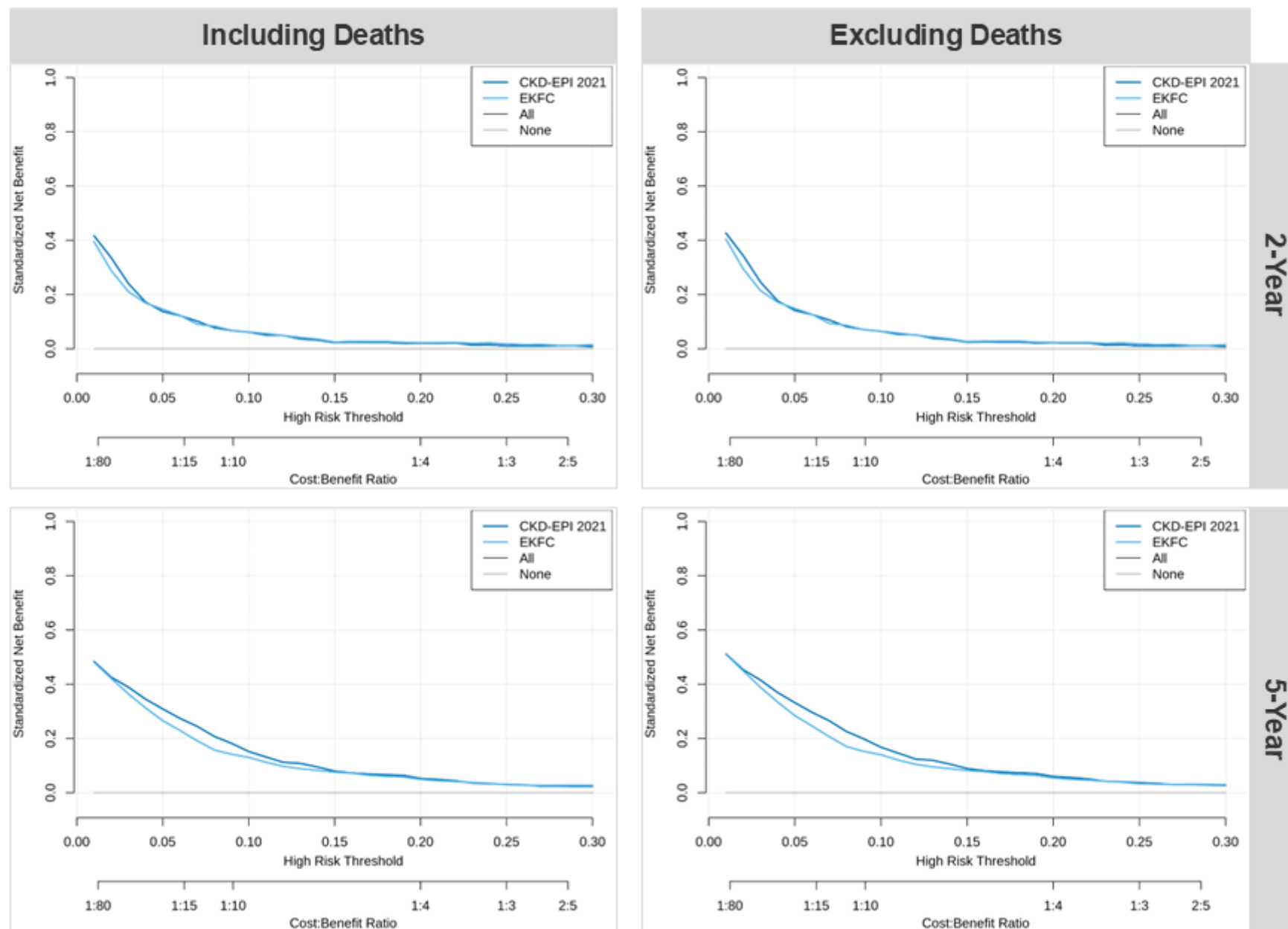


2-Year

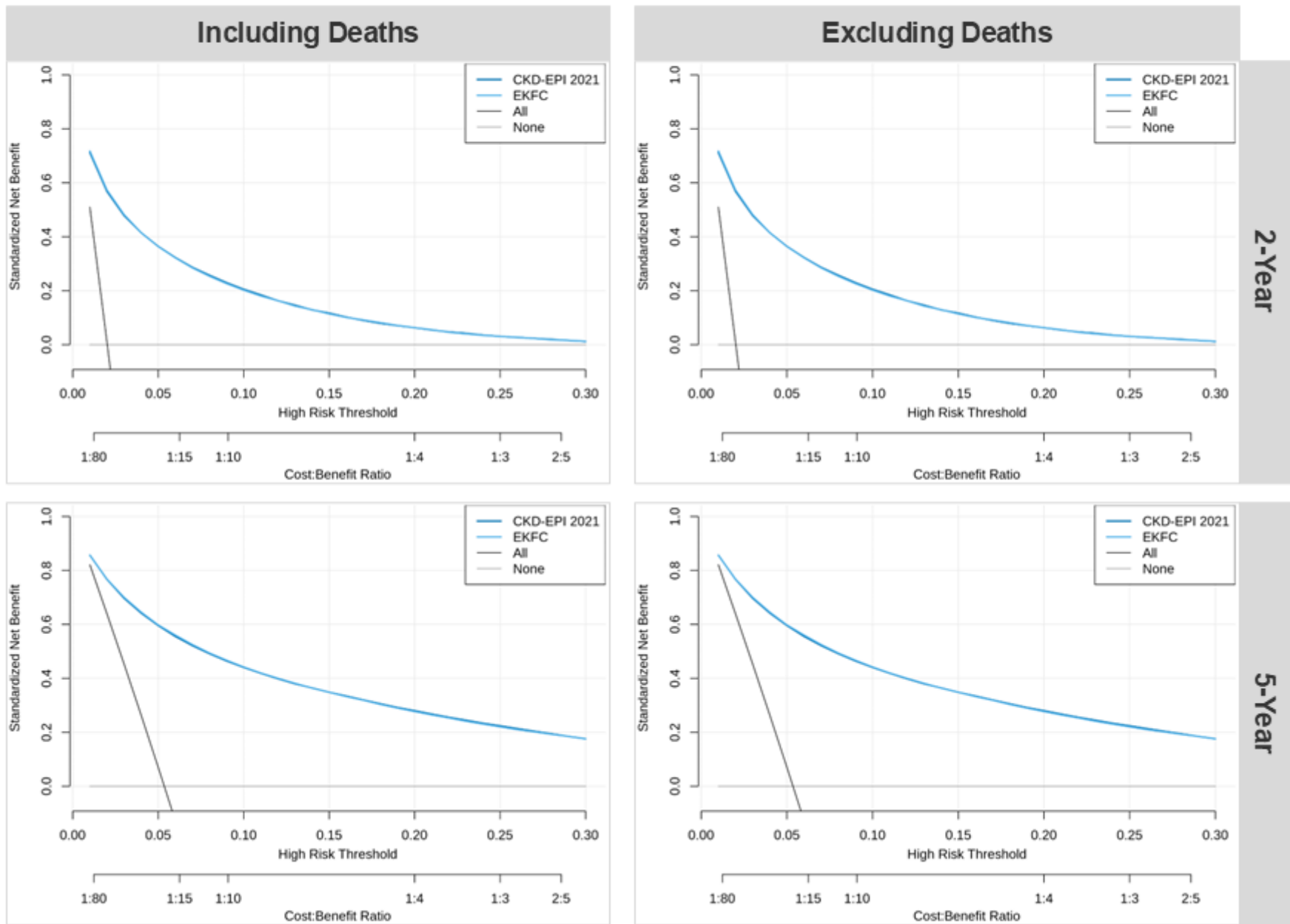


5-Year

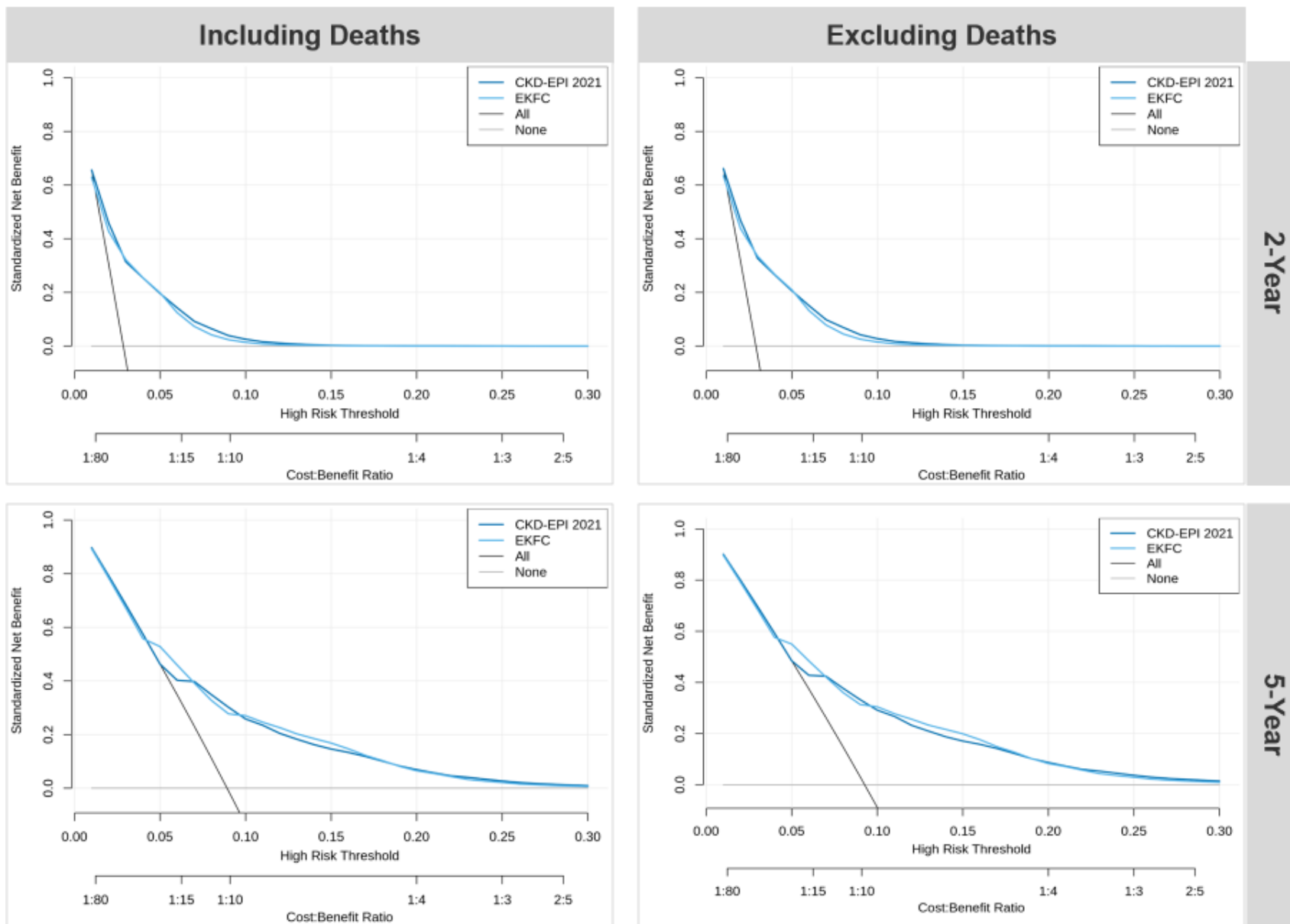
KRT Decision Curve Analysis — Overall



All-Cause Death Decision Curve Analysis — Overall



MAKE (unadjusted for age and sex) Decision Curve Analysis — Overall



Chapter 4: Supplemental Material

Appendix J. Sensitivity and specificity of outcome definitions

Outcome (component)	Data source & code / definition	Sens.	Spec.	PPV	Ref.
<i>Kidney Replacement Therapy (KRT)</i>					
Need for dialysis	CORR; treatment code $\neq$ 171/181	Reference-standard registry (mandatory across Canadian); not ICD-coded			
Kidney transplant	CORR; treatment code = 171/181	96%	—	98%	⁷⁵

Appendix K. Model discrimination, calibration and accuracy metrics

Table K1. Discrimination and calibration performance of the uncalibrated 4-variable KFRE using CKD-EPI 2021 (CK21) and EKFC eGFR inputs, by stratum and prediction horizon.

STRATUM	TIMEPOINT	MODEL	AUC (95% CI)	BRIER SCORE	O:E RATIO	CAL. INTERCEPT	CAL. SLOPE
OVERALL	2-year	CK21	0.929 (0.917, 0.941)	0.0149	0.751	−0.373	1.024
		EKFC	0.928 (0.916, 0.940)	0.0153	0.621	−0.600	1.124
FEMALE	5-year	CK21	0.913 (0.905, 0.921)	0.0383	0.894	−0.287	0.864
		EKFC	0.910 (0.901, 0.918)	0.0396	0.728	−0.602	0.932
	2-year	CK21	0.928 (0.909, 0.948)	0.0105	0.718	−0.402	1.039
		EKFC	0.928 (0.908, 0.947)	0.0107	0.567	−0.671	1.155
MALE	5-year	CK21	0.916 (0.903, 0.930)	0.0282	0.837	−0.363	0.914
		EKFC	0.914 (0.900, 0.928)	0.0294	0.653	−0.707	0.995
	2-year	CK21	0.926 (0.911, 0.941)	0.019	0.767	−0.357	1.014
		EKFC	0.925 (0.910, 0.940)	0.0194	0.65	−0.562	1.103
18 TO <40	5-year	CK21	0.906 (0.896, 0.917)	0.0478	0.927	−0.241	0.829
		EKFC	0.902 (0.891, 0.914)	0.049	0.773	−0.537	0.888
	2-year	CK21	0.897 (0.866, 0.929)	0.0685	0.877	−0.222	1.01
		EKFC	0.902 (0.872, 0.931)	0.0693	0.829	−0.317	1.043
40 TO ≤65	5-year	CK21	0.833 (0.797, 0.869)	0.1486	1.066	−0.047	0.646
		EKFC	0.839 (0.804, 0.874)	0.1474	1.008	−0.191	0.668
	2-year	CK21	0.910 (0.892, 0.927)	0.0297	0.922	−0.112	0.945
		EKFC	0.912 (0.895, 0.928)	0.0297	0.865	−0.195	1.019
66 TO <80	5-year	CK21	0.894 (0.882, 0.906)	0.0715	1.102	0.054	0.787
		EKFC	0.895 (0.883, 0.907)	0.0708	1.02	−0.089	0.845
	2-year	CK21	0.884 (0.851, 0.917)	0.0083	0.544	−0.694	0.860
		EKFC	0.887 (0.855, 0.920)	0.0088	0.399	−1.041	0.958
≥80	5-year	CK21	0.885 (0.865, 0.905)	0.0262	0.762	−0.481	0.822
		EKFC	0.886 (0.867, 0.906)	0.0277	0.561	−0.897	0.890
	2-year	CK21	0.941 (0.893, 0.990)	0.0041	0.400	−0.980	1.538
		EKFC	0.941 (0.891, 0.991)	0.0046	0.249	−1.487	1.676
	5-year	CK21	0.911 (0.876, 0.945)	0.0128	0.411	−1.115	1.137

< 3 MG/MMOL	2-year	EKFC	0.914 (0.880, 0.948)	0.0159	0.259	−1.672	1.238
		CK21	0.874 (0.780, 0.967)	0.0017	0.637	−0.457	1.34
		EKFC	0.871 (0.772, 0.970)	0.0017	0.401	−0.922	1.56
3-30 MG/MMOL	5-year	CK21	0.799 (0.737, 0.861)	0.0054	0.675	−0.473	0.987
		EKFC	0.786 (0.719, 0.852)	0.0056	0.426	−0.946	1.109
		CK21	0.835 (0.780, 0.891)	0.0073	0.501	−0.733	0.972
> 30 MG/MMOL	2-year	EKFC	0.830 (0.775, 0.886)	0.0076	0.372	−1.040	1.094
		CK21	0.819 (0.787, 0.851)	0.0253	0.646	−0.610	0.872
		EKFC	0.808 (0.775, 0.842)	0.0268	0.477	−0.947	0.97
> 30 MG/MMOL	5-year	CK21	0.839 (0.816, 0.863)	0.0588	0.825	−0.272	0.932
		EKFC	0.836 (0.812, 0.860)	0.0601	0.719	−0.454	1.025
		CK21	0.799 (0.782, 0.816)	0.1373	0.997	−0.120	0.655
		EKFC	0.791 (0.773, 0.808)	0.1406	0.863	−0.402	0.695

Table K2. Discrimination and calibration performance of the recalibrated 4-variable KFRE using CKD-EPI 2021 (CK21) and EKFC eGFR inputs, by stratum and prediction horizon.

STRATUM	TIMEPOINT	MODEL	AUC (95% CI)	BRIER SCORE	O:E RATIO	CAL. INTERCEPT	CAL. SLOPE
OVERALL	2-year	CK21	0.929 (0.917, 0.941)	0.0147	0.937	−0.083	1.043
		EKFC	0.928 (0.916, 0.940)	0.0148	0.92	−0.101	1.162
	5-year	CK21	0.913 (0.905, 0.921)	0.0383	0.904	−0.269	0.866
		EKFC	0.910 (0.901, 0.918)	0.0384	0.858	−0.329	0.967
FEMALE	2-year	CK21	0.928 (0.909, 0.948)	0.0104	0.904	−0.120	1.053
		EKFC	0.928 (0.908, 0.947)	0.0104	0.852	−0.183	1.185
	5-year	CK21	0.916 (0.903, 0.930)	0.0281	0.846	−0.346	0.916
		EKFC	0.914 (0.900, 0.928)	0.0283	0.777	−0.440	1.027
MALE	2-year	CK21	0.926 (0.911, 0.941)	0.0187	0.953	−0.063	1.035
		EKFC	0.925 (0.910, 0.940)	0.0189	0.956	−0.056	1.145
	5-year	CK21	0.906 (0.896, 0.917)	0.0478	0.936	−0.223	0.831
		EKFC	0.902 (0.891, 0.914)	0.0479	0.905	−0.261	0.925
18 TO <40	2-year	CK21	0.897 (0.866, 0.929)	0.0676	1.062	0.097	1.046
		EKFC	0.902 (0.872, 0.931)	0.0688	1.162	0.23	1.111

40 TO ≤65	5-year	CK21	0.833 (0.797, 0.869)	0.1485	1.074	−0.028	0.649
		EKFC	0.839 (0.804, 0.874)	0.147	1.134	0.107	0.714
	2-year	CK21	0.910 (0.892, 0.927)	0.0297	1.146	0.18	0.963
		EKFC	0.912 (0.895, 0.928)	0.03	1.272	0.306	1.051
66 TO <80	5-year	CK21	0.894 (0.882, 0.906)	0.0715	1.113	0.072	0.789
		EKFC	0.895 (0.883, 0.907)	0.0708	1.188	0.182	0.877
	2-year	CK21	0.884 (0.851, 0.917)	0.0079	0.69	−0.417	0.868
		EKFC	0.887 (0.855, 0.920)	0.0079	0.603	−0.557	0.977
≥80	5-year	CK21	0.885 (0.865, 0.905)	0.0261	0.771	−0.464	0.824
		EKFC	0.886 (0.867, 0.906)	0.0262	0.671	−0.629	0.917
	2-year	CK21	0.941 (0.893, 0.990)	0.0041	0.511	−0.711	1.553
		EKFC	0.941 (0.891, 0.991)	0.0042	0.381	−1.016	1.716
< 3 MG/MMOL	5-year	CK21	0.911 (0.876, 0.945)	0.0127	0.416	−1.099	1.139
		EKFC	0.914 (0.880, 0.948)	0.0139	0.314	−1.410	1.277
	2-year	CK21	0.874 (0.780, 0.967)	0.0017	0.822	−0.199	1.342
		EKFC	0.871 (0.772, 0.970)	0.0017	0.625	−0.473	1.565
3-30 MG/MMOL	5-year	CK21	0.799 (0.737, 0.861)	0.0054	0.685	−0.459	0.987
		EKFC	0.786 (0.719, 0.852)	0.0055	0.528	−0.722	1.114
	2-year	CK21	0.835 (0.780, 0.891)	0.0071	0.642	−0.467	0.978
		EKFC	0.830 (0.775, 0.886)	0.0072	0.573	−0.579	1.107
> 30 MG/MMOL	5-year	CK21	0.819 (0.787, 0.851)	0.0252	0.654	−0.594	0.873
		EKFC	0.808 (0.775, 0.842)	0.0255	0.583	−0.704	0.986
	2-year	CK21	0.839 (0.816, 0.863)	0.058	1.02	0.027	0.955
		EKFC	0.836 (0.812, 0.860)	0.0586	1.048	0.061	1.071
	5-year	CK21	0.799 (0.782, 0.816)	0.1371	1.006	−0.102	0.657
		EKFC	0.791 (0.773, 0.808)	0.1372	0.997	−0.111	0.734

Table K3. Discrimination and calibration performance of the uncalibrated 4-variable KFRE using CKD-EPI 2009 (CK09) and EKFC eGFR inputs, by stratum and prediction horizon.

STRATUM	TIMEPOINT	MODEL	AUC (95% CI)	BRIER SCORE	O:E RATIO	CAL. INTERCEPT	CAL. SLOPE
OVERALL	2-year	CK09	0.937 (0.926, 0.948)	0.012	0.629	-0.601	1.038
		EKFC	0.936 (0.925, 0.947)	0.012	0.624	-0.591	1.105
	5-year	CK09	0.923 (0.915, 0.930)	0.032	0.762	-0.551	0.870
		EKFC	0.919 (0.912, 0.927)	0.032	0.736	-0.578	0.927
FEMALE	2-year	CK09	0.941 (0.925, 0.957)	0.009	0.592	-0.635	1.079
		EKFC	0.941 (0.925, 0.957)	0.009	0.562	-0.680	1.161
	5-year	CK09	0.925 (0.913, 0.938)	0.024	0.709	-0.611	0.924
		EKFC	0.923 (0.910, 0.936)	0.024	0.658	-0.689	0.988
MALE	2-year	CK09	0.931 (0.916, 0.946)	0.016	0.648	-0.583	1.015
		EKFC	0.930 (0.915, 0.945)	0.016	0.658	-0.543	1.071
	5-year	CK09	0.917 (0.908, 0.927)	0.039	0.792	-0.516	0.835
		EKFC	0.914 (0.904, 0.924)	0.039	0.783	-0.510	0.885
18 TO <40	2-year	CK09	0.907 (0.878, 0.936)	0.064	0.792	-0.397	1.032
		EKFC	0.910 (0.883, 0.937)	0.064	0.825	-0.324	1.054
	5-year	CK09	0.834 (0.799, 0.869)	0.145	1.010	-0.206	0.629
		EKFC	0.837 (0.802, 0.871)	0.144	1.034	-0.139	0.654
40 TO ≤65	2-year	CK09	0.927 (0.912, 0.941)	0.024	0.785	-0.335	0.971
		EKFC	0.928 (0.914, 0.942)	0.023	0.866	-0.192	1.020
	5-year	CK09	0.912 (0.902, 0.922)	0.058	0.965	-0.199	0.802
		EKFC	0.912 (0.902, 0.923)	0.057	1.032	-0.067	0.854
66 TO <80	2-year	CK09	0.891 (0.859, 0.924)	0.007	0.448	-0.919	0.867
		EKFC	0.893 (0.861, 0.925)	0.007	0.413	-1.001	0.930
	5-year	CK09	0.895 (0.876, 0.913)	0.022	0.627	-0.756	0.829
		EKFC	0.895 (0.876, 0.914)	0.022	0.571	-0.864	0.882
≥80	2-year	CK09	0.938 (0.891, 0.985)	0.004	0.313	-1.246	1.469
		EKFC	0.940 (0.894, 0.986)	0.004	0.254	-1.463	1.577
	5-year	CK09	0.924 (0.895, 0.953)	0.012	0.317	-1.437	1.152
		EKFC	0.926 (0.898, 0.955)	0.013	0.257	-1.673	1.232

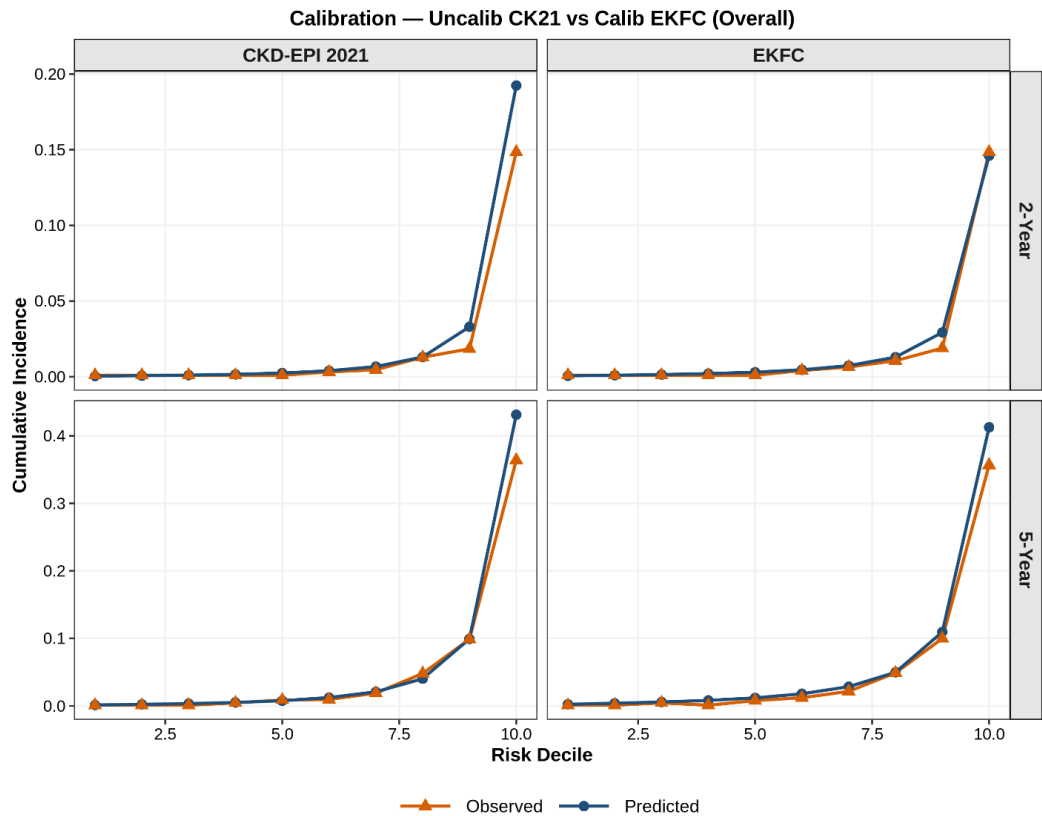
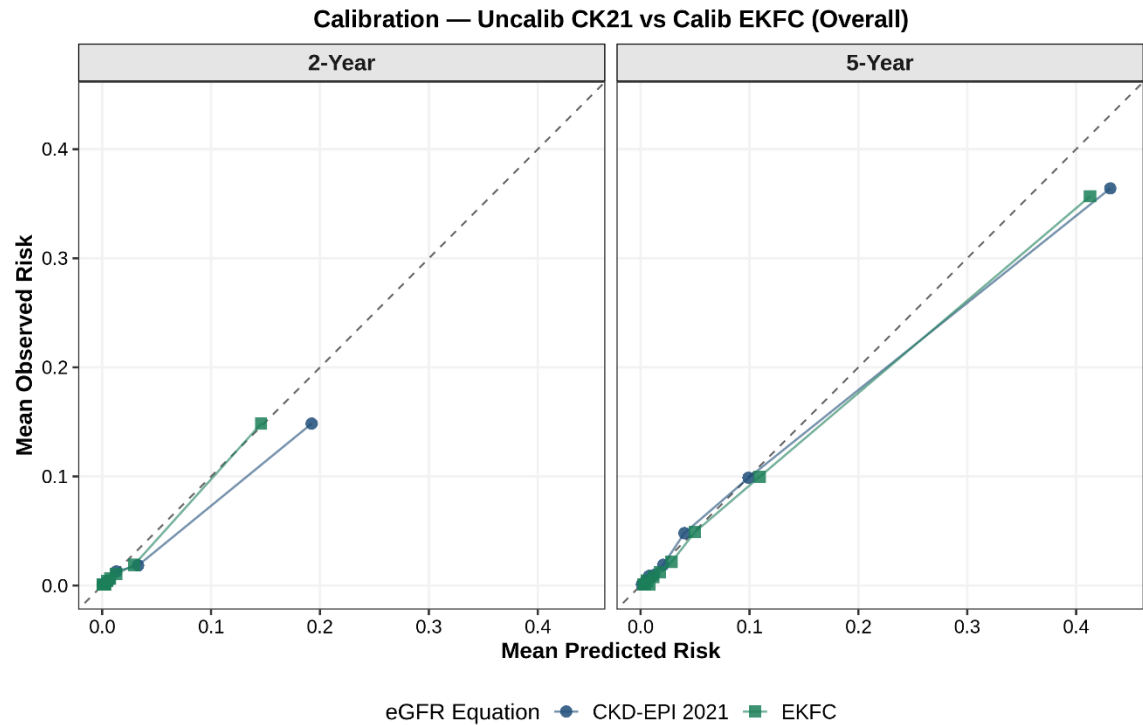
< 3 MG/MMOL	2-year	CK09	0.856 (0.761, 0.951)	0.001	0.494	-0.713	1.290
		EKFC	0.854 (0.757, 0.950)	0.001	0.416	-0.886	1.404
	5-year	CK09	0.806 (0.749, 0.862)	0.004	0.521	-0.735	0.990
		EKFC	0.796 (0.738, 0.855)	0.004	0.437	-0.911	1.055
3-30 MG/MMOL	2-year	CK09	0.845 (0.794, 0.897)	0.006	0.402	-0.964	0.996
		EKFC	0.843 (0.791, 0.894)	0.006	0.375	-1.028	1.071
	5-year	CK09	0.831 (0.801, 0.861)	0.022	0.521	-0.862	0.895
		EKFC	0.822 (0.790, 0.853)	0.023	0.481	-0.934	0.957
> 30 MG/MMOL	2-year	CK09	0.847 (0.824, 0.869)	0.056	0.706	-0.494	0.948
		EKFC	0.844 (0.821, 0.867)	0.055	0.724	-0.443	1.005
	5-year	CK09	0.808 (0.792, 0.824)	0.131	0.878	-0.386	0.653
		EKFC	0.800 (0.784, 0.817)	0.132	0.877	-0.368	0.688

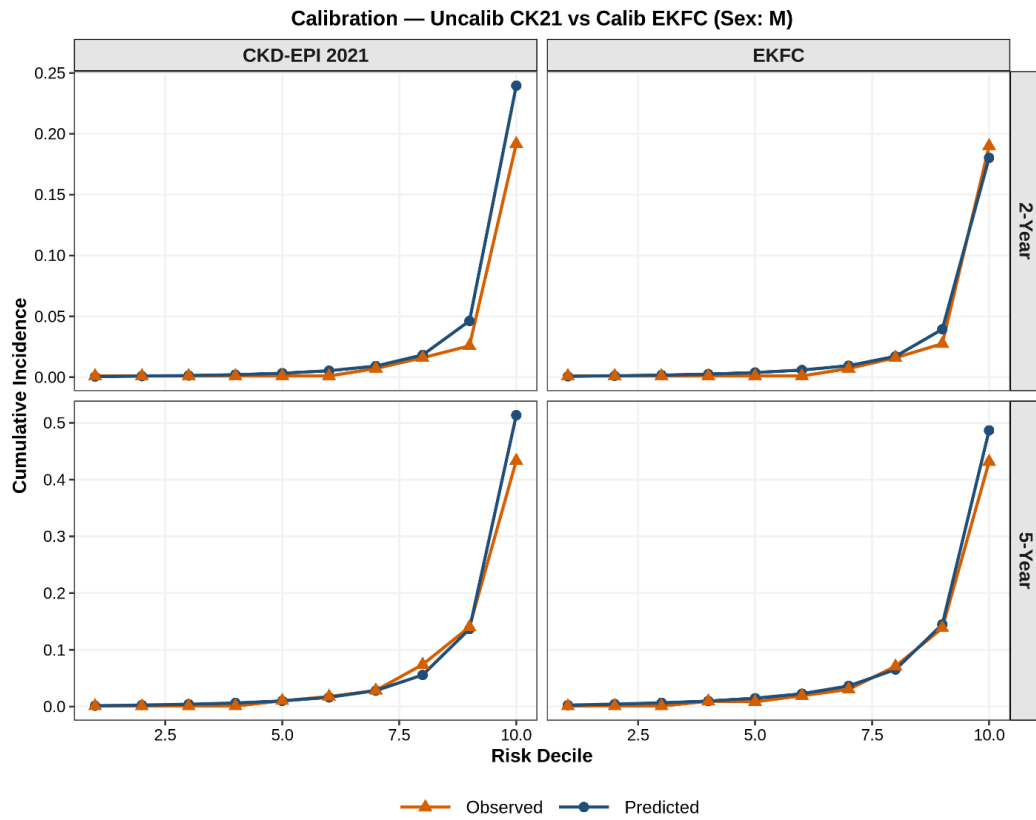
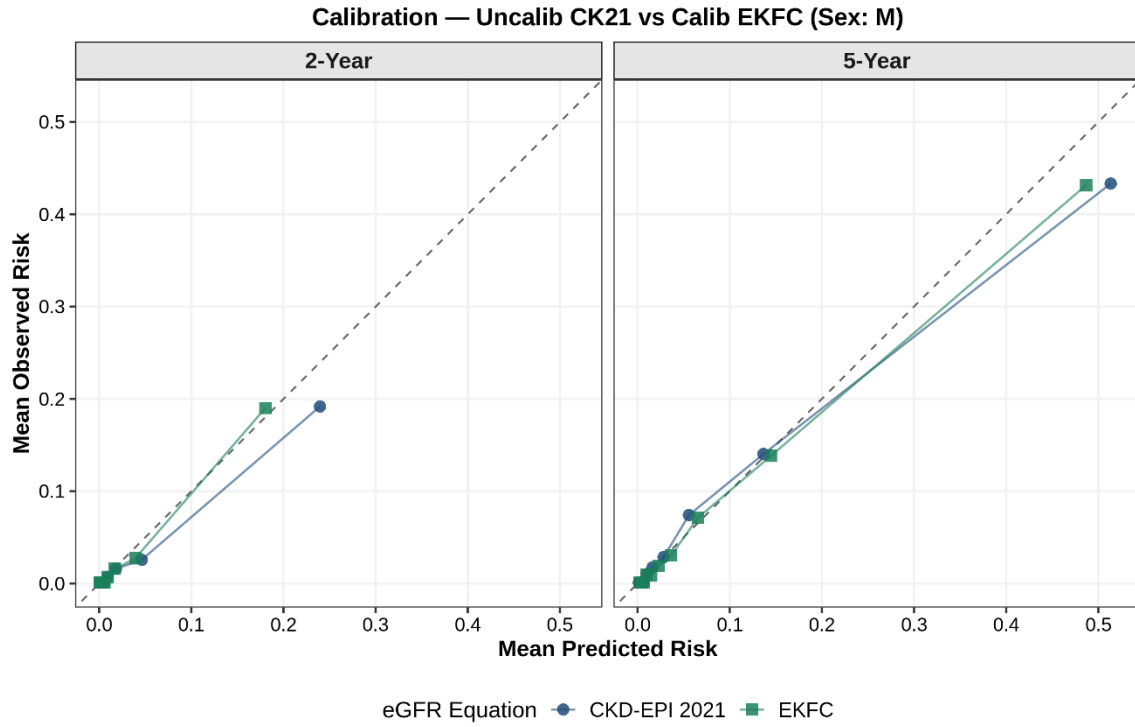
Table K4. Discrimination and calibration performance of the recalibrated 4-variable KFRE using CKD-EPI 2009 (CK09) and EKFC eGFR inputs, by stratum and prediction horizon.

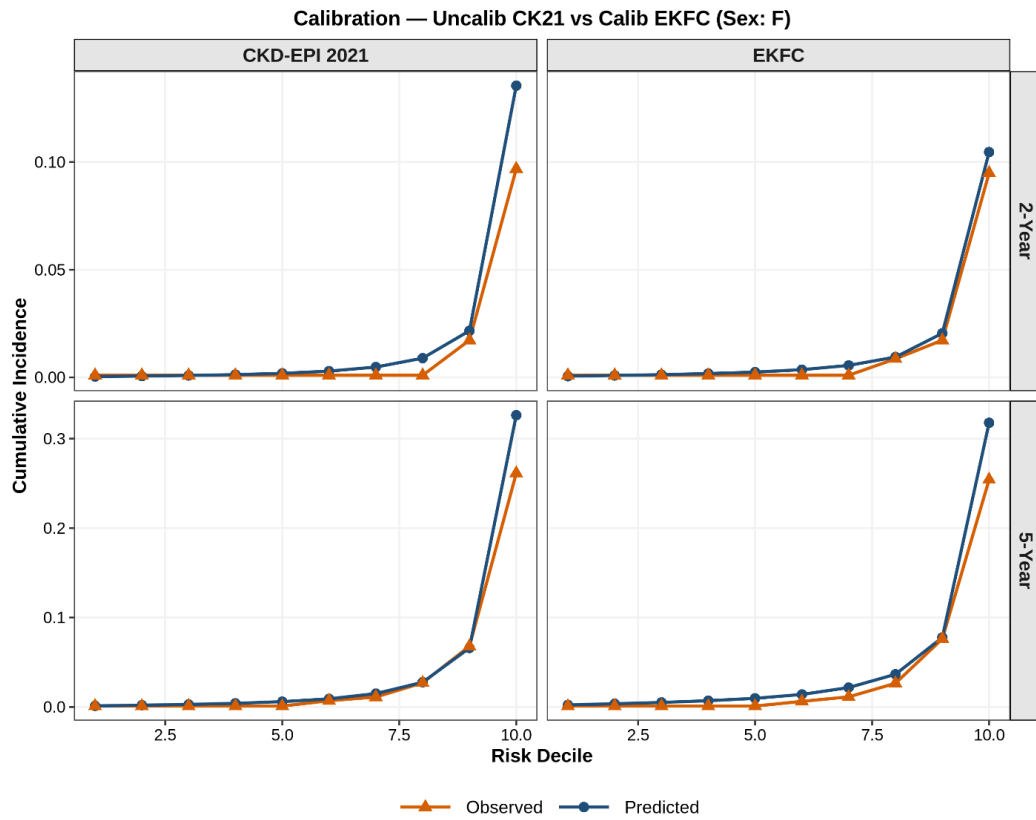
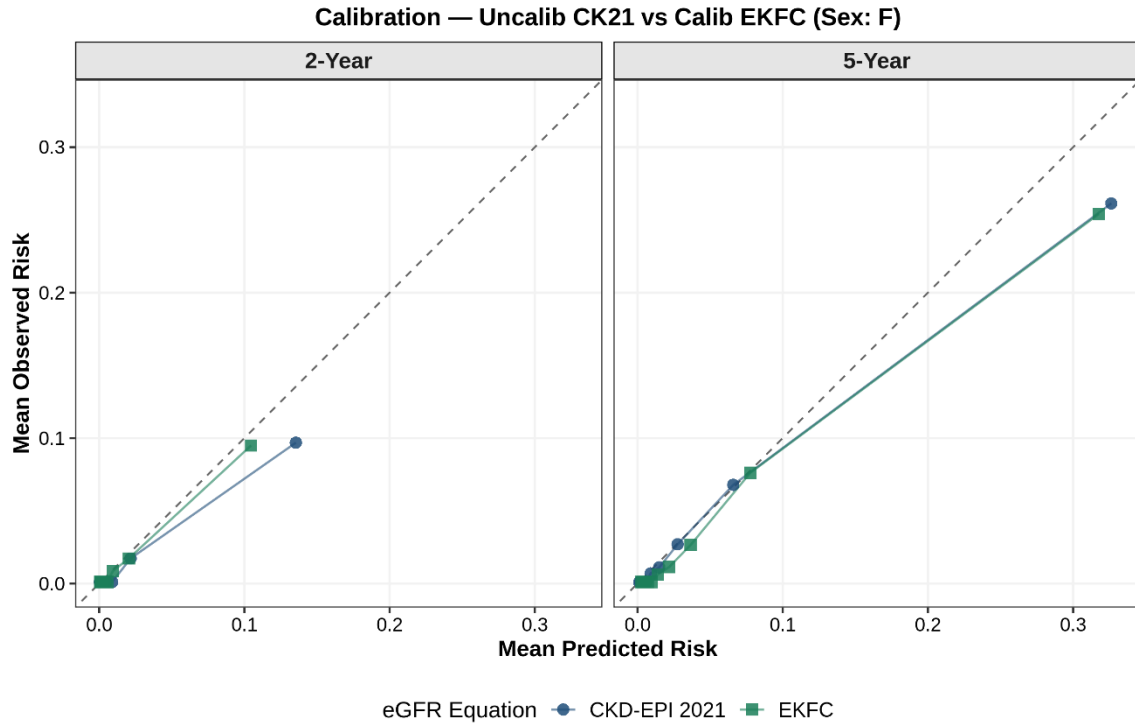
STRATUM	TIMEPOINT	MODEL	AUC (95% CI)	BRIER SCORE	O:E RATIO	CAL. INTERCEPT	CAL. SLOPE
OVERALL	2-year	CK09	0.937 (0.926, 0.948)	0.012	0.917	-0.107	1.071
		EKFC	0.936 (0.925, 0.947)	0.012	0.923	-0.097	1.139
	5-year	CK09	0.923 (0.915, 0.930)	0.031	0.868	-0.324	0.897
		EKFC	0.919 (0.912, 0.927)	0.031	0.865	-0.312	0.959
FEMALE	2-year	CK09	0.941 (0.925, 0.957)	0.008	0.876	-0.155	1.106
		EKFC	0.941 (0.925, 0.957)	0.008	0.841	-0.197	1.190
	5-year	CK09	0.925 (0.913, 0.938)	0.023	0.815	-0.390	0.947
		EKFC	0.923 (0.910, 0.936)	0.023	0.782	-0.430	1.017
MALE	2-year	CK09	0.931 (0.916, 0.946)	0.015	0.937	-0.083	1.051
		EKFC	0.930 (0.915, 0.945)	0.015	0.966	-0.043	1.107
	5-year	CK09	0.917 (0.908, 0.927)	0.038	0.898	-0.285	0.863
		EKFC	0.914 (0.904, 0.924)	0.039	0.914	-0.240	0.918
18 TO <40	2-year	CK09	0.907 (0.878, 0.936)	0.063	1.097	0.144	1.096
		EKFC	0.910 (0.883, 0.937)	0.063	1.153	0.218	1.121
	5-year	CK09	0.834 (0.799, 0.869)	0.144	1.110	0.042	0.663

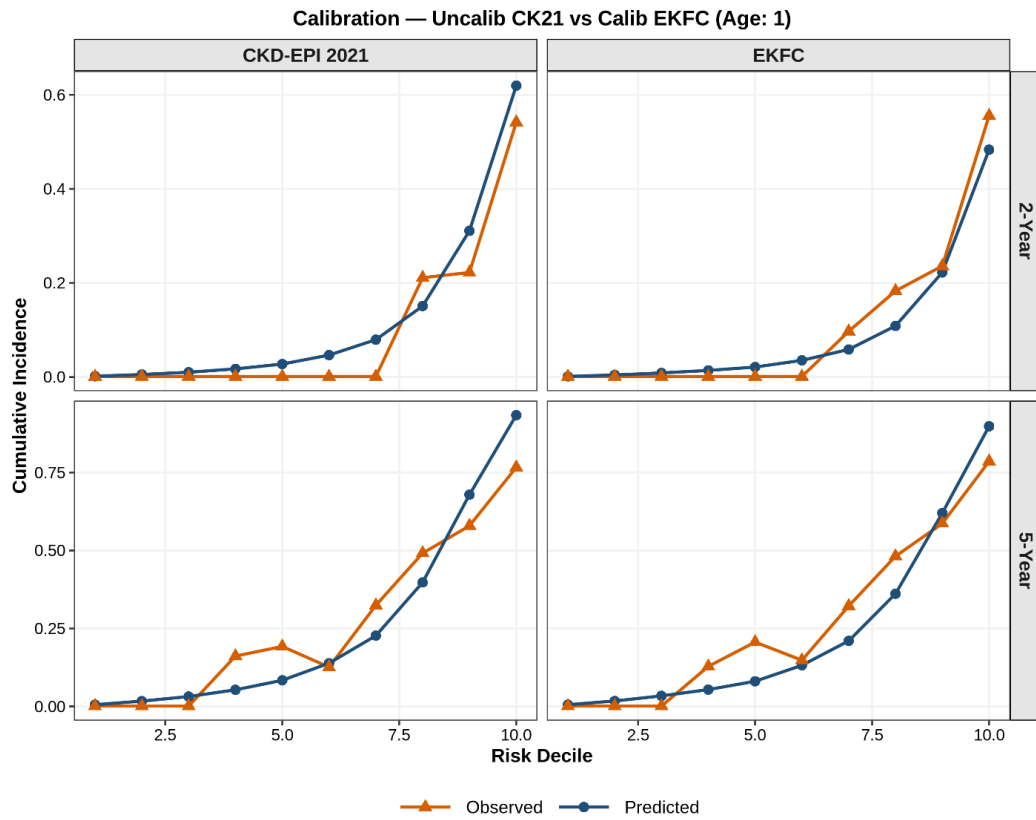
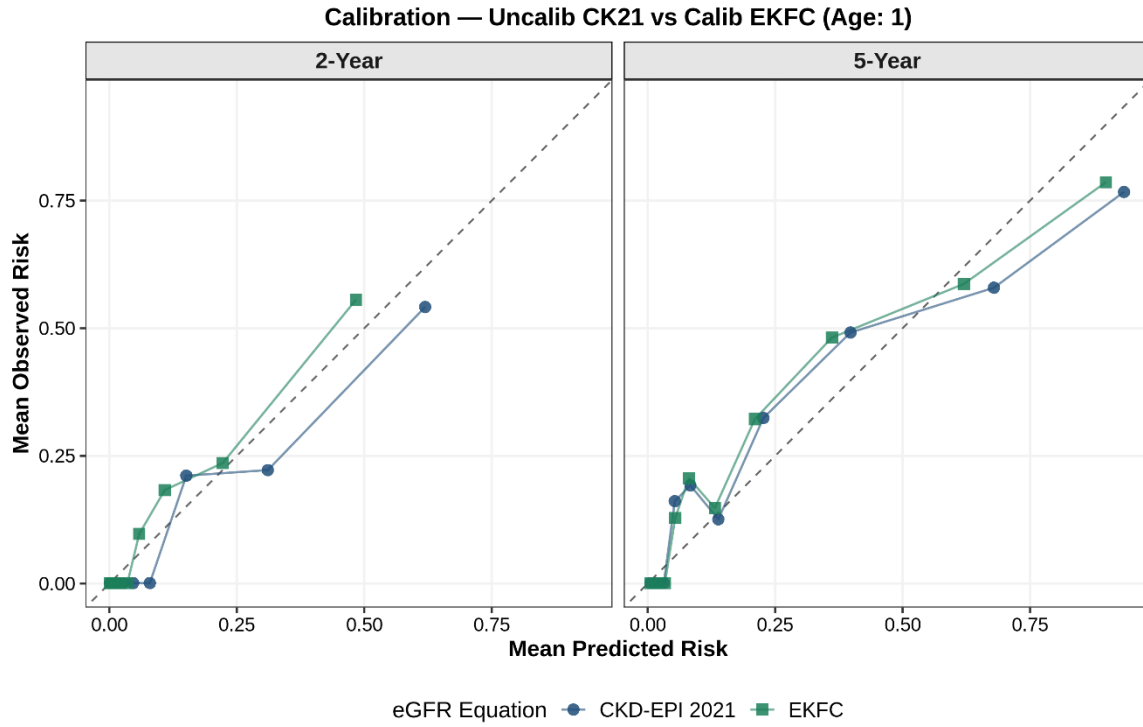
40 TO ≤65	2-year	EKFC	0.837 (0.802, 0.871)	0.144	1.161	0.150	0.696
		CK09	0.927 (0.912, 0.941)	0.023	1.133	0.163	1.004
		EKFC	0.928 (0.914, 0.942)	0.024	1.271	0.304	1.050
66 TO <80	5-year	CK09	0.912 (0.902, 0.922)	0.057	1.088	0.030	0.828
		EKFC	0.912 (0.902, 0.923)	0.057	1.199	0.198	0.883
		CK09	0.891 (0.859, 0.924)	0.006	0.670	-0.447	0.881
≥80	2-year	EKFC	0.893 (0.861, 0.925)	0.006	0.622	-0.523	0.947
		CK09	0.895 (0.876, 0.913)	0.021	0.725	-0.536	0.848
		EKFC	0.895 (0.876, 0.914)	0.021	0.681	-0.604	0.906
< 3 MG/MMOL	2-year	CK09	0.938 (0.891, 0.985)	0.004	0.474	-0.788	1.496
		EKFC	0.940 (0.894, 0.986)	0.004	0.387	-0.998	1.611
		CK09	0.924 (0.895, 0.953)	0.011	0.371	-1.224	1.177
3-30 MG/MMOL	5-year	EKFC	0.926 (0.898, 0.955)	0.012	0.310	-1.418	1.268
		CK09	0.856 (0.761, 0.951)	0.001	0.762	-0.275	1.293
		EKFC	0.854 (0.757, 0.950)	0.001	0.646	-0.441	1.408
> 30 MG/MMOL	2-year	CK09	0.806 (0.749, 0.862)	0.004	0.622	-0.551	0.993
		EKFC	0.796 (0.738, 0.855)	0.004	0.540	-0.691	1.058
		CK09	0.845 (0.794, 0.897)	0.006	0.612	-0.513	1.007
> 30 MG/MMOL	5-year	EKFC	0.843 (0.791, 0.894)	0.006	0.577	-0.572	1.082
		CK09	0.831 (0.801, 0.861)	0.021	0.613	-0.660	0.907
		EKFC	0.822 (0.790, 0.853)	0.022	0.585	-0.696	0.971
> 30 MG/MMOL	2-year	CK09	0.847 (0.824, 0.869)	0.053	1.012	0.016	0.989
		EKFC	0.844 (0.821, 0.867)	0.054	1.053	0.067	1.047
		CK09	0.808 (0.792, 0.824)	0.128	0.983	-0.143	0.683
	5-year	EKFC	0.800 (0.784, 0.817)	0.129	1.010	-0.085	0.724

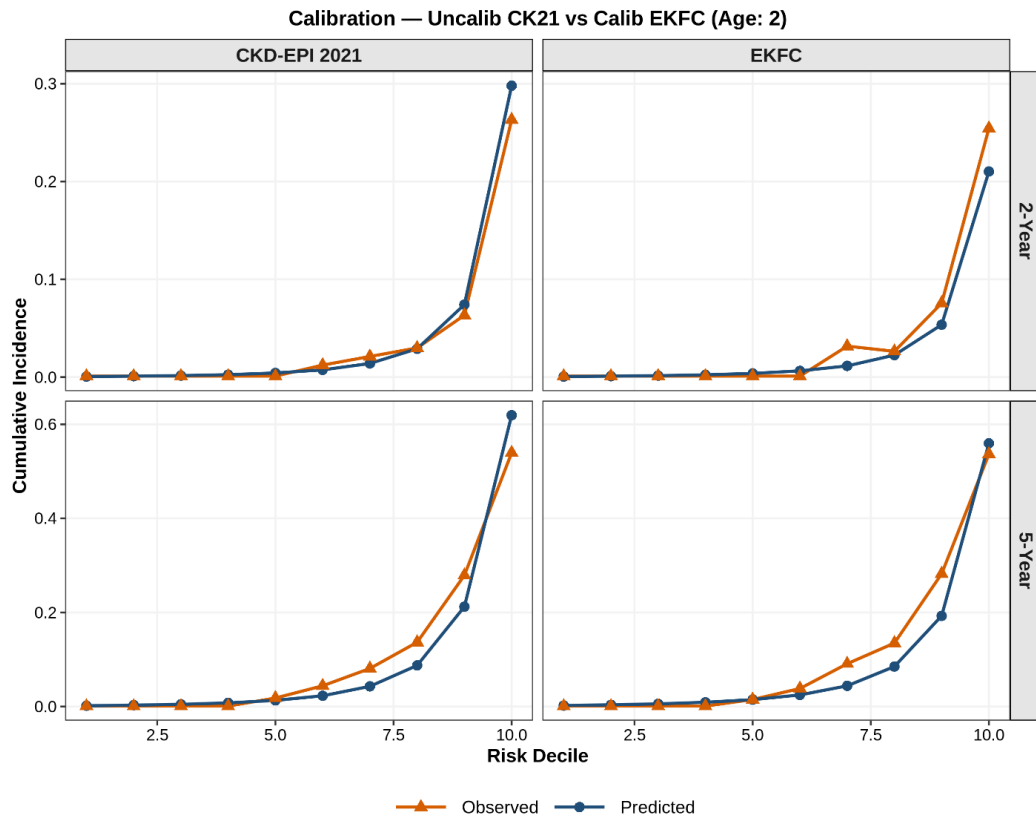
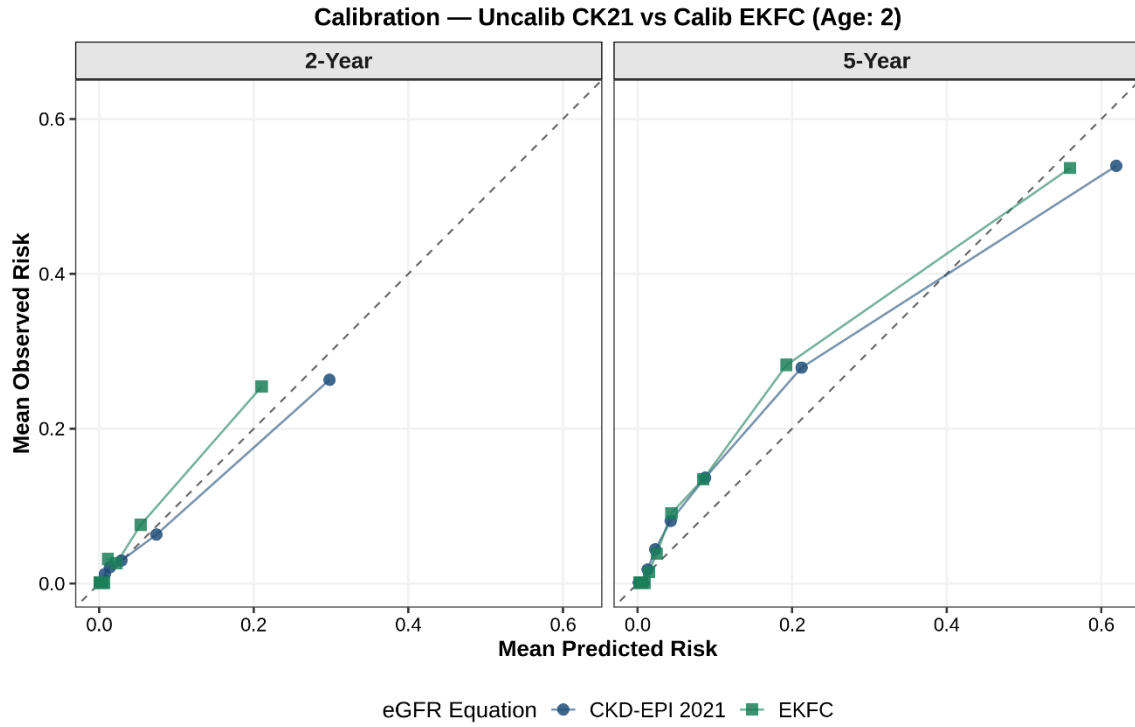
Appendix L1. Calibration line plots of observed versus predicted risk by deciles comparing uncalibrated CK21 to calibrated EKFC input to KRT at the 2- and 5-year horizons.

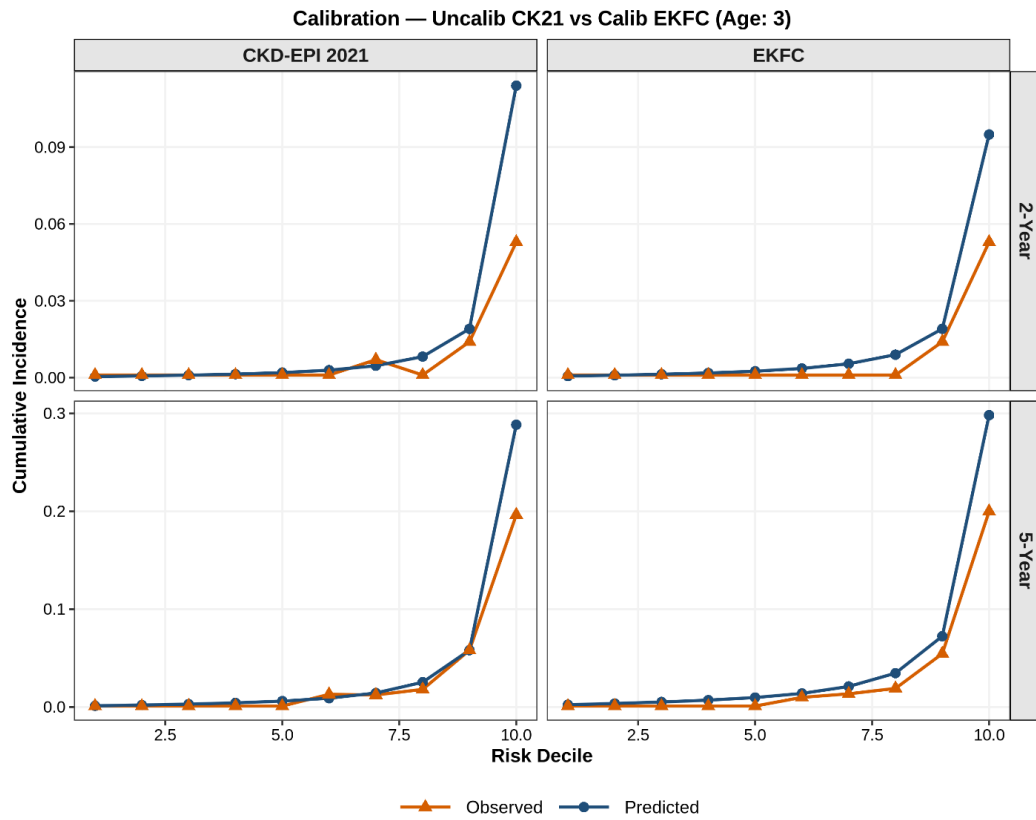
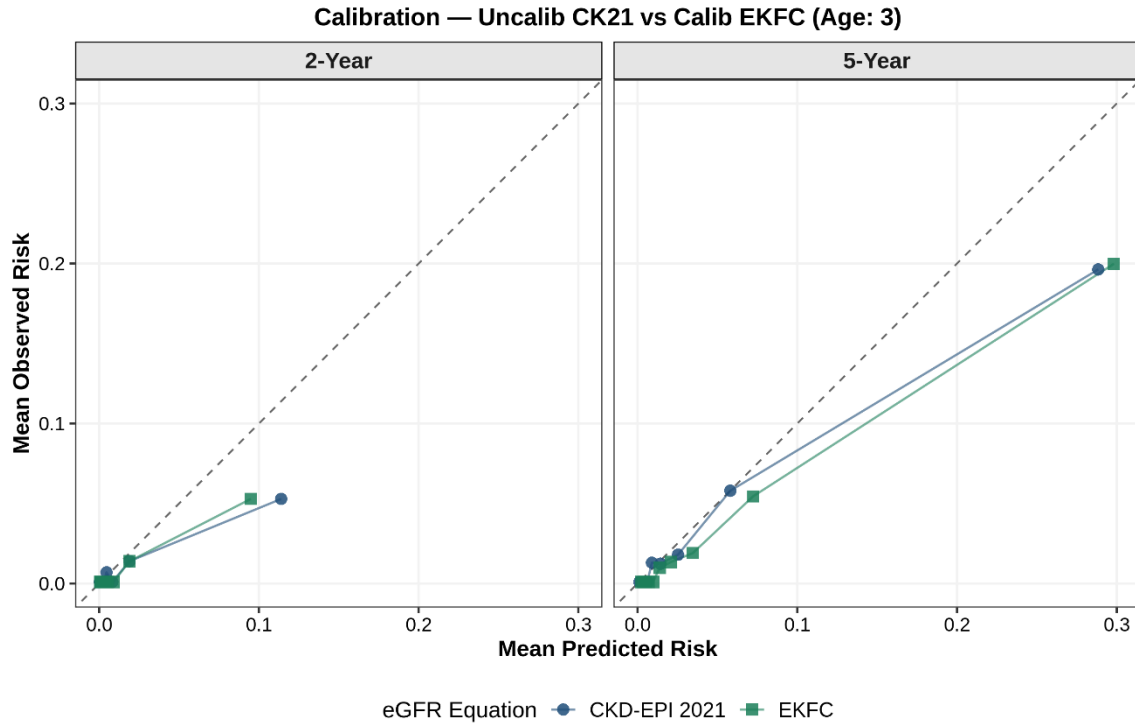


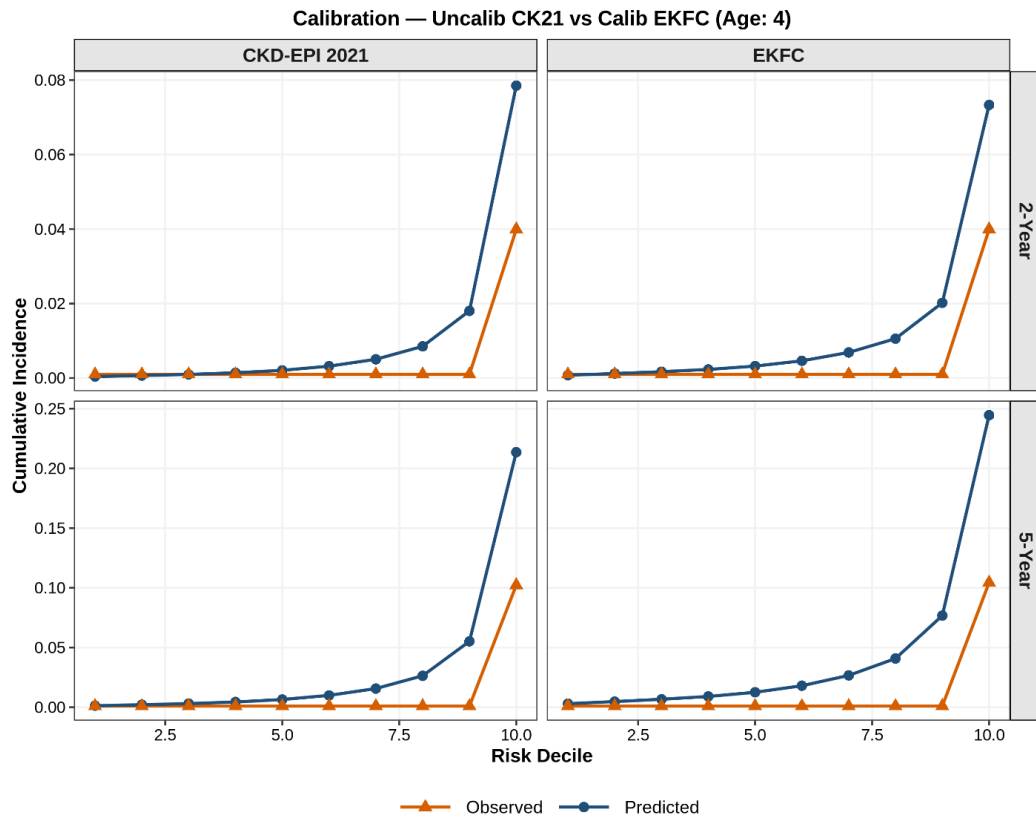
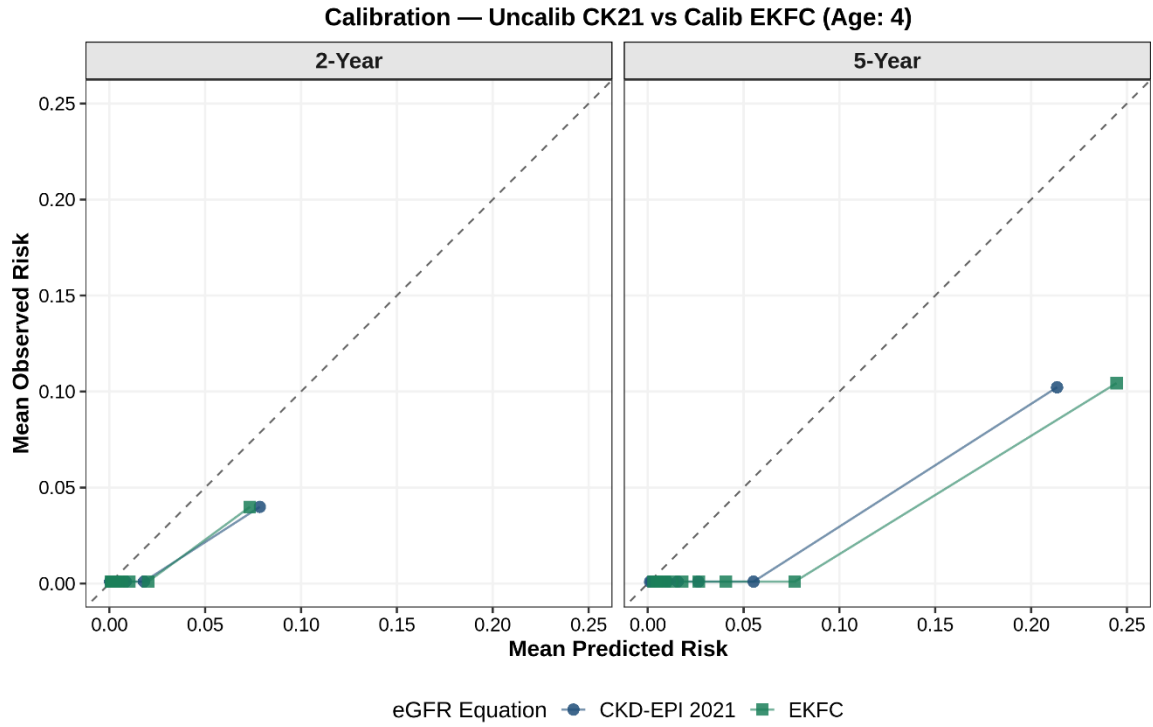


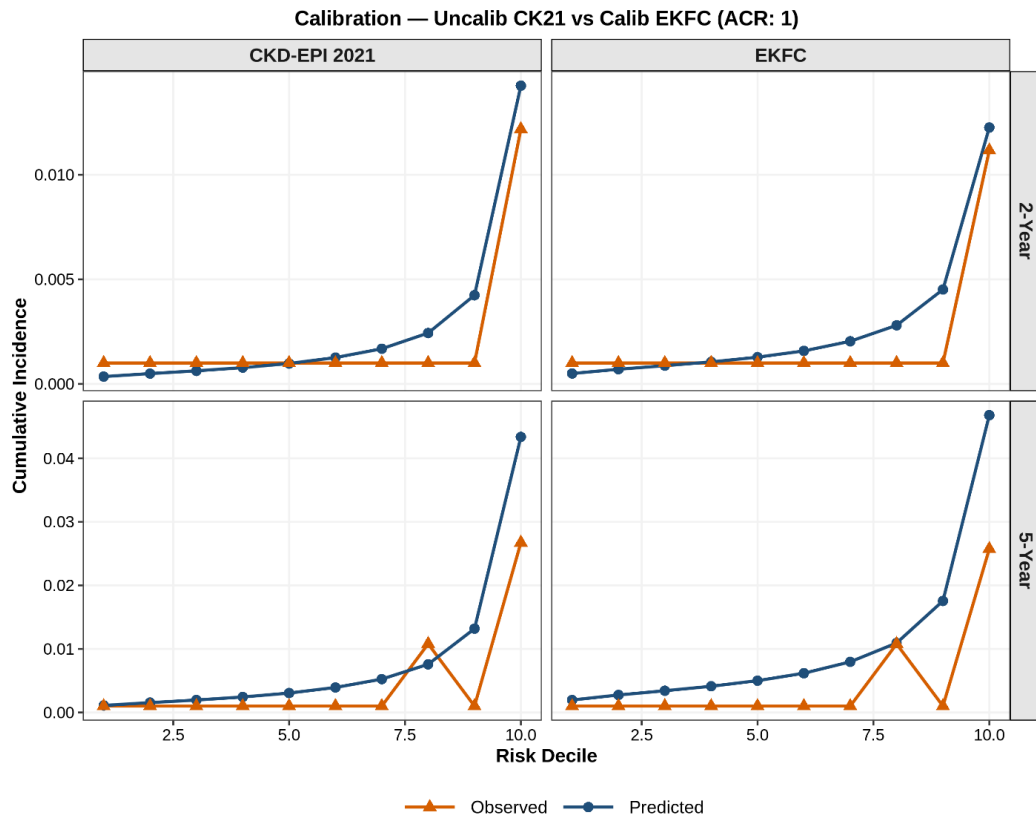
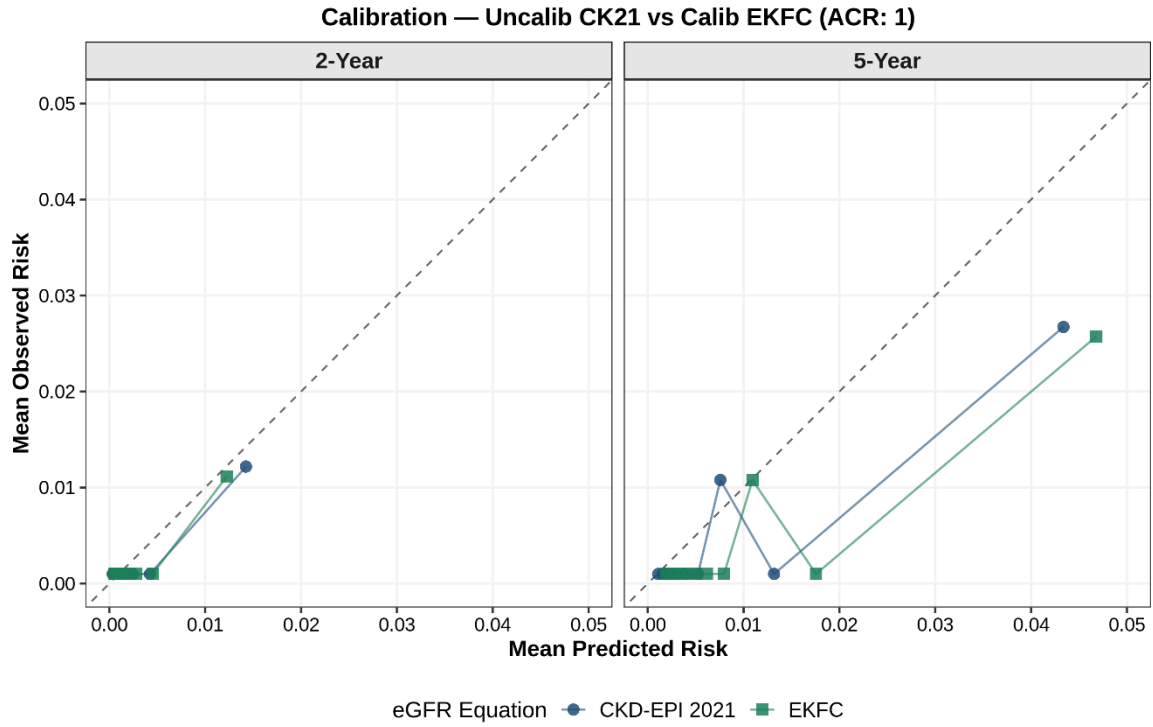


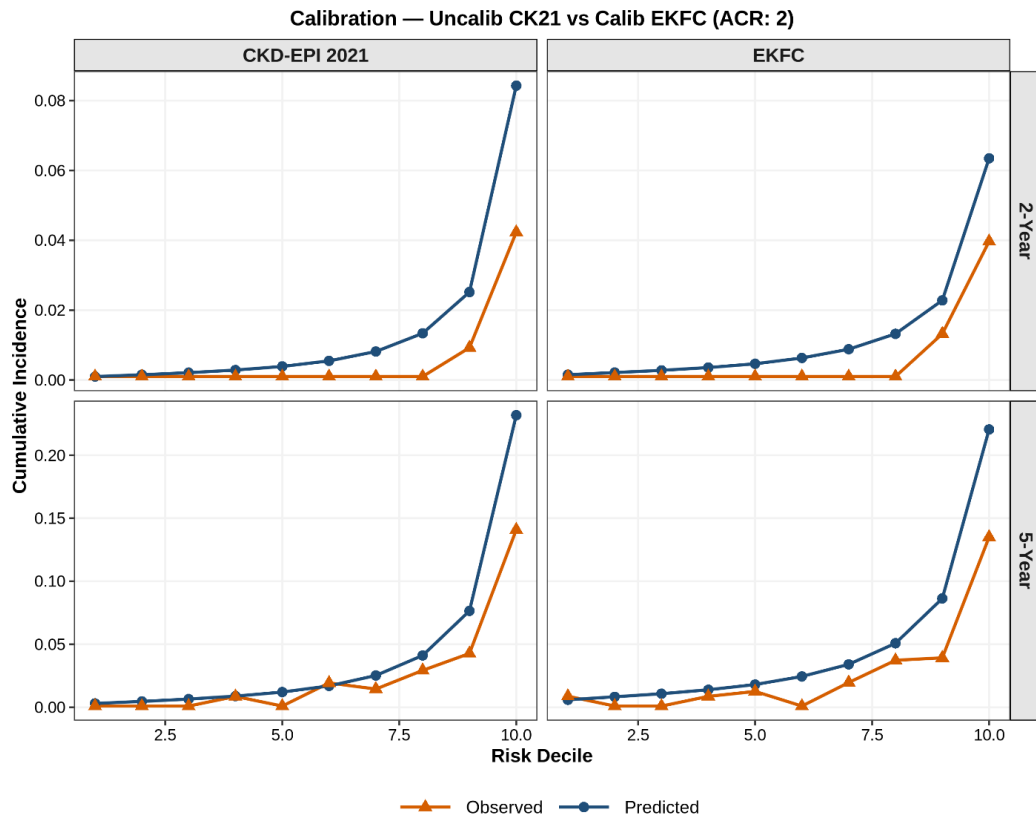
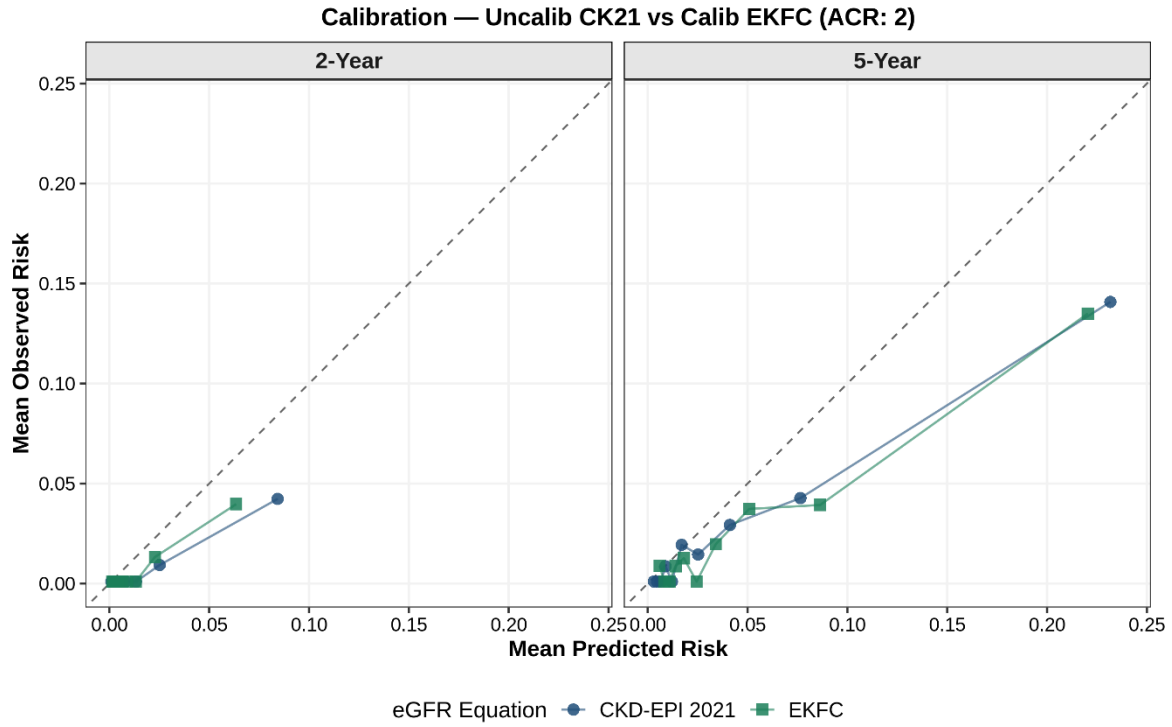


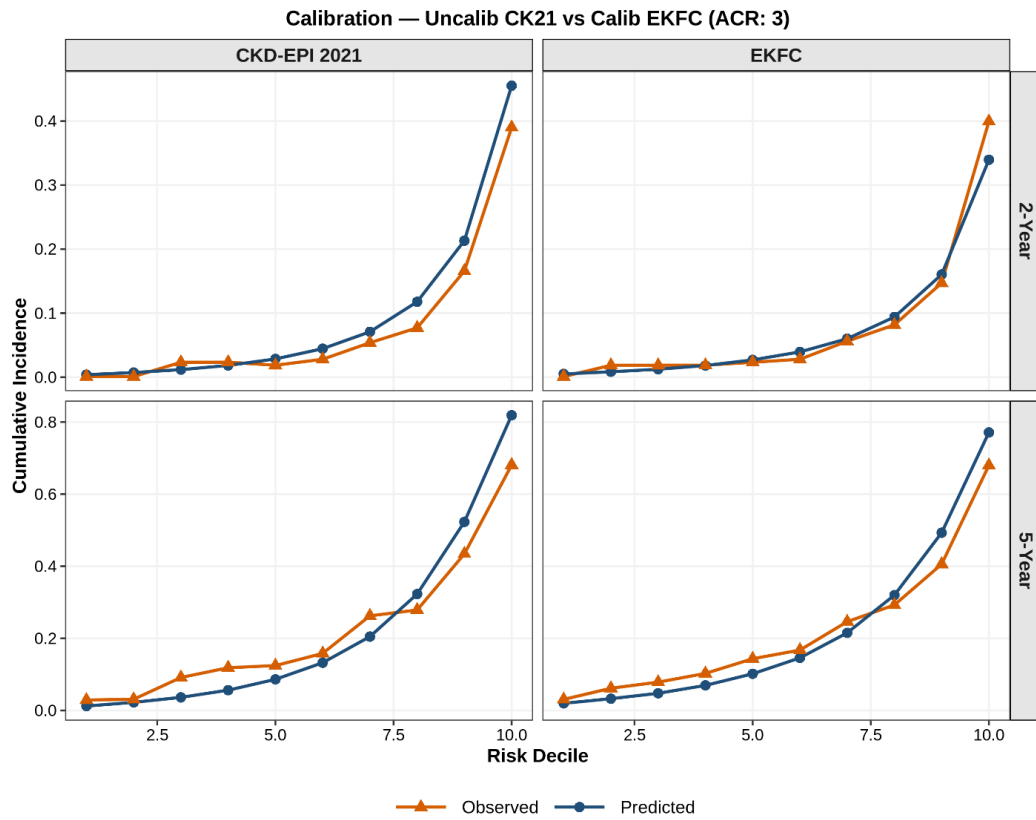
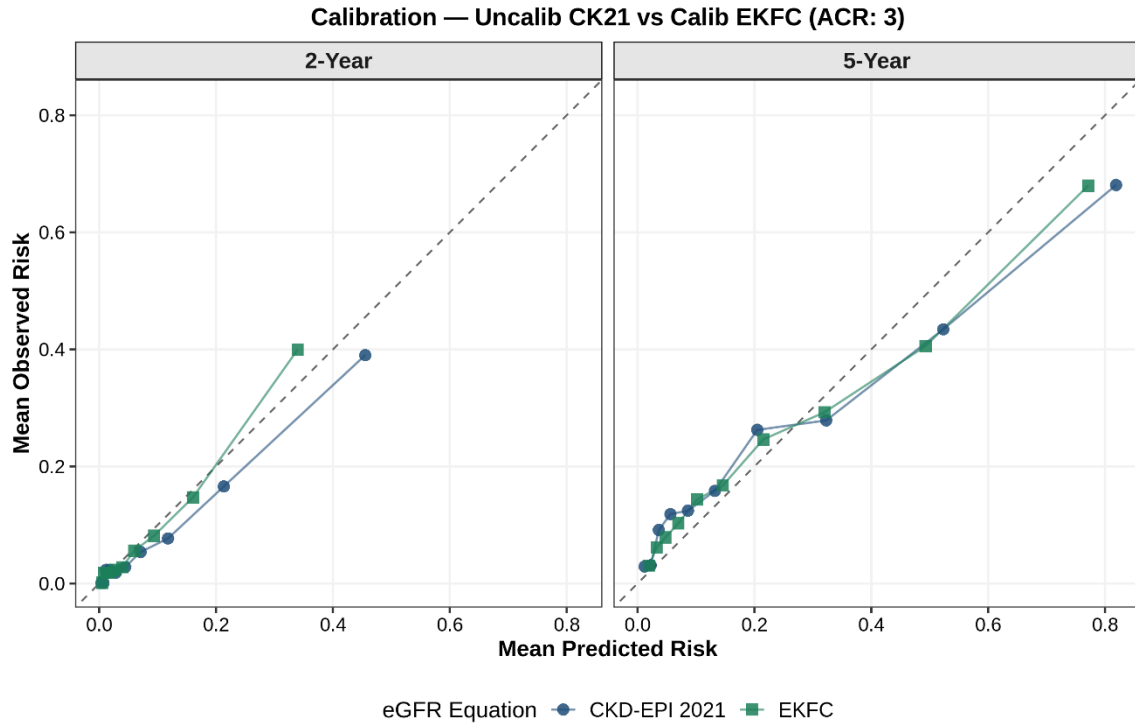




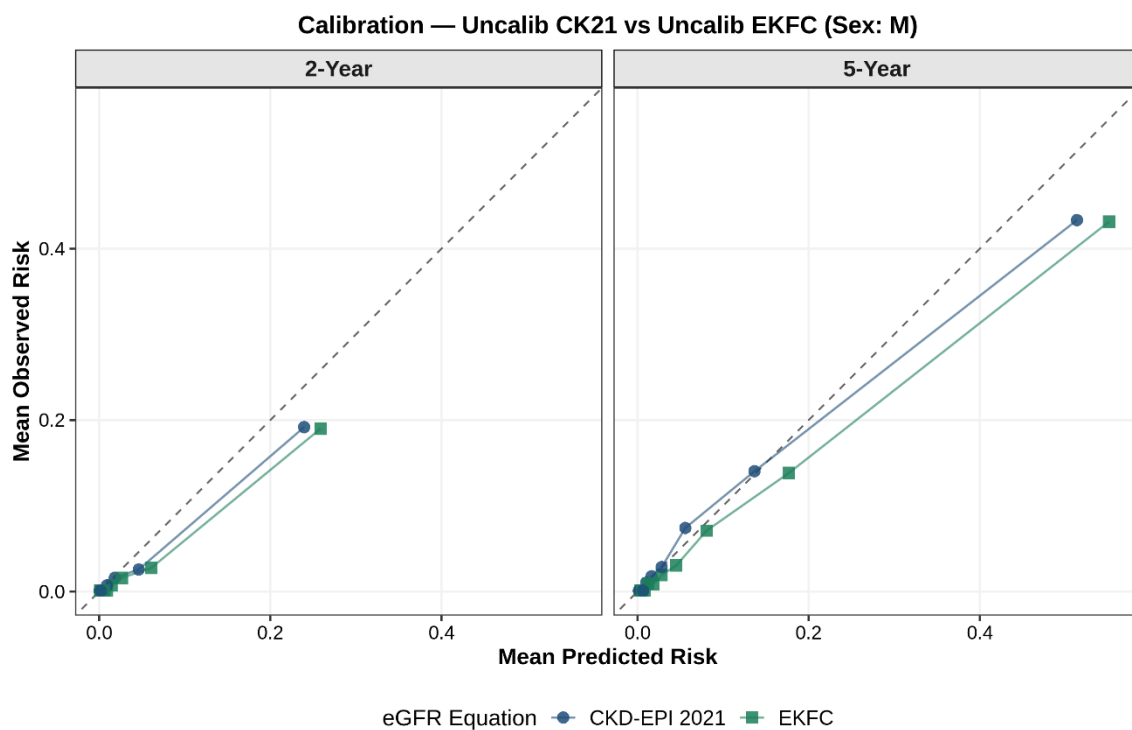
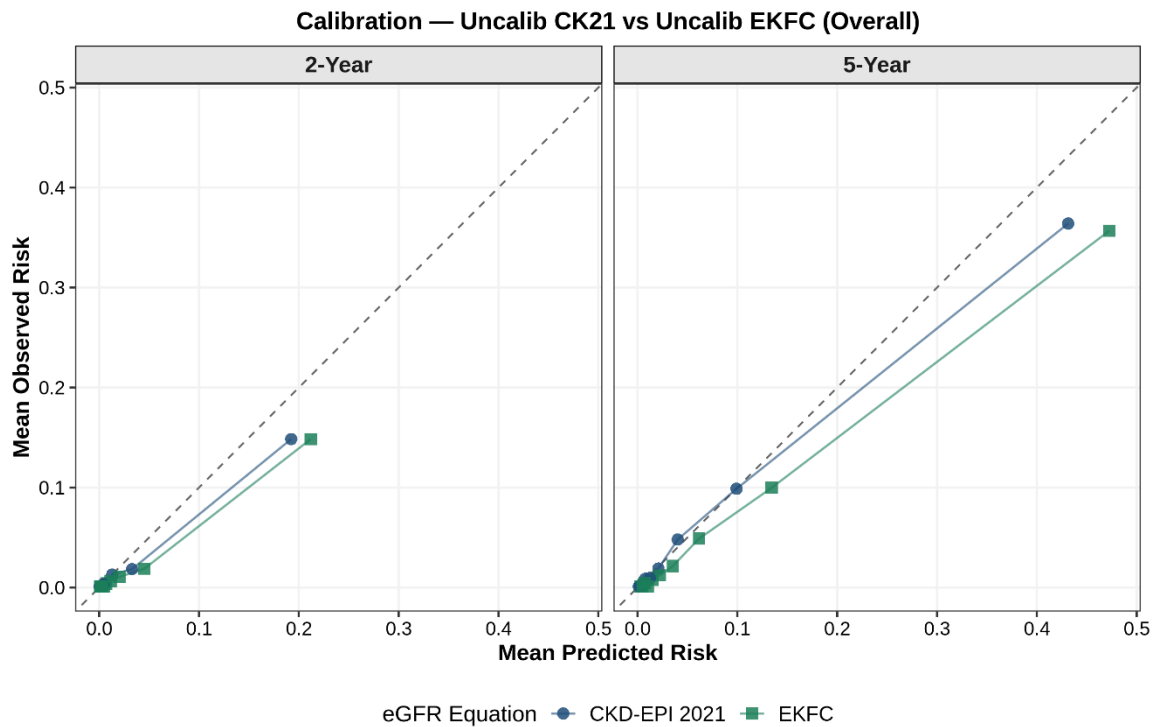




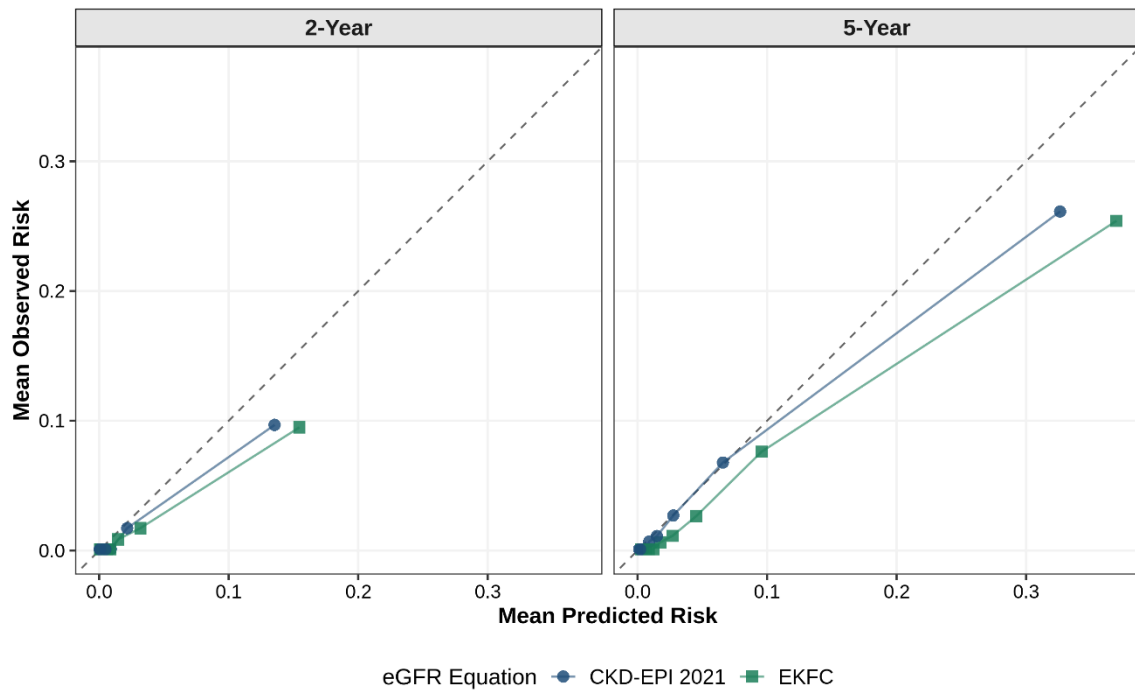




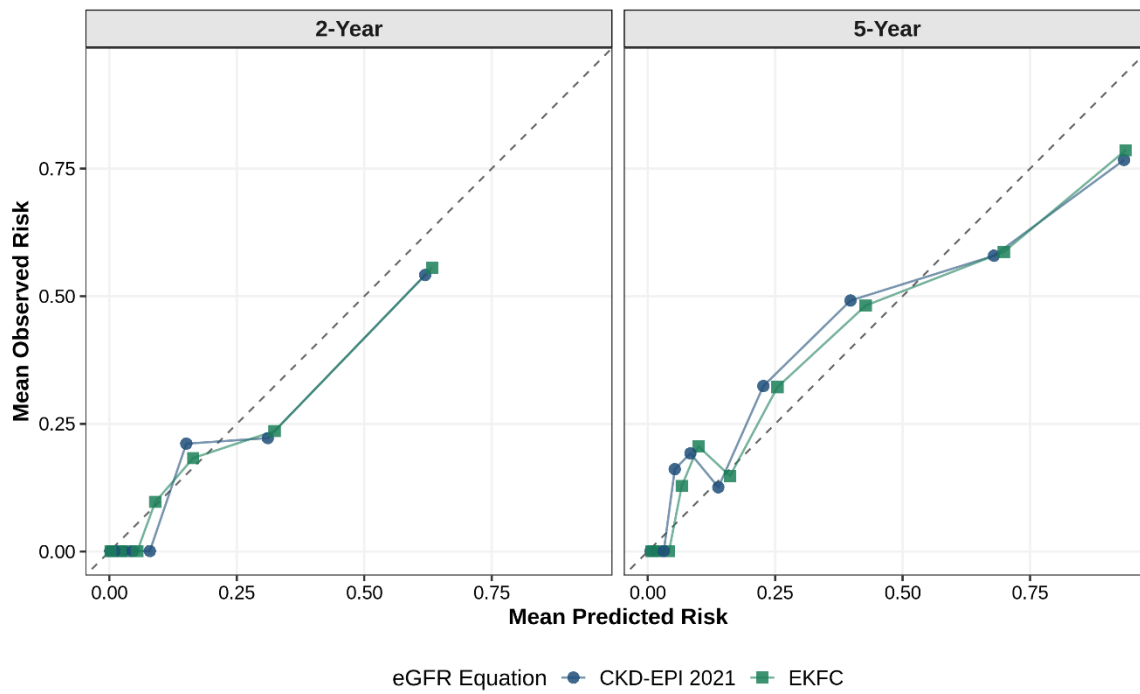
Appendix L2. Calibration line plots of observed versus predicted risk by deciles comparing uncalibrated CK21 to uncalibrated EKFC input to KRT at the 2- and 5-year horizons



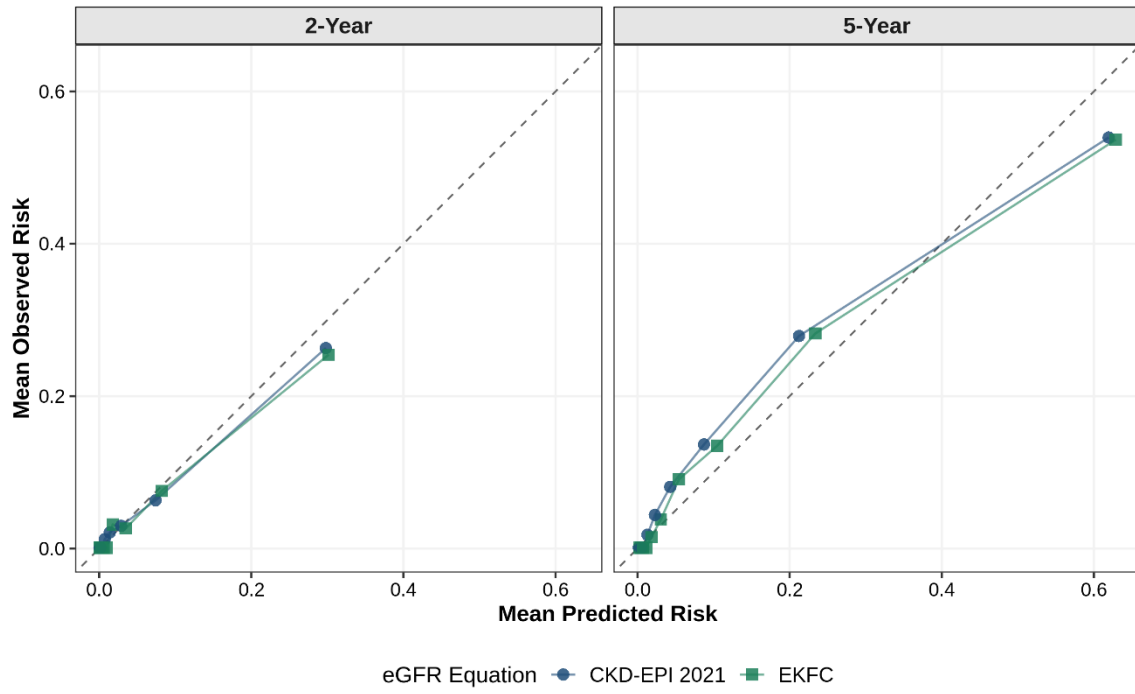
Calibration — Uncalib CK21 vs Uncalib EKFC (Sex: F)



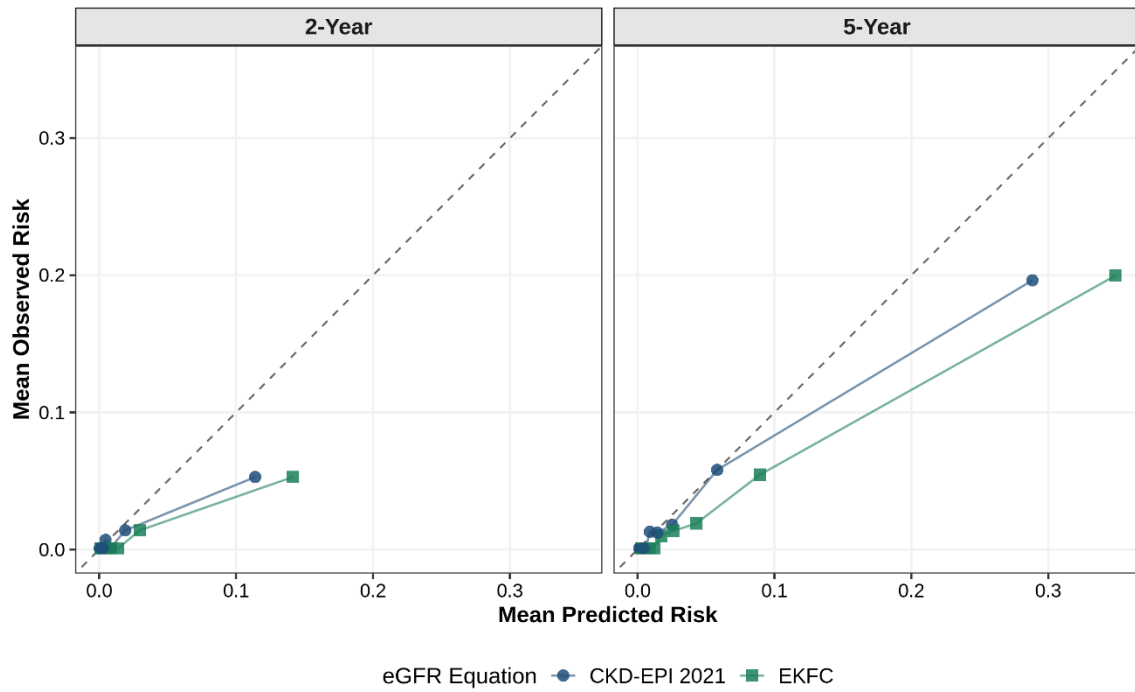
Calibration — Uncalib CK21 vs Uncalib EKFC (Age: 1)



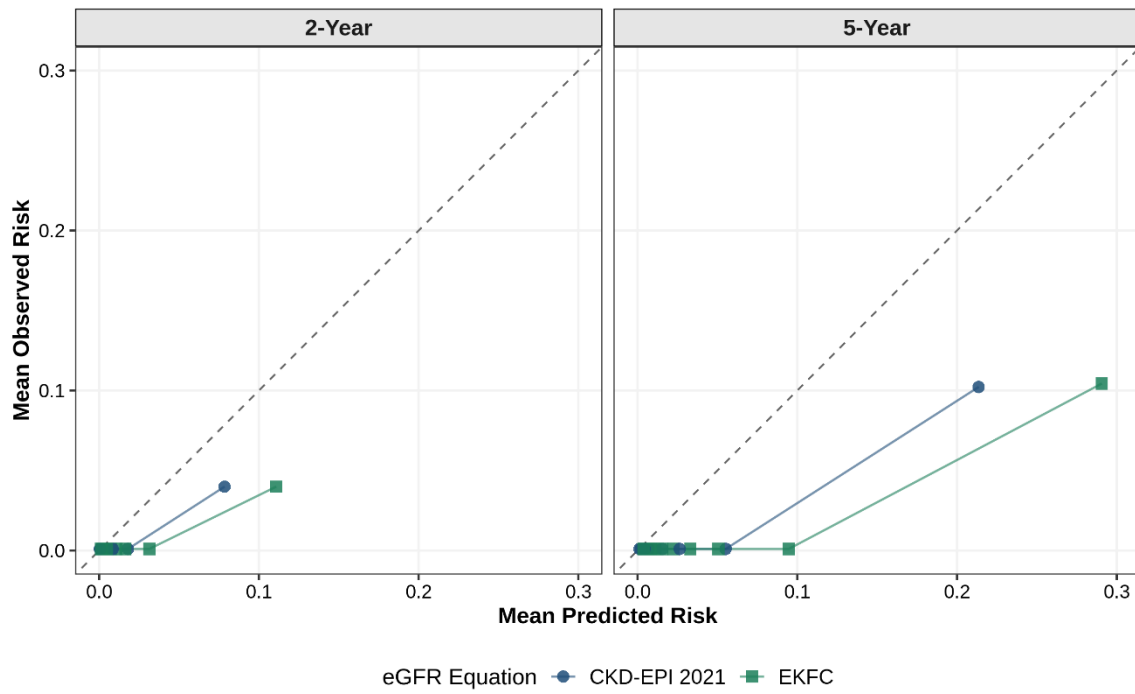
Calibration — Uncalib CK21 vs Uncalib EKFC (Age: 2)



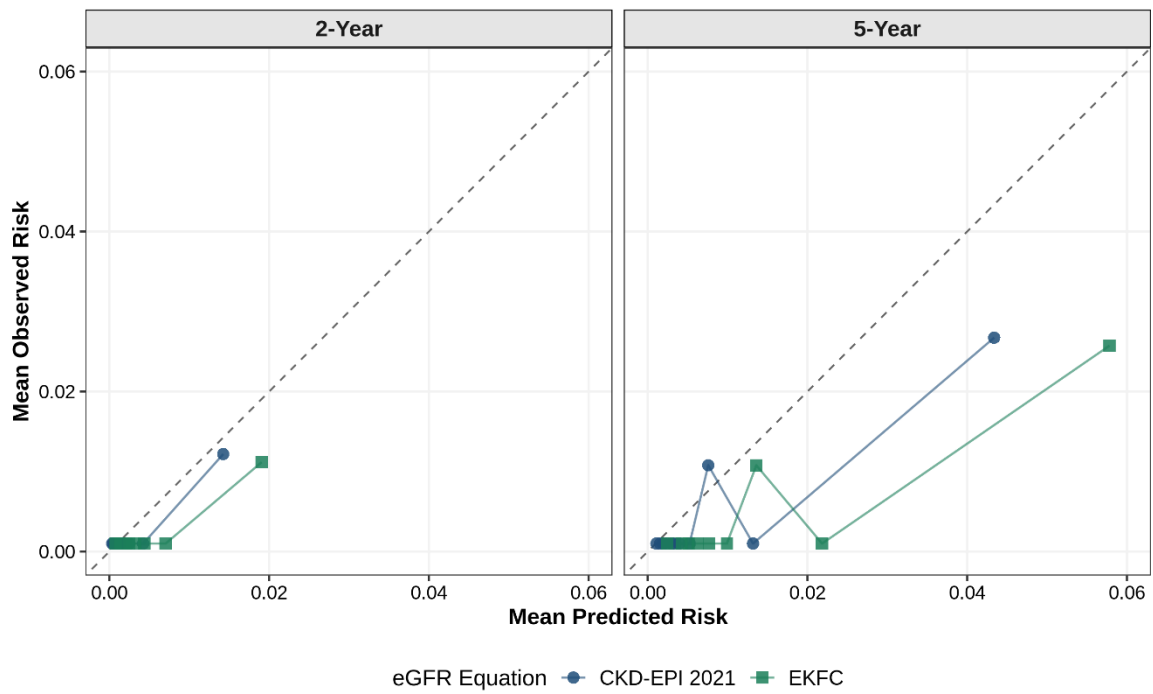
Calibration — Uncalib CK21 vs Uncalib EKFC (Age: 3)



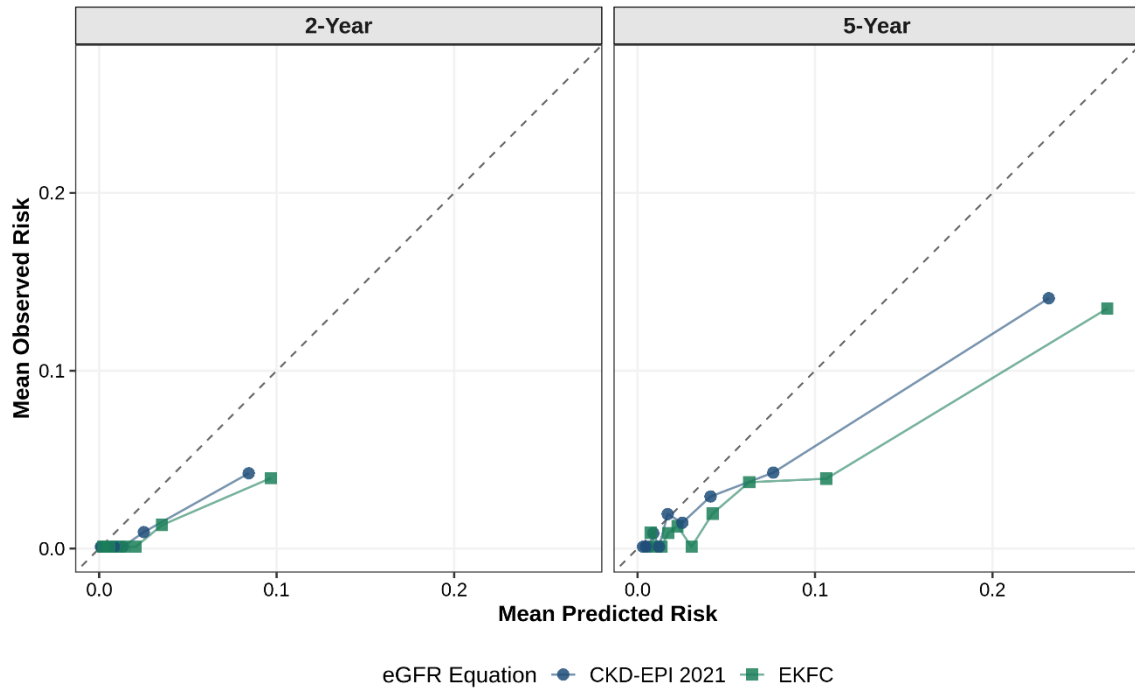
Calibration — Uncalib CK21 vs Uncalib EKFC (Age: 4)



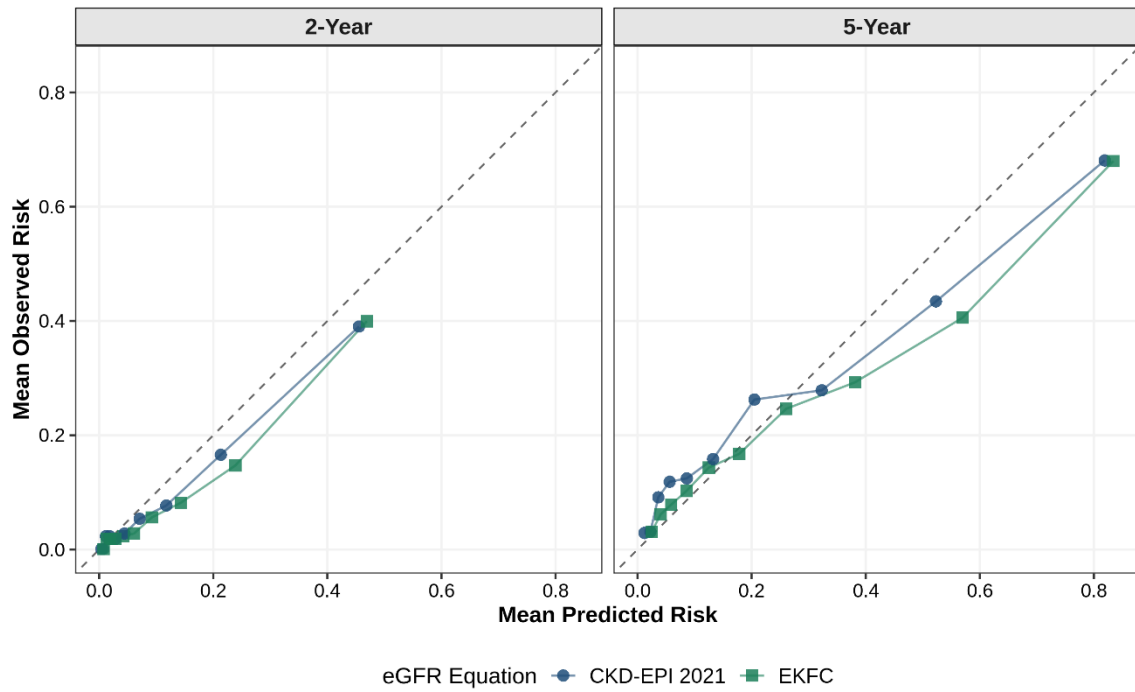
Calibration — Uncalib CK21 vs Uncalib EKFC (ACR: 1)



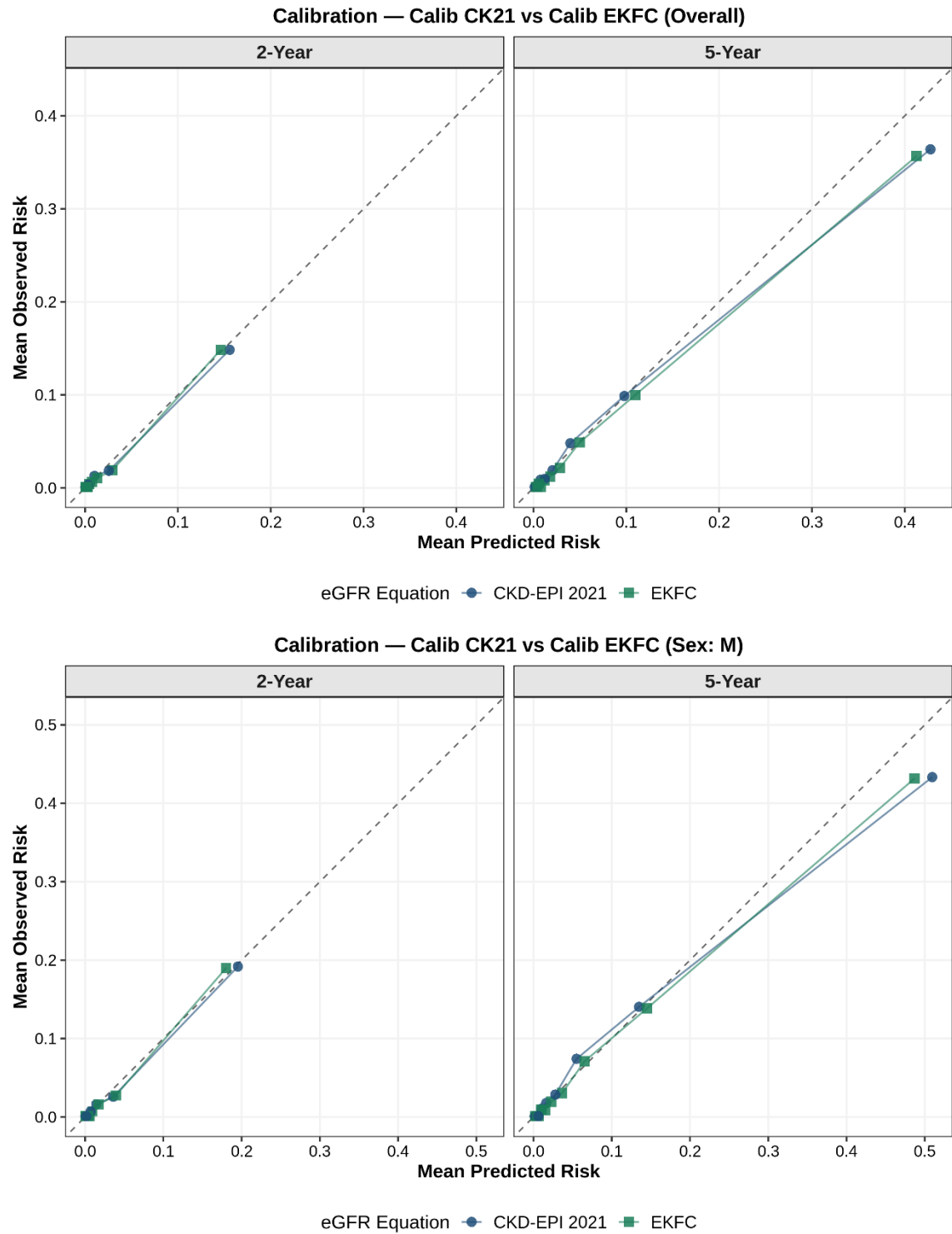
Calibration — Uncalib CK21 vs Uncalib EKFC (ACR: 2)



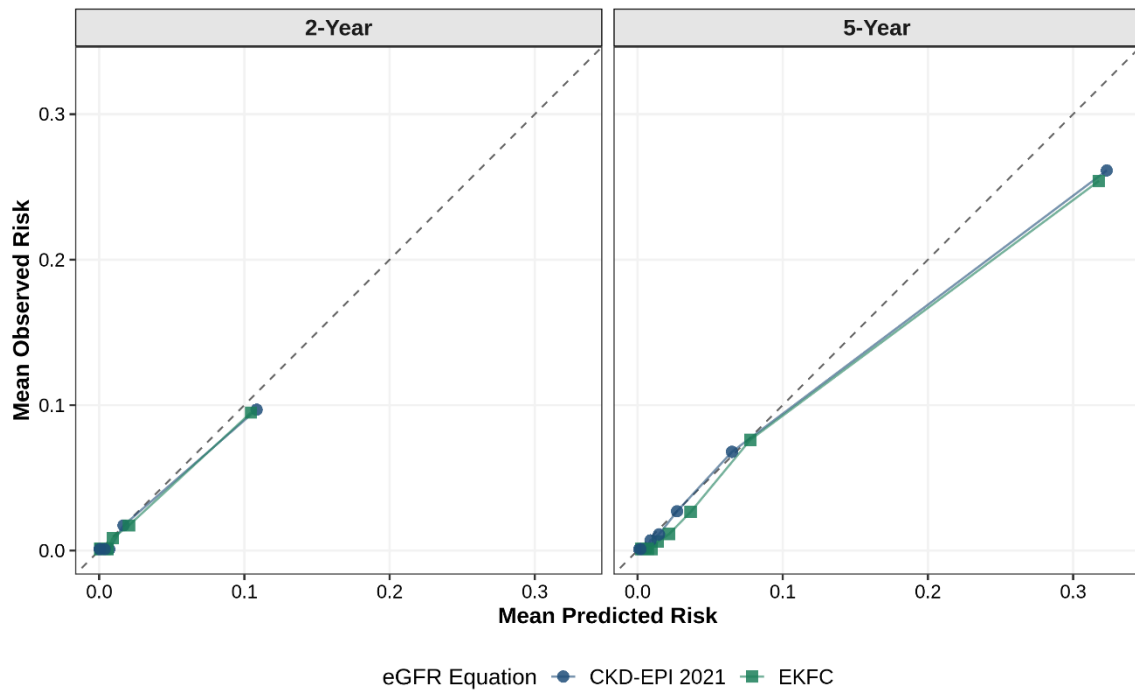
Calibration — Uncalib CK21 vs Uncalib EKFC (ACR: 3)



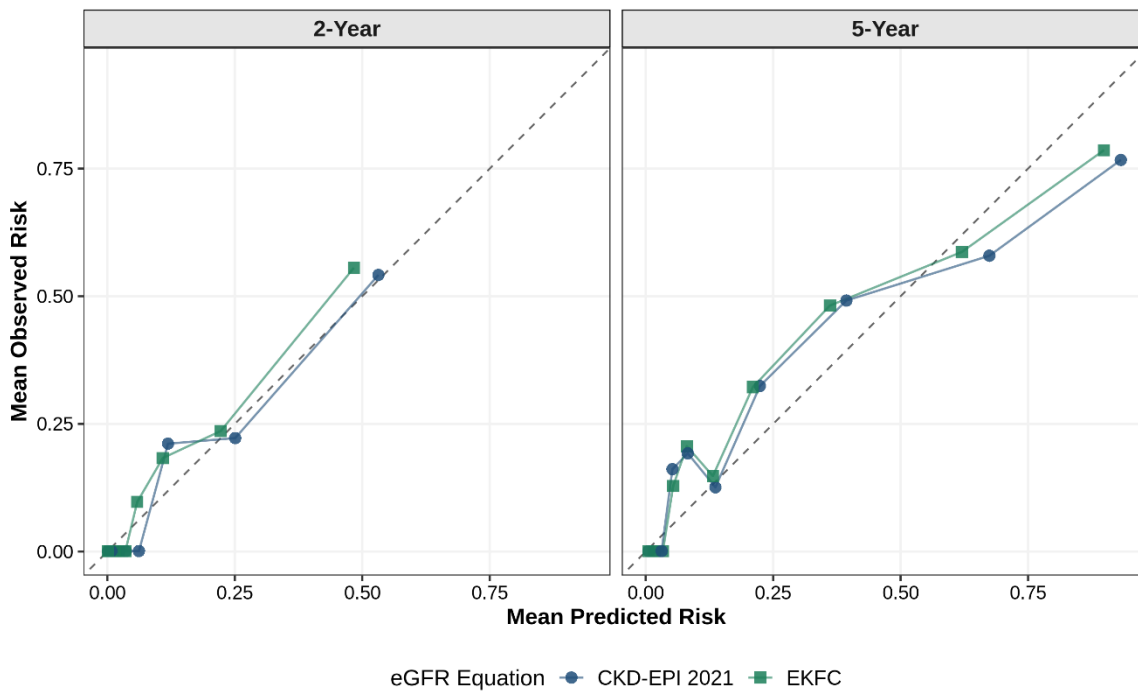
Appendix L3. Calibration line plots of observed versus predicted risk by deciles comparing calibrated CK21 to calibrated EKFC input to KRT at the 2- and 5-year horizons



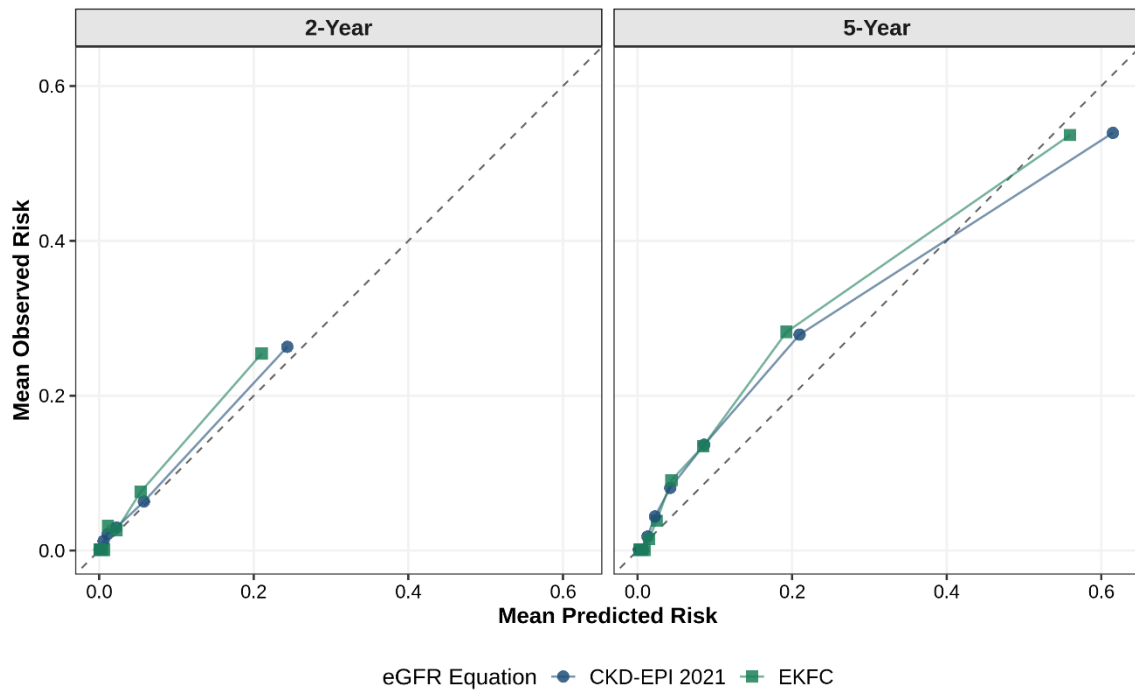
Calibration — Calib CK21 vs Calib EKFC (Sex: F)



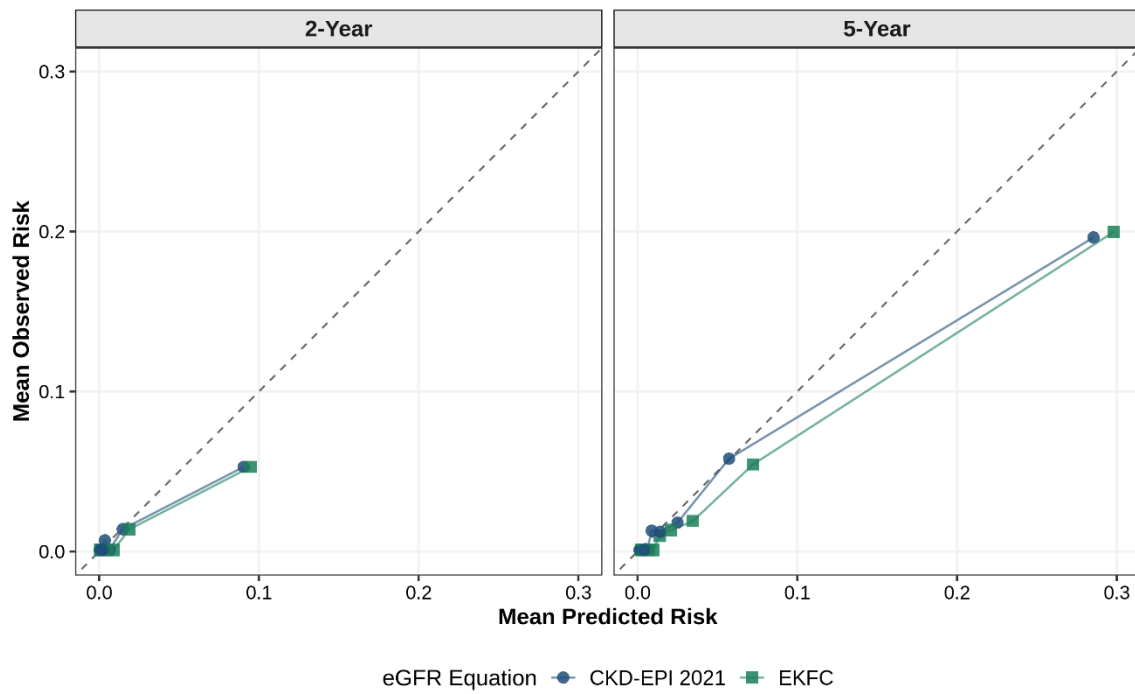
Calibration — Calib CK21 vs Calib EKFC (Age: 1)



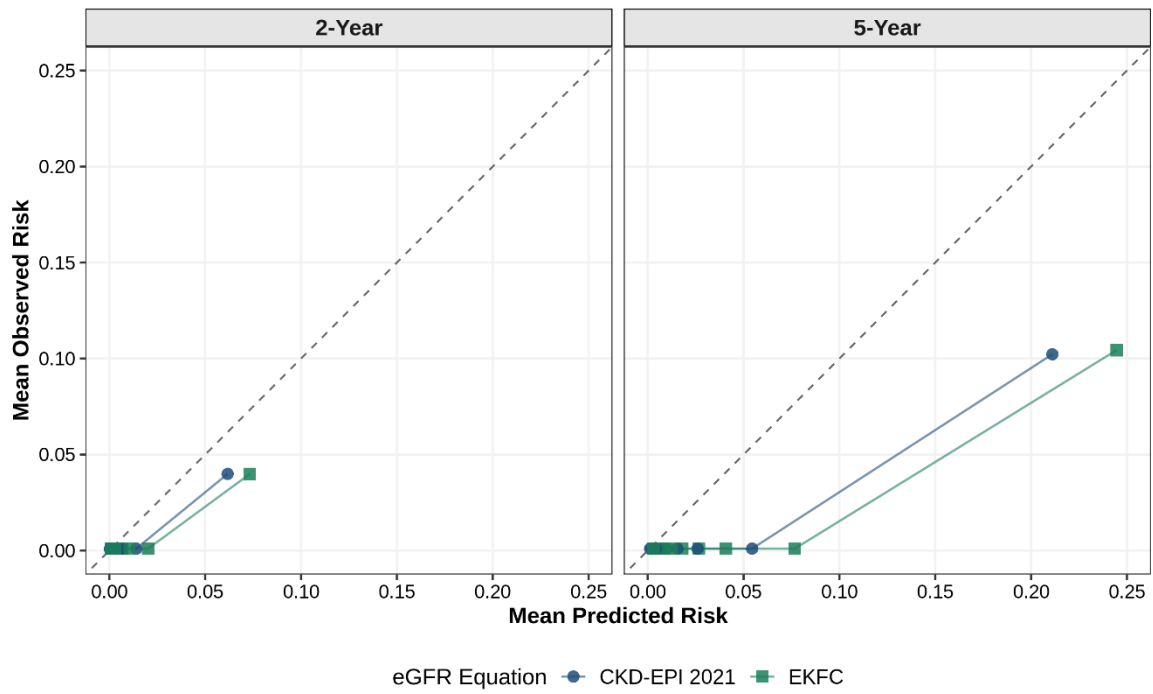
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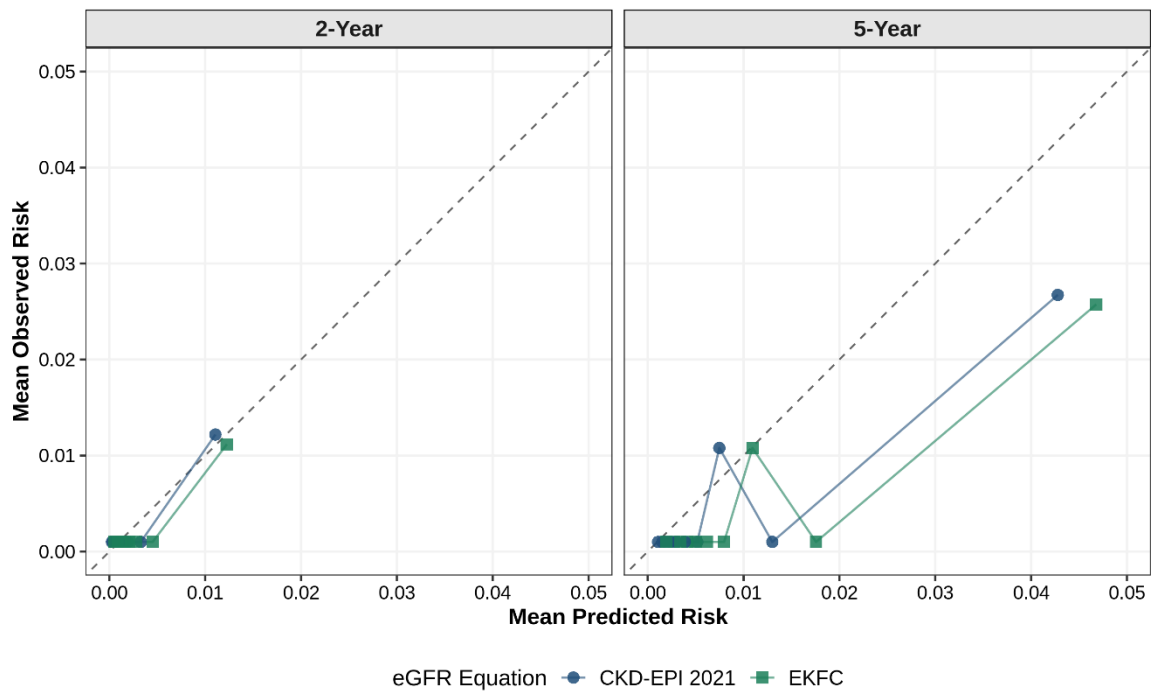
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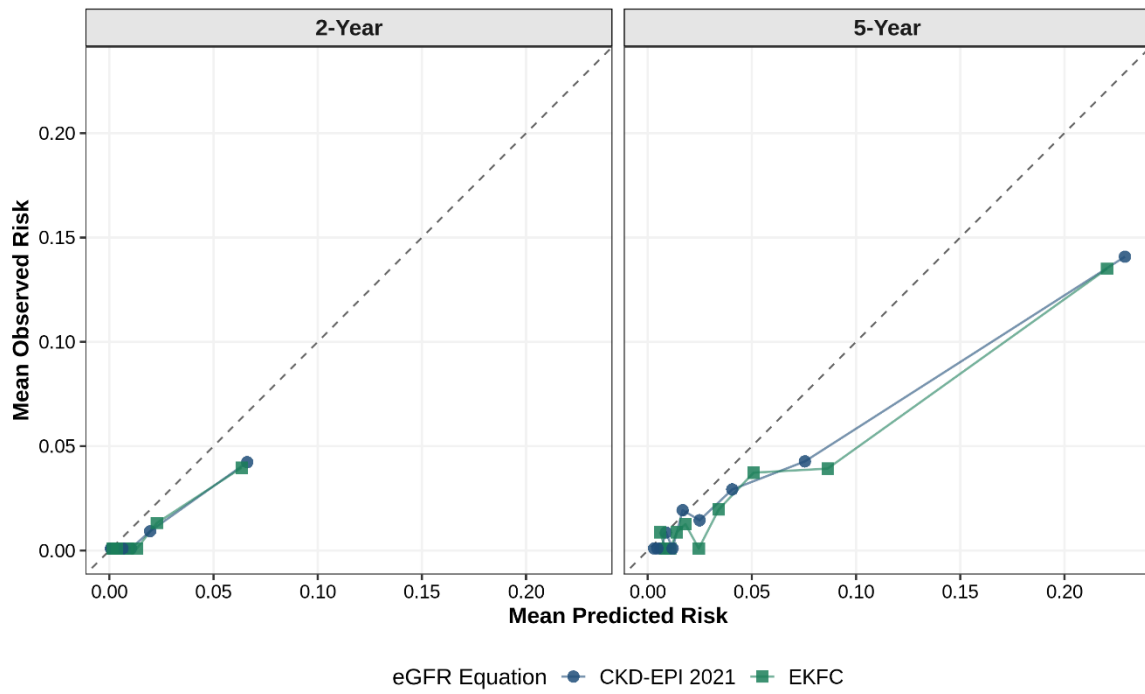
Calibration — Calib CK21 vs Calib EKFC (Age: 4)



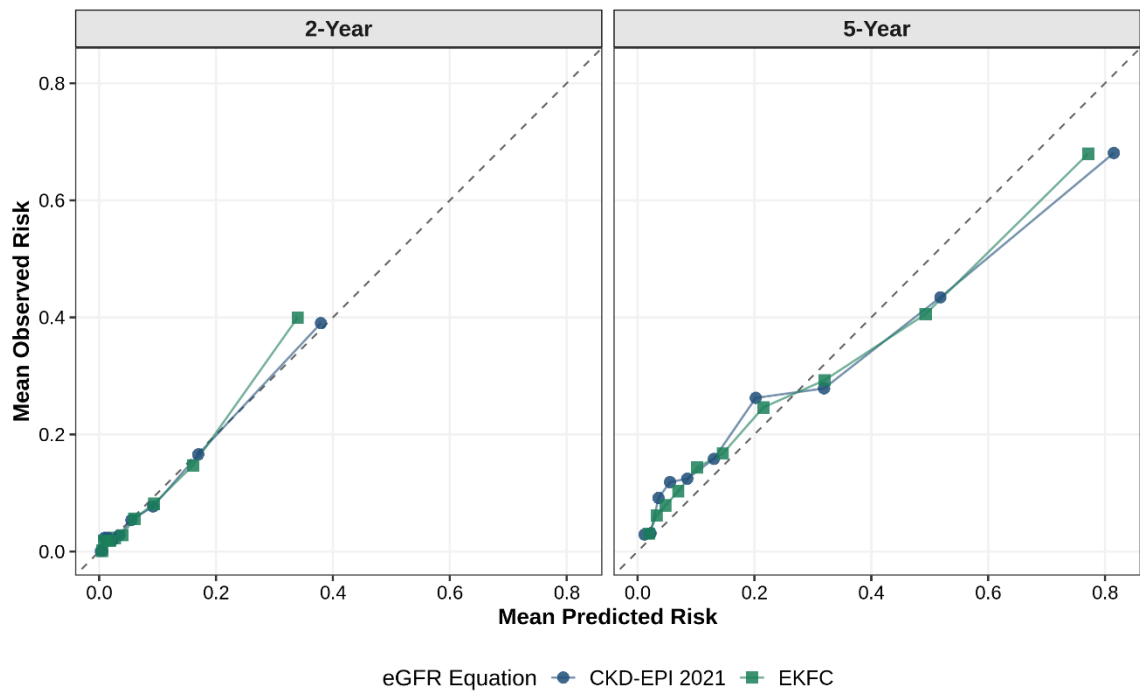
Calibration — Calib CK21 vs Calib EKFC (ACR: 1)



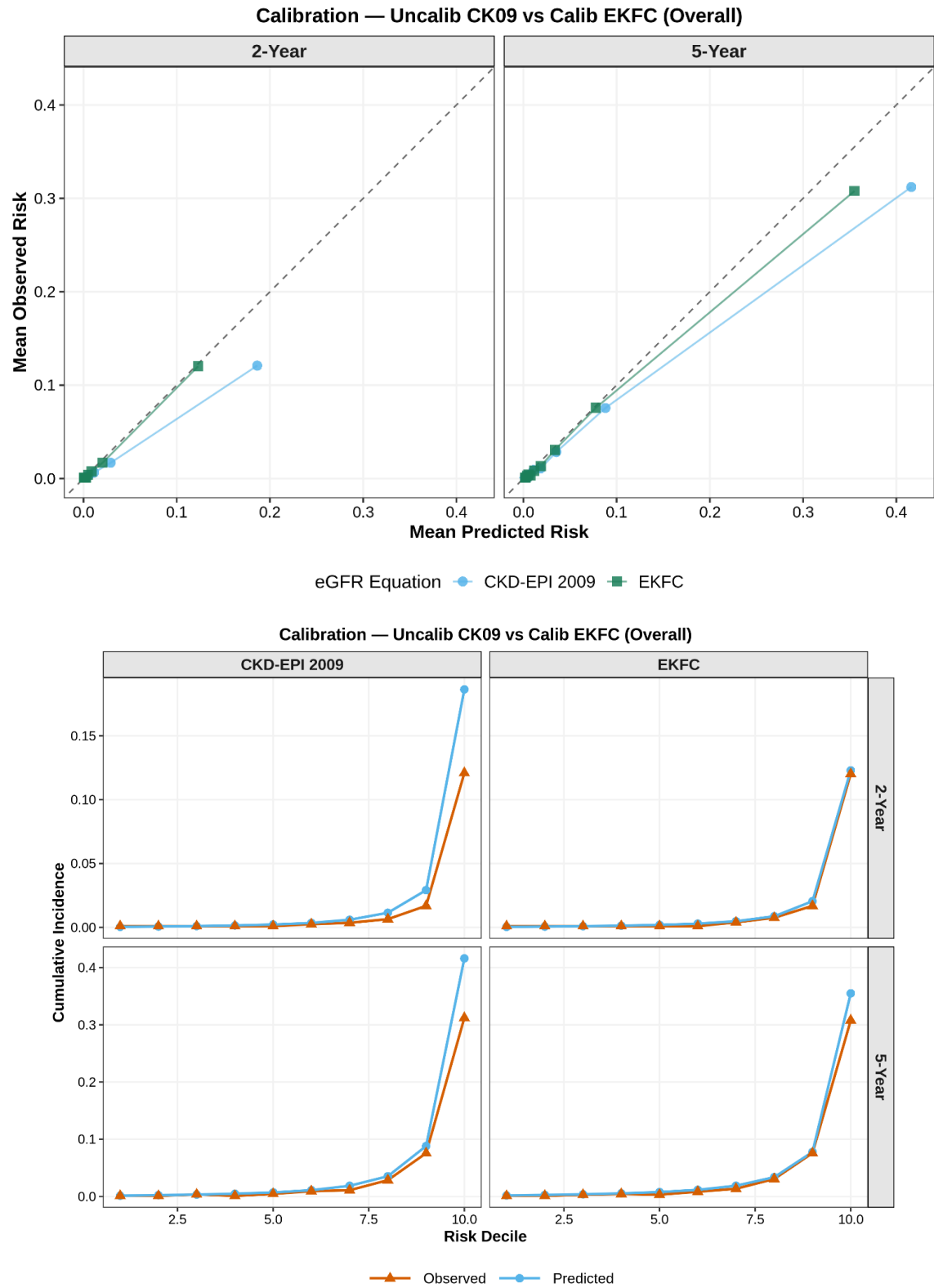
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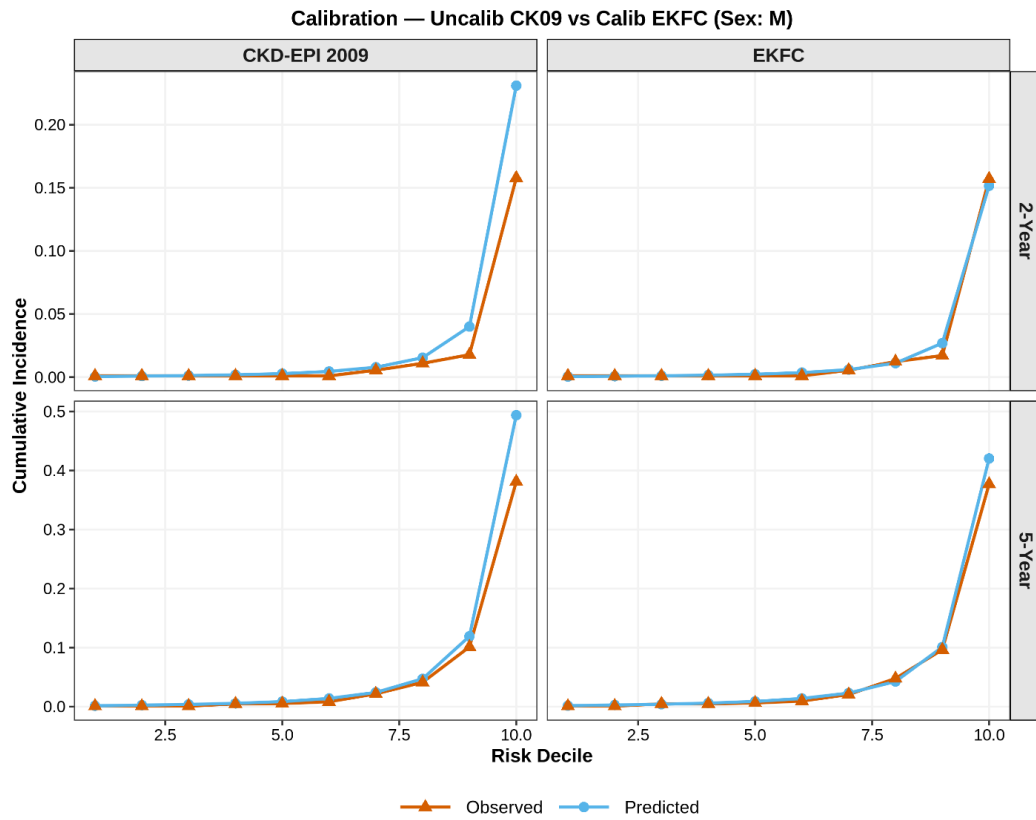
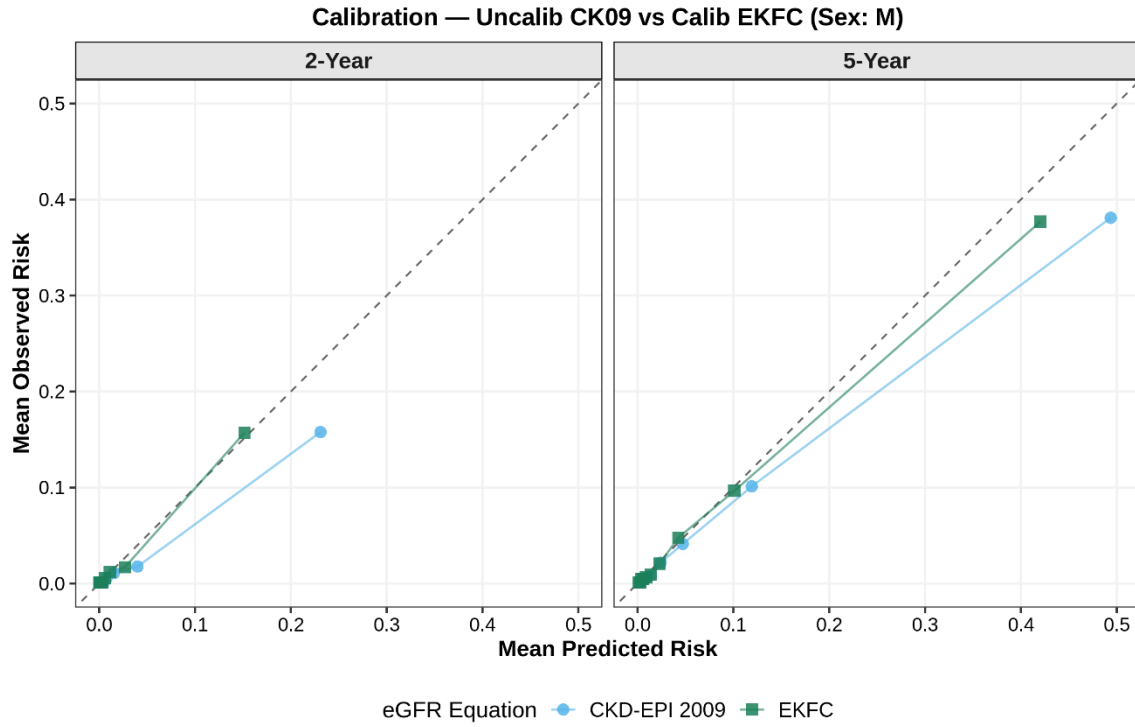


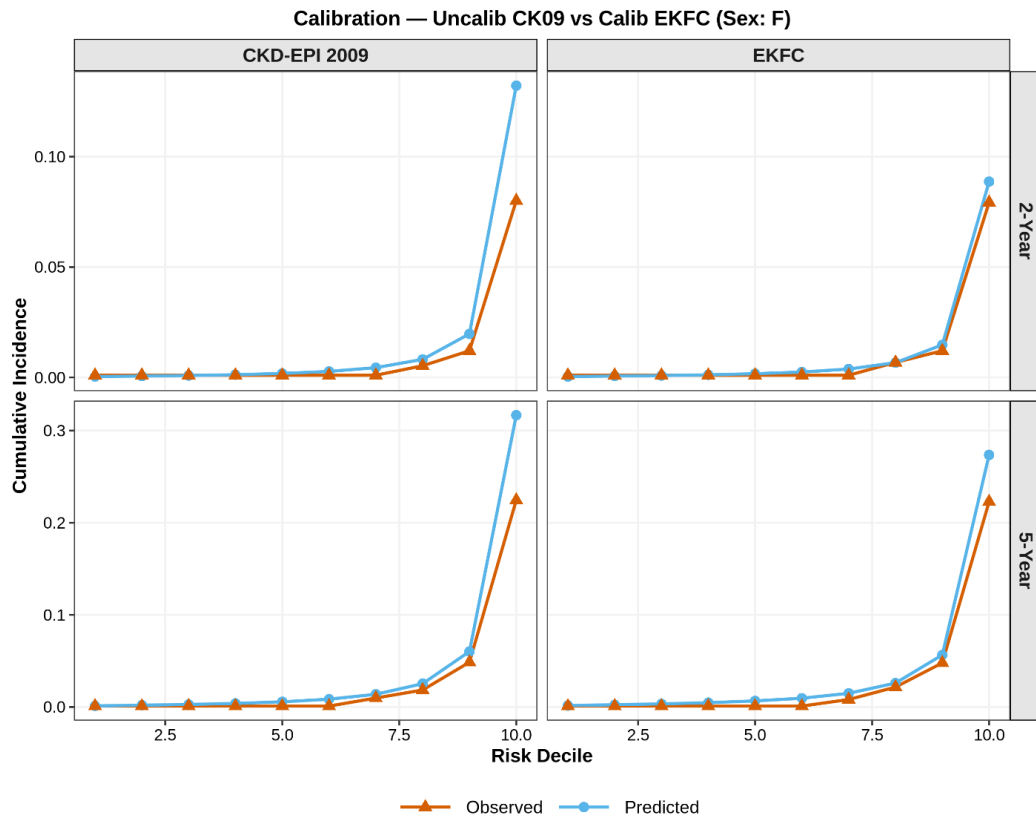
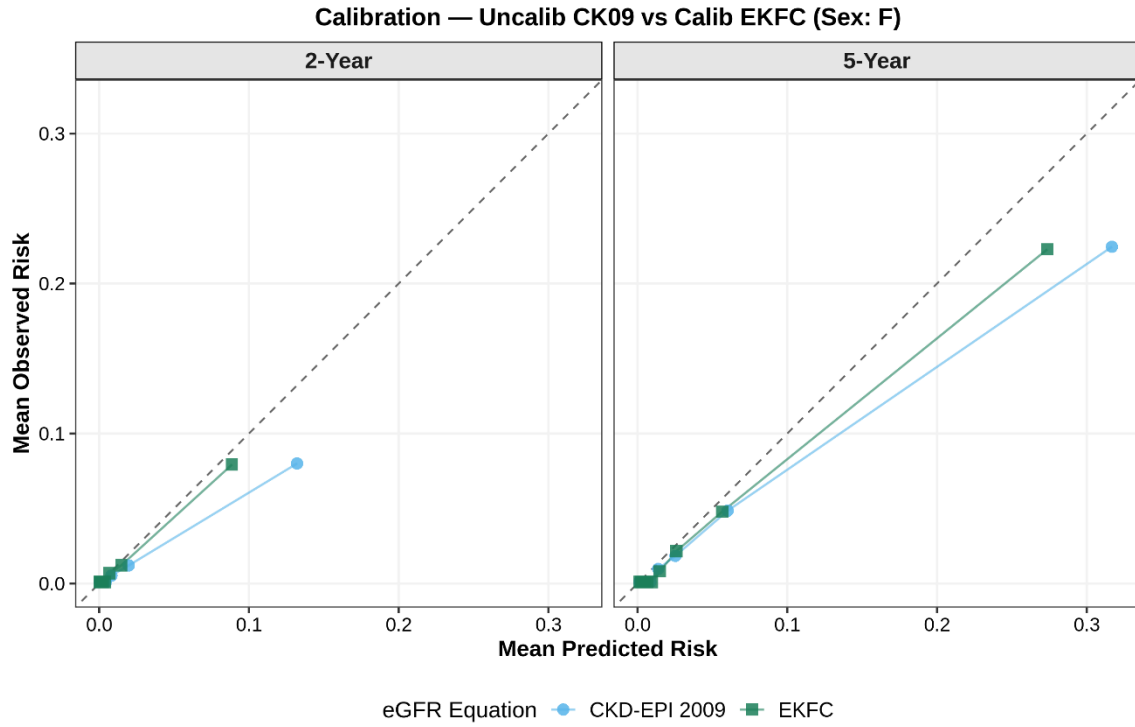
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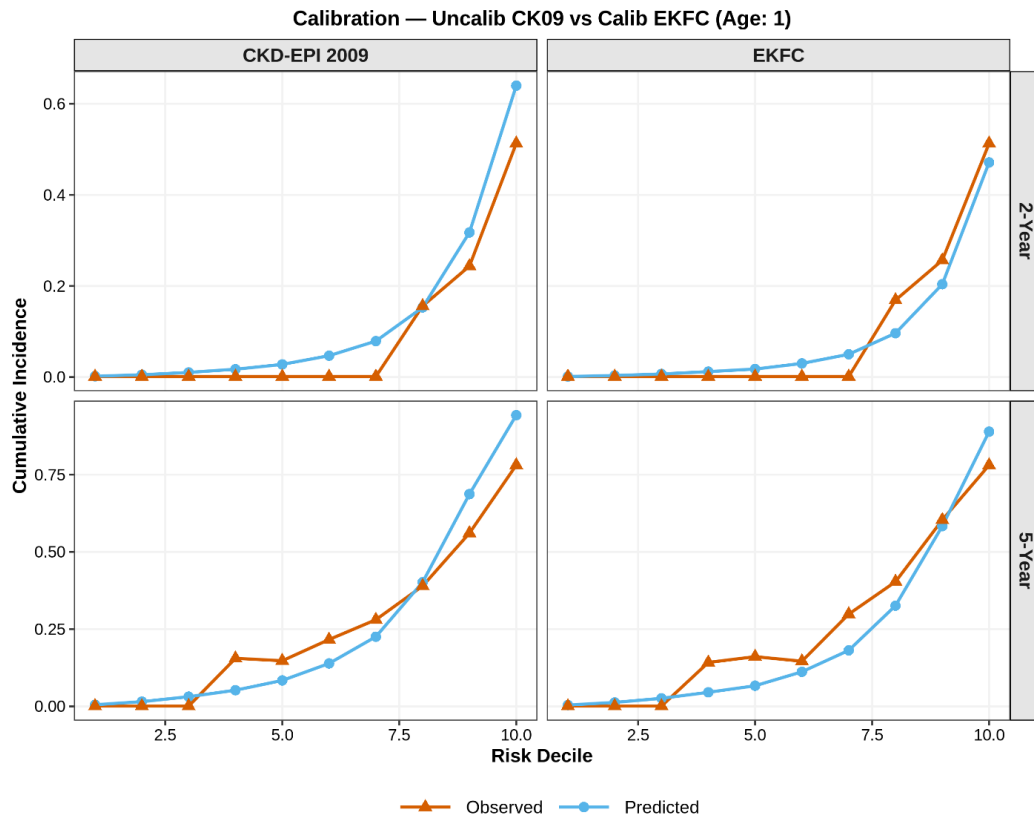
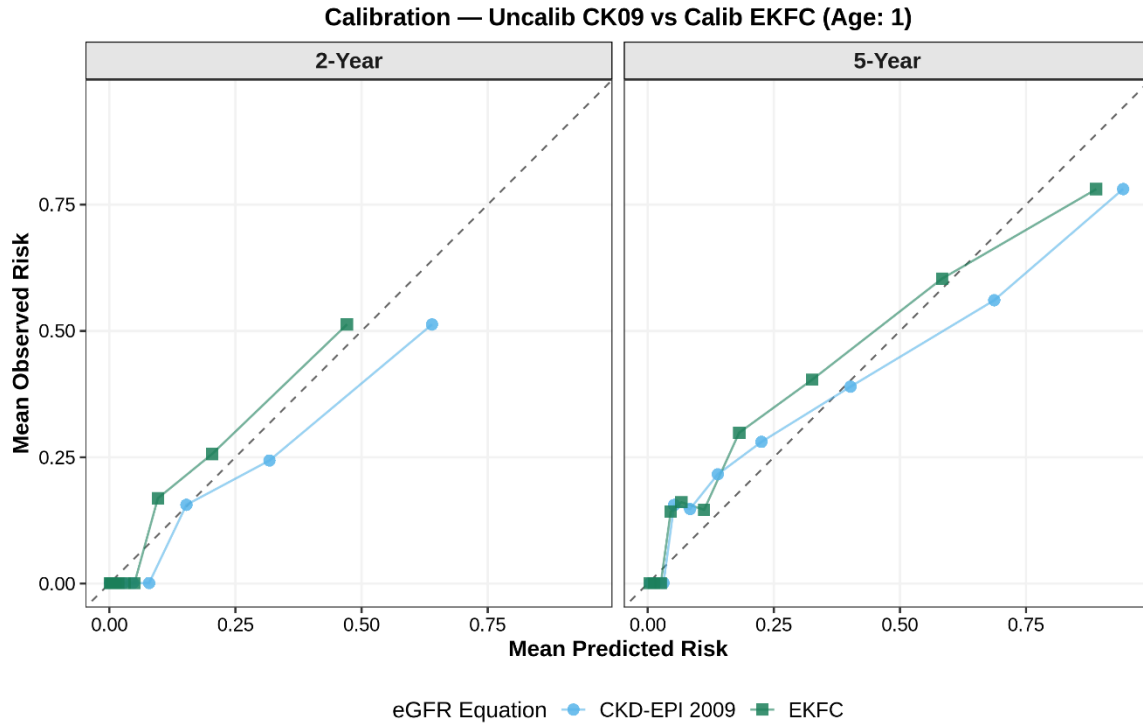


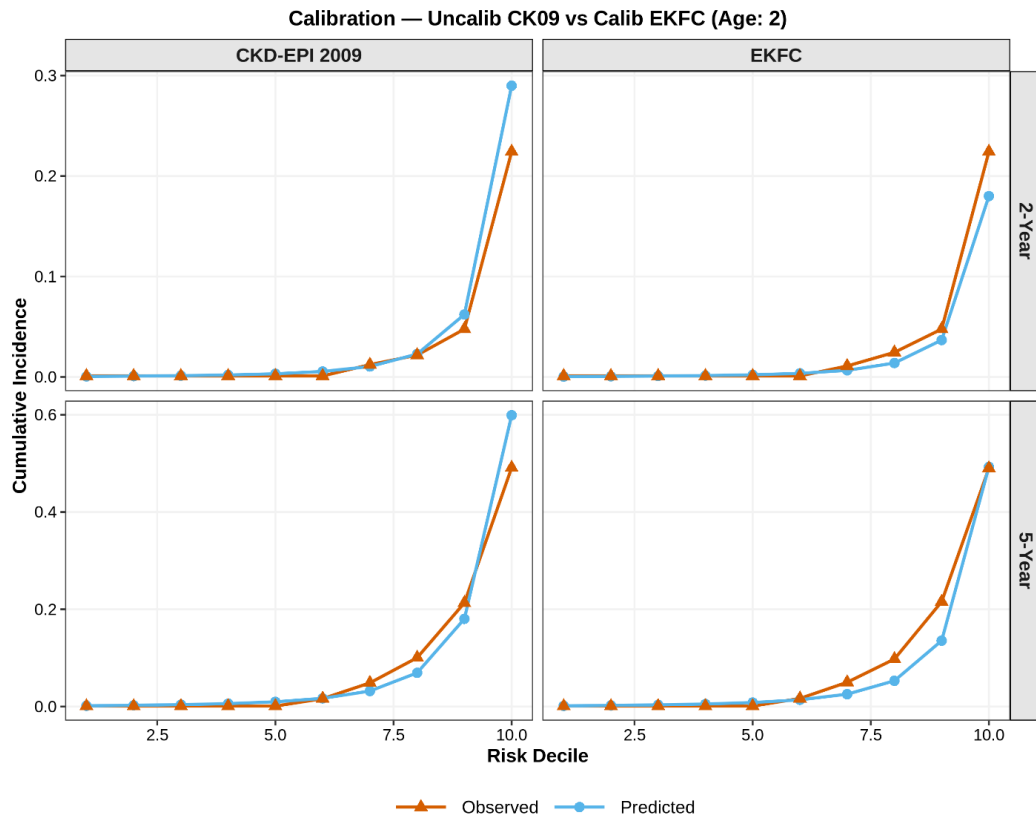
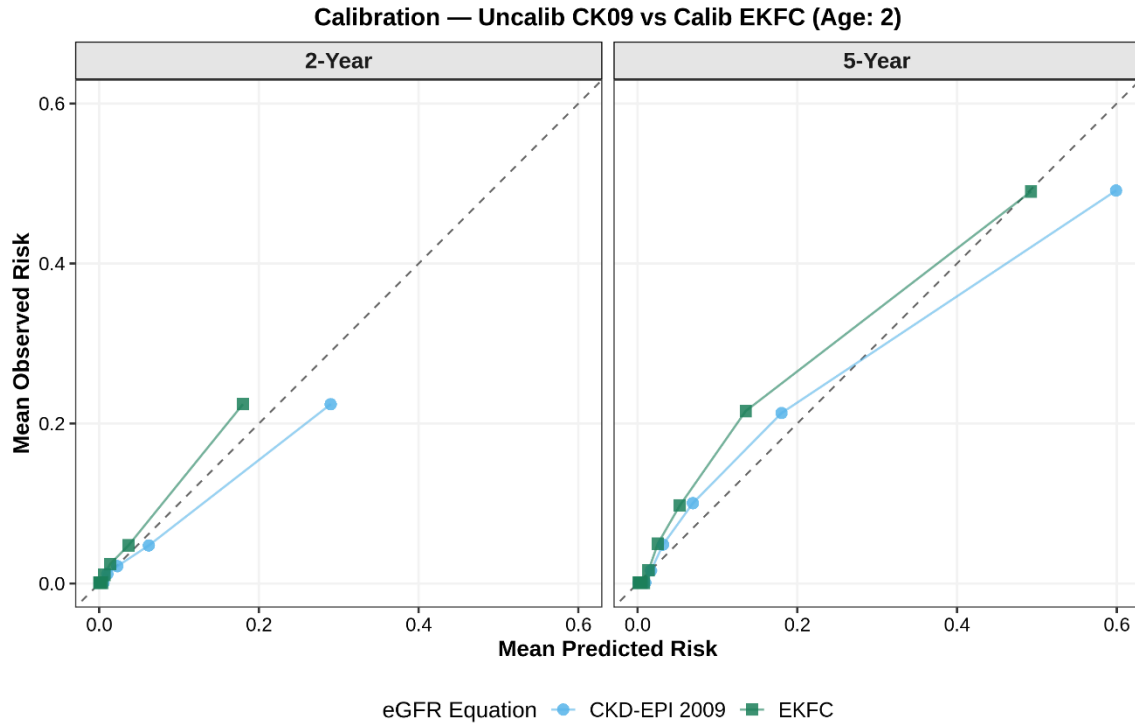
Appendix M1. Calibration line plots of observed versus predicted risk by deciles comparing uncalibrated CK09 to calibrated EKFC input to KRT at the 2- and 5-year horizons.

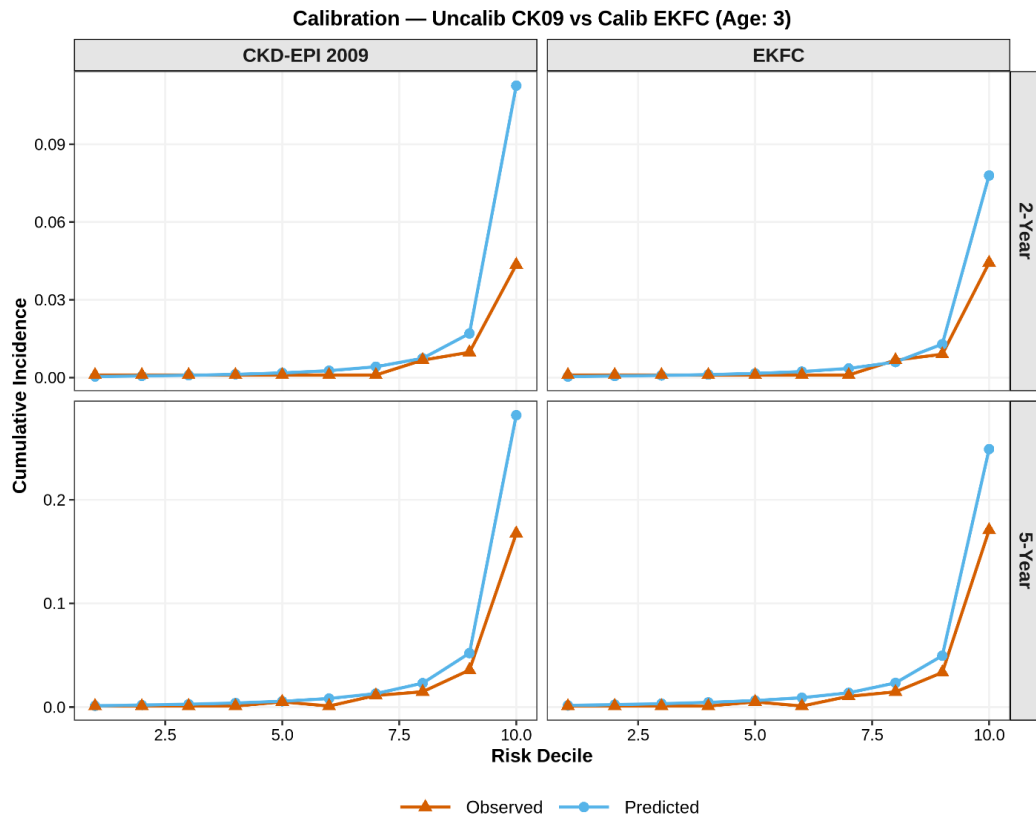
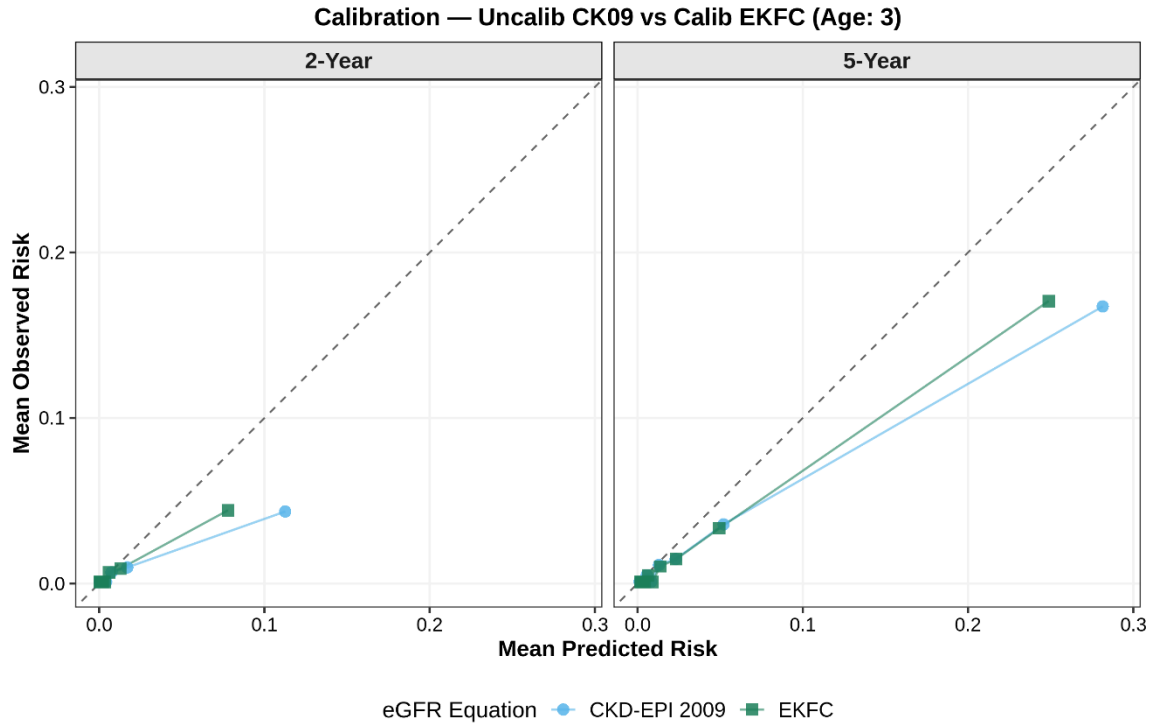


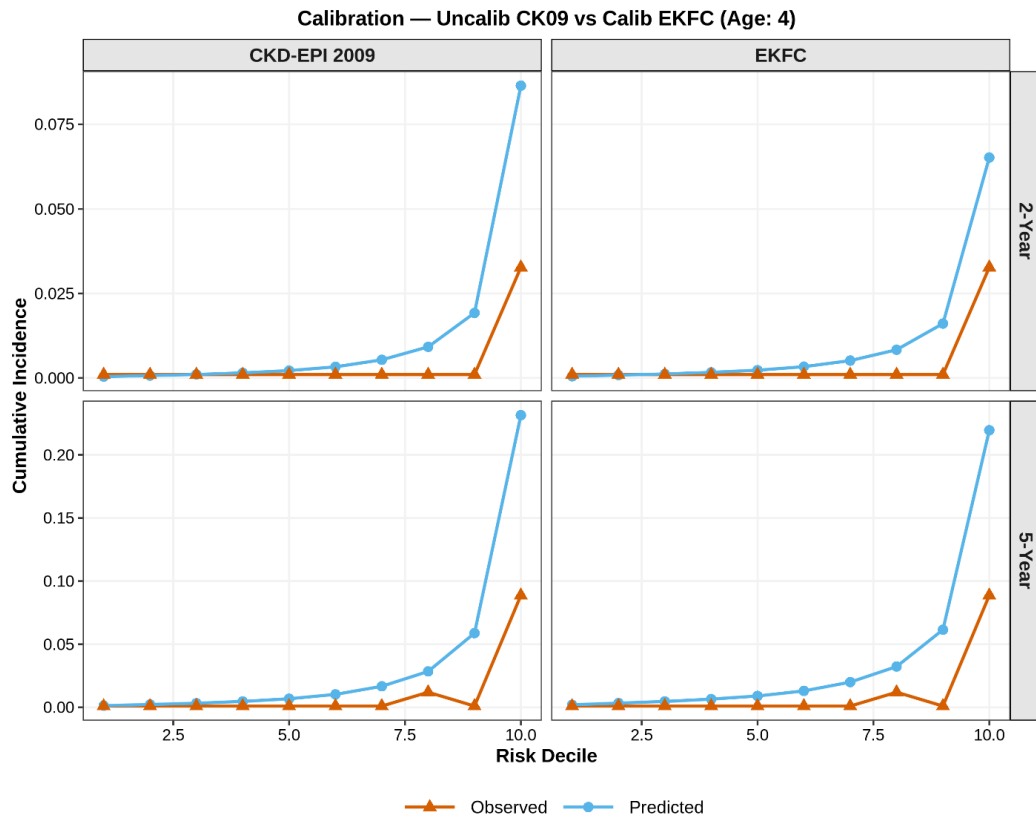
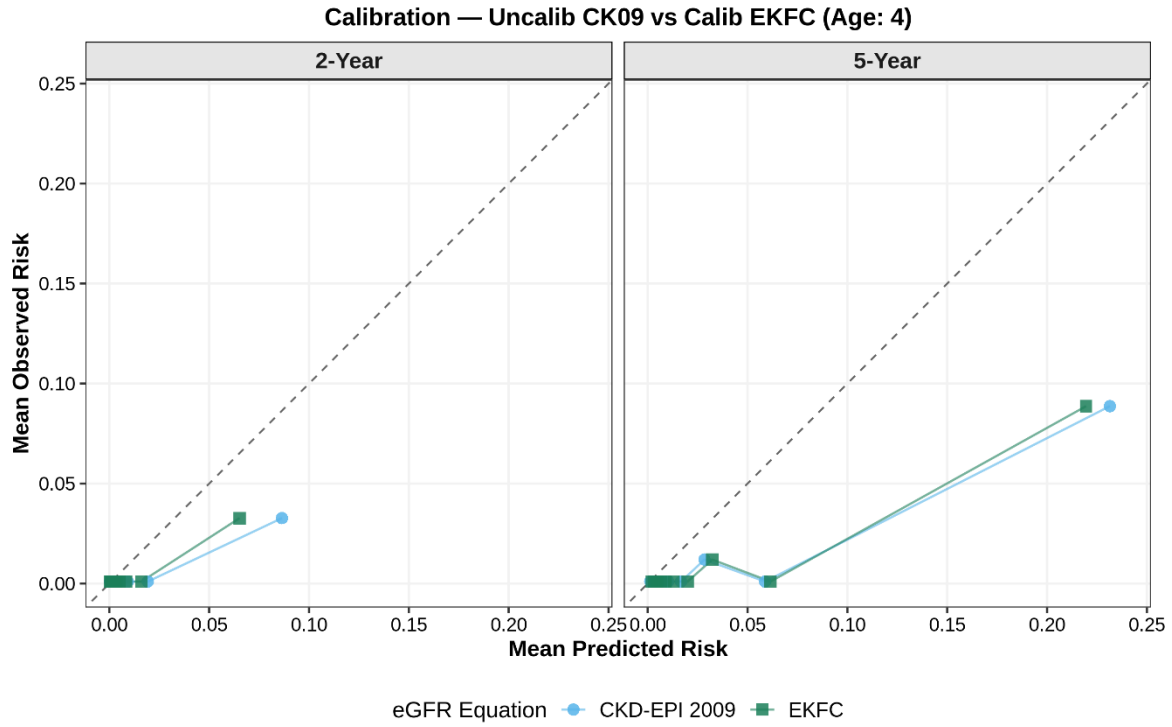


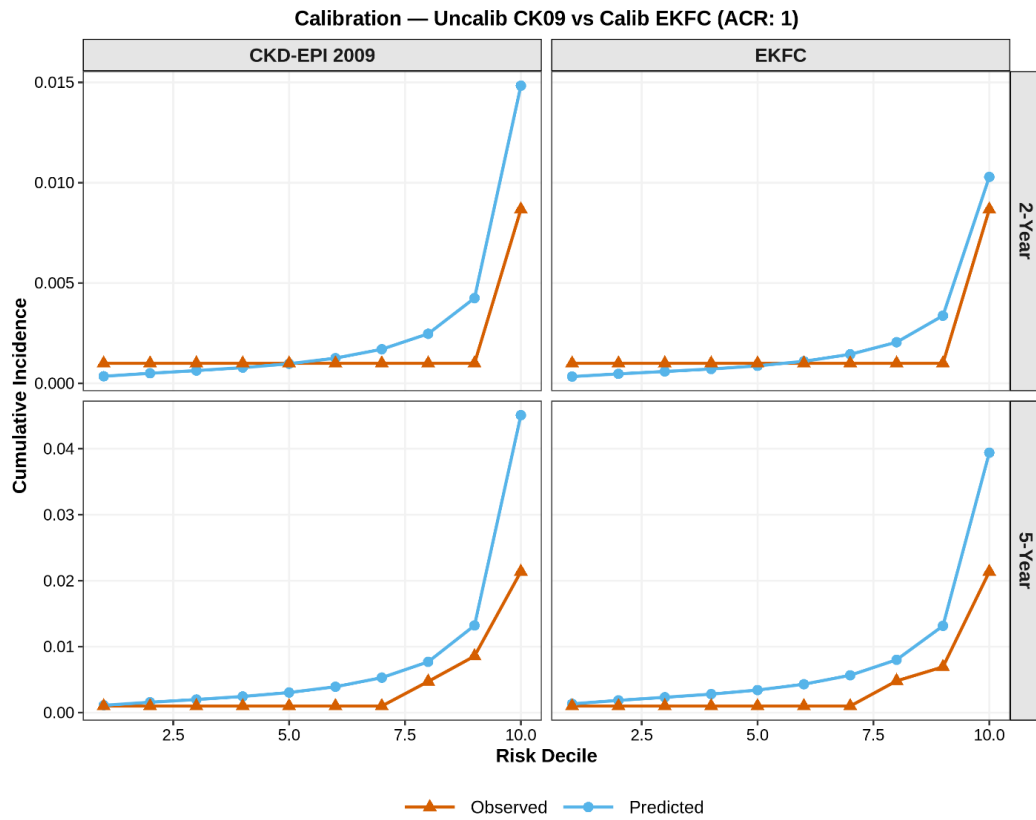
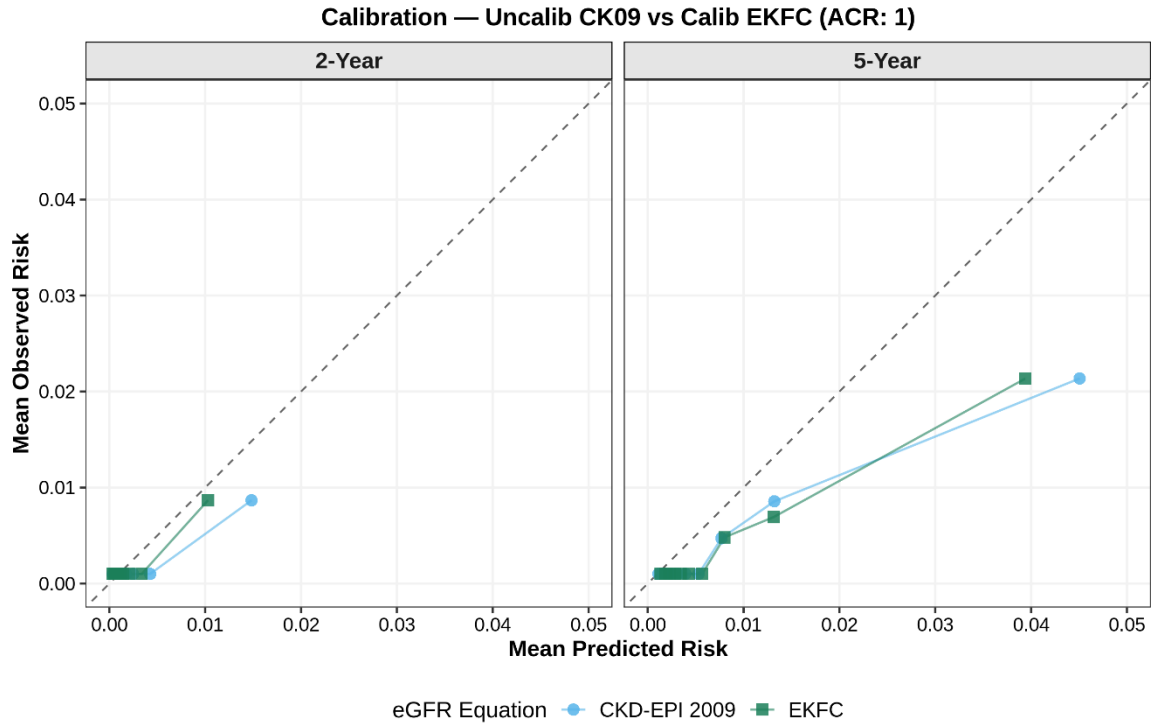


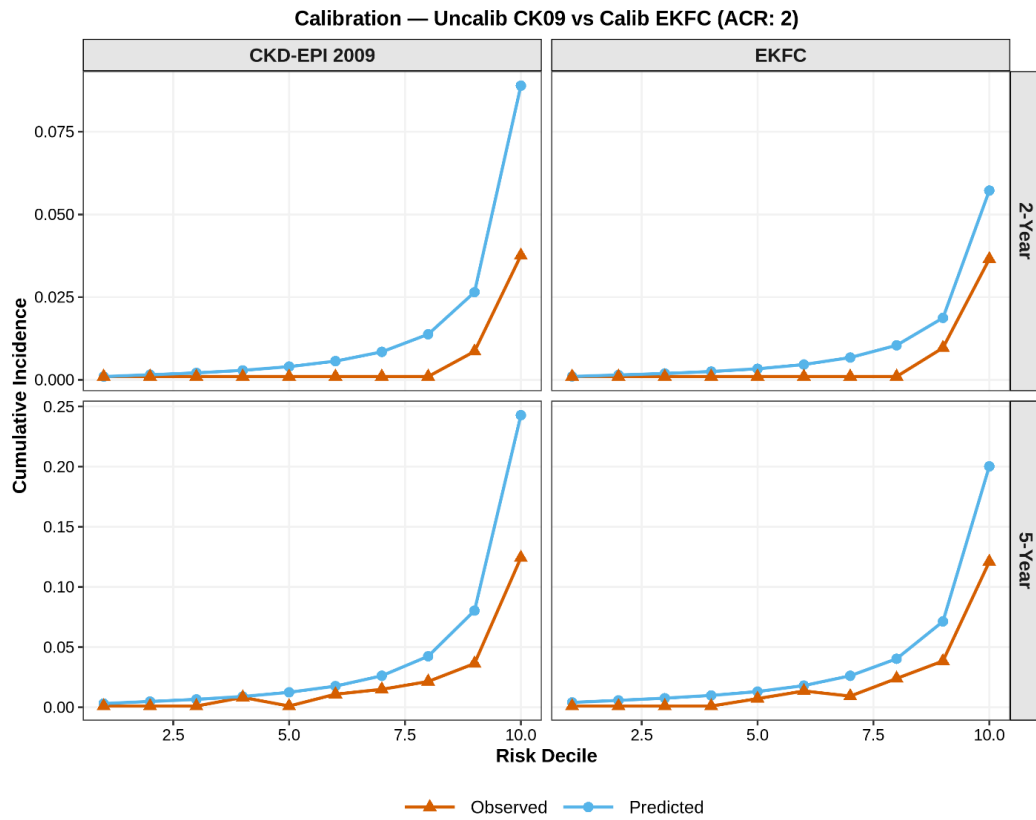
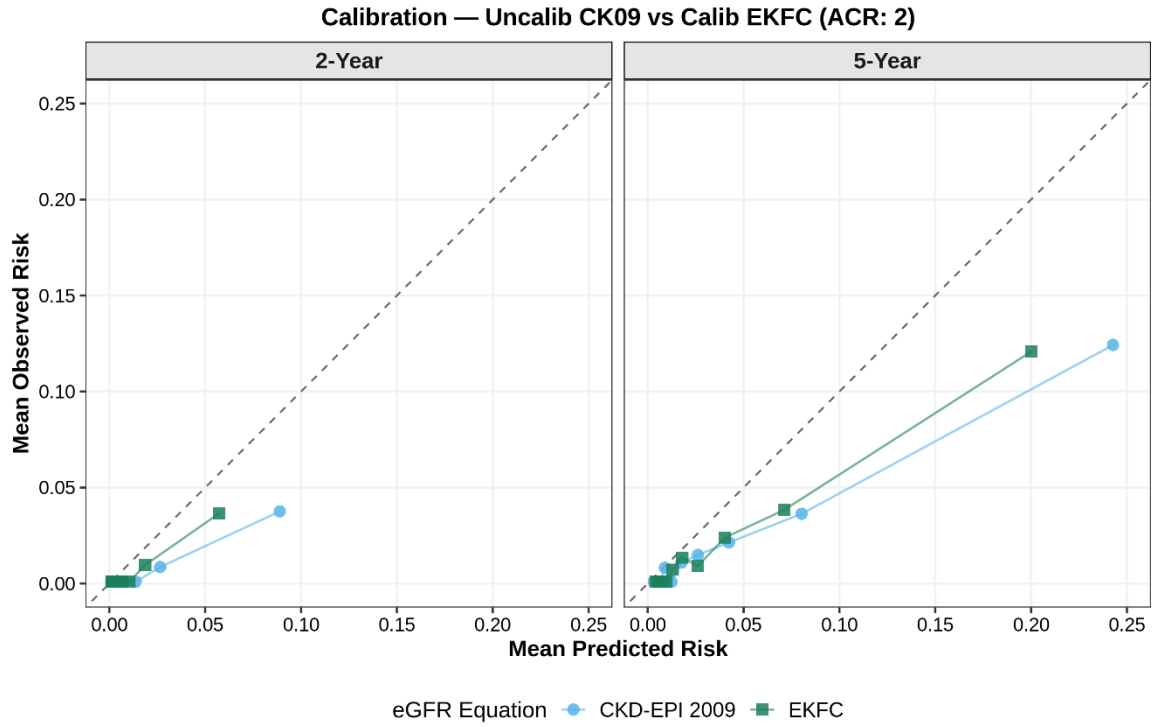


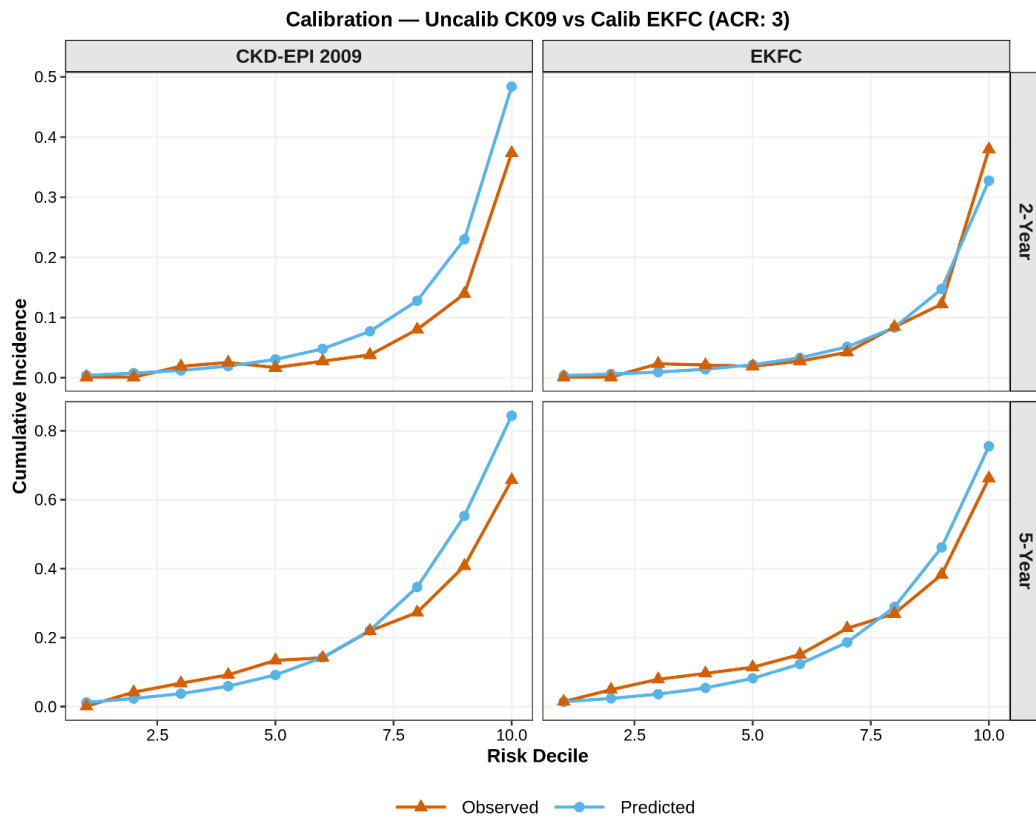
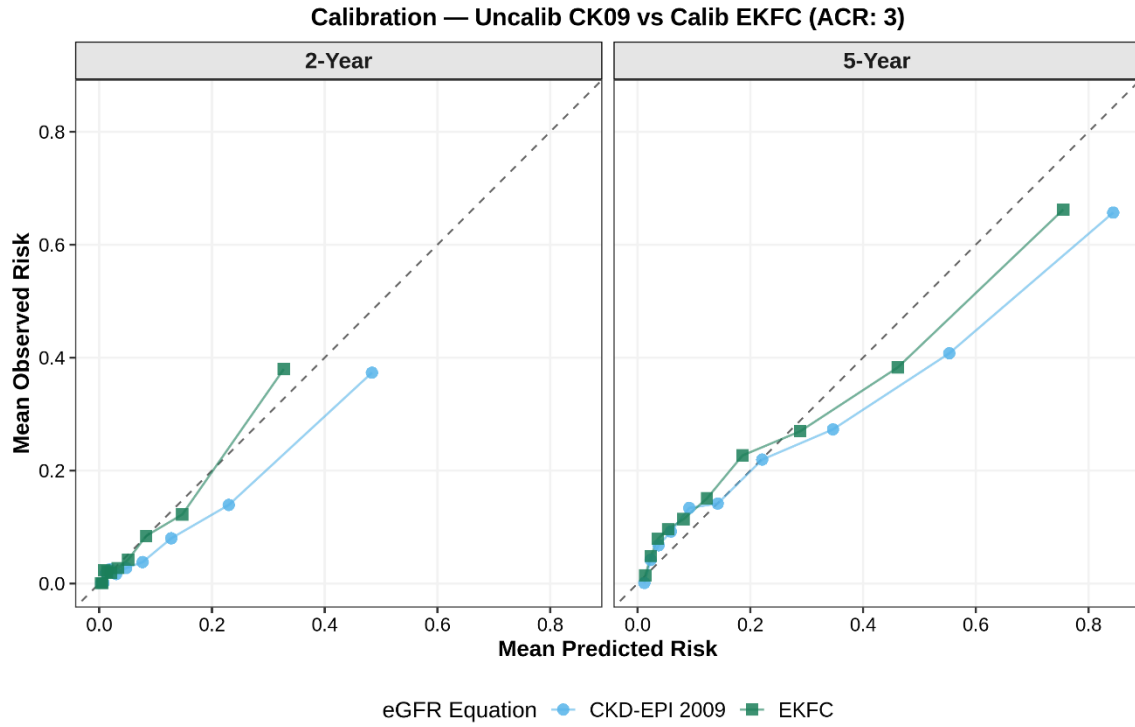




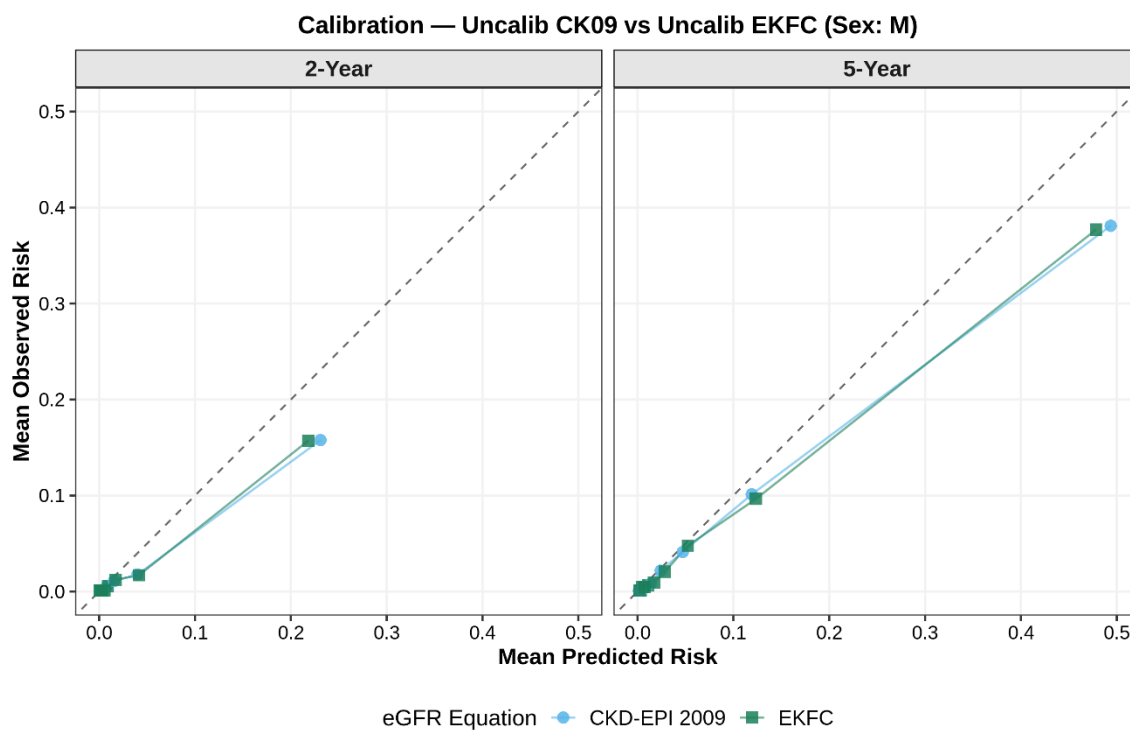
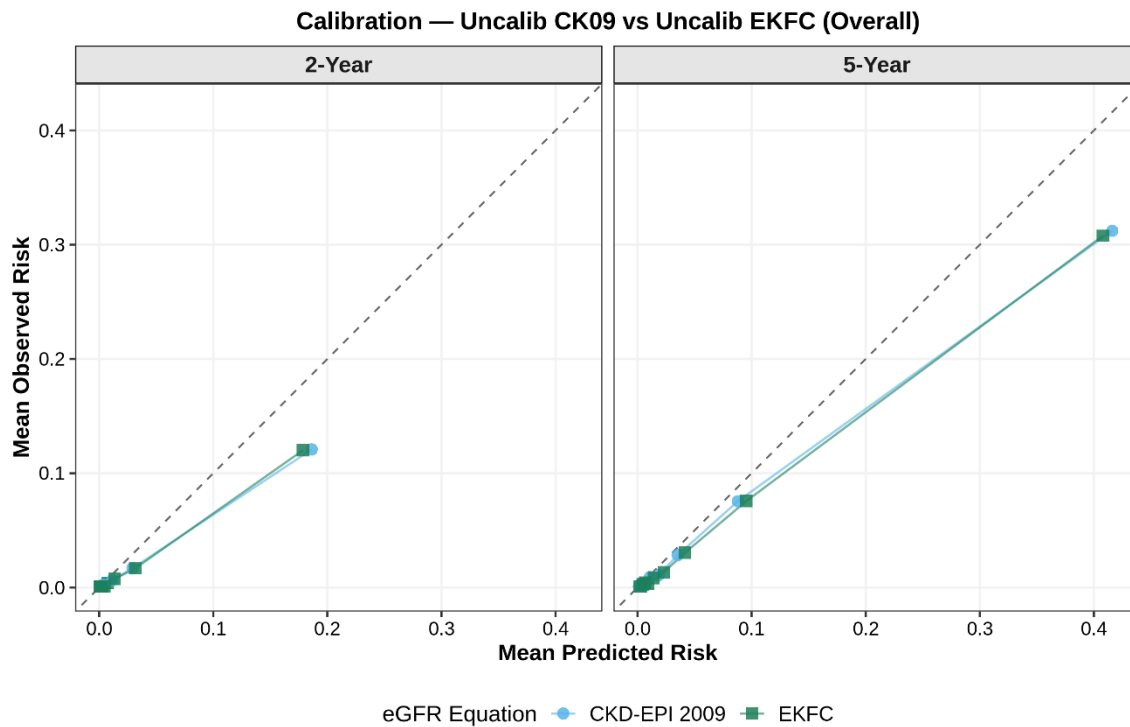




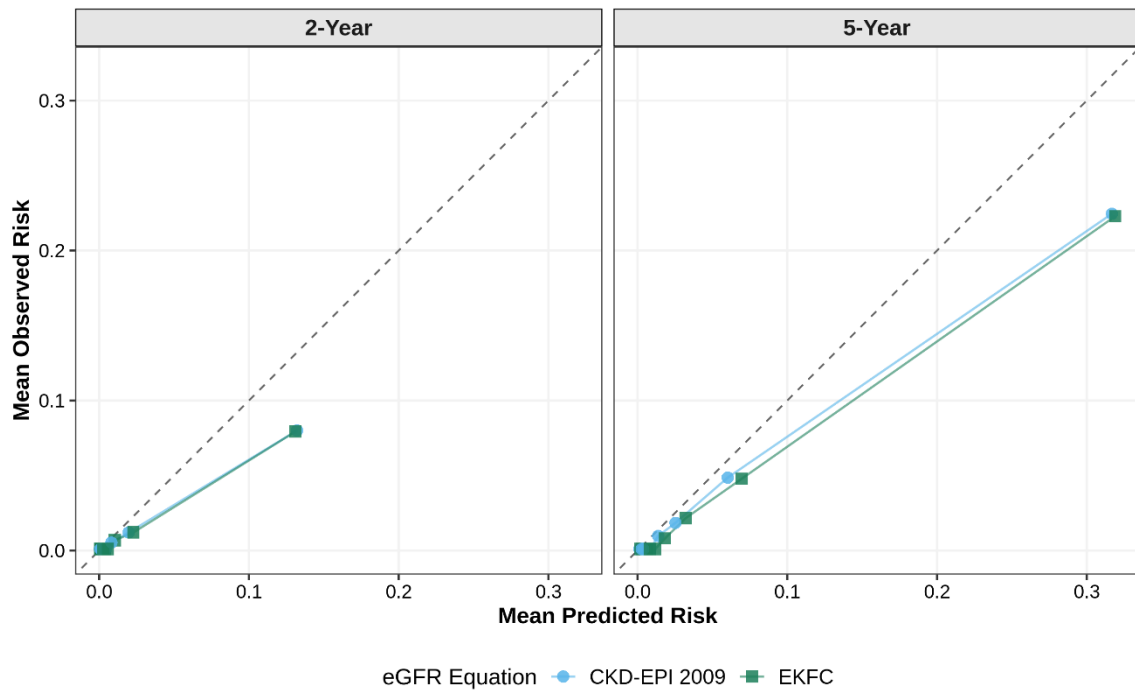




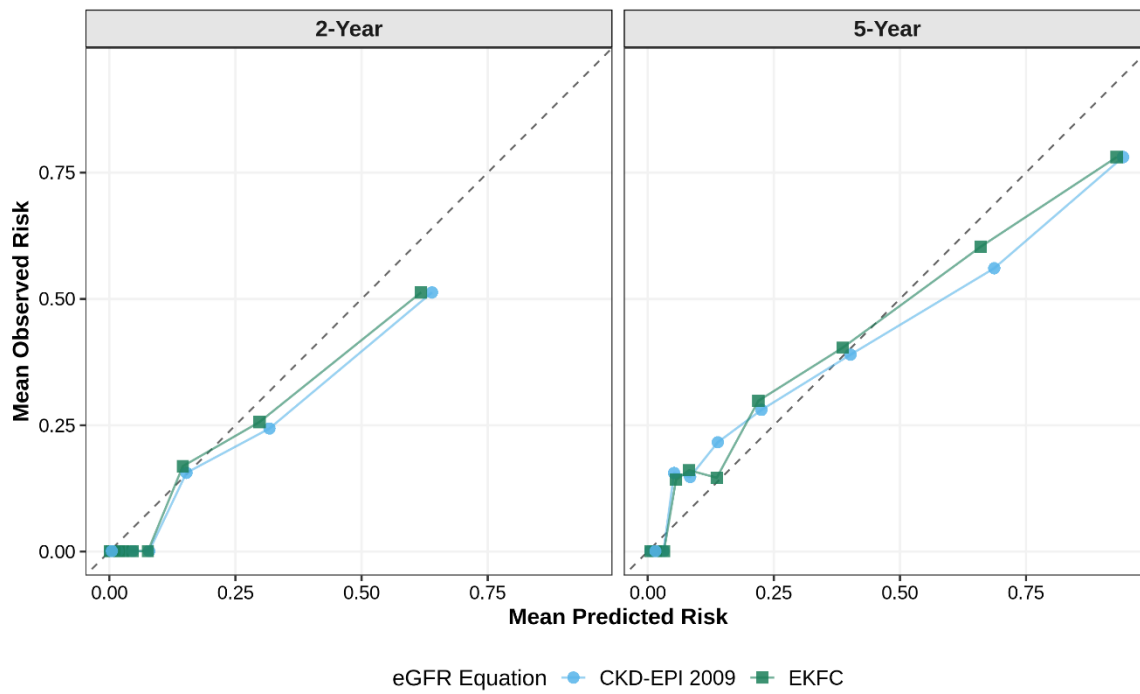
Appendix M2. Calibration line plots of observed versus predicted risk by deciles comparing uncalibrated CK09 to uncalibrated EKFC input to KRT at the 2- and 5-year horizons.



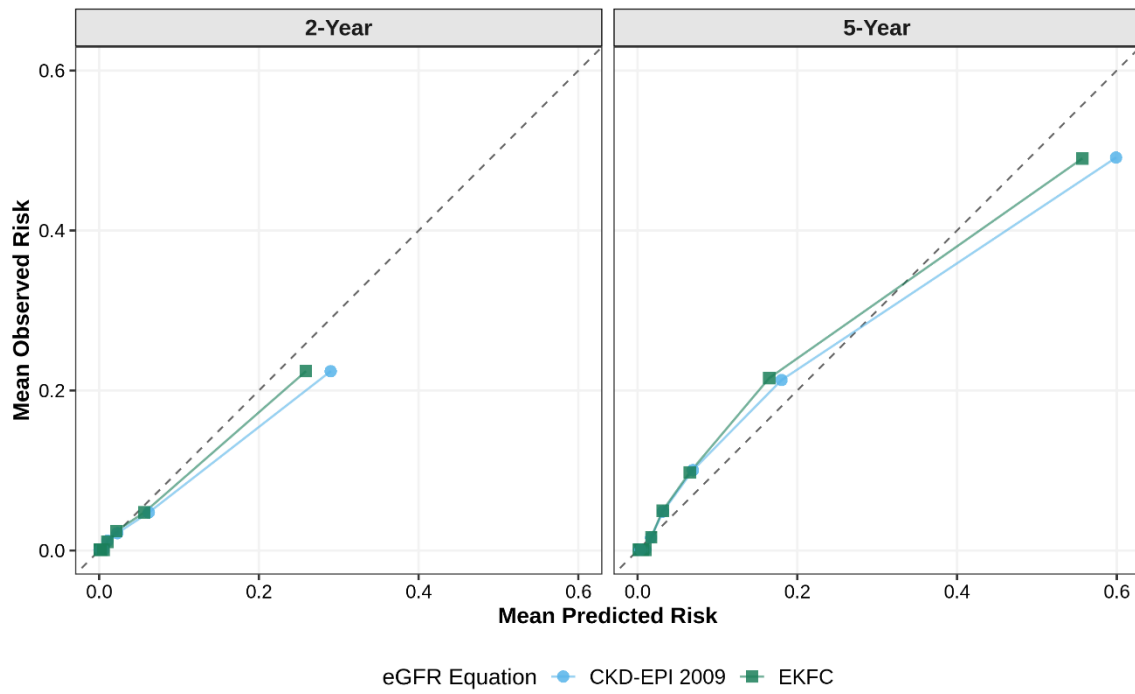
Calibration — Uncalib CK09 vs Uncalib EKFC (Sex: F)



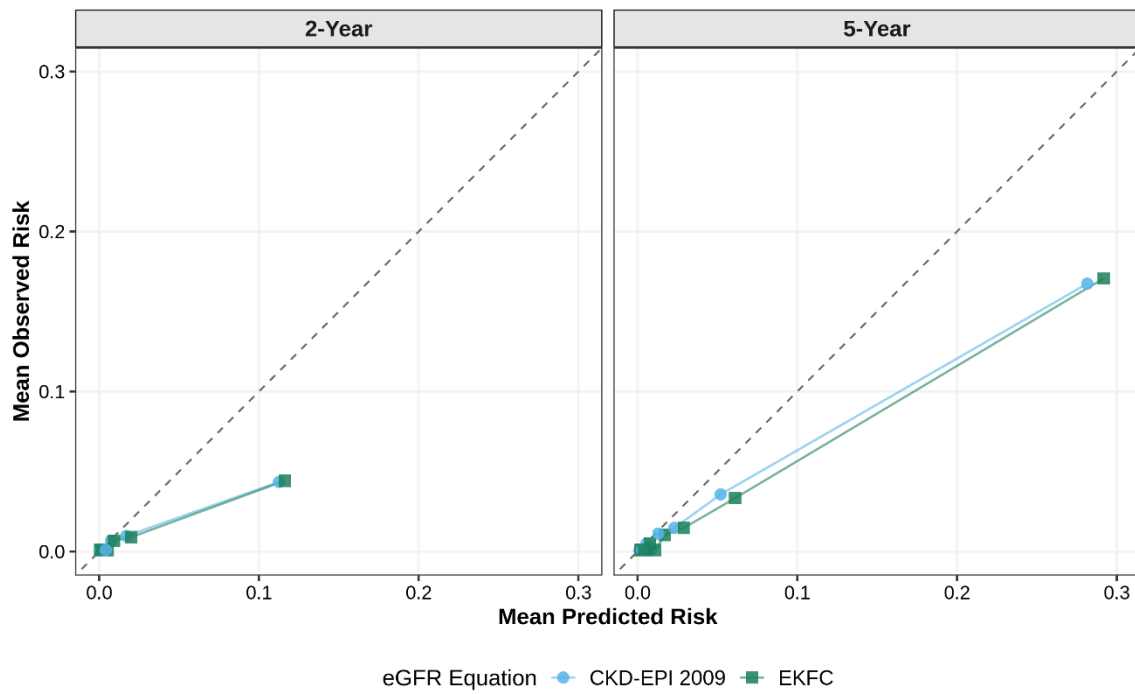
Calibration — Uncalib CK09 vs Uncalib EKFC (Age: 1)



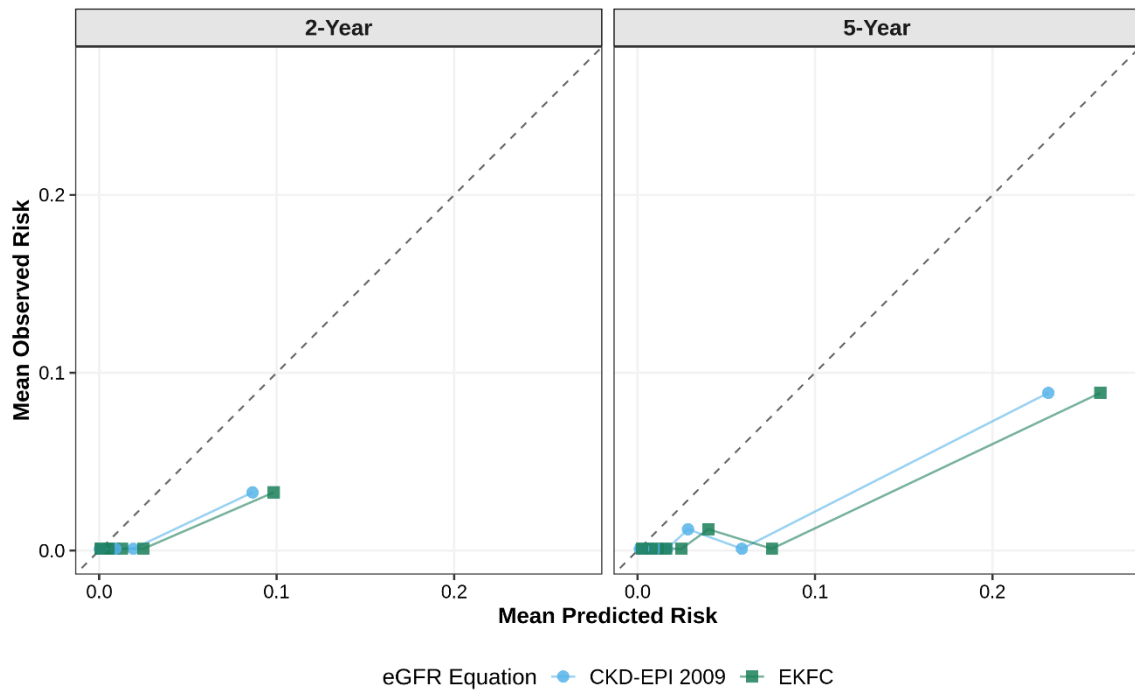
Calibration — Uncalib CK09 vs Uncalib EKFC (Age: 2)



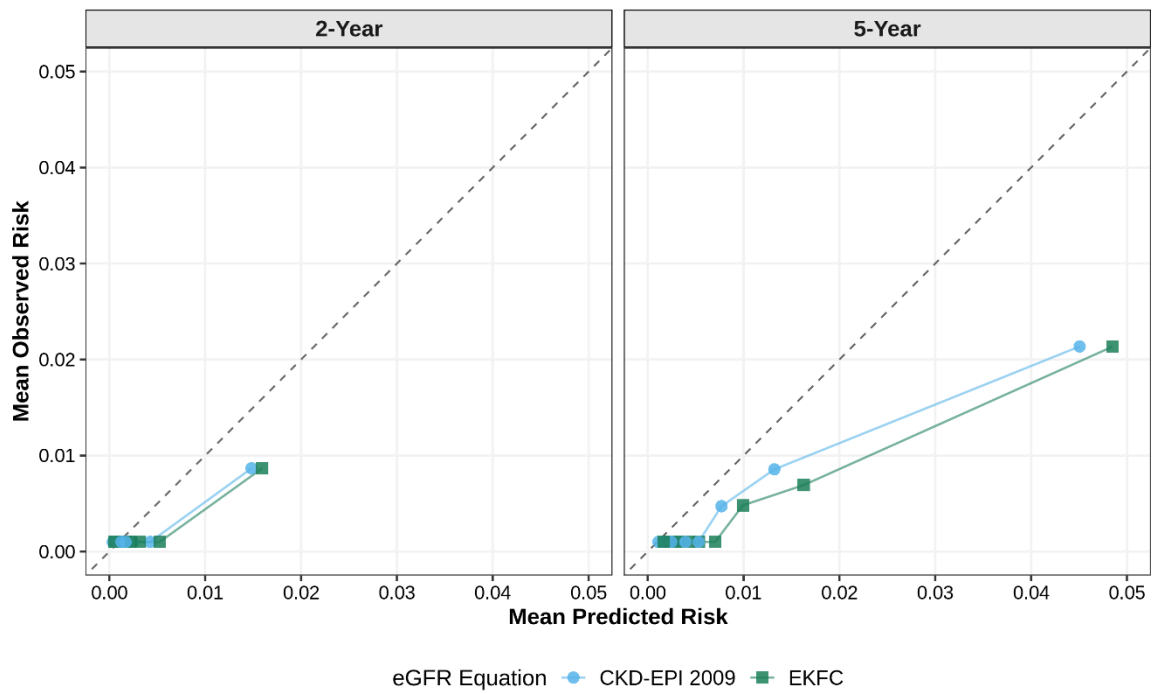
Calibration — Uncalib CK09 vs Uncalib EKFC (Age: 3)



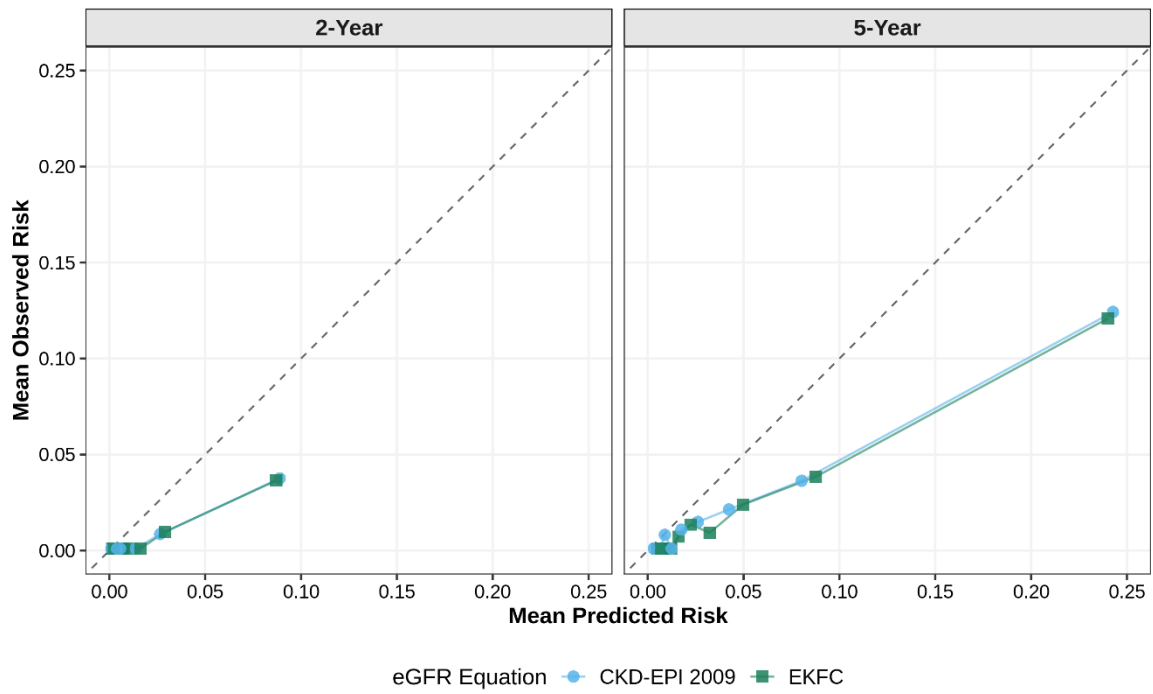
Calibration — Uncalib CK09 vs Uncalib EKFC (Age: 4)



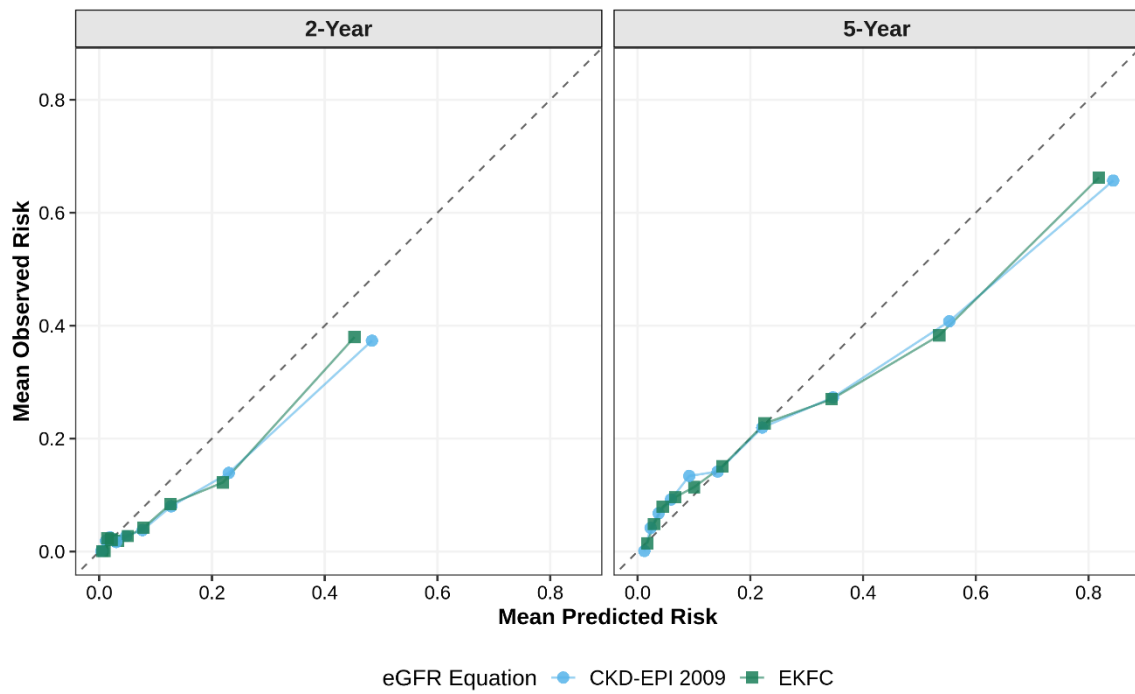
Calibration — Uncalib CK09 vs Uncalib EKFC (ACR: 1)



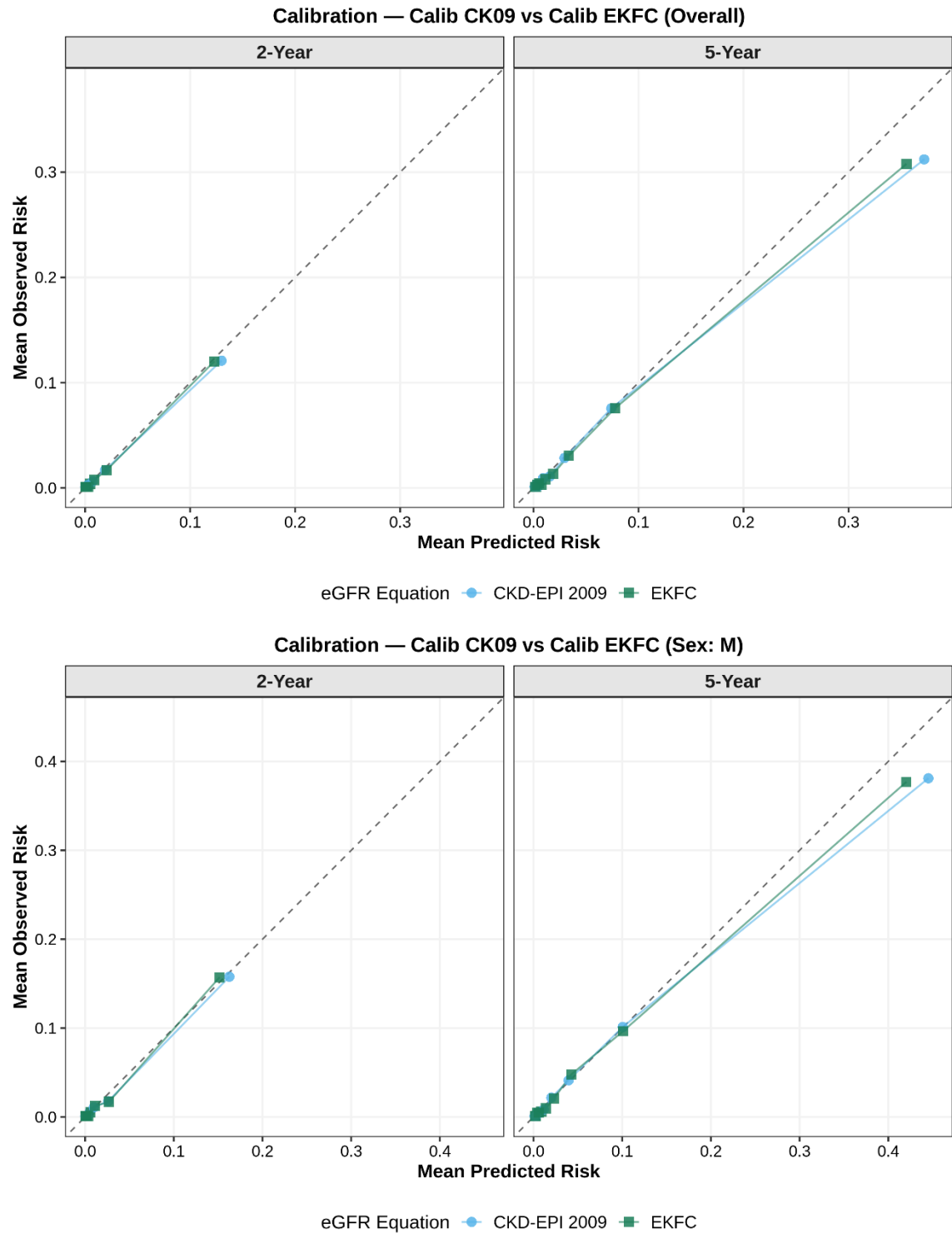
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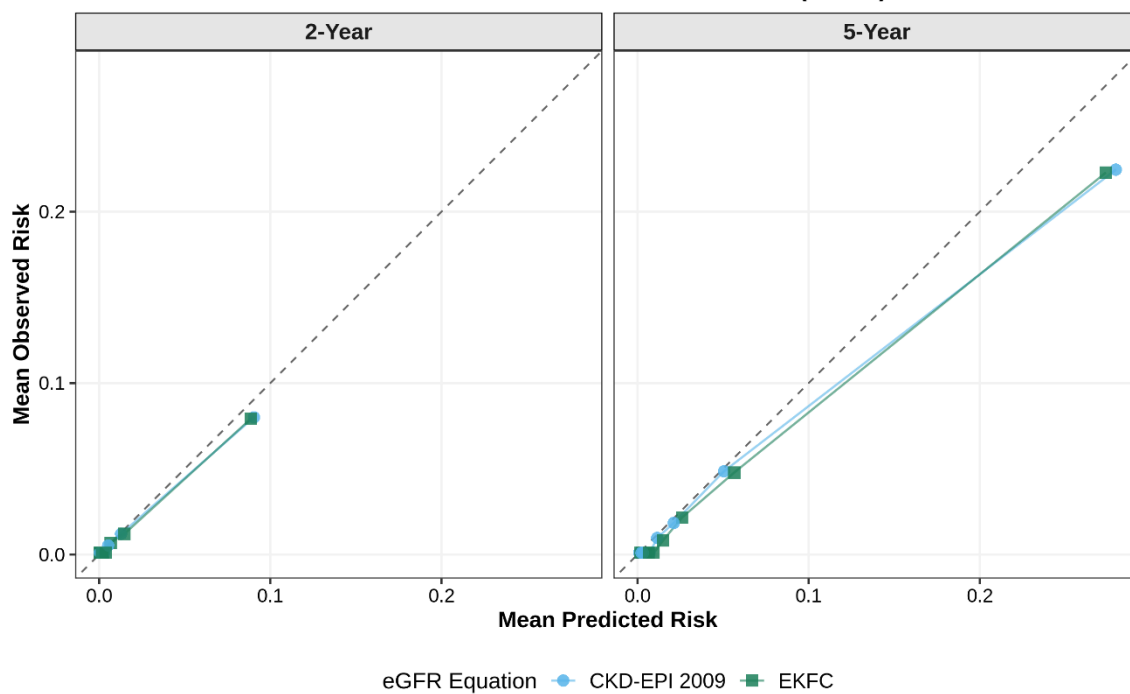
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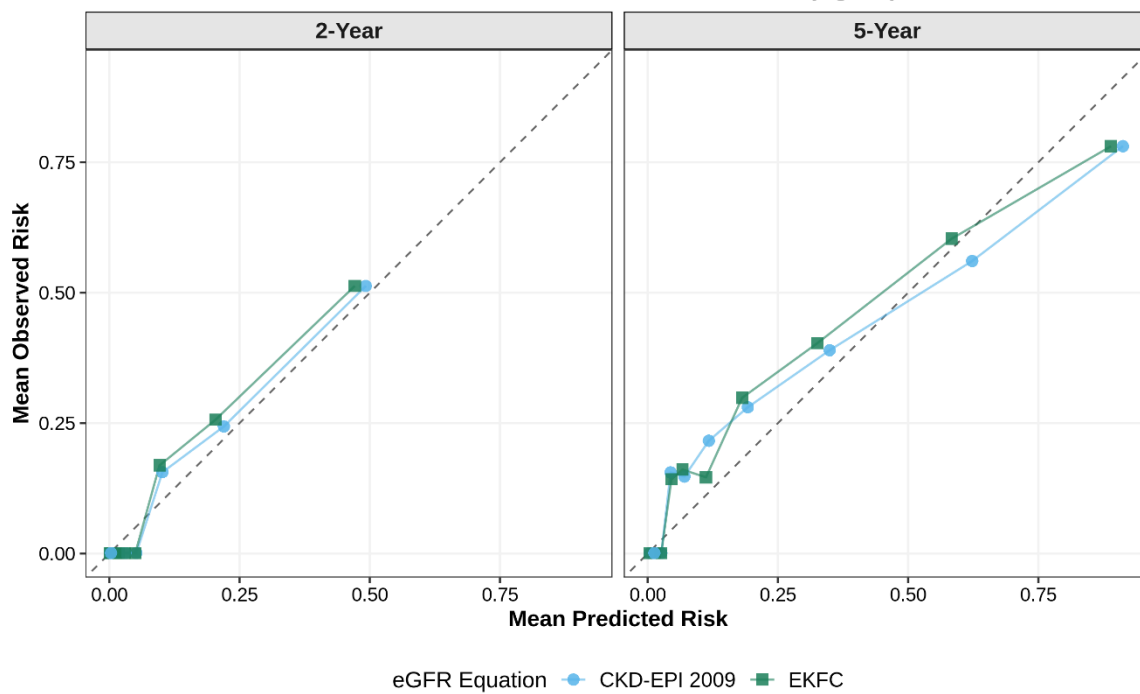
Appendix M3. Calibration line plots of observed versus predicted risk by deciles comparing calibrated CK09 to calibrated EKFC input to KRT at the 2- and 5-year horizons.



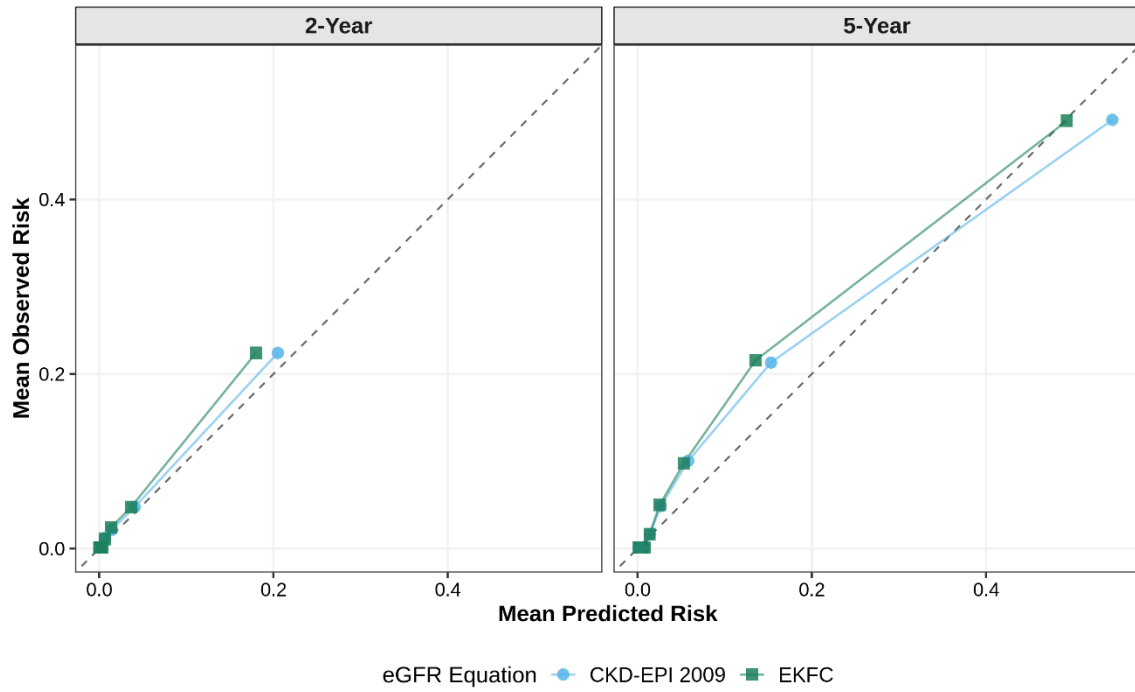
Calibration — Calib CK09 vs Calib EKFC (Sex: F)



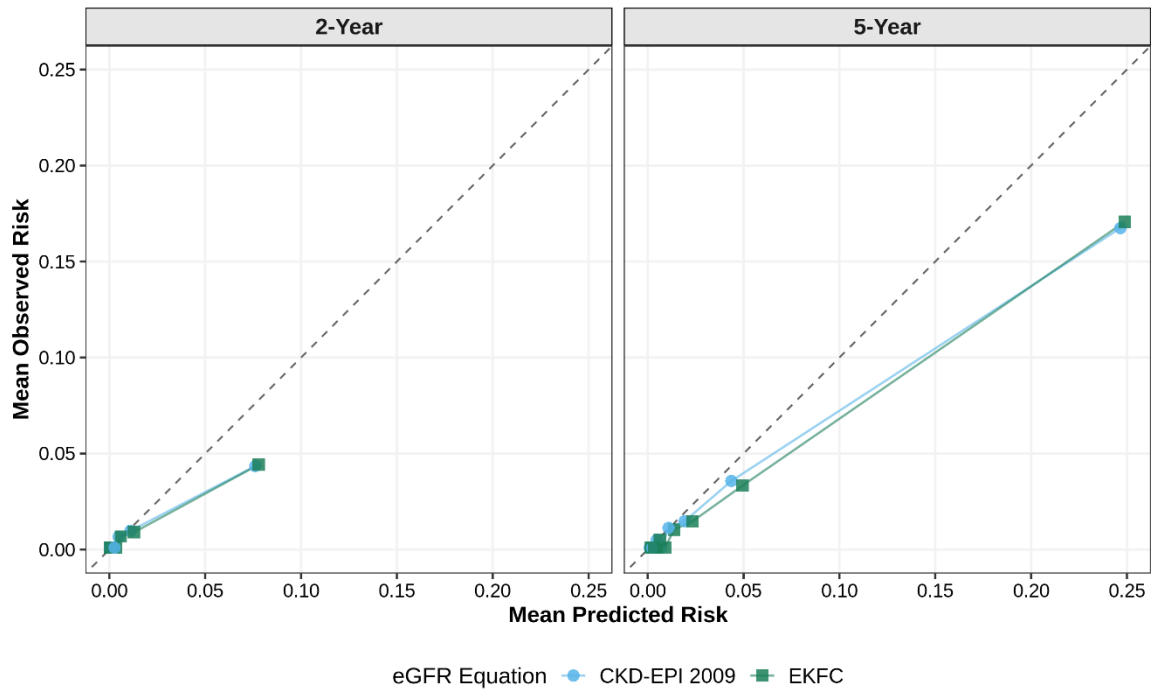
Calibration — Calib CK09 vs Calib EKFC (Age: 1)



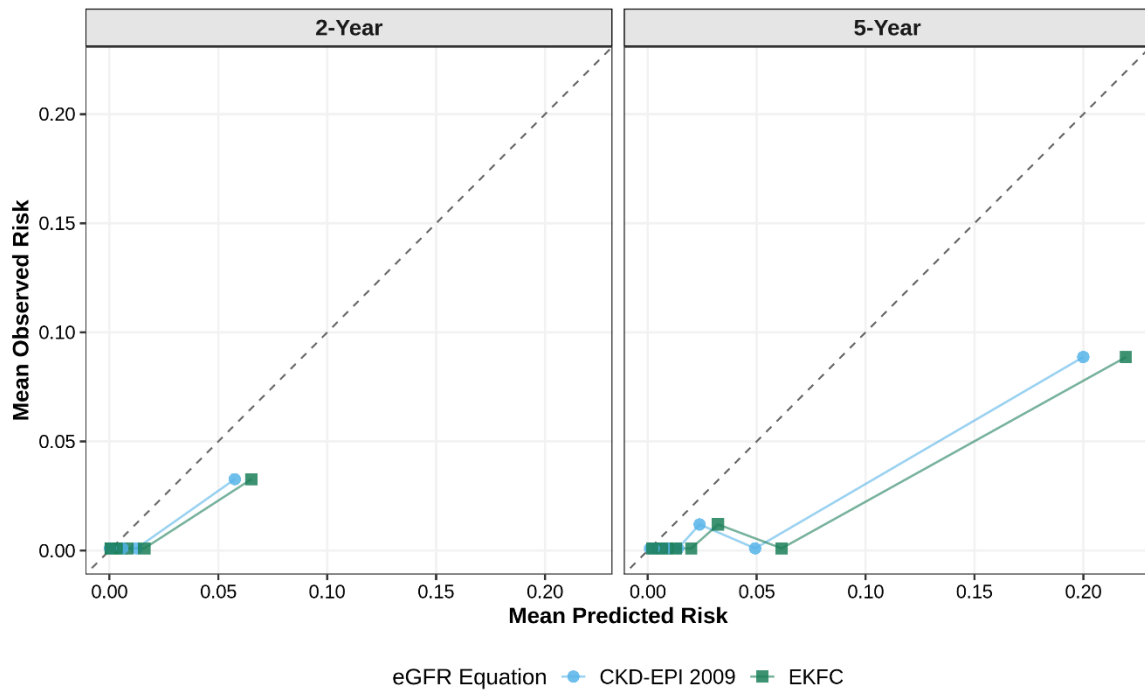
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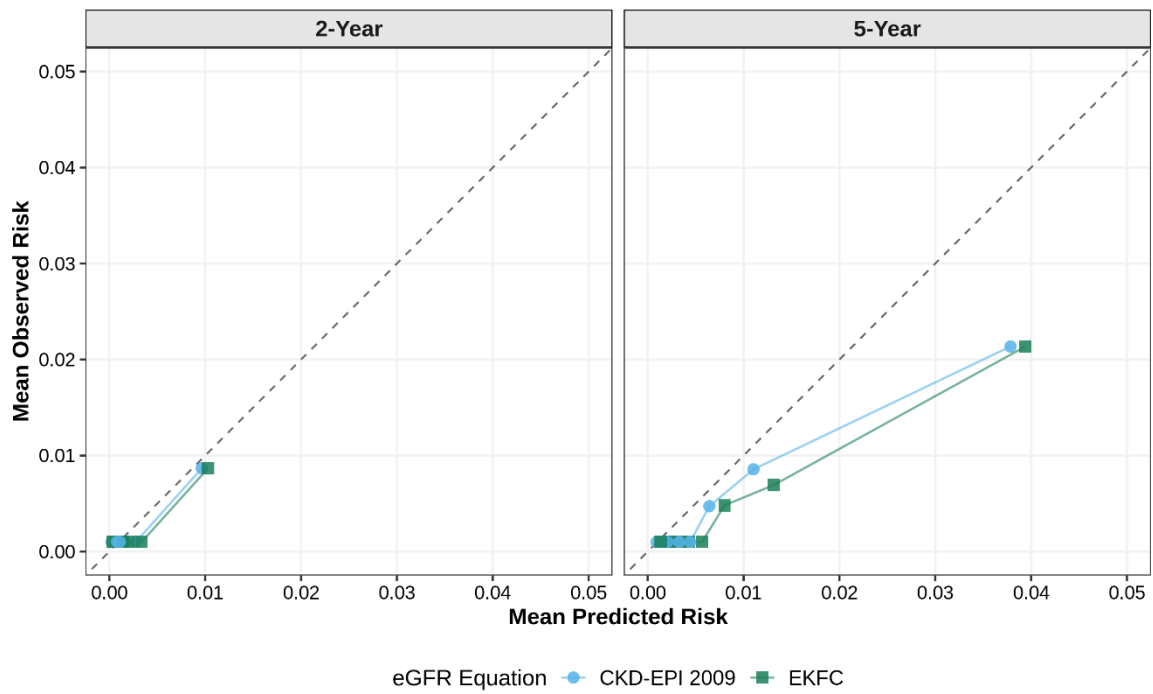
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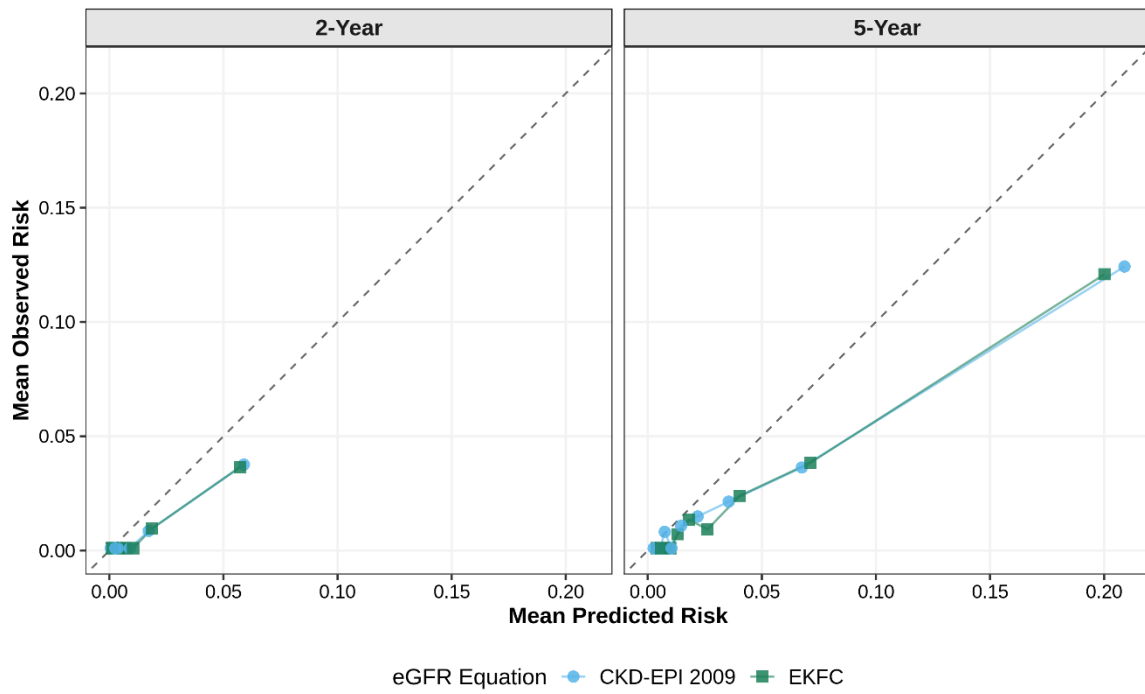
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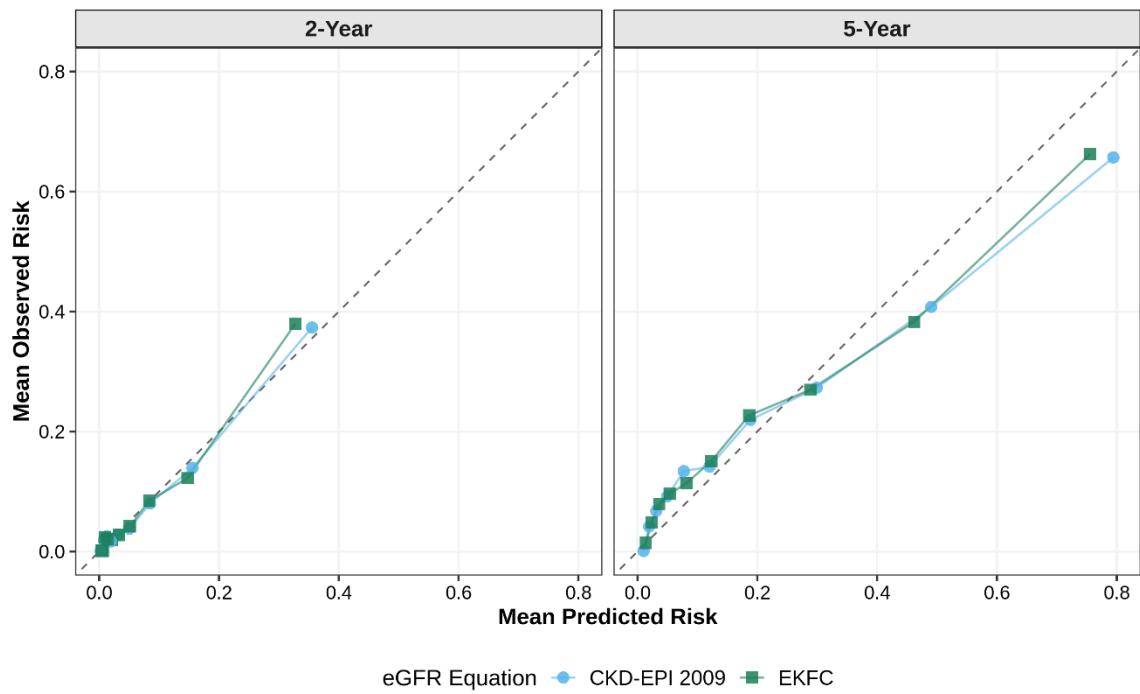
Calibration — Calib CK09 vs Calib EKFC (ACR: 1)



Calibration — Calib CK09 vs Calib EKFC (ACR: 2)

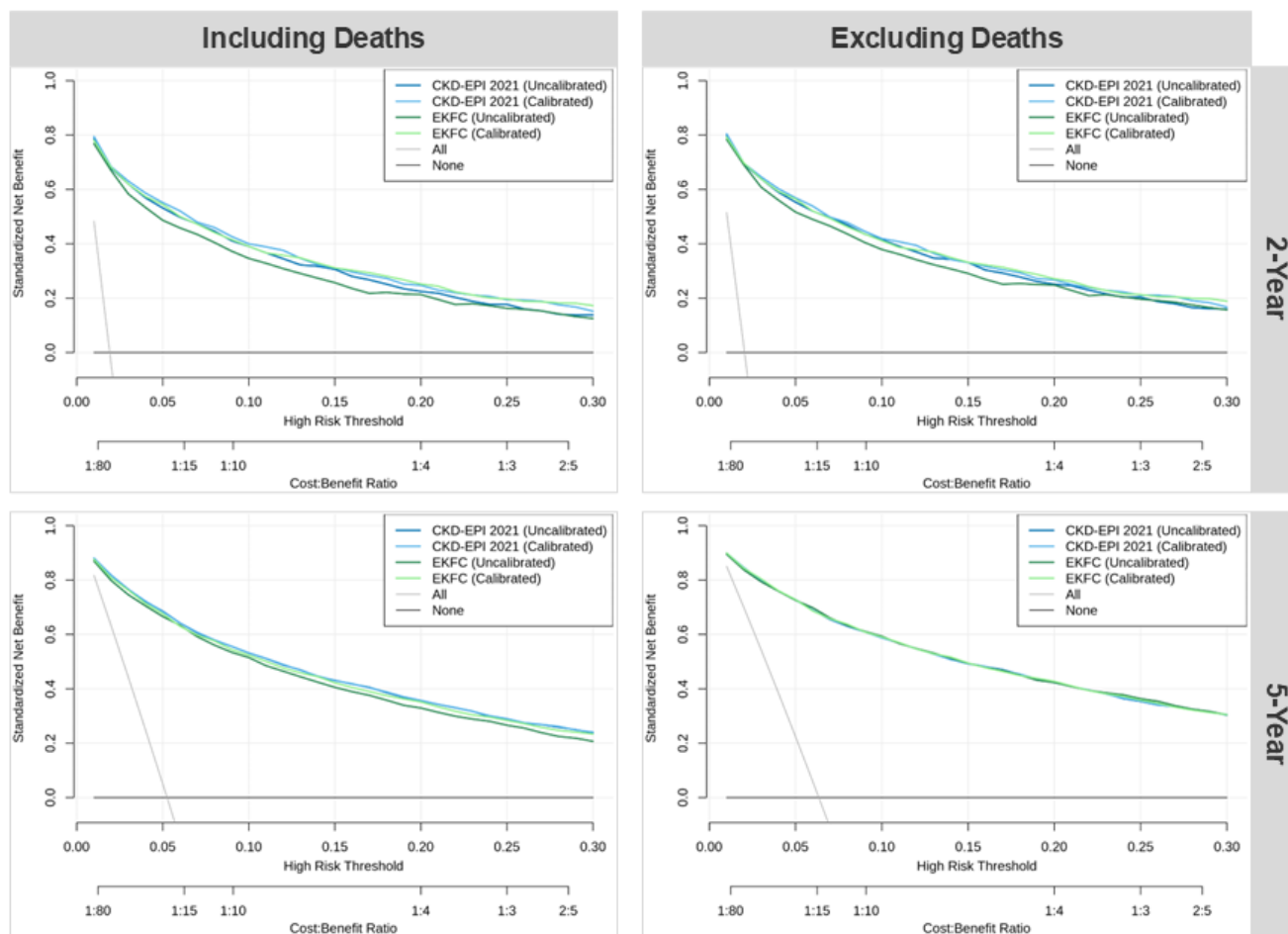


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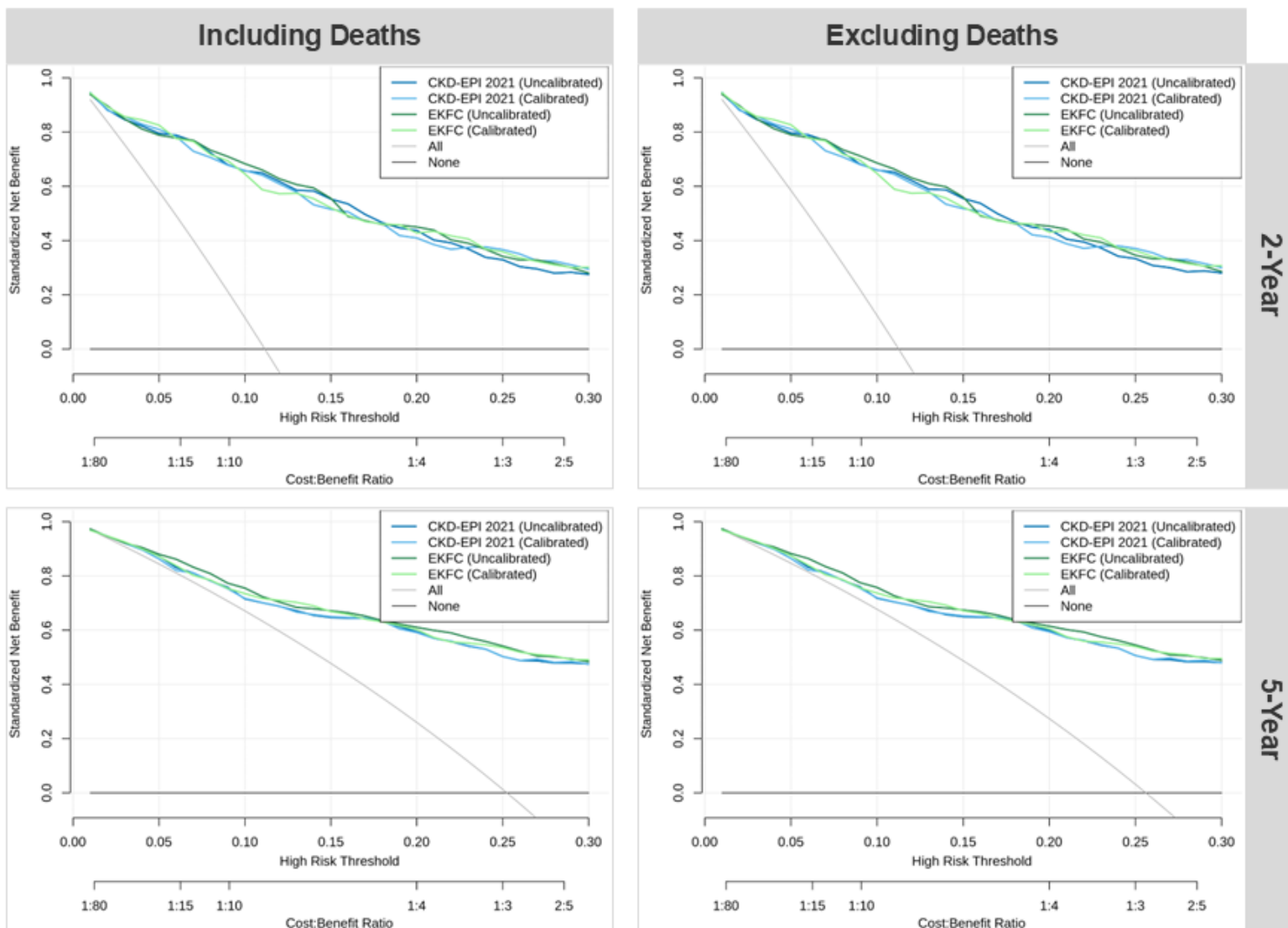


Appendix N. Decision Curve Analysis for KRT outcomes comparing KFRE inputs using CK21, EKFC, CK21 (recalibrated), EKFC (recalibrated) for the overall cohort, and for age 18 to <40, 40 to $\leq$ 65, 66 to <80, $\geq$ 80, male, female, ACR categories A1 (<3 mg/mmol), A2 (3-30 mg/mmol), and A3 (>30 mg/mmol) strata.

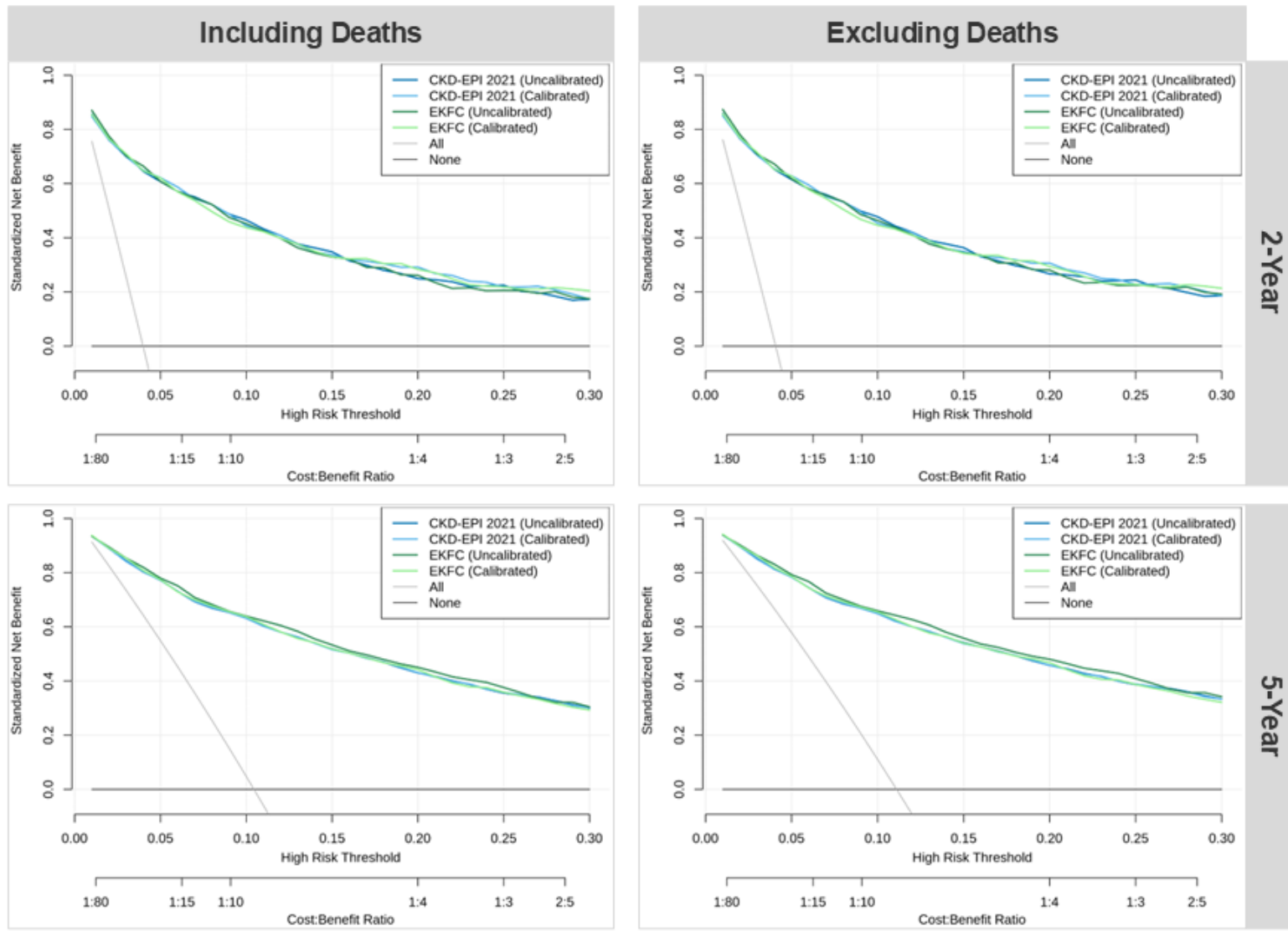
KRT Decision Curve Analysis — CK21 vs EKFC — Overall



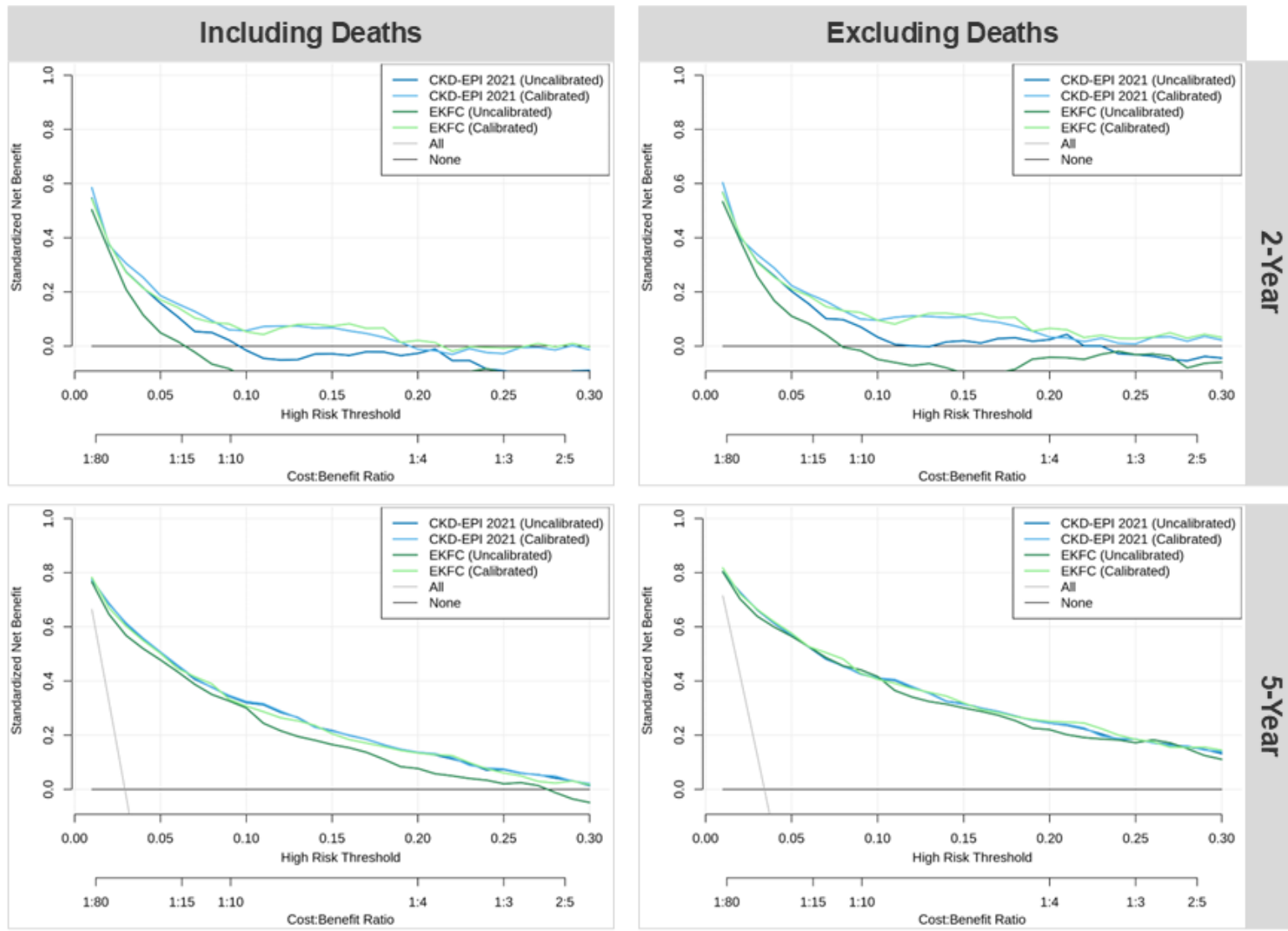
KRT Decision Curve Analysis — CK21 vs EKFC — Age 18 to <40



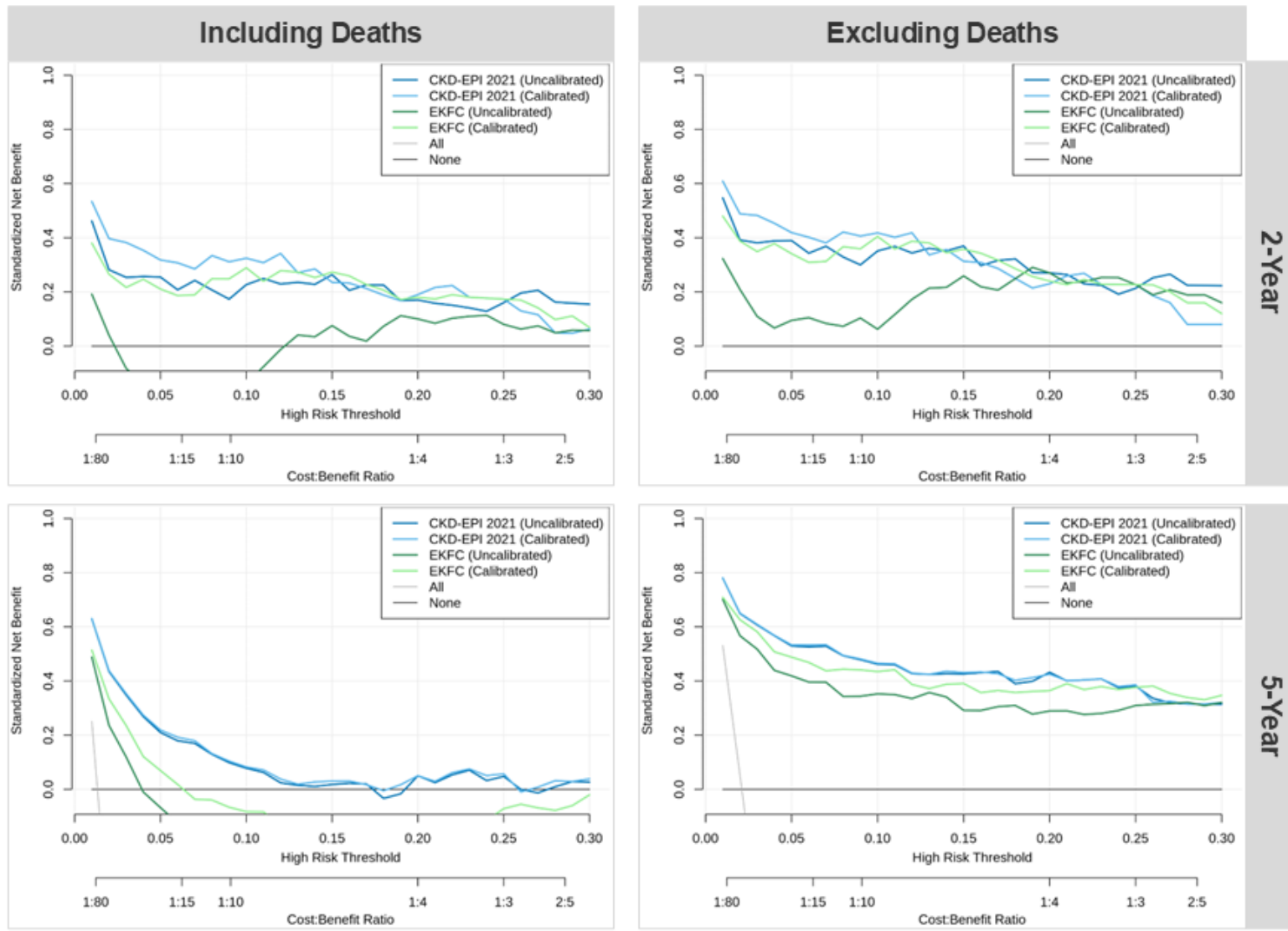
KRT Decision Curve Analysis — CK21 vs EKFC — Age 40 to ≤ 65



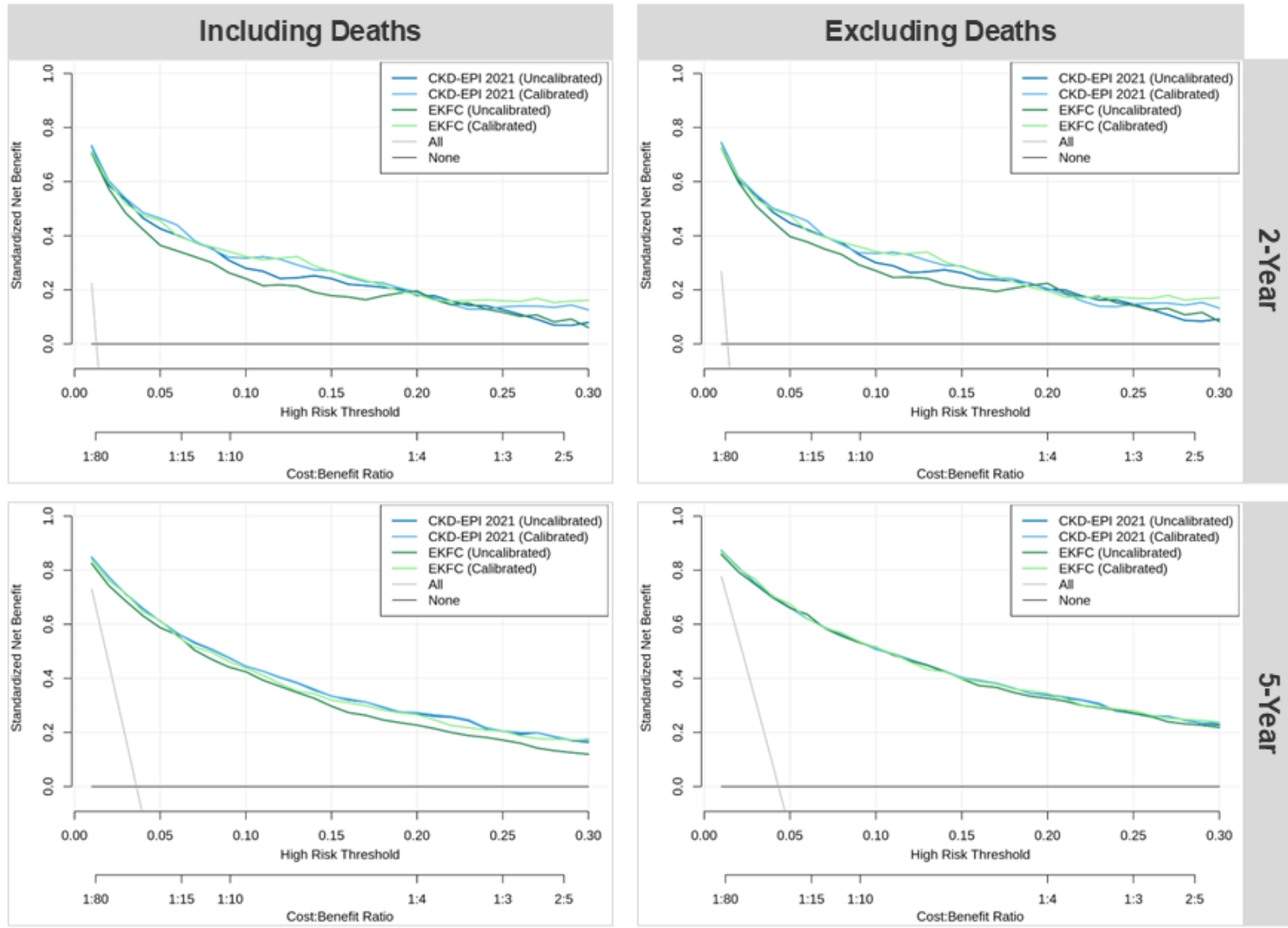
KRT Decision Curve Analysis — CK21 vs EKFC — Age 65 to <80



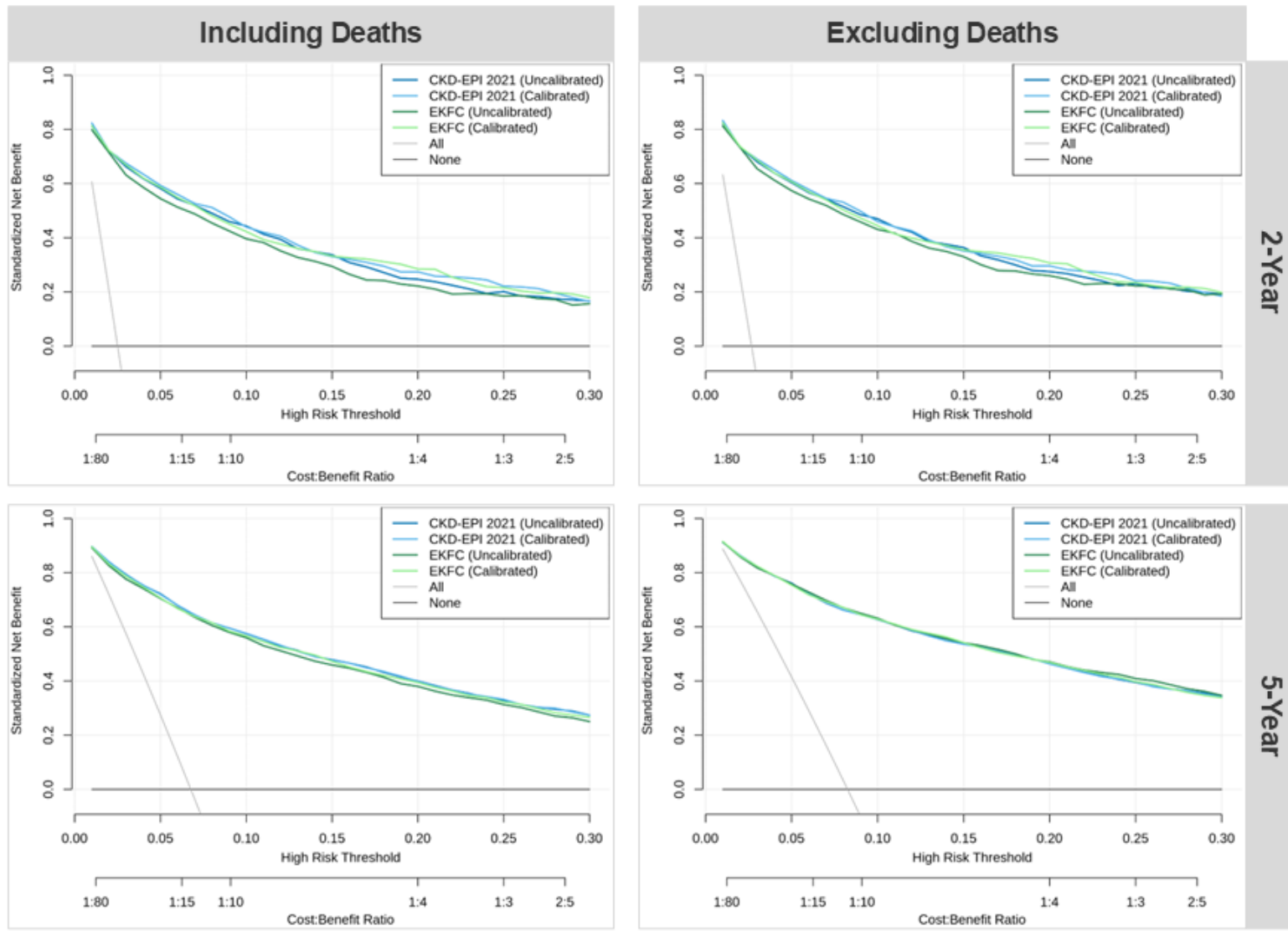
KRT Decision Curve Analysis — CK21 vs EKFC — Age 80+



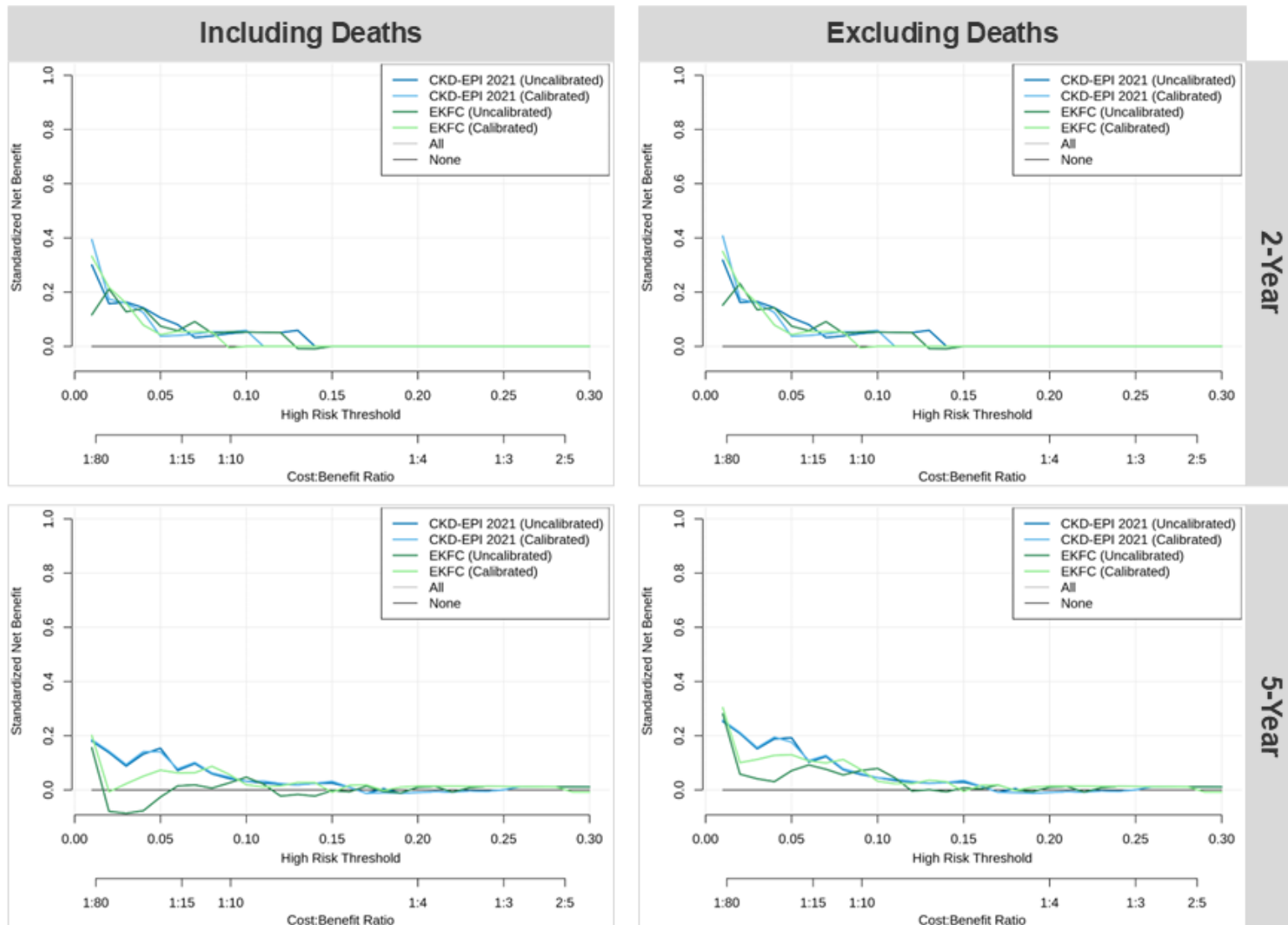
KRT Decision Curve Analysis — CK21 vs EKFC — Female



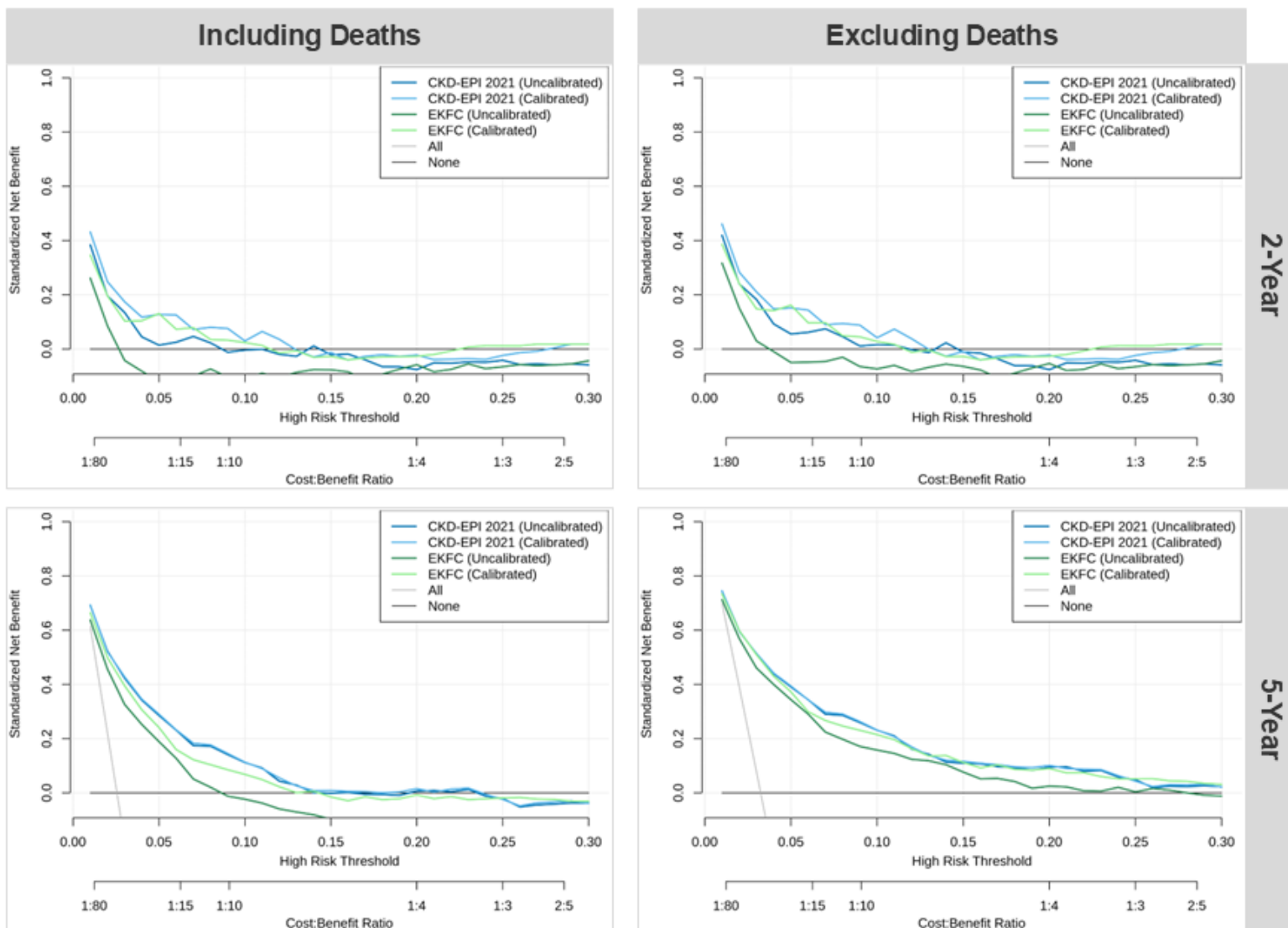
KRT Decision Curve Analysis — CK21 vs EKFC — Male



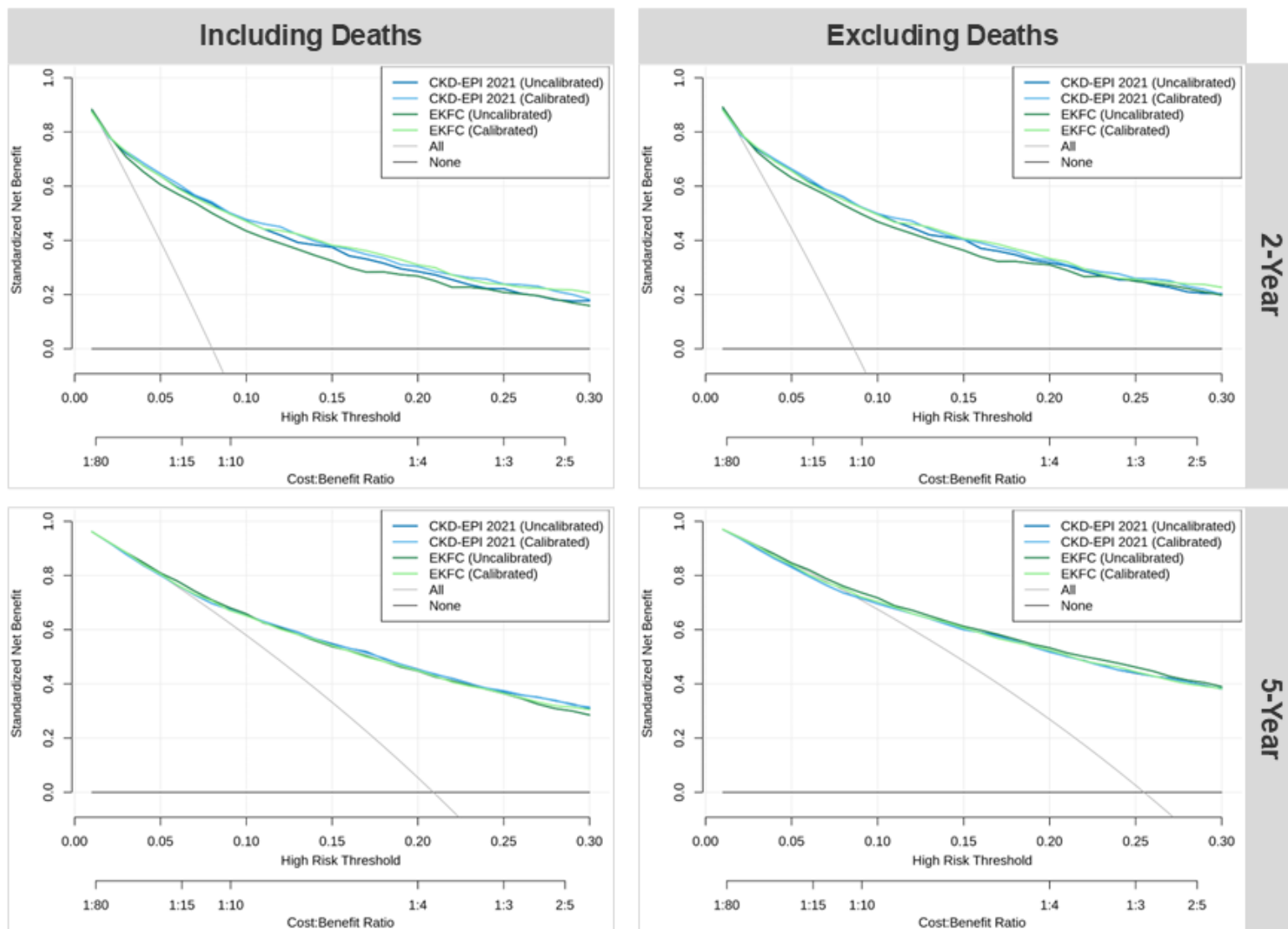
KRT Decision Curve Analysis — CK21 vs EKFC — Albuminuria A1 (<3 mg/mmol)



KRT Decision Curve Analysis — CK21 vs EKFC — Albuminuria A2 (3–30 mg/mmol)

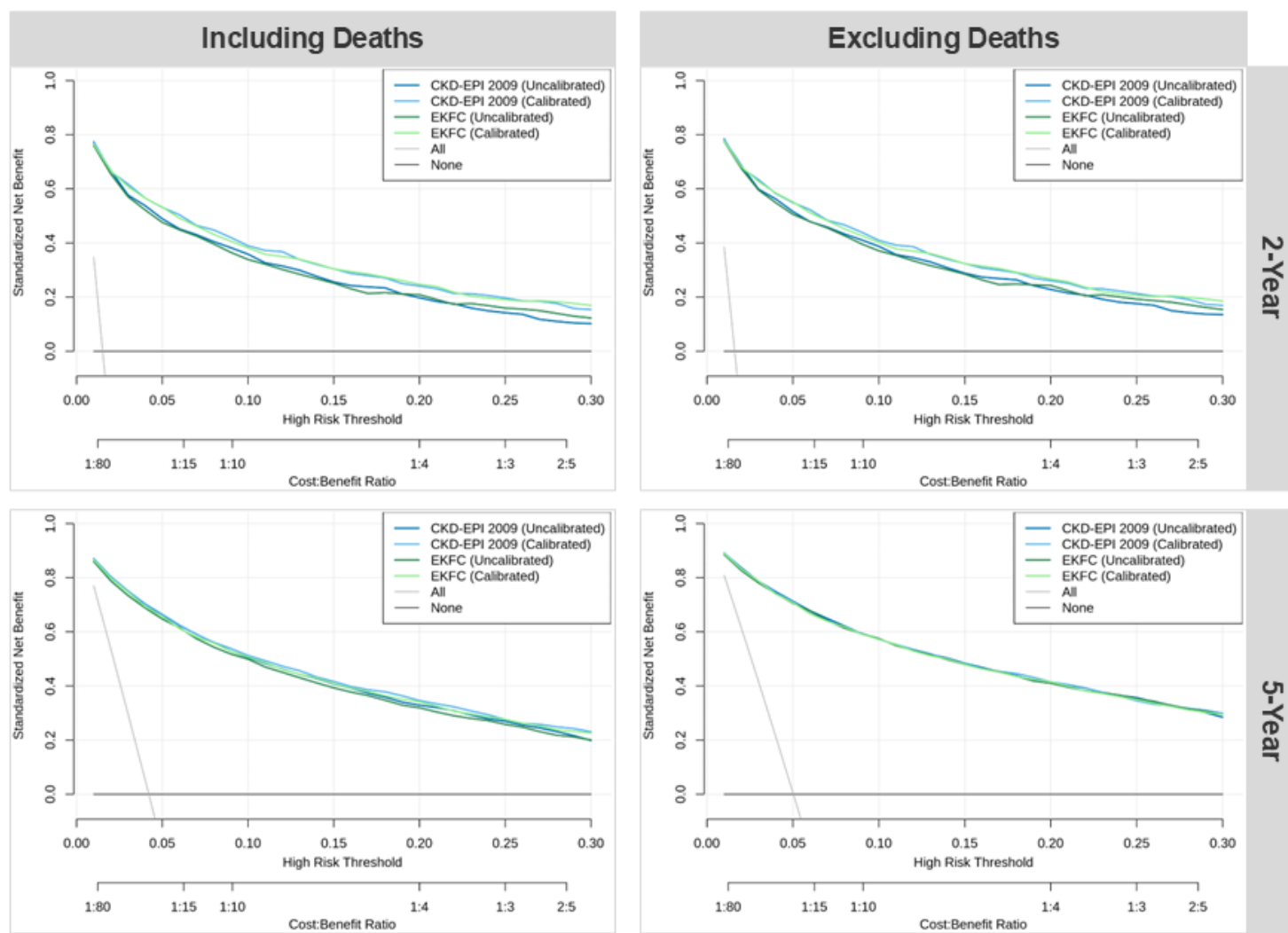


KRT Decision Curve Analysis — CK21 vs EKFC — Albuminuria A3 (>30 mg/mmol)

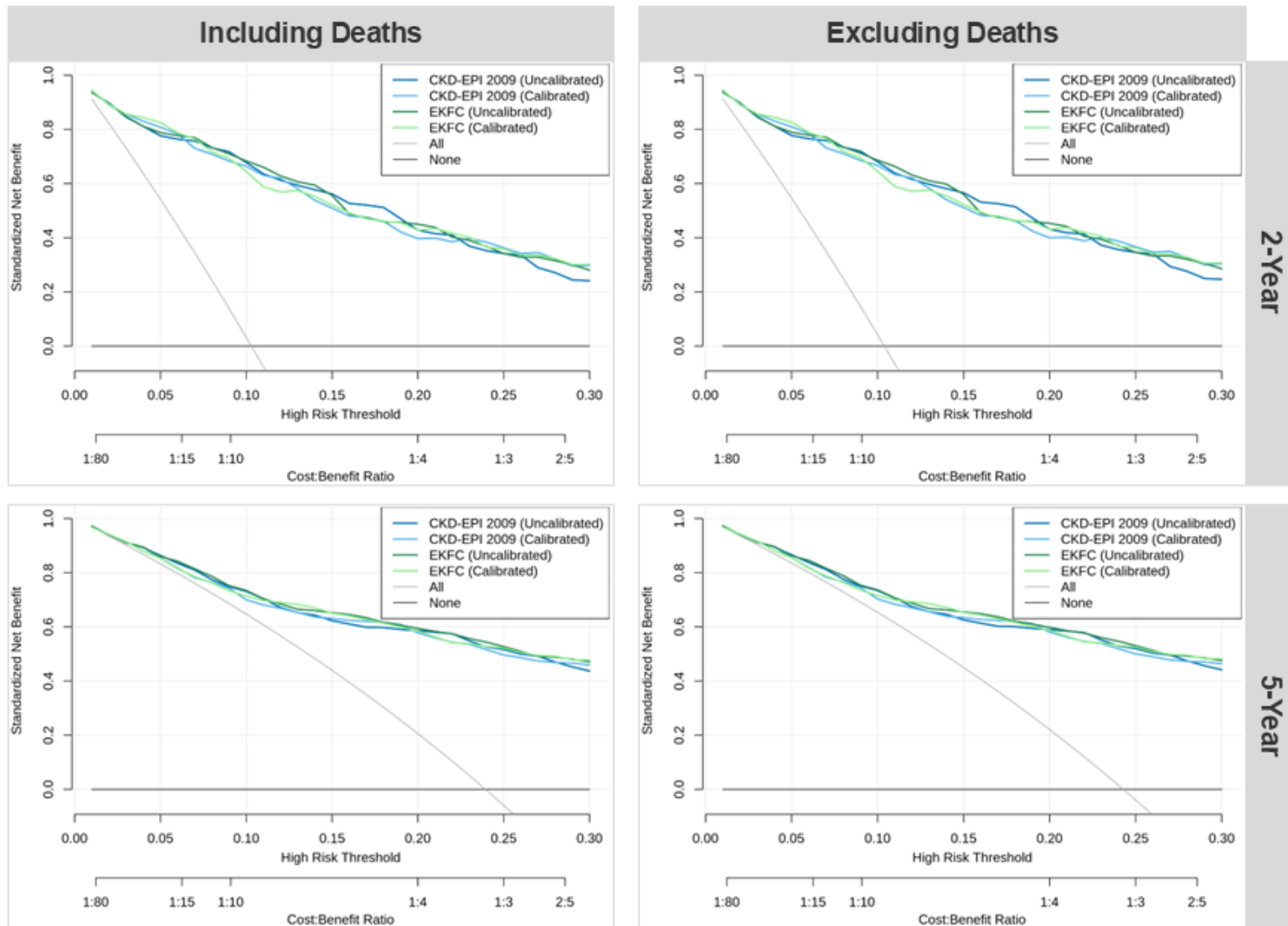


Appendix O. Decision Curve Analysis for KRT outcomes comparing KFRC inputs using CK09, EKFC, CK09 (recalibrated), EKFC (recalibrated) for the overall cohort, and for age 18 to <40, 40 to $\leq$ 65, 66 to <80, $\geq$ 80, male, female, ACR categories A1 (<3 mg/mmol), A2 (3-30 mg/mmol), and A3 (>30 mg/mmol) strata.

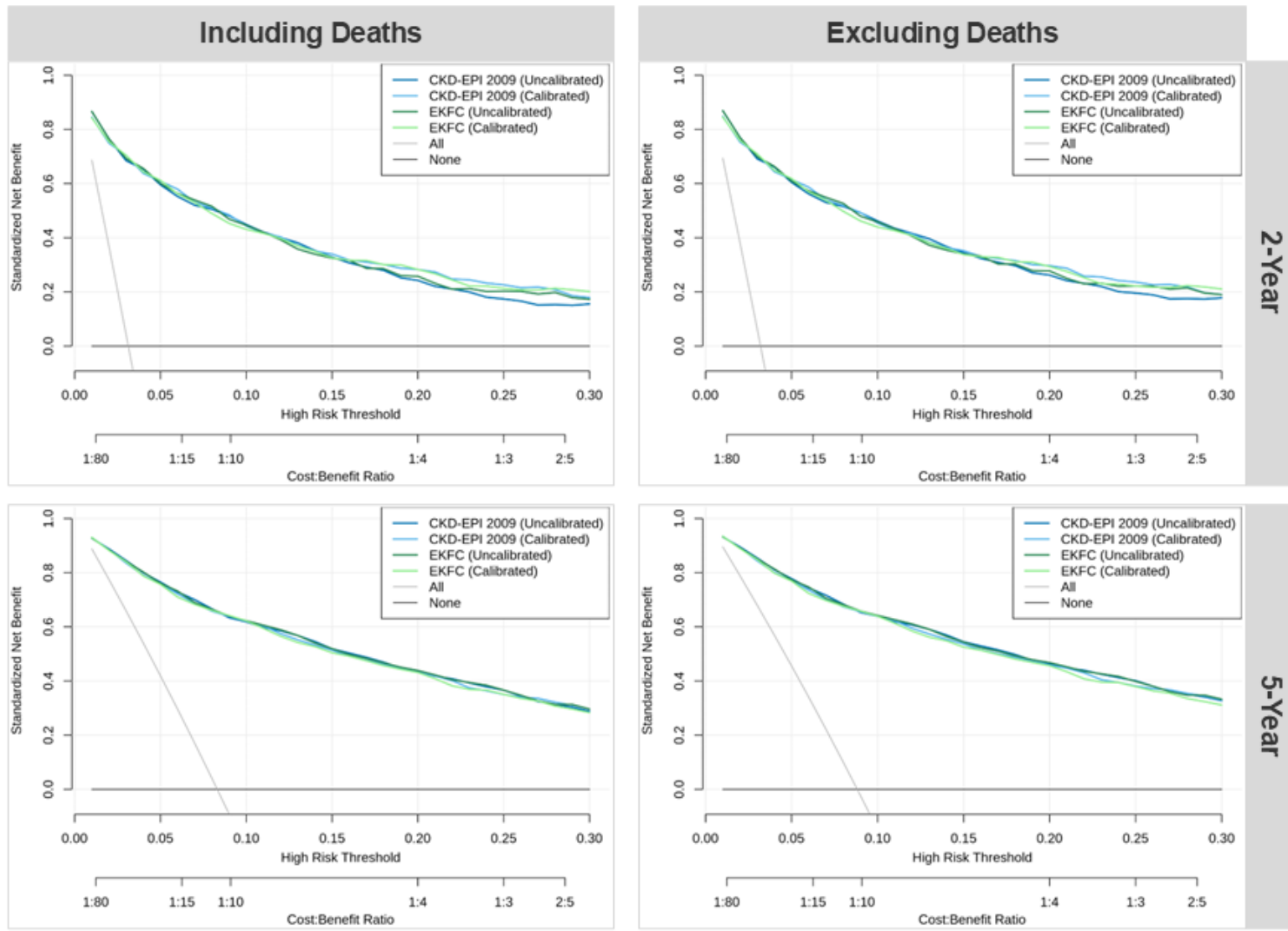
KRT Decision Curve Analysis — CK09 vs EKFC — Overall



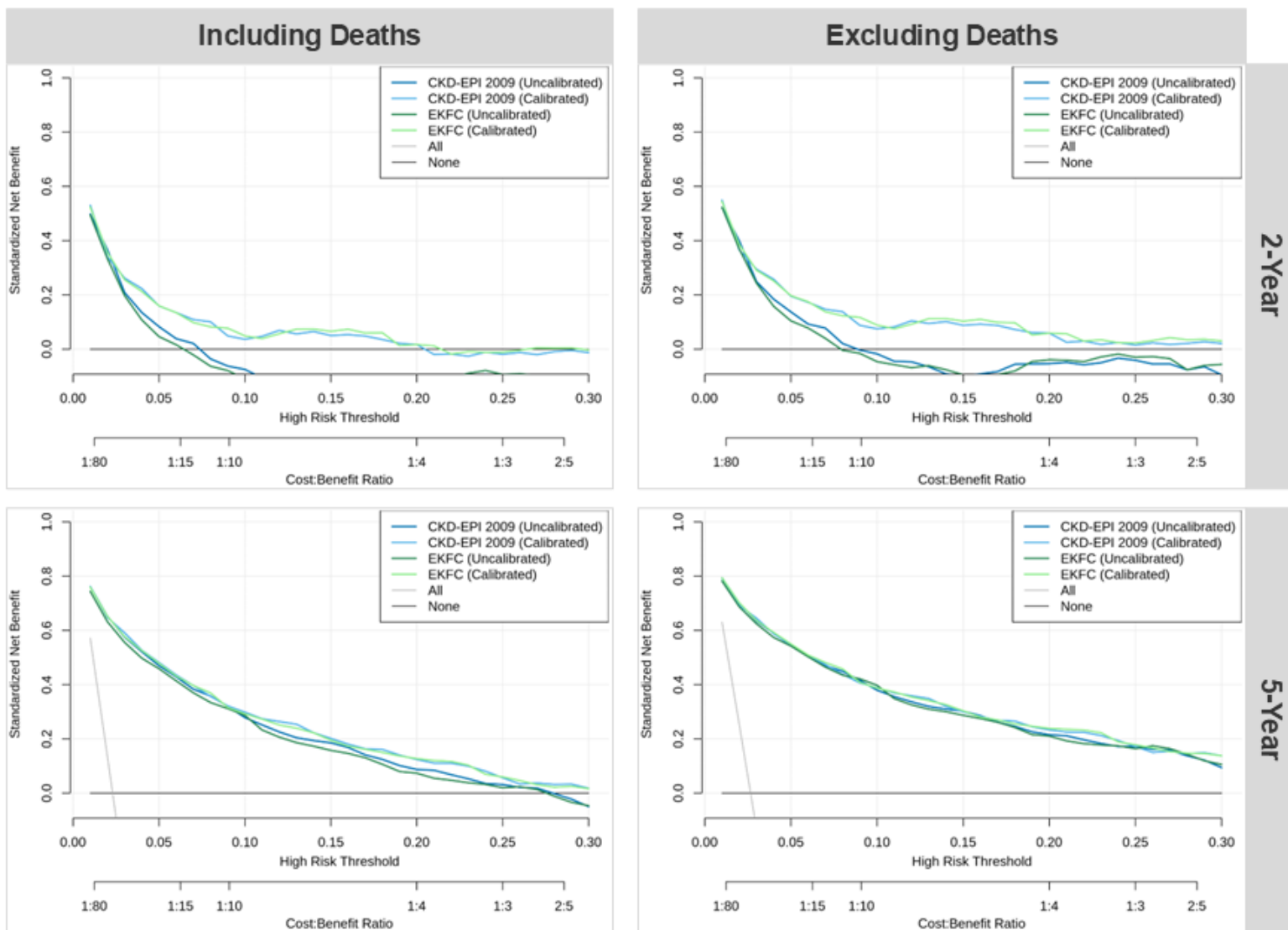
KRT Decision Curve Analysis — CK09 vs EKFC — Age 18 to <40



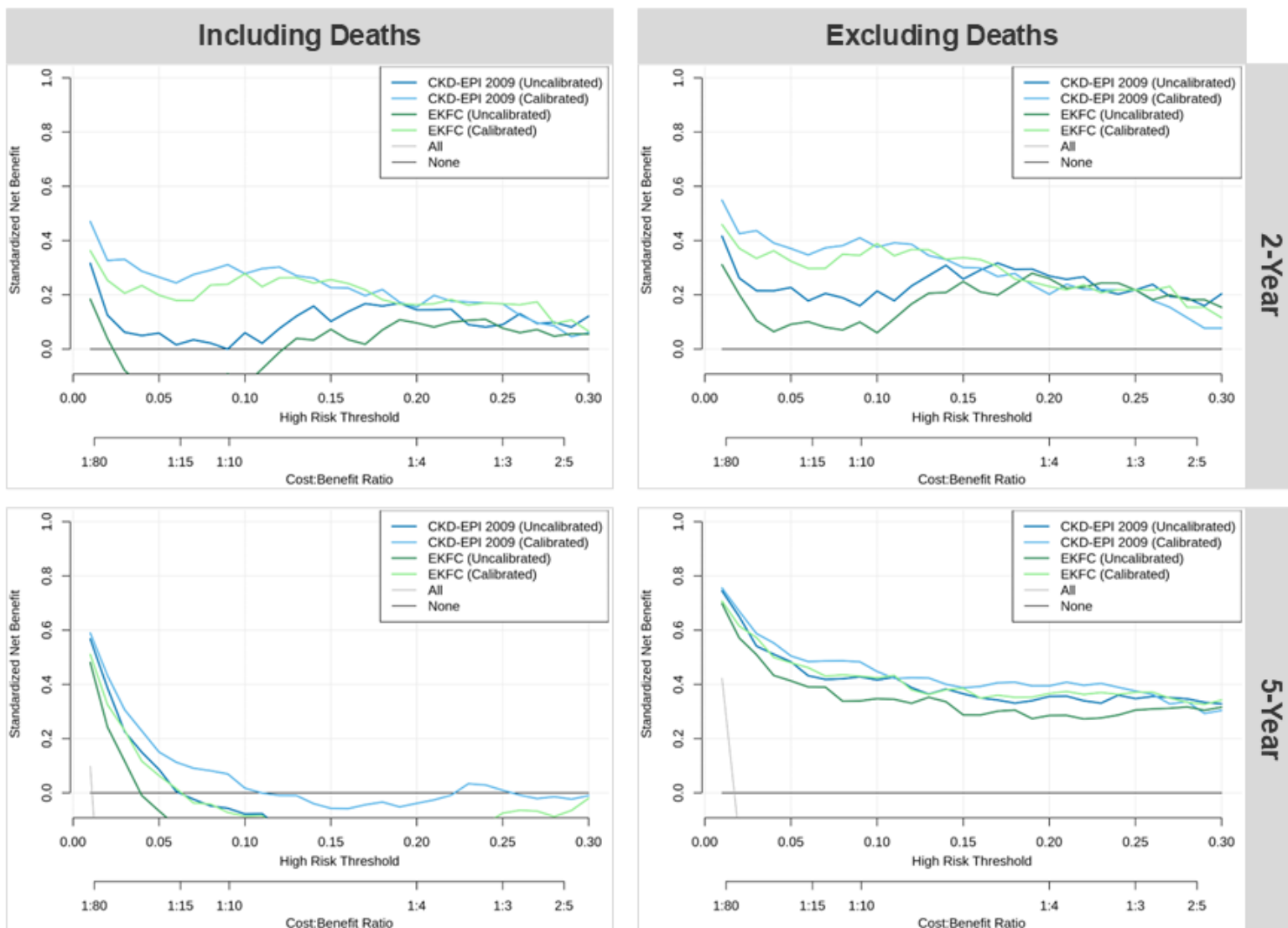
KRT Decision Curve Analysis — CK09 vs EKFC — Age 40 to ≤ 65



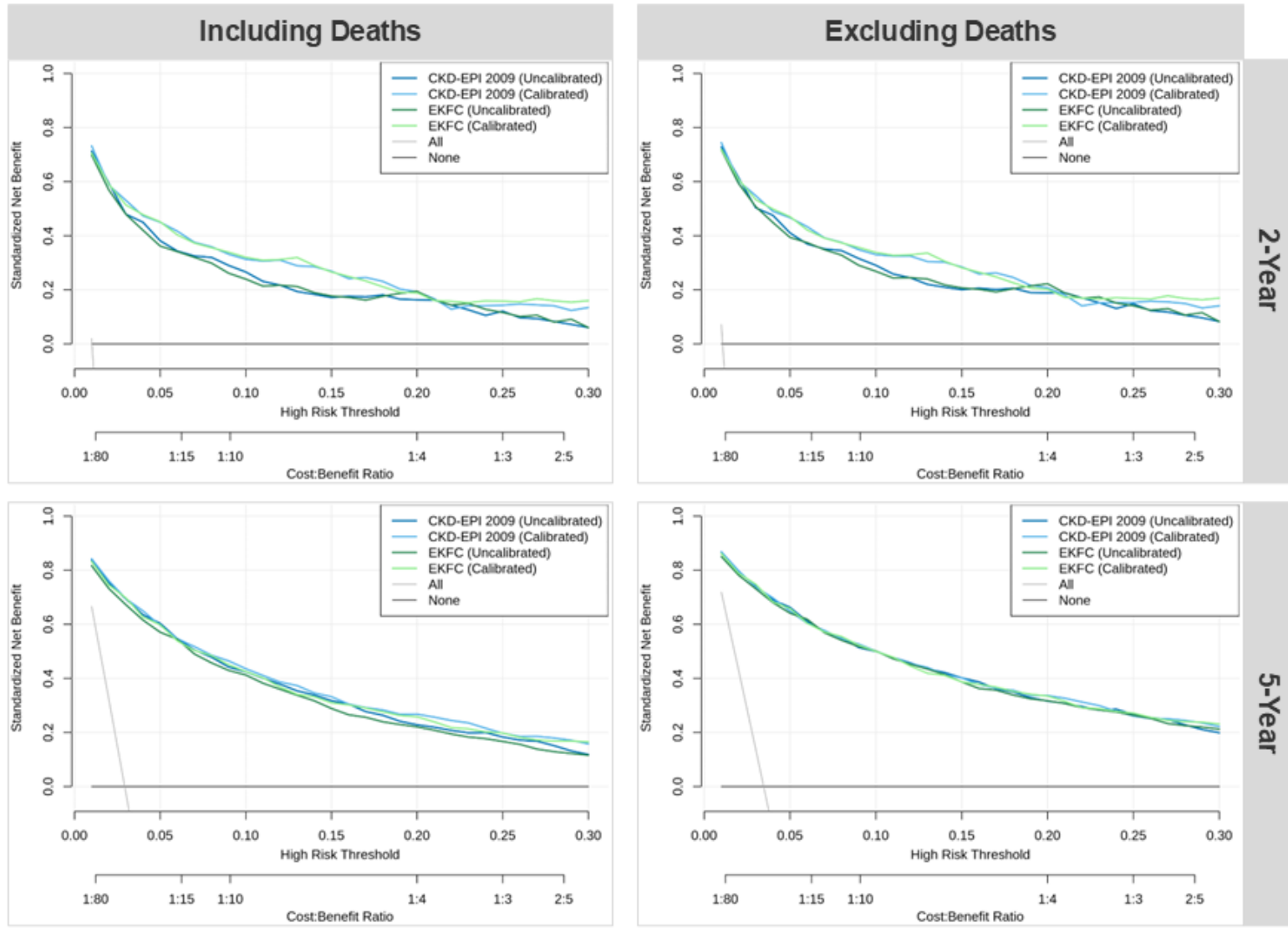
KRT Decision Curve Analysis — CK09 vs EKFC — Age 65 to <80



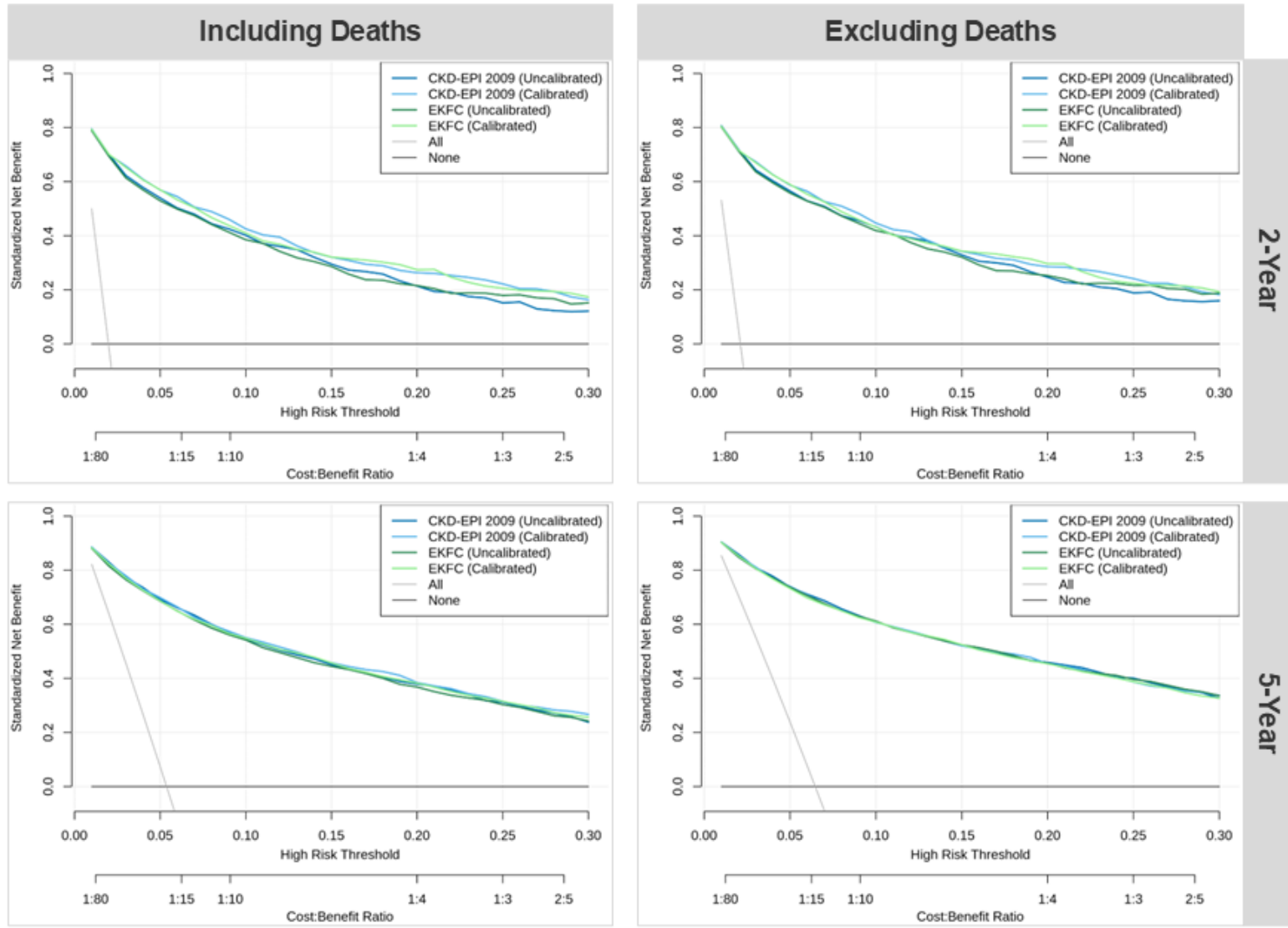
KRT Decision Curve Analysis — CK09 vs EKFC — Age 80+



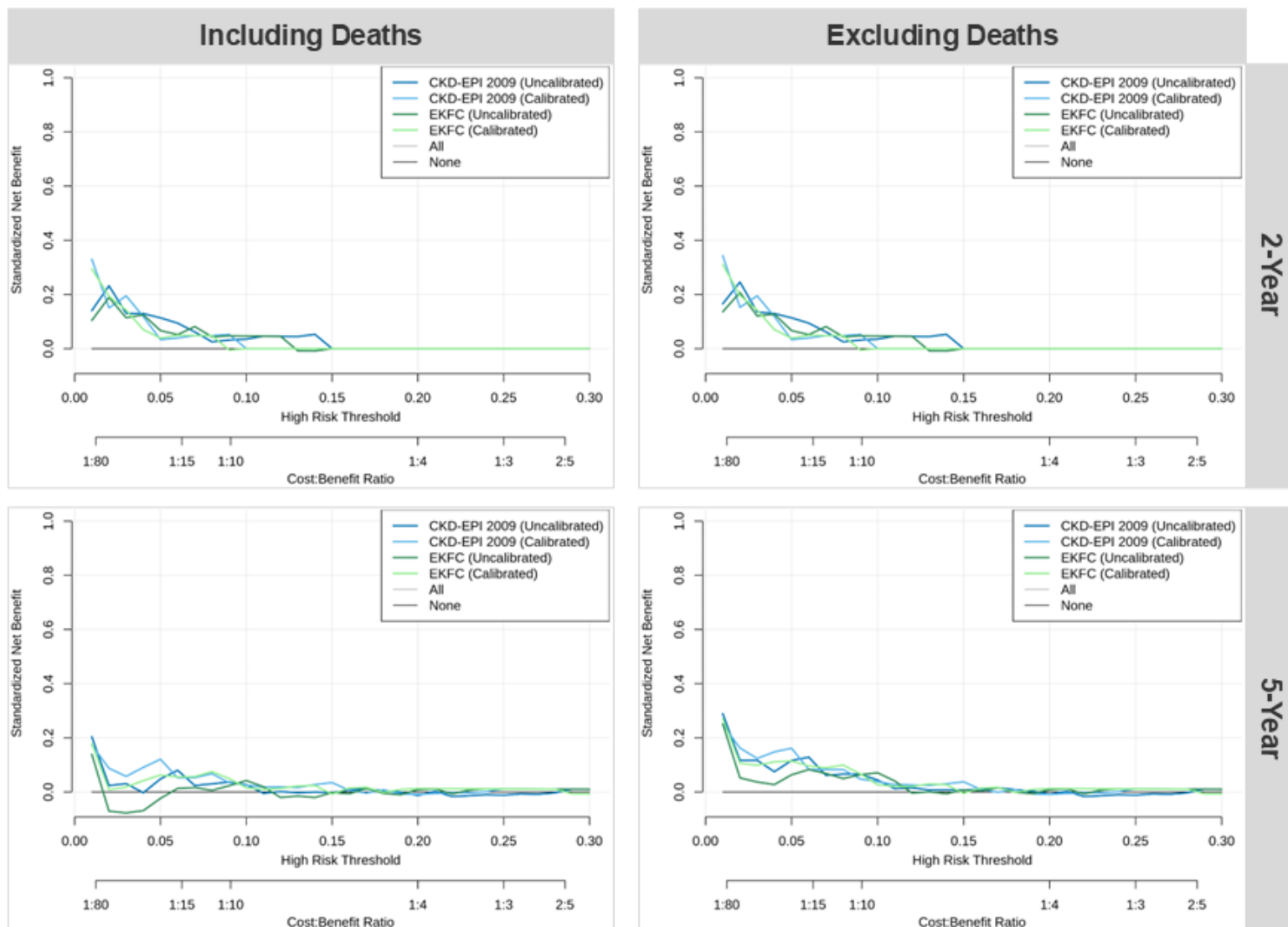
KRT Decision Curve Analysis — CK09 vs EKFC — Female



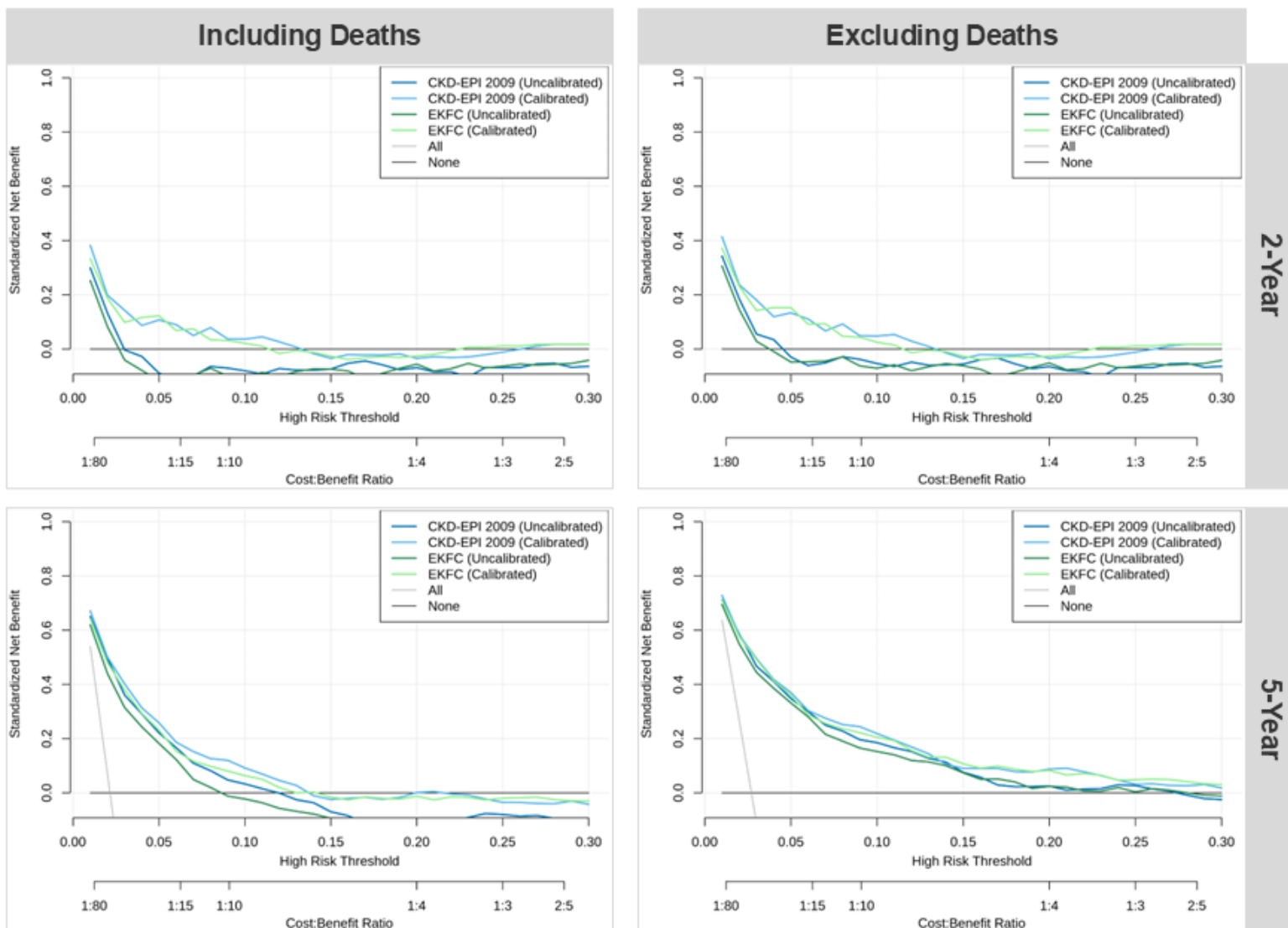
KRT Decision Curve Analysis — CK09 vs EKFC — Male



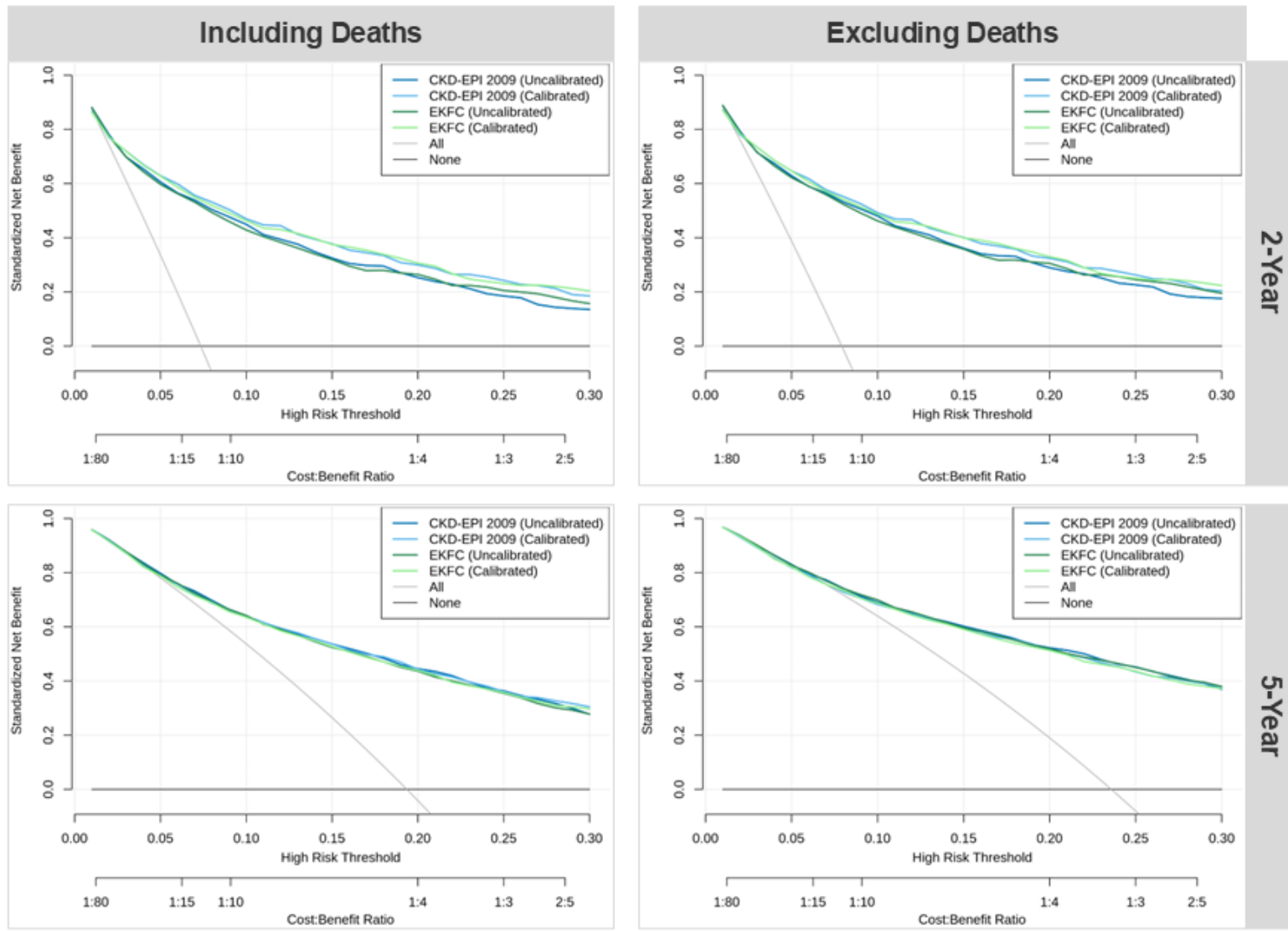
KRT Decision Curve Analysis — CK09 vs EKFC — Albuminuria A1 (<3 mg/mmol)



KRT Decision Curve Analysis — CK09 vs EKFC — Albuminuria A2 (3–30 mg/mmol)



KRT Decision Curve Analysis — CK09 vs EKFC — Albuminuria A3 (>30 mg/mmol)



Appendix P. Categorical NRI: Sensitivity analyses

Table P1. Categorical NRI for CK21 versus EKFC at 2- and 5-year horizons.

<i>Calibrated CK21 vs Calibrated EKFC</i>								
Timepoint	Death handling	N	Threshold	Reclassified	NRI Events	NRI Non-events	NRI Total	95% CI
2yr	Exclude	20,381	0.1	115	−0.014	0.001	−0.013	−0.032 to +0.004
2yr	Non-event	21,686	0.1	130	−0.014	0.001	−0.014	−0.030 to +0.004
5yr	Exclude	13,913	0.05	375	0.02	−0.022	−0.002	−0.012 to +0.009
5yr	Non-event	17,657	0.05	584	0.02	−0.030	−0.009	−0.020 to +0.002
<i>Uncalibrated CK21 vs Uncalibrated EKFC</i>								
Timepoint	Death handling	N	Threshold	Reclassified	NRI Events	NRI Non-events	NRI Total	95% CI
2yr	Exclude	20,381	0.1	243	0.024	−0.011	0.013	−0.001 to +0.029
2yr	Non-event	21,686	0.1	274	0.024	−0.012	0.012	−0.002 to +0.027
5yr	Exclude	13,913	0.05	723	0.04	−0.053	−0.013	−0.025 to −0.001
5yr	Non-event	17,657	0.05	1,088	0.04	−0.063	−0.023	−0.035 to −0.011

Table P2. Categorical NRI for CK09 versus EKFC at 2- and 5-year horizons.

<i>Calibrated CK09 vs Calibrated EKFC</i>								
<i>Timepoint</i>	Death handling	N	Threshold	Reclassified	NRI Events	NRI Non-events	NRI Total	95% CI
2yr	Exclude	26,299	0.1	98	−0.019	0.002	−0.017	−0.037 to 0.000
2yr	Non-event	27,877	0.1	110	−0.019	0.002	−0.017	−0.036 to +0.001
5yr	Exclude	18,201	0.05	262	0.004	−0.006	−0.002	−0.011 to +0.007
5yr	Non-event	22,717	0.05	386	0.004	−0.010	−0.006	−0.015 to +0.004
<i>Uncalibrated CK09 vs Uncalibrated EKFC</i>								
<i>Timepoint</i>	Death handling	N	Threshold	Reclassified	NRI Events	NRI Non-events	NRI Total	95% CI
2yr	Exclude	26,299	0.1	145	−0.017	0	−0.017	−0.034 to −0.002
2yr	Non-event	27,877	0.1	161	−0.017	0	−0.017	−0.032 to −0.003
5yr	Exclude	18,201	0.05	356	0.006	−0.013	−0.007	−0.015 to +0.001
5yr	Non-event	22,717	0.05	526	0.006	−0.018	−0.012	−0.020 to −0.004

Appendix Q. Density scatter plot comparing EKfC and CK21

