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**Kidney failure risk in multiple long-term conditions -
establishing validation in a population with multiple long-
term conditions and frailty, and exploration of patients’
and healthcare professionals’ perspectives of kidney
failure risk**

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Submitted in fulfilment of the requirements for the Degree of Doctor of
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School of Cardiovascular and Metabolic Health
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Abstract

Background

Chronic kidney disease (CKD) is increasingly common in adults and is associated with the presence of multiple long-term health conditions (multimorbidity) and/or frailty. Individuals with CKD and multimorbidity and/or frailty are at increased risk of their kidney disease progressing to kidney failure and of mortality compared to those without multimorbidity or frailty. A large number of kidney failure prognostic models have been developed to predict the risk of progression of CKD to kidney failure. The kidney failure risk equation (KFRE) is the most widely used and validated of these models and is recommended in clinical guidance. However, it is unclear if kidney failure prognostic models, including KFRE, have been developed with consideration for individuals with multimorbidity or frailty and if the presence of these impact how models perform or how they might be used in clinical practice.

Aims

The overall hypothesis was that the presence of multimorbidity and frailty in CKD negatively impacts the performance of the kidney failure risk equation and influences how it is used in the clinical care of individuals with multimorbidity and/or frailty.

This thesis aimed to:

- 1) Assess the prevalence of multimorbidity or frailty in studies that developed or validated kidney failure prognostic models for CKD.
- 2) Ascertain if the presence of multimorbidity or frailty in CKD impacted kidney failure prognostic model performance (focusing on the kidney failure risk equation) and if performance is influenced by the competing risk of mortality.
- 3) Evaluate if the performance of the kidney failure risk equation is impacted by the use of the biomarkers creatinine or cystatin-C in the

estimation of glomerular filtration rate (GFR) utilised in the model, in the context of multimorbidity or frailty.

- 4) Explore how multimorbidity and frailty influence patients' and healthcare professionals' understanding of CKD and perceptions of risk of kidney failure, and the potential use of the kidney failure risk equation in shared decision-making in these groups.

Methods

A systematic review of existing kidney failure prognostic models in CKD was performed, followed by two quantitative validation studies utilising data from a prospective research based cohort (UK Biobank) and a routine care population based cohort (Stockholm CREAtinine Measurements Project: SCREAM) and finally a qualitative descriptive study involving patients with CKD and multimorbidity and/or frailty and healthcare professionals involved in their care from primary and secondary care settings. Following completion of the described studies, triangulation of the findings was performed to establish findings of convergence (agreement), complementarity (added insight), and dissonance (discrepancy).

Results

There was a lack of reporting of multimorbidity and frailty in a systematic review of ninety-seven studies reporting 121 different kidney failure prognostic models. Only two studies reported prevalence of multimorbidity and one prevalence of frailty. Individual comorbidities were reported more frequently (diabetes: 67.0%, hypertension 54.6% and cardiovascular disease 39.2% of included studies). No studies assessed the impact of multimorbidity on prognostic model performance and a single study explored associations between frailty and risk of kidney failure and death but not the direct impacts on model performance.

Quantitative analysis confirmed that multimorbidity was common in CKD (14,998 of 24,489 individuals in UK Biobank: 61.2% and 30,147 of 42,902 individuals in SCREAM: 70.3%). Discrimination of KFRE was good in individuals with and without multimorbidity (area under receiver operating characteristic curve ≥ 0.86).

However, there was miscalibration, with underestimation of kidney failure risk in people with multimorbidity in UK Biobank (observed/expected (O/E) ratio 1.75 at 5-years; estimated GFR [eGFR] creatinine). Conversely, in SCREAM calibration-in-the-large (O/E ratio) at 5-years was 1.05 in the multimorbidity group (eGFR creatinine). Substituting creatinine with cystatin C to estimate GFR did not improve the performance of KFRE. The cumulative incidence of death was higher with multimorbidity groups compared to no multimorbidity. An updated model (using the same covariates as KFRE) considering competing mortality improved calibration performance over KFRE, O/E ratio 0.98 in multimorbidity group of the validation cohort (UK Biobank) at 5-years.

The prevalence of frailty in UK Biobank was 35% (8,533 of 24,489 individuals). Discrimination of KFRE was good (area under receiver operating characteristic curve ≥ 0.88 across all frailty sub-groups). Calibration was sub-optimal, with kidney failure at 5-years under-estimated in individuals with frailty (observed/expected (O/E) ratio 1.70). Substitution of creatinine with cystatin in the eGFR equation improved calibration-in-the-large (5-years O/E ratio 1.20). There was overestimation of kidney failure risk in analyses that do not account for competing mortality risk compared to those that do, particularly in individuals with frailty and at higher KFRE predicted risk levels.

Thirty-one patients and nineteen healthcare professionals participated in interviews or focus groups in the qualitative study. Patients were aged 46-94 years old, reported 3-10 long-term health conditions and had a clinical frailty scale of 1-7. The key factors that were found to influence understanding and perception of CKD and kidney failure risk were: 1) Variability in patients' knowledge and understanding of CKD, with many unaware of having received a diagnosis of CKD; 2) Work required to live with CKD alongside multimorbidity and/or frailty, including healthcare-associated work relating to complexity; 3) Relationships and interactions, where shared decision-making was facilitated by continuity and trust; 4) Context and priorities, including the level of prioritisation of CKD; and 5) Uncertainty.

Triangulation of findings identified that there were results from the four studies that agreed and complemented one another, but also some that were dissonant. There was agreement that frailty and multimorbidity impact KFRE performance

and its clinical applicability/use. The findings from the qualitative study explored the challenges that can arise from the uncertainties of risk prediction in people with frailty and multimorbidity and how risk information may be used informatively and relevantly in clinical practice. Dissonance arose because although the quantitative studies found the KFRE to be statistically adequate, the qualitative work uncovered its limitations in real-world use, and the systematic review showed minimal reporting of frailty and multimorbidity or evaluation these groups in the existing literature. Application of KFRE scores in clinical management of CKD patients with multimorbidity and frailty may have sub-optimal performance with a degree of uncertainty which should inform the discussion and shared decision-making with these group of patients.

Conclusions

Multimorbidity and frailty are common in CKD and impact the performance of KFRE. Risk prediction is improved for those with frailty when cystatin C-based eGFR equations are utilised in KFRE but not for those with multimorbidity. Accounting for competing risk of mortality is also important for kidney failure risk prognostication in both multimorbidity and frailty. An updated model (utilising the same covariates as KFRE) accounting for competing mortality risk improves calibration in multimorbidity.

Qualitative perspectives identified that CKD was often not a priority, compared to other long-term conditions, both for patients and HCPs. There was a desire from many patients to increase knowledge of CKD and kidney failure risk alongside other health problems. The potential value of KFRE was highlighted in reducing uncertainty, although optimal ways to communicate risk and uncertainty require further research.

Overall, these findings highlight that consideration of statistical model performance is important in ensuring that risk prediction is optimal for individuals with multimorbidity and frailty. However, implementation and clinical use of KFRE and other kidney failure risk prediction models is shaped by how CKD is understood and prioritised alongside the complexity and potential burden of multimorbidity and frailty.

Table of Contents

Abstract	ii
List of Tables	x
List of Figures	x
List of Supplemental Text	xvii
Awards	xviii
Other publications arising from this thesis	xix
Scientific presentations and abstracts	xxi
List of Accompanying Material	xxiv
Acknowledgements	xxv
Author's Declaration	xxvii
Abbreviations	xxix
1 Chapter: 1 Thesis Overview	1
1.1 Chapter summary	1
1.2 Introduction	1
1.3 Hypothesis	4
1.4 Research questions	4
1.5 Outline of chapters	5
2 Chapter: 2 Background	7
2.1 Chapter summary	7
2.2 Chronic kidney disease (CKD)	7
2.2.1 Chronic kidney disease definition and staging	7
2.2.2 Chronic kidney disease epidemiology, public health burden and health inequalities	10
2.2.3 eGFR equations and kidney function biomarkers	12
2.2.4 Chronic kidney disease progression and kidney failure	14
2.2.5 Symptoms and complications in chronic kidney disease	16
2.3 Multiple long-term conditions (MLTC)/Multimorbidity	18
2.3.1 Multimorbidity definition(s) and measurement	18
2.3.2 Epidemiology of multimorbidity	20
2.3.3 Impact of multimorbidity	21
2.4 Frailty	22
2.4.1 Frailty definition and measure(s)	22
2.4.2 Frailty epidemiology	27
2.4.3 Impact of frailty	28
2.5 Multimorbidity and frailty in CKD	28
2.5.1 Multimorbidity and frailty overlap	28
2.5.2 Multimorbidity and chronic kidney disease	30
2.5.3 Frailty and chronic kidney disease	31

2.6	Treatment burden	32
2.7	Prognostic risk prediction tools in CKD.....	33
2.7.1	Prognostic tools	33
2.7.2	Kidney failure prognostic tools in chronic kidney disease	36
2.7.3	Kidney Failure Risk Equation.....	38
2.7.4	Competing mortality risk in kidney failure risk prediction.....	39
2.8	Shared decision-making.....	40
2.8.1	Shared decision-making definitions and concepts.....	40
2.8.2	Models/frameworks of shared decision-making.....	41
2.8.3	Shared decision-making in CKD.....	43
2.8.4	Shared decision-making in complex patients.....	44
2.9	Conclusion	45
3	Chapter: 3 Methods	47
3.1	Chapter summary	47
3.2	Systematic review	48
3.2.1	Review planning and design.....	48
3.2.2	Eligibility criteria	48
	Search strategy	49
3.2.3	Screening.....	51
3.2.4	Data collection	51
3.2.5	Quality appraisal.....	53
3.2.6	Analysis and reporting	58
3.3	Description of datasets	58
3.3.1	UK Biobank.....	59
3.3.2	Stockholm CREAtinine Measurement project (SCREAM)	62
3.4	Assessment of kidney function	65
3.5	Assessment of albuminuria	66
3.6	Calculation of the Kidney Failure Risk Equation (KFRE)	67
3.7	Assessment of kidney failure and mortality outcomes.....	68
3.8	Defining long-term conditions and MLTC	69
3.8.1	Self-reported LTCs.....	70
3.8.2	Administrative healthcare data (diagnostic and prescribing codes).70	
3.9	Frailty measures and defining frailty cut-offs	71
3.9.1	Operational cut-offs.....	71
3.10	Validation of prognostic model and model performance measures....	72
3.11	Competing risk analyses.....	74
3.12	Qualitative interviews and focus groups.....	75
3.12.1	Study planning and design	75
3.12.2	Participants	75

3.12.3	Recruitment.....	75
3.12.4	Sample size.....	76
3.12.5	Data collection	77
3.12.6	Addressing potential bias	78
3.13	Normalisation Process Theory (NPT) and framework analysis	79
3.14	Triangulation.....	81
3.15	Patient and public involvement and engagement (PPIE)	81
4	Chapter: 4 Representation of multimorbidity and frailty in the development and validation of kidney failure prognostic prediction models: a systematic review	84
4.1	Reference	84
4.2	Chapter summary	84
4.3	Manuscript	85
5	Chapter: 5 Validation of the kidney failure risk equation in people with chronic kidney disease and multimorbidity: the effect of an update model accounting for competing mortality risks on model performance	113
5.1	Reference	113
5.2	Chapter summary	113
5.3	Manuscript	114
6	Chapter: 6 An analysis of frailty in adults with chronic kidney disease and validation of the kidney failure risk equation in sub-groups with frailty	147
6.1	Reference	147
6.2	Chapter summary	147
6.3	Manuscript	148
7	Chapter: 7 Exploration of patients' and health care professionals' perspectives of kidney failure risk in MULTIPLE Long-term conditions and frailTy (MULTIPOINT): a qualitative interview and focus group study	174
7.1	Reference	174
7.2	Chapter summary	174
7.3	Manuscript	175
8	Chapter: 8 Discussion	226
8.1	Chapter summary	226
8.2	Key/Summary of findings.....	226
8.2.1	Research question 1	226
8.2.2	Research questions 2	227
8.2.3	Research question 3	229
8.2.4	Research question 4	230
8.2.5	Research question 5	231
8.2.6	Triangulation of results	232
8.3	Findings in the context of other literature	233
8.4	Implications.....	236

8.4.1	Patients & carers	236
8.4.2	Healthcare professionals	238
8.4.3	Policy & healthcare services	240
8.4.4	Research	241
8.5	Strengths and limitations	242
8.5.1	Strengths	242
8.5.2	Limitations	243
8.6	Future directions	245
8.7	Conclusions	248
	References	251
	Appendices	279

List of Tables

Table 2-1. Staging of AKI	8
Table 2-2. Diagnostic criteria for AKI, AKD and CKD	9
Table 2-3. Characteristics of conditions that should be included in a multimorbidity measure from Ho et al. Delphi consensus study ⁶	19
Table 2-4. Overview of main frailty measures/tools.....	23
Table 2-5. Common measures of calibration	35
Table 3-1 Systematic review search strategy example	50
Table 3-2 Domains of the PROBAST risk of bias and applicability assessment tool	55
Table 4-1. Summary of kidney failure risk prediction models and multimorbidity/frailty measures reported for general CKD population.	97
Table 4-2. Baseline comorbidities recorded and included/added to externally validated kidney failure prediction models for general CKD population.	100
Table 5-1. Baseline characteristics.	125
Table 5-2. Kidney failure and death events over 2- and 5-years by cohort and multimorbidity status.	127
Table 5-3. Performance measures for validation of UK-calibrated KFRE using eGFRcr equation by cohort and multimorbidity status at 2-years.	129
Table 5-4. Performance measures for validation of UK-calibrated KFRE using eGFRcr equation by cohort and multimorbidity status at 5-years.	130
Table 5-5. Performance measures for validation of the competing mortality risk model using age, sex, log uACR, eGFRcr to predict kidney failure at 5-years..	139
Table 6-1. Baseline characteristics table.	158
Table 6-2. Kidney failure and death events over 2- and 5-years by frailty status.	160
Table 6-3. Performance measures for kidney failure risk equation by eGFR equation and frailty status at 2 years.	163
Table 6-4. Performance measures for kidney failure risk equation by eGFR equation and frailty status at 5-years.	164
Table 7-1. NPT coding framework for MULTIPOINT	183
Table 7-2. Participant characteristics.....	187
Table 7-3. Illustrative participant quotes by Normalisation Process Theory sub-constructs	191
Supplemental Table 4- 1. Full inclusion criteria	298
Supplemental Table 4- 2. Full exclusion criteria	298
Supplemental Table 4- 3. Medline (EBSCO interface) search strategy	299
Supplemental Table 4- 4. CINHALL (EBSCO interface) search strategy.....	300
Supplemental Table 4- 5. Cochrane Library - CENTRAL search strategy.....	301
Supplemental Table 4- 6. Overview of included studies - population, setting, CKD definitions, outcome definitions, eGFR equations used	302
Supplemental Table 4- 7. Summary of original models.....	315
Supplemental Table 4- 8. Baseline characteristics of included studies.....	328
Supplemental Table 4- 9. Summary of kidney failure risk prediction models and multimorbidity/frailty measures reported for renal specific disease aetiologies	336
Supplemental Table 4- 10. Summary of PROBAST tool assessment of individual studies.	338

Supplemental Table 4- 11. Competing risk of death consideration and performance measures included	341
Supplemental Table 5- 1. Long-term conditions included in multimorbidity definition.....	351
Supplemental Table 5- 2. Long-term conditions included in multimorbidity clusters	352
Supplemental Table 5- 3. Tripod checklist	353
Supplemental Table 5- 4. Kidney failure and mortality events by long-term condition count groups.....	355
Supplemental Table 5- 5. Kidney failure and mortality events by multimorbidity clusters	356
Supplemental Table 5- 6. Performance measures for validation of UK-calibrated KFRE by cohort, cystatin C-based eGFR equation and multimorbidity status at 2-years	357
Supplemental Table 5- 7. Performance measures for validation of UK-calibrated KFRE by cohort, cystatin-based eGFR equation and multimorbidity status at 5-years.	359
Supplemental Table 5- 8. Performance measures for validation of UK-calibrated KFRE by eGFR equation and LTC count in SCREAM cohort at 2-years	361
Supplemental Table 5- 9. Performance measures for validation of UK-calibrated KFRE by eGFR equation and LTC count in SCREAM cohort at 5-years	363
Supplemental Table 5- 10. Performance measures by eGFR equations and multimorbidity clusters at 2-years.....	365
Supplemental Table 5- 11. Performance measures by eGFR equations and multimorbidity clusters at 5-years.....	367
Supplemental Table 5- 12. Cumulative incidence of kidney failure by multimorbidity status	369
Supplemental Table 5- 13. Cumulative incidence of mortality by multimorbidity status	370
Supplemental Table 5- 14. Hazard ratio and 95% confidence intervals from cause-specific Cox model for kidney failure and mortality.....	371
Supplemental Table 5- 15. Individuals, characteristics, event numbers and performance for each risk group calculated by 5-year KFRE in UK Biobank	372
Supplemental Table 5- 16. Individuals, characteristics, event numbers and performance for each risk group calculated by 5-year KFRE in SCREAM.....	373
Supplemental Table 5- 17. Individuals, characteristics, event numbers and performance for each risk group calculated by 5-year updated KFRE accounting for competing mortality risk in UK Biobank	374
Supplemental Table 5- 18. Individuals, characteristics, event numbers and performance for each risk group calculated by 5-year updated KFRE accounting for competing mortality risk in SCREAM.....	375
Supplemental Table 5- 19. Baseline characteristics of individuals with predicted risk of kidney failure >5% by KFRE or competing risk model.....	376
Supplemental Table 5- 20. Sensitivity analysis: Performance measures for SCREAM cohort by eGFR equation and multimorbidity status using Non-North American calibrated 2-year KFRE	377
Supplemental Table 5- 21. Sensitivity analysis: Performance measures for SCREAM cohort by eGFR equation and multimorbidity status using Non-North American calibrated 5-year KFRE	378

Supplemental Table 5- 22. Sensitivity analysis: Performance measures for SCREAM cohort by eGFR equation and multimorbidity clusters using Non-North American calibrated 2-year KFRE	379
Supplemental Table 5- 23. Sensitivity analysis: Performance measures for SCREAM cohort by eGFR equation and multimorbidity clusters using Non-North American calibrated 5-year KFRE	380
Supplemental Table 5- 24. Sensitivity analysis: Additional performance measures for 2-year KFRE (utilising eGFRcr) by cohort and multimorbidity subgroups ...	381
Supplemental Table 5- 25. Sensitivity analysis: Additional performance measures for 5-year KFRE (utilising eGFRcr) by cohort and multimorbidity subgroup.....	381

Supplemental Table 6- 1. Long-term conditions included	409
Supplemental Table 6- 2. Tripod checklist	410
Supplemental Table 6- 3. Baseline characteristics by individual frailty measures and frailty status.....	412
Supplemental Table 6- 4. Kidney failure and death events over 2- and 5-years by frailty measures and frailty status	414
Supplemental Table 6- 5. DeLong's test for comparison of AUC by differing eGFR equations used in KFRE and cohort subgroups - frailty classified using all frailty measures	415
Supplemental Table 6- 6. DeLong's test for comparison of AUC by differing eGFR equations used in KFRE and cohort subgroups - frailty classified using a modified frailty phenotype	415
Supplemental Table 6- 7. DeLong's test for comparison of AUC by differing eGFR equations used in KFRE and cohort subgroups - frailty classified using frailty index (FI)	415
Supplemental Table 6- 8. DeLong's test for comparison of AUC by differing eGFR equations used in KFRE and cohort subgroups - frailty classified using laboratory frailty index (FI-lab).....	415
Supplemental Table 6- 9. Cumulative incidence of kidney failure by frailty status	416
Supplemental Table 6- 10. Cumulative incidence of mortality by frailty status	416
Supplemental Table 6- 11. Cumulative incidence of kidney failure by age groups	417
Supplemental Table 6- 12. Cumulative incidence of mortality by age group...	417
Supplemental Table 6- 13. Cumulative incidence of kidney failure by age and frailty status	418
Supplemental Table 6- 14. Cumulative incidence of mortality by age and frailty status	418
Supplemental Table 6- 15. Cumulative incidence of kidney failure by sex	419
Supplemental Table 6- 16. Cumulative incidence of mortality by sex	419
Supplemental Table 6- 17. Cumulative incidence of kidney failure by sex and frailty status	420
Supplemental Table 6- 18. Cumulative incidence of mortality by sex and frailty status	420
Supplemental Table 6- 19. Performance measures for KFRE by eGFR equation and frailty status assessed by individual frailty measures at 2 years	421
Supplemental Table 6- 20. Performance measures for KFRE by eGFR equation and frailty status assessed by individual frailty measures at 5 years	423

Supplemental Table 7- 1. Clinical coding (ICD-10 codes) used for identification of eligible patient participants	448
Supplemental Table 7- 2. COREQ (COnsolidated criteria for REporting Qualitative research) Checklist	449
Supplemental Table 7- 3. Expanded illustrative participant quotes by Normalisation Process Theory sub-constructs and themes.....	451

List of Figures

Figure 1-1 KDIGO staging and classification of CKD using eGFR and albuminuria with risk of adverse outcomes (mortality, progression of CKD, kidney failure) ¹ ..	2
Figure 2-1. Overview of AKI, AKD and CKD relationships and diagnostic criteria .	9
Figure 2-2 Common symptoms, prevalence and severity in individuals with CKD ¹	17
Figure 2-3. Special considerations for CKD care across the lifespan highlighted within KDIGO 2024 CKD guideline ¹	30
Figure 2-4. KDIGO proposed kidney failure risk thresholds ¹	39
Figure 4-1. Flow chart of study selection.....	94
Figure 4-2. Summary of risk of bias assessment.	105
Figure 4-3. Summary of applicability assessment.	105
Figure 5-1. Calibration curves for predicted versus observed 2-year and 5-year risk of kidney failure by Multimorbidity status in UK Biobank cohort.	132
Figure 5-2. Calibration curves for predicted versus observed 2-year and 5-year risk of kidney failure by Multimorbidity status in SCREAM cohort.	133
Figure 5-3. Cumulative incidence curves of kidney failure and mortality in UK Biobank and SCREAM: multimorbidity and no multimorbidity cohorts.	136
Figure 5-4. Kaplan-Meier estimates (dashed lines) and Aalen-Johansen estimates (solid lines) cumulative incidence curves for kidney failure by multimorbidity status and KFRE risk groups in UK Biobank and SCREAM.....	137
Figure 6-1. Euler diagram showing overlap between frailty measures/definitions.	159
Figure 6-2. Calibration curves for predicted versus observed 5-year risk of kidney failure by frailty status.	162
Figure 6-3. Cumulative incidence curves of kidney failure and mortality by frailty status	166
Figure 6-4. Kaplan-Meier estimates (dashed-lines_ and Aalen-Johansen estimates (solid lines) cumulative incidences curves for kidney failure by frailty status and KFRE risk groups	166
Figure 7-1. Key factors influencing patients' and healthcare professionals' understanding and perception of chronic kidney disease and kidney failure risk in the context of multimorbidity and frailty.	190
Figure 7-2. Key priorities emerging from the study for healthcare professionals, policy and researchers	220

Supplemental Figure 4- 1. Baseline co-morbidities recorded and included/added to externally validated kidney failure prediction models for renal specific aetiologies	344

Supplemental Figure 5- 1. Flow diagram of participant selection and exclusions in UK Biobank cohort	382
Supplemental Figure 5- 2. Flow diagram of participant selection and exclusions in SCREAM cohort.	383
Supplemental Figure 5- 3. Euler diagrams showing overlap between multimorbidity clusters in UK Biobank and SCREAM cohorts.....	384

Supplemental Figure 5- 4. Distribution of long-term condition counts: UK Biobank	385
Supplemental Figure 5- 5. Distribution of long-term condition counts: SCREAM	386
Supplemental Figure 5- 6. Histograms showing distribution of the predicted 2- year and 5-year risk of kidney failure by multimorbidity status in UK Biobank cohort. Predicted risk calculated by the UK calibrated KFRE using eGFRcr	387
Supplemental Figure 5- 7. Histograms showing distribution of the predicted 2- year and 5-year risk of kidney failure by multimorbidity status in SCREAM cohort. Predicted risk calculated by the UK calibrated KFRE using eGFRcr	388
Supplemental Figure 5- 8. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by multimorbidity status in UK Biobank cohort. Predicted risk is according to the UK calibrated KFRE using eGFRcys	389
Supplemental Figure 5- 9. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by multimorbidity status in UK Biobank cohort. Predicted risk is according to the UK calibrated KFRE using eGFRcrys	390
Supplemental Figure 5- 10. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by multimorbidity status in SCREAM cohort. Predicted risk is according to the UK calibrated KFRE using eGFRcys	391
Supplemental Figure 5- 11. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by multimorbidity status in SCREAM cohort. Predicted risk is according to the UK calibrated KFRE using eGFRcrys	392
Supplemental Figure 5- 12. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by LTC count and different eGFR equations used in KFRE for SCREAM cohort. Predicted risk is according to the UK calibrated KFRE	393
Supplemental Figure 5- 13. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure cardiometabolic multimorbidity and different eGFR equations used in KFRE for UK Biobank cohort. Predicted risk is according to the UK calibrated KFRE.....	396
Supplemental Figure 5- 14. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure cardiometabolic multimorbidity and different eGFR equations used in KFRE for SCREAM cohort. Predicted risk is according to the UK calibrated KFRE	397
Supplemental Figure 5- 15. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure complex multimorbidity and different eGFR equations used in KFRE for SCREAM cohort. Predicted risk is according to the UK calibrated KFRE	398
Supplemental Figure 5- 16. Kaplan-Meier estimates (dashed lines) and Aalen- Johansen estimates (solid lines) cumulative incidence curves for kidney failure by KFRE risk groups in SCREAM - comparison by multimorbidity status and age groups.....	399
Supplemental Figure 5- 17. Calibration plots with LOESS smoothing using cause- specific hazards approach and pseudo-observations for 5-year model (using eGFRcr) accounting for competing risk of mortality - UK Biobank cohort by multimorbidity status	400
Supplemental Figure 5- 18. Calibration plots with LOESS smoothing using cause- specific hazards approach and pseudo-observations for 5-year model (using eGFRcr) accounting for competing risk of mortality - SCREAM cohort by multimorbidity status	401
Supplemental Figure 5- 19. Calibration plots using sub-distribution hazard approach for 5-year model (using eGFRcr) accounting for competing risk of mortality - UK Biobank cohort by multimorbidity status	402

Supplemental Figure 5- 20. Calibration plots using sub-distribution hazard approach for 5-year model (using eGFRcr) accounting for competing risk of mortality -SCREAM cohort by multimorbidity status	403

Supplemental Figure 6- 1. Flow diagram of participant selection and exclusions UK Biobank cohort	425
Supplemental Figure 6- 2. Calibration curves for predicted versus observed 2-year risk of kidney failure by frailty status.....	426
Supplemental Figure 6- 3. Kaplan-Meier estimates (dashed lines) and Aalen-Johansen estimates (solid lines) cumulative incidence curves for kidney failure by frailty status, age groups and KFRE risk groups	427
Supplemental Figure 6- 4. Kaplan-Meier estimates (dashed lines) and Aalen-Johansen estimates (solid lines) cumulative incidence curves for kidney failure by frailty status, sex and KFRE risk groups	427
Supplemental Figure 6- 5. Calibration curves for predicted versus observed 2-year risk of kidney failure by frailty status - frailty phenotype	428
Supplemental Figure 6- 6. Calibration curves for predicted versus observed 5-year risk of kidney failure by frailty status - frailty phenotype	428
Supplemental Figure 6- 7. Calibration curves for predicted versus observed -year risk of kidney failure by frailty status - FI	429
Supplemental Figure 6- 8. Calibration curves for predicted versus observed 2-year risk of kidney failure by frailty status - FI	429
Supplemental Figure 6- 9. Calibration curves for predicted versus observed 5-year risk of kidney failure by frailty status - FI-lab	430
Supplemental Figure 6- 10. Calibration curves for predicted versus observed 2-year risk of kidney failure by frailty status - FI-lab	430

List of Supplemental Text

Supplemental Text 5- 1. Proteinuria conversion algorithm	345
Supplemental Text 5- 2. Interpretation of statistical performance measures utilised.....	346
Supplemental Text 5- 3. Description of Kaplan-Meier based calibration curve results for 2- and 5-year KFRE in UK Biobank and SCREAM cohorts.....	348
Supplemental Text 5- 4. Description of competing risk analysis results.....	349
Supplemental Text 5- 5. Sensitivity analyses	350
Supplemental Text 6- 1. Summary of included frailty measures.....	404
Supplemental Text 6- 2. UK Biobank algorithm for determination of kidney failure outcome	406
Supplemental Text 6- 3. UK calibrated four variable KFRE	406
Supplemental Text 6- 4. Explanation and interpretation of model performance measures utilised	406
Supplemental Text 6- 5. Competing risk analyses results.....	407
Supplemental Text 6- 6. Sensitivity and supplementary analyses	408
Supplemental Text 7- 1. Patient participant interview schedule.....	431
Supplemental Text 7- 2. Healthcare professional participant focus group schedule	440

Awards

- Top 30 Young Nephrologist Platform abstract at the 2024 European Renal Association Congress and congress travel grant winner for oral presentation “Validation of the Kidney Failure Risk Equation (KFRE) in individuals with chronic kidney disease and multimorbidity”
- Top scoring abstract and 2nd placed medical abstract oral presentation at the Scottish Renal Association Annual Conference 2024 for “An analysis of frailty in adults with chronic kidney disease and validation of the kidney failure risk equation in frailty sub-groups”
- NIHR Team Science Multiple Long-Term Conditions grant award - co-applicant. February 2025 to August 2026, £99,953
- Top Trainee Poster abstract at the 2025 American Society of Nephrology Kidney Week for “‘I’d Love It If Someone Gave Me Answers’: Exploration of Patients’ Perceptions of CKD and Kidney Failure Risk in the Context of Multimorbidity and Frailty”
- Top scoring abstract at the Scottish Renal Association Annual Conference 2025 for “I’d love it if someone gave me answers” - exploration of patients’ and health care professionals’ perspectives of chronic kidney disease and kidney failure risk in the context of multimorbidity and frailty: a qualitative interview and focus group study”
- Joint best poster prize at the University of Glasgow, College of Medical, Veterinary and Life Sciences, Clinical Research Open Day 2025 for “Analysis of the albuminuria testing, kidney failure risk equation implementation in routine clinical practice and health inequalities in chronic kidney disease care: a retrospective cohort study”

Other publications arising from this thesis

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Scientific presentations and abstracts

World Congress of Nephrology

2026. Poster presentation - “Integrating evidence and clinical application of the Kidney Failure Risk Equation (KFRE) in multimorbidity and frailty: a mixed-methods triangulation study”

2026. Poster presentation - “‘I’d Love It If Someone Gave Me Answers’: exploration of patients’ and healthcare professionals’ perspectives of chronic kidney disease and kidney failure risk in the context of multimorbidity and frailty: a qualitative interview and focus group study”

American Society of Nephrology Kidney Week

2024. Poster presentation - “Analysis of the kidney failure risk equation being incorporated into routine clinical practice for risk assessment”

2024. Poster presentation - “Impact of frailty on performance of the kidney failure risk equation using both creatinine and cystatin c based estimated glomerular filtration rates”

2025. Oral and poster presentation - “I’d Love It If Someone Gave Me Answers”: Exploration of Patients’ Perceptions of CKD and Kidney Failure Risk in the Context of Multimorbidity and Frailty”

European Renal Association Annual Congress

2024. Oral presentation - "Validation of the Kidney Failure Risk Equation (KFRE) in individuals with chronic kidney disease and multimorbidity"

2024. Poster presentation - "The representation of multimorbidity and frailty in the development and validation of kidney failure risk prediction models"

2025. Poster presentation - “Patients’ perspectives on the use of the Kidney Failure Risk Equation and shared decision-making in multimorbidity and frailty: a qualitative interview study”

Scottish Renal Association Annual Conference

2023. Oral presentation - "What is the representation of multimorbidity and frailty in the development and validation of kidney failure risk prediction models? - a systematic review"

2023. Oral presentation- "Validation of the kidney failure risk equation in UK Biobank participants with chronic kidney disease and multimorbidity or frailty"

2024. Oral presentation - “An analysis of frailty in adults with chronic kidney disease and validation of the kidney failure risk equation in frailty sub-groups”

2024. Poster presentation - "Analysis of the albuminuria testing, kidney failure risk equation implementation in routine clinical practice and health inequalities in chronic kidney disease care: a retrospective cohort study"

2025. Oral presentation - "I'd love it if someone gave me answers" - exploration of patients' and health care professionals' perspectives of chronic kidney disease and kidney failure risk in the context of multimorbidity and frailty: a qualitative interview and focus group study"

UK Kidney Week

2024. Oral presentation - "Validation of the Kidney Failure Risk Equation (KFRE) in individuals with chronic kidney disease and multimorbidity"

2024, Poster presentation - "Establishing validation of the kidney failure risk equation in UK Biobank participants with chronic kidney disease and multimorbidity or frailty"

2026, Poster presentation - "The main focus was something else" - exploration of health care professionals' perspectives of chronic kidney disease and kidney failure risk in multimorbidity and frailty"

Society of Academic Primary Care Annual Conference

2024. Lightening oral presentation - "Validation of the Kidney Failure Risk Equation (KFRE) to predict kidney failure and guide referrals from primary care for individuals with CKD who also experience multiple long-term health conditions or frailty."

Academic Departments of General Practice Scotland (NADEGS) Annual Conference

2025. Poster presentation - "Does clinical utility of the Kidney Failure Risk Equation in routine clinical practice vary by socioeconomic status?"

2025. Poster presentation - "Impact of frailty on performance of the Kidney Failure Risk Equation using creatinine and cystatin based eGFR"

NHS Research Scotland Health Research and Innovation Conference

2023. Poster presentation - "Establishing validation of the kidney failure risk equation in UK Biobank participants with chronic kidney disease and multimorbidity or frailty"

Kidney Research UK Driving Discoveries Conference

2024. Poster presentation - "Analysis of the kidney failure risk equation implementation in routine clinical practice and health inequalities in chronic kidney disease care"

University of Glasgow School of Cardiovascular and Metabolic Health Post-Graduate Researcher Symposium

2024. Poster presentation - “Analysis of the albuminuria testing, kidney failure risk equation implementation in routine clinical practice and health inequalities in chronic kidney disease care: a retrospective cohort study”

List of Accompanying Material

Appendix 1: Letter of permission to use KDIGO images and guidance

Appendix 2: Systematic review PROSPERO protocol

Appendix 3: Long-term condition ICD-10 code and definitions used in the Stockholm CREAtinine Measurements project dataset

Appendix 4: Long-term condition ICD-10 code and definitions used in the Stockholm CREAtinine Measurements project dataset

Appendix 5: Supplementary material for Chapter 4: Representation of multimorbidity and frailty in the development and validation of kidney failure prognostic prediction models: a systematic review

Appendix 6: Supplementary material for Chapter 5: Validation of the kidney failure risk equation in people with chronic kidney disease and multimorbidity: the effect of an update model accounting for competing mortality risks on model performance

Appendix 7: Supplementary material for Chapter 6: An analysis of frailty in adults with chronic kidney disease and validation of the kidney failure risk equation in sub-groups with frailty

Appendix 8: Supplementary material for Chapter 7: Exploration of patients' and health care professionals' perspectives of kidney failure risk and shared decision-making in MULTIPLE Long-term conditions and frailty (MULTIPOINT): a qualitative interview and focus group study

Appendix 9: Graphical summary of work for dissemination activities

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Author's Declaration

The work presented in this thesis was completed during a Clinical Research Fellowship supported by the Wellcome Trust as part of the Multimorbidity PhD programme for health professionals. All work was conducted by myself unless stated otherwise, under the supervision of my supervisory team. A number of colleagues and researchers collaborated on various aspects of the work presented. The contribution of other researchers is described in each chapter under the sub-sections titled: *Authors contributions*, and key contributions detailed below.

Chapters 4-8 are journal articles, published or submitted for publication. I acknowledge the contributions and support from the co-authors on each article. For each of these papers I was the primary author, wrote the first draft of each manuscript and revised the manuscript based on feedback from co-authors. In addition, co-authors contributed to the conceptualisation and planning of studies and interpretation of results. Other specific contributions are detailed below.

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I declare that I am the primary author of this thesis, including all statistical analysis and presentation of results. It has not previously been submitted for a higher degree.

Abbreviations

AAV - ANCA associated vasculitis
AGT - angiotensinogen
AKI - acute kidney injury
ALT - alanine aminotransferase test
AST - aspartate transaminase
AUC - area under receiver operating characteristic curve(s)
BNP - brain natriuretic peptide
CAD - coronary artery disease
CFS - Clinical Frailty Score
CCI - Charlson Comorbidity Index
CHARMS - Checklist for critical Appraisal of data extraction for systematic Reviews of prediction Modelling Studies
CHF - congestive heart failure
CI - confidence interval
CKD - chronic kidney disease
CKD-EPI - Chronic Kidney Disease Epidemiology Collaboration
CKD-PC - Chronic Kidney Disease Prognosis Consortium
COPD - chronic obstructive pulmonary disease
COREQ - Consolidated criteria for Reporting Qualitative Research
CRP - c-reactive protein
CTD - connective tissue disease
CVD - cardiovascular disease
DBP - diastolic blood pressure
DKD - diabetic kidney disease
ECI - Elixhauser Comorbidity Index
EGF - epidermal growth factor
eGFR - estimated glomerular filtration rate
eGFRcr - eGFR creatinine
eGFRcys - eGFR cystatin C
eGFRcr-cys - eGFR combined creatinine-cystatin C
EKFC - European Kidney Function Consortium
ESKD - end stage kidney disease
FGF23 - fibroblast growth factor 23
FI - frailty index
FI-lab - laboratory frailty index
FSGS - focal segmental glomerulosclerosis
Gd-IgA1 - galactose-deficient immunoglobulin A1
GFR - glomerular filtration rate
GGC - Greater Glasgow and Clyde
GGT - gamma-glutamyl transferase
GN - glomerulonephritis
GPs - general practitioners
Hb - Haemoglobin
HbA1C - glycated haemoglobin
HCP - healthcare professional
HDL - high density lipoprotein
HES - hospital episode statistics
ICD-10 - International Classification of Diseases-10
IDMS - isotope dilution mass spectrometry
IgAN - IgA Nephropathy

ISN/RPS - International Society of Nephrology and the Renal Pathology Society
 IQR - interquartile range
 KIM1 - kidney injury molecule 1
 KDIGO - Kidney Disease: Improving Global Outcomes
 KFRE - kidney failure risk equation
 KRT - kidney replacement therapy
 LDL - low density lipoprotein
 LTC - long-term condition
 MAP - mean arterial pressure
 MCV - mean cell volume
 MDT - multi-disciplinary team
 MeSH - medical subject heading
 MEST - mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T)
 MST - mesangial hypercellularity (M), segmental glomerulosclerosis (S), tubular atrophy/interstitial fibrosis (T)
 MLM - machine learning model
 MLTC - multiple long-term conditions
 MULTIPOINT - MULTIPLE Long-term conditions and frailty
 NHS - National Health Service
 NICE - National Institute for Health and Care Excellence
 NLR - neutrophil to lymphocyte ratio
 NPT - Normalisation Process Theory
 NRS PCRN - NHS Research Scotland Primary Care Research Network
 NT-pro-BNP - N-terminal pro-B-type natriuretic peptide
 ODSF - Ottawa Decision Support Framework
 OPDG - Ottawa Personal Decision Guide
 O/E - observed/expected
 OPCS4 - classification of interventions and procedures version 4
 PH - proportional-hazards
 PKD - polycystic kidney disease
 PPIE - Patient and Public Involvement and Engagement
 PRISMA-P - Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocols
 PROBAST - Prediction model Risk Of Bias Assessment Tool
 PROSPERO - International Prospective Register of Systematic Reviews
 PTH - parathyroid hormone
 PVD - peripheral vascular disease
 RASB - renin-angiotensin system blockade
 RBC - red blood cell
 REC - research ethics committee
 RLM - revised Lund-Malmö
 RQ - research question
 SCREAM - Stockholm CREATinine Measurements project
 SBP - systolic blood pressure
 SD - standard deviation
 SDM - shared decision-making
 SHARE - The Scottish Health Research Register and Biobank
 SIMD - Scottish Index of Multiple Deprivation
 T2DM - type two diabetes mellitus
 TIA - transient ischaemic attack
 TNFalphaR1 - tumour necrosis factor- α receptor 1
 TnT - troponin T

TRIPOD - Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis
uACR - urine albumin-creatinine ratio
UKKA - UK Kidney Association
uMMP7 - urinary matrix metalloproteinase 7
uNCR - urinary neutrophil gelatinase-associated lipocalin-to-creatinine ratio
uPCR - urine protein-to-creatinine ratio
UPE - urine protein excretion
WHO - World Health Organisation

1 Chapter: 1 Thesis Overview

1.1 Chapter summary

This chapter provides an overview of the thesis, introducing the central themes, research rationale, hypotheses, and research objectives. The chapter describes the research questions posed in detail, followed by a summary of each chapter and how these relate to the research objectives and questions.

1.2 Introduction

Chronic kidney disease (CKD) is defined as abnormality in structure or function of the kidney that is present for more than three months and has ongoing implications for health¹. CKD represents a major global burden, predicted to affect approximately 14% of adults worldwide and is projected to rise in prevalence². It is associated with significant morbidity, mortality and associated healthcare costs³. The disease trajectory is often complicated by the presence of other chronic health conditions and by frailty^{4, 5}.

Multimorbidity (or multiple long-term conditions (MLTC)) refers to the presence of two or more long-term conditions⁶, reflecting the complex nature of living with multiple chronic disease which can often interact to produce cumulative treatment demands and increased care needs. Frailty is defined as a state of reduced physiological reserve and increased vulnerability to stressors, including medications or illness⁷. Frailty is associated with susceptibility to adverse health outcomes such as falls, hospitalisation and mortality^{7, 8}. Although frailty and multimorbidity are distinct concepts, they often co-exist and share some overlapping mechanisms e.g. inflammation, metabolic dysregulation and sarcopenia - that are also prevalent in individuals with CKD. Both multimorbidity and frailty are more common in individuals with CKD compared with the general population and are increasingly recognised as determinants of health outcomes in people with CKD. However, they remain under-represented and explored in nephrology research and clinical guidance.

CKD is a spectrum, with staging of CKD (stages 1-5) determined by laboratory measures, estimated glomerular filtration rate (eGFR) - a blood measure of

kidney function, and albuminuria/proteinuria - the presence of increased levels of albumin/protein in the urine (Figure 1-1). CKD can progress to kidney failure (CKD stage 5), where there is a need for consideration of kidney replacement therapy (KRT) in the form of dialysis or kidney transplantation. Prediction of progression of CKD to kidney failure is an important part of CKD management and influences clinical decisions regarding referral, monitoring and treatment planning.

Figure 1-1 KDIGO staging and classification of CKD using eGFR and albuminuria with risk of adverse outcomes (mortality, progression of CKD, kidney failure)¹

KDIGO: Prognosis of CKD by GFR and albuminuria categories				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73 m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

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

Figure published with permission (Appendix 1).

Kidney failure prognostic models predict the risk of progression of CKD to the point of kidney failure. The kidney failure risk equation (KFRE) is currently the most widely validated and clinically adopted prognostic model for estimating the risk of progression from CKD to kidney failure^{9, 10}. KFRE incorporates routinely available clinical variables, age, sex, eGFR and urine albumin-creatinine ratio (uACR), to estimate an individual's probability of progressing to KRT within two or five years. KFRE is now recommended in both UK NICE (National Institute for Health and Care Excellence) CKD guidelines¹¹ and the international Kidney

Disease Improving Global Outcomes (KDIGO) CKD guidelines¹. However, clinical guidance typically focuses on single conditions or organs and does not account for the complexities of multimorbidity or frailty and the holistic management of patients, and robust evidence on the performance and applicability of KFRE in these populations is limited.

Individuals with CKD and multimorbidity or frailty may follow distinct disease trajectories compared to those with CKD alone, with evidence that multimorbidity is associated with renal progression¹² and major adverse kidney events (KRT, doubling of creatinine, eGFR <15 or >30% decline in eGFR)¹³. Additionally, competing mortality risk, which is particularly relevant for individuals with multimorbidity, frailty and older individuals, is not incorporated into KFRE calculations. Moreover, individuals living with multimorbidity and/or frailty may be more likely to opt for conservative management or be unsuitable for dialysis or transplantation, decisions that current prognostic models, including KFRE, do not account for. These factors may impact predictive accuracy of kidney failure prognostic models and how they are applied in clinical practice.

Beyond prognostic performance, the presence of multimorbidity and frailty may impact how patients and healthcare professionals interpret and utilise risk information. The presence of complex care needs, polypharmacy, fragmented care and treatment burden, all of which are associated with multimorbidity and frailty¹⁴, have the potential to influence how prognostic models are perceived, trusted and acted upon in clinical care and decision-making. Understanding how multimorbidity and frailty alongside CKD impact the performance and clinical utility of KFRE is therefore essential in exploring how it might be used for this group of people. Quantitative methods can identify the extent to which the presence of multimorbidity or frailty affects predictive validity, whilst qualitative methods can provide deeper insight into how patients and healthcare professionals interpret and use prognostic information in the real-world setting. Together, these complementary perspectives can inform how best to implement KFRE to support more personalised and holistic care for this group of people.

1.3 Hypothesis

This thesis focuses on testing the following hypothesis:

The presence of multimorbidity or frailty in addition to CKD impacts the performance of the kidney failure risk equation and the way it is utilised in clinical practice for such patients.

The thesis will explore how multimorbidity and frailty have been encompassed in existing kidney failure prognostic models, how they impact model performance of the kidney failure risk equation and how the presence of multimorbidity or frailty impacts perceptions and understanding of CKD, kidney failure and the use of the kidney failure risk equation in clinical practice.

1.4 Research questions

Research question 1 (RQ1):

What is the prevalence of multimorbidity or frailty in cohorts used to develop and/or validate kidney failure prediction models for CKD?

Research question 2 (RQ2):

How does the presence of multimorbidity impact the performance of the kidney failure risk equation and is it influenced by the competing risk of mortality?

Research question 3 (RQ3):

How does the presence of frailty impact the performance of the kidney failure risk equation and is it influenced by the competing risk of mortality?

Research question 4 (RQ4):

Is the kidney failure risk equation model performance influenced by the use of cystatin C based eGFR equations in place of creatinine based eGFR?

Research question 5 (RQ5):

Does the presence of multimorbidity or frailty impact how patients or healthcare professionals understand or perceive CKD, risk of kidney failure and the use of the kidney failure risk equation in shared decision-making?

1.5 Outline of chapters

This thesis is presented in journal, publication format. The results are presented as they have been submitted or published in peer-reviewed journals. The chapters presented are summarised below.

Chapter 2 gives a background of CKD, multimorbidity, frailty and how these problems are interconnected. Summarising the existing literature on the relationships between multimorbidity and frailty and CKD. Additionally, it gives background to kidney failure prognostic models including the kidney failure risk equation and the use of shared decision-making.

Chapter 3 describes the methods and data sources used in this thesis.

Chapter 4 presents the findings of a systematic review of the representation of multimorbidity and frailty in the development and validation of kidney failure prognostic prediction models (RQ1).

Chapter 5 presents the findings of a quantitative validation study of the kidney failure risk equation in people with CKD and multimorbidity in the UK Biobank and Stockholm CREAinine Measurements project cohorts (RQ2 and RQ4).

Chapter 6 presents the findings of a quantitative validation study of the kidney failure risk equation in people with CKD and frailty in the UK Biobank cohort (RQ3 and RQ4).

Chapter 7 presents the findings of the qualitative descriptive study investigating patients' and health care professionals' perspectives of CKD, kidney failure risk and use of the kidney failure risk equation in multimorbidity and frailty (RQ5).

Chapter 8 summarises the overall findings of the thesis, as well as considering the potential implications, strengths and limitations of the work and discusses directions for future research relating to the topics of the thesis (RQ6).

2 Chapter: 2 Background

2.1 Chapter summary

This chapter gives the background to the thesis. It provides a comprehensive overview of the epidemiology, definitions and clinical implications of chronic kidney disease, multimorbidity and frailty, including the overlap in conditions. This is then followed by discussion of prognostic tools for kidney failure, with a specific focus on the kidney failure risk equation. This chapter concludes with the background of treatment burden and shared decision-making in the management of CKD and in the context of complex patient groups such as those with multimorbidity or frailty.

2.2 Chronic kidney disease (CKD)

2.2.1 Chronic kidney disease definition and staging

CKD is typically defined as the presence of structural or functional abnormalities of the kidneys, persisting for a minimum of three months and that have implications for health¹. Abnormalities include a sustained reduction in estimated glomerular filtration rate (eGFR) ($<60\text{ml/min/1.73m}^2$), raised levels of albuminuria, imaging or histological abnormalities or changes in other biochemical markers, such as electrolyte disturbances.

Staging of CKD is based on the KDIGO classification¹, using eGFR categories (G1-G5) and albuminuria categories (A1-A3). The eGFR ‘G categories’ reflect declining levels of kidney function and the albuminuria ‘A categories’ capture increasing levels of albuminuria. These categories are combined in a two-dimensional grid, forming the CKD “heat map”, introduced in Chapter 1 (Figure 1-1)¹. The colour gradients in this grid represent increasing risk of adverse outcomes including kidney failure, cardiovascular disease, and mortality. This integrated approach highlights the additional prognostic information that albuminuria provides over and above eGFR in isolation.

CKD should, importantly, be distinguished from acute kidney injury (AKI) and acute kidney disease and disorders (AKD). AKI is defined as an abrupt decline in

kidney function that occurs over a period of hours or days, classified into three stages by changes in serum creatinine and/or urine output¹⁵ (Table 2-1).

Table 2-1. Staging of AKI

AKI Stage	Serum creatinine	Urine output
1	1.5-1.9 times baseline within the prior 7 days OR ≥0.3 mg/dl (≥26.5 µmol/l) increase within 48 hours	<0.5 ml/kg/h for 6-12 hours
2	2.0-2.9 times baseline	< 0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥4.0 mg/dl (≥353.6µmol/l) OR Initiation of kidney replacement therapy	Anuria for ≥ 12 hours

Adapted from KDIGO Clinical Practice Guideline for Acute Kidney Injury¹⁵

AKI is a clinical syndrome with a wide variety of aetiologies, including ischaemic injuries, nephrotoxic exposures, obstructive nephropathy and specific kidney disease (e.g. acute interstitial nephritis). AKD is defined as a decline in kidney function for less than 3 months, of which AKI is considered a subset. In contrast to AKI and CKD, AKD is a relatively new concept and therefore has limited epidemiological evidence surrounding it. Figure 2-1 provides a visual representation of the overlap between AKI, AKD and CKD and Table 2-2, an overview of the diagnostic criteria for each.

Figure 2-1. Overview of AKI, AKD and CKD relationships and diagnostic criteria

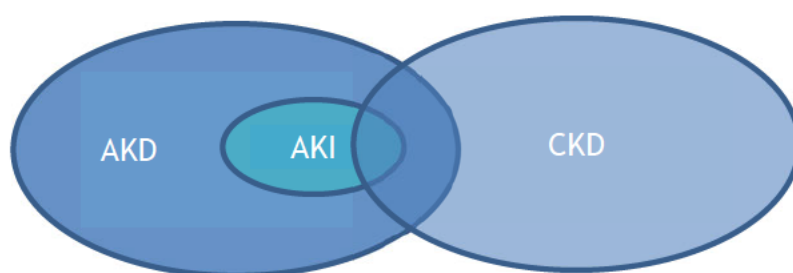


Table 2-2. Diagnostic criteria for AKI, AKD and CKD

	AKI	AKD	CKD
Duration	Within 7 days	<3 months	>3 months
Kidney function criteria	Increase in serum creatinine $\geq 50\%$ within 7 days OR increase in serum creatinine by ≥ 0.3 mg/dL ($26.5\mu\text{mol/L}$) within 2 days OR oliguria for ≥ 4 hours	AKI OR $\text{GFR} < 60\text{ml/min/1.73m}^2$ OR decrease in GFR by $\geq 35\%$ times baseline OR increase in serum creatinine $\geq 50\%$ times baseline	$\text{GFR} < 60\text{ml/min/1.73m}^2$
Structural criteria	Not defined	Marker of kidney damage (albuminuria, haematuria, pyuria most common)	Marker of kidney damage (albuminuria most common) OR small kidneys

Adapted from KDIGO Clinical Practice Guideline for Acute Kidney Injury¹⁵

Despite the differences in kidney function criteria and timing for diagnosis, AKI and AKD are relevant to CKD because episodes of AKI and AKD are associated with an increased risk of developing CKD and the progression of existing CKD¹⁶⁻¹⁸.

Risk factors for the development of CKD overlap closely with the presence of other major non-communicable diseases and risk factors for these. Key risk factors for CKD include diabetes/high fasting plasma glucose, hypertension, obesity and cardiovascular disease, as well as smoking, advancing age and a family history of kidney disease. However, the underlying aetiology of CKD is heterogenous including but not limited to diabetic kidney disease, hypertensive nephrosclerosis, glomerulonephritis, obstructive nephropathy, structural abnormalities and polycystic kidney disease and other hereditary/genetic kidney diseases. Identifying the underlying aetiology of CKD can inform prognosis and management, but in some individuals the cause of CKD may be mixed or uncertain, particularly in the presence of multiple long-term conditions.

2.2.2 Chronic kidney disease epidemiology, public health burden and health inequalities

CKD is estimated to affect approximately 13-15% of adults globally, with prevalence increasing². Estimates demonstrate that worldwide in 2023, CKD was the ninth leading cause of death, twelfth leading cause of disability-adjusted life years (DALYs) and that age-standardised prevalence of CKD has increased by 3.5% from estimates in 1990. CKD is more common in advancing age; therefore, prevalence and burden of CKD has increased as the overall population age has increased. Changing population risk profiles for diabetes, hypertension, cardiovascular disease and obesity and the subsequent rising prevalence of these diseases, have also contributed to the increasing burden of CKD. Additionally, improved survival from cardiovascular events including myocardial infarction and other improvements in healthcare treatments means that increasing numbers of people are living longer and developing CKD as consequence of other long-term diseases such as diabetes and hypertension.

The prevalence of CKD is higher in female sex compared to male but more men progress to kidney failure with kidney replacement therapy¹⁹, likely reflecting

differences in pathophysiology²⁰, risk factors profiles but also disparities in management, research participation and healthcare utilisation²¹.

In addition to demographic patterning of CKD seen across age and sex, socioeconomic and ethnic inequalities in the incidence, progression and access to care in CKD also exist^{22, 23}. Consistent evidence demonstrates that people living in the most deprived areas have a higher incidence of CKD and present later to nephrology services²⁴, with a UK cohort of 1657 patients showing that those living in the lowest socioeconomic quintile had lower eGFR at first nephrology assessment compared to those from higher socioeconomic quintiles²⁵. Within UK primary care data, it has also been demonstrated that nearly 55% of adults with CKD stage 3-5 in an ethnically diverse South London population were missing CKD coding, and that uncoded CKD was independently associated with deprivation and black Caribbean, black African, South Asian and “non-stated” ethnic groups compared to white ethnicity²². Additionally for patients that had uncoded CKD the quality of care, including prescribed guideline recommended medications, was lower compared to those with coded CKD. Globally, such inequities also exist, with CKD prevalence being highest in low- and middle-income countries, where the prevalence of CKD is around 18% but the prevalence of KRT and particularly kidney transplant is much lower than higher-income countries² related to healthcare infrastructure and poor access to KRT.

In addition to the impact of CKD on mortality and DALYs there are significant health system and economic implications. The majority of CKD care is provided in primary care/community settings, where increasing prevalence of CKD and multimorbidity and expanding treatment options contribute to the growing healthcare “workload”, for both patients and healthcare professionals. Research utilising a population-level health economic model for CKD, estimates the total annual cost of kidney disease in the UK to be around £7.0 billion²⁶. Globally, the healthcare system and economic costs of CKD are recognised to increase with advancing stage of CKD, with KRT resulting in large healthcare utilisation and associated costs^{27, 28}. In addition, individuals with CKD have an increased risk of hospitalisation compared to those without CKD²⁹, related to heart failure, infections and AKI³⁰. Subsequently, CKD represents a substantial and growing, global, clinical and economic burden.

2.2.3 eGFR equations and kidney function biomarkers

Assessment of kidney function is central to the diagnosis, staging and management of CKD. Measurement and estimation of kidney function/glomerular filtration capacity (GFR) can be conducted in several ways. Measured GFR (mGFR) is approximated by measuring plasma clearance of an exogenous substance, typically iohexol. Estimated GFR (eGFR) is calculated from the measurement of an endogenous biomarker, most commonly serum creatinine³¹.

Iohexol based mGFR is resource intensive and impractical for routine clinical use. Consequently, kidney function is usually assessed using eGFR. A range of creatinine-based eGFR equations have been developed. Serum creatinine is a breakdown product of creatine phosphate in skeletal muscle that is freely filtered at the glomerulus and is primarily eliminated through the kidneys, but with some active secretion from the proximal tubule in the kidney. Creatinine concentrations are therefore influenced by both GFR and non-GFR determinants, including age, sex, ethnicity, muscle mass, diet and some medications, e.g., trimethoprim which can impair tubular secretion of creatinine. Low muscle mass, as seen in frailty or sarcopenia, can result in low creatinine levels and overestimation of kidney function when using creatinine-based eGFR. Whereas high muscle mass can lead to raised serum creatinine levels and false underestimation of kidney function.

In parallel to refinements of creatinine-based equations which are later discussed, cystatin C emerged as an alternative and complementary kidney filtration biomarker that could be used in equations to derive eGFR. Cystatin C is a low molecular weight protein, produced by all nucleated cells, freely filtered by the glomerulus, with near-complete reabsorption in the proximal tubule and no renal tubular secretion³². It is not affected by muscle metabolism like creatinine and therefore is less influenced by factors such as age and sarcopenia. However, other non-GFR determinants impact cystatin C such as inflammation, smoking, thyroid disease, obesity and diabetes³³. It is evidenced from large general population and CKD specific cohorts that cystatin-based eGFR (cystatin C alone or in combination with creatinine), improve risk prediction for kidney failure, cardiovascular disease and mortality compared to eGFR calculated using creatinine in isolation^{34, 35}.

The development and refinement of calculations to estimate kidney function have been observed over the last 50 years. The Cockcroft-Gault equation, using sex, age, weight, and serum creatinine, was published in 1976 and was extensively employed to estimate creatinine clearance³⁶. A conceptual limitation is that Cockcroft-Gault estimates creatinine clearance rather than GFR and may therefore overestimate filtration due to tubular secretion of creatinine. Additionally, its dependence on body weight also introduces substantial variation in individuals at the extremes of weight or where there is altered body composition. The Modification of Diet in Renal Disease (MDRD) study subsequently used data collected from 1628 participants with kidney disease in a multicentre, controlled trial to improve the prediction of GFR using serum creatinine, resulting in the development of the MDRD eGFR formula, based on age, sex, serum creatinine and race, as a more accurate estimate of eGFR, superseding previously developed equations³⁷. The MDRD equation was later re-expressed for standardised (IDMS-traceable) creatinine assays, but despite this it remains biased towards underestimation at higher true GFR because it was primarily developed and validated in individuals with CKD. As a result, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed and published in 2009³⁸, similarly incorporating age, sex, race and serum creatinine levels, and was widely adopted in clinical practice. Alongside the refinement of creatinine-based equations, CKD-EPI developed cystatin C-based estimating equations in 2012, including a cystatin C and a combined creatinine-cystatin C equation³⁹. In external validation, the combined equation improved precision and overall accuracy compared with equations using either biomarker alone, and improved classification around the diagnostic threshold for CKD of 60 ml/min/1.73m². As with previous equations there are limitations with the 2009 CKD-EPI equation, with evidence demonstrating that inclusion of race within the equation results in overestimation of GFR in those categorised as Black race and may contribute to systemic racism in healthcare⁴⁰. Consequently, the 2021 CKD-EPI revision removed race from the updated eGFR equation⁴⁰. Importantly, the 2021 CKD-EPI work also evaluated race-free equations using cystatin C and combined creatinine-cystatin C. It was demonstrated that race-free creatinine-cystatin C equations were more accurate than race-free creatinine eGFR equations and produced smaller differences in performance between participants classed as Black and non-Black race⁴⁰. Other equations

such as the Lund-Malmö⁴¹, Berlin Initiative Study⁴² and European Kidney Function Consortium (EKFC)⁴³ equations have been developed specifically in European populations and therefore have better predictive performance in these populations. Due to variations in the derivation cohorts and the mathematical functions used, different equations will produce different eGFR estimates for the same creatinine levels^{44, 45}.

International guidelines, including KDIGO¹, recommend using creatinine-based eGFR and confirmatory testing with cystatin C in specific scenarios e.g., when creatinine-based eGFR may be unreliable or when more accurate risk stratification is needed. These recommendations acknowledge the complementary strengths and limitations of each biomarker.

In populations with multimorbidity or frailty, non-GFR determinants may bias the estimation of GFR and the prognostic utility of eGFR. As already described creatinine and cystatin C have different non-GFR determinants that should be considered and that may be present in the context of multimorbidity or frailty. The choice of biomarker and eGFR equation has practical implications for CKD staging, classification of progression and risk prediction and therefore may impact clinical decision-making such as drug dosing, specialist referral and KRT planning.

2.2.4 Chronic kidney disease progression and kidney failure

Progression of CKD varies widely amongst individuals, reflecting heterogeneity in underlying aetiology, comorbid conditions, and response to treatments. Progression is typically characterised by a sustained decline in eGFR and/or worsening albuminuria over time. Some individuals have stable function for many years, others experience slow or intermediate progressive decline, and a smaller number have rapidly progressive disease^{46, 47}. However, trajectories will also be influenced by factors such as intercurrent illnesses or medications and therefore clinically do not always follow one trajectory phenotype as described in the literature.

Factors associated with accelerated decline in kidney function overlap with the risk factors for the development of CKD, including poor blood pressure control,

repeated hyperglycaemia, persistent albuminuria/proteinuria and exposure to nephrotoxic medications such as non-steroidal anti-inflammatory drugs. AKI can also contribute to stepwise reductions in kidney function and increase the risk of progression of CKD to kidney failure¹⁶.

Kidney failure (CKD G5), also referred to as CKD stage 5 or end stage kidney disease, is defined by KDIGO as eGFR <15ml/min/1.73m or the need for initiation of KRT (dialysis or kidney transplantation)²¹. Progressive deterioration in kidney function is associated with a number of complications that are discussed in more detail in the following sub-section (2.2.5). There is variation in the nomenclature used to describe kidney function and kidney disease, with KDIGO proposing specific terminology that should be used within scientific publications following a Consensus Conference in 2019⁴⁸. Likewise, definitions of kidney failure used in research vary, although consensus for harmonisation of outcomes for use in clinical trials has been established through work by the International Society of Nephrology⁴⁹. Measures used as surrogate markers of future kidney failure and definitions of kidney failure events in research include, in combination or isolation, sustained eGFR thresholds (e.g., 40% or 50% decline in eGFR) [surrogate markers of future kidney failure], initiation of KRT alone, death from kidney failure and more recently meta-analyses also supporting the use of changes in eGFR slope as a surrogate endpoint for kidney failure particularly in clinical trial settings⁵⁰.

Kidney failure can have a profound impact for patients⁵¹. When an individual is approaching or presents with kidney failure they must consider, alongside healthcare professionals, treatment options relating to KRT, these include dialysis (haemodialysis or peritoneal dialysis), kidney transplantation (living or deceased donor) or conservative management (non-dialysis/transplantation management of kidney failure)¹. These decisions involve consideration of the balance between the potential benefits in survival or symptoms control versus possible burdens associated with treatments including time commitment, dialysis or transplant related risks/complications and impact on quality of life. If KRT is chosen plans must be made for dialysis access or transplant work-up.

Not all options may be suitable for each individual and discussion will be informed and guided by healthcare professionals working within a

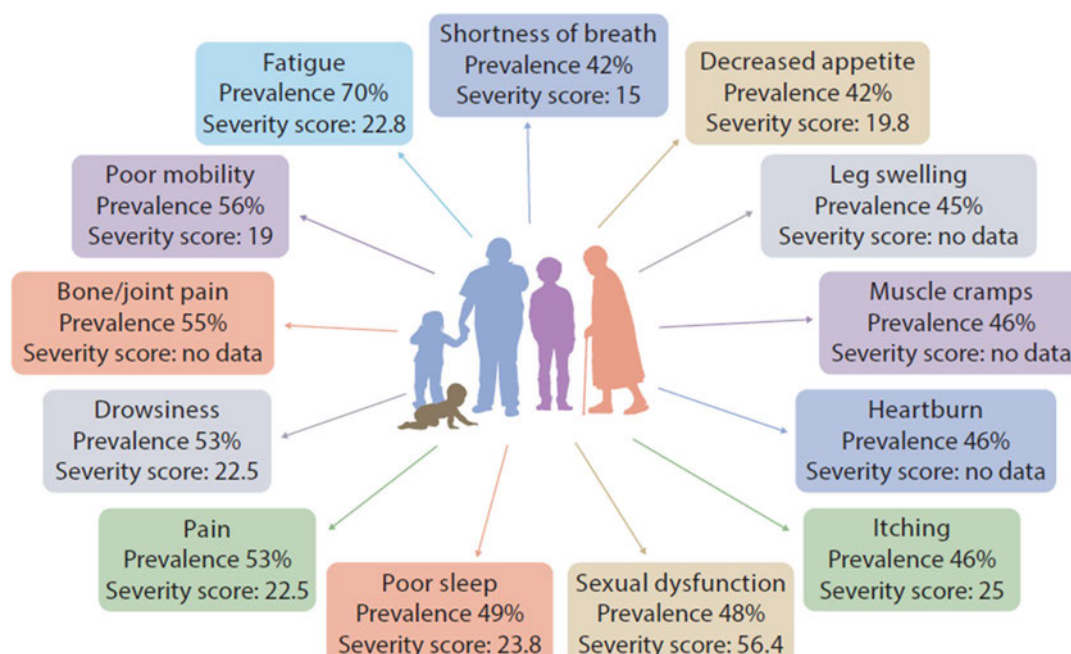
multidisciplinary team. For older individuals and those with substantial multimorbidity or frailty, the benefits of dialysis may be uncertain or modest compared to conservative care. However, evidence comparing the effectiveness of dialysis and conservative care in these groups of patients is lacking and relies mainly on small observational studies⁵². This topic is being addressed through the 'Prepare for Kidney Care' trial which aims to explore the survival, quality of life and experiences of patients and their families comparing dialysis and conservative care and is hoped to report findings in 2026⁵³.

At a health system level, as already discussed, kidney failure is associated with high costs relating to dialysis infrastructure, transplantation, inpatient care and management of complications. Unplanned or emergency initiation of dialysis, often in the context of late referral or missed opportunities for planning⁵⁴, is associated with worse clinical outcomes⁵⁵, higher healthcare costs⁵⁶ and negative psychological/quality of life^{57, 58} impacts for patients compared to planned initiation of KRT. Timely identification of individuals at highest risk of progression to kidney failure, accompanied by appropriate planning, is therefore a key goal of the management of CKD.

2.2.5 Symptoms and complications in chronic kidney disease

CKD is typically an asymptomatic condition until it progresses to the advanced stages, which contributes to its under-diagnosis and late presentation. As kidney function declines, a wide range of symptoms can emerge, including fatigue, pruritus, shortness of breath, sleep disturbance, cognitive difficulties, reduced appetite, pain and reduced mobility⁵⁹, these are represented with associated prevalence and severity scores in Figure 2-2. Symptoms may be multifactorial, including being caused by CKD, by other long-term conditions and/or related to side effects of prescribed medications. The overlap in symptoms and possible aetiologies, particularly in the presence of multiple long-term conditions, can make determining the cause of symptoms and treating them particularly challenging.

Figure 2-2 Common symptoms, prevalence and severity in individuals with CKD¹



KDIGO figure adapted from Fletcher et al. Symptom burden and health-related quality of life in chronic kidney disease: a global systematic review and meta-analysis. PLoS Med. 2022;19:e1003954.⁵⁹ published with permission (Appendix 1).

Progressive reduction in kidney function is associated with complications such as anaemia, metabolic acidosis, electrolyte dysfunction such as hyperkalaemia, fluid overload and CKD mineral bone disease, all of which become more common and severe with declining eGFR⁶⁰. Individual participant data meta-analysis from the CKD-PC shows that the adjusted prevalence of anaemia is around 12-15% of adults with CKD stage 3, increasing to approximately 57-61% by CKD stage 5. Metabolic acidosis similarly becomes more common as kidney function declines, with a serum bicarbonate <22 mmol/L being observed in 7-8% of adults with CKD stage 3 and 36-38% in those with CKD stage 5. CKD mineral bone disease is observed to occur early in the course of CKD, with progressive abnormalities in calcium, phosphate, vitamin D metabolites and parathyroid hormone. However, many of these complications are only evident if monitored or tested for by a

healthcare professional. Fluid overload and hypertension can contribute to breathlessness, oedema and cardiovascular strain. Collectively, these complications contribute substantially to excess risk of hospitalisation, cardiovascular events and death in individuals with CKD, as well as adding to the symptom burden and reduced quality of life observed in advanced CKD.

Alongside symptom burden, many individuals with CKD experience significant treatment burden^{51, 61}. Treatment burden encompasses the number and complexity of self-care tasks required to live with and manage CKD and other long-term conditions. For CKD this may relate to taking multiple medications often with complex dosing instructions, monitoring observations such as blood pressure or blood sugars, adapting to dietary and/or fluid restrictions, attending frequent appointments and navigating and interacting with multiple healthcare professionals and services. Treatment burden will be introduced in more detail in the subsequent subsection 2.6.

2.3 Multiple long-term conditions (MLTC)/Multimorbidity

2.3.1 Multimorbidity definition(s) and measurement

Multimorbidity, also referred to as multiple long-term conditions (MLTC), is defined as the coexistence of two or more long-term conditions (LTCs) within an individual⁶. This concept differs from comorbidity, which in general describes additional LTCs in relation to a single index disease⁶². In multimorbidity, no single disease is assumed to be primary, instead the focus is on the cumulative impact of multiple conditions on health, functioning and healthcare utilisation.

Differing multimorbidity classifications have been operationalised in both research and clinical practice⁶³. Definitions have included simple counts of LTCs, which are easy to calculate and interpret and are widely used in research and clinical settings. However, they treat all conditions as equal and do not account for difference in severity, prognosis or impact on quality of life. Weighted multimorbidity/comorbidity indices, such as the Charlson Comorbidity Index⁶⁴ or the Elixhauser Comorbidity Index,⁶⁵ assign different weights to conditions based on their associations with outcomes such as mortality or hospitalisation which

can provide a more nuanced measure of prognostic burden but potentially at the cost of greater complexity.

There is variation in relation to the number, type and severity of specific conditions included in multimorbidity definitions and measurements. A cross-sectional study using primary care data has demonstrated that the number and selection of conditions included in a multimorbidity measure results in large difference in multimorbidity prevalence and that this also varied across different sub-populations e.g., older vs younger age groups⁶⁶. A Delphi consensus exercise, completed in 2021, made reporting recommendations for multimorbidity studies to improve transparency and replicability and gained consensus on the characteristics that a long-term condition should have to be included in a multimorbidity measure (Table 2-3)⁶. Additionally, consensus was reached for 24 conditions that should always be included in multimorbidity measures and 35 conditions that should usually be included unless there is a good reason not to include them. However, due to the heterogeneity of multimorbidity and different clinical and research contexts there is no universal measurement or classification that can be/is being used, which complicates and limits comparison and synthesis of evidence from multimorbidity research.

Table 2-3. Characteristics of conditions that should be included in a multimorbidity measure from Ho et al. Delphi consensus study⁶

Characteristics of long-term condition
Currently active
Permanent in their effects
Requiring current treatment, care, or therapy
Requiring surveillance
Relapsing- remitting conditions requiring ongoing care

Data sources used to measure LTCs included in multimorbidity measures also vary. Sources include administrative coding from primary or secondary care data, and self-report questionnaires, each with strengths and limitations. For example, ascertainment of conditions has been shown to vary depending on whether primary or secondary care data is used⁶⁷, whereas self-reported LTCs may be influenced by recall or awareness.

The choice of multimorbidity measure should ideally be aligned with the outcome and context of interest, for example paediatric vs adult populations or CKD vs general population. There is a need to capture clinically relevant disease burden, but this is often balanced with feasibility to operationalise measures within research.

Besides the standard definition of multimorbidity, additional conceptual types of multimorbidity have also been proposed. Complex multimorbidity was identified as a potentially useful concept from the Ho et al consensus study⁶. However, consensus from this study was not reached on its definition. Complex multimorbidity is typically referred to as the presence of three or more LTCs affecting three or more body systems⁶⁸. Other typologies focus on specific patterns of conditions such as cardiometabolic multimorbidity¹³, mixed mental-physical multimorbidity or particular disease “clusters” identified using data-driven methods^{69, 70}. These distinctions highlight the importance of considering multimorbidity combinations and interactions as well as the number of conditions.

2.3.2 Epidemiology of multimorbidity

Multimorbidity is highly prevalent, increases with age and is socioeconomically patterned. A large systematic review and meta-analysis of studies published between 2020-2021 found the overall global prevalence of multimorbidity was 37.2% and has increased in prevalence over the last two decades⁷¹. In addition, they demonstrated variation based on:

- Geographical location, with the highest prevalence of multimorbidity being seen in South and North America (45.7% and 43.1% respectively).

- Sex, highlighting higher prevalence of multimorbidity in females (39.4%) compared to males (32.8%).
- Age, with as estimated 51.0% of adults >60 years old globally experiencing multimorbidity, compared to 44.4% in those ≥30 years old.

Evidence has shown that individuals living in more deprived areas tend to develop multimorbidity at a younger age, with multimorbidity occurring 10-15 years earlier in those living in the most deprived settings compared to those in the least socioeconomically deprived areas⁷². Furthermore, socioeconomic deprivation was associated with an increased prevalence mixed mental and physical multimorbidity⁷².

Minority ethnic populations are also disproportionately affected by multimorbidity, with data demonstrating increased prevalence of multimorbidity and earlier mortality in some groups compared to those of White ethnicity^{73, 74}. Individuals from minority ethnic groups are more likely to be exposed to discrimination or adverse life events that lead to an increased chance of living in socioeconomically deprived areas⁷⁵. Additionally, evidence highlights that these groups have poorer health related quality of life, worse experience of healthcare services and increased difficulty self-managing their own health needs⁷⁶. All of which may be factors in the earlier development of multimorbidity and increased prevalence seen in many minority ethnic populations.

Temporal trends and projections indicate that, as populations age and survival from acute events improves, the prevalence and complexity of multimorbidity will continue to rise, with major implications for health and social care services^{71, 77, 78}.

2.3.3 Impact of multimorbidity

Multimorbidity is associated with a wide range of adverse outcomes, including higher risk of mortality, hospitalisation and unscheduled healthcare use compared to individuals without multimorbidity⁷⁹⁻⁸¹. In addition to increased healthcare utilisation multimorbidity poses considerable other clinical challenges for healthcare professionals. Clinical guidelines typically focus on single diseases

and may offer conflicting advice when applied to people with multiple long-term conditions⁸². Evidence from clinical trials is often lacking, as trials often exclude individuals with substantial multimorbidity, and subsequently include fewer individuals with multimorbidity than the general population limiting generalisability and applicability of the findings⁸³. Healthcare professionals must therefore balance competing priorities, uncertainty and weigh potential harms and benefits of treatment in the context of multimorbidity.

Multimorbidity is also associated with greater functional decline and disability compared to those with fewer or no LTCs^{84, 85}. Additionally, polypharmacy (typically defined as the administration of more than five medications⁸⁶) is more commonly observed in individuals with multimorbidity⁸⁷ and is associated with increased risk of adverse drug reactions, drug-drug interactions, and medication errors⁸⁸. In addition to adverse clinical outcomes, multimorbidity is also associated with poorer quality of life⁸⁹, reduced ability to work⁹⁰ and to engage in social activities⁹¹.

Multimorbidity may also alter disease trajectories^{92, 93} and the perceived importance of any single condition⁹⁴. The order in which diseases occur within multimorbidity may influence the development of subsequent conditions or clinical outcomes.

From a patient's perspective conditions that are more symptomatic or that have a greater impact on daily functioning may be more salient than a condition that is asymptomatic⁹⁵, such as CKD despite the significant long-term implications of such chronic diseases. Recognising these differing perspectives and factors is crucial when considering communication and shared decision-making in individuals with multimorbidity.

2.4 Frailty

2.4.1 Frailty definition and measure(s)

Frailty is defined as a state of reduced physiological reserve that results in increased vulnerability to stressors⁷. Examples of physiological stressors that can

result in decompensation include minor illnesses, intercurrent infections and medication side effects.

Frailty is conceptually distinct from disability, comorbidity and multimorbidity. Disability refers to long-term physical, mental, intellectual or sensory impairments that may have a substantial negative effect on daily activities of living⁹⁶. Definitions of multimorbidity and comorbidity have been discussed earlier in this chapter but relate to the presence of multiple diseases/LTCs in relation to or in the context of each other. Frailty often co-occurs with multimorbidity and disability but can exist in isolation.

Although the definition of frailty is well established, there are a diverse range of measures and models used to quantify or identify frailty in clinical and research practice^{97, 98}(briefly described in Table 2-4). However, there is a lack of international consensus around which measure should be used.

Table 2-4. Overview of main frailty measures/tools

Frailty measure name	Description	Included measures	Classification/cut-offs
Frailty phenotype ⁸	Frailty based on specific physical criteria	Unintentional weight loss, self-reported exhaustion, weakness (low grip strength), low walking speed and low physical activity.	Frailty = presence of three or more criteria Pre-frailty = presence of one or two criteria Robust = none
Frailty index - Frailty index of cumulative deficits ⁹⁹	Based on a cumulative deficit model - the unweighted sum of age- and health-related	Varied “deficits” but may include long-term health conditions, laboratory or physical	Continuous score 0-1, cut-offs vary by specific index and by study

- Frailty index derived from comprehensive geriatric assessment¹⁰⁰ - Electronic frailty index¹⁰¹ - Laboratory frailty index^{102, 103}	“deficits”. Calculated as the proportion of deficits present out of the total number of potential deficits assessed.	measures, symptoms and/or functional impairments. Recommended a minimum of 30 are included, covering a range of physiological systems and domains.	Higher score = more frailty
Clinical frailty scale¹⁰⁴	Graphical image-based chart with corresponding written description.	Based on mobility, energy, physical activity and function.	Graded from 1 = very fit to 9 = terminally ill
FRAIL scale¹⁰⁵	Similar to frailty phenotype - based on specific physical measures	Fatigue, ambulation, resistance, illness and weight loss.	Frailty = presence of three or more criteria Pre-frailty = presence of one or two criteria Robust = none
Edmonton frailty scale¹⁰⁶	Assesses frailty across nine clinical subscales sub-scales.	Subscales - cognition, general health, physical performance,	Severe frailty = 12-17 Moderate frailty = 10-11

		functional independence, medication, social support, mood, nutrition and continence	Mild frailty = 8-9 Vulnerable = 6-7 Non frail ≤ 5
Groningen frailty indicator ¹⁰⁷	Frailty assessed using 15 questions, covering four domains.	Four domains - physical, cognitive, social and psychological.	Frailty ≥ 4
Hospital Frailty Risk Score ¹⁰⁸	Frailty measure calculated from electronic health records	Includes 109 health “deficits” from ICD-10 codes	Frailty risk: High >15 Intermediate 5-15 Low <5
Kihon Checklist ¹⁰⁹	Developed from components of the comprehensive geriatric assessment	25 self-reported items from the comprehensive geriatric assessment	Continuous score 0-25 Higher score = more frailty
Multidimensional prognostic instrument ¹¹⁰	Derived from eight comprehensive geriatric assessment components	Includes number of medications, activities of daily living, instrumental activities of daily living, cognition,	Frailty >0.66

		nutrition, risk of pressure sores, co-morbidity and living status	
Tilburg frailty indicator ¹¹¹	Questionnaire based measure of frailty	Assesses physical health, psychological wellbeing and social functioning	Frailty ≥ 5

A recently updated review of frailty measures in research has summarised the vast array of tools available for use in clinical and research settings⁹⁷. The study highlights significant variation in the domains included, thresholds for defining frailty and populations studied⁹⁷. Most research has been conducted in older adults, in high-income countries, with less evidence available in younger populations, those with multimorbidity and in low- and middle-income countries.

Comparative studies have examined how different frailty measures perform in predicting adverse outcomes such as mortality, hospitalisation, and functional decline^{112, 113}, with variation observed in frailty identification as well as associations with adverse outcomes. Reflecting the multidimensional nature of frailty, these tools differ in their approaches, complexity, data requirement and suitability for differing settings and populations. Each method has differing strengths and limitations and there is ongoing debate about which is best used for differing circumstances. Like multimorbidity measures, the frailty measure(s) utilised should be in keeping with the purpose of measurement, resources available and the population and setting in which measurement is occurring. The heterogeneity of measures complicates data synthesis and comparison across studies, emphasising the importance of transparent reporting of how frailty is defined and assessed.

2.4.2 Frailty epidemiology

Frailty, like multimorbidity, is common and increasing in prevalence^{114, 115}. However, the overall global prevalence of frailty is difficult to accurately assess with prevalence estimates varying by measure use, population studies, setting (e.g., community vs hospital, high income countries vs low- or middle-income countries). Additionally, the fluctuating, dynamic nature of frailty, where individuals can move between frailty states over time, makes assessment of prevalence and classification of frailty in research challenging. A large systematic review including publications up to April 2021 aimed to assess frailty prevalence at a population level¹¹⁶. They included 253 unique prevalence estimates for adults aged ≥ 50 years old from 62 different countries, reporting a pooled prevalence of frailty of 12%, using the frailty phenotype, and 24%, using the frailty index. Estimated prevalence varied by sex, with female sex having a higher pooled prevalence than males (15% and 11% respectively, measured by frailty phenotype).

Frailty is associated with advancing age but is not seen exclusively in older adults. Despite this the majority of frailty research has been conducted in older age groups, typically those over 65 years old¹¹⁶ (57% of included studies in a recent large systematic review). A large study conducted in UK Biobank has explored associations between frailty and mortality in middle-aged and older-aged populations¹¹⁷. The study found that frailty and pre-frailty, assessed by the frailty phenotype, was associated with increased risk of mortality in all age groups in both male and females, except for females aged 37-45 years. They additionally described associations between frailty and multimorbidity, finding that frailty was significantly associated with multimorbidity, and each additional long-term condition was associated with a significantly great odds of frailty and pre-frailty.

The epidemiology of frailty is also influenced by socioeconomic status, with increased prevalence and earlier frailty onset observed in more socioeconomically deprived groups. A recent large systematic review, including 383 observational studies from 64 different countries published up to April 2023, found that lower socioeconomic status (defined by a variety of socioeconomic indicators) was associated with higher frailty prevalence and that socioeconomic

patterning was most evident in relatively younger populations¹¹⁸. The study also demonstrated that the relationship and association between frailty and risk of mortality was independent of socioeconomic status.

2.4.3 Impact of frailty

As a consequence of the decompensation that occurs in frailty, individuals with frailty experience an increased risk of adverse events such as falls¹¹⁵, loss of independence, hospitalisation¹¹⁹, admission to residential care and premature death¹¹⁹ compared to individuals of a similar age with no frailty.

Individuals with frailty are more likely to have polypharmacy¹²⁰ and increased healthcare utilisation¹²¹ including attending multiple appointments, which may be associated with significant treatment burden. Both polypharmacy and healthcare utilisation associated with frailty have significant healthcare cost implications¹²¹.

From a clinical perspective, recognition of frailty has important implications for treatment decisions, prognostic discussions and advanced care planning. Similar to multimorbidity research findings, healthcare professionals perceive care and management of frailty as complex and out with clinical guideline recommendations¹²². Recognition of frailty has been shown to result in more holistic assessment and patient centredness^{123, 124}, with evidence relating to comprehensive geriatric assessment suggesting it may also improve clinical outcomes¹²⁵. In addition, acknowledgement of frailty can inform decision-making around appropriateness and intensity of interventions.

2.5 Multimorbidity and frailty in CKD

2.5.1 Multimorbidity and frailty overlap

Multimorbidity and frailty frequently co-occur¹²⁶, with the prevalence of frailty having been shown to increase with increasing numbers of LTCs¹¹⁷, and are thought to share some overlapping mechanisms and pathophysiology, including chronic inflammation, vascular changes and loss of muscle mass¹²⁷. However, they are conceptually distinct. As already described multimorbidity describes the presence of multiple long-term conditions, whereas frailty reflects

vulnerability arising from reduced physiological reserve and accumulative deficits.

Many individuals with multimorbidity are not frail and retain good functional capacity. Conversely, some individuals may experience frailty despite having relatively few diagnosed long-term health conditions¹²⁶, for example due to sarcopenia, malnutrition or social vulnerability. Studies have demonstrated that the concomitant presence of multimorbidity and frailty is associated with increased risk of adverse outcomes. However, each construct appears to contribute independently to prognosis and to healthcare needs and the presence of both has likely cumulative but distinct impacts^{117, 128}. Appreciation of these overlap and distinctions is important in both research and clinical practice as potential management decision and interventions are likely to be affected by these.

In the context of CKD, where both multimorbidity and frailty are more common than in people without CKD^{4, 129}, understanding how they intersect and the impact they have is particularly relevant. They may influence not only clinical outcomes but also individuals' capacities, priorities and responses, decision-making and treatment options. This is highlighted within the KDIGO 2024 CKD guideline¹ where it is specifically acknowledged that special considerations for care are required across the life span, detailing older adults with multimorbidity or frailty within this (Figure 2-3).

Figure 2-3. Special considerations for CKD care across the lifespan highlighted within KDIGO 2024 CKD guideline¹

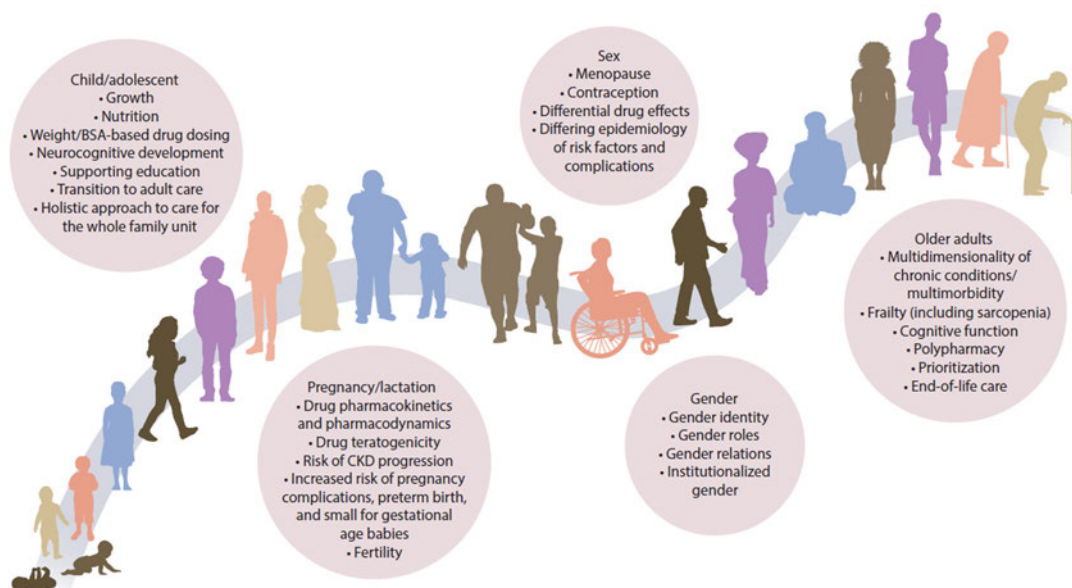


Figure published with permission (Appendix 1).

2.5.2 Multimorbidity and chronic kidney disease

People with CKD are more likely to have multiple long-term conditions than those without CKD, with a large cross-sectional study utilising Scottish primary care data⁴ demonstrating that 87.6% of adults with CKD had 2 or more LTCs in addition to CKD compared to 29.3% in those without CKD. In addition, evidence also shows as CKD progresses there is an increase in prevalence of LTCs⁶⁹.

Common co-occurring conditions for individuals with CKD include cardiovascular diseases, cerebrovascular disease, diabetes, musculoskeletal and mental health conditions^{69, 130}. Data-driven analyses, using large European population-based cohorts have identified distinct multimorbidity clusters across the spectrum of kidney function⁶⁹. The study identified cardiovascular conditions were more prominent within clusters at lower eGFR and that the presence of chronic pain and depression were common and associated with adverse outcomes (all-cause mortality and major adverse cardiovascular events) when in combination with physical conditions.

A recent systematic review and meta-analysis demonstrates that the presence of CKD and multimorbidity is associated with adverse outcomes, including increased risk of mortality, progression of kidney disease, hospitalisation and cardiovascular events, compared to CKD without multimorbidity¹². Additional

studies have also demonstrated the presence of multimorbidity prior to having CKD is associated with major adverse kidney events (MAKE): need for chronic KRT, doubling of serum creatinine, decline of eGFR to $<15 \text{ ml/min/1.73m}^2$ or 30% decline in eGFR from baseline¹³. Reporting that 92.7% of individuals who experienced MAKE had an eGFR $>60 \text{ ml/min/1.73m}^2$ at baseline. Within the same study they showed that increasing number of LTCs and specifically cardiometabolic multimorbidity were associated with increased risk of kidney events.

Multimorbidity may alter the clinical focus of consultations and management plans. As already highlighted, for some patients and healthcare professionals, conditions that cause immediate symptoms or are perceived as more urgent may take priority over asymptomatic or slowly progressive CKD⁹⁴. Treatment burden, and polypharmacy which are commonly seen in individuals with CKD and those with multimorbidity can lead to difficult decisions about which condition or treatment to prioritise, particularly if there are discordant treatments or decisions required. Guidelines and clinical trial evidence, such as specific pharmacological treatments are less likely to have been performed in or relate to populations with extensive multimorbidity^{83, 131}. Therefore, applying single-disease guidelines in isolation can lack evidence base, provide conflicting recommendations and be problematic due to lack of consideration of risk vs benefit profiles in patients with multimorbidity.

2.5.3 Frailty and chronic kidney disease

Frailty is more common and occurs earlier in people with CKD than in the general population, with prevalence increasing as eGFR declines and among those on dialysis, with a systematic review including studies up until September 2016 reporting frailty prevalence in patients on haemodialysis ranging from 14% to 73%¹²⁹. Frailty has been observed in younger adults with CKD, particularly those with advanced CKD^{5, 132}. Similar to frailty in the general population, prevalence of frailty in CKD is difficult to accurately assess (and subsequently varies widely across studies even when restricted to only validated frailty measures¹³³) due to the heterogeneity of frailty measures and lack of consensus on which of these to use in research and clinical practice. Other practical considerations include that fluctuations in health status may be more common

and impacted by factors such as anaemia or fluid overload in more advanced CKD.

Systematic reviews indicate that the presence of frailty in CKD is associated with increased risk of hospitalisation¹²⁹, poorer health-related quality of life¹³⁴ and mortality^{135, 136}. The presence of frailty also appears to influence the progression of CKD⁵ and outcomes following initiation of chronic KRT. Individuals identified as having frailty who initiate dialysis have increased risks of vascular access complications^{137, 138}, falls^{129, 139}, admission to hospital¹⁴⁰ and death¹³⁵ compared to non-frail individuals. The presence of frailty in CKD has also been associated with poorer outcomes after kidney transplantation¹⁴¹, including increased risk of mortality, surgical complications, graft failure and increased length of hospital stay compared to kidney transplant recipients without frailty.

The increased prevalence and earlier onset of frailty, alongside the associated adverse outcomes has resulted in guideline recommendations to screen for frailty in older individuals with advanced CKD (stage 3B or higher)¹⁴².

Recognition of frailty has the potential to inform discussions relating to treatment options, including whether to refer to specialist kidney services, to pursue dialysis or conservative care, how to tailor interventions and how to plan for future support needs. Incorporating frailty into prognostic assessments and conversations may help align treatment decisions more closely with an individual's values and goals. Therefore, the presence of screening could also have a potential role as part of general CKD assessment as well as part of a holistic pre-dialysis/transplant assessment or deciding to choose conservative care.

2.6 Treatment burden

The workload of healthcare that individuals must undertake in the treatment and management of health conditions and the associated impact this can have on individual functioning and wellbeing has been conceptualised and termed as 'treatment burden'¹⁴³. Treatment burden encompasses tasks such as self-monitoring, medication management, lifestyle modifications, attending appointments and coordination of care across multiple healthcare professionals and services (which are often siloed, or single organ focused). In CKD,

qualitative syntheses highlight that for patients this work can be substantial and may increase with disease progression and the addition of other long-term conditions¹⁴⁴.

The presence of multimorbidity and/or frailty has the potential to amplify treatment burden due to both increased healthcare workload and decreased ability to manage that workload¹⁴⁵. Individuals with multiple long-term conditions often receive recommendations and treatments from different specialists, which may be overlapping. However, treatments that are conflicting, may be difficult to integrate into daily life or result in significant burden¹⁴⁶. Polypharmacy increases the potential complexity of medication management and the risk of side effects. Furthermore, frailty and functional limitations may make travelling to appointments, collecting prescriptions or performing self-management tasks more difficult. The cumulative workload of health (treatment burden) can exceed an individual's capacity to cope, especially if social, financial or caregiving resources are limited. Conceptual models have been developed that describe the balance between healthcare workload and an individual's capacity to meet the demands, including the cumulative complexity model¹⁴⁶ and a framework for measuring treatment burden¹⁴⁷.

Increased treatment burden has been associated with non-adherence, disengagement from care, poorer clinical outcomes, and lower quality of life^{148, 149}. Additionally, treatment burden may influence how individuals understand CKD and other LTCs and how they perceive kidney failure. For some, the prospect of additional monitoring, investigations or interventions may add to what already feels like an overwhelming workload.^{144, 150} This has implications for communication, shared decision-making and implementation of risk-based approaches, including the use of prognostic models such as KFRE to guide referral and care.

2.7 Prognostic risk prediction tools in CKD

2.7.1 Prognostic tools

In healthcare prognostic tools, also commonly referred to as risk prediction tools, aim to estimate an individual's probability of experiencing a specified

outcome within a given time frame, based on a set of predictors (co-variates/variables - e.g., age, sex, blood measurements)¹⁵¹. The overall aim of prognostic models in health, is typically to facilitate decision-making and improve outcomes¹⁵². Accurate risk prediction can help healthcare professionals deliver precision medicine and more person-centred care, by identifying individuals at highest risk or who may benefit from specific treatments prior to burdensome or inappropriate management decisions. The application of prognostic models allows more informed patient communication, supports shared decision-making, and guides evidence-based practice¹⁵². A further potential use for prognostic models is to select patients with specific risks for inclusion in randomised control trials.

There are an increasing number of methodological and reporting resources available to support and improve the quality of prognostic research. These include:

- The TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) statement¹⁵³ - guidance on the information that should be reported for the development and/or validation of a multivariable prediction model for diagnosis or prognosis.
- PROBAST (prediction model risk-of-bias assessment tool) statement¹⁵⁴ - structured tool to assess the risk of bias and applicability of prediction model studies.
- CHARMS (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies) checklist¹⁵⁵ - guide for data extraction and critical appraisal of studies when performing systematic reviews of prognostic model studies.

Prognostic model research may develop a new model, validate (evaluate) a model, update a model or a combination of these. Model development involves selecting predictors and combining them into a prognostic model. Validation assesses the performance of the model in identifying the outcome of interest, this can be done within the same dataset that the model was developed (internal validation - for which there are a variety of methods e.g., bootstrapping, cross-validation, split) or in an independent population/dataset

(external validation). Models can then be updated (adding additional covariates) or recalibrated to improve performance and transportability. Model validation, in particular external validation, is necessary to ensure that a prognostic model performs consistently in different settings, demographics etc, as it is a recognised limitation of risk prediction models that there will be potential heterogeneity in model performance related to these factors¹⁵⁶.

Key performance concepts for the assessment of prognostic model performance include discrimination, calibration and overall model fit. Discrimination refers to the model's ability to distinguish between individuals who do and do not experience the outcome of interest (often assessed using the C-statistic¹⁵⁷ or area under the receiver operating characteristic curve¹⁵⁸). Discrimination measures typically range from 0.5 (no discrimination) to 1 (perfect discrimination). Calibration represents the agreement between predicted and observed risks across the range of predicted risk values. Calibration can be measured and represented in many ways each of which represent a slightly different aspect of calibration¹⁵⁹. Table 2-5 summarises common calibration measures used in the evaluation of prognostic models.

Table 2-5. Common measures of calibration

Calibration measure	What it assesses	Interpretation
Calibrations curves/plots	Plots observed risk against predicted risk, calibration over a range of predictions	The 45-degree line is the predicted risk (optimal calibration), plots above the line represent under-estimation and below the line over-estimation of risk
Observed/Expected (O/E) ratio	Overall calibration/calibration in the large, simple summary of overall calibration	Perfect calibration is an O/E value of 1, >1 demonstrates on average risk predictions are under-estimated and <1 over-estimated
Calibration intercept	How close estimated risks are to observed outcome	Ideal calibration is 0, a positive intercept represents over-estimation and a

	proportion, capturing global under/overprediction	negative intercept under-estimation of risk
Calibration slope	Level of variation in model prediction across the range of prediction (too extreme or too reserved), detecting overfitting/underfitting	Optimal calibration is a calibration slope equal to 1, <1 represents that risk predictions are too extreme (high predicted risks are too high and low risks too low), >1 demonstrates predictions are too reserved (high predicted risks too low and low risks too high)

Good calibration means that predicted probabilities correspond closely to observed outcome event rates. The overall fit of a model can be assessed using the Scaled Brier score, comparing the prediction of the model to a null model with no covariates^{160, 161}. A negative scaled brier score indicates that the predictions from the model are poorer than a null model, a score of 0% suggests predictions are no better or worse than a null model and positive values (up to 100%) demonstrate improved predictive accuracy from the model in comparison to a null model. Additional analyses, such as decision curve analyses¹⁶² can be used to evaluate the potential clinical utility and benefits of a prognostic model at different risk thresholds compared to a default strategy.

2.7.2 Kidney failure prognostic tools in chronic kidney disease

In CKD, prognostic models can help identify those at greatest risk of progression to kidney failure¹⁶³ or other adverse outcomes¹⁶⁴ (e.g. death^{163 165}, cardiovascular events¹⁶³, transplant graft survival¹⁶⁶). In particular, there has been an abundance of prognostic models developed to predict the risk of kidney failure in individuals with CKD and a number of systematic reviews exploring them^{163, 164, 167}. Existing models vary in their predictor covariates, derivation cohorts, target populations (e.g. primary care, nephrology clinic, advanced CKD populations), kidney failure outcome definitions and prediction time horizons. Some models include only routinely available variables such as age, sex, eGFR,

whilst others incorporate comorbidities, biomarkers or genetic variables that are less readily available.

Kidney failure prognostic models can be used in several ways in CKD care. They can guide clinical decision-making about timing of referral to kidney specialist care from primary care, helping identify individuals who may benefit from specialist input in secondary care assessment and those who can be safely managed/optimised in primary care¹. Additionally, they can inform decisions around if, and when to plan for KRT, including dialysis access planning and consideration of pre-emptive transplantation. They may also support discussions about prognosis and treatment options, contributing to shared decision-making in earlier CKD stages but this has not been well explored in the existing literature. The use of externally validated risk equations to estimate the absolute risk of kidney failure in individuals with CKD are now recommended in KDIGO guidance to help deliver personalised care but with the caveat that ensuring the prognostic tool is validated for “the appropriate outcome of interest, derived from the population of interest”¹. This is particularly relevant for individuals with multimorbidity or frailty as it is unclear if models have been developed or validated for/in these groups. Additionally, conservative care is not commonly included in kidney failure definitions when developing/validating such models and due to factors already discussed those with multimorbidity or frailty may be more likely to choose or require conservative care over KRT.

Previous systematic reviews have highlighted both the potential and the limitations of kidney failure prognostic models in CKD¹⁶⁸. Rampsek et al, identified a recent proliferation in kidney failure risk models including 42 studies, published up until December 2017, reporting the development and/or validation of models¹⁶⁷. Overall, the review judged the methodological quality and reporting standards to be suboptimal, with most studies (52%) not reporting adequate information to allow replication of the prediction model for use in practice and a lack of external validation of models. In addition, they identified no studies that assessed the impact of kidney failure risk prediction tools on outcomes. These findings were reinforced by van Rijn et al. who performed a systematic review that included 36 kidney failure risk prognosis models¹⁶³. They further highlighted the use of inconsistent kidney failure outcome definitions

and a lack of reporting of model equations to allow replication (78% of included studies).

2.7.3 Kidney Failure Risk Equation

Tangri et al developed the kidney failure risk equation (KFRE) in 2011⁹. The original study developed a range of different models using variables available in electronic health records, developing 4-, 6- and 8-variable KFRE models. The 8-variable KFRE (covariates: age, sex, eGFR, uACR, serum calcium, serum phosphate, serum bicarbonate and serum albumin) showed the best discrimination. However, the 4-variable KFRE is the most extensively validated and widely used kidney failure prognostic model for CKD populations (eGFR <60 ml/min/1.73m²).

The 4-variable KFRE uses age, sex, eGFR and uACR as predictor variables with two independent equations that can be used to calculate risk of kidney failure (need for KRT) at 2- and 5-year time horizons.

Cohorts used to develop and validate the KFRE models were two independent Canadian cohorts. The development cohort included 3449 patients with CKD stages 3-5 (eGFR 10-59 ml/min/1.73m²) referred to nephrology services in Ontario and was validated in 4942 patients referred to nephrologists in British Columbia. The development and validation cohorts included 386 and 1177 kidney failure events respectively, where kidney failure was defined as the need for dialysis or pre-emptive kidney transplantation. The 4-variable KFRE has subsequently been validated in several other studies including a large multinational meta-analysis utilising individual-participant level data through the CKD-PC¹⁰. Both in the original derivation and validation and subsequent external validation studies KFRE demonstrated robust performance (both discrimination and calibration), although some miscalibration was demonstrated requiring recalibration to improve this in different geographical locations (non-North American¹⁰ and UK primary care calibrated¹⁶⁹ KFRE) and based on other demographic factors such as race¹⁷⁰.

KFRE and other validated kidney failure prediction tools, have now been incorporated into clinical guidance, including UK NICE¹¹ (National Institute for

Health and Care Excellence) and international KDIGO¹ recommendations. Guidance endorses its use to guide referral to specialist kidney care services and KRT planning at suggested risk thresholds (Figure 2-4). However, full implementation and utilisation of KFRE is limited by factors such as lack of albuminuria testing in at risk individuals¹⁷¹, embedding it into IT systems¹⁷², lack of awareness of KFRE and time constraints.

Figure 2-4. KDIGO proposed kidney failure risk thresholds¹.

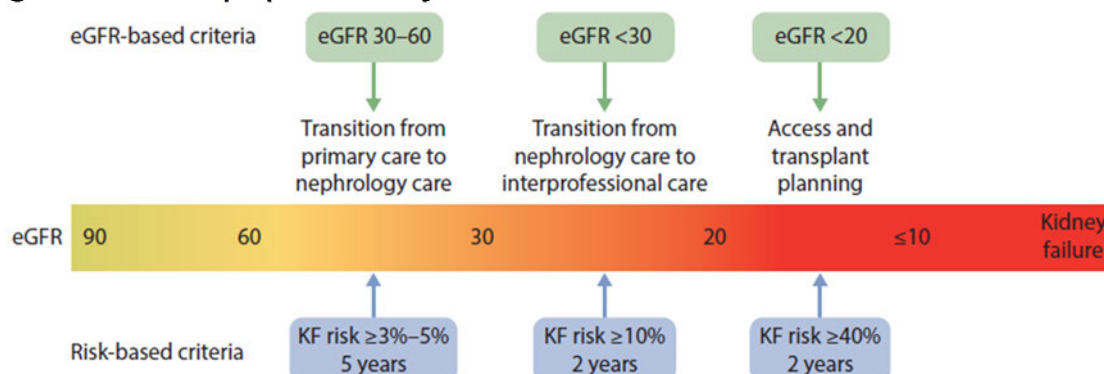


Figure published with permission (Appendix 1).

2.7.4 Competing mortality risk in kidney failure risk prediction

In prognostic modelling or survival analyses, a competing risk is an event that precludes the occurrence of the event of interest. In CKD, death before progression of CKD to kidney failure is a key competing event. If an individual dies, they can no longer go on to experience kidney failure and therefore the probability of kidney failure is influenced by their risk of death. This is particularly relevant in older individuals and those with multimorbidity or frailty, where mortality risk has been demonstrated to be substantially higher than those without multimorbidity or frailty.

Traditional survival analysis approaches such as Kaplan-Meier curves and Cox proportional hazard models typically treat competing events as censored observations, making the assumption that censoring is non-informative. When competing risks are common, this assumption is violated and can lead to misestimation of the cumulative incidence of the outcome of interest. In the context of kidney failure prediction, ignoring competing mortality may bias estimation of risk of progression to kidney failure, especially in sub-groups at increased risk of earlier mortality before they would reach kidney failure¹⁷³.

Competing risk approaches, such as the Fine-Gray subdistribution hazards model¹⁷⁴ and cause-specific hazards models¹⁷⁵, provide methodologies to account for competing events when estimating absolute risk. These approaches use cumulative incidence functions that more accurately reflect the probability of experiencing kidney failure in the presence of death as a competing event. The use of such methodologies has been limited by the complexity of the methods and lack of clear guidance on how to operationalise them. However, in 2022, van Geloven et al. published a comprehensive and accessible overview of these modern methods in line with the TRIPOD guidelines, allowing for wider adoption of competing risk methodologies¹⁷⁶.

Under- or overestimation of kidney failure risk has implications for clinical decision-making. Overestimating risk may prompt unnecessary referral to specialist services, potentially leading to increased treatment burden, anxiety and invasive procedures. Contrary to this, underestimating risk may delay essential planning, result in individuals missing out on medications that could slow kidney disease progression or unplanned KRT initiation. Evaluating how competing mortality affects KFRE across subgroups of multimorbidity and frailty are therefore central to understanding its suitability for guiding care in these groups.

2.8 Shared decision-making

2.8.1 Shared decision-making definitions and concepts

Shared decision-making (SDM) in healthcare has been defined as a collaborative process, that involves an individual (and their family/carer if applicable) and their healthcare professional, in which they share information, express treatment preferences and work together to reach a joint decision that reflects the best available evidence, risks and benefits, as well as a person's values and goals¹⁷⁷. It can encompass a variety of decisions including choosing investigations, referrals or treatments or choosing not to have these or to continue with current care. Decisions may relate to imminent decisions or to those in the future. In contrast to the previously commonly employed clinician-led ("paternalistic") decision-making model, SDM emphasises the patient as an active partner, empowered in making decisions rather than a passive recipient of

care. Core elements of SDM include bidirectional information exchange and understanding, deliberation around options, risks and benefits weighed against what matters to the individual and arriving at a mutually agreed plan¹⁷⁸.

SDM is conceptually distinct from informed consent and from standard patient information giving, however, SDM, consent and patient information giving will often be seen in combination. Informed consent focuses on an individual's understanding and receiving of full details relating to risks, benefits, and alternatives to a decision before proceeding with a decision.

SDM is important in clinical practice as it promotes patient autonomy and choice¹⁷⁸. There is also evidence, mainly observational data, that suggests SDM may improve individuals' health knowledge, alignment between care and an individual's values and in some settings, adherence to and satisfaction with care¹⁷⁹. These considerations are particularly relevant for CKD, where many decisions rely heavily on patient preference and involve balance between quantity and quality of life and must be revisited over time as kidney function, comorbidities, and life circumstances change.

2.8.2 Models/frameworks of shared decision-making

A number of conceptual models have been proposed to describe how SDM should occur in clinical encounters. Essential elements of a SDM model were proposed by Makoul and Clayman¹⁸⁰, including: define and/or explain the problem; discuss benefits/risks/costs; consider patient values/preferences; discuss patient ability/self-efficacy; knowledge and recommendations from the healthcare professional; ensure understanding; make or defer the decision; and ensure follow-up. A subsequent systematic review performed in 2019¹⁸¹, demonstrated a lack of consensus around SDM model components, with heterogeneity in models developed for different types of decisions and healthcare setting. However, there was some consistent overlap in elements such as describing treatment options, creating choice awareness, understanding patient preferences, tailoring information and reaching mutual agreement and making the choice, all of which were noted to be described in more than 50% of the SDM models included in the review.

Decision support frameworks sit alongside these interactional models. The Ottawa Decision Support Framework (ODSF)¹⁸², for example, conceptualises decision needs (e.g., knowledge gaps, values, expectations, support and decisional conflict) and proposes tailored decision support to address these needs to improve decision quality, reduce conflict and decrease decision delay. ODSF has been widely used in the development and evaluation of SDM aids/guides across different clinical settings¹⁸², including CKD. The Ottawa Personal Decision Guide (OPDG)¹⁸³ is one such decision guide that has been developed directly from the ODSF and is a well-established, commonly used decision aid, developed to help facilitate individuals making decisions and engage in SDM. The key components of the OPDG, aligned with the ODSF, are: knowledge; values; support; certainty; and decision-making.

Decision aids and risk communications tools are practical mechanisms for operationalising and supporting SDM. These tools can take the forms of leaflets, web-based resources, videos, or structured protocols, and typically provide a way of delivering balanced information about options, probabilities of benefits and harms and ways of exploring and clarifying an individual's values. A Cochrane systematic review of decision aids in long-term conditions suggests that they increase patients' knowledge, lead to more realistic expectations of benefits vs harms, reduce decision conflict and promote choices more consistent with patients' values¹⁸⁴. However, evidence on the impact on clinical outcomes are less consistent.

SDM frameworks intersect with the concept of health literacy in clinical encounters¹⁸⁵. Many SDM models assume that patients can understand health information and articulate their preferences¹⁸⁵. However, limited health literacy is common and can restrict meaningful participation, especially in more complex settings or decisions (e.g., in the presence of multiple long-term conditions or frailty)¹⁸⁶. These considerations have led to increasing emphasis on tailoring SDM to an individual's communication needs and literacy levels¹⁸⁵, explicitly inviting questions and checking understanding rather than assuming comprehension.

2.8.3 Shared decision-making in CKD

Within CKD, SDM is particularly relevant as many decisions are preference-sensitive, involve uncertainty and have significant consequences on an individual's daily life. Much of the research to date has focused on KRT decisions¹⁸⁷, including whether to pursue KRT or conservative care management, selection of dialysis modality^{188, 189} (haemodialysis versus peritoneal dialysis, in-centre versus home-based treatment) and timing of dialysis initiation. KDIGO CKD guidance explicitly states that patient specific prognostic information should be used to frame decisions about KRT and conservative care for individuals with CKD stage 5, including focusing on patient-centred outcomes such as quality of life, symptom burden and family/HCP support¹. KDIGO additionally state that “most people with CKD would choose to receive prognostic information about their individual risk of kidney failure as part of routine care”.

People living with CKD report mixed views on their preferences about information provision. A qualitative survey study of 163 patients with CKD (all stages)¹⁹⁰ reported diverse emotional responses, with patients often desiring more personalised information relating to prognosis and treatment strategies, including trajectories of CKD progression and life expectancy but with some individuals preferring to “live in the present” and avoid detailed information relating to the future to preserve hope or avoid anxiety. Authors concluded that the results emphasised the need to ensure individual preferences were accounted for and a personalised approach was taken when discussing the future with individuals living with CKD.

A range of interventions and decision aids have been developed to support SDM in CKD. Again, these relate mainly to decisions in advanced kidney disease^{191, 192}, including structured pre-dialysis education programmes, KRT modality decision aids and communication tools to support SDM in advanced care planning. A comprehensive scoping review published in 2022 identified 145 programmes/tools, including prognostic tools, education programmes, patient decision aids and multi-component interventions for SDM in advanced kidney disease¹⁹¹. Importantly, they highlighted that outcomes in the included studies were inconsistently measured and that there was a lack of evaluation of SDM

interventions/tools on outcomes. KDIGO 2024 CKD guidance does however, emphasise that SDM should be embedded within broader CKD care models that provide patient education, symptom management, psychosocial support and navigation of healthcare services¹.

Effective SDM and optimal care in CKD is limited by several barriers present at patient, healthcare professional and system levels. Time/system pressures¹⁸⁶, fragmented healthcare services, poor understanding of CKD and continuity/relationships between HCPs and patients have all been identified as factors that can limit SDM¹⁹² and management of CKD¹⁹³.

2.8.4 Shared decision-making in complex patients

SDM is clearly an important concept for all patients but may pose additional challenges for individuals who have CKD and multimorbidity and/or frailty. There is currently a small volume of research studying SDM in more complex patient groups, such as those with multimorbidity or frailty. Bujold et al. performed a systematic review and case-based qualitative synthesis exploring decision-making and outcomes in patients with complex care needs (including multimorbidity within their definition of patients with complex care needs) in primary care settings¹⁹⁴. Of the 26 included studies, 23 included individuals with multimorbidity. Time restraints and extensive problems/decisions to discuss were common in multimorbidity and decisional need and capacity to make decisions fluctuated over time, dependent on factors such as health status and social support. Additional barriers also included uncertainty and conflicting decision-making. Similar themes emerged in a qualitative study involving older patients (≥65 years) with multimorbidity and GPs from primary care settings¹⁹⁵, with acknowledgment from both perspectives that lack of clinical guidance in multimorbidity and clinical uncertainty contributed to medicolegal vulnerability for healthcare professionals, and that this was an additional barrier to SDM.

Concepts in multimorbidity and frailty such as treatment burden may impact an individual's preferences and the decisions they make, as described in the cumulative complexity model¹⁴⁶. Furthermore, caregiver or social support network are often involved in healthcare interactions including decision-making. Social support can enrich SDM by bringing additional perspectives and support

but may also introduce tensions when preferences or beliefs differ to that of the patients¹⁸⁶.

Prediction tools such as the KFRE and other kidney failure risk equations have potential to support SDM for complex patients by providing prognostic information relating to short- and medium-term risks of outcomes such as kidney failure and death. However, there is lacking evidence about the optimal way to communicate health risk in kidney disease¹⁹⁶. There are also potential negative consequences of discussing risk, such as misinterpretation of risk predictions¹⁹⁷, precipitating anxiety, or overloading a person who is already dealing with a large volume of information or balancing significant treatment burden⁶¹.

Overall, whilst SDM is widely endorsed in policy and clinical guidance, there remain important gaps in the evidence about how to best support SDM for people with CKD and multimorbidity or frailty and the HCPs caring for them. There is a lack of research exploring how kidney failure risk prediction tools are/could be used in communication with patients or how the presence of multimorbidity or frailty may impact understanding and perceptions of kidney disease or kidney failure in these populations and HCPs that warrants further exploration.

2.9 Conclusion

In summary, CKD is a common and growing global health problem associated with substantial morbidity, mortality, and healthcare utilisation. It frequently co-exists with multimorbidity and/or frailty, which themselves are associated with adverse outcomes and increased treatment burden. These overlapping conditions complicate disease trajectories, risk prediction and clinical decision-making for patients with CKD.

A variety of kidney failure prognostic models have been developed, with KFRE being the most widely implemented and cited. While KFRE and similar tools hold promise for improving risk stratification and supporting personalised, timely care, it is unclear how the presence of multimorbidity, frailty, competing mortality risk or the choice of kidney biomarker used influences their performance and use. Furthermore, the impact of treatment burden and need for shared decision-making are particularly salient in individuals with CKD and

multimorbidity or frailty and it is unclear how patients and healthcare professionals understand CKD and perceive kidney failure risk in the context of multimorbidity or frailty.

The subsequent chapters of this thesis address these gaps via the research questions outlined in Chapter 1.

3 Chapter: 3 Methods

3.1 Chapter summary

This chapter describes the methodological approaches used in this thesis. The alternative thesis format, in the form of published or submitted manuscripts, has been chosen to present the analyses and results of this thesis (chapters 4 to 9). Therefore, detailed descriptions of each piece of work, analyses and results are presented in the manuscript texts in the corresponding results chapters. This methods chapter provides an overview of the overarching methodological approaches, the rationale for these choices and the definitions and data sources utilised.

A mixed-methods approach was adopted, combining evidence synthesis in the form of a systematic review, large-scale quantitative analyses and validation studies using cohort datasets, and a qualitative study with patients and healthcare professionals. A concurrent data analysis approach was employed, followed by triangulation¹⁹⁸ of the analyses. Following analyses of each individual study, the findings of all studies were synthesised to identify areas of convergence (agreement), complementarity (added insight), and dissonance (contradiction). This integration of methods and triangulation of findings allowed for a comprehensive understanding of multimorbidity, frailty and risk prediction in CKD, addressing epidemiological, prognostic, experiential and implementational dimensions.

Specifically, chapters 4 to 8 comprise:

1. A systematic review of the published literature on kidney failure risk prediction models in CKD, with a focus on the consideration of multimorbidity and frailty¹⁹⁹.
2. Quantitative analysis of large cohort datasets, using UK Biobank and where relevant and possible, the Stockholm CREAtinine Measurement Project (SCREAM) cohort, including validation of the KFRE and consideration of the competing risk of mortality in:

- a. Subgroups defined by multimorbidity²⁰⁰, and
 - b. Subgroups defined by frailty²⁰¹.
3. The qualitative MULTIPPOINT (MULTIPLE Long-term conditions AND frailTy) descriptive study, exploring patients' and healthcare professionals' perspectives of kidney failure risk and shared decision-making in the context of CKD, multimorbidity and/or frailty, reporting findings from interviews and focus groups.

Together, these studies provided complementary perspectives and methodological triangulation, enabling a comprehensive and nuanced understanding of kidney failure risk prediction in CKD in the context of multimorbidity and frailty.

3.2 Systematic review

The first study conducted was a systematic review, to synthesise evidence and understand the existing evidence and any gaps relating to the development and validation of kidney failure prognostic models in CKD in individuals with multimorbidity or frailty¹⁹⁹.

3.2.1 Review planning and design

The systematic review was developed in line with the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P)²⁰² 2015 statement and the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS)¹⁵⁵ checklist. The protocol was developed and prospectively registered on PROSPERO, the International Prospective Register of Systematic reviews (PROSPERO: CRD42022347295). The protocol is included in the Appendix (Appendix 2).

3.2.2 Eligibility criteria

Inclusion and exclusion criteria are described in full in Chapter 4.

A decision was made to exclude studies that reported on prediction models that used only biopsy/pathology or genetic predictors only, as these would not be widely available to all individuals with CKD. Additionally, restricting inclusion to models with three or more predictor variables ensured that the review focused on multivariable prognostic models of sufficient complexity to capture the multifactorial nature of kidney failure risk, while maintaining clinical relevance by excluding models dependent on advanced or difficult-to-access biomarkers/variables.

Studies with a time to event (kidney failure) of less than 2 years were excluded as it was assessed by myself and in subsequent discussion with my supervisory team that a follow-up time of less than this was not as clinically meaningful and relevant when considering the impact of prognostic models on management and referral of individuals with CKD.

The focus of the work in this thesis is in adult populations with CKD, therefore, studies including paediatric or adolescent populations (individuals aged <18 years old) and those in the general population or groups without CKD were excluded. Due to the outcome of interest being progression from CKD to kidney failure studies including individuals with a history of kidney failure or kidney transplantation were not included.

Search strategy

A search strategy was developed in conjunction with a specialist librarian who has expertise in medical literature (Table 3-1). Medical subject headings (MeSH) and text terms were used to identify articles that referenced all of development, validation, prognostic models and kidney failure.

Table 3-1 Systematic review search strategy example

#1	(MH "Risk Assessment/MT")
#2	(MH "Prognosis")
#3	(MH "Disease Progression")
#4	AB (risk n3 (predict* OR model* OR progress* OR scor* OR factor* OR tool* OR equation*)) OR TI (risk n3 (predict* OR model* OR progress* OR scor* OR factor* OR tool* OR equation*))
#5	AB (predict* n4 (model* OR progress* OR scor* OR factor* OR tool* OR disease* OR equation*)) OR TI (predict* n4 (model* OR progress* OR scor* OR factor* OR tool* OR disease* OR equation*))
#6	S1 OR S2 OR S3 OR S4 OR S5
#7	(MH "Kidney Failure, Chronic/BL/CO/DI/EP/PP/TH/UR")
#8	(MH "Renal Insufficiency, Chronic/BL/CO/EP/PP/UR/TH/DI")
#9	(MH "Renal Replacement Therapy/MT/TD")
#10	AB (RRT OR KRT) OR TI (RRT OR KRT)
#11	AB ((kidney OR renal) AND replacement*) OR TI ((kidney OR renal) AND replacement*)
#12	AB CKD OR TI CKD
#13	AB "chronic kidney disease" OR TI "chronic kidney disease"
#14	AB ((kidney OR renal) AND failure) OR TI ((kidney OR renal) AND failure)
#15	AB ((end-stage* OR endstage*) AND (renal OR kidney)) OR TI ((end-stage* OR endstage*) AND (renal OR kidney))
#16	AB (chronic AND (renal OR kidney) AND (insufficiency OR impairment)) OR TI (chronic AND (renal OR kidney) AND (insufficiency OR impairment))
#17	AB (ESRD OR ESKD) OR TI (ESRD OR ESKD)
#18	AB nephropath* OR TI nephropath*
#19	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
#20	(MH "Humans")
#21	(MH "Adult")
#22	(MH "Middle Aged")
#23	S20 OR S21 OR S22
#24	Develop*
#25	Validat*
#26	S24 OR S25
#27	S6 AND S19 AND S23 AND S26
	Limit to English language

Three databases were searched (Medline (EBSCO interface), CINAHL Plus (EBSCO interface) and the Cochrane Library- CENTRAL (OVID interface)). Manual review of reference lists of included studies and relevant clinical guidelines was

performed to supplement database searching. Using multiple databases and searching reference lists reduced the likelihood of studies being missed.

Full search strategies for each database are included in Chapter 4. Results were collated using referencing software, with the initially identified studies imported into Rayyan systematic review software (<https://www.rayyan.ai/>), where duplicates were removed.

3.2.3 Screening

Titles and abstracts were screened independently, in Rayyan software, by myself and a second reviewer. Full text review, to confirm eligibility, was then performed by the same two reviewers (independently and in duplicate) in Covidence systematic review software (Covidence, Melbourne, Australia). Disagreements between reviewers at any stage were resolved by discussion with a third reviewer. The independent and duplicate screening process increased the reliability and rigor of study screening and inclusion.

3.2.4 Data collection

Data extraction and collection from the included studies was performed in Covidence software by myself, and one of four reviewers, using a pre-defined electronic data collection form within the software. Data collection was performed independently and in duplicate to ensure consistency and increase reliability.

The following information was extracted from each study:

- Author
- Publication year
- Country
- Population

- General CKD, subset of CKD e.g., IgA nephropathy, diabetic kidney disease
- Study design
 - Development, validation (internal/external), updated model
 - Consideration of the competing mortality risk
- Start/end dates
- Patient characteristics
 - Age
 - Sex
 - Ethnicity
 - eGFR
 - Co-morbidities
 - Multimorbidity measurements
 - Frailty measurements
- Sample size
 - Number of participants
 - Number of events
- Outcomes reported
 - Definitions used
 - Measurement of outcomes

- Timing of measurement
- Duration of follow-up
- Model details
 - Model name(s)
 - Method for selection of predictors
 - Model type
 - Model variables and number of variables
- Model performance measures
 - Calibration
 - Discrimination
 - Other

If studies reported on more than one prognostic model, data for each individual model was collected. Where data was missing, incomplete or unclear, study authors were contacted. For missing performance measures, we used methods described by Debray et al.²⁰³ to approximate measures where possible.

3.2.5 Quality appraisal

Risk of bias and applicability was independently assessed, using the Prediction model Risk of Bias Assessment Tool (PROBAST).¹⁵⁴ PROBAST is a risk of bias assessment tool that has been specifically developed, through a consensus process, for the assessment of risk of bias in systematic reviews of prediction model studies. It assesses risk of bias and applicability across four domains: participants, predictors, outcome and analysis. It uses a structure and rating system similar to other commonly used risk of bias tools, which allowed a

methodical and transparent way of assessing risk of bias and the applicability of included studies in the systematic review (Table 3-2).

Table 3-2 Domains of the PROBAST risk of bias and applicability assessment tool

Domain	Focus	Key considerations
Participants	Appropriateness of study population and data sources	Were participants representative of the target population?
		Were inclusion and exclusion criteria appropriate?
		Were data sources suitable for model development or validation?
Predictors	Definition, measurement, and timing of predictors	Were predictors clearly defined and measured consistently?
		Were predictor assessments made without knowledge of outcomes?
		Were all predictors available at the time the model would be used?

Outcome	Definition, determination and follow-up for outcomes	Was the outcome clearly defined and clinically relevant? Was the outcome assessed without prior knowledge of predictor information? Was the same outcome definition applied to all participants? Was follow-up sufficient to observe events of interest?
Analysis	Statistical methods and reporting	Were appropriate statistical models used? Were all participants included in the analysis? Was model overfitting addressed e.g., through internal validation or resampling? Were discrimination and calibration appropriately evaluated and reported?

		Were missing data handled appropriately?
Overall judgement	Synthesis across domains	Overall risk of bias/applicability based on the combined judgement across the four domains (participants, predictors, outcome and analysis) Low risk of bias/concern regarding applicability if all domains are rated low High risk of bias/concern regarding applicability if one or more domains are rated high Unclear risk of bias/concern regarding applicability if insufficient information is available to make a judgement in one or more domains
Domains of the PROBAST tool 1		

3.2.6 Analysis and reporting

This systematic review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRSIMA)²⁰⁴ guidelines.

Due to the heterogeneity of the included studies, particularly the wide range of prognostic models assessed, differences in outcome definitions and the variability in performance measures reported, statistical pooling through meta-analysis was not feasible. Instead, results were synthesised descriptively. Baseline characteristics were summarised quantitatively using means with standard deviations, medians with interquartile ranges and frequencies with percentages, as appropriate. A narrative synthesis approach was employed to describe and compare the findings across studies. This synthesis considered the types of kidney failure risk prediction models assessed, the populations studied, the consideration of multimorbidity or frailty within included studies and a specific focus on the most commonly validated model, KFRE.

Where possible, results were presented using structured summary tables (study characteristics and risk of bias assessments) and graphical representations to aid interpretation. The quality assessment results were summarised to highlight the strengths and limitations of the available evidence.

All analyses and data management were performed using R software version 4.3.0.

3.3 Description of datasets

Two datasets were chosen for the quantitative studies of the thesis. They were chosen based on availability of both creatinine and cystatin C data, as well as ease of availability and access. They are described in full in this section, including consideration of their strengths and weaknesses. Other datasets considered for the quantitative studies included the Secure Anonymised Information Linkage Databank (SAIL): a primary care database for the population of Wales and the Clinical Practice Research Datalink (CPRD): a UK primary care research database. However, both datasets would be biased by missing

albuminuria measurements and lack routine cystatin C testing necessary for the aims of the studies.

3.3.1 UK Biobank

3.3.1.1 Overview

UK Biobank is a prospective research cohort of over 500,000 adult participants aged 37-73 years, recruited between 2006 and 2010.²⁰⁵ Eligibility for recruitment was based on residence within an approximately 25-mile radius of one of the 22 assessment centres across England, Scotland or Wales.

At baseline, participants completed questionnaires and underwent physical measures, as well as blood and urine sampling. Baseline data available includes demographic, lifestyle factors, physical measures, blood and urine biomarkers, and extensive questionnaire data. Participants were subsequently linked to a number of other national health data sources and registries, including hospital episode statistics and death registries, enabling follow up of long-term outcomes.

For the purposes of this thesis, UK Biobank was particularly valuable because it included both serum creatinine and cystatin C, permitting calculation of multiple eGFR equations³⁴, in addition to urinary albumin creatinine ratio (uACR), which are two variables alongside age and sex required to calculate the KFRE.

3.3.1.2 Strengths

Several features of UK Biobank made it a strong data source for addressing the research questions posed in this thesis.

Firstly, the large sample size allowed sufficient numbers of participants with CKD (eGFR <60ml/min/1.73m²), to perform analyses on this subgroup, with sufficient numbers of kidney failure outcome events required for a statistically strong prognostic model validation study.

Secondly, the research cohort provides the availability of simultaneous serum creatinine and cystatin C and uACR, reducing selection and confounding bias which are often present in routine care databases. These kidney biomarkers were measured using reliable and standardised techniques.²⁰⁶ Specifically, serum and urine creatinine were quantified using reliable isotope dilution mass spectrometry (IDMS)-traceable methods²⁰⁷ on the Beckman Coulter AU5400 analyser, serum cystatin C using a latex-enhanced immunoturbidimetric method on the Siemens ADVIA 1800 analyser instrument, and urine microalbumin via immunoturbidimetric methods (reagents and calibrators from Randox Bioscience UK).

Thirdly, the rich baseline phenotyping included detailed demographic, lifestyle and clinical data with recording of varied and numerous long-term health conditions. This breadth allowed robust characterisation of multimorbidity, multimorbidity types (e.g., cardiometabolic, complex, LTC counts) and exploration of different frailty measures. Such frailty measures are rarely available in large population datasets and are particularly scarce in datasets that also include such wide cystatin C testing, a key requirement for this thesis.

Additionally, UK Biobank includes middle-aged adults as well as older adults, where frailty and multimorbidity are increasingly relevant and common in the context of CKD but remain under-explored in research.

Finally, linkage to hospitalisation and mortality records via HES and national death registers enabled outcome ascertainment of kidney failure and death. The long duration of follow-up (more than 10-years) allowed the outcomes to be assessed at both 2 and 5 years which was important for validation of KFRE at both time points, consistent with its original development and clinical use.

3.3.1.3 Limitations

The limitations of UK Biobank primarily relate to issues of representativeness and data completeness.

Participation in UK Biobank is not at random and is subject to participatory selection bias. The response rate was around 5%,²⁰⁸ leading to the well-

recognised phenomenon in research recruitment of healthy volunteer bias. Compared with the general UK population at recruitment, participants were on average healthier (fewer reported LTCs and lifestyle factors associated with adverse health outcomes e.g. smoking, obesity) and wealthier (fewer living in socioeconomically deprived areas).²⁰⁹ Although selection bias limits prevalence estimates, prior comparisons with nationally representative cohorts suggest that risk factor-outcome associations identified in UK Biobank remain broadly consistent, supporting its use for aetiological and prognostic research.^{119, 210}

The UK Biobank cohort additionally has poor representation from minority ethnic populations, with the majority of participants recorded as having White ethnicity (around 95%), which although reflecting the national population at the time of recruitment, limits the generalisability of findings to minority ethnic groups and to other countries with more diverse populations.²⁰⁸

Another limitation is that the upper age limit of the UK Biobank cohort was 73, excluding the oldest old, who are both more likely to have CKD and have increased likelihood of experiencing frailty and multimorbidity, central to the thesis.

Frailty measures were adapted for use in UK Biobank^{117, 211} and therefore may have limitations such as reduced validity, especially in younger participants/populations. Specific markers included in the frailty phenotype for UK Biobank that may have different causes or implications, include exhaustion and weight loss (importantly not specified as unintentional weight loss in the UK Biobank self-reported questionnaire).

A further limitation is the absence of linkage of UK Biobank participant data to national renal registries. Renal registries reliably record data relating to individuals who commence chronic kidney replacement therapy in the form of dialysis or transplant.²¹² Although, an algorithm for use in UK Biobank has been developed to identify kidney events,²¹³ it is less reliable than renal registry sources. Other methods of identifying kidney failure events, including follow-up blood testing were also limited. Only 4% of individuals in UK Biobank had repeat blood tests via UK Biobank and primary care data were linked for only 46% of participants, of whom just 25% had follow-up kidney function testing. It was

therefore not possible to include a sustained $\text{eGFR} < 15 \text{ ml/min}$ into the definition of kidney failure. Likewise, there is a lack of coding and recording of conservative care, a treatment option where individuals choose not to receive KRT but focus on quality of life with supportive care treatments and measures. Conservative care as a treatment option for kidney failure may be more commonly observed in individuals with multimorbidity or frailty. Due to these limitations, kidney failure events are likely overall to be incompletely captured in UK Biobank.

Despite these limitations, UK Biobank was a well-placed and invaluable data source in this thesis. Its size, availability of matched creatinine, cystatin and uACR data, long follow-up data and detailed baseline characterisation allowed rigorous validation of the KFRE in subgroups defined by multimorbidity and frailty.

3.3.2 Stockholm CREATinine Measurement project (SCREAM)

3.3.2.1 Overview

The SCREAM project is a large-scale, population-based healthcare utilisation cohort of around 2.9 million individuals residing in Stockholm, Sweden, who underwent serum creatinine testing between 2006 and 2021.²¹⁴ SCREAM was initially developed in 2010 by researchers at the Karolinska Institutet in collaboration with the Stockholm County healthcare provider to estimate CKD burden and evaluate prescribing practices in the context of impaired kidney function.

Healthcare and administrative data is linked anonymously between the following records and registers:

- Routine healthcare utilisation (administrative) data
- Routine laboratory results
- National registers, including:

- Prescribed drug register (pharmacy dispensation of prescribed drugs)
- Socioeconomic register
- Death register
- Cancer register (biopsy-verified cancer diagnoses)
- Birth register
- Quality registers, including:
 - Renal register (nephrology referred patients including need for KRT)
 - SWEDEHEART (patients admitted to healthcare with acute coronary syndrome)
 - SWEDEHF (patients admitted to healthcare with heart failure)
 - Swedish Dementia Registry (SveDem)

3.3.2.2 Strengths

In addition to UK Biobank, SCREAM provides complementary insights and has several unique strengths that make it a valuable resource for the research questions in this thesis.

Firstly, it is beneficial to have an international perspective, with data from a cohort outwith the UK where differences in healthcare systems, lifestyle and genetic factors may impact findings. With nearly 3 million individuals included and long-term follow-up, SCREAM provides a valuable large study of the general population. It captures all adults who had creatinine measured in routine care across Stockholm, reducing referral bias and enhancing the generalisability of findings to the broader CKD population compared with a research-based cohort. The large sample size again allowed sufficient numbers of kidney failure events

for validation of KFRE (the prognostic model of interest), particularly within the clinically relevant subgroup defined by multimorbidity.

Serum creatinine measurements were standardised across regional laboratories, reducing inter-laboratory variability. Cystatin C as a kidney biomarker was first discovered by a Swedish researcher, Anders Grubb and colleagues, in 1985²¹⁵ and due to his implementation efforts, it is now part of routine testing in Sweden²¹⁶. The availability of paired serum creatinine and cystatin C tests is therefore more prevalent in the SCREAM cohort compared to many other similar population-based routine healthcare cohorts.

The inclusion of high-quality registry data (hospitalisations, prescriptions, mortality and renal registry) facilitated detailed comorbidity ascertainment, multimorbidity counts and the capturing of death and kidney failure outcome events.

Additionally, SCREAM reflects routine clinical practice and allows comparison to UK Biobank, research cohort findings. This improves the external validity of the KFRE validation study findings in different and diverse populations.

3.3.2.3 Limitations

Despite these strengths, SCREAM also has limitations, largely due to the use of routinely collected healthcare data. A major limitation is that cystatin C and uACR were not routinely available across the full cohort during the study period. This restricted the sample size and possibly introduced selection bias due to missing baseline data. Similarly SCREAM requires at least one creatinine measurement in routine care for inclusion in the cohort which also introduces selection bias for individuals who have never had kidney function tests (SCREAM covers around 66% of the population of Stockholm).

SCREAM does not collect ethnicity data, as this is not permitted in Swedish data collection. Therefore, it is not possible to say with certainty how generalisable the results are based on ethnicity, but census data suggests it is a predominantly White-ethnic population and therefore generalisability of results will be limited by this. Additionally, life expectancy and baseline mortality prevalence differ

between Sweden and the UK, with higher life expectancy seen in Sweden compared to the UK²¹⁷. Differences in baseline survival and competing risk of death may impact the transportability of absolute risk estimates and outcome rates between populations.

Finally, SCREAM does not include any measures of frailty and therefore it was not possible to operationalise any of the frailty measures within this cohort and only UK Biobank was used for analyses relating to frailty subgroups.

Despite these limitations, SCREAM offered a large, representative, real-world dataset that complemented the detailed phenotyping available in UK Biobank. Its comprehensive laboratory and registry linkages enabled robust assessment of kidney outcomes and multimorbidity, alongside the wide availability of cystatin C testing provided an important advantage over many other routine healthcare datasets. SCREAM was therefore a valuable resource alongside UK Biobank that could be used to validate KFRE in multimorbidity subgroups within this thesis.

3.4 Assessment of kidney function

Kidney function was assessed using estimated glomerular filtration rate (eGFR). Three equations from the CKD Epidemiology Collaboration (CKD-EPI) were used:

- Creatinine-based equation (eGFR_{cr})
- Cystatin C-based equation (eGFR_{cys})
- Combined creatinine-cystatin C equation (eGFR_{cr-cys})

All three equations were chosen to allow the comparison of model performance when the different eGFR equations were employed in KFRE to answer the research question that one may be superior to the others in the context of CKD and multimorbidity or frailty for predicting future kidney failure.

The non-race adjusted 2009 CKD-EPI equation³⁸ was used to calculate eGFR_{cr} and the 2012 CKD-EPI equation⁴⁰ was used to measure eGFR_{cys} and eGFR_{cr-cys}. However, recent research²¹⁸ suggests that alternative equations, e.g., the

European Kidney Function Consortium (EKFC) equation and revised Lund-Malmö (RLM) equation may provide improved eGFR accuracy in European populations. Nevertheless, our approach of using CKD-EPI equations was chosen to remain consistent with how eGFR measurement is currently utilised in clinical practice and to allow comparability with KFRE development and previous validation studies based on observing that the majority of the studies had used a CKD-EPI equation to estimate GFR used in KFRE.

CKD was defined as an eGFR <60 millimetres per minute per 1.73 square metres (ml/min/1.73m²) at baseline, by any of the three eGFR equations (eGFR_{cr}, eGFR_{cys} or eGFR_{cr-cys}). This was in keeping with KDIGO¹ eGFR cut-off criteria for CKD and the definition used by Tangri et al.⁹ in the development of KFRE.

Creatinine and cystatin C measurements were used when they were performed on the same day, this occurred routinely in UK Biobank and typically occurred in SCREAM due to the clinical practices employed within laboratory testing that meant cystatin C testing is routinely performed alongside creatinine when kidney function tests are requested. We utilised outpatient serum creatinine and cystatin C tests only in SCREAM to limit the influence of acute illness on eGFR.²¹⁹ Participants in UK Biobank were assumed to be stable at the time of recruitment, due to its research-based nature and therefore a single blood test was used to calculate baseline eGFR.

3.5 Assessment of albuminuria

Participants in UK Biobank routinely had albuminuria measured at time of recruitment via uACR testing. However, individuals in the SCREAM cohort did not universally have albuminuria measurements. Participants from SCREAM were therefore included if they had either a quantifiable albuminuria measurement in the 12 months before or after creatinine and cystatin C measurement. This allowed pick-up of albuminuria tests that were related to reduced eGFR measurement that due to real-world practices are unlikely to be performed on the same day as blood testing. For individuals without albuminuria measurements within this time frame, uACR concentrations were estimated from urine protein-creatinine ratio (uPCR) or dipstick proteinuria measurements that were available in the time window, using a previously validated conversion

algorithm.²²⁰ This methodology was chosen as it reduced the selection bias that would be present if we only included individuals who had albuminuria formally tested (more frequently performed in individuals with diabetes or hypertension) and has been validated and shown to produce plausible estimates of albuminuria levels.

3.6 Calculation of the Kidney Failure Risk Equation (KFRE)

The four-variable KFRE is a prognostic model that uses the following four predictor variables:

- Age
- Sex
- eGFR
- uACR

KFRE was developed in Canadian cohorts⁹ and has since been widely validated multi-nationally.¹⁰ Regional calibration of the model has been performed producing equations that are specific to different populations and countries. The three main equations in use are the original KFRE, non-North American¹⁰ KFRE and UK calibrated¹⁶⁹ KFRE. KFRE models used are described in full in Chapters 5 and 6.

There are also differences in the KFRE equation, that should be noted, for calculating kidney failure risk at 2 and 5 years.

The UK-calibrated KFRE was selected for primary analyses given its relevance to UK Biobank participants, but we also chose to perform sensitivity analysis utilising the non-North American KFRE to account for potential differences between the UK Biobank cohort and the Swedish SCREAM population.

3.7 Assessment of kidney failure and mortality outcomes

To evaluate the performance of KFRE in the context of multimorbidity and frailty, and whilst assessing the impact of the competing risk of mortality, two outcomes were considered:

- Kidney failure
- All-cause mortality

Kidney failure was defined as requiring chronic dialysis or kidney transplantation (KRT). These were identified by different measures in each of the two datasets already described. In SCREAM data were linked with the national Swedish Renal Register²¹⁴ and in UK Biobank hospitalisation admission codes (International Classification of Diseases version 10 (ICD-10) and Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures version 4 (OPCS4 codes)) were used aligned with a previously established UK Biobank algorithm.²¹³ Strengths and limitations of these definitions are described earlier in this chapter.

All-cause mortality was defined as death by any cause prior to kidney failure. Mortality was identified in both datasets via linkage with national mortality registers.

Both datasets used in this thesis (UK Biobank and SCREAM) originate from countries with universal health coverage. This is an important strength as the majority of adverse health outcomes, including dialysis initiation, kidney transplantation and death, are captured within administrative healthcare systems and associated registries. However, some outcomes may still be under-ascertained. For example, events may have been missed if individuals accessed healthcare outside the study region or relocated during follow up.

Timing of outcome assessment is described in the relevant chapters.

3.8 Defining long-term conditions and MLTC

Multimorbidity (MLTC) was defined as the presence of two or more LTCs in addition to CKD. Previous research has identified that individuals with MLTC were at an increased risk of adverse kidney outcomes, including kidney failure¹³. This threshold was therefore selected to allow comparison between individuals with CKD alone and those with CKD plus multimorbidity, reflecting the thesis focus on use of KFRE in predicting kidney failure in individuals with multimorbidity compared to those without.

The LTCs that were considered for inclusion were based on the seminal paper by Barnett et al.⁷² which included 40 chronic conditions (inclusive of CKD). An alternative definition from the recent Delphi consensus study by Ho et al. was considered⁶. However, the Ho et al. definition yielded only slightly higher prevalence estimates of multimorbidity (36.4%) compared with the Barnett et al. list (34%)⁶⁶. The list of LTCs proposed by Barnett et al. has been used for a large number of multimorbidity studies including many studies performed in UK Biobank²²¹. Due to the replicability of this definition in UK Biobank it was chosen over other proposed lists.

LTC conditions were self-reported in UK Biobank and were assessed through ICD codes and prescribing data in SCREAM. In total, 42 and 26 LTCs, in addition to CKD, were captured in UK Biobank and SCREAM respectively, due to some LTCs lacking or have limited validation in health data. Therefore, the number of LTCs captured in SCREAM was restricted to those that could be reliably ascertained using established codes and algorithms²²². There were some differences in the LTCs used to define multimorbidity in this work, compared to the list originally proposed by Barnett et al.⁷², with the LTCs included being aligned with previous multimorbidity research conducted in UK Biobank²²¹. Differences in conditions were the inclusion of Meniere's disease (in place of hearing loss), osteoporosis, chronic fatigue syndrome, endometriosis, pernicious anaemia and polycystic ovary syndrome. Blindness and low vision and learning disabilities were excluded from our definition but were included in the Barnett et al. list.

The presence of LTCs was limited to those that existed prior to the index date (date of recruitment in UK Biobank or start of the study period in SCREAM) to

ensure the presence of multimorbidity at the time of prognostic tool assessment (the time the KFRE score was assessed and validated against).

In addition to categorising the presence or absence of multimorbidity, LTC counts were calculated (i.e. 0, 1, 2 etc LTCs in addition to CKD) and multimorbidity groupings were identified based on previous literature^{13, 68-70} (cardiometabolic, complex, and mixed physical and mental health multimorbidity). The LTCs identified for inclusion in the multimorbidity counts and groupings are described in full in Chapter 5.

3.8.1 Self-reported LTCs

In UK Biobank, conditions were self-reported by electronic questionnaire and nurse-led interviews. An unlimited lookback window was used to identify LTCs in UK Biobank, to maximise ascertainment of chronic conditions, under the assumption that if participants self-identified and reported having a LTC it was likely to be ongoing and relevant to their health status. However, one limitation of self-reporting LTCs is the possibility of recall bias, where individuals may not recall or be aware of health conditions.²²³ Therefore, self-reporting of LTCs even with the support of research nurses may result in some conditions not being reported.

3.8.2 Administrative healthcare data (diagnostic and prescribing codes)

In SCREAM, LTCs were identified through a combination of ICD codes, from primary and secondary care records, supplemented with prescribing data for depression and chronic pain (where specific diagnostic codes may be lacking) (Appendix 3). Routinely collected coding data are subject to limitations, particularly the under-reporting of chronic conditions²²⁴. Likewise, prescribing data has limited specificity for LTC identification, particularly when medications are used for multiple indications (e.g., gabapentinoids for chronic pain or epilepsy). We attempted to address this by only classing a LTC as being present where the indication for only one of the potential prescribing conditions exists (e.g., gabapentinoids for painful conditions if no ICD-10 code present for epilepsy diagnosis). The use of validated algorithms was chosen to again increase

replicability and reliability of the LTCs being included in the studies in the thesis²²².

3.9 Frailty measures and defining frailty cut-offs

Frailty was assessed using multiple measures:

- Frailty Phenotype: based on the five criteria described by Fried et al.⁸ (unintentional weight loss, self-reported exhaustion, low hand-grip strength, slow walking pace and low physical activity).
- Frailty Index (FI): based on a ‘cumulative deficit’ model of frailty developed by Rockwood and Mitnitski.⁹⁹
 - derived from self-reported deficits (symptoms, LTCs and function limitations)
 - based on laboratory and blood pressure (BP) measurements (FI-lab)

Both the frailty phenotype and FI have previously been adapted for use in UK Biobank analyses^{117, 211}. The FI-lab was derived in a similar manner, using the range of biochemical and physiological measures available, informed by prior methodological work^{102, 103}.

The FI-lab was originally chosen to allow the assessment and measurement of frailty in the SCREAM cohort. However, due to lack of availability of all the measurements included in the index, within a limited time point, it was not possible to produce this and conduct any frailty analyses within SCREAM.

Frailty measure components and measurements are summarised in full in Chapter 6.

3.9.1 Operational cut-offs

Frailty phenotype was based on the presence or absence of the five criteria described above. Participants were categorised as:

- Frail if they met three or more criteria
- Prefrail if they met one or two criteria
- Robust (non-frail) if they met none of the criteria

The frailty indices (FI and FI-lab) are constructed by unweighted counts/accumulation of deficits methods²²⁵. We followed methods standardized by Searle et al.²²⁶ The frailty indices were calculated by summing the total number of deficits present and dividing this by the total number of deficits assessed. This results in a continuous frailty score between 0 and 1. It is well established that the prevalence of frailty differs according to the measure applied and the cut-offs used. A cut-off of more than 0.25 was chosen to identifying individuals with frailty, as this has been evidenced in previous research as being a level that is associated with adverse outcomes such as mortality and is commonly used as a standard cut-off in other frailty research studies in UK Biobank, allowing comparability with prior studies^{103, 227}.

The decision to use more than one measure of frailty was based on the recognition that different tools reflect overlapping but distinct conceptualisations of what frailty is. The frailty phenotype primarily captures features of biological vulnerability and physical declines, whereas the FI reflects overall burden of accumulated health deficits that make an individual more vulnerable to fluctuations in health status and functioning. By applying three different measures, the rationale was that we could evaluate frailty from complementary perspectives and start to explore whether associations with the prediction of kidney failure risk and competing mortality varied depending on the measure used to identify frailty.

3.10 Validation of prognostic model and model performance measures

The four-variable KFRE was validated in CKD subgroups stratified by multimorbidity or frailty status dependent on the study. Model performance was assessed at 2 and 5 years using the following performance measures:

- Discrimination
 - Harrell's C-index (assesses concordance between predicted and observed outcomes)
 - Time-dependent area under receiver operating characteristic curves (AUC) (evaluates the ability of the model to distinguish between those who did and did not experience the outcome over specified time periods)
- Calibration
 - Calibration curves (visually compares observed versus predicted risks)
 - Calibration intercepts (general calibration - assesses whether predictions were systematically too high or too low)
 - Calibration slopes (quantifies the degree of under- or overfitting in predictions)
 - Observed/expected (O/E) ratios (calibration-in-the-large - a summary measurement of calibration)
- Overall model fit and prediction error
 - Brier scores (comparison of how close predicted probabilities are to observed outcomes)
 - Scaled Brier scores (model interpretation against a null model without covariates)

The choice of performance measures was shaped by methodological guidance for prognostic model validation in the presence of competing risks¹⁷⁶ and supported by the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) guidelines²²⁸. Where model discrimination,

calibration and overall performance are highlighted as being important for comprehensively assessing a prognostic model.

Models were compared across subgroups, differing eGFR equations and time horizons, as described in the respective chapters.

3.11 Competing risk analyses

Given that mortality was predicted to be a frequent competing event in populations with multimorbidity or frailty and CKD, competing risk analyses were conducted using both Cox-cause specific proportional hazards regression models and Fine-Gray subdistribution hazard models. I chose to perform competing risk analyses using the two different methods as they both have individual strengths and limitations.

The cause-specific Cox model develops separate hazard models for each event (kidney failure and death), where individuals experiencing the other event are treated as censored. These separate models are then combined to calculate the absolute risk of the primary event.¹⁷⁶ One advantage of the cause-specific Cox model is that it provides hazard ratios that are easily interpretable, as they directly represent the effects of the covariates on the occurrence of the specific event of interest. Additionally, the sum of absolute risks across competing outcomes is constrained to remain below 1, which is not the case with the Fine-Gray model. However, a practical limitation of the cause-specific Cox model is that calculating patient absolute risk predictions requires access to baseline hazard functions and covariate-specific hazard ratios over time which makes manual calculation difficult, with the reliance on digital app or scripts to facilitate their validation and use in clinical practice. In contrast the Fine-Gray model directly links covariates to the cumulative incidence (absolute risk) of the primary event by modelling the subdistribution hazard. Advantages of the Fine-Gray model include the ability to directly estimate the absolute risks for the primary event of interest (kidney failure) without the need to combine multiple models. Additionally, the Fine-Gray methodology is widely used in published competing risk prediction studies, permitting ease of comparison. However, subdistribution hazard ratios are less easy to interpret. For example, a subdistribution hazard ratio below one may suggest a variable is protective for

the event of interest but it could instead represent a risk factor for the event of interest if the variable is simultaneously a strong risk factor for a competing event.¹⁷⁶

Using both approaches allowed a fuller understanding and more robust assessment of the impact of the competing risk of mortality and the variables used in the KFRE to predict kidney failure.

3.12 Qualitative descriptive study

3.12.1 Study planning and design

The qualitative descriptive study planning and design was described in full and published in a protocol paper²²⁹ that is included in the Appendix (Appendix 3).

3.12.2 Participants

Eligible patients were adults with CKD, defined either as an eGFR below 60ml/min/1.73m² or by the presence of a clinical diagnosis code for CKD, and who also had two or more other LTCs or frailty (based on clinical coding). Healthcare professionals were eligible if they were directly involved in the management or care of individuals with CKD. This group included general practitioners, renal specialist registrars, specialty doctors, renal consultants, and specialist nurses.

3.12.3 Recruitment

Participants were recruited using a purposeful sampling strategy to gain diversity across age, sex, socioeconomic background, ethnicity and healthcare setting (primary or secondary care).

Recruitment took place across both primary and secondary care. In primary care participants were identified via the NHS Research Scotland Primary Care Networks (NRS PCRN). This is a valuable resource for identifying primary care practices willing to support advertised research studies. Within these primary care practices, searches of individuals who met the eligibility criteria were performed. Potential participants were subsequently screened by their own GP

and the research team to ensure suitability to take part before a letter of invitation was sent via post. This was an accessible and efficient way to identify potentially eligible individuals. However, limitations of this method included under-coding of frailty, making it more difficult to recruit individuals experiencing frailty to the study. There was also the additional challenge that some individuals were unaware of their CKD diagnosis.

In secondary care, recruitment occurred in kidney clinics, where HCPs identified potential participants who were then approached by the research team either in person when attending the kidney clinic or via telephone. Written study information was provided in person, by post or by email.

Additional recruitment routes and strategies including recruitment through SHARE (The Scottish Health Research Register and Biobank) and social media platforms were identified prior starting the study and were included in the study protocol but were not required due to a very positive response to the measures already described.

HCP participants were approached through practice managers (for primary care), renal clinical leads (for secondary care) and professional networks and contacts (for both primary and secondary care). Invitations and information sheets were distributed by email.

Through the process of data collection, it became apparent that general practice nurses had not previously been identified as individuals with a prominent role in CKD care and subsequently were not included in the original sampling frame. A targeted recruitment effort was therefore undertaken using professional networks and the NHS Scotland Continuous Professional Development General Practice Nurse group to ensure their perspectives were captured.

3.12.4 Sample size

A sample size of 30 patient participants and 20 HCPs (composed from primary and secondary care) was chosen based on previous qualitative research in similar populations/areas²³⁰⁻²³² to facilitate saturation of topic themes. The priority aim

of the research method and sample size was to gather a range of views and context rather than to achieve complete representativeness²³³. The split of primary care and secondary care individuals ensured we explored perspective from both settings.

3.12.5 Data collection

Patient participants were interviewed individually. This approach was chosen due to the clinically sensitive nature of discussions, giving participants the opportunity to share personal experiences and perspectives in a private setting without potential influence from peers. Flexibility in interview format, timing and setting were also chosen to support patient engagement, particularly for those who may have found group participation challenging.

Focus groups were chosen as the primary method of data collection for HCP participants. They were chosen to emulate natural interactions and team dynamics that exist within healthcare and multidisciplinary teams and to ensure a breadth of perspectives were sought. However, it was challenging to facilitate the logistics of ensuring all interested HCP participants who were engaged in taking part in the research were able to attend a focus group session due to clinical commitments and constraints. Therefore, in cases where participants could not attend a focus group session, individual interviews were offered to ensure their perspectives were not lost.

Interview and focus group schedules were developed using the Ottawa Decision Support Framework (ODSF)¹⁸² and the Ottawa Personal Decision Guide (OPDG),¹⁸³ a decision aid developed for and applied in shared decision-making contexts. This ensured that the domains relevant and important to decision-making were systematically covered during data collection.

The five areas of ODSF and OPDG that the guides were based on were:

- Knowledge - understanding decisions, including the benefits, risks and potential outcomes.

- Values - how personal preferences and priorities influence how options are considered and chosen.
- Support - role and availability of guidance, resources, or encouragement from others to help inform or facilitate decision-making.
- Certainty - level of confidence an individual has in understanding the options and the chosen course of action.
- Decision-making - the process by which knowledge, values and support are integrated to reach and action a choice.

The guides facilitated exploration of how shared decision-making related to CKD, multimorbidity, frailty, kidney failure risk and the use of the KFRE. Importantly, this complemented the Normalisation Process Theory (NPT) framework approach (described in Subsection 3.13) applied in the analysis, providing a dual focus on both shared decision-making and implementation in clinical practice.

Data from interviews and focus groups were digitally recorded to ensure accurate capture of the data. This was then followed by verbatim transcription and anonymisation through a University of Glasgow approved transcription service so that data was in a format to allow framework analysis using NVivo software (QSR International (UK) Ltd).

3.12.6 Addressing potential bias

It was acknowledged that I and the co-researcher involved in the qualitative data analysis had clinical backgrounds and that our experience could influence data collection and interpretation. Steps were taken to minimise potential bias in data collection and interpretation:

1. Development and piloting of interview and focus group guides.
2. Ensuring research aims were explicitly stated and emphasis was given that the focus was on gaining individuals perspectives, experiences and opinions, at the start of each interview/focus group session.

3. Reflexive notes were captured as part of field notes to highlight potential biases.
4. Performing co-analysis and check coding a sub-set of the data.

3.12.7 Overarching theoretical orientation

This thesis was underpinned by a pragmatist orientation, in which the research question determines the choice of method rather than adherence to a single philosophical position. This approach is suited to mixed-methods research, as it allows quantitative and qualitative methods to be combined. The questions addressed within the thesis required different approaches - whether KFRE performs accurately in individuals with multimorbidity or frailty required a quantitative analysis, while how patients and healthcare professionals understand CKD, kidney failure risk and use KFRE in the context of CKD and multimorbidity or frailty requires qualitative methods. An exclusively positivist or post-positivist position, which assumes a single measurable reality, would not allow the qualitative study. Similarly, an interpretivist position, which regards knowledge as socially constructed, would not fit quantitative validation. Mixed-methods design is about combining the results of both study types to answer research questions and therefore, adopting either theoretical position in isolation is not in keeping with this. Pragmatism was therefore the orientation most coherent with the research aims, questions and structure of the studies and thesis.

3.13 Normalisation Process Theory (NPT) and framework analysis

Analysis of the qualitative data followed a framework approach,²³⁴ guided by Normalisation Process Theory (NPT)^{235, 236}, which conceptualises implementations and utilisation of processes into daily life and clinical practice using four main constructs:

- Coherence - understanding and making sense of processes.
- Cognitive Participation - engagement and enrolment of individuals to processes and tasks.

- Collective Action - work and effort required to perform processes and tasks.
- Reflexive monitoring - appraisal and reflection of work and processes.

This theoretical framework has been widely applied in healthcare research to explore how clinical interventions or changes in practice are adopted, adapted and maintained, both from the perspectives of HCPs and in the context of patients' lives. It was therefore deemed suitable to enable insight into both the patient and health professional perspectives. In this thesis, NPT provided a structure to examine how KFRE might be integrated into shared decision-making processes, how patients and HCPs understood and perceived CKD and kidney failure risk in the context of multimorbidity and frailty and the work required for these processes in day-to-day life and clinical practice.

The five stages of framework analysis were followed, as described by Ritchie and Lewis²³⁷:

- Familiarisation
- Identification of a thematic framework
- Indexing
- Charting
- Mapping and interpretation

Coding was chosen to be both deductive (mapped to NPT constructs) and inductive (emerging themes) to ensure no relevant themes or topics were missed. Themes were developed iteratively primarily by myself, and a subgroup of them (10%) were checked by a second researcher with qualitative research training, experience of using NPT but a differing clinical background, enhancing the credibility and rigour through investigator triangulation.

3.14 Triangulation

Quantitative and qualitative methods were chosen to examine different aspects of the subject areas. Triangulation was selected as a mixed-methods approach to integrate the findings of the studies to advance the knowledge gained from the independent studies and provide more comprehensive, deeper understanding of the research topic¹⁹⁸. Additionally, mixed methods approaches such as triangulation allows complex research questions to be addressed more effectively by capturing both measurable outcomes and contextual experiences.

In this thesis, triangulation was conducted by comparing and integrating findings from the systematic review, validation studies and qualitative studies following the independent analysis of each study. Specifically, results were examined for areas of agreement (convergence), added insights (complementarity), and discrepancy (dissonance). This was performed using established triangulation protocol technique^{198, 238}. This method was originally developed for multiple qualitative methods but has been applied to mixed methods research. The process is conducted by developing a “convergence coding matrix”, where results from each individual study analysis are presented together and analysed to find the areas of agreement, partial agreement or disagreement. Additionally, areas of silence may be identified where a finding is identified in one study/analysis but not another. Through this process, the study aimed to develop a more robust and nuanced interpretation of the data, ensuring that conclusions were informed by multiple sources of evidence²³⁹ and to increase understanding of the findings.

3.15 Patient and public involvement and engagement (PPIE)

The involvement of Patient and Public Involvement and Engagement (PPIE) groups during this thesis has been invaluable. PPIE was embedded throughout the work of this thesis to ensure that the research addressed issues of direct relevance to people living with CKD. Involving public contributors provided opportunities to refine research aims, align study priorities with patients’ needs and to improve the clarity and accessibility of study materials. The approach was consistent with best practice in applied health research where meaningful

patient and public involvement helps to ensure that research is grounded in live experiences and realities of those most affected.²⁴⁰

PPIE input was sought at multiple stages of the research process:

- **Systematic review:** From the outset, the West of Scotland Kidney PPIE group helped refine the aims of the systematic review. Their feedback encouraged me to focus not only on the academic contributions of the work but also how the findings might be of practical relevance to patients and families impacted by CKD.
- **Quantitative studies:** During the development of studies validating KFRE in the context of frailty and multimorbidity, both the West of Scotland Kidney PPIE group and the University of Glasgow Medical, Veterinary and Life Sciences (MVLS) PPIE group provided feedback on study questions, aims and interpretation of results. They highlighted the importance of considering which outcomes were most important to patients, not only survival or disease progression, but quality of life, independence, and the ability to manage multiple conditions. These perspectives shaped the way I interpreted and presented the findings and the qualitative study that I went on to conduct.
- **Qualitative study:** Six individuals from the West of Scotland Kidney PPIE group contributed to the design of the qualitative work. They reviewed participant-facing materials (information sheets, consent forms, and interview guides) to ensure clarity, sensitivity, and accessibility. They also suggested recruitment approaches and themes for exploration, helping ensure that the study reflected patient priorities. Engagement with the broader MVLS PPIE group was also included to ensure that input was sought from individuals without direct CKD experience and aimed to ensure that study materials were understandable to a wider public audience. Finally, they were involved in reviewing themes and selecting quotes for inclusion in the manuscript of the qualitative study results.

The inclusion of PPIE was motivated by recognition that patient and public perspectives often differ from academic or clinical priorities. Involving PPIE

therefore ensured that the research conducted as part of this thesis remained aligned with issues that matter to individuals living with CKD and multimorbidity and frailty.

4 Chapter: 4 Representation of multimorbidity and frailty in the development and validation of kidney failure prognostic prediction models: a systematic review

4.1 Reference

Walker, H., Day, S., Grant, C. H., Jones, C., Ker, R., Sullivan, M.K., Jani, B. D., Gallacher, K., & Mark, P. B. (2024). Representation of multimorbidity and frailty in the development and validation of kidney failure prognostic prediction models: a systematic review. *BMC Medicine*, 22(1):452.

<https://doi.org/10.1186/s12916-024-03649-9>

4.2 Chapter summary

In this chapter, the consideration and reporting of multimorbidity and frailty in the development or validation of existing kidney failure prognostic models is explored through a systematic review of the literature.

4.3 Manuscript

Abstract

Background Prognostic models that identify individuals with chronic kidney disease (CKD) at greatest risk of developing kidney failure help clinicians to make decisions and deliver precision medicine. It is recognised that people with CKD usually have multiple long-term health conditions (multimorbidity) and often experience frailty. We undertook a systematic review to evaluate the representation and consideration of multimorbidity and frailty within CKD cohorts used to develop and/or validate prognostic models assessing the risk of kidney failure.

Methods We identified studies that described derivation, validation or update of kidney failure prognostic models in MEDLINE, CINAHL Plus and the Cochrane Library—CENTRAL. The primary outcome was representation of multimorbidity or frailty. The secondary outcome was predictive accuracy of identified models in relation to presence of multimorbidity or frailty.

Results Ninety-seven studies reporting 121 different kidney failure prognostic models were identified. Two studies reported prevalence of multimorbidity, and a single study reported prevalence of frailty. The rates of specific comorbidities were reported in a greater proportion of studies: 67.0% reported baseline data on diabetes, 54.6% reported hypertension and 39.2% reported cardiovascular disease. No studies included frailty in model development, and only one study considered multimorbidity as a predictor variable. No studies assessed model performance in populations in relation to multimorbidity. A single study assessed associations between frailty and the risks of kidney failure and death.

Conclusions There is a paucity of kidney failure risk prediction models that consider the impact of multimorbidity and/or frailty, resulting in a lack of clear evidence-based practice for multimorbid or frail individuals. These knowledge gaps should be explored to help clinicians know whether these models can be used for CKD patients who experience multimorbidity and/or frailty.

Systematic review registration This review has been registered on PROSPERO (CRD42022347295).

Keywords Prognosis, Chronic renal failure, CKD, Multimorbidity, Frailty, Guidelines, Systematic review

Key learning points

What was known:

- Individuals with CKD commonly experience multimorbidity and/or frailty.
- Multimorbidity and frailty are associated with adverse outcomes in CKD including disease progression.
- Clinical guidance recommends the use of validated risk prediction equations to guide referral to specialist kidney services, but it is unclear to what extent current prediction models have been developed with representative numbers of people with multimorbidity or frailty or if these syndromes impact model performance.

This study adds:

- Very few studies on kidney failure prognostic models reported multimorbidity or frailty prevalence or considered either as predictors.
- Kidney failure prognostic models have not been validated in relation to multimorbidity or frailty.

Potential impact:

- Clinical guidelines currently lack evidence for individuals with multimorbidity or frailty.
- Further research is required to support clinicians to know whether prognostic models recommended in clinical guidance can be used for individuals with CKD who experience multimorbidity and/or frailty.
- Validation of these models in sub-groups with multimorbidity and/or frailty will influence care for this population.

Background

Chronic kidney disease (CKD) is increasing in prevalence, with current estimates reporting 10-15% of adults having a diagnosis of CKD ²⁴¹. Progression of CKD leads to kidney failure in a small proportion of people. Various factors influence the risk of kidney failure such as age of CKD onset, sex, ethnicity, lifestyle, underlying disease aetiology, blood pressure and glycaemic control ²⁴². Additionally, non-renal comorbidities that are worsened by or occur as a sequelae of kidney disease may also influence the progression of kidney disease ^{69, 243}. Identification of individuals at greatest risk of progressing to kidney failure requiring kidney replacement therapy (KRT), frequently referred to as end-stage kidney disease (ESKD), can be accomplished in risk prediction models. The use of such risk prediction models in clinical practice potentially provides more precise and individualised care. Application of prognostic models allows more informed patient communication, facilitates shared decision-making and guides evidence-based practice including timing of referral to specialist care and decisions around KRT planning.

Individuals with CKD are more likely to have increased numbers of long-term conditions compared to those without CKD ⁴. Multimorbidity, the co-existence of two or more long-term conditions ⁶, differs conceptually from co-morbidities where the focus is on a primary disease alongside co-existing conditions ⁶². Both multimorbidity¹¹⁷ and CKD ^{5, 244} are associated with experiencing frailty. Frailty can be described as a vulnerability to decompensation and impaired or delayed resolution of homeostasis in response to stressors, such as illness or medications ^{7, 117}. Frailty is also associated with advancing CKD, increased risk of hospitalisation and mortality ¹²⁹. There is an overlap between multimorbidity and frailty, but they are distinct concepts. Some individuals experience co-occurrence of multimorbidity and frailty, while others experience one but not the other ¹²⁶. There are a number of ways of measuring multimorbidity including weighted scores such as the Charlson ⁶⁴ and Elixhauser ⁶⁵ Comorbidity indices or simpler long-term condition counts ⁶. Likewise, frailty can be measured in numerous ways with validated measures including but not limited to using cumulative deficit scores such as the frailty index ^{99, 226}, the Fried frailty

phenotype⁸ and the clinical frailty scale¹⁰⁴ based on clinical evaluation of an individual.

Patients with CKD and multimorbidity are at increased risk of mortality¹² and hospitalisation²⁴⁵ compared to CKD without multimorbidity. Multimorbidity has been shown to be associated with progression of CKD¹² and recent research highlights a cumulative risk of major adverse kidney events (KRT, doubling of creatinine, estimated glomerular filtration rate (eGFR) <15ml/min or >30% decline in eGFR) with increasing numbers of long-term conditions¹³.

Multiple risk prediction models have been developed to identify individuals at high risk of ESKD, with associated systematic reviews assessing their utility¹⁶⁷. The Kidney Disease: Improving Global Outcome (KDIGO) 2012 guidance recommended the use of risk prediction models to guide referral for KRT planning and 2021 National Institute for Health and Care Excellence (NICE) guidelines for management of CKD¹¹ recommended the four variable kidney failure risk equation (KFRE)⁹ to inform adults with CKD about their 5-year risk of need for KRT and to guide referral for specialist assessment. It is unclear to what extent current prediction models, including KFRE, have been developed with representative numbers of people with multimorbidity or frailty. Given these groups are at heightened risk of mortality, it is also unclear whether the competing risk of death has been appropriately factored into prediction tools. Heterogeneity between studies due to variation in study design, measurement of variables and outcomes and differences in case-mix may impact model performance²⁰³.

The systematic review aimed to describe, summarise and evaluate the representation of multimorbidity and frailty within cohorts used to develop, validate and/or update prediction models assessing the risk of kidney failure in individuals with CKD over a minimum of 2 years.

Key objectives are as follows:

1. Evaluate if prevalence of multimorbidity or frailty are reported in studies that develop and/or validate kidney failure prediction models.

2. Assess the impact of multimorbidity and/or frailty, if any, that has been studied on the validity of models in estimation of kidney failure risk.

Methods

The protocol for this systematic review was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number: CRD42022347295) and was prepared using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA-P) 2015 statement²⁰² and the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist¹⁵⁵.

Eligibility criteria

Articles eligible for inclusion were quantitative studies that developed, validated or updated a prognostic model for kidney failure, with the final model including a minimum of three predictors. The study population was adult patients with CKD, with a study outcome of kidney failure, ESKD or 50% reduction in baseline eGFR. Prediction models had to present at least one measure of model performance (calibration or discrimination).

Full inclusion and exclusion criteria are described in Supplemental Table 4-1 and 4-2.

Information sources and search strategy

An electronic search for published peer-reviewed articles was applied to MEDLINE (EBSCO interface), CINAHL Plus (EBSCO interface) and the Cochrane Library CENTRAL (OVID interface). Supplemented by manual review of reference lists of included studies and relevant clinical guidelines. Literature published up to 18 October 2023 was included. Full search strategies are presented in Supplemental Tables 4-3-4-5.

Data management

Studies identified were imported into Rayyan systematic review software (<https://www.rayyan.ai/>). Covidence systematic review software (Covidence, Melbourne, Australia) was used for full text review, data extraction and risk of bias assessment.

Data collection and analysis

Two reviewers (HW and SD) independently screened article titles and abstracts. Selected studies were reviewed independently, in full, to confirm eligibility. Differences were resolved by discussion with a third reviewer (PBM).

Data were extracted independently by HW and a second reviewer (SD, CHG, CJ or RK) into a pre-defined electronic data collection form including: study characteristics (author, publication year, country of origin, study design, start/end date, sample size), patient characteristics (including age, sex, ethnicity, eGFR, co-morbidities, multimorbidity/frailty measures), number of participants, number of events, outcomes (definitions, measurement, timing of measurement, duration of follow-up), model development (method for selection of predictors, model type, model variables) and model performance (calibration, discrimination measures). Where measures were not reported we followed previously described methods to calculate missing performance measures where possible ²⁰³.

Risk of bias

Two authors, HW and a second reviewer (SD, CHG, CJ or RK), independently reviewed the risk of bias using the Prediction model Risk Of Bias ASsessment Tool (PROBAST) ¹⁵⁴. PROBAST is a risk of bias assessment tool that has been developed through a consensus process specifically for assessment of risk of bias in systematic reviews of prediction model studies ¹⁵⁴. Differences were resolved by consensus with a third reviewer (PBM).

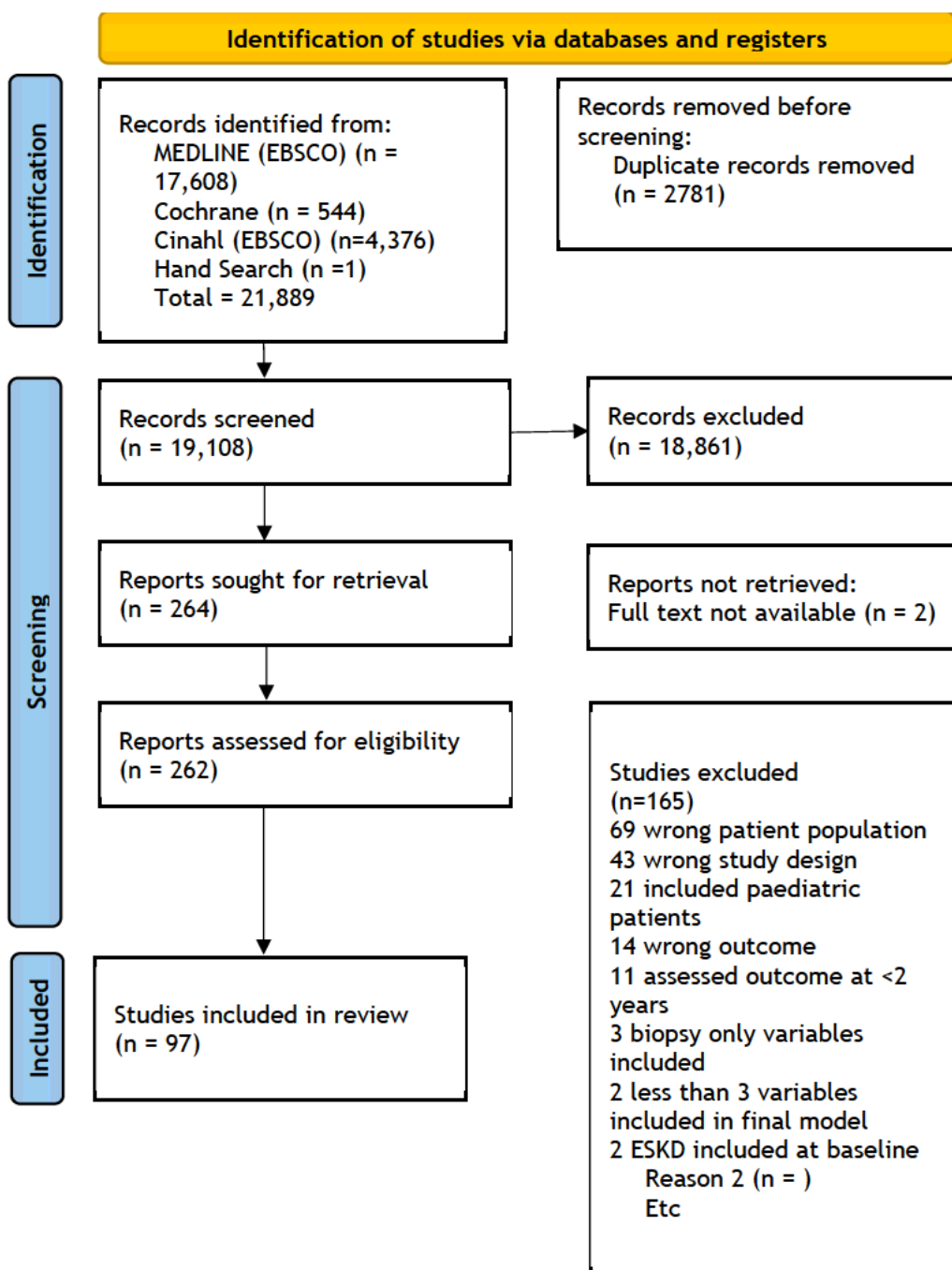
Summary measures and data synthesis

Baseline characteristics are summarised using means with standard deviations, medians with interquartile ranges and frequencies with percentages as appropriate. Included studies and overall findings were reported using narrative synthesis. Where possible, data are presented in summary tables and graphical representation. Analyses were performed using R software version 4.3.0.

Results

We identified 19,108 original articles, with 97 studies (full details of included studies in supplementary materials) meeting the inclusion criteria, and a resultant 121 original kidney failure prognostic models. Overall, there were 2,925,413 participants and 149,380 kidney failure outcome events. Included participants had mean age of 58.9 years (SD 9.6), 44.4% were female, with mean eGFR of 47.5ml/min/1.73m² (SD 10.7). Figure 4-1 details the study selection process.

Figure 4-1. Flow chart of study selection.



CKD definitions/sub-groups, populations and setting varied across included studies (Supplemental Table 4-6). Likewise, kidney failure outcome definitions and ascertainment (e.g., health records, laboratory data, coding or registry data) were not consistent.

Summaries of original models ²⁴⁶⁻²⁵⁵ and baseline characteristics of included studies are detailed in Supplemental Table 4-7 and 4-8.

Development studies

Fifty-four studies described the derivation of kidney failure prognostic models for use in CKD. There were a small number of prognostic models that were validated in studies included in the review, where the original development study did not meet inclusion criteria ²⁴⁶⁻²⁵⁵.

Thirty-one studies developed models for use in a general CKD population, although there was a wide variation in CKD definitions and eGFR cut-offs used across studies (Supplemental Table 4-6). The remaining included studies that developed/validated models to predict kidney failure in diabetic kidney disease (n = 15), IgA nephropathy (IgAN, n = 16), glomerular diseases (n = 2), focal segmental glomerulosclerosis (n = 1), ANCA-associated vasculitis (n = 1) and lupus nephritis (n = 1).

Multimorbidity and frailty within included studies

The majority of studies included did not report the overall multimorbidity or frailty of participants. Only two studies reported multimorbidity (reported by Elixhauser Comorbidity Index (ECI) ²⁵⁶ and Charlson Comorbidity Index (CCI) ²⁵⁷) and one study reported a frailty measure (self-reported general health scores as a proxy for frailty) ²⁵⁸. Two additional studies reported a number of hospitalisations ²⁵⁹ and medications along with annual hospital admissions ²⁶⁰ which could be considered a proxy for multimorbidity or frailty. The study that reported ECI, was a prognostic model for CKD stages 3-4 and type 2 diabetes mellitus. Mean ECI was 4.6 (SD2.6), mean index in individuals who experienced kidney failure compared to those who did not was higher (6.1 (SD2.9) vs 4.8 (SD2.6) respectively). The ECI was considered for inclusion in the model but was

not selected. However, ECI overlaps with individual comorbid conditions which form the index score, some of which were included in the model.

A single study that externally validated the 4-var KFRE in individuals with glomerulonephritides, reported baseline CCI ²⁵⁷ with a median score of 2 (IQR 1-3). Discrimination was adequate, AUC 0.77 (95%CI 0.72-0.83) ²⁵⁷ but calibration was not reported. Table 4-1 and Supplemental Table 4-9 summarise the prognostic models and reporting of multimorbidity/frailty measures.

No studies assessed the performance or validation of kidney failure prognostic models in populations specifically with CKD and multimorbidity. The single study that used a self-reported general health measure as a proxy for frailty assessed the clinical utility of a model and referral algorithms considering frailty, risk of kidney failure and risk of death but did not assess discrimination or calibration measures in the context of frailty ²⁵⁸.

Table 4-1. Summary of kidney failure risk prediction models and multimorbidity/frailty measures reported for general CKD population.

CKD population	Prediction models	Number of variables in the model	Number of external validation studies	Multimorbidity/frailty measure reported			
General CKD population	Johnson 2008	<10	1				
	Landray		2	Prouvot 2021 - Octogenerian cohort but no frailty measure reported			
	Marks*						
	Schroeder KPNW score						
	Tangri		3				
	KFRE-3						
	KFRE-4		36	Hallan 2019 - Self-reported general health score	Prouvot 2021 - Octogenerian cohort but no frailty measure reported	Stefan 2020 - Charlson co-morbidity index	Bellocchio 2021 - number of hospitalisations
	KFRE-6		5				
	KFRE-8		11				
	Belur MLMs x4		0				
	Dimitrov Renal Risk Index						
	Gibertoni CT-PIRP			Number of medications and annual hospital admissions as a proxy for disease severity			
	Hasegawa						
	Johnson 2007						
	Lim models 1-5						
	Smith						
	Tangri Dynamic model						
	Xu						
	Zacharias KFRT risk model						
	Zhu dynamic mode						
	Lee CKD stage 5 model						
	Maziarz model 1-2						
	Maziarz2 models 1-2						

	Xie model 1	10-20		
	Zhang models A-C			
	Led CKD stage 3 mode, CKD stage 4 model			
	Maziarz models 3-4			
	Maziarz2 models 3-4			
	Xie models 2-3			
	Zhang model D			
	Al-Wahsh			
	Dai			
	Edmonston, Edmonston +FGF23			
	Hsu base model, base model + urine biomarkers			
	Orlandi models 1-4			
	Sud			
	Yuan CKD3A model, CKD3B model			
	Grams Markov model	>20	3	Prouvot 2021 - Octogenerian cohort but no frailty measure reported
	Bellocchio PROGRESS-CKD		0	Number of hospitalisations
	Bai 5x MLMs	Unclear		

76.3% (n = 74) studies reported baseline data on one or more co-morbidities, primarily diabetes (67.0%, n = 65), hypertension (54.6%, n = 53), and cardiovascular disease (CVD) (39.2%, n = 38). Sixty-five studies including 1,610,586 participants reported on diabetes with a prevalence of 48.8%. A total of 1,565,364 participants from 54 studies reported on baseline hypertension with a pooled prevalence of 67.0%. Baseline CVD was reported in 39 studies, including 575,011 participants with a prevalence of 31.8%; however, there was heterogeneity in the definitions of CVD used across studies.

Forty-four studies considered the inclusion of one or more individual comorbidities as predictor variables in model development. Thirty-eight models went on to include one or more comorbidities as a variable in the reported models. Comorbidities included were most commonly diabetes (n = 28), hypertension (n = 19) and CVD (n = 18) but others also included chronic pulmonary disease, connective tissue disease, dementia, liver disease, anaemia, hyperlipidaemia, chronic viral disease and alcohol/drug misuse.

Table 4-2 and Supplemental Figure 4-1 summarise reporting and inclusion of individual comorbidities for all models that have been independently externally validated.

Table 4-2. Baseline comorbidities recorded and included/added to externally validated kidney failure prediction models for general CKD population.

Model	Study	Comorbidities recorded at baseline or included/added to model			
		Hypertension	Diabetes	CV disease	Other
KFRE-3	Bai 2022	✓	✓	✓	
	Naranjo 2021	✓	✓		
	Peeters 2013	✓	✓	✓	
	Jahan 2023		✓		
	Tangri 2011	✓	✓	✓	
	Tangri 2016	✓	✓		
	Ali 2021	✓	✓		
	Bundy 2022	✓	✓		
	Irish 2023	✓	✓		
	Chu 2023	✓	✓	✓	
KFRE-4	Da Silva 2022	✓	✓	✓	
	Grams 2018	✓	✓	✓	
	Hallan 2019		✓	✓	
	Grams 2023		✓	✓🟡	
	Ingwiller 2022	✓	✓		
	Kang 2020	✓	✓		
	Kwek 2022		✓		
	Lim 2019	✓	✓		
	Maher 2023	✓	✓	✓	
	Major 2019	✓	✓	✓	
	Massy 2023	✓	✓	✓	✓
	Naranjo 2021	✓	✓		
	Peeters 2013	✓	✓	✓	
	Prouvot 2021	✓	✓	✓	
	Ramspek 2021	✓	✓	✓	
	Stefan 2020	✓			
	Thanabalasingam 2022		✓	✓	

		Comorbidities recorded at baseline or included/added to model			
Model	Study	Hypertension	Diabetes	CV disease	Other
	Wang 2019	✓	✓	✓	
	Whitlock 2017		✓	✓	
	Yamanouchi 2018		✓🟡		
	Zacharias 2022	✓	✓	✓	
	Zhang 2023	✓	✓		
KFRE-6	Tangri 2011	✓	✓+	✓+	
	Ingwiller 2022	✓	✓+	+	
	Tangri 2016	✓	✓+	+	
	Kang 2020	✓	✓+	+	
KFRE-8	Tangri 2011	✓	✓	✓	
	Tangri 2016	✓	✓		
	Ingwiller 2022	✓	✓		
	Ali 2021	✓	✓		
	Jahan 2023		✓		
	Kang 2020	✓	✓		
	Kwek 2022		✓		
	Peeters 2013	✓	✓	✓	
	Ramspek 2021	✓	✓	✓	
	Tangri 2018	✓	✓	✓	✓
Markov model	Grams 2018		✓+	✓+	
	Prouvot 2021	✓	✓+	✓+	
	Ramspek 2021	✓	✓+	✓+	
	Thanabalasingam 2022		✓+	✓+	
Johnson 2008	Johnson 2008	✓+	✓+		
	Ramspek 2021	✓+	✓+	✓	
Landray	Landray 2010		✓	✓	
	Prouvot 2021	✓	✓	✓	
	Ramspek 2021	✓	✓	✓	
Marks	Prouvot 2021	✓	✓	✓	

		Comorbidities recorded at baseline or included/added to model			
Model	Study	Hypertension	Diabetes	CV disease	Other
Schroeder KPNW score	Ramspek 2021	✓	✓	✓	
		✓+	✓+	✓	

✓	Recorded at baseline
+	Included in model
+	Added to updated model

Model performance and observed and expected event numbers were not reported for the sub-groups of comorbidities in any study. Therefore, no meta-analysis of model performance by co-morbidities was possible. Due to the number of included studies reporting on multimorbidity or frailty no meta-analysis was possible.

Kidney failure risk equation

The prognostic model that was most extensively validated was the four variable KFRE (4-var KFRE) (n = 36). The 4-var KFRE performed well across most CKD populations and disease specific aetiologies, discrimination (AUC or c-index) ranged from 0.59 to 0.98 at 2 years, 0.78 to 0.91 at 3 years and 0.57 to 0.96 at 5 years, with some recalibration factors applied in different regions/countries.

Although most studies that validated KFRE did not report on multimorbidity, 75.7% (n = 28) reported on baseline diabetes with a mean prevalence of 42.9%. Only 48.6% (n = 18) reported on hypertension and 43.2% (n = 16) on CVD with baseline prevalence reported at 77.9% and 34.4%, respectively.

One study ²⁶¹ assessed the addition of previous CVD history into KFRE. Heart failure had a statistically significant association with kidney failure risk but did not improve overall model performance. A single study also assessed KFRE performance in the sub-groups by diabetes status and by those over 75 years compared to those 40-75 years old ²⁶².

Discrimination was similar across different age groups but was lower in those with type two diabetes mellitus compared to those without. Likewise, the performance of 4-var KFRE has been explored by renal disease aetiology ²⁶³. This study found that discrimination was adequate to excellent across all renal disease aetiologies explored but that calibration showed overestimation across all disease aetiologies with the exception of autosomal dominant polycystic kidney disease, where there was underestimation of kidney failure risk.

A further study ²⁵⁸ described validation of 4-var KFRE alongside the mortality risk equation for kidney disease (MREK) in patients over 65 years old although was

limited by restricting definition of ESKD to those receiving KRT and not conservative care of advanced CKD.

The 4-var KFRE was also the model most frequently updated, with effectiveness of updating the model depending on variables added, with small or no improvement in model performance reported.

Assessment of heterogeneity

Quantitative assessment of heterogeneity was not performed due to the inability to perform meta-analysis on included models.

Risk of bias and applicability assessment

Risk of bias was high, with 94% of studies having an overall high risk of bias. Summary of the PROBAST tool assessment of individual studies is presented in Supplemental Table 4-10 and overall and domain summaries for risk of bias and applicability assessment in Figure 4-2 and 4-3.

Figure 4-2. Summary of risk of bias assessment.

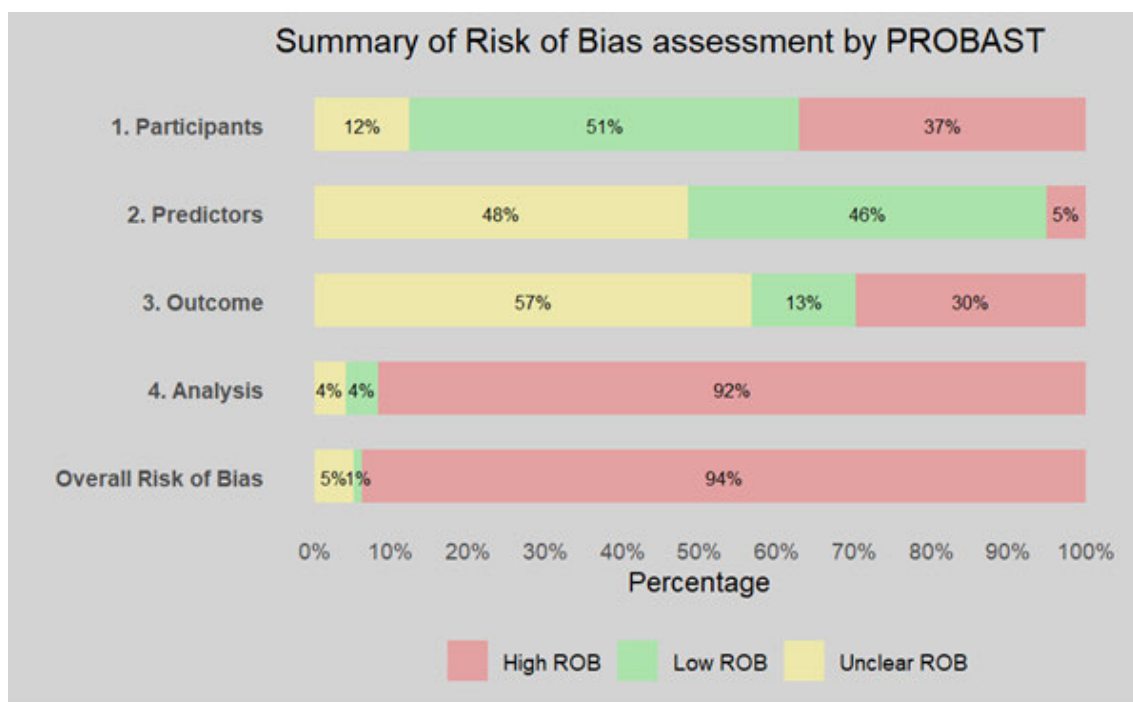
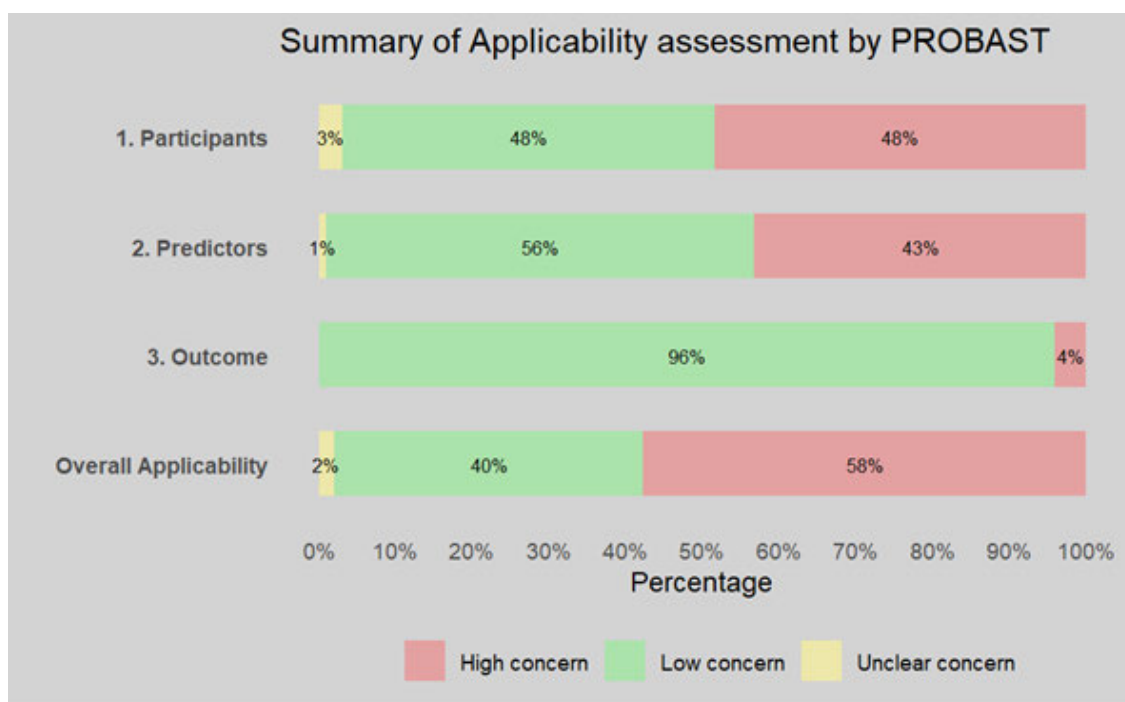


Figure 4-3. Summary of applicability assessment.



High risk of bias was attributable mainly to lack of assessment or consideration of the competing risk of death (68 of 97 studies, Supplemental Table 4-11). Inclusion bias occurred in 30% of studies, where eGFR was included in both outcome definition and prognostic model. Only 21 of the original models provided the full model formula to allow replication or application. Forty-three studies were classed as high risk of bias due to not reporting both discrimination and calibration measures or only reporting goodness-of-fit tests, such as Hosmer-Lemeshow test, for calibration. Only 70% of studies reporting calibration (n = 50) did so graphically, which is the preferred form of reporting calibration ¹⁵⁵.

There was a high concern regarding the applicability of 58% of the total included studies; this related to models focusing on the prediction of kidney failure in specific disease aetiologies of CKD such as IgA nephropathy rather than the general CKD population (48%) and the inclusion of model variables that were not routinely available in clinical practice (43%).

Discussion

Prognostic models for the prediction of kidney failure infrequently report or include measures of multimorbidity or frailty. Due to the large variety of relevant prognostic models and the lack of reporting of multimorbidity or frailty, comparison of model performance was limited. This review has defined a gap in the research relating to consideration of the competing risk of death in prognostic models for kidney failure. This is important as traditional survival analyses, where data is left censored and assumes that individuals lost to follow-up have the same risk of the outcome as individuals who continue to be followed up. However, if an individual dies before the outcome occurs (competing mortality), then they cannot experience the outcome event (kidney failure). This may lead to an over-prediction of kidney failure risk in individuals at higher risk of dying, such as those with multimorbidity or frailty. Competing mortality risk has been shown to impact predictive performance in other prognostic models and in older adults with more long-term conditions ^{264, 265}. The studies included in the review had a high risk of bias, primarily relating to lack of consideration of competing mortality risk and particular focus and attention should be given to ensuring future studies employ appropriate methodologies and report studies in line with TRIPOD guidelines.

In keeping with a recent large scoping review of prognostic models for patients with CKD ¹⁶⁸, including kidney failure prognostic models, our study found there was poor reporting of calibration. Calibration is important to consider alongside discrimination to assess overall model performance. There was also lack of reporting of full model formulas to allow replication or use of models. Similarly, the risk of bias findings in this review is consistent with a 2020 systematic review of prediction tools for kidney failure in CKD patients ¹⁶⁷.

The two studies that reported a multimorbidity baseline measure used a weighted score, making them difficult to interpret. Therefore, it is not possible to determine from the information provided whether participants had multimorbidity based on the standard definition of the presence of two or more long-term conditions ⁶. Within the studies that reported CCI and ECI, there is no comparison of model performance stratified by these measures.

Although baseline frailty or multimorbidity was not commonly reported in the existing prediction models, some studies were still relevant to these issues. Prouvout et al.²⁶⁶ evaluated the performance of four kidney failure prognostic models^{9, 253, 267, 268} in a cohort of octogenarian patients with advanced CKD. They found performance was poor across all models and highlighted that frailty may play a part in the poor performance of the prognostic models in this cohort. A 2016 systematic review of CKD and frailty¹²⁹ identified frailty as being associated with reducing eGFR and increased risk of adverse outcomes.

The inclusion of frailty may be limited by a lack of consensus on the optimal frailty measure to use in clinical practice or research settings. It is likely that frailty is not routinely available as a measure in observational data that are commonly used for the derivation or validation of prognostic models such as these. Frailty also fluctuates over time, with individuals moving between frailty states dependent on stressors such as illness or side effects from treatments. This may subsequently make it difficult to measure the true impact on subsequent kidney failure due to only capturing or accounting for an individual's frailty status at a single point in time.

Although the most frequently validated prognostic model, the 4-var KFRE, performed well in general CKD populations and aetiology specific CKD cohorts, there is evident heterogeneity between the populations and settings in which the model is validated. The performance of KFRE was reported as being lower in studies that focused on cohorts with glomerular diseases²⁶⁹ and diabetic kidney disease²⁷⁰. The study by Maher et al.¹⁷⁰ highlighted that incorporating ethnicity and its interactions with key variables like urine albumin creatinine ratio (uACR) and eGFR significantly improved KFRE's performance, for South Asian populations. Likewise, deficiencies in KFRE performance were noted by Grams et al. (2023)²⁶¹ with underprediction of kidney failure in the subgroup of individuals ≥ 65 years of age and over-estimation of risk at 5-year timeframes. Individuals are more likely to have increasing levels of multimorbidity and frailty as age increases and should be considered as factors that could impact model performance. Additionally, some studies that have considered the competing risk of death in KFRE have highlighted improvement in performance^{170, 261}. Of particular interest, is the finding that competing risk analysis improved

calibration in the subgroups of older adults (≥ 65 years old) and those with eGFR between 45 and 59 ml/min/1.73m² ²⁶¹.

A number of studies considered one or more individual comorbidities as predictor variables in model derivation, with the majority going on to include at least one comorbidity as a variable in the model developed. Comparison of these studies is limited by the variation in methodologies used to decide on predictor variable inclusion. Increasing numbers of machine learning models are being used to develop prognostic models for use in healthcare settings. Such methodologies allow consideration of a greater number of variables and exploration of more complex relationships than more traditional statistical methods. One such excluded study (no reported performance measures) developed a model using natural language processing to identify disease clusters based on ICD-9 codes, with improvements in classification accuracy using a machine learning model compared to more traditional models that included comorbidities²⁴³.

This systematic review has several strengths, including its extensive search strategy supporting the identification and comprehensive overview of available kidney failure prognostic models available for general and disease aetiology specific CKD populations. In addition, all review stages were performed in duplicate and independently adding to the robustness of study identification and data extraction. A further strength is the formal risk of bias and applicability assessment conducted using PROBAST. However, the overall finding of high risk of bias is not a novel one with a meta-review of prediction model systematic review literature identifying high risk of bias in the majority of studies and over time that this predominantly applied to the analysis domain ²⁷¹, as we have found in this study. This, however, highlights the ongoing need for prediction model studies to focus on improving methodological and model quality. The review is also limited by not all kidney failure prognostic model studies being included due to the lack of reporting of performance measures. Additionally, we were unable to perform meta-analysis due to the small number of studies reporting on multimorbidity or frailty.

This study has identified a gap in the research for the use of kidney failure prognostic models in adults with CKD and multimorbidity or frailty including how

the presence of these factors influences model performance. Additionally, understanding and comparison of model performance and use is limited by heterogeneity in CKD and kidney failure outcome definitions used and by differences in the timing of outcome assessment.

NICE and KDIGO guidelines both promote the use of prognostic models to predict the risk of kidney failure to guide the referral and treatment of patients with CKD. Validation of KFRE has been produced in multinational cohorts, varied settings and in different disease aetiologies but not specifically with a focus on multimorbidity or frailty. Given there is a high prevalence of multimorbidity and frailty in individuals with CKD it is essential that multimorbidity and frailty are represented within the cohorts used to develop, validate, and update available models. There is currently a lack of reporting of multimorbidity or frailty measures to say with certainty that such models are valid for use in individuals with multimorbidity or frailty.

Future research should focus on the assessment of validated prediction models that are recommended in clinical guidelines in those with multimorbidity or frailty compared to those without. Existing models may benefit from recalibration, updating or consideration of competing risks to improve performance, to take account of multimorbidity and/or frailty.

Conclusions

Multimorbidity and frailty are not yet well understood. In this review, we have been unable to determine how available prognostic models for kidney failure perform in individuals with multimorbidity and/or frailty. Further research is required to ensure that kidney failure prognostic and prediction models have sufficient clinical utility for use in these patients and should potentially be optimised, to take account of these conditions where appropriate.

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Authors' contributions

HW, MKS, BDJ, KG and PBM were involved in the conception/design of the work. HW, SD, CHG, CJ and RK were responsible for data acquisition & risk of bias/applicability assessment. HW performed analysis and interpretation of data. HW drafted the work and MKS, BDJ, KG and PBM critically revised it. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated of analysed during this study are included in this published article and its additional files.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

PBM reports lecture honoraria from Astrazeneca, Pharmacomsos, Bayer, Astellas, GSK and Boehringer Ingelheim outside the submitted work.

The other authors have no potential conflicts of interest to declare

5 Chapter: 5 Validation of the kidney failure risk equation in people with chronic kidney disease and multimorbidity: the effect of an update model accounting for competing mortality risks on model performance

5.1 Reference

Walker, H., Carrero, J-J., Sullivan, M.K., Field, R., Lees, J.S., Faucon, A-L., Fu, E.L., Jani, B.D., Gallacher, K. Mark, P.B. (2025). Validation of the kidney failure risk equation in people with chronic kidney disease and multimorbidity: the effect of an updated model accounting for competing mortality risks on model performance. *Nephrology Dialysis Transplantation*, 2025;. gfaf252.

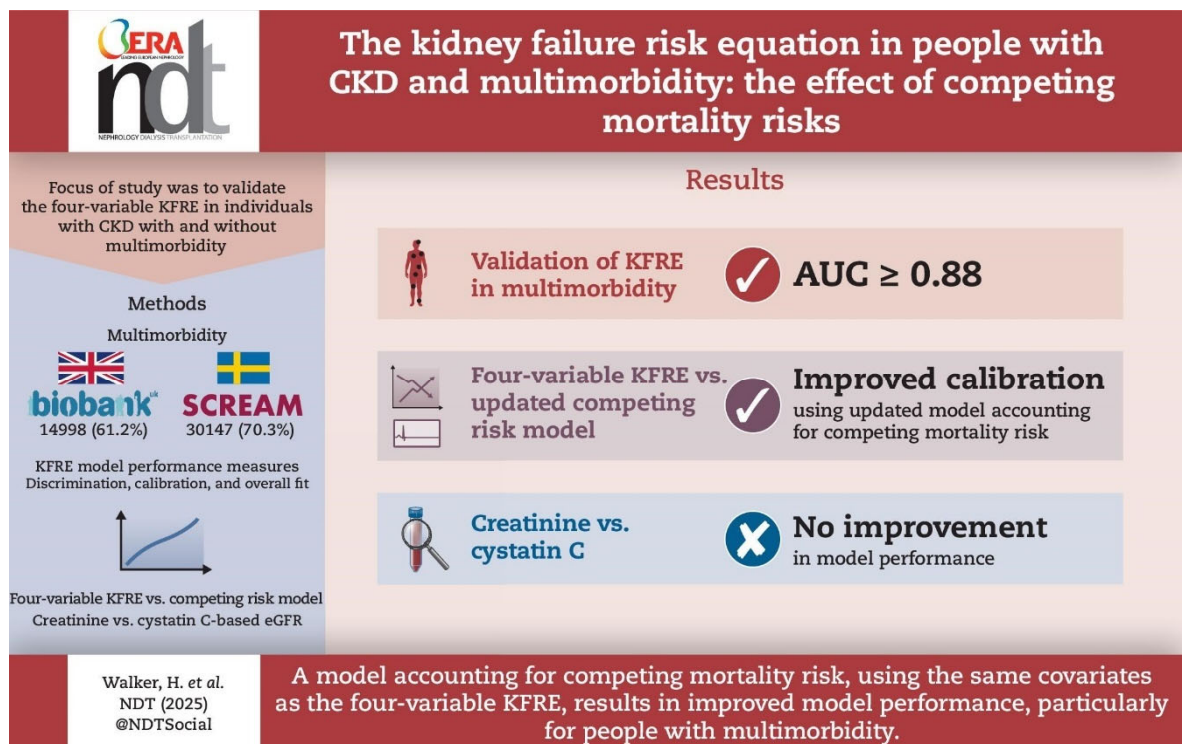
<https://doi.org/10.1093/ndt/gfaf252>

5.2 Chapter summary

This chapter presents analyses of the UK Biobank and SCREAM cohorts exploring how the presence of multimorbidity and different multimorbidity “cluster” groups, compared to no multimorbidity, affects the predictive performance of the Kidney Failure Risk Equation for patients with CKD and how the performance changes when competing mortality risks are accounted for (RQ2). In addition, the Kidney Failure Risk Equation performance is assessed comparing the use of cystatin-based eGFR (eGFR_{cys} and eGFR_{cr-cys}) compared to the creatinine eGFR (eGFR_{cr}) that is used as standard in the model (RQ4).

5.3 Manuscript

Graphical abstract



Abstract

Background and hypothesis Guidelines recommend using risk prediction models for predicting kidney failure in chronic kidney disease (CKD). Many people with CKD have multiple long-term conditions (multimorbidity), which influences outcomes including kidney failure and mortality. This study validated the four-variable Kidney Failure Risk Equation (KFRE) in individuals with CKD, with and without multimorbidity, comparing performance of KFRE using creatinine and cystatin C to calculate estimated glomerular filtration rate (eGFR) and updated the model to account for competing mortality risks.

Methods Observational cohort study using research-based (UK Biobank) and population-based cohorts (Stockholm Creatinine Measurements project: SCREAM). Multimorbidity was defined as two or more long-term conditions in addition to CKD. Kidney failure was defined as long-term dialysis or kidney transplantation. KFRE performance assessment included discrimination, calibration and overall fit at 2 and 5 years. An updated model (using the same variables as KFRE) accounting for competing mortality risks was developed and validated.

Results 14,998 of 24,489 individuals in UK Biobank (61.2%) and 30,147 of 42,902 individuals in SCREAM (70.3%) had multimorbidity. Discrimination of KFRE was good (area under curve ≥ 0.86 across eGFR equations in all cohorts, multimorbidity groups and time horizons). Kidney failure risk was underestimated in people with multimorbidity in UK Biobank (observed/expected (O/E) ratio 1.75 at 5-years; eGFR creatinine). Conversely, calibration-in-the-large (O/E ratio) at 5-years in SCREAM was 1.05 in the multimorbidity group (eGFR creatinine). Using cystatin C compared to creatinine did not improve model performance.

Cumulative incidence of death was higher with multimorbidity compared to no multimorbidity. An updated model considering competing mortality improved calibration performance over KFRE, O/E ratio 0.98 in multimorbidity group of the validation cohort (UK Biobank) at 5-years.

Conclusion Competing mortality risk is important when predicting kidney failure, particularly for people with multimorbidity. An updated model accounting for competing mortality risk, permits improved model performance.

Key learning points

What was known: The kidney failure risk equation has been recommended in clinical guidance to predict risk of kidney failure in chronic kidney disease. However, there is a lack of validation in individuals with multimorbidity compared to no multimorbidity, where risk of kidney failure and competing mortality risk is likely to be elevated.

This study adds: KFRE has good discrimination but demonstrated sub-optimal calibration in individuals with CKD and multimorbidity. An updated model accounting for competing mortality risk, using the same variables as KFRE, performs better for individuals with multimorbidity.

Potential impact: Competing mortality risk is important when predicting kidney failure, particularly for people with multimorbidity. By more accurately identifying those at greatest risk of developing kidney failure, a model accounting for competing mortality risk may impact individualised referral of individuals with multimorbidity and CKD, and subsequently impact treatment burden.

Keywords CKD, competing risk analysis, chronic renal failure, KFRE, prognostic model

Introduction

Chronic kidney disease (CKD) is a global healthcare problem³. A small proportion of people with CKD develop kidney failure requiring kidney replacement therapy (KRT). Individuals with CKD are also at increased risk of mortality compared to individuals without CKD²⁷², a potential competing risk of developing kidney failure. Prognostic models to predict the risk of kidney failure may help provide personalised healthcare aiding communication with patients²⁷³, guiding referrals to specialist kidney care²⁷⁴ and directing KRT preparation. The four-variable kidney failure risk equation (KFRE)⁹, comprised of age, sex, estimated Glomerular Filtration Rate (eGFR) and urine albumin-creatinine ratio (uACR), is the most widely used and validated kidney failure prognostic model for individuals with CKD.

Individuals with CKD have more long-term conditions (multimorbidity) compared to those without CKD⁴. Although prediction models such as KFRE are recommended for use in CKD¹, there is a lack of reporting of multimorbidity prevalence in studies that developed KFRE. No studies assess model performance in individuals with multimorbidity¹⁹⁹.

Certain combinations of conditions (or “clusters”) of multimorbidity are at higher risk of progressive kidney dysfunction¹³. Whether multimorbidity clusters impact KFRE performance is uncertain. Individuals with CKD and multimorbidity are also at increased risk of mortality⁶⁹. Current KFRE models used in clinical practice do not account for competing risk of mortality¹⁷³, which becomes increasingly relevant over longer prediction intervals and is more likely to impact individuals with multimorbidity²²¹. It is important to determine how mortality risk influences estimated kidney failure risk for patients with CKD and multimorbidity^{173, 275}.

Creatinine is the most commonly used biomarker to estimate GFR in routine clinical practice. Creatinine-based estimated glomerular filtration rate (eGFR) may not provide optimal accuracy in individuals with multimorbidity or ageing, due to loss of muscle mass that impacts creatinine levels^{276, 277}. Subsequently, multimorbidity may impact the accuracy of creatinine-based eGFR and bias the prognostic utility of KFRE. Cystatin C is an alternative biomarker that is

recommended in the Kidney Disease: Improving Global Outcomes (KDIGO) 2024 CKD clinical practice guidance¹ to be used when available for adults at risk of CKD and in certain clinical situations such as extremes of body habitus. Cystatin C is proposed as a more useful biomarker addressing risk of adverse outcomes, particularly in older patients^{216, 278}. Both biomarkers are impacted by differing non-GFR related factors: creatinine varies by age, sex, muscle mass and drugs that impact tubular secretion²⁷⁹, whereas cystatin C can fluctuate with chronic inflammation, smoking, increased adiposity²⁸⁰ and thyroid dysfunction²⁸¹. The use of eGFR cystatin C (eGFRcys) or combined creatinine-cystatin C (eGFRcr-cys), in place of eGFR creatinine (eGFRcr) in the KFRE, has not been explored for patients with multimorbidity.

We study the four-variable KFRE in individuals with and without multimorbidity, while assessing impact of competing mortality risks on model performance. We test if a model accounting for competing risk of mortality performed better in individuals with multimorbidity than current KFRE. Analyses also address the influence of creatinine compared to cystatin C based eGFR on performance of KFRE.

Materials and Methods

Data sources and study populations

Data were established from two databases:

- 1) UK Biobank, a prospective research cohort recruiting approximately half a million participants aged 37-73 years between 2006-2010 with sociodemographic, medical and biological data²⁰⁵. Participants consented to data linkage to healthcare records and national death registers. Ethical approval was granted from the NHS National Research Ethics Service (16/NW/0274).
- 2) The Stockholm Creatinine Measurements project (SCREAM), a population-based cohort covering the Stockholm region of Sweden with linked anonymised health and administrative data for approximately 2.9 million people between 2006-2021²¹⁴. The regional ethical review board in Stockholm approved the study (reference 2017/793-31); informed consent was waived as data were deidentified.

The study observation period in UK Biobank was date of recruitment until 31 March 2020 in Scotland and England and 28 February 2018 in Wales; and in SCREAM was between 1 January 2010 and 31 December 2021. Individuals were followed up for 2 and 5 years from the index date (recruitment date in UK Biobank or date of latest sample date (creatinine/cystatin C or quantifiable albuminuria/proteinuria) in SCREAM), or until date of kidney failure or death, whichever occurred earlier.

The four-variable KFRE, containing age, sex, eGFR and uACR was validated in both cohorts. Participants were included if they were aged ≥ 18 and had creatinine and cystatin C measurements occurring on the same day. Where multiple creatinine and cystatin C measurements were available, the first measurement per participant was included. If multiple measurements occurred on the same day, the median value was used. Individuals were included if eGFR < 60 millimetres per minute per 1.73 square metres (ml/min/1.73m²) at baseline by any eGFR equation (eGFRcr, eGFRcys or eGFRcr-cys). A single blood result

was used as participants were assumed to be stable on recruitment to UK Biobank. In SCREAM, only outpatient measurements were used²¹⁹. Participants were included if they had a quantifiable albuminuria/proteinuria measurement 12 months before or after creatinine and cystatin C measurement. Laboratory measurements outside the 0.1th and 99.9th percentiles of distribution were excluded, as they may represent laboratory error. Individuals established on KRT prior to the index date were excluded. When quantifiable uACR was unavailable, we estimated uACR concentrations from urine protein-creatinine ratio (uPCR) or dipstick proteinuria measurements using a validated conversion algorithm (Supplemental Text 5-1) derived from a meta-analysis of CKD cohorts²²⁰, which provides biologically plausible estimates that account for non-linear associations between these measures. When undetectable uACR values were present they were imputed with 0.1mg/mmol to allow calculation of KFRE.

eGFRcr was calculated using non race adjusted 2009 CKD-EPI equation³⁸. eGFRcys and eGFRcr-cys were measured using 2012 CKD-EPI equations⁴⁰.

Multimorbidity and long-term conditions

Multimorbidity was defined as presence of two or more long-term conditions (LTCs) in addition to CKD. LTCs included are described elsewhere⁷² and previously reported from UK Biobank²²¹. Among these, 42 and 26 LTCs, in addition to CKD, were captured in UK Biobank and SCREAM respectively; limited to conditions present before the index date, with an infinite lookback window (Supplemental Table 5-1). The number of LTCs captured in SCREAM was limited to those that could be validated in administrative healthcare data²²². In UK Biobank, conditions were self-reported by electronic questionnaire. In SCREAM, ICD-10 (International Classification of Diseases) codes, recorded in primary and secondary care records were used, with time windows based on validated algorithms for administrative data²²².

Additionally, LTC counts were calculated (i.e. 0, 1, 2 etc LTCs in addition to CKD) and multimorbidity clusters were constructed based on previous literature^{13, 68-70} (cardiometabolic, complex, and mixed physical and mental health multimorbidity; described in Supplemental Table 5-2).

Outcomes

Kidney failure was defined as requiring KRT within 2 and 5 years, defined as chronic dialysis or kidney transplantation. In SCREAM, KRT data were linked with the Swedish Renal Register, and hospital admission codes were used following an established UK Biobank algorithm²¹³. In competing risk analyses, all-cause mortality was identified through linkage to national death registers.

Sample size

A minimum sample size for external validation and development of a prognostic model was calculated based on published criteria, using the Cox-Snell R squared statistic and shrinkage factor of 0.9²⁸². A minimum sample size of 4,482 individuals with 106 kidney failure events was calculated for the 2-year period and 1,884 individuals with 108 kidney failure events for the 5-year period.

Statistical analysis

Baseline characteristics were summarised using means and standard deviations (SDs), medians and interquartile ranges (IQRs) and frequencies with percentages, where appropriate.

Predicted 2- and 5-year risks of kidney failure were calculated using the UK-calibrated version of KFRE¹⁶⁹. eGFRcr was substituted for eGFRcys and eGFRcr-cys to assess model performance with alternative biomarkers. Sensitivity analysis was performed using regionally calibrated non-North American KFRE equation in the SCREAM cohort¹⁰.

Validation of KFRE was examined in people with and without multimorbidity, across LTC counts and multimorbidity clusters, sample sizes permitting. Discrimination was assessed using time-dependent area under receiver operating characteristic curve(s) (AUC)¹⁵⁸ with 95% confidence intervals (CI) and Harrel's C-index, with 95% CI estimated from the bootstrap method^{157, 283}. Calibration was assessed by calibration curves¹⁵⁹, calibration intercept (to assess general calibration), calibration slope (assessing level of variation in model predictions) and calibration-in-the-large using the observed/expected (O/E) ratio. Prediction

error and model fit was measured using the Brier Score^{160, 161} (to assess how close predicted probabilities are to observed outcomes) and scaled Brier score²⁸⁴ (to allow model interpretation against a null model without covariates). Interpretation of statistical model performance measures is described in Supplemental Text 5-2.

Competing risk of death was considered because of high anticipated mortality rates amongst people with multimorbidity¹⁷³. Predicted risks for individuals were calculated using UK-calibrated KFRE and observed risks were estimated with Aalen-Johansen estimator. Aalen-Johansen cumulative incidence curves for kidney failure and death were plotted in patients with and without multimorbidity. Individuals were categorised into risk groups (KFRE risk <3%, 3-<5%, 5-<15%, 15-<25%, 25-<50% and $\geq 50\%$), as per previous validations^{10, 169}. Aalen-Johansen cumulative incidence curves were plotted by risk groups and compared to Kaplan-Meier curves to depict kidney failure risk when accounting for or not accounting for competing risks.

To account for competing risks, cause-specific, Cox proportional hazards, regression modelling was used to fit the same co-variables used in the 4-variable KFRE in the SCREAM cohort. Proportional hazard (PH) assumptions were assessed visually and numerically. Scaled Schoenfeld residual plots for both kidney failure and mortality appeared generally stable, except for eGFR in the kidney failure model. However, numerical tests demonstrated that all covariates for the kidney failure model and age and eGFR for the mortality model showed statistically significant violations of the PH assumption. Despite these violations, we continued with the cause-specific Cox proportional hazards model utilising the same covariates used in the four-variable KFRE, as the magnitude of the violations was modest and the model provides interpretable hazard ratios for the effects of covariates, with a focus of risk estimation at a single time point (five years). Additionally, sensitivity analysis using a Fine-Gray competing risk model was performed for calibration¹⁷⁶, as this is less influenced by PH assumption. For the Fine-Gray model, we formally assessed the proportional subdistribution hazards assumption both visually and numerically, using score tests based on modified Schoenfeld residuals. The proportional subdistribution hazards test indicated modest departures from proportionality, with eGFR showing the strongest evidence of time-variation. However, numerical tests demonstrated

that age, eGFR and log uACR for the kidney failure model and all covariates for the mortality model showed statistically significant violations of the PH assumption.

The competing risk model was then externally validated in UK Biobank. Discrimination, calibration plots and model fit were calculated for the competing risk model¹⁷⁶ at 5-years and compared by presence or absence of multimorbidity. Comparison of baseline characteristics was made between individuals with 5-year risk of kidney failure >5% (recommended threshold in guidelines for referral to kidney care services¹ as calculated by KFRE and by the competing risk model. Sensitivity analysis reporting additional performance measures: precision, recall, F1 score and area under the precision-recall curve (AUPRC) was performed for each cohort, subgroups and time horizon to focus on assessing model performance in imbalanced datasets²⁸⁵.

All analyses were performed using R (version 4.3.0) with tidyverse, nephron, dplyr, pROC, ggplot2, pmsampsize, predtools, magrittr, rms, survival, lubridate, sjPlot, survAUC, survminer, qwraps2, riskRegression, grid, gridExtra, geepack, kableExtra, boot, Hmisc, pseudo, pec, margins, lmtest, RColorBrewer, prodlm, reshape2, UpSetR, Metrics, caret, MLmetrics, PRROC, cmprsk, mstate, plotrix, knitr, splines, gtsummary, rsample, webshot, tidymodels, timeROC, crrSC, purr and viridis packages. Results are reported in accordance with TRIPOD guidelines (Supplemental Table 5-3)²²⁸.

Results

Baseline characteristics

24,489 individuals from UK Biobank and 42,902 individuals from SCREAM were included with mean age 62.8 years (SD 5.6) and 70.1 years (SD 14.1). 54% and 66% were female, respectively (Table 5-1). Supplemental Figure 5-1 and 5-2 represent participant selection and exclusions.

SCREAM participants were older, had greater female predominance, lower mean eGFR measured by eGFRcr and eGFRcys, higher albuminuria and higher prevalence of multimorbidity compared to UK Biobank participants.

In UK Biobank, 14,998 (61.2%) individuals had multimorbidity, of which 5,375 (21.9%) had cardiometabolic multimorbidity, 6,018 (24.6%) complex multimorbidity and 1,967 (8.0%) mixed physical and mental health multimorbidity. In SCREAM, 30,147 (70.3%) had multimorbidity, 17,854 (41.6%) cardiometabolic multimorbidity, 16,330 (38.1%) complex multimorbidity and 6,175 (14.4%) mixed physical and mental health multimorbidity. The overlap between the multimorbidity clusters identified were similar in UK Biobank and SCREAM (Supplemental Figure 5-3). Distribution of long-term conditions in each cohort are depicted in Supplemental Figure 5-4 and 5-5. Individuals with multimorbidity were older, had higher levels of albuminuria and had lower mean eGFRcys compared to those without multimorbidity, with these findings being more prominent in the SCREAM cohort. Mean eGFRcr was similar in those with and without multimorbidity in both cohorts.

Table 5-1. Baseline characteristics.

*	UK Biobank			SCREAM		
	Whole cohort (N = 24,489)	No multimorbidity (n = 9491)	Multimorbidity (n = 14998)	Whole cohort (N = 42,902)	No multimorbidity (n = 12755)	Multimorbidity (n = 30147)
Age (years)	62.8 ± 5.6	62.2 ± 6.0	63.3 ± 5.3	70.1 ± 14.1	62.4 ± 16.1	73.4 ± 11.7
Creatinine (μmol/L)	97.8 ± 38.5	95.6 ± 31.6	99.2 ± 62.2	121.2 ± 59.1	121.9 ± 62.5	121.0 ± 57.6
Cystatin C (mg/L)	1.3 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	1.6 ± 0.7	1.4 ± 0.6	1.7 ± 0.7
eGFR _{Cr} (ml/min/1.73m ²)	65.6 ± 16.0	66.3 ± 15.0	65.2 ± 16.5	50.8 ± 20.1	50.6 ± 17.9	50.9 ± 21.0
eGFR _{Cys} (ml/min/1.73m ²)	55.6 ± 13.1	59.6 ± 13.9	53.1 ± 11.9	45.5 ± 20.1	55.9 ± 22.9	41.1 ± 17.0
eGFR _{CrCys} (ml/min/1.73m ²)	62.4 ± 11.1	65.0 ± 9.5	60.8 ± 11.6	49.4 ± 17.5	55.1 ± 17.5	47.0 ± 16.9
uACR (mg/mmol)	5.4 ± 32.4	3.3 ± 18.8	6.7 ± 38.5	15.8 ± 46.0	12.6 ± 39.5	17.1 ± 48.4
Median (IQR)	0.0 (0.0, 1.5)	0.0 (0.0, 1.0)	0.5 (0.0, 1.9)	0.9 (0.0, 7.6)	0.4 (0.0, 5.7)	1.3 (0.0, 7.6)
Median (IQR)**	1.5 (0.8, 4.2)	1.3 (0.7, 3.0)	1.7 (0.9, 4.9)	5.3 (1.2, 22.8)	3.7 (0.9, 17.4)	5.8 (1.4, 7.6)
Sex n(%)						
Male	11,232 (45.9)	4,249 (44.8)	6,983 (46.6)	14,552 (33.9)	2,765 (21.7)	11,787 (39.1)
Female	13,258 (54.1)	5,242 (55.2)	8,015 (53.4)	28,350 (66.1)	9,990 (78.3)	18,360 (60.9)
LTC count						
Median (IQR)	2 (1, 3)	1 (0, 1)	3 (2, 4)	2 (1, 4)	1 (0, 1)	3 (2, 4)
Multimorbidity cluster n(%)						
Cardiometabolic	5375 (21.9)	N/A	5375 (35.8)	17854 (41.6)	N/A	17854 (59.2)
Complex	6018 (24.6)	N/A	6018 (40.1)	16330 (38.1)	N/A	16330 (54.2)
Mixed mental/physical	1967 (8.0)	N/A	1967 (13.1)	6175 (14.4)	N/A	6175 (20.5)
*Mean (SD) unless otherwise specified						
**Excluding undetectable uACR values						
eGFR _{Cr} , estimated glomerular filtration rate creatinine; eGFR _{Cys} , estimated glomerular filtration rate cystatin C; eGFR _{CrCys} , estimated glomerular filtration rate creatinine-cystatin C; uACR, urine albumin creatinine ratio.						

Kidney Failure and Mortality Events

Within 2- and 5-years there were 150 (0.6%) and 312 (1.3%) kidney failure events and 499 (2.0%) and 1,471 (5.8%) deaths in UK Biobank. In SCREAM there were 511 (1.2%) and 1,098 (2.6%) kidney failure events and 5,191 (12.1%) and 10,152 (23.7%) deaths in SCREAM, within 2- and 5-years respectively (Table 5-2). Both death and kidney failure event rates (per 1000 person years) were higher in those with multimorbidity compared to those without in UK Biobank but only death events were higher in the multimorbidity group in SCREAM (Table 5-2).

Kidney failure and mortality events by LTC count and multimorbidity clusters are presented in Supplemental Table 5-4 and 5-5. Based on minimum sample size calculations there were adequate kidney failure event numbers to perform validation in the following subgroups: cardiometabolic multimorbidity cluster groups in both cohorts and LTC count groups and complex multimorbidity group in the SCREAM cohort.

Table 5-2. Kidney failure and death events over 2- and 5-years by cohort and multimorbidity status.

	UK Biobank			SCREAM		
	Whole cohort (N = 24,489)	No multimorbidity (n = 9491)	Multimorbidity (n = 14998)	Whole cohort (N = 42,902)	No multimorbidity (n = 12755)	Multimorbidity (n = 30147)
Follow-up time (months)						
2-year cohort	23.7 ± 2.0	23.9 ± 1.5	23.6 ± 2.3	20.6 ± 6.7	21.8 ± 5.7	20.1 ± 7.1
5-year cohort	58.1 ± 8.4	58.9 ± 6.3	57.5 ± 9.5	41.3 ± 20.9	46.5 ± 19.1	39.1 ± 21.3
Death n(%)						
Within 2-year follow up	499 (2.0)	105 (1.1)	394 (2.6)	5191 (12.1)	569 (4.5)	4622 (15.3)
Per 1000 person years	10.3	2.3	13.3	70.5	11.5	91.5
Within 5-year follow up	1471 (5.8)	329 (3.5)	1142 (7.6)	10152 (23.7)	1287 (10.1)	8865 (29.4)
Per 1000 person years	12.4	7.1	15.9	68.7	26.0	90.2
Kidney failure n(%)						
Within 2-year follow up	150 (0.6)	29 (0.3)	121 (0.8)	511 (1.2)	167 (1.3)	344 (1.1)
Per 1000 person years	3.1	1.5	4.1	6.9	7.2	6.8
Within 5-year follow up	312 (1.3)	70 (0.7)	242 (1.6)	1098 (2.6)	375 (2.9)	723 (2.4)
Per 1000 person years	2.6	1.5	3.4	7.4	7.6	7.4

Discrimination

Discrimination of KFRE was good in individuals with and without multimorbidity, for all eGFR equations tested and across the 2-year and 5 years models (AUC ≥ 0.86 and c-index ≥ 0.86 in both cohorts - Table 5-3 and 5-4 and Supplemental Table 5-6 and 5-7).

Discrimination of KFRE was good across all eGFR equations for all LTC count groups (0- ≥ 5 LTCs) in SCREAM (2-year model; AUC ≥ 0.88 and c-index ≥ 0.91 , 5-year model; AUC ≥ 0.87 and c-index ≥ 0.91 - Supplemental Table 5-8 and 5-9), cardiometabolic multimorbidity in both cohorts (2-year model; AUC ≥ 0.84 and c-index ≥ 0.87 , 5-year model; AUC ≥ 0.87 and c-index ≥ 0.88 - Supplemental Table 5-8 and 5-9) and complex multimorbidity in SCREAM (2-year model; AUC 0.93 and c-index ≥ 0.92 , 5-year model; AUC ≥ 0.86 and c-index ≥ 0.91 - Supplemental Table 5-10 and 5-11).

Table 5-3. Performance measures for validation of UK-calibrated KFRE using eGFRcr equation by cohort and multimorbidity status at 2-years.

eGFR equation used in KFRE	Performance measure for 2-year KFRE	Whole cohort		Multimorbidity		No multimorbidity	
		UK Biobank	SCREAM	UK Biobank	SCREAM	UK Biobank	SCREAM
eGFRcr	AUC	0.88 (0.84-0.92)	0.89 (0.88-0.91)	0.88 (0.84-0.92)	0.90 (0.88-0.93)	0.86 (0.77-0.95)	0.94 (0.92-0.97)
	C-index	0.89 (0.86-0.92)	0.93 (0.92-0.94)	0.90 (0.87-0.93)	0.92 (0.91-0.94)	0.85 (0.75-0.93)	0.95 (0.93-0.95)
	O/E ratio	2.13 (1.97-2.29)	1.09 (1.01-1.18)	2.18 (2.01-2.36)	1.09 (0.99-1.20)	1.95 (1.59-2.31)	1.10 (0.95-1.25)
	Calibration intercept	0.19 (-0.09-0.47)	0.26 (0.16-0.35)	0.27 (-0.03-0.58)	0.25 (0.13-0.37)	-0.08 (-0.70-0.53)	0.26 (0.10-0.42)
	Calibration slope	0.69 (0.58-0.80)	1.35 (1.21-1.49)	0.67 (0.54-0.79)	1.17 (1.06-1.28)	0.83 (0.50-1.17)	1.43 (1.18-1.68)
	Brier score	0.005 (0.004-0.006)	0.009 (0.009-0.010)	0.007 (0.006-0.008)	0.010 (0.009-0.011)	0.003 (0.002-0.004)	0.009 (0.007-0.010)
	Scaled brier score (%)	14.90 (9.52-20.37)	31.07 (28.24-33.66)	15.10 (9.36-20.60)	27.26 (23.94-30.22)	13.53 (1.57-26.62)	39.29 (33.21-44.23)
AUC, Area under the receiver operator characteristic curves.							

Table 5-4. Performance measures for validation of UK-calibrated KFRE using eGFRcr equation by cohort and multimorbidity status at 5-years.

eGFR equation used in KFRE	Performance measure for 5-year KFRE	Whole cohort		Multimorbidity		No multimorbidity	
		UK Biobank	SCREAM	UK Biobank	SCREAM	UK Biobank	SCREAM
eGFRcr	AUC	0.90 (0.88-0.92)	0.88 (0.87-0.90)	0.90 (0.87-0.93)	0.88 (0.86-0.90)	0.89 (0.83-0.94)	0.89 (0.86-0.91)
	C-index	0.91 (0.89-0.93)	0.92 (0.91-0.93)	0.91 (0.88-0.93)	0.91 (0.90-0.92)	0.92 (0.88-0.95)	0.94 (0.93-0.95)
	O/E ratio	1.76 (1.65-1.87)	1.08 (1.02-1.14)	1.75 (1.62-1.87)	1.05 (0.98-1.13)	1.83 (1.59-2.06)	1.15 (1.04-1.25)
	Calibration intercept	0.46 (0.28-0.64)	0.02 (-0.10-0.07)	0.40 (0.20-0.61)	-0.05 (-0.16-0.05)	0.69 (0.33-1.04)	0.05 (-0.10-0.20)
	Calibration slope	0.78 (0.71-0.86)	1.00 (0.92-1.07)	0.76 (0.68-0.85)	1.00 (0.91-1.10)	0.91 (0.73-1.10)	0.94 (0.82-1.05)
	Brier score	0.009 (0.008-0.010)	0.023 (0.021-0.024)	0.011 (0.010-0.013)	0.023 (0.021-0.025)	0.005 (0.004-0.007)	0.022 (0.020-0.024)
	Scaled brier score (%)	30.86 (25.18-36.38)	36.57 (33.86-39.09)	31.14 (25.87-36.11)	35.32 (32.01-38.46)	29.27 (19.07-39.64)	39.49 (34.53-44.06)
AUC, Area under the receiver operator characteristic curves.							

Calibration

Calibration assessed without accounting for competing risk of mortality was inaccurate (Figure 5-1 and 5-2, Supplemental Text 5-1 and Supplemental Figure 5-8 and 5-9). Calibration-in-the-large, showed underestimation of kidney failure risk (O/E ratio range 1.01-2.18), except when eGFR_{cys} was used in the 2- and 5-year models in the SCREAM whole cohort and multimorbidity group and when eGFR_{cr-cys} was substituted in the 5-year KFRE and validated in the multimorbidity group (Table 5-3 and 5-4 and Supplemental Table 5-6 and 5-7). Full calibration quantitative results are presented in Table 5-3 and 5-4 and Supplemental Table 5-6 and 5-7.

There was no improvement in calibration performance (accounting for all calibration performance measures) when using eGFR_{cys} or eGFR_{cr-cys} compared to eGFR_{cr} (Table 5-3 and Table 5-4, Supplemental Table 5-6 and 5-7, Figure 5-1 and 5-2 and Supplemental Figures 5-6-5-11).

Calibration results for LTC count groups and multimorbidity clusters are presented in Supplemental Figures 5-12-5-15 and Supplemental Tables 5-8-5-11. Calibration-in-the-large and calibration slopes are similar across LTC counts but general calibration (assessed by calibration intercepts) changed from systematic underestimation of risk to overestimation of risk at 5 years as LTC counts increased. There was prominent underestimation of risk in the cardiometabolic multimorbidity cluster in UK Biobank assessed by O/E ratio (2 and 5-years).

Figure 5-1. Calibration curves for predicted versus observed 2-year and 5-year risk of kidney failure by Multimorbidity status in UK Biobank cohort.

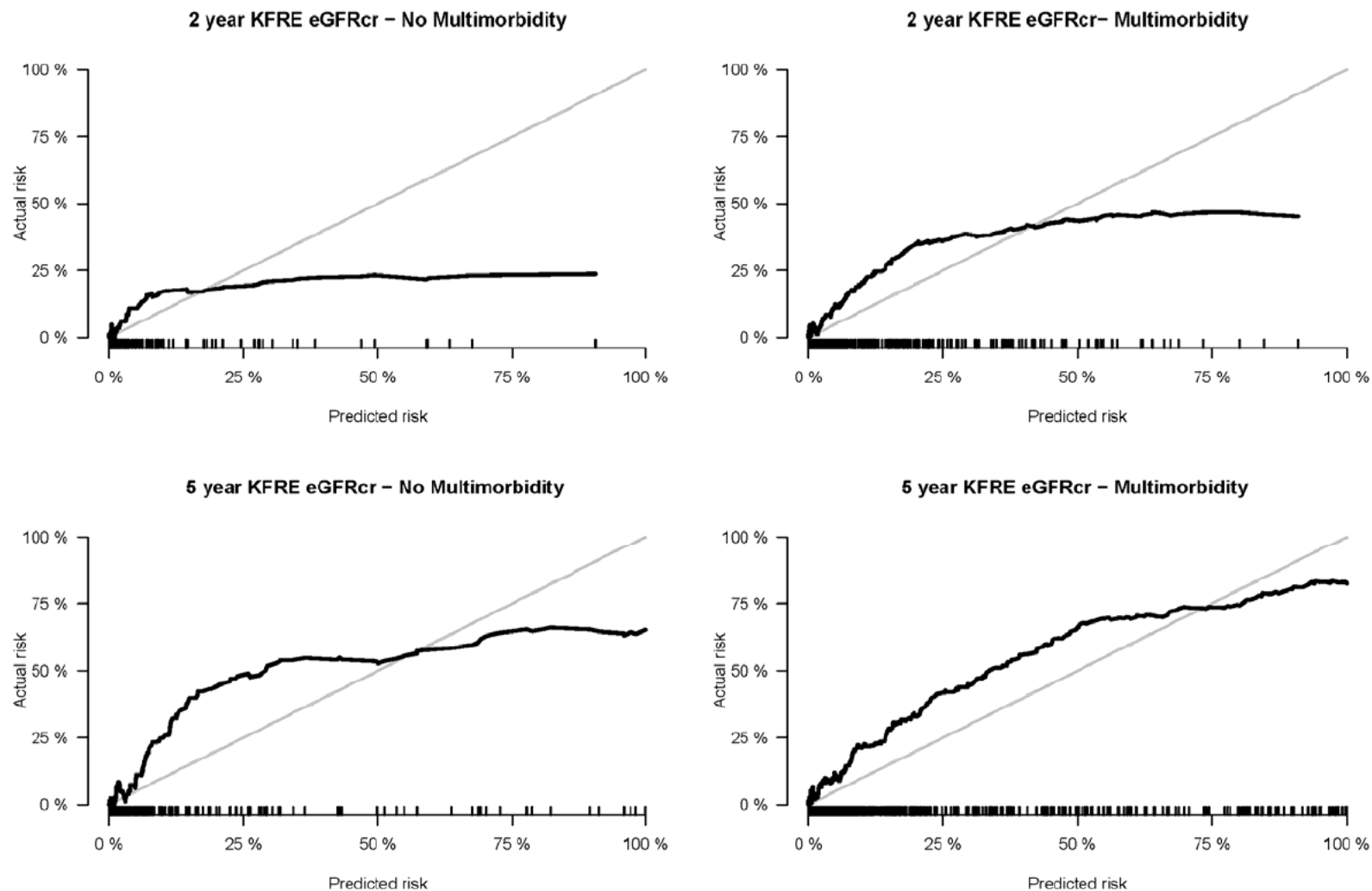
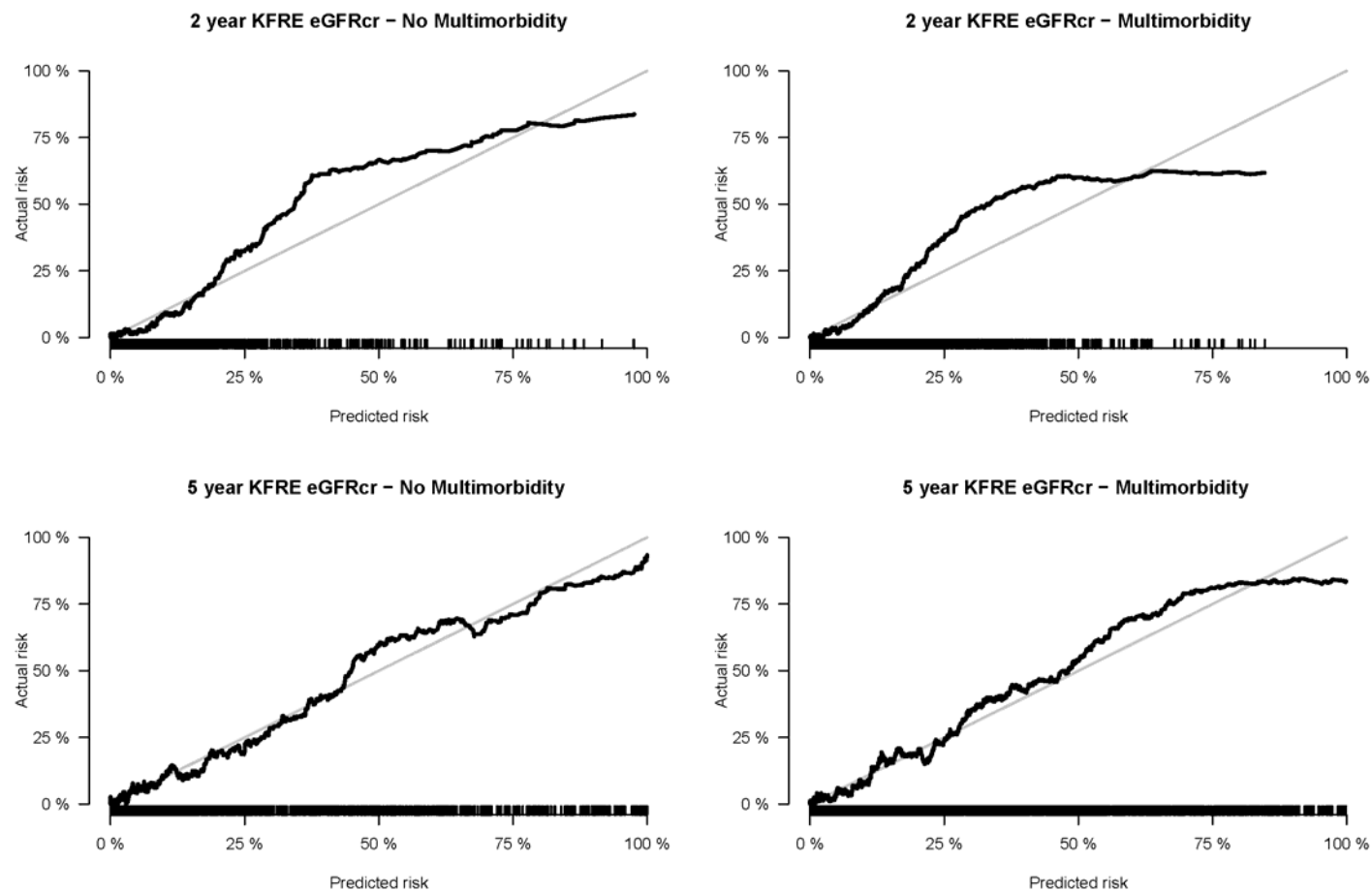


Figure 5-2. Calibration curves for predicted versus observed 2-year and 5-year risk of kidney failure by Multimorbidity status in SCREAM cohort.



Overall fit

Overall fit performance measures (Table 5-3 and 5-4 and Supplemental Table 5-6 and 5-7) were similar across different eGFR equations but was better in those without multimorbidity compared to those with multimorbidity in both cohorts and at both time points.

Brier scores were similar across LTC count groups but scaled Brier scores were lower in higher LTC counts ($3 \geq 5$). Overall fit performance measures for multimorbidity clusters and LTC counts are presented in Supplemental Tables 5-8-5-11.

Competing risk analysis

The 5-year cumulative incidence of kidney failure was 3.0% (95% CI: 2.7-3.2%) in the SCREAM multimorbidity cohort, and 1.6% (95% CI: 1.4-1.8%) in the UK Biobank multimorbidity cohort. Compared to a 5-year cumulative incidence of kidney failure of 3.6% (95% CI: 3.2-3.9%) and 0.7% (95% CI: 0.6-0.9%) in the SCREAM and UK Biobank no multimorbidity cohorts respectively (Supplemental Table 5-12).

There was a higher risk of death in the multimorbidity group, with a prominent increase in risk of death over time compared to the no multimorbidity group (Figure 5-3). The 5-year cumulative incidence of mortality was 34.0% (95% CI: 33.4-34.6%) and 7.2% (95% CI: 6.7-7.6%) in the SCREAM and UK Biobank multimorbidity cohorts respectively. In comparison, the 5-year cumulative incidence of mortality in the no multimorbidity groups was lower; SCREAM 11.1% (95% CI: 10.5-11.7%) and UK Biobank 3.3% (95% CI: 3.0-3.7%) (Supplemental Table 5-13).

Plots comparing survival analyses not accounting for competing risk (Kaplan-Meier survival curve) with analyses that do consider competing risk (Aalen-Johansen cumulative incidence curves) showed overestimation of kidney failure risk in the death-censored approach. This was most apparent in SCREAM, the multimorbidity subgroups and the higher KFRE-predicted risk groups (Figure 5-4). Cumulative risk of kidney failure was lower as age advanced but there was an increasing trend in overestimation of kidney failure risk using the death censored

approach for multimorbidity groups as age advanced in SCREAM (Supplemental Figure 5-16).

Figure 5-3. Cumulative incidence curves of kidney failure and mortality in UK Biobank and SCREAM: multimorbidity and no multimorbidity cohorts.

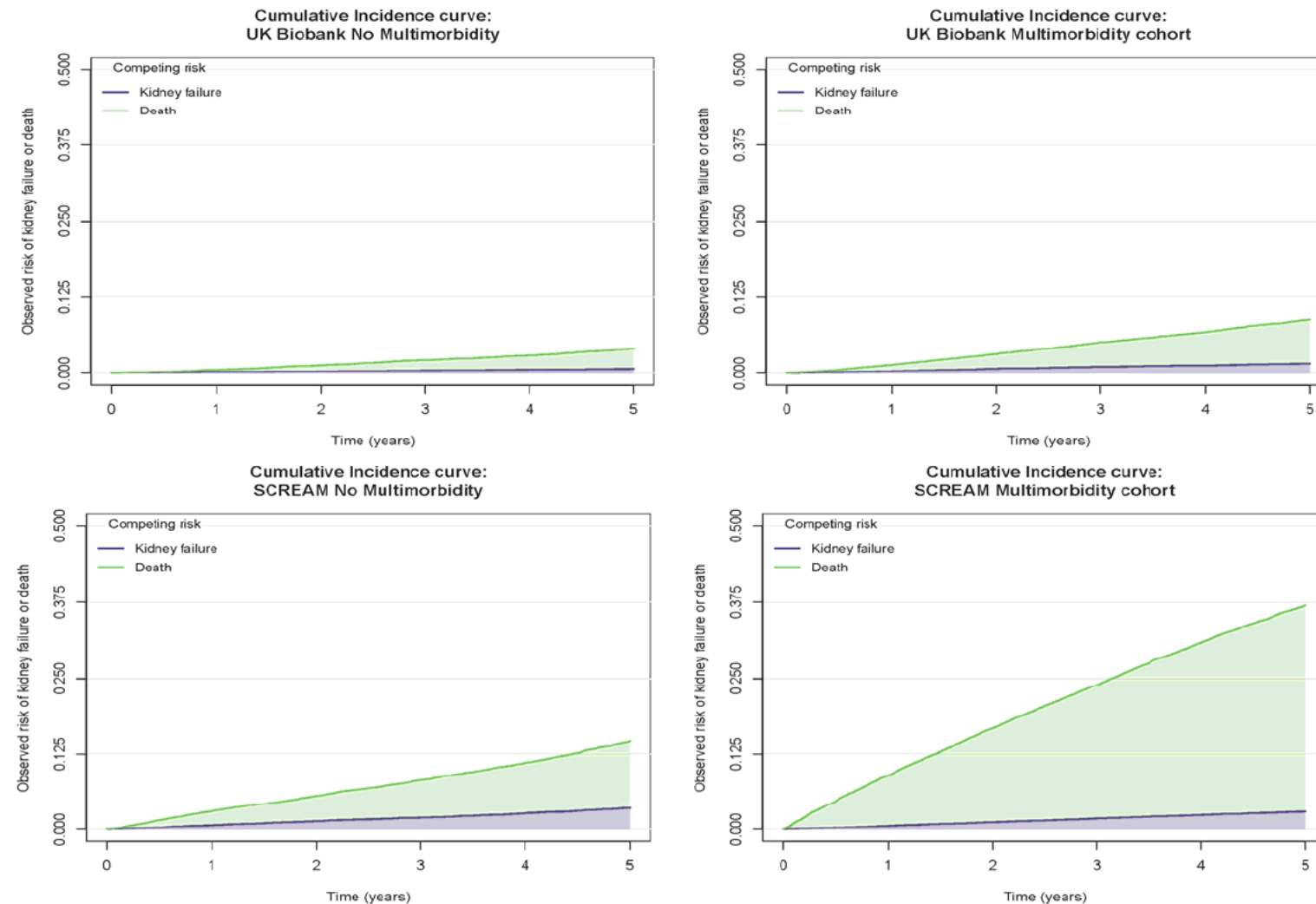
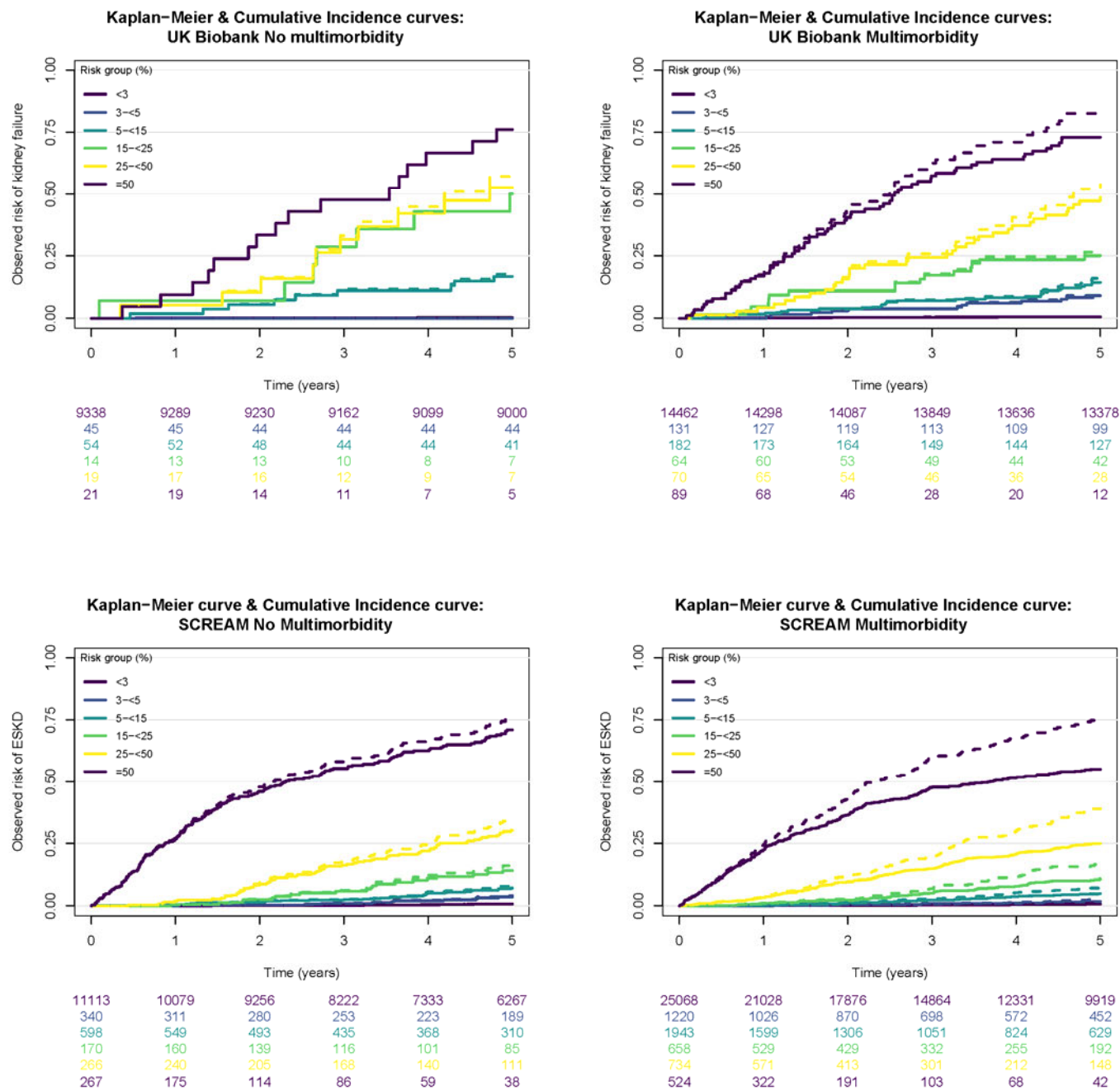


Figure 5-4. Kaplan-Meier estimates (dashed lines) and Aalen-Johansen estimates (solid lines) cumulative incidence curves for kidney failure by multimorbidity status and KFRE risk groups in UK Biobank and SCREAM.



Updated KFRE model considering competing mortality risk

A model considering competing risk of death (full model details including coefficients, baseline hazards and model terms Supplementary R Data Serialisation File 1 (online), Supplemental Table 5-14) improved performance measures compared to the UK calibrated 5-year KFRE in multimorbidity groups (Table 5-5, Supplemental Figure 5-17 and 5-18 and Supplemental Text 5-4), O/E ratio 0.98 in multimorbidity groups of both cohorts at 5-years. Improvements in calibration accuracy were predominantly in the multimorbidity groups. Overall fit of the competing risk model was also improved (increased scaled Brier scores) across both cohorts and multimorbidity groupings. Number of individuals, characteristics, event numbers and performance for each risk group for each cohort is reported in Supplemental Table 5-15 and 5-16 (KFRE model) and Supplemental Table 5-17 and 5-18 (updated KFRE accounting for competing mortality risk). Total referral numbers increased in both cohorts when a threshold of kidney failure risk >5% was applied using the competing risk model compared to KFRE. Individuals referred had lower levels of multimorbidity, fewer death events by 5 years and in the SCREAM cohort were younger (Supplemental Table 5-19). The number of kidney failure events within 5 years was greater when the competing risk model was used compared to KFRE.

Table 5-5. Performance measures for validation of the competing mortality risk model using age, sex, log uACR, eGFRcr to predict kidney failure at 5-years

Performance measure for competing risk model at 5-years	Whole cohort	Multimorbidity		No multimorbidity	
	UK Biobank	UK Biobank	SCREAM	UK Biobank	SCREAM
Discrimination					
Time dependent AUC	0.92 (0.90-0.94)	0.92 (0.89-0.93)	0.93 (0.91-0.94)	0.94 (0.91-0.97)	0.95 (0.93-0.96)
C-index	0.92 (0.90-0.93)	0.91 (0.89-0.93)	0.92 (0.90-0.93)	0.93 (0.91-0.96)	0.94 (0.93-0.96)
Calibration					
O/E ratio	0.93 (0.83-1.03)	0.98 (0.86-1.11)	0.98 (0.91-1.06)	0.79 (0.62-0.99)	0.83 (0.75-0.92)
Calibration intercept	-0.17 (-0.32- -0.02)	-0.17 (-0.33-0.00)	0.17 (0.08-0.27)	-0.17 (-0.48-0.14)	0.10 (-0.04-0.24)
Calibration slope	0.96 (0.87-1.06)	0.93 (0.83-1.04)	1.12 (1.03-1.21)	1.05 (0.86-1.25)	1.01 (0.90-1.11)
Overall fit					
Brier score	0.010 (0.008-0.010)	0.011 (0.010-0.013)	0.021 (0.019-0.022)	0.005 (0.004-0.006)	0.021 (0.019-0.024)
Scaled brier score (%)	28.25 (23.44-33.09)	27.61 (21.82-33.75)	27.98 (25.28-30.73)	29.99 (19.17-39.43)	37.54 (32.89-41.97)
AUC, Area under the receiver operator characteristic curves.					

Sensitivity analyses are presented in Supplemental Text 5-5, Supplemental Tables 5-20-5-25 and Supplemental Figure 5-19 and 5-20.

Discussion

In a research-based cohort of 24,489 individuals and population-based cohort of 42,902, 61.2% and 70.3% individuals respectively had multimorbidity. This study found that: 1. The 4-variable KFRE has good discrimination but sub-optimal calibration for CKD patients with and without multimorbidity. 2. There was no improvement in KFRE model performance when using eGFR_{cys} or eGFR_{cr-cys} compared to eGFR_{cr}. 3. A competing risk model developed, using the same variables as KFRE, performs better for all individuals with CKD, but particularly among people with multimorbidity. The competing risk model categorises more individuals as having >5% risk of kidney failure but more of these develop kidney failure and fewer die within 5 years.

Comparison of characteristics of our study population and the original cohorts used to develop KFRE, show that our cohorts had a higher baseline eGFR, lower levels of albuminuria, a higher proportion of females, lower kidney failure events and the UK Biobank cohort was younger⁹. However, the SCREAM cohort had a similar prevalence of cardiometabolic conditions as the KFRE development cohort⁹.

The importance of external validation of a prognostic model across different settings, populations and sub-groups due to variation in case mix and the impact that this can have on prognostic model performance has been highlighted¹⁵⁶. KFRE¹⁰ has been validated in 31 multinational cohorts, including >30 countries. In keeping with our findings, KFRE has good discrimination across all cohorts and additionally across subgroups of age, race and diabetes. However, KFRE over-estimates risk in some non-North American cohorts, requiring model recalibration. Validation in a UK cohort required recalibration, particularly in lower risk groups¹⁶⁹. Other studies highlight differences in model performance by ethnicity¹⁷⁰ and renal disease aetiologies²⁶³.

Using cystatin C based eGFR did not impact performance of KFRE. Existing evidence relating to cystatin C suggests eGFR_{cys} can improve risk stratification and discrimination of future kidney failure²⁸⁶, cardiovascular disease and mortality^{40, 278}. Although others have found no benefits of KFRE using eGFR_{cys} in mild to moderate CKD²⁸⁷. We found that individuals with multimorbidity had

similar eGFR_{cr} but lower mean eGFR_{cys} compared to those without multimorbidity. There may be subgroups of individuals with multimorbidity with discordant eGFR_{cr} and eGFR_{cys}, warranting exploration of the impact of this discrepancy on KFRE model performance and which subgroups may benefit from the use of cystatin C testing.

Albuminuria and eGFR are the co-variables with greatest contribution to predicting risk of kidney failure in KFRE⁹. Subgroups with multimorbidity in both cohorts had higher levels of albuminuria which may underpin the lesser impact of eGFR formulae compared to albuminuria. It is unclear if albuminuria seen in multimorbidity extends beyond simply being associated with diabetes which is a major component of multimorbidity. More accurate identification of high-risk individuals, and at an earlier time point, is imperative - particularly in an era where therapies such as sodium-glucose cotransporter-2 (SGLT2) inhibitors offer cardiovascular and renal benefits. These subgroups may stand to gain the most from early and tailored interventions, but consideration should also be given to the potential increased risk of adverse events or side effects that they may experience.

A lack of methodological guidance for competing risk analyses has likely contributed to a lack of use of these methods¹⁷⁶. Competing mortality risk impacts prognostic performance measures in other models in older adults and in those with multimorbidity^{176, 275}. There have been mixed findings from studies accounting for competing risk of mortality in KFRE^{9, 170, 261, 288}. Some studies accounting for competing mortality risk in KFRE highlight improvements in calibration in subgroups^{170, 261}. Grams et al. found an improvement in calibration at 5-years when accounting for competing risk of death amongst adults ≥ 65 years old and in those with eGFR between 45-59 ml/min/1.73m²²⁶¹. Ramspek et al. demonstrated models making predictions over longer time periods overestimate risk of kidney failure, specifically finding the 5-year 4-variable KFRE overpredicted kidney failure risk by 10% when not accounting for competing mortality¹⁷³. Likewise, Al-Wahsh et al. directly compared the prognostic performance of a standard Cox regression, cause-specific Cox regression and Fine and Gray models. They showed that, in individuals with more advanced CKD (stage 4), miscalibration was particularly evident in older adults and those with

more comorbidity (diabetes or cardiovascular disease) when longer prediction horizons were used²⁸⁸.

We highlight the high risk of mortality in individuals with CKD especially in those with multimorbidity. We demonstrate improvements in calibration and overall fit when a model, using the same co-variables, accounts for competing mortality risk, predominantly in multimorbidity subgroups. This is important for all individuals with CKD, although will have a greater impact in those at highest mortality risk e.g. those with multimorbidity⁶⁹ and when predicting risk over longer follow up²⁸⁸.

Some studies compare concurrent use of models assessing both kidney failure and mortality risk²⁵⁸ or a model predicting both simultaneously (KD predict)²⁸⁹. Such models are useful in understanding risk of death and kidney failure in relation to each other. It is uncertain if this approach helps communications between healthcare professionals and patients.

There are other validated prognostic models that may be used in clinical practice e.g. CKD-PC 'risks' model²⁶⁷ and KD-predict²⁸⁹ both of which account for or consider risk of mortality. Comparison and clinical utility studies are required to inform the best model for use in clinical practice.

Our study has several strengths. The combined datasets included over 63,000 individuals with over 10,000 kidney failure events, resulting in a large and precise validation study. We include cohorts from research and population-based cohorts to strengthen findings across different populations and settings¹¹⁹. This is the first study that we are aware of validating KFRE in those with multiple long-term conditions and that also considers the competing risk of mortality. We have also followed robust methodologies^{176, 228}.

We acknowledge some limitations. The cohorts may not be representative of populations outside Northern Europe. UK Biobank is a high-quality research database but consists of less socio-economically deprived individuals but with evidence that risk factor associations are generalisable²¹⁰. There was selection bias in SCREAM as participants missing baseline albuminuria data were excluded. Some groups, such as those with diabetes or hypertension, are more likely to

have albuminuria tested. We reduced this bias by converting dipstick proteinuria results in the SCREAM cohort (reflecting individuals having proteinuria tested as ‘screening’) and by including UK Biobank, where albuminuria was universally measured. Around 1.6 million individuals were excluded due to missing cystatin C measurements also contributing selection bias, as individuals may be more likely to have cystatin C measured when clinical characteristics - such as extremes of muscle mass, frailty, increased comorbidity or older age²⁹⁰ - may result in inaccuracies in creatinine-based eGFR. There were also differences in the measurements of LTCs between UK Biobank and SCREAM. Small kidney failure event numbers in some multimorbidity cluster groups (complex and mixed mental/physical multimorbidity in UK Biobank) limited our ability to conduct external validation. The kidney failure outcome definition we used did not include conservative (non KRT) kidney care which may be more common in individuals with multimorbidity and advancing age. Finally, we observed violation of PH assumptions in competing risk models (notably for eGFR and age), such violations may result in misinterpretation of time-specific hazards associations and bias interpretation of constant hazard ratios if effects vary meaningfully over time^{291, 292}. Our primary aim, however, was absolute risk estimation at a fixed 5-year horizon and comparability with the 4-variable KFRE, contexts in which modest departures are less consequential for predicted risks.

Conclusions

KFRE has good discrimination accuracy to predict kidney failure in individuals with multimorbidity but has less robust calibration and crucially does not account for competing risk of death. A model accounting for competing mortality risk improves model performance, particularly calibration, in individuals with multimorbidity.

Data availability statement

Data used for this study are available from UK Biobank and SCREAM. Access to data is through data application processes for each data source and fulfilment of ethics and GDPR regulations. Further details can be found via <https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access> for UK Biobank and by contacting juan.jesus.carrero@ki.se for SCREAM.

Analysis of UK Biobank was conducted as part of project 14151.

Code is available on Github for others to replicate our analysis:
https://github.com/h-j-walker/KFRE_validation.git.

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For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Authors' contributions

HW, JJC, MKS, BDJ, KG and PBM were involved in the conception/design of the work. HW, MKS and RF performed data analysis. All authors were involved in interpretation of data. HW drafted the work and JJC, MKS, RF, ALF, JSL, ELF, BDJ, KG, and PBM critically revised it. All authors, read and approved the final manuscript.

Conflict of interest statement

PBM reports lecture honoraria from AstraZeneca, Pharmacomso, Bayer, Astellas, GSK, Viforpharma and Boehringer Ingelheim outside the submitted work and research grants from AstraZeneca and Boehringer Ingelheim. JJC reports a relationship with Amgen, Astellas, AstraZeneca, NovoNordisk, Viforpharma, Boehringer Ingelheim, Nestle, Abbott that includes: funding grants and speaking and lecture fees. JSL reports personal lectureship honoraria from AstraZeneca, outside the submitted work.

The other authors have no potential conflicts of interest to declare.

6 Chapter: 6 An analysis of frailty in adults with chronic kidney disease and validation of the kidney failure risk equation in sub-groups with frailty

6.1 Reference

Walker, H., Carrero, J-J., Sullivan, M.K., Field, R., Lees, J.S., Hanlon, P., Faucon, A-L., Fu, E.L., Beridze, G. Jani, B.D., Gallacher, K. Mark, P.B. (2025). Frailty in Adults with CKD and Validation of the Kidney Failure Risk Equation in Frailty Subgroups. *Clinical Journal of the American Society of Nephrology*, 20(8), 1051-1062.

6.2 Chapter summary

This chapter presents an analysis of the UK Biobank cohort addressing how the presence of frailty, compared to no frailty, impacts the predictive performance of the kidney failure risk equation (RQ3) among patients with CKD, and the influence of cystatin C-based eGFR in place of eGFR calculated using creatinine (RQ4).

6.3 Manuscript

Key points

- The four-variable kidney failure risk equation (KFRE) does not accurately estimate kidney failure risk in frail individuals.
- Prognostication of kidney failure is improved in frail individuals with CKD by replacing eGFR creatinine with cystatin C-based eGFR in the KFRE model.
- Consideration of competing mortality risk is particularly important in those with frailty and higher KFRE risk predictions.

Abstract

Background Frailty is common amongst adults with CKD and its presence can influence clinical outcomes such as advancing CKD and mortality. Clinical guidelines recommend the use of the kidney failure risk equation (KFRE) to guide management of CKD. Our aim was to validate KFRE by frailty status and assess whether model performance could be improved by using cystatin C-based eGFR equations and to assess the impact of accounting for competing mortality risk.

Methods We studied adults from the prospective research cohort UK Biobank with CKD G3-5 (eGFR $<60\text{ mL/min/1.73m}^2$) by any of the three CKD Epidemiology Collaboration consortium eGFR equations: eGFR creatinine (eGFR_{cr}), eGFR cystatin C (eGFR_{cys}) and eGFR creatinine-cystatin C (eGFR_{cr-cys}). Frailty was assessed by a modified frailty phenotype and two cumulative deficit frailty indices. Kidney failure was defined as long-term dialysis or kidney transplantation. Model assessment included discrimination, calibration and overall fit at 2- and 5-years.

Results The prevalence of frailty by one or more measures was 35% (n=8,533). Those classed as frail had a higher discrepancy between eGFR_{cys} and eGFR_{cr} compared to the non-frail group (-15.8 versus -6.9 ml/min/1.73m²). Discrimination of KFRE was good (area under receiver operating characteristic

curve ≥ 0.88 across all frailty sub-groups and eGFR equations). Kidney failure at 5-years was under-estimated in individuals with frailty (observed/expected (O/E) ratio 1.70; 95% confidence interval, 1.55-1.85). Calibration-in-the-large improved when eGFR_{cr} was replaced by eGFR_{cys} (5-years O/E ratio 1.20; 95% confidence interval, 1.05-1.35). Overestimation of kidney failure risk in analyses that do not account for competing mortality risk compared to those that do, was most apparent in the frailty group and the higher KFRE predicted risk groups.

Conclusions KFRE under-estimates kidney failure risk for individuals with CKD and frailty. Risk prediction improved for those with frailty when cystatin C-based eGFR equations are utilized and when analyses account for competing risk of mortality. These factors should be considered when KFRE calculation is used in clinical practice in individuals with frailty.

Keywords chronic kidney disease, frailty, kidney failure risk equation, mortality, prediction model

Introduction

Frailty can be defined as a condition of increased susceptibility and vulnerability to stressors, such as adverse effects from medications or intercurrent illness, and decreased physiological reserve to be able to compensate for these⁷. People living with frailty experience disproportionate fluctuations in their health and functioning and are at increased risk of adverse events such as falls, delirium and hospitalisations^{7, 8}.

Chronic kidney disease (CKD) is a growing public health problem, with aging populations and increasing rates of risk factors such as type 2 diabetes²⁹³. Individuals with CKD are more likely to experience frailty than those without CKD^{244, 294}, with it occurring in around one in three adults with CKD¹³⁶. Frailty and CKD appear to be mutually exacerbated: frailty is associated with more severe CKD^{244, 295}; more severe albuminuria²⁹⁶ and the presence and severity of CKD^{129, 296} are associated with higher risk of frailty; and both frailty and advancing CKD are associated with higher risk of mortality^{136, 296}.

There is limited evidence to guide how CKD management should be altered in the presence of frailty¹⁴², with a particular lack of research in younger patients with frailty. Guidelines recommend the use of the kidney failure risk equation (KFRE) to guide clinical management in CKD^{1, 11}. However, validation of kidney failure prognostic models, including KFRE, is missing in individuals with frailty¹⁹⁹. KFRE⁹ estimates risk based on age, sex, estimated glomerular filtration rate (eGFR) and urine albumin-creatinine ratio (uACR). As part of the complex syndrome of frailty, individuals may be subject to loss of muscle mass that could bias the prognostic utility of creatinine-based eGFR equations²⁹⁷. Cystatin C has been proposed as a more accurate biomarker for assessing and estimating kidney function, compared to creatinine, particularly in older patients²⁷⁸. There is evidence to suggest that calculating eGFR using cystatin C alone (eGFR cystatin C [eGFRcys]) or in combination with creatinine (eGFR creatinine-cystatin C [eGFRcr-cys]), rather than creatinine alone (eGFR creatinine [eGFRcr]), improves risk stratification and discrimination of future kidney failure²⁸⁶, cardiovascular disease and death^{34, 40, 278}. The use of eGFRcys or eGFRcr-cys, in

place of eGFRcr, remains unexplored as a predictor of kidney failure for patients with frailty in KFRE.

The aims of this study were to: 1) validate KFRE in individuals with and without frailty; 2) explore if KFRE performance, in individuals with and without frailty, is impacted by eGFR equation utilised by substituting eGFRcr with eGFRcys or eGFRcr-cys; and 3) assess the impact of competing mortality risk in individuals with and without frailty.

We hypothesised that KFRE model performance would be affected negatively by the presence of frailty, and that cystatin C-based eGFR equations would improve model performance. Additionally, we anticipated that accounting for competing mortality risk would be important in frailty subgroups.

Methods

Data source and population

The study is based on data from UK Biobank, a prospective research cohort including around half a million individuals age 37-73 years²⁰⁵. Date of recruitment was between 2006 and 2010 and was considered as the index date. All individuals provided informed consent for data collection and electronic data linkage to healthcare records including Hospital Episode Statistics and national death registers. UK Biobank has full ethical approval, granted from the National Health Service (NHS) National Research Ethics Service (16/NW/0274). Permission to access and analyse data was granted as part of project 14151.

Individuals and data collection

Of 502,503 individuals recruited to UK Biobank, we excluded 46,868 individuals with missing biochemical data, 430,944 who did not have CKD and 52 with pre-existing kidney failure: leaving 24,489 eligible individuals for the analysis (Supplemental Figure 6-1).

CKD was defined as eGFR $<60\text{ml/min/1.73m}^2$ at baseline by any of the three CKD Epidemiology Collaboration (CKD-EPI) eGFR equations (eGFRcr, eGFRcys or eGFRcr-cys). A single blood result was used to define CKD because kidney function was assumed to be stable at the time of recruitment. eGFR was calculated using the 2009 CKD-EPI equation³⁸ for eGFRcr and 2012 CKD-EPI equations⁴⁰ for eGFRcys and eGFRcr-cys. Consistent with utilisation of eGFR calculations in clinical practice and to limit bias from potential missing ethnicity data, all individuals were classed as non-African American race.

Long-term health conditions (LTCs; Supplemental Table 6-1) were defined from self-reported questionnaires, completed on the index date, with support from research nurses. Biochemistry markers, including creatinine, cystatin C and uACR, were collected at recruitment (biochemical sampling procedures for UK Biobank have previously been described in full²⁰⁶). Serum and urine creatinine were measured using IDMS (isotope dilution mass spectrometry)-traceable methods on Beckman Coulter AU5400 instrument, serum cystatin C by latex

enhanced immunoturbidimetric method on a Siemens ADVIA 1800 instrument and urine microalbumin by immunoturbidimetric method using reagents and calibrators from Randox Bioscience UK. Walking pace, exhaustion, recent weight loss and physical activity were self-reported through the recruitment assessment centre questionnaire (Supplemental Text 6-1.). Grip strength was measured using a Jamar J00105 hydraulic hand dynamometer.

Frailty definitions

Frailty was assessed using three measures at baseline: a modified frailty phenotype, based on the Fried frailty phenotype⁸ and two cumulative frailty deficit indices; frailty index (FI, based on self-reported deficits)⁹⁹ and laboratory frailty index (FI-lab, based on laboratory and blood pressure (BP) measurements)¹⁰². The frailty phenotype and FI have both previously been adapted for use in UK Biobank^{117, 211}. The FI-lab was adapted for biochemical and BP data available in UK Biobank, on the basis of the available literature^{102, 103}. Frailty phenotype was based on the presence or absence of five criteria: weight loss, exhaustion, low grip strength, low physical activity and slow walking pace. Individuals were classed as frail if they met three or more criteria, pre-frail if they met one or two criteria and non-frail if they met none of five criteria. The frailty indices (FI and FI-lab) are based on an unweighted count/accumulation of deficits²²⁵ (LTCs, symptoms, functional limitations, biochemical laboratory abnormalities) standardised by Searle *et al*²²⁶. The frailty indices are calculated by dividing the number of deficits present by the total number of deficits assessed. Individuals were classed as frail if they had an FI or FI-lab of more than 0.25^{103, 227}. Frailty measures are summarised in Supplemental Text 6-1.

Outcomes

Kidney failure was defined as requiring kidney replacement therapy (KRT) (chronic maintenance dialysis or kidney transplantation), using hospital admission codes as per an established UK Biobank algorithm²¹³ (Supplemental Text 6-2). Outcomes were assessed within 2- and 5-years. All-cause mortality, for competing risk analyses, was identified through linkage to national death registers.

Individuals were followed up for 2- and 5-years from the index date, or until date of kidney failure or death, whichever occurred sooner.

Prediction model

The UK-calibrated version of the four variable KFRE¹⁶⁹ was used to predict the 2- and 5-year risk of kidney failure (Supplemental Text 6-3). Substitution of eGFR_{cr} by eGFR_{cys} and eGFR_{cr}-cys in KFRE was performed to assess model performance with alternative biomarkers.

Sample size

The minimum sample size required for external validation and development of a prognostic model was calculated²⁸². A minimum sample size of 4,482 individuals with 106 kidney failure events was required for 2-years and 1,884 individuals with 108 kidney failure events for the 5-year period, to ensure a margin of error of ≤ 0.05 .

Missing data

Individuals missing measures required for frailty phenotype assessment were included in the whole cohort analysis but excluded from frailty subgroup analyses. For frailty indices, if an individual had missing data for a deficit, the deficit was excluded from both the numerator and denominator²²⁶.

Statistical analysis

Baseline characteristics, including frailty and count of LTCs, were described using means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous variables, and frequencies with percentages for categorical variables. Comparisons of baseline demographics was performed using the two-sample t-test for continuous variables. The overlap between frailty (as defined by the different frailty measures) was presented through the construction of a Euler diagram⁶⁷. Event rates per 1000 person years were calculated for both kidney failure and death events.

Validation of KFRE was assessed across two subgroups (Supplemental Figure 6-1): (1) no frailty and (2) frailty (defined as frail by any one of the three frailty measures).

Model performance was assessed by discrimination (time-dependent, area under the receiver operating characteristics curve [AUC]¹⁵⁸ and Harrel's C-index, with 95% confidence intervals [CI] estimated from bootstrapping^{157, 283}), calibration (calibration curves¹⁵⁹, calibration intercept, calibration slope and calibration-in-the-large using observed/expected [O/E] ratio) and overall model fit (Brier score^{160, 161} and scaled Brier score²⁸⁴). Point estimates with 95% CI are presented for all model performance metrics. Where comparative analyses are made DeLong's test was reported for AUC in the Supplemental Materials.

Explanation of model performance measures is expanded in Supplemental Text 6-4.

If an individual dies they can no longer experience kidney failure; this is termed a competing event. Traditional Kaplan-Meier survival analyses treat competing death events as censored observations, which can bias estimates and prediction models. Given the anticipated high mortality rates amongst individuals with frailty^{173, 298}, we estimated risk using the Aalen-Johansen estimator to account for competing mortality. Individuals' predicted risk estimates were calculated using the UK-calibrated KFRE and observed risks by the Aalen-Johansen estimator. Aalen-Johansen cumulative incidence curves for kidney failure and death were plotted in individuals by frailty status. Individuals were categorised into risk groups based on KFRE risk (<3%, 3-<5%, 5-<15%, 15-<25%, 25-<50% and $\geq 50\%$), following previous validations^{10, 169}. Aalen-Johansen cumulative incidence curves were plotted by these risk groups and compared to Kaplan-Meier curves to depict kidney failure risk when accounting for or ignoring competing risks. Cumulative incidence of kidney failure and mortality and comparison of Aalen-Johansen cumulative incidence with Kaplan-Meier curves in frailty subgroups was stratified by age (<60 years old, ≥ 60 years old) and sex (male, female).

The study is reported in accordance with the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis) guidelines

(Supplemental Table 6-2)²²⁸. All analyses were performed using R software (version 4.3.0 or above).

Results

Baseline characteristics

Individuals included in the study (N=24,489) had a mean age of 62.8 years (SD 5.6), and the majority were female (54%). Mean eGFRcr was 66ml/min/1.73m² and eGFRcys 56 ml/min/1.73m². A total of 8,533 (35%) individuals were classified as frail by one or more frailty measures. The frail cohort was younger (62 years [SD 6] versus 63 [SD 6]; $P<0.001$) and had a higher eGFRcr (68ml/min/1.73m² [SD 18] versus 65ml/min/1.73m² [SD 15]; $p<0.001$), but lower eGFRcys (52ml/min/1.73m² [SD 12] versus 58ml/min/1.73m² [SD13]; $P<0.001$) compared with the non-frail cohort. Subsequently, those classed as frail had a higher discrepancy between eGFRcys and eGFRcr compared with the non-frail group (-16 versus -7ml/min/1.73m²; $P<0.001$; Table 6-1). The overlap between frailty measures in identifying frailty is depicted in a Euler diagram (Figure 6-1).

Baseline characteristics for individual frailty measure subgroups is presented in Supplemental Table 6-3.

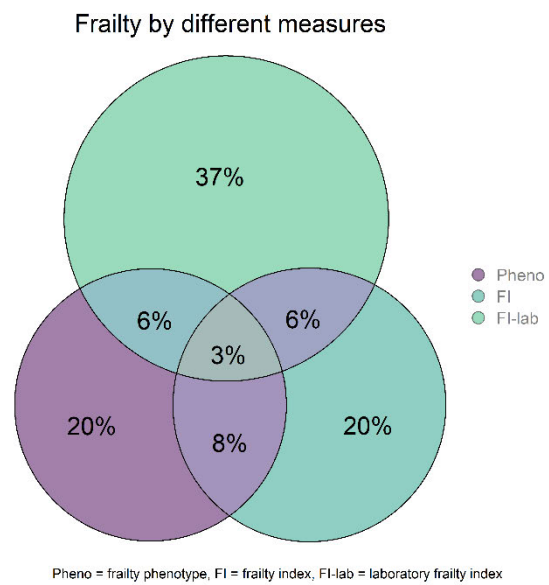
Table 6-1. Baseline characteristics table.

**	Whole cohort	No frailty	Frailty*
	n = 24,489	n = 15,865	n = 8,533
Age	62.8 ± 5.6	63.1 ± 5.6	62.4 ± 5.7
Creatinine (mg/dL)	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.5
Cystatin C (mg/L)	1.3 ± 0.3	1.3 ± 0.3	1.4 ± 0.4
eGFR _{Cr} (ml/min/1.73m ²)	65.6 ± 16.0	64.5 ± 14.8	67.7 ± 17.7
eGFR _{Cys} (ml/min/1.73m ²)	55.6 ± 13.1	57.6 ± 13.3	51.9 ± 11.7
eGFR _{CrCys} (ml/min/1.73m ²)	62.4 ± 11.1	63.2 ± 10.3	60.9 ± 12.3
eGFR creatinine cystatin discrepancy (eGFR _{Cys} -eGFR _{Cr}) (ml/min/1.73m ²)	-10.0 ± 19.5	-6.9 ± 19.9	-15.8 ± 17.4
uACR (mg/mmol)			
Median (IQR)	0.0 (0.0, 1.5)	0.0 (0.0, 1.2)	0.6 (0.0, 2.2)
Mean ± SD	5.4 ± 32.4	3.9 ± 26.1	8.3 ± 41.3
Sex, n(%)			
Male	11,232 (45.9)	7,538 (47.5)	3,664 (42.9)
Female	13,258 (54.1)	8,327 (52.2)	4,869 (57.1)
Follow-up time (months), mean ± SD			
2-year cohort	23.7 ± 2.0	23.8 ± 1.6	23.5 ± 2.6
5-year cohort	58.1 ± 8.4	58.7 ± 6.8	56.9 ± 10.7
Multimorbidity n (%)	14988 (61.2)	8454 (53.3)	6503 (76.2)
LTC count, median (IQR)	2 (1, 3)	2 (1, 2)	3 (1, 4)
Frailty			
FI score, median (IQR)	0.14 (0.09, 0.20)	0.12 (0.07, 0.16)	0.20 (0.13, 0.27)
FI-lab score, median (IQR)	0.18 (0.12, 0.25)	0.17 (0.12, 0.21)	0.29 (0.21, 0.33)
Missing frailty measure, n (%)	91 (0.4)	N/A	N/A

*based on being classed as frail by any of frailty phenotype, frailty index or laboratory frailty index

**Mean ± SD unless otherwise specified

Figure 6-1. Euler diagram showing overlap between frailty measures/definitions.



FI, frailty index; FI-lab, laboratory frailty index; Pheno, frailty phenotype.

Kidney failure and mortality events

There were 149 (0.6%) and 312 (1.3%) kidney failure and 499 (2.0%) and 1,471 (6.0%) death events within 2- and 5-years respectively. Death and kidney failure event rates were higher in those classed as frail compared with those without frailty (Table 6-2).

Kidney failure and mortality events by individual frailty measure subgroups are presented in Supplemental Table 6-4.

Table 6-2. Kidney failure and death events over 2- and 5-years by frailty status.

	Whole cohort n = 24,489	No frailty* n = 15,865	Frailty n = 8,533
Death, n(%)			
Within 2-year follow-up	1108 (4.5)	491 (3.1)	616 (7.2)
Per 1000 person-years	22.9	6.3	36.8
Within 5-year follow-up	1471 (5.8)	698 (4.4)	771 (9.0)
Per 1000 person-years	12.4	9.0	19.1
Kidney failure, n(%)			
Within 2-year follow-up	252 (1.0)	106 (0.7)	145 (1.7)
Per 1000 person-years	5.2	3.4	8.7
Within 5-year follow up	312 (1.3)	146 (0.9)	165 (1.9)
Per 1000 person-years	2.6	1.9	4.1

Model performance

The discriminatory ability of KFRE was consistent in the 2- and 5-year KFRE models and was similar across frailty subgroups analysed, regardless of eGFR equation used when assessed by AUC (AUC range 0.85-0.92) and by c-index (c-index range 0.92-0.94 for eGFRcys versus. 0.88-0.92 for eGFRcr with overlapping 95% CI) (Table 6-3 and 6-4). DeLong's test for comparison of AUC values for eGFR equation biomarker and frailty subgroups are reported in Supplemental Tables 6-5-6-8.

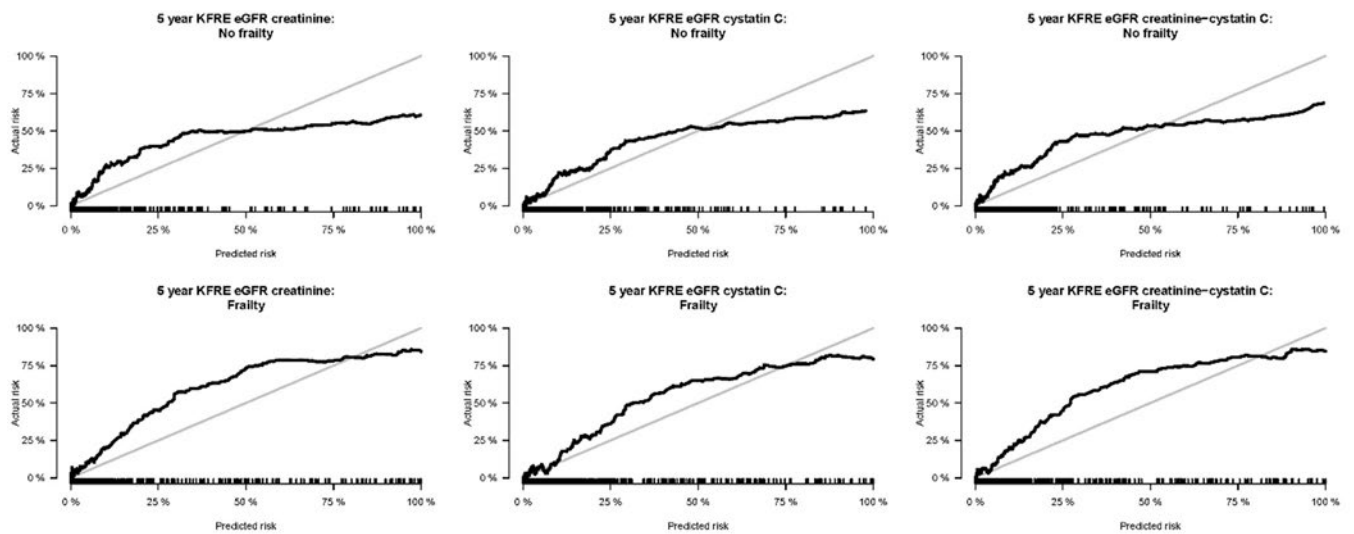
Calibration

Calibration curves display sub-optimal calibration in frail and non-frail groups at 2- and 5-years (Figure 6-2 and Supplemental Figure 6-2). Underestimation was present at lower predicted risk levels while overestimation was observed at higher predicted risk levels. Calibration-in-the-large demonstrated overall underestimation of kidney failure risk at both 2- and 5-years (5-year O/E ratio range 1.70-1.87 and 1.56-1.89, with eGFRcr and eGFRcr-cys, respectively), with some improvement when eGFRcys was substituted in KFRE (O/E ratio range 5-years; 1.20-1.47). Improvement in calibration-in-the-large was most prominent in the frailty subgroup (O/E ratio 5-years: eGFRcr 1.70; 95% CI, 1.55-1.85, eGFRcys 1.20; 95%CI 1.05-1.35). Calibration intercept demonstrated improvements with eGFRcys at 5-years (Table 6-3 and 6-4). Calibration slopes at all time points, eGFR equations and subgroups indicate that KFRE risk predictions are too extreme (calibration slope less than one), with high-risk predictions being too high and low-risk predictions too low (Table 6-4).

Overall fit

Overall fit was similar across the subgroups and eGFR equations used within KFRE when assessed by Brier score (Table 6-3 and 6-4). Scaled brier score showed superior model performance in the frail cohort compared to the non-frail cohort and with the 5-year compared to the 2-year KFRE equation but was similar across eGFR equations used (Table 6-3 and 6-4).

Figure 6-2. Calibration curves for predicted versus observed 5-year risk of kidney failure by frailty status.



The grey 45° line depicts perfect calibration, plots above this line represent underprediction by the prognostic model and plots below the line represent overprediction by the prognostic model. KFRE, kidney failure risk equation.

Table 6-3. Performance measures for kidney failure risk equation by eGFR equation and frailty status at 2 years.

eGFR equation used in KFRE	Performance measure for 2-year KFRE	Whole cohort	No frailty*	Frailty
eGFRcr	AUC	0.90 (0.87-0.92)	0.88 (0.83-0.92)	0.90 (0.87-0.94)
	C-index	0.89 (0.86-0.92)	0.88 (0.82-0.93)	0.90 (0.86-0.93)
	O/E ratio	2.12 (1.96-2.28)	2.07 (1.81-2.32)	2.18 (1.97-2.38)
	Calibration intercept	1.25 (1.05-1.46)	1.02 (0.70-1.35)	1.42 (1.16-1.68)
	Calibration slope	0.76 (0.68-0.84)	0.72 (0.60-0.83)	0.79 (0.66-0.91)
	Brier score	0.015 (0.004-0.006)	0.003 (0.003-0.004)	0.009 (0.007-0.010)
	Scaled brier score (%)	14.42 (8.98-19.82)	9.00 (1.02-16.80)	17.06 (10.22-23.86)
eGFRcys	AUC	0.91 (0.88-0.93)	0.89 (0.85-0.94)	0.91 (0.88-0.94)
	C-index	0.93 (0.92-0.95)	0.93 (0.90-0.95)	0.93 (0.90-0.95)
	O/E ratio	1.73 (1.57-1.89)	1.78 (1.53-2.04)	1.71 (1.50-1.91)
	Calibration intercept	1.08 (0.90-1.26)	1.05 (0.76-1.34)	1.11 (0.87-1.34)
	Calibration slope	0.83 (0.74-0.93)	0.84 (0.69-0.98)	0.82 (0.70-0.94)
	Brier score	0.005 (0.004-0.006)	0.003 (0.003-0.004)	0.009 (0.007-0.010)
	Scaled brier score (%)	14.38 (9.70-18.58)	9.51 (3.16-16.00)	16.91 (10.70-22.81)
eGFRcrcys	AUC	0.91 (0.88-0.93)	0.89 (0.85-0.94)	0.91 (0.88-0.95)
	C-index	0.93 (0.91-0.95)	0.92 (0.89-0.96)	0.92 (0.90-0.95)
	O/E ratio	2.11 (1.95-2.27)	2.17 (1.92-2.43)	2.09 (1.88-2.30)
	Calibration intercept	1.26 (1.07-1.46)	1.15 (0.84-1.46)	1.35 (1.10-1.60)
	Calibration slope	0.76 (0.68-0.85)	0.74 (0.61-0.86)	0.76 (0.65-0.88)
	Brier score	0.005 (0.004-0.006)	0.003 (0.003-0.004)	0.009 (0.007-0.010)
	Scaled brier score (%)	14.38 (10.21-19.25)	9.68 (2.51-16.67)	17.38 (10.67-23.76)
AUC, Area under the receiver operator characteristic curves; eGFRcr, estimated glomerular filtration rate creatinine; eGFRcys, estimated glomerular filtration rate cystatin C; eGFRcrcys, estimated glomerular filtration rate creatinine-cystatin C; KFRE, Kidney Failure Risk Equation; O/E, observed/expected. *Based on being classed as non-frail by any of frailty phenotype, frailty index or laboratory frailty index.				

Table 6-4. Performance measures for kidney failure risk equation by eGFR equation and frailty status at 5-years.

eGFR equation used in KFRE	Performance measure for 5-year KFRE	Whole cohort	No frailty*	Frailty
eGFRcr	AUC	0.90 (0.88-0.92)	0.88 (0.85-0.92)	0.91 (0.88-0.94)
	C-index	0.91 (0.89-0.93)	0.90 (0.86-0.93)	0.92 (0.90-0.94)
	O/E ratio	1.76 (1.65-1.87)	1.87 (1.70-2.03)	1.70 (1.55-1.85)
	Calibration intercept	0.46 (0.28-0.64)	0.40 (0.13-0.67)	0.53 (0.29-0.76)
	Calibration slope	0.78 (0.71-0.86)	0.75 (0.65-0.85)	0.82 (0.69-0.95)
	Brier score	0.009 (0.008-0.010)	0.007 (0.006-0.008)	0.012 (0.010-0.014)
	Scaled brier score (%)	30.86 (25.18-36.38)	22.41 (16.29-29.01)	37.77 (31.22-44.26)
eGFRcys	AUC	0.91 (0.89-0.93)	0.90 (0.86-0.93)	0.92 (0.88-0.95)
	C-index	0.94 (0.92-0.95)	0.93 (0.91-0.95)	0.94 (0.92-0.95)
	O/E ratio	1.30 (1.19-1.41)	1.47 (1.31-1.63)	1.20 (1.05-1.35)
	Calibration intercept	0.21 (0.06-0.36)	0.30 (0.07-0.53)	0.17 (-0.04-0.38)
	Calibration slope	0.87 (0.78-0.96)	0.88 (0.75-1.01)	0.88 (0.75-1.00)
	Brier score	0.009 (0.008-0.010)	0.007 (0.006-0.008)	0.012 (0.010-0.014)
	Scaled brier score (%)	30.52 (25.64-35.06)	22.66 (16.85-28.50)	36.88 (30.45-42.77)
eGFRcrcys	AUC	0.91 (0.89-0.93)	0.89 (0.86-0.93)	0.92 (0.89-0.95)
	C-index	0.94 (0.92-0.95)	0.93 (0.90-0.95)	0.94 (0.92-0.96)
	O/E ratio	1.69 (1.58-1.80)	1.89 (1.73-2.05)	1.56 (1.41-1.71)
	Calibration intercept	0.46 (0.29-0.63)	0.47 (0.21-0.72)	0.48 (0.26-0.70)
	Calibration slope	0.79 (0.71-0.87)	0.77 (0.66-0.88)	0.81 (0.69-0.93)
	Brier score	0.009 (0.008-0.010)	0.007 (0.006-0.008)	0.012 (0.010-0.014)
	Scaled brier score (%)	31.10 (26.58-35.75)	22.84 (16.78-29.07)	37.84 (31.30-44.22)
AUC, Area under the receiver operator characteristic curves; eGFRcr, estimated glomerular filtration rate creatinine; eGFRcys, estimated glomerular filtration rate cystatin C; eGFRcrcys, estimated glomerular filtration rate creatinine-cystatin C; KFRE, Kidney Failure Risk Equation; O/E, observed/expected. *Based on being classed as non-frail by any of frailty phenotype, frailty index or laboratory frailty index.				

Competing mortality risk

The 5-year cumulative incidence of kidney failure was 0.92% (95% CI, 0.77-1.07%) in the no frailty subgroup and 1.93% (95% CI, 1.64-2.23%) in the frailty subgroup. Likewise, the 5-year cumulative incidence of death was 4.22% (95% CI, 3.90-4.53%) and 8.41% (95% CI, 7.82-9.00%) in the no frailty and frailty groups, respectively (Figure 6-3 and Supplemental Table 6-9 and 6-10).

Plots comparing survival analyses that do not account for competing risk (Kaplan-Meier survival curve) with analyses that do (Aalen-Johansen cumulative incidence curves) showed overestimation of kidney failure risk in the death-censored approach (Kaplan-Meier estimates). This was most apparent in the frailty group and the higher KFRE predicted risk groups (Figure 6-4). Full competing risk analyses are described in Supplemental figure 6-3 and 6-4, Supplemental Tables 6-9-6-18, and Supplemental Text 6-5.

Sensitivity and supplementary analyses

Sensitivity and supplementary analyses are described in Supplemental Figure 6-5 and 6-10, Supplemental Table 6-19 and 6-20 and Supplemental Text 6-6.

Figure 6-3. Cumulative incidence curves of kidney failure and mortality by frailty status

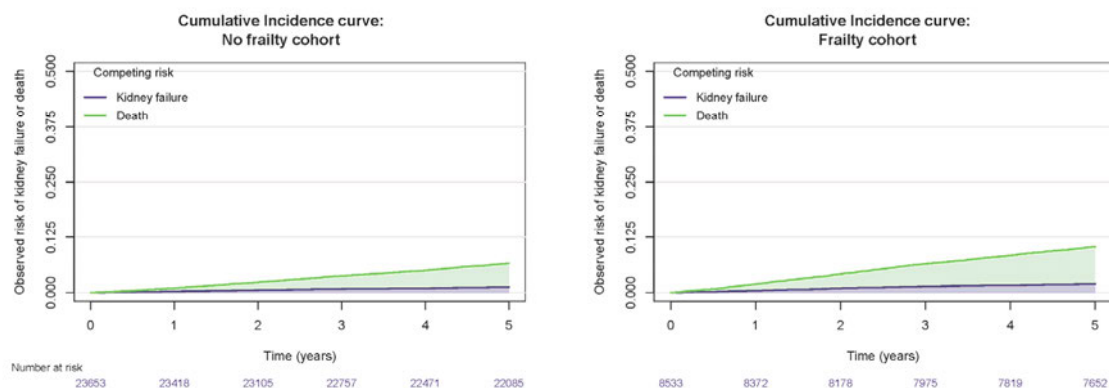
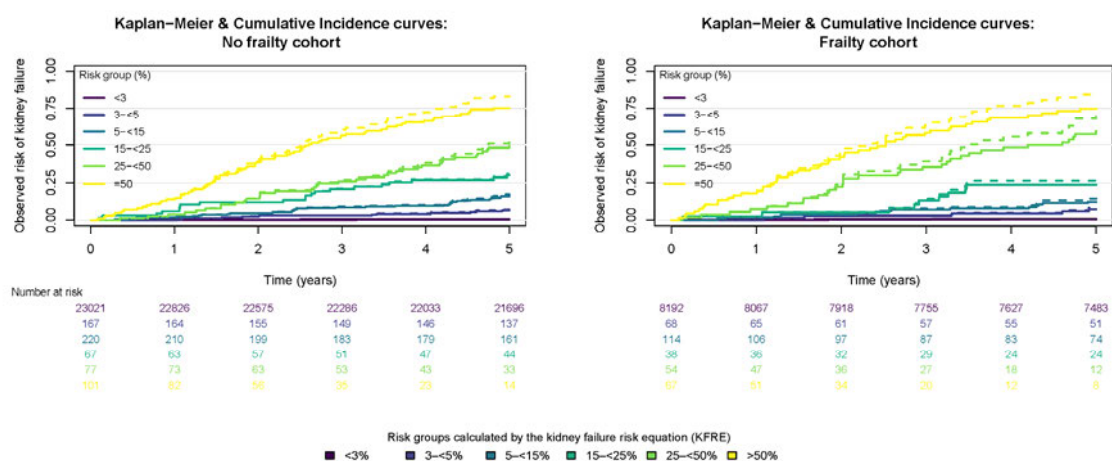


Figure 6-4. Kaplan-Meier estimates (dashed-lines) and Aalen-Johansen estimates (solid lines) cumulative incidences curves for kidney failure by frailty status and KFRE risk groups



Discussion

In this study conducted in the UK Biobank, we observed that (1) 34.8% of individuals with CKD were identified as having frailty; however, there was only a small degree of overlap between the measures utilised in identifying frailty. (2) The four-variable KFRE had a good discrimination but miscalibration for predicting kidney failure for individuals with CKD with frailty and that predictions were too extreme (*i.e.*, high-risk predictions being too high and low-risk predictions being too low). (3) Calibration improved when kidney function was estimated using cystatin C-based eGFR in the KFRE rather than eGFR_{cr}, with the greatest improvement observed in the frailty subgroups, although miscalibration remained. Higher cumulative incidences of both kidney failure and mortality were observed in individuals experiencing frailty compared with those without. Overestimation of kidney failure risk in analyses that do not account for competing mortality risk compared with those that do was most apparent in the frailty group and the higher KFRE predicted risk groups.

Frailty can occur at any age but its prevalence increases with aging. There is, however, no unified measure or consensus for the assessment of frailty²⁹⁹. The fluctuating nature of frailty may make it difficult to fully capture at a single point in time³⁰⁰, and the limited availability of longitudinal frailty data in large cohorts constrains our ability to assess change over time. In many population-based studies, frailty measures are not routinely collected at multiple time points, meaning cross-sectional assessment is required.

There is discordance between frailty phenotype and frailty index in an older adult population³⁰¹⁻³⁰⁴. We replicate this finding in a population with CKD with poor overlap between the three frailty measures. Conceptually, it is agreed that the clinical condition of frailty is associated with adverse health outcomes such as mortality and hospitalization, our study highlights that characteristics of frailty may vary and different frailty measures do not have equivalence within a CKD cohort, consistent with the wider literature. Further research is required to explore differences in types of frailty and predicting kidney failure risk. Information on frailty should be routinely collected in clinical research to improve our understanding of how to treat those with frailty and CKD and work

to develop consensus on how this is measured/reported and how to map between frailty measures is key³⁰⁵.

Guidance relating to frailty in CKD has mainly focused on older populations¹⁴². A systematic review of kidney failure prognostic models (including KFRE) highlights that no studies have validated models focusing on frailty in CKD¹⁹⁹. This may reflect complexities in measuring frailty and be limited by recording of frailty-relevant variables. Some studies have attempted to consider frailty in the context of kidney failure prognostic tool validation mainly focusing on older populations with CKD^{258, 266}. Our study includes a younger group of patients with CKD. Analyses stratified by age explored the impact of frailty on competing risk of kidney failure and mortality show that frailty and age both associate with higher cumulative risk of death but have opposite impacts on risk of kidney failure (lower risk of kidney failure in older age group compared to younger group and higher risk of kidney failure in frail group compared to non-frail group). The impact of not accounting for competing mortality risk was most evident in the frail group regardless of age but was also seen in the older non-frail group. Competing mortality risk should be considered even in younger patients identified as having frailty. Despite overestimation of kidney failure risk in some subgroups, measures of calibration-in-the-large demonstrated underprediction of risk with calibration slopes showing model predictions were too extreme suggesting that overprediction in some groups has led to bias and underprediction in other groups (non-frail, younger age groups and lower risk of kidney failure) where the competing risk of death is smaller.

We identified that frail individuals were younger than the non-frail sub-group, this reversal in the frailty-age relationship may be an example of Simpson's paradox³⁰⁶ and similar patterns have been observed in diabetes cohorts²²⁷.

We observed that using cystatin C-based eGFR KFRE resulted in improvements in calibration for KFRE, primarily in frailty sub-groups. It is unclear whether these improvements would translate into clinically relevant changes at an individual level. However, they may influence population-level risk stratification (for example, clinical guidelines), threshold based clinical decision and overall model calibration in vulnerable groups such as those with frailty. In addition, the frail group had a higher discrepancy between eGFR_{cys} and eGFR_{cr} compared to the

non-frail group. Our findings may be due to eGFR_{cys} and discrepancies between eGFR_{cys} and eGFR_{cr} having a closer relationship with frailty than eGFR_{cr}^{244, 307, 308} and reflecting non-muscle determinants of estimating kidney function, as well as the more explicit link between sarcopenia and frailty detected by the frailty phenotype model.

Although this study highlights the potential utility of eGFR_{cys} in improving risk prediction in frail individuals, we acknowledge that there are also limitations to the use of eGFR_{cys}³⁴. We propose an individualized approach when determining the biomarker(s) for estimating kidney function and the use of the combined creatinine-cystatin C based eGFR where available and appropriate, in keeping with Kidney Disease Improving Global Outcomes guidance¹. However, further research is required to explore the characteristics of individuals that have discordances between creatinine- and cystatin C-based eGFR and if routine use of cystatin C would impact prediction of kidney failure and improved the accuracy and clinical utility of KFRE, particularly in older populations.

The importance of accounting for competing mortality risk in predicting kidney failure in groups at increased risk of mortality, such as those with frailty has been demonstrated in this study. Others have considered competing mortality risk in the KFRE, highlighting improvements in KFRE performance with this approach^{170, 261}. Grams *et al.*²⁶¹ noted weaknesses in KFRE performance, with underprediction of kidney failure, in those ≥ 65 years of age and found competing risk analyses improved calibration for this group of patients. Our study expands previous work, using a large sample size and a specific focus on frailty in younger individuals with CKD.

Alternative validated prognostic tools exist that either use concurrent models to predict kidney failure and mortality risk²⁶⁷ or integrate risk prediction of both kidney failure and mortality simultaneously through a machine learning approach²⁸⁹. These tools are useful in understanding risks of kidney failure in the context of competing mortality risk. However, their performance has not been validated with a focus on individuals with frailty and remains an important research gap. Future comparative studies, including assessment of clinical utility would be beneficial in this area.

Previous research has identified that frailty is an independent predictor of mortality in patients referred for pre-dialysis education²⁹⁸. More accurate identification of individuals at highest risk of developing kidney failure and at an earlier time point is imperative, particularly in an era where we can utilise treatments, such as sodium-glucose cotransporter-2 (SGLT2) inhibitors, to improve cardiovascular and kidney outcomes³⁰⁹. However, it remains uncertain how prediction models impact communication or decision-making, particularly in more complex patient groups such as those living with frailty. Additionally, implementation studies are required to understand the impact of these risk prediction models on clinical outcomes.

Strengths of this study include that UK Biobank provides a large sample with rich phenotyping to permit the calculation of multiple frailty measures and an adequate number of kidney failure events for a validation study. We used robust methodologies for validation of prognostic models²²⁸. Evidence is lacking for optimal management of frail patients who are set to increase in number; therefore, an understanding of how prognostic models perform in such groups and how this impacts possible models of care is important. We used multiple frailty measures to capture frailty in the cohort. The frailty measured utilised are adapted frailty measures and may therefore have limitations when applied, particularly in younger populations, as some markers (such as exhaustion) may have different causes or implications when applied to younger populations and others (such as weight loss, which in UK Biobank is not specified as 'unintentional') differ from their original specification when used as frailty markers. In addition, kidney function was estimated using the CKD-EPI 2012 equation without race coefficient, we acknowledge that newer equations derived from European cohorts²¹⁸ may offer improved accuracy in UK populations, and future research could explore the impact of using more regional specific equations on risk prediction. The definition used for the outcome of kidney failure was not inclusive of conservative care, a pathway where patients choose not to receive KRT with a focus on providing supportive care to promote quality of life³¹⁰. Conservative care as a treatment for kidney failure may be more commonly observed in individuals experiencing frailty. Lastly, UK Biobank is a high quality research database but includes individuals from higher socioeconomic backgrounds, restricted age groups (upper age of

cohort 73 years), with fewer chronic health conditions than the general population. Despite this, evidence supports that risk factor associations in UK Biobank appear to be generalisable to those identified in nationally sampled cohort studies²¹⁰.

Frailty is common in CKD, but prevalence varies depending on measure of frailty used. Cystatin C-based eGFR equations improve calibration performance of KFRE in individuals with frailty but with persisting miscalibration. Competing mortality risk appears to be most clinically relevant to individuals with frailty and at higher predicted KFRE risks. Further work is required to assess the impact of frailty on other kidney failure prediction models, particularly those that consider the risk of mortality.

Disclosures

PBM reports lecture honoraria from AstraZeneca, Pharmacomso, Bayer, Astellas, Viforpharma, GSK and Boehringer Ingelheim outside the submitted work and research grants from AstraZeneca and Boehringer Ingelheim. JSL reports personal lectureship honoraria from AstraZeneca and consulting fees from Boehringer Ingelheim, outside the submitted work. The other authors have no potential conflicts of interest to declare.

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For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

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Authors' Contributions

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Project administration: Heather Walker.

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Supervision: Juan-Jesus Carrero, Katie Gallacher, Bhautesh Dinesh Jani, Patrick B. Mark, Michael K. Sullivan.

Validation: Michael K. Sullivan.

Visualization: Heather Walker.

Writing - original draft: Heather Walker.

Writing - review & editing: Giorgi Beridze, Juan-Jesus Carrero, Anne-Laure Faucon, Edouard L. Fu, Katie Gallacher, Peter Hanlon, Bhautesh Dinesh Jani, Jennifer S. Lees, Patrick B. Mark, Michael K. Sullivan, Heather Walker.

Data sharing statement

Data cannot be shared. Data used for this study are available from UK Biobank. Access to data is through data application processes for UK Biobank. Further details can be found via <https://www.ukbiobank.ac.uk/enable-your-research/apply-for-access>. Code is available on Github for others to replicate our analysis: https://github.com/h-j-walker/KFRE_validation.git.

7 Chapter: 7 Exploration of patients' and health care professionals' perspectives of kidney failure risk and shared decision-making in MULTIPLE Long-term conditions and frailty (MULTIPOINT): a qualitative interview and focus group study

7.1 Reference

Walker, H., Sullivan, M.K., Jani, B.J., Mark, P.B., Gallacher, K.I. Exploration of patients' and health care professionals' perspectives of kidney failure risk and shared decision-making in MULTIPLE Long-term conditions and frailty (MULTIPOINT): a qualitative interview and focus group study. Under review BMC Medicine June 2026.

7.2 Chapter summary

This chapter presents the findings of a qualitative descriptive study exploring patients and healthcare professionals understanding of CKD and perspectives of kidney failure risk in people with CKD and multimorbidity and/or frailty and expectations of the use of KFRE in guiding care and shared decision-making (RQ5).

7.3 Manuscript

Abstract

Background: People living with CKD frequently experience multiple long-term conditions (multimorbidity) and/or frailty. This population is under researched and shared decision-making about CKD can be challenging in the context of existing multimorbidity and/or frailty. Clinical guidelines recommend that care and referral of individuals with chronic kidney disease (CKD) is guided by the kidney failure risk equation (KFRE). This study aims to explore patients' and healthcare professionals' perspectives on kidney failure risk and shared decision-making in multimorbidity and/or frailty, with a secondary aim of examining perceptions of KFRE, as a guideline-recommended prognostic tools, in these populations.

Methods: Semi-structured interviews with patients with CKD and multimorbidity and/or frailty and focus groups for healthcare professionals (HCPs) caring for these groups from primary and secondary care settings in Glasgow, United Kingdom were conducted March 2024 - July 2025. Using a theory-informed abductive approach, data were analysed according to Normalisation Process Theory.

Results: Thirty-one patients (aged 46-94 years old; 3-10 long-term health conditions; clinical frailty scale of 1-7) and nineteen HCPs participated. Five interconnected factors shaped understanding of CKD, kidney failure risk and shared decision-making, each experienced differently by patients and HCPs: 1) Variable knowledge and understanding of CKD, with many patients unaware of their diagnosis and HCPs recognising challenges in addressing this within time-pressured consultations or where competing priorities exist; 2) Workload and burden of managing CKD within multimorbidity, including cognitive, practice and emotional demands for patients and completing clinical priorities and managing complexity for HCPs; 3) Relationships and interactions, where trust and continuity facilitated shared decision-making; 4) Context and priorities, including prioritisation of CKD by patients and HCPs; and 5) Pervasive uncertainty around prognosis, symptom attribution and when to discuss kidney failure risk. KFRE was unknown to patients

and most primary care HCPs, secondary care HCPs had greater awareness but expressed mixed views on its application.

Conclusions: CKD was often not a priority for patients or HCPs, compared to other long-term conditions. Many patients wanted to better understand CKD and kidney failure risk alongside other health problems. Trusting relationships, continuity of care and recognition of individual priorities were central to shared decision-making, but frequently undermined by healthcare system pressures. Methods of communicating kidney failure risk and uncertainty require further research. Findings provide insights into how an understanding of CKD and kidney failure risk can be embedded in the care of individuals with multimorbidity or frailty.

Trial registration: Ethical approval granted in August 2023 by the NHS Health Research Authority following a favourable opinion from the West of Scotland Research Ethics Committee (REC) 3 (IRAS ID: 325848, REC reference: 23WS/0119, Protocol number GN22RE559).

Keywords: Chronic kidney disease, multimorbidity, frailty, risk prediction, shared decision-making

Background

Globally there is a rising prevalence of chronic kidney disease (CKD)^{2, 241}. Many individuals with CKD will experience two or more long-term conditions, referred to as multimorbidity or multiple long-term conditions⁴. Both CKD and multimorbidity are associated with frailty¹¹⁷, a state of health where there is a reduced capacity to be able to respond to changes as a result of factors including illnesses or medication side effects^{7, 8}.

When CKD is detected or as kidney function declines to more advanced stages, individuals may face decisions relating to introduction of new treatments, lifestyle changes, referral to secondary care kidney specialists and future care planning, potentially including kidney replacement therapy (KRT) when individuals are approaching kidney failure - encompassing dialysis, kidney transplantation or conservative care⁽⁷⁾. In the context of multimorbidity or frailty decision making may be more complex and requires careful, person-centred deliberation. Management of individual conditions without consideration of the broader clinical and personal context may compound treatment burden and influence quality of life, particularly in this population³¹¹.

Shared decision-making, is a collaborative process that involves an individual and healthcare professional (HCP) reaching a joint decision that reflects the best available evidence, a person's values, preferences and priorities and risks and benefits of the decision¹⁷⁷. Existing qualitative literature has largely focused on shared decision-making for CKD in relation to KRT choices^{187, 230, 312-314} but shared decision-making in individuals with multimorbidity or frailty may involve unique challenges. Research conducted outside the context of CKD highlights how multimorbidity and clinical uncertainty can complicate or introduce barriers in communication and decision making and the challenges of utilising disease-specific guidelines in the presence of multimorbidity leading to conflict between evidence-based recommendations and patient-centred care^{195, 315}.

Prognostic tools are increasingly used in healthcare to support personalised care and inform clinical decision making¹⁵¹. These tools facilitate risk stratification,

identification of individuals at higher or lower risk of adverse outcomes and can be used to guide evidence-based treatment decisions³¹⁶. The most widely validated prognostic tool for predicting risk of progression to kidney failure in CKD is the Kidney Failure Risk Equation (KFRE)⁹, which uses four variables: age, sex, estimated GFR (eGFR) and urine albumin creatinine ratio (uACR). Both the 2021 National Institute for Health and Care Excellent (NICE)¹¹ and the Kidney Disease Improving Global Outcome (KDIGO) clinical guidelines for management of CKD¹ recommend using KFRE to support decisions about referral to specialist kidney care services for adults with CKD and to communicate an individual's five-year risk of progression to kidney failure. However, the effective use of prognostic tools depends not only on their statistical performance but on how risk is understood, communicated, and integrated into care. Adoption and implementation of KFRE on a national level in the UK has been variable, with barriers including a lack of standardisation of laboratory measures used, challenges with integration into IT platforms and paucity of albuminuria testing^{317, 318}. Evidence on the impact of KFRE, as well as how it is understood and used by patients and HCPs is limited²⁷⁴, with only a small number of studies exploring the use of KFRE in a risk-based approach to guiding care more broadly from patient, family and HCP perspectives^{319, 320}. Overall, there is a paucity of research examining how individuals with CKD and multimorbidity and/or frailty understand CKD, kidney failure risk, how such risk is discussed in practice and how prognostic tools such as KFRE are perceived and integrated into care for people with multimorbidity or frailty.

This study aims to explore patients' and healthcare professionals' perspectives on comprehension of CKD and kidney failure risk and shared decision-making, in the context of multimorbidity and/or frailty.

The primary objective is:

- To gain insights into how patients and HCPs perceive the risk of kidney failure when CKD occurs in conjunction with multimorbidity and/or frailty, and to examine how these perceptions shape communication and shared decision-making

The secondary objectives are:

- To examine and compare patients' preferences for discussing kidney failure risk to those of HCPs, in this population.
- To explore patient and HCPs expectations regarding the role of KFRE in supporting care and shared decision-making for individuals with multimorbidity and/or frailty.
- To identify barriers and enablers that may impact shared decision-making or the use of KFRE in guiding care, treatment and referral decisions in these patient groups.

The findings have the potential to inform more holistic and person-centred care and offer insight into shared decision-making approaches for this complex patient group.

Methods

A detailed description of the study design has been published in our protocol²²⁹. We conducted a qualitative study using in-depth semi-structured interviews with patients and focus groups with HCPs to explore perspectives and experiences of CKD, kidney failure risk and use of KFRE in the context of multimorbidity and frailty. Interviews were used for patient participants to allow exploration of sensitive and potentially distressing topics and to enhance ease of engagement in the study. Conversely, focus groups were primarily used for HCP participants to emulate multidisciplinary team interactions that exist within clinical practice. Interviews were used for HCP participants where individual availability prevented them from participating in a focus group session.

Individuals aged 18 years or older, with CKD and two or more other long-term conditions and/or frailty were recruited from primary and secondary care settings in NHS (National Health Service) Greater Glasgow and Clyde, UK. CKD was defined as either a sustained eGFR $<60\text{ml/min/1.73m}^2$ (calculated from creatinine using the CKD-EPI 2009 equation without incorporating the race coefficient³⁸) or by the presence of a diagnosis code for CKD in the clinical records. Frailty and long-term conditions were also based on diagnosis codes in clinical records (Supplementary Table 1). Identification of patients with frailty from clinical records proved challenging due to inconsistent frailty coding in primary care electronic records. As a consequence, only a small number of patient participants at the time of interview had a clinical frailty score indicating some degree of frailty (clinical frailty score ≥ 4) and the majority of participants had multimorbidity but were robust on frailty assessment (clinical frailty score 1-3). HCPs from the same region, involved in the care of people with CKD were recruited from general practices and secondary care renal services. Purposeful sampling techniques were employed to ensure variation in participant characteristics such as age, gender, ethnicity and socioeconomic status. A total of 217 postal invitations were sent to patients from four primary care practices, forty-one individuals responded to this initial interview and nineteen participated in interviews. Twenty-four secondary care patient participants were issued invitations during clinic visits and a total of

twelve responded and completed interviews. The total number of HCPs invited to participate in the study cannot be quantified due to the use of networks to disseminate invites via email, however, twenty-two HCPs responded to the invite. Baseline participant characteristics, including number of long-term conditions and clinical frailty score for patient participants was collected at the start of interview/focus group sessions.

Topic guides for the interviews and focus groups (Supplementary materials 1-2) were developed from the Ottawa Decision Support Framework¹⁸² and Ottawa Personal Decision Guide¹⁸³ (a decision making framework and decision aid developed to assist individuals in making decisions and participating in shared decision-making and discussed within the wider research team to ensure all appropriate topic areas were covered. Patient participant facing materials, including interview topic guides, were reviewed by individuals from the West of Scotland Kidney Patient and Public Involvement and Engagement (PPIE) group to ensure the content was appropriate, understandable and sensitive to the topics being discussed. Following their development, interview and focus group study guides were piloted by the PPIE group and a pilot focus group with HCPs from the research team. In addition to reviewing patient participant facing materials, PPIE input contributed to refining the research aims/questions, suggesting recruitment approaches and selecting patient quotes to be included in this publication, ensuring that the study and the findings aligned with the priorities of individuals living with CKD.

All interviews and focus groups were conducted by a single member of the research team (HW). Patient interviews were conducted in-person at participants' homes (30/31, 96.8%) or at the University of Glasgow (1/31, 3.2%). HCP focus groups were conducted in-person at the University of Glasgow (3 focus groups; 9 HCPs) or at NHS hospital sites (2 focus groups; 7 HCPs), with three HCPs participating in individual interviews online via video conference. Where sessions were conducted online, Microsoft Teams was used. Interviews and focus group sessions were audio-recorded, transcribed verbatim, and anonymised. Field notes

were compiled immediately following each session. Participants were recruited until data saturation was deemed complete.

Data were analysed abductively³²¹, using theory-led framework analysis, underpinned by Normalisation Process Theory (NPT)^{235, 236}. NPT provides a conceptual framework for examining how practices are adopted and sustained in routine settings³²². NPT has previously been applied to understand the patient experience of treatment burden associated with the management of chronic conditions³²³. In healthcare, it enables exploration of the mechanisms through which aspects of care become embedded in everyday practice. It was therefore deemed to be a useful lens to examine the processes of risk stratification and shared decision-making. The NPT-informed coding framework is presented in detail in Table 2. Data that fell outside of the coding frame were identified and examined to ensure important concepts were captured. This analysis aimed to enable exploration and understanding of the knowledge of CKD, communication of kidney disease, perceptions of kidney failure risk and expectations surrounding the use of the KFRE in the context of multimorbidity and/or frailty. As well as to provide insights into how these factors shape shared decision-making.

Table 7-1. NPT coding framework for **MULTIPOINT**

NPT Category	NPT sub-construct	Additional themes	
Understanding/Sense Making (Coherence): Making sense of CKD and kidney failure as part of multimorbidity and/or frailty	Understanding the kidneys & CKD (<i>Differentiation</i>)	Uncertainty	Prioritisation of CKD
	Considering what CKD & risk of kidney failure means for the individual (<i>Individual specification</i>)		
	Understanding the impact of CKD & risk of kidney failure for social/support networks (<i>Communal specification</i>)		
	Perception & value of KFRE in CKD/ multimorbidity/frailty & shared decision-making (<i>Internalisation</i>)		
Work of & roles in understanding & making decision (Cognitive Participation): Understanding how individuals work with HCPs and their support networks	Work involved related to living with CKD & multimorbidity/frailty (<i>Initiation</i>)		
	Understanding & engaging with others (HCPs/support networks) to understand their health & health decisions (<i>Enrolment</i>)		
	Determining roles & deciding if decisions made are the right thing to do (decision appraisal) (<i>Legitimation</i>)		

	Barriers & facilitators to understanding shared decision-making (<i>Activation</i>)		
Working with others & relationships/interactions in understanding CKD, kidney failure risk & shared decision-making (<i>Collective Action</i>): Working with HCPs, healthcare systems and their support networks to discuss/understand CKD and kidney failure risk and make shared decisions	Impact of multimorbidity/frailty on discussing kidney failure risk/using KFRE to guide care and make shared decisions (<i>Interactional workability</i>)		
	Role of relationships between individuals, support networks & HCPs (<i>Relational Integration</i>)		
	Allocation of work & decision-making (<i>Skillset workability</i>)		
	Impact of individuals' contexts & interactions between healthcare systems & individuals (<i>Contextual Integration</i>)		
Reflecting & appraising work required to understand CKD/kidney failure and making shared decisions in multimorbidity/frailty (<i>Reflexive monitoring</i>): Reflecting and evaluating the role of KFRE/risk prediction models in discussing kidney failure risk and shared decision-making	Finding information about CKD, kidney failure or impact of multimorbidity/frailty (<i>Systematisation</i>)		
	Review of decisions made with HCPs/support networks (<i>Communal Appraisal</i>)		
	Evaluating what is important to the individuals (<i>Individual Appraisal</i>)		
	Modifying decisions & discussions based on reflections (<i>Reconfiguration</i>)		

The five stages of framework analysis defined by Ritchie and Lewis were followed: familiarisation; identifying a thematic framework; indexing; charting; mapping and interpretation^{234, 237}. Development of the NPT-informed coding framework and constructs was an iterative process, with review, discussion and refinement of the framework and data interpretation conducted in parallel. Coding was led by HW, with a subset of transcripts independently reviewed by a second researcher (KG) to enhance rigour. NVivo data analysis software (version 14: QSR International (UK) Ltd.) was utilised for data management and analysis. The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist^{324, 325} was followed to report the findings of the study (Supplementary Table 7-2).

The research team comprised of primary and secondary care clinicians and researchers with expertise in kidney disease, multimorbidity and frailty care/management and qualitative methodologies. The principal researchers were a clinical research fellow and kidney doctor (HW; female PhD student) who conducted and analysed all participant interviews and focus groups and a clinical and academic general practitioner (KG; female Senior Clinical Research Fellow, PhD) who co-analysed and check-coded 10% of transcripts. Both researchers have experience in caring for individuals with CKD, multimorbidity and frailty and have completed formal training in qualitative research methods.

Ethical approval was obtained from the West of Scotland Research Ethics Committee 3 (IRAS ID: 325848; REC reference: 23WS/0119; Protocol number GN22RE559). All participants gave written informed consent.

Results

Participant characteristics

Thirty-one patient participants, 46-94 years (mean 74), 52% male, 3-10 long-term conditions, clinical frailty score 1-7, were interviewed. All patient participants met criteria for multimorbidity (≥ 2 long-term conditions in addition to CKD), eleven participants 35.5% had multimorbidity with some degree of frailty (vulnerable, mild/moderate/severe frailty; clinical frailty score ≥ 4) and of these three had multimorbidity with formal frailty (clinical frailty score ≥ 5). All patient participants were of white ethnicity but varied in socioeconomic status (Scottish Index of Multiple Deprivation (SIMD) quintile 1 [most deprived]; 32.3% and quintile 5 [least deprived]; 19.4%). The average patient participant interview was 34 minutes (range 20-79 minutes). Six patient participants had a family/support network member present during the interview.

Despite purposeful sampling strategies designed to recruit a diverse sample, all 31 patient participants were of white ethnicity. Efforts to recruit from non-white ethnic backgrounds were unsuccessful, likely reflecting a combination of factors including language barriers (invitation letters were in English only and inclusion criteria required participants to be able to read and communicate in English), likelihood of lower coding of CKD in minority ethnic groups and potential mistrust of healthcare professionals. This represents an important limitation of the study, discussed further in the Strengths and Limitations section.

Nineteen healthcare professionals involved in the care of patients with CKD (six renal consultants, three renal specialist trainees, five general practitioners, three renal specialist nurses and two primary care practice nurses) participated in focus groups or interviews. Of the nineteen HCPs, sixteen (84.2%) participated in in-person focus groups and three (15.8%) completed online individual interviews. The average HCP focus group and interview lengths were 51 minutes (range 43 to 57 minutes) and 38 minutes (29 to 48 minutes) respectively. Most HCPs (52.6%) had worked in their role for more than 10 years. Full participant characteristics are described in Table 7-2.

Table 7-2. Participant characteristics

Characteristic	Patient participants n = 31	Healthcare professional participants n = 19
Setting of recruitment (%)		
Primary Care	19 (61.3)	7 (36.8)
Secondary Care	12 (38.7)	12 (63.2)
Gender (%)		
Female	15 (48.4)	12 (63.2)
Male	16 (51.6)	7 (36.8)
Age (%)		
Mean	74.5	41.1
<50	1 (3.2)	9 (47.4)
50-64	6 (19.4)	1 (5.3)
65-74	8 (25.8)	-
≥75	16 (51.6)	-
Undisclosed	-	9 (47.4)
Ethnicity (%)		
White Scottish	30 (96.8)	14 (73.7)
White British	1 (3.2)	2 (10.5)
White Irish	0 (0)	2 (10.5)
Mixed	0 (0)	1 (5.3)

SIMD quintile (%)		
1 (most deprived)	10 (32.3)	-
2-4	15 (48.4)	-
5 (least deprived)	6 (19.4)	-
Number of LTCs (%)		
Range	3-10	
Mean	6.5	-
3-5	10 (32.3)	-
6-8	16 (51.6)	-
≥9	5 (16.1)	-
CFS (%)		
Range	1-7	
Mean	3	-
1-3 (robust)	20 (64.5)	-
4-5 (vulnerable/mild frail)	10 (32.3)	-
≥6 (frail)	1 (3.2)	-
Number of medications		
Range	4-16	
Mean	8.1	-
Median	7	-
Setting of interview/focus group (%)		

Home	30 (96.8)	-
University	1 (3.2)	9 (47.4)
Hospital	-	7 (36.8)
Online	-	3 (15.8)
Presence of carer/support network (%)	6 (19.4)	-
Time working in HCP role (years) (%)		
1-5	-	4 (21.1)
5-10	-	4 (21.1)
>10	-	11 (52.6)

Key themes

Key findings from the perspectives of patients and HCPs are presented under the 16 NPT sub-constructs (shown in Table 7-1), with key illustrative quotes (see Figure 7-1 for visual representation, Table 7-3 for selected illustrative quotes by NPT sub-constructs and Supplemental Table 7-3 for expanded quote examples).

Figure 7-1. Key factors influencing patients' and healthcare professionals' understanding and perception of chronic kidney disease and kidney failure risk in the context of multimorbidity and frailty.

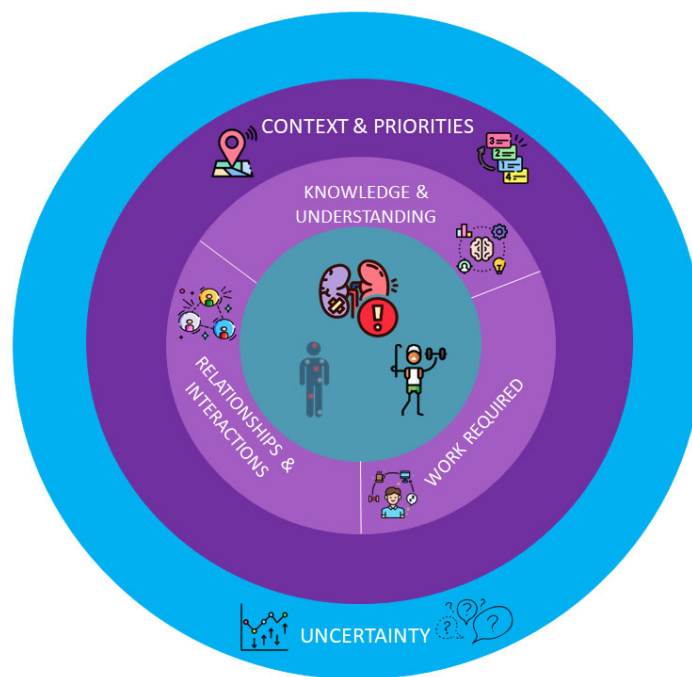


Table 7-3. Illustrative participant quotes by Normalisation Process Theory sub-constructs

NPT Category and sub-construct		Description/examples	Supporting quotes	
			Patients	HCPs
Understanding/Sense Making: Making sense of CKD and kidney failure as part of multimorbidity and/or frailty	Understanding the kidneys & CKD	• Pre-existing knowledge and understanding of the kidneys • Awareness at having CKD • Giving/receiving a diagnosis of CKD • Symptoms/asymptomatic nature of CKD • What will help the kidneys? • Discussing kidney failure	<i>"I had no idea that I had a problem, so I have no idea how it functions with anything else. I really have no idea at all."</i> (PCP02, Female, 84 years)	<i>"because kidney disease is- Can be relatively asymptomatic until it's quite advanced, it is one of these silent illnesses for a lot of people."</i> (HCP16, Female, Renal specialist nurse) <i>"patients are often wanting to know what they can modify, if anything."</i> (HCP12, Female, Renal specialist trainee)
	Considering what CKD & risk of kidney failure means for the individual	• Communication and setting expectations • Other LTCs • Individual preference for knowledge and understanding • Ongoing impact of CKD and day-to-day life	<i>"I don't ever remember being mentioned anything about my kidneys. Because I think I am too- I'm much more concerned with my asthma that's my main functioning thing."</i> (PCP02, Female, 84 years)	<i>"A lot of patients that come to clinic have absolutely no idea why they're there or what the kidneys actually do in the body, and then what consequence of kidney failure might look like because then that helps them work out what it will mean to them."</i> (HCP12, Female, Renal specialist trainee)
	Understanding the impact of CKD & risk of kidney failure for social/support networks	• Withholding information from others • Support network • Challenges with support networks • Using others experiences to understand CKD	<i>"I think if my family was involved, they would be saying, don't do this, don't do that... But no, I wouldn't let them be involved."</i> (PCP16, Female, 74 years)	<i>"Quite often they've spoken to lots of people, or they've had family members who've had a transplant or been on dialysis, and they actually know quite a lot already so it's a huge range of experience."</i> (HCP02, Male, Renal specialist trainee)

	NPT Category and sub-construct	Description/examples	Supporting quotes	
			Patients	HCPs
	Perception & value of KFRE in CKD/ multimorbidity/frailty & shared decision-making	• Perceptions of KFRE • Accuracy and precision • Value of KFRE • Implementation	<i>"I know in this area it's to quite a considerable extent guesswork, percentages, so I don't expect too much precision, one can't have it"</i> (PCP07, Male, 91 years) <i>"Some people would like to know. Sometimes you go to the doctor, you come out none the wiser. I think if you knew what was happening and what was going on, it would put your mind at ease a little."</i> (SCP01, Male, 86 years)	<i>"There are so many guidelines, and people get in a system of what they use for each thing. And I don't think the KFRE has sort of gone into primary care yet, and it's not become routine practice and it's just that it needs to be embedded."</i> (HCP03, Female, GP)
Work of & roles in understanding & making decision: Understanding how individuals work with HCPs and their support networks	Work involved related to living with CKD & multimorbidity /frailty	• Work involved in managing CKD and adapting (including medications, monitoring, appointments, self-care) • Emotional work • Self-blame • Patient roles and responsibilities • Communication/ conversations	<i>"I think probably you know if you have multiple health problems it's another thing to worry about isn't it you know but it's how to manage that what changes can you make to your lifestyle or etc you know what you'd be willing to do."</i> (PCP19, Female, 64 years)	<i>"The other thing I think is important in the setting of multiple health conditions is not just lack of information, but it's sometimes too much information and conflicting information.... I think that must be extremely confusing for people to go from pillar to post and be given different information each time."</i> (HCP11, Female, Renal specialist trainee)
	Understanding & engaging with others (HCPs/ support networks) to understand their health & health decisions	• Support network and roles • Facilitators to understanding and engagement	<i>"(My wife) comes with me because... my hearing's bad- even with the hearing aids in. So, she goes with me and then she understands a lot of the medical"</i>	<i>"I do think that we struggle to impart the information to people who have got poor health literacy and people who don't speak English as their first language. I think we're aware that we"</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
	Barriers to understanding and engagement	<i>jargon I wouldn't understand, you know, so she's my support"</i> (PCP13, Male, 81 years)	<i>struggle with that, and we have done some things to try and mitigate that but I think we can still do a lot more on that front."</i> (HCP05, Female, Renal consultant)
Determining roles & deciding if decisions made are the right thing to do (decision appraisal)	- SDM culture - Understanding decisions - Choosing roles in SDM - Agreeing/disagreeing with decisions and trust	<i>"it's a two-way conversation"</i> (SCP02, Male, 86 years) <i>"generally, we have a good chat about what's happening. He (GP) lets me know where my levels are, and it's good to have that information from somebody like that that I trust. And I rely on him to keep me in the right place, and I know if there's something that I need to be not doing or taking care of, he'll tell me that."</i> (PCP12, Male, 73 years)	<i>"there's a huge range. I think generally the people I'm seeing in clinic want you to be the driver of the decisions, but they want to feel that they're part of the discussion. But they're very much wanting you to give your opinion on what's the best line to go down, so it's like not the kind of authoritarian model that you're telling them what to do, but you're kind of guiding them."</i> (HCP12, Female, Renal specialist trainee)
Barriers & facilitators (to understanding shared decision-making)	- Barriers to SDM - Facilitators to SDM - Awareness and use of KFRE	<i>"I don't know if I've actually ever been given any information on it. The doctor I've seen this morning, he talked me through what I could understand...It's all double Dutch to me"</i> (SCP04, Male, 76 years)	<i>"We can't get translators for them just now, so often they're coming in and we're having to send them away... we don't have the resources to translate every letter into their language"</i> (HCP19, Female, Practice nurse) <i>"I was certainly not aware of this Kidney Risk Equation"</i> (HCP07, Male, GP)

NPT Category and sub-construct		Description/examples	Supporting quotes	
			Patients	HCPs
Working with others & relationships/interactions in understanding CKD, kidney failure risk & shared decision-making: Working with HCPs, healthcare systems and their support networks to discuss/understand CKD and kidney failure risk and make shared decisions	Impact of multimorbidity /frailty on discussing kidney failure risk/using KFRE to guide care and make shared decisions	• Other LTCs • Communicating and discussing risk • Ageing and declines in health • Healthcare systems	<i>"But it's all these different wee bits that I think, you know, trying to process that and you trust the consultants, you know what you are doing and things but it's hard, it's really hard to process."</i> (SCP07, Female, 46 years) <i>"It's not a lack of caring or a lack of care; it's just a new system that I don't think works terribly well as far as patients are concerned."</i> (PCP15, Male, 85 years)	<i>"when someone's got lots of other conditions, it almost feels as if the CKD is almost just a consequence of those things and I think it tends to just get underserved...you probably think, well, if we manage their heart failure, we manage their diabetes and we manage their other symptoms and the CKD will probably look after itself because we've actually got them on the drugs that are used for CKD anyway. So, it almost becomes an afterthought."</i> (HCP19, Male, GP)
	Role of relationships between individuals, support networks & HCPs	• Trust & continuity of care • Care setting (primary care, secondary care) • Healthcare system/processes	<i>"It's so difficult to get an appointment with the doctor that I, like most people, only use them for something that's urgent and acute."</i> (PCP05, Female, 73 years)	<i>"it's a different doctor I see every time and that's the biggest complaint. Every time we see a different doctor they change my medications, whereas we're the only constant people at clinic, we're always there."</i> (HCP16, Female, Renal specialist nurse)
	Allocation of work & decision-making	• Individual capacity and preferences • Role allocation • Decision aids	<i>"Generally speaking, one will go along with the best expert opinion, unless it conflicts violently with some other understanding that you have."</i> (PCP07, Male, 91 years)	<i>"Maybe you might not say it immediately and talk about all the long-term implications because potentially you have a patient who's got more than enough on their plate already, and you're just trying to give them enough information that's useful but not overwhelms them."</i> (HCP08, Female, GP)

	NPT Category and sub-construct	Description/examples	Supporting quotes	
			Patients	HCPs
	Impact of individuals' contexts & interactions between healthcare systems & individuals	- Individual context - Healthcare system - Time and resources - Acute versus chronic problems	<i>"any decision like referring you to a kidney specialist in Glasgow, means that I have to go to Glasgow. It's another burden on my planning day-to-day activities, and you've got to understand that as well, and someone here to say 'That's it, as far as I'm concerned. I'm not doing that.'"</i> (PCP07, Male, 91 years)	<i>"the time aspect of that is that you need time to deal with every aspect of someone's care and all the different conditions if there are other things that are a priority at that particular patient contact"</i> (HCP08, Female, GP)
Reflecting & appraising work required to understand CKD/kidney failure and making shared decisions in multimorbidity /frailty: Reflecting and evaluating the role of KFRE/risk prediction models in discussing kidney failure risk and shared decision-making	Finding information about CKD, kidney failure or impact of multimorbidity/frailty	- Information sources - Artificial Intelligence - Personal preferences - Health literacy - Interpretation of information - Information relevant to multimorbidity/frailty	<i>"I know I shouldn't do but I Google an awful lot [laughs] just to find out things when I need to."</i> (SCP10, Female, 63 years) <i>"I think it's really important that you've got a doctor that can put it in the layman's terms, because there's a lot of words round about the kidneys that you know I don't understand, so it's putting it to a level of terms and then I know what's happening, so."</i> (SCP05, Female, 63 years)	<i>"We used to use a lot of third sector information and resources as well for national kidney charities and things, or signpost patients to a lot of their websites and things, Kidney Care UK, we use a lot of their leaflets about and their website's good isn't it because you can change the language as well for patients."</i> (HCP15, Female, Renal specialist nurse) <i>"you might get a different opinion about how bad your CKD is from a diabetes specialist, from an ophthalmologist, from a cancer specialist because the thresholds and the boundaries of what is important with respect to your kidney function is different depending on the"</i>

NPT Category and sub-construct		Description/examples	Supporting quotes	
			Patients	HCPs
				<i>disease process and the treatment plan.</i> " (HCP10, Female, Renal consultant)
	Review of decisions made with HCPs/support networks	• Reflections and reviewing decisions • Monitoring (kidney function, KFRE) including awareness of kidney function & feedback mechanisms • Impact on quality of life	<i>"the other thing I do is when you come back with information, I tend to look up more about it and do more background research on it... So that I can understand it and then provide more support and help for mum if she needs it."</i> (PCP08 relative, Female)	<i>"you can't sense a lot of the problems that concern us prognostically, you can't sense what your proteinuria is doing or your eGFR or often your blood pressure. And you're much more concerned about something that may even be unrelated to your renal disease which blights your life."</i> (HCP05, Female, Renal consultant)
	Evaluating what is important to the individuals	• Individual priorities • Ageing and changing over time • Utilisation of resources • Differences in patients versus HCP focus • Self-care	<i>"I'm 65 this year, so I'm getting older, and as you get older, I'm going to get more issues... I'm here for a reason because I don't feel fine, how are we going to deal with it? Don't disregard it, just, let's- the more systems we have, I think the more systems you have in place just now, then you're reducing your need for operations because it's something you can deal with there and then. You can say, right, just by changing something, that's going help you, so that would work better for me."</i> (PCP10, Male, 64 years)	<i>"I think I always find the reason why that's important, the reason why we care about that, and we know what the implications of that could be and also the connection to other disease processes or illnesses they might have. Particularly where it can be asymptomatic for quite a period of time so to try and explain to someone if it's not something they're not feeling, what's going on and why we're bothered about it."</i> (HCP08, Female, GP)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
Modifying decisions & discussions based on reflections	- Reviewing and adjusting decisions - Seeking specialist or MDT care	<i>"I went to the hospital, and they took more blood and then they kept the treatment liaising between the hospital and the doctor (GP) where I had to go to the doctor and they kept monitoring me."</i> (PCP04, Male, 75 years)	<i>"we can contact secondary care for advice. It's not necessarily if we want their advice-based referral, but not necessarily this person needs an appointment because they're the people that are often really good at offering, and they're really helpful and they are very accessible."</i> (HCP08, Female, GP)
Uncertainty	- Awareness of CKD - Symptoms - Prognosis and trajectories - Which LTC is causing the problem and interaction of different LTCs - Predicting risk of kidney failure - KFRE (reducing uncertainty) - Decision-making - What kidney failure might entail - Functional status - Death and dying	<i>"I just wished somebody would tell me what was wrong with me."</i> (SCP12, Female, 73 years) <i>"I think that's probably a good tool (KFRE) for them. It's good for me to hear how they're assessing it when they say, 'This is-' It's not just a doctor looking at you going, 'Hmm, haw,' see what they think, but, 'I'm checking you on a standard basis,'"</i> (PCP12, Male, 73 years)	<i>"it's living with uncertainty as well isn't it and it's not exact prognostication that they can give, there's so many variables for people."</i> (HCP15, Female, Renal specialist nurse)
Prioritisation of CKD	- Symptoms/asymptomatic - Other LTCs (priority or perceived as more life threatening)	<i>"They all play a part. But probably my heart because that's the biggest thing. That's your biggest organ, isn't it. Maybe it's</i>	<i>"because symptomatically they're not particularly bad and the fact that they've got urine analysis that has their blood and protein, but they feel okay or</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
	- Existing knowledge of the kidneys and CKD - Awareness of having CKD - Competing risk of death more likely than reaching kidney failure - Prevention over cure	<i>no the biggest organ in your body, but it's the most important one."</i> (SCP03, Male, 58 years)	<i>their focus is on something else, it's not picked up."</i> (HCP14, Male, Renal specialist nurse)

Understanding and sense making

Patients reported variable levels of understanding of kidneys, CKD and kidney failure, and HCPs perceptions of patients' knowledge were congruent with this. For many patients, CKD was a confusing concept and was often dominated by other long-term conditions. HCPs also recognised that CKD was frequently not a priority in patients' lives and that the terminology of "Chronic Kidney Disease" made comprehension difficult, causing worry for individuals, and they acknowledged the consequences of limited understanding for self-management, perception of health status and risk of kidney failure as well as being a barrier to engaging in shared decision-making.

Understanding the kidneys and CKD

Patients and HCPs described challenges in making sense of CKD in the context of multimorbidity and/or frailty. Variable levels of understanding of kidneys, CKD and kidney failure risk were described by patients but with a desire to better understand these alongside other long-term conditions, with a particular focus on what they could do to help their kidneys.

"...so I don't know what else I can dae to make them any better apart fae keep taking the medicine."

(SCP04, Male, 76 years)

Many individuals lacked awareness or expressed surprise at having a diagnosis of CKD, a point that was also acknowledged by HCPs.

"I had no idea that I had a problem so I have no idea how it functions with anything else. I really have no idea at all."

(PCP02, Female, 84 years)

Additionally, HCPs emphasised that the asymptomatic nature of CKD may play a factor in awareness of diagnosis and understanding its importance. There was a lack of consensus relating to the optimal time in the patient journey to discuss kidney failure and HCPs felt that a lack of awareness of having CKD was also a limitation in patients' understanding and knowledge of kidney failure.

Considering what it means for the individual

Patients differed in how they integrated CKD into their self-understanding. Some dismissed it, often reflecting that they were never told about it or that other long-term conditions occupied their attention, whilst others expressed anxiety about its implications in day-to-day life, independence, or mortality. Living with multimorbidity or frailty complicated sense-making, with individuals often prioritising other conditions or scenarios that they viewed as more immediately threatening. For some individuals, this sense of competing conditions extended to feeling overwhelmed by the complexity of their health problems and that they were regarded as “too complicated”, leaving them feeling dismissed, overlooked or abandoned by healthcare professionals and the healthcare system. HCPs also acknowledged that CKD was often not a priority in healthcare interactions, especially if other conditions were causing acute problems. In Primary care, focused chronic disease education, particularly for practice nurses, also appeared to be lacking in the curriculum or continuous professional development education.

“It’s a second level diagnosis. You know if you had an MI, if you had a stroke... if you’ve got diabetes, these are the kind of top-level ones... even hypertension, I think almost has got a higher billing than CKD, even though they’re both asymptomatic.”

(HCP18, Male, GP)

Understanding the impact on support networks

Family members or social support networks often played a key role in helping patients interpret and manage kidney disease, sometimes acting as advocates in

discussions with HCPs. However, some individuals deliberately withheld information from their support networks to avoid worrying friends or family members.

“I think if my family was involved they would be saying, don’t do this, don’t do that... But no, I wouldn’t let them be involved.”

(PCP16, Female, 74 years)

HCPs commonly highlighted the role of involving family members particularly in facilitating shared decision-making, especially in frailty or more complex situations, but also observed challenges when family members had different priorities from patients or in the presence of language or cultural barriers.

“I think it’s really positive when family are there because often they will be able to remember a lot more additional details than the patient can on their own. But...when family cut across and don’t give an accurate account of what they’re experiencing and stuff, then that’s really challenging so it’s loads of positives and negatives.”

(HCP12, Female, Renal specialist trainee)

Perception and value of KFRE in shared decision-making

Many patients struggled to understand the concept of KFRE or how it could be used. For those who did understand KFRE, they saw it as potentially useful in giving a clearer picture of risk, likening it to a “warning light”. However, concerns about accuracy and uncertainty were common. For some, the idea of using KFRE scores provided reassurance that their condition was being monitored using a range of factors.

“that tool would allow people to talk, it flags up earlier lights, that’s not right, that’s not right, his blood pressure is...”

(PCP10, Male, 64 years)

HCPs valued KFRE as a tool for standardising communication and supporting referral decisions, but raised concerns about workload, integration within clinical systems and whether it captured the complexities of multimorbidity and frailty.

“There are so many guidelines, and people get in a system of what they use for each thing. And I don’t think the KFRE has sort of gone into primary care yet, and it’s not become routine practice and it’s just that it needs to be embedded.”

(HCP03, Female, GP)

Workload/burden and roles in understanding and making decisions

Managing CKD in the context of multimorbidity or frailty required considerable “healthcare workload” or burden for individuals and their networks. Engagement with support and HCP networks varied dependent on individual factors including their priorities, needs and contexts.

Workload involved

Patients described a range of healthcare related workload relating to living with CKD and multimorbidity and/or frailty including remembering appointments, arranging blood and urine tests, managing medications, adapting daily routines and interpreting information from different sources, with the perception that responsibility fell mainly on patients. This was often framed as part of the broader burden of living with multiple conditions.

“I think probably you know if you have multiple health problems it’s another thing to worry about isn’t it you know but its how to manage that what changes can you make to your lifestyle or etc you know what you’d be willing to do.”

(PCP19, Female, 64 years)

The emotional workload of living with kidney disease alongside other health problems was described and some individuals indicated self-blame for developing kidney disease or for declines in their kidney function.

“every time they asked me for a urine sample I kept saying I’d get it to them later, I’d get it to them later and that went on for a long time, you know. So if I had of put a urine sample in sooner it would have been detected”

(SCP05, Female, 63 years)

HCPs were aware of the emotional impact and worry that discussing CKD and kidney failure can have on individuals, influencing communication and timing of conversations with patients. Narratives from HCPs demonstrated that there was often an assumption that patients would not want to know, in part due to the perceived emotional workload.

“there’s always a balance of worrying people and giving them information...I suspect in primary care people don’t get as much information as they could. Whether they should or not I don’t know, because we try to personalise information for what we think’s helpful to people, and a lot of people with multimorbidity and frailty have so much else going on.”

(HCP03, Female, GP)

Understanding and engaging with others

Engagement with HCPs and support networks shaped patients’ experiences. Preferred sources of support e.g. GP, practice nurse, renal specialist nurse, kidney doctor, family member etc was diverse and personalised. Patients and HCPs highlighted nursing roles and non-medical allied health professional roles as

preferred HCPs for patients to seek advice and direct questions to, in addition to members of individuals support networks acting as advocates and asking/interpreting knowledge for patients.

“(My wife) comes with me because... my hearing’s bad- even with the hearing aids in. So, she goes with me and then she understands a lot of the medical jargon I wouldn’t understand, you know, so she’s my support”

(PCP13, Male, 81 years)

Patients from both primary and secondary care settings emphasised the need for clinicians to listen to and respect their concerns. HCPs acknowledged these dynamics, noting that engagement depended on trust, health literacy, “workload”/burden of engagement and patients’ preferences for involvement in understanding their health and making associated decisions.

“I do think that we struggle to impart the information to people who have got poor health literacy and people who don’t speak English as their first language.”

(HCP04, Male, Renal consultant)

Determining roles and decision appraisal

The shift in culture of decision making from HCP driven to shared decision-making was most apparent in discussions with HCPs.

“they want to feel that they’re part of the discussion. But they’re very much wanting you to give your opinion on what’s the best line to go down...”

(HCP12, Female, Renal specialist trainee)

Patients’ roles varied in how much they wanted to participate in decision-making and appeared to be influenced by societal expectations, trust/relationship with

HCPs and understanding of decisions. Deciding whether choices were “the right thing to do” often involved reflections with others, commonly family members, but also included comparison to others.

Barriers and facilitators

Barriers to shared decision-making included limited understanding of CKD, communication challenges, cultural differences and the complexity of multimorbidity/frailty.

“...The doctor I’ve seen this morning, he talked me through what I could understand...It’s all double Dutch to me.”

(SCP04, Male, 76 years)

Facilitators included continuity of care, strong patient-HCP relationships. shared decision-making was much more commonly described in situations where individuals perceived the decisions as being “bigger” such as decisions relating to KRT or need for invasive investigations/interventions such as renal biopsy, as well as in situations where individuals disagreed or felt uncertain about management decisions being proposed.

No patients had heard of the KFRE prior to participating in the study and there was limited awareness of KFRE or its integration into clinical guidelines by primary care HCPs. Patient participants were offered calculation of their KFRE score as part of participation in the study. Individuals who chose to proceed with this found discussions useful and reassuring. These reflections emerged in unrecorded post-interview discussions with the researcher and are therefore not part of the formal qualitative dataset but provide relevant contextual insight.

Additional barriers to the use of KFRE included lack of system integration, additional HCP workload, lack of urine albumin-creatinine ratio (uACR) results and difficulty in discussing and communicating risk with patients.

“I think the assumption is that you know what it (CKD and KFRE) is. But I think it's just you maybe find out through talking to other patients and things as much. Probably the doctors know much more, but they think that you probably know much more... I think it's just the professionals have a knowledge way beyond you and assume that even the basics you know.”

(PCP16, Female, 74 years)

Interactions and relations in understanding and shared decision-making

The presence of multimorbidity, frailty and interactions with healthcare systems and support networks shaped understanding of CKD and kidney failure risk and decision-making.

Impact of multimorbidity or frailty

Patients reported that they often prioritised other conditions over CKD, with kidney disease progression or kidney failure risk perceived as abstract until symptoms emerged. Frailty and ageing shaped expectations, with some individuals expressing acceptance of declines in health and functioning and acknowledgement of the inevitability of death.

“I’m basically disinterested, because I realise at my age things are going to go wrong. So, they’re bound to go wrong. But I’m perfectly happy the way I am at the moment, I don’t feel as though I’ve got any kidney problems.”

(SCP02, Male, 86 years)

Contrary to this, many HCPs felt that death was not something the patients often contemplated or were open about discussing. HCPs acknowledged the challenges of addressing kidney failure risk, including how best this should be communicated and at what time point in an individual’s journey. Context, complexity and individual capacity were again important in patients’ abilities to deal with and engage in discussions about kidney failure and risk. These difficulties were compounded by

healthcare systems largely organised around single-disease or single-organ models of care, which were recognised as contributing to fragmented care and a barrier to holistic, person-centred care.

Role of relationships

Trust and continuity in care were central to shared decision-making. Patients valued HCPs who understood their broader health and social context but varied in whether they felt primary care, secondary care, or a mixture of both were most important in understanding CKD in the context of multimorbidity or frailty. This was also acknowledged by HCPs.

A recurring reflection among both patients and HCPs was comparison of the current NHS system with how it functioned in the past. Negative sentiment was expressed in relation to perceived reductions in resources, time and continuity of care, including the lasting impact of the COVID-19 pandemic on service capacity. Participants felt this had eroded the systems that support effective shared decision-making.

"It's not a lack of caring or a lack of care; it's just a new system that I don't think works terribly well as far as patients are concerned." (PCP15, Male, 85 years).

This context shaped the relational dynamics that participants described, including the value placed on continuity of care and the difficulties that arose in its absence.

Allocation of workload and decision making

On a collective level the workload of understanding and shared decision-making was shared between patients and HCPs and tailored to individuals' capacity and preferences. Patients described relying on clinicians to guide decisions when they lacked knowledge, felt uncertain about decisions or if decisions were complex, and

they often trusted HCPs to make the right decisions for them or conveyed preferring a passive role in decision making.

“basically if a doctor gives me medication for any illness I just take it and hope for the best.”

(SCP04, Male, 76 years)

Navigating complex healthcare systems and explaining long-term conditions and treatments to others were areas of workload where patients felt increased responsibility and pressure.

Decision aids (formally recognised shared decision-making tools) were not commonly used by HCPs or encountered by patients in the context of CKD or kidney failure decision making. When prompted, HCPs expressed that decision aids were often perceived as rigid and lacked individualisation. Patients expressed a preference for preferring verbal communication relating to decisions over written or paper-based decision aid tools. The limited role of decision aids in shared decision-making in this population is an important finding, given their potential utility in guiding complex decisions.

Impact of context and interactions

Healthcare system level factors shaped patients' experiences, including difficulty accessing appointments, fragmented care (both within secondary care and between primary and secondary care) and limited resources. Acknowledging that provision of holistic and person-centred care often required extra time, knowledge outwith their remit or extra resources, HCPs identified that the healthcare system was not set up to optimally care for individuals with multimorbidity and that uncertainty around trajectories of health conditions also complicated this.

Recognition was given, by both HCPs and patients, that acute healthcare problems appeared to be given priority in access to care and chronic problems often felt ignored or forgotten.

“it’s quite a usual scenario where the patient will have had an incident whether cardiac or diabetic (a) couple of years previous(ly), where their kidney function at that point would have been 40%, but because it wasn’t particularly troublesome and the main focus was something else.”

(HACP14, Male, Renal specialist nurse)

Reflecting on and appraising the workload required for understanding and shared decision-making

KFRE implementation is not yet part of standardised care and practice within the area the study was conducted. Participants, both patients and HCPs, reflected on the role KFRE may play in discussing kidney failure risk and shared decision-making, as well as appraising the workload and processes required to understand CKD, kidney failure and making shared decisions in the context of multimorbidity or frailty.

Finding information about CKD, kidney failure or the impact of multimorbidity/frailty

In advance of consultations, following discussions or to better understand symptoms, patients often sought information from multiple sources including third sector organisations (charities or kidney societies), online resources, support groups, speaking to peers or discussions with HCPs.

“I know I shouldn’t do but I Google an awful lot [laughs] just to find out things when I need to.”

(SCP10, Female, 63 years)

“We used to use a lot of third sector information and resources as well for national kidney charities and things, or signpost patients to a lot of their websites and things, Kidney Care UK, we use a lot of their leaflets about

and their website's good isn't it because you can change the language as well for patients."

(HCP15, Female, Renal specialist nurse)

Individual preferences and health literacy again influenced information seeking behaviours, with some actively researching CKD and other long-term conditions, whilst others avoided information. Consequently, questions and misinterpretation or misinformation often existed in patients' knowledge and understanding of CKD, kidney failure and the concordances/discordances with medications or other long-term conditions.

"is it just the one kidney, is it both kidneys? You know, that kind of information would help as well because as you say you can go without one kidney, you cannae go without both of them"

(SCP09, Male, 73 years)

HCPs gave examples of reputable, or NHS endorsed resources that they sign-posted patients to, some of which had additional benefits of being available in non-English language, which was one barrier cited to understanding CKD, kidney failure risk and shared decision-making. Additionally, HCPs highlighted difficulty in finding information or support that was individually tailored or specific to people with multimorbidity or frailty. Of particular interest, artificial intelligence was discussed by HCPs as both a promising and challenging opportunity for individuals to be able to understand CKD in the context of multimorbidity.

Review of decisions made

Decisions made were commonly evaluated with family, friends or HCPs; with changes in symptoms or test results playing a significant role in appraisal of decisions. The impact of decisions on quality of life was a central consideration for patients.

Monitoring and having an awareness of kidney function level or eGFR was of importance to individuals, to allow understanding of the trajectory of their health and assessing impact of treatments, medications or changes in lifestyle. However, individuals, particularly in primary care, found it difficult to have these results fed-back to them. Whereas processes in secondary care were clearer including the use of health records accessible to patients (40) or individualised communication from HCPs with test results.

Evaluating what is important to individuals

Kidney health and related decisions were often weighted against other life priorities, including independence, quality of life, and impact on family. A key priority for patients was again what they could do individually to help their kidneys and other long-term conditions. Again, importance and urgency were often given to the condition(s) perceived to be the most life threatening or to be causing a large symptom burden.

For older individuals, justice and ensuring fair use of resources was commonly discussed with participants expressing awareness of their age, previous use of healthcare resources and perceptions that resources may be utilised by other individuals who could potentially benefit more from them.

HCPs acknowledged that there were often differences in patient and HCP priorities in healthcare encounters, with patients prioritising symptoms and HCPs focusing on measures such as blood pressure or kidney function.

“I think the patients understandably are sometimes more focused on symptoms than numbers and as a nephrologist, you’re focused a lot on the numbers. So, for example, we might be more concerned about the blood pressure levels that they have, whereas the patient might be more concerned about the fact that they’ve got cramps or itch. So I think there’s sometimes a disconnect there.”

(HCP12, Female, Renal specialist trainee)

Modifying decisions and discussions based on reflections

Adjusting to decisions over time as health status, priorities or experiences changed was described by both patients and HCPs. HCPs promoted individuals to re-evaluate decisions if they noted significant change in functional status and to reflect on their individual priorities particularly if they had more advanced frailty or a large burden of other long-term conditions.

“I have patients that have been focused on their (kidney) function, their percentages and when they’re getting near the end of their life I’m trying to steer them away from worrying about those factors and just focusing on how they are and how they’re feeling.”

(HCP15, Female, Renal specialist nurse)

Examples of personalised care and shared decision-making in primary care aligned to seeking specialist and multidisciplinary team guidance or assessment and in secondary care mainly related to KRT decisions.

Additional overarching themes beyond the NPT framework

Two overarching themes emerged that spanned multiple constructs and shaped how patients and HCPs interpreted and understood CKD, kidney failure risk and use of KFRE. These were 1) Uncertainty and 2) Prioritisation of CKD. These additional themes emerged across the NPT-informed framework and provide additional insights into how multimorbidity and frailty influence sense-making and shared decision-making. These themes are represented visually in Figure 1, which depicts them as a cross-cutting influences on other domains of the framework.

Uncertainty

Uncertainty was pervasive, encompassing prognosis, the meaning of symptoms and the role of CKD relative to other long-term conditions. Patients frequently described difficulties in predicting what CKD meant for their future, particularly in

the absence of symptoms. For many, not knowing whether a symptom was attributable to CKD or another long-term condition compounded feelings on confusion.

“I just wished somebody would tell me what was wrong with me.”

(PCP02, Female, 84 years)

Concerns and questions relating to what kidney failure might entail were often raised. Several participants inquired about what they should “look out for” as signs that kidney function was worsening and whether there were things they or HCPs could have done differently to prevent CKD. Uncertainty also stemmed from individuals being unaware they had CKD or it being mentioned incidentally, leaving them feeling helpless and wary of communication and healthcare services/professionals. Additionally, patients often described a sense of powerlessness, with CKD progression, multimorbidity and frailty being perceived as largely outside of their influence. However, some sought clarity about self-care actions they could engage with as a way of regaining a degree of control. This highlights both the importance of timely, transparent communication and the potential value of supporting patients with self-care strategies and autonomy that can foster a greater sense of agency in the face of uncertainty.

“I’ll just be ticking along. Until I discover that my kidneys are failing. If I can avoid dialysis I would want to avoid that, but obviously for a start I am not in control of that. I don’t know is there anything else that you can do to try and make your kidneys healthier?”

(SCP12, Female, 73 years)

KFRE was perceived by some HCPs as providing reassurance that formal assessment and risk evaluation had been performed when interacting between HCPs. However, uncertainty existed in how KFRE and risk of kidney failure should be communicated to patients. Specifically, relating to if this information would be useful or add

additional anxiety or complexity to discussions, that individuals would not meaningfully understand.

HCPs acknowledge that even when predicting risk of kidney failure whether that be with eGFR trajectories or KFRE scores, there was a large volume of uncertainty that remained and that conveying this uncertainty to patients whilst also enabling them to make shared decisions was a delicate balance.

“I show them a graphical representation of where I think their kidney function (eGFR) might be going and I show most patients in clinic to guide the discussions. And sometimes if I have time I kind of bring up the hypothetical things that might change in the future in terms of this is what we might be doing in terms of medications in the future, this is what we might be doing for blood pressure to let them know that this is a dynamic situation that might change.. I just think it’s like a hypothetical concept people can’t grasp.”

(HCP12, Female, Renal specialist trainee)

Prioritisation of CKD

The extent to which patients prioritised CKD varied, but many patients (particularly those in primary care) described it as a secondary concern compared with other long-term conditions or frailty related challenges. The largely asymptomatic nature of CKD contributed to this perception, with a surprising number of patients being unaware they even had the condition until they received the letter of participation for this study. Long-term conditions perceived as more imminently life-threatening, such as cardiovascular disease or cancer, were given more weight by patients in how they thought about their health status.

“They (patients) don’t seem as worried about their kidneys compared to their heart or their lungs, that seems to be their main priority.”

(HCP19, Female, Practice nurse)

In several cases, death was considered more imminent than kidney failure, acknowledged by both patients and HCPs, reducing the salience of CKD in personal health priorities. Patients often expressed this more frankly and openly whereas HCPs described conveying the message that individuals were unlikely to reach kidney failure in their lifetime without directly mentioning death.

Existing knowledge or prior experiences influenced prioritisation. Patients with existing awareness of kidneys or relationships with someone who had experienced kidney disease were more likely to give weight to CKD as a concern or priority. The prioritisation and awareness of CKD may compete with the ability to make shared decisions or to discuss kidney failure risk and may influence how risk information is processed and acted upon.

Discussion

Main findings

This study identified five interconnected, key factors influencing understanding and perceptions of CKD, kidney failure risk and shared decision-making in the context of multimorbidity and/or frailty (Figure 7-1), each relevant to both patients and HCPs but experienced differently across the two groups: 1) Variable knowledge and understanding of CKD, with many patients unaware of their diagnosis or lacking clarity about its implications and HCPs acknowledging gaps in education and recognising challenges in addressing patients knowledge/awareness of CKD in time-pressured consultations or where competing priorities exist; 2) The workload and burden required to live with and manage CKD alongside other long-term conditions and/or frailty, encompassing cognitive, practical and emotional demands for patients and competing clinical priorities, uncertainty and complexity for HCPs; 3) Relationships and interactions between individuals, HCPs, the healthcare system and support networks, where trust and continuity were important facilitators in shared decision-making for both groups and their absence a shared barrier; 4) Context and priorities, including relative prioritisation of CKD by patients and HCPs, with other more symptomatic problems or conditions perceived as more life-threatening being a more prominent concern and 5) Pervasive uncertainty, encompassing prognosis, attribution of symptoms, the role of KFRE, consideration of death as a more prominent risk and when or how to discuss kidney failure risk, experience by patients as uncertainty about their own futures and by HCPs as uncertainty about the timing and framing for these conversations.

KFRE was largely unknown to patients and, notably, to primary care HCPs. Amongst secondary care HCPs, awareness was more common, and some identified potential value in KFRE as a tool to standardise discussions and referrals. However, this was balanced with concerns and uncertainty about how numerical risk estimates should be communicated to patients, particularly those with multimorbidity or frailty, where competing priorities may make abstract prognostic information difficult to

interpret. However, in contrast, patients voiced a desire to discuss kidney failure risk, particularly if information can be contextualised within their lived experience, citing this may provide reassurance or offer a sense of preparedness should kidney failure become a likely event. In addition, individuals who chose to have their KFRE score calculated, as part of study participation, found discussions useful. This suggests that while HCP views on KFRE were nuanced, patient receptivity may be greater than that assumed by HCPs.

Barriers to implementation identified by both patients and HCPs included limited awareness of KFRE, lack of integration in clinical practice and IT systems and challenges relating to communicating risk, especially in the context of multimorbidity or frailty, where competing priorities and complexity complicate conversations.

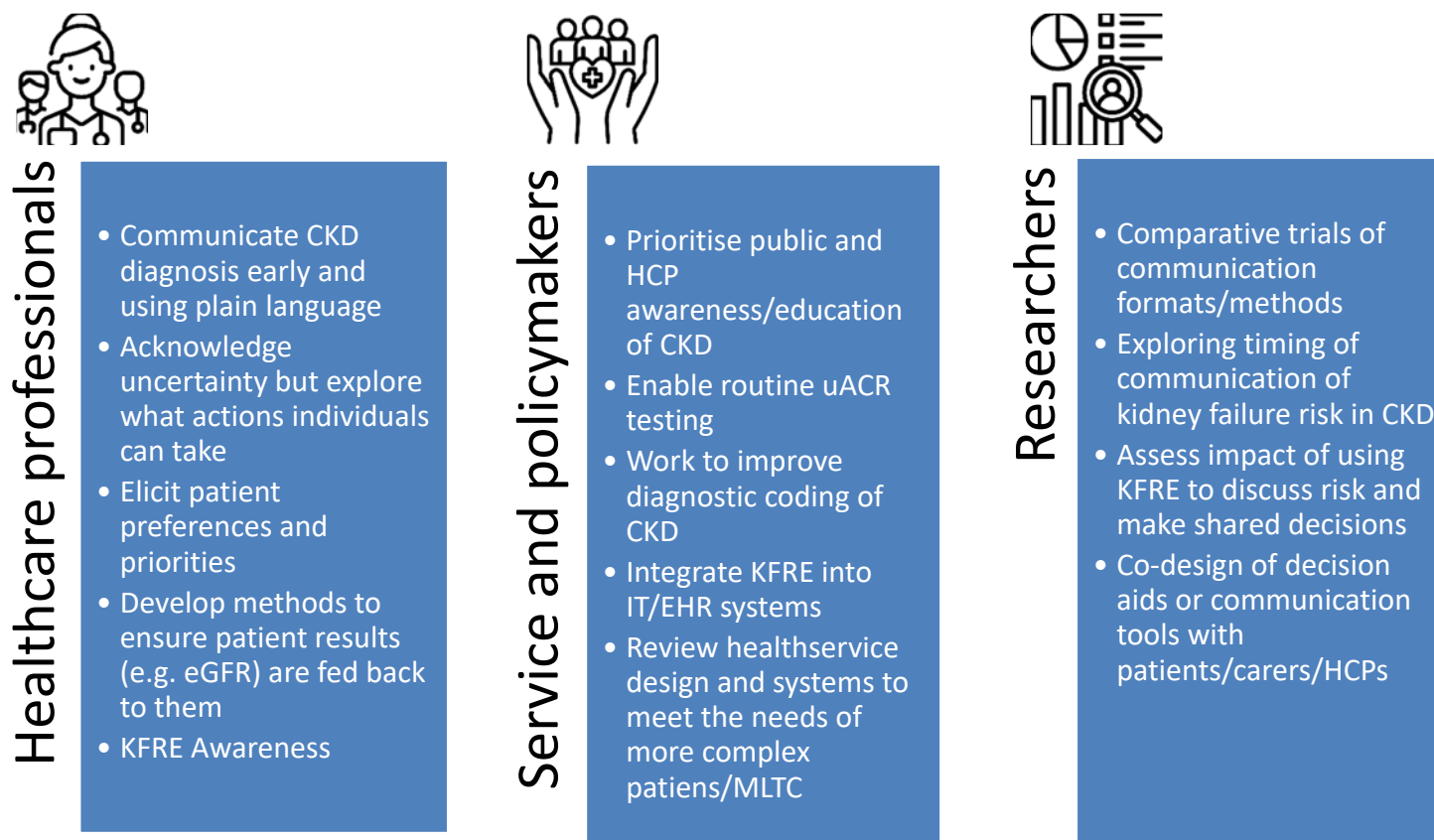
Our findings reinforce prior work showing that CKD is often “invisible” to patients until advanced stages^{326, 327}, with individuals frequently not recalling being told about CKD or having difficulty making sense of its implications³²⁸⁻³³⁰. Prioritisation of long-term conditions or treatments aligns with studies that have explored self-management⁹⁴ and treatment burden in multimorbidity⁹⁴. These studies have shown that patients often prioritise certain conditions over others based on factors such as symptom severity, perceived control and impact on daily life. Morris et al. found that individuals’ priorities may shift over time as their context, circumstance or health status changes⁹⁴. The systematic review of qualitative data exploring treatment burden in multimorbidity⁹⁴ found that patients prioritise long-term conditions to improve their capacity to manage treatment burden and workload associated with multimorbidity, particularly deprioritising conditions or treatments that they feel are less important or that do not result in observable changes in their conditions. In keeping with existing evidence, our findings also demonstrate how clinical uncertainty and decisional conflict complicates shared decision-making in multimorbidity and frailty^{331, 332}, particularly where single-organ or disease guidelines are not easily applicable or translated to patients with complex or nuanced needs^{195, 333}. Uncertainty is not unique to CKD, with substantial existing research across chronic illness and multimorbidity consistently

describing factors such as prognosis, unpredictable trajectories, reliability of evidence/treatments and complexity contributing to emotional workload and complicating shared decision-making³³⁴.

Our findings show that KFRE may mitigate some uncertainty for HCPs, but that communication of risk or discussing kidney failure in the absence of more severe CKD or symptoms is likely an abstract concept and may not align with patients' priorities. Existing research exploring the clinical use and implementation of KFRE in CKD care has demonstrated potential benefits for guiding referral and care delivery decisions^{274, 318-320, 335}, but has also raised concerns regarding changes to care for individuals with lower "risk" and capacity for CKD care to be delivered in primary/community care settings^{319, 320}. A recent mixed-methods study in US nephrology clinics found that integrating KFRE scores into electronic health records resulted in varied uptake of its use, with differing views on its value and practical implementation³³⁶. Our study extends this evidence by highlighting how multimorbidity, frailty and competing health priorities shape whether risk communication and information is perceived as meaningful, helpful or potentially burdensome. We also identified conflicting opinions between different HCP roles about the value of KFRE as a tool to guide care and referral, and whether providing a specific numerical estimate of kidney failure risk was something that should be discussed with individuals, including how and when such conversations should occur. This remains an underexplored, potential use for KFRE in clinical practice, although studies have explored how other prognostic models, such as cardiovascular risk calculators, are used to communicate risk in an NHS setting³³⁷. In keeping with the findings in this study, they demonstrated that while risk calculators can support structured conversations around risk and lifestyle modifications, HCPs were uncertain about how to explain numerical risk estimates or to adapt conversations to patients' health literacy, leading to variability in how risk information was shared and how it was interpreted and understood by patients. An ongoing cluster randomised control trial in Canada is currently studying the implementation of KFRE into primary care settings as a tool that is used by both patients and HCPs³³⁸ and will provide further evidence on its application in clinical care.

The findings of this study have strong implications relating to clinical practice, education and health policy. Key suggested priorities from the research are summarised in Figure 7-2. Firstly, greater emphasis is required on public and professional education to raise awareness of CKD as an important, largely preventable chronic disease, with significant associated health risks. Secondly, strategies for communication and shared decision-making must be tailored to individual preferences and contexts, focusing on their needs and priorities. Consideration should be given to healthcare system design and resources to best support a population living with multimorbidity and frailty. Focus is required to improve routine albuminuria testing in the community and primary care, to support earlier diagnosis, intervention and KFRE use. Related to this, the role of diagnostic coding also warrants attention, as formal coding of CKD can influence patient outcomes³³⁹, whether patients are informed of their diagnosis, albuminuria testing³⁴⁰ and the feasibility of KFRE calculation/use to guide care; important considerations for both research and policy. Finally, further research is required to explore effective methods of communicating and discussing risk with patients in CKD¹⁹⁶. Specifically, comparing formats of communication e.g. numerical formats (e.g. odds, percentage risk), visual aids/representations (e.g., trajectory graphs, icons, traffic-light stratification, risk ladders) and time horizons (e.g. specific time points 2- vs 5- years, time to event, short/medium/long term risk) as well as when in the CKD pathway these discussions should occur (e.g., at diagnosis, during key changes in eGFR/uACR trajectories, or when competing multimorbidity/frailty priorities change) and by which HCP/healthcare setting. This is particularly important in populations with multimorbidity or frailty where additional challenges including treatment burden and competing priorities may alter how risk is perceived or how it influences decision making.

Figure 7-2. Key priorities emerging from the study for healthcare professionals, policy and researchers



Strengths and limitations

Strengths of this study include that it was underpinned by the middle-range theory, NPT, to guide analysis, it involved the inclusion of patient and HCP perspectives across primary and secondary care, as well as the involvement of PPIE contributors in the design and interpretation of the study. The sample included diversity in deprivation levels, gender, age, occupation and number of long-term conditions. Although the study was in depth and conducted robustly, it was limited to a single geographic region in the UK. A critical limitation of this study is that all 31 patient participants were of white ethnicity. Glasgow is the most ethnically diverse local authority in Scotland, with approximately 19% of its population identifying as belonging to a non-white ethnic group, with Pakistani being the largest single minority at around 5%³⁴¹. Despite purposeful efforts to recruit a diverse sample, no non-white participants were successfully recruited. The modest proportional size of any individual minority ethnic group, alongside potential recruitment barriers described earlier (language requirements, likely under-coding of CKD in minority ethnic groups, and potential mistrust of healthcare services), likely contributed to this. The findings, including perspectives on risk communication, trust in healthcare relationships, and priorities around CKD management, should therefore be considered applicable primarily to white, English-speaking patients with CKD. No inference can be drawn regarding the perspectives of culturally and linguistically diverse patients, who may face additional or qualitatively different challenges including language barriers, differing cultural frameworks for understanding illness and risk, and potential inequities in access to and quality of CKD care. Future research must explicitly prioritise the inclusion of ethnically diverse populations in qualitative CKD research, using culturally adapted materials, inclusive recruitment strategies and the option of non-English language interviews. Additionally, there was difficulty identifying frailty in medical records, due to it being poorly coded, subsequently only a single participant at the time of interview was experiencing severe frailty (clinical frailty score 7 - severe frailty) and around one third were living with mild frailty (eight vulnerable (clinical frailty score 4) and two moderate frailty (clinical frailty score 5)), potentially limiting the applicability of the findings to individuals with more significant frailty. The findings are therefore most applicable to

individuals with CKD and multimorbidity; the experiences and perspectives of individuals with significant frailty require further dedicated research using purposive methods to identify formally frail participants. Potential bias may have been introduced in data collection and interpretation. We acknowledge that our clinical experience and professional backgrounds may have influenced data collection and interpretation. Secondary care patient participants may have met and been cared for by the researcher conducting the interviews and some HCPs were known to the researchers through clinical and academic activities. A number of steps were taken to enhance reflexivity and minimise potential bias or assumptions. These included the piloting of topic guides, ensuring participants were explicitly informed of the aims of the research to emphasise that the intention of the research was to understand their perspectives, experience and viewpoints and ensuring participants were informed of the researchers' role and background at the start of the interview/focus group to support transparency. Additionally co-analysis and code checking of a sub-set of transcripts by a second researcher, and the recording of reflexive and field notes throughout the study reduced the risk of bias in the interpretation of the data.

Conclusions

Many people living with CKD are unaware of the diagnosis or view CKD as a lower priority compared to other conditions. They typically want to better understand CKD and kidney failure risk alongside other health problems. Uncertainty and prioritisation of competing health problems shapes experiences of communication and shared decision-making. Relationships and interactions between individuals, HCPs, health systems and support networks are important, complex and vary by individual contexts. However, fostering trusting relationships, continuity and recognition of individual priorities are key to facilitating shared decision-making. Our study highlights the potentially useful role of KFRE in clinical practice, but further work is needed to ascertain how to best communicate risk and uncertainty with patients. Our findings provide insights into how an understanding of CKD and kidney failure risk can be embedded in the care of individuals with multimorbidity

or frailty. This study will inform care planning, healthcare systems and shared decision-making discussions about CKD and kidney failure in individuals with multimorbidity or frailty and other complex patient groups.

Many people living with CKD are unaware of the diagnosis or view CKD as a lower priority compared to other conditions. They typically want to better understand CKD and kidney failure risk alongside other health problems. Uncertainty and prioritisation of competing health problems shapes experiences of communication and SDM. Relationships and interactions between individuals, HCPs, health systems and support networks are important, complex and vary by individual contexts. However, fostering trusting relationships, continuity and recognition of individual priorities are key to facilitating SDM. Our study highlights the potentially useful role of KFRE in clinical practice, but further work is needed to ascertain how to best communicate risk and uncertainty with patients. Our findings provide insights into how an understanding of CKD and kidney failure risk can be embedded in the care of individuals with multimorbidity or frailty. This study will inform care planning, healthcare systems and shared decision-making discussions about CKD and kidney failure in individuals with multimorbidity or frailty and other complex patient groups.

Declarations

Ethical approval and consent to participate

Ethical approval was obtained from the West of Scotland Research Ethics Committee 3 (IRAS ID: 325848; REC reference: 23WS/0119; Protocol number GN22RE559). All participants gave written informed consent to participate in the study.

Consent for publication

All participants gave consent for the publication of the results of the study, including pseudonymised quotes from interviews or focus groups.

Availability of data and materials

The qualitative interview and focus group transcripts that form the primary dataset for this study contain potentially identifiable personal and health information and were collected under informed consent that did not include unrestricted public data sharing. Full transcripts cannot therefore be deposited in a publicly accessible open repository. Access to the anonymised dataset may be requested for legitimate research purposes, subject to review by the corresponding author and compliance with the terms of the original ethical approval (West of Scotland REC 3; IRAS ID: 325848; REC reference: 23WS/0119). Requests should be directed to the corresponding author. Aggregate data, the NPT coding framework (Table 2), illustrative quotes (Table 3 and Supplementary Table 3) and study materials (interview and focus group guides; Supplementary Texts 1-2) are published as part of this manuscript. All data generated or developed, peer-reviewed scientific publications and final PhD thesis will be archived in the University of Glasgow institutional data repository (Enlighten: Research Data; <https://researchdata.gla.ac.uk>).

Competing interests

PBM reports lecture honoraria from AstraZeneca, Pharmacomso, Bayer, Astellas, GSK, Viforpharma and Boehringer Ingelheim outside the submitted work

and research grants from AstraZeneca and Boehringer Ingelheim. HW, MKS, BDJ and KIG declare that they have no competing interests.

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For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Authors' contributions

HW, MKS, BDJ, PBM and KG were involved in the conception/design of the work. HW and KG performed data analysis. All authors were involved in interpretation of data. HW drafted the work and MKS, BDJ, PBM and KG critically revised it. All authors, read and approved the final manuscript.

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8 Chapter: 8 Discussion

8.1 Chapter summary

This chapter presents the key findings of the thesis and the results presented in chapters 4 to 7. A summary of the findings is presented for each research question, followed by triangulation of the results across the systematic review, quantitative validation studies and qualitative work. The findings are then discussed in the context of existing literature and considered in relation to the potential implications of the work for patients and carers, healthcare professionals, healthcare policy and services and future research. Finally, the overall strengths and limitations of the work are summarised, concluding with proposals for future research relating to the thesis topics and findings.

8.2 Key/Summary of findings

8.2.1 Research question 1

What is the prevalence of multimorbidity or frailty in cohorts used to develop and/or validate kidney failure prediction models for chronic kidney disease?

Research question 1 was addressed through systematic review of existing prognostic models that predict the risk of progression of CKD to kidney failure.

The systematic review¹⁹⁹ identified a large body of literature (97 studies) that report the development or validation of a vast number of existing kidney failure prognostic models for CKD (121 original prognostic models). Reporting of multimorbidity and frailty prevalence within the populations included in the studies was lacking. The prevalence of multimorbidity was reported in only two studies^{256, 257} (reported by Elixhauser Comorbidity Index⁶⁵ and Charlson Comorbidity Index⁶⁴) and frailty in a single study²⁵⁸ (using self-reported general health scores as a proxy for frailty measurement). Two additional studies reported measures that could be considered proxies for multimorbidity or frailty, with one reporting number of hospitalisations²⁵⁹ and one medications and annual hospital admission rates²⁶⁰. These findings mean that direct evidence relating to multimorbidity and frailty prevalence were largely missing in the existing literature. In contrast, reporting of specific co-morbidities were more

frequently observed, most commonly diabetes mellitus, hypertension and cardiovascular disease (in 67%, 55% and 39% of included studies respectively).

The assessment of prognostic model performance in relation to multimorbidity and frailty was absent. The single study that explicitly used a proxy for frailty (self-reported general health measure), explored associations between frailty and the risks of kidney failure and death²⁵⁸ but not how this impacted kidney failure model performance. The study highlighted, as expected, that mortality risk was higher in the group that had lower levels of self-reported health at baseline but that there was also a larger proportion of this group that experienced kidney failure compared to those in higher self-reported health groups.

The four variable-Kidney Failure Risk Equation⁹ was the most frequently validated prognostic tool (36 studies) but similarly lacked consideration of prognostic model performance in the context of multimorbidity or frailty. Finally, only 29 of the included studies (30%) accounted for or considered the competing risk of mortality, which is likely to be important in individuals with multimorbidity or frailty.

Overall, the systematic review addressing research question 1 highlighted substantial evidence gaps in the reporting of multimorbidity or frailty prevalence in cohorts used to develop or validate kidney failure prognostic models and in the assessment of model performance in the context of multimorbidity or frailty and considering competing mortality risk.

8.2.2 Research questions 2

How does the presence of multimorbidity impact the performance of the Kidney Failure Risk Equation and is it influenced by the competing risk of mortality?

Research question 2 was assessed through quantitative analysis across large European population-based and research-based cohorts²⁰⁰ (SCREAM and UK Biobank respectively) to validate the four-variable KFRE in individuals with and without multimorbidity and in multimorbidity cluster sub-groups, across two- and five-year time horizons.

Multimorbidity was common in addition to CKD, with around 61% of participants in UK Biobank and 70% in SCREAM being identified as having multimorbidity. In both cohorts KFRE demonstrated good discrimination across the two- and five-year time horizons for those with and without multimorbidity, with area under curve ≥ 0.86 , indicating good ability for the model to determine whether individuals would or would not develop future kidney failure. However, calibration was inconsistent and varied by cohort and multimorbidity status. In UK Biobank, KFRE consistently underestimated 5-year kidney failure risk in those with multimorbidity (observed/expected ratio 1.75 at 5-years). Conversely, in SCREAM calibration-in-the-large was closer to ideal for those with multimorbidity (observed/expected ratio 1.05 at 5-years). In both cohorts there was evidence of variation in calibration at different risk levels, with predominantly under-estimation at lower risk levels and over-estimation at higher levels in UK Biobank at 2- and 5-years and under-estimation across most risk levels at 2-years in SCREAM.

When assessing multimorbidity by number of long-term conditions, there was a shift from under- to over-estimation as the long-term condition count increased and in those with multiple cardiometabolic conditions (cardiometabolic multimorbidity).

Importantly, analyses demonstrated that individuals with multimorbidity had a higher cumulative incidence of death than those without multimorbidity, reinforcing the clinical relevance of considering competing mortality risk. An updated model for predicting kidney failure risk at 5-years, using the same covariates that form KFRE [age, sex, eGFR and uACR], but using methods accounting for competing mortality, improved calibration. This was most evident in those with multimorbidity (observed/expected ratio 0.98, both cohorts). Discrimination remained good in the updated model (area under curve ≥ 0.92 , both cohorts and multimorbidity subgroups).

Comparison of the impact of the updated competing risk model compared to KFRE, on referral numbers when a threshold of kidney failure risk $>5\%$ was employed, showed an increase in number of referrals when applying the competing risk model but that more of these individuals went on to develop

kidney failure than die first compared to KFRE. The magnitude of the increase varied by the population in which the models were applied to.

These findings suggest that KFRE can discriminate well in people with multimorbidity but underestimates absolute risk with less robust calibration, particularly when competing mortality is not considered. The updated model incorporating competing mortality risk improves model performance and may be more clinically useful in this complex population.

8.2.3 Research question 3

How does the presence of frailty impact the performance of the Kidney Failure Risk Equation and is it influenced by the competing risk of mortality?

Research question 3 was addressed using UK Biobank data to validate the four-variable KFRE at two- and five-years across subgroups defined by frailty²⁰¹, operationalised using both a modified frailty phenotype and two cumulative deficit frailty indices.

Frailty was common and was evident in 35% of participants with CKD. KFRE discrimination was good across all frailty sub-groups and the 2- and 5-year time horizons (area under curve ≥ 0.88), indicating that the model could identify those who would and would not experience kidney failure well regardless of the presence or absence of frailty. However, calibration was impacted by frailty status, with underestimation of kidney failure risk in individuals with frailty (observed/expected ratio 1.70 at 5-years).

Accounting for the competing mortality risk was important in individuals with frailty. Cumulative incidence analyses demonstrated that frailty was associated with both a higher risk of kidney failure and death compared to the no frailty subgroup. Survival analyses and plots demonstrated that overestimation of kidney failure risk was present and most evident in the frailty group and the higher KFRE predicted risk groups.

In summary, in addressing research question 3, it was demonstrated that frailty is common in CKD and impacts the calibration but not discrimination of KFRE.

Individuals with frailty are at higher risk of both kidney failure and death and ignoring competing mortality risk distorts estimation of kidney failure risk in this group.

8.2.4 Research question 4

Is the Kidney Failure Risk Equation model performance influenced by the use of cystatin C based eGFR equations in place of creatinine based eGFR?

Research question 4 was addressed alongside research questions 2 and 3 by comparing KFRE performance when eGFR was calculated using creatinine ($eGFR_{cr}$), cystatin C ($eGFR_{cys}$) or a combined creatinine-cystatin C equation ($eGFR_{cr-cys}$).

In multimorbidity analyses²⁰⁰, substituting $eGFR_{cr}$ with $eGFR_{cys}$ or $eGFR_{cr-cys}$ did not consistently improve model performance (discrimination, calibration or model fit) in either the UK Biobank or SCREAM cohorts or across the 2- or 5-year time horizons. These findings suggest that in broad multimorbidity populations, other variables such as albuminuria may be more influential drivers of risk than the specific biomarker used in the eGFR equation.

In contrast, the frailty analyses²⁰¹ indicated more influence from the eGFR biomarker utilised in the KFRE equation. Analyses demonstrated that replacing $eGFR_{cr}$ with $eGFR_{cys}$ improved calibration-in-the-large, especially in frailty subgroups at 5-years (observed/expected ratio 1.70, $eGFR_{cr}$ vs 1.20, $eGFR_{cys}$). However, discrimination remained similar and overall miscalibration remained. Individuals classified as having frailty had greater discrepancies between creatinine- and cystatin C-based eGFR, with lower $eGFR_{cys}$ relative to $eGFR_{cr}$, consistent with possible underlying sarcopenia and low muscle mass.

Overall, these findings suggests that some individuals or subgroups may benefit from cystatin C testing but are likely to be context specific; for example, in particular phenotypes characterised by frailty related sarcopenia and marked muscle mass loss. However, in CKD patients with broader multimorbidity without frailty, the benefits from use of Cystatin C may be limited.

8.2.5 Research question 5

Does the presence of multimorbidity or frailty impact how patients or healthcare professionals understand or perceive chronic kidney disease, risk of kidney failure and the use of the Kidney Failure Risk Equation in shared decision-making?

Research question 5 was explored through the MULTIPPOINT qualitative study that was comprised of interviews with patients living with CKD and multimorbidity and/or frailty and focus groups with healthcare professionals caring for these individuals. The study was conducted across primary and secondary care settings in a single region in Scotland. Qualitative analysis, underpinned by Normalisation Process Theory, identified five cross-cutting factors shaping how chronic kidney disease and kidney failure risk are understood and perceived in the context of multimorbidity or frailty and how KFRE might be used in these groups of individuals in practice:

1. **Variable CKD awareness and understanding:** Many individuals had limited awareness of having a diagnosis of CKD or did not understand the implications of CKD relative to their other long-term conditions.
2. **The “work” required to live with CKD plus other long-term conditions and/or frailty, including healthcare associated work:** Patient participants described substantial treatment burden and complexity, including polypharmacy, multiple appointments, self-management tasks and understanding their health conditions. Healthcare associated work was often related to complexity and uncertainty in the context of multimorbidity or frailty.
3. **Relationships and interactions between individuals, support networks, healthcare professionals and the health system:** Long-standing, trusting relationships were described as important by both healthcare professionals and patients in navigating complex care and decisions. Similarly, fragmented/siloed care systems and limited continuity made conversations about kidney failure and shared decision-making processes more difficult to initiate and build on over time.

4. **Context and priorities:** CKD was often deprioritised or perceived as less salient compared to other more symptomatic health conditions or those considered more urgent or life threatening, by both patients and healthcare professionals. Understanding of CKD and perceptions relating to kidney failure risk, including when to discuss this and how much detail to provide, were influenced by individuals' circumstances, motivations and competing health priorities.
5. **Uncertainty and the consideration of death:** Patients and healthcare professionals expressed pervasive uncertainty relating to prognosis, death, CKD trajectories, attribution of symptoms, the timing and likelihood of kidney failure and the role of KFRE in decision-making. For some patients, numerical risk estimates were viewed as potentially reassuring or empowering, whilst for others, they were abstract, difficult to interpret and could be anxiety provoking (intertwined with the fourth factor - individuals' context and priorities).

Healthcare professionals valued the potential function of KFRE in standardising referrals and discussions but anticipated difficulties in conveying risk values to patients. However, patients largely welcomed risk discussions when contextualised to their lived experience and their health literacy levels and highlighted the potential role of KFRE in reducing uncertainty. Implementation barriers included limited KFRE awareness, absent systems integration and limited time and communication challenges in more complex care situations such as in the presence of multimorbidity or frailty.

8.2.6 Triangulation of results

Triangulation of results from the four studies revealed convergence (findings validated one another), complementarity (findings enhanced one another) and dissonance (findings disagreed).

Convergence

All studies show that while KFRE is valid in general CKD populations, its application in patients with frailty and multimorbidity is less reliable and more complex in clinical practice/the real world.

Complementarity

Quantitative data shows how much risk prediction varies, whilst the qualitative data explains why and how clinicians and patients interpret and act on risk predictions and uncertainty that is present in many situations with multimorbidity and frailty.

Dissonance

Statistical adequacy contrasts with real-world usability and implementation. For example, competing risk models are more complicated to apply in practice. Additionally, there is lacking evidence and contrasting views about how to communicate KFRE risk scores to individuals, particularly in more complex patients such as those with multimorbidity or frailty. Application of KFRE scores in clinical management of CKD patients with multimorbidity and frailty may have sub-optimal performance with a degree of uncertainty which should inform the discussion and shared decision-making with these group of patients.

Overall, findings suggest that KFRE remains a valuable prognostic tool but requires contextual adaption for individuals with multimorbidity and frailty. Effective use depends on supportive systems, continuity of care, and communication strategies that acknowledge uncertainty and competing priorities.

8.3 Findings in the context of other literature

Current guidelines, including NICE¹¹ and KDIGO¹, recommend using KFRE in CKD to inform referrals, care planning and patient counselling, yet external validation has previously not focused on multimorbidity or frailty and lacks consideration of competing death, with the risk of mortality being higher in these subpopulations^{69, 136}. The validation work undertaken in this thesis demonstrates how accounting for competing risk and context-appropriate kidney

function biomarkers can improve calibration in selected subgroups. This work extends the KFRE and CKD literature in several ways. Previous multinational validations have demonstrated good discrimination but variable calibration across different settings and varying case mix, with the need for recalibration^{10, 169, 170}. Existing research exploring the risk of major adverse kidney events (MAKE - including kidney failure) in multimorbidity demonstrated that increasing number of LTCs, particularly cardiometabolic LTCs, was associated with an increased risk of MAKE¹³. The multimorbidity analyses in UK Biobank and SCREAM add to these findings by highlighting that calibration may vary by multimorbidity burden and disease clusters, with underestimation at higher LTC counts and cardiometabolic multimorbidity in some settings, and by demonstrating that competing risk models can improve calibration for this group of individuals whilst using the same predictors as KFRE²⁰⁰.

Similarly, the frailty analyses in this thesis show that KFRE underestimates kidney failure risk in frail individuals and that cystatin C-based eGFR can improve calibration, particularly in those with frailty and higher predicted kidney failure risk²⁰¹. These findings complement broader evidence that frailty, independent of age, is associated with more advanced CKD and substantially increased risk of mortality compared to those without frailty¹²⁹ but with inconsistent evidence relating to the performance of kidney failure prognostic models in these subgroups^{258, 266}. The findings from this thesis suggest that KFRE may require adaption, with alternative kidney function biomarkers and accounting for competing mortality risk, to improve performance for individuals with frailty.

The qualitative results reflect and align with established themes in multimorbidity literature including condition prioritisation⁹⁴, workload, treatment burden³⁴², and uncertainty³³⁴ which are central challenges observed in individuals living with and managing multimorbidity. Individuals often prioritise conditions that they perceive as more symptomatic, controllable or life-threatening, deprioritising those that appear asymptomatic or that they do not fully understand⁹⁴. Uncertainty relating to prognosis, disease trajectories and the applicability of disease-specific guidelines in complex patients has been shown to complicate shared decision-making³³¹⁻³³³. The qualitative work

presented in this thesis adds to the existing literature by highlighting how these factors exist in the context of CKD, multimorbidity and frailty, an existing gap in the literature, and the under-studied role of a prognostic tool such as KFRE in these circumstances. These findings align with a recent qualitative study conducted by Milders et al. exploring prognostic needs and perceptions about the future in patients with CKD, where uncertainty regarding the future was a common and central theme and although patients had diverse prognostic needs many wished more personalised prognostic information¹⁹⁰.

There is growing interest in prognostic models that jointly consider kidney failure and mortality risk, such as KD-predict²⁸⁹ or the use of multiple independent tools to predict both outcomes^{258, 267}. The quantitative work in this thesis supports this decision by demonstrating that competing mortality is particularly relevant for individuals with multimorbidity and frailty. Subsequently, models accounting for competing risk may better guide decisions about referral, preparedness for kidney replacement therapy and conservative management. However, the qualitative analyses highlight that beyond the statistical robustness of KFRE, consideration should be given to how it is implemented and utilised in ways that consider patient preferences, contexts, health literacy, the health systems, and the cumulative impacts of multimorbidity and frailty on patients' everyday lives.

In summary, collectively, these data extend the literature by:

- a) Quantifying the magnitude and direction of calibration errors in frailty/multimorbidity subgroups.
- b) Identifying possible ways of improving calibration e.g., competing mortality risk modelling and cystatin C incorporation where frailty is present.
- c) Highlighting practical considerations to improve understanding of CKD and kidney failure risk and prioritisation of CKD, particularly in the presence of other LTCs or frailty.

8.4 Implications

8.4.1 Patients & carers

Findings from Kidney Care UK, the UK's leading charity supporting kidney patients and their families, has consistently demonstrated that communication around CKD risk and CKD diagnosis is suboptimal³⁴³. The findings from this thesis reinforce the importance of earlier and clearer conversations about CKD and kidney failure risk with patients and their support networks, including ensuring transparent communication of a diagnosis of CKD. Many patients in the qualitative study described limited awareness of CKD as a diagnosis for them, alongside uncertainty about its implications and a desire for increased information about what they could do to protect or improve their kidney health. Routine, timely discussion of a CKD diagnosis, including education in understandable terms relating to kidney function, albuminuria, associated risks and relevant lifestyle or medication strategies, may help individuals to contextualise CKD alongside their other LTCs rather than perceiving it as a hidden or secondary concern. Ongoing work is required with healthcare professionals, healthcare systems and policy to make progress in this area.

Limited health literacy in individuals with CKD is common and estimated to be present in around 25% of patients with CKD³⁴⁴ and is associated with adverse clinical outcome such as hospitalisation, cardiovascular events and mortality³⁴⁵. The findings of this thesis suggest risk communication should be tailored to patients' priorities, health literacy and capacities. There is limited evidence relating to how best to communicate health risk in CKD¹⁹⁶ and exploring how and if risks from prognostic tools, such as KFRE, should be communicated to individuals. The impact of prognostic tools, such as cardiovascular risk calculators, have been shown to provide a structured base for communication relating to risk and self-care but that this did not translate into clear interpretation or understanding from patients³³⁷. Findings from the qualitative work in this thesis suggest that rather than presenting numerical KFRE risk estimates in isolation, risk discussions may be more helpful when linked to what matters to an individual, such as maintaining independence, avoiding hospitalisation, planning for day-to-day activities or the impact of potential treatments. In addition, using plain language, visual aids and clear time horizons

may support understanding. Furthermore, engaging with people to understand preferences relating to level of detail and understanding may help avoid overwhelming individuals who may be experiencing significant treatment burden due to multimorbidity^{149, 346} or frailty³⁴⁷.

The qualitative analyses also suggest that explicitly acknowledging uncertainty and competing risks could be beneficial. This supports findings from a 2022 systematic review and thematic synthesis of experiences of uncertainty in advanced multimorbidity³⁴⁸, that demonstrated that pervasive uncertainty can be distressing and can be improved by acknowledging it and considering what matters most to patients. For some individuals, having an awareness that death from other causes may occur before reaching kidney failure may reduce unnecessary anxiety and help orientate discussion towards an individuals' priorities for their remaining life. However, such discussion must be carefully tailored, as for some individuals this information may increase anxiety or distress, highlighting the importance of sensitive, patient-centred communication when addressing competing risks and prognosis. For others at higher risk of progression, understanding this balance may support timely access planning and engagement with interventions that reduce associated risks of adverse cardiovascular and kidney outcomes. This approach was demonstrated by Hallan et al. when considering concurrent prediction of kidney failure and mortality to illustrate how decisions relating to dialysis preparation in older adults could be shaped by competing risk estimates alongside patients' priorities and valuations of potential risks, burdens and benefits²⁵⁸.

Finally, the findings highlight a potential role for targeted kidney biomarker strategies in patient centred and individualised care. Bundy et al. found at a general population level, that KFRE discrimination and calibration were similar regardless of whether eGFR was derived from creatinine, cystatin C or combined creatinine-cystatin C equations²⁸⁷. Our findings in addition to these suggest that cystatin C may be most valuable when selectively applied in patients for whom creatinine based eGFR is likely to be biased or where clinical decisions are finely balanced. In line with KDIGO guidelines recommendations¹, cystatin C may be particularly relevant where frailty or low muscle mass are suspected, providing a more personalised assessment of kidney function and risk than creatinine alone.

Ensuring that patients and carers understand why additional tests are being performed and how results will influence shared decision-making will also be important in maintaining trust, understanding and engagement, consistent with multimorbidity literature showing that clear explanations, trusting relationships and shared decision-making are central to how patients weight up investigation and treatment choices³⁴⁹.

The findings included in this thesis have been disseminated to patients and members of the public in a variety of ways including:

- Through the West of Scotland Kidney PPIE group.
- Via national and international conferences where patient and public representatives were in attendance.
- A visual and graphical representation of the findings (Appendix 4) which will be sent to patient participants who contributed to interviews for the qualitative study and are also planned to be displayed in a public exhibition area of the University of Glasgow.

8.4.2 Healthcare professionals

For healthcare professionals, this thesis provides strong evidence that there is a requirement to ensure competing risk-aware prognostication in individuals with CKD and multimorbidity and/or frailty. Although the original KFRE development study by Tangri et al.⁹ showed that formally accounting for competing mortality had little impact on risk predictions at a general population level, the present findings highlight importance in populations with multimorbidity or frailty. This may be through updated KFRE models or alternative multi-outcome tools^{258, 267, 289}, that provide a more realistic picture of health trajectories and support more nuanced conversations regarding referral and management options²⁵⁸.

There is a large body of evidence demonstrating that many individuals are unaware of their risk of CKD or of having a diagnosis of CKD^{326, 327, 343}, early and explicit communication of a CKD diagnosis therefore remains essential. Qualitative analysis included in the thesis support that patients often discover

their CKD incidentally or late in the disease course and that delayed or vague explanations can erode trust and reduce opportunities for prevention and shared decision-making. Incorporating KFRE, or similar tools, into routine reviews where albuminuria and eGFR are discussed may support more structured, anticipatory conversations, especially if risk communication is framed relative to what individuals can do and how this information informs decision-making rather than purely for prognostication.

Persistent knowledge gaps and limited confidence in CKD detection and management have previously been described amongst non-nephrology healthcare professionals^{350, 351}. Additionally, medical education proposes that curricula that is single-disease/organ focused may result in under preparedness of healthcare professionals for the management of complexity that is seen in individuals with multimorbidity and frailty³⁵². Training and education for medical, nursing and allied health professionals are areas that have been highlighted as potential targets based on the findings of the work in this thesis. This includes adequate education about CKD, the importance of albuminuria testing, increased awareness of KFRE and cystatin C³⁵³ as an alternate kidney biomarker that can impact estimated kidney function relevant to some individuals (particularly as there is a move towards cystatin C testing becoming more readily available in routine care³⁵³). Additionally, skills in communicating risk in the context of multimorbidity and frailty, managing uncertainty and facilitating shared decision-making are important to improve the care provided for people living with multimorbidity or frailty, as already described. Recognition by healthcare professionals that CKD is often deprioritised, by both patients and healthcare professionals, may prompt more intentional efforts to ensure kidney health is considered and discussed if relevant and aligned with individuals' context and priorities.

Finally, the findings of this thesis suggest that assessment and documentation of frailty could be a valuable part of CKD care. Given the heterogeneity of frailty³⁵⁴, consideration is required around what frailty measure is used, what and how domains are captured, and if there are differences in the clinical implications based on method of measurement³⁵⁵. The use of validated frailty measures to assess frailty in clinical settings and recording of frailty assessments

for individuals with CKD may support discussions relating to prognostication, highlight the impacts of treatments (including monitoring of treatment burden) and identify individuals who may benefit from comprehensive geriatric assessment, more intensive supportive care or conservative care pathways. In addition, identification of individuals with CKD and frailty or reduced muscle mass would highlight individuals who may benefit from cystatin C testing.

8.4.3 Policy & healthcare services

Global prevalence estimates show that CKD is a rising major health issue². Public health and policy efforts to raise awareness of CKD as a common, largely preventable non-communicable disease remains essential. Recent advances include that the World Health Organisation (WHO), in 2025, for the first time formally recognising kidney disease as a non-communicable disease of increasing global priority within the WHO non-communicable disease agenda, with the aim of improving prevention, detection and management of CKD ^{356, 357}. However, at a national level in the UK, policy developments are still largely neglecting kidney disease as a priority³⁵⁸. In keeping with this there remains a lack of awareness and education in the public relating to kidney health and chronic kidney disease^{359, 360}.

The ability to calculate KFRE is limited by the availability of albuminuria testing³¹⁸. Enhancing albuminuria testing in primary care³⁶¹ or through screening programmes³⁶² has the potential improve the early detection of CKD and increase the feasibility of KFRE to be used for a greater number of individuals. Linked to this and relevant to the work in this thesis, focus on diagnostic coding of CKD and measuring of CKD incidence and prevalence are necessary. The coding of CKD is associated with individuals being informed of their diagnosis, albuminuria testing and lower risk of adverse outcomes³⁶³.

At a systems level, the results of this thesis also highlight the importance of data infrastructure and care design that support integrated, risk-informed CKD management. Embedding KFRE, or updated competing-risk models, within electronic health records could facilitate more consistent use by automating calculations from routinely collected creatinine and albuminuria data and prompting healthcare professionals when thresholds for referral or review are

met. Similarly, electronic health records could include structured fields for frailty status and multimorbidity measures, that may enable improved care, reduction in variation and be used in future research^{66, 364}.

Improving education, access to and pathways for cystatin C testing³⁵³ is also an important area that has been emphasised by this work. This is relevant for specific subpopulations such as those with frailty or reduced muscle mass. Guidance exists from KDIGO about when and for whom cystatin C testing should be requested but access and testing remain variables^{216, 365}. Implementation of laboratory ordering, reporting systems and electronic health records that enhance cystatin C in appropriate situations may be potentially beneficial for diagnostic assessment and risk prediction in individuals with frailty.

Finally, equity considerations are important for care pathways based on risk prediction models. Both frailty and multimorbidity are socioeconomically patterned^{72, 115, 118}, and there is a risk that algorithm/risk-based referral thresholds or model-driven decision support could unintentionally exacerbate disparities³⁶⁶ for example, delaying specialist care or over/under-treatment for some groups of individuals. Ongoing monitoring and evaluation of the implementation of KFRE and similar risk prediction models should include equity consideration and explore whether their use results in differences in access, treatment, or outcomes across socioeconomic, ethnic, and other sociodemographic groups³⁶⁷.

8.4.4 Research

The work in this thesis highlights several priorities for future research in kidney failure prediction and CKD care, both generally and in the context of multimorbidity and frailty. These priorities are outlined in detail in Section 9.5 and include routine subgroup validation and reporting of multimorbidity/frailty, comparative effectiveness and clinical utility studies to evaluate KFRE against other models, focus on implementation science approaches and methodologies to understand how to best integrate kidney failure risk tools into routine care, advancing kidney biomarker and trajectory research (including eGFR discordance and dynamic predictions following interventions), and exploring optimal risk communication in CKD care.

8.5 Strengths and limitations

There are several strengths and limitations to the work presented in this thesis, many of which are described in the discussion sections of the corresponding study manuscripts in Chapters 4 to 7. A summary of the main strengths and weaknesses of the work are detailed in this section.

8.5.1 Strengths

This thesis used mix-methods with explicit triangulation of results^{198, 239} presented in this chapter. By combining the systematic review, quantitative validation studies and qualitative study findings the work addresses epidemiological, prognostic, and experiential aspects of risk prediction in CKD. The qualitative work contextualises the findings and clarifies the practical limitations to the implementation of risk information provision in complex care.

The work provides a comprehensive and systematic evidence synthesis on the representation of multimorbidity and frailty in prognostic kidney failure models for CKD and their impact on model performance. The systematic review used robust methodology²⁰², including prospective protocol registration, and established prediction modelling reporting frameworks^{154, 155} to identify and characterise gaps in the development and validation of models for these groups of individuals.

The quantitative work used large-scale, complementary cohorts (UK Biobank and SCREAM) to conduct detailed validation of KFRE across multimorbidity and frailty. Together these cohorts included over 67,000 individuals, with around 45,000 being classified as having multimorbidity, and more than 1,400 kidney failure and 11,500 death events. The availability of both creatinine and cystatin C in these datasets allowed direct comparison of different eGFR equations in the prognostic model within the same cohorts. In addition, quantitative analyses used rigorous methods for prediction model evaluation, including multiple discrimination and calibration metrics, competing risk methods¹⁷⁶ and sensitivity analyses. Both multimorbidity and frailty were assessed and operationalised using existing and reproducible definitions^{103, 117, 211, 221}, that enables comparison

with other research and will allow future external validation or comparison studies to be performed.

The qualitative study was theoretically informed by Normalisation Process Theory²³⁶ and the Ottawa Decision Support Framework, and sought participation from patients and healthcare professionals from both primary and secondary care settings, enhancing relevance and generalisability.

8.5.2 Limitations

The representativeness of cohorts utilised in the work of this thesis is one of the main limitations. UK Biobank is susceptible to healthy volunteer bias and has limited representation of minority ethnic groups²⁰⁹. Furthermore, UK Biobank recruited individuals aged 37-73 years and therefore did not include the oldest old, the group in whom CKD, multimorbidity and frailty are most prevalent and in whom the competing risk of death is greatest. This introduces a further source of selection bias of relevance to the frailty and multimorbidity analyses. Older individuals not captured due to the age limitations of recruitment are likely to have had higher levels of frailty and have a subsequent higher mortality risk. Likewise individuals with more extreme frailty may have been less likely to be able to participate in the study. Frailty in UK Biobank was disproportionately identified in younger participants. This combination of age-truncated recruitment and mortality selection bias of individuals with the highest frailty is the likely explanation for the finding in the frailty validation that frail participants were younger than non-frail participants. This reversal of the expected frailty-age relationship may represent an example of Simpson's paradox³⁰⁶, whereby an association seen across a whole cohort differs from, or reverses, that seen within its subgroups because of an unevenly distributed confounding variable, in this case age. This has implications for the interpretation of the validation results. The burden and severity of frailty and multimorbidity are likely under-represented compared to a routine-care CKD population, and as age is a strongly weighted variable in KFRE associated with a lower predicted risk of kidney failure, the younger age of the frail and multimorbidity sub-groups may lower their predicted risk while frailty and multimorbidity themselves confer a higher risk that the equation does not fully capture, consistent with the underestimation of kidney failure risk observed in

UK Biobank. The baseline risk of kidney failure in UK Biobank was also lower than might have been expected, likely reflecting this same selection bias towards younger and healthier individuals. Together, these factors offer a likely explanation for the more severe underestimation of kidney failure risk seen in the multimorbidity group in UK Biobank compared with SCREAM. As the competing risk of death increases with age, the absence of the oldest old also means the influence of competing mortality on calibration is likely greater in the general CKD population than these results suggest, reinforcing the value of validation in cohorts such as SCREAM that include older, routinely managed patients. SCREAM is more representative of routine practice but is limited by being a single geographic area (with both datasets being limited to European populations) and does not collect ethnicity data, limiting generalisability across ethnic groups, other geographical areas and healthcare systems. In addition, selection bias was present as due to missing data in SCREAM, blood tests (serum creatinine) were necessary to ascertain CKD for inclusion and due to cystatin C and uACR not being universally available a large number of individuals were excluded due to missing data.

In UK Biobank, frailty measures were adapted from existing methods and may have differing associations in younger populations or when variables, e.g., weight loss, vary from the measures originally developed. There was limited overlap across frailty measures but due to small outcome numbers it was not possible to perform validation by frailty sub-definition. A further limitation is that frailty could not be assessed in SCREAM, precluding the replication of frailty analyses in a routine-care cohort. This is a general challenge with limited datasets available for research that include variables that can be utilised to measure and examine frailty.

Ascertainment of outcomes was a further limitation. The outcome of kidney failure focused on kidney replacement therapy, in keeping with the original development of KFRE¹⁰. However, conservative care is an established treatment choice for kidney failure and is particularly relevant to older individuals and those with multimorbidity or frailty where this is a more common treatment pathway. This may impact calibration and limits the understanding of prognostic utility for KFRE for these individuals.

The qualitative study, although in-depth, involved participants from a single UK region and excluded individuals who were at the end of life, unable to consent and those who were non-English speaking. Furthermore, despite a purposeful sampling technique there was a lack of ethnic diversity in participants who engaged in the study. These weaknesses may limit the generalisability of findings to some settings, ethnicities, cultures and populations.

8.6 Future directions

Building on the findings and implications of this thesis, several areas for future development and research are evident:

1. Standardising the reporting of frailty and multimorbidity in CKD

research: Future CKD prognostic studies, as well as other CKD research topics, should routinely report the prevalence of multimorbidity and frailty alongside the definitions used to assess these. Adopting consensus definitions for multimorbidity and working towards a greater understanding of differing frailty measures in CKD (expanded in point number 3) and consensus on which of these should be used in research - which is likely to be dependent on the research question and setting, would allow this and enhance comparability and relevance of the research.

2. Capturing frailty measure routinely in clinical care for CKD patients to inform care and to allow frailty research using routinely collected data.

Due to the higher prevalence of frailty in individuals with CKD compared to those without it is important to establish the incorporation of validated frailty measures into routine CKD assessment and recording them in structured electronic health record fields. This would provide the opportunity for care to be more personalised by highlighting if an individual is experiencing frailty or is at risk of it. Furthermore, observational studies using routinely collected data would become more feasible and informative due the possibility of performing research in larger cohorts/datasets, which are currently lacking frailty measures or variables required to assess frailty.

3. **Research mapping transitions in frailty status and frailty trajectories, differing frailty measures and their impact on outcomes.** Longitudinal data, with frailty measures, would be ideally placed to explore how frailty trajectories change over time, transitions between different frailty states and frailty interactions with multimorbidity. Research in this area is lacking primarily due to paucity of frailty measures in existing datasets but also due to scarceness of long-term follow-up in cohorts that do report frailty measures. There is also a need to explore the associations of differing frailty measures in CKD populations and their impact on outcomes such as mortality, kidney failure and hospitalisations, particularly in younger individuals, as existing frailty outcomes and association research in CKD primarily relates to older (>60 years old) populations¹²⁹ and those with kidney failure³⁶⁸. These research findings would inform which measures are most informative for prognostication and potentially which subgroups could benefit from tailored care pathways or interventions.
4. **Greater understanding of discordances between eGFR_{cr} and eGFR_{cys} in multimorbidity and frailty.** A recent large meta-analysis of participants in CKD Prognosis Consortium has demonstrated that large discordances between eGFR_{cr} and eGFR_{cys}, where eGFR_{cys} is $\geq 30\%$ lower than eGFR_{cr}, were associated with increased rates of mortality, cardiovascular event and kidney failure with KRT³⁶⁹. Large negative eGFR discrepancies were associated with several individual comorbidities. However, the association with multimorbidity and frailty and outcomes has not been explored. Likewise, the impact of eGFR discordance on KFRE model performance is unclear. These areas of research would support understanding in risk stratification and management of these patient groups.
5. **Routine sub-group validation of prognostic models in individuals with multimorbidity and/or frailty.** Building such analyses into validation studies as standard would help ensure models are adequate for populations where multimorbidity and frailty are most prevalent and may impact their use.

6. **Kidney failure prognostic model comparative and clinical utility studies.** Comparative evaluations are necessary to evaluate KFRE against other kidney failure and mortality prognostic models that incorporate mortality risk, such as KD predict²⁸⁹ or the CKD-PC advanced CKD ‘risks’ model²⁶⁷, particularly focusing on multimorbidity and frailty sub-populations. These studies should consider not only statistical performance but also how models influence clinical decisions, treatment burden and patient-reported outcomes. Analyses could benefit from the inclusion of impact and decision curve analyses which assess how model use and risk cut-offs might influence referrals, treatment decisions and patient-focused outcomes.
7. **Dynamic risk modelling.** Research using methods such as combining joint modelling and landmarking methodologies³⁷⁰ to create dynamic risk prediction models that can assess how risk changes over time or in response to intervention such as the introduction of kidney protective therapies such as SGLT2 inhibitors or other medications, which could help healthcare professionals and patients understand kidney failure risk over time and the impact of treatments on kidney failure risk in multimorbidity or frailty.
8. **Referral and management thresholds.** There is a large body of evidence validating the prognostic performance of KFRE but lacking research exploring the impact of KFRE on outcomes and when different risk thresholds should be used³³⁶. Future work exploring risk thresholds for use in different contexts such as referral to nephrology services, follow up frequency or planning for KRT and the impact that utilising KFRE has on outcomes would be informative and support future use.
9. **Integration of KFRE and other risk tools into routine care.** Implementation science approaches^{371, 372} are required to understand how best to integrate KFRE and other risk tools into routine care, with the UK Kidney Association having established a working group focusing on KFRE implementation in laboratory IT systems³⁷³. Co-designing work processes, decision aids and communication strategies with patients, carers and healthcare professionals could help address challenges such as alert

fatigue^{374, 375}, time constraints, IT barriers and variable health literacy³⁴⁴. Mixed-methods evaluations that assess both clinical and experiential outcomes (from patient and healthcare perspectives) would be particularly valuable.

10. **Optimising communication of kidney failure risk.** Further research would be beneficial in assessing different communication formats, timings and setting for discussing kidney failure risk in CKD, multimorbidity and frailty. This includes examining how patients and/or carers interpret or respond to numerical versus visual displays of risk, short- versus long-term time horizons and how best to align these conversations with evolving priorities and context and in the settings of uncertainty. Qualitative research or discrete choice experiments methods may be particularly useful in exploring these areas.
11. **Education and CKD prioritisation.** Updated estimates of global CKD prevalence and burden from the 2023 Global Burden of Disease Study² demonstrates that CKD is rising in prevalence and was the ninth leading cause of death globally and the 12th leading cause of disability-adjusted life years. The findings in this thesis, however, highlight that many individuals still unaware of having CKD and that it remains a lower priority to both patients and healthcare professionals compared to other LTCs. This should be a priority for policy and public health initiatives. UK based third sector charity, Kidney Care UK, has launched a national initiative at raising awareness about chronic kidney disease and encouraging early detection - “Blood Amazing Kidneys” campaign³⁷⁶. However, there is the opportunity for the government to influence policy and wider public health initiatives that could improve public awareness and promote early intervention in CKD, with the potential to lead to improved health outcomes in CKD.

8.7 Conclusions

This thesis aimed to test the hypothesis that the presence of multimorbidity or frailty, in addition to CKD, impacts both the performance of KFRE and the way it is used in clinical practice. The work demonstrates that multimorbidity and

frailty are common in CKD populations but have been largely neglected in the development and validation of kidney failure prognostic models to date.

Using large, complementary cohorts, the thesis shows that KFRE has good discrimination in individuals with multimorbidity and frailty but that calibration is sub-optimal and influenced by both case-mix and competing mortality risk. Multimorbidity and frailty are associated with higher risks of both kidney failure and death. Models that ignore competing mortality can underestimate risk in these groups. In addition, the work highlights a context specific role for cystatin C-based eGFR, with potential benefits for calibration amongst frail individuals but limited impact in multimorbidity.

The qualitative findings reveal that beyond statistical model performance, the clinical utility of KFRE is fundamentally shaped by how CKD is understood and prioritised, the burden and complexity of living with multiple conditions or frailty, the relationships and continuity with healthcare professionals, and the pervasive uncertainty that surrounds CKD and other health trajectories and treatment decisions. KFRE may in some situations provide structure and support for communication of risk and shared decision-making, but its value is constrained by limited awareness, communication challenges and competing priorities.

Overall, these findings highlight that risk prediction and shared decision-making in CKD with multimorbidity and frailty requires a personalised approach and consideration around implementation. This includes more consistent reporting and evaluation of multimorbidity and frailty in prognostic research, awareness of the impact of competing risks, potentially eGFR biomarker-tailored approaches to risk estimation and public health, healthcare systems, training, and communication strategies that support meaningful, patient centred understanding of CKD and use of risk information.

This thesis contributes a nuanced understanding of how prognostic models such as KFRE may support personalised care in complex CKD populations. It sets a foundation for future work to refine prediction tools, integrate frailty and multimorbidity explicitly into CKD prognostication as well as more widely in

evidence-based medicine and develop implementation approaches to support shared decision-making and person-centred care.

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Appendices

Appendix 1. Letter of permission to use KDIGO images and guidance



Global Science. Local Change.

Co-Chairs

Morgan Grams

Christoph Wanner

February 23, 2026

Heather Walker, MBChB
University of Dundee
Scotland, UK

Secretary/Treasurer

Michel Jadoul

Re: **Approval for referencing KDIGO guidance for the proposed thesis**

Executive Committee

Rolando Claire-Del Granado

Danielle Green

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Mark Sarnak

Ifeoma Ulasi

Marc Vervloet

Motoko Yanagita

Dear Dr. Walker,

We hereby grant you permission to reprint the Heat Map and Figures 4, 15, and 49 from the *Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease* provided it is properly acknowledged either in the footnote or caption or as a bibliographic citation for use in your thesis.

Kind regards,



Melissa A. Thompson, MS
Chief Operating Officer

www.KDIGO.org

**Representation of multimorbidity and frailty in
development and validation of kidney failure risk
prediction models: a systematic review**

*Heather Walker, Patrick Mark, Bhautesh Jani, Michael Sullivan, Scott Day, Katie
Gallacher*

Review methods were amended after registration. Please see the revision notes and
previous versions for detail.

Citation

Heather Walker, Patrick Mark, Bhautesh Jani, Michael Sullivan, Scott Day, Katie
Gallacher. Representation of multimorbidity and frailty in development and validation of
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from <https://www.crd.york.ac.uk/PROSPERO/view/CRD42022347295>

REVIEW TITLE AND BASIC DETAILS

Review title

Representation of multimorbidity and frailty in development and validation of kidney failure risk
prediction models: a systematic review

Review objectives

In patient cohorts used to develop and validate kidney failure risk prediction models what is the
representation of multimorbidity and frailty? What impact of multimorbidity and frailty, if any, has
been studied on the validity of risk prediction models in estimation kidney failure risk?

Keywords

Chronic kidney disease, Frailty, Kidney failure, Multimorbidity, Risk prediction, Validation

SEARCHING AND SCREENING

Searches 1 change

MEDLINE (EBSCO interface), CINAHL Plus (EBSCO interface) and the Cochrane Library (the
Cochrane Central Register of Controlled Trials (CENTRAL)) (OVID interface) will be searched.
We will then supplement this search with reviews of reference lists of included studies and
NICE guidelines. The search will be limited to papers published in the English language but

there will be no restriction of studies based on country of publication. The search will include literature published up until July 2022.

Additional search strategy information can be found in the attached PDF document (link provided below).

Study design

Quantitative studies that have developed or validated a risk prediction model for kidney failure will be considered for inclusion, with no restriction on sample size. The search will be limited to papers published in the English language but there will be no restriction of studies based on country of publication.

We will exclude review articles, drug intervention studies, qualitative studies and case reports, as well as excluding animal studies, studies with patients who have a renal transplant or studies including patients aged less than 18 years old.

ELIGIBILITY CRITERIA

Condition or domain being studied

Kidney failure. Risk prediction model(s). Multimorbidity. Frailty.

Population

Inclusion: Adult human population aged 18 years and over with chronic kidney disease (CKD), included in a cohort of a kidney failure risk prediction model development and/or validation.

Exclusion: Animal studies, studies including patients aged less than 18 years old or patients with a renal transplant.

Intervention(s) or exposure(s)

Multimorbidity/co-morbidities described and frailty.

Comparator(s) or control(s)

Patients with CKD but without multimorbidity and/or frailty.

OUTCOMES TO BE ANALYSED

Main outcomes

To systematically summarise the representation of multimorbidity and frailty within the cohorts that have been used to develop and validate kidney failure risk prediction models. Reporting if multimorbidity and frailty is reported in the studies used to develop and validate kidney failure risk prediction models and the impact this has of the validity (by comparison of discrimination and calibration measures) in estimating kidney failure risk.

Measures of effect

Frequencies and percentages for multimorbidity and frailty reported at time of the study

Discrimination and calibration measures used in the individual studies.

Additional outcomes

None.

Measures of effect

Not applicable.

DATA COLLECTION PROCESS

Data extraction (selection and coding)

The study selection process will be conducted independently by at least two individual reviewers. The results of the literature search will be imported into Rayyan. Title screening will be followed by abstract and full paper review, if necessary, prior to data extraction. Data charting and critical appraisal of sources of evidence will be conducted using established data extraction tools modified for this review.

Data extracted from each study will include: author, year, country of origin, study design, sample size, patient characteristics (including age, sex, ethnicity, eGFR/stage of CKD, comorbidities, multimorbidity, frailty), discrimination and calibration of the risk prediction tool.

Differences will be resolved by consensus or discussion with a third reviewer if required.

Risk of bias (quality) assessment

Two review authors will independently review the risk of bias in included studies by use of the Cochrane risk of bias tool/standards (1) and the Prediction model Risk Of Bias ASsessment Tool (PROBAST)(2). Differences will be resolved by consensus or discussion with a third reviewer.

1. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.0: Cochrane; 2019 [updated updated July 2019]. Available from: www.training.cochrane.org/handbook.

2. Moons KGM, Wolff RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. *Ann Intern Med*. 2019;170(1):W1-w33.

PLANNED DATA SYNTHESIS

Strategy for data synthesis

Baseline characteristics will be summarised using quantitative descriptive statistics, means and standard deviations for normally distributed continuous data or medians and interquartile ranges for skew data. Categorical variables will be summarised using frequencies and percentages. If possible, odds ratios will be calculated for patients with multimorbidity against people without multimorbidity and an equivalent kidney failure risk. The random effects model will be used to calculate the average effects and 95% confidence interval. Heterogeneity will be assessed using Cochran's Q statistic test (p values <0.1 will be considered as statistically significant) and I² statistic. The included studies and overall findings will be reported using narrative synthesis.

Analysis of subgroups or subsets

Subgroup analysis based on socio-demographic factors will be undertaken if relevant for included studies.

REVIEW AFFILIATION, FUNDING AND PEER REVIEW

Review team members

- Dr Heather Walker, University of Glasgow
- Dr Patrick Mark, University of Glasgow

- Dr Bhautesh Jani, University of Glasgow
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Funding source

Dr Heather Walker has fellowship funding and support via Wellcome Trust for the Multimorbidity PhD programme for Health Professionals

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TIMELINE OF THE REVIEW

Review timeline

Start date: 22 November 2022. End date: 31 May 2023

Date of first submission to PROSPERO

22 November 2022

Date of registration in PROSPERO

23 November 2022

CURRENT REVIEW STAGE

Publication of review results

The intention is to publish the review once completed. The review will be published in English

Stage of the review at this submission ¹ change

Review stage	Started	Completed
Pilot work	✓	
Formal searching/study identification	✓	
Screening search results against inclusion criteria		
Data extraction or receipt of IP		
Risk of bias/quality assessment		
Data synthesis		

Review status

The review is currently planned or ongoing.

ADDITIONAL INFORMATION

PROSPERO version history

- Version 1.1 published on 24 Nov 2022
- Version 1.0 published on 23 Nov 2022

Review conflict of interest

None known

Country

Scotland

Medical Subject Headings

Aged; Frail Elderly; Frailty; Humans; Multimorbidity; Renal Insufficiency

Revision note 1 change

Change in search databases and search terms due to search terms not picking up all expected studies.

Disclaimer

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BMJ Open Exploration of patients' and healthcare professionals' perspectives on kidney failure risk and the use of the kidney failure risk equation in MULTIPLE Long-term conditions and frailty (MULTIPOINT) study: a qualitative interview and focus group study protocol

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ABSTRACT

Introduction Clinical guidelines recommend the use of the kidney failure risk equation (KFRE) to guide the referral of individuals with chronic kidney disease (CKD) to secondary kidney care services. People living with CKD frequently experience multiple long-term conditions (multimorbidity) and/or frailty. This may impact patients' or carers' perceptions of kidney failure in the context of other health problems and associated risks and emphasises the need for shared decision-making. This paper presents the research protocol for the exploration of patients' and healthcare professionals' perspectives on kidney failure risk and the use of the KFRE in the MULTIPLE Long-term conditions and frailty study. This study aims to investigate patient and healthcare professionals' perspectives and expectations of the use of KFRE in individuals with CKD and multimorbidity and/or frailty, with a focus on shared decision-making.

Methods and analysis Analysis of semistructured interviews with adults who have CKD and multimorbidity and/or frailty and focus groups with healthcare professionals (who are involved in caring for patients with CKD). Framework analysis, underpinned by normalisation process theory, will be used to develop codes and explore themes from the interviews and focus groups. Patient and public involvement has been pivotal to the study conceptualisation and will continue to be embedded throughout the study.

Ethics and dissemination The study protocol has undergone peer review by the NHS Greater Glasgow and Clyde Research and Innovation team and has been granted ethical approval in August 2023 by the NHS Health Research Authority following a favourable opinion from the West of Scotland Research Ethics Committee (REC) 3 (IRAS ID: 325848, REC reference: 23WS/0119, Protocol number GN22RE559).

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study explores the use of a kidney failure prognostic model in the shared decision-making and clinical management of people with chronic kidney disease and multiple long-term health conditions and/or frailty, through rigorous methods underpinned by middle range theory (normalisation process theory).
- ⇒ The qualitative interview and focus group approach will aid the understanding of patients' and healthcare professionals' perspectives on kidney failure risk in the context of multimorbidity and/or frailty.
- ⇒ All aspects of the study have been developed in partnership with patient and public representatives.
- ⇒ Individuals approaching the end of life, those unable to provide informed consent or those who do not speak English are excluded from the study, which limits the validation of our findings in these populations.
- ⇒ Participants are recruited from a single region of Scotland, UK. This potentially may reduce the diversity of the study population.

The results of the research will be disseminated through peer-reviewed publications and conferences, as well as to patient and public involvement groups who have been involved in the study and through knowledge exchange events.

INTRODUCTION

People with chronic kidney disease (CKD) are frequently impacted by multiple long-term health conditions, also referred to as multimorbidity.¹ In addition, individuals

with CKD are more likely to experience frailty than those without CKD.² Frailty refers to an elevated risk of rapid health deterioration and reduced ability to recover from illness which is typically due to a diminished physiological capacity.^{3,4}

An important risk faced by a small proportion of people with CKD is the progression to kidney failure requiring treatment with kidney replacement therapy (KRT), in the form of long-term dialysis or kidney transplantation. Accurate risk prediction of kidney failure in CKD is important to allow clinicians to provide personalised healthcare. The Kidney Disease: Improving Global Outcome (KDIGO) 2012 Clinical Practice Guideline for CKD⁵ and the 2021 National Institute for Health and Care Excellence (NICE) guidelines for management of CKD⁶ recommend using the four-variable Kidney Failure Risk Equation (KFRE),⁷ composed of age, sex, estimated glomerular filtration rate and urine albumin creatinine ratio. This can inform adults with CKD about their 5-year risk of need for KRT and it can help guide referral of adults with CKD for assessment from primary care to secondary care kidney specialists. Despite this recommendation, there remain barriers to KFRE being used for all people with CKD, with various possible reasons for this.⁸

Multimorbidity is associated with a heightened risk of mortality,⁹ higher healthcare service utilisation, polypharmacy, high treatment burden and reduced quality of life.¹⁰ Treatment of single diseases, compared with holistic and generalised care approaches, can exacerbate these problems.¹¹ Multimorbidity, frailty and associated factors such as treatment burden may influence how individuals wish information about kidney failure risk, assessment and management be communicated to them and how they make decisions around future care. Shared decision-making (SDM) can play an important role in helping individuals reach health-related decisions unique to their circumstances, preferences and priorities. SDM has been defined as 'an approach where clinicians and patients share the best available evidence when faced with the task of making decisions, and where patients are supported to consider options, to achieve informed preferences'.¹² Its utilisation in people with multiple long-term conditions may result in improved understanding of risks and benefits, enhance communication between healthcare professionals (HCPs) and patients and reduce difficulties around decision-making.^{13,14}

To date, there has been limited research on communication and SDM in the CKD population, with a focus mainly on KRT decisions.^{15–20} More recently, there has been an acknowledgement that SDM is likely to be beneficial and preferred by patients with CKD, in decision-making scenarios.²¹ However, there is a lack of high-quality studies relating to the impact of SDM on clinical outcomes.²⁰ A recent scoping review assessing interventions that support SDM in advanced kidney disease highlighted prognostic tools, including KFRE, that may be used to support treatment modality decisions.¹⁹ It is unclear how best to communicate the

risk of kidney failure in patients with CKD who are frail and/or multimorbid or how SDM should be used when using prognostic tools such as KFRE. A small number of studies have examined the patient, family and HCP perspective on the use of the KFRE for a risk-based approach to guiding care.^{22,23} However, there is a paucity of research exploring the use of KFRE in more complex populations such as those with multimorbidity or frailty.

Despite this lack of research in the CKD population, decision-making about treatments has been studied in primary care populations, with a recent systematic review focusing on patients in primary care with complex care needs, identifying the types of decisional needs across a range of settings and contexts²⁴ and demonstrating that SDM was associated with positive outcomes. Within this study, it was acknowledged that decisions concerning areas other than treatment options have been under-researched and warrant further consideration. A recent qualitative study examined the experience of decision-making from the perspective of older adults with multimorbidity and general practitioners (GPs).²⁵ Themes identified from this study included the barrier of clinical uncertainty in communication and SDM and the difficulty of applying single organ or disease-specific guidelines in patients with multimorbidity, which may be applicable to implementing the KFRE in patients with multimorbidity and/or frailty.

Current literature does not address the use of SDM in the context of decisions relating to communication of the risk of kidney failure, referral to secondary care kidney specialists or the use of risk prediction models (such as KFRE) in making healthcare-related decisions in this context. Moreover, there is a lack of understanding around SDM in individuals with CKD who also experience multimorbidity and/or frailty. This study will explore these topics.

Aims and objectives

The overall aim of this study is to explore patient and HCP perspectives and expectations of the use of KFRE in individuals with CKD and multimorbidity and/or frailty, with a focus on SDM.

The study objectives are as follows:

- ▶ To understand patient and HCP perceptions of kidney failure risk in the context of multimorbidity and frailty.
- ▶ To explore how patients with CKD and multimorbidity and/or frailty wish to discuss kidney failure risk and if this differs from HCP's perspectives.
- ▶ To investigate patient and HCP expectations about how the KFRE should be used in the care and decision-making process of individuals with multimorbidity and/or frailty.
- ▶ To identify what barriers and challenges exist in using the KFRE to guide treatment and referral in individuals with multimorbidity and/or frailty.

METHODS AND ANALYSIS

Study design

Semistructured interviews and focus groups will be conducted and analysed to explore patient and HCP perspectives on kidney failure risk and use of the KFRE in individuals with multimorbidity and/or frailty.

The study will involve framework analysis^{26, 27} of in-depth individual patient interviews and HCP focus groups. Patients and HCPs are being recruited to allow an exploration of the topic of SDM. Individual interviews for patients are being used to allow exploration of the potentially distressing subject of kidney failure risk and to provide insights into personal feelings and perspectives on this topic. Interviews were also chosen for patients to allow flexibility and enhance ability to participate as we recognise that some individuals may find participating in focus groups challenging or burdensome. Focus groups are being used for HCP participants to capture a breadth of perspectives and build on interactions that exist within multidisciplinary teams.

Study setting and participant recruitment

Purposeful sampling will be used to recruit participants with experiences relevant to the research aims and objectives and to gain a variation in characteristics such as age, gender, ethnicity and healthcare role.^{28, 29}

Scottish primary care practices and secondary care kidney hospital departments in the Greater Glasgow and Clyde (GGC) Health Board, which provide renal services to a population of approximately 1.2million, will be approached to recruit patients with CKD and multimorbidity and/or frailty and HCPs.

Potential participants from primary care will be identified through the National Health Service Research Scotland Primary Care Research Network (NRS PCRN), which will recruit through National Health Service (NHS) primary care practices. We will also recruit through SHARE (The Scottish Health Research Register and Biobank) who have a list of individuals registered with primary care practices across Scotland who are willing to be contacted to participate in research. Participants will be identified through an IT system search of primary care records (identified via CKD coding and long-term condition and frailty coding where available), with subsequent screening by the patient's own GP and the research team. Potential participants will be sent written information and an invitation letter by post.

Patients from secondary care kidney clinics will be screened by their named HCP to ensure they meet the inclusion criteria and are willing to be approached to participate in the study. These potential participants will then be approached by the research team via telephone or when attending clinic, to discuss the research project. Written information and an invitation letter will be provided in person, by email or by post.

Potential participants will also be approached through social media platforms, third-sector organisations and patient and public involvement and engagement (PPIE)

groups. They will be invited to contact the research team directly or return an expression of interest form.

HCPs involved in discussing kidney disease and risk of kidney failure with patients will be identified by practice managers (primary care), renal clinical leads (secondary care) and professional contacts and networks (both primary and secondary care). HCPs will include doctors (specialty registrars (doctors in renal specialty training), specialty doctors (doctors who have chosen to work in renal but do not hold a training or consultant post), consultants and GPs) and specialist nurses. Clinical staff identified will then be screened by the research team to ensure they meet the inclusion criteria. All potentially suitable individuals will be contacted via email with a participant information sheet and invitation attached. An overview of the participant recruitment strategy is summarised in [figure 1](#).

Once potential participants have expressed an interest, a researcher will contact them to arrange a suitable time for interview/focus group.

Inclusion and exclusion criteria

Study inclusion and exclusion criteria are described in [table 1](#).

Study sample size

The aim is to recruit approximately 30 patient participants in total (20 from primary care and 10 from secondary care) to allow adequate sampling for saturation of themes. This split will allow us to explore the perspectives of both individuals who have CKD but may not have discussed kidney failure or attended specialist assessment and individuals who have experienced this process.

A mixture of approximately 20 primary and secondary care HCPs will be recruited to participate in a focus group. Focus groups will include around five individuals each and will be run as separate focus groups for primary and secondary care HCPs to explore if there are differences in the perspectives of these populations.

Sample sizes are appropriate to the study design, as qualitative research prioritises covering a range of views and contexts relevant to the topic rather than achieving representativeness. Sample sizes have been informed by previous qualitative research in similar populations/areas.^{17, 30, 31}

Consent

Participants will be sent a participant information sheet and consent documents prior to participating in their interview/focus group session. Individuals will be able to contact the research team directly (by email or telephone) if they wish to ask questions and will be given an opportunity to discuss the study further at the time of the interview/focus group. Written informed consent will be obtained from participants immediately prior to the interview/focus group.

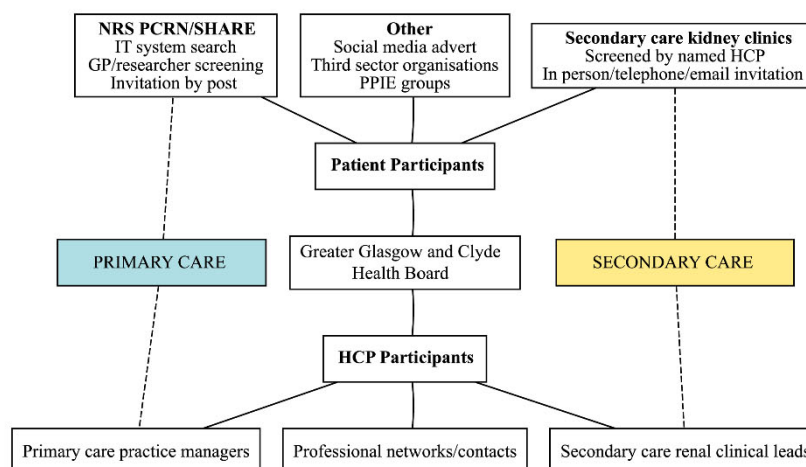


Figure 1 Participant recruitment strategy diagram. HCP, healthcare professional; NRS PCRN, National Health Service Scotland Primary Care Research Network; PPIE, patient and public involvement and engagement; SHARE, The Scottish Health Research Register and Biobank.

Data collection

Interview and focus group schedules will be developed based on the research questions, the Ottawa Decision Support Framework (ODSF) and the Ottawa Personal Decision Guide³² (OPDG) (a decision aid developed to help individuals make decisions and facilitate SDM based on the ODSF).³³ The interview and focus group questions/guides were constructed based on the components of ODSF and OPDG (knowledge, values, support, certainty and decision-making). The ODSF and OPDGs were chosen over other SDM frameworks and guides due to their established use across a range of health decisions.³³ This enables the adaptation of their themes for use in the context of SDM relating to risk of kidney failure and the use of the KFRE to guide care. Additionally, their

use ensures important topics relevant to individuals making health-related decisions are captured within the study. ODSF was chosen above other SDM frameworks.

Although the study has a focus on SDM, the study also aims to explore individuals' perceptions of kidney failure risk in the context of multimorbidity and frailty, communication of kidney failure risk, the use of KFRE in the care/treatment of individuals with multimorbidity and/or frailty and what barriers and challenges exist in using the KFRE in clinical practice. Patient participant interviews and HCP focus group guides are provided in online supplemental Text 1 and 2.

At the time of interviews and focus groups, participants will be asked to provide basic demographic information including age, gender, ethnic group, postcode (to allow

Table 1 Participant inclusion and exclusion criteria

	Patient participants	Healthcare professional participants
Inclusion criteria	- Adults (aged ≥18 years) with a diagnosis of CKD (defined as eGFR<60 mL/min/1.73 m²) and multiple long-term conditions (2 or more) or frailty defined by primary care read codes. - Able to read and communicate in English. - Able to provide informed consent.	- Involved in the care of patients with CKD and explaining risk of kidney failure. - Able to provide informed consent.
Exclusion criteria	- Children and young people aged <18 years. - Individuals already established on chronic kidney replacement therapy, in the form of dialysis or a transplant. - Patients approaching end of life. - Unable to give informed consent. - Unable to read or communicate in English.	- Not involved in the care of patients with CKD. - Unable to provide informed consent.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

Scottish Index of Multiple Deprivation (SIMD) decile to be determined) and their main healthcare setting experience. Additionally, patient participants will be asked about long-term conditions that they currently have, medications they are prescribed and to complete, with assistance from the interviewer, a clinical frailty scale as measurements of multimorbidity and frailty.

Interviews and focus groups will be performed/facilitated by one member of the research team (HW). Interviews will take place in the participants' homes, in a secondary care clinic room or online via Zoom video conferencing software, depending on participant preference. Focus groups will take place in a hospital or GP practice meeting room or online, dependent on suitability/participant preference. Interviews will be offered to those who cannot attend focus groups. Interviews and focus groups will be digitally recorded and transcribed verbatim.

Data analysis

Data collection has been developed around the components of the ODSF. An alternative framework has been chosen for data analysis. Framework analysis,^{36,37} underpinned by normalisation process theory (NPT),^{34,35} will be used to develop codes and explore themes from the interview and focus group transcripts. The five stages of framework analysis, as described by Ritchie and Lewis, will be followed: familiarisation, identifying a thematic framework, indexing, charting, mapping and interpretation.^{36,37} NPT is a middle-range theory^{38,39} that has been developed to understand the implementation, organisation and utilisation of processes and practices that are embedded, integrated and sustained in day-to-day life.³⁸ The theory is divided into four mechanisms: coherence (making sense of processes), cognitive participation (engagement, organisation and commitment of individuals to tasks), collective actions (enablement of efforts and resources for practices including doing tasks and communicating knowledge) and reflexive monitoring (appraisal of cost and benefits of tasks and reorganising based on this evaluation).³⁴ It has been used to understand the implementation of healthcare interventions from an HCP perspective,³⁹ the embedding of treatments in the everyday life of a patient⁴⁰ and to understand the treatment burden and the burden of self-care practices in patients with chronic diseases.⁴⁰ NPT, therefore, provides a way of exploring and understanding the social processes that allow new models of care to be incorporated in healthcare settings. Self-care practices and SDM have similarities, for example, both involve patient roles/responsibilities and interactions with HCPs. We propose that NPT is a useful framework to aid understanding of how SDM is implemented and embedded in a patient's life and health journey, and how HCPs implement and sustain a new process (here KFRE) in the SDM care of patients.

The analysis will primarily be conducted by the lead researcher on the project (HW), and 10% of transcripts

will be check-coded by a second individual (KIG) to reduce unconscious bias within the analysis.

The analysis will be performed by using NVivo data analysis (V.14 (QSR International (UK))).

Ethics and dissemination

Ethical approval was granted in August 2023 by the NHS Health Research Authority following a favourable opinion from the West of Scotland Research Ethics Committee (REC) 3 (IRASID: 325848, REC reference: 23WS/0119, Protocol number GN22RE559).

There is a possibility that individuals recruited from primary care may be unaware of their CKD diagnosis prior to recruitment, making this information new to them. This could be viewed as both a potential risk and a benefit. Individuals taking part in the research will be offered the chance to have their kidney failure risk score calculated and discussed with them. Discussing the possibility of worsening kidney function could be difficult and this topic will be approached sensitively, with the option to withdraw from the study if desired, and encouragement to speak to their usual health professional if upset occurs. Distress protocols for participants and researchers have been developed in case any distress related to the study occurs.

The findings of the study will be reported following the Consolidated criteria for Reporting Qualitative Research checklist.⁴¹

Findings will be published in a peer-reviewed, open-access journal, in line with Wellcome's research output guidance—to allow work to be accessed free of cost and without restriction. Permission will be sought on consent forms for future use of fully anonymised data for the purposes of teaching or research (secondary analysis) for up to 10 years after the study has ended.

Findings will be disseminated to academic colleagues through presentations at national and international conferences.

Results from the study will be fed back to PPIE groups that have been involved in the study, prior to and following publication. Results will also be feedback to participating GP practices via NRS PCRN and included in SHARE newsletters. A lay report will be produced and disseminated through the third-sector and social media. To share information and exchange the results of the study, a knowledge exchange event for participants, patients, carers and members of the public following the completion of the project is planned. Kidney research charities and community groups, as well as our PPIE groups, will be approached to help advertise and widen the reach of our knowledge exchange event.

Dissemination to clinicians will be facilitated through a national KFRE implementation group and sharing of findings with clinical guidance policy makers such as NICE and KDIGO.

Equity of access to the study

This study is being conducted in GGC, Scotland. The location provides diversity in ethnicity and socioeconomic



deprivation.⁴² Efforts will be made to recruit individuals proportionate to the background demographics of the Scottish population (based on age, gender, ethnic group and SIMD) where possible within the constraints of time and resources of the study.

Patient and public involvement and engagement

The study development has been informed by six people with lived experience of CKD (the University of Glasgow West of Scotland Kidney PPIE group). They will continue to identify the key areas they feel PPIE would be useful, advise on recruitment of participants and aid dissemination of results with themselves and the wider public.

The study has had further engagement with a similar sized group of patients who do not all specifically have experience of kidney disease (MVLS PPIE group), as we acknowledge the views and ideas of people who have not yet experienced kidney failure might be different to those who have.

The West of Scotland Kidney PPIE group contributed to the development and refinement of participant-facing materials, including participant information sheets, consent forms and interview schedules.

There is future planned involvement for the above PPIE groups in reviewing themes that are identified from the thematic analysis.

Strengths and limitations

This study is designed to explore the understanding of patient and HCP perspectives on kidney failure risk in the context of multimorbidity and/or frailty and how KFRE might be used in SDM. The resulting data and recommendations will be dependent on individuals who participate in the interviews and focus group sessions. The study aims to recruit patients and HCPs from both primary and secondary care, to minimise bias and increase the generalisability of results. However, participants will be recruited from a single region in Scotland, UK, which may limit the diversity of the study participants. Additionally, individuals approaching the end of life, those unable to provide informed consent and those who cannot speak English are excluded from participating in the study, limiting the validation of findings in these populations.

A key strength of this study is that all aspects have been developed in partnership with the patient and public representatives. The study concept and aims and study materials have been reviewed by PPIE groups, as already described. This has ensured that the study has a more patient-centred focus and that participant-facing materials are understandable and accessible to participants.

Underpinning data analysis with middle-range theory will provide strength in informing how SDM can be used in individuals with CKD also experiencing multimorbidity or frailty to explore kidney failure risk.

Impact

We anticipate that the findings from this project have the potential to influence clinical practice, guidelines and

policy in relation to the management of patients with CKD with the added complexities of multimorbidity and/or frailty. In particular, findings will have the potential to promote a more holistic and comprehensive approach and provide an understanding of how best to explore and undertake SDM around kidney failure risk with this subgroup of patients. The study will provide insights into how KFRE or similar prediction tools might be used or impact these individuals and their care.

CONCLUSION

This qualitative study will explore patient and HCP perspectives on kidney failure risk and the use of KFRE in individuals with CKD and multimorbidity and/or frailty. Framework analysis, underpinned by NPT, will guide themes and support recommendations from the study. This under-researched topic is key for guiding HCPs, policy and clinical guidance for this group of patients.

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Contributors HW, MKS, BDJ, PBM and KIG were involved in the conception of the work. HW and KIG designed the methodology, ethical approvals and drafted and revised the protocol. All authors approved the final protocol. HW is the guarantor.

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Competing interests PBM reports lecture honoraria from Astrazeneca, Pharmacosmos, Bayer, Astellas, GSK and Boehringer Ingelheim outside the submitted work.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Appendix 4: Long-term condition ICD-10 code and definitions used in the Stockholm CREATinine Measurements project dataset

Long-term condition	ICD-10 codes		Time	Number required to confirm diagnosis		Prescribing data supplementation requirements
	Inclusions	Exclusions		Hospitalisations	Claims	
Alcohol misuse	E52, F10, G621, I426, K292, K700, K703, K709, T51, Z502, Z714, Z721	N/A	Past 2 years	1	2	N/A
Asthma	J45	N/A	Past 2 years	1	N/A	N/A
Atrial fibrillation	I480	N/A	Past 2 years	1	2	N/A
Cancer	C81, C82, C83, C84, C85, C88, C900, C902, C96, C77, C78, C79, C80, C18, C19, C20, C21, C33, C34, C384, C450, C4671, C50, C53, C61, D010, D011, D012, D013, D022, D05, D075	N/A	Past 2 years	1	2	N/A

Chronic liver disease	K703, K743, K744, K745, K746, I850, I859, I982, I983, K650, K658, K659, K670, K671, K672, K673, K678, K767, K930, R18	N/A	N/A	1	2	N/A
Coronary heart disease	I21, I22	N/A	N/A	1	N/A	N/A
Dementia	F00, F01, F02, F03, F051, G30, G311	N/A	Past 2 years	1	2	N/A
Depression	F204, F313, F314, F315, F32, F33, F341, F412, F432	N/A	Past 2 years	1	2	Four or more prescriptions within a year N06AF, N06AX22, N06AX12, N06AB04, N06AX21, N06AB10, N06AB03, N06AB08, N06AF05, N06AF01, N06AX03, N06AX11, N06AG02, N06AX06, N06AB05, N06AF03, N06AX18, N06AB06, N06AF04, N06AX05, N06AX02, N06AX16, N06AX09, N06AX26

Diabetes	E10, E11, E12, E13, E14	N/A	Past 2 years	1	2	N/A
Epilepsy	G40, G41	N/A	Past 2 years	1	2	N/A
Heart failure	I099, I255, I420, I425, I426, I427, I428, I429, I43, I50	N/A	Past 2 years	1	2	N/A
Hypertension	I10, I11, I12, I13, I15	N/A	Past 2 years	1	2	N/A
Inflammatory bowel disease	K50, K51	N/A	Past 3 years	2	2	N/A
Irritable bowel syndrome	K58	C18, C19, C20, C21, C25, C56, C785, C796, D017, D019, D371, D372, D373, D374, D375, K50, K51, K702, K703, K740, K742, K746, K860, K861, K90, K912	Past 2 years	1	2	N/A
Multiple sclerosis	G35, G36, G37, H46	N/A	Past 3 years	2	2	N/A

Painful conditions	F454, M081, M255, M432, M433, M434, M435, M436, M45, M461, M463, M464, M469, M47, M480, M481, M488, "M489, M508, M509, M51, M531, M532, M533, M538, M539, M54, M608, M609, M633, M790, M791, M792, M796, M797, M961	N/A	Two or more codes at least 30-days apart	2	2	Four or more prescriptions within a year N02B, N02A, N02C, N02CC, N02BA01, N02BA51, N02BA71, N02CC05, N02BA02, N02BA10, N02AE01, N02BA03, N02CX02, N02AC01, N02AC04, N02AC54, N02BA11, N02AA08, N02AA58, N02CA01, N02CC06, N02CA02, N02CA52, N02AB03, N02CC07, N02AA03, N02CA07, N02AX05, N02CA04, N02AA01, N02BA13, N02AA09, N02BG10, N02AF02, N02CC02, N02BG06, N02AA02, N02AA10, N02BE01, N02BE51, N02BE71, N02AB02, N02CX01, N02CC04, N02BA06, N02BA04, N02CC01, N02AX06, N02AX02, N02AX52, N02BG08, N02CC03

						If no epilepsy: N03AF01, N03AX12, N03AX16
Parkinson's disease	G20, G21, G22	N/A	N/A	1	1	N/A
Peptic ulcer disease	K257, K259, K267, K269, K277, K279, K287, K289	N/A	Past 2 years	1	2	N/A
Peripheral vascular disease	I702	N/A	N/A	1	1	N/A
Psoriasis	L400, L401, L402, L403, L404, L408, L409	N/A	N/A	1	1	N/A
Chronic Pulmonary disorders	I278, I279, J40, J41, J42, J43, J44, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J684, J701, J703	N/A	Past 2 years	1	2	N/A
Rheumatoid arthritis	M05, M06, M315, M32, M33, M34, M351, M353, M360	N/A	Past 2 years	1	2	N/A
Schizophrenia	F20, F21, F3232, F25	N/A	Past 2 years	1	2	N/A
Severe constipation	K558, K560, K564, K567,	C17, C18, C19, C20,	Past 2 years	1	2	N/A

	K590, K631, K634, K638, K928	C21, C451, C48, C51, C52, C53, C54, C55, C56, C57, C58, C60, C61, C62, C63, C64, C65, C66, C67, C68, C785, C786, D017, D019, D371, D372, D373, D374, D375, K50, K51, K660, N736, N994				
Stroke/Transient ischaemic attack (TIA)	G450, G451, G452, G453, G458, G459, H341, I60, I61, I63, I64	N/A	N/A	1	1	N/A
Thyroid disorders	E00, E01, E02, E03, E890	N/A	Past 2 years	1	2	N/A
Viral hepatitis	B16, B180, B181	N/A	Past 6 months	2	2	N/A

Appendix 5: Supplementary material for Chapter 4: Representation of multimorbidity and frailty in the development and validation of kidney failure prognostic prediction models: a systematic review

Supplemental Table 4- 1. Full inclusion criteria

Inclusion Criteria	Definition
Population	Adult patients aged 18 years or older with CKD (definition as per individual studies) with no previous history of kidney failure or pre-emptive kidney transplantation.
Study Design	Articles reporting the development and/or validation or update of a prediction model with at least one measure to assess model performance.
Year of publication	From inception to 18 th October 2023
Minimum of 3 predictors in model	Articles reporting the development and/or validation or update of a prediction model using a minimum of three predictor variables. At least one of these predictors should be a clinical or demographic variable.
Outcome	Kidney failure/ESKD (as per individual study definitions) or 50% reduction in baseline eGFR.
Time-to-event	Minimum of 2 years.

Supplemental Table 4- 2. Full exclusion criteria

Exclusion Criteria	Definition
Population	Adult patients aged less than 18 years old, the general population or groups without CKD and individuals with a history of kidney failure or kidney transplantation.
Study Design	Articles reporting drug intervention studies, qualitative studies, narrative or systematic reviews. Articles that report the identification of prognostic factors associated with the outcome.
Predictors in model	Articles reporting prediction models using biopsy/pathology or genetic predictors only.
Full text not available	Articles for which the full text is not accessible online or through accessible library resources.
Language	Articles not available in English language.

Supplemental Table 4- 3. Medline (EBSCO interface) search strategy

#1	(MH "Risk Assessment/MT")
#2	(MH "Prognosis")
#3	(MH "Disease Progression")
#4	AB (risk n3 (predict* OR model* OR progress* OR scor* OR factor* OR tool* OR equation*)) OR TI (risk n3 (predict* OR model* OR progress* OR scor* OR factor* OR tool* OR equation*))
#5	AB (predict* n4 (model* OR progress* OR scor* OR factor* OR tool* OR disease* OR equation*)) OR TI (predict* n4 (model* OR progress* OR scor* OR factor* OR tool* OR disease* OR equation*))
#6	S1 OR S2 OR S3 OR S4 OR S5
#7	(MH "Kidney Failure, Chronic/BL/CO/DI/EP/PP/TH/UR")
#8	(MH "Renal Insufficiency, Chronic/BL/CO/EP/PP/UR/TH/DI")
#9	(MH "Renal Replacement Therapy/MT/TD")
#10	AB (RRT OR KRT) OR TI (RRT OR KRT)
#11	AB ((kidney OR renal) AND replacement*) OR TI ((kidney OR renal) AND replacement*)
#12	AB CKD OR TI CKD
#13	AB "chronic kidney disease" OR TI "chronic kidney disease"
#14	AB ((kidney OR renal) AND failure) OR TI ((kidney OR renal) AND failure)
#15	AB ((end-stage* OR endstage*) AND (renal OR kidney)) OR TI ((end-stage* OR endstage*) AND (renal OR kidney))
#16	AB (chronic AND (renal OR kidney) AND (insufficiency OR impairment)) OR TI (chronic AND (renal OR kidney) AND (insufficiency OR impairment))
#17	AB (ESRD OR ESKD) OR TI (ESRD OR ESKD)
#18	AB nephropath* OR TI nephropath*
#19	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
#20	(MH "Humans")
#21	(MH "Adult")
#22	(MH "Middle Aged")
#23	S20 OR S21 OR S22
#24	Develop*
#25	Validat*
#26	S24 OR S25
#27	S6 AND S19 AND S23 AND S26
	Limit to English language

Supplemental Table 4- 4. CINHAL (EBSCO interface) search strategy

#1	(MH "Risk Assessment/MT")
#2	(MH "Prognosis")
#3	(MH "Disease Progression")
#4	AB (risk n3 (predict* OR model* OR progress* OR scor* OR factor* OR tool* OR equation*)) OR TI (risk n3 (predict* OR model* OR progress* OR scor* OR factor* OR tool* OR equation*))
#5	AB (predict* n4 (model* OR progress* OR scor* OR factor* OR tool* OR disease* OR equation*)) OR TI (predict* n4 (model* OR progress* OR scor* OR factor* OR tool* OR disease* OR equation*))
#6	S1 OR S2 OR S3 OR S4 OR S5
#7	(MH "Kidney Failure, Chronic/BL/CO/DI/EP/PP/TH/UR")
#8	(MH "Renal Insufficiency, Chronic/BL/CO/EP/PP/UR/TH/DI")
#9	(MH "Renal Replacement Therapy/MT/TD")
#10	AB (RRT OR KRT) OR TI (RRT OR KRT)
#11	AB ((kidney OR renal) AND replacement*) OR TI ((kidney OR renal) AND replacement*)
#12	AB CKD OR TI CKD
#13	AB "chronic kidney disease" OR TI "chronic kidney disease"
#14	AB ((kidney OR renal) AND failure) OR TI ((kidney OR renal) AND failure)
#15	AB ((end-stage* OR endstage*) AND (renal OR kidney)) OR TI ((end-stage* OR endstage*) AND (renal OR kidney))
#16	AB (chronic AND (renal OR kidney) AND (insufficiency OR impairment)) OR TI (chronic AND (renal OR kidney) AND (insufficiency OR impairment))
#17	AB (ESRD OR ESKD) OR TI (ESRD OR ESKD)
#18	AB nephropath* OR TI nephropath*
#19	S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18
#20	(MH "Human")
#21	(MH "Adult")
#22	(MH "Middle Age")
#23	S20 OR S21 OR S22
#24	Develop*
#25	Validat*
#26	S24 OR S25
	S6 AND S19 AND S23 AND S26
	Limit to English language

Supplemental Table 4- 5. Cochrane Library – CENTRAL search strategy

#1	MeSH descriptor: [Risk Assessment] this term only
#2	MeSH descriptor: [Prognosis] this term only
#3	MeSH descriptor: [Disease Progression] this term only
#4	(risk near/3 (predict* or model* or progress* or scor* or factor* or tool* or equation*)):ti,ab
#5	(predict* near/4 (model* or progress* or scor* or factor* or tool* or disease* or equation*)):ti,ab
#6	#1-#5
#7	MeSH descriptor: [Kidney Failure, Chronic] this term only
#8	MeSH descriptor: [Renal Insufficiency, Chronic] this term only
#9	MeSH descriptor: [Renal Replacement Therapy] this term only
#10	(RRT or KRT):ti,ab
#11	((kidney or renal) and replacement*):ti,ab
#12	CKD:ti,ab
#13	chronic kidney disease:ti,ab
#14	((kidney or renal) and failure):ti,ab
#15	((end-stage* or endstage*) and (renal or kidney)):ti,ab
#16	(chronic and (renal or kidney) and (insufficiency or impairment)):ti,ab
#17	(ESRD or ESKD):ti,ab
#18	nephropath*:ti,ab
#19	#7-#18
#20	MeSH descriptor: [Humans] this term only
#21	MeSH descriptor: [Adult] this term only
#22	MeSH descriptor: [Middle Aged] this term only
#23	{or #20-#22}
#24	Develop*:ti,ab
#25	Validat*:ti,ab
#26	#6 and #19 and #23 and #25

Supplemental Table 4- 6. Overview of included studies – population, setting, CKD definitions, outcome definitions, eGFR equations used

Author	Model	Year	Cohort	CKD definition	Setting	Outcome definition	eGFR equation used
Ali ³⁷⁷	KFRE-4 KFRE-8	2021	Patients referred to advanced kidney care service	eGFR<30	Secondary care	KRT or conservative care	CKD-EPI
Al-Wahsh ²⁸⁸	Al-Wahsh	2021	General Canadian population data with stage 4 CKD	eGFR 15- <30	Primary & secondary care	KRT or eGFR<10	CKD-EPI
Bai ³⁷⁸	5 MLMs KFRE-3	2022	Chinese CKD population	CKD stages 1-5	Secondary care	KRT	Not reported
Bai ³⁷⁹	Renal Risk Score	2021	Chinese AAV cohort	AAV on renal biopsy	Secondary care	KRT	CKD-EPI
Barbour ³⁸⁰	IgA prediction tool Updated IgA prediction tool	2022	European pts from VALIGA study, Chinese, Japanese + European/American pts from Oxford study	Biopsy proven IgAN	Secondary care	eGFR <15 mL/min/1.73m ² , KRT or a permanent reduction in eGFR to <50% of the value at baseline	CKD-EPI
Barbour ³⁸¹	IgA prediction tool Clinical model Limited model	2019	Multi-ethnic cohort from VALIGA study, Oxford study, 2 Chinese & 1 Japanese cohorts	Biopsy proven IgAN	Secondary care	eGFR <15 mL/min/1.73m ² , KRT or a permanent reduction in eGFR to <50% of the value at baseline	CKD-EPI
Barbour ³⁸²	Clinical model Clinical model + MEST score	2016	Pooled cohorts from VALIGA, Oxford + North American	Biopsy proven IgAN	Secondary care	eGFR <15 mL/min/1.73m ² or a permanent reduction in eGFR to <50% of the value at baseline	MDRD

			validation studies with IgAN				
Bellocchio ²⁵⁹	PROGRESS-CKD KFRE-4 KFRE-6	2021	FMC Nephro-Care cohort (Euclid) + GCKD study cohort	eGFR<60 non-dialysis dependent	Secondary care	KRT	CKD-EPI 2009
Belur ³⁸³	4 MLMs, Cox PH model KFRE-8	2020	Adult patients with DKD/T2DM from RENAAL, IDNT + ALTITUDE trials	T2DM + proteinuria (proteinuria levels set for each trial)	Clinical trial	KRT or doubling of serum creatinine from baseline	MDRD
Bon ³⁸⁴	IgA prediction tool with and without ethnicity	2023	French biopsy cohort	Biopsy proven IgAN	Secondary care	KRT or sustained reduction in eGFR <50% of baseline value	CKD-EPI 2009
Bundy ²⁸⁷	KFRE-4	2022	CRIC study participants	eGFR 20-70	Study data	KRT	CKD-EPI (compares old & new equations and Cr, Cys + CrCys equations)
Chen ³⁸⁵	Chen MLM + cox regression model	2019	Chinese IgAN cohort	Biopsy proven IgAN, eGFR ≥ 30 + proteinuria $\geq 0.5\text{g/day}$	Secondary care	eGFR < 15 mL/min/1.73 m ² for more than 3 months or KRT or 50% reduction in eGFR	CKD-EPI
Cheng ³⁸⁶	Cheng - clinical model Lab model Lab-medication model	2020	Chinese hospitalised patients with DKD	Biopsy proven DKD, eGFR 30-60 or albuminuria	Secondary care	KRT	CKD-EPI

	Full model						
Chu ³⁸⁷	KFRE-4	2023	CKD Outcomes and Practice Patterns Study (CKDOPPS) cohort	eGFR<60	Secondary care	KRT	CKD-EPI
da Silva ³⁸⁸	KFRE-4	2023	CKD population referred for vascular access	eGFR<60	Secondary care	KRT	CKD-EPI
da Silva ³⁸⁹	KFRE-4	2022	Patients referred to Portuguese nephrology clinic	eGFR<60	Secondary care	KRT	CKD-EPI
Dai ³⁹⁰	Dai	2021	CKD population identified from administrative claims database	CKD stage 3 or 4 (eGFR 15-60 or ICD-9/10 code)	Administrative claims database (Primary & secondary care)	≥1 medical claim for stage 5 CKD (ICD-10-CM: N18.5) or ESRD (ICD-10-CM: N18.6); ≥1 medical claim for dialysis therapy or kidney transplantation; an eGFR <15	MDRD
Desai ³⁹¹	TREAT ESRD model + cardiac biomarkers	2011	TREAT trial participants	eGFR 20-60 + T2DM + anaemia	Clinical trial	KRT (sustained for at least 30 days or death within 30 days), a physician recommendation to initiate dialysis therapy with documented patient refusal	MDRD
Dimitrov ³⁹²	Renal Risk Index	2003	REIN study participants	CrCl 20-70 or >1g/24hrs proteinuria	Clinical trial data	Not described	measured GFR unlabelled iohexol

Edmonston³⁹³	Edmonston + FGF23	2019	CRIC study participants	eGFR 20-70	Secondary care study data	KRT	CRIC study equation
Fenton³⁹⁴	KFRE-4 + FLCs	2018	RIISC study participants with CKD	eGFR<30 or 30-59 with decline $\geq 5\text{ml/min}$ over 1 yr or $\geq 10\text{ml}$ over 5yrs or ACR $\geq 70\text{mg/mmol}$	Secondary care study data	KRT	CKD-EPI
Floyd³⁹⁵	RRS (Brix)	2023	Multinational biopsy cohort	Biopsy proven Anti-GBM disease	Secondary care and registries	KRT	CKD-EPI
Forsblom³⁹⁶	Forsblom	2014	FinnDiane cohort study participants with T1DM + nephropathy	DKD - T1DM + macroalbuminuria ($\geq 300\text{mg/day}$ or $\geq 200\text{mcg/min}$)	Study data primary & secondary care	KRT	CKD-EPI
Gibertoni²⁶⁰	CT-PIRP	2019	PIRP project participants	Patients referred to nephrology centres by primary care physicians	Primary and secondary care	KRT	CKD-EPI
Grams²⁶⁷	Markov model KFRE-4	2018	CKD prognosis consortium (CKD-PC)	eGFR <30	Primary & secondary care	KRT	CKD-EPI 2009
Grams²⁶¹	KFRE-4 plus other variables	2023	CKD prognosis consortium (CKD-PC)	eGFR <60	Primary & secondary care	KRT	CKD-EPI 2021 + 2009
Haaskjold³⁹⁷	IgA prediction tool IgA CDSS (Schen et al.)	2023	Norwegian Kidney Biopsy Registry	Biopsy proven IgAN, eGFR>30	Biopsy Registry	KRT, eGFR<15ml/min/1.73m ² or decline in eGFR of 50%	Not reported

Hallan ²⁵⁸	KFRE-4	2019	HUNT study CKD 4 participants aged >65 years old	eGFR<45	Cohort study data	KRT	CKD-EPI
Hasengawa ³⁹⁸	Hasegawa	2019	CKD-Japan Cohort (CKD-JAC)	eGFR<60	Secondary care	KRT	Japanese eGFR equation
Hoshino ³⁹⁹	Hoshino	2015	Japanese biopsy cohort	Biopsy proven DKD	Secondary care	KRT	Unclear
Hsu ⁴⁰⁰	Hsu	2017	CRIC study cohort	eGFR 20-70	Study data secondary care	KRT or reduction in eGFR to <50% of the value at baseline	CRIC study equation
Hundemer ²⁶³	KFRE-4	2020	Canadian CKD patients referred to tertiary multi-care kidney clinic	Referred to Multi-Care Kidney clinic	Secondary care	KRT	CKD-EPI
Hwang ⁴⁰¹	Oxford model IgA prediction tool	2021	Patients >20 yrs old with IgAN on biopsy	Biopsy proven IgAN	Secondary care	eGFR <15ml/min/1.73m ² , KRT or reduction in eGFR to <50% of the value at baseline	CKD-EPI
Ingwiller ⁴⁰²	KFRE-4 KFRE-6 KFRE-8	2022	French CKD cohort	eGFR<60, non-dialysis	Secondary care	KRT	CKD-EPI
Irish ⁴⁰³	KFRE-4	2023	Australian, New Zealand and Tasmanian CKD cohort	eGFR<60	Study data	KRT Sensitivity analysis using eGFR<10 ml/min/1.73m ² and <7.5 ml/min/1.73m ²	CKD-EPI
Jahan ⁴⁰⁴	KFRE-3, KFRE-4, KFRE-8	2023	Patients under the care of an Australian CKD MDT programme	eGFR<60, non-dialysis dependent	Secondary care	KRT	Not reported

Jiang ⁴⁰⁵	Jiang	2019	Chinese biopsy cohort	Biopsy proven DKD	Secondary care	KRT	CKD-EPI
Johnson ⁴⁰⁶	Johnson 2008	2008	Health maintenance organisation CKD cohort	eGFR 15-59	Primary & secondary care	KRT	MDRD
Johnson ⁴⁰⁷	Johnson 2007	2007	Health maintenance organisation CKD cohort	eGFR<60	Health maintenance organisation	KRT	MDRD
Kang ⁴⁰⁸	KFRE-4, KFRE-6, KFRE-8	2020	Adult patients with CKD3-5 Korean population	eGFR<60	Secondary care	KRT	MDRD
Knoop ⁴⁰⁹	ARR	2015	Norwegian kidney biopsy registry IgAN cohort	Biopsy proven IgAN	Secondary care registry	KRT	CKD-EPI
Kong ⁴¹⁰	RRS (Brix)	2023	Chinese biopsy cohort	Biopsy proven MPO AAV	Secondary care	KRT	Not reported
Kwan ⁴¹¹	Kwan	2020	CRIC study participants with DKD	eGFR 20-70, diabetes + albuminuria	Study data secondary care	KRT	CRIC study equation, CKD-EPI
Kwek ⁴¹²	KFRE-4, KFRE-8	2022	Multi-ethnic Singapore cohort referred to renal hospital department	eGFR<60	Secondary care	KRT	CKD-EPI
Landray ²⁶⁸	Landray	2010	CRIB study participants with CKD	eGFR<60	Secondary care study data	KRT	MDRD
Lee ⁴¹³	Lee	2018	Sout Korean hospital cohort	eGFR<60ml	Secondary care	KRT	CKD-EPI, MDRD

Lennartz⁴¹⁴	KFRE-4 + resistive index	2016	CARE FOR HOME + Hannover cohort participants	CKD 2-4, CrCl <75% of their normal value for age and sex, proteinuria ≥150 mg/d or hypertension, or other established CKD	Secondary care	KRT or insertion of a peritoneal dialysis catheter	MDRD
Lim⁴¹⁵	Lim KFRE-4	2019	Singapore Epidemiology of Eye Disease study participants with CKD	eGFR<60 or albuminuria >30mg/g	Secondary care study data	eGFR <15ml/min/1.73m ² , serum creatinine >500 μmol/L or KRT	CKD-EPI
Lin⁴¹⁶	Lin	2023	Action to Control Cardiovascular Risk in Diabetes (ACCORD) clinical trial	CKD + T2DM (not fully described)	Clinical trial	KRT or eGFR <15ml/min/1.73m ² ,	MDRD
Maher¹⁷⁰	KFRE-4, KFRE-4 + ethnicity	2023	UK primary care cohort	eGFR<60	Primary care	KRT	CKD-EPI, MDRD
Major¹⁶⁹	KFRE-4	2019	UK primary care cohort	eGFR<60	Primary care	KRT	CKD-EPI, MDRD
Massy⁴¹⁷	KFRE + Urine Peptidome	2023	French CKD-Renal Epidemiology and Information Network (REIN) cohort	eGFR<60	Secondary care	KRT	CKD-EPI
Maziarz⁴¹⁸	Maziarz	2015	American safety net healthcare systems, homeless cohort	eGFR<60	Primary and secondary care Urban	KRT	MDRD

					poor population		
Maziarz ⁴¹⁹	Maziarz2	2014	American safety net healthcare systems	eGFR<60	Primary and secondary care (homeless and poor population)	KRT	MDRD
Naranjo ⁴²⁰	KFRE-3, KFRE-4	2021	American electronic health records system	eGFR<60	Secondary care outpatient	KRT or CKD stage 5	CKD-EPI
Orlandi ⁴²¹	Orlandi	2018	CRIC study participants	eGFR 20-70	Primary and secondary care study data	≥50% decrease in eGFR from baseline or KRT	CRIC study equation
Ouyang ⁴²²	Barbour IgA prediction tool 2019, KFRE-4	2021	Multicentre Chinese biopsy cohort	Biopsy proven IgAN + eGFR>15	Secondary care	50% decline in eGFR, eGFR <15ml/min/1.73m ² or KRT	CKD-EPI
Park ⁴²³	Hass classification, Oxford classification models	2014	Korean biopsy cohort	Biopsy proven IgA	Secondary care	doubling of the baseline serum creatinine concentration or KRT	CKD-EPI
Peeters ⁴²⁴	KFRE-3, KFRE-4, KFRE-8	2013	MASTERPLAN cohort	eGFR<60	Clinical trial	KRT	MDRD
Pesce ⁴²⁵	Pesce, Berthoux	2016	Multinational IgAN cohorts	Biopsy proven IgAN	Secondary care	KRT	CKD-EPI
Prouvot ²⁶⁶	Grams, KFRE-4, Landray, Marks	2021	PSPA participants >75 years old	eGFR <20ml	Secondary care	KRT	MDRD

Ramspek¹⁶⁷	Grams, KFRE-4, KFRE-8, Landray, Marks, KPNW score (Schroeder et al. 2016), Johnson 2008	2021	EQUAL study participants ≥ 65 years old and SRR cohort	eGFR 8-30ml	Secondary care	KRT	CKD-EPI, MDRD
Sato⁴²⁶	Japanese histologic classification 2013	2015	Japanese biopsy cohort	Biopsy proven IgAN	Secondary care	50% decline in eGFR or KRT	Japanese eGFR equation
Schena⁴²⁷	Schena (CDSS - ANN model, Berthoux, Tanaka, Barbour models)	2021	VALIGA cohort study participants and Greek hospital biopsy cohort	Biopsy proven IgA	Secondary care	eGFR<15ml/min/1.73m ² or KRT	MDRD
Schroeder⁴²⁸	Schroeder	2017	American health maintenance organisation	eGFR 15-59	Secondary care outpatients	KRT	CKD-EPI
Sheer²⁵⁶	Sheer	2022	American administrative claims data cohort	eGFR 15-59 or UACR ≥ 30 mg/g	Primary & secondary care	KRT or CKD stage 5/eGFR <15ml/min/1.73m ² (>1 eGFR value on different dates)	Not reported
Smith⁴²⁹	Smith	2013	Academic Study cohort	eGFR15-59	Secondary care study data	KRT	CKD-EPI
Stefan²⁵⁷	KFRE-4, KFRE + renal chronicity score	2020	Canadian Biopsy cohort	Biopsy proven glomerular disease	Secondary care	KRT	CKD-EPI

Sud ⁴³⁰	Sud	2014	Patients referred to secondary care nephrology clinic	eGFR<60	Secondary care	KRT or all-cause mortality	CKD-EPI
Sun ⁴³¹	Sun	2020	Chinese biopsy cohort	Biopsy proven DKD + eGFR >30	Secondary care	KRT or death due to chronic renal failure or ESRD	Not reported
Tangri ¹⁰	KFRE-4, KFRE-6, KFRE-8	2016	CKD prognosis consortium (CKD-PC)	eGFR<60	Primary & secondary care	KRT	CKD-EPI 2009
Tangri ⁴³²	Dynamic model, KFRE=8	2017	CKD patients referred to Canadian CKD outpatient clinic	eGFR <60	Secondary care outpatient	KRT	CKD-EPI 2009
Tangri ⁹	KFRE-4, KFRE-6, KFRE-8	2011	CKD patients referred to Canadian CKD outpatient clinic	eGFR <60	Secondary care	KRT	CKD-EPI 2009
Thanabalasingam ⁴³³	Grams, KFRE-4	2022	CKD patients referred to Canadian CKD MDT outpatient clinic	eGFR<60	Secondary care	KRT	CKD-EPI
van den Brand ⁴³⁴	KFRE-4 KFRE-4 + slope eGFR	2019	MASTERPLAN and NephroTest cohorts	eGFR 30-60	Secondary care study data	KRT, death due to kidney failure or eGFR <15ml/min/1.73m ²	CKD-EPI 2009
Wang ²⁶²	KFRE-4	2019	Singapore primary care cohort	eGFR <60	Primary care	Serum creatinine ≥880 μmol/L, eGFR/CrCl <15ml/min/1.73m ² , KRT	CKD-EPI, MDRD
Wang ⁴³⁵	Wang	2017	Chinese biopsy cohort	Biopsy proven, glomerular disease, urine protein	Secondary care	eGFR<15ml/min or KRT	CKD-EPI

				>0.3g/24hrs, eGFR $\geq$ 15			
Wang ⁴³⁶	RRS	2023	Multicentre Chinese biopsy cohort	Biopsy proven ANCA GN	Secondary care	KRT	CKD-EPI, MDRD
Whitlock ⁴³⁷	KFRE-4	2017	Unreferred Canadian general primary care CKD cohort	eGFR<60	Primary care	KRT	CKD-EPI
Wu ⁴³⁸	Wu	2022	Chinese biopsy cohort	Biopsy proven MPO AAV	Secondary care	KRT or death	CKD-EPI
Xie ⁴³⁹	Clinical Progression Risk Score, Goto, RENAAL (Keane et al.), Berthoux models	2012	Chinese biopsy cohort	Biopsy proven IgAN	Secondary care	KRT	MDRD modified for Chinese population
Xie ⁴⁴⁰	Xie	2016	American safety- net healthcare system, CKD cohort	eGFR<60, non- dialysis dependent	Primary & secondary care	KRT or death	MDRD
Xu ⁴⁴¹	Xu	2021	Dryad Digital Repository	CKD stage 2-5 + visited a nephrology centre	Secondary care study data	KRT or >50% decline in eGFR	Not reported
Yamanouchi ²⁷⁰	KFRE-4, D- score, KFRE + D-score	2018	Multicentre Japanese biopsy cohort	Biopsy confirmed DKD, eGFR<60	Secondary care	KRT or death from uraemia	MDRD
Yang ⁴⁴²	MEST score + MMP7	2020	Chinese biopsy cohort	Biopsy proven IgAN, eGFR $\geq$ 30	Secondary care	$\geq$ 40% decline in eGFR (two measurements at least 30 days apart),	CKD-EPI

						KRT, eGFR <15ml/min/1.73m ² , KRT or death	
Ye ⁴⁴³	Ye	2022	CRIC study participants with T2DM	eGFR 20-70	Secondary care study data	KRT	CKD-EPI
Yuan ²⁴²	Yuan	2020	Chinese hospital CKD cohort	eGFR 30-60 (eGFR cut-off <43ml/min used in models)	Secondary care	Sustained eGFR<15ml/min/1.73m ²	CKD-EPI for Chinese patients
Zacharias ⁴⁴⁴	KFRT risk model, KFRE- 4	2022	SKS, CKD-REIN, GCKD, MMKD cohorts	CKD stages 1-5	Study data	KRT	CKD-EPI
Zacharias ⁴⁴⁵	KFRE-4 plus NMR spectroscopy, KFRE-4	2019	GCKD cohort	eGFR 30-60 or >60 + overt proteinuria	Secondary care	KRT	CKD-EPI
Zhang ⁴⁴⁶	Zhang	2022	Chinese chronic disease management clinic cohort	eGFR<60	Secondary care	KRT or death	CKD-EPI
Zhang ⁴⁴⁷	IgA prediction tool (Barbour)	2020	Chinese biopsy cohort	Biopsy proven IgAN cohort		50% decline in eGFR, eGFR <15ml/min/1.73m ² or KRT	CKD-EPI
Zhang ⁴⁴⁸	Zhang LN model	2021	Chinese biopsy cohort	Biopsy proven LN	Secondary care	All-cause mortality, persistent decline in eGFR to 50% of baseline level, KRT	CKD-EPI
Zhang ⁴⁴⁹	Zhang DKD model	2021	Chinese multicentre biopsy cohort	Biopsy proven DKD	Secondary care	KRT or all-cause mortality	CKD-EPI

Zhang ²⁶⁹	KFRE-4 + pathology	2023	China Kidney Biopsy Cohort Study	Biopsy proven glomerular disease	Secondary care	KRT or $\geq 40\%$ decrease in eGFR	CKD-EPI 2009
Zhu ⁴⁵⁰	Zhu dynamic model	2020	African American Study of Kidney Disease and Hypertension (AASK) study cohort	eGFR 20-65 and hypertension	Clinical trial	KRT or death	measured GFR
Zhu ⁴⁵¹	Zhu FSGS model	2022	Chinese biopsy cohort	Biopsy proven FSGS, eGFR ≥ 15	Secondary care	KRT or eGFR $< 15\text{ml/min/1.73m}^2$	MDRD modified eGFR for Chinese patients
Zou ⁴⁵²	Zou MLM	2022	Chinese biopsy cohort	Biopsy proven DKD, T2DM, eGFR > 15	Secondary care	KRT or eGFR $< 15\text{ml/min/1.73m}^2$	CKD-EPI

*Baseline comorbidity data reported for overall cohort from which study sample was taken, not reported for participants included in final model development/validation cohorts

Supplemental Table 4- 7. Summary of original models

Author	Year	Model	Number of variables	Variables
Al-Wahsh	2021	Al-Wahsh	15	Age (10 years), age (squared term), male sex, log ACR, eGFR, CVD, diabetes, male sex*eGFR, CVD*eGFR, diabetes*eGFR, diabetes*log ACR, CVD*age, CVD*age squared, CVD*log ACR, CVD*diabetes.
Bai	2021	5x MLM	Unclear	-
Barbour	2016	MEST score + clinical data	3 (clinical data at biopsy model)	eGFR, proteinuria, MAP (at time of biopsy)
			3 (clinical data over 2 years model)	eGFR, proteinuria, average MAP (over 2 years)
			8 (clinical data + MEST model)	eGFR, proteinuria, MAP, MEST1T2
Barbour	2019	IgA prediction tool	3 (clinical model)	eGFR, MAP, proteinuria
			7 (clinical model + MEST)	eGFR, MAP, proteinuria, M1, E1, S1, T1/T2
			13 (full model with race)	eGFR, MAP, proteinuria, M1, E1, S1, T1/T2, proteinuria x T1/T2, proteinuria x MAP, age, race, RASB, immunosuppression
			13 (full model without race)	eGFR, MAP, proteinuria, M1, E1, S1, T1/T2, proteinuria x T1/T2, proteinuria x MAP, age, RASB, immunosuppression, proteinuria x RASB
Bellocchio	2021	PROGRESS-CKD	34	age, gender, body mass index, smoking status, albumin, uACR, calcium, eGFR, slope of linear regression of eGFR over last 12 months, Haemoglobin, phosphate, urine protein, PTH, sodium, ferritin, aetiology of kidney disease (diabetes, hypertension, GN, PKD), comorbidities

				(cerebrovascular disease, chronic pulmonary disease, CHF, CTD, CAD, dementia, diabetes with organ damage, diabetes without complications, hemiplegia, hypertension, mild liver disease, mod-severe liver disease, PVD), number of hospitalisations, SBP
Belur	2020	4x MLMs	4 (final feed forward neural network model)	uACR, albumin, uric acid, creatinine
			5 (FNN 3)	uACR, albumin, phosphorus, Haemoglobin, creatinine
			7 (FNN 2)	age, uACR, serum albumin, serum uric acid, Haemoglobin, SBP and creatinine
			8 (FNN 1)	age, uACR, serum albumin, phosphorus, serum uric acid, Haemoglobin, SBP and creatinine
Chen	2019	Chen MLMs + cox regression	3 (simplified scoring scale model)	tubular atrophy/interstitial fibrosis, global sclerosis, and urine protein excretion
			10 (XGBoost prediction model)	tubular atrophy/interstitial fibrosis (%), albumin, global sclerosis (%), hypertension before biopsy, uric acid, microscopic haematuria/RBC count, age, urine protein, mean mesangial score, creatinine
Cheng	2020	Cheng	3 (Clinical model)	age, gender, oral hypoglycaemic drug use
			5 (Lab model)	haemoglobin, NLR, serum cystatin C, eGFR, 24-hour urine protein
			6 (Lab medication model)	haemoglobin, NLR, serum cystatin C, eGFR, 24-hour urine protein, hypoglycaemic drug use
			8 (Full model)	age, gender, haemoglobin, NLR, serum cystatin C, eGFR, 24-hour urine protein, and the use of oral hypoglycaemic drugs

Dai	2021	Dai	12	age, gender, CKD stage, CKD stage switch, hypertension, diabetes mellitus, hyperkalaemia, CHF, PVD, iron deficiency anaemia, prospective episode risk group score, poor adherence to RASB
Desai	2011	TREAT ESRD model + cardiac biomarkers	17 (TREAT ESRD model)	age, sex, race, body mass index, insulin use, eGFR, urea, log uPCR, albumin, prior stroke, prior PVD, prior CHF, cardiac arrhythmia, Haemoglobin, log ferritin, CRP, history of AKI
			18 (TREAT ESRD + cardiac biomarkers model)	age, sex, race, body mass index, insulin use, eGFR, urea, log uPCR, albumin, prior stroke, prior PVD, prior CHF, cardiac arrhythmia, Haemoglobin, log ferritin, CRP, history of AKI, TnT/BNP levels (grouped as one)
Dimitrov	2003	Renal Risk Index	3	serum creatinine concentration (>2.4 mg/dL), 24hr UPE rate (>=3g/dl), Calcium*Phosphate product (>=32.64 mg/dl)
Edmonston	2019	Edmonston +FGF23	11 (Edmonston model)	age, sex, race, diabetes, CHF, hypertension medications, SBP, cholesterol, eGFR, albumin, uACR
			12 (Edmonston model + FGF23)	age, sex, race, diabetes, CHF, hypertension medications, SBP, cholesterol, eGFR, albumin, uACR, FGF23
Forsblom	2014	Forsblom	3 (model 1)	eGFR (2 fractional polynomial), duration of type 1 diabetes mellitus (linear form), HbA1C
			4 (model 2)	eGFR (2 fractional polynomial), duration of type 1 diabetes mellitus (linear form), HbA1C, TNFalphaR1 (-0.5 fractional polynomial))
Gibertoni	2019	CT-PIRP	6	gender, age, proteinuria, baseline eGFR, phosphate levels, diabetes
Grams	2018	Markov model	30	Age, sex, race, eGFR, albumin-to-creatinine ratio, systolic blood pressure, smoking status, diabetes mellitus, history of CVD, age*male, age*black race, age CVD, age*smoker, age*SBP, age* diabetes, age*eGFR, age*uACR, CVD*male, CVD*black race, CVD*SBP, CVD*eGFR, CVD*uACR, smoker*black

				race, smoker*SBP, smoker*diabetes, smoker*eGFR, smoker*uACR, diabetes*eGFR, diabetes*uACR, eGFR*uACR
Hasengawa	2019	Hasegawa	8	age, sex, eGFR, albuminuria, SBP, diabetes, serum albumin + Haemoglobin
Hoshino	2015	Hoshino	3 (model 1)	age, eGFR, proteinuria
			7 (model 2)	Proteinuria, eGFR, pathological score of diabetic nephropathy (D- score) [glomerular classes, tubular atrophy/interstitial fibrosis, interstitial inflammation, hyalinosis, arteriosclerosis]
			8 (model 3)	age, eGFR, urinary protein + (D-score)
Hsu	2017	Hsu	12 (Base model)	age, sex, race/ethnicity, clinical centre, albumin/ creatinine ratio, estimated glomerular filtration rate; diabetes mellitus; cardiovascular disease; systolic blood pressure, body mass index, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, and education
			13 (Base model plus urine biomarker)	age, sex, race/ethnicity, clinical centre, albumin/ creatinine ratio, estimated glomerular filtration rate; diabetes mellitus; cardiovascular disease; systolic blood pressure, body mass index, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker use, education and urine biomarker
Jiang	2019	Jiang	4	urinary protein excretion, CKD stage, extra capillary hypercellularity, glomerular hyalinosis
Johnson	2008	Johnson 2008	6	age, sex, eGFR, diabetes, anaemia, hypertension
Johnson	2007	Johnson 2007	6	age, sex, hypertension, diabetes, eGFR, anaemia

Kwan	2020	Kwan	9 (clinical model)	Baseline data of age, race, sex, smoked >100 cigarettes in lifetime, body mass index, HbA1c, mean arterial pressure, urine albumin, and eGFR
			13 (metabolite model)	aconitic acid, citric acid (nucleotide metabolism: tricarboxylic acid [TCA] cycle); uracil (nucleotide metabolism: purine); 3-hydroxyisobutyrate, 2-methylacetoacetate, 3- hydroxyisovalerate, 2-ethyl-3-hydroxypropionate, 3-methylcrotonylglycine, tiglylglycine (amino acid metabolism: valine, leucine, and isoleucine); homovanillic acid (amino acid metabolism: phenylalanine and tyrosine); glycolic acid, 3-methyladipic acid, and 3-hydroxypropionate
			22 (clinical metabolite model)	Baseline data of age, race, sex, smoked >100 cigarettes in lifetime, body mass index, HbA1c, mean arterial pressure, urine albumin, and eGFR + aconitic acid, citric acid (nucleotide metabolism: tricarboxylic acid [TCA] cycle); uracil (nucleotide metabolism: purine); 3-hydroxyisobutyrate, 2-methylacetoacetate, 3- hydroxyisovalerate, 2-ethyl-3-hydroxypropionate, 3-methylcrotonylglycine, tiglylglycine (amino acid metabolism: valine, leucine, and isoleucine); homovanillic acid (amino acid metabolism: phenylalanine and tyrosine); glycolic acid, 3-methyladipic acid, and 3-hydroxypropionate
Landray	2010	Landray	4	log creatinine, log phosphate, log uACR, and sex
Lee	2018	Lee	4 (CKD stage 5 model)	haemoglobin, urea, MDRD eGFR, urinary protein
			10 (CKD stage 4 model)	age, sex, diabetes mellitus, GN, PKD, haemoglobin, urea, calcium, MDRD eGFR, urinary protein
			10 (CKD stage3 model)	age, sex, DM, PKD, albumin, haemoglobin, phosphorus, potassium, CKD-EPI eGFR, urinary protein
Lim	2019	Lim	3 (model 1)	age, sex, eGFR

			4 (model 2)	age, sex, eGFR, uACR
			5 (model 3)	age, sex, eGFR, uACR, race
			6 (model 4)	age, sex, eGFR, uACR, diabetes, hypertension
			6 (model 5)	age, sex, eGFR, uACR, diabetes, hyperlipidaemia
Lin	2023	Lin	12	female sex, race, smoking status, age at type 2 diabetes mellitus, diagnosis, SBP, heart rate, HbA1c, eGFR, uACR, retinopathy event occurring in last year, antihypertensive drug use, interaction term between SBP and female
Maziarz	2015	Maziarz	4 (model 1)	age, sex, race-ethnicity and eGFR
			6 (model 2)	age, sex, race-ethnicity, eGFR, dipstick proteinuria and an interaction between eGFR and dipstick
			12 (model 3)	age, sex, race-ethnicity, eGFR, dipstick proteinuria and an interaction between eGFR and dipstick, health insurance coverage, comorbidities (diabetes mellitus, CVD, hypertension, substance abuse and chronic viral disease)
			16 (model 4)	age, sex, race-ethnicity, eGFR, dipstick proteinuria and an interaction between eGFR and dipstick, health insurance coverage, comorbidities (diabetes mellitus, CVD, hypertension, substance abuse and chronic viral disease), additional laboratory variables (albumin, calcium, haemoglobin and cholesterol)
Maziarz	2014	Maziarz2	4 (model 1)	age, sex, race-ethnicity and eGFR
			6 (model 2)	age, sex, race-ethnicity, eGFR, dipstick proteinuria and an interaction between eGFR and dipstick

			12 (model 3)	age, sex, race-ethnicity, eGFR, dipstick proteinuria and an interaction between eGFR and dipstick, health insurance coverage, comorbidities (diabetes mellitus, CVD, hypertension, substance abuse and chronic viral disease)
			16 (model 4)	age, sex, race-ethnicity, eGFR, dipstick proteinuria and an interaction between eGFR and dipstick, health insurance coverage, comorbidities (diabetes mellitus, CVD, hypertension, substance abuse and chronic viral disease), additional laboratory variables (albumin, calcium, haemoglobin and cholesterol)
Orlandi	2018	Orlandi	11 (model 1)	age, race, sex, eGFR, albuminuria, diabetes, systolic blood pressure, body mass index, waist circumference, NT-pro-BNP, serum albumin
			12 (model 2)	age, race, sex, eGFR, albuminuria, diabetes, systolic blood pressure, body mass index, waist circumference, NT-pro-BNP, serum albumin, haematuria
			13 (model 3)	age, sex, eGFR, albuminuria, diabetes, waist circumference, NT-pro-BNP, FGF-23, Calcium, PTH, serum albumin, uric acid, triglycerides
			14 (model 4)	age, sex, eGFR, albuminuria, diabetes, waist circumference, NT-pro-BNP, FGF-23, Calcium, PTH, serum albumin, uric acid, triglycerides, haematuria
Pesce	2016	Pesce	6	Gender, age, histological grading, serum creatinine, 24hr proteinuria, hypertension
Schena	2021	Schena (CDSS - ANN model)	13	age, sex, SBP, DBP, serum creatinine MESTC, 24-hour proteinuria, RASB, immunosuppression

Schroeder	2017	Schroeder KPNW score	8	age, sex, eGFR, haemoglobin, presence of proteinuria or albuminuria, systolic blood pressure, antihypertensive use, and the Diabetes Complications Severity Index
Sheer	2022	Sheer	21 (logistic regression with backward elimination model)	age, sex, race, CHF, PVD, hypertension (complicated), COPD, fluid/electrolyte disorder, complicated diabetes, liver failure, anaemia, smoking, eGFR category, uACR category, LDL category, HDL category, serum creatinine, HbA1c, adherence to insulin, diuretics, physician encounters
			22 (LASSO model)	sex, race, CHF, PVD, hypertension (complicated), COPD, fluid/electrolyte disorder, complicated diabetes, liver failure, anaemia, smoking, eGFR category, uACR category, serum creatinine, HbA1c, metformin, insulin, statins, beta blockers, calcium channel blockers, diuretics, physician encounters
Smith	2013	Smith	5	CVD, eGFR, triglyceride, uPCR, uNCR
Sud	2014	Sud	12	age, sex, DBP, eGFR, albumin, phosphate, bicarbonate, urea nitrogen, albuminuria, HF, hypertension, diabetes
Sun	2020	Sun	4 (clinical model)	cystatin C, eGFR, BNP, log uACR
			5 (clinical-pathological model)	Pathological grade, cystatin C, eGFR, BNP, log uACR
			5 (clinical-medication model)	RASB use, cystatin C, eGFR, BNP, log uACR
			7 (full model)	Age, pathological grade, RASB use, cystatin C, eGFR, BNP, log uACR
Tangri	2011	KFRE	3-var KFRE	age, sex, eGFR

			4-var KFRE	age, sex, log uACR, eGFR
			6-var KFRE	age, sex, log uACR, eGFR, diabetes, hypertension
			8-var KFRE	age, sex, eGFR, uACR, albumin, phosphate, bicarbonate, calcium
Tangri	2017	Dynamic model	8	age, sex, eGFR, uACR, albumin, phosphate, bicarbonate, calcium (dynamic laboratory measures except uACR)
van den Brand	2019	van den Brand - cox PH model	4 (cox PH model with time varying eGFR)	age, sex, uACR, eGFR at 2 year follow up
			5 (cox PH model with slope eGFR)	age, sex, uACR, eGFR at landmark time and eGFR slope
			6 (shared parameter joint model)	sex, age, uACR, current eGFR, eGFR slope + follow up time
Wang	2017	Wang	5 (model 1)	eGFR, urine protein, blood pressure, age, sex
			6 (model 2)	urinary fibrinogen, eGFR, urine protein, blood pressure, age, sex
Wu	2022	Wu	3 (clinical model)	age, eGFR, proteinuria
			4 (clinical model +MMP7)	age, eGFR, proteinuria, uMMP7
			6 (clinpath model)	age, eGFR, proteinuria, % normal glomeruli, tubular atrophy/interstitial fibrosis
			7 (clinpath model + MMP7)	age, eGFR, proteinuria, % normal glomeruli, tubular atrophy/interstitial fibrosis, uMMP7

Xie	2012	Clinical Progression Risk Score	4	eGFR, Haemoglobin, serum albumin, SBP
Xie	2016	Xie	5 (model 1)	eGFR, dipstick proteinuria, residual associations with age, sex, and race-ethnicity
			11 (model 2)	eGFR, dipstick proteinuria, residual associations with age, sex, and race-ethnicity, health insurance coverage, comorbidities (diabetes mellitus, CVD, hypertension, substance abuse and chronic viral disease)
			15 (model 3)	eGFR, dipstick proteinuria, serum albumin, calcium, cholesterol and haemoglobin, residual associations with age, sex, and race-ethnicity, health insurance coverage, comorbidities (diabetes mellitus, CVD, hypertension, substance abuse and chronic viral disease)
Xu	2021	Xu	5	Disease aetiology, proteinuria (+/-), Haemoglobin, creatinine, uPCR
Yamanouchi	2018	D-score	5	glomerular lesions, tubular atrophy/interstitial fibrosis, interstitial inflammation, arteriolar hyalinosis, arteriosclerosis
Yang	2020	MEST score + MMP7	3 (clinical model)	MAP, proteinuria, eGFR
			8 (clinical model + MEST-C)	MAP, proteinuria, eGFR, MEST-C
			9 (clinical model + MEST-C + urinary biomarker)	MAP, proteinuria, eGFR, MEST-C, urinary biomarker (5 different biomarkers added individually)
			13 (clinical model + MEST-C + all urinary biomarkers)	MAP, proteinuria, eGFR, MEST-C + uMMP7 + AGF, + EGF + KIM1 + serum Gd-IgA1

Ye	2022	Ye	8	age at diabetes diagnosis, sex, body mass index, SBP, eGFR, uPCR, CHF, myocardial infarction
Yuan	2020	Yuan	30 (CKD3A model)	Albumin, proteinuria, total protein, total bilirubin, direct bilirubin, albumin-to-globulin ratio, haemoglobin, serum calcium, eGFR, blood haematocrit, total cholesterol, ALT, HDL, urine specific gravity, serum creatinine, urea, age, blood glucose, red blood cells, potassium, LDL, triglycerides, lymphocyte percentage, diabetes, neutrophil percentage, monocyte percentage, eosinophil percentage, mean corpuscular haemoglobin concentration, urine glucose, urine pH
			30 (CKD3B model)	Serum creatinine, eGFR, total protein, total cholesterol, urea, eosinophil percentage, albumin, mean corpuscular haemoglobin, total bilirubin, diabetes, AST, eosinophil count, sodium, HDL, chloride, proteinuria, age, direct bilirubin, LDL, urine glucose, MCV, triglycerides, lymphocyte count, globulin, HDL:total cholesterol ratio, red blood cell volume distribution, glucose, platelet volume distribution width, red blood cell count, haemoglobin
Zacharias	2022	KFRT risk model	6	serum creatinine, serum cystatin C, UACR, serum urea, Haemoglobin, serum albumin (all log transformed)
Zhang	2022	Zhang	3 (model A)	Age, eGFR, urine protein
			8 (model B)	Age, eGFR, urine protein, haemoglobin, serum uric acid, cardiovascular disease, primary disease, chronic disease management adherence
			8 (model C)	Age, eGFR, urine protein, alpha-blockers, beta-blockers, calcium supplements, Chinese herbal decoction, Chinese patent medicines for dispelling turbidity
			13 (model D)	Age, eGFR, urine protein, haemoglobin, serum uric acid, cardiovascular disease, primary disease, chronic disease management adherence, alpha-

				blockers, beta-blockers, calcium supplements, Chinese herbal decoction, Chinese patent medicines for dispelling turbidity
Zhang	2021	Zhang LN model	8	Haemoglobin, eGFR, serum albumin, sex, ISN/RPS class, tubular atrophy/interstitial fibrosis, proteinuria (tertiles), proteinuria/albumin interaction
Zhang	2021	Zhang DKD model	3 (model 1)	Baseline eGFR, urine proteinuria, albumin
			3 (model 2)	Modified arteriosclerosis score. Baseline eGFR and urine proteinuria.
Zhu	2020	Zhu dynamic model	8	Four longitudinal biomarkers (eGFR, urine protein, albumin, SBP) plus gender, age at time of prediction, eGFR slope and blood pressure volatility
Zhu	2022	Zhu FSGS model	3	eGFR, haematuria, percentage of sclerosis
Zou	2022	Zou MLM	5	cystatin C, Haemoglobin, serum albumin, urinary total protein, eGFR
Berthoux*(123)	2011	ARR	3	hypertension, proteinuria of ≥ 1 g/24 h and severe pathologic lesions
Brix*(124)	2018	Renal Risk Score	3	Normal glomeruli (%), tubular atrophy/interstitial fibrosis (%), renal function at time of diagnosis (eGFR)
Cattran*(125)	2009	Oxford classification	4	Mesangial hypercellularity score, segmental glomerulosclerosis, endocapillary proliferation, tubular atrophy/interstitial fibrosis
Goto*(126)	2009	Goto	8	Sex, age, SBP, proteinuria, haematuria, serum albumin, eGFR, histological grade
Haas*(127)	1997	Haas classification	5	Mesangial hypercellularity, glomerular sclerosis, focal proliferative GN, diffuse proliferative GN, tubular atrophy/loss
Kawamura*(128)	2013		4 (model 1)	glomerular lesion percentage score, initial MAP, proteinuria, eGFR,

		Japanese histologic classification 2013	6 (model 2)	glomerular lesion percentage score, initial MAP, proteinuria, eGFR, immunosuppressive therapy, RASB
Keane*(129)	2006	RENAAL	4	Mesangial hypercellularity, segmental glomerulosclerosis, endocapillary hypercellularity, tubular atrophy/interstitial fibrosis
Marks*(130)	2015	Marks	4	Age, sex, eGFR, proteinuria
Sethi*(131)	2017	Renal chronicity score	4	Glomerulosclerosis, interstitial fibrosis, tubular atrophy, arteriolosclerosis
Tanaka*(132)	2013	Tanaka	5	Urinary protein excretion, eGFR, MST

*Original study developing model not included in the review

Supplemental Table 4- 8. Baseline characteristics of included studies

Author	Year	Participants (n)	Outcome events (n)	Death events (n)	Female n (%)	Age Mean (SD)	eGFR (mean)	Diabetes (%)	Hypertension (%)	CVD (%)
Ali	2021	743	331	164	281 (37.8)	67.5 (15.0)	15.7 (3.7)	39.8	97.3	-
Ali 2021 2-year validation		743	257	101	-			-	-	-
Al-Wahsh	2021	14619	3265	6582	7549 (51.6)	74.1 (12.8)	27.2 (2.9)	67.6	-	56.7
Al-Wahsh 2021 validation		2295	722	875	1143 (49.8)	71.9 (14)	24.7 (3.7)	-	-	34.7
Bai	2022	748	70	Not reported	329 (44.0)	57.8 (17.6)	48.8 (26.1)	55.5	74.6	23.7
Bai	2021	65	34	8	33 (50.8)	61.8 (10.2)	12.9 (11.5)	-	-	-
Barbour	2022	2507	385	Not reported	1033 (41.2)	37 (12.6)	82.7 (37.8)	-	-	-
Barbour 2022 validation		722	123	Not reported	324 (44.9)	37 (12.6)	81 (31.9)	-	-	-
Barbour	2019	2781	492	35	1173 (42.2)	36.4 (12.8)	82.7 (38.0)	-	-	-
Barbour 2019 validation		1146	213	0	581 (50.7)	35.6 (13.4)	89.2 (35.2)	-	-	-
Barbour	2016	901	162	Not reported	261 (29.0)	38.8 (14.9)	68.5 (29.8)	-	-	-
Bellocchio	2021	9407	1817	Excluded	-	-	-	-	-	-
Bellocchio 2021 validation		3684	80	Excluded	-	-	-	-	-	-
Belur	2020	11789	1280	Not reported	-	-	-	-	-	-
Bon	2023	473	98	32	127 (26.8)	37.3 (17.1)	84.7 (30.8)	-	-	-
Bundy	2022	3873	856	Not reported	1751 (45.2)	57.8 (10.9)	44.4 (25.3)	48.2	91.3	
Chen	2019	1022	74	Not reported	496 (48.5)	34.6 (9.4)	90.7 (29.2)	0	42.8	-
Chen 2019 validation		1025	114	Not reported	512 (50.0)	35 (9.8)	85.2 (31.7)	0	32.8	-

Cheng	2020	641	272	Excluded	260 (40.6)	56.0 (11.9)	56.6 (72.4)	100	70.0	9.0*
Cheng 2020 validation		280	138	Excluded	167 (59.6)	51.7 (10.4)	55.4 (33.9)	100	79.6	11.8*
Chu	2023	1641	268	180	799 (48.7)	68.6 (13)	28.3 (12.6)	57.8	91.8	31.7*
da Silva	2023	256	159	40	91 (35.5)	70.4 (12.9)	16.1 (10.4)	-	-	-
da Silva	2022	360	23	86	164 (45.6)	74.9 (12.2)	33.4 (12.1)	45.3	90.6	47.8
Dai	2021	74114	2476	Excluded	42419 (57.2)	74.4 (9.7)	-	40.0	89.7	27.1*
Desai	2011	1000	222	185	558 (55.8)	67.7 (10.7)	34.9 (11.7)	100	-	38.8*
Dimitrov	2003	344	80	Not reported	-	-	-	-	-	-
Edmonston	2019	3879	929	823	1737 (44.8)	57.7	42.8 (13.5)	48.5	86.1	22.0
Fenton	2018	556	60	34 - excluded from analysis	205 (36.9)	63.7 (18.6)	26 (11.1)	35.3	-	21.6*
Floyd	2023	174	106	53 - unclear how many before or after ESKD	99 (56.9)	58 (18.7)	8.2 (6.0)	-	-	-
Forsblom	2014	459	130	59	200 (43.6)	41.6 (10.6)	57.7 (28.4)	100	92.6	19.0*
Gibertoni	2019	2265	536	657	790 (34.9)	71.2 (12.9)	29 (13.1)	32.6	-	-
Gibertoni 2019 validation		2051	not reported	not reported	679 (33.1)	74.8 (13)	29.6 (18.7)	38.1	-	-
Grams	2018	264296	31541	123985				-	-	-
Grams	2023	91578	4609	Not reported	49452 (54.0)	73 (11)	43 (13)	-		36.0*
Grams 2023 validation		142591	3693	Not reported	65592 (46.0)	74 (11)	45 (12)	-	-	32.0*
Haaskjold	2023	306	151	17	72 (23.5)	37.4 (14)	79.3 (32.6)	-	-	-

Hallan	2019	1188	42	462	675 (56.8)	79.9 (6.8)	35.8 (7.8)	17.2	-	22.8*
Hasengawa	2019	1017	206	27	375 (36.9)	60.6 (11.6)	28.8 (12.5)	38.7	84.0	-
Hasengawa 2019 validation		1017	216	30	359 (35.3)	61.1 (11.1)	27.5 (12.1)	91.5	84.0	-
Hoshino	2015	205	unclear 121	Not reported	55 (26.8)	55.9 (13)	44.4 (22.9)	100	-	-
Hsu	2017	2466	581	Not reported	1131 (45.9)	59.5 (10.8)	43.6 (17.8)	49.7	-	34.4
Hundemer	2020	1293	541	144	501 (38.7)	68 (14.8)	15.3 (5.2)	-	-	-
Hundemer 2-year KFRE cohort		637	406	111	245 (38.5)	67.3 (14.9)	15 (5.9)	-	-	-
Hwang	2021	545	53	Not reported	250 (45.9)	40.0 (14.1)	88.1 (31.7)	5.0	32.1	-
Ingwiller	2022	314	157	Excluded	109 (34.7)	67.1 (13.0)	-	50	-	-
Irish	2023	12861	285	2607	6635 (51.6)	70.7 (10.4)	50.3 (9.3)	55.0	41.2	-
Irish	2023	10429	276	Not reported	5314 (51.0)	70.8 (10.6)	49.9 (9.6)	58.9	50.8	-
Irish	2023	4969	202	Not reported	2479 (49.9)	68.3 (11.9)	48.3 (11)	53.0	48.6	-
Jahan	2023	406	71	112	195 (48.0)	70.9 (12.2)	30.9 (11.7)	53.9	-	-
Jiang	2019	110	48	2	31 (28.1)	52.0 (9.5)	-	100	91.8	25.5
Johnson	2008	9782	323	3130	6184 (63.2)	73 (10)	-	27.6	90.2	-
Johnson	2007	6541	369	2678	4091 (62.5)	74 (-)	-	31.3	85.2	-
Kang	2020	13244	3706	Not reported	5562 (42.0)	59.9 (14.6)	36.1 (17.1)	29.0	47.4	-
Knoop	2015	1134	251	69	305 (26.9)	38 (16)	-	-	36.2	-

Kong	2023	255	73	Not reported	119 (46.7)	58.9 (8.4)	-	12.5	48.2	-
Kwan	2020	1001	359	159	437 (43.7)	59.9 (9.4)	40.6 (11.2)	100	92.5	-
Kwek	2022	1128	252	383	475 (42.1)	67.1 (11.8)	33.0 (16.6)	64.6	-	-
Landray	2010	382	190	150	134 (35.1)	61.5 (14.3)	21.8 (10.7)	17.3	-	44.8
Landray 2010 validation		213	66	65	76 (35.7)	65.1 (13.5)	21.6 (13.6)	26.8	-	43.2
Lee	2018	1625	530	Not reported	897 (55.2)	57.3 (10.6)	39.4 (15.7)	39.4	37.5	-
Lee 2018 validation		1618	473	Not reported	879 (54.3)	58.5 (11.6)	40.6 (25.6)	38.7	34.7	-
Lennartz	2016	403	52	Not reported	168 (41.7)	64.6 (12.6)	45.8 (16)	37.2	-	-
Lennartz 2016		370	49	Not reported	-	-	-	-	-	-
Lennartz 2016 validation		162	23	Not reported	67 (41.4)	49.8 (16.4)	80.2 (47.6)	13.0	-	-
Lim	2019	1970	32	Not reported	1050 (53.3)	62.4 (10.2)	76.0 (24.2)	44.8	77.9	-
Lin	2023	6982	312	Not reported	2629 (37.7)	66.1 (7.4)	79.2 (28.5)	100	-	24.9*
Lin validation cohort 2		2954	545	Not reported	1051 (35.6)	67.4 (8.1)	55.0 (15.3)	100	-	99.9*
Lin validation cohort 3		1907	670	Not reported	844 (44.3)	52 (9.8)	40.7 (12.9)	100	-	17.4*
Maher	2023	27017	290	5421	15717 (58.2)	76.6 (10.3)	48 (9.9)	30.54	70.3	33.2
Maher cohort 2		2728	104	230	1442 (52.9)	70.2 (11.6)	48.1 (10.6)	53.2	69.7	29.0
Major	2019	35539	429	death rate 55.9 per 1000 person years (95% CI 54.8- 57.)	20436 (57.5)	75.9 (10.6)	48.2 (9.8)	31.5	41.7	32.0

Major 2 years		35539	176	death rate 55.9 per 1000 person years (95% CI 54.8- 57.)	-	-	-	-	-	-
Massy	2023	1000	262	108	310 (31.0)	69 (11.9)	28 (11)	43	92	57
Massy 2023 validation		326	28	61	130 (40.0)	70.3 (13.4)	36 (13)	38.0	-	45.1
Maziarz	2015	28779	1730	Not reported	14876 (51.7)	60.3 (14.2)	-	22.8	47.0	27.6
Maziarz	2014	982	71	Not reported	314 (32.0)	49.6 (10.9)	-	15.6	31.1	15.0
Maziarz 2015 domiciled cohort		15564	888	Not reported	8452 (54.3)	59.3 (13.6)	-	22.9	48.5	19.4
Naranjo	2021	976299	29653	Death incidence per 1000 person years 69.28 (69.02-69.53)	583827 (59.8)	73 (10)	46 (11)	22.7-	49.4	-
Orlandi	2018	3272	1071	480	1405 (42.9)	57 (11)	44 (16)	50.5	88.4	22.8*
Ouyang	2021	2300	288	10	1194 (51.9)	35.7 (11.9)	76.9 (39.7)	-	-	-
Park	2014	500	52	Not reported	285 (57.0)	37.1 (12)	87.3 (28.5)	-	24.4	-
Peeters	2013	595	114	59	184 (30.9)	60.8 (12.1)	33.3 (11.7)	25.0	-	30.1
Pesce	2016	1040	241	Not reported	321 (30.9)	34.9 (13.4)	86.8 (27.4)	-	41.8	-
Prouvot	2021	573	287	238	246 (42.9)	82.3 (5.2)	12.7 (3.7)	39.4	97.9	31.4*
Ramspek	2021	1580	458	330	545 (34.5)	76.1 (8.0)	18.5 (4.7)	42.1	91.7	62.2
Ramspek 2021 - SRR cohort		13489	2764	3357	5220 (38.7)	73.7 (11.5)	21.9 (5.7)	36.4	73.2	33.1

Sato	2015	198	51	0	103 (52.0)	42 (10.1)	71.3 (25.9)	-	42.9	-
Schena	2021	948	210	Not reported	263 (27.7)	40.6 (14)	67.3 (33.4)	-	30.3	-
Schena 2021 - Thessaloniki cohort		167	23	Not reported	47 (28.1)	40.1 (15.5)	69.6 (31.6)	-	34.7	-
Schroeder	2017	22460	737	Not reported	13378 (59.7)	74.6 (10.1)	46.8 (10.1)	34.3	85.1	-
Schroeder 2017 - validation cohort		16553	360	Not reported	10270 (62.0)	74.7 (9)	47.5 (9.8)	27.0	81.9	-
Sheer	2022	169876	7928	Not reported	90841 (53.5)	75.2 (6.1)	47.9 (9.7)	100	21.3	-
Smith	2013	158	40	20	40 (25.3)	69 (12)	32 (11)	25.3	-	46.8
Stefan	2020	625	78	Not reported	269 (43.0)	46.7 (14.6)	55.9 (29.6)	-	50.1	-
Sud	2014	3273	459	540	1426 (43.6)	70	36 (13)	50.0	75.7	41.9*
Sun	2020	478	225	Not reported	186 (38.9)	51.7 (10.4)	-	100	-	-
Tangri	2016	721357	23829	Not reported	167974 (23.3)	74 (10)	46 (11)	-	-	-
Tangri	2017	3004	344	Not reported	1262 (42.0)	69 (14)	36 (13)	38.0	87.0	42.0*
Tangri	2011	3449	386	Not reported	1503 (43.6)	70 (14)	36 (13)	37.1	-	40.2*
Tangri 2011 validation		4942	1177	Not reported	2109 (42.7)	69 (14)	31 (11)	38.6	-	26.4*
Thanabalasingam	2022	442	159	206	196 (44.3)	73 (12)	20 (6.2)	56.1	-	54.8
Thanabalasingam 4-year cohort		442	145	161				-	-	-
Thanabalasingam 2-year cohort		442	90	91				-	-	-
van den Brand	2019	505	55	45	157 (31.1)	58 (13)	50 (18)	-	-	-
van den Brand 2019 Nephro Test cohort		1385	72	94	443 (32.0)	58 (15)	51 (18)	-	-	-

Wang	2019	17271	491	3241	8810 (51.0)	75 (9)		58.6	98.5	25.2
Wang 2019 2 year follow up		17444	330	1927	8773 (50.3)	76 (9)		58.9	98.2	25.3
Wang	2017	402	68	Not reported	169 (42.0)	40.7 (14.1)	82 (43.1)	-	-	-
Wang	2023	272	82	Not reported	147 (54.0)	60 (12.7)	18.8 (18.0)	-	-	-
Wang 2023 validation of updated model		117	33	Not reported	62 (53.0)	61.2 (7.9)	18 (17.0)	-	-	-
Whitlock	2017	1512	151	419	753 (49.8)	66.8 (13.2)	42.3 (-)	75.9	-	37.9
Wu	2022	90	26	8	49 (54.4)	52.7 (15.9)	29.2 (28.4)	-	-	-
Wu 2022 validation		60	19	5	33 (55.0)	53.9 (14.7)	27.4 (27.3)	-	-	-
Xie	2012	619	67	Not reported	305 (49.3)	36 (12.3)	87.9 (44.4)	-	46.8	-
Xie	2016	28779	1730	7628	14965 (52.0)	60 (14)	49 (10.7)	22.8	47.0	28.0
Xu	2021	1045	260	Not reported	315 (30.1)	67.3 (13.6)	32.95 (18.9)	37.7	90.3	26.8
Yamanouchi	2018	198	92	0	55 (27.8)	59 (11)	35.2 (14.7)	100	-	-
Yamanouchi 2018 validation		98	49	0	30 (30.6)	61 (10)	35.9 (15.3)	100	-	-
Yang	2020	554	61	0	271 (48.9)	38.1 (9.7)	72.5 (27.5)	-	28.5	-
Yang 2020 validation		392	37	0	193 (49.2)	35.1 (11.5)	81.4 (30.4)	-	51.3	-
Ye	2022	1432	457	260	612 (42.7)	61.6 (7.8)	41 (13)	100	93.2	24.3*
Yuan	2020	1090	455	Not reported	476 (43.7)	50.0 (11.4)	45.6 (16.2)	21.0	30.6	2.7
Zacharias	2022	4915	200	Not reported	1956 (39.8)	60 (11.9)	49.4 (18.2)	26.4	96.1	22.7

Zacharias 2022 CKD-REIN cohort		1912	445	Not reported	637 (33.3)	66.2 (13.0)	34.1 (13.3)	42.3-	90.8	39.0
Zacharias 2022 SKS cohort		949	150	Not reported	353 (37.2)	65.2 (14.1)	30.8 (16.7)	29.3	93.9	32.2
Zacharias 2022 MMKD cohort		202	75	Not reported	69 (34.2)	46.3 (12.3)	47.4 (30.0)	0	89.1	11.9
Zacharias	2019	4640	185	Supplementary materials but unable to access	1814 (39.1)	60.2 (11.9)	49.4 (18.2)	-	-	-
Zhang	2022	459	149	1	227 (49.5)		32.3 (21.0)	21.1	71.0	15.5
Zhang 2022 validation		326	25	0	140 (42.9)		35.6 (20.8)	20.6	72.1	11.0
Zhang	2020	1373	186	Not reported	607 (44.2)	35.7 (13.4)	83.3 (41.6)	-	-	-
Zhang	2021	376	37	5	330 (87.8)	31.7 (10.4)	113.8 (30.6)	-	-	-
Zhang	2021	135	62	5	38 (28.1)	52.1 (10.4)	48 (30.7)	100	93.3	-
Zhang	2023	4982	444	87	2587 (51.9)	37.7 (14.8)	92.6 (28.5)	15.3	41.7	-
Zhu	2020	992	449	Not reported separately	-	-	-	-	-	-
Zhu	2022	99	8	Not reported	47 (47.5)	44.3 (16.3)	-	17.2	61.6	-
Zou	2022	390	158	Not reported	117 (30.0)	51 (9.6)	66.6 (34.1)	100	95.1	-

*Definitions of CVD vary across studies

Supplemental Table 4- 9. Summary of kidney failure risk prediction models and multimorbidity/frailty measures reported for renal specific disease aetiologies

CKD population	Prediction models	Number of variables in the model	Number of external validation studies	Multimorbidity/frailty measure reported
IgA Nephropathy	Barbour 2019 IgA prediction tool clinical model, clinical model + MEST, full model with race	<10	7	
	Berthoux ARR*		4	
	Cattran Oxford classification*		2	
	Haas classification*		1	
	Goto*			
	Keane RENAAL*			
	Kawamura Japanese histologic classification 2013 models 1-2*			
	Tanaka*		0	
	Barbour clinical data at biopsy model, 2-year data model, clinical data + MEST score			
	Chen Cox regression model			
	Pesce			
	Xie Clinical Progression Risk Score			
	Yang clinical mode, clinical model + MEST-C, clinical model + MEST-C + urinary + MMP7			
	10-20	7		
		Schena CDSS		2
		Chen MLM,		0
		Yang clinical model + MEST-C + all urinary biomarkers		
AAV or Anti-GBM disease	Brix Renal risk score*	<10	4	
	Wu (MPO AAV) clinical model, clinical model + MMP7, clinpath model, clinpath model + MMP7		0	

Diabetic kidney disease	Cheng clinical model, Lab model, Lab-medication model, Full model	<10	0	
	Forsblom models1-2			
	Hoshino models 1-3			
	Jiang			
	Kwan clinical model			
	Sun clinical model, clinical-pathological model, clinical-medication model, full model			
	Yamanouchi D-score^			
	Ye			
	Zhang DKD models 1-2			
	Zou MLM			
	Desai TREAT ESRD model + cardiac biomarkers	10-20		
	Kwan metabolite model			
	Lin			
	Kwan clinical metabolite model	>20		Elixhauser comorbidity index + Physician encounters
	Sheer logistic regression model, LASSO model			
Glomerular diseases	Sethi Renal Chronicity Score*	<10		
	Wang models 1-2			
Lupus nephritis	Zhang LN model			
FSGS	Zhu FSGS model			

Supplemental Table 4- 10. Summary of PROBAST tool assessment of individual studies.

Author	Year	Risk of Bias				Applicability			Overall	
		1. Participants	2. Predictors	3. Outcome	4. Analysis	1. Participants	2. Predictors	3. Outcome	Risk of Bias	Applicability
Ali	2021	+	+	?	?	+	+	+	?	+
Al-Wahsh	2021	+	?	-	-	+	+	+	-	+
Bai	2022	-	+	?	-	-	-	+	-	-
Bai	2021	+	+	?	-	+	+	+	-	+
Barbour	2022	+	-	-	-	-	+	+	-	-
Barbour	2019	-	+	-	-	-	-	+	-	-
Barbour	2016	+	+	-	-	-	-	+	-	-
Bellocchio	2021	-	+	?	-	-	+	+	-	-
Belur	2020	+	+	-	?	-	+	+	-	-
Bon	2023	-	?	-	-	-	-	+	-	-
Bundy	2022	+	+	?	-	+	-	+	-	-
Chen	2019	?	?	-	-	-	-	+	-	-
Cheng	2020	-	?	?	-	-	-	+	-	-
Chu	2023	+	?	?	-	+	+	+	-	+
da Silva	2023	-	?	?	-	?	+	+	-	?
da Silva	2022	-	?	-	-	+	+	+	-	+
Dai	2021	-	?	-	-	-	-	+	-	-
Desai	2011	+	+	?	-	-	+	+	-	-
Dimitrov	2003	+	+	?	-	-	+	+	-	-
Edmonston	2019	+	+	+	-	-	-	+	-	-
Fenton	2018	+	+	?	-	+	+	+	-	+
Floyd	2023	-	?	-	-	-	-	+	-	-
Forsblom	2014	+	+	?	-	-	-	+	-	-
Gibertoni	2019	?	+	?	-	-	+	+	-	-
Grams	2018	+	?	?	+	+	+	+	?	+
Grams	2023	+	?	?	-	+	+	+	-	+
Haaskjold	2023	+	?	?	-	-	-	+	-	-
Hallan	2019	+	+	?	-	-	+	+	-	-
Hasengawa	2019	-	+	?	?	-	-	+	?	-
Hoshino	2015	-	?	?	-	-	-	+	-	-
Hsu	2017	+	+	-	-	+	-	+	-	-

Hundemer	2020	-	?	?	-	+	+	+	-	+
Hwang	2021	+	?	-	-	-	-	+	-	-
Ingwiller	2022	-	-	?	-	+	+	+	-	+
Irish	2023	+	?	?	-	+	+	+	-	+
Jahan	2023	+	?	?	-	+	+	+	-	+
Jiang	2019	-	+	?	-	-	-	+	-	-
Johnson	2008	+	?	?	-	+	+	+	-	+
Johnson	2007	+	?	?	-	+	+	+	-	+
Kang	2020	-	?	?	-	+	+	+	-	+
Knoop	2015	?	?	?	-	-	-	-	-	-
Kong	2023	-	?	?	-	-	-	+	-	-
Kwan	2020	+	+	?	-	-	+	+	-	-
Kwek	2022	-	?	?	-	+	+	+	-	+
Landray	2010	+	+	?	-	+	+	+	-	+
Lee	2018	-	-	?	-	+	+	+	-	+
Lennartz	2016	-	+	?	-	?	+	+	-	-
Lim	2019	-	+	+	-	+	+	+	-	+
Lin	2023	?	+	-	-	-	+	+	-	-
Maher	2023	+	?	?	+	+	+	+	?	+
Major	2019	-	?	?	-	+	+	+	-	+
Massy	2023	+	+	+	-	+	-	+	-	-
Maziarz	2015	?	?	-	-	+	+	+	-	+
Maziarz	2014	?	?	+	-	+	+	+	-	+
Naranjo	2021	?	+	-	-	+	?	+	-	+
Orlandi	2018	+	+	-	-	+	+	+	-	+
Ouyang	2021	-	?	-	-	-	-	+	-	-
Park	2014	-	?	-	-	-	-	-	-	-
Peeters	2013	-	+	?	-	+	+	+	-	+
Pesce	2016	-	?	?	-	-	-	+	-	-
Prouvot	2021	+	+	?	-	+	+	+	-	+
Ramspek	2021	+	-	?	?	+	+	+	-	+
Sato	2015	-	?	-	-	-	-	-	-	-
Schena	2021	-	?	-	-	-	-	+	-	-
Schroeder	2017	+	+	+	-	+	+	+	-	+
Sheer	2022	-	+	-	-	-	+	+	-	-

Smith	2013	?	+	?	-	+	-	-	-	-
Stefan	2020	-	+	?	-	-	-	+	-	-
Sud	2014	?	-	?	-	+	-	+	-	-
Sun	2020	+	+	?	-	-	-	+	-	-
Tangri	2016	+	?	?	-	+	+	+	-	+
Tangri	2017	+	?	?	-	+	+	+	-	+
Tangri	2011	+	?	?	-	+	+	+	-	+
Thanabalasingam	2022	+	?	?	-	+	+	+	-	+
van den Brand	2019	-	+	-	-	+	+	+	-	+
Wang	2019	-	+	?	-	-	-	+	-	-
Wang	2017	+	?	-	-	+	-	+	-	-
Wang	2023	+	?	-	-	+	+	+	-	+
Whitlock	2017	+	?	?	-	+	+	+	-	+
Wu	2022	?	+	+	-	-	-	+	-	-
Xie	2012	-	?	?	-	-	+	+	-	-
Xie	2016	+	?	?	-	+	+	+	-	+
Xu	2021	?	?	-	-	?	+	+	-	?
Yamanouchi	2018	+	?	?	-	-	-	+	-	-
Yang	2020	+	+	+	-	-	-	+	-	-
Ye	2022	?	+	+	+	-	+	+	?	-
Yuan	2020	-	?	?	-	+	+	+	-	+
Zacharias	2022	+	+	+	-	+	-	+	-	-
Zacharias	2019	+	+	+	+	+	-	+	+	-
Zhang	2022	+	+	-	-	-	-	+	-	-
Zhang	2020	+	+	-	-	-	-	+	-	-
Zhang	2021	+	+	-	-	-	-	+	-	-
Zhang	2021	+	?	?	-	+	+	+	-	+
Zhang	2023	-	+	+	-	-	-	+	-	-
Zhu	2020	-	+	+	-	-	+	+	-	-
Zhu	2022	-	?	+	-	-	-	+	-	-
Zou	2022	+	?	-	-	-	-	+	-	-

Supplemental Table 4- 11. Competing risk of death consideration and performance measures included

Author	Year	Discrimination measure	Calibration measure	Competing risk of death considered
Ali	2021	AUC	Calibration plot	Yes
Al-Wahsh	2021	c-index	Calibration plot, Brier score	Yes
Bai	2022	AUC	-	No
Bai	2021	AUC	-	Yes
Barbour	2022	c-index	Calibration curves/slopes	No
Barbour	2019	c-index	Calibration plots	No
Barbour	2016	c-index	Calibration plots	No
Bellocchio	2021	AUC	Calibration plots	No
Belur	2020	AUC	Calibration plots	No
Bon	2023	AUC	-	No
Bundy	2022	AUC	Calibration plots	No
Chen	2019	c-index	O:E by deciles, Hosmer-Lemeshow test	No
Cheng	2020	c-index	Calibration curves, Hosmer-Lemeshow test	No
Chu	2023	c-index	-	No
da Silva	2023	AUC	Hosmer-Lemeshow test	No
da Silva	2022	AUC	Hosmer-Lemeshow test	No
Dai	2021	AUC	O:E by deciles	No
Desai	2011	c-index	-	Yes
Dimitrov	2003	AUC	-	No
Edmonston	2019	AUC	-	No
Fenton	2018	c-index	Hosmer-Lemeshow test	No
Floyd	2023	c-index	-	No
Forsblom	2014	AUC, c-index	R2	Yes
Gibertoni	2019	Visual inspection of K-M curves	Calibration plots	Yes
Grams	2018	c-index	R2	Yes
Grams	2023	c-index	Calibration slope	Yes
Haaskjold	2023	AUC	Calibration plots	No
Hallan	2019	AUC	Calibration curves, Hosmer-Lemeshow test	Compared to risk of death using MREK
Hasengawa	2019	Time varying AUC	-	Yes
Hoshino	2015	c-index	-	No
Hsu	2017	c-index	-	No
Hundemer	2020	AUC	Calibration curves, Hosmer-Lemeshow test, Brier score	Yes
Hwang	2021	AUC	Calibration plots	No

Ingwiller	2022	AUC	Hosmer-Lemeshow test	No
Irish	2023	c-index	O:E, Brier score	No
Jahan	2023	AUC	O:E	Yes
Jiang	2019	c-index	Calibration plot	No
Johnson	2008	c-index	calibration quintiles/curves, Hosmer-Lemeshow test	No
Johnson	2007	c-index	-	No
Kang	2020	Time dependent AUC	calibration plot, Brier score	No
Knoop	2015	AUC	-	No
Kong	2023	Time dependent AUC	Calibration plot	No
Kwan	2020	AUC	-	Yes
Kwek	2022	c-index	Calibration curves	No
Landray	2010	AUC	O:E	No
Lee	2018	c-index	Brier score	No
Lennartz	2016	c-index	Calibration plots	No
Lim	2019	c-index	Nam-D'Agostino X2 statistic, Brier score	No
Lin	2023	c-index	Brier score	No
Maher	2023	c-index	O:E, calibration plots, intercept/slope	Yes
Major	2019	c-index, Somer's D	Calibration plots	No
Massy	2023	c-index	O:E absolute risk	Yes
Maziarz	2015	AUC	Prediction error	No
Maziarz	2014	AUC	Prediction error	No
Naranjo	2021	c-index	Calibration plots, Greenwood-Nam-D'Agostino statistic	No
Orlandi	2018	c-index	Calibration plot	No
Ouyang	2021	c-index	Calibration curves, Hosmer-Lemeshow test	No
Park	2014	c-index	-	No
Peeters	2013	AUC	Calibration plots, Hosmer-Lemeshow test	No
Pesce	2016	AUC	-	No
Prouvot	2021	AUC	Calibration plot, Hosmer-Lemeshow test	No
Ramspek	2021	c-index	Calibration plots	Yes
Sato	2015	-	Hosmer-Lemeshow test	N/A (no recorded deaths)
Schena	2021	c-index	May-Hosmer test	No
Schroeder	2017	c-index	Calibration curves	No
Sheer	2022	c-index	-	No
Smith	2013	c-index	R2	No
Stefan	2020	AUC	Hosmer-Lemeshow test	No

Sud	2014	c-index	X2 statistic Nam and D'Agostino	Yes
Sun	2020	c-index	Hosmer-Lemeshow test	No
Tangri	2016	c-index	Calibration plots (quintiles), Brier score	No
Tangri	2017	c-index	Calibration curves/deciles, X2 statistic (Nam and D'Agostino)	No
Tangri	2011	c-index	Calibration plots, X2 statistic (Nam and D'Agostino)	Yes
Thanabalasingam	2022	AUC, c-index	Calibration plots	Yes for Grams
van den Brand	2019	AUC	Calibration curves	No
Wang	2019	AUC	Brier	Yes
Wang	2017	AUC	-	No
Wang	2023	c-index	O:E by quintiles, Hosmer- Lemeshow test	No
Whitlock	2017	c-index	-	No
Wu	2022	c-index	R2	No
Xie	2012	AUC	R2	No
Xie	2016	AUC	Prediction error	No
Xu	2021	AUC	Calibration curve	No
Yamanouchi	2018	AUC	-	N/A (no recorded deaths)
Yang	2020	c-index	-	N/A (no recorded deaths)
Ye	2022	c-index	Calibration plot	Yes
Yuan	2020	AUC	-	No
Zacharias	2022	c-index	Calibration curves	Yes
Zacharias	2019	c-index	-	Yes
Zhang	2022	c-index	Calibration curve	N/A composite outcome of death
Zhang	2020	c-index	Calibration slope	No
Zhang	2021	AUC	-	N/A composite outcome of death
Zhang	2021	c-index	Calibration plot	N/A composite outcome of death
Zhang	2023	AUC, c-index	Calibration plots	No
Zhu	2020	AUC	Brier	N/A composite outcome of death
Zhu	2022	c-index	Calibration plots	No
Zou	2022	AUC	-	No

Supplemental Figure 4- 1. Baseline co-morbidities recorded and included/added to externally validated kidney failure prediction models for renal specific aetiologies

Comorbidities recorded at baseline or included/added to model					
Model	Study	Hypertension	Diabetes	CV disease	Other
Oxford Classification	Park 2014	✓			
	Hwang 2021	✓	✓		
Barbour IgA prediction tool	Schena 2021	✓	✓		
	Knoop 2015	✓+			
Berthoux ARR	Pesce 2016	✓+			
	Schena 2021	✓+			
	Xie 2012	✓+			
Brix RRS	Kong 2023	✓	✓		
Haas classification	Park 2014	✓+			
Goto	Xie 2012	✓			
Keane RENAAL		✓			

✓

Recorded at baseline

+

Included in model

Appendix 6: Supplementary material for Chapter 5: Validation of the kidney failure risk equation in people with chronic kidney disease and multimorbidity: the effect of an update model accounting for competing mortality risks on model performance

Supplemental Text 5- 1. Proteinuria conversion algorithm

Predicted urine ACR from urine PCR (uPCR) = $\exp(5.3920 + 0.3072 \times \log(\min(uPCR/50, 1)) + 1.5793 \times \log(\max(\min(uPCR/500, 100), 0.1)) + 1.1266 \times \log(\max(uPCR/500, 1)))$

Predicted urine ACR from dipstick proteinuria = $\exp(2.43738 + 0.7539 \times (\text{if trace}) + 1.7243 (\text{if } +) + 3.3475 \times (\text{if } ++) + 4.6399 \times (\text{if } >+))$

Supplemental Text 5- 2. Interpretation of statistical performance measures utilised

Discrimination

Discrimination describes the ability of a prognostic model to correctly separate those who do or do not experience the outcome event. It is commonly assessed by the area under the receiver operating characteristic curve (AUC) and/or Harrell's C-index. Harrell's c-index measures overall discrimination by assessing the proportion of all comparable pairs where the model correctly predicts which individual experiences the event first. However, does not explicitly account for time. In comparison, the time-dependent AUC considers changes in risk over time. It evaluates discrimination at specific time points, allowing assessment of how well a prediction model distinguishes between outcomes at different time horizons. Discrimination (using both measures) range from 0.5 (no discrimination) to 1 (perfect discrimination).

Calibration

Calibration describes the agreement and correspondence between the predicted risk attributed from a prognostic model and the true observed risk that is measured and can be measured in a number of ways:

- Calibration curves - assess calibration over the whole range of predicted risk (0 to 1) by plotting the observed risks against the predicted risk (represented by the 45-degree line). Observation above the 45 degree represents under-estimation of risk and those below represents over-estimation of risk.
- Calibration intercept - assesses general calibration by assessing how close the estimated risks are to the overall observed outcome proportion. The ideal calibration intercept is 0, a positive intercept represents that the model systematically overestimates the outcome, and a negative intercept indicates the mode underestimates the outcome.
- Calibration slope - measures the level of variation in model predictions across the range of predictions. The perfect calibration slope is 1, a slope <1 suggests that model predictions are too far apart/extreme (high

predicted risks are too high and low predicted risks are too low) and a slope >1 indicates that the predictions are too modest (i.e., the high predicted risks are too low and the low predicted risks are too high).

- Calibration in the large: observed/expected (O/E) ratio - an overall measure of calibration. An O/E ratio of 1 indicates perfect calibration in the large (i.e. the number of observed events matches the number of expected events), a ratio >1 indicates that on average the model predictions are underestimated (i.e. there are more observed events than the model predicts), and a ratio <1 that the predictions are overestimated (the model predicts more outcome events than are observed).

Prediction error and model fit

- Brier Score - assesses how close the predicted probabilities are to observed outcomes. Brier Score can range from 0 (best) to 1 (worst).

Scaled Brier Score - provides interpretation of the model against a null model without covariates. Scaled brier score can range from negative values (indicates predication from the model are worse than a null model) to 100% (indicates perfect predictive accuracy from the model). A scaled brier score of 0% would indicate that the predictions from a model are no better or worse than a null model.

Supplemental Text 5- 3. Description of Kaplan-Meier based calibration curve results for 2- and 5-year KFRE in UK Biobank and SCREAM cohorts

Calibration curves in UK Biobank revealed under-estimation at lower risk levels and over-estimation of risk at higher risk levels at 2-years for those with and without multimorbidity (Figure 5-1). Improved calibration of 2-year KFRE was evident in the SCREAM cohort in both those with and without multimorbidity but with under-estimation across most risk levels (Figure 5-2). In UK Biobank, there was under-estimation of risk at 5-years across most risk levels in patients with multimorbidity (Figure 5-1). In the no multimorbidity group in UK Biobank, at 5-years, there was underestimation at lower risk levels but overestimation at higher risk levels (Figure 5-1). In comparison, calibration at 5-years in SCREAM was good in those with and without multimorbidity (Figure 5-2).

Supplemental Text 5- 4. Description of competing risk analysis results

There was improved discrimination across both cohorts and multimorbidity statuses when measured by AUC (competing risk model; range 0.92-0.95, UK calibrated 5-year KFRE;0.88-0.90). However, discrimination measured by c-index showed similar results in both models. Calibration plots are presented in Supplemental Figure 5-17 and 5-18. Calibration-in-the-large (O/E ratios) were closer to 1 for the competing risk model, demonstrating improved calibration. Likewise, calibration intercepts were closer to 0 (ideal) for UK Biobank but not SCREAM. Demonstrating slight underestimation in the UK Biobank cohort and slight over-estimation in the SCREAM cohort but with similar results across multimorbidity status. Calibration slopes showed improvements (closer to 1) in the UK Biobank cohort but were similar in the SCREAM cohort compared to the non-competing risk 5-year KFRE

Supplemental Text 5- 5. Sensitivity analyses

Analyses validating the non-North American calibrated KFRE in the SCREAM cohort provided similar results (Supplemental Tables 5-20-5-23). Calibration in the large (as measured using O/E ratios) demonstrated worsening in the direction of over-estimation of the risk of kidney failure for all multimorbidity status groups and the cardiometabolic multimorbidity cluster but remained unchanged for complex multimorbidity. The calibration intercept became negative and moved closer to 0 (ideal calibration) at 2-years in all groups. At 5-years KFRE calibration intercepts displayed increasingly negative values (systematic underestimation of risk). Overall fit assessed using the scaled Brier score showed similar results in the whole SCREAM cohort and multimorbidity group with the 2-year KFRE (all eGFR equations). Whereas small improvements were demonstrated in the no multimorbidity group compared to when the UK calibrated KFRE was used. Scaled Brier scores were similar for the 5-year KFRE using eGFRcr and eGFRcr-cys for all multimorbidity groupings but there were small reductions in the score when using eGFRcys, primarily for the whole cohort and multimorbidity group.

Supplemental Table 5- 1. Long-term conditions included in multimorbidity definition

Physical health conditions	Mental health conditions
Painful conditions	Depression
Hypertension	Anxiety*
Asthma	Alcohol problems*
Atrial Fibrillation	Other psychoactive substance abuse*
Coronary Heart Disease	Dementia
Dyspepsia*	Schizophrenia/bipolar disorder
Diabetes	Anorexia or bulimia*
Thyroid disorders	
Connective tissue disorders	
Chronic Obstructive Pulmonary Disease (COPD)	
Irritable bowel syndrome	
Treated constipation	
Stroke/Transient Ischaemic Attack (TIA)	
Chronic kidney disease	
Diverticular disease*	
Peripheral vascular disease	
Heart failure	
Prostate disorders	
Glaucoma*	
Epilepsy	
Psoriasis/eczema	
Inflammatory Bowel Disease	
Migraine*	
Chronic sinusitis*	
Bronchiectasis*	
Parkinson's disease	
Multiple Sclerosis	
Viral Hepatitis	
Chronic Liver disease	
Osteoporosis*	
Chronic fatigue syndrome*	
Endometriosis*	
Meniere's disease*	
Pernicious Anaemia*	
Polycystic ovary*	
Cancer	

*Included in UK Biobank LTCs only

Supplemental Table 5- 2. Long-term conditions included in multimorbidity clusters

Multimorbidity cluster	LTC included
Cardiometabolic	Hypertension, coronary heart disease, peripheral vascular disease, atrial fibrillation, heart failure, stroke/transient ischaemic attack, diabetes
Complex	Involvement of three or more LTCs from three or more body systems (neoplasm, haematological, endocrine/metabolic, mental health, neurological, ophthalmological, ontological, cardiovascular, respiratory, gastrointestinal, musculoskeletal, gynaecological, other)
Mixed physical and mental health	At least 1 physical and 1 mental health condition from Supplementary Table 1

Supplemental Table 5- 3. Tripod checklist

Section/Topic		Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	112
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	114-115
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	116-117
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	117
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	118-119
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	118-119
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	118-119
	5b	Describe eligibility criteria for participants.	
	5c	Give details of treatments received, if relevant.	N/A
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	120-122
	6b	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	118-120
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	Explain how the study size was arrived at.	120
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	118-119
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	120
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	120-122
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	121-122
Risk groups	11	Provide details on how risk groups were created, if done.	121

Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Table 5.1 140
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	Table 5.1 Sup figures 5.1-5.2
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 5.1
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 5.1
Model performance	16	Report performance measures (with CIs) for the prediction model.	127-133 Table 5.3-5.4 Sup tables 5.6-5.11 Sup figures 5.6-5.11
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	137 Table 5.5 Sup tables 5-17-5.19 Sup figures 5.7-5.18 Sup text 5.4
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	142-143
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	140-141
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	140-143
Implications	20	Discuss the potential clinical use of the model and implications for future research.	140-143
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	144
Funding	22	Give the source of funding and the role of the funders for the present study.	144

Supplemental Table 5- 4. Kidney failure and mortality events by long-term condition count groups

Long-term conditions count	Individuals		RRT outcome events n (%)				Death (no prior RRT) events n (%)			
	UK Biobank	SCREAM	UK Biobank		SCREAM		UK Biobank		SCREAM	
			2-years	5-years	2-years	5-years	2-years	5-years	2-years	5-years
0	3200	4806	<5 (0.1)	<5 (0.1)	61 (1.3)	138 (2.9)	21 (0.7)	75 (2.3)	125 (2.6)	314 (6.5)
1	6291	7949	27 (0.4)	67 (1.1)	106 (1.3)	237 (3.0)	84 (1.3)	254 (4.0)	444 (5.6)	973 (12.2)
2	6538	9169	47 (0.7)	100 (1.5)	114 (1.2)	259 (2.8)	134 (2.1)	395 (6.4)	860 (9.4)	1780 (19.4)
3	4472	8329	37 (0.8)	73 (1.6)	94 (1.1)	207 (2.5)	111 (2.5)	325 (7.3)	1076 (12.9)	2195 (26.4)
4	2345	5983	23 (1.0)	38 (1.6)	58 (1.0)	119 (2.0)	92 (3.9)	236 (10.1)	1039 (17.4)	1984 (33.2)
≥5	1643	6666	14 (0.9)	31 (1.9)	78 (1.2)	138 (2.1)	57 (3.5)	186 (11.3)	1647 (24.7)	2906 (43.6)

Supplemental Table 5- 5. Kidney failure and mortality events by multimorbidity clusters

Multimorbidity cluster	Individuals		RRT outcome events n (%)				Death (no prior RRT) events n (%)			
	UK Biobank	SCREAM	UK Biobank		SCREAM		UK Biobank		SCREAM	
			2-years	5-years	2-years	5-years	2-years	5-years	2-years	5-years
Cardiometabolic	5375	17854	61 (1.1)	126 (2.3)	246 (1.4)	492 (2.8)	189 (3.5)	567 (10.5)	3133 (17.5)	6026 (33.8)
Complex	6018	16330	53 (0.9)	102 (1.7)	157 (1.0)	338 (2.1)	177 (1.7)	532 (8.8)	2996 (18.3)	5561 (34.1)
Mixed mental/physical health	1967	6175	12 (0.6)	29 (1.5)	60 (1.0)	123 (2.0)	55 (2.8)	157 (8.0)	1145 (18.5)	2118 (34.3)

Supplemental Table 5- 6. Performance measures for validation of UK-calibrated KFRE by cohort, cystatin C-based eGFR equation and multimorbidity status at 2-years

eGFR equation used in KFRE	Performance measure for 2-year KFRE	Whole cohort		Multimorbidity		No multimorbidity	
		UK Biobank	SCREAM	UK Biobank	SCREAM	UK Biobank	SCREAM
eGFR _{cys}	AUC	0.90 (0.86-0.93)	0.89 (0.88-0.91)	0.89 (0.86-0.93)	0.90 (0.88-0.92)	0.88 (0.80-0.97)	0.95 (0.92-0.97)
	C-index	0.93 (0.92-0.95)	0.94 (0.93-0.94)	0.93 (0.90-0.94)	0.93 (0.91-0.93)	0.94 (0.91-0.97)	0.96 (0.95-0.97)
	O/E ratio	1.74 (1.58-1.90)	0.86 (0.77-0.95)	1.75 (1.57-1.92)	0.78 (0.67-0.88)	1.75 (1.38-2.11)	1.14 (0.99-1.29)
	Calibration intercept	0.23 (-0.02-0.48)	0.10 (0.00-0.19)	0.22 (-0.06-0.49)	-0.01 (-0.13-0.10)	0.30 (-0.29-0.88)	0.38 (0.22-0.54)
	Calibration slope	0.78 (0.66-0.90)	1.49 (1.34-1.64)	0.75 (0.62-0.89)	1.47 (1.29-1.65)	0.91 (0.58-1.25)	1.48 (1.22-1.73)
	Brier score	0.005 (0.004-0.006)	0.010 (0.009-0.011)	0.007 (0.006-0.008)	0.010 (0.009-0.011)	0.003 (0.002-0.004)	0.009 (0.008-0.010)
	Scaled brier score (%)	14.80 (10.00-19.29)	28.33 (25.84-30.76)	15.11 (9.83-20.19)	24.82 (22.01-27.68)	13.04 (3.18-22.83)	35.67 (30.83-40.02)
eGFR _{cr} _{cys}	AUC	0.89 (0.86-0.93)	0.90 (0.89-0.91)	0.89 (0.85-0.93)	0.91 (0.88-0.93)	0.88 (0.79-0.97)	0.95 (0.87-0.92)
	C-index	0.94 (0.91-0.95)	0.94 (0.93-0.95)	0.93 (0.90-0.95)	0.92 (0.91-0.94)	0.93 (0.90-0.97)	0.96 (0.95-0.97)
	O/E ratio	2.13 (1.97-2.29)	1.06 (0.97-1.15)	2.13 (1.96-2.31)	1.01 (0.91-1.12)	2.11 (1.74-2.47)	1.19 (1.04-1.34)
	Calibration intercept	0.28 (0.02-0.55)	0.28 (0.19-0.38)	0.30 (0.01-0.60)	0.23 (0.11-0.35)	0.22 (-0.40-0.83)	0.39 (0.23-0.55)
	Calibration slope	0.71 (0.59-0.82)	1.45 (1.30-1.60)	0.68 (0.56-0.80)	1.44 (1.26-1.62)	0.83 (0.51-1.14)	1.44 (1.18-1.70)
	Brier score	0.005 (0.004-0.006)	0.010 (0.009-0.011)	0.007 (0.006-0.008)	0.010 (0.009-0.011)	0.003 (0.002-0.004)	0.009 (0.008-0.010)
	Scaled brier score (%)	14.81 (10.21-19.25)	28.33 (28.49-33.54)	15.12 (10.41-21.03)	24.82 (24.55-30.68)	13.04 (2.66-25.61)	35.67 (33.84-43.58)

AUC, Area under the receiver operator characteristic curves.

Supplemental Table 5- 7. Performance measures for validation of UK-calibrated KFRE by cohort, cystatin-based eGFR equation and multimorbidity status at 5-years.

eGFR equation used in KFRE	Performance measure for 5-year KFRE	Whole cohort		Multimorbidity		No multimorbidity	
		UK Biobank	SCREAM	UK Biobank	SCREAM	UK Biobank	SCREAM
eGFRcys	AUC	0.90 (0.86-0.93)	0.88 (0.87-0.90)	0.91 (0.88-0.94)	0.88 (0.86-0.89)	0.89 (0.84-0.95)	0.90 (0.87-0.92)
	C-index	0.94 (0.92-0.95)	0.93 (0.92-0.93)	0.93 (0.88-0.94)	0.93 (0.91-0.92)	0.95 (0.93-0.97)	0.95 (0.94-0.95)
	O/E ratio	1.30 (1.19-1.41)	0.81 (0.75-0.87)	1.28 (1.15-1.40)	0.73 (0.65-0.80)	1.43 (1.20-1.67)	1.12 (1.02-1.22)
	Calibration intercept	0.21 (0.06-0.363)	-0.31 (-0.38- -0.23)	0.17 (-0.01-0.35)	-0.44 (-0.53- 0.34)	0.38 (0.07-0.70)	0.09 (-0.05-0.23)
	Calibration slope	0.87 (0.78-0.96)	1.02 (0.95-1.09)	0.84 (0.75-0.94)	1.02 (0.94-1.11)	1.03 (0.78-1.28)	0.99 (0.87-1.10)
	Brier score	0.009 (0.008-0.010)	0.023 (0.022-0.025)	0.011 (0.010-0.013)	0.024 (0.022-0.026)	0.005 (0.004-0.007)	0.022 (0.020-0.024)
	Scaled brier score (%)	30.52 (25.64-35.06)	35.43 (32.54-38.15)	31.05 (25.72-36.21)	33.34 (30.02-36.55)	28.03 (19.06-36.89)	39.30 (33.88-43.66)
eGFRcrcls	AUC	0.89 (0.89-0.93)	0.89 (0.87-0.90)	0.91 (0.88-0.94)	0.88 (0.87-0.90)	0.90 (0.84-0.95)	0.90 (0.87-0.92)
	C-index	0.94 (0.92-0.95)	0.93 (0.92-0.94)	0.93 (0.91-0.94)	0.92 (0.91-0.93)	0.96 (0.94-0.97)	0.95 (0.94-0.96)
	O/E ratio	1.69 (1.58-1.80)	1.03 (0.97-1.09)	1.65 (1.52-1.77)	0.96 (0.88-1.03)	1.86 (1.63-2.10)	1.22 (1.12-1.32)
	Calibration intercept	0.46 (0.29-0.63)	-0.04 (-0.12-0.04)	0.40 (0.21-0.59)	-0.13 (-0.23- -0.03)	0.70 (0.37-1.02)	0.18 (0.04-0.33)
	Calibration slope	0.79 (0.71-0.87)	1.01 (0.93-1.08)	0.77 (0.68-0.86)	1.01 (0.92-1.10)	0.96 (0.72-1.21)	0.96 (0.84-1.08)
	Brier score	0.009 (0.008-0.010)	0.022 (0.021-0.024)	0.011 (0.010-0.013)	0.023 (0.021-0.024)	0.005 (0.004-0.007)	0.021 (0.019-0.024)
	Scaled brier score (%)	31.10 (26.58-35.75)	38.28 (35.60-40.70)	31.46 (26.42-36.61)	36.75 (33.52-39.70)	29.27 (19.94-38.24)	41.51 (36.92-45.94)

AUC, Area under the receiver operator characteristic curves.

Supplemental Table 5- 8. Performance measures for validation of UK-calibrated KFRE by eGFR equation and LTC count in SCREAM cohort at 2-years

eGFR equation used in KFRE	Performance measure for 2-year KFRE (95% CI)	Long term condition count					
		0 (n=4806)	1 (n=7949)	2 (n=9169)	3 (n=8329)	4 (n=5983)	≥5 (n=6666)
eGFRcr	AUC	0.90 (0.88-0.93)	0.88 (0.87-0.913)	0.90 (0.88-0.931)	0.90 (0.87-0.93)	0.90 (0.88-0.93)	0.90 (0.87-0.93)
	C-index	0.95 (0.92-0.98)	0.95 (0.94-0.97)	0.91 (0.89-0.94)	0.92 (0.90-0.94)	0.93 (0.90-0.96)	0.93 (0.92-0.95)
	O/E ratio	1.13 (0.88-1.38)	1.08 (0.89-1.27)	1.10 (0.92-1.28)	1.07 (0.87-1.27)	1.04 (0.78-1.30)	1.16 (0.94-1.39)
	Calibration intercept	0.31 (0.05-0.56)	0.23 (0.02-0.44)	0.25 (0.04-0.46)	0.21 (-0.03-0.44)	0.27 (-0.03-0.56)	0.29 (0.03-0.55)
	Calibration slope	1.50 (1.07-1.93)	1.39 (1.08-1.69)	1.27 (1.01-1.53)	1.28 (0.98-1.57)	1.71 (1.09-2.33)	1.24 (0.90-1.59)
	Brier score	0.008 (0.006-0.010)	0.009 (0.007-0.011)	0.010 (0.008-0.011)	0.010 (0.008-0.011)	0.008 (0.006-0.010)	0.012 (0.009-0.014)
	Scaled brier score (%)	42.71 (33.76-50.9)	37.31 (31.30-43.80)	29.99 (24.28-35.62)	26.32 (19.62-32.24)	29.31 (21.82-36.47)	23.13 (18.40-28.45)
eGFRcys	AUC	0.90 (0.88-0.92)	0.90 (0.86-0.93)	0.90 (0.88-0.92)	0.90 (0.86-0.93)	0.90 (0.88-0.92)	0.90 (0.86-0.93)
	C-index	0.96 (0.95-0.97)	0.96 (0.95-0.97)	0.92 (0.90-0.94)	0.92 (0.89-0.94)	0.93 (0.91-0.95)	0.93 (0.91-0.94)
	O/E ratio	1.29 (1.04-1.54)	1.07 (0.89-1.26)	0.94 (0.76-1.13)	0.80 (0.60-1.00)	0.67 (0.41-0.92)	0.69 (0.46-0.91)
	Calibration intercept	0.48 (0.23-0.73)	0.33 (0.12-0.53)	0.16 (-0.04-0.36)	-0.02 (-0.24-0.21)	-0.06 (-0.34-0.22)	-0.18 (-0.43-0.08)
	Calibration slope	1.45 (1.04-1.86)	1.47 (1.15-1.80)	1.52 (1.21-1.82)	1.41 (1.10-1.73)	1.67 (1.16-2.17)	1.29 (0.93-1.64)
	Brier score	0.009 (0.007-0.011)	0.009 (0.008-0.011)	0.010 (0.008-0.012)	0.010 (0.008-0.012)	0.008 (0.006-0.010)	0.012 (0.009-0.014)
	Scaled brier score (%)	35.63 (28.69-42.03)	35.67 (30.12-40.90)	27.52 (22.52-32.59)	22.23 (16.07-27.85)	28.18 (21.32-34.60)	21.43 (15.62-27.01)
eGFRcrcys	AUC	0.91 (0.88-0.93)	0.90 (0.87-0.93)	0.91 (0.88-0.93)	0.90 (0.87-0.93)	0.91 (0.88-0.93)	0.90 (0.87-0.93)
	C-index	0.96 (0.94-0.98)	0.96 (0.95-0.97)	0.92 (0.89-0.94)	0.92 (0.90-0.95)	0.94 (0.92-0.96)	0.93 (0.92-0.95)

	O/E ratio	1.27 (1.02-1.52)	1.15 (0.97-1.34)	1.12 (0.93-1.30)	1.01 (0.81-1.22)	0.92 (0.66-1.17)	0.98 (0.75-1.20)
	Calibration intercept	0.44 (0.19-0.70)	0.36 (0.15-0.57)	0.31 (0.10-0.51)	0.20 (-0.03-0.43)	0.22 (-0.06-0.50)	0.18 (-0.08-0.43)
	Calibration slope	1.48 (1.04-1.92)	1.41 (1.10-1.73)	1.42 (1.12-1.72)	1.35 (1.04-1.66)	1.87 (1.23-2.51)	1.32 (0.95-1.70)
	Brier score	0.008 (0.006-0.010)	0.009 (0.007-0.011)	0.010 (0.008-0.011)	0.010 (0.008-0.011)	0.008 (0.006-0.010)	0.011 (0.009-0.014)
	Scaled brier score (%)	40.89 (33.26-48.85)	37.70 (31.58-43.89)	30.14 (24.28-35.05)	25.81 (19.21-31.33)	30.63 (23.71-37.40)	23.79 (18.52-28.88)
AUC, Area under the receiver operator characteristic curves.							

Supplemental Table 5- 9. Performance measures for validation of UK-calibrated KFRE by eGFR equation and LTC count in SCREAM cohort at 5-years

eGFR equation used in KFRE	Performance measure for 5-year KFRE (95% CI)	Long term condition count					
		0 (n=4806)	1 (n=7949)	2 (n=9169)	3 (n=8329)	4 (n=5983)	≥5 (n=6666)
eGFRcr	AUC	0.88 (0.86-0.90)	0.87 (0.85-0.89)	0.88 (0.86-0.89)	0.87 (0.85-0.89)	0.88 (0.86-0.90)	0.87 (0.85-0.89)
	C-index	0.93 (0.91-0.95)	0.94 (0.93-0.95)	0.91 (0.90-0.93)	0.91 (0.89-0.93)	0.92 (0.89-0.94)	0.92 (0.90-0.94)
	O/E ratio	1.18 (1.02-1.35)	1.13 (1.00-1.26)	1.14 (1.02-1.26)	1.08 (0.94-1.21)	0.97 (0.78-1.15)	0.96 (0.78-1.13)
	Calibration intercept	0.01 (-0.24-0.26)	0.08 (-0.11-0.26)	0.11 (-0.07-0.28)	-0.01 (-0.20-0.19)	-0.26 (-0.51- -0.02)	-0.24 (-0.47- -0.01)
	Calibration slope	0.89 (0.72-1.05)	0.97 (0.82-1.12)	1.05 (0.88-1.21)	1.02 (0.85-1.19)	0.98 (0.76-1.21)	0.89 (0.71-1.07)
	Brier score	0.021 (0.017-0.025)	0.023 (0.020-0.026)	0.023 (0.020-0.026)	0.024 (0.020-0.027)	0.025 (0.020-0.030)	0.024 (0.020-0.029)
	Scaled brier score (%)	39.30 (30.39-46.88)	39.56 (33.18-45.51)	40.35 (34.47-44.99)	33.80 (27.69-39.81)	18.65 (24.43-39.23)	30.56 (22.58-38.25)
eGFRcys	AUC	0.88 (0.86-0.89)	0.86 (0.84-0.89)	0.88 (0.86-0.89)	0.86 (0.84-0.89)	0.87 (0.86-0.89)	0.86 (0.84-0.89)
	C-index	0.95 (0.93-0.96)	0.95 (0.94-0.96)	0.92 (0.91-0.94)	0.91 (0.89-0.93)	0.92 (0.90-0.94)	0.92 (0.90-0.93)
	O/E ratio	1.24 (1.07-1.40)	1.07 (0.94-1.19)	0.93 (0.81-1.05)	0.78 (0.64-0.91)	0.61 (0.42-0.79)	0.56 (0.39-0.74)
	Calibration intercept	0.14 (-0.08-0.36)	0.07 (-0.10-0.24)	-0.13 (-0.29-0.03)	-0.41 (-0.58- -0.23)	-0.59 (-0.82- -0.37)	-0.70 (-0.91- -0.49)
	Calibration slope	0.98 (0.78-1.18)	0.98 (0.84-1.13)	1.02 (0.87-1.16)	0.99 (0.84-1.14)	1.12 (0.88-1.35)	0.99 (0.80-1.18)
	Brier score	0.021 (0.017-0.025)	0.023 (0.020-0.026)	0.024 (0.021-0.027)	0.025 (0.022-0.029)	0.024 (0.020-0.029)	0.024 (0.019-0.028)
	Scaled brier score (%)	39.12 (31.51-46.93)	39.31 (33.47-44.40)	37.32 (31.98-42.25)	29.39 (22.30-35.16)	21.46 (21.97-38.66)	33.17 (24.49-40.78)
eGFRcrcys	AUC	0.88 (0.87-0.90)	0.87 (0.85-0.90)	0.88 (0.87-0.90)	0.87 (0.85-0.90)	0.88 (0.87-0.90)	0.87 (0.85-0.90)
	C-index	0.95 (0.93-0.96)	0.95 (0.94-0.96)	0.92 (0.91-0.94)	0.91 (0.90-0.93)	0.92 (0.91-0.94)	0.92 (0.90-0.94)

	O/E ratio	1.29 (1.13-1.46)	1.19 (1.06-1.31)	1.13 (1.01-1.25)	1.00 (0.86-1.14)	0.84 (0.66-1.03)	0.79 (0.62-0.97)
	Calibration intercept	0.17 (-0.07-0.41)	0.20 (0.02-0.38)	0.11 (-0.06-0.28)	-0.10 (-0.28-0.09)	-0.30 (-0.54- -0.07)	-0.36 (-0.58- -0.14)
	Calibration slope	0.90 (0.72-1.08)	1.00 (0.84-1.16)	1.02 (0.87-1.17)	0.98 (0.82-1.14)	1.01 (0.80-1.23)	0.96 (0.77-1.16)
	Brier score	0.020 (0.016-0.024)	0.022 (0.019-0.026)	0.023 (0.019-0.026)	0.024 (0.020-0.027)	0.025 (0.020-0.030)	0.023 (0.019-0.028)
	Scaled brier score (%)	41.35 (33.91-48.67)	41.55 (35.75-47.18)	40.96 (35.71-46.16)	33.79 (27.46-39.46)	19.98 (27.27-42.00)	34.28 (26.95-41.46)
AUC, Area under the receiver operator characteristic curves.							

Supplemental Table 5- 10. Performance measures by eGFR equations and multimorbidity clusters at 2-years

eGFR equation used in KFRE	Performance measure for 2-year KFRE (95% CI)	Multimorbidity cluster		
		Cardiometabolic		Complex
		UK Biobank n=5375	SCREAM n=17854	SCREAM n=16330
eGFR _{cr}	AUC	0.84 (0.77-0.90)	0.90 (0.87-0.93)	0.93 (0.91-0.95)
	C-index	0.87 (0.82-0.91)	0.92 (0.91-0.93)	0.93 (0.91-0.94)
	O/E ratio	2.06 (1.81-2.31)	1.11 (0.98-1.23)	1.03 (0.88-1.19)
	Calibration intercept	0.15 (-0.28-0.59)	0.27 (0.13-0.42)	0.19 (0.01-0.37)
	Calibration slope	0.64 (0.46-0.81)	1.31 (1.11-1.51)	1.37 (1.11-1.63)
	Brier score	0.010 (0.007-0.012)	0.012 (0.010-0.013)	0.009 (0.007-0.010)
	Scaled brier score (%)	13.70 (5.76-21.36)	26.84 (23.23-30.59)	25.71 (20.89-30.59)
eGFR _{cys}	AUC	0.86 (0.80-0.93)	0.90 (0.87-0.93)	0.93 (0.91-0.95)
	C-index	0.90 (0.87-0.94)	0.92 (0.91-0.93)	0.92 (0.90-0.94)
	O/E ratio	1.51 (1.26-1.76)	0.78 (0.65-0.90)	0.65 (0.49-0.80)
	Calibration intercept	0.04 (-0.35-0.43)	-0.02 (-0.16-0.12)	-0.17 (-0.34-0.00)
	Calibration slope	0.71 (0.52-0.91)	1.34 (1.15-1.53)	1.58 (1.29-1.87)
	Brier score	0.010 (0.007-0.012)	0.012 (0.011-0.014)	0.009 (0.00-0.010)
	Scaled brier score (%)	14.57 (6.44-21.90)	23.85 (20.47-27.16)	23.57 (18.68-28.05)
eGFR _{cr} _{cys}	AUC	0.86 (0.79-0.92)	0.90 (0.88-0.93)	0.93 (0.91-0.95)

	C-index	0.90 (0.86-0.94)	0.92 (0.91-0.94)	0.93 (0.91-0.94)
	O/E ratio	1.92 (1.67-2.17)	1.02 (0.89-1.14)	0.90 (0.74-1.05)
	Calibration intercept	0.16 (-0.25-0.57)	0.24 (0.10-0.38)	0.13 (-0.05-0.30)
	Calibration slope	0.65 (0.47-0.83)	1.38 (1.18-1.59)	1.52 (1.23-1.80)
	Brier score	0.010 (0.007-0.12)	0.012 (0.011-0.013)	0.009 (0.007-0.010)
	Scaled brier score (%)	14.53 (6.44-21.76)	26.77 (23.52-30.39)	26.54 (22.18-30.39)
AUC, Area under the receiver operator characteristic curves.				

Supplemental Table 5- 11. Performance measures by eGFR equations and multimorbidity clusters at 5-years

eGFR equation used in KFRE	Performance measure for 5-year KFRE (95% CI)	Multimorbidity cluster		
		Cardiometabolic		Complex
		UK Biobank n=5375	SCREAM n=17854	SCREAM n=16330
eGFR _{cr}	AUC	0.87 (0.83-0.91)	0.88 (0.85-0.90)	0.87 (0.84-0.89)
	C-index	0.88 (0.85-0.91)	0.91 (0.90-0.92)	0.92 (0.90-0.93)
	O/E ratio	1.72 (1.54-1.89)	1.01 (0.92-1.10)	1.04 (0.93-1.15)
	Calibration intercept	0.49 (0.22-0.76)	-0.09 (-0.21-0.03)	-0.11 (-0.26-0.04)
	Calibration slope	0.82 (0.68-0.97)	1.01 (0.90-1.12)	0.96 (0.83-1.08)
	Brier score	0.016 (0.013-0.020)	0.026 (0.024-0.029)	0.022 (0.020-0.025)
	Scaled brier score (%)	31.33 (23.59-38.03)	35.42 (31.53-39.33)	32.36 (27.77-36.71)
eGFR _{cys}	AUC	0.87 (0.82-0.92)	0.87 (0.85-0.89)	0.86 (0.84-0.89)
	C-index	0.90 (0.88-0.93)	0.91 (0.90-0.92)	0.91 (0.90-0.93)
	O/E ratio	1.17 (0.99-1.34)	0.69 (0.60-0.78)	0.64 (0.53-0.75)
	Calibration intercept	0.08 (-0.16-0.33)	-0.45 (-0.56- -0.34)	-0.58 (-0.71- -0.44)
	Calibration slope	0.83 (0.69-0.97)	1.05 (0.94-1.16)	1.03 (0.90-1.16)
	Brier score	0.016 (0.013-0.019)	0.026 (0.023-0.029)	0.023 (0.020-0.025)
	Scaled brier score (%)	31.22 (23.84-39.31)	35.45 (31.28-39.34)	30.56 (25.33-35.23)
eGFR _{cr} _{cys}	AUC	0.87 (0.82-0.92)	0.88 (0.86-0.90)	0.87 (0.84-0.90)

	C-index	0.90 (0.87-0.93)	0.92 (0.91-0.93)	0.92 (0.91-0.93)
	O/E ratio	1.55 (1.38-1.72)	0.91 (0.82-1.00)	0.89 (0.78-1.00)
	Calibration intercept	0.41 (0.15-0.66)	-0.15 (-0.27- -0.04)	-0.23 (-0.38- -0.09)
	Calibration slope	0.79 (0.6-0.93)	1.04 (0.93-1.15)	0.98 (0.85-1.10)
	Brier score	0.016 (0.013-0.019)	0.025 (0.023-0.028)	0.022 (0.019-0.024)
	Scaled brier score (%)	31.53 (23.48-39.21)	37.91 (34.45-41.57)	34.03 (29.44-38.42)
AUC, Area under the receiver operator characteristic curves.				

Supplemental Table 5- 12. Cumulative incidence of kidney failure by multimorbidity status

Time frame	Cumulative incidence of kidney failure - Estimate (95% CI)			
	UK Biobank		SCREAM	
	No Multimorbidity	Multimorbidity	No Multimorbidity	Multimorbidity
1-year	0.0016 (0.0008-0.0024)	0.0033 (0.0024-0.0043)	0.0070 (0.0055-0.0085)	0.0059 (0.0051-0.0068)
2-year	0.0028 (0.0018-0.0039)	0.0077 (0.0063-0.0091)	0.0140 (0.0119-0.0161)	0.0122 (0.0109-0.0135)
3-year	0.0046 (0.0033-0.0060)	0.0107 (0.0091-0.0124)	0.0197 (0.0172-0.0223)	0.0184 (0.0167-0.0200)
4-year	0.0061 (0.0045-0.0077)	0.0129 (0.0111-0.0147)	0.0268 (0.0238-0.0299)	0.0240 (0.0221-0.0259)
5-year	0.0074 (0.0057-0.0091)	0.0161 (0.0141-0.0181)	0.0356 (0.0320-0.0391)	0.0295 (0.0274-0.0316)

Supplemental Table 5- 13. Cumulative incidence of mortality by multimorbidity status

Time frame	Cumulative incidence of mortality - Estimate (95% CI)			
	UK Biobank		SCREAM	
	No Multimorbidity	Multimorbidity	No Multimorbidity	Multimorbidity
1-year	0.0043 (0.0030-0.0056)	0.0106 (0.0090-0.0122)	0.0232 (0.0205-0.0258)	0.0848 (0.0815-0.0880)
2-year	0.0104 (0.0084-0.0125)	0.0241 (0.0216-0.0265)	0.0428 (0.0391-0.0464)	0.1551 (0.1508-0.1593)
3-year	0.0173 (0.0147-0.0199)	0.0402 (0.0371-0.0433)	0.0632 (0.0588-0.0677)	0.2212 (0.2162-0.2262)
4-year	0.0234 (0.0203-0.0264)	0.0544 (0.0508-0.0580)	0.0843 (0.0790-0.0895)	0.2856 (0.2800-0.2912)
5-year	0.0334 (0.0298-0.0370)	0.0715 (0.0673-0.0756)	0.0111 (0.1050-0.1171)	0.3400 (0.3339-0.3460)

Supplemental Table 5- 14. Hazard ratio and 95% confidence intervals from cause-specific Cox model for kidney failure and mortality

Covariate	Hazard ratio (95% CI)	
	Kidney failure	Mortality
Age	0.45 (0.43-0.48)	3.73 (3.61-3.85)
eGFR	0.10 (0.09-0.10)	0.87 (0.85-0.89)
lnACR	4.51 (3.83-5.31)	1.36 (1.31-1.41)
Sex (male)	3.68 (3.31-4.08)	1.05 (1.01-1.10)

Supplemental Table 5- 15. Individuals, characteristics, event numbers and performance for each risk group calculated by 5-year KFRE in UK Biobank

	KFRE risk groups (as calculated by 5-year KFRE) - UK Biobank					
	<3%	3- <5%	5- <15%	15- <25%	25- <50%	≥50%
	n = 23800	n = 176	n = 236	n = 78	n = 89	n= 110
Age	62.9 ± 5.5	61.4 ± 7.0	61.0 ± 6.9	59.1 ± 7.5	59.5 ± 7.8	59.3 ± 7.4
eGFRcr mean (SD)	66.7 ± 14.8	38.0 ± 6.8	32.8 ± 6.7	26.5 ± 6.2	22.7 ± 5.7	13.0 ± 6.1
eGFRcys mean (SD)	56.5 ± 12.2	35.9 ± 10.1	30.2 ± 7.7	26.7 ± 7.2	22.5 ± 6.5	15.4 ± 5.6
uACR median	0.0 (0.0, 1.3)	13.1 (4.2, 47.3)	18.3 (5.8, 62.5)	37.3 (14.3, 88.9)	68.4 (31.6, 153.4)	102.6 (39.0, 239.2)
Sex, n(%)						
Male	10,750 (45)	117 (66)	170 (72)	52 (67)	62 (70)	81 (74)
Female	13,050 (55)	59 (34)	66 (28)	26 (33)	27 (30)	29 (26)
Multimorbidity						
n(%)	14,462 (61)	131 (74)	182 (77)	64 (82)	70 (79)	89 (81)
Mean LTC count	2.1 ± 1.5	2.4 ± 1.4	2.7 ± 1.5	2.7 ± 1.5	2.7 ± 1.3	2.7 ± 1.3
Kidney failure within 2 years	65 (0)	5 (3)	10 (4)	8 (10)	17 (19)	45 (41)
Kidney failure within 5 years	117 (0)	12 (7)	35 (15)	23 (29)	44 (49)	81 (74)
Death within 2 years	443 (2)	10 (6)	17 (7)	<5 (<6)	11 (12)	14 (13)
Death within 5 years	1,349 (6)	22 (12)	42 (18)	9 (12)	21 (24)	28 (25)
Sensitivity (recall)	33.4	3.9	11.5	7.5	14.4	26.6
PPV	0.5	6.8	14.8	29.5	49.4	73.6

Supplemental Table 5- 16. Individuals, characteristics, event numbers and performance for each risk group calculated by 5-year KFRE in SCREAM

	KFRE risk groups (as calculated by 5-year KFRE) - SCREAM					
	<3% n = 36181	3- <5% n = 1561	5- <15% n = 2541	15- <25% n = 828	25- <50% n = 1000	≥50% n= 791
Age	70.1 ± 14.0	81.8 ± 13.5	71.7 ± 13.9	71.7 ± 12.8	69.4 ± 15.1	62.2 ± 17.1
eGFRcr mean (SD)	55.4 ± 18.0	34.1 ± 7.0	28.7 ± 6.9	22.8 ± 5.6	18.5 ± 5.7	12.6 ± 4.8
eGFRcys mean (SD)	49.2 ± 19.1	33.2 ± 13.2	27.6 ± 11.1	22.3 ± 7.9	18.9 ± 7.5	14.5 ± 4.9
uACR median	0.4 (0.0, 3.3)	8.9 (4.2, 38.1)	18.6 (7.6, 40.2)	38.18 (12.2, 75.0)	38.1 (23.1, 138.9)	138.9 (38.1, 141.9)
Sex, n(%)						
Male	13,292 (37)	307 (20)	468 (18)	138 (17)	194 (19)	153 (19)
Female	22,889 (63)	1,254 (80)	2,073 (82)	690 (83)	806 (81)	638 (81)
Multimorbidity						
n(%)	25,068 (69)	1,220 (78)	1,943 (76)	658 (79)	734 (73)	524 (66)
Mean LTC count	2.6 ± 1.8	3.0 ± 1.8	3.0 ± 1.8	3.1 ± 1.8	2.8 ± 1.8	2.5 ± 1.8
Kidney failure within 2 years	147 (0)	17 (1)	89 (4)	63 (8)	193 (19)	409 (52)
Kidney failure within 5 years	202 (1)	27 (2)	115 (5)	82 (10)	235 (24)	437 (55)
Death within 2 years	6,417 (18)	424 (27)	804 (32)	320 (39)	451 (45)	369 (47)
Death within 5 years	7,469 (21)	487 (31)	930 (37)	369 (45)	503 (50)	394 (50)
Sensitivity (recall)	18.4	2.5	10.5	7.5	21.4	39.8
PPV	0.6	1.7	4.5	9.9	23.5	55.2

Supplemental Table 5- 17. Individuals, characteristics, event numbers and performance for each risk group calculated by 5-year updated KFRE accounting for competing mortality risk in UK Biobank

	KFRE risk groups (as calculated by updated KFRE accounting for competing mortality risk) - UK Biobank					
	<3% n = 22897	3- <5% n = 539	5- <15% n = 599	15- <25% n = 149	25- <50% n = 157	≥50% n= 148
Age	63.0 ± 5.4	61.4 ± 7.0	61.0 ± 7.4	59.8 ± 7.8	58.7 ± 7.6	58.6 ± 7.6
eGFRcr mean (SD)	67.6 ± 14.3	46.0 ± 6.7	40.1 ± 6.9	31.6 ± 6.5	26.0 ± 6.2	15.3 ± 6.8
eGFRcys mean (SD)	56.1 ± 11.9	47.6 ± 15.5	39.4 ± 13.6	30.7 ± 11.1	16.1 ± 8.7	17.4 ± 6.6
uACR median	0.0 (0.0, 1.2)	2.7 (0.8, 9.6)	5.4 (1.8, 24.0)	14.7 (2.9, 56.2)	20.8 (5.2, 78.2)	57.0 (22.5, 146.4)
Sex, n(%)						
Male	12,989 (57)	90 (17)	97 (16)	31 (21)	31 (20)	19 (13)
Female	9,908 (43)	449 (83)	502 (84)	118 (79)	126 (80)	129 (87)
Multimorbidity						
n(%)	13,822 (60)	387 (72)	438 (73)	109 (73)	120 (76)	122 (82)
Mean LTC count	2.1 ± 1.5	2.5 ± 1.5	2.5 ± 1.5	2.5 ± 1.5	2.6 ± 1.4	2.6 ± 1.2
Kidney failure within 2 years	43 (0)	7 (1)	18 (3)	7 (5)	26 (17)	49 (33)
Kidney failure within 5 years	80 (0)	11 (2)	47 (8)	26 (17)	52 (33)	96 (65)
Death within 2 years	404 (2)	26 (5)	33 (6)	<5 (<3)	18 (11)	15 (10)
Death within 5 years	1,250 (5)	57 (11)	82 (14)	17 (11)	35 (22)	30 (20)
Sensitivity (recall)	25.6	4.5	15.1	8.3	16.7	30.8
PPV	0.3	2.0	7.8	17.4	33.1	64.9

Supplemental Table 5- 18. Individuals, characteristics, event numbers and performance for each risk group calculated by 5-year updated KFRE accounting for competing mortality risk in SCREAM

	KFRE risk groups (as calculated by updated KFRE accounting for competing mortality risk) - SCREAM					
	<3% n = 35189	3- <5% n = 2428	5- <15% n = 3202	15- <25% n = 857	25- <50% n = 733	≥50% n= 493
Age	70.9 ± 13.7	69.6 ± 14.1	68.5 ± 14.5	65.9 ± 14.4	61.4 ± 14.2	49.0 ± 15.5
eGFRcr mean (SD)	55.9 ± 17.9	33.6 ± 9.6	27.8 ± 9.5	22.2 ± 9.2	18.6 ± 8.4	15.0 ± 7.1
eGFRcys mean (SD)	49.5 ± 18.8	33.5 ± 16.6	27.2 ± 13.9	21.4 ± 9.9	18.9 ± 8.6	16.2 ± 6.4
uACR median	0.40 (0.00, 3.80)	6.69 (1.30, 31.02)	10.10 (3.50, 38.08)	38.08 (7.57, 101.89)	38.08 (13.09, 138.88)	38.08 (33.60, 138.88)
Sex, n(%)						
Male	12,393 (35)	602 (25)	820 (26)	276 (32)	236 (32)	225 (46)
Female	22,796 (65)	1,826 (75)	2,382 (74)	581 (68)	497 (68)	268 (54)
Multimorbidity						
n(%)	24,620 (70)	1,781 (73)	2,392 (75)	607 (71)	490 (67)	257 (52)
Mean LTC count	2.6 ± 1.8	2.8 ± 1.8	2.9 ± 1.9	2.7 ± 1.9	2.5 ± 1.8	2.0 ± 1.7
Kidney failure within 2 years	64 (0)	41 (2)	149 (5)	134 (16)	240 (33)	290 (59)
Kidney failure within 5 years	97 (0)	56 (2)	191 (6)	165 (19)	280 (38)	309 (63)
Death within 2 years	6,457 (18)	608 (25)	1,010 (32)	300 (35)	278 (38)	132 (27)
Death within 5 years	7,529 (21)	685 (28)	1,152 (36)	339 (40)	308 (42)	139 (28)
Sensitivity (recall)	8.8	5.1	17.4	15.0	25.5	28.1
PPV	0.3	2.3	6.0	19.3	38.2	62.7

Supplemental Table 5- 19. Baseline characteristics of individuals with predicted risk of kidney failure >5% by KFRE or competing risk model

	UK Biobank		SCREAM	
	KFRE n=513	Competing risk model n=1053	KFRE n=5160	Competing risk model n=5285
Age (years)	60 (7)	60 (8)	70 (15)	65 (16)
Sex n(%)				
Male	365 (71.2)	875 (83.1)	4,207 (81.5)	3,728 (70.5)
Female	148 (28.8)	178 (16.9)	953 (18.5)	1,577 (29.4)
eGFR creatinine (ml/min/1.73m ²)	26 (10)	33 (11)	23 (9)	24 (10)
uACR (mg/mmol)	96 (160)	53 (120)	68 (87)	55 (83)
Age categories (years)				
18 to 44	17 (3.3)	49 (4.7)	394 (7.6)	635 (12.0)
45 to 64	319 (62.2)	609 (57.8)	1,091 (21.1)	1,439 (27.2)
65 to 74	177 (34.5)	395 (37.5)	1,416 (27.4)	1,546 (29.3)
75 plus	N/A	N/A	2259 (43.8)	1665 (31.5)
LTC count				
0	12 (2.3)	37 (3.5)	421 (8.2)	541 (10.2)
1	96 (18.7)	227 (21.6)	880 (17.1)	998 (18.9)
2	150 (29.2)	310 (29.4)	1,100 (21.3)	1,124 (21.3)
3	126 (24.6)	243 (23.1)	1,042 (20.2)	999 (18.9)
4	72 (14.0)	127 (12.1)	742 (14.4)	700 (13.2)
5 or more	57 (11.1)	109 (10.4)	975 (18.9)	923 (17.5)
Multimorbidity clusters				
Cardiometabolic	218 (42.5)	439 (41.7)	2,781 (53.9)	2,574 (48.7)
Mixed mental and physical	47 (9.2)	80 (7.6)	707 (13.7)	760 (14.4)
Complex	189 (36.8)	334 (31.7)	2,041 (39.6)	1,983 (37.5)
Event within 5 years				
Kidney failure	183 (35.7)	221 (21.0)	869 (16.8)	945 (17.9)
Death	100 (19.5)	164 (15.6)	2,196 (42.6)	1,938 (36.7)

Supplemental Table 5- 20. Sensitivity analysis: Performance measures for SCREAM cohort by eGFR equation and multimorbidity status using Non-North American calibrated 2-year KFRE

eGFR equation used in KFRE	Performance measure for 2-year KFRE (95% CI)	Whole cohort	Multimorbidity	No multimorbidity
eGFRcr	AUC	0.92 (0.90-0.93)	0.90 (0.88-0.93)	0.94 (0.92-0.97)
	C-index	0.93 (0.92-0.94)	0.92 (0.91-0.94)	0.95 (0.94-0.97)
	O/E ratio	0.83 (0.75-0.92)	0.83 (0.72-0.93)	0.85 (0.70-1.00)
	Calibration intercept	-0.07 (-0.16-0.03)	-0.07 (-0.20-0.05)	-0.06 (-0.23-0.10)
	Calibration slope	1.35 (1.21-1.49)	1.32 (1.15-1.48)	1.43 (1.18-1.68)
	Brier score	0.009 (0.008-0.010)	0.010 (0.009-0.010)	0.008 (0.007-0.010)
	Scaled brier score (%)	32.48 (29.16-35.59)	28.85 (24.82-32.60)	40.38 (33.83-46.28)
eGFRcys	AUC	0.92 (0.90-0.93)	0.90 (0.88-0.92)	0.95 (0.92-0.97)
	C-index	0.94 (0.93-0.94)	0.92 (0.91-0.93)	0.96 (0.95-0.97)
	O/E ratio	0.65 (0.56-0.74)	0.58 (0.48-0.69)	0.87 (0.72-1.02)
	Calibration intercept	-0.23 (-0.32- -0.13)	-0.34 (-0.45- -0.22)	0.06 (-0.10-0.21)
	Calibration slope	1.49 (1.34-1.64)	1.47 (1.29-1.65)	1.48 (1.22-1.73)
	Brier score	0.010 (0.009-0.010)	0.010 (0.009-0.011)	0.009 (0.007-0.010)
	Scaled brier score (%)	29.14 (25.91-28.65)	24.69 (20.63-28.65)	38.28 (32.87-42.99)
eGFRcrcys	AUC	0.92 (0.90-0.94)	0.91 (0.88-0.93)	0.95 (0.92-0.97)
	C-index	0.94 (0.93-0.95)	0.92 (0.91-0.94)	0.96 (0.95-0.97)
	O/E ratio	0.80 (0.72-0.89)	0.76 (0.66-0.87)	0.92 (0.77-1.07)
	Calibration intercept	-0.04 (-0.14-0.05)	-0.09 (-0.21-0.03)	0.07 (-0.09-0.23)
	Calibration slope	1.45 (1.30-1.60)	1.44 (1.26-1.62)	1.44 (1.18-1.70)
	Brier score	0.010 (0.009-0.010)	0.010 (0.009-0.011)	0.009 (0.007-0.010)
	Scaled brier score (%)	29.14 (30.09-36.12)	24.69 (25.63-33.07)	38.28 (35.51-46.77)
AUC, Area under the receiver operator characteristic curves.				

Supplemental Table 5- 21. Sensitivity analysis: Performance measures for SCREAM cohort by eGFR equation and multimorbidity status using Non-North American calibrated 5-year KFRE

eGFR equation used in KFRE	Performance measure for 5-year KFRE	Whole cohort	Multimorbidity	No multimorbidity
eGFRcr	AUC	0.88 (0.87-0.90)	0.88 (0.86-0.90)	0.89 (0.86-0.91)
	C-index	0.92 (0.91-0.93)	0.91 (0.90-0.92)	0.94 (0.93-0.95)
	O/E ratio	0.82 (0.76-0.88)	0.79 (0.72-0.87)	0.89 (0.79-0.99)
	Calibration intercept	-0.42 (-0.51- -0.34)	-0.45 (-0.56- -0.35)	-0.35 (-0.50- -0.20)
	Calibration slope	1.00 (0.92-1.07)	1.00 (0.91-1.10)	0.94 (0.82-1.05)
	Brier score	0.023 (0.022-0.025)	0.023 (0.021-0.025)	0.023 (0.020-0.025)
	Scaled brier score (%)	35.28 (31.84-38.55)	34.57 (30.51-38.28)	37.23 (31.46-42.88)
eGFRcys	AUC	0.88 (0.87-0.90)	0.87 (0.86-0.89)	0.90 (0.87-0.92)
	C-index	0.93 (0.92-0.93)	0.92 (0.91-0.92)	0.95 (0.94-0.95)
	O/E ratio	0.81 (0.75-0.87)	0.73 (0.65-0.80)	1.12 (1.02-1.22)
	Calibration intercept	-0.71 (-0.79- -0.63)	-0.84 (-0.93- -0.74)	-0.31 (-0.45- -0.18)
	Calibration slope	1.02 (0.95-1.09)	1.02 (0.94-1.11)	0.99 (0.87-1.10)
	Brier score	0.024 (0.023-0.026)	0.025 (0.024-0.027)	0.023 (0.020-0.025)
	Scaled brier score (%)	32.17 (28.42-35.45)	28.71 (24.27-33.06)	38.16 (31.77-43.77)
eGFRcrcys	AUC	0.89 (0.87-0.90)	0.88 (0.87-0.90)	0.90 (0.87-0.92)
	C-index	0.93 (0.92-0.94)	0.92 (0.91-0.93)	0.95 (0.94-0.96)
	O/E ratio	0.77 (0.72-0.83)	0.72 (0.64-0.79)	0.95 (0.84-1.05)
	Calibration intercept	-0.44 (-0.52- -0.36)	-0.53 (-0.63- -0.43)	-0.22 (-0.36- -0.07)
	Calibration slope	1.01 (0.93-1.08)	1.01 (0.92-1.10)	0.96 (0.84-1.08)
	Brier score	0.022 (0.021-0.024)	0.023 (0.021-0.025)	0.021 (0.019-0.024)
	Scaled brier score (%)	37.77 (34.66-40.70)	36.13 (32.12-39.93)	41.08 (35.27-46.22)
AUC, Area under the receiver operator characteristic curves.				

Supplemental Table 5- 22. Sensitivity analysis: Performance measures for SCREAM cohort by eGFR equation and multimorbidity clusters using Non-North American calibrated 2-year KFRE

eGFR equation used in KFRE	Performance measure for 2-year KFRE (95% CI)	Multimorbidity cluster	
		Cardiometabolic n=17854	Complex n=16330
eGFR _{cr}	AUC	0.90 (0.87-0.93)	0.93 (0.91-0.95)
	C-index	0.92 (0.91-0.93)	0.93 (0.91-0.94)
	O/E ratio	0.84 (0.71-0.96)	1.03 (0.88-1.19)
	Calibration intercept	-0.05 (-0.19-0.10)	-0.13 (-0.31-0.05)
	Calibration slope	1.31 (1.11-1.51)	1.37 (1.11-1.63)
	Brier score	0.012 (0.010-0.013)	0.009 (0.007-0.010)
	Scaled brier score (%)	28.75 (24.24-33.56)	27.27 (21.66-32.75)
eGFR _{cys}	AUC	0.90 (0.87-0.93)	0.93 (0.91-0.95)
	C-index	0.92 (0.91-0.93)	0.92 (0.90-0.94)
	O/E ratio	0.59 (0.46-0.71)	0.65 (0.49-0.80)
	Calibration intercept	-0.34 (-0.48- -0.20)	-0.49 (-0.67- -0.32)
	Calibration slope	1.34 (1.15-1.53)	1.58 (1.29-1.87)
	Brier score	0.012 (0.011-0.014)	0.009 (0.008-0.010)
	Scaled brier score (%)	23.93 (19.27-28.25)	22.00 (14.84-27.54)
eGFR _{cr} _{cys}	AUC	0.90 (0.88-0.93)	0.93 (0.88-0.91)
	C-index	0.92 (0.91-0.94)	0.93 (0.91-0.94)
	O/E ratio	0.77 (0.64-0.89)	0.90 (0.74-1.05)
	Calibration intercept	-0.08 (-0.22-0.06)	-0.20 (-0.37- -0.02)
	Calibration slope	1.38 (1.18-1.59)	1.52 (1.23-1.80)
	Brier score	0.012 (0.010-0.013)	0.008 (0.007-0.010)
	Scaled brier score (%)	28.95 (24.41-32.89)	27.99 (22.60-33.07)
AUC, Area under the receiver operator characteristic curves.			

Supplemental Table 5- 23. Sensitivity analysis: Performance measures for SCREAM cohort by eGFR equation and multimorbidity clusters using Non-North American calibrated 5-year KFRE

eGFR equation used in KFRE	Performance measure for 5-year KFRE (95% CI)	Multimorbidity cluster	
		Cardiometabolic n=17854	Complex n=16330
eGFRcr	AUC	0.87 (0.85-0.90)	0.87 (0.84-0.89)
	C-index	0.91 (0.90-0.92)	0.91 (0.90-0.93)
	O/E ratio	0.76 (0.67-0.85)	1.04 (0.93-1.15)
	Calibration intercept	-0.49 (-0.61- -0.37)	-0.51 (-0.66- -0.36)
	Calibration slope	1.01 (0.90-1.12)	0.96 (0.83-1.08)
	Brier score	0.027 (0.024-0.029)	0.023 (0.020-0.025)
	Scaled brier score (%)	34.58 (29.92-39.85)	31.42 (26.00-36.99)
eGFRcys	AUC	0.87 (0.85-0.89)	0.86 (0.84-0.89)
	C-index	0.91 (0.90-0.92)	0.91 (0.90-0.93)
	O/E ratio	0.69 (0.60-0.78)	0.64 (0.53-0.75)
	Calibration intercept	-0.85 (-0.96- -0.74)	-0.98 (-1.12- -0.85)
	Calibration slope	1.05 (0.94-1.16)	1.03 (0.91-1.16)
	Brier score	0.028 (0.026-0.031)	0.025 (0.023-0.028)
	Scaled brier score (%)	31.27 (25.54-36.19)	23.71 (16.29-30.49)
eGFRcrcys	AUC	0.88 (0.86-0.90)	0.87 (0.84-0.90)
	C-index	0.92 (0.91-0.92)	0.92 (0.91-0.93)
	O/E ratio	0.68 (0.59-0.77)	0.89 (0.78-1.00)
	Calibration intercept	-0.55 (-0.67- -0.44)	-0.63 (-0.78- -0.49)
	Calibration slope	1.04 (0.93-1.15)	0.98 (0.85-1.10)
	Brier score	0.026 (0.023-0.028)	0.022 (0.020-0.025)
	Scaled brier score (%)	37.53 (32.87-41.97)	32.54 (26.83-37.95)
AUC, Area under the receiver operator characteristic curves.			

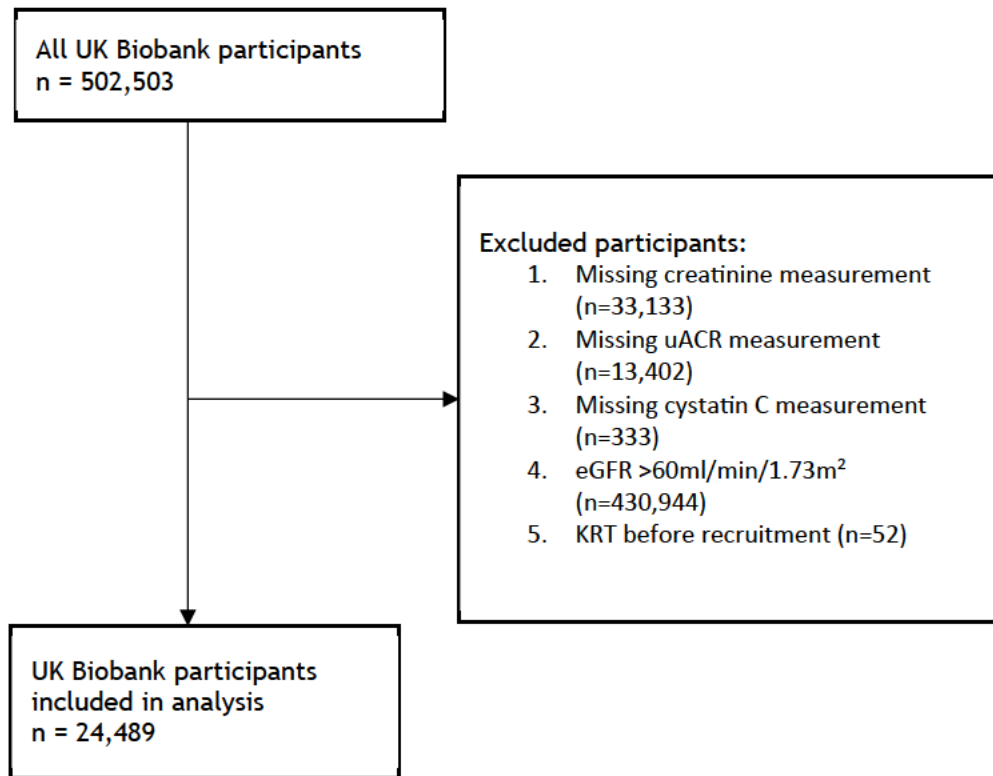
Supplemental Table 5- 24. Sensitivity analysis: Additional performance measures for 2-year KFRE (utilising eGFRcr) by cohort and multimorbidity subgroups

Performance measure for 2-year KFRE	Whole cohort		Multimorbidity		No multimorbidity	
	UK Biobank	SCREAM	UK Biobank	SCREAM	UK Biobank	SCREAM
Precision	0.26	0.27	0.27	0.24	0.22	0.34
Recall	0.45	0.71	0.46	0.70	0.38	0.75
F1 score	0.33	0.39	0.34	0.36	0.28	0.46
AUPRC	0.24 (0.17-0.32)	0.46 (0.42-0.50)	0.24 (0.17-0.34)	0.41 (0.37-0.45)	0.25 (0.08-0.40)	0.55 (0.50-0.61)
AUC, Area under the receiver operator characteristic curves.						

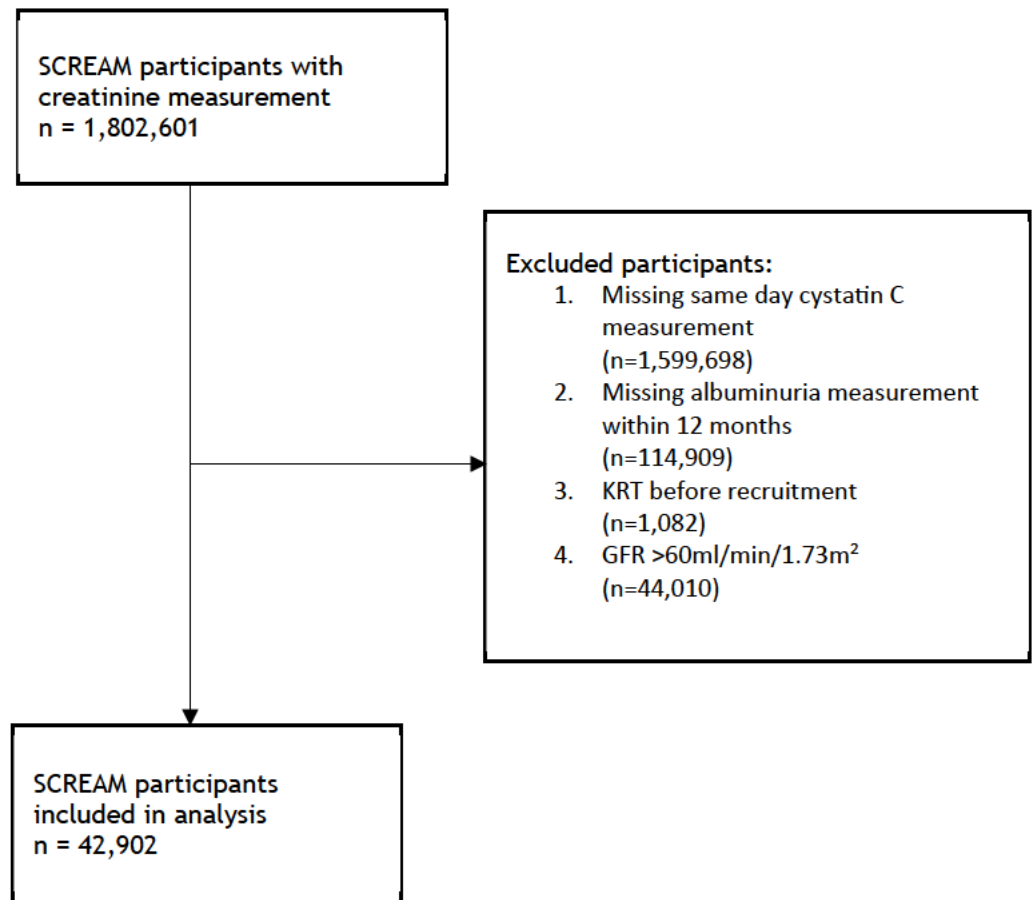
Supplemental Table 5- 25. Sensitivity analysis: Additional performance measures for 5-year KFRE (utilising eGFRcr) by cohort and multimorbidity subgroup

Performance measure for 5-year KFRE	Whole cohort		Multimorbidity		No multimorbidity	
	UK Biobank	SCREAM	UK Biobank	SCREAM	UK Biobank	SCREAM
Precision	0.36	0.17	0.35	0.15	0.39	0.23
Recall	0.59	0.81	0.58	0.80	0.60	0.83
F1 score	0.44	0.28	0.44	0.25	0.47	0.36
AUPRC	0.45 (0.38-0.51)	0.46 (0.43-0.49)	0.44 (0.38-0.52)	0.41 (0.37-0.45)	0.47 (0.34-0.59)	0.56 (0.51-0.61)
AUC, Area under the receiver operator characteristic curves.						

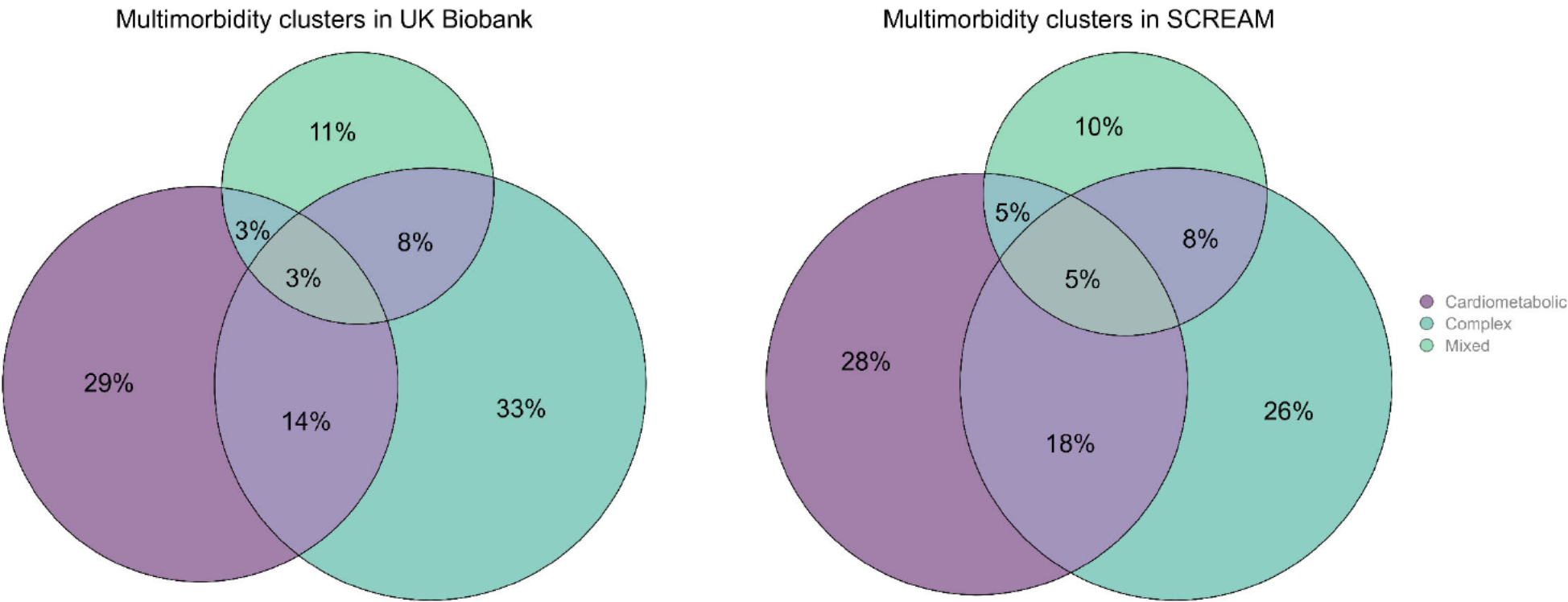
Supplemental Figure 5- 1. Flow diagram of participant selection and exclusions in UK Biobank cohort



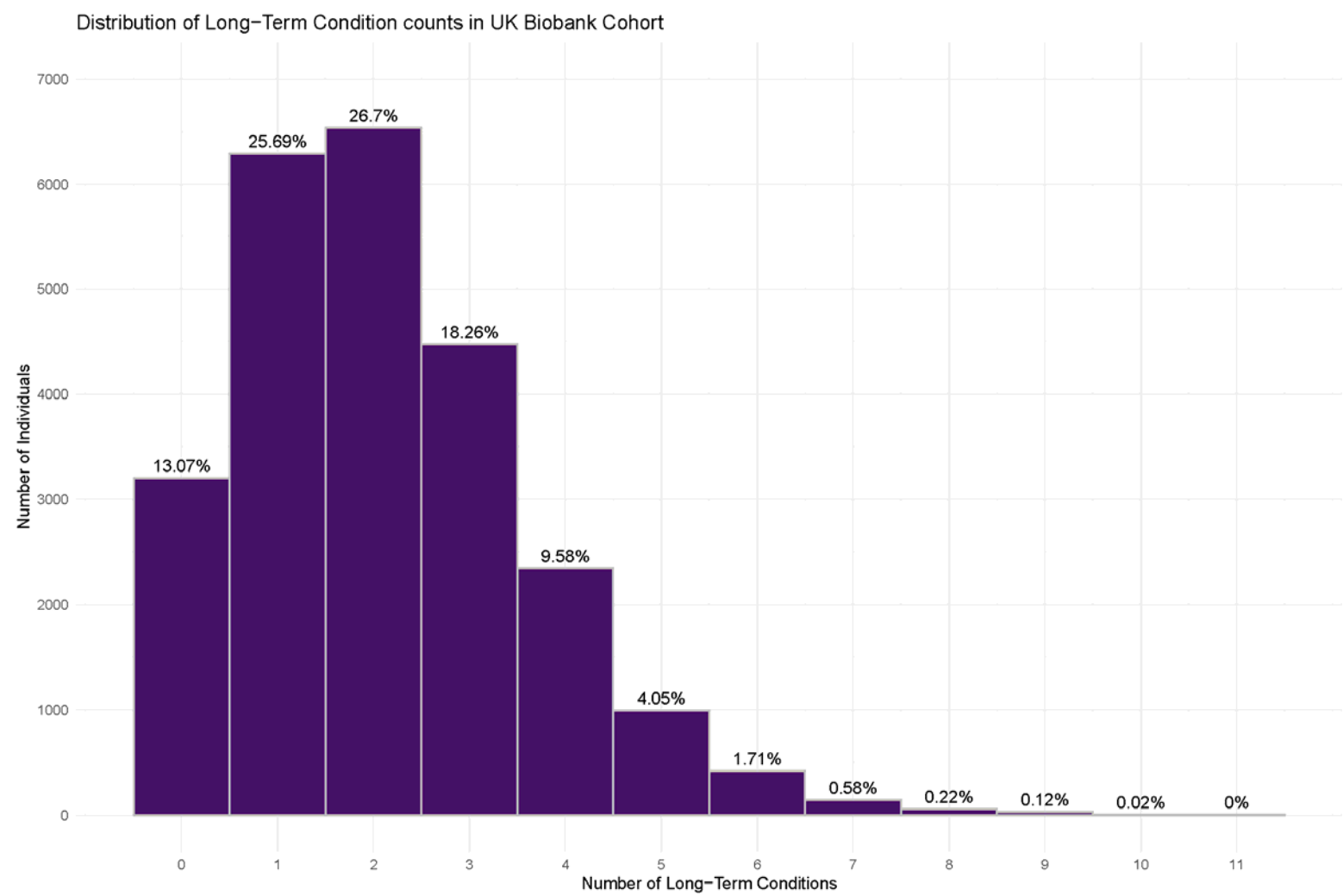
Supplemental Figure 5- 2. Flow diagram of participant selection and exclusions in SCREAM cohort.



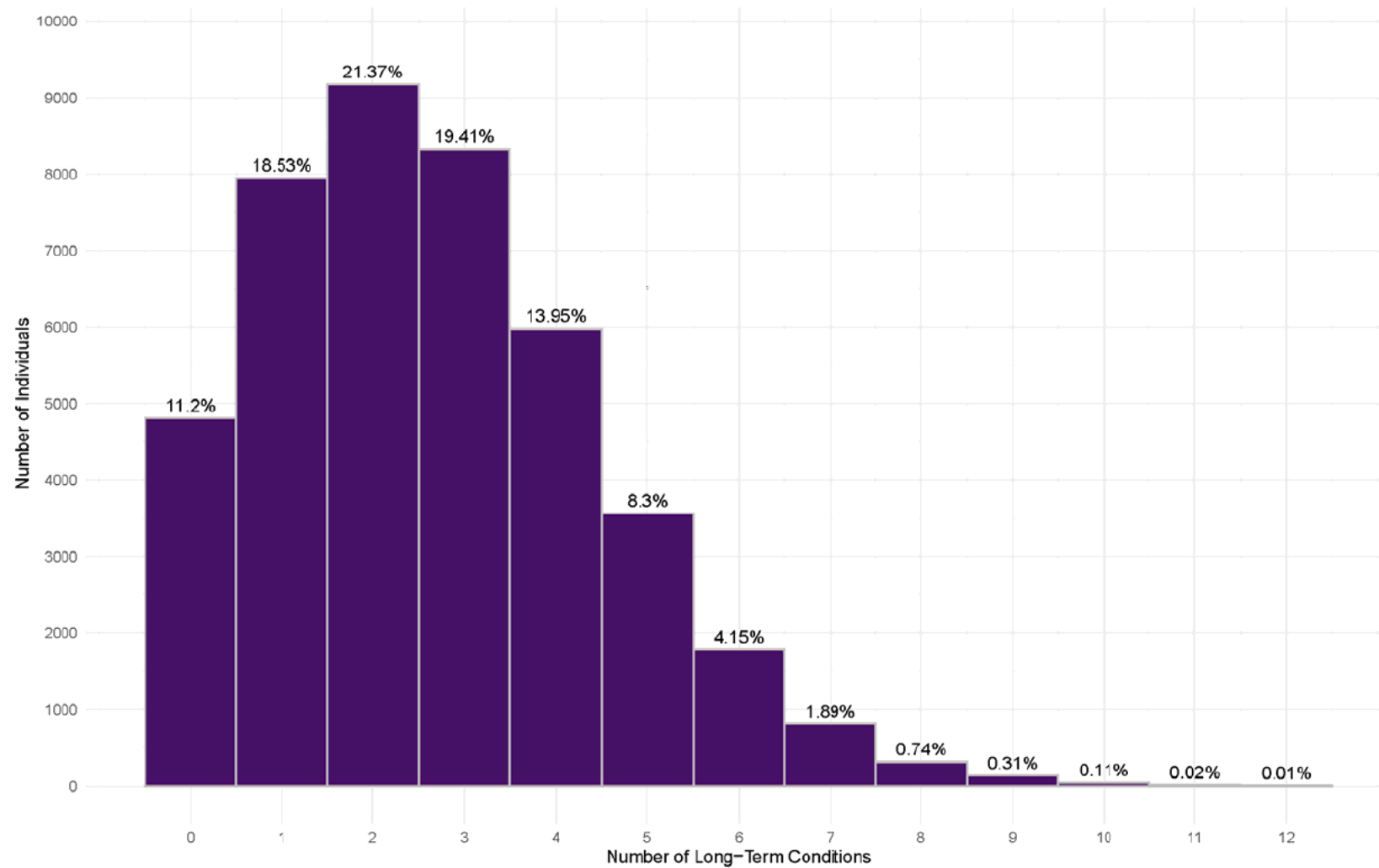
Supplemental Figure 5- 3. Euler diagrams showing overlap between multimorbidity clusters in UK Biobank and SCREAM cohorts



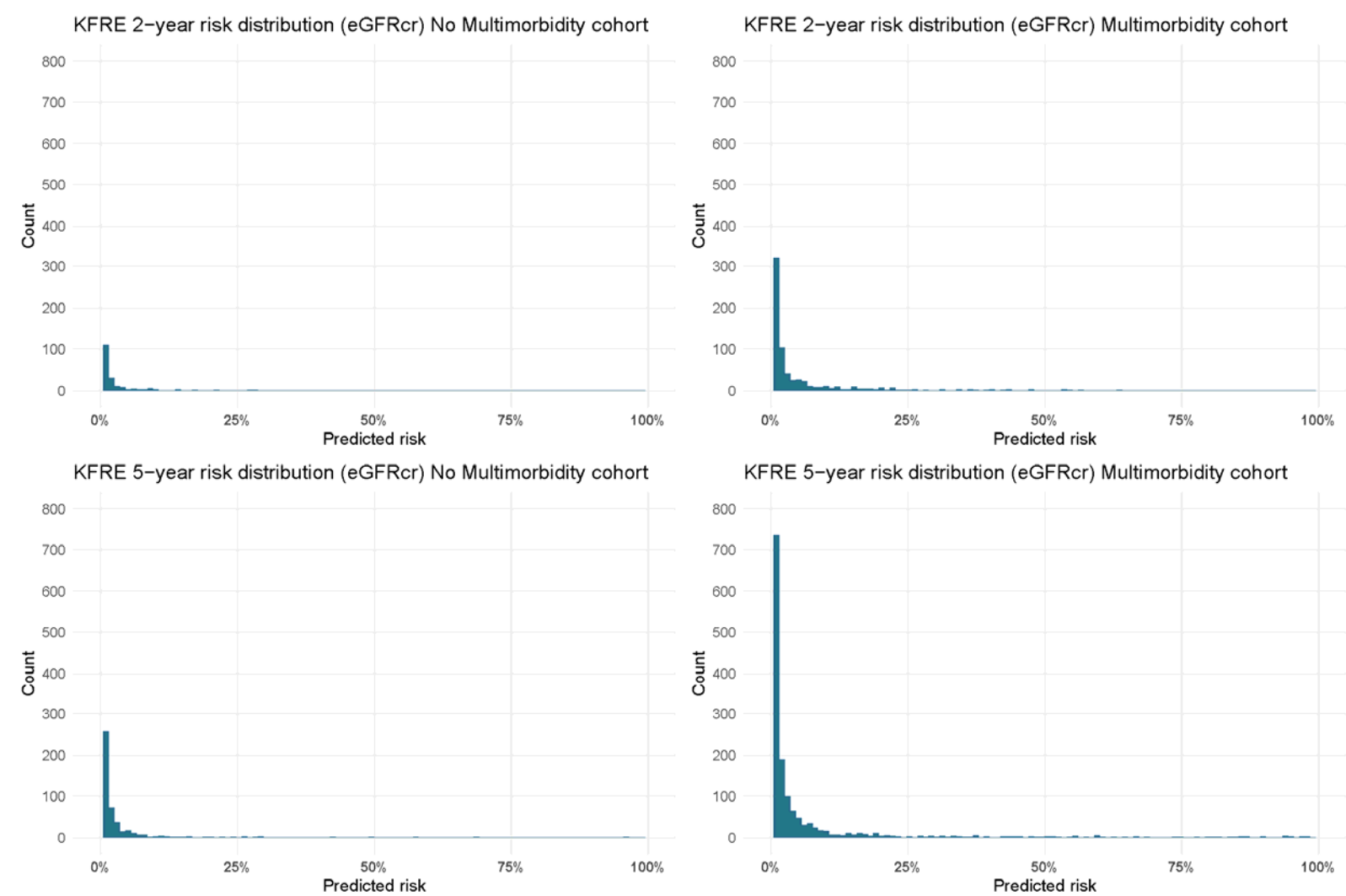
Supplemental Figure 5- 4. Distribution of long-term condition counts: UK Biobank



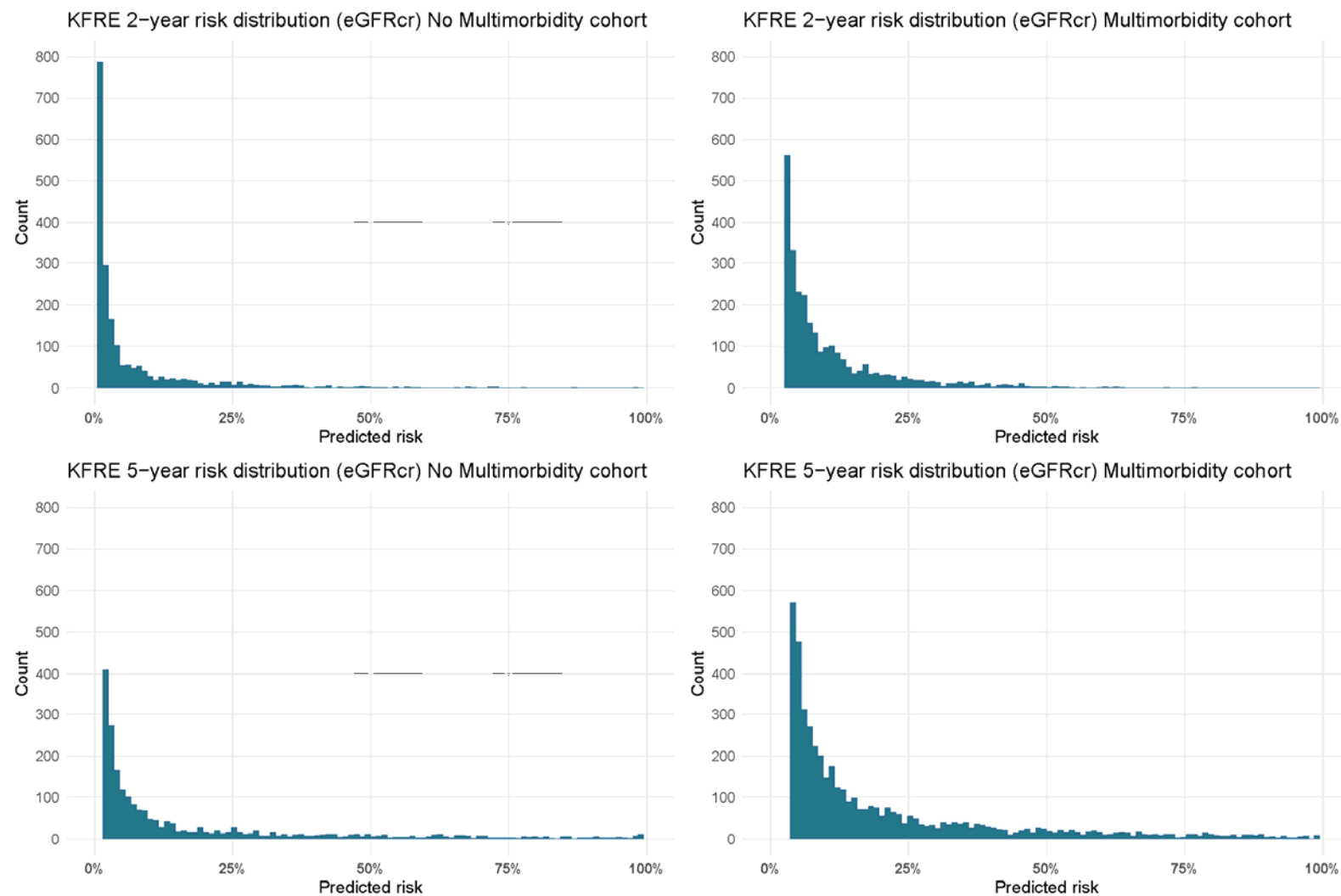
Supplemental Figure 5- 5. Distribution of long-term condition counts: SCREAM



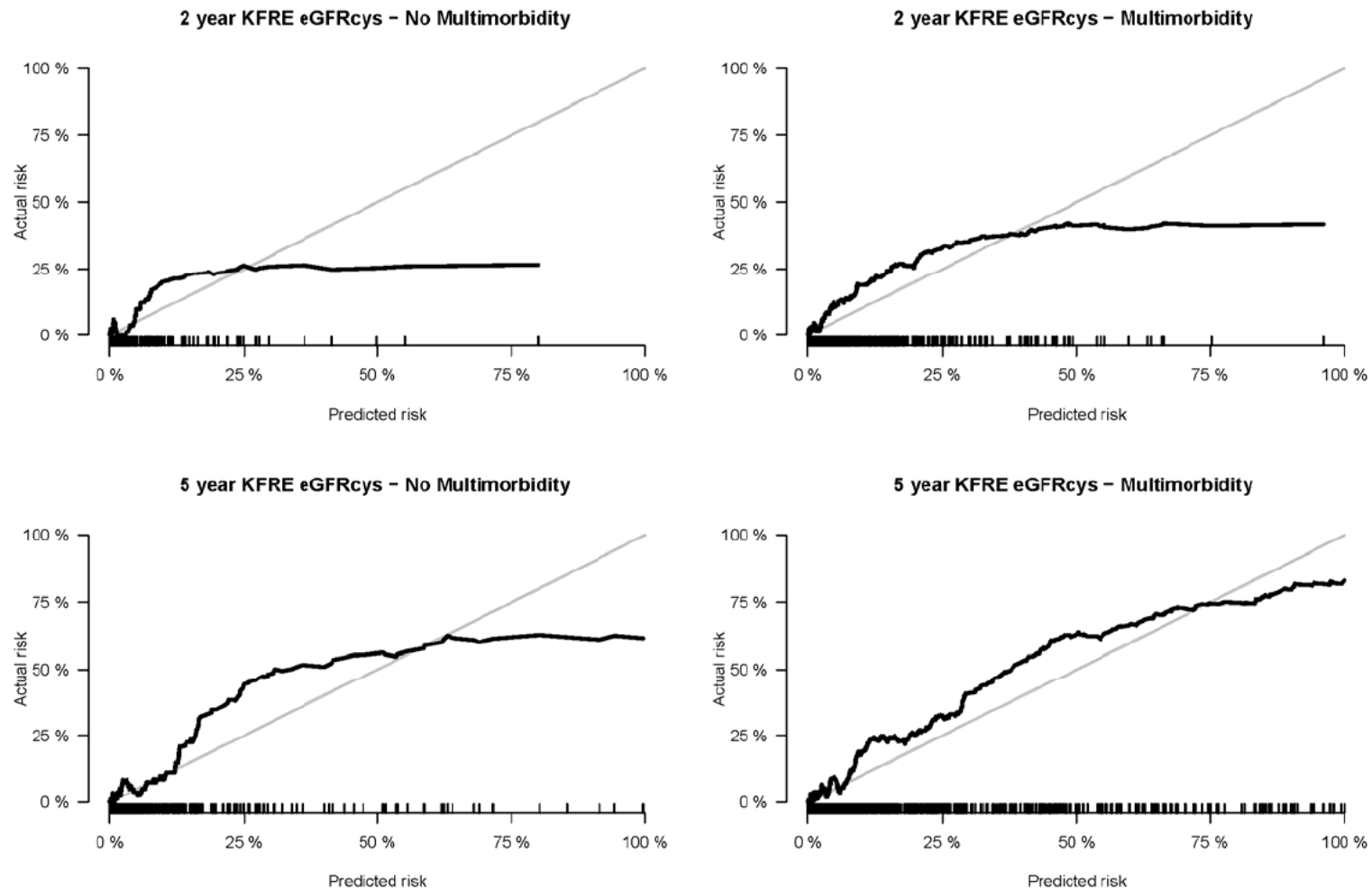
Supplemental Figure 5- 6. Histograms showing distribution of the predicted 2-year and 5-year risk of kidney failure by multimorbidity status in UK Biobank cohort. Predicted risk calculated by the UK calibrated KFRE using eGFRcr



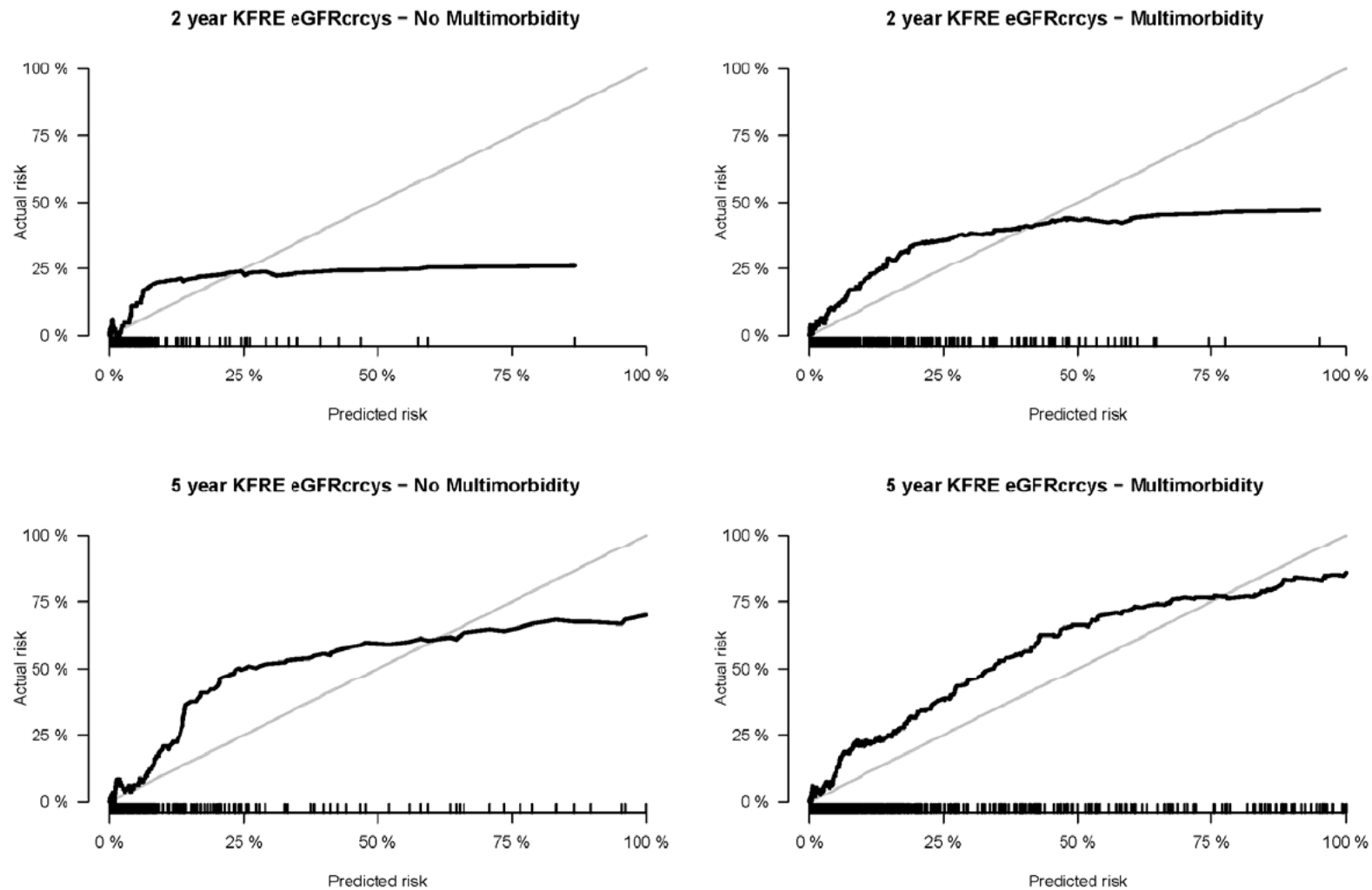
Supplemental Figure 5- 7. Histograms showing distribution of the predicted 2-year and 5-year risk of kidney failure by multimorbidity status in SCREAM cohort. Predicted risk calculated by the UK calibrated KFRE using eGFRcr



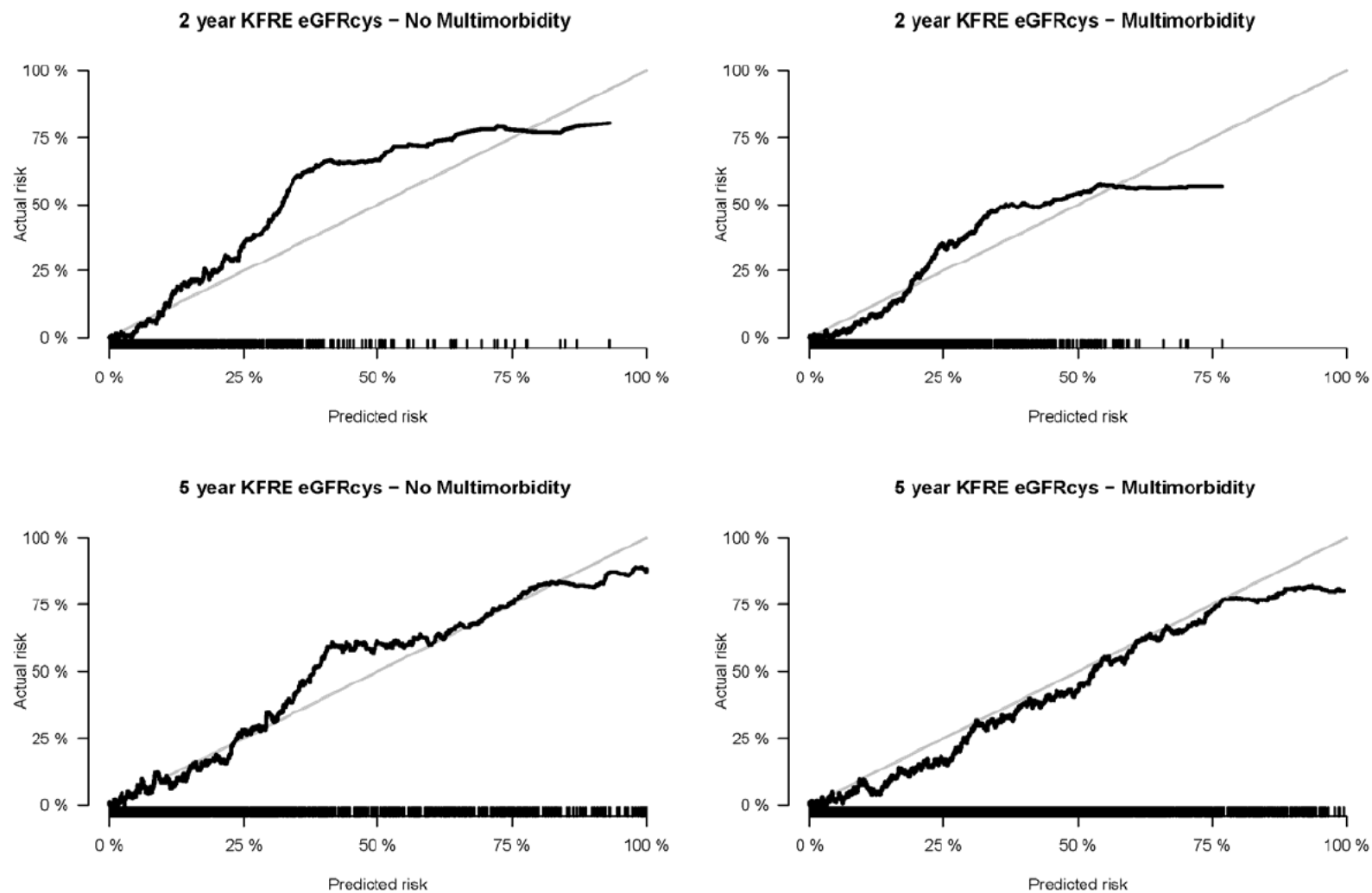
Supplemental Figure 5- 8. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by multimorbidity status in UK Biobank cohort. Predicted risk is according to the UK calibrated KFRE using eGFRcys



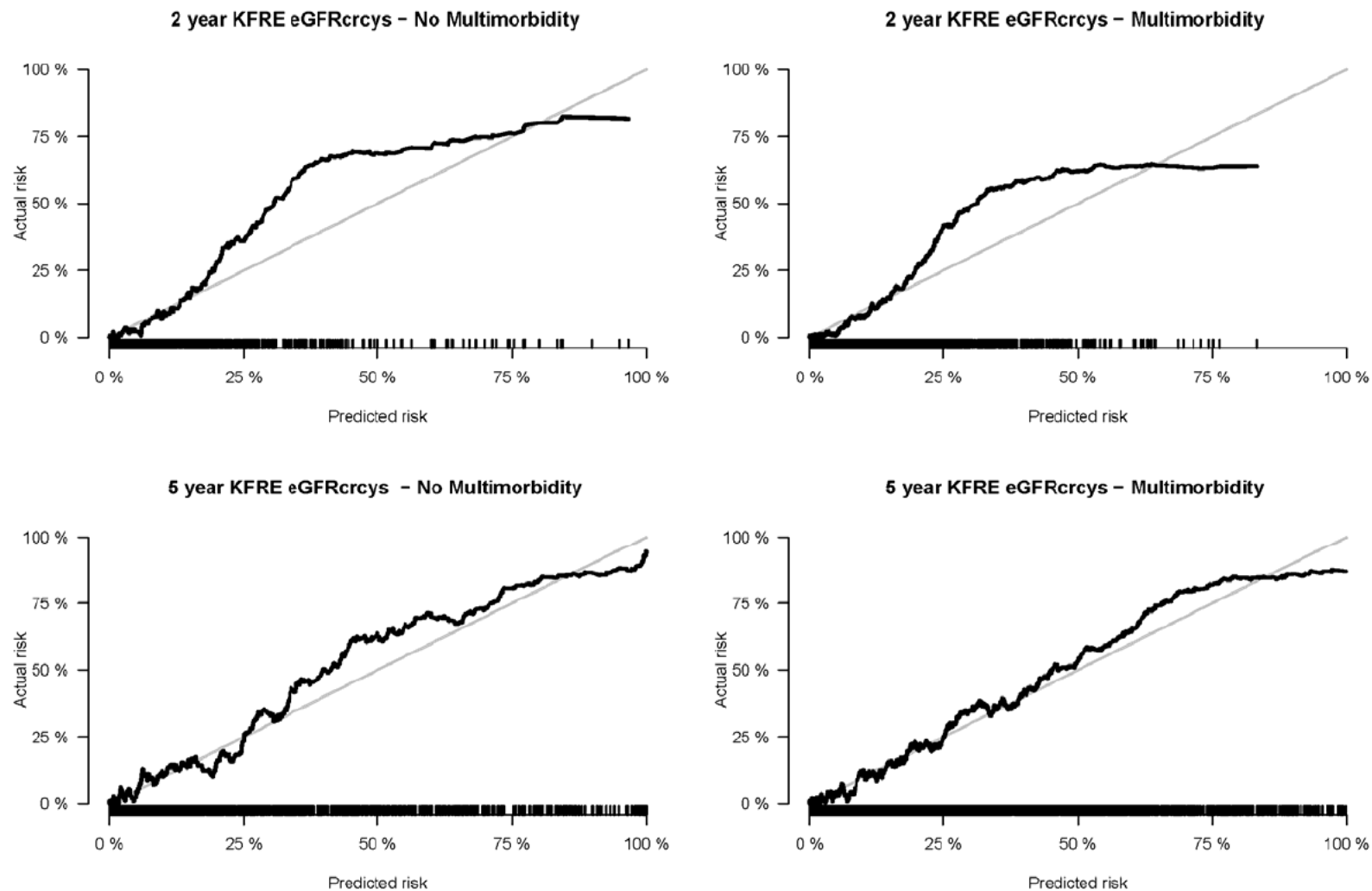
Supplemental Figure 5-9. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by multimorbidity status in UK Biobank cohort. Predicted risk is according to the UK calibrated KFRE using eGFRrcrys



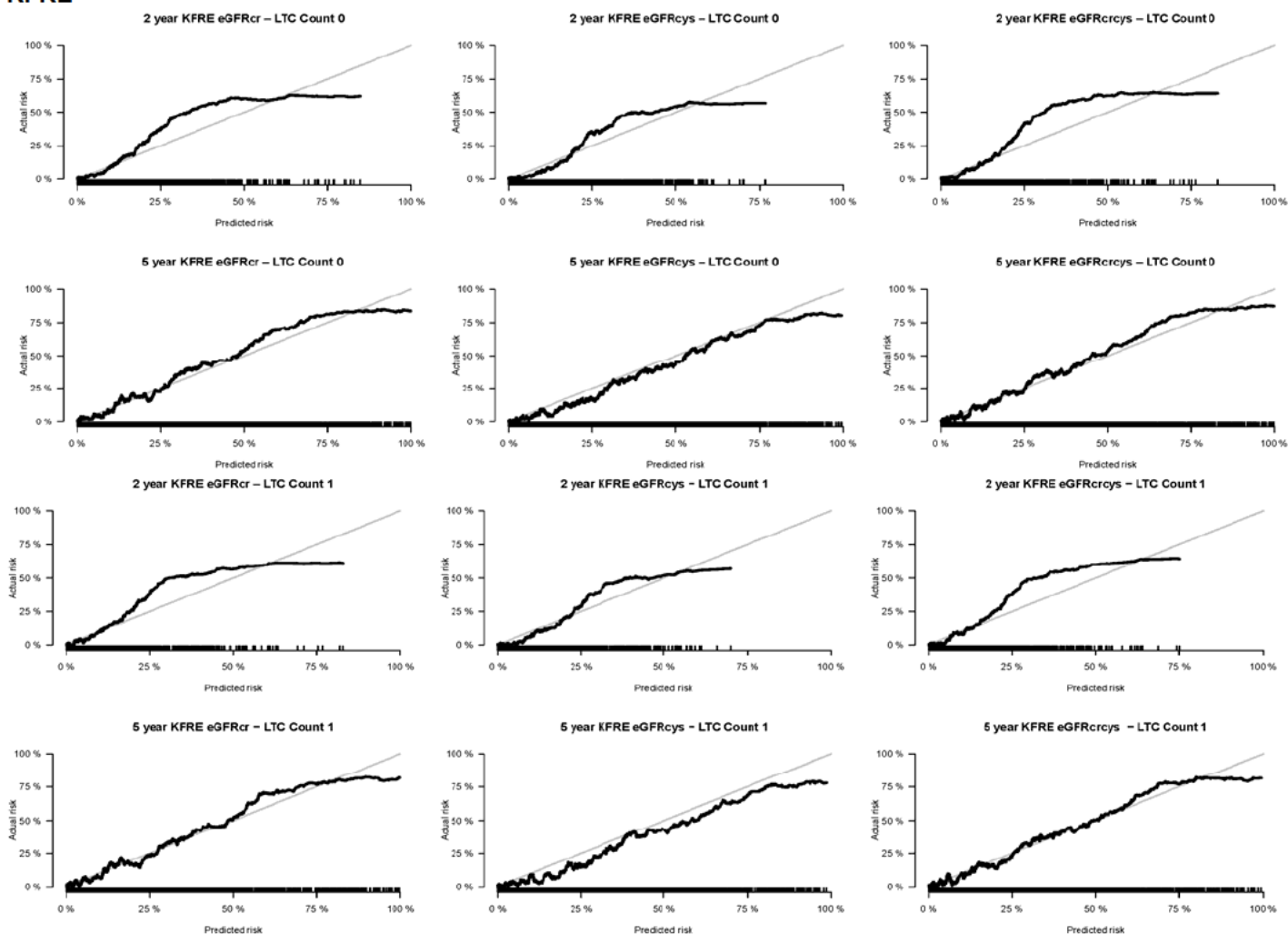
Supplemental Figure 5- 10. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by multimorbidity status in SCREAM cohort. Predicted risk is according to the UK calibrated KFRE using eGFRcys

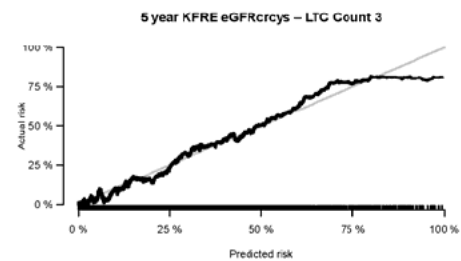
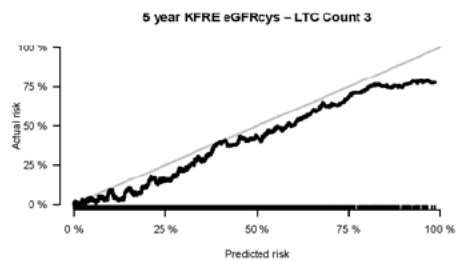
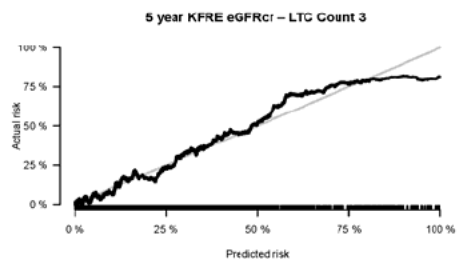
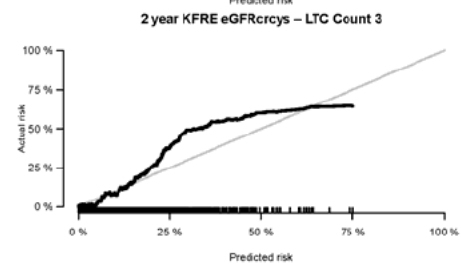
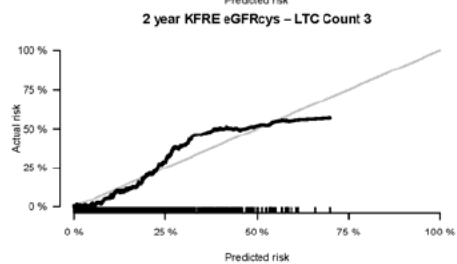
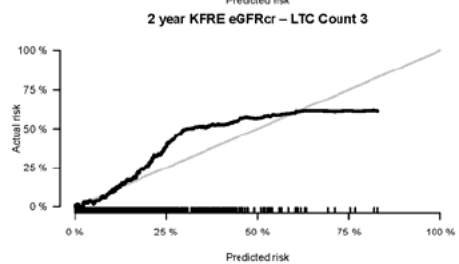
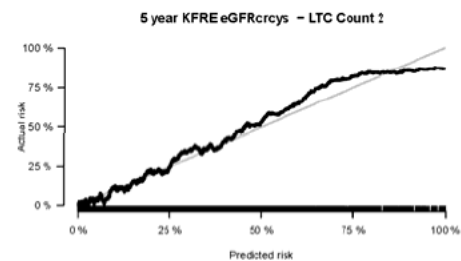
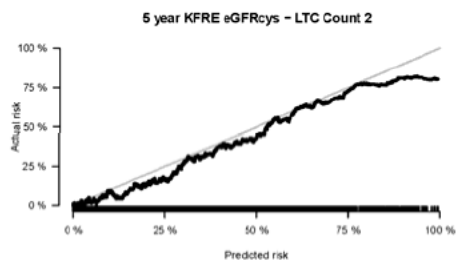
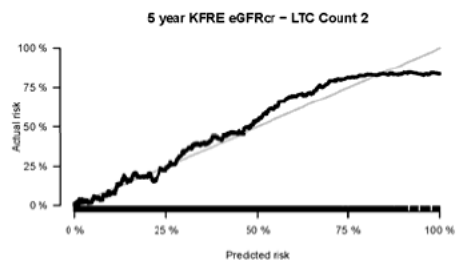
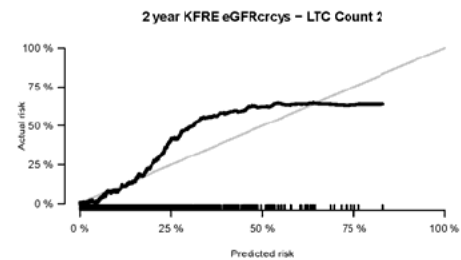
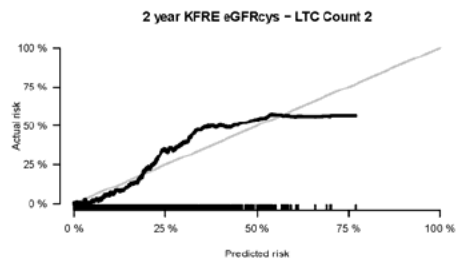
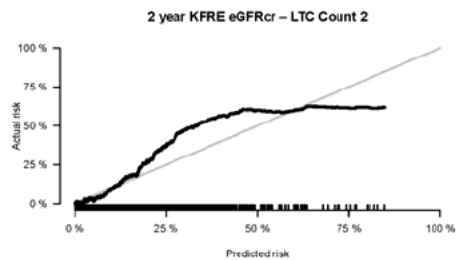


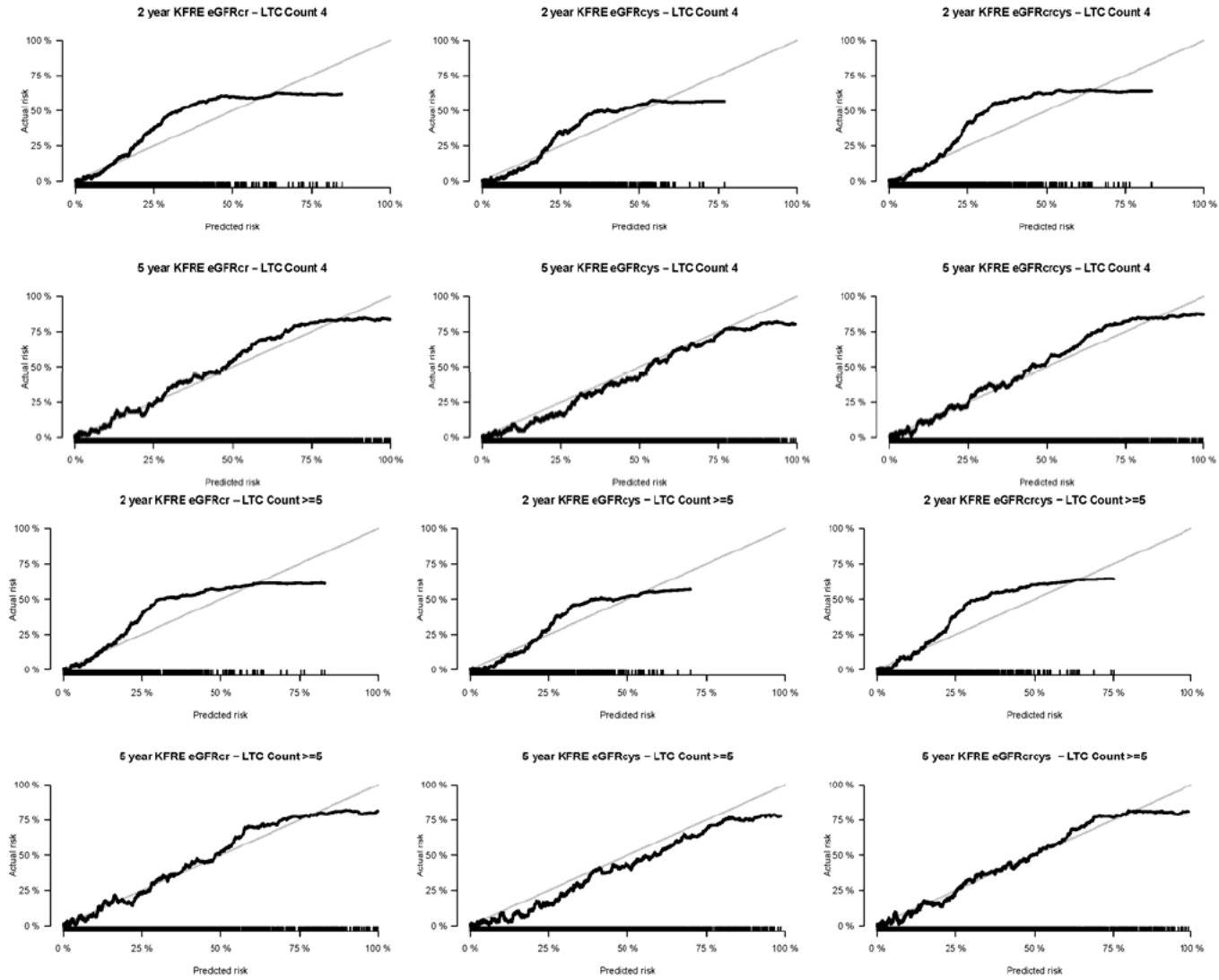
Supplemental Figure 5- 11. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by multimorbidity status in SCREAM cohort. Predicted risk is according to the UK calibrated KFRE using eGFRrcrys



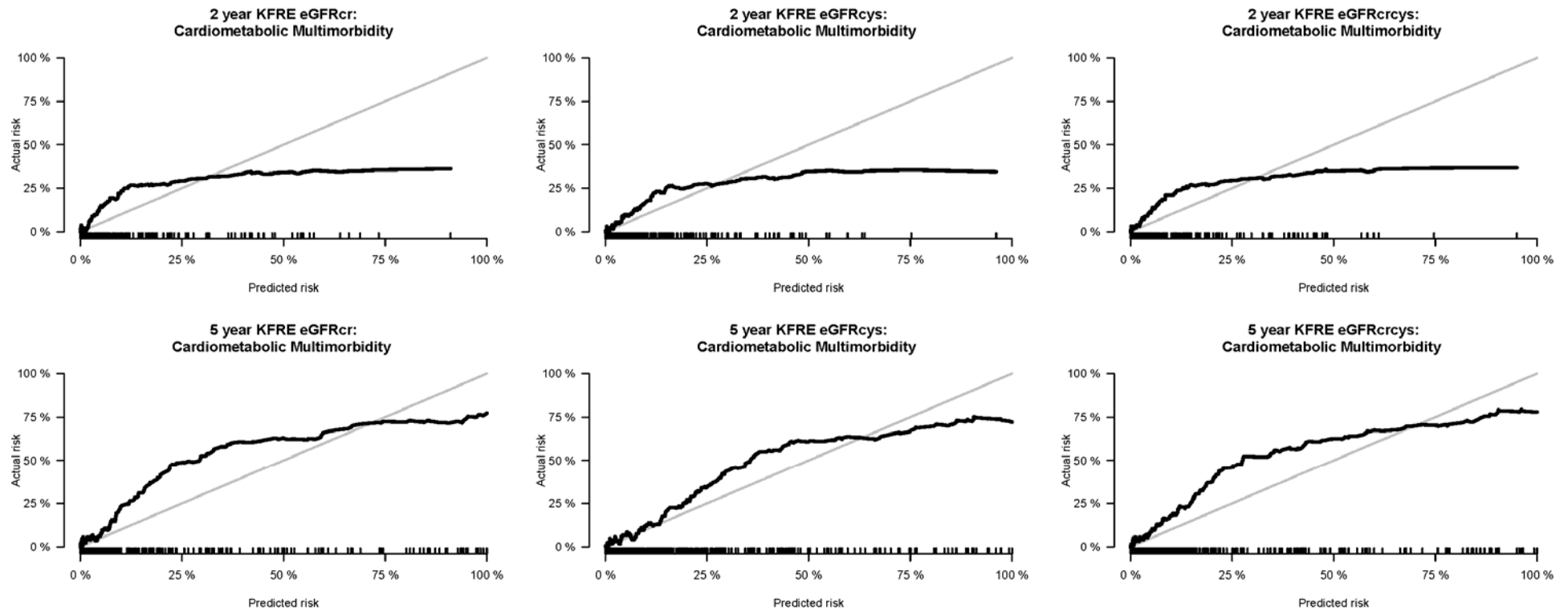
Supplemental Figure 5- 12. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure by LTC count and different eGFR equations used in KFRE for SCREAM cohort. Predicted risk is according to the UK calibrated KFRE



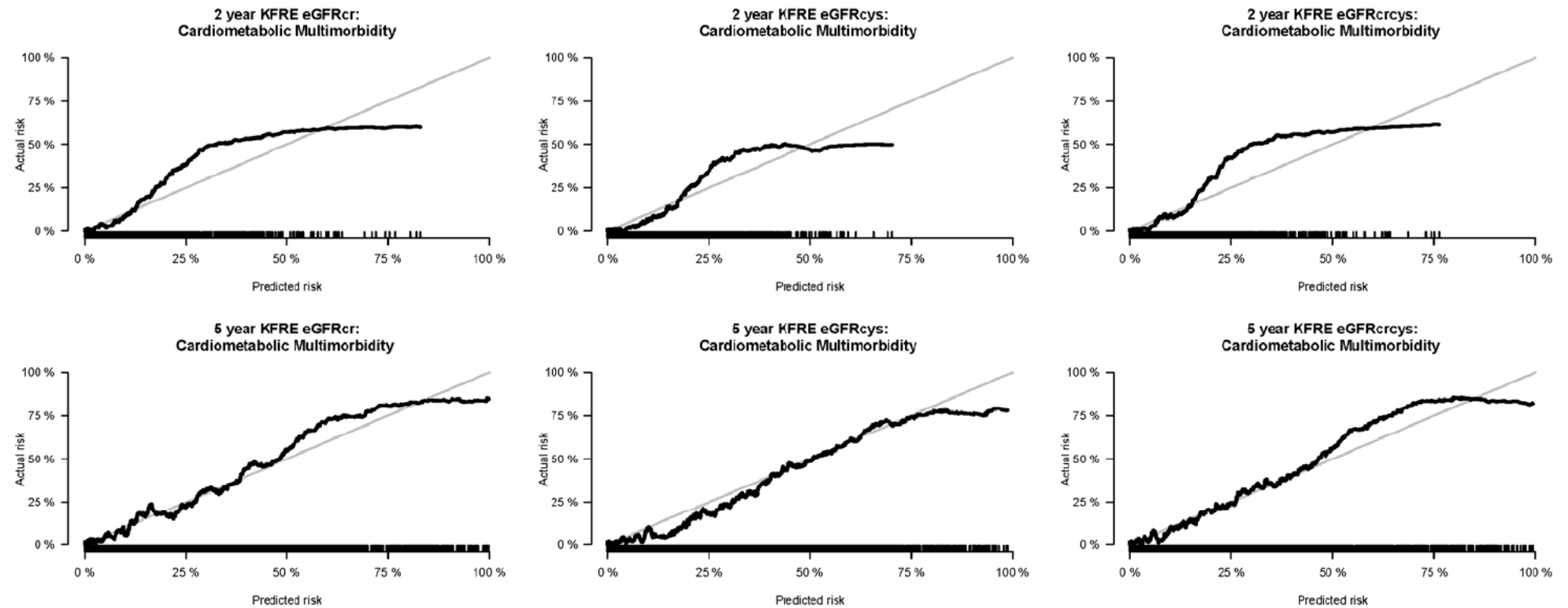




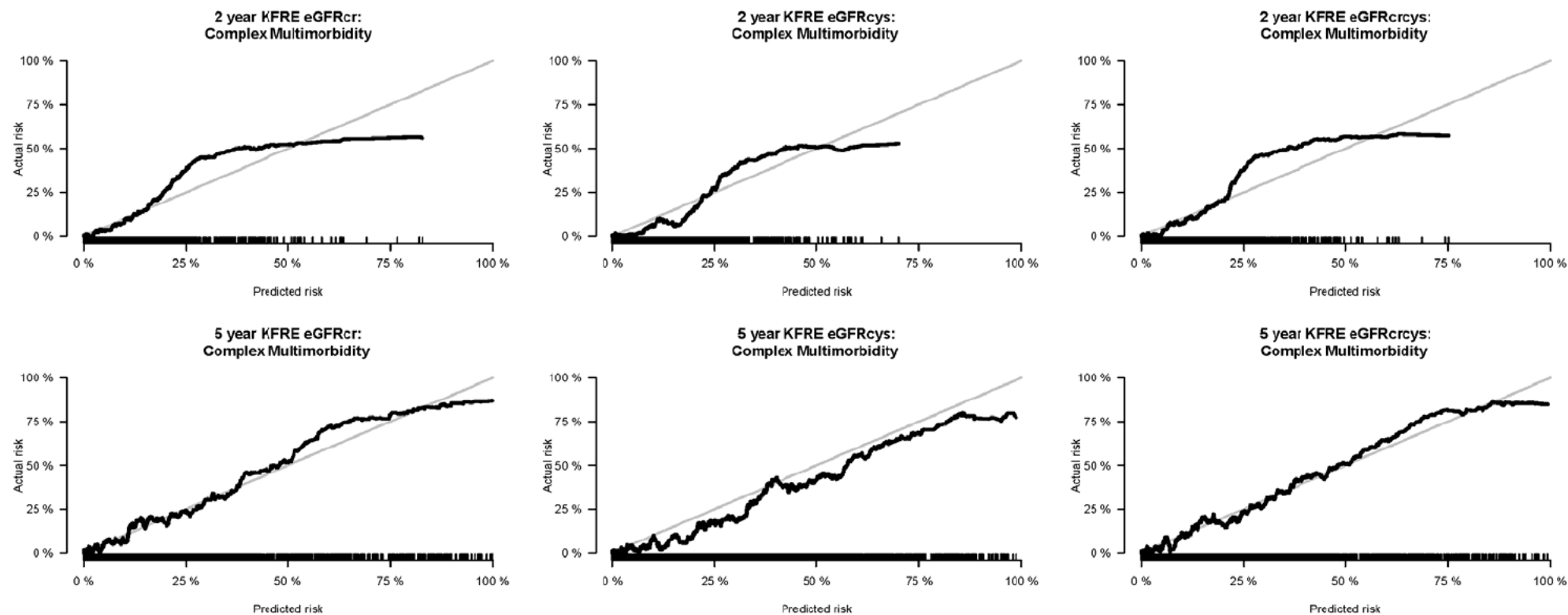
Supplemental Figure 5- 13. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure cardiometabolic multimorbidity and different eGFR equations used in KFRE for UK Biobank cohort. Predicted risk is according to the UK calibrated KFRE



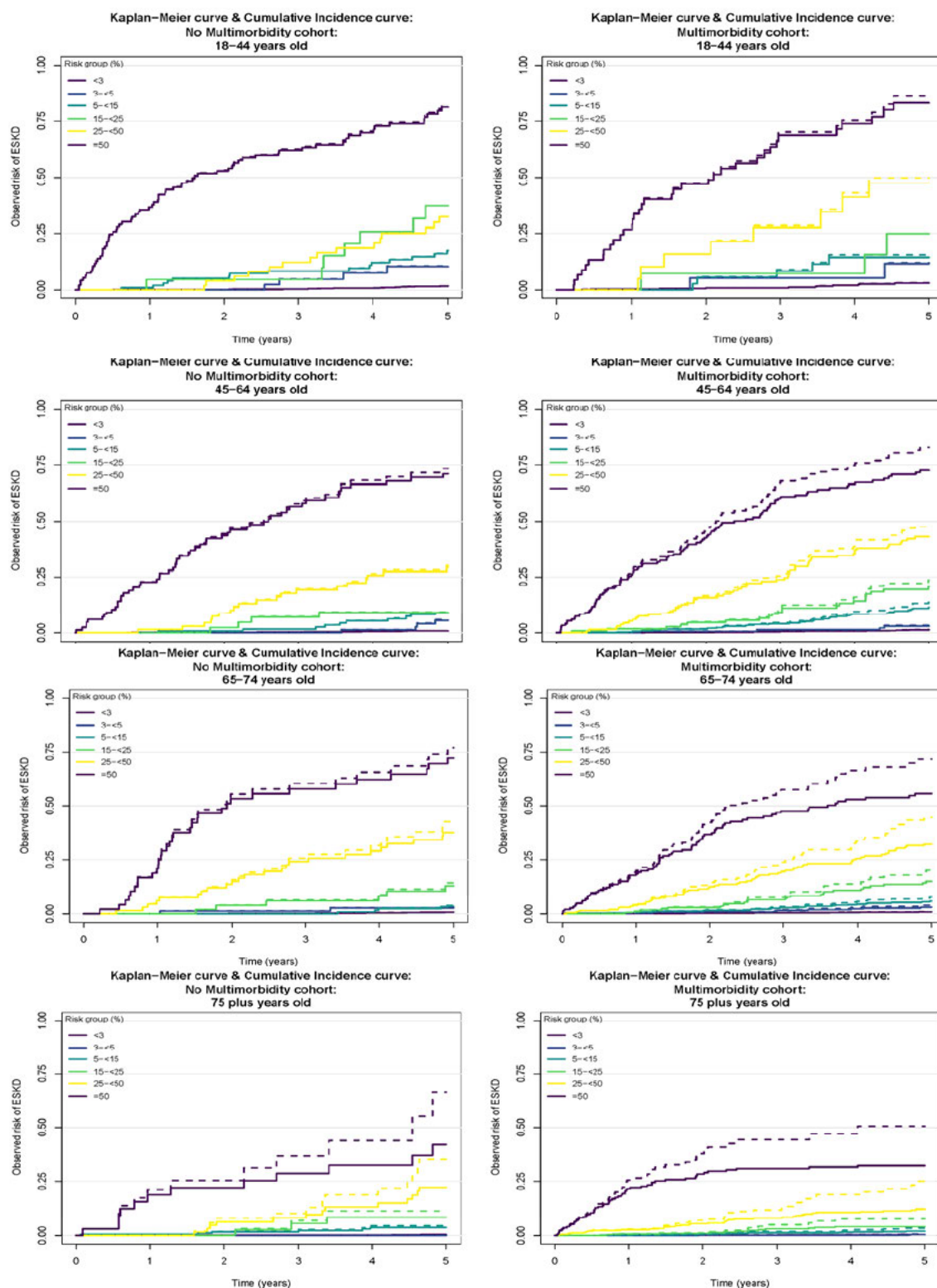
Supplemental Figure 5- 14. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure cardiometabolic multimorbidity and different eGFR equations used in KFRE for SCREAM cohort. Predicted risk is according to the UK calibrated KFRE



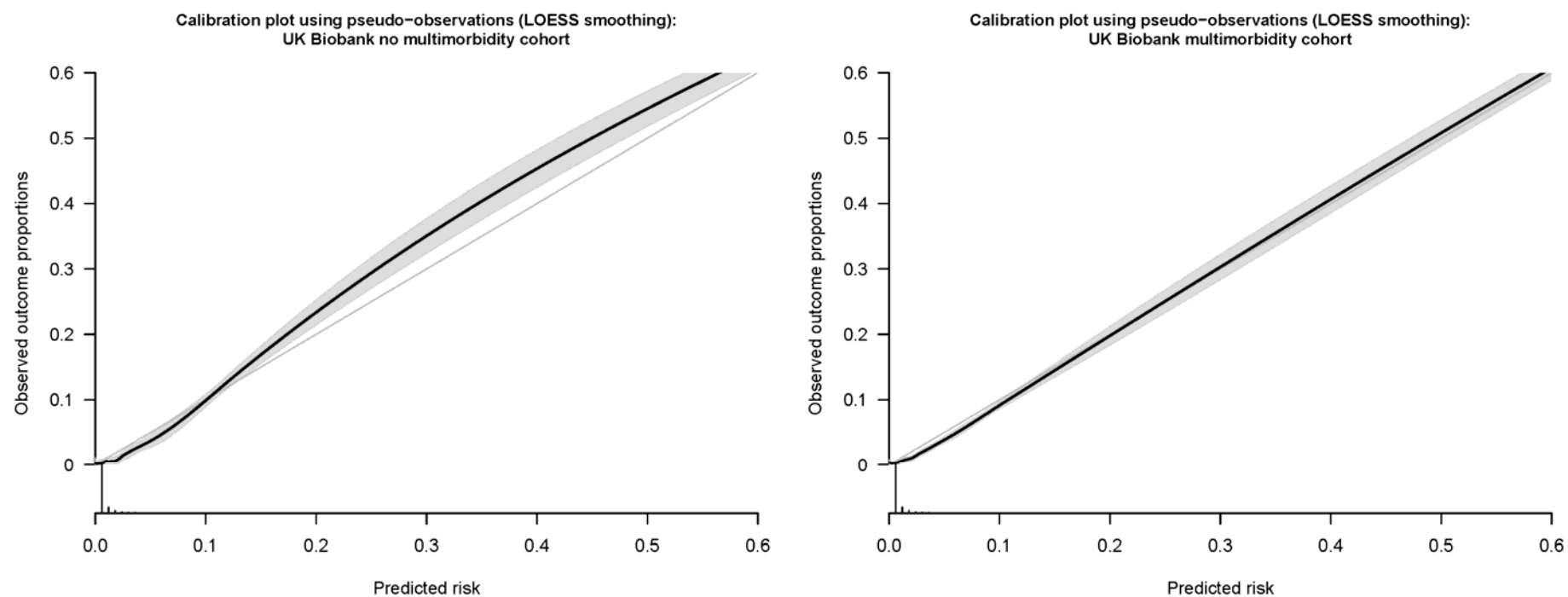
Supplemental Figure 5- 15. Calibration curves for predicted versus observed 2- and 5-year risk of kidney failure complex multimorbidity and different eGFR equations used in KFRE for SCREAM cohort. Predicted risk is according to the UK calibrated KFRE



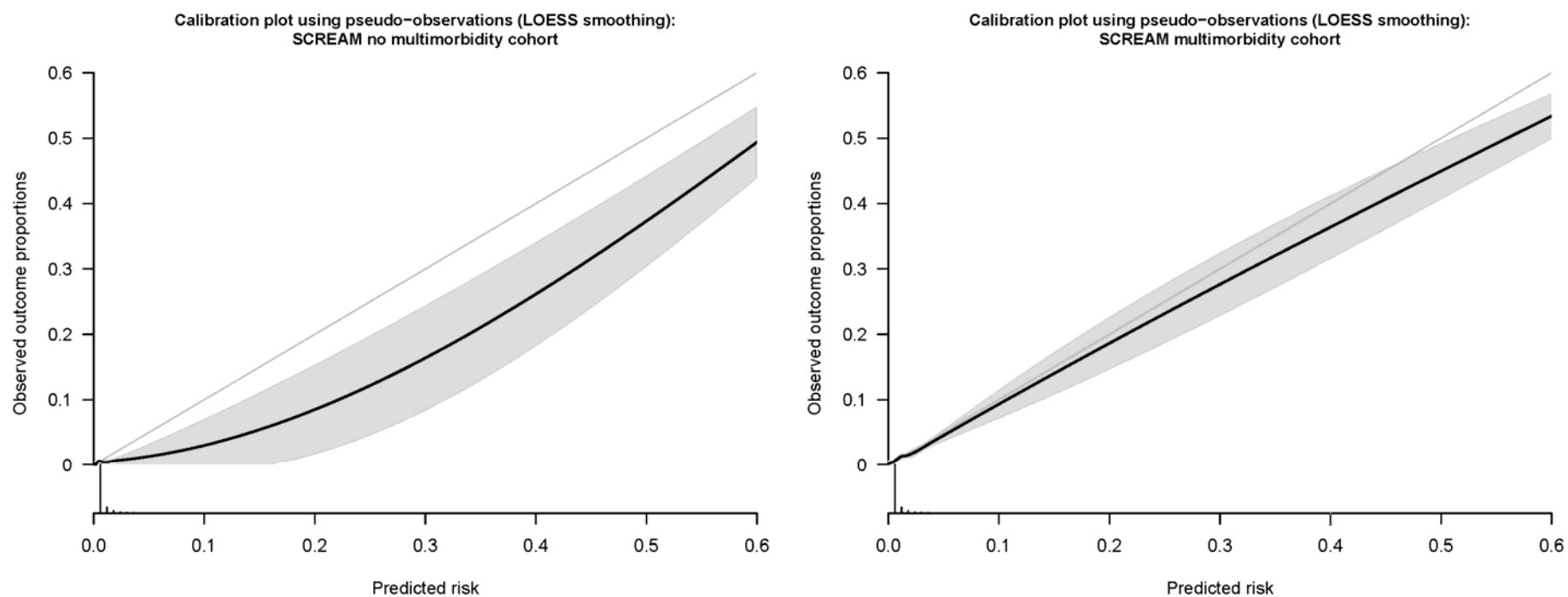
Supplemental Figure 5- 16. Kaplan-Meier estimates (dashed lines) and Aalen-Johansen estimates (solid lines) cumulative incidence curves for kidney failure by KFRE risk groups in SCREAM – comparison by multimorbidity status and age groups



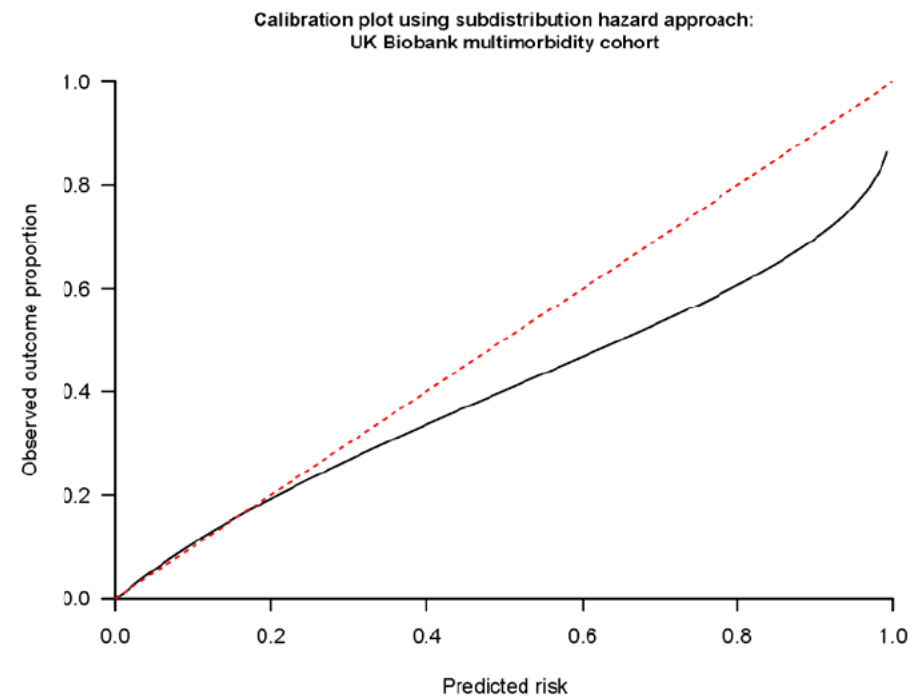
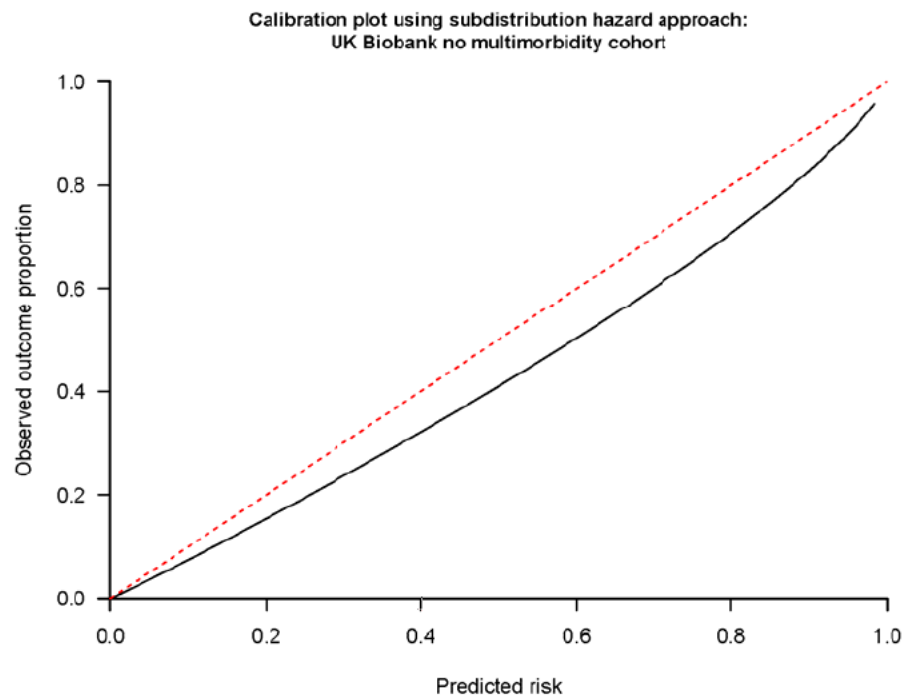
Supplemental Figure 5- 17. Calibration plots with LOESS smoothing using cause-specific hazards approach and pseudo-observations for 5-year model (using eGFRcr) accounting for competing risk of mortality – UK Biobank cohort by multimorbidity status



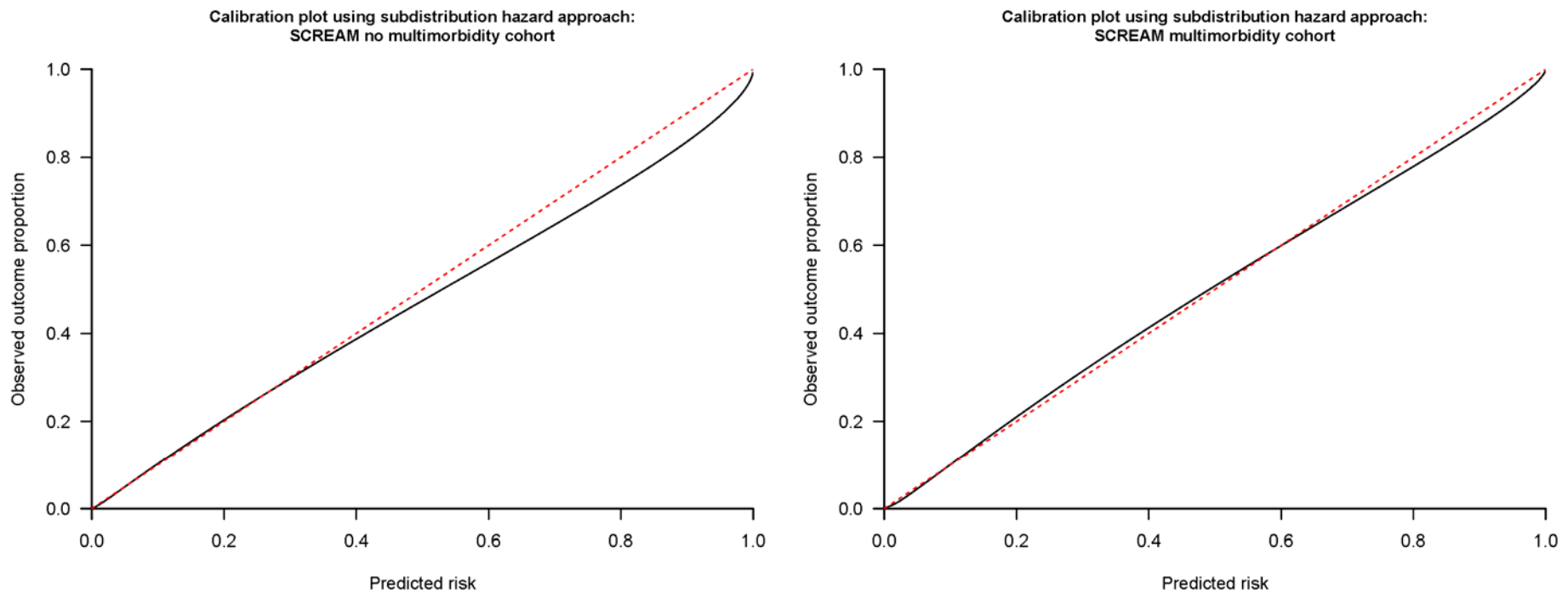
Supplemental Figure 5- 18. Calibration plots with LOESS smoothing using cause-specific hazards approach and pseudo-observations for 5-year model (using eGFRcr) accounting for competing risk of mortality – SCREAM cohort by multimorbidity status



Supplemental Figure 5- 19. Calibration plots using sub-distribution hazard approach for 5-year model (using eGFRcr) accounting for competing risk of mortality – UK Biobank cohort by multimorbidity status



Supplemental Figure 5- 20. Calibration plots using sub-distribution hazard approach for 5-year model (using eGFRcr) accounting for competing risk of mortality –SCREAM cohort by multimorbidity status



Appendix 7: Supplementary material for Chapter 6: An analysis of frailty in adults with chronic kidney disease and validation of the kidney failure risk equation in sub-groups with frailty

Supplemental Text 6- 1. Summary of included frailty measures

Frailty phenotype five criteria definitions:

- weight loss - “Compared with one year ago, has your weight changed?” (reduced = yes, other response = no)
- exhaustion - “Over the past two weeks, how often have you felt tired or had little energy?” (more than half the days or nearly every day= yes, other response = no)
- grip strength – highest valid reading (as assessed by Jamar J00105 hydraulic hand dynamometer) was used. Weakness = grip strength in the lowest 20% at baseline, adjusted for gender and body mass index as per definitions used by Fried et al.⁸
- low physical activity - none (no physical activity in the last 4 weeks), low (light DIY activity only in the past 4 weeks), medium (heavy DIY activity, walking for pleasure, or other exercises in the past 4 weeks), high (strenuous sports in the past 4 weeks). (none or light activity with a frequency of once per week or less = yes ‘low physical activity’)
- slow walking pace - “How would you describe your usual walking pace?” (slow = yes, other = no)

Individuals were classed as frail if they met three or more criteria, pre-frail if they met one or two criteria and non-frail if they met none of five criteria.

Frailty index

Conditions/variables assessed for inclusion were:

- glaucoma, cataracts, hearing difficulty, migraine, dental problems, self-described nervous personality, severe anxiety/panic attacks, long standing illness or disability, common to feel loneliness, sense of misery, fractures/broken bones in the last 5-years, diabetes, myocardial infarction, angina, stroke, high blood pressure, hypothyroidism, deep vein thrombosis, high cholesterol, wheeze in the last year, pneumonia, chronic bronchitis/emphysema, rheumatoid arthritis, osteoarthritis, gout, osteoporosis, hayfever/allergic rhinitis/eczema, psoriasis, cancer diagnosis, multiple cancers diagnosed, chest pain, head and/or neck pain, back pain, stomach/abdominal pain, hip pain, knee pain, whole body pain, facial pain, sciatica, gastric reflux, hiatus hernia, gall stones, diverticulitis (presence/absence = 1/0).
- Self-rated health (0=excellent, 0.25=good, 0.5=fair, 1=poor)
- Frequency of tiredness/lethargy in the last two weeks (0=not at all, 0.25=several days, 0.5=more than half of the time, 1= nearly every day)
- Experience of sleeplessness/insomnia (0=never/rarely, 0.5=sometimes, 1=usually)
- Frequency of depressed feelings in last two weeks (0=not at all, 0.5 = several days, 0.75 = more than half of the time, 1= nearly every day)
- Falls in the last year (0=no falls, 0.5=once fall, 1=more than one fall)

Laboratory frailty index – variables assessed for calculation of laboratory frailty index

Variable	Units	Lower limit cut-off	Upper limit cut-off	UK Biobank variable code
Albumin	g/L	35	50	30600-0.0
AST (IU/L)	U/L		40	30650-0.0
SBP (mmHg)	mmHg	90	140	sbp
DBP	mmHg	60	90	dbp
Calcium	mmol/L	2.2	2.6	30680-0.0
Glucose	mmol/L (does not state fasted)	3.9	11.0	30740-0.0
Hb	g/dL	13.0 (male) 11.5 (female)	18.0 (male) 16.0 (female)	30020-0.0
Mean corpuscular volume (fL)	fL (femtolitres)	83	101	30040-0.0
Alkaline phosphatase	U/L	30	130	30610-0.0
Phosphate	mmol/L	0.8	1.5	30810-0.0
Total Protein	g/L	60	80	30860-0.0
Lymphocytes	X10 ⁹ cells/L	1.1	5.0	30120-0.0
Eosinophils	X10 ⁹ cells/L	0.02	0.5	30150-0.0
Platelet count	X10 ⁹ cells/L	150	410	30080-0.0
ALT	U/L	N/A	50	30620-0.0
Cholesterol	mmol/l	N/A	5	30690-0.0
CRP	mg/L	N/A	5	30710-0.0
GGT	U/L	N/A	70 M 40 F	30730-0.0
HbA1C	mmol/mol	25	48	30750-0.0
HDL cholesterol	mmol/l	1	N/A	30760-0.0
LDL	mmol/l	N/A	3.0	30780-0.0
Total bilirubin	µmol/L	N/A	20	30840-0.0
Triglycerides	mmol/L	0.2	2.3	30870-0.0
Vitamin D	nmol/l	50	N/A	30890-0.0

Supplemental Text 6- 2. UK Biobank algorithm for determination of kidney failure outcome
 Kidney failure was defined as requiring maintenance kidney replacement therapy (KRT); chronic maintenance dialysis or kidney transplantation. An established and pre-specified UK Biobank algorithm²¹³, using hospital admission data (ICD-10 and OPCS4 codes) was utilised to determine which individuals experienced the outcome of kidney failure. Individuals with codes indicating a kidney transplant or peritoneal dialysis are assumed to be kidney failure cases. For individuals with codes for haemodialysis, they were only deemed to have experienced kidney failure if there was an associated indicator of CKD prior to or within 365 days of receiving the KRT (to exclude cases of AKI requiring KRT).

Supplemental Text 6- 3. UK calibrated four variable KFRE

2-year KFRE = $1 - 0.9878^{\exp((-0.2201 * (\text{age} / 10 - 7.036)) + (0.2467 * (\text{male} - 0.5642)) - (0.5567 * (\text{eGFR} / 5 - 7.222)) + (0.451 * (\log(\text{uACR} / 0.113) - 5.137)))}$

5-year KFRE = $1 - 0.957^{\exp((-0.2201 * (\text{age} / 10 - 7.036)) + (0.2467 * (\text{male} - 0.5642)) - (0.5567 * (\text{eGFR} / 5 - 7.222)) + (0.451 * (\log(\text{uACR} / 0.113) - 5.137)))}$

Supplemental Text 6- 4. Explanation and interpretation of model performance measures utilised

Model performance was assessed in the following categories:

- Discrimination (how well the model can discriminate between those who do or do not experience the outcome) using time-dependent area under the receiver operating characteristic curve (AUC)¹⁵⁸ with 95% confidence intervals (CI) and Harrel's C-index, with 95% CI estimated via bootstrapping with 1000 samples^{157, 283}.
- Calibration (assessment of whether the risk assigned to individuals corresponds to their true risk) by calibration curves¹⁵⁹, calibration intercept (to assess general calibration), calibration slope (to examine the degree of variation in model predictions) and calibration-in-the-large using the observed/expected (O/E) ratio.
- Overall model fit using the Brier score^{160, 161} and the scaled Brier score²⁸⁴.

Supplemental Text 6- 5. Competing risk analyses results

Cumulative incidence of kidney failure was lower as age advanced (5-year cumulative incidence of kidney failure <60 years old 2.62% vs ≥60 years old 0.91%) with an increased risk in mortality in the older age group compared to the younger age group (Supplemental Table 6-11 and 6-12). There was an overestimation of kidney failure risk using the death censored approach compared to the competing risk approach for frailty groups in younger age groups (<60 years) but not the younger non-frail cohort (<60 years) at higher kidney failure risk prediction levels (>50% predicted risk of kidney failure) and in both frail and non-frail groups in older age groupings (≥60 years old) (Supplemental Tables 6-11-6-14 and Supplemental Figure 6-4). Cumulative incidence of both kidney failure and mortality was higher in males compared to females and was higher in the frailty subgroups in both sexes (Supplemental Tables 6-15-6-18). Survival analyses stratified by sex demonstrated an earlier separation of survival curves accounting for and not accounting for competing risk of death in the female frailty subgroups compared to the male subgroups (Supplemental figure 6-4).

Supplemental Text 6- 6. Sensitivity and supplementary analyses

KFRE model performance by individual frailty measures are presented in Supplemental Table 6-19 and 6-20 and Supplemental Figure 6-10. Discrimination was regardless of which eGFR equation was used in KFRE. Improvements in calibration were observed when utilising eGFR_{cys} at both 2- and 5-years; greatest improvement in calibration slope in frailty subgroup assessed by frailty phenotype but with some overlap in 95%CI and in calibration-in-the-large and calibration intercept for those classed as frail by FI.

Supplemental Table 6- 1. Long-term conditions included

Physical health conditions	Mental health conditions
Painful conditions	Depression
Hypertension	Anxiety
Asthma	Alcohol problems
Atrial Fibrillation	Other psychoactive substance abuse
Coronary Heart Disease	Dementia
Dyspepsia	Schizophrenia/bipolar disorder
Diabetes	Anorexia or bulimia
Thyroid disorders	
Connective tissue disorders	
Chronic Obstructive Pulmonary Disease (COPD)	
Irritable bowel syndrome	
Treated constipation	
Stroke/Transient Ischaemic Attack (TIA)	
Chronic kidney disease	
Diverticular disease	
Peripheral vascular disease	
Heart failure	
Prostate disorders	
Glaucoma	
Epilepsy	
Psoriasis/eczema	
Inflammatory Bowel Disease	
Migraine	
Chronic sinusitis	
Bronchiectasis	
Parkinson's disease	
Multiple Sclerosis	
Viral Hepatitis	
Chronic Liver disease	
Osteoporosis	
Chronic fatigue syndrome	
Endometriosis	
Meniere's disease	
Pernicious Anaemia	
Polycystic ovary	
Cancer	

Supplemental Table 6- 2. Tripod checklist

Section/Topic	n	Checklist Item	Page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	146
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	147-148
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	149-150
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	150
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	151
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	151
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	151
	5b	Describe eligibility criteria for participants.	Sup figure 6.1 151-152
	5c	Give details of treatments received, if relevant.	N/A
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	152-153
	6b	Report any actions to blind assessment of the outcome to be predicted.	N/A
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	151, 153
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	N/A
Sample size	8	Explain how the study size was arrived at.	153
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	153
Statistical analysis methods	10c	For validation, describe how the predictions were calculated.	153 Sup text 6.3
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	154 Sup text 6.4
	10e	Describe any model updating (e.g., recalibration) arising from the validation, if done.	N/A
Risk groups	11	Provide details on how risk groups were created, if done.	154
Development vs. validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	Table 6.1
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the	Table 6.2 Sup

		outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	figure 6.1
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 6.1
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 6.1
Model performance	16	Report performance measures (with CIs) for the prediction model.	160-163
Model-updating	17	If done, report the results from any model updating (i.e., model specification, model performance).	160-163
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	169-170
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	167-169
	19b	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	167-170
Implications	20	Discuss the potential clinical use of the model and implications for future research.	167-170
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	172
Funding	22	Give the source of funding and the role of the funders for the present study.	171

Supplemental Table 6- 3. Baseline characteristics by individual frailty measures and frailty status

**	Phenotype: No frailty n = 9,459	Phenotype: Frailty n = 2,828	Phenotype: Pre-frailty n = 11,455	Missing frailty phenotype n = 747	FI: No frailty n = 21,565	FI: Frailty n = 2,924	FI-lab: No frailty n = 19,019	FI-lab: Frailty n = 5,349	Missing FI-lab n = 121
Age, mean±SD	62.9 ± 5.7	62.5 ± 5.5	62.9 ± 5.6	62.4 ± 5.7	62.9 ± 5.6	62.4 ± 5.7	63.1 ± 5.5	62.0 ± 5.8	62.5 ± 6.0
Creatinine (μmol/L), mean±SD	1.1 ± 0.3	1.1 ± 0.6	1.1 ± 0.5	1.1 ± 0.5	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.4	1.1 ± 0.6	1.1 ± 0.5
Cystatin C (mg/L), mean±SD	1.2 ± 0.3	1.4 ± 0.4	1.3 ± 0.3	1.4 ± 0.5	1.3 ± 0.3	1.4 ± 0.4	1.3 ± 0.3	1.4 ± 0.4	1.3 ± 0.3
eGFRcr (ml/min/1.73m ²), mean±SD	64.0 ± 14.2	68.2 ± 18.6	66.2 ± 16.3	68.1 ± 18.9	65.5 ± 15.8	66.8 ± 17.1	65.0 ± 15.2	68.0 ± 18.1	65.6 ± 19.7
eGFRcys (ml/min/1.73m ²), mean±SD	59.1 ± 13.7	50.0 ± 11.4	54.6 ± 12.2	50.1 ± 12.0	56.23± 13.2	51.2 ± 11.1	56.7 ± 13.2	52.1 ± 12.1	54.0 ± 13.5
eGFRcrcys (ml/min/1.73m ²), mean±SD	63.9 ± 9.8	59.8 ± 13.2	62.0 ± 11.1	60.0 ± 13.3	62.8 ± 10.9	60.1 ± 12.0	62.8 ± 10.6	61.1 ± 12.5	61.3 ± 13.4
eGFR creatinine cystatin discrepancy (eGFRcys-eGFRcr) (ml/min/1.73m ²), mean±SD	-4.8 ± 20.3	-18.3 ± 16.1	-11.7 ± 18.6	-18.0 ± 17.4	-9.2 ± 19.8	-15.7 ± 16.1	-8.3 ± 19.6	-15.9 ± 18.0	-11.5 ± 20.4
uACR (mg/mmol)									
Median (IQR)	0.0 (0.0, 1.2)	0.7 (0.0, 2.4)	0.4 (0.0, 1.6)	0.5 (0.0, 2.2)	0.0 (0.0, 1.5)	0.6 (0.0, 2.0)	0.0 (0.0, 1.3)	0.8 (0.0, 2.7)	0.6 (0.0, 2.3)
Mean±SD	4.0 ± 25.7	9.1 ± 45.1	5.4 ± 32.9	9.0 ± 41.1	5.1 ± 30.8	7.7 ± 42.3	4.0 ± 26.0	10.3 ± 48.3	10.3 ± 46.5
Sex, n(%)									
Male	4,695 (49.6)	1,138 (40.2)	5,066 (44.2)	333 (44.6)	9,993 (46.3)	1,239 (42.4)	8,886 (46.7)	2,302 (43.0)	44 (36.4)
Female	4,764 (50.4)	1,690 (59.8)	6,389 (55.8)	414 (55.4)	11,572 (53.7)	1,685 (57.6)	10,133 (53.3)	3,047 (57.0)	77 (63.6)
LTC count									
Median (IQR)	1 (1, 2)	3 (2, 4)	2 (1, 3)	3 (1, 4)	2 (1, 3)	4 (3, 5)	2 (1, 3)	2 (1, 3)	2 (1, 3)
Frailty									
Median FI score (IQR)	0.11 (0.06, 0.15)	0.23 (0.17, 0.29)	0.15 (0.10, 0.21)	0.19 (0.13, 0.27)	0.13 (0.08, 0.18)	0.29 (0.27, 0.32)	0.13 (0.09, 0.20)	0.16 (0.10, 0.22)	0.13 (0.07, 0.21)

Median lab-FI score (IQR)	0.17 (0.12, 0.25)	0.21 (0.17, 0.29)	0.21 (0.12, 0.25)	0.22 (0.17, 0.29)	0.17 (0.12, 0.25)	0.21 (0.17, 0.29)	0.17 (0.12, 0.21)	0.30 (0.29, 0.35)	N/A
Missing frailty phenotype	N/A	N/A	N/A	747 (100)	530 (2.46)	217 (7.42)	484 (2.54)	259 (4.84)	4 (3.31))
Missing lab-FI	49 (0.5)	16 (0.6)	52 (0.5)	4 (0.5)	100 (0.5)	21 (0.7)	N/A	N/A	121 (100)
eGFRcr, estimated glomerular filtration rate creatinine; eGFRcys, estimated glomerular filtration rate cystatin C; eGFRcrcys, estimated glomerular filtration rate creatinine-cystatin C; FI, frailty index; FI-lab, laboratory frailty index; LTC, long-term condition; uACR, urine albumin creatinine ratio. ** Mean±SD unless otherwise specified.									

Supplemental Table 6- 4. Kidney failure and death events over 2- and 5-years by frailty measures and frailty status

	Phenotype: No frailty n = 9,459	Phenotype: Frailty n = 2,828	Phenotype: Pre-frailty n = 11,455	Missing frailty phenotype n = 747	FI: No frailty n = 21,565	FI: Frailty n = 2,924	FI-lab: No frailty n = 19,091	FI-lab: Frailty n = 5,349	Missing FI- lab n = 121
Follow-up (months), mean±SD									
2-year cohort	23.86 ± 1.43	23.35 ± 3.18	23.75 ± 1.88	23.19 ± 3.48	23.75 ± 1.91	23.53 ± 2.62	23.79 ± 1.71	23.48 ± 2.79	23.55 ± 2.42
5-year cohort	58.92 ± 6.25	56.01 ± 12.07	58.03 ± 8.34	55.43 ± 13.02	58.24 ± 8.00	56.72 ± 10.78	58.45 ± 7.43	56.69 ± 11.05	57.51 ± 9.84
Death n(%)									
Within 2-year follow-up	105 (1.11)	119 (4.21)	227 (1.98)	48 (6.43)	389 (1.80)	110 (3.76)	291 (1.52)	205 (3.83)	3 (2.48)
Per 1000 person-years	2.26	21.63	4.10	13.91	3.72	19.19	3.14	19.59	5.17
Within 5-year follow-up	344 (3.64)	308 (10.89)	719 (6.28)	100 (13.39)	1171 (5.43)	300 (10.26)	965 (5.05)	497 (9.29)	9 (7.44)
Per 1000 person years	7.41	23.33	12.98	28.98	11.19	21.71	10.42	19.67	15.52
Kidney failure, n(%)									
Within 2-year follow-up	24 (0.25)	38 (1.34)	78 (0.68)	9 (1.20)	119 (0.55)	30 (1.03)	93 (0.49)	54 (1.01)	2 (1.65)
Per 1000 person-years	1.28	6.91	3.44	6.23	2.79	5.23	2.47	5.16	8.42
Within 5-year follow-up	68 (0.72)	78 (2.76)	152 (1.33)	14 (1.87)	263 (1.22)	49 (1.68)	206 (1.08)	104 (1.94)	2 (1.65)
Per 1000 person-years	1.46	5.91	2.74	4.06	2.51	3.55	2.22	4.12	3.45

Supplemental Table 6- 5. DeLong's test for comparison of AUC by differing eGFR equations used in KFRE and cohort subgroups – frailty classified using all frailty measures

eGFR equation used in KFRE	p-value					
	2-years			5-years		
	Whole cohort	No frailty*	Frailty	Whole cohort	No frailty*	Frailty
eGFRcr vs eGFRcys	0.002	0.07	0.02	<0.001	0.07	0.06
eGFRcr vs eGFRcrcys	<0.001	0.02	<0.001	<0.001	0.02	<0.001
eGFRcys vs eGFRcrcys	0.75	0.68	0.94	0.55	0.68	0.24

*based on being classed as non-frail by any of frailty phenotype, frailty index or laboratory frailty index

Supplemental Table 6- 6. DeLong's test for comparison of AUC by differing eGFR equations used in KFRE and cohort subgroups – frailty classified using a modified frailty phenotype

eGFR equation used in KFRE	p-value							
	2-years				5-years			
	Whole cohort	No frailty*	Pre-frailty	Frailty	Whole cohort	No frailty*	Pre-frailty	Frailty
eGFRcr vs eGFRcys	0.002	0.34	0.005	0.79	<0.001	0.02	0.004	0.42
eGFRcr vs eGFRcrcys	<0.001	0.17	<0.001	0.14	<0.001	0.007	<0.001	0.35
eGFRcys vs eGFRcrcys	0.75	0.68	0.22	0.26	0.55	0.43	0.58	0.02

*based on being classed as non-frail by frailty phenotype

Supplemental Table 6- 7. DeLong's test for comparison of AUC by differing eGFR equations used in KFRE and cohort subgroups – frailty classified using frailty index (FI)

eGFR equation used in KFRE	p-value					
	2-years			5-years		
	Whole cohort	No frailty*	Frailty	Whole cohort	No frailty*	Frailty
eGFRcr vs eGFRcys	0.002	0.03	0.02	<0.001	0.004	0.16
eGFRcr vs eGFRcrcys	<0.001	0.001	0.003	<0.001	<0.001	0.01
eGFRcys vs eGFRcrcys	0.75	0.73	0.30	0.55	0.50	0.82

*based on being classed as non-frail by frailty index

Supplemental Table 6- 8. DeLong's test for comparison of AUC by differing eGFR equations used in KFRE and cohort subgroups – frailty classified using laboratory frailty index (FI-lab)

eGFR equation used in KFRE	p-value					
	2-years			5-years		
	Whole cohort	No frailty*	Frailty	Whole cohort	No frailty*	Frailty
eGFRcr vs eGFRcys	0.002	0.02	0.03	<0.001	0.005	0.04
eGFRcr vs eGFRcrcys	<0.001	0.001	0.004	<0.001	<0.001	0.001
eGFRcys vs eGFRcrcys	0.75	0.97	0.47	0.55	0.77	0.91

*based on being classed as non-frail by laboratory frailty index

Supplemental Table 6- 9. Cumulative incidence of kidney failure by frailty status

Time frame	Cumulative incidence of kidney failure - Estimate % (95% CI)	
	No frailty	Frailty
1-year	0.18 (0.11-0.24)	0.43 (0.29-0.57)
2-year	0.37 (0.27-0.46)	0.97 (0.76-1.18)
3-year	0.54 (0.43-0.66)	1.38 (1.13-1.63)
4-year	0.67 (0.54-0.79)	1.70 (1.42-1.97)
5-year	0.92 (0.77-1.07)	1.93 (1.64-2.23)

Supplemental Table 6- 10. Cumulative incidence of mortality by frailty status

Time frame	Cumulative incidence of mortality - Estimate % (95% CI)	
	No frailty	Frailty
1-year	0.47 (0.36-0.57)	1.46 (1.21-1.72)
2-year	1.17 (1.00-1.34)	3.20 (2.83-3.57)
3-year	2.05 (1.83-2.28)	5.16 (4.69-5.62)
4-year	2.94 (2.68-3.21)	6.68 (6.15-7.21)
5-year	4.22 (3.90-4.53)	8.41 (7.82-9.00)

Supplemental Table 6- 11. Cumulative incidence of kidney failure by age groups

Time frame	Cumulative incidence of kidney failure - Estimate % (95% CI)	
	<60 years old	≥60 years old
1-year	0.76 (0.52-0.99)	0.13 (0.08-0.18)
2-year	1.42 (1.10-1.74)	0.35 (0.27-0.43)
3-year	1.86 (1.50-2.23)	0.56 (0.45-0.66)
4-year	2.22 (1.82-2.62)	0.70 (0.58-0.82)
5-year	2.62 (2.19-3.05)	0.91 (0.77-1.04)

Supplemental Table 6- 12. Cumulative incidence of mortality by age group

Time frame	Cumulative incidence of mortality - Estimate % (95% CI)	
	<60 years old	≥60 years old
1-year	0.72 (0.49-0.95)	0.84 (0.71-0.97)
2-year	1.58 (1.24-1.91)	1.96 (1.76-2.16)
3-year	2.47 (2.05-2.89)	3.31 (3.06-3.57)
4-year	3.29 (2.80-3.77)	4.50 (4.21-4.79)
5-year	4.33 (3.78-4.88)	6.04 (5.70-6.38)

Supplemental Table 6- 13. Cumulative incidence of kidney failure by age and frailty status

Time frame	Cumulative incidence of kidney failure - Estimate % (95% CI)			
	No frailty		Frailty	
	<60 years old	≥60 years old	<60 years old	≥60 years old
1-year	0.58 (0.31-0.84)	0.08 (0.03-0.13)	1.03 (0.60-1.46)	0.23 (0.12-0.35)
2-year	1.06 (0.70-1.42)	0.20 (0.12-0.27)	1.92 (1.34-2.50)	0.66 (0.46-0.85)
3-year	1.41 (1.00-1.83)	0.33 (0.23-0.43)	2.48 (1.82-3.14)	1.02 (0.77-1.26)
4-year	1.67 (1.22 -2.12)	0.42 (0.31-0.54)	3.00 (2.27-3.72)	1.27 (0.99-1.54)
5-year	2.09 (1.58-2.59)	0.64 (0.50-0.77)	3.37 (2.60-4.13)	1.45 (1.16-1.75)

Supplemental Table 6- 14. Cumulative incidence of mortality by age and frailty status

Time frame	Cumulative incidence of mortality - Estimate % (95% CI)			
	Non-frail		Frail	
	<60 years old	≥60 years old	<60 years old	≥60 years old
1-year	0.35 (0.14-0.56)	0.49 (0.37-0.62)	1.26 (0.79-1.74)	1.53 (1.23-1.83)
2-year	0.74 (0.44-1.04)	1.28 (1.08-1.47)	2.81 (2.11-3.51)	3.33 (2.89-3.77)
3-year	1.16 (0.78-1.53)	2.27 (2.01-2.53)	4.40 (3.53-5.27)	5.41 (4.85-5.96)
4-year	1.74 (1.28-2.19)	3.24 (2.93-3.55)	5.57 (4.59-6.54)	7.05 (6.42-7.68)
5-year	2.57 (2.01-3.13)	4.62 (4.25-4.98)	6.93 (5.85-8.00)	8.91 (8.21-9.61)

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Supplemental Table 6- 15. Cumulative incidence of kidney failure by sex

Time frame	Cumulative incidence of kidney failure - Estimate % (95% CI)	
	Female	Male
1-year	0.17 (0.10-0.24)	0.37 (0.26-0.49)
2-year	0.30 (0.21-0.40)	0.91 (0.73-1.08)
3-year	0.48 (0.36-0.60)	1.26 (1.05-1.46)
4-year	0.65 (0.51-0.79)	1.48 (1.25-1.70)
5-year	0.75 (0.61-0.90)	1.89 (1.64-2.14)

Supplemental Table 6- 16. Cumulative incidence of mortality by sex

Time frame	Cumulative incidence of mortality - Estimate % (95% CI)	
	Female	Male
1-year	0.45 (0.33-0.56)	1.26 (1.05-1.46)
2-year	1.06 (0.89-1.24)	2.84 (2.53-3.15)
3-year	1.83 (1.60-2.06)	4.67 (4.27-5.05)
4-year	2.64 (2.37-2.91)	6.13 (5.68-6.57)
5-year	3.58 (3.26-3.89)	8.15 (7.64-8.65)

Supplemental Table 6- 17. Cumulative incidence of kidney failure by sex and frailty status

Time frame	Cumulative incidence of kidney failure - Estimate % (95% CI)			
	No frailty		Frailty	
	Female	Male	Female	Male
1-year	0.07 (0.01-0.13)	0.29 (0.17-0.41)	0.35 (0.18-0.51)	0.55 (0.31-0.78)
2-year	0.12 (0.05-0.19)	0.64 (0.46-0.82)	0.62 (0.40-0.84)	1.45 (1.06-1.83)
3-year	0.25 (0.14-0.36)	0.86 (0.65-1.07)	0.88 (0.62-1.15)	2.05 (1.59-2.50)
4-year	0.36 (0.23-0.49)	1.01 (0.78-1.23)	1.15 (0.85-1.45)	2.43 (1.93-2.93)
5-year	0.49 (0.34-0.64)	1.39 (1.13-1.66)	1.21 (0.90-1.52)	2.89 (2.35-3.43)

Supplemental Table 6- 18. Cumulative incidence of mortality by sex and frailty status

Time frame	Cumulative incidence of mortality - Estimate % (95% CI)			
	Non-frail		Frail	
	Female	Male	Female	Male
1-year	0.26 (0.15-0.37)	0.69 (0.50-0.88)	0.74 (0.50-0.98)	2.43 (1.93-2.93)
2-year	0.62 (0.46-0.79)	1.78 (1.48-2.08)	1.81 (1.43-2.18)	5.05 (4.34-5.76)
3-year	1.12 (0.89-1.34)	3.09 (2.70-3.48)	3.06 (2.58-3.54)	7.94 (7.06-8.81)
4-year	1.74 (1.46-2.02)	4.27 (3.87-4.73)	4.19 (3.63-4.75)	9.99 (9.01-10.95)
5-year	2.57 (2.23-2.91)	6.04 (5.50-6.57)	5.30 (4.67-5.93)	12.55 (11.48-13.62)

Supplemental Table 6- 19. Performance measures for KFRE by eGFR equation and frailty status assessed by individual frailty measures at 2 years

eGFR equation used in KFRE	Performance measure for 2-year KFRE	Whole cohort	No frailty Frailty phenotype	Pre-frailty Frailty phenotype	Frailty Frailty phenotype	No frailty FI	Frailty FI	No frailty FI-lab	Frailty FI-lab
eGFRcr	AUC	0.88 (0.847-0.92)	0.88 (0.78-0.98)	0.86 (0.81-0.92)	0.92 (0.86-0.97)	0.87 (0.83-0.92)	0.90 (0.84-0.96)	0.87 (0.82-0.92)	0.89 (0.83-0.95)
	C-index	0.89 (0.86-0.92)	0.90 (0.82-0.98)	0.88 (0.84-0.92)	0.89 (0.83-0.95)	0.90 (0.86-0.93)	0.87 (0.80-0.94)	0.88 (0.84-0.93)	0.90 (0.86-0.94)
	O/E ratio	2.12 (1.96-2.28)	1.53 (1.13-1.93)	2.30 (2.08-2.52)	2.22 (1.90-2.53)	1.95 (1.77-2.13)	3.20 (2.84-3.56)	2.37 (2.17-2.57)	1.79 (1.53-2.06)
	Calibration intercept	0.16 (-0.13-0.44)	-0.41 (-1.33-0.50)	0.06 (-0.37-0.49)	0.48 (0.00-0.96)	0.04 (-0.27-0.36)	0.80 (0.20-1.39)	0.23 (-0.14-0.61)	0.04 (-0.40-0.48)
	Calibration slope	0.68 (0.57-0.79)	0.65 (0.36-0.93)	0.62 (0.49-0.75)	0.74 (0.48-1.01)	0.78 (0.55-0.80)	0.81 (0.48-1.13)	0.70 (0.56-0.84)	0.63 (0.45-0.80)
	Brier score	0.005 (0.004-0.006)	0.002 (0.0001-0.003)	0.006 (0.005-0.007)	0.011 (0.007-0.014)	0.005 (0.004-0.006)	0.009 (0.006-0.012)	0.004 (0.003-0.005)	0.008 (0.006-0.011)
	Scaled brier score (%)	14.42 (8.98-19.82)	9.36 (-5.31-24.15)	11.19 (4.11-17.85)	20.90 (10.48-30.77)	14.51 (8.11-20.28)	13.89 (5.83-23.32)	11.85 (6.10-17.86)	17.59 (7.01-26.89)
eGFRcys	AUC	0.89 (0.86-0.93)	0.89 (0.79-0.99)	0.88 (0.83-0.94)	0.92 (0.86-0.98)	0.88 (0.84-0.93)	0.93 (0.88-0.98)	0.88 (0.84-0.93)	0.91 (0.85-0.96)
	C-index	0.93 (0.92-0.95)	0.96 (0.94-0.98)	0.92 (0.90-0.95)	0.91 (0.86-0.96)	0.93 (0.91-0.95)	0.93 (0.90-0.95)	0.93 (0.91-0.95)	0.93 (0.91-0.95)
	O/E ratio	1.73 (1.57-1.89)	1.33 (0.94-1.74)	1.98 (1.76-2.20)	1.67 (1.36-2.00)	1.68 (1.50-1.86)	1.96 (1.61-2.32)	1.98 (1.78-2.19)	1.42 (1.15-1.68)
	Calibration intercept	0.20 (-0.06-0.45)	-0.00 (-0.67-0.67)	0.24 (-0.14-0.62)	0.26 (-0.19-0.71)	0.17 (-0.11-0.45)	0.33 (-0.27-0.93)	0.37 (0.03-0.70)	-0.01 (-0.38-0.37)
	Calibration slope	0.77 (0.65-0.89)	0.73 (0.35-1.10)	0.73 (0.58-0.88)	0.75 (0.52-0.98)	0.78 (-0.11-0.45)	0.72 (0.48-0.96)	0.80 (0.64-0.97)	0.74 (0.53-0.95)
	Brier score	0.005 (0.004-0.006)	0.002 (0.001-0.003)	0.006 (0.005-0.007)	0.011 (0.008-0.015)	0.005 (0.004-0.006)	0.009 (0.006-0.012)	0.004 (0.003-0.005)	0.008 (0.006-0.011)
	Scaled brier score (%)	14.38 (9.70-18.58)	11.95 (0.39-23.29)	11.60 (5.56-17.86)	18.03 (8.29-26.45)	14.49 (6.69-16.56)	13.75 (5.31-22.55)	11.82 (6.99-16.56)	17.98 (8.79-26.77)

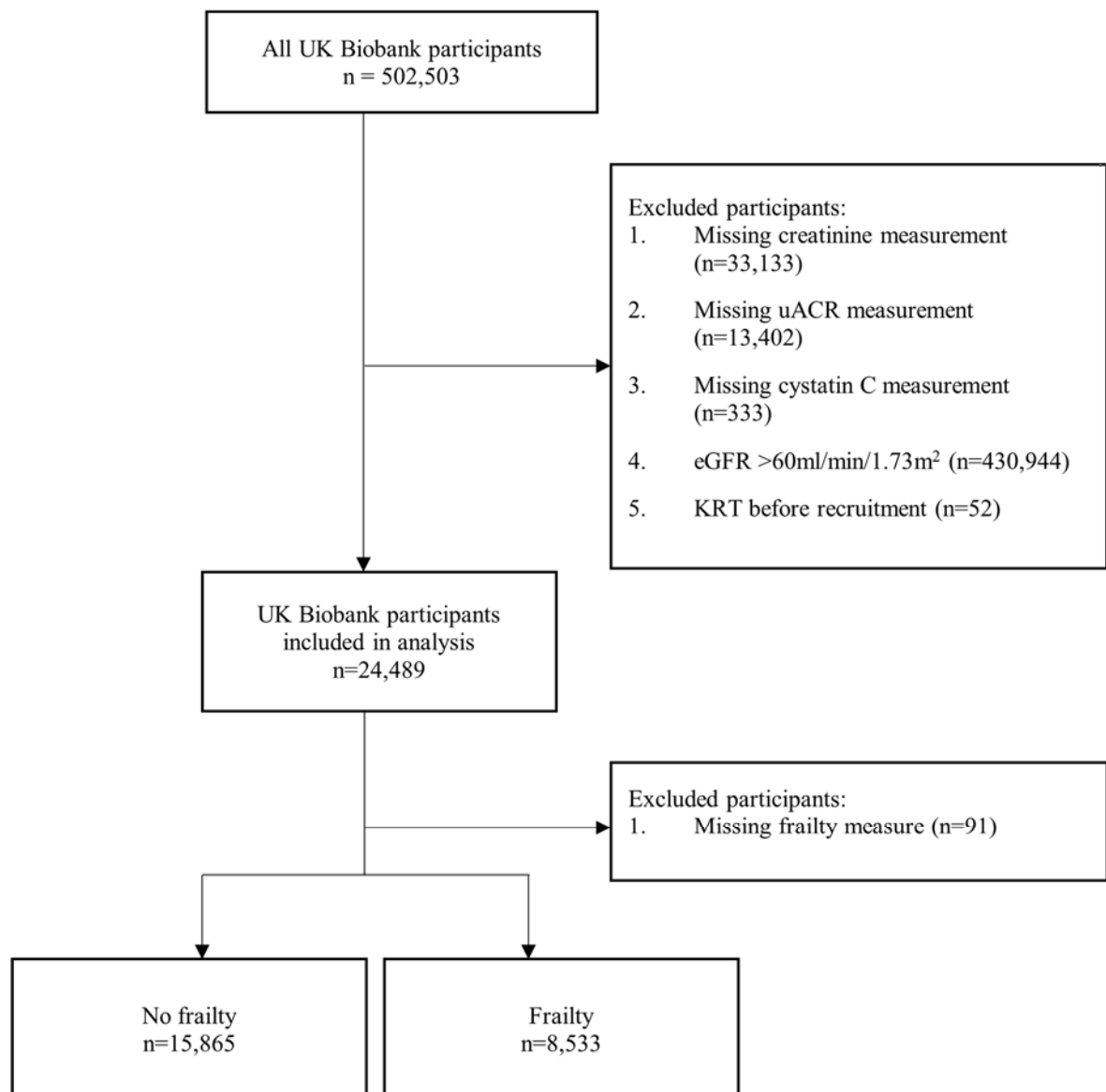
eGFR _{cr} cys	AUC	0.89 (0.86-0.93)	0.89 (0.80-0.99)	0.88 (0.83-0.93)	0.92 (0.87-0.98)	0.88 (0.84-0.93)	0.92 (0.87-0.98)	0.88 (0.84-0.93)	0.90 (0.85-0.96)
	C-index	0.93 (0.91-0.95)	0.95 (0.92-0.98)	0.92 (0.89-0.95)	0.91 (0.85-0.97)	0.93 (0.91-0.96)	0.92 (0.88-0.96)	0.93 (0.90-0.96)	0.93 (0.90-0.95)
	O/E ratio	2.11 (1.95-2.27)	1.63 (1.23-2.03)	2.36 (2.13-2.58)	2.06 (1.74-2.38)	2.00 (1.82-2.18)	2.71 (2.35-3.06)	2.43 (2.23-2.64)	1.72 (1.45-1.98)
	Calibration intercept	0.25 (-0.02-0.52)	-0.07 (-0.82-0.70)	0.22 (-0.19-0.62)	0.42 (-0.05-0.89)	0.18 (-0.12-0.48)	0.64 (0.03-1.25)	0.41 (0.05-0.76)	0.06 (-0.34-0.46)
	Calibration slope	0.70 (0.58-0.81)	0.65 (0.34-0.96)	0.64 (0.51-0.78)	0.72 (0.49-0.95)	0.70 (0.57-0.83)	0.72 (0.47-0.98)	0.73 (0.57-0.88)	0.65 (0.47-0.83)
	Brier score	0.005 (0.004-0.006)	0.002 (0.001-0.003)	0.006 (0.005-0.007)	0.011 (0.007-0.014)	0.005 (0.004-0.006)	0.009 (0.006-0.012)	0.004 (0.003-0.005)	0.008 (0.006-0.010)
	Scaled brier score (%)	14.38 (10.21-19.25)	11.31 (-0.09-23.50)	11.75 (5.42-18.37)	19.83 (10.61-29.20)	14.94 (9.19-20.33)	14.05 (5.28-22.70)	12.15 (7.21-16.79)	18.35 (8.82-27.63)
AUC, Area under the receiver operator characteristic curves; FI, self-reported measures frailty index; FI-lab, laboratory measures frailty index									

Supplemental Table 6- 20. Performance measures for KFRE by eGFR equation and frailty status assessed by individual frailty measures at 5 years

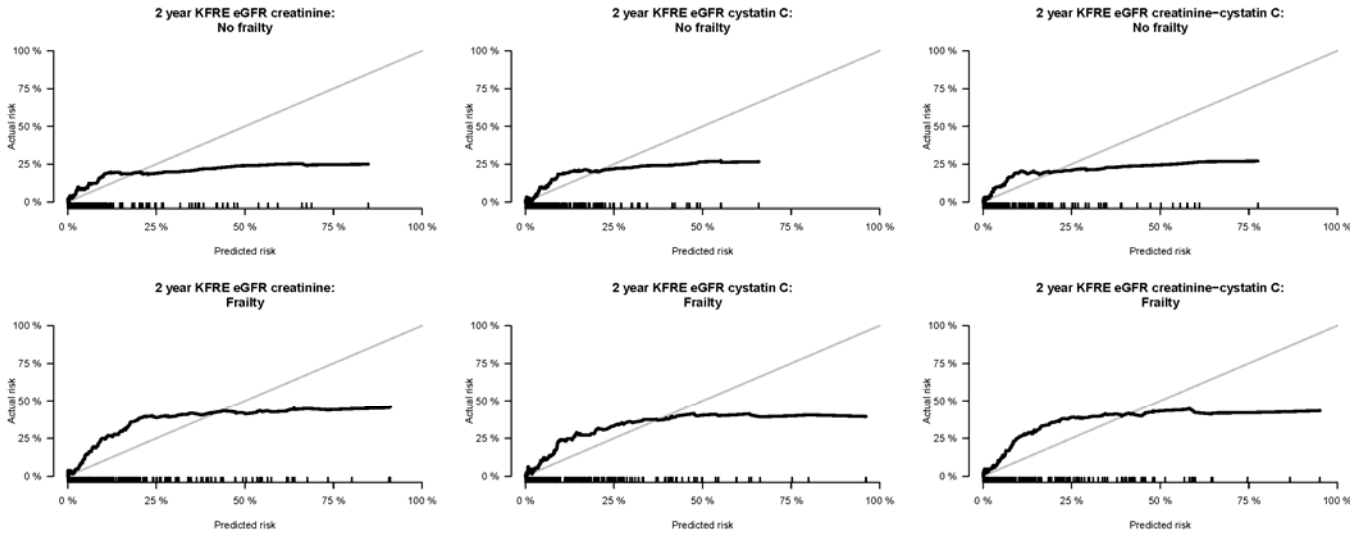
eGFR equation used in KFRE	Performance measure for 5-year KFRE	Whole cohort	No frailty Frailty phenotype	Pre-frailty Frailty phenotype	Frailty Frailty phenotype	No frailty FI	Frailty FI	No frailty FI-lab	Frailty FI-lab
eGFRcr	AUC	0.90 (0.88-0.92)	0.89 (0.84-0.95)	0.88 (0.85-0.92)	0.93 (0.90-0.97)	0.90 (0.87-0.92)	0.92 (0.87-0.96)	0.90 (0.87-0.93)	0.90 (0.86-0.95)
	C-index	0.91 (0.89-0.93)	0.89 (0.84-0.95)	0.90 (0.88-0.93)	0.93 (0.90-0.96)	0.91 (0.89-0.93)	0.89 (0.84-0.95)	0.90 (0.88-0.93)	0.92 (0.90-0.95)
	O/E ratio	1.76 (1.65-1.87)	1.63 (1.39-1.86)	1.78 (1.62-1.94)	1.86 (1.64-2.08)	1.74 (1.62-1.86)	1.88 (1.60-2.16)	1.96 (1.82-2.10)	1.49 (1.30-1.68)
	Calibration intercept	0.46 (0.28-0.64)	0.29 (-0.12-0.71)	0.35 (0.09-0.60)	0.76 (0.43-1.10)	0.45 (0.25-0.64)	0.53 (0.13-0.93)	0.57 (0.36-0.79)	0.33 (0.02-0.63)
	Calibration slope	0.78 (0.71-0.86)	0.74 (0.60-0.88)	0.77 (0.66-0.88)	0.79 (0.61-0.97)	0.78 (0.70-0.86)	0.83 (0.58-1.08)	0.80 (0.70-0.89)	0.79 (0.64-0.94)
	Brier score	0.009 (0.008-0.010)	0.006 (0.004-0.007)	0.009 (0.008-0.011)	0.016 (0.012-0.020)	0.008 (0.007-0.010)	0.012 (0.009-0.016)	0.008 (0.007-0.009)	0.012 (0.010-0.015)
	Scaled brier score (%)	30.86 (25.18-36.38)	21.69 (12.15-30.84)	28.13 (21.01-35.48)	42.19 (33.17-50.94)	31.26 (6.10-17.86)	28.61 (18.50-38.50)	26.46 (21.00-32.17)	39.09 (30.52-47.27)
eGFRcys	AUC	0.91 (0.89-0.93)	0.91 (0.85-0.96)	0.90 (0.86-0.93)	0.93 (0.89-0.97)	0.90 (0.88-0.93)	0.93 (0.88-0.97)	0.90 (0.88-0.93)	0.91 (0.87-0.95)
	C-index	0.94 (0.92-0.95)	0.93 (0.90-0.97)	0.93 (0.91-0.95)	0.93 (0.91-0.96)	0.94 (0.93-0.95)	0.93 (0.90-0.96)	0.93 (0.91-0.95)	0.94 (0.93-0.96)
	O/E ratio	1.30 (1.19-1.41)	1.31 (1.08-1.55)	1.36 (1.20-1.52)	1.29 (1.07-1.51)	1.34 (1.22-1.46)	1.14 (0.86-1.42)	1.50 (1.36-1.63)	1.05 (0.86-1.24)
	Calibration intercept	0.21 (0.06-0.36)	0.23 (-0.12-0.59)	0.22 (0.00-0.45)	0.32 (0.04-0.60)	0.26 (0.10-0.43)	-0.02 (-0.42-0.38)	0.40 (0.21-0.58)	-0.06 (-0.33-0.21)
	Calibration slope	0.87 (0.78-0.96)	0.85 (0.67-1.03)	0.86 (0.74-0.98)	0.99 (0.77-1.22)	0.89 (0.79-0.99)	0.78 (0.56-1.00)	0.94 (0.83-1.06)	0.83 (0.69-0.97)
	Brier score	0.009 (0.008-0.010)	0.006 (0.004-0.007)	0.009 (0.008-0.011)	0.016 (0.012-0.020)	0.008 (0.007-0.010)	0.012 (0.009-0.016)	0.008 (0.007-0.009)	0.012 (0.010-0.015)

	Scaled brier score (%)	30.52 (25.64-35.06)	22.41 (12.61-31.05)	26.98 (20.18-33.33)	42.32 (32.57-50.72)	30.95 (25.70-35.90)	28.05 (14.72-39.40)	27.31 (22.33-32.80)	36.32 (26.93-44.90)
eGFRcrlys	AUC	0.91 (0.89-0.93)	0.90 (0.85-0.96)	0.90 (0.86-0.93)	0.94 (0.90-0.97)	0.90 (0.88-0.93)	0.93 (0.88-0.97)	0.91 (0.88-0.93)	0.91 (0.87-0.95)
	C-index	0.94 (0.92-0.95)	0.93 (0.89-0.97)	0.93 (0.91-0.95)	0.94 (0.91-0.97)	0.94 (0.92-0.95)	0.92 (0.88-0.96)	0.93 (0.91-0.95)	0.94 (0.93-0.96)
	O/E ratio	1.69 (1.58-1.80)	1.69 (1.46-1.93)	1.74 (1.58-1.90)	1.66 (1.44-1.88)	1.71 (1.59-1.83)	1.60 (1.32-1.87)	1.94 (1.80-2.07)	1.37 (1.18-1.56)
	Calibration intercept	0.46 (0.29-0.63)	0.43 (0.04-0.82)	0.41 (0.16-0.65)	0.65 (0.34-0.96)	0.48 (0.30-0.67)	0.37 (-0.02-0.76)	0.61 (0.40-0.81)	0.24 (-0.05-0.54)
	Calibration slope	0.79 (0.71-0.87)	0.76 (0.60-0.92)	0.77 (0.66-0.88)	0.86 (0.67-1.05)	0.79 (0.71-0.88)	0.77 (0.55-0.99)	0.83 (0.73-0.93)	0.77 (0.63-0.90)
	Brier score	0.009 (0.008-0.010)	0.006 (0.004-0.007)	0.009 (0.008-0.011)	0.016 (0.012-0.020)	0.008 (0.007-0.010)	0.012 (0.009-0.016)	0.008 (0.007-0.009)	0.012 (0.010-0.015)
	Scaled brier score (%)	31.10 (26.58-35.75)	22.54 (13.20-32.01)	27.86 (20.61-34.53)	42.75 (34.74-51.77)	31.50 (26.70-36.34)	28.85 (16.97-39.15)	27.20 (21.86-32.51)	38.31 (29.08-47.32)

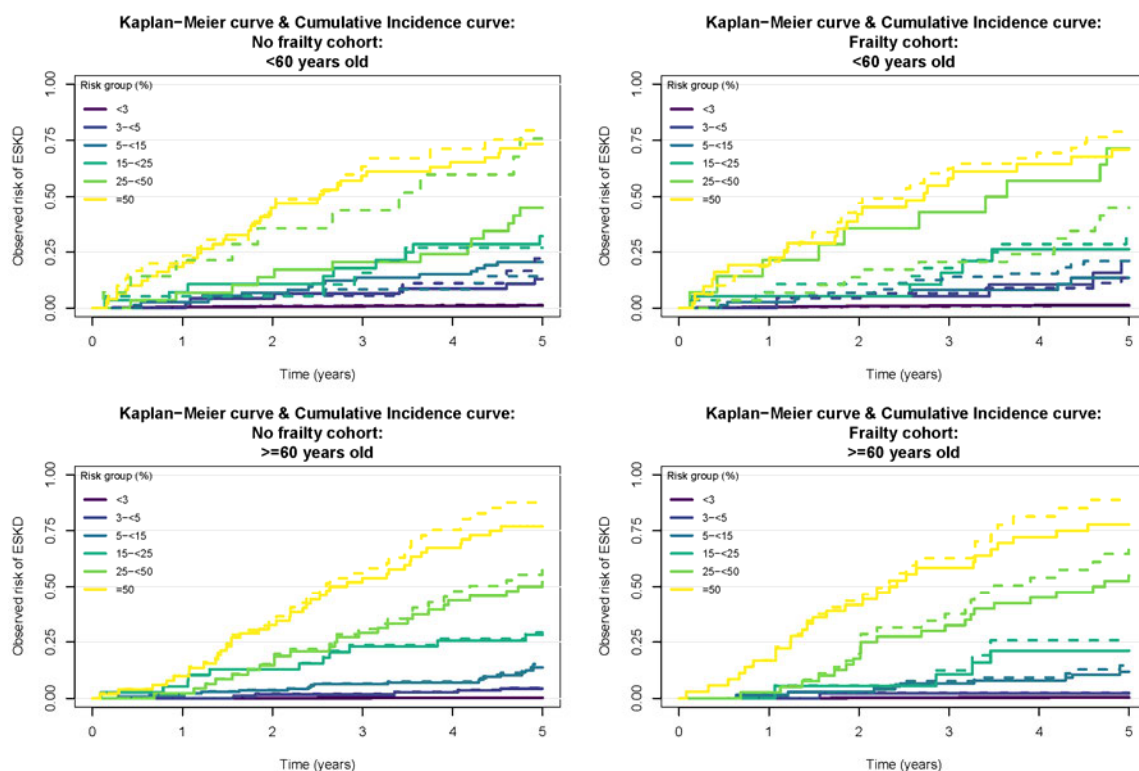
Supplemental Figure 6- 1. Flow diagram of participant selection and exclusions UK Biobank cohort



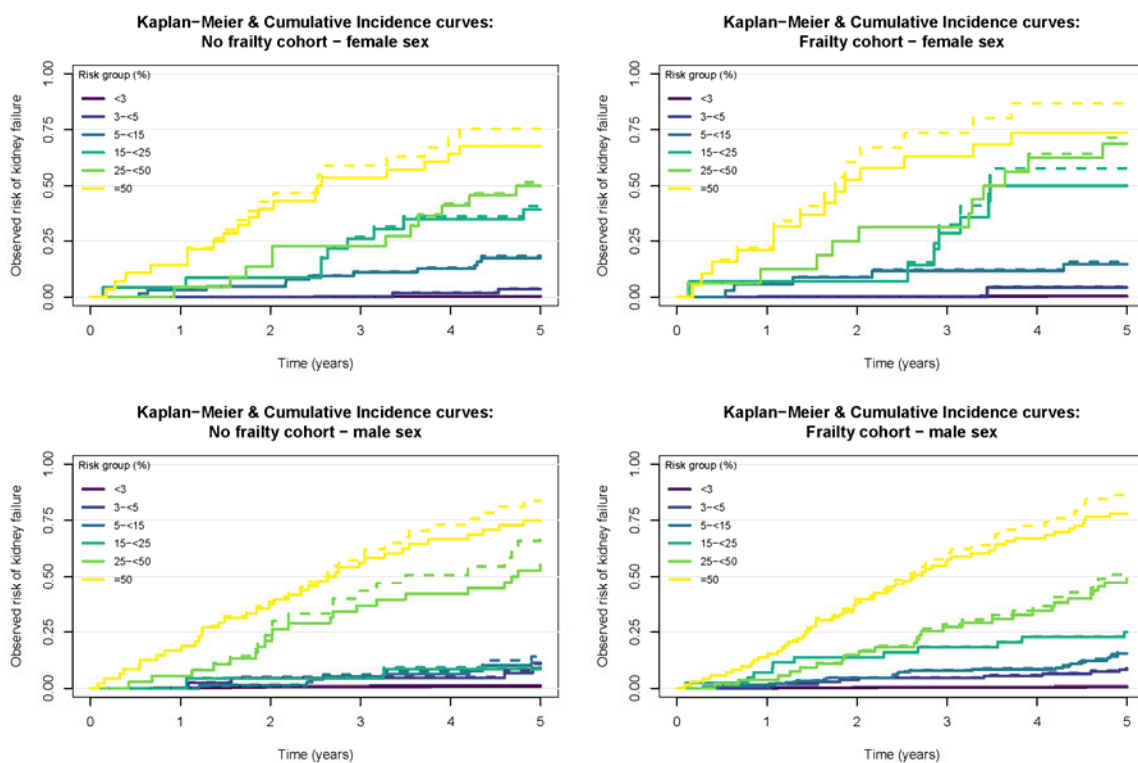
Supplemental Figure 6- 2. Calibration curves for predicted versus observed 2-year risk of kidney failure by frailty status



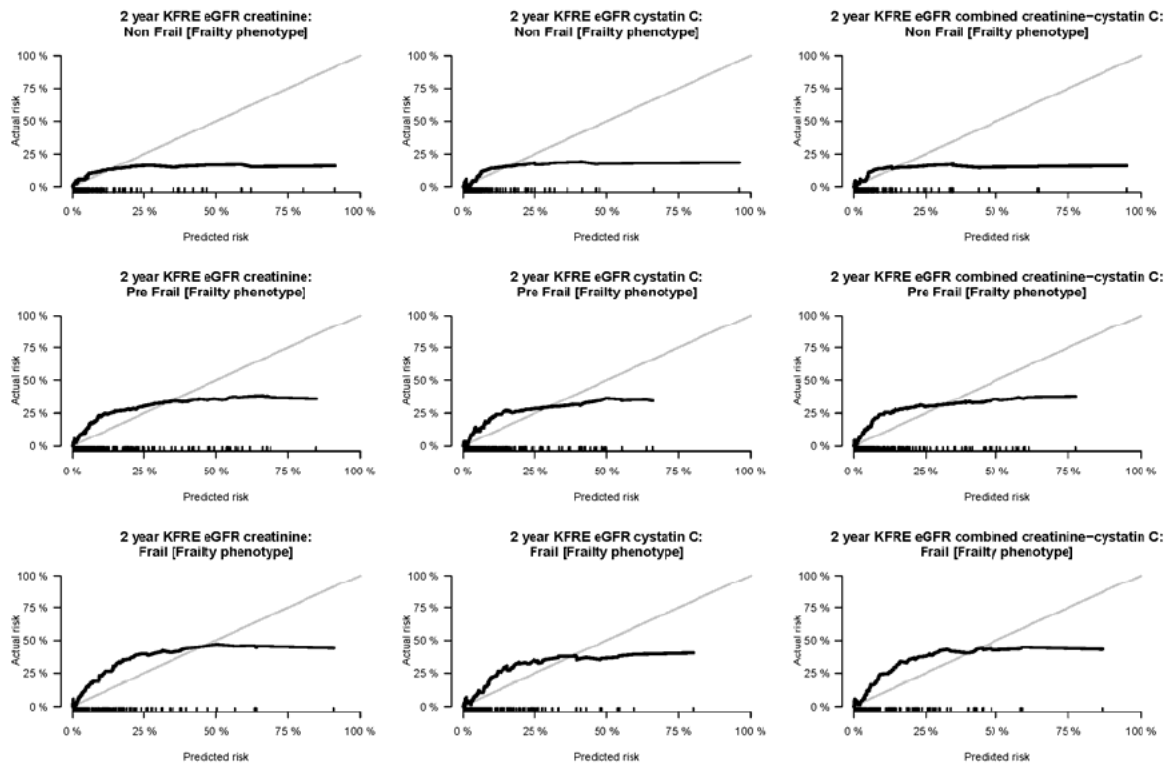
Supplemental Figure 6- 3. Kaplan-Meier estimates (dashed lines) and Aalen-Johansen estimates (solid lines) cumulative incidence curves for kidney failure by frailty status, age groups and KFRE risk groups



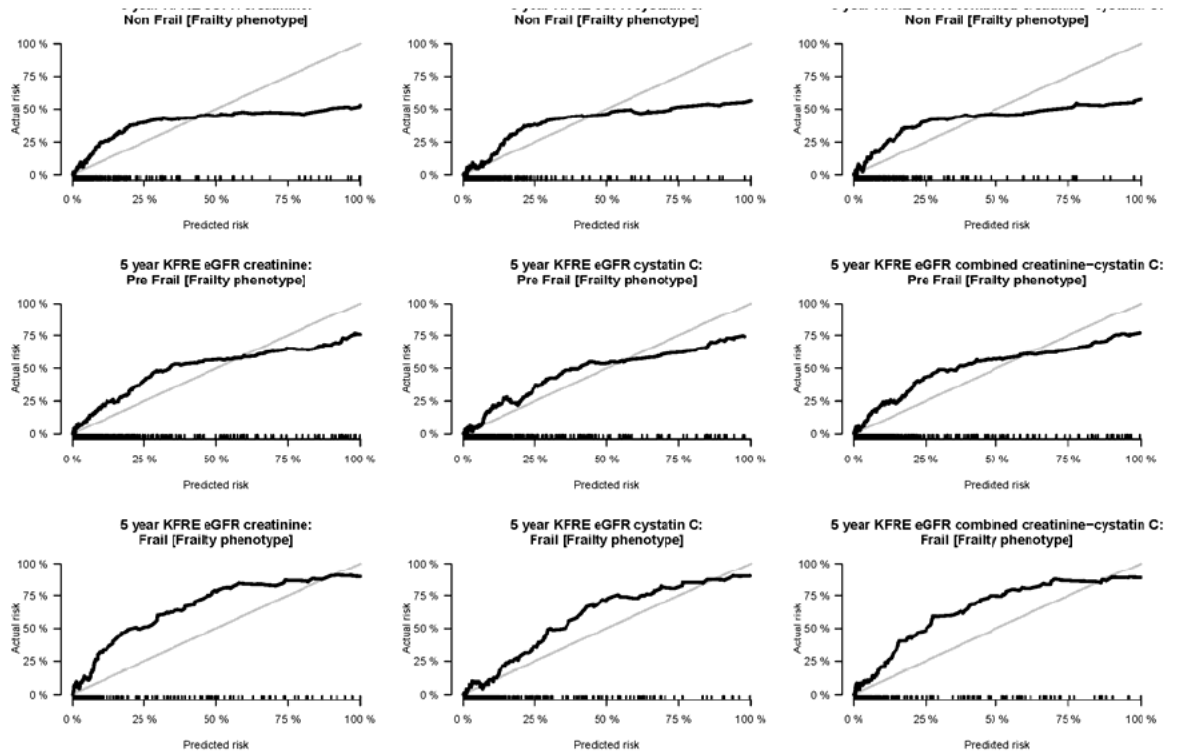
Supplemental Figure 6- 4. Kaplan-Meier estimates (dashed lines) and Aalen-Johansen estimates (solid lines) cumulative incidence curves for kidney failure by frailty status, sex and KFRE risk groups



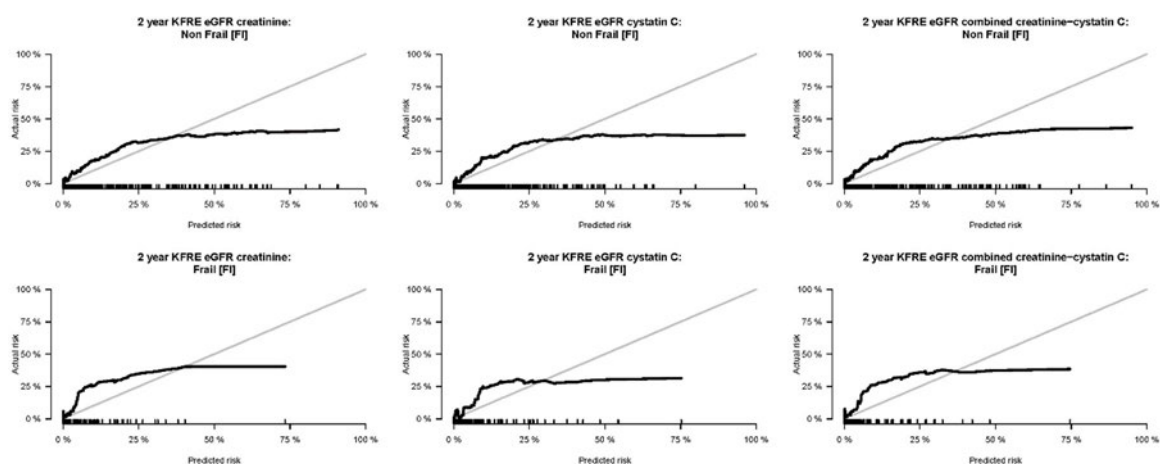
Supplemental Figure 6- 5. Calibration curves for predicted versus observed 2-year risk of kidney failure by frailty status - frailty phenotype



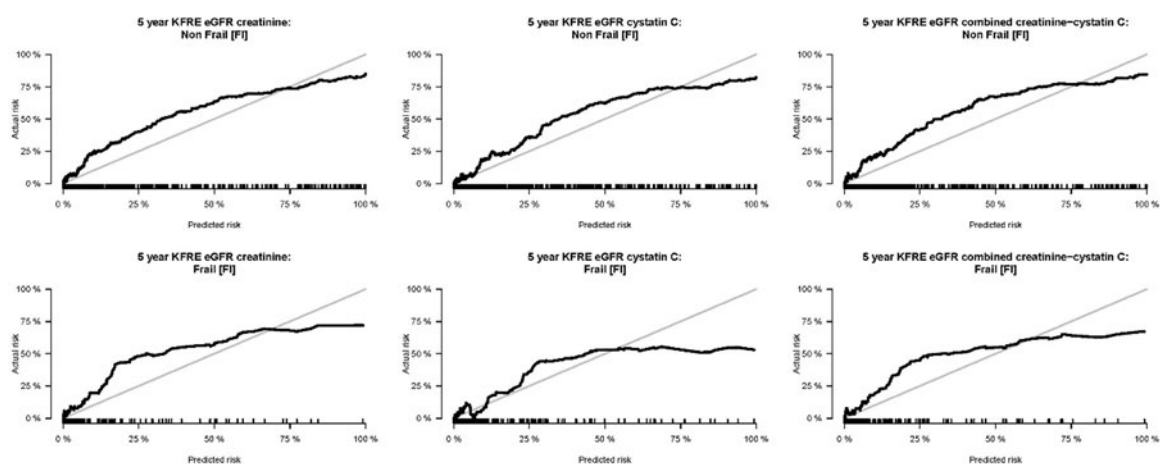
Supplemental Figure 6- 6. Calibration curves for predicted versus observed 5-year risk of kidney failure by frailty status - frailty phenotype



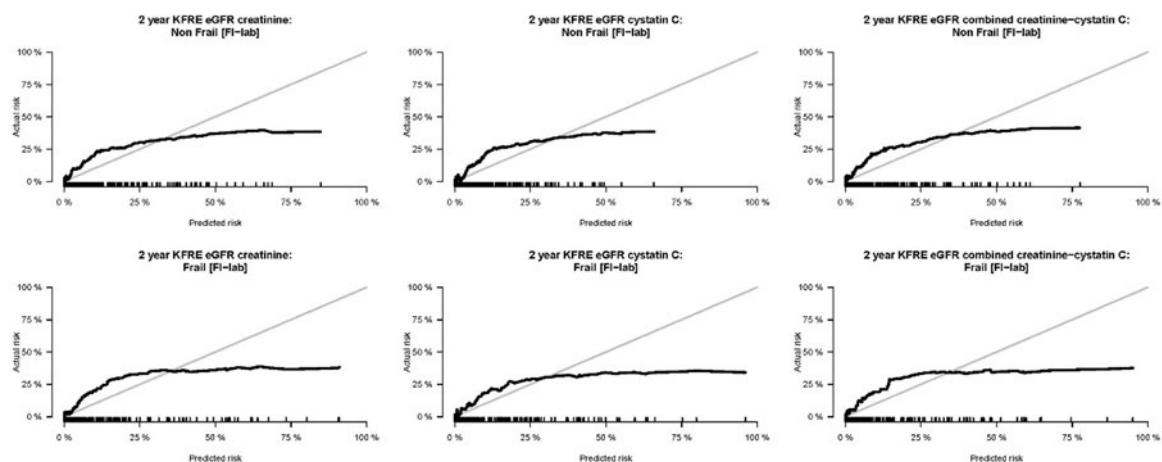
Supplemental Figure 6- 8. Calibration curves for predicted versus observed 2-year risk of kidney failure by frailty status - FI



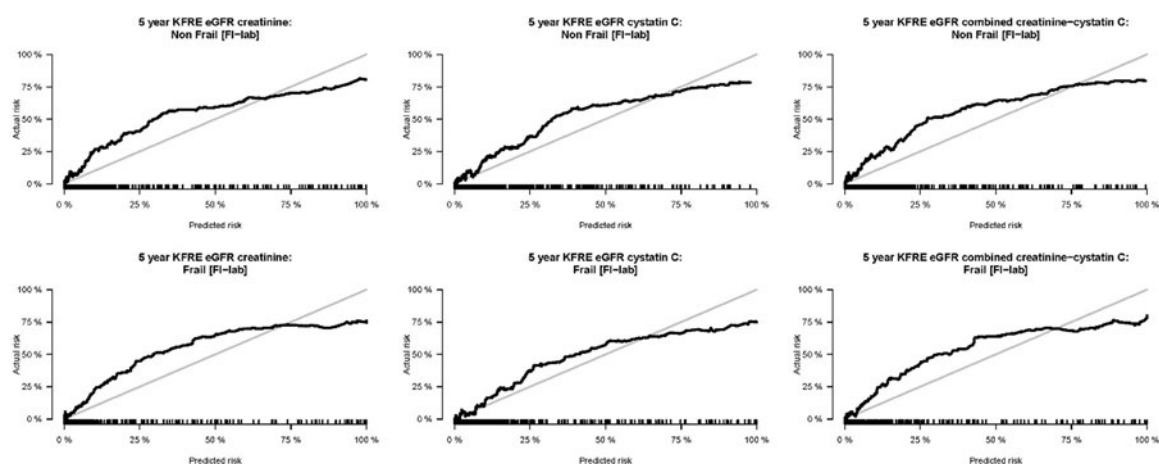
Supplemental Figure 6- 7. Calibration curves for predicted versus observed -year risk of kidney failure by frailty status - FI



Supplemental Figure 6- 10. Calibration curves for predicted versus observed 2-year risk of kidney failure by frailty status - FI-lab



Supplemental Figure 6- 9. Calibration curves for predicted versus observed 5-year risk of kidney failure by frailty status - FI-lab



Appendix 8: Supplementary material for Chapter 7: Exploration of patients' and health care professionals' perspectives of kidney failure risk in MULTIPLE long-term conditions and frailty (MULTIPOINT): a qualitative interview and focus group study

Supplemental Text 7- 1. Patient participant interview schedule

INTERVIEW GUIDE: Kidney failure risk in multiple long-term conditions and frailty – exploration of patients' and healthcare professionals' perspectives of kidney failure risk

Background Information for the Interviewer

In situations where there is a lack of knowledge, questions will be posed in a manner which takes account of such a limitation.

The interview will be semi-structured in format, and thus the exact wording and prompts used may vary between patients to encourage the patient to share their views and allow them an opportunity to talk at length about their thoughts, ideas and feelings about their illnesses and shared decision-making in healthcare.

Not all questions may be asked and participants will be able to guide the topics.

Introduction Procedure with Patients

1. Give complete name.
2. Identify self as a researcher from the Department of Cardiovascular and Metabolic Health at the University of Glasgow.
3. Give short explanation of the purpose of the study:

'I would like you to help me understand your thoughts and ideas around the risk of kidney failure in people with kidney disease, multiple long-term conditions, and frailty. I am interested in particular in how this topic should be explored and discussed between patients and healthcare professionals and what the expectations of using a tool called the Kidney Failure Risk Equation in the decision-making process and guiding care are.

The Kidney Failure Risk Equation or KFRE is a tool that uses an individual's age, sex, a blood test that measures kidney function called estimated glomerular filtration rate and a urine test that looks for protein to see how well the kidneys are working called urine albumin

creatinine ratio to estimate the chance of their kidney problem progressing to kidney failure. The tool calculates the risk of kidney failure as a percentage risk over the next 5 years, so for example a 10% risk means that out of 100 people with that score, 10 will develop kidney failure over the next 5 years. Recent NICE guidelines have suggested that people who have a more than 5% risk of kidney failure (as calculated using the KFRE tool) within 5 years should be referred to hospital kidney doctors.

Please feel assured that no one will be able to identify you from what you say when talking to me and everything you tell me will be treated in the strictest confidence.'

If at any time you want to stop, or have a break, please let me know.

'I will be recording the interview, so I can remember all that you have said to me.'

'Do you have any questions about the study or anything you would like me to explain further?'

PARTICIPANT PROFILE

Subject ID:

Age:

Gender:

- ☐ Male
- ☐ Female
- ☐ Non-binary
- ☐ Other
- ☐ Would rather not say

What is your ethnic group?

Choose one option that best describes your ethnic group or background

White

- ☐ Scottish
- ☐ Other British
- ☐ Irish
- ☐ Gypsy/Traveller
- ☐ Polish
- ☐ Any other White ethnic group, please describe

Mixed or Multiple ethnic groups

- ☐ Any Mixed or Multiple ethnic groups, please describe

Asian, Asian Scottish or Asian British

- ☐ Pakistani, Pakistani Scottish or Pakistani British
- ☐ Indian, Indian Scottish or Indian British

- ☐ Bangladeshi, Bangladeshi Scottish or Bangladeshi British
- ☐ Chinese, Chinese Scottish or Chinese British
- ☐ Any other Asian group, please describe

African

- ☐ African, African Scottish or African British
- ☐ Any other African group, please describe

Caribbean or Black

- ☐ Caribbean, Caribbean Scottish or Caribbean British
- ☐ Black, Black Scottish or Black British
- ☐ Any other Caribbean or Black group, please describe

Other ethnic group

- ☐ Arab, Arab Scottish or Arab British
- ☐ Any other ethnic group, please describe

Main setting of current healthcare for kidney disease:

- ☐ Hospital Setting
- ☐ Community/GP practice
- ☐ Other

How long have you had kidney disease for? (Please provide as close an estimate as you can but don't worry if you don't know the exact date)

Please list any medical conditions that you have:

Please list any medications that you take:

With the assistance of your interviewer please use the following scale to pick the best description of your current activity and functional status:

Clinical Frailty Scale*	
	1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.
	2 Well – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally , e.g. seasonally.
	3 Managing Well – People whose medical problems are well controlled , but are not regularly active beyond routine walking.
	4 Vulnerable – While not dependent on others for daily help, often symptoms limit activities . A common complaint is being “slowed up”, and/or being tired during the day.
	5 Mildly Frail – These people often have more evident slowing , and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.
	6 Moderately Frail – People need help with all outside activities and with keeping house . Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.
	7 Severely Frail – Completely dependent for personal care , from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).
	8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.
	9. Terminally Ill - Approaching the end of life. This category applies to people with a life expectancy <6 months , who are not otherwise evidently frail .

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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**DALHOUSIE UNIVERSITY**
Inspiring Minds

Date and Time of Interview:

The interviewer will explore the following general areas in an open fashion:

- **Knowledge**
- **Values**
- **Support**
- **Certainty**
- **Decision-making**

Knowledge of kidney disease and kidney failure

What information do you feel is necessary to make decisions about the care you receive for your kidney disease?

What information do you feel is necessary for you to understand your risk of kidney failure (where treatments are required to do the job the kidneys would usually do (dialysis) or a kidney donated from someone else)?

Do you feel that information provision is currently adequate?

If not, how could it improve?

What facilitates and prevents good information provision?

How do you wish to discuss or explore your risk of kidney failure?

Do you feel this differs to your healthcare professional's perspectives?

If so how?

Knowledge of multimorbidity and frailty

What do you feel the impact of having kidney disease and other long term medical conditions or being frail is on your healthcare?

What information do you think you need to understand the needs or competing needs/risks of your multiple long-term conditions and kidney disease?

Do you think that other long term health conditions or frailty are discussed adequately alongside your kidney disease?

If not, how could this be improved?

Who should discuss other long term health conditions alongside kidney disease e.g., hospital kidney doctors/specialist kidney nurses / primary care GP or nurse/mixture?

Communication

How well do hospital teams and/or primary care teams communicate with and to you?

What facilitates and prevents the above communication?

Priorities/key values

What matters to you most in relation to your kidney disease and other long-term conditions/frailty?

What risks and benefits or pros and cons are important to you?

Support

What support do you have or feel you need to make decisions about your healthcare?

Who do you discuss your health and care and any related decisions with?

Do you think an individual's social network (friends, family, neighbours) influence their role in shared decision-making (making health decisions with health professionals)?

If so, how?

Uncertainty

How certain do you feel about the choices you make in relation to your kidney disease and other long-term conditions?

Are there any areas you feel uncertain about?

If so, how do you manage these uncertainties?

Do you discuss uncertainties with your healthcare professional?

Do you think you would be more or less likely to want to be referred to hospital kidney doctors/discuss your risk of kidney failure if you have reached a point in life when you have lots of health conditions or are frail?

Choices/decisions

How do you think the kidney failure risk equation (a tool that can estimate the chance of someone's kidney problem progressing to kidney failure) should be used in the care of individuals with multiple long-term conditions and/or frailty?

How do you think the kidney failure risk equation (a tool that can estimate the chance of someone's kidney problem progressing to kidney failure) should be used in the decision-making process of individuals with multiple long-term conditions and/or frailty?

How do you think the decision to refer people with multiple long-term conditions/frailty and kidney disease to hospital kidney doctors should be made? Should it involve the kidney failure risk equation and if so how?

What facilitates and prevents the use of the Kidney Failure Risk Equation being used to guide care/treatment/referral to hospital kidney doctors?

Shared decision-making

What role do you prefer to take in making choices or decisions related to your health and healthcare?

Who do you think should make decisions?

How often should these decisions be reviewed and by whom?

Do you think that shared decision-making is helpful to people with kidney disease and multiple long-term conditions?

Do you think that shared decision-making (making health decisions with health professionals) is helpful to people with kidney disease and frailty?

What do you think facilitates and prevents shared decision-making?

What are your thoughts on decision aids/tools that might help you make decisions?

At close of interview

The interviewer will ask the participant if there are any issues, they would like to mention which haven't been covered.

Thank the participant and reiterate that all they have discussed is confidential.

FOCUS GROUP GUIDE: Kidney failure risk in multiple long-term conditions and frailty – exploration of patients’ and healthcare professionals’ perspectives of kidney failure risk

Background Information for the Interviewer

In situations where there is a lack of knowledge, questions will be posed in a manner which takes account of such a limitation.

The focus group will be semi-structured in format, and thus the exact wording and prompts used may vary between groups to encourage individuals to share their views and allow them an opportunity to talk at length about their thoughts, ideas and feelings about the Kidney Failure Risk Equation and multimorbidity and shared decision-making in healthcare.

Not all questions may be asked and participants we be able to guide the topics.

Introduction Procedure with Participants

1. Give complete name.
2. Identify self as a researcher from the Department of Cardiovascular and Metabolic Health at the University of Glasgow.
3. Give short explanation of the purpose of the study:

‘I would like you to help me understand your thoughts and ideas around the risk of kidney failure in people with kidney disease, multiple long-term conditions/multimorbidity and frailty. I am interested in particular in how this topic should be explored and discussed between patients and healthcare professionals and what the expectations of using a tool called the Kidney Failure Risk Equation in the decision-making process and guiding care are.

The Kidney Failure Risk Equation or KFRE is a tool that uses an individual’s age, sex, a blood test that measures kidney function called estimated glomerular filtration rate and a urine test that looks for protein to see how well the kidneys are working called urine albumin creatinine ratio to estimate the chance of their kidney problem progressing to kidney failure. The tool calculates the risk of kidney failure as a percentage risk over the next 5 years, so for example a 10% risk means that out of 100 people with that score, 10 will develop kidney failure over the next 5 years. Recent NICE guidelines have suggested that people who have

a more than 5% risk of kidney failure (as calculated using the KFRE tool) within 5 years should be referred to hospital kidney doctors.

Please feel assured that no one will be able to identify you from what you say when talking to me and everything you tell me will be treated in the strictest confidence.'

'If at any time you want to stop, or have a break, please let me know.'

'I will be recording the focus group, so I can remember everything that has been discussed.'

'Do you have any questions about the study or anything you would like me to explain further?'

PARTICIPANT PROFILE

Subject ID:

Age:

Gender:

- ☐ Male
- ☐ Female
- ☐ Non-binary
- ☐ Other
- ☐ Would rather not say

What is your ethnic group?

Choose one option that best describes your ethnic group or background

White

- ☐ Scottish
- ☐ Other British
- ☐ Irish
- ☐ Gypsy/Traveller
- ☐ Polish
- ☐ Any other White ethnic group, please describe

Mixed or Multiple ethnic groups

- ☐ Any Mixed or Multiple ethnic groups, please describe

Asian, Asian Scottish or Asian British

- ☐ Pakistani, Pakistani Scottish or Pakistani British
- ☐ Indian, Indian Scottish or Indian British

- ☐ Bangladeshi, Bangladeshi Scottish or Bangladeshi British
- ☐ Chinese, Chinese Scottish or Chinese British
- ☐ Any other Asian group, please describe

African

- ☐ African, African Scottish or African British
- ☐ Any other African group, please describe

Caribbean or Black

- ☐ Caribbean, Caribbean Scottish or Caribbean British
- ☐ Black, Black Scottish or Black British
- ☐ Any other Caribbean or Black group, please describe

Other ethnic group

- ☐ Arab, Arab Scottish or Arab British
- ☐ Any other ethnic group, please describe

Profession:

- ☐ Renal consultant
- ☐ Renal doctor in training
- ☐ Renal specialist nurse
- ☐ GP
- ☐ Practice nurse
- ☐ Other - Please state:

Do you work in the:

- ☐ Hospital Setting
- ☐ Primary Care

- ☐ Other

How long have you worked in this job?

- ☐ <1 year
- ☐ 1-5 years
- ☐ 5-10 years
- ☐ >10 years

Please describe your role in caring for and discussing risks of kidney failure to patients with CKD:

Date and Time of Focus Group

The facilitator will explore the following general areas in an open fashion:

- **Knowledge**
- **Values**
- **Support**
- **Certainty**
- **Decision-making**

Knowledge of kidney disease and kidney failure

What information do you feel patients require about chronic kidney disease?

What information do you feel patients require about their risk of kidney failure?

Do you feel that information provision is currently adequate?

If not, how could it improve?

What facilitates and prevents good information provision?

How and when should the risk of kidney failure be discussed or explored with patients?

Knowledge of multimorbidity and frailty

What are your perceptions of the risk of kidney failure in patients who have CKD, multimorbidity and/or frailty?

What needs or competing needs/risks do you think these patients should be informed of?

Who should discuss other long term health conditions alongside kidney disease e.g., hospital doctors/specialist kidney nurses /primary care GP or nurse/mixture?

Communication

How well do you feel you communicate about kidney disease and kidney failure risk with these types of patients (multimorbidity/frailty and CKD)?

What facilitates and prevents the above communication?

Priorities/key values

What are your key priorities in caring for these patients?

What do you think matters most to patients in relation to their kidney disease and other long-term conditions/frailty?

How do you explore this with patients and gather this information?

Support

What support do you have or feel you need to make decisions for these patients?

Does an individual's social network (friends, family, neighbours) influence their role in shared decision-making?

If so, how?

Uncertainty

Are there areas of uncertainty in caring for and managing patients with CKD, multimorbidity and/or frailty?

If so, how do you manage these uncertainties?

Do you discuss these uncertainties with patients?

Do you think you would be more or less likely to refer patients to secondary care nephrology services/discuss their risk of kidney failure if they had multimorbidity and/or were frail?

Choices/decisions

How do you think the kidney failure risk equation (a tool that can estimate the chance of someone's CKD progressing to kidney failure) should be used in the care of individuals with multimorbidity and/or frailty?

How do you think the kidney failure risk equation (a tool that can estimate the chance of someone's CKD progressing to kidney failure) should be used in the decision-making process of individuals with multimorbidity and/or frailty?

How do you think the decision to refer people with multimorbidity and kidney disease to secondary care nephrology services should be made? Should it involve the kidney failure risk equation and if so how?

What facilitates and prevents the use of the Kidney Failure Risk Equation being used to guide care/treatment/referral to secondary care nephrology services?

Do you take into account an individual's multimorbidity/frailty when assessing their risk of kidney failure/referring to secondary care?

Shared decision-making

What role do you think patients should take in making choices or decisions related to their health and healthcare?

Who do you think should make decisions?

When thinking specifically about referring to secondary care nephrology services/discussing risk of kidney failure: How often should these decisions be reviewed and by whom?

Do you think that shared decision-making is helpful to people with kidney disease and multiple long-term conditions?

Do you think that shared decision-making is helpful to people with kidney disease and frailty?

What do you think facilitates and prevents shared decision-making?

What are your thoughts on decision aids/tools that might help patients make decisions?

At close of focus group

The facilitator will ask the participant if there are any issues they would like to mention which haven't been covered.

Thank the participants and reiterate that all they have discussed is confidential.

Supplemental Table 7- 1. Clinical coding (ICD-10 codes) used for identification of eligible patient participants

Inclusion criteria					Exclusions
CKD	AND	Two or more LTCs	OR	Frailty	
N18.3, N18.4 eGFR <60ml/min/1.73m ²		I05 – I99, E00 – E35, E70 – E90, J40 - J47, J60 - J70, G10 – G99, R52.1,R52.2, C00- C97,D33, F00 – F03, F10 - F19, F20 - F29, F30 - F39,F40-F48, F50, F84, M00 – M25, M47.0 – M47.9, M79.7, M45, M46, M32, M80-M85, K76.9, K50-K52, K86.0, K86.1,K27, N80,N39.0, D51.0, D60, D61, D63, D64, D46, D55 – D59, D57, H54, H90, H91, H81.0, B20 - B24, A69.2, A15 – A19, G93.3, Q00-Q99,		R54, 2Jd., 2Jd1., 2Jd2., 38DW., 38Qk., 38Ql., 69D9., 38GD.	E85.3, N16.5, N18.5, Q60.1, T82.4, T86.1, Y60.2, Y61.2, Y62.2, Y84.1, Z49, Z94.0, Z99.2, H54.2, H54.3

Supplemental Table 7- 2. COREQ (CONsolidated criteria for REporting Qualitative research) Checklist

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
<i>Personal characteristics</i>			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	180
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	183
Occupation	3	What was their occupation at the time of the study?	183
Gender	4	Was the researcher male or female?	183
Experience and training	5	What experience or training did the researcher have?	183
<i>Relationship with participants</i>			
Relationship established	6	Was a relationship established prior to study commencement?	180, 215
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	215
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	215
Domain 2: Study design			
<i>Theoretical framework</i>			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	179-180, 215
<i>Participant selection</i>			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	179
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	Referenced protocol paper
Sample size	12	How many participants were in the study?	184
Non-participation	13	How many people refused to participate or dropped out? Reasons?	184
<i>Setting</i>			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	Table 8.2
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	Table 8.2
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	184, Table 7.2
<i>Data collection</i>			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	180, Supplemental text 7.1 & 7.2
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	N/A
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	180
Field notes	20	Were field notes made during and/or after the inter view or focus group?	180, 215
Duration	21	What was the duration of the inter views or focus group?	184

Data saturation	22	Was data saturation discussed?	180
Transcripts returned	23	Were transcripts returned to participants for comment and/or correction?	No
Domain 3: analysis and findings			
<i>Data analysis</i>			
Number of data coders	24	How many data coders coded the data?	183
Description of the coding tree	25	Did authors provide a description of the coding tree?	Tables 8.1 & 8.3
Derivation of themes	26	Were themes identified in advance or derived from the data?	Both 180-183, 207
Software	27	What software, if applicable, was used to manage the data?	183
Participant checking	28	Did participants provide feedback on the findings?	180, 215
<i>Reporting</i>			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	197-209, Table 8.3, Supplemental table 8.3
Data and findings consistent	30	Was there consistency between the data presented and the findings?	197-209, Table 8.3, Supplemental table 8.3
Clarity of major themes	31	Were major themes clearly presented in the findings?	197-209, Figure 8.1, Table 8.3
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	No

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 - 357

Supplemental Table 7- 3. Expanded illustrative participant quotes by Normalisation Process Theory sub-constructs and themes

NPT Category and sub-construct		Description/examples	Supporting quotes	
			Patients	HCPs
Understanding/Sense Making: Making sense of CKD and kidney failure as part of multimorbidity and/or frailty	Understanding the kidneys & CKD	Pre-existing knowledge and understanding of the kidneys	<i>"no knowing how the kidneys work, I know fluid goes in, it's got to go through your system and the kidneys pee it oot...I don't know what else I can dae to make them any better apart fae keep taking the medicine."</i> (SCP04, Male, 76 years) <i>"I don't really know anything about it."</i> (PCP13, Male, 81 years)	<i>"first of all, patients need to know what their kidneys roughly do. A lot of patients that come to clinic have absolutely no idea why they're there or what the kidneys actually do in the body, and then what consequence of kidney failure might look like because then that helps them work out what it will mean to them."</i> (HCP12, Female, Renal specialist trainee)
		Awareness at having CKD	<i>"I had no idea that I had a problem so I have no idea how it functions with anything else. I really have no idea at all."</i> (PCP02, Female, 84 years) <i>"they're taking samples and they wanted to see me again in three months' time and take blood and that was it, they never said anything at all about it, about any"</i>	<i>"I would say, as a ballpark figure like 80% or 90%, won't generally know the specific reason they've been referred. Often because it's in the context of other things going on...But as soon as you then start going into well, your kidneys aren't very good, they're not functioning well or they're leaking protein... you can see people are quite lost about what's going on."</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>part of my kidneys actually, just nothing.</i> (SCP09, Male, 73 years)	(HCP13, Male, Renal specialist trainee)
	Giving/receiving a diagnosis of CKD	<i>"they'll just say oh you've got a kidney disease and- But I really don't know what kidney disease is."</i> (PCP03, Female, 65 years) <i>"it was fairly well explained in that they told me it was down to – that your urine goes frothy because of the protein, and it's lacking because your thingamy is no passing through your kidneys properly."</i> (SCP03, Male, 58 years)	<i>"I think a lot of people would say it in a kind of reassuring way, this is more for GPs or doctors to know about than it is for you to have a diagnosis."</i> (HCP07, Male, GP) <i>"we've just made a kind of basic letter to say "We've noticed a slight change in your kidney function and we suspect CKD."</i> (HCP19, Female, Practice nurse)
	Symptoms/asymptomatic nature of CKD	<i>"I just accepted it because to me it wasn't affecting me in any way then. But I didn't know I had kidney disease. Nothing was happening that made me think I had (it)."</i> (PCP01, Female, 94 years) <i>"I wouldn't know what symptoms to look for, you know, what exactly does a kidney do?"</i>	<i>"because kidney disease is- Can be relatively asymptomatic until it's quite advanced, it is one of these silent illnesses for a lot of people."</i> (HCP16, Female, Renal specialist nurse)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		(SCP02, Male, 86 years)	
	What will help the kidneys	<i>"it's not bad at the moment but again what could I be doing to either slow down the deterioration or whatever?"</i> (PCP17, Female, 75 years)	<i>"patients are often wanting to know what they can modify, if anything."</i> (HCP12, Female, Renal specialist trainee)
	Discussing kidney failure	<i>"is it just the one kidney, is it both kidneys? You know, that kind of information would help as well because as you say you can go without one kidney, you cannae go without both of them, so you're gonnae be getting yourself nearer towards renal failure and dialysis. So I think as much information as early as possible would help people."</i> (SCP09, Male, 73 years)	<i>"I think people don't like to start talking to people that are old and vulnerable or young and vulnerable about the fact that they're going to need dialysis or even transplantation, that distinct possibility. I think it's a difficult one for them to do."</i> (HCP14, Male, Renal specialist nurse)
Considering what CKD & risk of kidney failure means for the individual	Communication and setting expectations	<i>"I just keep being told that I'm very complex when I go to the hospital and I was sort of- I was that unpopular patient I'm afraid and I know that exists that nobody can do anything for you. They told me 10 years ago well it's more now about 13 years ago that they wouldn't go back in</i>	<i>"I feel that I've maybe not gotten access to a lot of patient resources... maybe I need to get posters up to highlight to people... they don't realise they have been getting tested because it's not, you don't chat about this stuff at the dinner table, let's face it."</i> (HCP19, Female, Practice nurse)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>unless it was a matter of life and death.”</i> (PCP03, Female, 65 years)	
	Other LTCs	<i>“I don’t ever remember being mentioned anything about my kidneys. Because I think I am too- I’m much more concerned with my asthma that’s my main functioning thing.”</i> (PCP02, Female, 84 years)	<i>“people just think the heart’s the big issue and then you bring into the fact, well, there’s a change in your kidney function, they’re not running at 100%, but they’re still functioning but we need to keep an eye on it or there’s a risk of, you know, that a heart attack or further complications and they just look at you. What do you mean, my kidneys affect my heart.”</i> (HCP19, Female, Practice nurse)
	Individual preference for knowledge and understanding	<i>“as far as this is concerned, I’m fact basically disinterested...I’m perfectly happy the way I am at the moment.”</i> (SCP02, Male, 86 years) <i>“I’m the kind of person who likes to know, especially if there’s the possibility of a change in behaviour, or lifestyle or something, that would make things better, then I would like all the information I could get.”</i> (PCP05, Female, 73 years)	<i>“one patient doesn’t want to know the same as the other person. So some people are quite happy to be sort of led down what’s going on and just take it step by step, but some people want to come in and they want to know all the studies that have been done in this specific condition. So I think the amount people want to know from the outset is also very different as well.”</i> (HCP12, Female, Renal specialist trainee)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
	Ongoing impact of CKD and day-to-day life	<i>“what information do I need- You know, what are the likely outcomes for further deterioration? I mean obviously my life is quite active, but if somebody was to say to me, you know, within the next five years you might not be able to go to the gym, lead the life that you're living then, you know, I would then be asking is there anything I can do to prevent that, to slow that process down.”</i> (SCP08, Male, 75 years)	<i>“if they've got other conditions, so if they've got hypertension or diabetes, they're getting their blood pressure, they're getting their eGFR, they're getting their urine dipped annually anyway, so in terms of what is happening to them, they may not perceive it that differently. So, like you say, you've given them that additional bit of information but it might not have such a meaningful change on what they're experiencing I suppose.”</i> (HCP08, Female, GP) <i>“A lot of patients that come to clinic have absolutely no idea why they're there or what the kidneys actually do in the body, and then what consequence of kidney failure might look like because then that helps them work out what it will mean to them.”</i> (HCP12, Female, Renal specialist trainee)
Understanding the impact of CKD & risk of kidney failure for social/support networks	Withholding information from others	<i>“Most people that know me don't know I'm ill because I hide it and I carry on and I do the best I can all the time.”</i> (PCP03, Female, 65 years)	<i>“I think it gets very messy I find when family aren't involved at all because then I think when family feel blindsided with how bad someone is, as I say, because they've not had any</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>"Family's got their own things going on so I don't burden them. I'll maybe say, I was up for a blood test or something and back, such and such, but I don't tell an awful lot of detail with them."</i> (SCP09, Female, 74 years)	<i>symptoms, often they don't see them deteriorating."</i> (HCP12, Female, Renal specialist trainee)
	Support network	<i>"I think I had the support that I needed, certainly from my family."</i> (PCP08, Female, 84 years) <i>"I might talk to my daughter about it and my friend. I was at a wee club this morning and we do discuss- It's all my age group, it's supposed to be yoga but it's really bingo and tea and talk. We discuss things like that, you know, if- Us all, you know, the latest problem."</i> (PCP18, Female, 85 years)	<i>"I would say the vast majority of the time the family being there is really helpful because then I think they chip in with a few questions at the end that the patient's maybe just a bit too overwhelmed to ask. Especially if it's the same family member that comes each time to the clinic, so I generally find them helpful."</i> (HCP12, Female, Renal specialist trainee)
	Challenges with support networks	<i>"it's mainly me because I think if my family was involved they would be saying, don't do this, don't do that."</i> (PCP16, Female, 74 years)	<i>"it's really challenging when someone's made a decision and then it's sometimes they discuss it with the family and then come back and make a different decision, I think that's challenging. I think it's really positive</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
			<i>when family are there because often they will be able to remember a lot more additional details than the patient can on their own. But...when family cut across and don't give an accurate account of what they're experiencing and stuff, then that's really challenging so it's loads of positives and negatives."</i> (HCP12, Female, Renal specialist trainee)
	Using others experiences to understand CKD	<i>"Well as you go through life you learn a bit more you have clients you have friends who have been through all these stages so you just know vaguely what's what."</i> (PCP02, Female, 84 years)	<i>"Patients fed back that it was really helpful speaking to other patients on dialysis, when the come up to the education clinics."</i> (HCP15, Female, Renal specialist nurse) <i>"Quite often they've spoken to lots of people, or they've had family members who've had a transplant or been on dialysis, and they actually know quite a lot already so it's a huge range of experience."</i> (HCP02, Male, Renal specialist trainee)
Perception & value of KFRE in CKD/ multimorbidity/frailty & shared decision-making	Perceptions of KFRE	<i>"that tool would allow people to talk, it flags up earlier lights, that's</i>	<i>"when we use the Kidney Failure Risk Equation as an indicator of time and probability, we present it in a kind of</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>not right, that's not right, his blood pressure is..."</i> (PCP10, Male, 64 years) <i>"I'm no saying it should be the one and only qualifying thing, but if it helps diagnosis..."</i> (SCP03, Male, 58 years)	<i>funny way in that for most people it's not going to be 70, 80, 90, 100% five-year risk. It's going to be the most people that we see in clinic, you know, 1, 2, 3, 4, 5, 10, 15% which means that there is still up to 85% or more chance that they will not end up with kidney failure.</i> <i>And I think the way that it's currently presented can sometimes terrify people that they are going to develop a condition that they're probably not going to develop, and that we should actually be talking to them about all the other things that might happen instead and how to prevent that from happening...I think it needs much broader consideration than just a blanket we should refer above this threshold, there's a lot more nuance to it. Some of it is dependent on the cause of the albuminuria, for example, which is usually the thing that's driving the KFRE in many cases."</i> (HCP10, Female, Renal consultant)
	Accuracy and precision	<i>"I know in this area it's to quite a considerable extent guesswork, percentages, so I don't expect too</i>	<i>"you don't have a crystal ball, people do not behave... You know, all these decision-making tools, everything helps. They finesse our decisions, they</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>much precision, one can't have it."</i> (PCP07, Male, 91 years)	<i>allow us- But they still, on an individual level, they guide, they're not certainties, and that's part of clinical judgement, even though it's flawed as well. But it does mean that for each one of these decision-making aids or whatever you're still always surprised by somebody who doesn't quite fit with the data, or the data doesn't give enough precision for that individual patient."</i> (HCP01, Male, Renal consultant)
	Value of KFRE	<i>"You can do that wee tool to help you guide that side of things to start the communication because it could be, sometimes it's I need to change my lifestyle, because I've got relaxed after a year...realising that, yes, it's causing an issue for me."</i> (PCP10, 64, Male years) <i>"Some people would like to know. Sometimes you go to the doctor, you come out none the wiser. I think if you knew what was happening and what was going on, it would put your mind at ease a little."</i>	<i>"I personally don't give them the risk score I, as I said, show them a graphical representation of where I think their kidney function might be going and I show most patients in clinic to guide the discussions."</i> (HCP12, Female, Renal specialist trainee) <i>"the other situation that I'm using it is when it's about a referral for the GP to explain to the GP why they don't need to come to a renal clinic. Or occasionally when I'm discharging a patient back to the GP who we've maybe been following for a year or so and saying we can be reassured"</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		(SCP01, Male, 86 years)	<i>because the Kidney Failure Risk Equation says X.</i> (HCP04, Male, Renal consultant)
	Implementation	<i>"I didn't realise that I had to have a yearly urine test and they asked for it the last time."</i> (PCP03, Female, 65 years)	<i>"There are so many guidelines, and people get in a system of what they use for each thing. And I don't think the KFRE has sort of gone into primary care yet, and it's not become routine practice and it's just that it needs to be embedded."</i> (HCP03, Female, GP)
Work of & roles in understanding & making decision: Understanding how individuals work with HCPs and their support networks	Work involved related to living with CKD & multimorbidity /frailty	Work involved in managing CKD and adapting (including medications, monitoring, appointments, self-care)	<i>"I think probably you know if you have multiple health problems it's another thing to worry about isn't it you know but it's how to manage that what changes can you make to your lifestyle or etc you know what you'd be willing to do."</i> (PCP19, Female, 64 years) <i>"someone's capacity to cope with several conditions, you know, CKD and other conditions and if we're asking them to do self-management and lifestyle changes and things like that, then the wider social network does become really important because have they got other people that could help them with all the other things that they need to do so that they can focus on this? That's really variable and it's really important because there's no point just telling someone what they need to do if they don't have space or the means in their life to do it."</i> (HCP08, Female, GP)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
	Emotional work	<i>"The more information you can give somebody, the more choices you've got, I find really important because it's an anxious moment... no communication with anybody, and this is what gets you anxious, what's going on here."</i> (PCP10, Male, 64 years)	<i>"there's always a balance of worrying people and giving them information...I suspect in primary care people don't get as much information as they could. Whether they should or not I don't know, because we try to personalise information for what we think's helpful to people, and a lot of people with multimorbidity and frailty have so much else going on."</i> (HCP03, Female, GP)
	Self-blame	<i>"every time they asked me for a urine sample, I kept saying I'd get it to them later, I'd get it to them later and that went on for a long time, you know. So if I had of put a urine sample in sooner it would have been detected."</i> (SCP05, Female, 63 years)	<i>"The most common one (question) is why did this or how does it come about? Is it because I've been taking co-codamol my whole life?"</i> (HCP19, Female, Practice nurse)
	Patient roles and responsibilities	<i>"I phoned up the receptionist and she said, 'Your bloods are fine.' And I always say, 'Well what's my, you know eGFR?'"</i> (PCP03, Female, 65 years)	<i>"I think it's useful to discuss with them if there's anything they can do to slow it down...a big part of what we would do if somebody was diagnosed would be to give them a nurse appointment, and discuss what they can do to sort of, you know, improve cardiovascular health generally in that discussion of kidney disease."</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
			(HCP03, Female, GP).
	Communication/conversations	<i>“because I’ve got all these other issues wrong it all impacts, and I think that’s quite hard to process. So I think for my care, I think having the doctors talk to each other would be good as well.”</i> (SCP07, Female, 46 years) <i>“there was two nurses used to come and dae the blood pressure and things like that and they knew mair than the doctors, I thought, because they were telling me something tae dae wi me that they werenae telling me. They were telling me how things worked, basically. Whereas the doctor tells you, Aye you’re fine, just get you down here.”</i> (SCP04, Male, 76 years)	<i>“I think maybe at that stage I don’t really offer much, and we worry about it...all you can do is maintain a healthy life, like all the things that we would normally say to do ...I probably don’t go much further into it, and we’ll keep a check on it every year. Maybe if it started drifting down further then I would maybe go in a bit more, but I don’t think I go in too hard right away to worry them.”</i> (HCP09, Female, GP) <i>“The other thing I think is important in the setting of multiple health conditions is not just lack of information, but it’s sometimes too much information and conflicting information.... I think that must be extremely confusing for people to go from pillar to post and be given different information each time.”</i> (HCP11, Female, Renal specialist trainee)
Understanding & engaging with others (HCPs/support	Support network and roles	<i>“(My wife) comes with me because... my hearing’s bad- even with the hearing aids in. So,</i>	<i>“older people often relying on younger carers to get them to appointments and things like that. So yeah, and</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
networks) to understand their health & health decisions		<i>she goes with me and then she understands a lot of the medical jargon I wouldn't understand, you know, so she's my support."</i> (PCP13, Male, 81 years)	<i>clearly people's health information or the way they live as well is strongly influenced by their social network and their family."</i> (HCP07, Male, GP)
	Facilitators to understanding and engagement	<i>"it's only relatively recently that I've thought, Yes, I've got something to contribute to this discussion. And once I'd started doing that, mostly their people are willing to listen."</i> (PCP08, Female, 84 years) <i>"The doctors they keep in touch and everything else so if I've got any problems I would get in touch with them."</i> (PCP04, Male, 75 years)	<i>"Any long-term condition, you need to understand that condition because these are not diseased people that need fixed, they are managing a chronic disorder and so they have to understand that as best they can. Because although we need to understand it and treat them well, for them to do really well, they have to get their heads around that, they have to be engaged."</i> (HCP05, Female, Renal consultant)
	Barriers to understanding and engagement	<i>"You know they would use all these fancy names...I kind of knew it, what it meant in my own head, saying it in my terms is better you know because we're not all great medical minded or you know about the human body."</i> (SCP05, Female, 63 years)	<i>"I do think that we struggle to impart the information to people who have got poor health literacy and people who don't speak English as their first language. I think we're aware that we struggle with that and we have done some things to try and mitigate that but I think we can still do a lot more on that front."</i> (HCP05, Female, Renal consultant)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
Determining roles & deciding if decisions made are the right thing to do (decision appraisal)	SDM culture	<i>"it's a two-way conversation"</i> (SCP02, Male, 86 years)	<i>"obviously it's their decision, but that they're appropriately informed making any decision, absolutely informed, and that might involve family, carers etc. They make an appropriate decision, and once they've made an appropriate decision, that may not be set in stone but at least guides us where we want to be."</i> (HCP01, Male, Renal consultant)
	Understanding decisions	<i>"the doctor tried to talk me out of it because he said that I would probably have to have dialysis. I said I didn't care, I couldn't live with it and they sent a dialysis nurse out and she was really good. She explained everything to us... I still said, no I wanted to go ahead with it. So they decided that, okay then they would do it."</i> (PCP16, Female, 74 years)	<i>"What they don't like is being made to feel like they're having to make the decision on their own, especially if it's a complex area that they don't really feel fully informed to make that decision about. But then you also get patients that just shut down the conversation and say, 'Just do what you want, Doc. I'll do whatever you say.'"</i> (HCP12, Female, Renal specialist trainee)
	Choosing roles in SDM	<i>"generally we have a good chat about what's happening. He (GP) lets me know where my levels are, and it's good to have that information from somebody like that that I trust. And I rely on him</i>	<i>"there's a huge range. I think generally the people I'm seeing in clinic want you to be the driver of the decisions but they want to feel that they're part of the discussion. But they're very much wanting you to give your opinion on</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>to keep me in the right place, and I know if there's something that I need to be not doing or taking care of, he'll tell me that.</i> (PCP12, Male, 73 years)	<i>what's the best line to go down, so it's like not the kind of authoritarian model that you're telling them what to do, but you're kind of guiding them.</i> (HCP12, Female, Renal specialist trainee)
	Agreeing/disagreeing with decisions and trust	<i>"why a biopsy? Because there's risks involved – from my point of view, risks involved there, too much for me, at my age. It tells you if they do something wrong with a kidney you could end up with dialysis and things like that. For what I might have left in my life I don't want to be going into the hospital on dialysis. So the biopsy, as far as I'm concerned, I really wouldn't want it. That's the only thing. I was a wee bit concerned about because people come out – it was as if they were trying to push you into it."</i> (SCP04, Male, 76 years)	<i>"We had a patient who had a cognitive impairment, so he didn't retain information but he insisted that there was really nothing wrong with him and he was absolutely fine and felt great and wanted dialysis. But it took for him to be brought into hospital for a period of assessment and observation and actually a challenge to try and sit for a period of time for them to prove to him that he wouldn't be right for him."</i> (HCP16, Female, Renal specialist nurse)
Barriers & facilitators (to understanding shared decision-making)	Barriers to SDM	<i>"I don't know if I've actually ever been given any information on it. The doctor I've seen this morning, he talked me through what I could</i>	<i>"There's so much information to impart and I think also one patient doesn't want to know the same as the other person. So some people are quite happy to be sort of led down what's</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>understand...It's all double Dutch to me."</i> (SCP04, Male, 76 years)	<i>going on and just take it step by step, but some people want to come in and they want to know all the studies that have been done in this specific condition. So I think the amount people want to know from the outset is also very different as well."</i> (HCP13, Male, Renal specialist trainee) <i>"We can't get translators for them just now, so often they're coming in and we're having to send them away... we don't have the resources to translate every letter into their language."</i> (HCP19, Female, Practice nurse)
	Facilitators to SDM	<i>"Having a good family and a good doctor that understands you."</i> (SCP05, Female, 64 years)	<i>"I work in <Place>, so medical paternalism is still strong here. They, most, a lot of them don't want things explained. They just want us to own the problem and us to tell them what they need to do. Whereas, <Place> down the way or whatever, it's a different level of understanding."</i> (PCP18, Male, GP)
	Awareness and use of KFRE	<i>"I think it (KFRE) would be a good thing for patients to know,</i>	<i>"I was certainly not aware of this Kidney Risk Equation."</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>obviously it's just a rough indicator these things because they can't say for definite, but, yeah, I think it would be interesting to see what the stats show.</i>" (SCP07, Female, 46 years) <i>"if I'd known about it (KFRE) I think I would have asked about it, and it's predictive outcomes because surely there are certain directions that this disease might go in."</i> (SCP08, Male, 75 years)	(HCP07, Male, GP) <i>"95% of my referrals don't have it (KFRE) at the minute. But some do, and I find those very- It's the most helpful, because clearly their GP has thought about it, thought about risk, thought about their patient and referred on."</i> (PHCP01, Male, Renal consultant)
Working with others & relationships/interactions in understanding CKD, kidney failure risk & shared decision-making: Working with HCPs, healthcare systems and their support networks to discuss/understand CKD and kidney failure risk and make shared	Impact of multimorbidity /frailty on discussing kidney failure risk/using KFRE to guide care and make shared decisions	Other LTCs	<i>"But it's all these different wee bits that I think, you know, trying to process that and you trust the consultants, you know what you are doing and things but it's hard, it's really hard to process."</i> (SCP07, Female, 46 years) <i>"when someone's got lots of other conditions, it almost feels as if the CKD is almost just a consequence of those things and I think it tends to just get underserved because I think you probably think, well, if we manage their heart failure, we manage their diabetes and we manage their other symptoms and the CKD will probably look after itself because we've actually got them on the drugs that are used for CKD anyway. So, it almost becomes an afterthought. I think it's only once you see an inexorable decline, in the eGFR and there's nothing that you can stop."</i>

NPT Category and sub-construct		Description/examples	Supporting quotes	
			Patients	HCPs
				(HCP19, Male, GP)
		Communicating and discussing risk	<i>"I've never really thought about it (kidney failure) because of, well, what I'd been told previous, and what was already on the letter that the GP had sent. I never felt I was in any danger of anything progressing. But I suppose that's the confidence the letter gives you, and I just assumed.."</i> (PCP06, Male, 81 years)	<i>"if we can give someone some numbers to try and convey that risk, although that's often a difficult thing in itself, like how do you do that?"</i> (HCP07, Male, GP) <i>"they also find it difficult knowing when is the best time to start talking about it."</i> (HCP14, Male, Renal specialist nurse)
		Ageing and declines in health	<i>"from being physically able relatively recently, I'm now physically declining, I know that. I don't see very well, my balance is poor, and it's just generally everything is not as fine and fit as it was last year. It's inevitable when you're in your eighth decade I reckon."</i> (PCP08, Female, 84 years)	<i>"we take it terribly careful, like I think your kidneys are probably going to outlive you. They go great. They're not thinking, Oh well, that's bad. We phrase it very carefully, we are positive... I don't think we're hiding things from them. We are stating the truth but we choose the way we say it."</i> (HCP06, Female, Renal consultant)
		Healthcare systems	<i>"they're disconnected"</i> (SCP12, Female, 73 years) <i>"It's not a lack of caring or a lack of care; it's just a new system that</i>	<i>"when you're having to ask three or four different specialties about a medicine or a treatment plan, that's introducing delays because there's the email to the other specialty or the phone call or the letter or waiting for</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>I don't think works terribly well as far as patients are concerned."</i> (PCP15, Male, 85 years)	<i>the appointment. And it just means that every single time you're wanting to do something different or give some advice, you're waiting for weeks or sometimes months to collate all that information from a whole bunch of different people. And then formulate some kind of intelligible plan and then see a patient again, so everything just takes much, much longer for people who've got lots of things going on. And actually in many cases you want things done more quickly to try and prevent the problems."</i> (HCP10, Female, Renal consultant)
Role of relationships between individuals, support networks & HCPs	Trust & continuity of care	<i>"There's different people taking over different roles at the GPs so you don't just see your GP anymore so I go and get my bloods taken and it's somebody different every time and it's- Who then takes your blood pressure as well, but I don't really understand what they're taking it for and they'll dip your urine and things as well. So they don't have an understanding of what the results are and then you know that if there's a problem somebody else</i>	<i>"it's a different doctor I see every time and that's the biggest complaint. Every time we see a different doctor they change my medications, whereas we're the only constant people at clinic, we're always there."</i> (HCP16, Female, Renal specialist nurse)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>will phone you with the results or if you're worried about yourself you phone. And sometimes you see the nurse and then sometimes you see the advanced nurse practitioner so it's a bit disjointed."</i> (PCP03, Female, 65 years)	
	Care setting (primary care, secondary care)	<i>"there's like five or six of them (GPs) there, so if <name> can't do, <name> will come and talk to me, if he can't, <name> will do it. They all know what's going on, so in that sense it's easy, whereas in the hospital, there's one person. I mean, this is the problem now, the person I dealt with six weeks ago, I've now got somebody else."</i> (PCP10, Male, 64 years)	<i>"I think in principle for people with multiple long-term conditions in terms of the workload that they have to do and the burden of treatments and the burden of appointments and things like that. And the stress of having to meet multiple different people all at once, the feedback is that having somebody that you know, somebody that you trust giving you all the information that you need about all the things you need to know about, that seems to be the kind of favoured healthcare delivery thing. And failing that, having everybody who's involved sitting down at once and discussing it."</i> (HCP10, Female, Renal consultant)
	Healthcare system/processes	<i>"It's so difficult to get an appointment with the doctor that I, like most people, only use them</i>	<i>"it's an issue when there's multiple health problems and also if they've not been able to access other healthcare</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>for something that's urgent and acute."</i> (PCP05, Female, 73 years)	<i>professionals. So quite frequently things get brought up in our clinics that because they've not been able to see another specialty for months on end or they can't get an appointment with their GP or whatever, and that's definitely gotten worse since Covid with the kind of squeeze on healthcare in general and the delay in elective appointments. So quite often people are wanting to talk about a symptom that belongs to another specialty but they're looking for advice and help from you because they trust you, and they come to your clinic very often and they respect what you've got to say, even if you think that's not really your kidney issue."</i> (HCP12, Female, Renal specialist trainee)
Allocation of work & decision-making	Individual capacity and preferences	<i>"I think some people can take information, some people can't. It just depends on your personality. I would rather have the information."</i> (PCP12, Male, 73 years)	<i>"Maybe you might not say it immediately and talk about all the long-term implications because potentially you have a patient who's got more than enough on their plate already, and you're just trying to give them enough information that's useful but not overwhelms them."</i> (HCP08, Female, GP)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
	Role allocation	<i>“Generally speaking, one will go along with the best expert opinion, unless it conflicts violently with some other understanding that you have.”</i> (PCP07, Male, 91 years)	<i>“The feedback I get from patients where I work in <Place>, a more deprived area, is that they want you as the doctor to tell them what to do.”</i> (HCP07, Male, GP) <i>“at the end of the day, it's a patient's choice whether they want to take the tablets or not. Most people go along with that fine.”</i> (HCP17, Female, Practice nurse)
	Decision aids	<i>“I’ve had like, conversations where I’ve been told this or that yeah but not, never written down no.”</i> (SCP06, Male, 60 years)	<i>“Some of the decision tools I find are helpful. I think they’d be more helpful if you have time to go through the tool with them rather than completing it on their own, and there’s just not enough time in our clinics to go through a decision tool with them...I’d only do it for a selected population of patients that I felt that that decision tool would not be an extra burden. They are seeming to want to work through those pros and cons and we’ve kind of done a little bit of that in the discussion, so I feel like, one, they’ll be able to read it because that’s not guaranteed.”</i> (HCP12, Female, Renal specialist trainee)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
Impact of individuals' contexts & interactions between healthcare systems & individuals	Individual context	<i>"any decision like referring you to a kidney specialist in Glasgow, means that I have to go to Glasgow. It's another burden on my planning day-to-day activities, and you've got to understand that as well, and someone here to say 'That's it, as far as I'm concerned. I'm not doing that.'"</i> (PCP07, Male, 91 years)	<i>"that chap had his 60th wedding anniversary and his granddaughter's wedding to live for. And he made his granddaughter's wedding and he didn't quite make his 60th wedding anniversary, and it was absolutely the right decision for him and his wife to carry on and have dialysis."</i> (HCP05, Female, Renal consultant)
	Healthcare system	<i>"I don't know because if I make appointment I usually get the advanced nurse practitioner, but she's very good and she always sorts me out she's just very experienced so, but it's very difficult to get see a GP just now. But in the old days I had a great relationship with my GP and they know you don't they?"</i> (PCP03, Female, 65 years)	<i>"why people phone us as well is to I've coming for this, what am I going for? If I'm going for this renal appointment and going for that renal appointment, do I need to go to both? Some of them will just not go to one because they've got another one. Therefore, you miss out on your vascular access... You help them prioritise what will support them."</i> (HCP14, Male, Renal specialist nurse)
	Time and resources	<i>"Time. I think what is wrong is the GPs don't have the time."</i> (PCP15, Male, 85 years)	<i>"the time aspect of that is that you need time to deal with every aspect of someone's care and all the different conditions if there are other things that</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>"I go to my doctors you're getting a five or ten minute thingamy, d'you know what I mean, and if I try and sit and tell him how I'm feeling for the last two weeks because I'm struggling with thingamy, he'll say, Well we'll deal with this the now."</i> (SCP03, Male, 58 years)	<i>are a priority at that particular patient contact."</i> (HCP08, Female, GP)
	Acute versus chronic problems	<i>"the fact that they obviously don't see my condition as acute and immediately dangerous."</i> (PCP05, Female, 73 years)	<i>"it's quite a usual scenario where the patient will have had an incident whether cardiac or diabetic couple of years previous where their kidney function at that point would have been 40% but because it wasn't particularly troublesome and the main focus was something else."</i> (HCP14, Male, Renal specialist nurse)
Reflecting & appraising work required to understand CKD/kidney failure and making shared decisions in multimorbidity /frailty: Reflecting and evaluating the role of	Finding information about CKD, kidney failure or impact of multimorbidity/frailty	Information sources <i>"I know I shouldn't do but I Google an awful lot [laughs] just to find out things when I need to."</i> (SCP10, Female, 63 years) <i>"We're going to get a kidney charity in (to talk to us) this year, so we do wellness sessions (in work) every month."</i> (SCP07, Female, 46 years)	<i>"we've just made a kind of basic letter to say "We've noticed a slight change in your kidney function and we suspect CKD" and we actually signpost them to the CKD website, and I'll just tell you exactly what one it is on my letter, it's the Kidney Care UK website that we link them to."</i> (HCP19, Female, Practice nurse)

NPT Category and sub-construct		Description/examples	Supporting quotes	
			Patients	HCPs
		Artificial Intelligence	-	<i>"Lots of the younger, more dynamic patients that I've spoken to recently also use ChatGPT...AI would be extraordinarily helpful... if you had a tool that would allow you to do that, kind of move a slider up and down to increase or decrease the complexity of the language and the patient can select the information they want to have, I think that would be extremely useful."</i> <i>(HCP10, Female, Renal consultant)</i>
		Personal preferences	<i>"because I don't know how bad my kidney disease is and so I don't know what the effects, in fact I don't really know what the full function of the kidney is. So, this is just my stupidity as far as health is concerned... I wouldn't know what symptoms to look for, you know, what exactly does a kidney do? I'm not particularly interested, actually."</i> <i>(SCP02, Male, 85 years)</i>	<i>"There may be a small number of patients that don't want to know that may be frightened. You know that you know, are don't tell me this, I'm fine. You know, they don't want to know. Most people will take advice on board and they'll know, you know. But this I think it's a mixture of people different, you know, personalities. How they how they cope with their chronic disease and some are very positive and others maybe shy away from that. It's just everybody's different, you know, I don't think there's anything."</i> <i>(HCP17, Female, Practice nurse)</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
	Health literacy	<i>"I think it's really important that you've got a doctor that can put it in the layman's terms, because there's a lot of words round about the kidneys that you know I don't understand, so it's putting it to a level of terms and then I know what's happening, so."</i> (SCP05, Female, 63 years)	<i>"I am not aware of within our service people formally assessing what people have understood from the discussions they've had with us and perhaps if we did then we might be surprised. I do think that we struggle to impart the information to people who have got poor health literacy."</i> (HCP04, Male, Renal consultant)
	Interpretation of information	<i>"is it just the one kidney, is it both kidneys? You know, that kind of information would help as well because as you say you can go without one kidney, you cannae go without both of them."</i> (SCP09, Male, 73 years) <i>"You know they would use all these fancy names. And you've no – though I kind of knew it, what it meant in my own head, saying it in my terms is better you know because we're no all great medical minded or you know about the human body. I knew about the kidney function, what it was for and all that kind of stuff. But I mean does it affect us perhaps, you know like your</i>	<i>"We used to use a lot of third sector information and resources as well for national kidney charities and things, or signpost patients to a lot of their websites and things, Kidney Care UK, we use a lot of their leaflets about and their website's good isn't it because you can change the language as well for patients."</i> (HCP15, Female, Renal specialist nurse)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>bladder. Does it affect aw that? I daedna know, you know.</i> (SCP05, Female, 63 years)	
	Information relevant to multimorbidity/frailty	-	<i>“you might get a different opinion about how bad your CKD is from a diabetes specialist, from an ophthalmologist, from a cancer specialist because the thresholds and the boundaries of what is important with respect to your kidney function is different depending on the disease process and the treatment plan.”</i> (HCP10, Female, Renal consultant)
	Review of decisions made with HCPs/support networks		
	Reflections and reviewing decisions	<i>“the other thing I do is when you come back with information, I tend to look up more about it and do more background research on it... So that I can understand it and then provide more support and help for mum if she needs it.”</i> (PCP08 relative, Female)	<i>“Oftentimes if someone has a stronger family or wider social network to support them, they have more capacity to address those things (engagement and management). And I suppose maybe that also means they have other people to talk to about their conditions or if they’ve been given some new information.”</i> (HCP08, Female, GP)
	Monitoring (kidney function, KFRE) including awareness of kidney function and feedback mechanisms	<i>“knowing like what your kidney was functioning at so that they could guide you on what you should be doing, you know, rather</i>	<i>“you can’t sense a lot of the problems that concern us prognostically, you can’t sense what your proteinuria is doing or your eGFR or often your blood pressure. And you’re much more</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>than like just going blind through it."</i> (PCP16, Female, 74 years)	<i>concerned about something that may even be unrelated to your renal disease which blights your life."</i> (HCP05, Female, Renal consultant) <i>"a lot of the time I think patients are not informed in a sort of understandable method about what their kidney function's like. Even if you phone up yourself for GP blood results you get, they're fine, they're normal or there's no change or something. That's not tangible for people. I think what they need to understand and there needs to be maybe more discussion about is like percentage function, or your percentage function is, or in keeping with your age. That's much more understandable for an individual."</i> (HCP15, Female, Renal specialist nurse)
	Impact on quality of life	<i>"(It matters most to) remain healthy and well-being as well not just physical health wellbeing and I look after my well-being and I'm conscious of that- that I'm not going to die before my father."</i> (PCP19, Female, 64 years)	<i>"quality of life's very important, but as you say very much depends on the person. Because, you know, it can be very different pictures for different people, and people have their own priorities of what they want to be able to do, you know. Sometimes living long enough to make a certain event is simply important to someone."</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
Evaluating what is important to the individuals			(HCP02, Female, GP)
	Individual priorities	<i>"That has really blown my mind how I can have normal kidneys and then deteriorate so quickly, and that's the thing on my mind the most. That's the forefront, kidneys, kidneys, kidneys, to the point where people forget that I've got rheumatoid but it's that that's caused the kidneys."</i> (SCP07, Female, 46 years)	<i>"I think I always find the reason why that's important, the reason why we care about that and we know what the implications of that could be and also the connection to other disease processes or illnesses they might have. Particularly where it can be asymptomatic for quite a period of time so to try and explain to someone if it's not something they're not feeling, what's going on and why we're bothered about it."</i> (HCP08, Female, GP)
	Ageing and changing over time	<i>"I can't be bothered to spend time getting new blood and as for a kidney donor by the time you find me one I would have popped my clogs, you know, it's no point. It is no point as far as I'm concerned. If I was much, much younger say 20 years younger that's different, but at this stage well, I mean, come on I'll be locking up glass soon."</i> (PCP02, Female, 84 years)	<i>"it is one of these silent illnesses for a lot of people. Particularly as they age as well, they'll say, it's down to this, I'm tired because I'm older and I think one of the things that stuck with me when I started this job, I went out to see somebody in their 90s and I think he had about 7% function of something but I said how do you feel and he said, well I don't know I've never been 90-odd before. So I feel 90-odds. So a lot of the symptoms can be explained away with other ailments and other illnesses or age. So I think it's trickier"</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
			<i>to get people to recognise symptoms for it as well.</i> (HCP15, Female, Renal specialist nurse)
	Utilisation of resources	<i>“I’m 65 this year, so I’m getting older, and as you get older, I’m going to get more issues... I’m here for a reason because I don’t feel fine, how are we going to deal with it? Don’t disregard it, just, let’s- the more systems we have, I think the more systems you have in place just now, then you’re reducing your need for operations because it’s something you can deal with there and then. You can say, right, just by changing something, that’s going help you, so that would work better for me.”</i> (PCP10, Male, 64 years) <i>“I’m concerned about the cost effectiveness of it (KRT) there’s no point in my stage of life to have all the expense.”</i> (PCP02, Female, 84 years)	<i>“secondary care is under so much stress and primary care starting to get that stress too, because people are living older, CKD is now recognised.”</i> (PCP19, Female, Practice nurse)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
	Differences in patients versus HCP focus	<i>"The trouble is, the more expert a person is in a particular area, the more they will focus on that particular area rather than the generality of treatment. So, you've got to allow understanding I think there. I think they've got to try and realise that they've got to have informed priorities."</i> (PCP07, Male, 91 years)	<i>"I think the patients understandably are sometimes more focused on symptoms than numbers and as a nephrologist, you're focused a lot on the numbers. So, for example, we might be more concerned about the blood pressure levels that they have, whereas the patient might be more concerned about the fact that they've got cramps or itch. So I think there's sometimes a disconnect there... And we specifically don't ask questions about things which we know are problematic because we know we're not good at treating them, so itch and fatigue."</i> (HCP12, Female, Renal specialist trainee)
	Self-care	<i>"I think like it's good having the information and knowing what you can do yourself to either prevent it or know if there's risks involved here that, you know that should I be looking for something or not."</i> (PCP03, Female, 65 years)	<i>"I think we could prevent or slow down the progression if we intervened beforehand and explained to them what they need to do about sorting things."</i> (HCP16, Female, Renal specialist nurse)
Modifying decisions & discussions based on reflections	Reviewing and adjusting decisions	<i>"it flags up where it's dropped down, you ask the next question, what's your lifestyle like just now,</i>	<i>"I have patients that have been focused on their function, their percentages and when they're getting</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>what are you doing, what's changed in your life? Has anything changed? Your dietary conditions, are you eating more, are you doing this, are you doing that? All right, and then okay, let's try not doing that for a wee while, and see if that builds it back up, or they might just say no, we've got an infection, let's just give you these antibiotics, whatever, to try and see if that levels off again."</i> (PCP10, Male, 64 years)	<i>near the end of their life I'm trying to steer them away from worrying about those factors and just focusing on how they are and how they're feeling, you need to take my bloods, I don't need to take your bloods because they're not really going to change how we manage things. So you've taught them all that for years and years and then I'm trying to unteach them at the end of their life not to worry so much about that so that's a different aspect to it."</i> (HCP15, Female, Renal specialist nurse)
	Seeking specialist or MDT care	<i>"I went to the hospital and they took more blood and then they kept the treatment liaising between the hospital and the doctor (GP) where I had to go to the doctor and they kept monitoring me."</i> (PCP04, Male, 75 years) <i>"they've got a pharmacist now in the practice, which I don't think they had years ago, and often, when there's something to do with mediations, he may have an idea and he'll say, 'I'll check that with</i>	<i>"we can contact secondary care for advice. It's not necessarily if we want their advice-based referral, but not necessarily this person needs an appointment because they're the people that are often really good at offering, and they're really helpful and they are very accessible."</i> (HCP08, Female, GP)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>the pharmacist and I'll come back to you on that."</i> (PCP12, Female, 73 years)	
Uncertainty	Awareness of CKD	<i>"It's never occurred to me that the kidney disease I had then- Well, that's another question. Do I still have it? Is it just in abeyance? So, that's the biggest question really. But it's never occurred to me that the problems with my heart or with my gut were related, so that's a question. Are they? Is it all part of the same thing?"</i> (PCP05, Female, 73 years)	<i>"if I see a new person in the kidney clinic, I always just go over, just let you know this is a kidney clinic, you've been referred up from your GP, you may not have any problems, it may just have been picked up on a blood test. And every now and again somebody says oh, I thought it was the whatever clinic, you know, a completely different one."</i> (HCP05, Female, Renal consultant)
	Symptoms	<i>"Could the kidney problems be causing tiredness as well?"</i> (SCP09, Male, 73 years) <i>"I would like to know more about it, but I can hardly discuss if I've not got any symptoms, you know, any problems, but I would like to know about it."</i> (PCP18, Female 85 years)	<i>"Sometimes they're bringing up symptoms that we personally don't think are anything to do with their kidney disease, but they're really important to them and they're worried that they might be because why would we expect them to know how kidney disease manifests?"</i> (HCP12, Female, Renal specialist trainee)
	Prognosis and trajectories	<i>"What are the likelihood of this going wrong at some stage in the future. Clearly it's necessary to</i>	<i>"I think as soon as you say you've got kidney disease, kidney failure is a possibility, it's well, when's that going</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		<i>keep my kidney function, as bad as it is, it's still effective enough to keep me alive and, so it would be interesting to know- I keep on asking them, and they never really tell me how long.</i> (SCP08, Male, 75 years)	<i>to happen? How much longer have I got?"</i> (HCP10, Female, Renal consultant) <i>"it's living with uncertainty as well isn't it and it's not exact prognostication that they can give, there's so many variables for people."</i> (HCP15, Female, Renal specialist nurse)
	Which LTC is causing the problem and interaction of different LTCs	<i>"I just wished somebody would tell me what was wrong with me."</i> (SCP12, Female, 73 years)	<i>"we don't know what comorbidities, apart from the very obvious ones, how that might impact on someone's kidney health and kidney experience like dialysis and stuff. So someone might have a terrible aortic stenosis but actually their function of the heart is fine so they'll be fine on dialysis until something catastrophic happens and that's probably quite a good experience for the person. Whereas someone who's got some chronic heart failure that's actually looking okay might really do very badly, we just don't really know. That's a real challenge, I find it's often then we have a perception that they're going to do very badly when we don't really know because of some</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
			<i>comorbidity, and so then makes the decision-making and informing the person really challenging. If you've got lots of comorbidities, you don't know how they're going to respond to whatever treatment it is, whether it's immunosuppression, dialysis or whatever, I think that's really difficult.</i> " (HCP13, Male, Renal specialist trainee)
	Predicting risk of kidney failure	<i>"what I know about my kidneys is that I've been told that it's at 22% normal function. If it goes below 10% I need dialysis or a transplant, but my question to you is how likely is that, will it definitely go below 10% definitely?"</i> (SCP06, Male, 60 years)	<i>"I show them a graphical representation of where I think their kidney function might be going and I show most patients in clinic to guide the discussions. And sometimes if I have time I kind of bring up the hypothetical things that might change in the future in terms of this is what we might be doing in terms of medications in the future, this is what we might be doing for blood pressure to let them know that this is a dynamic situation that might change...but I personally find a percentage number not a helpful bit of information to give because I don't think people take that onboard and they don't understand it. I see that when you calculate their QRISK for statins as well, I just think it's like a</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
			<i>hypothetical concept people can't grasp. Like what does it mean if I've got a 10% chance of this happening in five years? Whereas I think actually showing them their actual blood tests and how they've changed over time makes that a wee bit easier to understand."</i> <i>(HCP12, Female, Renal specialist trainee)</i>
	KFRE (reducing uncertainty)	<i>"I think that's probably a good tool for them. It's good for me to hear how they're assessing it when they say, 'This is-' It's not just a doctor looking at you going, 'Hmm, haw,' see what they think, but, 'I'm checking you on a standard basis.'"</i> <i>(PCP12, Male, 73 years)</i>	<i>"I think it is a helpful tool to highlight actually the risk to the kidney itself and have some way of conveying that level of risk to patients that, you know, this isn't just about your general cardiovascular disease health. It is about that, but it's also about the kidneys themselves and have a discussion that your kidney function can decline over time with age, but actually there are things that we can do to try and slow that decline. And it's highlighted it for us now and if we can give someone some numbers to try and convey that risk, although that's often a difficult thing in itself, like how do you do that? And we've already got little smiley faces for cardiovascular</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
			<i>disease risk and QRISK and ASSIGN Score, so that in itself is an issue.”</i> (HCP07, Male, GP) <i>“I’ve certainly used it in clinic, that does give some indication of the degree of threat that faces that particular patient.”</i> (HCP10, Female, Renal consultant)
	Decision-making	<i>“It’s the way that you feel having to tell somebody you’ve got this, and you don’t know what I can do about it.”</i> (PCP10, Male, 64 years)	<i>“What I do make them aware of is over time, if things change, we will have different discussions and possible different management plans.”</i> (HCP19, Female, Practice nurse)
	What kidney failure might entail	<i>“What exactly dialysis is. How long does it last. You know, is there a risk while you’re going through the dialysis, because I know that that’s a very high possibility. And I was just told that the doctors and that would keep my family informed, my next of kin informed, who is my own brother, you know that you’d be very truthful as to what was going on through the dialysis and you know what exactly it does you know with the blood and all that.”</i>	<i>“The most commonly asked question, how long will it be until I get to kidney failure? Surprisingly people don’t ask what else might happen to me before I get to kidney failure and I think that’s a very relevant question that the Kidney Failure Risk Equation doesn’t address the way it’s currently set up.”</i> (HCP10, Female, Renal consultant)

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		(SCP05, Female, 63 years)	
	Functional status	<i>"I'm not afraid of dying. I'm more afraid of being stuck in an old folks' home or a hospice and being in terrible... pain... But I don't want to be in pain."</i> (PCP09, Female, 74 years)	<i>"it can be very different pictures for different people, and people have their own priorities of what they want to be able to do, you know. Sometimes living long enough to make a certain event is simply important to someone. You know, it's amazing how personal goals, like, come out of nowhere, that you didn't expect people to say, so I think it's just what the patient wants."</i> (HCP03, Female, GP)
	Death and dying	<i>"I want to be there for my daughter, that's my main thing and I thought like last week I'm not going to be and that was hard."</i> (SCP07, Female, 46 years) <i>"When I feel so weak and wobbly, I'm very tired and lightheaded and I know I've got to go and have a lie down. I think, Oh right, I know the end is near. You know, it's not kind of depression, it's just the facts are all pointing that I'm towards the end of my life, which I know is realistic."</i>	<i>"It took me a long time to realise it, you can be in your 80s and you still haven't accepted the fact that you're going to die one day and there's still people out there absolutely terrified of dying, absolutely terrified."</i> (HCP16, Female, Renal specialist nurse)

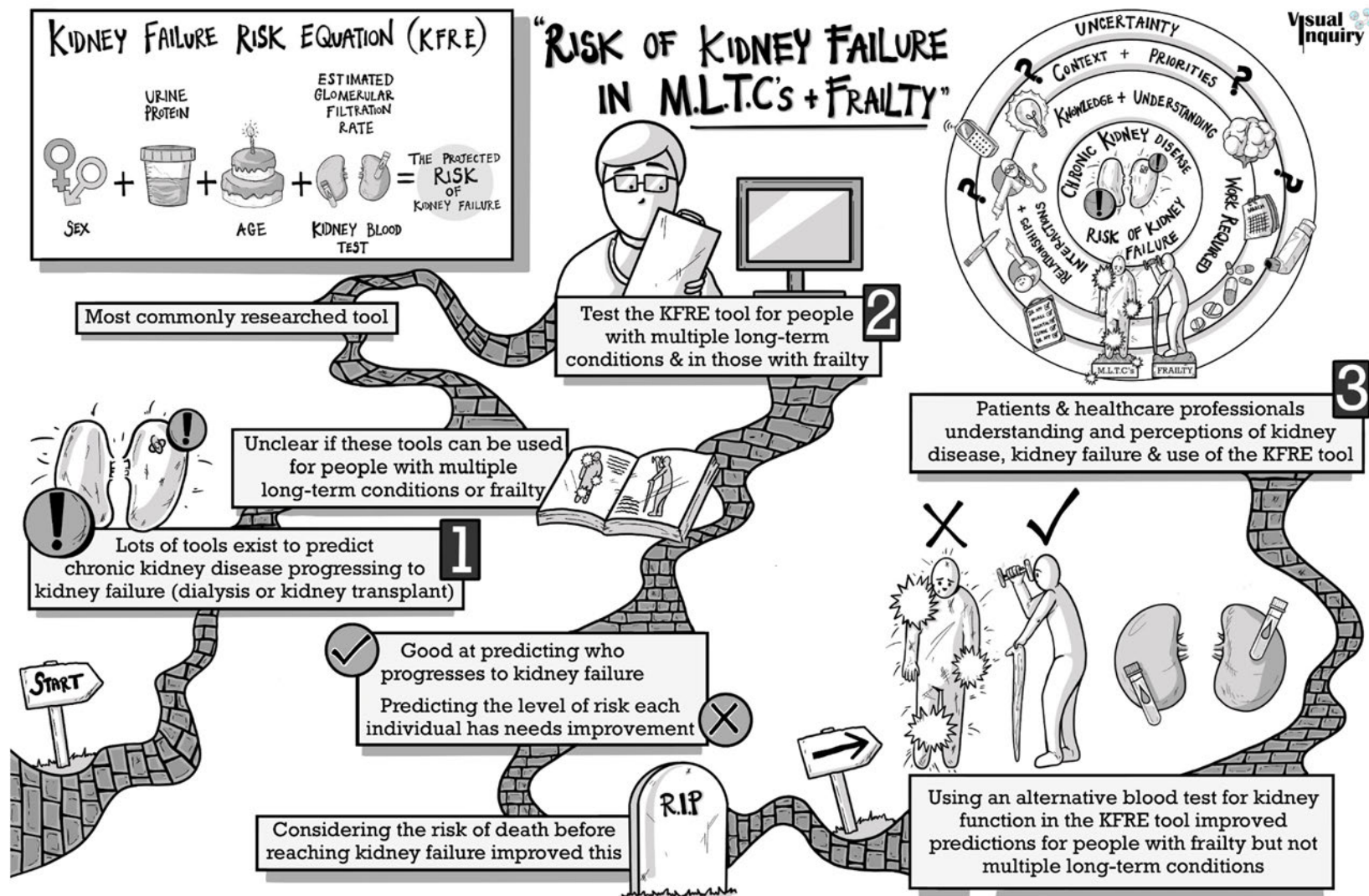
NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		(PCP08, Female, 84 years)	
Prioritisation of CKD	Symptoms/asymptomatic	<i>"As I say, right now I feel good. I've nothing wrong with me. I don't feel ill. Just keep taking the medication, hopefully I'm gonna be all right."</i> (SCP04, Male, 76 years)	<i>"because symptomatically they're not particularly bad and the fact that they've got urine analysis that has their blood and protein but they feel okay or their focus is on something else, it's not picked up."</i> (HCP14, Male, Renal specialist nurse)
	Other LTCs (priority or perceived as more life threatening)	<i>"They all play a part. But probably my heart because that's the biggest thing. That's your biggest organ, isn't it. Maybe it's not the biggest organ in your body, but it's the most important one."</i> (SCP03, Male, 58 years) <i>"I don't think I'd given the kidney disease possibility a high priority. I think other things are more likely."</i> (PCP08, Female, 84 years)	<i>"there is so little understanding both with patients and with non-nephrology specialists that the kidneys have a role not just in kidney health and keeping people off dialysis, but that there are implications for how they control other processes around the body that protect them from having other events, cardiovascular events, infections and things like that. And if those processes go wrong, the risk of all these other things increase so I think understanding a bit about the kidneys and the implications for when the kidneys go wrong."</i> (HCP10, Female, Renal consultant) <i>"I think people are quite often not very interested in chronic kidney disease. You know, if you tell them that they</i>

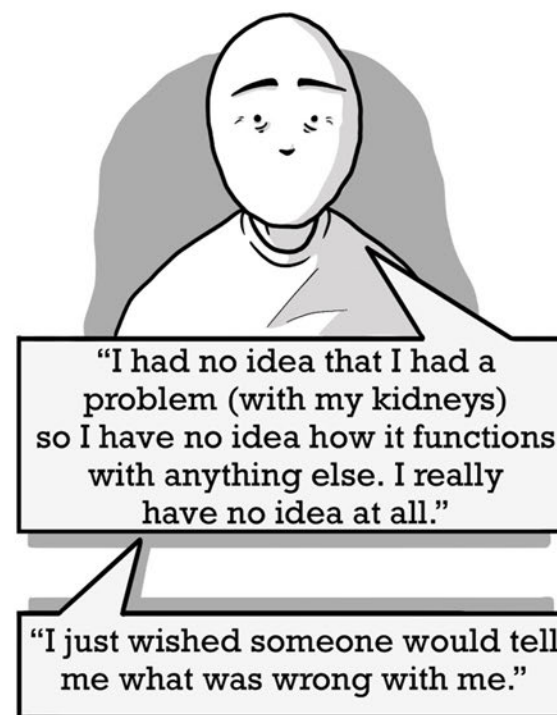
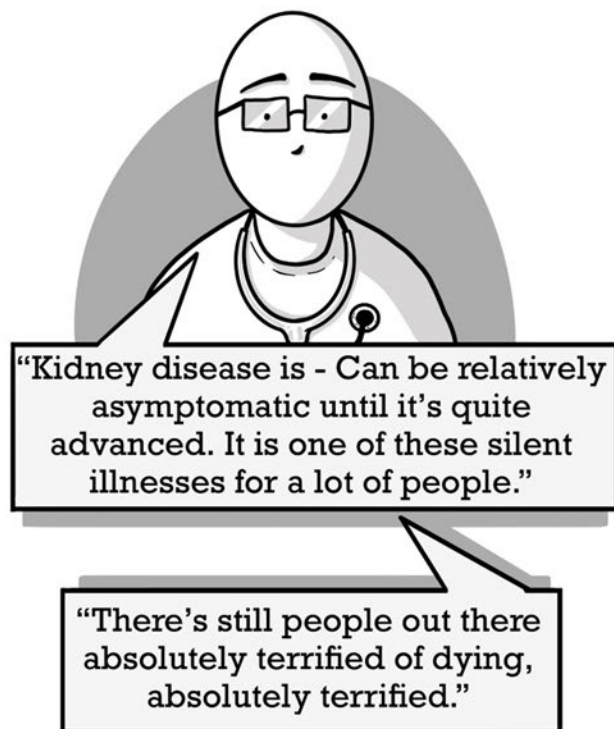
NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
			<i>have angina they're instantly panicked, but I just don't think people know much about chronic kidney disease."</i> (HCP02, Female, GP)
	Existing knowledge of the kidneys and CKD	<i>"My wife's family are all medical people, my daughter is also a consultant anaesthetist amongst other things, so that and I've always had some general interest in biophysics. In fact, I taught medical students when I was a lecturer at Edinburgh, so I know quite a bit about it."</i> (PCP07, Male, 91 years) <i>"she (my wife) was on dialysis all that time"</i> (SCP04, Male, 76 years)	<i>"I've not specifically sat down and been taught this is what you should be saying, what you shouldn't be saying, I've just kind of picked up from colleagues. I did do the NES general practice nurse course. They never actually covered CKD, they covered asthma, diabetes, COPD, they maybe touched on CKD, but I don't remember there actually being a module on it."</i> (HCP19, Female, Practice nurse)
	Awareness of having CKD	<i>"I didn't know I had kidney disease, nobody said to me you've kidney disease. I was quite surprised when I got the letter through the post that's what it's about. And obviously, maybe I should have known about that but- and then obviously the heart thing; that's a- these are all priority things, dangerous things that you think."</i>	<i>"I think what sometimes happens is that these patients sometimes get their CKD management piggybacked in on the top of another co-existing (disease), so I think they often sometimes the hypertension recall is a little bit better, diabetes recall is a little better. Say oh while you are here, we'll do your CKD while you're at it. I think it gets tagged on to another condition, far more commonly than some of the</i>

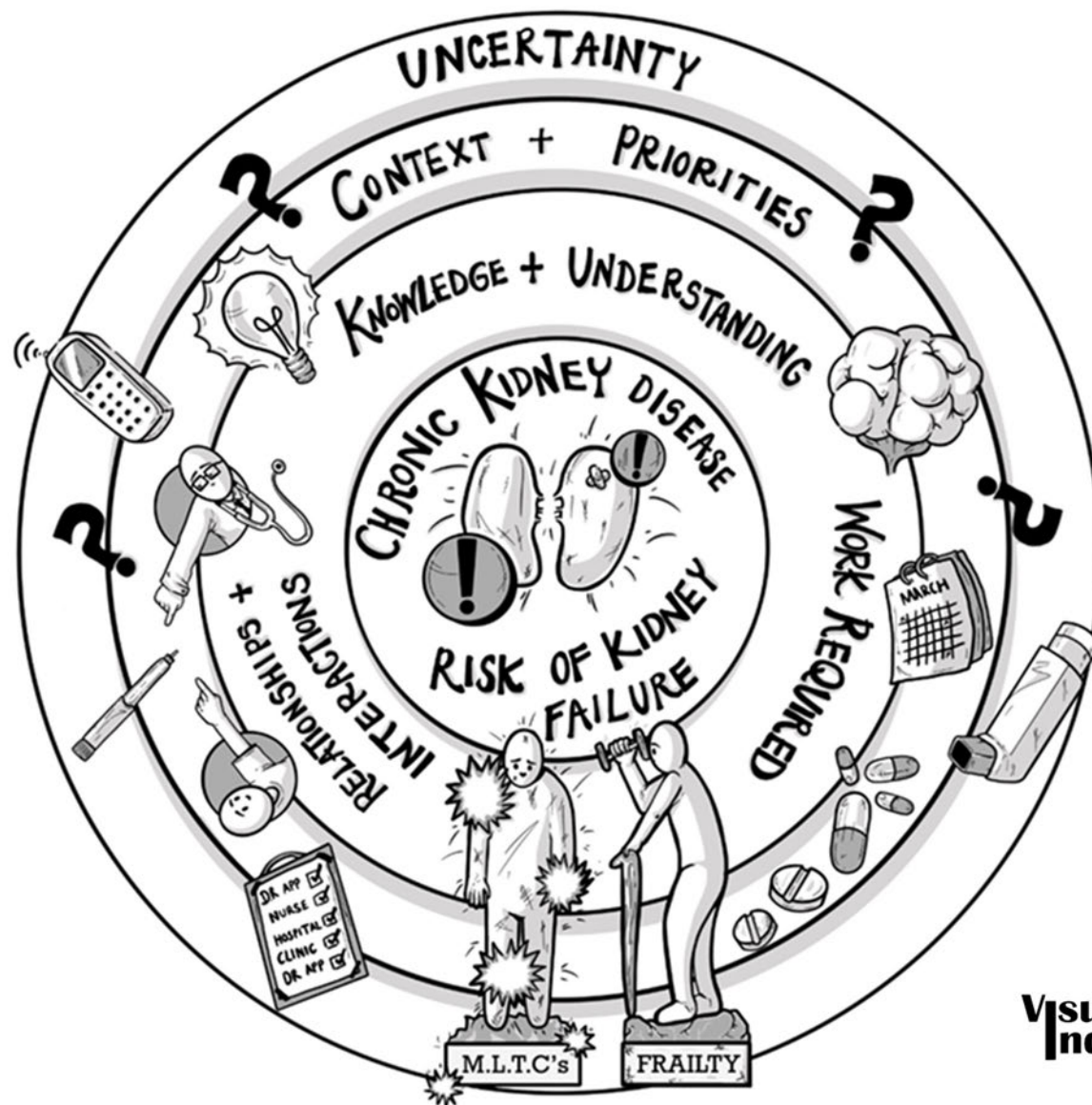
NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
		(PCP13, Male, 81 years)	<i>other ones do, because I don't think it's one of the big four or five.</i>" (HCP18, Male, GP) <i>"often patients, they don't pick up on the diagnosis, I don't know if it's because of how we tell them."</i> (HC07, Male, GP)
	Competing risk of death more likely than reaching kidney failure	<i>"Not at 63, I'm sorry, d'you know what I mean. I'm no interested. I'm gaun tae go anyway, you know, so just make me happy."</i> (SCP05, Female, 63 years)	<i>"sometimes they say, "I don't know why you're worrying about this, doctor," if we're looking at a graph and they say, "Because I don't think I'm going to be here in five years' time." And they're probably right, that's possible."</i> (HCP06, Female, Renal consultant)
	Prevention over cure	<i>"More knowledge so they could maybe just be on the verge of having a kidney problem and if it's caught early it could maybe save somebody all the grief that I went through."</i> (SCP12, Female, 73 years)	<i>"given the progression of people going on to dialysis is going to absolutely triple or whatever it is in the next 10 years seemingly, the projection. The focus surely should be on the preventative side in primary care."</i> (HCP14, Male, Renal specialist nurse) <i>"a lot of what we see is related to obesity, to type two diabetes which is a metabolic disorder, a lot of our patients then get on to have more evidence of hepatic dysfunction, and I think a lot of</i>

NPT Category and sub-construct	Description/examples	Supporting quotes	
		Patients	HCPs
			<i>our hypertensive diseases, it's all related. So if that could be treated early on, we wouldn't have to be doing what we're doing but that's the whole of healthcare, isn't it?</i> (HCP05, Female, Renal consultant)

Appendix 9: Graphical summary of work for dissemination activities







Visual Inquiry