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Accuracy of glomerular filtration rate estimation using creatinine and cystatin C for identifying and monitoring moderate chronic kidney disease: the eGFR-C study

Edmund J Lamb,[1*] Jonathan Barratt,[2] Elizabeth A Brettell,[3] Paul Cockwell,[4] R Neil Dalton,[5] Jon J Deeks,[3,6,7] Gillian Eaglestone,[8] Tracy Pellatt-Higgins,[9] Philip A Kalra,[10] Kamlesh Khunti,[11] Fiona C Loud,[12] Ryan S Ottridge,[3] Aisling Potter,[1] Ceri Rowe,[1] Katie Scandrett,[6] Alice J Sitch,[6,7] Paul E Stevens,[8] Claire C Sharpe,[13] Bethany Shinkins,[14] Alison Smith,[14] Andrew J Sutton[14] and Maarten W Taal[15]

[1]Clinical Biochemistry, East Kent Hospitals University NHS Foundation Trust, Canterbury, UK
[2]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
[3]Birmingham Clinical Trials Unit, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[4]Renal Medicine, Queen Elizabeth Hospital Birmingham and Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
[5]WellChild Laboratory, Evelina London Children's Hospital, St. Thomas' Hospital, London, UK
[6]Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[7]NIHR Birmingham Biomedical Research Centre, University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[8]Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust, Kent, UK
[9]Centre for Health Services Studies, University of Kent, Canterbury, UK
[10]Department of Renal Medicine, Salford Royal Hospital Northern Care Alliance NHS Foundation Trust, Salford, UK
[11]Diabetes Research Centre, University of Leicester, Leicester, UK
[12]Kidney Care UK, Alton, UK
[13]Faculty of Life Sciences and Medicine, King's College London, London, UK
[14]Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
[15]Department of Renal Medicine, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

[*]Corresponding author

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Abstract

Accuracy of glomerular filtration rate estimation using creatinine and cystatin C for identifying and monitoring moderate chronic kidney disease: the eGFR-C study

Edmund J Lamb[1*] Jonathan Barratt[2] Elizabeth A Brettell[3] Paul Cockwell[4] R Neil Dalton[5] Jon J Deeks[3,6,7] Gillian Eaglestone[8] Tracy Pellatt-Higgins[9] Philip A Kalra[10] Kamlesh Khunti[11] Fiona C Loud[12] Ryan S Ottridge[3] Aisling Potter[1] Ceri Rowe[1] Katie Scandrett[6] Alice J Sitch[6,7] Paul E Stevens[8] Claire C Sharpe[13] Bethany Shinkins[14] Alison Smith[14] Andrew J Sutton[14] and Maarten W Taal[15]

[1]Clinical Biochemistry, East Kent Hospitals University NHS Foundation Trust, Canterbury, UK
[2]Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
[3]Birmingham Clinical Trials Unit, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[4]Renal Medicine, Queen Elizabeth Hospital Birmingham and Institute of Inflammation and Ageing, University of Birmingham, Birmingham, UK
[5]WellChild Laboratory, Evelina London Children's Hospital, St. Thomas' Hospital, London, UK
[6]Test Evaluation Research Group, Institute of Applied Health Research, University of Birmingham, Birmingham, UK
[7]NIHR Birmingham Biomedical Research Centre, University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
[8]Kent Kidney Care Centre, East Kent Hospitals University NHS Foundation Trust, Kent, UK
[9]Centre for Health Services Studies, University of Kent, Canterbury, UK
[10]Department of Renal Medicine, Salford Royal Hospital Northern Care Alliance NHS Foundation Trust, Salford, UK
[11]Diabetes Research Centre, University of Leicester, Leicester, UK
[12]Kidney Care UK, Alton, UK
[13]Faculty of Life Sciences and Medicine, King's College London, London, UK
[14]Academic Unit of Health Economics, Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
[15]Department of Renal Medicine, University Hospitals of Derby and Burton NHS Foundation Trust, Derby, UK

[*]Corresponding author elamb@nhs.net

Background: Estimation of glomerular filtration rate using equations based on creatinine is widely used to manage chronic kidney disease. In the UK, the Chronic Kidney Disease Epidemiology Collaboration creatinine equation is recommended. Other published equations using cystatin C, an alternative marker of kidney function, have not gained widespread clinical acceptance. Given higher cost of cystatin C, its clinical utility should be validated before widespread introduction into the NHS.

Objectives: Primary objectives were to: (1) compare accuracy of glomerular filtration rate equations at baseline and longitudinally in people with stage 3 chronic kidney disease, and test whether accuracy is affected by ethnicity, diabetes, albuminuria and other characteristics; (2) establish the reference change

value for significant glomerular filtration rate changes; (3) model disease progression; and (4) explore comparative cost-effectiveness of kidney disease monitoring strategies.

Design: A longitudinal, prospective study was designed to: (1) assess accuracy of glomerular filtration rate equations at baseline (*n* = 1167) and their ability to detect change over 3 years (*n* = 875); (2) model disease progression predictors in 278 individuals who received additional measurements; (3) quantify glomerular filtration rate variability components (*n* = 20); and (4) develop a measurement model analysis to compare different monitoring strategy costs (*n* = 875).

Setting: Primary, secondary and tertiary care.

Participants: Adults (≥ 18 years) with stage 3 chronic kidney disease.

Interventions: Estimated glomerular filtration rate using the Chronic Kidney Disease Epidemiology Collaboration and Modification of Diet in Renal Disease equations.

Main outcome measures: Measured glomerular filtration rate was the reference against which estimating equations were compared with accuracy being expressed as P30 (percentage of values within 30% of reference) and progression (variously defined) studied as sensitivity/specificity. A regression model of disease progression was developed and differences for risk factors estimated. Biological variation components were measured and the reference change value calculated. Comparative costs of monitoring with different estimating equations modelled over 10 years were calculated.

Results: Accuracy (P30) of all equations was ≥ 89.5%: the combined creatinine–cystatin equation (94.9%) was superior ($p < 0.001$) to other equations. Within each equation, no differences in P30 were seen across categories of age, gender, diabetes, albuminuria, body mass index, kidney function level and ethnicity.

All equations showed poor (< 63%) sensitivity for detecting patients showing kidney function decline crossing clinically significant thresholds (e.g. a 25% decline in function). Consequently, the additional cost of monitoring kidney function annually using a cystatin C-based equation could not be justified (incremental cost per patient over 10 years = £43.32).

Modelling data showed association between higher albuminuria and faster decline in measured and creatinine-estimated glomerular filtration rate.

Reference change values for measured glomerular filtration rate (%, positive/negative) were 21.5/−17.7, with lower reference change values for estimated glomerular filtration rate.

Limitations: Recruitment of people from South Asian and African-Caribbean backgrounds was below the study target.

Future work: Prospective studies of the value of cystatin C as a risk marker in chronic kidney disease should be undertaken.

Conclusions: Inclusion of cystatin C in glomerular filtration rate-estimating equations marginally improved accuracy but not detection of disease progression. Our data do not support cystatin C use for monitoring of glomerular filtration rate in stage 3 chronic kidney disease.

Trial registration: This trial is registered as ISRCTN42955626.

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Report Supplementary Material 2 Health-economic analyses relating to Chapter 4

Supplementary material can be found on the NIHR Journals Library report page (https://doi.org/10.3310/HYHN1078).

Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

ACE	angiotensin-converting enzyme
ACR	albumin-to-creatinine ratio
AE	adverse event
AKI	acute kidney injury
A2RB	angiotensin 2 receptor blocker
BCTU	Birmingham Clinical Trials Unit
BIS	Berlin Initiative Study
BMI	body mass index
BP	blood pressure
BSA	body surface area
CAPA	Caucasian, Asian, paediatric and adult
CCB	calcium channel blocker
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease-Epidemiology Consortium
CV	coefficient of variation
CV_A	analytical variation
CV_G	interindividual (between-subject) variation
CV_I	intraindividual (within-subject) variation
EDTA	ethylenediaminetetraacetic acid
eGFR	estimated glomerular filtration rate
EKFC	European Kidney Function Consortium
ESKD	end-stage kidney disease
FAS	full age spectrum
FN	false negative
FP	false positive
GFR	glomerular filtration rate
GP	general practitioner
HTA	Health Technology Assessment
ID-MS	isotope dilution mass spectrometry
IQR	interquartile range
KDIGO	Kidney Disease Improving Global Outcomes
LMR	Lund–Malmö revised
LTFU	lost to follow-up
MDRD	Modification of Diet in Renal Disease
mGFR	measured glomerular filtration rate
MI	myocardial infarction
MIQUEST	Morbidity Information QUery and Export SynTax
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NKF-KDOQI	National Kidney Foundation – Kidney Disease Outcomes Quality Initiative
NPV	negative predictive value
P30	percentage of estimated GFR results within 30% of measured GFR
PPV	positive predictive value
RAAS	renin–angiotensin–aldosterone system
RCV	reference change value
RMSE	root mean square error
SAEs	serious adverse events
SGLT2	sodium-glucose cotransporter-2 inhibitor
TN	true negative
TP	true positive

Plain language summary

What is the problem?

Chronic kidney disease, which affects approximately 14% of the adult population, often has no symptoms but, in some people, may later develop into kidney failure. Kidney disease is most often detected using a blood test called creatinine. Creatinine does not identify everyone with kidney disease, or those most likely to develop more serious kidney disease. An alternative blood test called cystatin C may be more accurate, but it is more expensive than the creatinine test.

What did we do?

We compared the accuracy of these two tests in more than 1000 people with moderate kidney disease. Participants were tested over 3 years to see if the tests differed in their ability to detect worsening kidney function. We also wanted to identify risk factors associated with loss of kidney function, and how much the tests normally vary to better understand what results mean. We compared the accuracy and costs of monitoring people with the two markers.

What did we find?

Cystatin C was found slightly more accurate than the creatinine test at estimating kidney function when comparing the baseline single measurements (95% accurate compared to 90%), but not at detecting worsening function over time. This means that the additional cost of monitoring people over time with cystatin C to detect kidney disease progression could not be justified. Kidney test results could vary by up to 20% between tests without necessarily implying changes in underlying kidney function – this is the normal level of individual variation.

What does this mean?

Cystatin C marginally improved accuracy of kidney function testing but not ability to detect worsening kidney function. Cystatin C improves identification of moderate chronic kidney disease, but our results do not support its use for routine monitoring of kidney function in such patients.

Scientific summary

Background

Chronic kidney disease (CKD) is commonly identified using estimation of glomerular filtration rate (GFR) and/or detection of albuminuria [urinary albumin-to-creatinine ratio (ACR)]. Ideally, GFR is measured using reference procedures, but these are cumbersome and impractical for clinical practice. Estimation of GFR using equations based on serum creatinine with adjustments for age, gender and black ethnicity has been widely used. In the UK, the Modification of Diet in Renal Disease (MDRD) study equation and more recently the Chronic Kidney Disease Epidemiology Collaboration creatinine (CKD-EPI$_{creatinine}$) equation have been recommended. Other more recently published equations, including CKD-EPI cystatin C-containing equations (CKD-EPI$_{cystatin}$, CKD-EPI$_{creatinine\text{-}cystatin}$), the Berlin Initiative Study equations, the Caucasian, Asian, Pediatric and Adult equation, the Lund–Malmö revised equation, the full age spectrum equation, the European Kidney Function Consortium equation and the 2021 revisions of the CKD-EPI equations, have not yet gained widespread acceptance in clinical practice.

In addition to the accurate identification of CKD, the ability of tests to identify which individuals with CKD have higher risk of progressive or mortal disease is a crucial issue. Many people with stage 3 CKD are not at increased risk of CKD progression and there are concerns that CKD detection using creatinine-based approaches may identify some individuals who are at low risk and unlikely to benefit from active management. Equations utilising serum cystatin C, an alternative marker of GFR, instead of, or in addition to, creatinine have been proposed. Given the higher unit cost of cystatin C compared to creatinine, its diagnostic accuracy and clinical utility should be validated ahead of widespread introduction into the NHS.

Objectives

Primary objectives

The comparative performance of GFR-estimating equations in assessing and monitoring measured glomerular filtration rate (mGFR) in people with stage 3 CKD (GFR 30–59 ml/minute/1.73 m^2) was evaluated. The aims of the study were to:

1. estimate and compare the accuracy of the MDRD and three CKD-EPI equations
2. estimate the accuracy of the GFR-estimating equations according to ethnic group (particularly Caucasian, South Asian and African-Caribbean), baseline diabetes, albuminuria and other characteristics
3. evaluate and compare how accurately these GFR-estimating equations track and detect change in mGFR over 3 years
4. establish the biological variability of mGFR and estimated glomerular filtration rate (eGFR)
5. estimate which GFR-estimating equation, together with ACR, or ACR alone, most accurately predicts mortality and CKD progression
6. estimate and model disease progression (decline in GFR or increase in ACR) and differences in progression between ethnic groups (Caucasian, South Asian and African-Caribbean), baseline diabetes and albuminuria status and other potential risk factors
7. explore the comparative cost-effectiveness of monitoring strategies for identifying people who have CKD progression utilising different GFR-estimating equations.

Secondary objectives

1. Estimate and compare the accuracy of more recently published GFR-estimating equations.
2. Evaluate and compare how accurately these newer equations reflect and detect change in GFR over 3 years.

3. Estimate and compare the performance of the MDRD and CKD-EPI equations using the Haycock instead of the Du Bois equation for body surface area (BSA) adjustment.
4. Assess the impact of cystatin C calibration on the performance of the CKD-EPI equations.
5. Assess the impact of creatinine methodology [enzymatic vs. isotope-dilution mass spectrometry (ID-MS)] on the performance of the MDRD and creatinine-based CKD-EPI equations.

Methods

1. Main study. A 3-year prospective longitudinal cohort study using 6-monthly GFR estimates and baseline and final mGFR values was undertaken to assess and compare the accuracy of each estimate of GFR and change in GFR.
2. Substudy of disease progression. Predictors of progression of GFR in a subset of the cohort who received annual GFR measurements were modelled.
3. Substudy of biological variation. Components of variability in mGFR and eGFR were quantified.
4. An economic evaluation tested the consequences of implementing creatinine- and/or cystatin C-based eGFR for monitoring subjects who are initially stage 3 CKD.

Glomerular filtration rate was measured using iohexol clearance. Iohexol was measured by ID-MS. Creatinine was measured by a commercial enzymatic assay and by ID-MS. Cystatin C was measured by a commercial immunoassay. Both creatinine and cystatin C methods were internationally standardised.

Setting

Primary, secondary and tertiary care. Recruitment occurred across six centres in England.

Participants

Adults (≥ 18 years) with stage 3 CKD proportionally enriched to include people more likely to have progressive kidney disease (i.e. those with proteinuria and/or diabetes) and including South Asian and African-Caribbean people.

Interventions

Estimated GFR using the MDRD and three CKD-EPI equations, using either creatinine or cystatin C or a combination of both, in addition to urinary ACR. Other GFR-estimating equations were also studied.

Main outcome measures

Measured GFR was the reference test against which GFR-estimating equations were compared. Accuracy of GFR-estimating equations was expressed as P30, the percentage of estimated values within 30% of mGFR, with P30 ≥ 90% considered acceptable. P30 incorporates elements of bias and imprecision. The ability of eGFR equations to both track and detect change in mGFR over time gave an estimate of temporal error. For each individual, the average change per year in eGFR and mGFR was derived and error, the difference between the annual change in mGFR and eGFR, calculated. Large error was accepted as ≥ 3 ml/minute/1.73 m^2/year, or > 5%/year difference between mGFR and eGFR. Ability of equations to detect change was studied based on whether or not eGFR detected overall change, or decline only, in mGFR over 3 years against threshold changes variously defined as (1) > 10 ml/minute/1.73 m^2; (2) > reference change value (RCV) (a > 21.5% increase or a > 17.7%

decrease); (3) > 25% change; and (4) > 25% change and a change in disease stage. Sensitivity and specificity of eGFRs to identify progressive disease were evaluated. Estimated GFRs, in addition to urinary ACR, were also tested as predictors of progression and mortality.

In the substudy of disease progression the change in mGFR, and the difference between mGFRs and eGFRs (bias), assessed every 12 months, were modelled over time using a longitudinal linear random coefficients regression model, to estimate average and variability in disease progression and bias. A model of disease progression based on mGFR was developed and differences in progression for risk factors estimated.

In the biological variation substudy, analytical (CV_A) and individual (CV_I) components of variation were calculated and used to derive the RCV for significant changes in serial results for both mGFR and eGFR.

Results from the main study informed a measurement model analysis. The trajectory of participants mGFR and eGFR over 10 years was used to estimate the proportion meeting the National Institute for Health and Care Excellence (NICE) definition of accelerated progression or of progression to CKD stage G4, assuming an annual testing schedule, and the number of participants expected to be incorrectly managed at each of the evaluated monitoring time points using different estimating equations. Based on the findings, the comparative costs of monitoring with GFR-estimating equations were calculated.

Sample size

1. Main study. Complete baseline data *n* = 1167. Three-year follow-up GFR data *n* = 875.
2. Disease progression substudy. *n* = 278.
3. Biological variation substudy. *n* = 20.

Results

All estimates of GFR relating to the primary study objectives were negatively biased compared to mGFR. There was no difference in median bias (ml/minute/1.73 m^2) against mGFR between the MDRD (−3.7), CKD-$EPI_{creatinine}$ (−2.8), CKD-$EPI_{cystatin}$ (−4.1) and CKD-$EPI_{creatinine\text{-}cystatin}$ (−3.9) equations. Accuracy (P30) of the CKD-$EPI_{cystatin}$ equation (89.5%) did not differ from that of the MDRD (89.5%) and CKD-$EPI_{creatinine}$ (90.2%) equations: accuracy of the CKD-$EPI_{creatinine\text{-}cystatin}$ equation (94.9%) was superior ($p < 0.001$) to these equations. Similar performance characteristics were observed for more recently described GFR-estimating equations. Accuracy of cystatin C-containing equations was critically influenced by the commercial assay used, for example median bias of CKD-$EPI_{cystatin}$ equation changed from −9.8 to −4.1 when Siemens as opposed to Abbott assay was used, with a corresponding increase in P30 from 72.5% to 89.5%. To a lesser extent, a consistent positive bias (4.7 µmol/l) in the creatinine assay compared to the ID-MS reference method also increased the negative bias of GFR estimates.

P30 of eGFR equations was unaffected by whether mGFR was adjusted for BSA using the Du Bois or the Haycock equation. Nevertheless, use of Haycock-adjusted mGFR reduced negative bias of all GFR-estimating equations by approximately 1.4 ml/minute/1.73 m^2.

P30 of the main study GFR-estimating equations was examined by categories of age, gender, diabetes, albuminuria, body mass index (BMI), level of GFR and ethnic group: no significant differences were seen across any of these categories for any of the study equations. Interpretation of accuracy data across ethnic groups was limited by the small sample size of South Asian (*n* = 66) and African-Caribbean (*n* = 60) groups. However, removal of the African-Caribbean adjustment factor from the MDRD and CKD-$EPI_{creatinine}$ equations led to reduced point estimates of accuracy amongst African-Caribbean individuals (e.g. P30 for the CKD-$EPI_{creatinine}$ equation decreased from 81.7% to 70.0%).

When monitoring changes in GFR over time, all GFR equations tended to underestimate GFR decline. In relation to the tolerance limits (± 3 ml/minute/1.73 m^2/years or ± 5%/years) of the slope of change for mGFR, equations achieved > 70% concordance. The CKD-EPI$_{creatinine-cystatin}$ equation had better concordance than the other three primary study equations ($p < 0.05$ for ± 3 ml/minute/1.73 m^2/years), although confidence intervals overlapped in all cases. All newer equations that incorporated both creatinine and cystatin C also achieved higher point estimates of agreement than their corresponding creatinine-only equations.

In relation to detection of decline in mGFR, irrespective of which threshold change was studied, while the specificity of GFR-estimating equations was reasonable (> 83% in all cases), sensitivity for detecting change was < 63% in all cases. There was no clear difference in sensitivity or specificity between the four main study equations. For all equations and all thresholds, there was no clear evidence of improved performance of cystatin-containing equations compared to their matched creatinine-only equation.

In the substudy of disease progression, modelling data showed a strong association between albuminuria status and rate of progression in mGFR and CKD-EPI$_{creatinine}$ eGFR, with those with albuminuria having faster progression (steeper decline). Higher baseline mGFR values were associated with faster progression rate for mGFR. African-Caribbean ethnicity increased (slower decline) and South Asian ethnicity decreased (faster decline) the estimate of progression slope for mGFR and CKD-EPI$_{creatinine}$ GFR. However, recruitment of ethnic minority participants in particular to the substudy fell short of target, limiting the strength of any conclusions.

Within-subject biological variation of mGFR was 6.7%, with similar, although in some cases significantly lower, biological variation of eGFR (5.0, 5.3, 5.3 and 5.0% for MDRD, CKD-EPI$_{creatinine}$, CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine-cystatin}$ equations, respectively). Derived RCVs (%, positive/negative) were 21.5/−17.7 (mGFR), 15.1/−13.1 (MDRD), 15.9/−13.7 (CKD-EPI$_{creatinine}$), 15.9/−13.8 (CKD-EPI$_{cystatin}$) and 15.1/−13.1 (CKD-EPI$_{creatinine-cystatin}$).

We observed 62 deaths during the 3-year follow-up period. The study was not powered for hard end points. However, in agreement with earlier studies, regression models including each GFR-estimating equation separately demonstrated mortality was associated with lower eGFR, increasing age and male gender. An association with categorical albuminuria was not observed. There was no evidence of superiority of CKD-EPI equations, including the cystatin C-containing equations, as predictors of death compared to the MDRD equation.

A measurement model analysis found no evidence to suggest that any of the estimating equations were superior for identifying CKD progression based on NICE-defined clinical end points. The average incremental per patient costs (compared to MDRD) of monitoring over a 10-year period using the cystatin C-based equations were estimated (CKD-EPI$_{cystatin}$ £42.20; CKD-EPI$_{creatinine-cystatin}$ £43.32).

Conclusions

Most GFR equations achieved acceptable accuracy as judged by P30. There was little difference between the equations in accuracy, with evidence of superior accuracy for the CKD-EPI$_{creatinine-cystatin}$ equation. Across several important characteristics (age, gender, diabetes, albuminuria, BMI, GFR level) we found no difference in accuracy of GFR-estimating equations. In relation to GFR estimation in African-Caribbean individuals, there was evidence to suggest caution should be exercised before advocating simple removal of the black race factor from the original CKD-EPI equations.

In the longitudinal study, the CKD-EPI$_{creatinine-cystatin}$ displayed slightly better concordance with mGFR than the other main study equations when tracking patients, but all study equations underestimated the mGFR decline. The sensitivity of GFR equations to detect clinically relevant threshold changes in mGFR,

either overall or when considering decline in GFR only, was ≤ 63% for all equations. This is of concern given that such thresholds, including the NICE definition of accelerated progression and the change recognised as being true as determined by biological variation (RCV), were studied.

Overall, data comparing the accuracy of different GFR-estimating equations demonstrated no notable benefit of using a cystatin C-containing equation in detecting GFR change. The measurement model underpinning the health economic analysis focused on the comparative accuracy of the estimating equations to detect accelerated progression. The analysis estimated accuracy over a longer trajectory than the main study and factored in measurement error, but found no clear benefit of using a cystatin C-based estimating equation. There was therefore no evidence to suggest that adding cystatin C measurement to current GFR monitoring protocols would be cost-effective.

The disease progression modelling of the substudy data noted faster progression associated with higher baseline GFR and albuminuria; the latter consistent with other studies. Any conclusions relating to the influence of ethnicity were tempered by poor recruitment of ethnic minority individuals.

The biological variability data have implications for monitoring of patients with CKD and clinical ability to understand CKD progression, both in clinical practice and research. The information presented provides an evidence base allowing clinicians to have meaningful discussions with their patients about the implications of changes in their GFR results.

Inclusion of cystatin C in GFR-estimating equations was associated with marginal improvements in accuracy, but no clear advantages in terms of detecting GFR change over time. Problems of standardisation of cystatin C assays remain, despite the introduction of an international standard. The use of cystatin C increases the economic cost of CKD monitoring with little apparent gain. These data do not support the use of cystatin C for the routine monitoring of GFR in people with stage 3 CKD. Further research is warranted to investigate specific patient groups that may benefit from cystatin C use.

Trial registration

This trial is registered as ISRCTN42955626 www.controlled-trials.com/ISRCTN42955626 (accessed 26 July 2023).

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Chapter 1 Introduction

Background and rationale

Globally, the overall prevalence of all stages of chronic kidney disease (CKD) is estimated to be 9%. In the UK a model developed using data from the Health Survey for England– 2009 and 2010 and the 2011 Census predicted the prevalence of CKD stages 3–5 [glomerular filtration rate (GFR) < 60 ml/minute/1.73 m^2] in people aged 16 years and older to be 6.1% (2.6 million people).[1] The prevalence was higher in women than in men (7.4% vs. 4.7%) and there was a clear association between increasing age and prevalence. Overall, prevalence increased from 0.1% in people aged 16–34 years to 32.7% in those aged 75 years and over. Based on the projected population increase and assuming no change in the age-specific prevalence of CKD stages 3–5 and no improvement in the prevention and management of CKD stages 3–5, estimates of CKD prevalence are expected to increase to 8.3% of the population by 2036, representing roughly 4.2 million people.

The progression of CKD to kidney failure requiring consideration of kidney replacement therapy (dialysis and/or transplantation) is associated with a huge physical and mental health burden for individuals affected, including premature morbidity and mortality. There are also significant social and economic burdens for those individuals, their families and communities and the NHS. Data from the latest report from the UK Renal Registry suggest that the current rates of kidney replacement treatment are between 110 and 150 per million population per year.[2] Department of Health estimates of the annual cost of kidney failure treatment in England were approximately £1.5 billion in 2012 and were predicted to rise to £3.2 billion by 2027.[3] A secondary analysis of 7246 patients (2498 on dialysis) with moderate-to-severe CKD contributing 28,261 years of patient data from the Study of Heart and Renal Protection randomised trial has also been used to model costs.[4] Inclusion of non-fatal cardiovascular events, deaths, all hospital admissions, routine dialysis treatments and recorded outpatient/day-case attendances in UK 2011 prices led to estimates that those on maintenance dialysis incurred annual hospital costs of £18,986 in the year of initiation and £23,326 annually thereafter. Patients with a functioning kidney transplant incurred hospital care costs of £24,602 in the year of transplantation and £1148 annually thereafter. Non-fatal major vascular events increased annual costs in the year of the event by £6133 for patients on dialysis and by £4350 for patients not on dialysis.

Research has demonstrated that increasing severity of CKD is associated with greater risk for adverse outcomes which include cardiovascular disease, acute kidney injury (AKI), mortality (both all-cause and cardiovascular) as well as progression of CKD to kidney failure.[5–8] The increased risk for CKD progression in adults is driven by common, potentially modifiable risk factors, such as hypertension, diabetes and obesity as well as less modifiable genetic risk factors such as renin–angiotensin–aldosterone system (RAAS) genes.[9] Earlier recognition of CKD and improved identification of those at risk of adverse outcomes would enable earlier intervention, improved outcomes and avoidance of unnecessary costs. Blood pressure (BP) control and treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin 2 receptor blockers (A2RBs) have renoprotective benefits in people with CKD, particularly in those with diabetes and albuminuria[10–12] but also in non-diabetic nephropathy.[13] A subsequent cost-effectiveness study suggested that ramipril delayed progression to kidney failure and prolonged patient survival by 1.5–2.2 and 1.2–1.4 years, respectively, and saved US$16,605–23,894 lifetime and US$2422–4203 annually direct costs per patient.[14]

More recently, a number of large placebo-controlled randomised controlled trials have shown that treatment with sodium-glucose cotransporter-2 (SGLT2) inhibitors in people with CKD not only substantially reduces the risk of kidney failure, AKI and hospitalisation for heart failure, but also moderately reduces the risk of cardiovascular death and myocardial infarction (MI).[15–19] Data on lifetime benefits for people with CKD suggest that treatment with a combination of ACE inhibitors/A2RBs and

SGLT2 inhibitors in patients with albuminuric CKD without diabetes is expected to substantially increase kidney failure-free survival.[20] For a 50-year-old patient until the age of 75 years, the estimated survival free from kidney failure or death was 17.0 [95% confidence interval (CI), 12.4 to 19.6] years with the combination therapy and 9.6 (95% CI, 8.4 to 10.7) years with no treatment with any of these agents.

Chronic kidney disease is commonly identified using estimation of GFR and/or detection of protein in the urine (albuminuria/proteinuria). GFR is accepted as the best overall measure of kidney function and is central to diagnosis, staging and management of CKD. Ideally, GFR is measured using reference procedures which follow the clearance of an infused exogenous substance [e.g. inulin, ^{125}I-iothalamate, ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) or iohexol] which is neither reabsorbed from nor secreted into the renal tubule.[21] However, these methods are cumbersome and impractical for general kidney disease detection, monitoring and management. Estimation of GFR [estimated glomerular filtration rate (eGFR)] using equations based on serum creatinine with adjustments for age, gender and, until recently, black ethnicity has been widely used as surrogate measures of GFR. In England, the National Institute for Health and Care Excellence (NICE) have made recommendations regarding which individuals should be tested for the presence of CKD (e.g. those with diabetes or hypertension) and have stated that GFR should be estimated 6-monthly in people with stage 3 CKD (GFR 30–59 ml/minute/1.73 m^2),[22] comprising approximately 6–7% of the overall UK population.[23,24] (Note that the International CKD staging system actually requires knowledge of both GFR and albuminuria to define stage. In this report, stage 3 CKD refers to all individuals with a GFR of 30–59 ml/minute/1.73 m^2 irrespective of albuminuria status.) The aim of disease detection is to identify and manage individuals at increased risk of progression to kidney failure (GFR < 15 ml/minute/1.73 m^2) and/or increased risk of morbidity and mortality compared to individuals without CKD. In addition to the accurate identification of CKD, the ability of tests to identify which individuals with CKD have higher risk of progressive or mortal disease is a crucial issue. Many people with stage 3 CKD are not at increased risk of progressive disease and there are concerns that CKD detection using creatinine-based approaches may be identifying some individuals who are at low risk and unlikely to benefit from active management.[25]

Creatinine has many limitations as a marker of kidney function, including its relationship to muscle mass and age, and susceptibility of its measurement to analytical, drug and dietary interferences. An alternative marker of GFR, cystatin C, is less susceptible to the problems affecting creatinine measurement and interpretation of creatinine results. Early studies demonstrated the superiority of cystatin C measurement compared with creatinine for the detection of kidney disease.[26] Equations utilising serum cystatin C instead of, or in addition to, creatinine have been studied. Generally, such equations have demonstrated modest improvement in accuracy for estimating GFR compared to creatinine-only equations.[27,28] Furthermore, accumulating evidence suggests that cystatin C gives improved risk prediction for death and kidney failure compared to creatinine.[29,30] However, there have been no large, prospective studies of the value of cystatin C to identify and track changes in kidney function in a representative population of NHS patients. Given the higher costs of cystatin C compared to creatinine (approximately £3.80/test compared to £0.43/test for creatinine) and the scale of testing across the NHS, it is critical that its diagnostic accuracy and prognostic ability are carefully validated ahead of widespread introduction into the NHS.

Measuring glomerular filtration rate

Standard clearance of inulin, including urine collection, remains the ‘gold-standard’ method for GFR measurement but few studies use this. Most evaluations of GFR equations have used radiolabelled plasma clearance methods which are assumed to be closely related to inulin clearance. Radiolabelled iothalamate plasma clearance was the method used for developing estimating equations that are the standard of care in routine clinical practice, the Modification of Diet in Renal Disease (MDRD) study[31] and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[32] GFR-estimating equations (see below), while the CKD-EPI equation validation data set used a variety of reference GFR methods

including iohexol.[32] Although regarded as the reference approach for assessment of kidney function, it is increasingly appreciated that non-inulin plasma clearance methods are not all equivalent.[33] Furthermore, as with any physiological measurement, GFR has an intrinsic biological variability, an understanding of which is critical to appreciation of disease-related change. Using a variety of reference markers, values (coefficient of variation, CV%) ranging between 5.5% and 11.6% have been reported for the biological variation of GFR.[34] However, most of these estimates were from older studies that did not conform to recommended processes for deriving and reporting biological variation estimates.[35,36]

Estimating glomerular filtration rate

A variety of equations have been developed to estimate GFR (*Table 1*). The MDRD Study equation, which estimates GFR adjusted for body surface area (BSA), was originally developed in 1999.[31] A simplified ('4-variable') version of the equation which requires knowledge only of serum creatinine concentration, age, gender and race (black or other) was later published and subsequently re-expressed for use with a standardised serum creatinine assay.[37,38] Generally, the MDRD equation has been seen to perform better, and offer practical advantages, over other GFR equations that had been used previously. Its use has been endorsed by national professional healthcare organisations including in the UK.[39,40] However, accuracy of the equation is suboptimal. In the CKD field, accuracy of GFR-estimating equations is commonly expressed as the P30, the percentage of eGFR values within 30% of 'true' GFR. This metric captures aspects of both imprecision (measurement error) and bias (systematic over- and/or underestimation). Reported P30 values for the MDRD equation typically range between 73% and 93%.[41] The MDRD equation has also been criticised on the basis that it significantly underestimates GFR (particularly in individuals with GFR > 60 ml/minute/1.73 m^2) and has poor precision.[32]

An alternative equation, the CKD-EPI$_{creatinine}$ equation, was published in 2009 and is claimed to partially address this issue, producing less biased estimates of GFR at higher levels of kidney function,[32] although reportedly less accurate estimates as GFR falls below 60 ml/minute/1.73 m^2.[41] P30 values for the CKD-EPI$_{creatinine}$ equation are slightly superior to those of the MDRD equation in studies that have undertaken a head-to-head comparison.[41] The NICE CKD guidance first published in 2008 recommended the MDRD equation for routine clinical care. The guidance was updated in 2014 and this recommendation was changed to the CKD-EPI equation, a recommendation that was continued in the 2021 CKD guideline. However, currently many laboratories in England continue to report eGFR using the MDRD equation.

Cystatin C, a small-molecular-weight protein, has been proposed as an improved marker of GFR compared to creatinine.[49,50] In 2010 an international standard for cystatin C became available which paved the way for the development of generalisable cystatin C-based GFR-estimating equations, either alone or in conjunction with creatinine.[51] Following publication of the original CKD-EPI$_{creatinine}$ equation, the CKD-EPI Collaboration published two further CKD-EPI equations: one based on cystatin C (CKD-EPI$_{cystatin}$) and one using both cystatin C and creatinine (CKD-EPI$_{creatinine\text{-}cystatin}$).[28] Members of the current study group have independently validated the latter equations in older people in the UK.[52]

During the period of the current study, further equations have been published and validated, including the Berlin Initiative Study (BIS) equations BIS1 (creatinine-based) and BIS2 (creatinine and cystatin C based),[42] the Lund–Malmö revised (LMR) equation,[53] the Caucasian, Asian, Pediatric and Adult (CAPA) equation,[43] the full age spectrum creatinine (FAS$_{creatinine}$)[44] and FAS$_{creatinine\text{-}cystatin}$ equations,[45] the European Kidney Function Consortium (EKFC) equation,[47] and recently in 2021 revised versions of the CKD-EPI equations [CKD-EPI(2021)$_{creatinine}$ and CKD-EPI(2021)$_{creatinine\text{-}cystatin}$].[48] These equations are described in further detail later.

TABLE 1 Equations used to eGFR

Abbreviation	GFR equation expressed as a single equation
MDRD[38]	GFR (ml/minute/1.73 m^2) = 175 × (SCr × 0.01131)$^{-1.154}$ × (age)$^{-0.203}$ × (1.212 if patient is black) × (0.742 if patient is female)
CKD-EPI$_{creatinine}$[32]	GFR (ml/minute/1.73 m^2) = 141 × min(SCr × 0.01131/κ, 1)$^{\alpha}$ × max(SCr × 0.01131/κ, 1)$^{-1.209}$ × 0.993^{age} × 1.018 (if female) × 1.159 (if black), where SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1
CKD-EPI$_{cystatin}$[28]	GFR (ml/minute/1.73 m^2) = 133 × min(SCys/0.8, 1)$^{-0.499}$ × max(SCys/0.8, 1)$^{-1.328}$ × 0.996^{Age} × 0.932 (if female), where min indicates the minimum of SCys/κ or 1, and max indicates the maximum of SCys/κ or 1
CKD-EPI$_{creatinine\text{-}cystatin}$[28]	GFR (ml/minute/1.73 m^2) = 135 × min(SCr × 0.01131/κ, 1)$^{\alpha}$ × max(SCr × 0.01131/κ, 1)$^{-0.601}$ × min(SCys/0.8, 1)$^{-0.375}$ × max(SCys/0.8, 1)$^{-0.711}$ × 0.995^{Age} × 0.969 (if female) × 1.08 (if black), where SCr is serum creatinine, SCys is serum cystatin C, κ is 0.7 for females and 0.9 for males, α is −0.248 for females and −0.207 for males, min indicates the minimum of SCr/κ or 1, and max indicates the maximum of SCr/κ or 1
BIS1$_{creatinine}$[42]	GFR (ml/minute/1.73 m^2) = 3736 × (SCr × 0.01131)$^{-0.87}$ × age$^{-0.95}$ × 0.82 (if female)
BIS2$_{creatinine\text{-}cystatin}$[42]	GFR (ml/minute/1.73 m^2) = 767 × SCys$^{-0.61}$ × (SCr × 0.01131)$^{-0.40}$ × age$^{-0.57}$ × 0.87 (if female)
CAPA$_{cystatin}$[43]	GFR (ml/minute/1.73 m^2) = 130 × SCys$^{-1.069}$ × age$^{-0.117}$ −7
FAS$_{creatinine}$[44]	GFR (ml/minute/1.73 m^2) = 107.3/(SCr/Q) for 2 ≤ age ≤ 40 GFR (ml/minute/1.73 m^2) = [107.3/(SCr/Q)] × 0.988$^{(age-40)}$ for age > 40 where Q values are the mean or median serum creatinine concentration for age-/sex-specific healthy reference populations
FAS$_{creatinine\text{-}cystatin}$[45]	$FAS_{combi} = \frac{107.3}{\alpha \times \frac{Scr}{Q_{crea}} + (1-\alpha) \times \frac{ScysC}{Q_{cysC}}} \times \left[0.988^{(Age-40)} \text{ when age } 40 \text{ years}\right]$. where Q values are the mean or median serum creatinine or cystatin C concentration for age-/sex-specific healthy reference populations. When α = 0.5, the denominator is equal to the weighted average of the two normalised biomarkers
LMR$_{creatinine}$[46]	eX − 0.0158 × age + 0.438 × ln(age), where X varies by gender and serum creatinine concentration (refer to paper)
EKFC$_{creatinine}$[47]	GFR (ml/minute/1.73 m^2) = 107.3 × (SCr/Q)$^{-0.322}$ for age 2–40 and SCr/Q < 1 GFR (ml/minute/1.73 m^2) = 107.3 × (SCr/Q)$^{-1.132}$ for age 2–40 and SCr/Q ≥ 1 GFR (ml/minute/1.73 m^2) = 107.3 × (SCr/Q)$^{-0.322}$ × 0.990$^{(Age\ -\ 40)}$ for age > 40 and SCr/Q < 1 GFR (ml/minute/1.73 m^2) = 107.3 × (SCr/Q)$^{-1.132}$ × 0.990$^{(Age\ -\ 40)}$ for age > 40 and SCr/Q ≥ 1 where Q values are the mean or median serum creatinine concentration for age-/gender-specific healthy reference populations
CKD-EPI(2021)$_{creatinine}$[48]	GFR (ml/minute/1.73 m^2) = 142 × min(Scr/κ,1)$^{\alpha}$ × max(Scr/κ,1)$^{-1.200}$ 0.9938^{age} × 1.012 (if female), where Scr is serum creatinine, κ is 0.7 for females and 0.9 males, α is −0.241 for females and −0.302 for males, min indicates the minimum of Scr/κ or 1, max indicates the maximum of Scr/κ or 1
CKD-EPI(2021)$_{creatinine\text{-}cystatin}$[48]	GFR (ml/minute/1.73 m^2) = 135 × min(Scr/κ,1)$^{\alpha}$ × max(Scr/κ,1)$^{-0.544}$ × min (Scys/0.8,1)$^{-0.323}$ × max(Scys/0.8,1)$^{-0.778}$ × 0.9961^{age} × 0.963 (if female), where Scr is serum creatinine Scys is serum cystatin C, κ is 0.7 for females and 0.9 males, α is −0.219 for females and −0.144 for males, min indicates the minimum of Scr/κ or 1, max indicates the maximum of Scr/κ or 1

Note
Age is given in years, SCr in μmol/l, SCys in mg/l, weight in kilograms.

Estimating glomerular filtration rate in British ethnic minority populations

People from South Asian and African-Caribbean backgrounds are at a three- to fivefold increased risk of developing established kidney failure requiring transplantation or dialysis compared to Caucasians. However, the proportion of the population from South Asian and African-Caribbean backgrounds with an eGFR of < 60 ml/minute/1.73 m^2 is not similarly over-represented at a population level.[54] There is debate regarding whether individuals of South Asian and African-Caribbean ethnic backgrounds are at higher risk of CKD progression compared to Caucasians.[55–58] People of South Asian and African-Caribbean ethnicity are also less likely to undergo kidney transplantation when they reach established kidney failure and are at greater risk of complications from diabetes and high BP than the rest of the population.

The black race adjustment factors in the CKD-EPI and MDRD equations were founded on the premise that the relationship between serum creatinine concentration and kidney function is different amongst people of black ethnicity. Creatinine concentration is positively related to muscle mass and the historical assumption has been that individuals of black ethnicity will have a higher serum creatinine concentration at any given level of GFR due to increased muscle mass. Hence, two inflationary adjustment factors have been included: 1.212 in the MDRD equation and 1.159 in the $CKD\text{-}EPI_{creatinine}$ equation (*Table 1*). In the development of these equations, predominantly in North American cohorts, use of these adjustment factors improved the agreement between mGFR ('true') and eGFR.

When widespread use of GFR estimation was first introduced into the UK (and other countries), it was recommended that the same adjustment factors for people of black ethnicity should be applied to African-Caribbean individuals in the UK, although the lack of UK evidence supporting this was acknowledged. NICE have recently reviewed the evidence in this area.[59] While GFR-estimating equations have been validated in African-Caribbean communities from North America[60] and endemic Asian populations,[61–66] there remains no independent validation in British South Asian or African-Caribbean populations.[59] There is increasing concern, both in the UK and elsewhere,[67] that GFR adjustment may have contributed to falsely high GFR estimations amongst people of black ethnicity, potentially exacerbating pre-existing inequalities in access to health care in some individuals (e.g. access to certain drugs that are prescribed based on GFR level, access to advanced kidney care planning).

Adjusting GFR estimations for black ethnicity/race assumes that all individuals self-identifying as black share the same ancestry. There is increasing concern that the adjustment for ethnicity does not reflect the wide diversity within individuals of black ethnicity, with the adjustment based on outdated and unfounded biological assumptions for differences between ethnic groups at the expense of better understanding of social (e.g. dietary), environmental and ancestral (e.g. accuracy of self-reported ethnicity amongst individuals of mixed race) determinants. For some individuals of black ethnicity, such adjustment could lead to an overestimation of their GFR levels, and potential inequality in delivery of care. In the 2021 NICE CKD guideline the recommendation to adjust for ethnicity, present in earlier versions, was removed on the basis that adjusting for ethnicity when estimating GFR may not be valid or accurate.[59] The guideline committee recommended further research to establish, in adults, children and young people from black, Asian and other minority ethnic groups with CKD living in the UK, which existing GFR estimations are the most accurate.[59]

Progression of kidney disease

There is no consistent definition of what constitutes progression of kidney disease. Many studies have used a doubling of serum creatinine, corresponding to an approximate halving of GFR, as an end-point defining progression, but this is insufficiently sensitive to be useful in clinical practice. Kidney Disease Improving Global Outcomes (KDIGO) have defined progression as a move to a higher disease category [e.g. stage 3A (GFR 45–59 ml/minute/1.73 m^2) to stage 3B (GFR 30–44 ml/minute/1.73 m^2)]

accompanied by a fall in GFR of ≥ 25% (e.g. a decline from 50 to 35 ml/minute/1.73 m^2) or an increase in albuminuria.[27] They defined rapid progression as a sustained decline in GFR of > 5 ml/minute/1.73 m^2/year (e.g. a decline from 60 to < 54 ml/minute/1.73 m^2 in 1 year).[27] NICE originally defined progression as a decline in GFR of more than 5 ml/minute/1.73 m^2/year, or more than 10 ml/minute/1.73 m^2/5 years.[40] More recently, NICE have defined accelerated progression as a sustained decrease in GFR of 25% or more and a change in GFR category within 12 months, or a sustained decrease in GFR of 15 ml/minute/1.73 m^2 per year.[59]

Progression is not necessarily common even amongst people with known CKD, for example amongst people with stage 3 CKD only 1.3% progressed to stage 5 CKD (established kidney failure, typically requiring dialysis or transplantation) over 5 years.[68] Amongst community-dwelling older (> 65 years) adults with stage 3 CKD, Hemmelgarn *et al.* reported mean decline of GFR of 3.6 and 2.8 ml/minute/1.73 m^2/year, respectively, in male and female subjects with diabetes and somewhat lower values amongst subjects without diabetes (1.9 and 1.1 ml/minute/1.73 m^2/year amongst males and females, respectively).[69] In the Ramipril Efficacy in Nephropathy study proteinuric (> 1 g/24 hours) non-diabetic subjects with GFRs in the approximate range 30–50 ml/minute/1.73 m^2 showed a decline of GFR of 7.0 ml/minute/1.73 m^2/year with slightly lower values being observed in those receiving RAAS blockade.[70]

There are some data, mainly restricted to small studies in people with diabetes, describing disease progression in terms of decline in reference GFR measurements.[71,72] Generally, disease progression in people with diabetes has been described as following a broadly linear decline, being influenced by BP and albuminuria and ameliorated by antihypertensive medication/RAAS blockade.[71,73,74] A similar pattern has been observed using estimated rather than measured glomerular filtration rate (mGFR).[75]

Identifying and predicting progressive kidney disease and clinical risk

A significant problem is the ability of GFR-estimating equations to identify progression of kidney disease against background change in GFR (i.e. that due to 'normal' ageing; commonly cited as approximately 1 ml/minute/1.73 m^2/year) given the biological and measurement variability of both reference and eGFR. The intraindividual variation (CV_I) of the main determinant (serum creatinine) of eGFR has been reported as 4.3%[76] to which should be added analytical variation (CV_A) of approximately 3.0%.[39] These data can be used to calculate the critical difference or reference change value (RCV) for serum creatinine using the equation:[35]

$$RCV = 2^{1/2} \cdot Z \cdot (CV_A{}^2 + CV_I{}^2)^{1/2} \quad (1)$$

where Z is the number of standard deviations (SDs) appropriate to the probability.

For 95% probability (Z = 1.96), the derived RCV for serum creatinine is approximately 14.5% (i.e. this is the difference that can be considered 'real' with 95% probability). Substituting this level of variation into change in eGFR, it can be calculated that an individual with a GFR of 60 ml/minute/1.73 m^2 will need to fall below approximately 50 ml/minute/1.73 m^2 before the change can be considered a significant decrease. Some,[77,78] although not the majority,[79–82] of data suggest that the biological variation of serum cystatin C is greater than that of creatinine. If this were the case, then it would clearly impact on the ability of cystatin C-based GFR-estimating equations to detect changes in true GFR vis-à-vis serum creatinine.

Glomerular filtration rate changes of this order exceed the limit that most nephrologists would consider clinically significant. However, there is little prospective longitudinal data assessing the relative abilities of GFR-estimating equations to detect change in underlying 'true' GFR. In a 1-year prospective study of 71 patients with autosomal dominant polycystic kidney disease, the MDRD and CKD-$EPI_{creatinine}$

equations underestimated the change in iohexol mGFR (mean change 8.4 ml/minute/1.73 m^2) by > 50%.[83] A retrospective but larger (3532 participants with CKD followed for a mean of 2.6 years) study also addressed the accuracy of GFR-estimating equations compared to ^{125}I-iothalamate mGFR over time in people with kidney disease.[84] The authors concluded that GFR-estimating equations accurately reflected changes in mGFR over time. Neither of these studies included eGFR data derived using cystatin C. Observational data suggest that for identification of progressive CKD the combination of eGFR using cystatin C and albumin-to-creatinine ratio (ACR) ranks highest, followed by eGFR using cystatin C alone, then the combination of ACR and eGFR using creatinine, and finally eGFR using creatinine alone.[85] The combined use of cystatin C and creatinine in a GFR-estimating equation, which is claimed to be less influenced by ethnicity, has not been tested as a predictor of progression.

In addition to identifying change in kidney function, there is evidence to suggest that baseline GFR estimates using cystatin C may be better able to predict patients likely to have progressive decline in kidney function, and increased risk of other outcomes including mortality, than equations based upon creatinine.[30,85] This closer relation to clinical risk was one of the justifications for inclusion of cystatin C GFR estimation in certain patients, as an adjunct to creatinine-based GFR estimations, in the 2014 NICE CKD guidance.[22]

Evidence explaining why this study was needed and remains relevant

Chronic kidney disease is common, with an estimated population prevalence in England in 2016 of 13.9%.[86] Most commonly, it is detected using eGFR and/or albuminuria. Estimation of GFR on every blood creatinine request received by laboratories is recommended by NICE.[59] Circa 50 million GFR estimates are produced by UK NHS laboratories every year. As discussed earlier, NICE have recently removed the recommendation to adjust GFR estimates for individuals of black ethnicity. Of note, the guideline committee also recently expressed doubts that P30 accuracy was a good enough measure to make a recommendation on the use of one GFR-estimating equation over another because P30 covers a wide range compared to P15, which would be preferred if there were enough data.[22,59]

The NICE guideline group originally also included cystatin C measurement, as a confirmatory test, in their guidance on CKD detection and diagnosis, in agreement with that from KDIGO.[22,27] However, this recommendation has been withdrawn, on the basis of an absence of good evidence for the accuracy of cystatin C-containing GFR equations and concerns that, although such equations may reduce false-positive (FP) tests for CKD, they may also increase false-negative (FN) results.[59] Conversely, a task force from the National Kidney Foundation and American Society of Nephrology have recommended increased, routine and timely use of cystatin C, especially to confirm creatinine-based eGFR in adults for clinical decision-making.[67] While the clinical utility of cystatin C remains uncertain, the increasing availability of cystatin C assays on large, automated laboratory test platforms may increase the pressure on NHS laboratories to introduce this test, which is significantly more expensive than creatinine testing.

The NICE guidelines have made a research recommendation for a large study to establish the diagnostic accuracy of cystatin C-based equations to estimate GFR as a measurement of kidney function in adults, children and young people in the UK.[59] There is also a further research recommendation to determine which biomarkers or factors, other than ethnicity, improve the diagnostic accuracy of GFR estimations in adults, children and young people from black, Asian and other minority ethnic groups with CKD living in the UK.[59] While introduction of routine GFR estimations is generally deemed to have brought significant health advantages,[87] there is also concern that individuals without CKD may be inappropriately identified as having CKD.[25] Further, the ability of tests to identify which individuals with CKD will have high-risk (i.e. progressive disease and/or increased mortality risk) disease is seen as a crucial issue. A significant problem has been the ability of GFR-estimating equations to identify progression of kidney disease given the biological variability of its main determinant (serum creatinine). There are few prospective studies of the ability of GFR-estimating equations to monitor progression and no studies at

all in adults of the monitoring ability of GFR-estimating equations incorporating cystatin C; there have been no prospective validations of GFR-estimating equations in British ethnic minority populations. The present study addresses these important issues.

The study

While there is significant published literature describing the accuracy of creatinine-based GFR estimation against reference methods, there are few data addressing the ability of GFR-estimating equations, including those incorporating cystatin C, to detect change in GFR. Furthermore, there are no data addressing the accuracy of these equations in British ethnic minority populations. The study protocol was published in 2014.[88] The study assessed whether eGFR using either creatinine or cystatin C or a combination of both was superior at detecting changes in GFR as measured by a reference GFR method. The utility of baseline eGFR and urinary ACR to predict who were more likely to show progressive kidney disease was also tested. We chose plasma iohexol clearance as the reference measure of GFR for our study because it is equivalent to inulin clearance, is widely used in clinical and research practice, is not radioactive, can be measured accurately and precisely, and is relatively cheap.[89–91] We chose to study the CKD-EPI and MDRD equations because they are internationally accepted GFR-estimating equations anchored to both creatinine and cystatin C reference methodology and therefore likely to generate data that will be valid in perpetuity. During the study several other GFR-estimating equations have been published and gained credence: these have also been evaluated here.

The study population was a large cohort of people with stage 3 CKD including people of South Asian and African-Caribbean ethnicity and participants with diabetes and albuminuria. A substudy modelled disease progression in a smaller cohort. The study built on the findings of previous research but used a prospective design with regular reference GFR measurements: the impact of medication on disease progression was estimated and included in the model. We also used a classical study design to establish the intraindividual biological variability of both mGFR and eGFR: this information was used as one of the tools in defining progression and assessing the ability of GFR-estimating equations to detect it. A cost analysis exploring the impact of including cystatin C in GFR-estimating equations in a monitoring context was undertaken.

To address these issues, a study in three parts was undertaken to provide the required portfolio of evidence to identify the optimal estimate of GFR to use in clinical practice:[88]

1. Main study. A large 3-year prospective longitudinal cohort study using 6-monthly estimates of GFR and baseline and final reference GFR values was undertaken to assess and compare the accuracy and precision of each estimate of GFR and change in GFR. The study included adults (n = 1229) with stage 3 CKD (GFR 30–59 ml/minute/1.73 m^2) recruited across six centres. The cohort was enriched for participants more likely to have progressive kidney disease (i.e. those with albuminuria and/or diabetes) and those from South Asian and African-Caribbean ethnic groups.
2. Substudy of disease progression. We modelled predictors of progression of GFR in a subset of the cohort (n = 278) who received annual mGFR tests, in addition to 6-monthly GFR estimates and urinary ACR measurements, assessing risk factors and over time.
3. Substudy of biological variation. We undertook a substudy in 20 participants investigating sources of variability to estimate the components of measurement error in each measure and estimate of GFR.

We used the results from the comparative accuracy study to inform a measurement model analysis. In this, the trajectory of participants' mGFR and eGFR over 10 years was used to estimate the proportion meeting the NICE threshold of accelerated progression (see *Progression of kidney disease*), assuming an annual testing schedule, and the number of participants expected to be incorrectly managed at each of

the evaluated monitoring time points using the different estimating equations. Based on the findings, the comparative costs of monitoring with GFR-estimating equations were estimated.

Specific objectives

Primary objectives

The study evaluated the comparative performance of GFR-estimating equations, including those incorporating cystatin C, in assessing and monitoring GFR in people with stage 3 CKD. The data were analysed to assess the impact of ethnicity, albuminuria, diabetes and other characteristics on equation performance. The aims of the study were:

1. to estimate and compare the accuracy of GFR-estimating equations at baseline based on the MDRD equation and three CKD-EPI equations using either creatinine or cystatin C or a combination of both in individuals with stage 3 CKD
2. to estimate the accuracy of the GFR-estimating equations according to ethnic group (particularly Caucasian, South Asian and African-Caribbean), and baseline diabetes, albuminuria, age, gender, BMI and mGFR level
3. to evaluate and compare how accurately these GFR-estimating equations track mGFR and detect change in mGFR over 3 years
4. to estimate the biological variability of mGFR and eGFR
5. to establish which GFR-estimating equation, together with urinary ACR, or ACR alone, most accurately predicts mortality and those individuals that have progressive loss of kidney function (CKD progression)
6. to estimate and model disease progression (decline in GFR or increase in ACR) and differences in progression between ethnic groups (Caucasian, South Asian and African-Caribbean), baseline diabetes and albuminuria status and other potential risk factors
7. to explore the comparative cost effectiveness of monitoring strategies for identifying people who have progressive loss of kidney function (CKD progression) utilising different GFR-estimating equations.

Secondary objectives

1. To estimate and compare the accuracy of more recent GFR-estimating equations that have been published while the study has been ongoing including BIS1 and BIS2 equations, CAPA equation, LMR equation, $FAS_{creatinine}$ equation, $FAS_{creatinine\text{-}cystatin}$ equation, EKFC equation and the 2021 revisions of the CKD-EPI equations (*Table 1*).
2. To evaluate and compare how accurately these newer GFR-estimating equations reflect and detect change in GFR over 3 years.
3. To estimate and compare the performance of the MDRD equation and CKD-EPI equations using the Haycock equation[92] for BSA adjustment instead of the Du Bois equation.[93]
4. To assess the impact of cystatin C calibration on the performance of the CKD-EPI equations.
5. To assess the impact of creatinine methodology [enzymatic vs. isotope dilution mass spectrometry (ID-MS)] on the performance of the MDRD equation and creatinine-based CKD-EPI equations.

Chapter 2 Methods

Main study: prospective longitudinal cohort study

The main study comprised a prospective longitudinal test evaluation cohort study in which adults (≥ 18 years) with stage 3 CKD (GFR 30–59 ml/minute/1.73 m^2) had baseline investigations of kidney function (mGFR and eGFR and albuminuria) and were then followed for 3 years, with 6-monthly estimates of GFR and a repeat reference mGFR at the end of the study (*Figure 1*).[88]

Recruitment

Adults with stage 3 CKD were recruited to the study at six centres, with a target case mix as follows:

1. Birmingham – 50% Caucasian, 25% South Asian, 25% African-Caribbean from secondary care
2. Canterbury – predominantly Caucasian cohort from secondary care
3. Derby – predominantly Caucasian cohort from primary care
4. Leicester – 50% Caucasian, 50% South Asian, from primary and secondary care
5. Salford – predominantly Caucasian cohort from secondary care
6. London – Kings College Hospital – 50% Caucasian, 50% African-Caribbean from secondary care.

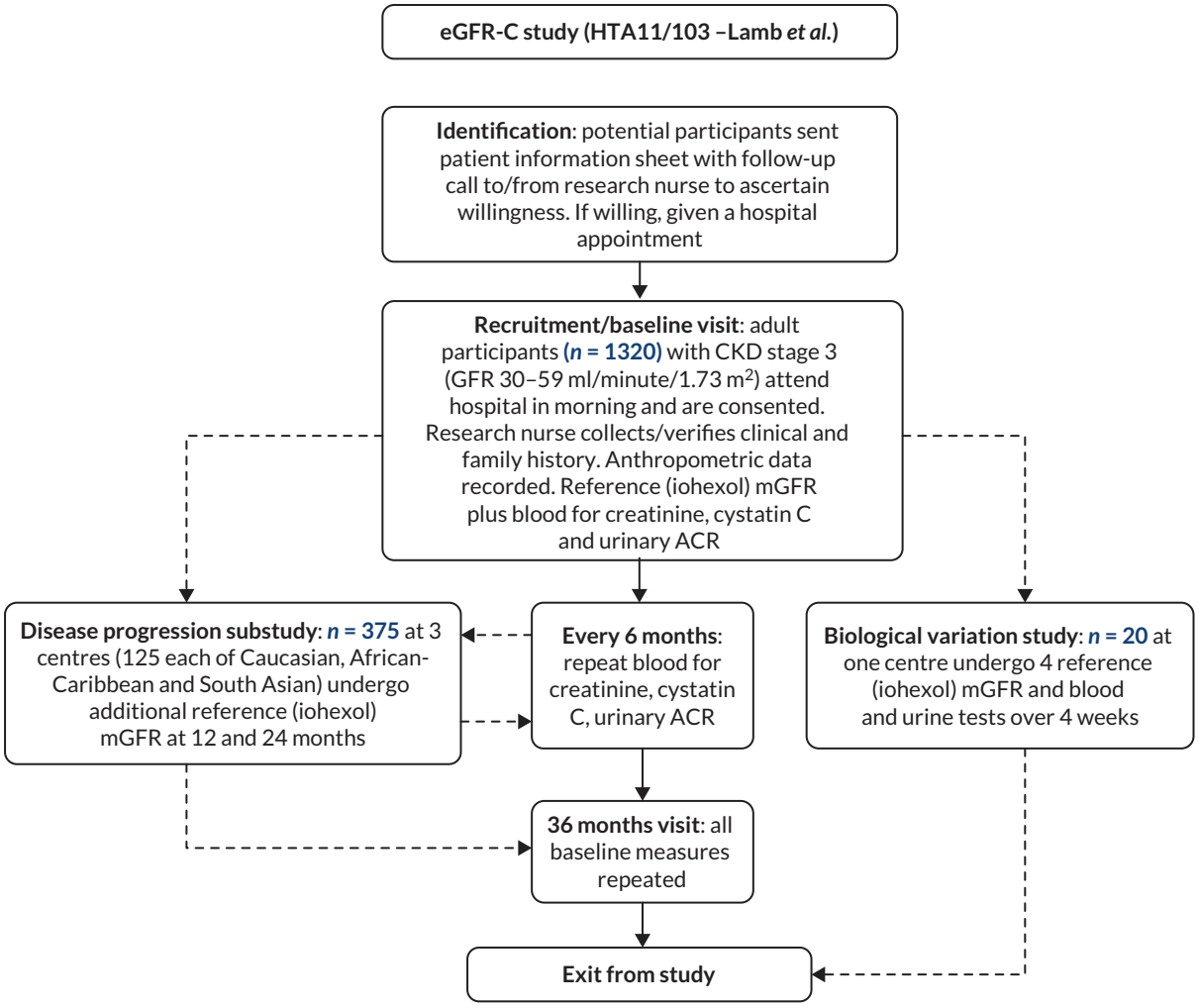

FIGURE 1 Outline of study.

Participants were recruited from both primary and secondary/tertiary care. Recruitment in secondary/tertiary care was primarily from CKD clinics. Potential participants were identified by the research nurse/co-investigator at each of the recruiting centres from the individual renal unit databases. Recruitment from primary care utilised the following approaches. In Leicester, letters were sent to general practitioners (GPs) inviting them to participate. Research active practices were approached by the Clinical Research Network and consenting practices were given instructions to help identify eligible people from the CKD register, for example using READ code searches. MIQUEST (Morbidity Information QUery and Export SynTax) software was used to extract an up-to-date data set. The practices sent invitation letters with a stamped envelope to eligible people. The invitation was sent out with the patient information sheet. Potential recruits were given a dedicated study phone line to use to indicate willingness to participate and the research assistant then telephoned willing participants to further discuss the study and schedule hospital attendance. Signed informed consent was obtained upon hospital attendance for the reference GFR test (see below). In Derbyshire, a similar process was followed except that eligible participants were identified from a database of participants from the Renal Risk in Derby study,[94] a cohort study of persons with CKD in primary care.

Inclusions

Individuals aged 18 years and older having stage 3 CKD (eGFR measurements between 30 and 59 ml/minute/1.73 m^2 inclusive sustained over at least 3 months prior to recruitment) were included. Recruitment was targeted such that approximately 20% would have severely increased albuminuria (ACR > 30 mg/mmol) and a similar proportion would have diabetes, since such prevalences are fairly typical of the CKD population being studied, at least in secondary care. Albuminuria and diabetes prevalence were monitored during the course of the study to ensure reasonable representation.

Exclusions

History of untoward reactions to iodinated contrast media or allergy to topical iodine, pregnant or breastfeeding, known current alcohol or drug abuse, kidney transplant recipient, people whose life expectancy would make study completion unlikely,[95] inability to consent, for example due to cognitive impairment, inability to comply with study schedule and follow-up, amputation of whole or part limb, recent (last 6 months) episode of AKI, as defined by the Acute Kidney Injury Network criteria[96] and sickle cell disease.

Sampling and data collection

Baseline visit: Participants were asked to attend hospital in the morning after having been advised to consume a light breakfast (no meat or fish). A clinical and drug history was recorded using a standardised questionnaire taken by research nurses on the day of hospital attendance. Vascular disease was defined as the presence of MI (including ST-elevation myocardial infarction and non-ST elevation myocardial infarction), angina, congestive cardiac failure (heart failure) or a requirement for coronary intervention (angioplasty, coronary artery bypass graft or pacemaker), cerebrovascular or peripheral vascular disease. Information on ethnicity was gathered using a modified version of the 2011 UK Census Questionnaire, with ethnicity being mapped to the following codes:

Caucasian 31, 32, 33, 34; South Asian 39, 40, 41; African-Caribbean 44, 45, 46.

Height was measured to the nearest 0.1 cm with a rigid stadiometer. Body weight was measured in light indoor clothing to the nearest 0.1 kg. Waist circumference was recorded to the nearest 0.1 cm at the mid-point between the lower costal margin and the level of the anterior superior iliac crest. Brachial BP was measured as recommended by the British and Irish Hypertension Society [https://bihsoc.org/resources/bp-measurement/measure-blood-pressure/ (accessed 26 July 2023)] three times in the sitting position using standardised Omron M7 digital sphygmomanometers (Omron Healthcare, Milton Keynes, UK). The average of the second and third BP readings was recorded.

Baseline blood was taken for serum creatinine and cystatin C, and a urine sample was collected for ACR. Blood samples were also taken for haemoglobin and glycated haemoglobin (only if known to have diabetes) measurement. Further aliquots of serum and urine were stored for potential analysis of future markers of GFR or disease progression. Blood samples were collected using standard venepuncture and phlebotomy procedures including the use of a tourniquet. Blood was collected in appropriate Greiner Vacuette™ tubes [www.gbo.com (accessed 26 July 2023)] following the manufacturer's recommended order of draw. The urine sample was taken into a plain Sterilin pot. Samples were transported to the local laboratory, where plasma/serum was separated within 4–6 hours of venepuncture by centrifuging at 2000 *g* for 10 minutes. Aliquots of serum/plasma and urine were then stored at −80 °C pending transportation to the central laboratories [St. Thomas's (iohexol, ID-MS creatinine) or Canterbury (enzymatic creatinine, cystatin C, ACR) depending on analyte] and analysis.

Glomerular filtration rate was measured using an iohexol clearance method.[97] A 5 ml bolus of Omnipaque 240 (518 g/l iohexol corresponding to 240 g/l of iodine, GE Healthcare [www.gehealthcare.co.uk/ (accessed 12 April 2023)] followed by 10 ml of normal saline was injected into the antecubital vein. Blood samples were collected at 5, 120, 180 and 240 minutes after injection. Exact time of the samples in relation to the bolus injection was accurately recorded. Participants were allowed free access to fluids during the collection procedure but were asked to refrain from protein intake (i.e. biscuits/toast would be permitted) and to refrain from excessive exercise. Samples were stored at −80 °C prior to analysis. Iohexol was determined using an ID-MS method (see below) and GFR calculated.[98]

Glomerular filtration rate was estimated using published GFR-estimating equations: the simplified ID-MS traceable version of the MDRD equation and the three CKD-EPI equations ($CKD\text{-}EPI_{creatinine}$, $CKD\text{-}EPI_{cystatin}$ and $CKD\text{-}EPI_{creatinine\text{-}cystatin}$) for the primary study objectives. For the secondary study objectives, the BIS1 and BIS2, CAPA, LMR, $FAS_{creatinine}$, $FAS_{creatinine\text{-}cystatin}$, EKFC and the 2021 revisions of the CKD-EPI equations were studied (*Table 1*).

Follow-up: Participants were followed for 3 years. All the above measurements and the clinical history were repeated at 36 months. At each 6-month interval, blood samples of all participants were taken for serum creatinine, according to standard care,[40] in addition to cystatin C and a urine sample was collected for ACR: GFR was estimated as above. All measurements were undertaken in accordance with standard operating procedures by trained staff. Nursing staff familiar with these procedures at the Canterbury centre cascade trained other recruiting centres. Clinicians and others involved in patient care were blinded to the reference measured (iohexol) GFR and cystatin C-based eGFR results for the duration of the study. During the course of the study, participants were given advice regarding the management of their CKD according to standard evidence-based practice.[40]

Laboratory analyses

Iohexol was measured using electrospray isotope dilution tandem mass spectrometry on an ABSCIEX API6500 Q-trap (ABSCIEX, Warrington, UK) mass spectrometer.[97] Iohexol stock standard, 10 mmol/l, was prepared by diluting Omnipaque 300 solution (647 g/l) in deionised water and stored in 1 ml aliquots at −80 °C. Aqueous iohexol calibrators (0, 10, 100 and 500 µmol/l) were prepared from the stock iohexol standard by dilution and stored in 0.5 ml aliquots at −80 °C. Iohexol stable isotope, d5-iohexol (Toronto Research Chemicals Inc., Toronto, ON, Canada), was obtained from 2BScientific Ltd, Upper Heyford, UK, dissolved in deionised water at circa 10 mmol/l, and stored at −80 °C. Plasma control samples were prepared by spiking a plasma pool with iohexol stock standard at 10, 100 and 400 µmol/l. Calibrators, controls, patient samples and stable isotope stock solutions were thawed from frozen on a roller mixer at room temperature for no more than 60 minutes, and then centrifuged for 4 minutes at 1500 *g* at 4 °C (Eppendorf 5810R centrifuge, VWR International Ltd, Lutterworth, UK). Working iohexol stable isotope was prepared by diluting the circa 10 mmol/l solution 1 : 200 with deionised water. Calibrators, controls and samples were pipetted (20 µl) into 2 ml microcentrifuge tubes [000-MICR-200, Elkay Laboratory Products (UK) Ltd, Basingstoke, UK] and 50 µl working iohexol stable isotope, followed by 200 µl acetonitrile (Rathburn Chemicals Ltd, Walkerburn, UK) were added to each

tube. Samples were capped, vortex-mixed for 5 seconds and centrifuged for 5 minutes at 20,800 *g* at 4 °C (Eppendorf 5417R centrifuge, VWR International Ltd, Lutterworth, UK). Supernatants (200 µl) were then transferred into a 96 deep well plate and loaded onto the autosampler. The sample (2 µl) was automatically injected into a mobile phase stream of acetonitrile : water (1: 1) with 0.025% formic acid using a Hewlett-Packard 1100 Series autosampler and pump (Applied Biosystems, Warrington, UK) at 250 µl/minute. Chromatography was performed on a Chirobiotic T 100 × 2.1 mm column with a 2 cm × 4.0 mm guard column (Sigma-Aldrich Company Ltd, Poole, UK).

Tandem mass spectrometry was performed in positive ion multiple reaction monitoring mode: iohexol 821.849/602.8, d5-iohexol 826.849/607.8. Data acquisition time was 6 minutes with a pause time of 5.0070 milliseconds between transitions and a scan speed of 10 Da/s. Iohexol concentrations were calculated in Analyst 1.6 (ABSCIEX, Warrington, UK) using the ratio of sample peak area to stable isotope peak area. Between-day imprecision (CV, %) was 1.0%, 0.8% and 1.5% at 10, 100 and 400 µmol/l, respectively. The laboratory participated in an international proficiency testing scheme [EQUALIS, https://equalis.se/en/ (accessed 5 April 2023)] for iohexol measurement with good performance.

Iohexol concentrations were log-transformed (natural log) and plotted as a function of time. GFR was calculated from the slope-intercept method using a single compartment model:[99,100]

$$\begin{aligned}\text{GFR}\,(\text{ml/min}) \;=\; & 0.693 \times \text{iohexol volume of distribution}\;(\text{l}) \\ & \times 1000/\text{half-life of iohexol}\;(\text{minutes})\end{aligned} \tag{2}$$

To ensure integrity of the iohexol procedure (dose administration, sample collection, sample labelling, and iohexol analysis), the iohexol data were rigorously reviewed for every mGFR. The 5-minute sample enabled identification of procedures where the iohexol was given subcutaneously in error, or where saline flushing of the infusion line was suboptimal, as demonstrated by low and high iohexol concentrations respectively. In addition, all procedures where the iohexol concentration versus time correlation coefficient (*r*) was < 0.98 (< 6% of total procedures) were re-analysed to check for any within-assay sample transposition.

Glomerular filtration rate was adjusted for BSA using the Du Bois equation[93] and corrected for the fast exponential.[98] In a separate analysis, GFR was adjusted for BSA using an alternative approach (Haycock equation[92]) to assess the impact of these adjustments on the accuracy of GFR estimation.

Serum creatinine was measured using an enzymatic assay on an Abbott Architect analyser [Abbott Diagnostics Ltd, www.abbott.co.uk/ (accessed 12 April 2023)] standardised to the reference material, NIST SRM 967 and 914. Between-day imprecision (CV, %) was 0.8%, 0.3% and 0.4% at concentrations of 75, 176 and 760 µmol/l, respectively. The laboratory participated in an international proficiency testing scheme [UKNEQAS, https://birminghamquality.org.uk/ (accessed 5 April 2023)] for creatinine measurement and GFR estimation with satisfactory performance. Additionally, serum creatinine was measured using ID-MS on an ABSCIEX API6500 Q-trap mass spectrometer.

Cystatin C was measured by a turbidimetric immunoassay on an Abbott Architect analyser. Between-day imprecision was 2.3% and 1.6% at concentrations of 0.9 and 4.0 mg/l, respectively. The laboratory participated in an international proficiency testing scheme (EQUALIS) for cystatin C measurement and GFR estimation with good performance.

During the course of the study, we became aware of published data describing a significant positive bias of the Abbott cystatin C assay.[101] This was supported by information from the EQUALIS proficiency testing scheme and our own re-analysis of historical stored samples (data not presented here). To investigate this, a recovery study was undertaken in which lyophilised human serum cystatin C ERM-DA471/IFCC [Sigma-Aldrich Chemical Co., www.sigmaaldrich.com (accessed 5 April 2023)] was added

to pooled non-uraemic serum to give samples with a range of expected concentrations covering 1.47–3.41 mg/l. These samples were analysed and the mean recovery calculated.

To further explore this bias, in a subset of samples (n = 106) covering a representative range of concentrations cystatin C was also measured by a particle-enhanced nephelometric immunoassay according to the manufacturer's instructions on a Siemens BN Prospec analyser [www.siemens.com (accessed 12 April 2023)]. Between-batch imprecision (n = 38) for the Siemens assay was 3.5% at 0.87 mg/l and 3.6% at 4.64 mg/l. Both Abbott and Siemens assays were calibrated against the internationally certified reference material ERM-DA471/IFCC for cystatin C.[51]

Prior to analysis, samples were thawed at room temperature, mixed by inversion and centrifuged prior to measurement. For the biological variation study, all samples from each individual subject were measured in duplicate in random order in a single assay. Each of the biomarker analyses was undertaken by a single operator blinded to participant data using a single instrument. Creatinine and cystatin C measurements were undertaken in an accredited laboratory by scientists registered with the Health and Care Professions Council.

Substudy of disease progression

Participants in the substudy underwent additional testing to that described in the main study, with a reference mGFR each year over the 3-year study period (i.e. four reference GFR measures in total) (*Figure 1*). Serum creatinine and cystatin C measurements to inform the eGFR equations and ACR measurements were taken every 6 months. Four eGFR equations were investigated [MDRD, CKD-EPI$_{creatinine}$, CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ (*Table 1*)]. CKD-EPI$_{creatinine}$ is the NICE-recommended equation and was the primary result to compare to mGFR.

It was planned to recruit at least 375 participants in the substudy enriched to include equal numbers of South Asian, African-Caribbean and Caucasian participants, and approximately equal numbers with and without diabetes and/or albuminuria (high and low risk).

The majority of participants in the substudy were recruited from the Birmingham, Leicester and London centres. An additional two centres (Canterbury and Salford) were later added to increase recruitment to the substudy.

The aim was to develop a model of disease progression based on reference GFR measurement and to estimate differences in progression for risk factors. The target number of subjects for inclusion was considered to provide a range of values over the main factors considered to influence disease progression and allow assessment of covariates in the statistical model. Inclusions/exclusions and laboratory methods for this substudy were as described above.

Further assessment of covariates was performed by combining the data from the disease progression substudy with the main study, and fitting the final covariate models for the substudy to the full data set. The evaluable population included those participants from the main study or substudy with paired mGFR and eGFR at two time points or more.

Substudy of intraindividual biological variability

At one centre (Canterbury) a study was undertaken to define the normal biological variability of a reference GFR test in addition to the eGFR tests. Participants with stage 3 CKD (n = 20) underwent four iohexol reference measures of GFR over 4 successive weeks, with standardisation for time of day (morning after a light breakfast) and day of week. Inclusions/exclusions and laboratory methods for this

substudy were as above (see *Recruitment*). Individuals participating in this substudy were eligible for inclusion in the main study and the substudy of disease progression if they were happy to do so.

Sample size calculations

Main study: prospective longitudinal cohort study

The sample size calculation for the main study focused on the ability to detect differences in accuracy of measurement between the MDRD equation and the CKD-EPI$_{cystatin}$ equation. We also made secondary comparisons with the other equations. While it is relatively easy to estimate the relationship between each equation and the reference standard in smaller samples, a relatively large sample is required to have adequate statistical power to make the comparison in accuracy. Similarly, while it is possible to show a relationship between eGFR and progression within a cohort, to show that one equation predicts progression better than another is more challenging.

The measure of accuracy we used was the P30, the percentage of eGFR values within 30% of 'true' GFR. Describing percentiles of the distribution of the differences between estimated and mGFR was endorsed as a useful measure of accuracy by the National Kidney Foundation – Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) in 2002 and has been widely used subsequently in the GFR field.[102] The approach captures aspects of both imprecision (measurement error) and bias (systematic over- and/or underestimation). NKF-KDOQI suggested that GFR equations should achieve a P30 value in excess of 90%. Having undertaken initial algebraic sample size calculations based on comparing variance estimates of measurement error, we defined our final sample size based on a simulation study to estimate differences in P30 and estimates of rate of change which are not amenable to algebraic solution. Our simulations modelled the full structure of the study including random variability, and computed statistical power through noting the percentage of simulations yielding statistically significant results for analysis of each outcome. Power estimates were based on 1000 simulations.

Values of P30 for the alternative eGFR equations have previously been estimated to range between 73% and 95% across the literature.[41] The original MDRD validation cohort achieved a P30 of 91%,[31] whereas in the CKD-EPI cohort, this fell to 81%, compared to 84% for the CKD-EPI equation itself.[32] In the external validation data sets of Inker *et al.*[28] the CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations achieved P30 values of 86% and 92%, respectively. In our recent study of GFR-estimating equation performance in older people, the MDRD equation achieved a P30 of 81% compared to 86% for the CKD-EPI$_{creatinine\text{-}cystatin}$ equation.[52]

We evaluated the ability of the present study to detect a difference of 5% in P30, between 81% and 86%, which is of a magnitude considered clinically important and likely to occur with the expected scale of differences in imprecision between the equations. With 1000 evaluable subjects our simulations showed 87% power for detecting a difference at the 5% level. We thus aimed to recruit 1300 people, which, allowing for 15–20% dropout, would deliver over 90% power. This calculation was conservative in that it only took imprecision into account. In the presence of systematic bias (a reasonable assumption) the power was estimated to be greater than this. In relation to estimating equation performance amongst the ethnic groups, the proposed sample size of these subgroups allowed P30 estimates to be reported with 95% CIs of 10%.

The annual rate of change over 3 years can be estimated by the observed difference between follow-up and baseline measurements or by using regression techniques for estimated and mGFR. Padala *et al.* proposed two cut-points for estimating accuracy of rates of change comparing estimated to mGFR: > 3 ml/minute/1.73 m^2/year error and > 5% error.[84] Our simulations predicted that with the magnitude of measurement error that corresponds with P30 measures of 81% and 86% the study would have over

90% power to detect differences in the proportions with > 3 ml/minute/1.73 m^2/year error and over 80% power to detect differences in proportions with > 5% error.

Ideally, we would like to have been able to detect differences in progression to stage 4 CKD between estimating equations. While it is possible to estimate a relationship with progression for each equation, a study would need to have 10,000 participants to be able to have 90% power to detect a difference in predictive abilities to stage 4 CKD between equations. Therefore, our study did not have power to evaluate this as an outcome, but it was considered in the model-based analysis.

Substudy of disease progression

A target sample size of 375 was chosen based on practical considerations to allow investigation of 12 covariates of interest (gender, age, diabetes, duration of diabetes, ethnicity, albuminuria, baseline GFR, BP, BMI, waist circumference, smoking status and presence of vascular disease) in addition to variables for time, drug effects and random effects. Another consideration was to include a reasonable number of subjects in each of the ethnic groups and high- and low-risk subgroups. General sample size formulae[103] for multiple regression models indicate that a sample of 300 individuals, with 15–20% attrition, will provide 90% power to detect a change in R^2 of 0.11 (medium-to-small effect size[103]) attributed to 20 independent variables, 6 controlled independent variables and a significance level of 0.05.

Study of intraindividual biological variation

Sample sizes in biological variation studies are somewhat dictated by the practical limitations and costs of handling the large numbers of analyses generated while minimising the effects of pre-analytical and analytical variation. However, biological variation studies are known to be robust to the effects of sample size. For example, using 4 samples on 10 subjects, Gowans *et al*. estimated a CV_I for creatinine of 4.1%,[76] whereas Keevil *et al.* using 10 samples from 12 subjects obtained a CV_I of 4.9%.[77]

The sample size was based on the precision of CV_I, which was estimated to be 10%. With 20 participants recruited, tested on 4 occasions and assayed in duplicate and assuming data are log-normally distributed, an approximate 95% CI for CV_I has limits ± 2% (absolute).

Statistical methods

Main study: prospective longitudinal cohort study

Data were analysed to address three main questions.

Which of the glomerular filtration rate-estimating equations is the most accurate assessment of measured glomerular filtration rate?

The baseline creatinine or cystatin C result obtained using the baseline sample from the iohexol-mGFR procedure was used to estimate GFR. Measured GFR was accepted as the reference measure of GFR against which each GFR-estimating equation was compared. The performance of the GFR-estimating equations was evaluated as proposed by NKF-KDOQI[102] by assessing accuracy, bias and precision. Accuracy was assessed by establishing the proportion of GFR estimates within 30% (P30) of iohexol-mGFR and also as root mean square error (RMSE). For the primary objectives, we compared P30 values between GFR-estimating equations using McNemar's test for paired data. We also reported P15 (the proportion of GFR estimates within 15% of iohexol mGFR) values for each estimating equation, but the study was not powered to detect differences in P15 values between equations. The mean difference between estimated and mGFR provided a measure of bias. The median difference provided a second measure of bias that was valid and less influenced by outliers. Data were also visually examined using bias plots (eGFR minus mGFR against mGFR) with lowess (locally weighted scatterplot smoothing). Precision was assessed as the interquartile range (IQR) of the differences between mGFR and eGFR. Exploratory analyses of GFR accuracy were also undertaken in which data were stratified by age (< 50, 50–59, 60–69, 70–79 and ≥ 80 years), gender (male/female), diabetes (diabetic or not diabetic as

recorded in medical history), albuminuria (< 3.0, 3.0–29.9 or ≥ 30.0 mg/mmol, corresponding to normal, moderately and severely increased albuminuria in the international classification of CKD),[27] BMI (< 30 or ≥ 30 kg/m^2, corresponding to healthy/overweight and obese/severely obese)[104] and level of kidney function (mGFR < 45 or ≥ 45 ml/minute/1.73 m^2). Accuracy was also studied by race (Caucasian, South Asian, African-Caribbean, with ethnicity being self-reported and classified as described in *Sampling and data collection*).

Which glomerular filtration rate-estimating equation most accurately tracks glomerular filtration rate over time?

For each individual, the difference between baseline and 3-year follow-up eGFR was calculated and the change per year was derived by averaging change over the time between baseline and 3-year follow-up. Similarly, the difference between baseline and 3-year follow-up mGFR was calculated and the change per year was derived by averaging change over the time between baseline and 3-year follow-up. The outcome of interest was error, the difference between the annual change in mGFR and eGFR. Large error was accepted as ≥ 3 ml/minute/1.73 m^2/year, or > 5%/year difference in slope between mGFR and eGFR. Differences in the slopes of estimated and mGFR were therefore considered present when the slope for eGFR exceeded ± 3 ml/minute/1.73 m^2/year or ± 5%/year of the mGFR slope. The primary analysis used observed eGFR compared to observed mGFR, both calculated as absolute change per year calculated from difference between 3-year and baseline measurements. The rate of change was calculated using actual calendar sampling date rather than nominal date in cases where follow-up period was not exactly 3 years.

Different approaches were explored in two sensitivity analyses: in the first, as described by Padala *et al.*,[84] (1) change in eGFR values derived from a linear regression model (change per year calculated from a linear regression model fitted per person using all available measurements, i.e. up to seven measurements per individual) was compared to observed mGFR (calculated as per the primary analysis); and in the second (2) change in eGFR values derived from linear regression models, as above in (1), was compared to estimated change in mGFR from a mixed-effects linear regression model (coefficient from a single mixed-effects model obtained using all available measures for all individuals, i.e. up to four measurements per individual including additional mGFRs from the substudy).

The percentage of participants demonstrating large error when comparing change over time between the eGFR and mGFR values, for each GFR-estimating equation for the primary objectives, was compared. The numbers meeting the two criteria were compared with McNemar's test.

Which glomerular filtration rate-estimating equation most accurately detects change in glomerular filtration rate?

We also calculated, for each participant, whether their change in mGFR (reference test) and eGFRs (index tests) was ≥ 10 ml/minute/1.73 m^2 over the 3 years and compared these to calculate the sensitivity (i.e. percentage of patients with a change in mGFR ≥ 10 ml/minute/1.73 m^2 over the 3 years in whom a change ≥ 10 ml/minute/1.73 m^2 was also observed in the GFR estimate), specificity (i.e. percentage of patients without a change in mGFR ≥ 10 ml/minute/1.73 m^2 over the 3 years in whom a change ≥ 10 ml/minute/1.73 m^2 was also not observed in the GFR estimate), positive predictive value (PPV) and negative predictive value (NPV) for each of the eGFRs. The 10 ml/minute/1.73 m^2 cut-point was chosen as it was felt by clinical members of the study group to be a useful metric in practice, representing significant loss of renal function, and mapping to the original 2008 NICE definition of progression (albeit defined over 5 years, not 3 years).[40] A further analysis was undertaken based on whether participants showed a change of > 25% in mGFR and eGFR over the 3 years,[59] and separately a change of > 25% in combination with a change in disease category.[27] The sensitivity, specificity, positive and NPVs for the four eGFRs of interest to the primary outcome were calculated using standard approaches. A separate analysis was undertaken based on the biological variation of mGFR, as defined in the substudy (see *Study of intraindividual biological variation*). A true change in GFR was assumed to be a value that exceeded or equalled the RCV derived for the reference (measured) GFR test. The above

analyses were all repeated looking only at declines in mGFR and eGFR rather than changes in either direction, for example a decline of > 10 ml/minute/1.73 m^2/year, > 25%/year or greater than the RCV.

Which glomerular filtration rate-estimating equation, together with albumin-to-creatinine ratio, or albumin-to-creatinine ratio alone, most accurately predicts mortality and those people who have progressive loss of kidney function (chronic kidney disease progression)?

An analysis was undertaken to identify factors associated with loss of kidney function (defined in terms of decline in mGFR but also in terms of an increase in albuminuria category, as defined by KDIGO). Baseline eGFR, ACR and other relevant baseline variables (age, gender, ethnicity) were investigated as potential factors associated with progression. Baseline ACR was categorised into the three clinical ACR stages: < 3.0, 3.0–29.9 and ≥ 30.0 mg/mmol. We used logistic regression to model the relationship between the baseline factors and loss of kidney function, separately for each of the eGFRs. Logistic and Cox regression models were also used to study the relationship between these baseline variables and death within the study and time to death, respectively, as outcomes.

Substudy of disease progression

Analysis was undertaken using Stata/IC version 16.1.

The rate of decline (ml/minute/1.73 m^2/year) in mGFR and the difference between mGFRs and eGFRs (bias), assessed every 12 months, were modelled over time using a longitudinal linear random coefficients regression model, to estimate average and variability in disease progression and bias.[84] The random coefficients model included random effects for intercept and slope, allowing a different intercept and slope for each individual within the model. Rates of change in mGFR and bias were estimated from the slopes of the regression model, and reported with 95% CIs. Participants were included in the analysis if they had measurements recorded on more than one occasion during the study. Measured GFR was modelled on the natural and log-transformed scales. Parameters of the model for mGFR and bias were estimated using maximum likelihood. Between- and within-patient variability in the rate of decline of mGFR was also estimated.

Diagnostic plots of residuals, fitted values and marginal predictors for intercept and slope were assessed for normal distribution and constant variance assumptions and goodness of fit. The final models for mGFR and eGFRs on the natural scale indicated that normal distribution assumptions and goodness of fit were acceptable; for ACR, the diagnostic plots of log-transformed data were acceptable, and there was evidence of non-normality on the natural scale.

Covariates explored in the disease progression model for mGFR were as described earlier (see *Substudy of disease progression*). The time-varying covariates in the model were BMI, waist circumference, systolic BP and diastolic BP, the mean of the second and third BP measurements at each time was used for systolic and diastolic BP.

The effect of covariates on the population average intercept and longitudinal time effect (progression) was assessed. The method of backward elimination was used to remove covariates that were not significant from the model. As this was an exploratory analysis and the sample size was relatively small, parameters were retained in the model if the *p*-value was < 0.20. This enabled detection of possible associations which may be more significant in a larger sample. Where there was evidence of an interaction with time, indicating a difference in progression between categories defined by the covariate (e.g. between males and females), a factor was included in the model to estimate separate intercepts for categories of the covariate as well as separate slopes. Similarly, for continuous covariates in the model, if there was evidence that progression changed with different values of the covariate, an estimate of the change in intercept for the covariate was also included in the model.

The effect of drug class on the rate of progression was explored for drug classes where at least 10 participants in the substudy were taking medication within that class. Drug classes included in the analysis were thiazide diuretics, loop diuretics, beta-blockers, calcium channel blockers (CCBs), ACE inhibitors, A2RBs, alpha-blockers, statins, xanthine oxidase inhibitors (allopurinol) and antiplatelet agents.

It was originally planned to use the population Fisher information matrix optimal design algorithms (R open source software) to calculate the D-optimal[105] sampling times from the disease progression model based on reference GFR for people with diabetes and/or albuminuria, and for those with neither of these conditions. We intended to select optimal monitoring strategies from a set of designs with sampling every 6 months and compare monitoring strategies with a number of sampling points (between two and six). However, the mGFR disease progression model was linear and therefore these methods were not needed, as the optimal design solution is simplified for linear models, intuitively the slope is estimated optimally by the two design points with the greatest spread.[105] More frequent monitoring will increase accuracy of estimation.

Additional disease progression modelling was performed on eGFR (CKD-EPI$_{creatinine}$ and CKD-EPI$_{cystatin}$) and ACR measured every 6 months. The covariates and drug classes explored in the mGFR analysis were also explored in the eGFRs and ACR models. Parameter estimates, 95% CIs and estimates of within- and between-patient variability were compared to those for mGFR.

While our longitudinal cohort did not have adequate power to detect differences in progression, our data on mGFR and eGFR over time (study 1), patterns and determinants of progression (study 2), and intraindividual biological variation (study 3) were combined in a measurement model to evaluate the impact of alternative monitoring strategies on detection of NICE's combined progression criteria (see *Clinical guidelines*) and/or progression to stage 4 CKD. True GFR values were modelled over time for representative cohorts of people, and the comparative performance of alternative monitoring strategies in detecting progression (varying in choice of eGFR equation) was simulated utilising estimates of measurement error and accuracy. Outcome variables that were assessed included FP progression rates, and the sensitivity and delays in detecting progression.

Further assessment of covariates was performed by combining the data from the disease progression substudy with the main study and fitting the final covariate models for the substudy to the full data set. The main purpose of this was to check the inferences are consistent across the two data sets, as the full data set had more participants and hence more covariate information, while the substudy has more time points so progression is better defined.

Study of intraindividual biological variation

Data were log-transformed and normality tests were performed using the Shapiro–Wilk test. Outliers between duplicate measurements and of within-subject variance were excluded using Cochran's test and outliers amongst mean values of subjects were excluded using Reed's test.[35] Sensitivity analyses were also performed without exclusion of identified outliers. Log transformation was used to simplify calculation and because it improved the normality of the data as assessed by an increase in Shapiro–Wilk W statistic and visual examination of the distributions.

Terminology used was as proposed by Simundic *et al.*[106] Analytical (CV$_A$), individual (CV$_I$) and between-subject (CV$_G$) components of variation were calculated using standard approaches[35] of linear random-effects modelling with restricted maximum likelihood estimation (allowing for the clustering of observations within time points and repeated observations per patient) (Stata version 15). Exact geometric CVs $[\sqrt{(\exp(S^2) - 1)} \times 100]$[107,108] were calculated. CIs for SDs and CVs were estimated as described by Burdick and Graybill.[109] Differences in measures of CV, comparing the eGFR measures to mGFR, were investigated using multilevel models accounting for the clustering of test observations within individuals, using unstructured covariance matrices, in addition to the clustering of test results (multiple results per person, observation points and assessments). The critical difference (RCV) for

significant changes in serial results with 95% probability was calculated using the approach for log-normal data giving a negative and positive limit.[110] The derived RCV for the reference GFR was used to test the ability of eGFR equations to detect a true change in GFR. The number of specimens (*n*) required to produce a precise estimate of the homeostatic set-point with 95% confidence within ± 10% was calculated as:

$$n = [1.96 \cdot (CV_I^2 + CV_A^2)^{1/2}/10]^2 \quad (3)$$

For each biomarker, the index of individuality (II) was calculated as:

$$II = (CV_I^2 + CV_A^2)^{1/2}/CV_G \quad (4)$$

To confirm kidney function was stable across the study period, the iohexol GFR measures were modelled to identify trend with time using a multilevel linear regression model (allowing for clustering of assessments within time points and observations within individuals).

Secondary objectives

Secondary analyses covered a range of more recently published equations and modified versions of the equations evaluated in the primary analysis.

To estimate and compare the accuracy of more recent GFR-estimating equations that have been published while the study has been ongoing (BIS1 and BIS2 equations, CAPA equation, LMR equation, $FAS_{creatinine}$ equation, $FAS_{creatinine\text{-}cystatin}$ equation, EKFC equation and the 2021 revisions of the CKD-EPI equations, *Table 1*)

The P30 statistic was calculated to enable comparison of each of these equations to the reference mGFR, as in the primary analysis.

To evaluate and compare how accurately these newer GFR-estimating equations reflect and detect change in GFR over 3 years

Equations were subjected to the same analysis as described above (see *Which glomerular filtration rate-estimating equation most accurately tracks glomerular filtration rate over time?* and *Which glomerular filtration rate-estimating equation most accurately detects change in glomerular filtration rate?*).

To estimate and compare the performance of the MDRD and CKD-EPI equations using the Haycock equation for body surface area adjustment instead of the Du Bois equation

For the equations specified in the primary analysis, we calculated the P30 for the baseline measurements (comparing mGFR to eGFRs) using the Haycock equation for BSA adjustment rather than the more widely used Du Bois equation.

To assess the impact of cystatin C calibration on the performance of the cystatin C GFR-estimating equations

Samples (*n* = 106) covering a representative range of concentrations were measured by both methods (i.e. Abbott and Siemens). These observations were analysed using both Deming regression and linear regression analyses to generate an equation to adjust the Abbott results in the entire baseline study cohort to mimic Siemens results. These adjusted results were then used to estimate GFR in equations incorporating cystatin C and generated comparisons with mGFR for baseline and follow-up measurements, as per main study.

To assess the impact of creatinine methodology (enzymatic vs. isotope dilution mass spectrometry) on the performance of the MDRD equation and creatinine-based CKD-EPI equations

P30 for the baseline eGFR data was calculated using the ID-MS creatinine method and compared to that obtained with the enzymatic creatinine assay. We also undertook direct comparison of the ID-MS and enzymatic creatinine assays using regression and bias plot analyses.

Clinical accuracy and health economic analysis of monitoring with different estimated glomerular filtration rate equations

If cystatin C-based eGFR was found to be an improved approach to monitoring progression of CKD, then this would have cost implications for the healthcare sector. Cystatin C is more expensive than creatinine (£3.80 vs. £0.43); however, prompt identification of worsening kidney disease function may reduce additional treatment costs, offsetting the additional cost of testing. Furthermore, more accurate identification of individuals at high risk using cystatin C may reduce costs due to overdiagnosis and provide better management of low-risk individuals.[25,85]

A systematic review was conducted to identify previous studies that have assessed the cost-effectiveness of test-based strategies for CKD using a decision-analytic model. This review was conducted and published at the beginning of the project and then updated in the last year of the project (full details and results can be found in *Appendix 2*). A key objective was to examine how existing models have captured the clinical impact of monitoring kidney function over time, given that we only have accuracy data available from this study.

To better understand definitions around kidney disease progression and triggers for clinical action (which have been updated since the initiation of this study), we then summarised the latest key clinical guidelines (see *Clinical guidelines*). We then used the data and results from this study to compare the accuracy of the different estimating equations for predicting CKD progression (using the definitions warranting clinical action based on the latest clinical guidelines) – we describe this as 'clinical accuracy' [see *Comparative accuracy of estimated glomerular filtration rate equations for predicting accelerated progression (measurement model analysis)*]. This analysis is based on a simulated measurement model, which considers a 10-year horizon of annual GFR monitoring, with GFR estimation error simulated onto mGFR values based on the bias profile information derived from the current study.

A cost–utility analysis was planned to estimate the health and economic consequences of implementing cystatin C-based eGFR or a combination of both cystatin C and creatinine-based eGFR for monitoring subjects who are initially stage 3 CKD compared to MDRD (creatinine-based) eGFR alone. In the absence of an accuracy improvement, a comparative cost analysis was reported to demonstrate the economic implications of implementing cystatin C based equations for monitoring those who are initially stage 3 CKD (see *Comparative cost of monitoring with different estimated glomerular filtration rate equations*).

Serious adverse events

The only study-related safety risk to participants involved the administration of iohexol (contrast medium) required for the reference GFR measure, which does not form part of routine clinical practice and takes approximately 5 hours to complete. The associated risks may include risk from venepuncture and vein cannulation, idiosyncratic reaction to iohexol and a theoretical risk of deteriorating kidney function with injection of iohexol.

These risks are in all cases extremely low. The following adverse events (AEs) that could be reasonably 'expected' for this group of patients during the course of the study were:

- nausea
- mild urticaria, with or without pruritus
- transient sensation of mild warmth
- haematomas and ecchymoses around injection site
- bronchospasm.

These represent minimal risk to participants, so for the purposes of this study these AEs did not require reporting to the eGFR-C Study Office. Serious adverse events (SAEs) occurring within 24 hours of iohexol administration (and not listed as 'expected' as defined above) were reportable to the eGFR-C Study Office on an SAE form. The assessment of relatedness and expectedness to the administration of iohexol is a clinical decision based on all available information at the time. SAEs outside of this time frame could also be reported if it was the opinion of the investigator that there was a possible causal relationship to another aspect of the study. An independent clinical assessment of relatedness and expectedness would also be undertaken.

Study oversight and ethical approval

All co-investigators were members of the project management group. Annual face-to-face meetings were held at the Birmingham Clinical Trials Unit (BCTU) with approximately bimonthly teleconferences. The project management group reviewed issues including recruitment against target, data management, nursing aspects, training issues (e.g. with the reference GFR technique), laboratory issues and statistical interpretation.

There was an independent study steering committee (Trial Steering Committee equivalent). This comprised an independent chairperson (Dr Charlie Tomson, Consultant Nephrologist and Immediate Past-President of the Renal Association), one other independent nephrologist (Professor Hugh Gallagher), a patient representative, the study statistician, an independent statistician (Professor Rafael Perera, Director of MaDOX, University of Oxford), the chief investigator, the study lead research nurse and one co-applicant. This group met at the beginning of the study and thereafter up to 6-monthly intervals depending on progress.

The study budget was managed by East Kent Hospitals University NHS Foundation Trust with subcontracts being arranged with the other participating organisations.

The Health Technology Assessment (HTA) grant award commenced on 1 August 2013. Approval from the National Research Ethics Service was obtained (reference 13/LO/1349, approved 9 October 2013). Written informed consent was obtained from all participants. Participant information leaflets were prepared in collaboration with the patient representative on the study group [Mrs Fiona Loud, Director of the former Kidney Alliance and now Policy Director of Kidney Care UK (www.kidneycareuk.org/, accessed 12 April 2023)] and were circulated for comment to patient groups at the recruiting units and to the Research Design Service south-east public patient involvement group. Recruitment and retention strategies were adjusted to meet the needs of the specific ethnic minority groups including the production of translated material and use of translators where required for non-English speakers.

Data from this study were handled by the BCTU, a full-time research facility dedicated to, and with substantial experience in, the design and conduct of clinical research. Data were collected, analysed and reported using secure data collection procedures and anonymisation was used.

Chapter 3 Results

Recruitment and flow of participants through the study

The aim of the study was to recruit 1320 individuals in total, including 300 who would participate in the substudy of disease progression and 20 who would participate in the biological variation substudy.[88] The first participant was recruited in April 2014 (see *Appendix 1*, *Table 36*) but not all centres opened to recruitment at the same time. It was anticipated that with 6 recruiting centres a recruitment rate of approximately 72 participants per month was realistic, but this rate was difficult to achieve. Recruitment to the substudy of disease progression was particularly difficult, possibly due to its more intensive testing regime. Recruitment of Asian and African-Caribbean individuals was also more difficult than expected, and target population sizes had to be modified accordingly. Recruitment and retention were reviewed and discussed regularly at study management group meetings. Various changes to the study were made to improve recruitment, including extending primary care recruitment beyond the two centres originally envisaged, modifying and translating participant information sheets. Retention in the study was encouraged through newsletters and sending final appointment reminder letters. In January 2017 revised sample size/power calculations indicated that under the proposed analysis method for the primary outcomes, with 1167 evaluable subjects the study had > 87% power to detect a 5% difference in P30 between equations at baseline, and with 875 evaluable subjects at study end had > 85% power to compare proportions of equations with a more than 3 ml/minute/1.73 m^2/year error over 3 years. Following discussion between the study management group, the independent study steering committee and the funder, recruitment was terminated due to low ongoing recruitment rates.

Main study: prospective longitudinal cohort study

In total, 29,845 people were screened for potential suitability for study inclusion: 15,340 were deemed unsuitable at an early stage from informatics and clinic lists due to not having CKD stage 3. Other identified reasons for unsuitability included that they were too unwell, had recently had AKI, were unable to consent, were known alcohol or drug abusers, had had a previous reaction to iodine, were amputees, were under 18 years of age or were pregnant or breastfeeding. People considered suitable for study inclusion (n = 6209) were approached in person and/or sent participant information sheets. A further 4000 individuals were contacted through their primary care provider. Reasons for declining to participate were recorded in 928 cases. The major reasons for declining were that the participants were not interested in research; that they had too many medical appointments; that the 5-hour appointment time was too long; that too much travel was involved; that they were already in other research studies; and that the study involved too many injections.

A total of 1229 participants were recruited to the main study between April 2014 and January 2017, representing 95% of the target recruitment number. Recruitment was primarily from secondary/tertiary care, with 72 patients being recruited from primary care. Details of cumulative recruitment per month and recruitment by site and withdrawal by site may be found in *Appendix 1* (see *Appendix 1*, *Tables 37* and *38*). *Figure 2* shows the flow of participants through the study, using the format recommended by the Consolidated Standards of Reporting of Trials.[111]

Of the 1229 participants recruited to the study, 1205 and 1180 respectively had evaluable estimated and mGFRs at baseline, with 1167 (95.0%) having both eGFRs and mGFRs recorded. At 36 months 976 participants remained in the study, of whom 875 (71.2%) had evaluable estimated and mGFRs at both baseline and 36 months. The last patient visit occurred in January 2020. Following laboratory analyses and data queries, the study database was locked on 30 April 2021 (see *Appendix 1*, *Table 36*).

Overall, 253 (20.6%) participants withdrew from the study. Consent was withdrawn by 112 (9.1%), 79 (6.4%) were lost to follow-up (LTFU) and there were 62 (5.0%) deaths. Causes of death were cancer (16),

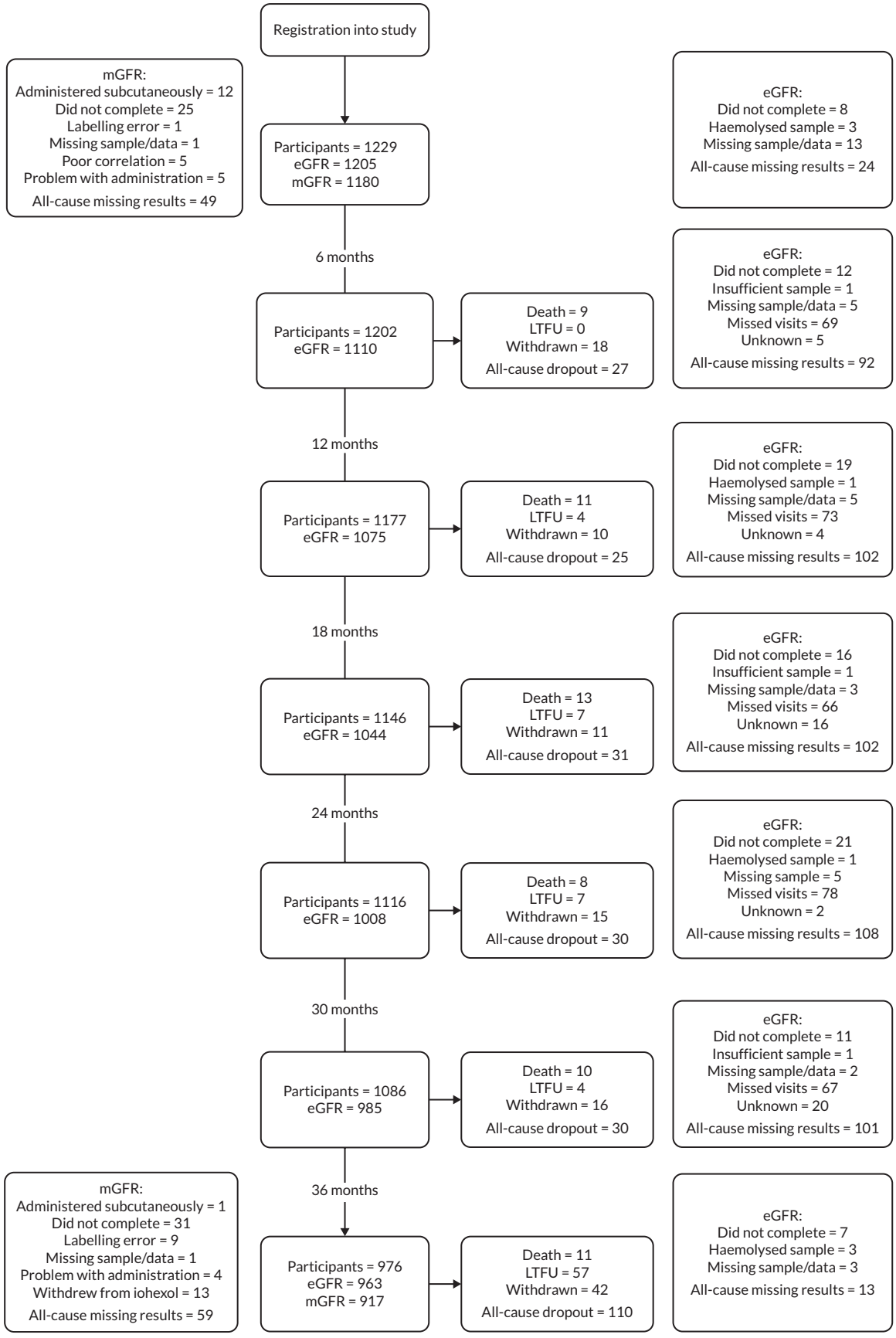

FIGURE 2 Consolidated Standards of Reporting Trials flow diagram illustrating recruitment and follow-up in the prospective longitudinal cohort study.

cardiovascular disease (14), respiratory disease (11), kidney disease (4), cerebrovascular (1), liver disease (1), other (6) and unknown (9). In addition to death and loss to follow-up, reasons for withdrawing from the study included illness (60), commencement of kidney replacement therapy (12), inability to complete sampling (9), suspected reaction to iohexol (5), loss from area (3), carer commitment (2), other reasons (7) and no reason given (14). A further 25 participants were unable to complete their 36-month mGFR test, increasing the total effective dropout rate to 22.6%. Study dropout appears to escalate at the final time point of the study: this reflects closure of records of participants that the research teams had been trying to retain in the study up to this point (e.g. the participant was no longer contactable).

Substudy of disease progression

Fewer participants were recruited to the substudy than planned. In addition, due to difficulties in recruiting participants from some ethnic groups, more than the planned number of Caucasian participants and fewer South Asian and African-Caribbean participants were recruited. A total of 278 participants were recruited to the substudy of patterns of disease progression between April 2014 and December 2016, representing 93% of the target recruitment number. Of these, 128 (46%) had diabetes and/or albuminuria. There were 196 Caucasian (70%), 47 African-Caribbean (17%) and 35 South Asian participants (13%) in the substudy.

Figure 3 shows the flow of participants through the substudy. Of the 278 participants recruited to the study, 269 and 273 respectively had evaluable mGFRs and at least one eGFR recorded at baseline, with 265 (95%) having both estimated and mGFRs recorded. Attrition was 22.7% for the substudy, with 215 participants remaining in the study at the end of year 3. Of these, 214 and 198 respectively had evaluable estimated and mGFRs, with 197 (71%) having both mGFRs and at least one eGFR recorded. The last patient visit occurred in December 2019.

Overall, 63 (22.7%) participants dropped out of the study. Consent was withdrawn by 31, 22 were LTFU and there were 10 deaths. Of those who were LTFU, 50% were African-Caribbean. Causes of death were cancer (2), cardiovascular disease (4), respiratory disease (2) and unknown (2). In addition to death and loss to follow-up, reasons for withdrawing from the study included illness (20), suspected reaction to iohexol (1), loss from the area (1), other reasons (1) and no reason given (8). A further 17 participants were unable to complete their 36-month mGFR test, increasing the total effective dropout rate to 28.8%. Seventeen participants crossed over from the substudy to the main study (i.e. withdrawing from additional iohexol-mGFR tests). One patient crossed over to the main study at one time point but subsequently returned to the substudy. Patients have been included in the substudy analysis if data were collected at more than one time point.

The number of participants recruited was sufficient to perform the planned analysis and investigate the 12 covariates of interest. There were only three participants with type I diabetes; therefore type of diabetes was not included in the analysis model. Smoking status changed very little during the study and the number of current smokers was small so only baseline smoking status was used in the analysis. Similarly, most participants with diabetes were diagnosed before the study began and baseline diabetes status was used in the analysis model and the duration of diabetes was calculated at baseline. Vascular disease was defined as described above (see *Sampling and data collection*). Due to the low numbers of South Asian and African-Caribbean participants, separate variance parameters were not included in the analysis models for these ethnic groups. It was assumed that variability is similar across ethnic groups. Differences between ethnic groups were explored, and estimates and CIs were calculated. Inferences drawn from the substudy analysis results should be interpreted more cautiously due to the limited number of South Asian and African-Caribbean participants.

Study of intraindividual biological variation

Participants (n = 20) were recruited to the study between August 2014 and July 2015.[97] *Figure 4* shows the flow of participants through the study. All 20 patients attended all four iohexol-mGFR procedures except one patient who missed their final appointment. Results from five iohexol clearances (five

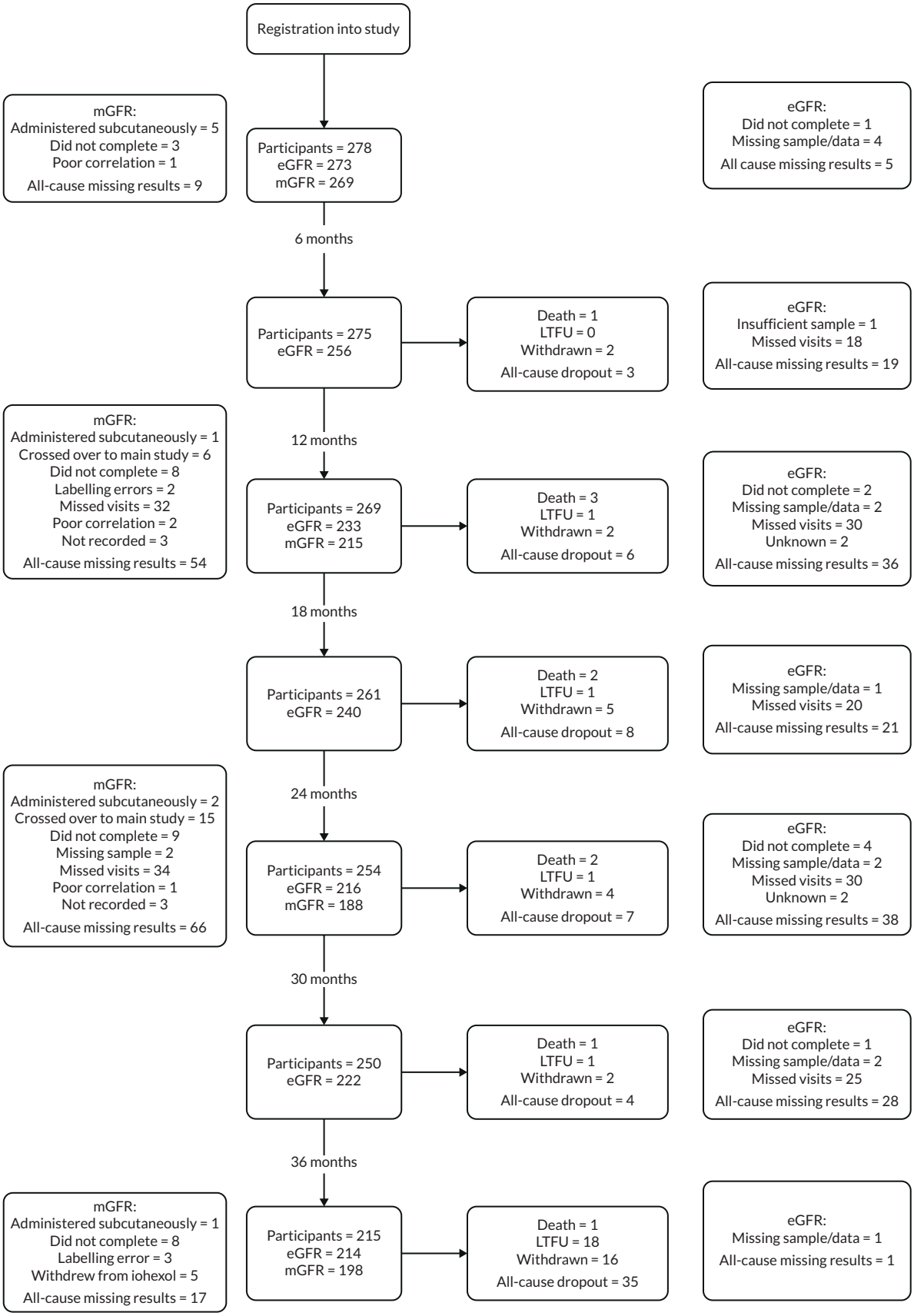

FIGURE 3 Consolidated Standards of Reporting Trials flow diagram illustrating recruitment and follow-up in the substudy of disease progression.

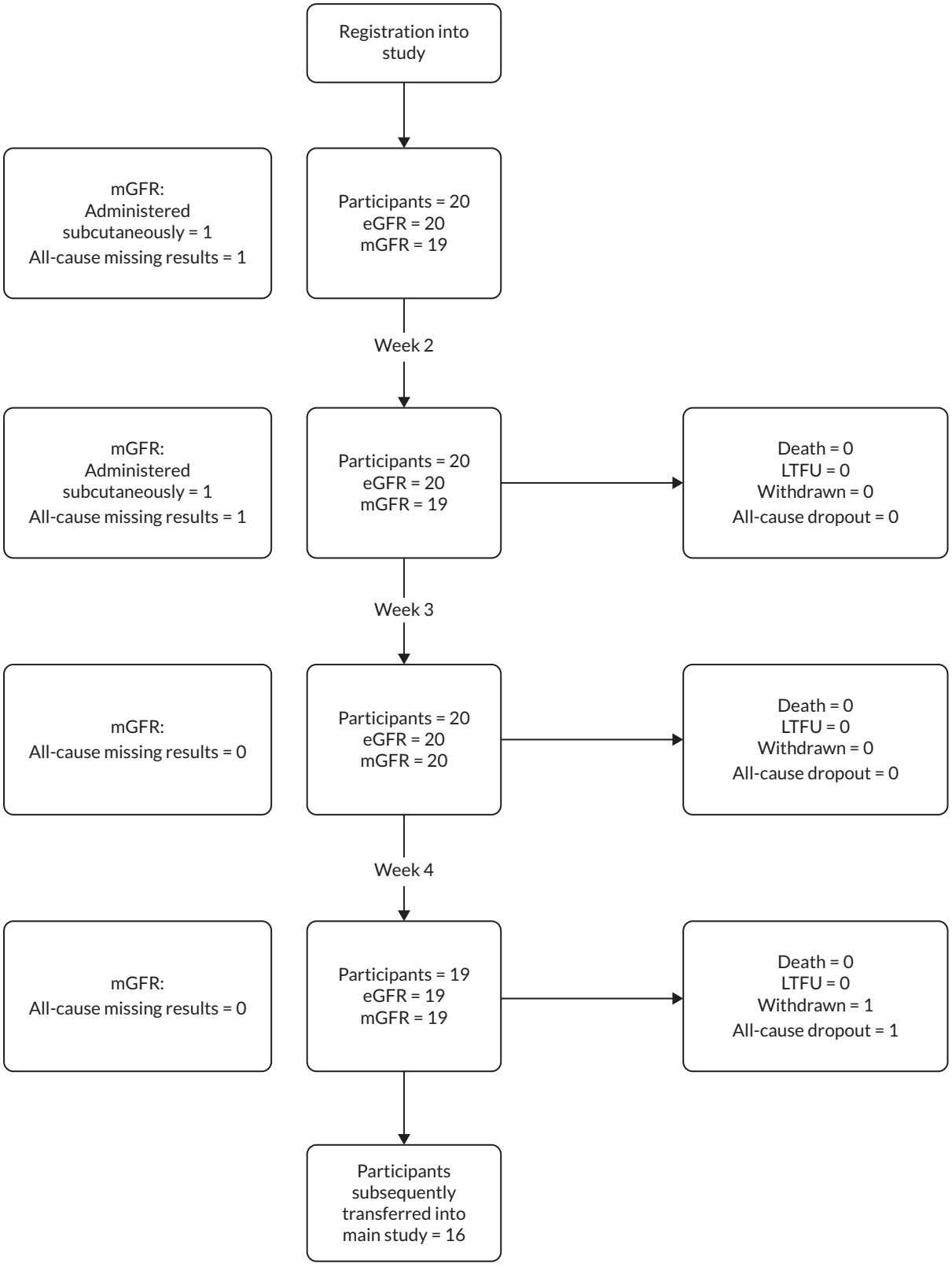

FIGURE 4 Consolidated Standards of Reporting Trials flow diagram illustrating recruitment and follow-up in the study of intraindividual biological variation.

separate patients) were excluded before analysis, as the dose given was not fully administered or it was given subcutaneously. Medications were held constant during the 4 weeks of the study, except that two patients received a 1-week course of amoxicillin (500 mg tds) due to chest infection. Sixteen of the participants subsequently entered the main study, with their first iohexol-mGFR being used as their baseline test.

Baseline characteristics of the study subjects

Main study: prospective longitudinal cohort study

Characteristics of the study subjects are shown in *Table 2*. The median age of participants was 67.5 years; 714 (58%) were male and 1066 (87%) were Caucasian. Diabetes was a pre-existing diagnosis in 28.3% of participants. The median mGFR at baseline was 46.8 ml/minute/1.73 m^2 and 56.8% had albuminuria (ACR ≥ 3 mg/mmol). There were 71 people in the baseline cohort with mGFR below 30 ml/minute/1.73 m^2 and 211 people with mGFR ≥ 60 ml/minute/1.73 m^2, with a total range of values from 11.9 to 103.7 ml/minute/1.73 m^2.

Substudy of disease progression

Characteristics of the study participants are shown in *Table 3*. The characteristics of those who remained in the study at the end of year 3 were similar to those at baseline. The proportion of participants in the substudy who were current smokers was low. There were very few missing values for the participant characteristics and continuous covariates at baseline. Analysis was performed on observed data and missing values were not estimated.

The evaluable population for disease progression modelling included those participants with paired mGFR and eGFR at two or more time points. We included individuals with at least two times so the data for each individual could contribute to the random intercept and slope terms in the model, and by including those with both mGFR and eGFR at two time points comparisons of mGFR and eGFR models were based on the same samples.

Study of intraindividual biological variation

Characteristics of the study subjects are shown in *Table 4*. Application of Cochran and Reed's tests led to the exclusion of between one and three duplicate measurements for mGFR or eGFR and to the exclusion of one outlying within-subject measurement for iohexol clearance. Overall, no patient was completely excluded and all calculations of biological variation for mGFRs and eGFRs were based on a minimum of 3 weeks' data in all individuals.

Primary study: objectives and results

Accuracy of Glomerular Filtration Rate-estimating equations including the Modification of Diet in Renal Disease equation and three Chronic Kidney Disease-Epidemiology Consortium equations using either creatinine or cystatin C or a combination of both in people with stage 3 chronic kidney disease: baseline analysis

During the course of the study, we became aware of significant published concerns regarding bias of the Abbott cystatin C assay. Re-analysis of some historical stored samples suggested to us that the Abbott assay had undergone a significant change in standardisation around the time when the present study commenced (data not shown). In a laboratory analytical recovery study, the Abbott cystatin C assay was found to over-recover added international reference preparation cystatin C by an average of 109.1%. Given the potential negative impact of this on cystatin C eGFR, this was further explored by comparing cystatin C values with those obtained with an alternative assay (Siemens). Cystatin C results obtained using the Siemens method were lower than those using the Abbott assay, the relationship between the two methods being described by the linear regression equation Siemens = −0.08 + 0.94(Abbott). CIs

TABLE 2 Baseline characteristics of the main prospective longitudinal cohort study population

Characteristics	All participants recruited	All participants with mGFR and eGFR at baseline[a]	All participants with mGFR and eGFR at baseline and 3-year follow-up[b]
n	1229	1167	875
Age, years	67.5 (58.2–74.5)	67.5 (58.3–74.5)	67.1 (58.1–73.6)
M : F, *n*	714 : 515	680 : 487	505 : 370
Ethnicity			
Caucasian, *n* (%)	1066 (86.7)	1014 (86.9)	773 (88.3)
African-Caribbean, *n* (%)	68 (5.5)	60 (5.1)	36 (4.1)
South Asian, *n* (%)	67 (5.5)	66 (5.7)	46 (5.3)
Other, *n* (%)[c]	28 (2.3)	27 (2.3)	20 (2.3)
Height, cm	170 (162–176)	170 (162–176)	170 (163–176)
Weight, kg	84.6 (72.6–97.7)	84.1 (72.5–97.3)	84.7 (73–97.2)
Du Bois BSA, m^2	1.96 (1.80–2.11)	1.96 (1.80–2.10)	1.96 (1.81–2.11)
Haycock BSA, m^2	2.02 (1.84–2.20)	2.02 (1.84–2.19)	2.02 (1.86–2.19)
BMI, kg/m^2	29.0 (25.8–33.5)	29.0 (25.8–33.3)	29.0 (25.7–33.4)
Medication recorded (*n*, %)	Thiazide diuretic (128, 10.4), loop diuretic (193, 15.7), potassium-sparing diuretic (27, 2.2), beta-blocker (326, 26.5), CCB (394, 32.1), ACE inhibitor (435, 35.4), A2RB (362, 29.5), alpha-blocker (160, 13.0), HMG CoA reductase inhibitor (668, 54.4), allopurinol (143, 11.6), antiplatelet drugs (387, 31.5)	Thiazide diuretic (123, 10.5), loop diuretic (180, 15.4), potassium-sparing diuretic (26, 2.2), beta-blocker (314, 26.9), CCB (376, 30.6), ACE inhibitor (411, 35.2), A2RB (348, 29.8), alpha-blocker (153, 13.1), HMG CoA reductase inhibitor (635, 54.4), allopurinol (137, 11.7), antiplatelet drugs (367, 31.4)	Thiazide diuretic (94, 10.7), loop diuretic (114, 13.0), potassium-sparing diuretic (18, 2.1), beta-blocker (223, 25.5), CCB (273, 31.2), ACE inhibitor (317, 36.2), A2RB (267, 30.5), alpha-blocker (111, 12.7), HMG CoA reductase inhibitor (463, 52.9), allopurinol (105, 12.0), antiplatelet drugs (258, 29.5)
Comorbidity recorded (*n*, %)[d]	Diabetes mellitus (348, 28.3), ischaemic heart disease (189, 15.4), angina (91, 7.4), heart failure (57, 4.6), cerebrovascular disease (92, 7.5), TIA (51, 4.1), stroke (42, 3.4), HBV (20, 1.6), malignancy (203, 16.5)	Diabetes mellitus (324, 27.8), ischaemic heart disease (177, 15.2), angina (88, 7.5), heart failure (55, 4.7), cerebrovascular disease (85, 7.3), TIA (48, 4.1), stroke (37, 3.2), HBV (18, 1.5), malignancy (191, 16.4)	Diabetes mellitus (220, 25.1), ischaemic heart disease (120, 13.7), angina (60, 6.9), heart failure (30, 3.4), cerebrovascular disease (56, 6.4), TIA (29, 3.3), stroke (26, 3.0), HBV (14, 1.6), malignancy (134, 15.3)
Smoking status			
Non-smoker, *n* (%)	612 (49.8)	590 (50.6)	453 (51.8)
Current smoker, *n* (%)	110 (9.0)	101 (8.7)	63 (7.2)
Former smoker, *n* (%)	502 (40.9)	474 (40.6)	357 (40.8)
Unknown, *n* (%)	5 (0.4)	2 (0.2)	2 (0.2)
Urine albumin concentration			
< 3 mg/mmol, *n* (%)	498 (40.5)	483 (41.4)	375 (42.9)
3–30 mg/mmol, *n* (%)	421 (34.3)	396 (33.9)	295 (33.7)

continued

TABLE 2 Baseline characteristics of the main prospective longitudinal cohort study population (*continued*)

Characteristics	All participants recruited	All participants with mGFR and eGFR at baseline[a]	All participants with mGFR and eGFR at baseline and 3-year follow-up[b]
> 30 mg/mmol, *n* (%)	277 (22.5)	269 (23.1)	195 (22.3)
Missing, *n* (%)	33 (2.7)	19 (1.6)	10 (1.1)
Serum creatinine, µmol/l	129 (108–153) *n* = 1209	129 (107–154) *n* = 1167	132 (109–162) *n* = 875
Serum cystatin C, mg/l (Siemens)	1.53 (1.28–1.81) *n* = 1209	1.53 (1.28–1.81) *n* = 1167	1.55 (1.26–1.84) *n* = 875
Serum cystatin C, mg/l (Abbott)	1.71 (1.45–2.01) *n* = 1209	1.71 (1.45–2.01) *n* = 1167	1.73 (1.43–2.04) *n* = 875
CKD GFR category ('stage') at baseline based on mGFR, *n* (%)			
1 *n* (%)	7 (0.6)	7 (0.6)	5 (0.6)
2, *n* (%)	204 (17.3)	204 (17.5)	163 (18.6)
3A, *n* (%)	458 (38.8)	452 (38.7)	366 (41.8)
3B, *n* (%)	440 (37.3)	434 (37.2)	303 (34.6)
4, *n* (%)	69 (5.8)	68 (5.8)	38 (4.3)
5, *n* (%)	2 (0.2)	2 (0.2)	0 (0)
Measured GFR, ml/minute/1.73 m^2	46.8 (38.7–56.3) *n* = 1180	47.0 (38.7–56.4) *n* = 1167	48.1 (40.2–57.2) *n* = 875
MDRD, ml/minute/1.73 m^2	44.1 (36.2–52.0) *n* = 1205	44.0 (36.2–52.0) *n* = 1167	44.6 (37.1–52.4) *n* = 875
CKD-EPI$_{creatinine}$, ml/minute/1.73 m^2	44.8 (36.9–53.8) *n* = 1205	44.8 (36.7–53.8) *n* = 1167	45.7 (37.7–54.2) *n* = 875
CKD-EPI$_{cystatin}$, ml/minute/1.73 m^2 (Siemens)	42.1 (33.7–53.4) *n* = 1205	42.3 (33.8–53.4) *n* = 1167	43.6 (35.0–54.3) *n* = 875
CKD-EPI$_{cystatin}$, ml/minute/1.73 m^2 (Abbott)	36.3 (29.3–45.3) *n* = 1205	36.4 (29.4–45.5) *n* = 1167	37.5 (30.4–46.3) *n* = 875
CKD-EPI$_{creatinine-cystatin}$, ml/minute/1.73 m^2 (Siemens)	42.6 (34.7–52.2) *n* = 1205	42.7 (34.6–52.4) *n* = 1167	43.4 (35.9–53.3) *n* = 875
CKD-EPI$_{creatinine-cystatin}$, ml/minute/1.73 m^2 (Abbott)	39.3 (32.2–48.1) *n* = 1205	39.4 (32.2–48.1) *n* = 1167	40.2 (33.3–48.9) *n* = 875

HBV, hepatitis B virus; HMG CoA, hydroxymethyl glutaryl CoA reductase; TIA, transient ischaemic attack.
a Participants with mGFR and ANY eGFR results at baseline were included.
b Participants with mGFR and ANY eGFR results at both baseline and follow-up were included.
c 'Other' includes participants with ethnic backgrounds other than Caucasian, South Asian or African-Caribbean, plus three individuals where data were not recorded.
d Only comorbidities affecting a minimum of 20 individuals in the baseline recruited cohort are listed.

Note
Values for continuous data are shown as median (IQR).

TABLE 3 Baseline characteristics of the substudy of disease progression population

Characteristics	All participants recruited	All participants with paired mGFR and eGFR on at least two occasions
n	278	239
Age, years	65.0 (56.0–74.0)	65.0 (57.0–73.0)
M : F, *n*	180 : 98	161 : 78
Ethnicity		
Caucasian, *n* (%)	196 (70.5)	174 (72.8)
African-Caribbean, *n* (%)	47 (16.9)	35 (14.6)
South Asian, *n* (%)	35 (12.6)	30 (12.6)
Height, cm	170 (163–177)	170 (164–178)
Weight, kg	85.5 (72.8–98.0)	85.1 (72.0–97.3)
BSA, m^2	1.98 (1.79–2.12)	1.98 (1.79–2.12)
BMI, kg/m^2	29.3 (25.6–33.3)	28.7 (25.3–33.2)
Medication record (*n*, %)[a]	Thiazide diuretic (28, 10.1), loop diuretic (56, 20.1), beta-blocker (80, 28.8), CCB (111, 39.9), ACE inhibitor (111, 39.9), A2RB (79, 28.4), alpha-blocker (49, 17.6), HMG CoA reductase inhibitor (148, 53.2), allopurinol (33, 11.9), antiplatelet drugs (86, 30.9)	Thiazide diuretic (26, 10.9), loop diuretic (45, 18.8), beta-blocker (65, 27.2), CCB (94, 39.3), ACE inhibitor (92, 38.5), A2RB (68, 28.4), alpha-blocker (40, 16.7), HMG CoA reductase inhibitor (126, 52.7), allopurinol (32, 13.4), antiplatelet drugs (71, 29.7)
Comorbidity (*n*, %)[a]	Diabetes mellitus (73, 26.6), ischaemic heart disease (33, 12.0), heart failure (15, 4.4), cerebrovascular disease (22, 8.0), TIA (12, 4.4), stroke (10, 3.6), angina (15, 5.5), malignancy (40, 14.6)	Diabetes mellitus (60, 25.1), ischaemic heart disease (28, 11.8), heart failure (10, 4.2), cerebrovascular disease (19, 8.0), TIA (11, 4.6), angina (12, 5.0), malignancy (36, 15.1)
Smoking status		
Non-smoker, *n* (%)	156 (56.5)	132 (55.2)
Current smoker, *n* (%)	27 (9.8)	23 (9.6)
Former smoker, *n* (%)	93 (33.7)	84 (35.2)
Urine albumin concentration < 3 mg/mmol, *n* (%)	100 (36.0)	92 (38.5)
Urine albumin concentration 3–30 mg/mmol, *n* (%)	102 (36.7)	86 (36.0)
Urine albumin concentration > 30 mg/mmol, *n* (%)	76 (27.3)	61 (25.5)
Serum creatinine, µmol/l	135 (114–167) *n* = 276	135 (115–170) *n* = 238
Serum cystatin C, mg/l (Siemens)	1.56 (1.29–1.80) *n* = 276	1.57 (1.27–1.81) *n* = 238
Measured GFR, ml/minute/1.73 m^2	47.2 (38.2–57.9) *n* = 269	47.2 (38.4–58.2) *n* = 235
MDRD, ml/minute/1.73 m^2	42.8 (35.2–52.5) *n* = 273	43.2 (34.8–52.8) *n* = 236
$CKD\text{-}EPI_{creatinine}$, ml/minute/1.73 m^2	43.6 (36.2–53.4) *n* = 273	44.6 (35.4–53.6) *n* = 236

continued

TABLE 3 Baseline characteristics of the substudy of disease progression population (*continued*)

Characteristics	All participants recruited	All participants with paired mGFR and eGFR on at least two occasions
CKD-EPI$_{cystatin}$, ml/minute/1.73 m^2	42.1 (34.8–54.0) *n* = 273	42.1 (34.9–54.5) *n* = 236
CKD-EPI$_{creatinine\text{-}cystatin}$, ml/minute/1.73 m^2	42.1 (35.1–52.8) *n* = 273	42.1 (35.2–54.4) *n* = 236

HBV, hepatitis B virus; HMG CoA, hydroxymethyl glutaryl CoA reductase; TIA, transient ischaemic attack.
a Only medications and comorbidities affecting a minimum of 10 individuals in the baseline recruited cohort are listed.

Note
Values for continuous data are shown as median (IQR).

TABLE 4 Characteristics of the intraindividual biological variation study population

Characteristic	
n	20
Age, years	71 (50–80)
M : F	10 : 10
Caucasian (*n*)	20
Height, cm	170.5 (154–194)
Weight, kg	79.5 (47.1–118.1)
BSA, m^2	1.99 (1.42–2.47)
BMI, kg/m^2	28.2 (19.6–40.9)
Medication record (*n*)	Thiazide diuretic (3), loop diuretic (3), potassium sparing diuretic (2), beta-blocker (7), CCB (4), ACE inhibitor (8), A2RB (6), alpha-blocker (1), isosorbide mononitrate (1), HMG CoA reductase inhibitor (13), allopurinol (4), antiplatelet drugs (7)
Comorbidity (*n*)	Type 2 diabetes mellitus (3), ischaemic heart disease (7), angina (1), heart failure (2)
Smoking status – current/former (*n*)	1/10
Urine albumin concentration < 3 mg/mmol (*n*)	9
Urine albumin concentration 3–30 mg/mmol (*n*)	7
Urine albumin concentration > 30 mg/mmol (*n*)	4
Serum creatinine, µmol/l	124 (79–182)
Serum cystatin C, mg/l (Abbott)	1.67 (1.01–2.30)
Measured GFR, ml/minute/1.73 m^2	49.0 (30.8–71.6)[a]
MDRD, ml/minute/1.73 m^2	42.2 (31.5–61.4)
CKD-EPI$_{creatinine}$, ml/minute/1.73 m^2	43.0 (30.8–62.8)
CKD-EPI$_{cystatin}$, ml/minute/1.73 m^2	36.8 (23.5–67.1)
CKD-EPI$_{creatinine\text{-}cystatin}$, ml/minute/1.73 m^2	38.2 (27.2–65.4)

HMG CoA, hydroxymethyl glutaryl coenzyme A.
a Excludes data from five failed iohexol procedures (five separate patients).

Note
Values for continuous data are shown as median (range). Anthropometric data are based on baseline measurements. Estimated and measured[a] GFR, creatinine and cystatin C data are calculated using all values over the 4 weeks.

for the intercept and slope were −0.12, −0.03 and 0.92, 0.96, respectively (see *Appendix 1*, *Figure 14*). Deming regression produced a similar equation (see *Appendix 1*, *Table 39*).

Glomerular Filtration rate estimates of cystatin C containing CKD-EPI equations were recalculated using a recalibration of cystatin C values based on this regression equation. The rationale for this recalibration is considered further in the *Discussion* section of this report. In this section (*Accuracy of glomerular filtration rate-estimating equations including the Modification of Diet in Renal Disease equation and three Chronic Kidney Disease-Epidemiology Consortium equations using either creatinine or cystatin C or a combination of both in people with stage 3 chronic kidney disease: baseline analysis*), results for both the initial (Abbott) cystatin C equations and the recalibrated (Siemens) cystatin C containing equations are shown to illustrate the impact of calibration. In subsequent sections of the results chapter, only the recalibrated cystatin C-containing equations are shown.

All estimates of GFR relating to the primary study objectives were negatively biased overall compared to mGFR (see *Table 5* and *Figure 5*). As would be predicted, recalibration of the cystatin C-containing equations with Siemens results improved the negative bias. There was no difference in bias overall against mGFR between the MDRD, CKD-EPI$_{creatinine}$, CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations. However, both the MDRD and CKD-EPI$_{creatinine}$ equations demonstrated positive bias at lower levels of GFR and increasing negative bias at higher levels of GFR: this effect was largely attenuated when the CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations were used (*Figure 6*). CKD-EPI equations incorporating recalibrated cystatin C values showed an improvement in performance (P30, 95% CI) compared to the same equations using Abbott cystatin C results (*Table 5*); for example, CKD-EPI$_{cystatin}$ 72.5 (69.8 to 75.0) versus 89.5 (87.6 to 91.2) when adjusted values were used. Accuracy (P30) of the recalibrated CKD-EPI$_{cystatin}$ equation did not differ from that of the MDRD and CKD-EPI$_{creatinine}$ equations (*Table 6*), while accuracy of the recalibrated CKD-EPI$_{creatinine\text{-}cystatin}$ equation was superior to that of all of these equations (94.9% CI 93.5 to 96.1) (see *Table 6* and *Figure 5*). In general, P15 values followed a similar rank order between equations to P30 values but were significantly lower.

Accuracy of glomerular filtration rate-estimating equations according to age, gender, diabetes, albuminuria, body mass index, measured glomerular filtration rate level and ethnic group (particularly Caucasian, South Asian and African-Caribbean)

Performance (P30) of GFR-estimating equations was examined by categories of age, gender, diabetes, albuminuria, BMI, level of GFR (*Table 7*) and ethnic group (particularly Caucasians, South Asian and African-Caribbean) (*Table 8*). For each characteristic, data for equations incorporating cystatin C utilised cystatin C values obtained following assay recalibration (see *Accuracy of glomerular filtration rate-estimating equations including the Modification of Diet in Renal Disease equation and three Chronic Kidney Disease-Epidemiology Consortium equations using either creatinine or cystatin C or a combination of both in people with stage 3 chronic kidney disease: baseline analysis*). Although in some cases point estimates suggest differences with certain characteristics (e.g. inferior performance in people with higher BMI), for none of the equations were any of the changes significant (i.e. confidence intervals of the P30 estimates were overlapping across categories).

In the overall cohort, removal of the race adjustment factors had no impact (overlapping CIs) on the median bias or accuracy (P30) of the MDRD, CKD-EPI$_{creatinine}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations (see *Table 5*). There was no evidence (overlapping CIs) of a difference in accuracy of any of the equations across ethnic groups (*Table 8*). Removal of the adjustment factor for African-Caribbean ethnicity in the MDRD, CKD-EPI$_{creatinine}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations resulted in decreased point estimates of P30 for these participants, although this only achieved significance ($p < 0.05$) for the MDRD equation (see *Table 8*). The 2021 revisions of the CKD-EPI equations, which were specifically remodelled to address concerns around interethnic performance, were also included here for comparison.

TABLE 5 Performance of the GFR-estimating equations at baseline compared to mGFR

Equation	Bias (eGFR minus mGFR), mean difference (SD) (95% CI), ml/minute/1.73 m²	Bias (eGFR minus mGFR), median difference (IQR), ml/minute/1.73 m²	Accuracy, percentage of estimates within 30% of mGFR (P_{30}) (95% CI)	Accuracy, percentage of estimates within 15% of mGFR (P_{15}) (95% CI)	Accuracy, RMSE, ml/minute/1.73 m²
MDRD	**−3.8 (9.2) (−4.3 to −3.3)**	**−3.7 (−9.7 to 2.4)**	**89.5 (87.6 to 91.2)**	**52.0 (49.1 to 54.9)**	**9.09**
MDRD (no race adjustment)	−4.2 (9.3) (−4.7 to −3.7)	−4.0 (−10.1 to 2.0)	88.4 (86.5 to 90.2)	51.0 (48.1 to 53.9)	9.25
CKD-EPI$_{creatinine}$	**−2.5 (9.1) (−3.0 to −1.9)**	**−2.8 (−8.2 to 3.5)**	**90.2 (88.4 to 91.9)**	**56.0 (53.1 to 58.8)**	**8.83**
CKD-EPI$_{creatinine}$ (no race adjustment)	−2.8 (9.2) (−3.3 to −2.3)	−2.9 (−8.6 to 3.4)	89.6 (87.7 to 91.3)	55.4 (52.5 to 58.2)	8.97
CKD-EPI$_{cystatin}$	**−3.4 (9.1) (−3.9 to −2.9)** *−9.9 (7.9) (−10.3 to −9.4)*	**−4.1 (−9.3 to 1.5)** *−9.8 (−14.9 to −5.3)*	**89.5 (87.6 to 91.2)** *72.5 (69.8 to 75.0)*	**52.4 (49.5 to 55.3)** *30.6 (28.0 to 33.3)*	**7.58** *7.60*
CKD-EPI$_{creatinine-cystatin}$	**−3.7 (7.3) (−4.1 to −3.3)** *−7.2 (7.1) (−7.6 to −6.8)*	**−3.9 (−8.4 to 1.1)** *−7.2 (−11.7 to −2.4)*	**94.9 (93.5 to 96.1)** *90.4 (88.6 to 92.0)*	**60.4 (57.5 to 63.2)** *45.7 (42.8 to 48.6)*	**7.07** *7.08*
CKD-EPI$_{creatinine-cystatin}$ (no race adjustment)	−3.9 (7.3) (−4.3 to −3.4) *−7.3 (7.1) (−7.8 to −6.9)*	−4.0 (−8.5 to 0.9) *−7.4 (−11.9 to −2.6)*	94.7 (93.2 to 95.9) *89.9 (88.0 to 91.6)*	60.1 (57.2 to 62.9) *45.2 (42.3 to 48.1)*	7.09 *7.10*
CKD-EPI(2021)$_{creatinine}$	0.0 (9.3) (−0.6 to 0.5)	−0.4 (−6.0 to 6.1)	88.0 (86.0 to 89.8)	57.5 (54.6 to 60.4)	8.99
CKD-EPI(2021)$_{creatinine-cystatin}$	−1.1 (7.6) (−1.5 to −0.6) *−5.2 (7.2) (−5.6 to −4.8)*	−1.3 (−6.1 to 3.7) *−5.3 (−9.9 to −0.4)*	94.9 (93.4 to 96.1) *94.2 (92.7 to 95.4)*	66.1 (63.3 to 68.8) *55.2 (52.3 to 58.1)*	7.06 *7.07*
BIS1$_{creatinine}$	1.0 (12.9) (0.2 to 1.7)	−0.6 (−6.5 to 6.6)	85.9 (83.7 to 87.8)	53.2 (50.3 to 56.1)	10.94
BIS2$_{creatinine-cystatin}$	−1.8 (8.6) (−2.3 to −1.3) *−5.0 (8.4) (−5.5 to −4.5)*	−2.2 (−7.0 to 2.5) *−5.1 (−10.2 to −0.7)*	93.2 (91.6 to 94.6) *93.1 (91.5 to 94.5)*	65.0 (62.1 to 67.7) *52.6 (49.7 to 55.5)*	8.31 *8.38*
CAPA$_{cystatin}$	−2.2 (9.0) (−2.7 to −1.7) *−8.5 (8.0) (−9.0 to −8.1)*	−2.8 (−7.9 to 3.0) *−8.6 (−13.6 to −3.3)*	91.0 (89.2 to 92.6) *78.6 (76.1 to 80.9)*	56.6 (53.7 to 59.4) *37.4 (34.7 to 40.3)*	7.82 *7.79*
FAS$_{creatinine}$	−3.5 (9.2) (−4.1 to −3.0)	−3.7 (−9.3 to 2.5)	89.4 (87.5 to 91.1)	54.2 (51.2 to 57.0)	9.10
FAS$_{creatinine-cystatin}$	−2.9 (7.9) (−3.3 to −2.4) *−5.5 (7.9) (−5.9 to −5.0)*	−3.0 (−7.9 to 2.0) *−5.4 (−10.6 to −0.6)*	94.4 (93.0 to 95.7) *92.6 (91.0 to 94.1)*	61.0 (58.1 to 63.8) *53.0 (50.1 to 55.9)*	7.89 *7.92*
LMR$_{creatinine}$	−6.2 (9.1) (−6.7 to −5.6)	−6.4 (−11.9 to −0.2)	84.2 (82.0 to 86.2)	45.3 (42.4 to 48.2)	8.93
EKFC$_{creatinine}$	−4.4 (9.0) (−4.9 to −3.8)	−4.4 (−10.0 to 1.3)	89.4 (87.5 to 91.1)	52.5 (49.6 to 55.4)	8.87

Note
Equations that were part of the primary study objectives are shown in bold. Data for equations incorporating cystatin C are shown as both those utilising cystatin C values obtained following assay recalibration (upper row) and those obtained before assay recalibration (lower row, italics) (see also *Impact of cystatin C calibration on the performance of more recent cystatin C containing glomerular filtration rate-estimating equations*).

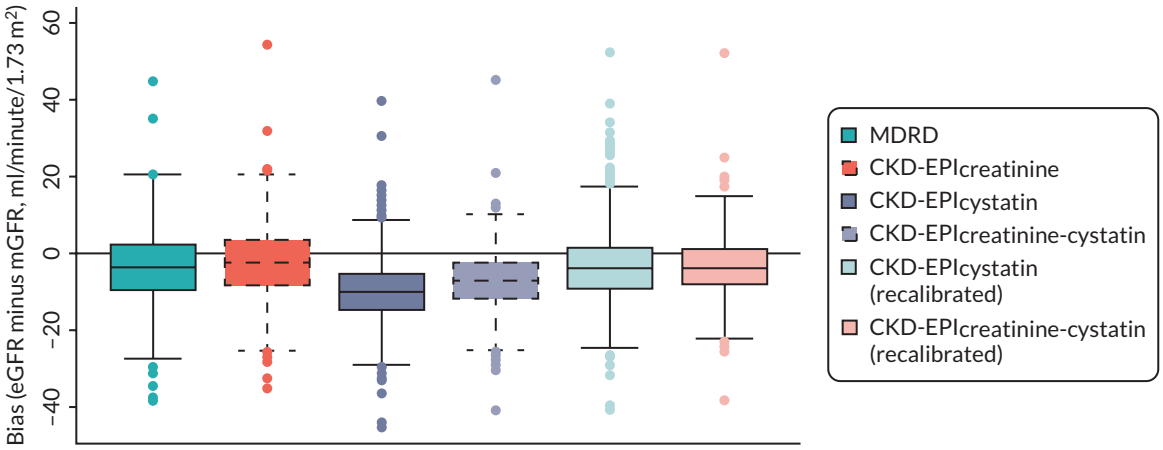

FIGURE 5 Bias of GFR-estimating equations compared to mGFR shown as box and whisker plots. The box shows the median and the first (Q1) and third quartiles (Q3). The whiskers span all data points within 1.5 IQR of the nearer quartile, with Tukey outliers outside of this range (< Q1−1.5 IQR or > Q3 + 1.5 IQR). The CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations are shown both before and after recalibration against the Siemens assay.

Performance of glomerular filtration rate-estimating equations at detecting changes in measured glomerular filtration rate over 3 years

The median mGFR (ml/minute/1.73 m^2) at baseline was 48.1 falling to 43.6 at 3-year follow-up. The equivalent changes for the eGFRs were: 44.6–41.5 (MDRD); 45.7–42.0 (CKD-EPI$_{creatinine}$); 43.6–40.4 (CKD-EPI$_{cystatin}$); and 43.4–40.6 (CKD-EPI$_{creatinine\text{-}cystatin}$). Of the 875 participants with mGFR and eGFR at both baseline and 3-year follow-up, 7 (0.8%) reached kidney failure (mGFR < 15) at follow-up. Of the 875 participants over the study duration, 268 (30.6%) had a change in GFR > 10; 235 (26.8%) had a decline in GFR > 10; 272 (31.1%) had a GFR decline of > RCV; 156 (17.8%) had a GFR decline of > 25%; and 139 (15.9%) had a GFR decline of > 25% in combination with a change in disease category.

As opposed to assessments of equation accuracy at baseline (see *Table 5*), in the analyses shown in this section which relate to monitoring GFR over time, the 'race adjustment factor removed' versions of equations are not shown. This adjustment involves scaling an element of the equation in African-Caribbean individuals only by a constant factor on each occasion, so monitoring an individual over time will have no impact on the ability of an equation to reflect change over time. This was confirmed empirically, and the data have not been included to aid clarity. In all tables in this section, data for equations incorporating cystatin C utilise cystatin C values obtained following assay recalibration (see *Accuracy of glomerular filtration rate-estimating equations including the Modification of Diet in Renal Disease equation and three Chronic Kidney Disease-Epidemiology Consortium equations using either creatinine or cystatin C or a combination of both in people with stage 3 chronic kidney disease: baseline analysis*).

Concordance of glomerular filtration rate-estimating equations with measured glomerular filtration rate within a tolerance of 3 ml/minute/1.73 m^2/year or five percentage points over 3 years

The abilities of GFR-estimating equations to track mGFR within 3 ml/minute/1.73 m^2 or within five percentage points of the observed change in mGFR are summarised in *Tables 9* and *10*. For the three CKD-EPI equations, an exploratory analysis was undertaken to compare differences in baseline characteristics between those identified as having a change within 3 ml/minute/1.73 m^2 mGFR and those in whom the eGFR was > 3 ml/minute/1.73 m^2 different from the change in mGFR: no clear differences were identified (see *Appendix 1*, *Table 40*).

Sensitivity analysis for change over time

Sensitivity analyses used alternative methods to estimate the change in eGFR (using a linear regression model per person) and mGFR (multilevel model) (*Table 11*).

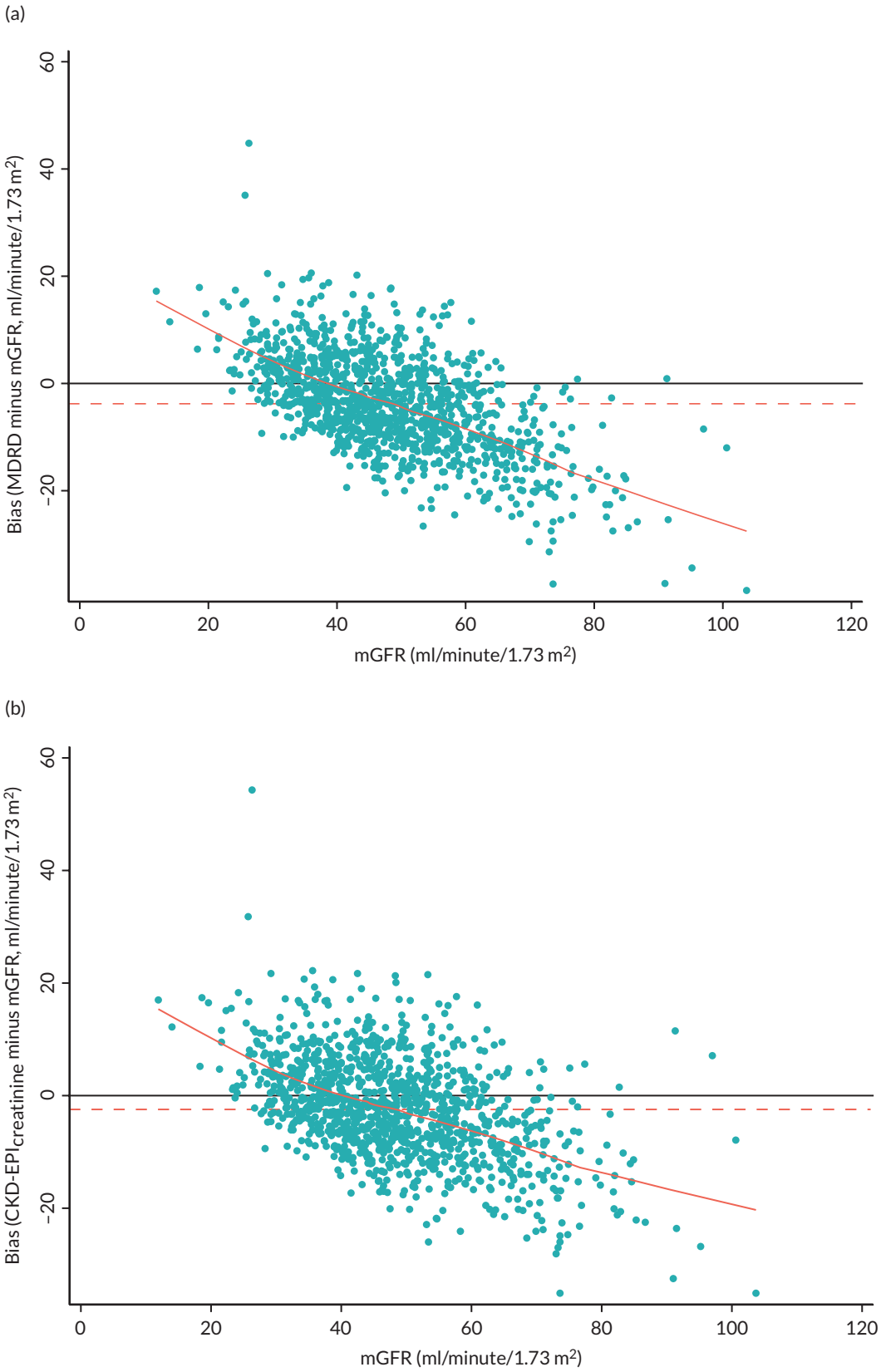

FIGURE 6 Bias of GFR-estimating equations compared to mGFR shown as lowess plots. Bias plots for the baseline cohort (*n* = 1167) are shown with lowess (locally weighted scatterplot smoothing) function (red solid line). The solid black line shows zero bias, and the dashed red line shows mean bias. The CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations are shown both after (c, d) and before (e, f) recalibration against the Siemens assay. (a) MDRD eGFR vs. mGFR; (b) CKD-EPI$_{creatinine}$ eGFR vs. mGFR; (c) CKD-EPI$_{cystatin}$ eGFR vs. mGFR (Siemens); (d) CKD-EPI$_{creatinine\text{-}cystatin}$ eGFR vs. mGFR (Siemens); (e) CKD-EPI$_{cystatin}$ eGFR vs. mGFR (Abbott); and (f) CKD-EPI$_{creatinine\text{-}cystatin}$ eGFR vs. mGFR (Abbott).

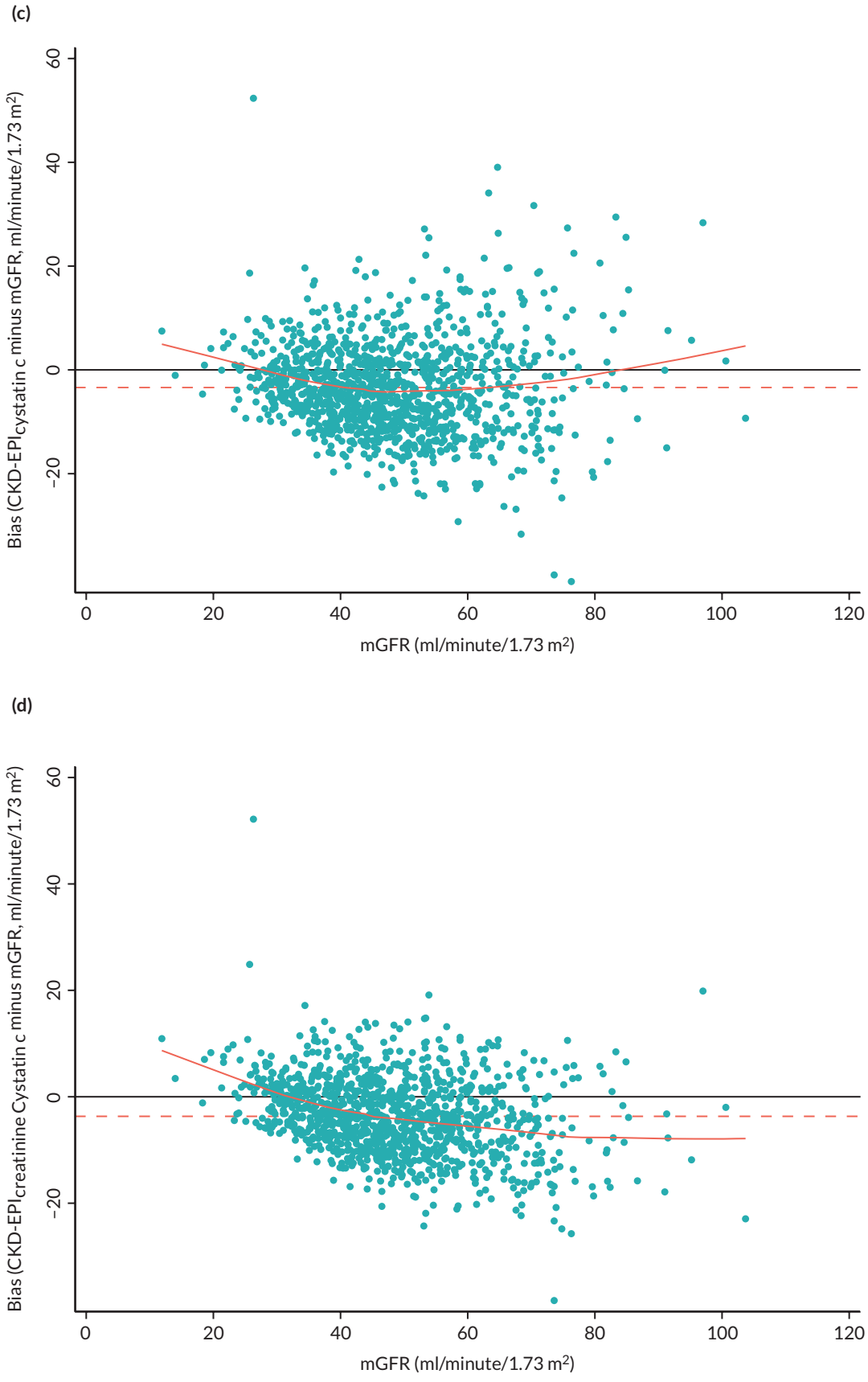

FIGURE 6 Bias of GFR-estimating equations compared to mGFR shown as lowess plots. Bias plots for the baseline cohort (n = 1167) are shown with lowess (locally weighted scatterplot smoothing) function (red solid line). The solid black line shows zero bias, and the dashed red line shows mean bias. The CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations are shown both after (c, d) and before (e, f) recalibration against the Siemens assay. (a) MDRD eGFR vs. mGFR; (b) CKD-EPI$_{creatinine}$ eGFR vs. mGFR; (c) CKD-EPI$_{cystatin}$ eGFR vs. mGFR (Siemens); (d) CKD-EPI$_{creatinine\text{-}cystatin}$ eGFR vs. mGFR (Siemens); (e) CKD-EPI$_{cystatin}$ eGFR vs. mGFR (Abbott); and (f) CKD-EPI$_{creatinine\text{-}cystatin}$ eGFR vs. mGFR (Abbott). (*continued*)

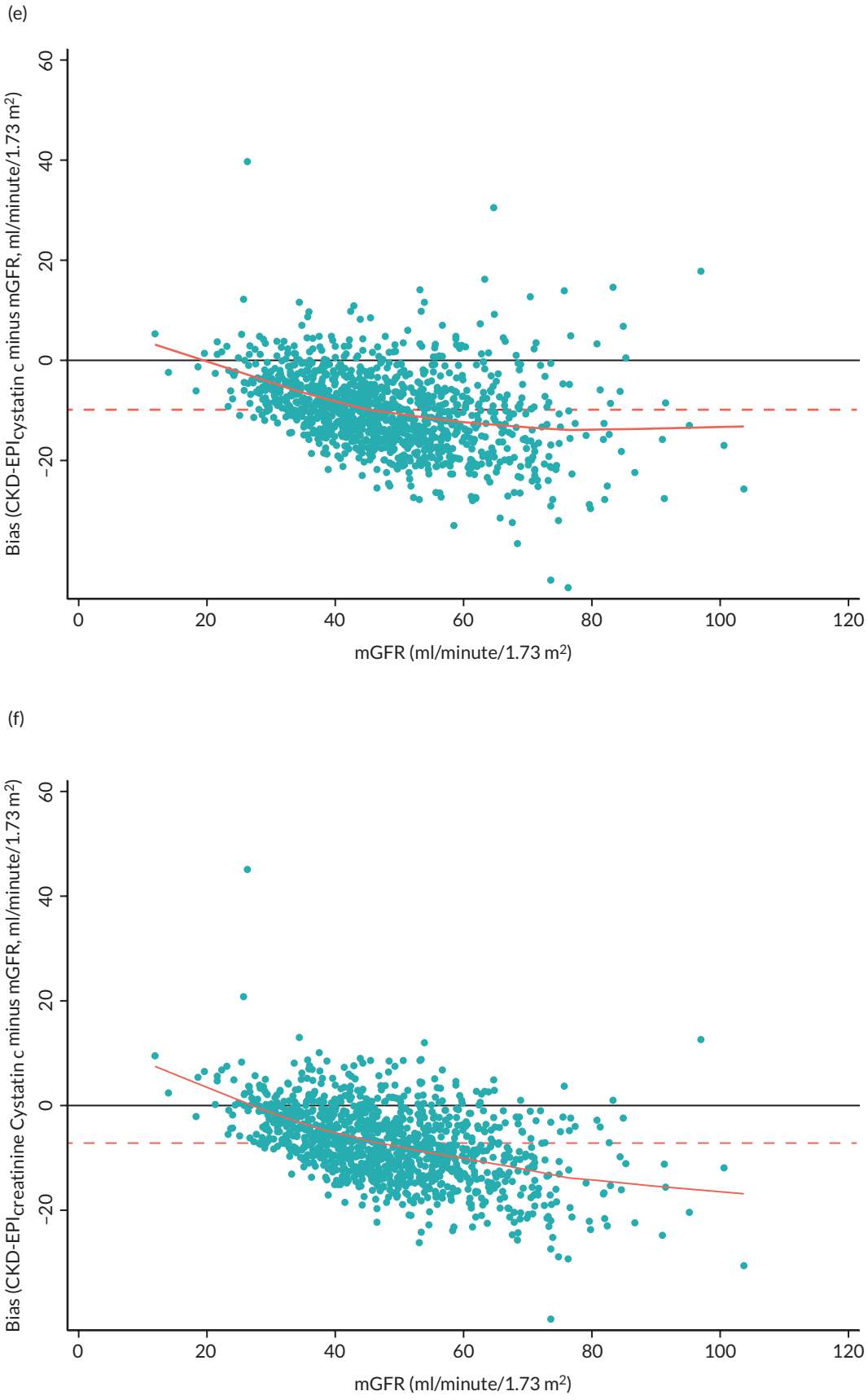

FIGURE 6 Bias of GFR-estimating equations compared to mGFR shown as lowess plots. Bias plots for the baseline cohort (n = 1167) are shown with lowess (locally weighted scatterplot smoothing) function (red solid line). The solid black line shows zero bias, and the dashed red line shows mean bias. The CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations are shown both after (c, d) and before (e, f) recalibration against the Siemens assay. (a) MDRD eGFR vs. mGFR; (b) CKD-EPI$_{creatinine}$ eGFR vs. mGFR; (c) CKD-EPI$_{cystatin}$ eGFR vs. mGFR (Siemens); (d) CKD-EPI$_{creatinine\text{-}cystatin}$ eGFR vs. mGFR (Siemens); (e) CKD-EPI$_{cystatin}$ eGFR vs. mGFR (Abbott); and (f) CKD-EPI$_{creatinine\text{-}cystatin}$ eGFR vs. mGFR (Abbott). (*continued*)

TABLE 6 Comparison of GFR-estimating equation performance at baseline

	Test A		
Test B	**MDRD**	**CKD-EPI$_{creatinine}$**	**CKD-EPI$_{cystatin}$**
MDRD			
CKD-EPI$_{creatinine}$	0.8 (−0.5 to 2.0) p = 0.2529		
CKD-EPI$_{cystatin}$	0.0 (−2.5 to 2.5) p > 0.999 *−17.0 (−20.2 to −13.8) p < 0.001*	−0.8 (−3.3 to 1.7) p = 0.5783 *−17.7 (−20.9 to −14.6) p < 0.001*	
CKD-EPI$_{creatinine-cystatin}$	5.5 (3.6 to 7.4) p < 0.001 *0.9 (−1.2 to 3.0) p = 0.4031*	4.7 (2.9 to 6.5) p < 0.001 *0.2 (−1.9 to 2.2) p = 0.9322*	5.5 (3.8 to 7.2) p < 0.001 *17.9 (15.5 to 20.4) p < 0.001*

Note
The table shows % difference (95% CI) for P30 test B – P30 test A together with a p-value. McNemar's test was used to compare the P30 values of the equations against each other. For the cystatin C-containing equations, the lower values in italics in each cell refer to the results before the equations were recalibrated.

Ability of glomerular filtration rate-estimating equations to detect a change in measured glomerular filtration rate > 10 ml/minute/1.73 m^2 over 3 years

For this analysis, we were interested in the clinically meaningful results of a change in GFR > 10 ml/minute/1.73 m^2 over 3 years (in either direction), which we considered a positive result and, consequently, a change in GFR ≤ 10 ml/minute/1.73 m^2 over 3 years (in either direction) negative. We have also investigated the outcome of a GFR decline only of > 10 ml/minute/1.73 m^2 over 3 years. Using the observed data, we calculated whether a positive or negative result was achieved for each estimated equation (index tests) and compared these to the result from mGFR (the reference standard) (*Table 12*).

Ability of glomerular filtration rate-estimating equations to detect a change in measured glomerular filtration rate greater than the reference change value over 3 years

Table 13 shows the ability of GFR estimations to detect a change in mGFR exceeding the RCV. The bounds of the RCV are asymmetric, so we have a different positive and negative percentage change indicating a meaningful change and a positive result; we also consider change only in the negative direction. Of the main equations assessed, MDRD had the highest specificity for change overall (79.9%) and for detecting decline (87.4%), but CIs for all equations overlapped for specificity and sensitivity.

Ability of glomerular filtration rate-estimating equations to detect a change in measured glomerular filtration rate of > 25% over 3 years

Of the four main study equations, the sensitivity of the eGFRs to detect change in mGFR > 25% (in either direction) over 3 years was between 44.1% and 55.3%; and the specificity ranged from 84.0% to 88.4% (*Table 14*). The PPV (percentage of eGFR-positive participants that were mGFR-positive) ranged between 48.1% and 54.5%, whereas the NPV (percentage of eGFR-negative participants that were mGFR-negative) ranged between 85.3% and 87.7%. Sensitivity, specificity, PPV and NPV all increased when using only a reduction in GFR of > 25%, but in all cases CIs of equations overlapped.

Ability of glomerular filtration rate-estimating equations to detect a change in measured glomerular filtration rate of > 25% over 3 years in combination with a change in disease stage

All main study equations had relatively poor sensitivity (< 56%) and good specificity (> 93%) at detecting change in mGFR of > 25% over 3 years (in either direction) in combination with a change in disease stage. Marker characteristics (sensitivities, specificities, PPV, NPV) improved slightly when only a decline in GFR was considered. There were no differences in performance between the main study equations (*Table 15*).

TABLE 7 Performance of the GFR-estimating equations at baseline compared to mGFR stratified by age, gender, diabetes, albuminuria, BMI and level of mGFR

Equation	Demographic/clinical category				
	Age (years)				
	< 50 (*n* = 149)	**50–59 (*n* = 177)**	**60–69 (*n* = 376)**	**70–79 (*n* = 368)**	**≥ 80 (*n* = 97)**
MDRD	85.2 (78.5 to 90.5)	87.0 (81.1 to 91.6)	89.1 (85.5 to 92.1)	92.9 (89.8 to 95.3)	88.7 (80.6 to 94.2)
$CKD\text{-}EPI_{creatinine}$	87.9 (81.6 to 92.7)	88.7 (83.1 to 93.0)	88.8 (85.2 to 91.8)	92.9 (89.8 to 95.3)	91.8 (84.4 to 96.4)
$CKD\text{-}EPI_{cystatin}$	90.6 (84.7 to 94.8)	92.1 (87.1 to 95.6)	87.0 (83.1 to 90.2)	90.5 (87.0 to 93.3)	88.7 (80.6 to 94.2)
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	97.3 (93.2 to 99.3)	94.4 (89.9 to 97.3)	93.6 (90.7 to 95.9)	95.7 (93.0 to 97.5)	94.8 (88.4 to 98.3)
	Gender				
	Males (*n* = 680)	**Females (*n* = 487)**			
MDRD	88.2 (85.6 to 90.6)	91.2 (88.3 to 93.5)			
$CKD\text{-}EPI_{creatinine}$	88.5 (85.9 to 90.8)	92.6 (89.9 to 94.8)			
$CKD\text{-}EPI_{cystatin}$	90.3 (87.8 to 92.4)	88.3 (85.1 to 91.0)			
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	94.4 (92.4 to 96.0)	95.7 (93.5 to 97.3)			
	Diabetes				
	Non-diabetic (*n* = 843)	**Diabetic (*n* = 324)**			
MDRD	89.6 (87.3 to 91.5)	89.2 (85.3 to 92.4)			
$CKD\text{-}EPI_{creatinine}$	90.7 (88.6 to 92.6)	88.9 (85.0 to 92.1)			
$CKD\text{-}EPI_{cystatin}$	89.9 (87.7 to 91.9)	88.3 (84.4 to 91.6)			
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	95.1 (93.5 to 96.5)	94.4 (91.4 to 96.7)			
	Albuminuria category				
	A0 < 3 mg/mmol (*n* = 483)	**A1 3.0–29.9 mg/mmol (*n* = 396)**	**A2 ≥ 30 mg/mmol (*n* = 269)**		
MDRD	90.9 (88.0 to 93.3)	89.6 (86.2 to 92.5)	87.0 (82.4 to 90.8)		
$CKD\text{-}EPI_{creatinine}$	91.7 (88.9 to 94.0)	90.4 (87.1 to 93.1)	87.7 (83.2 to 91.4)		
$CKD\text{-}EPI_{cystatin}$	91.9 (89.1 to 94.2)	86.9 (83.1 to 90.0)	89.2 (84.9 to 92.7)		
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	95.7 (93.4 to 97.3)	95.5 (92.9 to 97.3)	92.9 (89.2 to 95.7)		

TABLE 7 Performance of the GFR-estimating equations at baseline compared to mGFR stratified by age, gender, diabetes, albuminuria, BMI and level of mGFR (*continued*)

Equation	Demographic/clinical category	
	BMI	
	< 30 kg/m² (*n* = 668)	**≥ 30 kg/m² (*n* = 499)**
MDRD	90.4 (87.9 to 92.5)	88.2 (85.0 to 90.9)
$CKD\text{-}EPI_{creatinine}$	91.2 (88.8 to 93.2)	89.0 (85.9 to 91.6)
$CKD\text{-}EPI_{cystatin}$	90.9 (88.4 to 92.9)	87.6 (84.4 to 90.3)
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	96.0 (94.2 to 97.3)	93.6 (91.1 to 95.6)
	Measured GFR (ml/minute/1.73 m²)	
	GFR < 45 (*n* = 504)	**GFR ≥ 45 (*n* = 663)**
MDRD	87.7 (84.5 to 90.4)	90.8 (88.3 to 92.9)
$CKD\text{-}EPI_{creatinine}$	88.1 (84.9 to 90.8)	91.9 (89.5 to 93.8)
$CKD\text{-}EPI_{cystatin}$	87.7 (84.5 to 90.4)	90.8 (88.3 to 92.9)
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	93.7 (91.2 to 95.6)	95.9 (94.1 to 97.3)

Note
Results represent accuracy, percentage of estimates within 30% of mGFR [P30 (95% CI)].

TABLE 8 Ethnicity: performance of the GFR-estimating equations at baseline compared to mGFR in participants according to ethnicity

Equation	Reported ethnicity[a]				Difference (95% CI) for African-Caribbeans with and without adjustment factor; *p*-values (*n* = 60)[b]
	Caucasian (*n* = 1014)	South Asian (*n* = 66)	African-Caribbean (*n* = 60)	African-Caribbean, adjustment factor removed (*n* = 60)	
MDRD	**89.8 (87.8 to 91.6)**	**87.9 (77.5 to 94.6)**	**83.3 (71.5 to 91.7)**	**63.3 (49.9 to 75.4)**	**−20.0 (−35.4 to −4.6); *p* = 0.0118**
CKD-EPI$_{creatinine}$	**90.8 (88.9 to 92.5)**	**86.4 (75.7 to 93.6)**	**81.7 (69.6 to 90.5)**	**70.0 (56.8 to 81.2)**	**−11.7 (−23.8 to 0.4); *p* = 0.0654**
CKD-EPI$_{cystatin}$	**89.6 (87.6 to 91.5)**	**86.4 (75.7 to 93.6)**	**90.0 (79.5 to 96.2)**	**N/A**	**N/A**
CKD-EPI$_{creatinine-cystatin}$	**95.0 (93.4 to 96.2)**	**93.9 (85.2 to 98.3)**	**95.0 (86.1 to 99.0)**	**90.0 (79.5 to 96.2)**	**−5.0 (−12.2 to 2.2); *p* = 0.2500**
CKD-EPI(2021)$_{creatinine}$	88.9 (86.8 to 90.7)	84.8 (73.9 to 92.5)	75.0 (62.1 to 85.3)	N/A	N/A
CKD-EPI(2021)$_{creatinine-cystatin}$	95.1 (93.6 to 96.3)	92.4 (83.2 to 97.5)	93.3 (83.8 to 98.2)	N/A	N/A

a Ethnicity data were unavailable in 3 individuals and 24 individuals were of non-Caucasian, South Asian or African-Caribbean origin. Twenty-seven individuals were therefore excluded from this analysis.
b McNemar test was used.

Note
Results represent accuracy, percentage of estimates within 30% of mGFR [P30 (95% CI)]. Equations that form part of the primary study objectives are shown in bold. N/A, not applicable: the original version of these equations did not contain an African-Caribbean adjustment factor.

TABLE 9 Performance of eGFR equations: change per year within 3 ml/minute/1.73 m^2 or within 5% of mGFR

Equation	Difference in change per year (eGFR – mGFR) within 3 ml/minute/1.73 m^2		Absolute difference in % change (eGFR – mGFR) within 5%	
	n/N	%, (95% CI)	*n/N*	%, (95% CI)
MDRD	**660/875**	**75.4 (72.4 to 78.2)**	**655/875**	**74.9 (71.8 to 77.7)**
CKD-EPI$_{creatinine}$	**640/875**	**73.1 (70.1 to 76.1)**	**627/875**	**71.7 (68.5 to 74.6)**
CKD-EPI$_{cystatin}$	**662/875**	**75.7 (72.7 to 78.5)**	**646/875**	**73.8 (70.8 to 76.7)**
CKD-EPI$_{creatinine-cystatin}$	**688/875**	**78.6 (75.8 to 81.3)**	**662/875**	**75.7 (72.7 to 78.5)**
CKD-EPI(2021)$_{creatinine}$	635/875	72.6 (69.5 to 75.5)	631/875	72.1 (69.0 to 75.1)
CKD-EPI(2021)$_{creatinine-cystatin}$	683/875	78.1 (75.2 to 80.8)	665/875	76.0 (73.0 to 78.8)
BIS1$_{creatinine}$	668/875	76.3 (73.4 to 79.1)	718/875	82.1 (79.4 to 84.5)
BIS2$_{creatinine-cystatin}$	712/875	81.4 (78.6 to 83.9)	729/875	83.3 (80.7 to 85.7)
CAPA$_{cystatin}$	664/875	75.9 (72.9 to 78.7)	664/875	75.9 (72.9 to 78.7)
FAS$_{creatinine}$	681/875	77.8 (74.9 to 80.5)	699/875	79.9 (77.1 to 82.5)
FAS$_{creatinine-cystatin}$	703/875	80.3 (77.6 to 82.9)	728/875	83.2 (80.6 to 85.6)
LMR$_{creatinine}$	651/875	74.4 (71.4 to 77.3)	633/875	72.3 (69.3 to 75.3)
EKFC$_{creatinine}$	669/875	76.5 (73.5 to 79.2)	653/875	74.6 (71.6 to 77.5)

Note
Equations that form part of the primary study objectives are shown in bold. *n* indicates the number of individuals that had a change within 3 ml/minute/1.73 m^2 or within 5% of mGFR.

TABLE 10 Comparison of GFR-estimating equation performance over time: (a) change per year within 3 ml/minute/1.73 m^2 of mGFR; and (b) difference in change per year compared to mGFR within 5 percentage points

Test B	Test A		
	MDRD	**CKD-EPI$_{creatinine}$**	**CKD-EPI$_{cystatin}$**
MDRD			
CKD-EPI$_{creatinine}$	(a) −2.3 (−3.8 to −0.7), p = 0.0029 (b) −3.2 (−4.5 to −1.9), p < 0.0001		
CKD-EPI$_{cystatin}$	(a) 0.2 (−3.1 to 3.5), p = 0.9442 (b) −1.0 (−4.2 to 2.2), p = 0.5607	(a) 2.5 (−0.9 to 5.9), p = 0.1567 (b) 2.2 (−1.1 to 5.4), p = 0.1973	
CKD-EPI$_{creatinine-cystatin}$	(a) 3.2 (0.6 to 5.8), p = 0.0134 (b) 0.8 (−1.7 to 3.3), p = 0.5692	(a) 5.5 (2.8 to 8.2), p < 0.0001 (b) 4.0 (1.6 to 6.4), p = 0.0010	(a) 3.0 (0.7 to 5.3), p = 0.0103 (b) 1.8 (−0.6 to 4.3), p = 0.1523

Note
The table shows % difference (95% CI) for test B – test A together with a *p*-value. McNemar's test was used to compare the values of the equations against each other.

To estimate and model disease progression (decline in glomerular filtration rate or increase in albumin-to-creatinine ratio) and differences in progression between ethnic groups (Caucasian, South Asian and African-Caribbean), and baseline diabetes and albuminuria status and other potential risk factors

In the substudy of disease progression, 239 participants with paired mGFR and eGFR on at least 2 occasions were evaluable and included in the disease progression covariate models. There were no obvious changes in the covariates BP, BMI and waist circumference (*Table 16*) or mGFR or eGFR over time (*Table 17*), although there was a tendency towards lower GFR and higher ACR values over time (see *Appendix 1*, *Figures 15–17*).

TABLE 11 Sensitivity analysis performance of eGFR equations: change per year within 3 ml/minute/1.73 m^2 of mGFR

	Sensitivity analysis 1		Sensitivity analysis 2	
Equation	***n/N***	**% (95% CI)**	***n/N***	**% (95% CI)**
MDRD	681/875	77.8 (74.9 to 80.5)	723/875	82.6 (79.9 to 85.1)
CKD-EPI$_{creatinine}$	673/875	76.9 (74.0 to 79.7)	704/875	80.5 (77.7 to 83.0)
CKD-EPI$_{cystatin}$	655/875	74.9 (71.8 to 77.7)	694/875	79.3 (76.5 to 82.0)
CKD-EPI$_{creatinine-cystatin}$	685/875	78.3 (75.4 to 81.0)	726/875	83.0 (80.3 to 85.4)

Note
Sensitivity analysis 1: change in eGFR (change per year estimated from linear regression models; one model fitted per person using all available measurements) was compared to the observed change in mGFR (calculated as change per year from difference between 3 years and baseline measurements). Sensitivity analysis 2: change in eGFR (change per year estimated from linear regression model; one model fitted per person using all available measurements) was compared to change in mGFR (estimated from a multilevel linear regression model using all available measures).

The difference between estimated and mGFR (bias) at each time point is summarised in *Table 18*. The baseline differences (bias) between estimated and mGFR in the substudy were similar to those observed in the main study, and did not change during the course of the study, although the bias at baseline was larger than observed at later time points for all eGFRs except CKD-EPI$_{creatinine}$ (see also *Appendix 1*, *Figure 17*).

The estimated slopes (progression) and variance estimates for mGFRs and eGFRs and bias (eGFR minus mGFR) from the random coefficients regression model without covariates are presented in *Table 19*.

The rates of decline were steepest for mGFR and CKD-EPI$_{creatinine}$ eGFR, and slope estimates were similar. The rates of decline were slowest for cystatin C eGFR. The model-predicted slopes for mGFR and CKD-EPI$_{creatinine}$ and CKD-EPI$_{cystatin}$ eGFR are shown in *Appendix 1*, *Figure 18*.

The variability of slopes was larger for the eGFRs compared to mGFR and the residual variability was lower. This is likely due to the difference in the number of observations for each individual for mGFR and eGFR. In the regression model for eGFRs, more data points are included for each individual (includes 6-monthly data), resulting in less shrinkage towards the population mean slope, more variability between slopes and lower residual variability (variability between observations and individual slope fitted values).

There was little evidence of decline in bias (difference) over time based on the difference between CKD-EPI$_{creatinine}$ GFR and mGFR (slope estimate 0.101, 95% CI −0.272 to 0.474). Similarly for the difference between MDRD and mGFR, the slope estimate was 0.325 and 95% CI −0.038 to 0.688. In contrast, differences of mGFR from CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine-cystatin}$ showed an incline in slope over time indicated by the positive slope estimates with 95% CI not overlapping zero (e.g. 0.840, CI 0.441 to 1.24 for difference between CKD-EPI$_{cystatin}$ GFR and mGFR), suggesting an increase in bias (i.e. eGFR minus mGFR) over time. The median bias was negative at all times for CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine-cystatin}$ (i.e. these estimates of GFR were always lower than the mGFR), but the median bias at later time points was closer to zero compared to the median bias at baseline (*Table 18*).

Prior to conducting the random coefficients regression modelling with covariates, correlations between the covariates to be included in the model were explored to identify collinearity (*Table 20*). Correlations were calculated using the data from baseline and from all time points for evaluable participants (i.e. those with estimated and mGFR available on at least two time points). The final covariate models for mGFR, eGFR and ACR should be interpreted bearing in mind the observed associations between covariates. Where collinearity exists, some covariates associated with the GFR measure were excluded from the final multiple regression model. A correlation of 0.3 or higher and < 0.5 was considered

TABLE 12 Ability of eGFR to detect change (upper table) and decline only (lower table) in mGFR > 10 ml/minute/1.73 m^2 over 3 years

Change in GFR								
	> |10|		≤ |10|		% (95% CI)			
Equation	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
MDRD	**104**	**164**	**104**	**503**	**38.8 (32.9 to 44.9)**	**82.9 (79.6 to 85.8)**	**50.0 (43.0 to 57.0)**	**75.4 (72.0 to 78.6)**
CKD-EPI$_{creatinine}$	**119**	**149**	**127**	**480**	**44.4 (38.4 to 50.6)**	**79.1 (75.6 to 82.2)**	**48.4 (42.0 to 54.8)**	**76.3 (72.8 to 79.6)**
CKD-EPI$_{cystatin}$	**134**	**134**	**121**	**486**	**50.0 (43.9 to 56.1)**	**80.1 (76.7 to 83.2)**	**52.5 (46.2 to 58.8)**	**78.4 (74.9 to 81.6)**
CKD-EPI$_{creatinine-cystatin}$	**123**	**145**	**111**	**496**	**45.9 (39.8 to 52.1)**	**81.7 (78.4 to 84.7)**	**52.6 (46.0 to 59.1)**	**77.4 (73.9 to 80.6)**
CKD-EPI(2021)$_{creatinine}$	120	148	143	464	44.8 (38.7 to 50.9)	76.4 (72.9 to 79.8)	45.6 (39.5 to 51.9)	75.8 (72.2 to 79.2)
CKD-EPI(2021)$_{creatinine-cystatin}$	129	139	126	481	48.1 (42.0 to 54.3)	79.2 (75.8 to 82.4)	50.6 (44.3 to 56.9)	77.6 (74.1 to 80.8)
BIS1$_{creatinine}$	103	165	73	534	38.4 (32.6 to 44.5)	88.0 (85.1 to 90.5)	58.5 (50.9 to 65.9)	76.4 (73.1 to 79.5)
BIS2$_{creatinine-cystatin}$	103	165	67	540	38.4 (32.6 to 44.5)	89.0 (86.2 to 91.3)	60.6 (52.8 to 68.0)	76.6 (73.3 to 79.7)
CAPA$_{cystatin}$	126	142	121	486	47.0 (40.9 to 53.2)	80.1 (76.7 to 83.2)	51.0 (44.6 to 57.4)	77.4 (73.9 to 80.6)
FAS$_{creatinine}$	101	167	72	535	37.7 (31.9 to 43.8)	88.1 (85.3 to 90.6)	58.4 (50.7 to 65.8)	76.2 (72.9 to 79.3)
FAS$_{creatinine-cystatin}$	99	169	64	543	36.9 (31.1 to 43.0)	89.5 (86.7 to 91.8)	60.7 (52.8 to 68.3)	76.3 (73.0 to 79.3)
LMR$_{creatinine}$	112	156	107	500	41.8 (35.8 to 47.9)	82.4 (79.1 to 85.3)	51.1 (44.3 to 57.9)	76.2 (72.8 to 79.4)
EKFC$_{creatinine}$	108	160	95	512	40.3 (34.4 to 46.4)	84.3 (81.2 to 87.1)	53.2 (46.1 to 60.2)	76.2 (72.8 to 79.4)

continued

TABLE 12 Ability of eGFR to detect change (upper table) and decline only (lower table) in mGFR > 10 ml/minute/1.73 m^2 over 3 years (*continued*)

Decline in GFR								
	> |10|		≤ |10|		% (95% CI)			
Equation	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
MDRD	**96**	**139**	**68**	**572**	**40.9 (34.5 to 47.4)**	**89.4 (86.7 to 91.7)**	**58.5 (50.6 to 66.2)**	**80.5 (77.3 to 83.3)**
CKD-EPI$_{creatinine}$	**111**	**124**	**87**	**553**	**47.2 (40.7 to 53.8)**	**86.4 (83.5 to 89.0)**	**56.1 (48.8 to 63.1)**	**81.7 (78.6 to 84.5)**
CKD-EPI$_{cystatin}$	**109**	**126**	**81**	**559**	**46.4 (39.9 to 53.0)**	**87.3 (84.5 to 89.8)**	**57.4 (50.0 to 64.5)**	**81.6 (78.5 to 84.4)**
CKD-EPI$_{creatinine-cystatin}$	**107**	**128**	**79**	**561**	**45.5 (39.0 to 52.1)**	**87.7 (84.9 to 90.1)**	**57.5 (50.1 to 64.7)**	**81.4 (78.3 to 84.3)**
CKD-EPI(2021)$_{creatinine}$	112	123	96	544	47.7 (41.1 to 54.3)	85.0 (82.0 to 87.7)	53.8 (46.8 to 60.8)	81.6 (78.4 to 84.4)
CKD-EPI(2021)$_{creatinine-cystatin}$	111	124	88	552	47.2 (40.7 to 53.8)	86.3 (83.3 to 88.8)	55.8 (48.6 to 62.8)	81.7 (78.5 to 84.5)
BIS1$_{creatinine}$	99	136	65	575	42.1 (35.7 to 48.7)	89.8 (87.2 to 92.1)	60.4 (52.4 to 67.9)	80.9 (77.8 to 83.7)
BIS2$_{creatinine-cystatin}$	92	143	57	583	39.1 (32.9 to 45.7)	91.1 (88.6 to 93.2)	61.7 (53.4 to 69.6)	80.3 (77.2 to 83.1)
CAPA$_{cystatin}$	103	132	80	560	43.8 (37.4 to 50.4)	87.5 (84.7 to 90.0)	56.3 (48.8 to 63.6)	80.9 (77.8 to 83.8)
FAS$_{creatinine}$	96	139	62	578	40.9 (34.5 to 47.4)	90.3 (87.8 to 92.5)	60.8 (52.7 to 68.4)	80.6 (77.5 to 83.4)
FAS$_{creatinine-cystatin}$	89	146	54	586	37.9 (31.6 to 44.4)	91.6 (89.1 to 93.6)	62.2 (53.8 to 70.2)	80.1 (77.0 to 82.9)
LMR$_{creatinine}$	104	131	81	559	44.3 (37.8 to 50.9)	87.3 (84.5 to 89.8)	56.2 (48.7 to 63.5)	81.0 (77.9 to 83.9)
EKFC$_{creatinine}$	102	133	75	565	43.4 (37.0 to 50.0)	88.3 (85.5 to 90.7)	57.6 (50.0 to 65.0)	80.9 (77.8 to 83.8)

Note
Equations that were part of the primary study objectives are shown in bold.

TABLE 13 Ability of eGFR to detect a change in mGFR greater than the RCV over 3 years (+ 21.5%/−17.7%, upper table) or a decline only in GFR greater than the RCV (−17.7%, lower table)

Change in GFR								
	> RCV (> 21.5% or < −17.7%)		≤ RCV		% (95% CI)			
Equation	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
MDRD creatinine	**170**	**144**	**113**	**448**	**54.1 (48.5 to 59.7)**	**79.9 (76.3 to 83.1)**	**60.1 (54.1 to 65.8)**	**75.7 (72.0 to 79.1)**
CKD-EPI$_{creatinine}$	**179**	**135**	**133**	**428**	**57.0 (51.3 to 62.6)**	**76.3 (72.6 to 79.8)**	**57.4 (51.7 to 62.9)**	**76.0 (72.3 to 79.5)**
CKD-EPI$_{cystatin}$	**191**	**123**	**144**	**417**	**60.8 (55.2 to 66.3)**	**74.3 (70.5 to 77.9)**	**57.0 (51.5 to 62.4)**	**77.2 (73.4 to 80.7)**
CKD-EPI$_{creatinine-cystatin}$	**189**	**125**	**121**	**440**	**60.2 (54.5 to 65.6)**	**78.4 (74.8 to 81.8)**	**61.0 (55.3 to 66.4)**	**77.9 (74.2 to 81.2)**
CKD-EPI(2021)$_{creatinine}$	175	139	127	434	55.7 (50.0 to 61.3)	77.4 (73.7 to 80.8)	57.9 (52.2 to 63.6)	75.7 (72.0 to 79.2)
CKD-EPI(2021)$_{creatinine-cystatin}$	190	124	124	437	60.5 (54.9 to 66.0)	77.9 (74.2 to 81.3)	60.5 (54.9 to 66.0)	77.9 (74.2 to 81.3)
BIS1$_{creatinine}$	150	164	73	488	47.8 (42.1 to 53.5)	87.0 (83.9 to 89.7)	67.3 (60.7 to 73.4)	74.8 (71.3 to 78.1)
BIS2$_{creatinine-cystatin}$	164	150	66	495	52.2 (46.5 to 57.9)	88.2 (85.3 to 90.8)	71.3 (65.0 to 77.1)	76.7 (73.3 to 80.0)
CAPA$_{cystatin}$	183	131	128	433	58.3 (52.6 to 63.8)	77.2 (73.5 to 80.6)	58.8 (53.1 to 64.4)	76.8 (73.1 to 80.2)
FAS$_{creatinine}$	168	146	87	474	53.5 (47.8 to 59.1)	84.5 (81.2 to 87.4)	65.9 (59.7 to 71.7)	76.5 (72.9 to 79.7)
FAS$_{creatinine-cystatin}$	160	154	71	490	51.0 (45.3 to 56.6)	87.3 (84.3 to 90.0)	69.3 (62.9 to 75.1)	76.1 (72.6 to 79.3)
LMR$_{creatinine}$	186	128	143	418	59.2 (53.6 to 64.7)	74.5 (70.7 to 78.1)	56.5 (51.0 to 62.0)	76.6 (72.8 to 80.0)
EKFC$_{creatinine}$	176	138	116	445	56.1 (50.4 to 61.6)	79.3 (75.7 to 82.6)	60.3 (54.4 to 65.9)	76.3 (72.7 to 79.7)

continued

TABLE 13 Ability of eGFR to detect a change in mGFR greater than the RCV over 3 years (+ 21.5%/−17.7%, upper table) or a decline only in GFR greater than the RCV (−17.7%, lower table) (*continued*)

Decline in GFR								
	> RCV (< −17.7%)		≤ RCV		% (95% CI)			
Equation	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
MDRD	**156**	**116**	**76**	**527**	**57.4 (51.2 to 63.3)**	**87.4 (84.5 to 89.9)**	**67.2 (60.8 to 73.2)**	**82.0 (78.8 to 84.9)**
$CKD\text{-}EPI_{creatinine}$	**166**	**106**	**97**	**506**	**61.0 (55.0 to 66.9)**	**83.9 (80.7 to 86.8)**	**63.1 (57.0 to 69.0)**	**82.7 (79.4 to 85.6)**
$CKD\text{-}EPI_{cystatin}$	**168**	**104**	**102**	**501**	**61.8 (55.7 to 67.6)**	**83.1 (79.8 to 86.0)**	**62.2 (56.1 to 68.0)**	**82.8 (79.6 to 85.7)**
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	**170**	**102**	**85**	**518**	**62.5 (56.5 to 68.3)**	**85.9 (82.9 to 88.6)**	**66.7 (60.5 to 72.4)**	**83.5 (80.4 to 86.4)**
$CKD\text{-}EPI(2021)_{creatinine}$	162	110	91	512	59.6 (53.5 to 65.4)	84.9 (81.8 to 87.7)	64.0 (57.8 to 69.9)	82.3 (79.1 to 85.2)
$CKD\text{-}EPI(2021)_{creatinine\text{-}cystatin}$	170	102	84	519	62.5 (56.3 to 68.3)	86.1 (83.0 to 88.7)	66.9 (60.8 to 72.7)	83.6 (80.4 to 86.4)
$BIS1_{creatinine}$	145	127	64	539	53.3 (47.2 to 59.4)	89.4 (86.6 to 91.7)	69.4 (62.6 to 75.6)	80.9 (77.7 to 83.8)
$BIS2_{creatinine\text{-}cystatin}$	149	123	58	545	54.8 (48.7 to 60.8)	90.4 (87.7 to 92.6)	72.0 (65.3 to 78.0)	81.6 (78.4 to 84.5)
$CAPA_{cystatin}$	160	112	88	515	58.8 (52.7 to 64.7)	85.4 (82.3 to 88.1)	64.5 (58.2 to 70.5)	82.1 (78.9 to 85.1)
$FAS_{creatinine}$	158	114	73	530	58.1 (52.0 to 64.0)	87.9 (85.0 to 90.4)	68.4 (62.0 to 74.3)	82.3 (79.1 to 85.2)
$FAS_{creatinine\text{-}cystatin}$	147	125	56	547	54.0 (47.9 to 60.1)	90.7 (88.1 to 92.9)	72.4 (65.7 to 78.4)	81.4 (78.2 to 84.3)
$LMR_{creatinine}$	172	100	100	503	63.2 (57.2 to 69.0)	83.4 (80.2 to 86.3)	63.2 (57.2 to 69.0)	83.4 (80.2 to 86.3)
$EKFC_{creatinine}$	164	108	90	513	60.3 (54.2 to 66.2)	85.1 (82.0 to 87.8)	64.6 (58.3 to 70.4)	82.6 (79.4 to 85.5)

Note
Equations that were part of the primary study objectives are shown in bold.

TABLE 14 Ability of eGFR to detect a change (upper table) and decline (lower table) in mGFR > 25% over 3 years

Change in GFR								
	> |25%|		≤ |25%|		% (95% CI)			
Equation	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
MDRD	**83**	**105**	**80**	**607**	**44.1 (36.9 to 51.6)**	**88.4 (85.7 to 90.7)**	**50.9 (43.0 to 58.8)**	**85.3 (82.4 to 87.8)**
CKD-EPI$_{creatinine}$	**91**	**97**	**94**	**593**	**48.4 (41.1 to 55.8)**	**86.3 (83.5 to 88.8)**	**49.2 (41.8 to 56.6)**	**85.9 (83.1 to 88.4)**
CKD-EPI$_{cystatin}$	**102**	**86**	**110**	**577**	**54.3 (46.8 to 61.5)**	**84.0 (81.0 to 86.7)**	**48.1 (41.2 to 55.1)**	**87.0 (84.2 to 89.5)**
CKD-EPI$_{creatinine-cystatin}$	**104**	**84**	**87**	**600**	**55.3 (47.9 to 62.6)**	**87.3 (84.6 to 89.7)**	**54.5 (47.1 to 61.7)**	**87.7 (85.0 to 90.1)**
CKD-EPI(2021)$_{creatinine}$	89	99	93	594	47.3 (40.0 to 54.7)	86.5 (83.7 to 88.9)	48.9 (41.4 to 56.4)	85.7 (82.9 to 88.2)
CKD-EPI(2021)$_{creatinine-cystatin}$	103	85	94	593	54.8 (47.4 to 62.0)	86.3 (83.5 to 88.8)	52.3 (45.1 to 59.4)	87.5 (84.7 to 89.9)
BIS1$_{creatinine}$	70	118	47	640	37.2 (30.3 to 44.6)	93.2 (91.0 to 94.9)	59.8 (50.4 to 68.8)	84.4 (81.7 to 86.9)
BIS2$_{creatinine-cystatin}$	81	107	45	642	43.1 (35.9 to 50.5)	93.4 (91.3 to 95.2)	64.3 (55.3 to 72.6)	85.7 (83.0 to 88.1)
CAPA$_{cystatin}$	98	90	95	592	52.1 (44.7 to 59.5)	86.2 (83.4 to 88.7)	50.8 (43.5 to 58.0)	86.8 (84.0 to 89.3)
FAS$_{creatinine}$	77	111	62	625	41.0 (33.9 to 48.3)	91.0 (88.6 to 93.0)	55.4 (46.7 to 63.8)	84.9 (82.1 to 87.4)
FAS$_{creatinine-cystatin}$	80	108	44	643	42.6 (35.4 to 50.0)	93.6 (91.5 to 95.3)	64.5 (55.4 to 72.9)	85.6 (82.9 to 88.1)
LMR$_{creatinine}$	94	94	109	578	50.0 (42.6 to 57.4)	84.1 (81.2 to 86.8)	46.3 (39.3 to 53.4)	86.0 (83.2 to 88.5)
EKFC$_{creatinine}$	87	101	80	607	46.3 (39.0 to 53.7)	88.4 (85.7 to 90.7)	52.1 (44.2 to 59.9)	85.7 (82.9 to 88.2)

continued

TABLE 14 Ability of eGFR to detect a change (upper table) and decline (lower table) in mGFR > 25% over 3 years (*continued*)

Decline in GFR								
	> |25%|		≤ |25%|		% (95% CI)			
Equation	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
MDRD	**76**	**80**	**51**	**668**	**48.7 (40.6 to 56.8)**	**92.9 (90.8 to 94.7)**	**59.8 (50.8 to 68.4)**	**89.3 (86.9 to 91.4)**
CKD-EPI$_{creatinine}$	**84**	**72**	**65**	**654**	**53.8 (45.7 to 61.8)**	**91.0 (88.6 to 93.0)**	**56.4 (48.0 to 64.5)**	**90.1 (87.7 to 92.2)**
CKD-EPI$_{cystatin}$	**89**	**67**	**71**	**648**	**57.1 (48.9 to 64.9)**	**90.1 (87.7 to 92.2)**	**55.6 (47.6 to 63.5)**	**90.6 (88.3 to 92.7)**
CKD-EPI$_{creatinine-cystatin}$	**92**	**64**	**64**	**655**	**59.0 (50.8 to 66.8)**	**91.1 (88.8 to 93.1)**	**59.0 (50.8 to 66.8)**	**91.1 (88.8 to 93.1)**
CKD-EPI(2021)$_{creatinine}$	82	74	64	655	52.6 (44.4 to 60.6)	91.1 (88.8 to 93.1)	56.2 (47.7 to 64.4)	89.8 (87.4 to 91.9)
CKD-EPI(2021)$_{creatinine-cystatin}$	91	65	65	654	58.3 (50.2 to 66.2)	91.0 (88.6 to 93.0)	58.3 (50.2 to 66.2)	91.0 (88.6 to 93.0)
BIS1$_{creatinine}$	68	88	41	678	43.6 (35.7 to 51.8)	94.3 (92.3 to 95.9)	62.4 (52.6 to 71.5)	88.5 (86.0 to 90.7)
BIS2$_{creatinine-cystatin}$	73	83	35	684	46.8 (38.8 to 54.9)	95.1 (93.3 to 96.6)	67.6 (57.9 to 76.3)	89.2 (86.8 to 91.3)
CAPA$_{cystatin}$	85	71	59	660	54.5 (46.3 to 62.5)	91.8 (89.5 to 93.7)	59.0 (50.5 to 67.1)	90.3 (87.9 to 92.3)
FAS$_{creatinine}$	74	82	45	674	47.4 (39.4 to 55.6)	93.7 (91.7 to 95.4)	62.2 (52.8 to 70.9)	89.2 (86.7 to 91.3)
FAS$_{creatinine-cystatin}$	74	82	35	684	47.4 (39.4 to 55.6)	95.1 (93.3 to 96.6)	67.9 (58.3 to 76.5)	89.3 (86.9 to 91.4)
LMR$_{creatinine}$	88	68	74	645	56.4 (48.2 to 64.3)	89.7 (87.3 to 91.8)	54.3 (46.3 to 62.2)	90.5 (88.1 to 92.5)
EKFC$_{creatinine}$	82	74	59	660	52.6 (44.4 to 60.6)	91.8 (89.5 to 93.7)	58.2 (49.6 to 66.4)	89.9 (87.5 to 92.0)

Note
Equations that form part of the primary study objectives are shown in bold.

TABLE 15 Ability of eGFR to detect a change in mGFR > 25% over 3 years and a change in disease category (e.g. GFR category 3A–3B)

Change in GFR								
	> 25% and change in stage		≤ 25% and no change in stage		% (95% CI)			
Equation	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
MDRD	**76**	**94**	**32**	**673**	**44.7 (37.1 to 52.5)**	**95.5 (93.7 to 96.9)**	**70.4 (60.8 to 78.8)**	**87.7 (85.2 to 90.0)**
CKD-EPI$_{creatinine}$	**82**	**88**	**38**	**667**	**48.2 (40.5 to 56.0)**	**94.6 (92.7 to 96.2)**	**68.3 (59.2 to 76.5)**	**88.3 (85.8 to 90.5)**
CKD-EPI$_{cystatin}$	**93**	**77**	**46**	**659**	**54.7 (46.9 to 62.3)**	**93.5 (91.4 to 95.2)**	**66.9 (58.4 to 74.6)**	**89.5 (87.1 to 91.7)**
CKD-EPI$_{creatinine-cystatin}$	**94**	**76**	**38**	**667**	**55.3 (47.5 to 62.9)**	**94.6 (92.7 to 96.2)**	**71.2 (62.7 to 78.8)**	**89.8 (87.4 to 91.9)**
CKD-EPI(2021)$_{creatinine}$	80	90	38	667	47.1 (39.4 to 54.9)	94.6 (92.7 to 96.2)	67.8 (58.6 to 76.1)	88.1 (85.6 to 90.3)
CKD-EPI(2021)$_{creatinine-cystatin}$	93	77	43	662	54.7 (46.9 to 62.3)	93.9 (91.9 to 95.6)	68.4 (59.9 to 76.1)	89.6 (87.1 to 91.7)
BIS1$_{creatinine}$	65	105	23	682	38.2 (30.9 to 46.0)	96.7 (95.1 to 97.9)	73.9 (63.4 to 82.7)	86.7 (84.1 to 89.0)
BIS2$_{creatinine-cystatin}$	73	97	21	684	42.9 (35.4 to 50.7)	97.0 (95.5 to 98.1)	77.7 (67.9 to 85.6)	87.6 (85.1 to 89.8)
CAPA$_{cystatin}$	90	80	43	662	52.9 (45.1 to 60.6)	93.9 (91.9 to 95.6)	67.7 (59.0 to 75.5)	89.2 (86.8 to 91.4)
FAS$_{creatinine}$	70	100	28	677	41.2 (33.7 to 49.0)	96.0 (94.3 to 97.3)	71.4 (61.4 to 80.1)	87.1 (84.6 to 89.4)
FAS$_{creatinine-cystatin}$	72	98	19	686	42.4 (34.8 to 50.2)	97.3 (95.8 to 98.4)	79.1 (69.3 to 86.9)	87.5 (85.0 to 89.7)
LMR$_{creatinine}$	84	86	45	660	49.4 (41.7 to 57.2)	93.6 (91.6 to 95.3)	65.1 (56.2 to 73.3)	88.5 (86.0 to 90.7)
EKFC$_{creatinine}$	78	92	36	669	45.9 (38.2 to 53.7)	94.9 (93.0 to 96.4)	68.4 (59.1 to 76.8)	87.9 (85.4 to 90.1)

continued

TABLE 15 Ability of eGFR to detect a change in mGFR > 25% over 3 years and a change in disease category (e.g. GFR category 3A–3B) (*continued*)

Decline in GFR								
	> 25% and change in stage		≤ 25% and no change in stage		% (95% CI)			
Equation	TP	FN	FP	TN	Sensitivity	Specificity	PPV	NPV
MDRD	**70**	**69**	**23**	**713**	**50.4 (41.8 to 58.9)**	**96.9 (95.3 to 98.0)**	**75.3 (65.2 to 83.6)**	**91.2 (89.0 to 93.1)**
CKD-EPI$_{creatinine}$	**76**	**63**	**29**	**707**	**54.7 (46.0 to 63.1)**	**96.1 (94.4 to 97.3)**	**72.4 (62.8 to 80.7)**	**91.8 (89.7 to 93.7)**
CKD-EPI$_{cystatin}$	**80**	**59**	**29**	**707**	**57.6 (48.0 to 65.9)**	**96.1 (94.4 to 97.3)**	**73.4 (64.1 to 81.4)**	**92.3 (90.2 to 94.1)**
CKD-EPI$_{creatinine-cystatin}$	**83**	**56**	**29**	**707**	**59.7 (51.1 to 67.9)**	**96.1 (94.4 to 97.3)**	**74.1 (65.0 to 81.9)**	**92.7 (90.6 to 94.4)**
CKD-EPI(2021)$_{creatinine}$	74	65	29	707	53.2 (44.6 to 61.7)	96.1 (94.4 to 97.3)	71.8 (62.1 to 80.3)	91.6 (89.4 to 93.4)
CKD-EPI(2021)$_{creatinine-cystatin}$	82	57	30	706	59.0 (50.3 to 67.3)	95.9 (94.2 to 97.2)	73.2 (64.0 to 81.1)	92.5 (90.4 to 94.3)
BIS1$_{creatinine}$	64	75	18	718	46.0 (37.6 to 54.7)	97.6 (96.2 to 98.5)	78.0 (67.5 to 86.4)	90.5 (88.3 to 92.5)
BIS2$_{creatinine-cystatin}$	66	73	16	720	47.5 (39.0 to 56.1)	97.8 (96.5 to 98.8)	80.5 (70.3 to 88.4)	90.8 (88.6 to 92.7)
CAPA$_{cystatin}$	77	62	26	710	55.4 (46.7 to 63.8)	96.5 (94.9 to 97.7)	74.8 (65.2 to 82.8)	92.0 (89.8 to 93.8)
FAS$_{creatinine}$	68	71	20	716	48.9 (40.4 to 57.5)	97.3 (95.8 to 98.3)	77.3 (67.1 to 85.5)	91.0 (88.8 to 92.9)
FAS$_{creatinine-cystatin}$	67	72	14	722	48.2 (39.7 to 56.8)	98.1 (96.8 to 99.0)	82.7 (72.7 to 90.2)	90.9 (88.7 to 92.8)
LMR$_{creatinine}$	79	60	31	705	56.8 (48.2 to 65.2)	95.8 (94.1 to 97.1)	71.8 (62.4 to 80.0)	92.2 (90.0 to 94.0)
EKFC$_{creatinine}$	74	65	28	708	53.2 (44.6 to 61.7)	96.2 (94.5 to 97.5)	72.5 (62.8 to 80.9)	91.6 (89.4 to 93.5)

Notes
Equations that form part of the primary study objectives are shown in bold.
The upper table describes change in either direction and the lower table describes decline only.

TABLE 16 Summary of continuous covariates over time for evaluable participants

Characteristic	Time (years)			
	Baseline	1	2	3
Systolic BP (mmHg)	130 (118–142) 239	127 (117–140) 224	130 (118–142) 201	129 (116–144) 208
Diastolic BP (mmHg)	78 (72–86) 239	78 (71–86) 224	77 (71–85) 201	77 (69–84) 208
BMI (kg/m^2)	28.7 (25.3–33.2) 239	28.6 (25.6–33.8) 224	28.8 (25.5–32.8) 200	28.9 (25.4–33.1) 209
Waist circumference (cm)	101 (91–111) 239	102 (93–111) 224	102 (93–113) 199	102 (91–113) 205

Note
Evaluable participants were those in whom paired mGFR and eGFR were available on at least two occasions. Values are shown as median (IQR) *n*.

TABLE 17 Summary of mGFR and eGFR and ACR over time for evaluable participants

Time (years)	GFR–ml/minute/1.73 m^2					Urine ACR–mg/mmol
	Measured GFR	MDRD	CKD-EPI$_{creatinine}$	CKD-EPI$_{cystatin}$	CKD-EPI$_{creatinine-cystatin}$	
Baseline	47.2 (38.4–58.2) 235	43.2 (34.8–52.8) 236	44.6 (35.4–53.6) 236	42.1 (34.9–54.5) 236	42.1 (35.2–54.4) 236	5.0 (1.6–27.4) 236
0.5	Not applicable	43.1 (34.8–51.8) 227	42.9 (35.1–53.5) 227	40.2 (32.4–52.4) 227	41.3 (33.5–50.7) 227	5.9 (1.7–30.4) 219
1.0	44.8 (35.5–55.9) 215	42.2 (34.1–50.9) 221	41.8 (34.3–51.5) 221	41.4 (32.3–55.5) 221	40.8 (33.3–54.4) 221	5.7 (1.6–30.1) 221
1.5	Not applicable	40.6 (32.0–48.5) 217	40.7 (31.9–49.6) 217	40.6 (30.1–52.2) 217	40.1 (30.7–51.7) 217	6.8 (1.6–46.2) 212
2.0	45.7 (34.8–56.6) 187	41.2 (32.0–53.1) 198	41.6 (31.8–54.9) 198	40.5 (29.6–57.9) 198	40.7 (29.8–54.7) 198	7.4 (2.0–41.0) 200
2.5	Not applicable	39.4 (31.7–51.2) 190	39.0 (30.7–53.0) 190	37.3 (27.9–53.3) 190	38.1 (28.9–53.1) 190	6.3 (1.7–38.8) 186
3.0	43.8 (32.9–54.3) 197	41.2 (30.8–52.7) 209	41.1 (30.5–53.5) 209	41.4 (30.4–56.7) 209	40.9 (30.4–55.3) 209	6.2 (1.8–29.8) 208

Note
Evaluable participants were those in whom paired mGFR and eGFR were available on at least two occasions. Values are shown as median (IQR) *n*. (See also *Appendix 1*, *Figures 15* and *16*.)

TABLE 18 Summary of bias (eGFR minus mGFR) over time for evaluable participants

Time (years)	Bias (eGFR – mGFR)– ml/minute/1.73 m^2			
	MDRD	CKD-EPI$_{creatinine}$	CKD-EPI$_{cystatin}$	CKD-EPI$_{creatinine-cystatin}$
Baseline	−4.7 (−11.0 to 2.0), 232	−3.8 (−9.6 to 3.5), 232	−3.5 (−9.4 to 2.6), 232	−4.2 (−9.0 to 1.1), 232
1	−3.4 (−9.4 to 3.1), 212	−3.0 (−8.0 to 3.2), 212	−1.9 (−7.3 to 4.0), 212	−3.3 (−7.1 to 2.0), 212
2	−3.8 (−8.2 to 2.0), 184	−3.0 (−7.2 to 2.6), 184	−1.1 (−6.9 to 4.7), 184	−2.2 (−6.2 to 1.8), 184
3	−4.0 (−9.0 to 1.0), 196	−4.0 (−8.0 to 1.8), 196	−1.4 (−6.3 to 4.4), 196	−2.5 (−6.4 to 2.6), 196

Note
Evaluable participants were those in whom paired mGFR and eGFR were available on at least two occasions. Values shown are the median of the differences (IQR), *n*.

TABLE 19 Slope and variability estimates from random coefficients model (excluding covariates)

Outcome measure	Slope (rate of change), ml/minute/1.73 m^2/year		Variance estimate	
	Estimate	95% CI	Between slopes	Residual
Measured GFR	−1.47	−1.85 to −1.09	2.33	28.5
MDRD	−1.33	−1.69 to −0.967	4.76	20.1
CKD-EPI$_{creatinine}$	−1.56	−1.94 to −1.19	5.14	23.0
CKD-EPI$_{cystatin}$	−0.743	−1.17 to −0.314	7.88	22.7
CKD-EPI$_{creatinine-cystatin}$	−1.01	−1.39 to −0.632	6.19	17.5
Difference MDRD – mGFR	0.325	−0.038 to 0.688	0.707	33.1
Difference CKD-EPI$_{creatinine}$ – mGFR	0.101	−0.272 to 0.474	0.734	35.0
Difference CKD-EPI$_{cystatin}$ – mGFR	0.840	0.441 to 1.24	1.78	34.7
Difference CKD-EPI$_{creatinine-cystatin}$ – mGFR	0.619	0.266 to 0.971	1.07	29.3

moderate, and correlations of 0.5 or above high. *Table 20* shows the correlation coefficients for each covariate pair. The highest correlation was seen between waist circumference and BMI (0.856). Waist circumference was also moderately correlated with gender (0.337) and diabetes status (0.384). BMI and diabetes status were moderately correlated (0.383), as were systolic and diastolic BP (0.400). All other correlations were < 0.3, although there were a number of correlations between 0.2 and 0.3 which could have impacted covariate selection in the model.

Regression modelling to explore the effect of each covariate individually on the intercept and progression slope was conducted prior to modelling the combined covariates in the full models. For mGFR, the individual unadjusted covariate regression models had coefficients with a *p*-value of < 0.2 for the intercept term for all covariates with the exception of BMI and smoking status. Similarly, the individual regressions had coefficients with $p < 0.2$ for the rate of change (progression) for covariates age, diabetes status, ethnicity group, albuminuria, BMI, waist circumference and smoking status (data not shown).

Measured glomerular filtration rate random coefficients final covariate model

Estimates from the random coefficients final covariate model for mGFR for both the substudy and the combined substudy and main study data combined are shown in *Table 21*. All covariates were controlled for other terms in the model, that is the estimated coefficients show the additional effect of the covariate after all other variables in the model have been accounted for.

TABLE 20 Correlation coefficient estimates between baseline covariates used in the random coefficients models

Covariate	Gender	Age (years)	Diabetes (yes/no)	Ethnicity group	Proteinuria	Systolic BP (mmHg)	Diastolic BP (mmHg)	BMI (kg/m^2)	Waist circumference (cm)	Smoking status (yes/no)
Age (years)	0.105	1.00								
Diabetes (yes/no)	0.130	0.120	1.00							
Ethnicity group	0.058	0.249	0.190	1.00						
Albuminuria	0.154	0.271	0.111	0.152	1.00					
Systolic BP (mmHg)	0.154	0.285	−0.033	0.140	0.166	1.00				
Diastolic BP (mmHg)	0.022	−0.287	−0.247	0.074	0.146	0.400	1.00			
BMI (kg/m^2)	0.084	−0.046	0.383	0.130	0.059	−0.141	−0.137	1.00		
Waist circumference (cm)	0.337	0.135	0.384	0.144	0.077	−0.077	−0.190	0.856	1.00	
Smoking status (yes/no)	0.179	0.231	0.063	0.146	0.182	0.100	0.098	0.143	0.203	1.00
Vascular disease (yes/no)	0.164	0.215	0.092	0.127	0.014	−0.002	−0.219	0.092	0.136	0.123

Note
Spearman's rank correlation was used for continuous variable pairs, Cramer's V for categorical variable pairs, point-biserial correlation for continuous and categorical (binary) variables and eta correlation coefficient for continuous and categorical (> 2 levels) variable pairs. Albuminuria was categorised by ACR as < 3 mg/mmol, 3–30 mg/mmol and > 30 mg/mmol.

TABLE 21 Measured GFR covariate model

Model term/covariate	Measured GFR (ml/minute/1.73 m²)	
	Substudy data only	Main study and substudy data combined
Intercept constant (Caucasian, no albuminuria, no CCB antagonists)	0.202 (−4.518 to 4.922), 0.933	0.042 (−1.857 to 1.943), 0.965
Age (years)	−0.036 (−0.081 to 0.008), 0.111	−0.019 (−0.038 to −0.001), 0.042
Baseline mGFR (ml/minute/1.73 m²)	0.957 (0.916 to 1.000), < 0.001	0.984 (0.968 to 1.000), < 0.001
Ethnicity group		
African-Caribbean	0.146 (−1.401 to 1.693), 0.853	0.096 (−0.788 to 0.979), 0.832
South Asian	−0.660 (−2.308 to 0.998), 0.433	−0.270 (−1.12 to 0.585), 0.536
Albuminuria		
3–30 mg/mmol	0.527 (−0.708 to 1.761), 0.403	0.123 (−0.353 to 0.600), 0.612
> 30 mg/mmol	−0.069 (−1.533 to 1.395), 0.927	−0.021 (−0.584 to 0.541), 0.941
Systolic BP (mmHg)	0.031 (0.006 to 0.056), 0.016	0.015 (0.004 to 0.025), 0.008
Slope constant (progression rate of change) (ml/minute/1.73 m²/year)	1.051 (−0.800 to 2.902), 0.266	2.121 (1.226 to 3.016), < 0.001
Ethnicity group * slope		
African-Caribbean	1.014 (−0.198 to 2.226), 0.101[a]	1.113 (0.171 to 2.055), 0.021
South Asian	−0.655 (−1.917 to 0.606), 0.309	−0.218 (−1.095 to 0.659) 0.625
Albuminuria * slope		
3–30 mg/mmol	−0.935 (−1.758 to −0.112), 0.026	−0.549 (−0.959 to −0.140), 0.009
> 30 mg/mmol	−1.619 (−2.631 to −0.607), 0.002	−1.521 (−2.007 to −1.036), < 0.001
Baseline mGFR * slope	−0.037 (−0.069 to 0.005), 0.025	−0.064 (−0.080 to −0.048), < 0.001

a See note in text regarding effect of one individual on impact of African-Caribbean ethnicity slope factor.

Note
For the substudy, terms were retained in the model where $p < 0.2$ and intercept terms retained where the interaction with slope $p < 0.2$. Associations observed to be significant in the substudy were then assessed in the combined data set. Units for progression are ml/minute/1.73 m²/year. Values show regression coefficient (95% CI), *p*-value.

The coefficients for each of the categorical variates in the regression model correspond to the difference from the reference category, for example the albuminuria coefficients for the two higher categories correspond to the difference from those with no albuminuria (< 3 mg/mmol). To estimate the intercept for a particular subgroup, the regression coefficients of the constant term and each of the covariate main effect terms (not interactions) are used. As an example consider the estimated intercept from the mGFR substudy final model for a baseline mGFR of 60 ml/minute/1.73 m², ACR of 10 mg/mmol, age 70 years, South Asian ethnicity, and systolic BP 120 mmHg: the estimate of intercept is 0.202 − (0.036 × 70) + (0.957 × 60) − 0.660 + 0.527 + (0.031 × 120), which is equal to 58.7 ml/minute/1.73 m². Similarly, progression can be estimated using the slope constant term and the coefficients of the interactions with the slope (the terms appearing below the slope constant term in the table). For the example given above, the estimate of progression would be 1.051 − 0.655 − 0.935 − (0.037 × 60), which is equal to a rate of change of −2.76 ml/minute/1.73 m²/year.

In the substudy data, the intercept (including covariates) was the expected mean value of mGFR when the time was equal to zero (baseline). In the final model, this was derived using baseline mGFR, age (increasing age lowers the intercept) and systolic BP (higher systolic BP increases the intercept) ($p < 0.2$).

Of these, baseline-mGFR was the main determinant. Intercept terms were also included in the model for covariates which were associated with slope. In the final model, the rate of change in mGFR over time was associated with baseline GFR, ethnicity group and albuminuria ($p < 0.2$). Baseline GFR increased the intercept by 0.957 ml/minute/1.73 m^2 (95% CI 0.916 to 1.000) for each unit of baseline GFR, and decreased the progression slope (steeper decline) by −0.037 ml/minute/1.73 m^2/year (95% CI −0.069 to 0.005) for each unit. African-Caribbean ethnicity increased the progression slope (slower decline) by 1.01 ml/minute/1.73 m^2/year (95% CI −0.198 to 2.226). However, inspection of the individual data revealed one participant (ID 19877) who had much higher values of mGFR at baseline and at 3 years in the African-Caribbean ethnicity group. Sensitivity analysis excluding this participant (ID 19877) showed no evidence of effects of ethnicity on progression or intercept ($p > 0.2$).

The rate of decline was steeper for those with higher levels of albuminuria: the slope decreased by −0.935 ml/minute/1.73 m^2/year (95% CI −1.758 to −0.112) for those with ACR between 3 and 30 mg/mmol (inclusive) and −1.619 ml/minute/1.73 m^2/year (95% CI −2.631 to −0.607) for those with ACR > 30 mg/mmol.

Age and systolic BP were associated with the intercept only. There was a decrease of −0.036 ml/minute/1.73 m^2 (95% CI −0.081 to −0.008) for each year of age, and an increase of 0.031 ml/minute/1.73 m^2 (95% CI 0.006 to 0.056) for each unit of systolic BP (mmHg).

Plots of the fitted and observed data by participants for the final covariate model for mGFR are shown for completeness in *Report Supplementary Material 1*.

The parameter estimates from the model using the full data set were similar to those from the substudy for all covariates (*Table 21*). The association between African-Caribbean ethnicity and progression (i.e. with African-Caribbean ethnicity being associated with reduced progression) was more significant when the model was fitted to the full data set ($p = 0.021$). Sensitivity analysis excluding the data for one participant (ID 19877) discussed earlier made very little difference to the statistical significance of this association ($p = 0.032$) (see *Appendix 1*, *Figure 19*). It should be noted that the number of evaluable participants in the full data set was still quite low for African-Caribbean ($n = 46$) and South Asian ($n = 51$) ethnicity groups.

Figure 7 illustrates the changes in mGFR progression over time for albuminuria status. The median mGFR of those with albuminuria declines more steeply compared to those who do not have albuminuria. The equivalent figure for the combined main and substudy data may be found in *Appendix 1*, *Figure 20*.

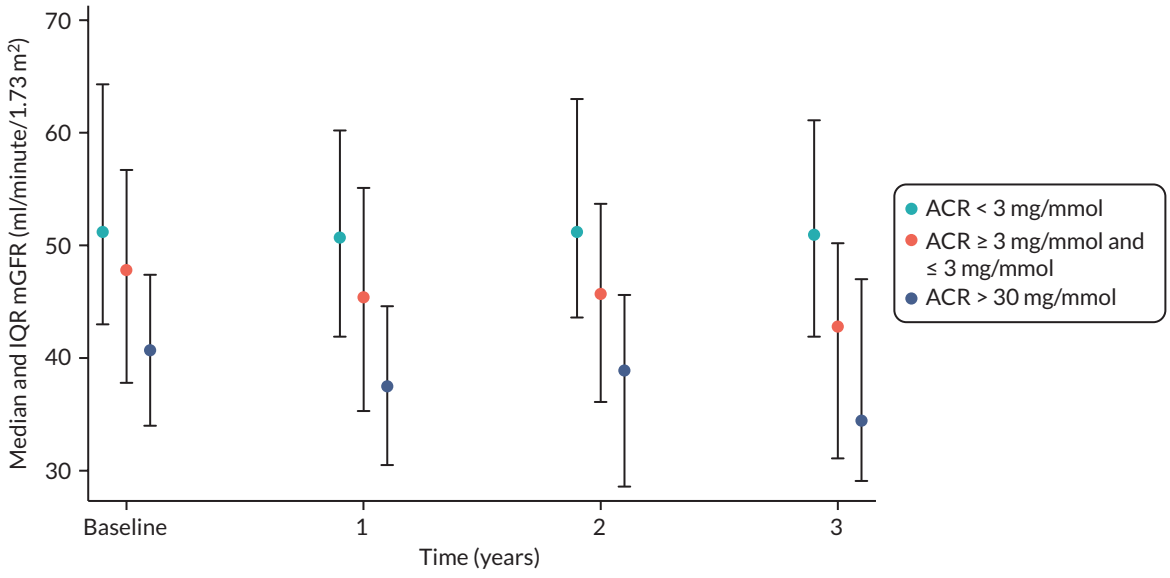

FIGURE 7 Median and IQR mGFR over time by albuminuria status (substudy data).

Creatinine estimated glomerular filtration rate random coefficients final covariate model

The individual covariate regression models for CKD-EPI$_{creatinine}$ had coefficients with a *p*-value of < 0.2 for the intercept term for all covariates with the exception of ethnicity group and systolic BP. Similarly, the individual regressions had coefficients with $p < 0.2$ for the rate of change (progression) for covariates age, diabetes status, ethnicity group, albuminuria, diastolic BP, waist circumference and smoking status (data not shown).

Table 22 shows the estimates from the random coefficients regression final covariate model for CKD-EPI$_{creatinine}$ for all main study and substudy data compared to the model estimates including the substudy data only.

TABLE 22 Estimated GFR CKD-EPI$_{creatinine}$ covariate model

Model term/covariate	CKD-EPI$_{creatinine}$ (ml/minute/1.73 m^2)	
	Substudy data only	Main study and substudy data combined
Intercept constant (Caucasian, no diabetes, no albuminuria, no beta-blockers, no A2RB)	7.971 (3.462 to 12.480), 0.001	5.125 (2.819 to 7.431), < 0.001
Age (years)	−0.038 (−0.080 to −0.003), 0.069	−0.017 (−0.039 to 0.004), 0.109
Baseline CKD-EPI$_{creatinine}$ (ml/minute/1.73 m^2)	0.945 (0.905 to 0.985), < 0.001	0.909 (0.888 to 0.930), < 0.001
Diabetes (yes)	−0.094 (−1.294 to 1.106), 0.878	−0.515 (−1.099 to 0.067), 0.083
Ethnicity group		
African-Caribbean	0.786 (−0.604 to 2.177), 0.268	0.952 (−0.144 to 2.048), 0.089
South Asian	−0.621 (−2.150 to 0.908), 0.426	0.174 (−0.876 to 1.224), 0.745
Albuminuria		
3–30 mg/mmol	−0.180 (−1.207 to 0.847), 0.731	0.056 (−0.449 to 0.562), 0.828
> 30 mg/mmol	0.138 (−1.033 to 1.308), 0.818	0.651 (0.073 to 1.228), 0.027
BMI (kg/m^2)	−0.085 (−0.173 to 0.003), 0.058	−0.0001 (−0.040 to 0.040), 0.995
Beta-blocker (yes)	−0.434 (−1.460 to 0.592), 0.407	−0.222 (−0.741 to 0.297), 0.402
A2RB (yes)	−0.695 (−1.665 to 0.275), 0.160	−0.669 (−1.160 to −0.177), 0.008
Slope constant (progression rate of change) (ml/minute/1.73 m^2/year)	−1.082 (−1.749 to −0.414), 0.001	−1.197 (−1.498 to −0.895), < 0.001
Diabetes * slope	1.058 (0.153 to 1.964), 0.022	0.037 (−0.403 to 0.477), 0.870
Ethnicity group * slope		
African-Caribbean	0.161 (−0.992 to 1.315), 0.784	−0.046 (−0.935 to 0.842), 0.919
South Asian	−1.011 (−2.249 to 0.227), 0.109	−0.581 (−1.419 to 0.256), 0.173
Albuminuria * slope		
3–30 mg/mmol	−0.251 (−0.942 to 0.440), 0.477	0.048 (−0.276 to 0.371), 0.772
> 30 mg/mmol	−0.861 (−1.685 to −0.037), 0.040	−0.479 (−0.858 to −0.099), 0.013
Beta-blocker * slope	−0.598 (−1.348 to 0.152), 0.118	0.043 (−0.300 to 0.385), 0.808
A2RB * slope	−0.609 (−1.335 to 0.117), 0.100	−0.235 (−0.560 to 0.090) 0.156

Note
For the substudy, terms were retained in the model where $p < 0.2$ and intercept terms retained where the interaction with slope $p < 0.2$. Associations observed to be significant in the substudy were then assessed in the combined data set. Units for progression are ml/minute/1.73 m^2/year. Values show regression coefficient (95% CI), *p*-value.

In the substudy, intercept was associated with baseline CKD-EPI$_{creatinine}$, age, BMI and A2RB medication ($p < 0.2$). Intercept terms were also included in the model for covariates which were associated with slope. In the final model, the rate of change in CKD-EPI$_{creatinine}$ over time is associated with ethnicity group, albuminuria and diabetes status, and beta-blocker and A2RB medication ($p < 0.2$).

Albuminuria decreased the progression slope (steeper decline) by −0.861 ml/minute/1.73 m^2/year (95% CI −1.685 to −0.037) for those with ACR > 30 mg/mmol. South Asian ethnicity decreased the progression slope (steeper decline) by −1.011 ml/minute/1.73 m^2/year (95% CI −2.249 to 0.227). Diabetes increased the slope (slower decline) by 1.058 ml/minute/1.73 m^2/year (95% CI 0.153 to 1.964): this seems counterintuitive and may be partially due to the lower intercept for those with diabetes. The coefficient is the combined effect of diabetes status with all other covariates in the model and diabetes status is correlated with BMI which is also included in the model and could affect the coefficient for this covariate. The rate of decline was steeper for those prescribed beta-blocker medication, the slope decreasing by −0.598 ml/minute/1.73 m^2/year (95% CI −1.348 to 0.152), and for those prescribed A2RBs, who had a decrease in slope of −0.609 ml/minute/1.73 m^2/year (95% CI −1.335 to 0.117). The intercept also decreased by −0.695 ml/minute/1.73 m^2 (95% CI −1.665 to 0.275) for those taking A2RBs.

Age, baseline CKD-EPI$_{creatinine}$ and BMI were associated with intercept only. There was a decrease of −0.038 ml/minute/1.73 m^2 (95% CI −0.080 to −0.003) for each year of age, an increase of 0.945 ml/minute/1.73 m^2 (95% CI 0.905 to 0.985) for each unit of baseline CKD-EPI$_{creatinine}$ and a decrease of −0.085 ml/minute/1.73 m^2 (−0.173 to 0.003) for each BMI unit (kg/m^2).

Using the full data set, diabetes status was associated with the intercept estimates of CKD-EPI$_{creatinine}$ ($p = 0.083$), but not associated with progression, and the association of BMI with the intercept was no longer significant, but BMI and diabetes status were highly correlated so it is likely these effects are presenting in a different way in the model. Using the full data set, there was no longer an association between the use of beta-blocker medication and progression, but there was a statistically significant association between A2RB use and the intercept levels of CKD-EPI$_{creatinine}$. Other covariate estimates for the full data set were similar to those seen for the substudy.

Figures 8–10 illustrate CKD-EPI$_{creatinine}$ progression over time in the substudy for diabetes, albuminuria and ethnicity groups, respectively. In *Figure 8* the decline in the medians of those who have and those who do not have diabetes appears to be similar, the differences seen in the model could be due to the differences in the intercepts of those with and without diabetes, and the correlation between BMI and diabetes status. In *Figure 9* the steeper decline over time is more obvious for those with albuminuria, compared to those who do not have albuminuria. The equivalent figure for the combined main and substudy data may be found in *Appendix 1*, *Figure 21*. *Figure 10* suggests a steeper decline for people of South Asian ethnicity. The equivalent figure for the combined main and substudy data may be found in *Appendix 1* (*Figure 22*).

Cystatin C estimated glomerular filtration rate random coefficients final covariate model

The individual covariate regression models for CKD-EPI$_{cystatin}$ had coefficients with a p-value of < 0.2 for the intercept term for all covariates with the exception of albuminuria and diastolic BP. The individual regressions had coefficients with $p < 0.2$ for the rate of change (progression) for covariates gender, baseline CKD-EPI$_{cystatin}$, albuminuria, systolic and diastolic BP, BMI, waist circumference and smoking status (data not shown).

Table 23 shows the estimates from the random coefficients regression final covariate model for CKD-EPI$_{cystatin}$. For the substudy, intercept was associated with baseline CKD-EPI$_{cystatin}$, gender, ethnicity group, BMI, waist circumference and smoking status ($p < 0.2$). Intercept terms were also included in the model for covariates which were associated with slope. In the final model, the rate of change in CKD-EPI$_{cystatin}$

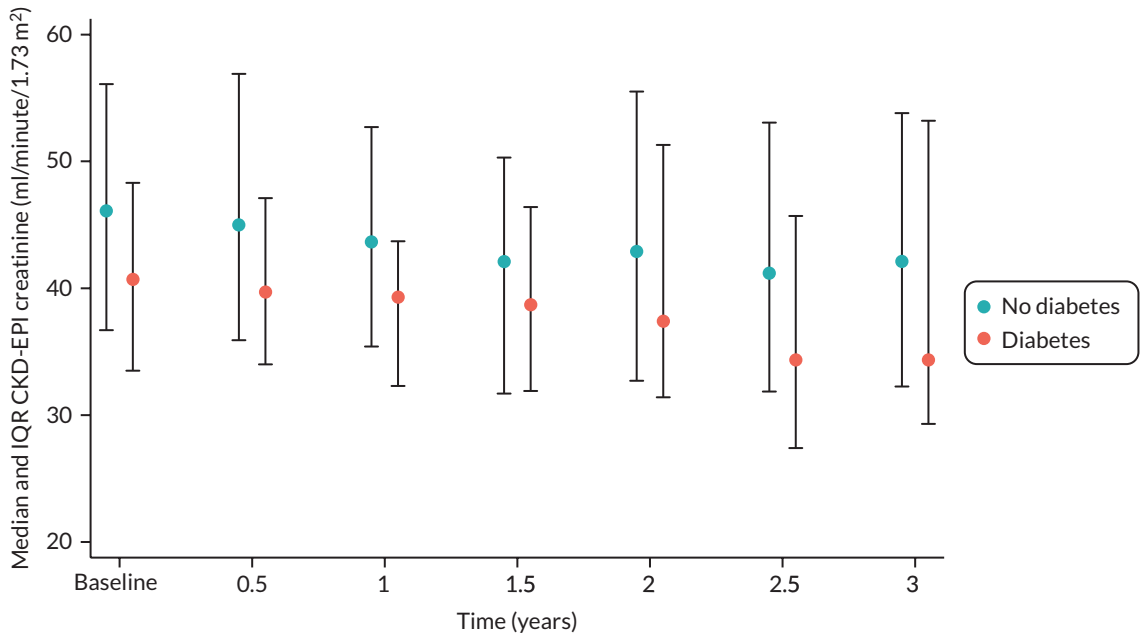

FIGURE 8 Median and IQR CKD-EPI$_{creatinine}$ over time by diabetes status (substudy data).

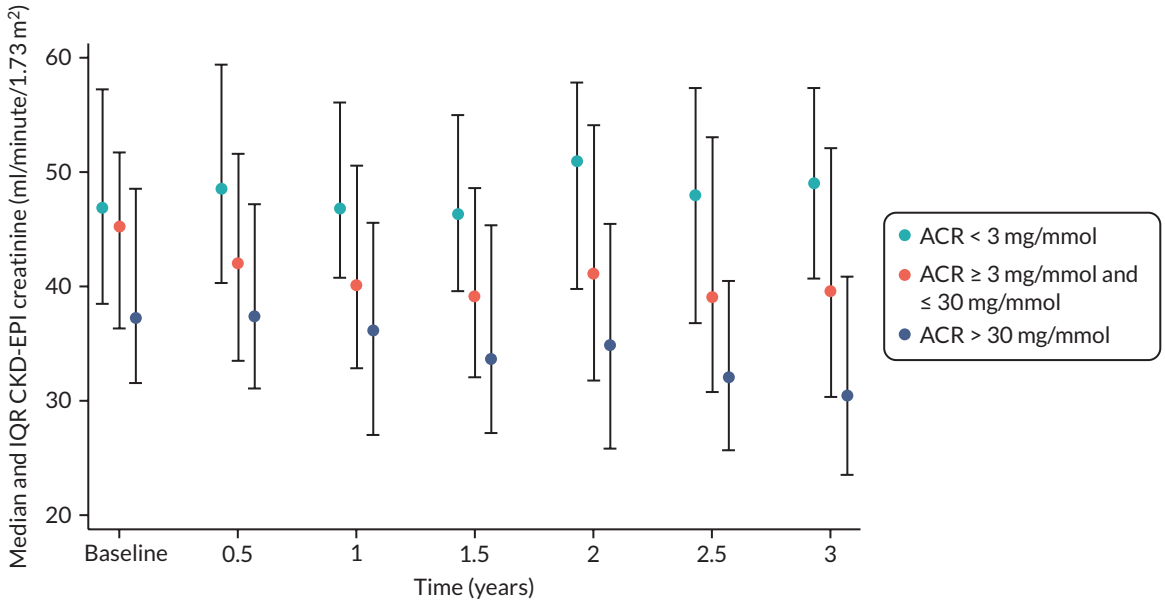

FIGURE 9 Median and IQR CKD-EPI$_{creatinine}$ over time by albuminuria status (substudy data).

over time was associated with baseline CKD-EPI$_{cystatin}$, diastolic BP, BMI and beta-blocker and A2RB medication ($p < 0.2$).

Baseline CKD-EPI$_{cystatin}$ increased the intercept by 0.991 ml/minute/1.73 m^2 (95% CI 0.957 to 1.025) for each unit of baseline CKD-EPI$_{cystatin}$, and increased the progression slope (slower decline) by 0.031 ml/minute/1.73 m^2/year (95% CI 0.003 to 0.060) for each unit. The rate of decline was also steeper for those prescribed beta-blocker medication, the slope decreasing by −0.997 ml/minute/1.73 m^2/year (95% CI −1.826 to −0.168), and for those prescribed A2RBs, who had a decrease in the slope of −0.855 ml/minute/1.73 m^2/year (95% CI −1.633 to −0.077). Diastolic BP decreased the progression slope (steeper decline) by −0.024 ml/minute/1.73 m^2/year (95% CI −0.052 to 0.004) for each mmHg unit of BP. BMI

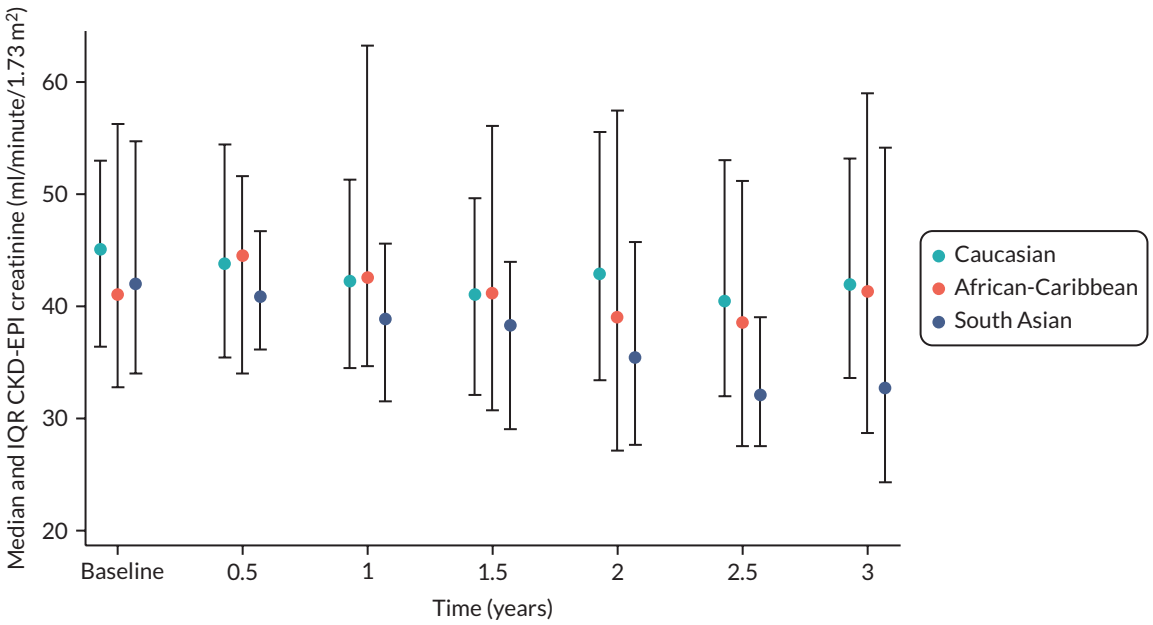

FIGURE 10 Median and IQR CKD-EPI$_{creatinine}$ over time by ethnicity group (substudy data).

decreased the intercept by −0.220 ml/minute/1.73 m^2 (95% CI −0.366 to −0.073) for each unit (kg/m^2), and increased the progression slope (slower decline) by 0.077 ml/minute/1.73 m^2/year (95% CI 0.005 to 0.148).

Gender, ethnicity group, waist circumference and smoking status were associated with the intercept only. There was an increase of 0.046 ml/minute/1.73 m^2 (95% CI −0.011 to 0.103) for each unit change in waist circumference (cm), a decrease of −0.768 ml/minute/1.73 m^2 (95% CI −1.895 to 0.358) for males, an increase of 1.082 ml/minute/1.73 m^2 (95% CI −0.300 to 2.463) for African-Caribbean ethnicity and a decrease in intercept of −1.547 ml/minute/1.73 m^2 (95% CI −3.203 to 0.108) for those who currently smoke.

Using the full data set, BMI and waist circumference were no longer associated with the intercept estimates of CKD-EPI$_{cystatin}$, and BMI was no longer associated with progression. The effect of smoking status changed: using the substudy data only, there was an association between current smokers and the intercept, whereas using the full data set there was an association between ex-smokers and the intercept. This change may be due to the increased number of ex-smokers in the full data set (n = 367), compared to the number of current smokers (n = 70). Using the full data set, there was no longer an association between the use of beta-blocker medication and progression. Other estimates for the full data set were similar to those seen for the substudy data.

Figure 11 illustrates the changes in CKD-EPI$_{cystatin}$ progression over time by ethnicity group. Those of African-Caribbean ethnicity have a different profile over time compared to the other ethnicity groups, although there was little evidence to suggest a difference in progression over time, but the intercept was higher for African-Caribbeans in the final model. The equivalent figure for the combined main and substudy data may be found in *Appendix 1*, *Figure 23*.

Urinary albumin-to-creatinine ratio random coefficients final covariate model

The individual covariate regression models for log-transformed urinary ACR had intercept coefficients with a p-value of < 0.2 for all covariates with the exception of diabetes, BMI, waist circumference and vascular disease. The individual regressions had coefficients with p < 0.2 for the rate of change (progression) for covariates diabetes status, ethnicity group, albuminuria, baseline log ACR, systolic and diastolic BP and waist circumference (data not shown).

TABLE 23 Estimated GFR CKD-EPI$_{cystatin}$ covariate model

Model term/covariate	CKD-EPI$_{cystatin}$ (ml/minute/1.73 m^2)	
	Substudy data only	Main study and substudy data combined
Intercept constant (Caucasian, females, non-smoker, no beta-blockers, no A2RB)	1.862 (−3.446 to 7.190), 0.493	0.914 (−1.784 to 3.612), 0.507
Baseline CKD-EPI$_{cystatin}$ (ml/minute/1.73 m^2)	0.991 (0.957 to 1.025), < 0.001	0.963 (0.946 to 0.980), < 0.001
Males	−0.768 (−1.895 to 0.358), 0.181	0.574 (0.016 to 1.132), 0.044
Ethnicity group		
African-Caribbean	1.082 (−0.300 to 2.463), 0.125	0.975 (−0.151 to 2.101), 0.090
South Asian	−0.110 (−1.603 to 1.382), 0.885	−0.372 (−1.449 to 0.703), 0.497
Diastolic BP (mmHg)	0.008 (−0.034 to 0.050), 0.708	0.009 (−0.013 to 0.031), 0.429
BMI (kg/m^2)	−0.220 (−0.366 to −0.073), 0.003	−0.004 (−0.078 to 0.071), 0.927
Waist circumference (cm)	0.046 (−0.011 to 0.103), 0.115	−0.006 (−0.036 to 0.023), 0.677
Smoking status		
Current smoker	−1.547 (−3.203 to 0.108), 0.067	−0.078 (−1.024 to 0.868), 0.872
Ex-smoker	−0.012 (−1.077 to 1.053), 0.983	−0.535 (−1.060 to −0.009), 0.046
Beta-blockers (yes)	0.065 (−0.982 to 1.112), 0.903	−0.274 (−0.825 to 0.272), 0.323
A2RB (yes)	0.486 (−0.511 to 1.483), 0.339	−0.095 (−0.609 to 0.418), 0.717
Slope constant (progression rate of change) (ml/minute/1.73 m^2/year)	−2.047 (−5.488 to 1.393), 0.244	−0.142 (−1.739 to 1.455), 0.861
Baseline CKD-EPI$_{cystatin}$ * slope	0.031 (0.003 to 0.060), 0.031	0.011 (−0.003 to 0.025), 0.118
Diastolic BP * slope	−0.024 (−0.052 to 0.004), 0.094	−0.016 (−0.029 to −0.002), 0.022
BMI * slope	0.077 (0.005 to 0.148), 0.035	0.006 (−0.027 to 0.038), 0.727
Beta-blockers * slope	−0.997 (−1.826 to −0.168), 0.018	0.018 (−0.354 to 0.390), 0.924
A2RB * slope	−0.855 (−1.633 to −0.077), 0.031	−0.389 (−0.739 to −0.038), 0.030

Note
For the substudy, terms were retained in the model where $p < 0.2$ and intercept terms retained where the interaction with slope $p < 0.2$. Associations observed to be significant in the substudy were then assessed in the combined data set. Units for progression are ml/minute/1.73 m^2/year. Values show regression coefficient (95% CI), *p*-value.

Table 24 shows the estimates from the random coefficients regression final covariate model for log ACR. For the substudy, intercept was associated with baseline log ACR, albuminuria (ACR category), age, systolic BP, diabetes, smoking status and loop diuretic medication ($p < 0.2$). Intercept terms were also included in the model for covariates associated with slope. In the final model, the rate of change in log ACR over time was associated with baseline log ACR, diabetes status, ethnicity group, albuminuria (ACR category), diastolic BP, smoking status and loop diuretic and CCB medication ($p < 0.2$).

There was a 0.605% increase in ACR intercept (95% CI 0.557% to 0.653%) for each 1% increase in baseline ACR, and a −0.118% decrease in slope (slower incline) (95% CI −0.146% to −0.092%) for each 1% increase in baseline ACR. Albuminuria (ACR category) increases both the intercept and the slope (steeper incline), larger increases were seen for those with ACR higher than 30 mg/mmol, ACR intercept increased by 472% (95% CI 360% to 611%) and slope increased by 57.6% (95% CI 39.2% to 78.6%) for those with ACR > 30 mg/mmol. Diastolic BP increased the slope (steeper incline) by 0.170% (95% CI −0.060% to 0.411%), for each increasing unit of BP (mmHg). For current smokers, there was an increase in progression

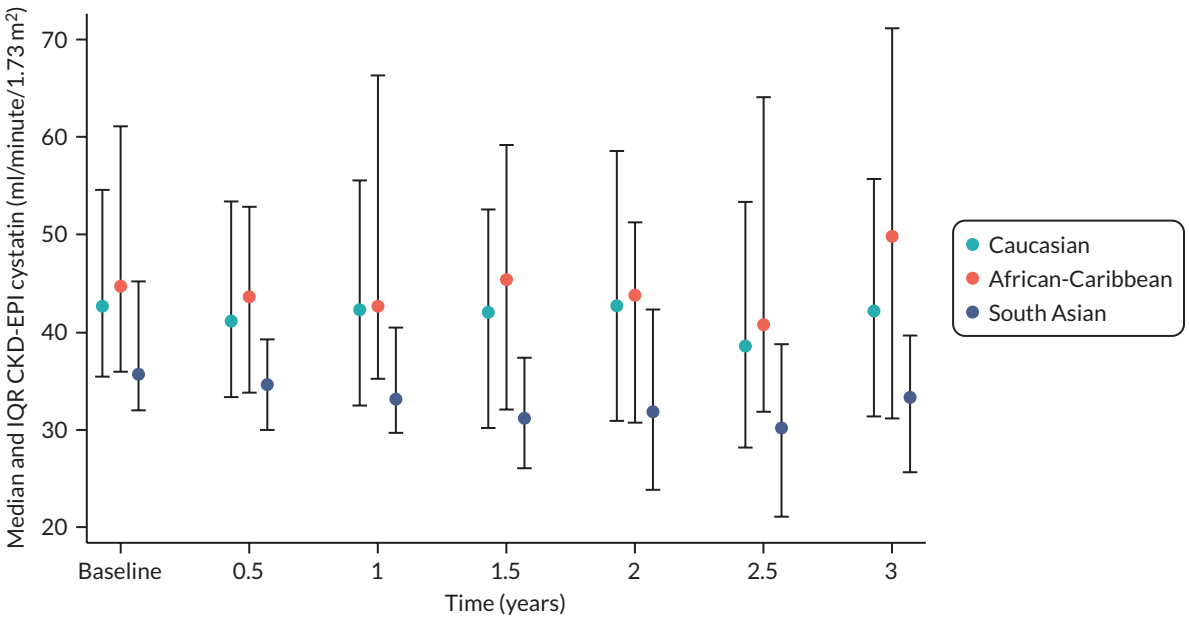

FIGURE 11 Median and IQR CKD-EPI$_{cystatin}$ over time by ethnicity group (substudy data).

TABLE 24 Urinary ACR (log-transformed) covariate model

	Log-transformed ACR (mg/mmol)	
Model term/covariate	**Substudy data only**	**Main study and substudy data combined**
Intercept (Caucasian, no diabetes, no albuminuria, non-smoker, no loop diuretics, no CCB)	−4.88% (−31.2% to 60.8%), 0.816	1.21% (−19.4% to 27.3%), 0.916
Age (years)	−0.499% (−0.896% to 0.100%), 0.011	−0.200% (−0.399% to 0.030%), 0.101
Baseline ACR (log mg/mmol)[+]	0.605% (0.557% to 0.653%), < 0.001	0.533% (0.508% to 0.558%), < 0.001
Diabetes (yes)	10.1% (0.300% to 21.2%), 0.049	5.44% (0.300% to 10.7%), 0.038
Ethnicity group		
African-Caribbean	2.02% (−13.8% to 11.4%), 0.756	3.15% (−7.69% to 15.1%), 0.587
South Asian	−7.87% (−19.7% to 5.76%), 0.243	−1.09% (−10.8% to 9.75%), 0.839
Albuminuria		
3–30 mg/mmol	129% (101% to 160%), < 0.001	178% (160% to 198%), < 0.001
> 30 mg/mmol	472% (360% to 611%), < 0.001	713% (625% to 812%), < 0.001
Systolic BP (mmHg)	0.300% (0.100% to 0.602%), 0.002	0.200% (0.100% to 0.300%), 0.001
Diastolic BP (mmHg)	−0.200% (−0.598% to 0.300%), 0.470	−0.200% (−0.399% to 0.100%), 0.133
Smoking status		
Current smoker	4.39% (−10.6% to 21.9%), 0.587	−3.82% (−12.1% to 5.34%), 0.404
Ex-smoker	−4.11% (−12.9% to 5.44%), 0.387	−4.21% (−8.88% to 0.702%), 0.092
Loop diuretic (yes)	12.5% (1.01% to 25.4%), 0.032	3.46% (−3.34% to 10.7%), 0.330
CCB (yes)	0.401% (−7.87% to 9.31%), 0.936	−1.49% (−6.29% to 3.56%), 0.557
Slope (progression rate of change) (% mg/mmol/year)	−12.5% (−27.9% to 6.18%), 0.175	−5.35% (−14.2% to 4.39%), 0.274
Baseline ACR * slope[a]	−0.118% (−0.146% to −0.092%), < 0.001	−0.090% (−0.103% to −0.077%), < 0.001

continued

TABLE 24 Urinary ACR (log-transformed) covariate model (*continued*)

Model term/covariate	Log-transformed ACR (mg/mmol)	
	Substudy data only	Main study and substudy data combined
Ethnicity group * slope		
African-Caribbean	12.0% (2.74% to 22.0%), 0.010	10.8% (3.87% to 18.3%), 0.002
South Asian	10.6% (1.01% to 21.0%), 0.030	8.98% (2.63% to 15.7%), 0.005
Albuminuria * slope		
3–30 mg/mmol	25.6% (16.6% to 35.4%), < 0.001	15.4% (11.2% to 19.7%), < 0.001
> 30 mg/mmol	57.6% (39.2% to 78.6%), < 0.001	41.8% (33.2% to 50.7%), < 0.001
Diastolic BP * slope	0.170% (−0.060% to 0.411%), 0.147	0.100% (−0.020% to 0.220%), 0.103
Smoking status * slope		
Current smoker	12.4% (1.31% to 24.7%), 0.028	6.82% (1.41% to 12.6%), 0.014
Ex-smoker	7.25% (0.702% to 14.1%), 0.029	4.71% (1.82% to 7.79%), 0.001
Loop diuretic * slope	−10.1% (−16.3% to −3.54%), 0.003	−3.15% (−6.67% to 0.501%), 0.094
CCB * slope	4.29% (−1.19% to 10.1%), 0.129	3.56% (0.803% to 6.50%), 0.012

a For baseline ACR, coefficients show per cent change in ACR based on 1% change in baseline ACR.

Note
For the substudy, terms were retained in the model where $p < 0.2$ and intercept terms retained where the interaction with slope $p < 0.2$. Associations observed to be significant in the substudy were then assessed in the combined data set. Units for progression are percentage change in mg/mmol/year. Values show regression coefficient (95% CI) expressed as percentage change in ACR per one unit change in the covariate[a], *p*-value.

(steeper incline) of 12.4% (95% CI 1.31% to 24.7%). For ex-smokers, the slope increased (steeper incline) by 7.25% (95% CI 0.702% to 14.1%). For African-Caribbean ethnicity, there was an increase in slope of 12.0% (95% CI 2.74% to 22.0%), compared to an increase in slope of 10.6% (95% CI 1.01% to 21.0%) for those of South Asian ethnicity. The rate of incline was slower for those prescribed loop diuretic medication, the slope decreasing by −10.1% (95% CI −16.3 to −3.54%); in contrast, the rate of incline was faster for those prescribed CCB who had an increase in slope of 4.29% (95% CI −1.19% to 10.1%).

Age and systolic BP were associated with the intercept only. Age decreased the ACR intercept by −0.499% (95% CI −0.896% to 0.100%) for each increasing year of age, and there was an increase of 0.300% (95% CI 0.100% to 0.602%) for each increasing unit of systolic BP (mmHg).

The parameter estimates of covariates associated with progression from the model using the full data set were similar to those from the substudy for all covariates in the final model. The parameter estimates for covariates associated with the intercept were different for some covariates using the full data set. Diastolic BP and smoking status were associated with intercept estimates of log ACR ($p < 0.2$) using the full data set, and there was no significant association between loop diuretic use and intercept levels of log ACR. Smoking status showed an association between ex-smokers and the intercept, which is likely a result of having more ex-smokers in the full data set ($n = 367$). Other estimates for the full data set were similar to those seen for the substudy data.

Figures 12 and *13* illustrate the changes in log-transformed ACR progression over time for albuminuria status and ethnicity groups, respectively. In *Figure 12* the profiles of those with albuminuria incline more steeply compared to those who do not have albuminuria, although the data show high variability. The equivalent figure for the combined main and substudy data may be found in *Appendix 1*, *Figure 24*.

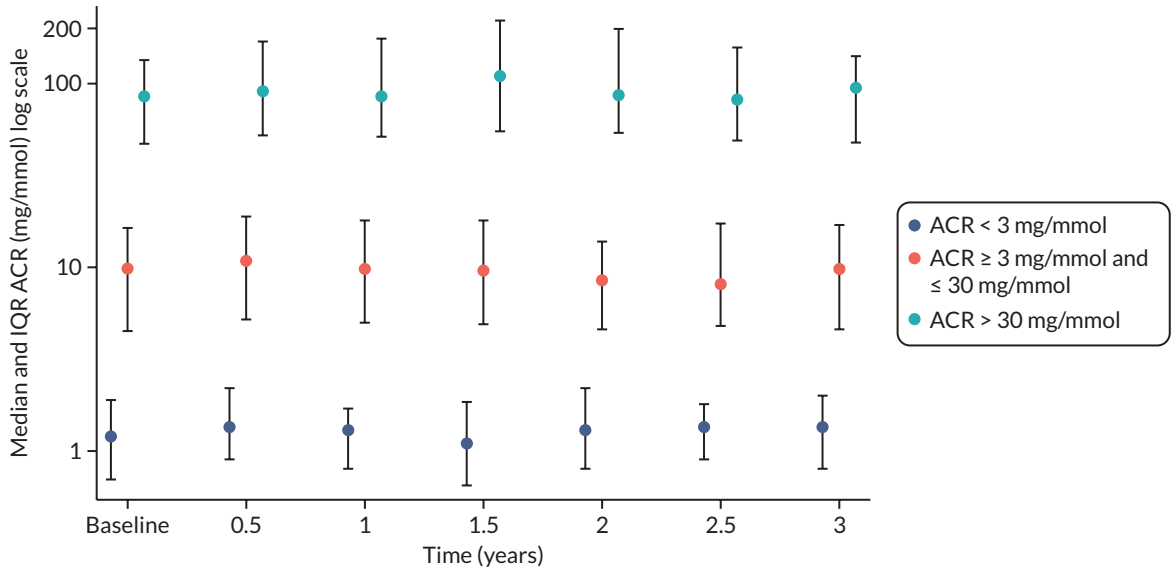

FIGURE 12 Median and IQR ACR over time by albuminuria status (substudy data).

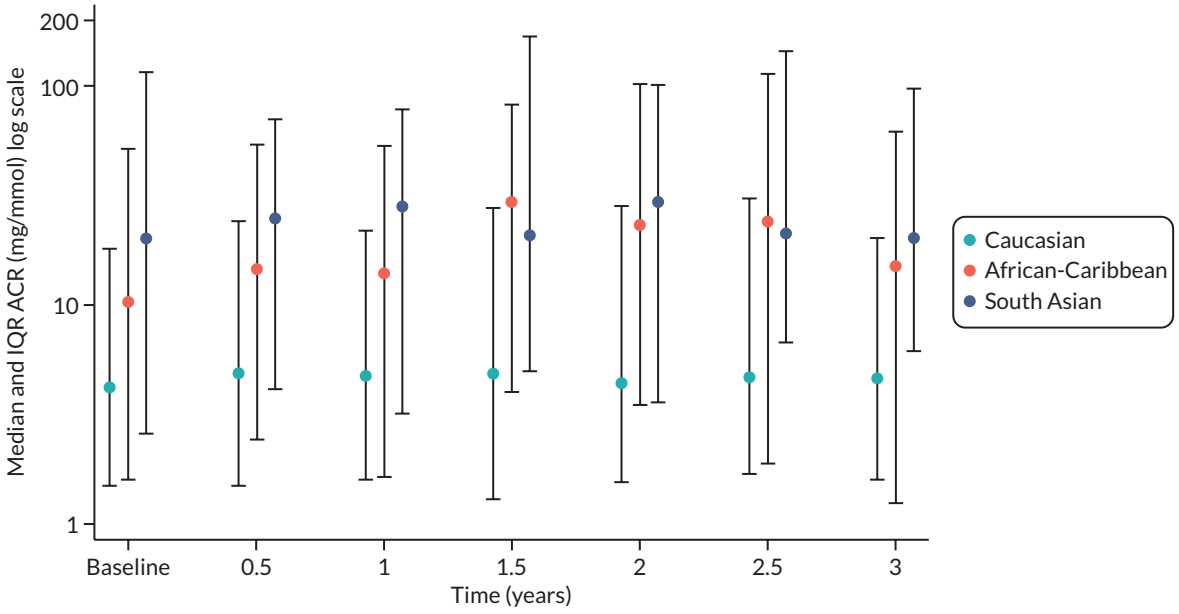

FIGURE 13 Median and IQR ACR over time by ethnicity group (substudy data).

Figure 13 supports a steeper incline overall for those with African-Caribbean and South Asian ethnicity. The equivalent figure for the combined main and substudy data may be found in *Appendix 1*, *Figure 25*.

The biological variability of measured and estimated glomerular filtration rate

Estimates of components of biological variation are given in *Table 25*.[97] The geometric exact CV_I value (95% CI) for mGFR was 6.7% (5.6 to 8.2). CV_I values for the eGFR equations were broadly equivalent: MDRD 5.0% (4.3 to 6.1), CKD-EPI$_{creatinine}$ 5.3% (4.5 to 6.4), CKD-EPI$_{cystatin}$ 5.3% (4.5 to 6.5), and CKD-EPI$_{creatinine\text{-}cystatin}$ 5.0% (4.3 to 6.2) to each other. Modelling to investigate differences showed the CV_I for MDRD and CKD-EPI$_{creatinine\text{-}cystatin}$ eGFRs to be significantly (at 5% level) lower than for mGFR (difference −1.8%, $p = 0.027$ and difference −1.8%, $p = 0.022$ respectively). Using the MDRD equation, positive and negative RCVs were 15.1% and 13.1%, respectively. For example, if the baseline MDRD GFR (ml/minute/1.73 m^2) in an individual is 59, significant increases or decreases would be to values > 68 or < 51, respectively.

TABLE 25 Summary of components of variation for creatinine and cystatin C and mGFR and eGFR

				Estimated GFR			
	Measured GFR	**Creatinine**	**Cystatin C**	**MDRD**	**CKD-EPI$_{creatinine}$**	**CKD-EPI$_{cystatin}$**	**CKD-EPI$_{creatinine-cystatin}$**
Geometric exact							
CV_A (%)	2.3 (1.9 to 2.7)	0.7 (0.6 to 0.8)	0.6 (0.5 to 0.7)	0.8 (0.7 to 0.9)	0.8 (0.7 to 1.0)	0.7 (0.6 to 0.9)	0.6 (0.5 to 0.7)
CV_I (%)	6.7 (5.6 to 8.2)	4.4 (3.7 to 5.3)	4.0 (3.4 to 4.9)	5.0 (4.3 to 6.1)	5.3 (4.5 to 6.4)	5.3 (4.5 to 6.5)	5.0 (4.3 to 6.2)
CV_G (%)	16.7 (12.5 to 24.9)	20.0 (15.0 to 29.6)	19.0 (14.4 to 28.2)	17.8 (13.4 to 26.0)	19.3 (15.5 to 29.2)	25.2(18.9 to 37.5)	20.2 (15.2 to 30.0)
Positive RCV (%)	21.5	13.0	11.8	15.1	15.9	15.9	15.1
Negative RCV (%)	−17.7	−11.5	−10.6	−13.1	−13.7	−13.8	−13.1
Homeostatic set point	2	1	1	1	1	1	1
Index of individuality	0.4	0.2	0.2	0.3	0.3	0.2	0.3

Notes
All CV values are expressed as percentages. 95% CIs were calculated using methods of Burdick and Graybill.[109]
Table reproduced with permission from: Rowe *et al.* [97]

Sensitivity analyses were carried out without outlier detection and deletion. Data were similar to those obtained following outlier removal, with analyses after outlier removal estimating slightly reduced CVs.

Modelling to identify any trends over time resulted in non-significant slopes [coef = −0.005; 95% CI (−0.020 to 0.009); p = 0.488], thus providing no evidence of a change in disease state (kidney function) over the duration of the study.

Ability of glomerular filtration rate-estimating equations, together with albumin-to-creatinine ratio, or albumin-to-creatinine ratio alone, to predict those people that have progressive loss of kidney function (chronic kidney disease progression) and to predict mortality

We investigated the association between baseline factors and CKD progression. Models were developed for each of the main study equations using CKD progression defined as (1) a 25% decrease in mGFR and/or an increase in ACR category within the study period (*Table 26*) and (2) decrease in mGFR exceeding the RCV, and/or an increase in ACR category within the study period (*Table 27*). All models demonstrated an association between lower baseline eGFR and increased risk of renal progression within the study follow-up period.

Models including all of the GFR equations demonstrated an association between lower baseline eGFR and renal progression, defined as a decrease in GFR exceeding the RCV, and/or an increase in ACR category within the study follow-up period (see *Table 27*). For every 1 ml/minute/1.73 m^2 higher eGFR at baseline, there was a 4% reduction in the odds of progressing.

To evaluate the outcome of death in this cohort, two regression models were fitted: a logistic model (*Table 28*) with death within the study as an outcome and a Cox regression model (*Table 29*) to evaluate time to death.

Secondary study objectives results

Accuracy of more recent GFR-estimating equations including BIS1 and BIS2 equations, CAPA equation, LMR equation, FAS creatinine equation, FAS creatinine–cystatin equation, EKFC equation and 2021 CKD-EPI equations: baseline analysis

Performance characteristics of the more recent GFR-estimating equations are described in *Table 5*. With the exception of the CKD-EPI(2021)$_{creatinine}$ and BIS1$_{creatinine}$ equations, all of the newer GFR-estimating equations were negatively biased compared to mGFR (negative median bias with non-overlapping CIs). Biases of the cystatin C containing equations, before recalibration (see *Impact of cystatin C calibration on the performance of more recent cystatin C containing glomerular filtration rate-estimating equations*), tended to be greater than those of the creatinine containing equations, with equations incorporating both cystatin C and creatinine having intermediate bias. Several of the equations [BIS2$_{creatinine\text{-}cystatin}$, FAS$_{creatinine\text{-}cystatin}$, CKD-EPI(2021)$_{creatinine\text{-}cystatin}$] achieved P30 values in excess of 90%. The overall performance (P30) of the CKD-EPI(2021)$_{creatinine\text{-}cystatin}$ and BIS2$_{creatinine\text{-}cystatin}$ equations was superior to that of their respective creatinine-only equations [CKD-EPI(2021)$_{creatinine}$ and BIS1$_{creatinine}$].

Ability of the newer glomerular filtration rate-estimating equations to reflect and detect changes in glomerular filtration rate over 3 years

The ability of the newer GFR-estimating equations to reflect and detect change in GFR over time is shown in *Tables 9* and *12*–*15*. As observed for the four primary equations, the newer equations, compared to mGFR, all estimated change in GFR within either 3 ml/minute/1.73 m^2/years or difference in % observed change within 5%/years (absolute difference) for > 70% of patients (see *Table 9*).

The sensitivity and specificity of the newer equations to detect change in mGFR > 10 ml/minute/1.73 m^2 were similar to that of the primary study equations (see *Table 12*). Similar observations were seen for

TABLE 26 Ability of models incorporating the various equations to predict a 25% decrease in mGFR and/or an increase in urinary ACR category within the study period

	MDRD			CKD-EPI$_{creatinine}$			CKD-EPI$_{cystatin}$			CKD-EPI$_{creatinine-cystatin}$		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Estimated GFR (ml/minute/1.73 m^2)	0.96	(0.95 to 0.98)	< 0.001	0.96	(0.95 to 0.98)	< 0.001	0.96	(0.95 to 0.98)	< 0.001	0.96	(0.94 to 0.97)	< 0.001
Ethnicity												
African-Caribbean	1.47	(0.70 to 3.07)	0.310	1.34	(0.64 to 2.80)	0.438	1.55	(0.73 to 3.29)	0.253	1.48	(0.70 to 3.13)	0.307
South Asian	1.79	(0.95 to 3.34)	0.070	1.79	(0.96 to 3.36)	0.069	1.59	(0.84 to 2.98)	0.152	1.64	(0.87 to 3.09)	0.124
Age (years)	1.00	(0.98 to 1.01)	0.701	0.99	(0.98 to 1.01)	0.238	0.99	(0.97 to 1.00)	0.059	0.99	(0.97 to 1.00)	0.093
Female	0.83	(0.61 to 1.13)	0.235	0.87	(0.64 to 1.18)	0.359	0.85	(0.63 to 1.16)	0.311	0.86	(0.63 to 1.17)	0.347
ACR category												
3–30 mg/mmol	0.96	(0.68 to 1.35)	0.799	0.95	(0.68 to 1.34)	0.786	0.86	(0.60 to 1.22)	0.388	0.87	(0.62 to 1.24)	0.448
> 30 mg/mmol	0.80	(0.53 to 1.21)	0.299	0.80	(0.53 to 1.21)	0.285	0.68	(0.45 to 1.04)	0.075	0.70	(0.46 to 1.06)	0.094
Vascular disease	1.09	(0.75 to 1.58)	0.664	1.09	(0.75 to 1.58)	0.667	1.06	(0.73 to 1.55)	0.757	1.06	(0.73 to 1.55)	0.743

OR, odds ratio.

Note
Ethnicity reference is Caucasian; sex reference was male; urinary ACR category reference is < 3 mg/mmol.

TABLE 27 Ability of models incorporating the various equations to predict a decrease in mGFR exceeding the RCV, and/or an increase in ACR category within the study period

	MDRD			$CKD\text{-}EPI_{creatinine}$			$CKD\text{-}EPI_{cystatin}$			$CKD\text{-}EPI_{creatinine\text{-}cystatin}$		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Estimated GFR (ml/minute/1.73 m^2)	0.96	(0.95 to 0.98)	< 0.001	0.96	(0.95 to 0.98)	< 0.001	0.96	(0.95 to 0.98)	< 0.001	0.96	(0.94 to 0.97)	< 0.001
Ethnicity												
African-Caribbean	1.47	(0.70 to 3.07)	0.310	1.34	(0.64 to 2.80)	0.438	1.55	(0.73 to 3.29)	0.253	1.48	(0.70 to 3.13)	0.307
South Asian	1.79	(0.95 to 3.34)	0.070	1.79	(0.96 to 3.36)	0.069	1.59	(0.84 to 2.98)	0.152	1.64	(0.87 to 3.09)	0.124
Age (years)	1.00	(0.98 to 1.01)	0.701	0.99	(0.98 to 1.01)	0.238	0.99	(0.97 to 1.00)	0.059	0.99	(0.97 to 1.00)	0.093
Female	0.83	(0.61 to 1.13)	0.235	0.87	(0.64 to 1.18)	0.359	0.85	(0.63 to 1.16)	0.311	0.86	(0.63 to 1.17)	0.347
ACR category												
3–30 mg/mmol	0.96	(0.68 to 1.35)	0.799	0.95	(0.68 to 1.34)	0.786	0.86	(0.60 to 1.22)	0.388	0.87	(0.62 to 1.24)	0.448
> 30 mg/mmol	0.80	(0.53 to 1.21)	0.299	0.80	(0.53 to 1.21)	0.285	0.68	(0.45 to 1.04)	0.075	0.70	(0.46 to 1.06)	0.094
Vascular disease	1.09	(0.75 to 1.58)	0.664	1.09	(0.75 to 1.58)	0.667	1.06	(0.73 to 1.55)	0.757	1.06	(0.73 to 1.55)	0.743

OR, odds ratio.

Note
Ethnicity reference is Caucasian; sex reference is male; urinary ACR category reference is < 3 mg/mmol.

TABLE 28 Logistic regression models including each eGFR equation to predict mortality (within the study period)

	MDRD			$CKD\text{-}EPI_{creatinine}$			$CKD\text{-}EPI_{cystatin}$			$CKD\text{-}EPI_{creatinine\text{-}cystatin}$		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Estimated GFR (ml/minute/1.73 m^2)	0.97	(0.94 to 1.00)	0.042	0.97	(0.94 to 1.00)	0.040	0.94	(0.91 to 0.97)	< 0.001	0.95	(0.92 to 0.98)	< 0.001
Ethnicity												
African-Caribbean	0.58	(0.08 to 4.42)	0.600	0.54	(0.07 to 4.14)	0.556	0.61	(0.08 to 4.67)	0.631	0.56	(0.07 to 4.30)	0.578
South Asian	0.79	(0.18 to 3.48)	0.760	0.79	(0.18 to 3.48)	0.758	0.59	(0.13 to 2.61)	0.484	0.66	(0.15 to 2.92)	0.583
Age (years)	1.07	(1.04 to 1.11)	< 0.001	1.07	(1.03 to 1.10)	< 0.001	1.05	(1.02 to 1.09)	0.002	1.06	(1.03 to 1.09)	0.001
Female	0.53	(0.28 to 1.00)	0.051	0.55	(0.29 to 1.04)	0.065	0.53	(0.28 to 1.00)	0.049	0.54	(0.29 to 1.02)	0.059
ACR category												
3–30 mg/mmol	1.21	(0.64 to 2.27)	0.561	1.21	(0.64 to 2.27)	0.562	0.94	(0.49 to 1.80)	0.853	1.03	(0.54 to 1.96)	0.924
> 30 mg/mmol	1.30	(0.62 to 2.69)	0.486	1.29	(0.62 to 2.69)	0.489	0.91	(0.43 to 1.93)	0.815	1.04	(0.49 to 2.18)	0.923
Vascular disease	1.59	(0.89 to 2.82)	0.114	1.59	(0.89 to 2.81)	0.115	1.58	(0.89 to 2.80)	0.120	1.58	(0.89 to 2.80)	0.119

OR, odds ratio.

Note
Ethnicity reference was Caucasian; sex reference was male; urinary ACR category reference was < 3 mg/mmol.

TABLE 29 Cox regression models including each eGFR equation to predict mortality (time to event)

	MDRD			$CKD\text{-}EPI_{creatinine}$			$CKD\text{-}EPI_{cystatin}$			$CKD\text{-}EPI_{creatinine\text{-}cystatin}$		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Estimated GFR (ml/minute/1.73 m^2)	0.97	(0.95 to 1.00)	0.068	0.98	(0.95 to 1.00)	0.065	0.95	(0.92 to 0.97)	< 0.001	0.95	(0.93 to 0.98)	0.001
Ethnicity												
African-Caribbean	0.56	(0.08 to 4.13)	0.571	0.53	(0.07 to 3.91)	0.533	0.64	(0.09 to 4.67)	0.657	0.57	(0.08 to 4.22)	0.585
South Asian	0.81	(0.19 to 3.38)	0.774	0.81	(0.19 to 3.38)	0.772	0.68	(0.16 to 2.82)	0.590	0.73	(0.17 to 3.03)	0.662
Age (years)	1.07	(1.04 to 1.11)	< 0.001	1.07	(1.03 to 1.10)	< 0.001	1.06	(1.02 to 1.09)	0.001	1.06	(1.03 to 1.10)	< 0.001
Female	0.53	(0.28 to 0.97)	0.040	0.54	(0.29 to 1.00)	0.050	0.53	(0.28 to 0.97)	0.040	0.54	(0.29 to 0.99)	0.048
ACR category												
3–30 mg/mmol	1.17	(0.64 to 2.15)	0.608	1.17	(0.64 to 2.15)	0.609	0.92	(0.50 to 1.71)	0.802	1.01	(0.55 to 1.87)	0.970
> 30 mg/mmol	1.19	(0.59 to 2.42)	0.629	1.19	(0.59 to 2.41)	0.633	0.84	(0.41 to 1.73)	0.637	0.95	(0.46 to 1.95)	0.887
Vascular disease	1.58	(0.91 to 2.73)	0.101	1.58	(0.91 to 2.73)	0.102	1.57	(0.91 to 2.69)	0.105	1.57	(0.91 to 2.71)	0.102

Note
Ethnicity reference was Caucasian; sex reference was male; urinary ACR category reference was < 3 mg/mmol.

the other change metrics investigated: GFR change in excess of the RCV, change in excess of 25% and change in excess of 25% in addition to a change in the GFR category (see *Tables 13–15*).

Influence of body surface area adjustment method on accuracy (P30) of glomerular filtration rate-estimating equations: Haycock equation compared to the Du Bois equation

Accuracy of the GFR equations was unaffected by the method of BSA adjustment (*Table 30*). Bias and precision data for these analyses may be found in *Appendix 1* (see *Appendix 1*, *Table 41*).

Impact of cystatin C calibration on the performance of more recent cystatin C containing glomerular filtration rate-estimating equations

As noted with the original CKD-EPI cystatin C containing equations (see *Table 5*), in all cases, substitution of recalibrated cystatin C values into the newer GFR-estimating equations was associated with a decrease in bias, with non-overlapping CIs, and with an increase in P30, in some cases with non-overlapping CIs compared to the equivalent non-cystatin C containing equation (e.g. BIS1 compared to BIS2). Relative improvement in performance tended to be more marked in the cystatin-only equations compared to the creatinine–cystatin equations (see *Table 5*).

Impact of creatinine method on accuracy of glomerular filtration rate-estimating equations: enzymatic compared to isotope dilution mass spectrometry method

There was no evidence of an effect of creatinine method on the performance of creatinine-based GFR-estimating equations; for example, $CKD\text{-}EPI_{creatinine}$ using enzymatic creatinine P30 was 90.2 (88.4 to 91.9) compared to 89.0 (87.1 to 90.8) for ID-MS-creatinine (*Table 31*).

Creatinine results obtained using the enzymatic method were higher than those using the ID-MS assay, the relationship between the two methods being described by the linear regression equation; enzymatic = 3.23 + 1.01(ID-MS), R^2 0.969 (see *Appendix 1*, *Figure 26*). Deming regression produced a similar equation [enzymatic = 1.20 + 1.03(ID-MS)].

Bias plot analysis demonstrated a constant mean positive bias of 4.7 µmol/l (CI 4.3 to 5.0) for the enzymatic compared to the ID-MS assays (see *Appendix 1*, *Figure 27*).

TABLE 30 Accuracy of GFR-estimating equations using two different (Du Bois and Haycock) methods of adjusting for BSA

Equation	Du Bois BSA adjustment	Haycock BSA adjustment
MDRD	89.5 (87.6 to 91.1)	89.5 (87.6 to 91.2)
$CKD\text{-}EPI_{creatinine}$	90.2 (88.4 to 91.9)	90.1 (88.2 to 91.7)
$CKD\text{-}EPI_{cystatin}$	89.5 (87.6 to 91.2)	90.7 (88.9 to 92.3)
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	94.9 (93.5 to 96.2)	95.3 (94.0 to 96.5)

Note
Data shown as percentage of estimates within 30% of mGFR (P30), % (95% CI). *n* = 1167 in both cases.

TABLE 31 Performance (P30) of GFR-estimating equations using ID-MS compared to enzymatic measurement of serum creatinine

	Enzymatic creatinine		ID-MS creatinine	
Equation	*n/N*	P30 (%, 95% CI)	*n/N*	P30 (%, 95% CI)
MDRD	1044/1167	89.5 (87.6 to 91.1)	1054/1167	89.6 (87.7 to 91.3)
$CKD\text{-}EPI_{creatinine}$	1053/1167	90.2 (88.4 to 91.9)	1047/1167	89.0 (87.1 to 90.8)
$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	1108/1167	94.9 (93.5 to 96.1)	1112/1167	95.3 (93.9 to 96.4)

Chapter 4 Health economics: comparative clinical accuracy and cost of annual monitoring using glomerular filtration rate-estimating equations

Introduction

This chapter presents the health-economic analysis. *Systematic review of economic evaluations* presents a brief summary of findings from a systematic review of model-based economic evaluations, which is provided in full in *Appendix 2*. *Clinical guidelines* provides a summary of key clinical guidelines for monitoring CKD in the UK, focusing on the recommended criteria for identifying those with progressive disease. *Comparative accuracy of estimated glomerular filtration rate equations for predicting accelerated progression (measurement model analysis)* reports on the clinical accuracy of the different estimating equations for predicting CKD progression compared to mGFR, based on a simulated measurement model over a 10-year horizon. *Comparative cost of monitoring with different estimated glomerular filtration rate equations* presents the comparative costs of monitoring with GFR estimating equations, followed by a description of the implications of the results of the measurement model and the wider literature on longer-term costs and outcomes in *Longer-term differences in costs and outcomes*.

Systematic review of economic evaluations

A systematic review was conducted to identify previous studies that have assessed the cost-effectiveness of test-based strategies for CKD using a decision-analytic model. The objective was not to draw conclusions about the cost effectiveness of different testing strategies; rather the aim was to examine how economic models have been previously implemented in this setting. Full details of the systematic review, including Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagrams and results tables, can be found in *Appendix 2* (see *Figures 32* and *33*, *Tables 42–44*). Here, we provide a brief summary of the key findings.

Across the initial (February 2015)[112] and updated (February 2020) literature searches, 28 studies were included in the review. All of the identified studies evaluated screening strategies in at-risk groups or general populations not currently diagnosed with CKD. No studies which assessed test-based monitoring strategies for patients with known CKD (i.e. matching the role of monitoring being considered in this HTA) were identified. The majority of studies (n = 24) evaluated proteinuria or albuminuria tests, with only six studies focusing on GFR estimation.

Eight studies did not incorporate any measure of diagnostic accuracy into the model, despite evaluating test-based strategies. Of the 20 studies that did explicitly incorporate diagnostic accuracy into their models, the majority were based on data from a single published study. In terms of modelling the impact of test inaccuracies, patients with FN results were assumed to remain in 'untreated' health states, and thereby could not benefit from treatment for CKD until future screening rounds, leading to higher risks of progression to later CKD stages. In the case of FP results, the most common consequence modelled was the unnecessary cost of additional/confirmatory testing. In most cases, confirmatory testing was assumed to have perfect accuracy, thus removing all FP cases at this stage. Of those studies that evaluated repeated testing scenarios and explicitly accounted for diagnostic accuracy in the model, the majority assumed that the same diagnostic accuracy values would apply over time.

The majority of studies used a cohort Markov model approach to model disease progression. [N.B. Markov models, also known as cohort transition models, track the movement of a group (i.e. cohort) of patients through mutually exclusive health states (e.g. GFR levels or CKD stages), which are each associated with state-specific health-related quality of life and cost values; the movement of patients between modelled health states occurs at fixed time points (e.g. every month, or year) and is dictated by defined transition probabilities.] Of those studies that tracked progression according to GFR levels, the stages of CKD were most often split into five GFR 'stages'. Most studies assumed a step-by-step process of disease progression (i.e. patients could only move up one health state in the ladder of progression per model cycle), and only a minority explicitly allowed for the possibility of the reversibility in CKD severity.

The cost of testing related to screening activities captured in the included studies was typically limited to the unit cost of the screening test alone. Eight studies also included the cost of a physician/GP visit associated with the initial screening test(s) undertaken.

The most common issue apparent from the study quality assessment concerned a failure of all but four studies to discuss all of the issues relevant to users, which in this case meant that studies did not include any discussion regarding the impact of test diagnostic accuracy on the modelled outcomes, or the impact of testing from the patient perspective (e.g. costs incurred, anxiety.

Following the completion of our systematic review, Perera *et al.* published a highly relevant report that focused on long-term monitoring in primary care for CKD and chronic heart failure.[113] A short summary of this report is provided below. Perera *et al.* reported a programme of research exploring the optimal monitoring of individuals with CKD in primary care.[113] Pertinent to our research was an economic evaluation exploring the cost-effectiveness of monitoring CKD in primary care, using evidence generated for other components of the research programme. Qualitative interviews with clinicians and stakeholders highlighted that a key objective of GFR monitoring is to guide treatments to manage cardiovascular disease risk in those with CKD. However, the authors concluded that this finding was at odds with guideline recommendations at the time, as statins are recommended for all individuals with CKD and an eGFR < 60 ml/minute/1.73 m^2 who are pre-dialysis, and eGFR has no impact on recommendations for antiplatelet agents for secondary prevention.[59,114]

Perera *et al.* also conducted a systematic review to synthesise the effects of medication on the progression of stages G3 (GFR 30–59 ml/minute/1.73 m^2) and G4 (GFR 15–29 ml/minute/1.73 m^2) CKD. Their review focused on four classes of drugs: antihypertensives, lipid-modifying drugs, glycaemic control medications in patients with diabetes and sodium bicarbonate. Nineteen studies provided data for patients with CKD stages G3 and G4. The key conclusions were:

1. Pooled estimates showed no significant differences in renal function for those taking antihypertensive drugs compared to a control group (either placebo, no drug intervention or a comparator drug from one of the three other classes).
2. There were no significant differences in cardiovascular events or mortality in studies of antihypertensives.
3. Estimated GFR was 4% higher in those taking lipid-modifying drugs. Treatment with lipid-modifying drugs led to a significant reduction in the risk of CVD (risk ratio = 0.64, 95% CI 0.52 to 0.80) and all-cause mortality (risk ratio = 0.74, 95% CI 0.56 to 0.98).
4. Estimated GFR was 6% higher in those taking glycaemic control drugs. There were no significant differences in cardiovascular events or mortality in studies of glycaemic control medications.
5. No data were identified for the effects of sodium bicarbonate medication.

As the treatments that may slow progression are already indicated for those with G3 disease onwards, the authors concluded that there is no evidence to support the impact of monitoring GFR in those with CKD on the management of cardiovascular disease. GFR monitoring, therefore, cannot be justified on this basis.

Perera *et al.* did however explore whether it would be cost-effective to monitor GFR in individuals with impaired renal function (an eGFR of < 90 ml/minute/1.73 m^2) but no CKD (defined as albuminuria or an eGFR of < 60 ml/minute/1.73 m^2). It was estimated that the most cost-effective interval of GFR monitoring (based on a £20,000 per QALY cost-effectiveness threshold) in this group is every 3 years for individuals aged < 60 years, every 4 years for individuals aged 60–69 years, and not cost-effective in those aged 70 years and above.

One of the key conclusions of the overall research programme was 'monitoring individuals with CKD is difficult to justify by the usual logic of treatment initiation or titration. Alternative ways of quantifying its benefit might be required'.[113]

Clinical guidelines

An update of the NICE clinical guideline 'Chronic kidney disease: assessment and management (NG203)' was published in 2021.[59] The guideline covers the care and treatment of people with, or at risk of, CKD with the aim of preventing or delaying progression and reducing the risk of complications associated with CKD. Here we summarise the recommendations pertinent to our research question.

According to the NICE guideline, the recommended minimum frequency of monitoring those with GFR categories 3a and 3b is annual GFR estimation and ACR measurements. NICE recommend obtaining a minimum of three GFR estimations over a period of not < 90 days to identify the rate of progression of CKD. Additionally, in adults with a new finding of reduced GFR, to repeat the GFR within 2 weeks to exclude causes of acute deterioration of GFR, for example, AKI or starting RAAS therapy.

The guideline defines the exact criteria for accelerated progression of CKD in adults as either (1) a sustained decrease in GFR of 25% or more and a change in GFR category within 12 months, or (2) a sustained decrease in GFR of 15 ml/minute/1.73 m^2 or more per year. Such individuals are considered at increased risk of progression to kidney failure.[59] NICE recommend that, when assessing CKD progression, the current rate of decline of GFR is extrapolated and taken into account when planning intervention strategies, particularly if it suggests that the person might need kidney replacement therapy in their lifetime.

In the original current study protocol, the main outcome of interest for the health-economic analysis was listed as progression to CKD stage G4. In light of the updated NICE clinical guidelines on identifying progression in this patient population, it was decided to instead focus the analysis on the role of GFR monitoring for identifying accelerated progression based on the NICE criteria. Progression to CKD stage G4 is reported as a secondary analysis.

Comparative accuracy of estimated glomerular filtration rate equations for predicting accelerated progression (measurement model analysis)

The aim of this analysis was to construct a *measurement model* describing the trajectory of patients mGFR and eGFR over 10 years, based on extrapolating mGFR and eGFR bias data from the study. This model was used to assess the proportion of patients meeting the NICE threshold of accelerated progression (see *Clinical guidelines*), assuming an annual testing schedule, and the number of patients expected to be incorrectly managed at each of the evaluated monitoring time points using the different estimating equations. The outcomes produced from this measurement model were used to inform the subsequent cost analysis presented in *Comparative cost of monitoring with different estimated glomerular filtration rate equations*.

Methods

Data

Study participants who had complete data on mGFR and eGFR at baseline and 36 months were used to inform this analysis (n = 875) (see *Table 2*).

Measured glomerular filtration rate trajectories

Each individual's absolute change in mGFR over the 3-year follow-up period was calculated by a simple subtraction of the baseline mGFR from the 36-month mGFR. Assuming a linear model of GFR change over time, as suggested by the above statistical analysis (see *Chapter 3*), the annual change (calculated as the 3-year change divided by three) was then used to interpolate individuals' mGFR values at the year 1 and year 2 time points. Extrapolation was similarly conducted to estimate annual GFR measurements beyond the study follow-up period, up to 10 years from baseline.

Patients' true GFR categories over time (required for the first element of the NICE progression criteria) were classified using individuals' longitudinal GFR measurements and according to the CKD GFR classification (all units in ml/minute/1.73 m^2):

- G1: GFR ≥ 90
- G2: 90 > GFR ≥ 60
- G3a: 60 > GFR ≥ 45
- G3b: 45 > GFR ≥ 30
- G4: 30 > GFR ≥ 15
- G5: GFR < 15.

The primary analysis of the measurement model focused on evaluating when patients would meet NICE's combined *progression criteria* (see *Clinical guidelines*), based on the individual's annual mGFR. A secondary outcome looking at the number of patients transitioning into CKD category G4 or higher (GFR < 30 ml/minute/1.73 m^2) was also conducted.

Estimated glomerular filtration rate equations

Information on the diagnostic accuracy of the eGFR values was calculated, according to how well they were able to accurately predict the NICE progression criteria. The four primary equations included in the statistical analysis were evaluated: MDRD, CKD-EPI$_{creatinine}$, CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$.

The eGFR values at baseline and year 3 were based on the patients' recorded GFR estimations at those time points. Estimated GFR values for other time points (years 1, 2 and 4–10) were estimated as a function of the underlying mGFR value (derived from the linear trajectories of mGFR previously described) plus a simulated *measurement error factor* representing the expected measurement error incurred with each GFR-estimating equation. The estimation of GFR values is represented by the following measurement error equation:

$$\text{eGFR}_{simi} = \text{mGFR}_i + \text{Lnorm}\left(\text{bias}_i,\ \text{SD}_i\right) \tag{5}$$

where mGFRi is the underlying 'true' GFR measurement taken from the model of mGFR trajectories described previously; bias$i$ is the expected measurement bias associated with the given eGFR equation at the given level of mGFRi, applied within a lognormal distribution; and SDi is the expected SD of the measurement bias at the given level of mGFRi. The adopted equation above follows the standard approach used in the modelling literature, whereby error in repeated measurements is assumed to be log-normally distributed.[115]

Rather than assuming a fixed level of bias for each of the eGFR equations (as reported in previous chapters), the above approach allows the expected bias associated with GFR estimations to change

depending on the underlying level of mGFR. This is important since, in the laboratory context, test measurement error often varies over the measurement range: for example, being lower or higher at certain regions of the measurement range.

The individual-level bias values used in the measurement error equation were derived from *bias profiles* for each of the GFR equations, which show the relationship between the expected level of measurement error occurring for each GFR equation across the range of observed mGFR values (see *Appendix 1*, *Figures 28–31*). These bias profiles were obtained using available information on the difference between reported mGFR and eGFR values for each annual sampling point from the study (separate profiles are presented for baseline, year 1, year 2 and year 3), and fitting a loess regression model to the data to estimate the mean expected bias over the measurement range. [N.B. the baseline profile was not actually used in the simulation (at baseline the directly reported mGFR and eGFR values were used) but is included in the results here for interest.] Since repeated GFR estimations were not undertaken at fixed mGFR time points, we could not obtain different SD values over the measurement range – instead, the simplifying assumption was made that SD would remain fixed for each GFR equation over the measurement range, using the aggregate SD values (reported in *Table 18*).

In the simulation, eGFR values were based on the observed values where both mGFR and eGFR values were available for the whole cohort (i.e. at baseline and year 3). For all other years, eGFR values were simulated by applying the above bias profile and SD data within the previously reported measurement error equation.

The same approach as outlined for mGFR was undertaken with the eGFR values, to calculate the proportion of patients classified as progressing according to NICE guidelines, at each time point. The eGFR progression outcomes were then compared against those obtained using mGFR, to calculate the clinical accuracy of the GFR-estimating equations.

Analysis and outcomes

The measurement model extrapolated mGFR and eGFR values over a 10-year period. The results are based on a two-stage simulation process: an 'inner loop', sampling with replacement from the main study data (n = 875) to produce a bootstrap data set of 20,000 patients; followed by an 'outer loop', repeating the bootstrap process 1000 times with different random number sequences (to account for first-order uncertainty). Mean and 95% credible intervals were calculated from the 1000 samples, for the following outcomes:

1. the percentage of patients [out of the starting cohort (n = 20,000)] tested each year
2. the percentage of all annual test results that are positive (i.e. meet the threshold for progression)
3. the percentage of annual positive test results that are:
    a. FPs
    b. true positives (TPs)
4. the percentage of all annual test results that are negative (i.e. do not meet the threshold for progression)
5. the percentage of annual negative test results that are:
    a. FNs
6. for FNs:
    a. the average delay time (in years) patients experience between their FN result and eventually being identified (for those identified within the analysis 10-year period)
    b. the percentage of patients that are not identified during the analysis period
7. cumulative sensitivity and specificity values (e.g. for cumulative sensitivity: up to year X, out of all the patients who experienced a true progression event, how many have been correctly identified)
8. cumulative PPV and NPV values (e.g. for cumulative PPV: up to year X, out of all positive test results, how many patients were truly progressing at that time point).

Note that in all analyses the proportion of patients tested reduces over time, according to the number of patients assumed to be removed from annual monitoring due to identified progression. Patients were assumed to be removed from the monitoring cohort once they reached one of two outcomes: (1) a TP test result, (2) a *delayed positive* test result – that is patients whose first point of progression was not identified, but who received a subsequent positive test result (which may or may not be a TP in that year, depending on the patient's subsequent progression status). All other patients with FP test results were assumed to return to the standard monitoring cohort following confirmatory testing.

In addition to the primary analysis, the analysis was repeated with progression defined as anyone transitioning into CKD category G4 or above.

Assumptions

Key assumptions underpinning the simulation analysis are listed below:

1. Measured GFR represents true measurement (measurement error in the mGFR is not considered).
2. Measured GFR exhibits a linear change over time.
3. Random variability in the eGFR measurement error (i.e. SD) is constant over the measurement range.
4. Patients receiving a TP or delayed positive eGFR test result (i.e. a positive test following a previous missed progression event) are assumed to undergo a change in management and are taken out of the annual monitoring cohort.
5. All patients are assumed to comply with annual testing.

Results

Measured glomerular filtration rate outcomes

According to the study data, when considering all study participants with complete mGFR and eGFR data at baseline and year 3 (n = 875), mGFR declined by an average of −4.83 ml/minute/1.73 m^2 over 3 years, equivalent to an annual decline of −1.61 ml/minute/1.73 m^2. Focusing only on patients exhibiting a *decline* in mGFR (n = 631), the average annual drop was −2.96 ml/minute/1.73 m^2, compared to an average rise of 1.89 ml/minute/1.73 m^2 per year in patients who exhibited stable or increasing mGFR (n = 244).

Table 32 shows the cumulative proportion of patients meeting the NICE accelerated progression criteria according to their mGFR, as well as the numbers progressing into GFR category 4 or above, based on the 10-year measurement model of mGFR trajectories. From these results, we observe that for the study cohort, the NICE individual criteria stipulating a decrease in GFR of ≥ 15 ml/minute/1.73 m^2 per year only identified one patient and therefore provides minimal utility in this context. Note however that under the criteria of an absolute drop in mGFR, when assuming a constant linear decline in GFR, any patients meeting these criteria would be identified in year 1. Thus, the utility of this criteria is also limited by the assumption of a linear decline in mGFR.

The second NICE progression criteria, stipulating both a decrease in GFR ≥ 25% and a change in GFR category within 12 months, return a comparatively higher number of patients: 10 (1.1%) by year 3 and 125 (14.3%) by year 10. This is therefore the major component of the NICE combined GFR progression criteria.

A higher number of patients are seen to meet the criteria of a stage shift in the GFR category (to category 4 +), compared to the NICE progression criteria. This reflects the fact that a significant proportion of patients progress into GFR category 4 (or 5) without exhibiting a significant relative or absolute decline in their GFR: typically, the average relative decline in GFR for those patients

TABLE 32 Cumulative number of patients meeting NICE accelerated progression criteria and CKD stage shift (4 +) criteria based on patients' mGFR trajectories

Year	Individual NICE criteria (cumulative *N*, %)		NICE combined progression criteria: (1) or (2)	Progression to GFR category 4 + (GFR < 30 ml/minute/1.73 m²)
	(1) Decrease in GFR of ≥ 15 ml/minute/1.73 m²/year	(2) A sustained decrease in GFR ≥ 25% and a change in GFR category within 12 months		
Baseline	–	–	–	–
Year 1	1 (0.1)	0 (0)	1 (0.1)	23 (2.6)
Year 2	1 (0.1)	5 (0.6)	6 (0.7)	40 (4.6)
Year 3	1 (0.1)	10 (1.1)	10 (1.1)	88 (10.1)
Year 4	1 (0.1)	23 (2.6)	23 (2.6)	141 (16.1)
Year 5	1 (0.1)	45 (5.1)	45 (5.1)	194 (22.2)
Year 6	1 (0.1)	66 (7.5)	66 (7.5)	244 (27.9)
Year 7	1 (0.1)	90 (10.3)	90 (10.3)	276 (31.5)
Year 8	1 (0.1)	105 (12.0)	105 (12.0)	312 (35.6)
Year 9	1 (0.1)	117 (13.4)	117 (13.4)	348 (39.8)
Year 10	1 (< 0.1)	125 (14.3)	125 (14.3)	371 (42.4)

progressing into stage 4 or above was ~10–18%, with only a minority of patients, thus meeting the 25% decline requirement required by the NICE progression criteria.

Estimated glomerular filtration rate outcomes

Estimated glomerular filtration rate bias profiles

The bias profiles for each of the primary eGFR equations are provided in *Appendix 1*, *Figures 28–31*). Note that the bias profile at baseline is shown for interest only – this was not used in the simulation analysis.

Combined National Institute for Health and Care Excellence progression criteria

Full results tables and a Markov model structure for the accuracy outcomes of the primary eGFR equations (MDRD, CKD-EPI$_{creatinine}$, CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$, respectively) for the combined NICE progression criteria are provided in *Report Supplementary Material 2*. These tables provide information on the proportion of patients who test positive and negative over the 10-year analysis; the proportion of FP and FN test results; the average delay experienced for patients with FN results; and the proportion of FN results never correctly identified over the analysis period. *Table 33* reports a summary of the cumulative sensitivity, specificity, PPVs and NPVs results. The reported credible intervals represent the 5th and 95th percentile of the mean simulated results [based on 1000 simulations of bootstrap (n = 20,000) analyses].

Overall, clinical accuracy results when looking at annual time frames are lower than those previously reported in the statistical analysis of 3-year progression outcomes, due to the fact that it is harder to obtain (e.g.) a 25% drop over 1 year versus 3 years, as the NICE accelerated progression criteria demands. In general, no significant difference is observed between the eGFR equations in terms of the 10-year clinical accuracy results. In year 1, it appears that the cystatin-based equations have significantly higher sensitivity compared to MDRD and CKD-EPI$_{creatinine}$; however, these results should be interpreted

TABLE 33 Ten-year clinical accuracy simulation results (NICE combined progression criteria)

Year	MDRD		CKD-EPI$_{creatinine}$		CKD-EPI$_{cystatin}$		CKD-EPI$_{creatinine-cystatin}$	
Cumulative sensitivity and specificity [mean (%) (95% credible interval)]								
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Year 1	21.8 (7.5 to 38.5)	85.8 (82.9 to 88.4)	34.1 (14.6 to 50.0)	84.3 (81.1 to 87.0)	98.3 (95.8 to 100)	80.0 (77.6 to 82.5)	90.9 (81.0 to 100)	85.6 (83.3 to 88.1)
Year 2	47.5 (42.3 to 53.0)	84.4 (82.6 to 85.8)	49.0 (43.4 to 54.7)	83.4 (81.4 to 85.1)	40.3 (33.7 to 54.3)	78.6 (77.3 to 80.1)	43.1 (35.7 to 56.7)	84.9 (83.6 to 86.5)
Year 3	50.7 (40.6 to 61.9)	82.4 (81.2 to 83.6)	51.8 (42.7 to 62.7)	81.5 (80.3 to 82.7)	45.7 (34.0 to 57.6)	77.5 (76.3 to 78.8)	47.4 (35.8 to 59.6)	82.8 (81.1 to 85.0)
Year 4	50.0 (41.8 to 60.3)	82.9 (82.1 to 83.6)	51.1 (43.0 to 61.3)	82.3 (81.5 to 83.1)	44.7 (33.3 to 55.8)	77.2 (76.4 to 78.2)	46.4 (35.6 to 57.8)	83.2 (82.6 to 84.2)
Year 5	50.1 (42.2 to 60.3)	82.3 (81.5 to 83.1)	51.1 (43.2 to 61.3)	81.8 (80.9 to 82.7)	44.6 (33.3 to 55.5)	77.3 (76.6 to 78.0)	46.3 (35.6 to 57.7)	83.2 (82.6 to 83.9)
Year 6	45.7 (41.5 –51.7)	82.0 (81.1 to 82.8)	46.0 (41.8 to 52.2)	81.6 (80.6 to 82.4)	42.2 (36.0 to 48.7)	77.5 (76.8 to 77.9)	43.3 (37.3 to 50.4)	83.2 (82.7 to 83.7)
Year 7	42.8 (39.4 to 47.1)	82.0 (80.9 to 82.7)	43.0 (39.5 to 47.3)	81.6 (80.5 to 82.4)	39.8 (35.2 to 45.0)	77.8 (77.0 to 78.2)	40.3 (35.7 to 45.7)	83.5 (82.8 to 83.9)
Year 8	42.6 (39.4 to 46.8)	81.9 (80.8 to 82.7)	42.8 (39.5 to 47.1)	81.6 (80.4 to 82.4)	39.5 (35.2 to 44.6)	78.1 (77.2 to 78.5)	40.0 (35.7 to 45.4)	83.6 (82.9 to 84.1)
Year 9	42.6 (39.4 to 46.8)	81.9 (80.6 to 82.6)	42.7 (39.5 to 47.1)	81.5 (80.3 to 82.3)	39.5 (35.2 to 44.5)	78.3 (77.3 to 78.7)	39.9 (35.7 to 45.2)	83.7 (82.9 to 84.3)
Year 10	40.0 (37.1 to 43.3)	81.9 (80.5 to 82.7)	40.4 (37.6 to 43.6)	81.6 (80.2 to 82.4)	37.9 (34.5 to 41.8)	78.5 (77.5 to 79.0)	37.5 (33.9 to 41.9)	84.0 (82.9 to 84.5)

TABLE 33 Ten-year clinical accuracy simulation results (NICE combined progression criteria) (*continued*)

Year	MDRD		CKD-EPI$_{creatinine}$		CKD-EPI$_{cystatin}$		CKD-EPI$_{creatinine-cystatin}$	
PPV and NPV [mean (%) (95% credible interval)]								
	PPV	**NPV**	**PPV**	**NPV**	**PPV**	**NPV**	**PPV**	**NPV**
Year 1	0.0 (0.0 to 0.3)	100.0 (99.8 to 100)	0.1 (0.0 to 0.4)	100.0 (99.8 to 100)	0.1 (0.0 to 1.0)	100.0 (100 to 100)	0.2 (0.0 to 1.3)	100.0 (100 to 100)
Year 2	3.4 (1.5 to 7.3)	99.3 (98.4 to 99.7)	3.3 (1.5 to 7.0)	99.3 (98.4 to 99.7)	2.0 (1.1 to 4.2)	99.1 (98.0 to 99.7)	3.1 (1.6 to 6.5)	99.2 (98.2 to 99.8)
Year 3	2.6 (1.3 to 4.5)	99.5 (98.9 to 99.7)	2.5 (1.2 to 4.4)	99.5 (98.8 to 99.7)	1.8 (0.8 to 3.3)	99.3 (98.7 to 99.7)	2.5 (1.1 to 4.4)	99.4 (98.8 to 99.7)
Year 4	2.2 (1.0 to 3.6)	99.5 (99.2 to 99.8)	2.1 (1.0 to 3.5)	99.5 (99.2 to 99.8)	1.5 (0.6 to 2.7)	99.4 (98.9 to 99.7)	2.1 (0.9 to 3.7)	99.5 (99.1 to 99.8)
Year 5	1.8 (0.8 to 2.8)	99.6 (99.3 to 99.8)	1.8 (0.8 to 2.8)	99.6 (99.3 to 99.8)	1.3 (0.5 to 2.2)	99.5 (99.2 to 99.8)	1.8 (0.7 to 3.0)	99.6 (99.2 to 99.8)
Year 6	3.2 (1.6 to 4.4)	99.2 (98.9 to 99.5)	3.1 (1.6 to 4.3)	99.2 (98.9 to 99.5)	2.4 (1.2 to 3.5)	99.0 (98.7 to 99.4)	3.2 (1.6 to 4.7)	99.1 (98.8 to 99.5)
Year 7	3.9 (2.6 to 4.9)	98.8 (98.5 to 99.1)	3.8 (2.6 to 4.8)	98.8 (98.5 to 99.1)	3.0 (1.9 to 3.9)	98.7 (98.4 to 99.0)	4.0 (2.6 to 5.2)	98.8 (98.5 to 99.1)
Year 8	3.5 (2.3 to 4.6)	98.9 (98.5 to 99.2)	3.4 (2.3 to 4.5)	98.9 (98.5 to 99.2)	2.7 (1.7 to 3.7)	98.8 (98.4 to 99.1)	3.6 (2.3 to 4.9)	98.9 (98.5 to 99.2)
Year 9	3.1 (2.0 to 4.2)	99.0 (98.6 to 99.3)	3.1 (2.0 to 4.1)	99.0 (98.7 to 99.3)	2.5 (1.6 to 3.4)	98.9 (98.6 to 99.2)	3.3 (2.1 to 4.5)	99.0 (98.7 to 99.3)
Year 10	4.0 (3.1 to 5.0)	98.6 (98.3 to 98.9)	3.9 (3.1 to 4.9)	98.6 (98.3 to 98.9)	3.2 (2.4 to 3.9)	98.5 (98.1 to 98.8)	4.1 (3.1 to 5.1)	98.6 (98.2 to 98.9)

Note
Cumulative sensitivity, specificity, PPV and NPV results for the four primary eGFR equations, NICE combined progression criteria.

with caution due to the very low number of true progression events that occurred in year 1. Over the remainder of the time horizon the cystatin-based equations performed consistently lower than the other equations in terms of sensitivity, and higher in terms of specificity; although for both cystatin-based equations the credible intervals overlapped with the other GFR equations.

Overall, there was no evidence to suggest that any of the estimating equations are superior for identifying progression, as defined by NICE.[59] This reflects the findings of the statistical analysis presented in *Chapter 3*.

Secondary analysis

Progression to glomerular filtration rate stage 4 +

The complete results tables for the secondary analysis (progression to CKD stage G4 +) are provided in *Report Supplementary Material 2*. *Table 34* provides the summary results showing the cumulative sensitivity, specificity, PPV and NPV results for the primary eGFR equations.

Based on these results, it appears that all of the GFR-estimating equations perform poorly in terms of identifying patients progressing into higher CKD GFR categories, with sensitivity values below 45% across the modelled timeline (and significantly lower than this at several time points for all of the tests). Excluding year 1, the CKD-EPI$_{cystatin}$ equation is consistently the lowest performer in terms of sensitivity and specificity, while either the MDRD or CKD-EPI$_{creatinine\text{-}cystatin}$ equations tended to yield the highest levels of sensitivity, with the CKD-EPI$_{creatinine}$ equation achieving the highest mean specificity values. However, as in the primary analysis evaluating the performance of the GFR equations at identifying NICE accelerated progression, in this analysis we again observe that the credible intervals of the results for all of the GFR equations overlapped. There is therefore no evidence to suggest that any of the estimating equations are superior for identifying progression into higher CKD GFR stages.

Comparative cost of monitoring with different estimated glomerular filtration rate equations

The economic analysis in this chapter focuses on the respective cost of monitoring individuals using the different GFR-estimating equations, based on the results from the measurement model analyses which estimate test accuracy for accelerated progression (defined by NICE criteria) over a 10-year period.

The analysis focuses on the cost of monitoring with eGFR and does not include the costs associated with additional testing (e.g. urine albumin) or treatment. In line with the assumptions of the measurement model analysis, monitoring costs are included up to the point that an individual receives a TP or delayed positive eGFR result when patients are assumed to undergo a change in management and are taken out of the annual monitoring cohort. Those who receive a FP or TP result are assumed to undergo an additional GFR estimation in line with clinical guidance[59] and return to the annual monitoring cohort.

Appointment costs

Appointment costs were only assigned to annual monitoring visits. Based on clinical advice, repeat tests due to a FP test result were unlikely to result in an additional clinical appointment, other than an outpatient phlebotomy appointment (£4).[116]

The 2019/20 NHS National Cost Collection data provide costs for consultant and non-consultant-led appointments based on whether it is an initial or follow-up appointment.[116] For the purposes of our analysis and, given that the study cohort was primarily recruited in secondary care (i.e. post referral to specialist nephrologist), we assumed that our cohort had already had an initial appointment with a nephrologist and that monitoring appointments should be costed at the slightly lower follow-up rate.

TABLE 34 Ten-year clinical accuracy simulation results (CKD stage shift progression criteria)

Year	MDRD		CKD-EPI$_{creatinine}$		CKD-EPI$_{cystatin}$		CKD-EPI$_{creatinine-cystatin}$	
Cumulative sensitivity and specificity [mean (%) (95% credible interval)]								
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Year 1	1.9 (0.0 to 22.6)	91.1 (90.0 to 92.4)	2.8 (0.0 to 27.9)	91.4 (90.3 to 92.8)	5.8 (0.0 to 29.8)	89.3 (87.6 to 91.3)	3.3 (0.0 to 34.8)	90.9 (89.1 to 92.5)
Year 2	24.4 (11.0 to 36.2)	91.2 (90.3 to 92.5)	24.9 (11.1 to 37.8)	91.5 (90.6 to 92.8)	18.5 (7.6 to 31.6)	88.6 (87.5 to 89.9)	21.8 (9.3 to 35.3)	90.7 (89.5 to 92.0)
Year 3	33.8 (27.8 to 40.6)	90.9 (89.3 to 92.3)	32.2 (27.0 to 37.6)	90.9 (89.1 to 92.4)	33.1 (29.1 to 38.3)	86.9 (83.6 to 89.1)	33.4 (28.9 to 37.9)	87.7 (84.0 to 90.9)
Year 4	41.2 (34.8 to 46.3)	91.6 (90.8 to 92.5)	39.6 (34.1 to 44.1)	91.6 (90.7 to 92.6)	34.9 (26.0 to 43.2)	87.7 (85.2 to 89.4)	43.6 (38.2 to 48.2)	89.0 (86.4 to 90.9)
Year 5	40.0 (34.6 to 44.1)	91.4 (90.7 to 92.2)	38.7 (34.0 to 43.1)	91.5 (90.8 to 92.3)	33.9 (26.0 to 39.4)	88.1 (86.1 to 89.5)	42.1 (37.9 to 46.5)	89.4 (87.3 to 90.9)
Year 6	39.1 (34.7 to 42.6)	91.3 (90.6 to 92.0)	38.0 (34.3 to 41.5)	91.4 (90.7 to 92.2)	33.7 (27.3 to 37.8)	88.4 (86.8 to 89.6)	40.8 (37.4 to 44.3)	89.7 (87.9 to 91.0)
Year 7	37.8 (34.5 to 40.4)	91.5 (90.7 to 92.2)	37.1 (34.3 to 39.9)	91.6 (90.9 to 92.4)	33.1 (28.6 to 36.3)	88.9 (87.6 to 90.0)	38.9 (36.5 to 41.6)	90.1 (88.7 to 91.3)
Year 8	36.5 (33.5 to 38.9)	91.7 (90.8 to 92.5)	35.9 (33.4 to 38.3)	91.9 (91.1 to 92.7)	32.3 (28.1 to 35.5)	89.5 (88.3 to 90.5)	37.3 (34.8 to 39.6)	90.7 (89.4 to 91.8)
Year 9	35.7 (32.7 to 38.2)	92.1 (91.0 to 92.8)	35.2 (32.6 to 37.1)	92.2 (91.2 to 93.0)	31.8 (27.8 to 35.2)	90.0 (89.0 to 91.0)	36.3 (33.7 to 38.3)	91.2 (90.1 to 92.2)
Year 10	35.5 (32.7 to 37.8)	92.3 (91.1 to 93.1)	35.0 (32.5 to 36.9)	92.5 (91.4 to 93.3)	31.7 (27.9 to 35.0)	90.4 (89.6 to 91.4)	36.1 (33.7 to 38.0)	91.6 (90.7 to 92.6)

continued

TABLE 34 Ten-year clinical accuracy simulation results (CKD stage shift progression criteria) (*continued*)

Year	MDRD		$CKD\text{-}EPI_{creatinine}$		$CKD\text{-}EPI_{cystatin}$		$CKD\text{-}EPI_{creatinine\text{-}cystatin}$	
PPV and NPV [mean (95% credible interval)]								
	PPV	NPV	PPV	NPV	PPV	NPV	PPV	NPV
Year 1	0.4 (0.0 to 3.9)	97.1 (94.8 to 99.0)	0.5 (0.0 to 5.0)	97.1 (94.8 to 99.1)	0.8 (0.0 to 4.3)	97.1 (94.7 to 99.3)	0.6 (0.0 to 6.4)	97.1 (94.8 to 99.1)
Year 2	6.6 (3.1 to 12.9)	97.8 (96.9 to 98.8)	6.9 (3.2 to 13.2)	97.8 (96.9 to 98.8)	4.0 (1.8 to 6.9)	97.6 (96.6 to 98.6)	5.6 (2.5 to 10.8)	97.7 (96.8 to 98.7)
Year 3	11.6 (9.1 to 14.6)	97.3 (96.3 to 98.1)	11.1 (8.9 to 14.2)	97.2 (96.3 to 98.0)	8.4 (6.3 to 10.3)	97.1 (96.2 to 98.1)	9.1 (6.6 to 11.8)	97.2 (96.2 to 98.0)
Year 4	15.9 (12.3 to 18.8)	97.3 (96.8 to 97.7)	15.4 (12.3 to 17.9)	97.3 (96.8 to 97.7)	10.5 (6.6 to 13.9)	96.9 (96.4 to 97.4)	14.1 (9.8 to 17.2)	97.4 (96.9 to 97.7)
Year 5	13.7 (9.9 to 17.5)	97.5 (96.8 to 98.1)	13.4 (9.9 to 16.4)	97.4 (96.7 to 98.1)	9.5 (5.5 to 13.8)	97.2 (96.5 to 97.7)	12.7 (8.4 to 16.8)	97.6 (96.8 to 98.1)
Year 6	13.9 (10.3 to 17.2)	97.3 (96.5 to 97.9)	13.6 (10.4 to 16.4)	97.3 (96.4 to 97.9)	10.0 (6.3 to 13.9)	97.1 (96.3 to 97.6)	13.1 (9.1 to 16.9)	97.4 (96.5 to 97.9)
Year 7	15.1 (11.8 to 17.7)	96.9 (96.3 to 97.5)	15.0 (11.9 to 17.4)	96.9 (96.2 to 97.5)	11.2 (7.8 to 14.3)	96.7 (96.1 to 97.2)	14.3 (10.5 to 17.2)	97.0 (96.3 to 97.5)
Year 8	15.5 (12.6 to 17.6)	96.7 (96.1 to 97.4)	15.4 (12.7 to 17.3)	96.7 (96.1 to 97.4)	11.8 (8.6 to 14.4)	96.5 (96.0 to 97.1)	14.9 (11.2 to 17.3)	96.7 (96.2 to 97.4)
Year 9	15.3 (13.3 to 17.2)	96.7 (96.1 to 97.0)	15.3 (13.4 to 17.4)	96.7 (96.1 to 97.0)	11.8 (9.4 to 13.9)	96.5 (96.0 to 96.8)	14.9 (12.1 to 16.9)	96.7 (96.2 to 97.1)
Year 10	14.8 (12.6 to 16.4)	96.8 (96.2 to 97.2)	14.8 (12.7 to 16.4)	96.8 (96.2 to 97.2)	11.5 (9.0 to 13.6)	96.7 (96.1 to 97.0)	14.5 (11.6 to 16.4)	96.9 (96.3 to 97.2)

Note
Cumulative sensitivity, cumulative specificity, cumulative PPV and cumulative NPV results for CKD stage shift progression criteria.

We weighted the proportion of consultant-led versus non-consultant-led appointments by the total number of appointments in each category in the cost collection data (88.8% consultant-led, consultant-led follow-up appointment: £170.93, non-consultant-led follow-up appointment: £145.85). Post referral to a nephrologist, a significant proportion of individuals are referred back and monitored in primary care (estimated to be 80% in a recent NICE economic model).[59] We therefore applied this weighting to the costings for the annual monitoring appointments, applying the cost of a GP appointment instead (£33.19).[117]

Test costs

The costs of the CKD-EPI$_{creatinine}$ and CKD-EPI$_{cystatin}$ tests were calculated as part of the study, taking into account the cost of reagents, staff and overheads. The cost of a CKD-EPI$_{creatinine}$ test was estimated to be £0.43 and the cost of a CKD-EPI$_{cystatin}$ test was £3.80. The cost of a CKD-EPI$_{creatinine\text{-}cystatin}$ test was calculated as the cost of a CKD-EPI$_{cystatin}$ test plus the cost of a CKD-EPI$_{creatinine}$ test. In some primary care settings, laboratory tests are charged at a fixed rate which is based on the annual cost of the whole service divided by the number of tests conducted each year. This tariff cost may vary by region, but it is typically more than the cost of a creatinine test and notably less than a cystatin C test. Here we have used the true estimated direct costs of the tests rather than the tariff cost, even if monitoring took place in primary care, to reflect the increased cost to the NHS overall.

Results

The breakdown and total cost of monitoring the study cohort (n = 875) over a 10-year period are presented in *Table 35*. As there were no notable differences in accuracy between the different GFR equations, the primary driver of the differences observed in costs is due to the higher unit cost of the cystatin C test.

Longer-term differences in costs and outcomes

In an earlier-stage CKD cohort (CKD stage G3), the main clinical justification for monitoring GFR is to promptly detect disease progression and offer interventions that may prevent or delay it. It is therefore the comparative sensitivity of the different testing strategies that would drive any differences in long-term costs and outcomes. In our measurement model analysis, we simulated the comparative accuracy of the GFR equations in an annual monitoring context and found no consistent improvement in sensitivity when applying GFR equations based on or incorporating cystatin C compared to creatinine alone. These results echo the findings of the statistical analysis of the 3-year cohort data reported in *Chapter 3*. We therefore have no evidence to support an analysis of the longer-term cost and health consequences of implementing a cystatin-based GFR equation.

TABLE 35 Estimated cost of monitoring n = 875 individuals over a 10-year period using different GFR equations

	MDRD	CKD-EPI$_{creatinine}$	CKD-EPI$_{cystatin}$	CKD-EPI$_{creatinine\text{-}cystatin}$
Cost of annual monitoring	£508,968.22 (98.58%)	£508,968.22 (98.55%)	£538,054.00 (97.26%)	£542,064.99 (97.81%)
Cost of repeat testing due to FP	£6829.73 (1.32%)	£6952.89 (1.35%)	£14,289.60 (2.58%)	£11,256.99 (2.03%)
Cost of repeat testing due to TP	£515.76 (0.10%)	£520.53 (0.10%)	£896.03 (0.16%)	£891.51 (0.16%)
Total cost (n = 875)	£516,313.71	£516,441.63	£553,239.63	£554,213.50
Average per patient cost	£590.07	£590.22	£632.27	£633.39
Incremental per patient cost	–	£0.15	£42.20	£43.32

In anticipation of cystatin-based GFR equations demonstrating an improvement in sensitivity, we developed a Markov model in R to capture the impact of identifying individuals whose CKD is progressing earlier. We would like to make the code for this model structure freely available for future research and adaptation as it may be useful in two key contexts: (1) if a more sensitive means of detecting progression is identified, and (2) if a novel intervention for preventing or delaying progression in individuals with CKD stage 3a/b is found. Details about the model structure and parameterisation can be found in *Report Supplementary Material 2*, along with a link to the R code.

When reviewing the literature and developing the model, we struggled to find evidence which quantified the impact of GFR monitoring on the rate of CKD progression. The most recently available evidence at the time was a NIHR programme report by Perera *et al.* which synthesised the evidence on the impact of monitoring GFR on cardiovascular disease management in those with G3 CKD.[113] Given that statin treatment is already recommended for all those with CKD category G3[59] and the use of antihypertensives is based on BP and urinary ACR,[59] Perera *et al.* concluded that monitoring eGFR in those with CKD is unlikely to be a driver of cardiovascular therapy indication.[113] Since the time of this programme, there have been a number of publications on the impact of glycaemic medications both on progression of CKD and on cardiovascular disease events in individuals with CKD.[17] This led to a new recommendation by NICE in November 2021 on the use of SGLT2 inhibitors in adults with CKD and type 2 diabetes who are taking an A2RB or an ACE inhibitor.[59] The use of this medication is dependent on ACR and eGFR threshold, and therefore may provide a means of quantifying the impact of monitoring GFR on longer-term costs and outcomes. Thus, it is important to note that if we had found that cystatin C was more sensitive than the creatinine alone equations, the health economic argument would likely be centred on the use of eGFR monitoring to trigger the use of these new hypoglycaemic medications.

Chapter 5 Discussion

Main study: prospective, longitudinal cohort study

We have studied GFR-estimating equations that were in widespread use in clinical practice at the inception of the study. We have also reported data describing the performance of equations that have been published during the progress of the study, including some recent equations specifically designed to address concerns about the use of ethnic adjustment factors in individuals of African descent. We have studied accuracy of these equations in a cross-sectional baseline analysis and also the ability of these equations to reflect and detect changes in mGFR over 3 years, in relation to several clinically relevant thresholds. We have explored possible causes for differences in the performance of some of the equations, in particular, issues related to the calibration of cystatin C. In the following discussion, comments relating to the characteristics of the cystatin C equations are based upon the use of recalibrated cystatin C data, except where calibration itself is the issue under consideration (see *The impact of calibration on cystatin C and glomerular filtration rate estimation*).

Which glomerular filtration rate-estimating equation is the most diagnostically accurate assessment of measured glomerular filtration rate?

Accuracy of the main study glomerular filtration rate-estimating equations

The main study estimated that GFR equations were negatively biased overall compared to mGFR. Median bias ranged from −2.8 to −4.1 ml/minute/1.73 m^2, with no evidence of a difference in bias between these equations. The overall bias we have observed for these equations is of a very similar order to that observed when the equations were originally validated.[28,32] However, the creatinine-based equations (MDRD and CKD-$EPI_{creatinine}$) demonstrated a clear shift in bias depending on the level of GFR (positively biased at lower levels of GFR, approximately < 35 ml/minute/1.73 m^2, and negatively biased at higher levels, approximately > 50 ml/minute/1.73 m^2). Inclusion of cystatin C within the equations largely attenuated this effect. Within the target population of the present study (i.e. individuals with GFR 30–59 ml/minute/1.73 m^2), the impact of this effect was less dramatic than at more extreme levels of GFR, but the data suggest that cystatin C-containing equations may perform more consistently in terms of bias across a wider range of GFR levels. This could be an important advantage in terms of disease detection. It is widely accepted that the MDRD equation displays negative bias at levels of GFR > 60 ml/minute/1.73 m^2 and this was one of the drivers for its replacement with the CKD-$EPI_{creatinine}$ equation in clinical practice.[32,41] The bias-GFR level effect we have observed for the CKD-$EPI_{creatinine}$ equation is not consistent with other studies. Although Levey *et al.* observed a slight increase in negative bias at higher levels of GFR,[32] in large European studies Pottel *et al.* observed positive bias for the CKD-$EPI_{creatinine}$ equation which was fairly constant across the GFR range studied and across adult (> 30 years) age ranges,[44,47] while Björk *et al.* report positive bias at GFR levels up to 90 ml/minute/1.73 m^2.[118] Comparisons with other studies are complicated by factors including the demographics of the populations and the range of GFRs studied, and by methodological differences in reference and test methodologies.

Twenty years ago the NKF-K/DOQI suggested a P30 minimal performance target of 90% for GFR equations, a position that was later adopted by KDIGO (2012).[27,102] Many equations, particularly creatinine-based equations, have not achieved this level of performance, including in their original published descriptions.[32,44,47] While the MDRD equation achieved a P30 of 92% in the stage 3 CKD GFR range in its development cohort,[38] this was not sustained in a validation data set.[32]

Encouragingly, in the present study, all of the primary equations achieved P30 > 89%. In relation to the primary study question of which equation is the most accurate in this population, the MDRD, CKD-$EPI_{creatinine}$ and CKD-$EPI_{cystatin}$ equations provide similar assessments of mGFR. The CKD-$EPI_{creatinine}$

equation is the NICE-endorsed equation. We found no evidence of the superiority of this equation over the MDRD equation, which it supplanted in the NICE 2014 guideline.[22] These observations pertain only to performance in a predominantly stage 3 CKD cohort and other data would have informed the NICE decision at that time, for example the reported increasing negative bias and poorer precision of the MDRD equation at higher levels of GFR. We also observed no benefit of using cystatin C in isolation in an equation. However, the CKD-EPI$_{creatinine-cystatin}$ equation demonstrated somewhat superior performance to the other three equations with a P30 point estimate of 94.9% and CI that did not overlap 90%. Performance of the CKD-EPI$_{creatinine-cystatin}$ equation was also superior to that of all of the secondary study equations that did not incorporate cystatin C.

Accuracy of more recently described glomerular filtration rate-estimating equations

More recently published creatinine-based equations generally had similar slight negative bias compared to mGFR, with CIs overlapping those of the main study equations and P30 values > 89%. The exceptions to this were CKD-EPI(2021)$_{creatinine}$ (zero bias, P30 88.0%), the BIS1$_{creatinine}$ equation (slight positive bias 1.0 ml/minute/1.73 m^2, P30 85.9%) and the LMR$_{creatinine}$ equation, which performed poorly in this study (negative bias 6.2 ml/minute/1.73 m^2, P30 84.2%). More recently published cystatin-based and combined creatinine–cystatin C-based equations were negatively biased compared to mGFR. Equations that incorporated both creatinine and cystatin C demonstrated improved performance, with the CKD-EPI(2021)$_{creatinine-cystatin}$, BIS2$_{creatinine-cystatin}$ and FAS$_{creatinine-cystatin}$ equations achieving P30 values equivalent to those of the CKD-EPI$_{creatinine-cystatin}$ equation. However, we found no evidence to suggest that any of the newer equations were superior to the CKD-EPI$_{creatinine-cystatin}$ equation in this setting.

Our observations and conclusions are limited to a predominantly stage 3 CKD adult cohort. Furthermore, there may be good reasons for recommending other equations in specific situations and beyond the sole consideration of accuracy performance. The BIS1 (creatinine-based) and BIS2 (creatinine and cystatin C-based) equations were developed in a predominantly non-CKD community-dwelling population of older (> 70 years) adults. The blood creatinine concentration/GFR relationship is often different in older compared to younger adults, potentially leading to inaccuracies in GFR estimation when equations derived in younger adults are applied to older people. The authors observed low bias for the BIS2 equation and recommend the use of this equation, in preference to the CKD-EPI equations, in older adults.[42] The LMR equation[53] is a creatinine-based equation that has also demonstrated good performance in older Caucasian adults.[46] The CAPA equation was developed in northern European and Japanese cohorts. It is solely cystatin C-based and no adjustments are required for race or gender.[43] A recognised limitation of many equations, including the CKD-EPI and BIS equations, has been their lack of applicability across all age groups and lack of continuity as individuals cross age thresholds (e.g. from adolescence to adulthood). The FAS$_{creatinine}$ [44] and FAS$_{creatinine-cystatin}$ equations[45] address this issue. Observed creatinine or cystatin C concentrations are utilised in these equations as ratios to the age- and gender-matched median concentrations, obtained from large reference interval studies. The EKFC equation extended this general approach but also introduced different exponential coefficients depending on whether the creatinine concentration was above or below the age and gender-related median.[47] This produced an equation with good accuracy and precision compared to earlier equations, although validation was only undertaken in Caucasian populations. As a general consideration, equations that utilise only cystatin C are likely to be less influenced by racial differences or recent ingestion of meat.[119] In 2021, amidst growing concerns about the use of race adjustment in GFR-estimating equations, new CKD-EPI equations that omitted race were developed. This issue is discussed later.

Assessing the accuracy of glomerular filtration rate estimation: P30 versus P15

The P30 is the most commonly used metric to measure the accuracy of GFR equations, yet it was defined in the absence of clinical and statistical rationale.[120] The arbitrary choice of a 30% margin is actually rather broad and can span multiple GFR categories, especially at higher GFR values. Other stricter criteria such as the P5, P10 and P15 (where 5, 10 and 15 represent the acceptable percentage

margin of error between estimated and mGFR) provide an alternative to the P30 and NICE advise that the P5 and P15 are also useful for clinical decision-making.[59] Calculation of the P15 was not originally specified in the statistical analysis plan (and the sample size calculation did not consider the P15), but the decision was made to include it to reflect the current view from NICE.

The P15 values of different equations generally fell in similar rank order to P30 values with some exceptions {e.g. while both the original and 2021 revised CKD-EPI$_{creatinine\text{-}cystatin}$ equations achieved P30 values of 94.9%, the P15 value of the remodelled 2021 equation was superior to that of the original equation [66.1% (63.3 to 68.8) compared to 60.4% (57.5 to 63.2)]}. All of the combined creatinine–cystatin equations achieved P15 values > 60%, whereas all of the creatinine-only equations achieved P15 values < 58%.

The benchmark value for the P30 is often quoted as 90%, but there does not appear to be any standard or published aspiration in terms of what the P15 should be. Porrini *et al.* however state that to be clinically meaningful, a GFR-estimating equation should achieve a P10 of 90%[120] – a much stricter criterion than the same 90% threshold for the P30. The P15 values we observed were all much lower than 90% illustrating that current equations are unlikely to meet this target.

While we would agree that the P30 range is rather broad for clinical decision-making, it is questionable how much further progress can be made in improving on this situation using current approaches. In addition to issues relating to the accuracy of creatinine measurement, and those which can be compensated for in estimating equations (e.g. age, gender), there are a large number of non-glomerular influences on serum creatinine concentration including tubular secretion, extrarenal elimination, differences in skeletal muscle mass,[121] dietary intake[119,122] and differences in creatinine production rate which may be genetically determined.[123] Although non-glomerular influences on serum cystatin C concentration are generally considered less important than those of creatinine, cystatin C concentration has been reported to be affected by factors such as lean mass,[124] glucocorticoid treatment,[125] smoking status[126,127] and also genetic influences.[128] Some progress may be made by the use of multimarker approaches. The addition of beta-trace protein and beta-2 microglobulin did not lead to incremental improvements in GFR estimation in one study,[129] but in the future, the use of multimarker metabolite profiling may hold promise.[130] However, an issue which will affect the upper limits of accuracy of any approach is the biological and analytical variability of the reference mGFR procedure itself (see *Study of intraindividual biological variation*).

The impact of calibration on cystatin C and glomerular filtration rate estimation

Using the Abbott cystatin C assay we observed significant negative bias of CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ GFR-estimating equations. This was unexpected based on earlier data from members of the study group.[52] Cystatin C assays are calibrated against an international reference preparation (ERM-DA471/IFCC) developed with the aim of achieving improved agreement between assays from different manufacturers.[51] ERM-DA471/IFCC was originally verified as being commutable for use in the Abbott immunoassay.[51] However, during the course of this study, evidence emerged of continuing discordance between different manufacturers methods.[131] A report in 2017 described a significant positive bias of some 16–20% of the Abbott cystatin C assay, resulting in significantly negatively biased GFR estimates.[101] Re-analysis of some historical stored samples in the present study supported this report. Communication with Abbott Diagnostics confirmed that they had seen a shift in their calibration but that the assay remained within their manufacturing tolerance.

We further explored this issue through a laboratory recovery study, which confirmed an average over-recovery of 9.1% in the Abbott cystatin C assay, sufficient to cause negative bias of GFR estimates of the order we observed (see *Table 5* and *Figure 5*). We also undertook a comparison study against the Siemens BN Prospec assay, which further supported a positive bias of the Abbott assay. In a recent study, the Siemens method on the BN Prospec analyser was the only commercially available assay achieving prespecified performance criteria in relation to bias and precision.[101] After careful

consideration, we decided that our Abbott cystatin C data should be recalibrated against the Siemens BN Prospec assay, to ensure that our study data represented the performance of cystatin C-based GFR-estimating equations under internationally standardised conditions. Following recalibration, the negative bias of the CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations was significantly improved and indistinguishable from that of the MDRD and CKD-EPI$_{creatinine}$ equations.

The positive bias of the Abbott cystatin C assay illustrates the difficulty when transferring reference calibrator values to field methods. The issues are particularly complex with immunoassay where the major 'reagent' is antibody-based. There are multiple potential sources of variation. For example, there may be subtle differences in the antigens that different manufacturers use to inoculate the antibody-producing animals. The animal species used to make the antibodies may also influence the speed and affinity of the reaction with the antigen. Consequently, antibodies used by different manufacturers may have differing selectivity, affinity and avidity for cystatin C in the sample, and they may be differentially affected by matrix effects present in human serum samples (other proteins, salt, phospholipids, complement, drugs and other substances), and possibly also by genetic variation.[128] This issue is important: there is an assumption that the introduction of the international standard for cystatin C has resulted in globally aligned assays. Although there is evidence that between-method agreement has improved following the introduction of the standard, evidence from this study and others indicates that further efforts are required to improve assay comparability in this area.[101,131] Additionally, in contrast to the situation with creatinine, there is currently no certified reference measurement procedure for cystatin C to definitively establish target values for the reference material.[132]

Attention to accuracy of standardisation of cystatin C assays has important clinical and research implications. This was illustrated in a UK primary care study of older patients with stage 3 CKD, where the use of the Abbott cystatin C assay classified a greater proportion as having more advanced CKD than the use of GFR$_{creatinine}$, with associated increased monitoring costs, leading the authors to refute the recommendation of the NICE 2014 guideline in relation to use of cystatin C.[133]

Influence of body surface area adjustment method on accuracy (P30) of glomerular filtration rate-estimating equations: Haycock equation compared to the Du Bois equation

To adjust GFR for differences in body size, mGFR is commonly adjusted for BSA, with a population average BSA value of 1.73 m^2 being used.[134] The Du Bois equation was first reported in 1916 and enabled estimation of BSA from height and weight of an individual based on a laboratory comparison with direct measurements of BSA in a relatively small number (n = 9) of individuals.[93] The Haycock equation was developed in a larger cohort of individuals but still only included 19 adult subjects.[92] The method involved reducing the limbs and trunk to a series of cylinders, or a sphere in the case of the head, measuring the length of the cylinders and calculating and summing surface area from these measurements. The BSA equation was then derived using multiple regression analysis to solve BSA from height and weight measurements.

While many studies in this field have used the Du Bois equation to adjust their reference mGFR, including the MDRD equation,[31] there is no consensus on this point. Indeed in some publications, including some of those used in the development data set of the CKD-EPI equation, the BSA adjustment method is not described.[60,135] The Haycock equation is the preferred method of the British Nuclear Medicine Society when adjusting GFR for BSA.[100] Other BSA equations have also been described.[136] Estimated GFR values are already adjusted for BSA because BSA was taken into account when the equations were originally derived using regression modelling against measured BSA-adjusted GFR.

In the present study, all eGFR equations were equally accurate in terms of P30 whether the mGFR was adjusted using the Du Bois or the Haycock equation. This accords with other reports.[136,137] The Haycock equation will give higher BSA results, and consequently lower adjusted GFR results, in individuals of higher BMI. For example, in an individual weighing 100 kg of height 1.75 m, the Haycock BSA estimate

will be 3.9% higher than Du Bois. Our cohort had a median BMI of 29.0, with 43% of individuals having BMI > 30. Consequently, the Haycock BSA was slightly higher than the Du Bois estimate (2.02 vs. 1.96 m^2), with slightly lower BSA-adjusted mGFR (*Table 2*). The impact of using Haycock-adjusted mGFR would be to reduce the negative bias of all the GFR-estimating equations by approximately 1.4 ml/minute/1.73 m^2 (see *Appendix 1*, *Table 41*).

Although the validity of GFR adjustment for BSA has been questioned,[134] the practice remains widespread. Our data indicate that the difference between Du Bois and Haycock BSA GFR adjustments is small. Nevertheless, the adjustment method does have an impact which is larger in individuals with higher BMI and will contribute to between-study comparisons of GFR equation performance. It would seem sensible for the scientific and clinical community to reach an agreement on the adjustment method that should be used and for authors in this field to ensure such information is available in published reports.

Impact of creatinine method on accuracy of glomerular filtration rate-estimating equations: enzymatic compared to isotope dilution mass spectrometry method

An enzymatic creatinine assay was used throughout the study. Such assays are less susceptible to interferences than older colorimetric (Jaffe) methods, although are not immune to such effects. Accuracy of the main study equations did not differ in terms of P30 irrespective of whether GFR was estimated using enzymatic or ID-MS creatinine results. However, regression and bias plot analysis demonstrated that enzymatic creatinine results were slightly higher than ID-MS results, with a mean positive bias of 4.7 µmol/l that was fairly consistent across the concentration range of the study cohort. Between-method differences are not unexpected, and even within-method differences across different laboratories. The consistency of the bias across the concentration range suggests a sample matrix interference in the enzymatic assay as opposed to a standardisation issue. The enzymatic assay demonstrated excellent performance in external quality assessment schemes throughout the study period, although it is widely appreciated that external quality assessment materials do not always reflect performance in clinical samples (i.e. the test materials are not necessarily commutable). According to recommendations of the National Kidney Disease Education Program, the low imprecision of the assay (analytical between-day imprecision < 0.9%) was consistent with optimal assay performance in relation to biological variation and the bias in relation to the reference method (ID-MS) was acceptable.[39]

Nevertheless, it is clearly the case that substitution of ID-MS creatinine values for the enzymatic ones would, on average, have increased GFR estimates and reduced the negative bias we observed against mGFR. The purpose of our study was to evaluate the performance of GFR equations using analytical methods representing typical clinical laboratory conditions. We therefore chose not to use ID-MS creatinine results for our analyses. It is the case however, as with cystatin C, that the accuracy of commercial creatinine methods remains a critical issue when considering the accuracy of GFR-estimating equations.

Influence of baseline diabetes and albuminuria, age, gender, body mass index, measured glomerular filtration rate level and ethnicity (Caucasian, South Asian and African-Caribbean), on accuracy of glomerular filtration rate-estimating equations

In unadjusted analyses, accuracy of the main study equations at baseline did not change significantly across any of the characteristics studied (i.e. age, gender, BMI, kidney function, ethnic origin and in the presence and absence of diabetes). Many studies have described differences in the performance of GFR-estimating equations across different characteristics (e.g. age,[138,139] gender,[138] level of GFR,[32,138,140,141] BMI[138,139]). While we did not observe any of these described effects it should be noted that our study was not powered to address these issues, we only undertook unadjusted analyses with P30 as a fairly crude overall indicator of equation performance, and our cohort was, by design, restricted to a relatively narrow level of kidney function.

The performance of GFR-estimating equations in non-Caucasian ethnic groups has always been an area of debate. As discussed earlier, this interest has heightened recently with the recommendation by the National Kidney Foundation-American Society of Nephrology[67] that black race adjustment factors should no longer be used and by the publication of revised CKD-EPI equations that were remodelled without the inclusion of a black race adjustment factor.[48] Similarly, the 2021 revision of the NICE CKD guideline no longer includes a recommendation to adjust for black ethnicity.[59]

One of the aims of the present study was to evaluate the performance of GFR-estimating equations in South Asian and African-Caribbean ethnic groups living in the UK. Unfortunately, the study under-recruited from these populations and any conclusions we can draw are limited by the small sample size of these groups (see *Table 8*). Overall, however, we found no evidence of a difference in the accuracy of the main study equations across the three ethnic groups. Simple removal of the African-Caribbean factor did not alter the performance of the MDRD, CKD-EPI$_{creatinine}$ or CKD-EPI$_{creatinine\text{-}cystatin}$ equations in the overall cohort (see *Table 5*), but this is predictable given that African-Caribbean participants represented only 5.1% of the overall cohort. However, removal of the African-Caribbean adjustment factor from the MDRD and CKD-EPI$_{creatinine}$ equations, as proposed by NICE,[59] did lead to reduced point estimates of P30/accuracy amongst African-Caribbean individuals. This decrease only achieved significance for the MDRD equation, which is probably explained by the heavier weighting of the adjustment factor in this equation (i.e. MDRD 1.212; CKD-EPI$_{creatinine}$ 1.159; CKD-EPI$_{creatinine\text{-}cystatin}$ 1.08). This finding is at odds with a large (n = 1888), retrospective, UK-based study using ^{51}Cr-EDTA mGFR as the reference test compared to MDRD and CKD-EPI$_{creatinine}$-based eGFR.[142] Amongst the black participants (n = 266), MDRD and CKD-EPI$_{creatinine}$ estimates of GFR demonstrated significant positive median bias (16.0 and 20.0 ml/minute/1.73 m^2, respectively), which was ameliorated by removal of the ethnic adjustment factors (bias 1.0 and 7.0 ml/minute/1.73 m^2 for MDRD and CKD-EPI$_{creatinine}$, respectively). Additionally, the study also observed significant positive bias of MDRD and CKD-EPI$_{creatinine}$-based eGFR amongst the white participants (n = 1622, 12.0 and 14.0 ml/minute/1.73 m^2, respectively) and poor accuracy overall in black and white participants (P30 < 78% in all cases).[142] Demographic, methodological and clinical differences between this cohort and ours make direct comparison difficult. As conceded by the authors, one potential source of this bias may have been that many participants had their GFR measured in preparation for chemotherapy as treatment for (predominantly haematological) cancer and may therefore have had lower than expected muscle mass.[143] While the removal of inflationary ethnic adjustment factors will inevitably lower estimates of GFR, further research is required to establish whether this improves or worsens overall accuracy in black people.

There are theoretical reasons why simple removal of the African-Caribbean factor from the 2009 CKD-EPI equations may be inappropriate, specifically that the equations were developed using regression modelling that included race as a factor. The CKD-EPI consortium observed a worsening of bias of eGFR amongst black individuals using the original 2009 equation as a result of racial factor removal from the CKD-EPI$_{creatinine}$ equation, from a positive bias of 3.7 ml/minute/1.73 m^2 to a negative bias of 7.1 ml/minute/1.73 m^2. The bias was reduced using a new CKD-EPI(2021)$_{creatinine}$ equation developed using regression modelling that had included only age, gender and serum creatinine concentration, but not race, as variables. However, the CKD-EPI(2021)$_{creatinine}$ equation did not perform as well as the original equation in non-black individuals. The equation that incorporated both creatinine and cystatin C [CKD-EPI(2021)$_{creatinine\text{-}cystatin}$] was less biased and more accurate amongst black individuals than the original CKD-EPI$_{creatinine\text{-}cystatin}$ equation but had the reverse effects amongst non-black individuals. Overall differences in accuracy between black and non-black individuals were reduced using the CKD-EPI(2021)$_{creatinine\text{-}cystatin}$ equation compared to the original CKD-EPI$_{creatinine\text{-}cystatin}$ equation, equations with creatinine alone and the CKD-EPI$_{cystatin}$ equation.[48] A report published simultaneously by the Chronic Renal Insufficiency Cohort Study investigators reached broadly similar conclusions.[144] In the present study, the CKD-EPI(2021)$_{creatinine}$ and CKD-EPI$_{creatinine\text{-}cystatin}$ equations demonstrated equivalent performance compared to their respective original CKD-EPI equations in the overall cohort (see *Table 5*) and amongst Caucasians and South Asians. However, the CKD-EPI(2021)$_{creatinine}$ equation had a reduced point estimate of accuracy amongst African-Caribbean individuals.

Our data represent one of the first evaluations of the CKD-EPI(2021) equations in a UK population. While further evaluation across a broader spectrum of GFR values is required, the data presented here would not preclude future use of the CKD-EPI(2021) equations amongst the Caucasian UK population, but further validation in ethnic minority groups is still required. Simple removal of the racial adjustment factors from the original CKD-EPI equations, as (indirectly) proposed by NICE,[59] has minimal impact on performance in the population overall, but further research is required to reassure that this does not have a deleterious effect on performance in African-Caribbean individuals.

Concordance of glomerular filtration rate-estimating equations with measured glomerular filtration rate within a tolerance of 3 ml/minute/1.73 m^2/year or five percentage points over 3 years

The ability of estimating equations to track mGFR over 3 years was assessed by analysing agreement in two separate analyses (estimated change per year within 3 ml/minute/1.73 m^2 of mGFR change per year and change per year for eGFR within 5 percentage points of the % change in mGFR per year). To clarify, this analysis compared the slopes of change for mGFR and eGFR and did not compare absolute values. Agreement was considered present when the eGFR slope lay within ±3 ml/minute/1.73 m^2/years (or ± 5%/years) of the slope of change for mGFR. In both situations, the main study equations achieved > 70% agreement with mGFR. We observed that the CKD-EPI$_{\text{creatinine-cystatin}}$ equation generally had better concordance with mGFR than the other three primary study equations. This difference was significant compared to all three other equations when considering concordance within a change of ±3 ml/minute/1.73 m^2/years and compared to the CKD-EPI$_{\text{creatinine}}$ equation when considering change within ± 5%/years of mGFR. However, CIs overlapped in all cases. Performance of the CKD-EPI$_{\text{creatinine}}$ equation was inferior to that of the MDRD and CKD-EPI$_{\text{creatinine-cystatin}}$ equations but not compared to the CKD-EPI$_{\text{cystatin}}$ equation.

In the above analyses, the observed changes in mGFR and eGFR per year were used (i.e. final mGFR/eGFR minus initial mGFR/eGFR to calculate change per year in either ml/minute/1.73 m^2 and for percentage change using the calculated change per year in GFR and comparing this to the initial GFR measurement to generate a percentage change per year). Additional sensitivity analyses were undertaken estimating the change per year and percentage change per year using all the data points available in the study (up to three mGFR and seven eGFR time points per participant) to enable analyses using two different regression modelling approaches. The approaches were: (1) linear regression models to estimate the slope for each individual for the eGFR measurements and observed differences in mGFR and (2) linear regression models to estimate the slope for each individual for the eGFR measurements and a single multilevel model allowing individual predictions of mGFR slopes. Both these approaches, using the change in eGFR calculated from linear regression and using the change in mGFR calculated using a multilevel model, suggested the changes in eGFRs were within the specified tolerances (3 units and 5%) for more participants than when using only the observed data to calculate change over time, for all main study equations. For example, for the CKD-EPI$_{\text{creatinine}}$ equation, the main analysis for tolerance within ±3 ml/minute/1.73 m^2/years of change demonstrated 73.1% concordance with mGFR; in sensitivity analyses 1 and 2, this increased to 76.9% and 80.5%, respectively. In these sensitivity analyses, the CKD-EPI$_{\text{creatinine-cystatin}}$ equation again consistently had the highest point estimates compared to the other equations, although CIs overlapped in most cases. While the modelling methods used in these sensitivity analyses allowed data at all time points to be used, they also removed the variability in the measurements. This would not be observable in practice, hence the apparent superior performance of all estimating equations in these analyses compared to the main analysis using just the observed changes over time. The approaches using interim data points with statistical methods to describe the change over time, as performed by Padala *et al.*,[84] give a more accurate estimate of the true change in estimated and mGFR over time, but this does not reflect the observed changes that would be seen in practice.

Of the more recent study equations, when considering concordance within ±3 ml/minute/1.73 m^2/years or ± 5%/years of mGFR, those equations that included both creatinine and cystatin C [CKD-EPI(2021)$_{\text{creatinine-cystatin}}$, BIS2$_{\text{creatinine-cystatin}}$, FAS$_{\text{creatinine-cystatin}}$] achieved higher point estimates of agreement

than their corresponding creatinine-only equations [CKD-EPI(2021)$_{creatinine}$, BIS1$_{creatinine}$, FAS$_{creatinine}$ respectively], although CIs overlapped in all cases. Of these more recent study equations, BIS2$_{creatinine-cystatin}$ performed best, but with CIs overlapping with CKD-EPI$_{creatinine-cystatin.}$

The limits of ± 3 ml/minute/1.73 m^2/years (or ± 5%/years) were selected based on the earlier study of Padala *et al.* where the authors considered that such errors would be considered large in clinical terms.[84] Padala *et al.* concluded that CKD-EPI$_{creatinine}$ eGFR accurately reflected changes in mGFR over time, with only 15.3% of their participants having an error that exceeded ± 3 ml/minute/1.73 m^2/years, similar to the results in the present study. However, given that the overall median change in mGFR in the present study was −1.5 ml/minute/1.73 m^2/years (i.e. from 48.1 to 43.6 ml/minute/1.73 m^2 over 3 years), with similar magnitude overall changes in eGFRs, concordance within a change of ± 3 ml/minute/1.73 m^2/years (or ± 5%/years) represents a fairly wide degree of tolerance. Even given biological and analytical variability, the majority of patients would have been unlikely to show excursions of eGFR outside of these limits. Only 30.6% of the study population showed a change in GFR of > 10 ml/minute/1.73 m^2 (approximately 3.3 ml/minute/1.73 m^2/year) over the study period. In other words, achievement of > 70% concordance, or higher, depending on the statistical approach used, is not altogether surprising and may not represent a strenuous test of the ability of GFR-estimating equations to monitor change. Similar considerations would presumably apply to the study of Padala *et al.*, where the average rate of change was −2.25 ml/minute/1.73 m^2/year. It should also be considered, given the median baseline mGFR in our cohort was 48.1 ml/minute/1.73 m^2, that tolerance limits of ± 3 ml/minute/1.73 m^2/years or ± 5%/years equate very closely (and would be equivalent at a GFR of 60 ml/minute/1.73 m^2). This is reflected in the similar performance of all of the equations against these two limits (e.g. 75.4% or 74.9% concordance respectively for MDRD eGFR): in retrospect, use of quantitatively similar thresholds has added little value to the data.

There have been earlier longitudinal studies of the ability of creatinine-based eGFR to track mGFR over time.[145–148] A consistent feature of all studies has been that eGFR underestimated the decline in mGFR. In a study comparable to ours in terms of duration (minimum 2.6 years), GFR range of the study cohort (25–55 ml/minute/1.73 m^2) and estimating equation used (MDRD), Xie *et al.* observed eGFR to underestimate the slope of iothalamate mGFR decline by 28%, with 42% of individuals having an eGFR slope that differed from the mGFR slope by ≥ 2 ml/minute/1.73 m^2, similar to the discordance observed in the present study.[148] The annual change in mGFR seen in the present cohort was smaller than that observed by Xie *et al.* (−1.5 vs. −3.9 ml/minute/1.73 m^2/years), but we also observed that changes in eGFR were smaller than changes in mGFR (MDRD −1.0, CKD-EPI$_{creatinine}$ −1.2, CKD-EPI$_{cystatin}$ −1.1, and CKD-EPI$_{creatinine-cystatin}$ −0.9 ml/minute/1.73 m^2/years). Possible reasons for this are discussed in *Ability of glomerular filtration rate-estimating equations to detect change in measured glomerular filtration rate over 3 years*. In keeping with Xie *et al.*,[148] we found no differences in baseline characteristics that could predict whether individual eGFRs would be discordant with mGFR. The annual underestimation of change we observed was small but could potentially have significant clinical implications where eGFR measurements are being used to plan future renal care.

Most studies have focused on the value of creatinine-based GFR estimates when monitoring GFR over time. A relatively small (*n* = 20) early study suggested that cystatin C may have advantages over creatinine in this respect.[149] However, studies of patients with type 1 diabetes (*n* = 977) and of patients with human immunodeficiency virus infection (*n* = 184) found no additional benefit of using cystatin-containing CKD-EPI equations compared to CKD-EPI$_{creatinine}$ when monitoring GFR over time.[150,151] Our data concur with these latter reports. While there was some evidence of improved concordance for the CKD-EPI$_{creatinine-cystatin}$ equation within the tolerance limits studied, the underestimation of mGFR slope certainly appears no better with this equation. Indeed, slope estimates derived from random coefficients models in the substudy [see *To estimate and model disease progression (decline in glomerular filtration rate or increase in albumin-to-creatinine ratio) and differences in progression between ethnic groups (Caucasian, South Asian and African-Caribbean), and baseline diabetes and albuminuria status and other potential risk*

factors] show reduced slope estimates (i.e. less steep decline in GFR over time) for cystatin-containing equations compared to mGFR and creatinine-based GFR estimates.

Ability of glomerular filtration rate-estimating equations to detect change in measured glomerular filtration rate over 3 years

The performance characteristics (sensitivity, specificity, NPV, PPV) of GFR-estimating equations were studied in relation to their ability to detect several different thresholds of change in mGFR over 3 years: (1) > 10 ml/minute/1.73 m^2; (2) > RCV (a > 21.5% increase or a > 17.7% decrease); (3) > 25% change; and (4) > 25% change in combination with a change in disease stage. The rationale for studying these thresholds is described earlier (see *Progression of kidney disease* and *Which glomerular filtration rate-estimating equation most accurately detects change in glomerular filtration rate?*).

A change in GFR > 10 ml/minute/1.73 m^2 was observed in 30.6% of the cohort. The sensitivity (% of patients with a positive result from mGFR that were also positive using the estimating equation) was ≤ 50% in all cases, whether change in GFR or decline in GFR only was being considered. The specificity (% of patients with a negative result from mGFR that were also negative using the estimating equation) exceeded 79% for all primary study equations and was improved (point estimates > 86%) when only a decline in GFR was considered.

Consequently, GFR-estimating equations have relatively poor PPVs for identifying change in GFR exceeding 10 ml/minute/1.73 m^2 (TPs), but good NPVs where GFR change has not exceeded 10 ml/minute/1.73 m^2 [true negatives (TNs)], particularly when only decline in GFR is being considered.

Similar equation performance in terms of sensitivity for detecting both overall change and decline only were observed when other threshold changes in mGFR were considered, either changes in excess of the RCV (> + 21.5%/−17.7%) or the larger change > 25% overall or > 25% decline only. In our cohort, changes in excess of the RCV or of 10 ml/minute/1.73 m^2 are numerically similar thresholds, and this is illustrated by the similar sensitivities and specificities of these two criteria.

In all scenarios, specificity was good, particularly for the larger > 25% change in GFR studied and when considering a decline in GFR only, where point estimates in excess of 90% were observed. Combining 25% change in GFR with a change in disease category, as recommended by KDIGO when defining progression,[27] made little difference to the point estimates of sensitivity, but the more stringent criteria for positivity did increase the specificity of all equations, and NPVs were in excess of 90%.

There was no clear difference in sensitivity or specificity (overlapping CIs) between the four main study equations at all thresholds studied. Sensitivity and specificity estimates of newer GFR-estimating equations had similar point estimates to the main study equations. For all equations and all metrics, there was no clear evidence of improved performance of cystatin-containing equations compared to their matched creatinine-only equation.

In relation to detection of disease progression, the performance of estimating equations is poor and may appear somewhat at odds with the high concordance noted earlier between estimated and mGFR change when considering annual change within 3 ml/minute/1.73 m^2 or 5% of mGFR. The earlier analysis assessed whether the eGFR change was within a certain tolerance (± 3 ml/minute/1.73 m^2/years or ± 5%/years) of the mGFR change. However, as noted above, the majority of individuals did not show large excursions of GFR from baseline. When assessing the sensitivity and specificity of GFR-estimating equations to detect change, changes in both estimated and mGFR are converted to binary measures (either positive or negative) with no tolerance (i.e. mGFR and eGFR either show the difference of the magnitude investigated or do not). Sensitivity estimates are based only on the minority (e.g. 30.6% or 21.4% for the ≥ 10 ml/minute/1.73 m^2 or > 25% criteria respectively) of individuals showing a larger change in mGFR that also show a larger change in eGFR, rather than studying the whole group.

Conversely, specificity estimates will be based on the majority of individuals who did not show a large change in mGFR that also did not show a large change in eGFR.

Definitions of progressive kidney disease vary (see *Progression of kidney disease*). It is important to consider whether, in the clinical context, estimates of GFR allow for detection of progressive kidney disease over a useful time frame. Our data, based on change detection over 3 years, suggest that reported 'normal' mean age-related decline in GFR of 1 ml/minute/1.73 m^2/years,[152] or reported rates of decline of between 2.8 and 3.6 ml/minute/1.73 m^2/years in older adults with diabetes and moderate CKD[69] would not be reliably detected by eGFR measurement. It is possible that reported mean GFR declines of 7.0 ml/minute/1.73 m^2/year amongst proteinuric (> 1 g/24 hours) patients would be detected by a programme of annual monitoring of individual patient's GFR.[70] NICE have recently defined accelerated progression as a sustained fall in GFR in excess of 25% and a progression in disease category [e.g. G3a (GFR 45–59 ml/minute/1.73 m^2) to G3b (GFR 30–44 ml/minute/1.73 m^2)] in a 12-month period, or a sustained decline in GFR of 15 ml/minute/1.73 m^2 over a 12-month period.[59] Of concern, assuming our data gathered over 3 years are reflective of the ability of eGFR to detect annual change, monitoring of GFR would not reliably permit detection of accelerated progression by this definition. While the NICE accelerated progression criteria concur broadly with our biological variation estimates as being consistent with true change (see *Study of intraindividual biological variation*), monitoring patients with annual eGFR would detect such changes only approximately half of the time. Part of this limitation will be due to the poor accuracy of GFR equations: as noted earlier, at best, current equations only achieve a P30 of around 90%, and the P30 itself is a rather broad metric of accuracy. It should also be considered that the reference mGFR test has its own intrinsic biological and analytical variability, which is in fact greater than that of GFR-estimating equations (see *Study of intraindividual biological variation*).

In terms of progression, there are theoretical reasons why one might consider that creatinine-based equations will be suboptimal at detecting change, in particular decline, in GFR. Changes in tubular secretion and extrarenal elimination of creatinine will increase as renal disease progresses, potentially blunting the response of eGFR to declining kidney function.[121] Creatinine is a product of muscle creatine metabolism, being continuously formed at a rate of 1.6–1.7% of creatine mass per day. Creatine is synthesised in a two-part process. The first step, the synthesis of guanidinoacetate, occurs in the kidney, implying that as renal functional mass declines (i.e. GFR declines) the production rate of guanidinoacetate (and creatinine) will fall.[153] Furthermore, as kidney disease progresses there is a tendency for muscle mass to decrease with a high prevalence of sarcopenia, itself possibly driven, in part, by reduced synthesis of creatine and resulting in a change in the usual plasma creatinine–GFR relationship. However, given that plasma cystatin C concentration is considered to be less dependent on muscle mass, it is disappointing that equations incorporating cystatin C did not demonstrate improved sensitivity. Modelling within the substudy demonstrated a decline in progression slope over time for the CKD-$EPI_{cystatin}$ equation (see *Substudy of disease progression*) which could have countered the ability to detect change.

Substudy of disease progression

Modelling of disease progression in the substudy

Recruitment to the substudy fell short of target, probably partly due to the more intensive nature of the study design, requiring four iohexol reference GFR procedures in total. Results should be interpreted cautiously as estimates derived in small subgroups are more sensitive to influence by extreme values, in particular ethnicity group and smoking status. There were only 35 African-Caribbean participants and 30 South Asian participants, and only 23 current smokers in the evaluable population.

There was evidence of collinearity among some of the covariates, which should be considered when interpreting the results. The covariates were selected based on known or purported associations with kidney disease progression observed in previous studies (e.g. ethnicity,[57,58] diabetes,[69] proteinuria[70]). All

of the unadjusted covariates were associated with GFR and/or ACR intercept or progression in single covariate regression models with the exception of vascular disease.

The final multiple regression random coefficients models showed a strong association between albuminuria status and rate of progression in mGFR and CKD-EPI$_{creatinine}$ eGFR. In each case, those with albuminuria had faster progression (steeper decline), consistent with the body of evidence in this area.[70,154]

Higher baseline values of mGFR were associated with a faster rate of progression for mGFR. A similar observation has been made by others.[155] This effect was not seen for CKD-EPI$_{creatinine}$ eGFR. There is some evidence to support the finding of higher baseline GFR being associated with steeper GFR decline, possibly reflecting hyperfiltration in some individuals even in the presence of normal or slightly reduced overall GFR (i.e. hyperfiltration in remaining nephrons).[156] A further confounding influence here could be the nature of the primary renal disease: it is known that different primary renal diseases may progress at different rates. For example, on average, patients with autosomal dominant polycystic kidney disease progress at a significantly higher rate, as to a lesser extent do patients with diabetic nephropathy, than those with other primary causes of kidney disease.[155] Primary cause of kidney disease was not recorded in the present study. In the case of the CKD-EPI$_{cystatin}$ eGFR model, although there was still progression overall, higher baseline values were associated with slower progression of CKD-EPI$_{cystatin}$ eGFR. It is possible that this may have been influenced by the decreased progression slope, and perhaps by the reduction in bias over time compared to the mGFR, that was observed for CKD-EPI$_{cystatin}$ (see below).

There was some evidence of an ethnicity group association with progression for mGFR, CKD-EPI$_{creatinine}$ and ACR. African-Caribbean ethnicity increased the estimate of the progression slope (slower decline) and South Asian ethnicity decreased the estimate of the progression slope (faster decline) for mGFR and CKD-EPI$_{creatinine}$ GFR, respectively. For mGFR, sensitivity analysis excluding one extreme value in the African-Caribbean group reduced this association. Both South Asian and African-Caribbean ethnicity increased the estimates of progression slope (faster progression) for ACR. Overall, there was no evidence to suggest African-Caribbean ethnicity, but some evidence to suggest South Asian ethnicity, was associated with increased decline in GFR, in keeping with some,[56–58] but not all [55] reports. However, as noted above, recruitment of ethnic minority participants in particular to the substudy fell short of target, thereby limiting the strength of any conclusions that can be drawn.

Diabetes status was strongly associated with progression for CKD-EPI$_{creatinine}$ eGFR but not for the other measures, with those with diabetes exhibiting slower GFR decline as estimated by the CKD-EPI$_{creatinine}$ equation. As discussed earlier (see *Ability of glomerular filtration rate-estimating equations to detect change in measured glomerular filtration rate over 3 years*), underestimation of decline in creatinine-based eGFR has been reported previously.[145–148]

There were four drug types (loop diuretic, CCB, A2RB and beta-blocker) that were associated with progression, as measured by at least one of the mGFR, eGFR or ACR. The group sizes for each of these types were reasonable, the smallest subgroup was for loop diuretics with just under one-fifth of evaluable participants prescribed this medication (n = 45, 18.8%). Participants taking CCBs had faster progression based on ACR (steeper incline). There is evidence that the use of CCBs, in particular L-type CCBs (e.g. amlodipine, nifedipine, verapamil, diltiazem), may increase albuminuria due to selective vasodilation of afferent arterioles in the kidney.[157] Faster progression in eGFRs (CKD-EPI$_{creatinine}$ and CKD-EPI$_{cystatin}$) was seen for those prescribed beta-blockers or A2RB. It should be considered that the effect of specific types of medication on progression may be more related to the population prescribed the medication than the effect of the medicine itself, and estimates should be interpreted in this way.

Random coefficient regression models were also fitted to the differences between the eGFRs and mGFRs (bias), without covariates. These models of the bias suggested an incline in slope over time for

CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine-cystatin}$, eGFRs were lower than mGFR and the model suggests that the biases became smaller over time. This was not evident for the other eGFRs.

Findings from the substudy warrant external validation in a large sample to further define the predictive model.

Application of substudy models to the full data set

The full data set is larger and hence contains more covariate information compared to the substudy, although with fewer measurement times, progression is less well-defined. To check consistency of inferences across the data sets the final models from the substudy were fitted to the full data set.

The model estimates from the combined data set were very similar to the estimates from the substudy data, supporting the covariate models, with a few exceptions.

African-Caribbean ethnicity and progression for mGFR were significantly associated, with a slower decline seen in African-Caribbean as observed in the substudy. This association persisted even in a sensitivity analysis excluding an outlying participant.

An association between smoking status and CKD-EPI$_{cystatin}$, but not mGFR or CKD-EPI$_{creatinine}$, was observed. Using the substudy data only current smoking lowered the intercept for CKD-EPI$_{cystatin}$ GFR by 1.5 ml/minute/1.73 m^2; using the full study data set being an ex-smoker lowered the intercept for CKD-EPI$_{cystatin}$ by 0.5 ml/minute/1.73 m^2. This difference may be due to the increased number of ex-smokers in the full data set (n = 367), compared to the number of current smokers (n = 70). As discussed earlier, this is consistent with earlier multivariable analyses demonstrating an association between current cigarette smoking and increased serum cystatin C concentration.[126,127]

Study of intraindividual biological variation

To our knowledge, this is the first study to simultaneously establish the biological variation of mGFR and eGFR in patients with CKD. Data from this aspect of the study have previously been published.[97] We observed the within-subject biological variation of mGFR to be 6.7%, with similar, although in some cases significantly lower, biological variation of eGFR (5.0%, 5.3%, 5.3% and 5.0% for the MDRD, CKD-EPI$_{creatinine}$, CKD-EPI$_{cystatin}$ and CKD-EPI$_{creatinine-cystatin}$ equations, respectively). Taking analytical and within-subject biological variability into account produced RCVs (%, positive/negative) of 21.5/−17.7 (mGFR), 15.1/−13.1 (MDRD), 15.9/−13.7 (CKD-EPI$_{creatinine}$), 15.9/−13.8 (CKD-EPI$_{cystatin}$) and 15.1/−13.1 (CKD-EPI$_{creatinine-cystatin}$).

Although there have been several previous studies of the biological variation of GFR, few have followed the rigour of design required of a biological variation study.[35,36] Nevertheless, several of these earlier studies report biological variability of GFR of a similar magnitude to that observed here, despite a variety of techniques and study designs; 4.5%,[79] 5.7%,[91] 6.3%,[158] 5.5%,[159] with some authors reporting higher estimates – 9.8%[99] and 8.0%.[160] Some of the differences observed may reflect the underlying level of kidney function in the groups studied: both Levey *et al.*[158] and Brochner-Mortensen *et al.*[159] report higher variation estimates in individuals with GFR < 30 ml/minute/1.73 m^2. Other factors including length of time between repeat procedures (10 months) and total study duration (12 years),[99] inattention to hydration status, fasting and exercise before and during the test[160] may also have increased the variability reported in some studies.

When considering any change in a patient's results, healthcare practitioners need to be able to distinguish true change ('signal') from the 'noise' of variability. In clinical practice, biological variation is best considered in terms of the RCV, which takes both biological and analytical variation of mGFR into account: the positive and negative RCVs of mGFR were 21.5% and −17.7%, respectively. These

values describe the change in mGFR in excess of which can be considered true with 95% certainty. For example, if the baseline mGFR in an individual is 59 ml/minute/1.73 m^2, significant increases or decreases would be to values > 72 or < 48 ml/minute/1.73 m^2. Given the lower CV_I and CV_A of eGFR, slightly lower RCVs may be applied when monitoring patients using GFR-estimating equations (e.g. if an individual's baseline MDRD eGFR was 59, significant increases or decreases would be to values > 68 or < 51 ml/minute/1.73 m^2, respectively). However, it must be remembered that our biological variation estimates were obtained under idealised conditions, over a relatively short observation period, with optimisation of preanalytical variables and precise laboratory methods. In an uncontrolled operational clinical environment, it is likely that biological and analytical variation, and hence RCVs, would increase.

The within-subject biological variation of serum creatinine we observed (4.4%) was in broad agreement with values reported in other studies in both healthy (4.1–7.6%)[76–79,81,82,161–163] and diseased (5.7–9.9%)[78,164–166] cohorts. Enzymatic creatinine methods are less prone to interference than Jaffe methods and the use of an enzymatic assay in the present study improves confidence in the estimate of biological variation we have reported. While calculation of CV_I excludes any contribution due to CV_A, it cannot account for biological variability of non-creatinine chromogens (e.g. bilirubin, glucose, ketones, protein and certain drugs) that are known to interfere in Jaffe methods of creatinine measurement. Similarly, our reported within-subject biological variation of cystatin C (4.0%) is similar to most (3.1%,[167] 4.1%,[162] 4.5%[79,81] and 4.8%[164]) but not all (6.8%,[163] 8.6%[78] and 13.3%[77]) previous estimates. As for mGFR, differences in study design and data analysis may account for differences in reported estimates of variation: for example, most of these studies did not report their approach to outlier detection; the time interval between repeat sampling was prolonged in some studies.[163]

Depending on the equation used, eGFR is based on the concentration of creatinine, cystatin C or both. Therefore, eGFR will have a similar CV_I to creatinine or cystatin C, mathematically inflated by the power function in the respective equation. The point estimates for CV_I of the four studied equations lie between 5.0% and 5.3% and have overlapping CIs.

It is uncertain why the CV_I of the eGFR should be lower than that of the mGFR. Probably the complexity of the iohexol clearance procedure, involving multiple measurements and blood samplings, contributes to a higher CV_I for mGFR than eGFR. However, it is also possible that the variability of eGFR is somewhat attenuated compared to physiological fluctuations in mGFR, as noted, in an extreme example, following a renal insult in an AKI episode where there is a delay between the fall in GFR and the consequent rise in blood creatinine concentration.

These data have implications for the use of mGFR versus eGFR in clinical practice and research. Within-subject biological variation of mGFR was similar to that of eGFR, implying that significant change in kidney function should be considered to have taken place, or not taken place, with quantitatively similar temporal differences in estimated or mGFR. However, this should not be interpreted as an indication that eGFR should replace mGFR when an accurate assessment of GFR is required. As noted above (see *Ability of glomerular filtration rate-estimating equations to detect change in measured glomerular filtration rate over 3 years*), eGFR had poor sensitivity for detecting changes in mGFR. Reference techniques are considered more accurate than eGFR primarily because they are not influenced by the non-GFR determinants of endogenous filtration markers. Reference GFR measurements will remain important as the benchmark in clinical research studies and also to inform clinical situations in which more accurate knowledge of GFR is important. These situations include certain chemotherapies (e.g. carboplatin); the use of any drug that is nephrotoxic or renally excreted and has a narrow therapeutic margin; the assessment of potential living-related kidney donors; and the assessment of GFR in patients with muscle-wasting disorders, including spina bifida and paraplegia.

The strengths of this aspect of the overall study include that it followed a strict design to minimise pre-analytical variation and investigator bias.[36] Outliers were excluded using a formal exclusion protocol: sensitivity testing was undertaken using excluded data to confirm that the presented results were

representative. Estimation of components of variation was derived using a nested analysis of variance approach, which takes into account analytical variation for estimation of within-subject biological variation. The studied patient group represents a major population in which monitoring of kidney function to detect worsening disease is regularly undertaken and which is mandated in international guidance.[22,27,59] Prescribed medication was unaltered during the study, with the exception of two patients who received a course of amoxicillin. No patient showed significant trends in GFR during the study period, confirming that the variation we have reported is physiological and not pathological in nature.

Our biological variation study had some limitations.[97] The cohort studied was recruited from a single centre and was exclusively Caucasian: biological variability estimates may not be transferable to other ethnic groups. Although the study was adequately powered to answer the primary question,[168] we were unable to investigate whether variability is higher at differing levels of GFR or albuminuria. Although previous studies have observed statistically significant differences in CV_I when individuals are stratified for level of GFR/albuminuria,[164] such effects are unlikely to be of practical importance.[162] Our mGFR data were based on a plasma iohexol clearance procedure. While constant infusion urinary inulin clearance would be considered the reference measure of GFR, single-bolus plasma clearance of iohexol demonstrates good agreement with this technique and is widely used in clinical practice.[169] In terms of CV_I, plasma clearance techniques are likely to produce lower values than urinary clearance techniques due to problems of inaccurate urine collection. We have chosen to calculate RCVs representing 95% probability, as is conventional. However, if a lower probability was considered clinically acceptable, then the RCV would be smaller.[161]

Ability of glomerular filtration rate-estimating equations, together with albumin-to-creatinine ratio, or albumin-to-creatinine ratio alone, to predict people who have progressive loss of kidney function (chronic kidney disease progression) and to predict mortality

Several previous large studies have shown an association between kidney disease progression and level of GFR and albuminuria.[85,170,171] In the present study, logistic models demonstrated that lower baseline eGFR (using any of the four main study equations) predicted renal disease progression, defined as either a 25% decrease in mGFR or a decrease in mGFR exceeding the RCV and/or an increase in ACR category within the study period. There were no clear differences between the GFR equations and no impact of the ACR category on the ORs. Conversely, in the substudy of disease progression (see *Substudy of disease progression*), higher levels of baseline mGFR were associated with faster decline of mGFR, and albuminuria was fairly consistently associated with renal disease progression. The apparent contradiction between these two findings probably reflects the statistical approaches used. The substudy analyses used changes in actual values, whereas the logistic models studied fixed percentage changes at a point in time. Individuals with higher initial values of GFR have the biggest potential for decline in absolute terms, but this does not necessarily mean a large percentage change. The substudy analysis explored covariates associated with progression for all eligible participants, not only those who meet the criteria for renal progression. The results of the main study and substudy analyses should be interpreted differently as 30% or less of eligible participants met the criteria for renal progression in the main study analysis.

Previous studies have also identified independent associations between decreased levels of GFR,[7,172,173] male gender,[174,175] increasing albuminuria[7,173] and mortality amongst patients with CKD. Studies have observed differences between the MDRD and CKD-EPI equations as predictors of risk (e.g. Matsushita *et al.*)[176]. Several studies have observed a stronger association between cystatin C eGFR and risk of death compared to creatinine-based eGFR.[30,177,178]

In this study of 1159 individuals, we observed 62 deaths during the 3-year follow-up period. The study was not powered for hard end points. In agreement with earlier studies, regression models including each GFR-estimating equation separately and addressing both death within the study and time to death as outcomes, each demonstrated mortality within the study follow-up period was associated with lower eGFR, increasing age and male gender. An association with categorical albuminuria was not observed. As with the models addressing progression, we found no evidence of superiority of CKD-EPI equations as predictors compared to the MDRD equation, or of a strengthened association with cystatin C-containing GFR equations. Results were similar across the models showing a decrease in both odds and hazard for mortality as eGFR increased, with no clear differences between the GFR equations. Point estimates suggested a decrease in the hazard ratio and OR for the cystatin C-containing equations compared to the creatinine-based equations, but the CIs across the models overlapped.

Overall, our data are in agreement with reported associations between eGFR and both mortality risk and renal progression. However, we did not find evidence to support superiority of any equation in these contexts including of those estimating GFR using cystatin C.

Strengths and limitations of the study

We have undertaken a large, prospective, longitudinal study of the clinical performance of contemporary GFR-estimating equations in a UK population of people with moderate CKD, which included participants of South Asian and African-Caribbean ethnicity. The accuracy of GFR-estimating equations was assessed at baseline in 1167 participants, 875 of whom subsequently provided a second reference GFR measure after 3 years. A health economic analysis was included.

All analytical methods used in the study were rigorously quality-assured. The strengths of the study include the use of a reference GFR test including a three-point iohexol clearance procedure, with the final sample being taken at 4 hours post injection. This time interval has generally been considered suitable for patients with GFR > 30 ml/minute/1.73 m^2, with a longer collection period being recommended for individuals with lower GFRs.[179] More recently, it has been suggested that the threshold of 30 ml/minute/1.73 m^2 is too low and that patients with higher levels of GFR should also be tested using an extended clearance period.[180] The potential impact of not using an extended collection period in individuals with low GFR is that GFR will be overestimated. The use of three time points in the present study enabled confirmation of linear decline in iohexol concentration using regression analysis (r > 0.99 in the vast majority of study subjects), with no suggestion that delayed clearance in those with lower GFR was an issue. Furthermore, our data are not suggestive of this being a problem, given the relatively close alignment of eGFR and mGFR. On a pragmatic note, our study protocol was developed with patient involvement: it is our belief that prolonged test duration, beyond 240 minutes, would have adversely affected recruitment into the study. Further research is needed in this area leading to the development of a standardised protocol for GFR measurement using plasma iohexol clearance. More generally, the issue of standardisation of the reference methodology itself in GFR studies, including choice of marker (i.e. inulin, iohexol or iothalamate clearance techniques),[181] whether urinary or plasma clearance is studied, the timing of sample collection, patient preparation, BSA correction method and laboratory analytical approach remains a pertinent issue, with important clinical and research practice implications;[182] it must be remembered that both eGFR and mGFR have error compared to 'true' GFR.

Creatinine and cystatin C were measured in centralised laboratories reducing any between-laboratory variability in our data. Patients were asked to avoid meat intake on the day of the test visit. Meat is known to acutely increase blood creatinine concentration, causing suppression of eGFR.[119] While this increases the accuracy of our data, these idealised sampling conditions may be unreflective of the clinical situation.

An enzymatic creatinine method was used. These are less prone to interference than the widely used Jaffe methods and their specificity facilitates standardisation against ID-MS reference methodology. Additional assurance was provided by direct comparison of our enzymatic creatinine results against an ID-MS method with good agreement. Nevertheless, we observed some bias compared to the ID-MS method, the removal of which would have improved the performance of the estimating equations against mGFR. This represents a true field situation and illustrates that accuracy of creatinine measurement remains an issue contributing to variation in GFR estimation between laboratories.

The critical importance of laboratory method accuracy is often under-appreciated. We also explored the issue of cystatin C calibration on GFR equation performance to an extent not usually considered in such studies. An adjustment was made to address a standardisation issue with the cystatin C assay. Nevertheless, a limitation of our study is that our cystatin C recalibration was based on regression analysis using a subset of our cohort (n = 106). Ideally, we would have tested this analysis in a validation cohort. However, the sample size and measurement range used in this study met globally accepted standards for method comparison studies in laboratory medicine, and the approach to recalibration was tested using two regression approaches with relatively tight CIs.[183] Within the context of a research study, we were able to study and adjust accordingly the calibration of our commercial cystatin C method: it should be appreciated that this is not an adjustment that would be available to most clinical diagnostic laboratories.

By design, our study was limited to CKD stage 3. However, despite the inclusion criteria targeting individuals with stable stage 3 CKD as determined by MDRD eGFR, at baseline 26% of those recruited had mGFR outside 30–59 ml/minute/1.73 m^2. This is to be expected given biological variation and the performance characteristics of GFR-estimating equations in terms of accuracy and precision compared to mGFR. For example, if a GFR-estimating equation has a P30 of 90%, for individuals with mGFR 59 ml/minute/1.73 m^2, then the eGFR will lie within 41 and 77 ml/minute/1.73 m^2 90% of the time; in 10% of cases, it will lie outside of this range. This has allowed for some general observations to be made regarding the performance of the equations outside of stage 3 CKD, but the strength of any conclusions in this respect is limited.

The primary cause of kidney disease was not recorded in our study, potentially limiting the generalisability of our data and the granular detail to which statistical models could be developed. Modelling also suggested a linear pattern of GFR decline, which is not a universal finding.[184–186]

The study aimed to recruit a minimum of 20% of individuals with diabetes and 20% with albuminuria (ACR > 30 mg/mmol) and this was achieved. However, we encountered difficulties with adequate recruitment of people from South Asian and African-Caribbean backgrounds. Although there were no consistent reasons why patients from these ethnic backgrounds declined to take part in the study, the acceptance rate in these populations was lower and in keeping with previous experience. Barriers to participation in research among ethnic minority populations are complex and may include challenges with the language, mistrust of researchers, poor awareness and stigma of research, cultural factors and beliefs about research, unawareness of benefits of research and inaccessibility to research, particularly in deprived populations as well as concerns of costs of time and money.[187,188] Anecdotally, patients said they had caring responsibilities, were unhappy with being included in research and could not take time off from work. It is recognised that specific strategies can be used to increase recruitment from patients from different ethnic backgrounds and future studies should include the use of validated and culturally competent toolkits to ensure these populations are better represented.[189] During the COVID-19 pandemic and the accompanying vaccination trials, much was learnt regarding reasons for non-participation and barriers from ethnic minority groups. Mechanisms which we would take forward in future studies would include the use of ‘research buddies’ and ‘community champions’ in addition to public patient involvement strategies more focused on black and ethnic minority groups, for example the design of study materials.[190,191]

Suggestions for further research

We observed no clear advantage to the use of cystatin C-containing GFR-estimating equations for the monitoring of kidney function in patients with stage 3 CKD. This does not preclude the use and investigation of cystatin C in other settings and for different purposes, including for identification of CKD and prediction of outcomes. Both the MDRD and CKD-EPI$_{creatinine}$ equations demonstrated a negative bias at GFR levels > 50 ml/minute/1.73 m^2, which was not apparent with cystatin C-containing equations. There would be merit in extending this observation by studying the relative specificity of cystatin C and creatinine-eGFR for CKD at such levels of GFR, including in patients with GFR correlating to stage 2 CKD (60–89 ml/minute/1.73 m^2). There are other specific populations in which it is reasonable to suspect cystatin C eGFR may offer advantages over creatinine, in particular due to the relationship of the latter with muscle mass. Such populations would include children and people with unusual muscle mass (e.g. amputees, people with advanced malignancy). A growing concern is how best to estimate GFR in transgender people, where the assignment of sex for this purpose can be complex. Cystatin C equations are less influenced by gender and may offer advantages in this scenario. Further research in this population is warranted.

The use, or not, of adjustment for race when estimating GFR remains an important issue. Our data suggest that simple removal of the African-Caribbean adjustment factor from the MDRD and, to a lesser extent, the original CKD-EPI$_{creatinine}$ equations may reduce accuracy in such populations. Although our African-Caribbean cohort was relatively small, we did observe that the original CKD-EPI$_{creatinine\text{-}cystatin}$ and the 2021 CKD-EPI$_{creatinine\text{-}cystatin}$ equations performed well in African-Caribbean people and equally well across Caucasian and South Asian ethnic groups. Further research is required to confirm this observation, which could lend stronger impetus to the use of cystatin C in routine practice.

Assessment of the accuracy of GFR-estimating equations has for many years been based upon the use of P30 values. This metric has recently been questioned, with NICE suggesting that P5, P10 and P15 values should be used instead.[59] Future research should evaluate the sensitivity of these metrics to bias effects and applicability across a range of GFR. As noted above, some of the achieved P30 value is a product of between- and within-study variation in the GFR reference method itself and there is a need for research and standardisation in this area.

While cystatin C appears to offer little benefit for monitoring GFR in the population we have studied, and only marginal benefit in terms of diagnostic accuracy, there is an increasing literature describing the advantages of cystatin C compared to creatinine in relation to prognosis.[29,30] Prospective, large-scale studies of the value of cystatin C in this respect are warranted, including in combination with other markers (e.g. albuminuria) and as a component of established risk equations (e.g. the kidney failure risk equation).[59,192]

Chapter 6 Conclusions

The estimation of GFR using prediction equations is important in clinical practice for both the detection and diagnosis of CKD, and for monitoring individual patients over time. Especially in relation to detection and diagnosis, accuracy compared to a reference measured GFR test is important. Our conclusions are confined to the study of patients with predominantly stage 3 CKD. In this cohort, all of the main study equations achieved acceptable accuracy as judged by P30. There was little difference between the equations in accuracy, but the CKD-EPI$_{\text{creatinine-cystatin}}$ equation had a slightly higher P30 and there was some evidence that bias across the GFR range was more consistent when cystatin C was included in the equation. Since the inception of the study, many newer GFR-estimating equations have been described. Many of these newer equations have been developed in European populations and in theory could be more applicable to a UK population, compared to the MDRD and CKD-EPI equations, which were predominantly developed in North American populations. However, while most of the newer equations demonstrated acceptable accuracy, none were superior to the CKD-EPI$_{\text{creatinine-cystatin}}$ equation.

Across several important characteristics (age, gender, BMI, levels of mGFR and albuminuria) we found little difference in accuracy of GFR-estimating equations. Due to difficulties in recruitment, we were not able to fully address the accuracy of the equations in British South Asian and African-Caribbean populations. However, we found some evidence to suggest a cautious approach should be taken before advocating simple removal of the black race factor from the original CKD-EPI equations or introducing the more recently reported CKD-EPI(2021) equations.

In the longitudinal study, we observed that CKD-EPI$_{\text{creatinine-cystatin}}$ displayed slightly better concordance with mGFR than the other main study equations when tracking patients, but all study equations underestimated the mGFR decline. The sensitivity of GFR equations to detect several clinically relevant threshold changes in mGFR, either overall or when considering decline in GFR only, was < 63% for all equations. This is of concern given that such thresholds, including the NICE definition of accelerated progression and the change recognised as being true as determined by biological variation data, were studied. It must be borne in mind that some of the observed changes in mGFR could represent FP signals, given the higher within-person variability of mGFR compared to eGFR (see below).

Overall, our data comparing the accuracy of different GFR-estimating equations demonstrated no notable benefit of using a cystatin or creatinine–cystatin-based estimating GFR equation in predicting CKD progression over time. The measurement model underpinning the health economic analysis focused on the comparative accuracy of the estimating equations to detect accelerated progression according to NICE's definition or of progression to CKD G4. The analysis estimated accuracy over a longer trajectory than the main study and factored in measurement error, but also found no clear benefit of using a cystatin C-based estimating equation. There was therefore no evidence to suggest that adding a cystatin C measurement to current GFR monitoring protocols would be cost-effective.

The evidence presented in the health economics chapter highlighted the current challenge in justifying and quantifying the health impact of monitoring eGFR in those with CKD G3. It is unclear what interventional decisions would be made as a result of monitoring eGFR at this earlier stage, as the cardiovascular and renal progression therapies which currently have an evidence base for use are not changed in patients with CKD G3 based on change in GFR, but on monitoring of BP and/or ACR.

The disease progression modelling of the substudy data suggested a linear decline over time for mGFR and eGFR. There were associations between GFR or ACR and all of the covariates selected for modelling in this study, with the exception of vascular disease. The final models included those covariates where there was evidence of association, following adjustment for other covariates in the model. In particular, there was a strong association between albuminuria and mGFR and CKD-EPI$_{\text{creatinine}}$ eGFR, with faster progression associated with albuminuria. There were also associations between four drug types (loop

diuretic, CCB, A2RB and beta-blocker) and progression, in each case progression was faster for those taking medication, which is most likely a reflection of the characteristics of the population prescribed these medications. Fitting the final models to the full study data set confirmed the inferences found in the substudy data, with only a few exceptions; of note is the change of the association with smoking status on the intercept for CKD-EPI$_{cystatin}$ and ACR; data from the full study suggested an association with ex-smokers which was not evident in the substudy analysis.

We described the biological variability of mGFR and eGFR in a carefully designed study.[97] The data generated have implications for monitoring of patients with CKD and clinical ability to understand CKD progression, both in clinical practice and in clinical trials, whether using mGFR or eGFR. Within-subject biological variation of mGFR is similar to that of eGFR and, in terms of variability, suggests no real advantage to the use of mGFR when monitoring patients over time. There were no clear differences in biological variability when measured by the different GFR-estimating equations. Most importantly, the information presented provides an evidence base allowing clinicians to have meaningful discussions with their patients about the implications of changes in their GFR results.

We have found evidence that inclusion of cystatin C in GFR-estimating equations leads to marginal improvements in accuracy and more consistent bias across the range of GFR values studied. However, there were no clear advantages to the inclusion of cystatin C in terms of monitoring patients over time. Problems of standardisation of cystatin C assays remain, despite the introduction of an international standard. Cystatin C may find niche applications of benefit, for example when managing children with CKD and in adults with unusual creatinine–GFR relationships (e.g. amputees). The independence of cystatin C from racial and dietary influences offers further advantages. Cystatin C may offer advantages over creatinine in the prediction of risk and outcomes in patients with CKD.[30] However, given that the use of cystatin C increases the economic cost of CKD management with little apparent gain, our data do not support the use of cystatin C for the monitoring of GFR in people with stage 3 CKD.

Additional information

Contributions of authors

Edmund J Lamb (https://orcid.org/0000-0002-5154-7351) (Consultant Clinical Scientist in Clinical Biochemistry) was the chief investigator for the study and was involved in all aspects of the research from original proposal to submission of final report.

Jonathan Barratt (https://orcid.org/0000-0002-9063-7229) (Professor of Renal Medicine) was principal investigator for recruitment in Leicester, provided critical review of the results throughout the study and reviewing and editing the study report.

Elizabeth A Brettell (https://orcid.org/0000-0002-0669-3085) (Trial Management Team Leader) was the Clinical Trials Unit co-investigator involved in planning and developing the study and responsible for oversight of study management.

Paul Cockwell (https://orcid.org/0000-0003-1975-266X) (Consultant Nephrologist and Honorary Professor of Nephrology) was involved in development of the study protocol, principal investigator for recruitment in Birmingham, critical review of the results throughout the study and reviewing and editing the study report.

R Neil Dalton (https://orcid.org/0000-0001-9201-5266) (Professor and Consultant Clinical Scientist in Paediatrics) was a co-principal investigator involved in all aspects of the research, from original proposal to submission of final report, with primary responsibility for the iohexol measurements.

Jon J Deeks (https://orcid.org/0000-0002-8850-1971) (Professor of Biostatistics) was the senior statistician and was involved in developing the study proposal, planning the analysis, overseeing the analysis, and contributed to the final report.

Gillian Eaglestone (https://orcid.org/0000-0001-9860-8679) (Senior Research Nurse in Renal Medicine) was the lead research nurse for the study and was involved in protocol development, patient recruitment and data collection.

Tracy Pellatt-Higgins (https://orcid.org/0000-0002-2543-461X) was one of the study statisticians and was involved in planning and developing the methodology for the substudy of disease progression, analysing the substudy data, and writing and reviewing the final report.

Philip A Kalra (https://orcid.org/0000-0001-7652-1572) (Professor of Nephrology) was involved in development of the study protocol, principal investigator for recruitment in Salford, critical review of the results throughout the study and reviewing and editing the study report.

Kamlesh Khunti (https://orcid.org/0000-0003-2343-7099) (Professor of Primary Care Diabetes and Vascular Medicine) was co-principal investigator in Leicester and provided input in recruitment of diverse populations and reviewing the final report.

Fiona C Loud (https://orcid.org/0000-0001-7706-5396) (Director of Kidney Alliance at the start of this study, subsequently Policy Director of the British Kidney Patient Association, now known as Kidney Care UK) provided lay input, recommendations on patient involvement and patient representation on participation sheets and study news.

Ryan S Ottridge (https://orcid.org/0000-0002-8685-2145) (Trial Management Team Leader) was the trial manager responsible for data quality, and day-to-day management and administrative support of the study.

Aisling Potter (https://orcid.org/0000-0003-4366-1039) (Research Scientist) undertook laboratory analyses, data entry and analysis for the study and contributed to writing and reviewing the final report.

Ceri Rowe (https://orcid.org/0000-0002-6150-1816) (Clinical Scientist) undertook laboratory analyses, statistical analysis and report writing for the biological variation substudy of the project and contributed to writing and reviewing the final report.

Katie Scandrett (https://orcid.org/0000-0001-6111-2805) (Research Associate in Biostatistics) was responsible for analysing data from the main study and contributed to writing and reviewing the final report.

Alice J Sitch (https://orcid.org/0000-0001-7727-4497) (Associate Professor of Biostatistics) was the study statistician (main and biological variability study) and was involved in planning and developing the study, analysing the data, observing further analysis of the data, writing and reviewing the final report.

Paul E Stevens (https://orcid.org/0000-0001-7606-0649) (Consultant Nephrologist) was involved in the original proposal and development of the study protocol. He was principal investigator for recruitment in Canterbury, critically reviewed results throughout the study and reviewed and edited the final report.

Claire C Sharpe (https://orcid.org/0000-0003-1704-8492) (Professor in Renal Medicine) was a co-principal investigator and contributed to the original proposal, patient recruitment, discussion of data analysis and reviewing and editing the final report.

Bethany Shinkins (https://orcid.org/0000-0001-5350-1018) (Associate Professor of Health Economics) took over as lead health economist from Andrew Sutton (Andrew left his post) part-way through the project. She was involved in planning and developing the health economic statistical and economic analysis, supervising the economic evaluation systematic review update, and writing and reviewing the final report.

Alison Smith (https://orcid.org/0000-0001-7709-1869) (Lecturer in Health Economics) undertook the economic evaluation systematic review update and the health economic statistical analysis, was involved in the economic analysis, and writing and reviewing the final report.

Andrew J Sutton (https://orcid.org/0000-0001-7008-4770) (Health Economist) was the Lead health economist in the early stages of the study. He wrote the health economics section of the original research proposal, and protocol, and was responsible for planning and conducting the initial economic evaluation systematic review. He has reviewed the final report.

Maarten W Taal (https://orcid.org/0000-0002-9065-212X) (Professor of Medicine and Honorary Consultant Nephrologist) was a co-principal investigator and contributed to the grant application, protocol design, participant recruitment and discussion of data interpretation as well as review of the final report.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it is important that there are safeguards to make sure that they are stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration by the CI and the co-sponsors. Access to anonymised data may be granted following review, no earlier than 6 months after this publication.

Ethics statement

Approval for this research study was obtained from the National Research Ethics Service (NRES Committee South East Coast – Surrey, reference 13/LO/1349, approved 9 October 2013).

Information governance statement

University of Birmingham is committed to handling all personal information in line with the UK Data Protection Act (2018) and the General Data Protection Regulation (EU GDPR) 2016/679. Under the Data Protection legislation, University of Birmingham is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer here: https://www.birmingham.ac.uk/privacy.

Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/HYHN1078.

Primary conflicts of interest: Paul Cockwell is President of the UK Kidney Association. R Neil Dalton is Director of SpOtOn Clinical Diagnostics Ltd. Claire Sharpe and Philip Kalra have received honoraria from pharmaceutical companies for consultancy work and lectures within the field of chronic kidney disease (CKD) but are not directly related to the present study. Philip Kalra reports grants, consulting fees, and honoraria from various organisations; and travel support from Pharmacosmos and Vifor. Kamlesh Khunti has received honoraria and grants from pharmaceutical companies within the field of CKD and diabetes but not directly related to the present study. He is also member of the Kidney Disease Improving Global Outcomes (KDIGO) CKD in Diabetes Guideline Group, the COVID-19 Reviewing Committee and the HS&DR Funding Committee. Edmund Lamb reports travel support from KDIGO CKD, and NICE CKD. Fiona Loud reports grants from AstraZeneca, Pfizer, and Novartis; speaking fees from various institutions; and travel support from Astellas. Ceri Rowe reports travel support from Association for Clinical Biochemistry and Laboratory Medicine. Claire Sharpe reports grants, consulting fees, and honoraria from various organisations. Paul Stevens reports grant from NIHR (HTA 16/31/127). All other authors declare they have no competing interests. All authors have completed the unified competing interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare (1) no financial support for the submitted work from anyone other than their employer; (2) no financial relationships with commercial entities that might have an interest in the submitted work; (3) no spouses, partners, or children with relationships to commercial entities that might have an interest in the submitted work; and (4) no non-financial interests that may be relevant to the submitted work.

Publications

Lamb EJ, Brettell EA, Cockwell P, Dalton RN, Deeks JJ, Harris K, *et al*. The eGFR-C Study. Accuracy of glomerular filtration rate (GFR) estimation using creatinine and cystatin C and albuminuria for monitoring disease progression in patients with stage 3 chronic kidney disease: a prospective longitudinal study in a multiethnic population. *BMC Nephrol* 2014;**15**:13. http://doi.org/10.1186/1471-2369-15-13

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Appendix 1 Supplementary information for *Chapters 2* and *3*

TABLE 36 Study milestones

Date	Milestone
13 June 2013	eGFR-C trial launch meeting, Birmingham
1 August 2013	Grant start date
9 October 2013	REC approval
15 October 2013	NSA 1 – Addition of ISRCTN number to protocol
2 December 2013	Study steering committee meets
28 February 2014	R&D approval
8 April 2014	First participant
13 May 2014	Study steering committee meets
1 June 2014	Substantial amendment 1 – adding consent for long-term follow-up via NHS Digital
17 October 2014	REC annual progress report submitted
19 November 2014	Study steering committee meets
26 November 2014	Investigator meeting (face to face), Birmingham
29 January 2015	Trial monitoring review meeting, HTA, London
2 February 2015	Substantial amendment 2 – adding summary information sheet
20 February 2015	NSA 2 – correcting version error in substantial amendment 2
30 March 2015	NSA 3 – adding primary care PIC site recruitment at King's College Hospital, London
14 May 2015	Study steering committee meets
15 May 2015	Substantial amendment 3 – adding participant newsletters
6 July 2015	Variation to contract 1 agreed by funder – 12 months funded extension
8 July 2015	NSA 4 – adding primary care PIC site recruitment for all sites; notifying of 12-month extension to trial
11 September 2015	REC annual progress report submitted
5 November 2015	Study steering committee meets
24 November 2015	Investigator meeting (face to face), Birmingham
1 December 2015	Substantial amendment 4 – updating participant information sheet
16 December 2015	NSA 5 – minor update to consent form
7 January 2016	NSA 6 – seeking REC approval to send trial newsletters to potential participants
20 January 2016	NSA 7 – changes to substudy recruitment targets
13 April 2016	Substantial amendment 5 – changes to PIC site recruitment process
11 May 2016	Study steering committee meets
13 May 2016	NSA 8 – adding Derby CCGs to PIC sites for region; adding HTA logo to documents

continued

TABLE 36 Study milestones (*continued*)

Date	Milestone
21 September 2016	Variation to contract 2 agreed by funder – 5 months funded extension
5 October 2016	Substantial amendment 6 – adding IRAS number to documents; notifying of 5 month extension to trial
11 October 2016	REC annual progress report submitted
15 November 2016	Study steering committee meets
25 January 2017	Last participant recruited
14 February 2017	Substantial amendment 7 – updates to SAE process
12 July 2017	Study steering committee meets
10 October 2017	REC annual progress report submitted
29 November 2017	Study steering committee meets
25 July 2018	Study steering committee meets
10 October 2018	REC annual progress report submitted
14 November 2018	Study steering committee meets
8 January 2019	NSA 9 – addition of GDPR information leaflet
15 May 2019	Substantial amendment 8 – adding final appointment reminder letter
10 July 2019	Study steering committee meets
8 October 2019	REC annual progress report submitted
9 January 2020	Follow up completed
27 February 2020	Study steering committee meets
9 June 2020	Analysis of samples complete at Kent laboratory
18 July 2020	Analysis of samples complete at London laboratory
21 September 2020	Variation to contract 3 agreed by funder – 12 months unfunded extension
10 October 2020	NSA 10 – change to trial/grant end date
6 November 2020	REC annual progress report submitted
30 April 2021	Trial database closed to data entry
2 June 2021	End of trial notified to REC

CCGs, Clinical Commissioning Groups; GDPR, General Data Protection Regulation; IRAS, Integrated Research Application System; ISRCTN, International Standard Randomised Control Trial Number; NSA, non-substantial amendment; PIC, Participant identification centres; R&D, research and development; REC, Research Ethics Committee.

TABLE 37 Cumulative and actual recruitment per month throughout the study recruitment phase

Month	Month	Cumulative number of participants recruited	Monthly number of participants recruited
1	February 2014	0	0
2	March 2014	0	0
3	April 2014	1	1
4	May 2014	10	9
5	June 2014	26	16
6	July 2014	51	25
7	August 2014	83	32
8	September 2014	124	41
9	October 2014	173	49
10	November 2014	231	58
11	December 2014	263	32
12	January 2015	325	62
13	February 2015	378	53
14	March 2015	440	62
15	April 2015	509	69
16	May 2015	555	46
17	June 2015	598	43
18	July 2015	639	41
19	August 2015	677	38
20	September 2015	716	39
21	October 2015	763	47
22	November 2015	799	36
23	December 2015	826	27
24	January 2016	863	37
25	February 2016	903	40
26	March 2016	946	43
27	April 2016	986	40
28	May 2016	1019	33
29	June 2016	1061	42
30	July 2016	1097	36
31	August 2016	1126	29
32	September 2016	1144	18
33	October 2016	1173	29
34	November 2016	1210	37
35	December 2016	1236	26
36	January 2017	1249	13

TABLE 38 Recruitment and dropout rates by recruiting sites

	Total participants recruited	Total dropouts	% dropouts
Derby	218	43	19.7
East Kent	278	32	11.5
King's	157	36	22.9
Salford	231	68	29.4
Birmingham	165	25	15.2
Leicester	180	49	27.2
Total	**1229**	**253**	**20.6**

TABLE 39 Linear and Deming regression analysis of the relationship between the Abbott and Siemens cystatin C assays

	Linear regression			Deming regression		
	Estimate	95% CI	*p*	Estimate	95% CI	*p*
Abbot cystatin C	0.94	0.92 to 0.96	< 0.001	0.95	0.92 to 0.97	< 0.001
Constant	−0.08	−0.12 to −0.03	< 0.001	−0.09	−0.13 to −0.06	< 0.001

TABLE 40 Comparison of baseline characteristics for the three CKD-EPI equations between those identified as having a change within 3 ml/minute/1.73 m^2 of mGFR and those in whom the eGFR was > 3 ml/minute/1.73 m^2 different from the change in mGFR

$CKD\text{-}EPI_{creatinine}$	Change within 3 ml/minute/1.73 m^2 of mGFR	Change ≥ 3 ml/minute/1.73 m^2 of mGFR
n	640/875	235/875
Age, years	67 (59–74)	66 (58–73)
M : F, *n*	371 : 269	134 : 101
Ethnicity		
Caucasian, *n* (%)	568 (88.8)	205 (87.2)
African-Caribbean, *n* (%)	21 (3.3)	15 (6.4)
South Asian, *n* (%)	33 (5.2)	13 (5.5)
Other (missing), *n* (%)[a]	18 (2.8)	2 (0.9)
Height, cm	170 (163–177)	169 (161–176)
Weight, kg	84.6 (72.8–97.1)	84.7 (73.9–97.4)
BMI, kg/m^2	28.8 (25.7–33.1)	30.0 (25.9–34.1)
Smoking status		
Non-smoker, *n* (%)	343 (53.6)	110 (46.8)
Current smoker, *n* (%)	42 (6.6)	21 (8.9)
Former smoker, *n* (%)	253 (39.5)	104 (44.3)
Unknown, *n* (%)	2 (0.3)	0 (0)

TABLE 40 Comparison of baseline characteristics for the three CKD-EPI equations between those identified as having a change within 3 ml/minute/1.73 m² of mGFR and those in whom the eGFR was > 3 ml/minute/1.73 m² different from the change in mGFR (*continued*)

CKD-EPI$_{creatinine}$	**Change within 3 ml/minute/1.73 m² of mGFR**	**Change ≥ 3 ml/minute/1.73 m² of mGFR**
Diabetes (yes), *n* (%)	152 (23.8)	68 (28.9)
Urine albumin concentration	4.7 (1.4–26.3)	4.0 (1.5–27.0)
< 3 mg/mmol, *n* (%)	254 (39.7)	99 (42.1)
3–30 mg/mmol, *n* (%)	219 (34.2)	73 (31.1)
> 30 mg/mmol, *n* (%)	145 (22.7)	55 (23.4)
Missing, *n* (%)	22 (3.4)	8 (3.4)
Serum creatinine, µmol/l	133.7 (112.2–162)	129.8 (102.5–157.6)
Serum cystatin C, mg/l	1.7 (1.5–2.0)	1.7 (1.4–2.1)
Measured GFR, ml/minute/1.73 m²	45.9 (36.4–54.7)	50.2 (43.4–58.6)
CKD-EPI$_{cystatin}$	**Change within 3 ml/minute/1.73 m² of mGFR**	**Change ≥ 3 ml/minute/1.73 m² of mGFR**
n	652/875	223/875
Age, years	67 (59–74)	67 (56–73)
M : F, *n*	371 : 269	134 : 101
Ethnicity		
Caucasian, *n* (%)	568 (88.8)	205 (87.2)
African-Caribbean, *n* (%)	21 (3.3)	15 (6.4)
South Asian, *n* (%)	33 (5.2)	13 (5.5)
Other (missing), *n* (%)[a]	18 (2.8)	2 (0.9)
Height, cm	171 (163–177)	168 (161–174)
Weight, kg	85.6 (73.9–98.2)	81.3 (70.9–95.0)
BMI, kg/m²	29.1 (25.8–33.5)	28.6 (25.5–33.0)
Smoking status		
Non-smoker, *n* (%)	343 (53.6)	110 (46.8)
Current smoker, *n* (%)	42 (6.6)	21 (8.9)
Former smoker, *n* (%)	253 (39.5)	104 (44.3)
Unknown, *n* (%)	2 (0.3)	0 (0)
Diabetes (yes), *n* (%)	152 (23.8)	68 (28.9)
Urine albumin concentration	5.5 (1.5–31.6)	3.1 (1.4–17.4)
< 3 mg/mmol, *n* (%)	99 (42.1)	254 (39.7)
3–30 mg/mmol, *n* (%)	73 (31.1)	219 (34.2)
> 30 mg/mmol, *n* (%)	55 (23.4)	145 (22.7)
Missing, *n* (%)	8 (3.4)	22 (3.4)

continued

TABLE 40 Comparison of baseline characteristics for the three CKD-EPI equations between those identified as having a change within 3 ml/minute/1.73 m^2 of mGFR and those in whom the eGFR was > 3 ml/minute/1.73 m^2 different from the change in mGFR (*continued*)

CKD-EPI$_{cystatin}$	**Change within 3 ml/minute/1.73 m^2 of mGFR**	**Change ≥ 3 ml/minute/1.73 m^2 of mGFR**
Serum creatinine, µmol/l	135.1 (114.0–164.3)	120.0 (99.0–144.0)
Serum cystatin C, mg/l	1.8 (1.5–2.1)	1.5 (1.3–1.9)
Measured GFR, ml/minute/1.73 m^2	46.5 (37.3–54.5)	51.1 (40.4–59.5)
CKD-EPI$_{creatinine-cystatin}$	**Change within 3 ml/minute/1.73 m^2 of mGFR**	**Change ≥ 3 ml/minute/1.73 m^2 of mGFR**
n	689/875	186/875
Age, years	67 (58–74)	67 (58–74)
M : F, *n*	407 : 282	98 : 88
Ethnicity		
Caucasian, *n* (%)	611 (88.7)	162 (87.1)
African-Caribbean, *n* (%)	25 (3.6)	11 (5.9)
South Asian, *n* (%)	37 (5.4)	9 (4.8)
Other (missing), *n* (%)[a]	16 (2.3)	4 (2.2)
Height, cm	170 (163–177)	168 (161–176)
Weight, kg	85.0 (73.3–97.8)	82.7 (70.8–96.5)
BMI, kg/m^2	29.0 (25.7–33.5)	29.0 (25.6–33.1)
Smoking status		
Non-smoker, *n* (%)	362 (52.5)	91 (48.9)
Current smoker, *n* (%)	47 (6.8)	16 (8.6)
Former smoker, *n* (%)	278 (40.4)	79 (42.5)
Unknown, *n* (%)	2 (0.3)	0 (0)
Diabetes (yes), *n* (%)	170 (24.7)	50 (26.9)
Urine albumin concentration	5.4 (1.5–30.2)	3.1 (1.2–15.0)
< 3 mg/mmol, *n* (%)	264 (38.3)	89 (47.9)
3–30 mg/mmol, *n* (%)	232 (33.7)	60 (32.3)
> 30 mg/mmol, *n* (%)	167 (24.2)	33 (17.7)
Missing, *n* (%)	26 (3.8)	4 (2.2)
Serum creatinine, µmol/l	135.0 (113.0–163.0)	119.8 (98.3–145.2)
Serum cystatin C, mg/l	1.8 (1.5–2.1)	1.6 (1.3–2.0)
Measured GFR, ml/minute/1.73 m^2	46.5 (37.0–54.9)	50.8 (40.6–59.5)

a Other includes participants with ethnic backgrounds other than Caucasian, South Asian or African-Caribbean, or in whom this information was not recorded

Note
Continuous variables shown as median (IQR).

TABLE 41 Influence of BSA adjustment method on bias and precision of GFR-estimating equations: Haycock equation compared to the Du Bois equation

Equation		Du Bois BSA adjustment	Haycock BSA adjustment
MDRD	Mean bias (SD)	−3.8 (9.2)	−2.4 (9.0)
	Median bias (IQR)	−3.7 (−9.7 to 2.4)	−2.3 (−8.4 to 3.5)
	RMSE	9.09	8.90
CKD-EPI$_{creatinine}$	Mean bias (SD)	−2.5 (9.1)	−1.1 (8.9)
	Median bias (IQR)	−2.8 (−8.2 to 3.5)	−1.2 (−6.9 to 4.8)
	RMSE	8.83	8.66
CKD-EPI$_{cystatin}$	Mean bias (SD)	−3.4 (9.1)	−2.0 (8.9)
	Median bias (IQR)	−4.1 (−9.3 to 1.5)	−2.8 (−7.7 to 2.7)
	RMSE	7.58	7.25
CKD-EPI$_{creatinine-cystatin}$	Mean bias (SD)	−3.7 (7.3)	−2.3 (7.1)
	Median bias (IQR)	−3.9 (−8.4 to 1.1)	−2.6 (−6.9 to 2.3)
	RMSE	7.07	6.82

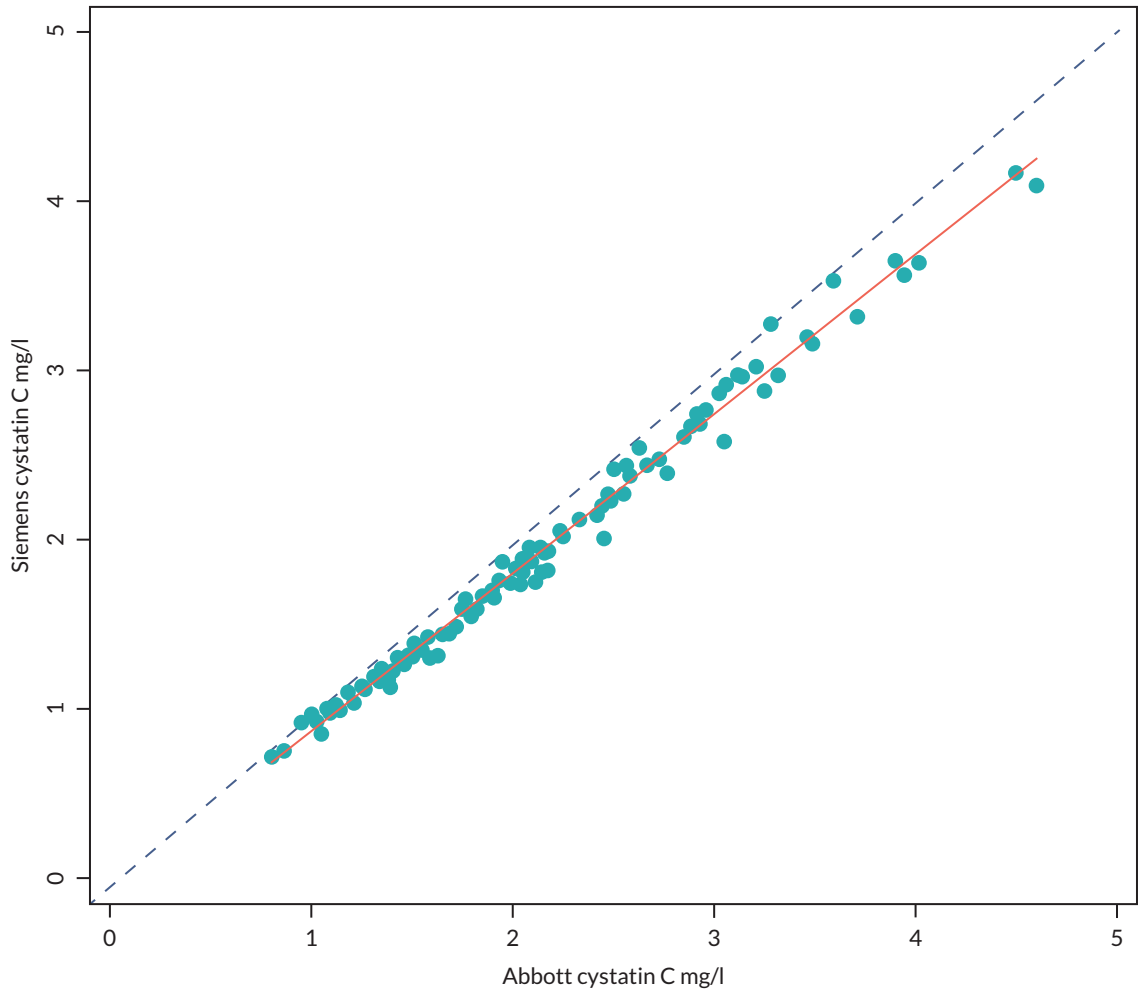


FIGURE 14 Scatter plot comparing Abbott and Siemens cystatin C measurements. The solid line shows the linear regression line of best fit and the dotted line shows the line of identity.

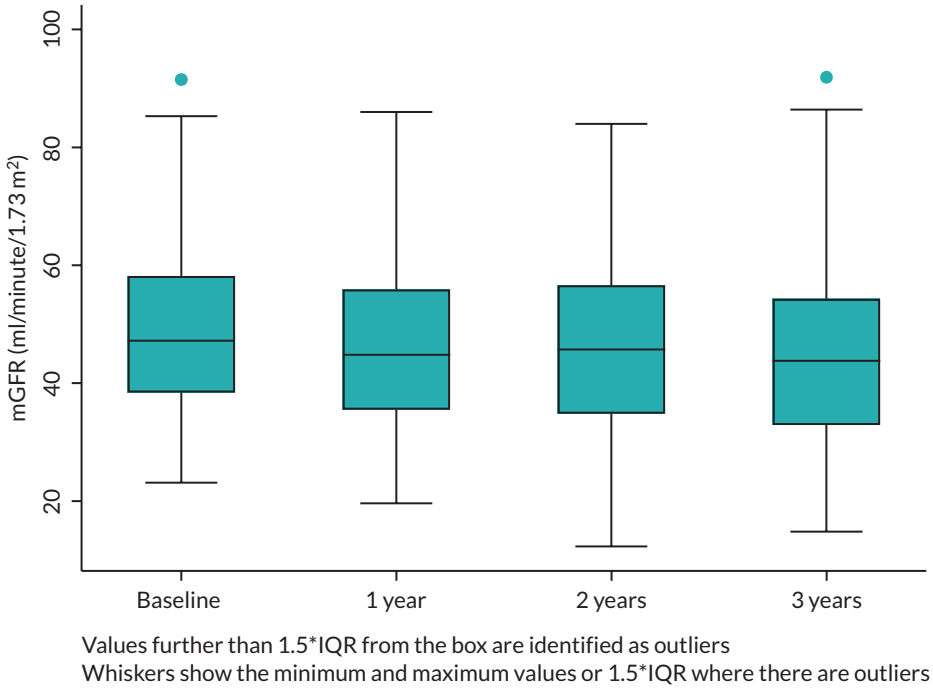


FIGURE 15 Box and whisker plot of mGFR over time in the substudy of disease progression.

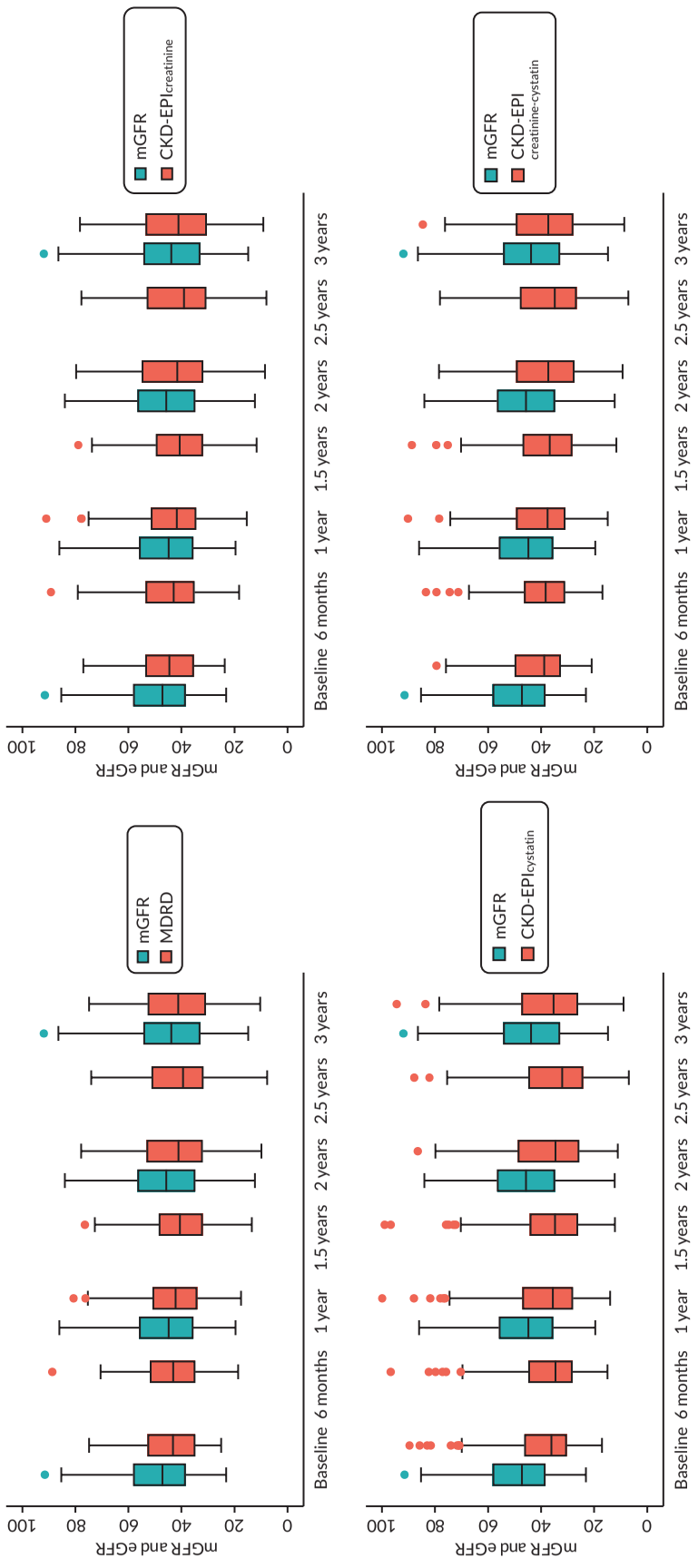
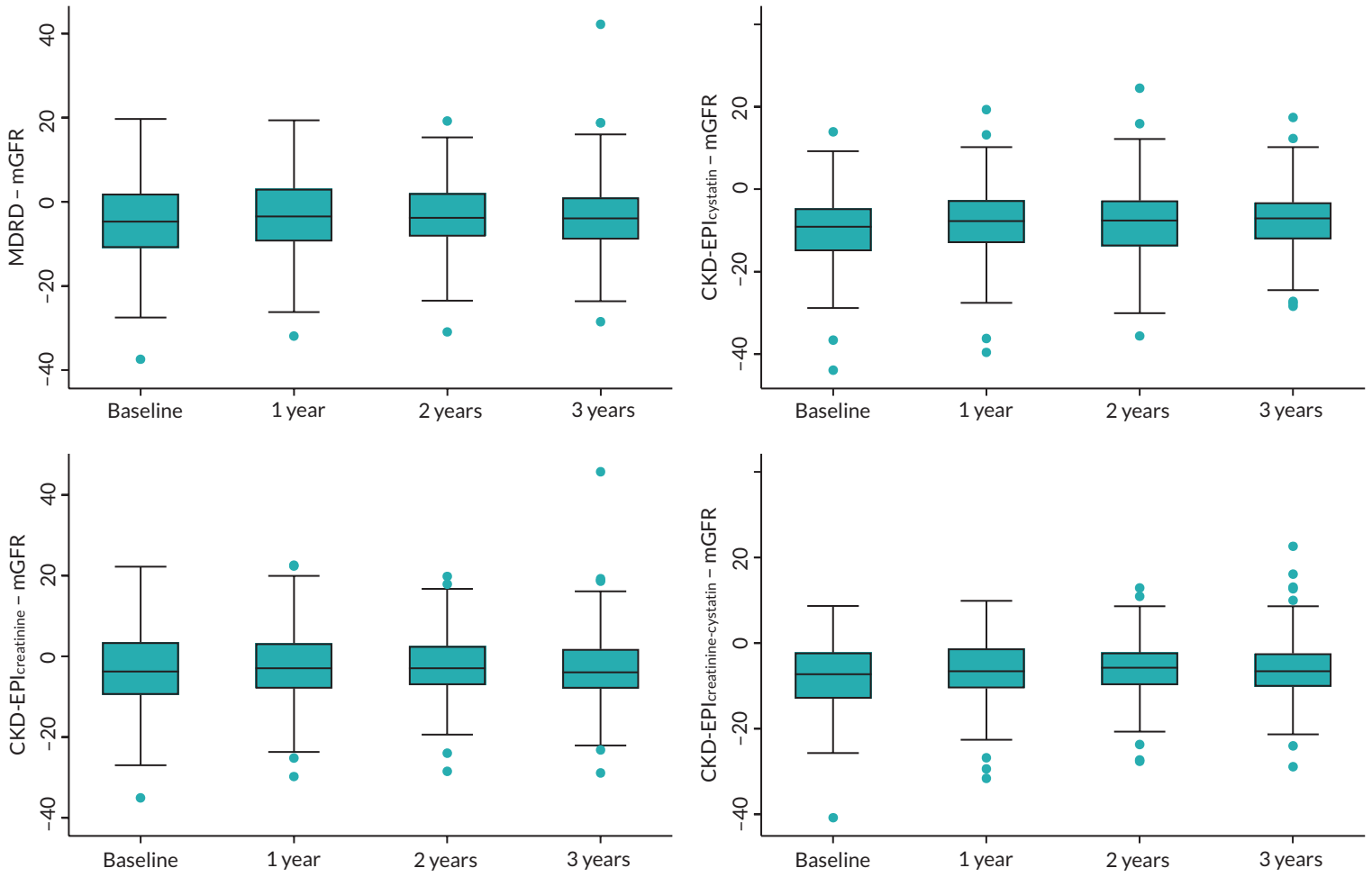


FIGURE 16 Box and whisker plots of mGFRs and eGFRs over time in the substudy of disease progression.



Values further than 1.5*IQR from the box are identified as outliers
Whiskers show the minimum and maximum values or 1.5*IQR where there are outliers
Units for measured and estimated GFR are ml/minute/1.73 m^2

FIGURE 17 Box and whisker plots of difference (bias) between mGFRs and eGFRs in the substudy of disease progression.

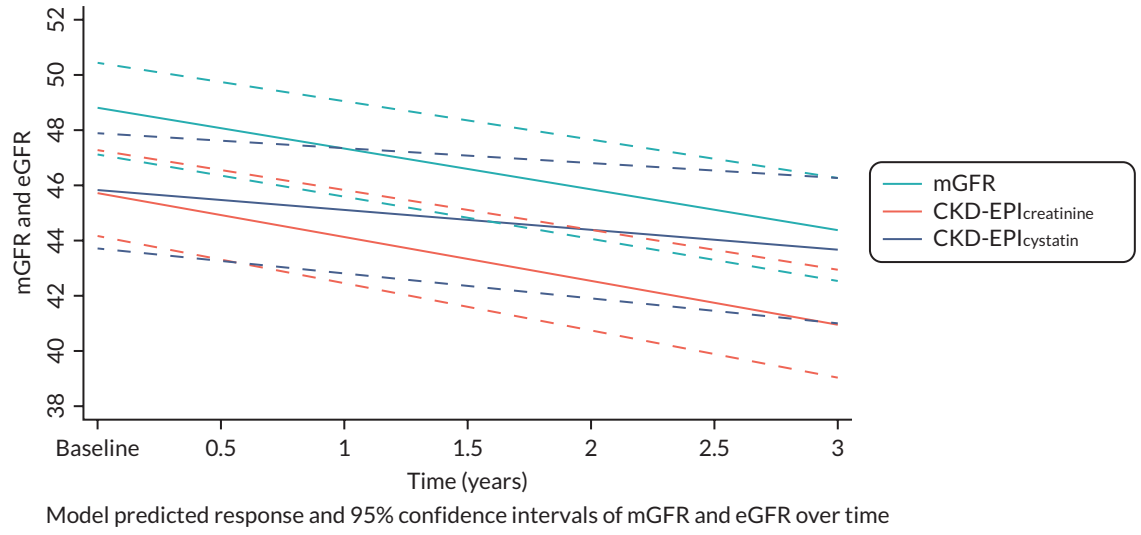


FIGURE 18 Model predicted slopes for mGFR and CKD-EPI$_{creatinine}$ and CKD-EPI$_{cystatin}$ eGFR.

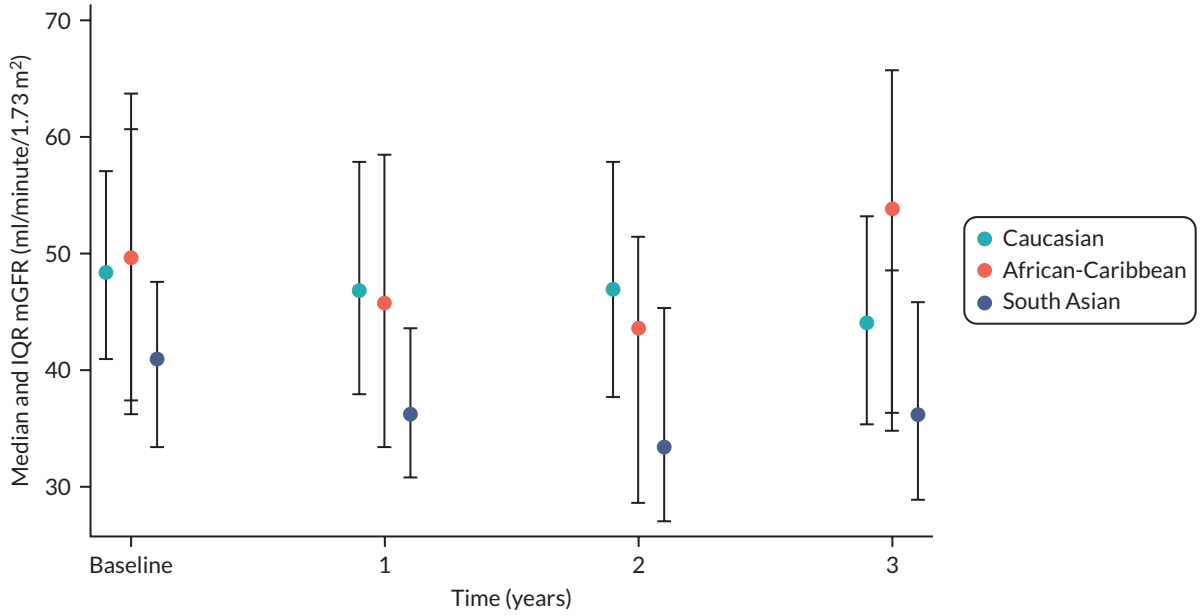


FIGURE 19 Median and IQR mGFR over time by ethnicity group (main study and substudy data combined).

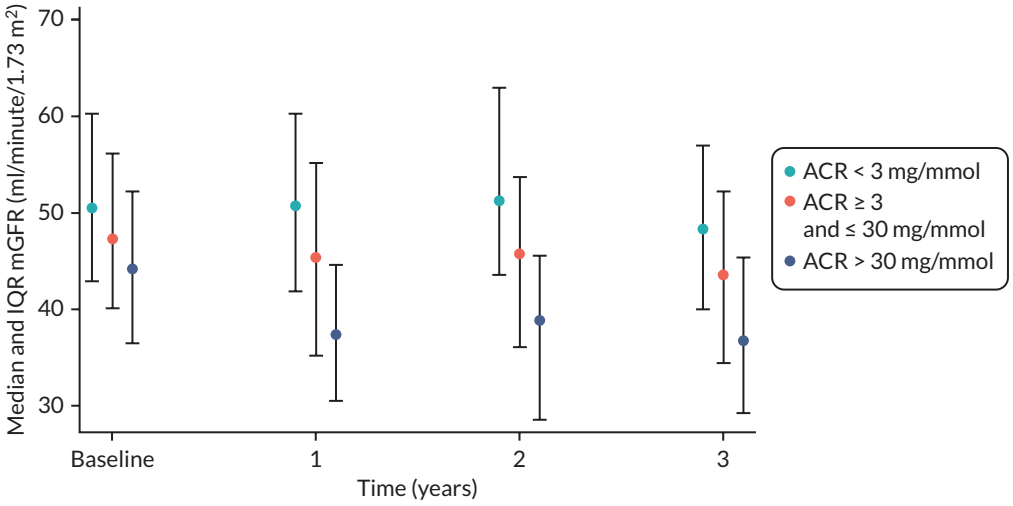


FIGURE 20 Median and IQR mGFR over time by albuminuria status (main study and substudy data combined).

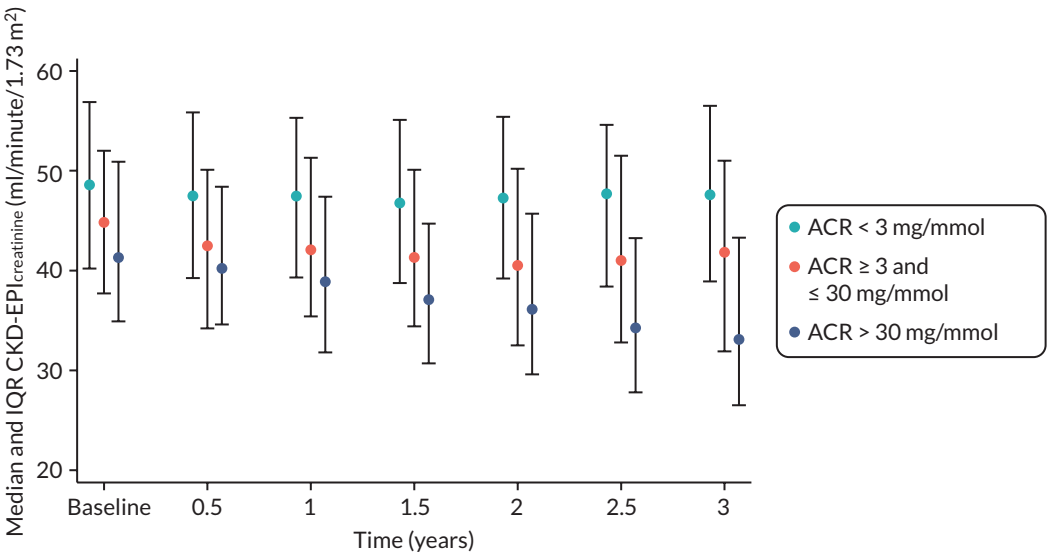


FIGURE 21 Median and IQR CKD-EPI$_{creatinine}$ over time by albuminuria status (main study and substudy data combined). The steeper decline over time is more obvious for those with albuminuria, compared to those who do not have albuminuria, particularly those with ACR > 30 mg/mmol.

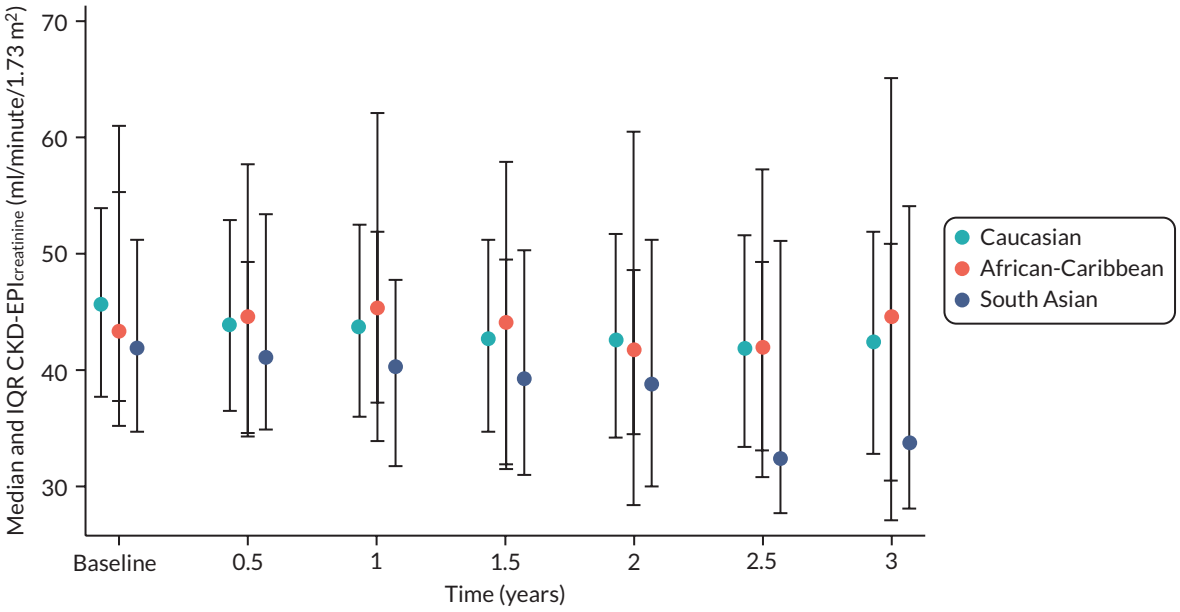


FIGURE 22 Median and IQR CKD-EPI$_{creatinine}$ over time by ethnicity group (main study and substudy data combined). The data suggest a steeper decline for South Asian ethnicity.

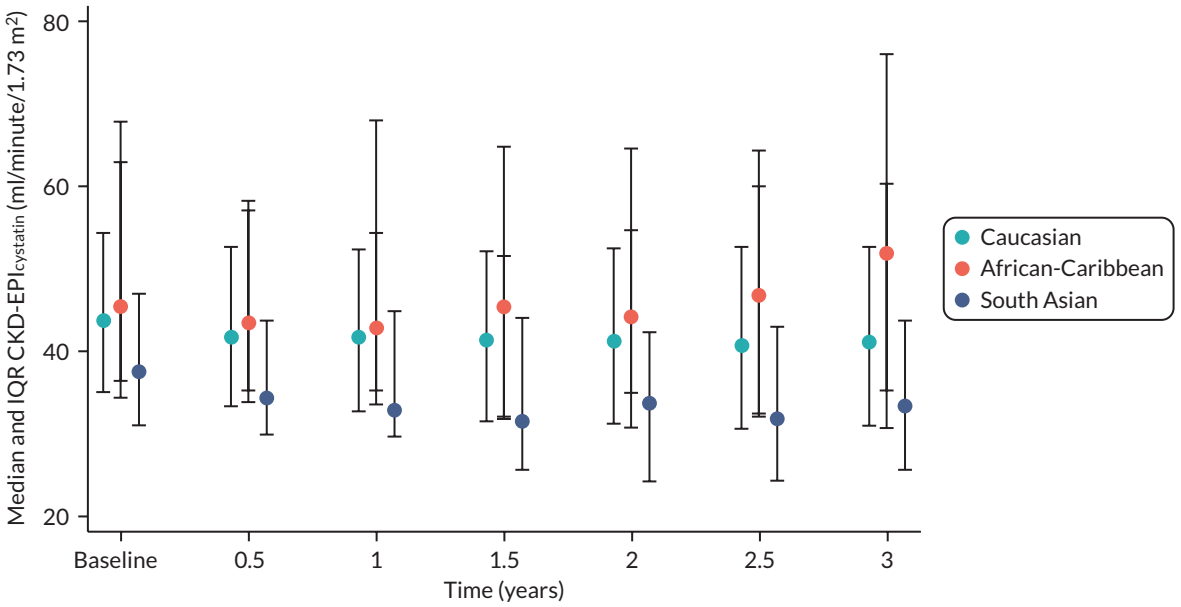


FIGURE 23 Median and IQR CKD-EPI$_{cystatin}$ over time by ethnicity group (main study and substudy data combined).

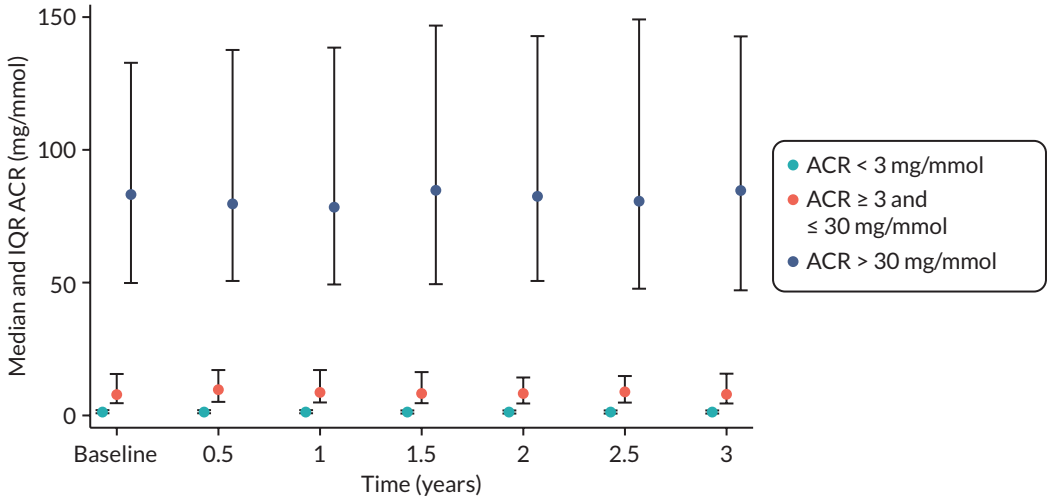


FIGURE 24 Median and IQR ACR over time by albuminuria status (main study and substudy data combined). The model suggested that those with albuminuria incline more steeply, although this is not very apparent from examination of the median and quartiles.

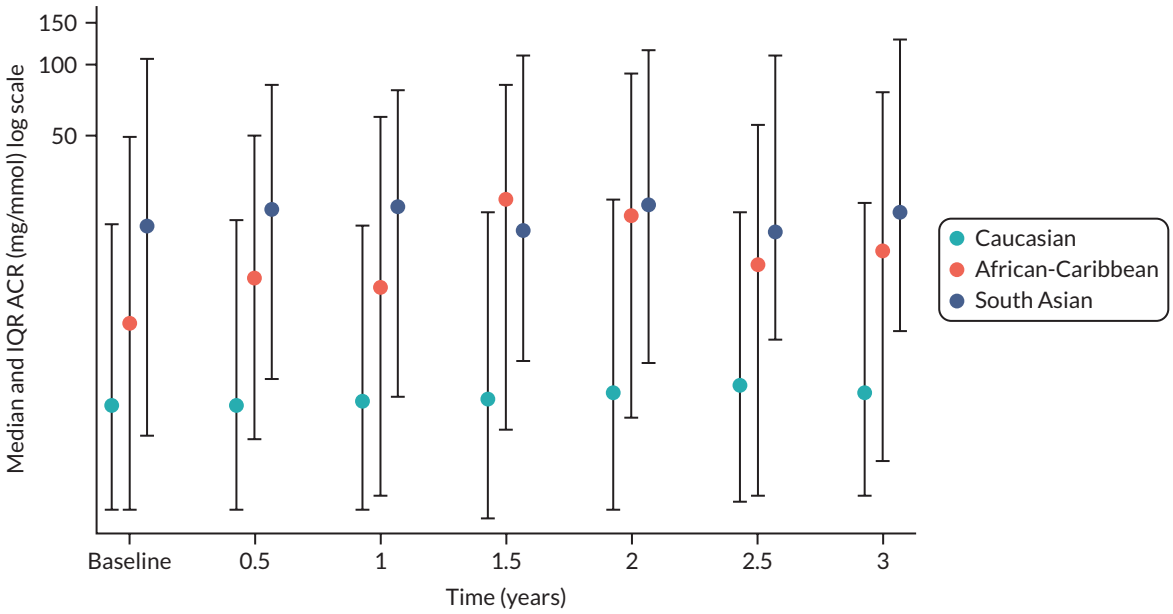


FIGURE 25 Median and IQR ACR over time by ethnicity group (main study and substudy data combined). The model suggests a steeper incline overall for those with African-Caribbean and South Asian ethnicity: plots of the median and quartiles show an incline for African-Caribbean individuals, but this is not so obvious for South Asian ethnicity.

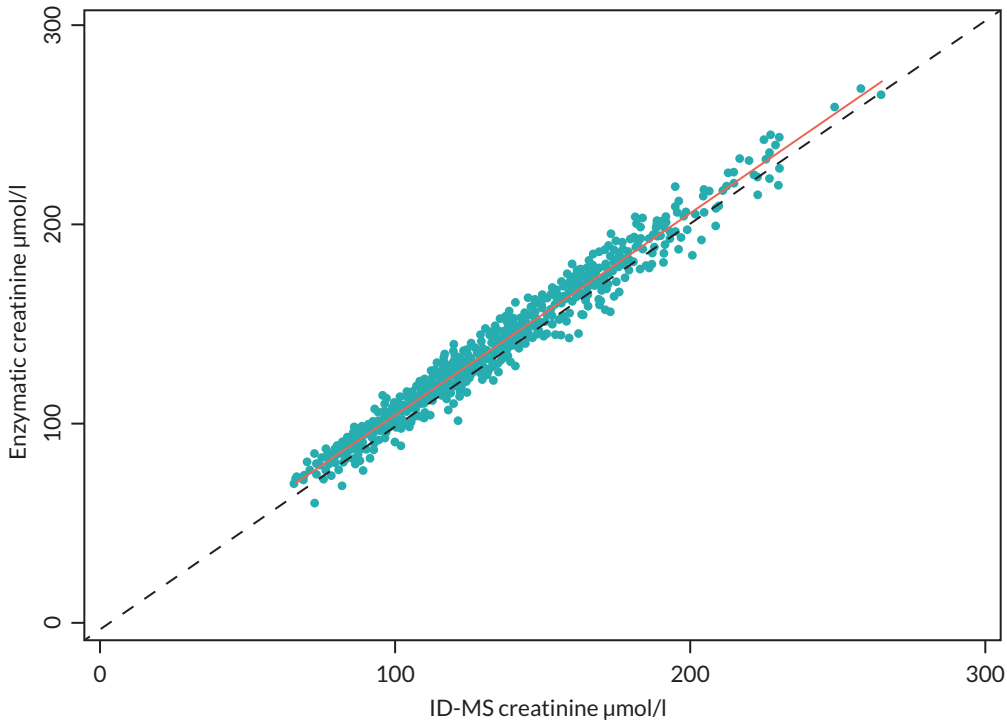


FIGURE 26 Linear regression analysis comparing creatinine results obtained using the enzymatic (field) and ID-MS (reference) methods. The dashed black line indicates unity and the red line shows the regression line. The relationship between the two methods was described by the linear regression equation: enzymatic = 3.23 + 1.01(ID-MS), R^2 0.969.

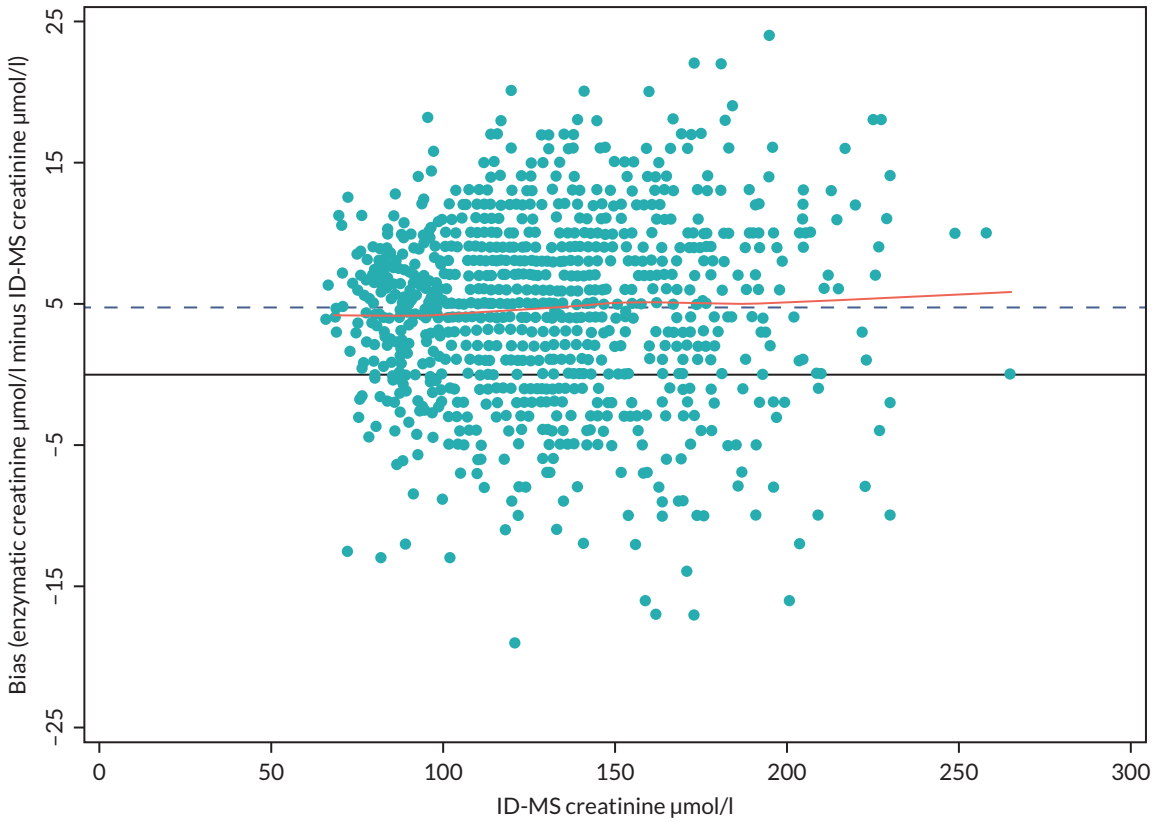


FIGURE 27 Bias plot comparison of creatinine results obtained using the enzymatic (field) and ID-MS (reference) methods. The solid black line indicates zero bias and the dashed red line shows mean bias. A lowess (locally weighted scatterplot smoothing function) curve (red solid line) is also shown.

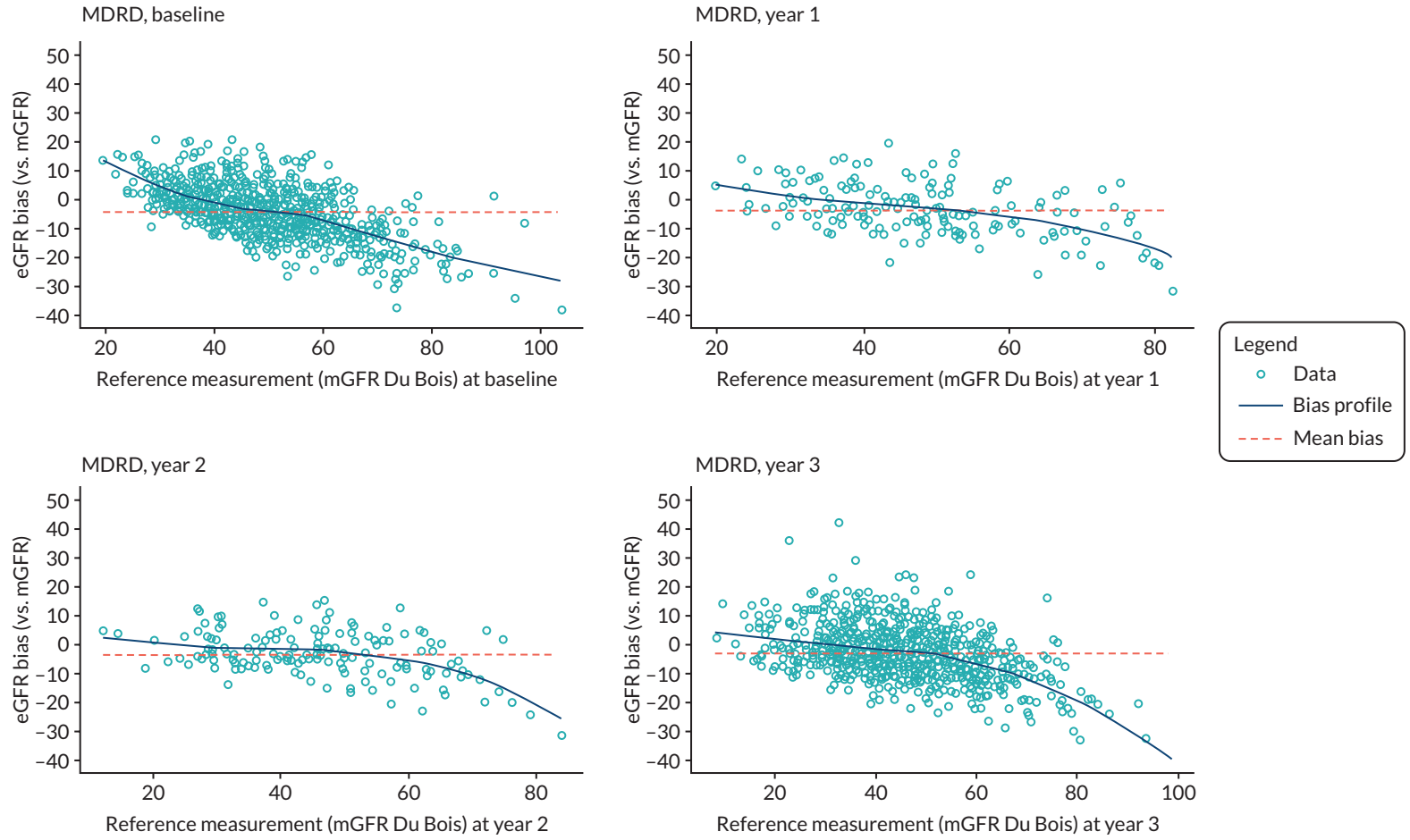


FIGURE 28 Bias profiles for the MDRD equation based on annual data from the main study. The individual scatter points represent the available study data on mGFR vs. eGFR at each annual sampling point (n = 875 at baseline and year 3; n = 212 at year 1; and n = 184 at year 2); the solid blue lines representing the expected mean eGFR bias over the mGFR range, based on a fitted loess regression curve; and the red dotted line in each plot indicates the overall mean bias calculated for the given eGFR equation at each time sampling point.

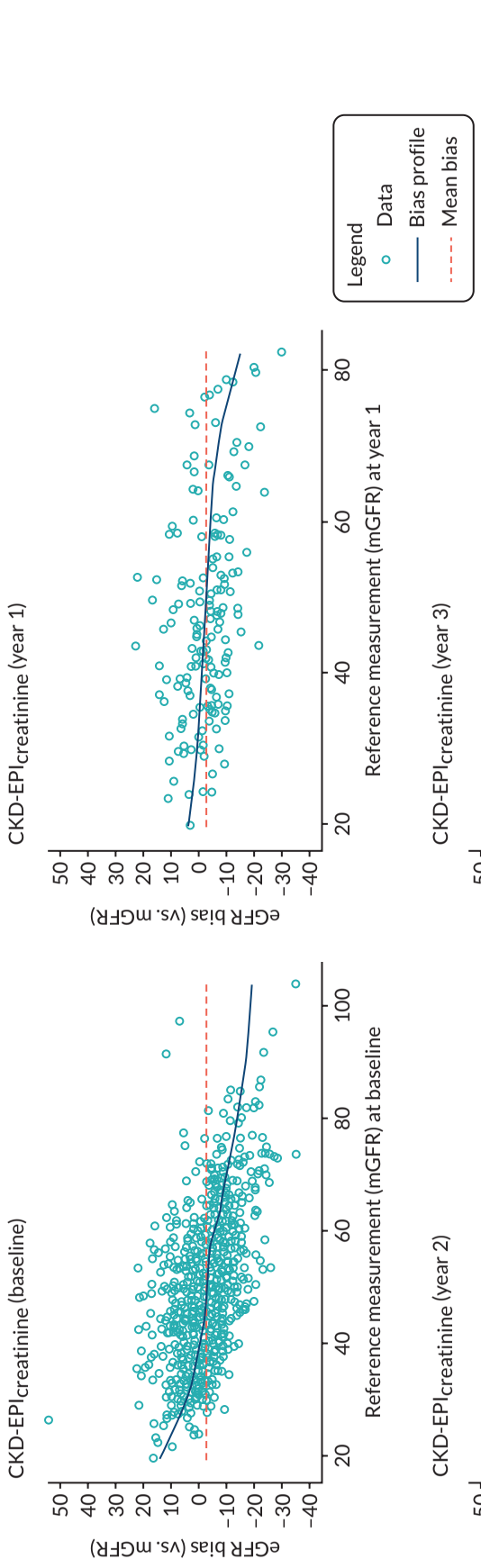


FIGURE 29 Bias profiles for the CKD-EPI$_{creatinine}$ equation based on annual data from the main study. The individual scatter points represent the available study data on mGFR vs. eGFR at each annual sampling point (n = 875 at baseline and year 3; n = 212 at year 1; and n = 184 at year 2); the solid blue lines representing the expected mean eGFR bias over the mGFR range, based on a fitted loess regression curve; and the red dotted line in each plot indicates the overall mean bias calculated for the given eGFR equation at each time sampling point.

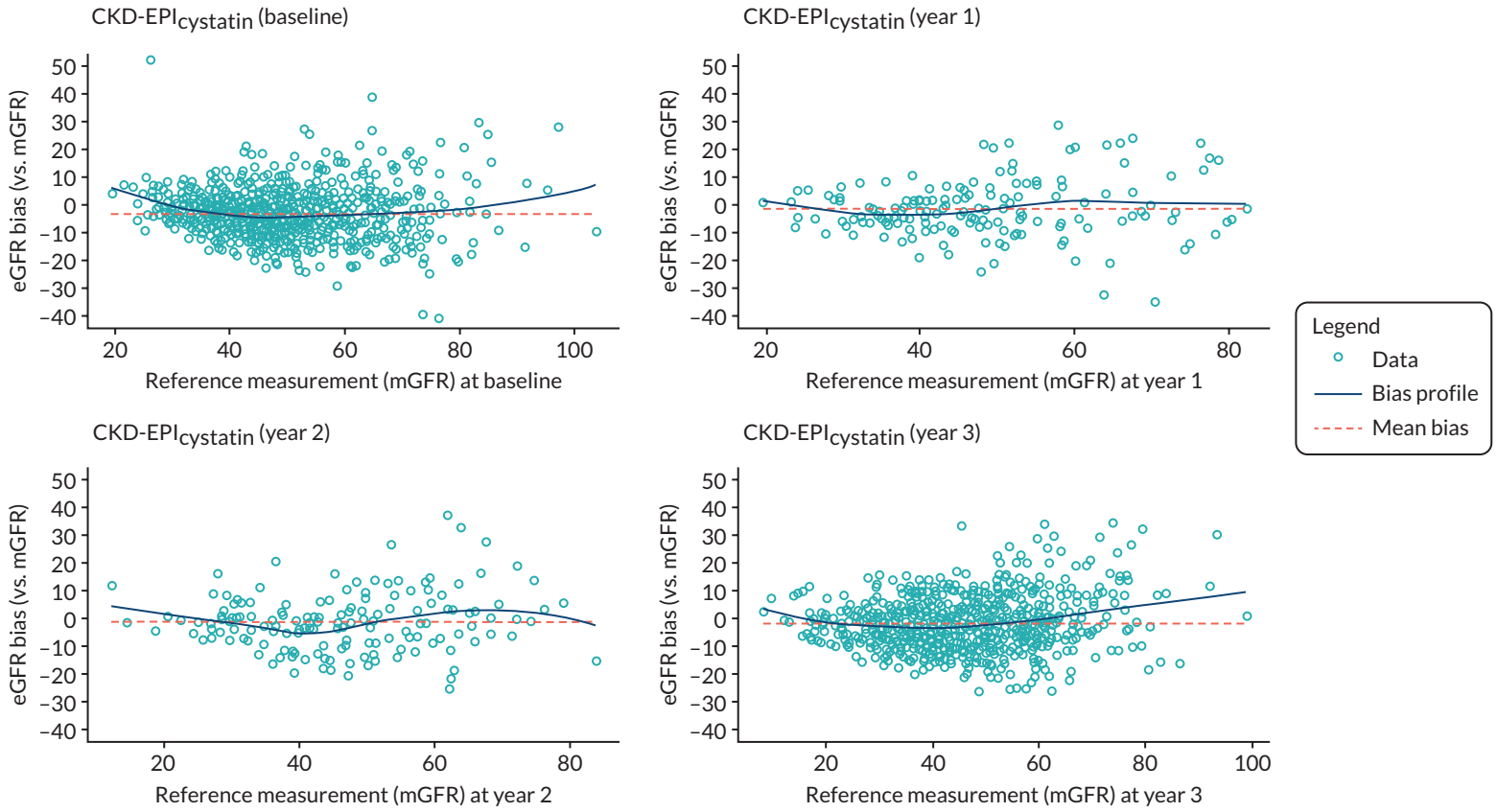


FIGURE 30 Bias profiles for the CKD-EPI$_{cystatin}$ equation based on annual data from the main study. The individual scatter points represent the available study data on mGFR vs. eGFR at each annual sampling point (n = 875 at baseline and year 3; n = 212 at year 1; and n = 184 at year 2); the solid blue lines representing the expected mean eGFR bias over the mGFR range, based on a fitted loess regression curve; and the red dotted line in each plot indicates the overall mean bias calculated for the given eGFR equation at each time sampling point.

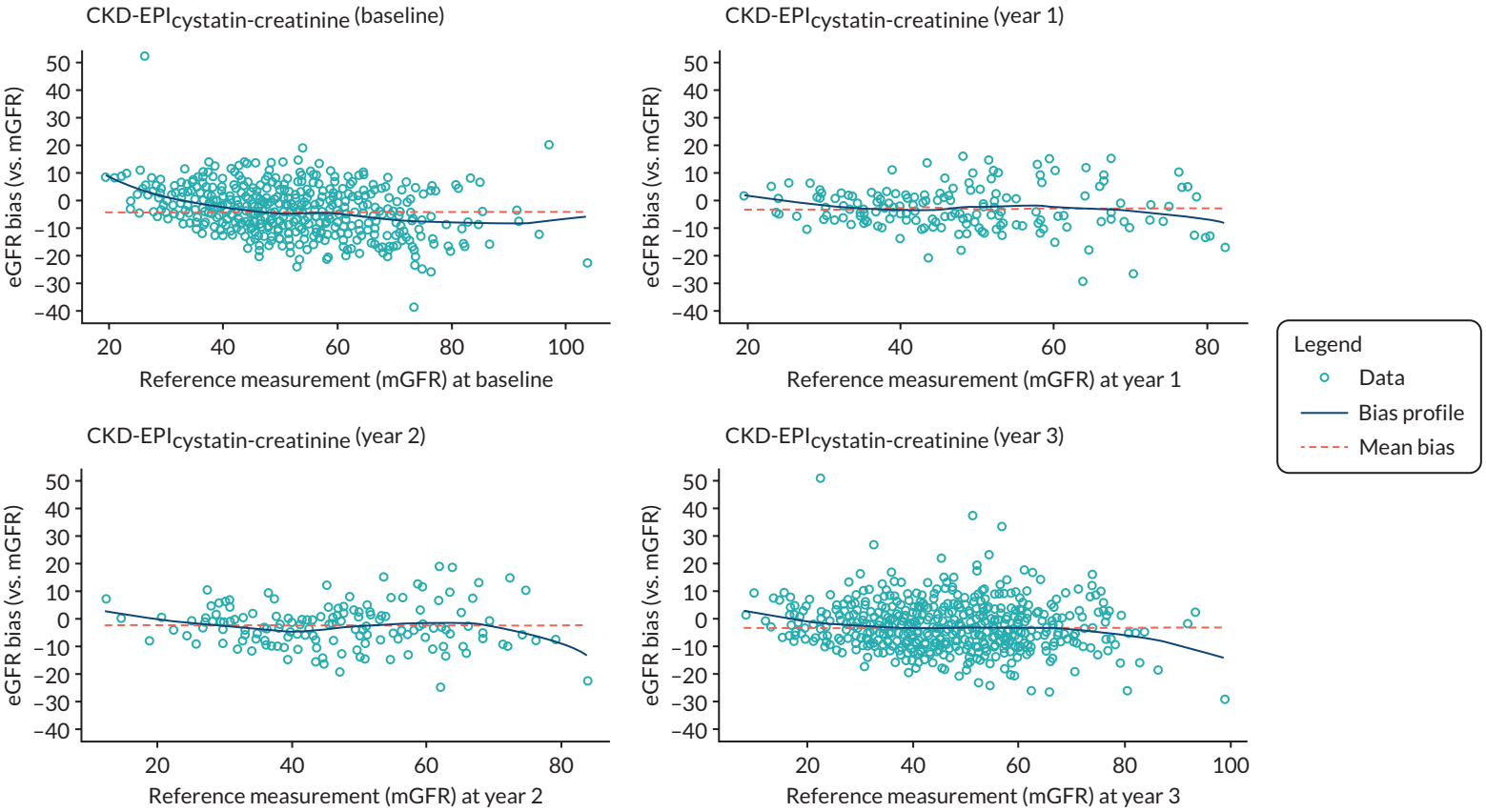


FIGURE 31 Bias profiles for the CKD-EPI$_{\text{creatinine-cystatin}}$ equation based on annual data from the main study. The individual scatter points represent the available study data on mGFR vs. eGFR at each annual sampling point (n = 875 at baseline and year 3; n = 212 at year 1; and n = 184 at year 2); the solid blue lines representing the expected mean eGFR bias over the mGFR range, based on a fitted loess regression curve; and the red dotted line in each plot indicates the overall mean bias calculated for the given eGFR equation at each time sampling point.

Appendix 2 Health economics systematic review

Systematic review of economic evaluations

A systematic review was conducted to identify previous studies that have assessed the cost-effectiveness of test-based strategies for CKD (including screening, diagnostic and monitoring-based strategies) using a decision-analytic model (e.g. decision tree, Markov model or microsimulation model). An original version of this review was conducted towards the beginning of the project (searches run February 2015) and published in *PLOS ONE*.[112] The review has since been updated for this report (searches run February 2020). The objective was not to draw conclusions about the cost-effectiveness of different testing strategies – rather the aim was to examine how economic models have been implemented in this setting to date. This section reports the methods and findings of the review.

Methods

An initial search was conducted on 17 February 2015 and published in *PLOS ONE*.[112] This review was subsequently updated (searches conducted on 4 February 2020) to ensure that the latest research in this area was captured before finalising the de novo economic model. As far as possible, the same methods (i.e. search strategies, screening and data extraction processes) were used in both the original and updated searches; however, it should be noted that different researchers were involved in the original and updated reviews, due to a change of research group undertaking the health economic analysis over the course of this project. Any differences in the methods employed in the original and update reviews are highlighted in the sections below.

Searches

Articles were identified through searches of electronic databases and hand-searching of the bibliographies of the included studies. In the original review (February 2015), the following databases were searched:

- CINAHL (EBSCO) 1981–present
- EconLit (EBSCO) 1886–present
- EMBASE Classic + EMBASE (Ovid) 1947–present
- Ovid MEDLINE(R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily 1946–present
- PsycInfo (Ovid) 1806–present
- The HTA database, accessed via the Cochrane Library (Wiley)
- The NHS Economic Evaluation Database (EED), accessed via the Cochrane Library (Wiley).

In the updated review (February 2020), all the above databases were searched except for NHS EED, which stopped having new content added to it in January 2015. The original search of NHS EED in February 2015 would therefore have already identified any relevant records available in NHS EED for this review.

The search strategy was customised for each database and included free-text terms and medical subject headings (MeSH) terms where appropriate. The following concepts were covered: CKD, diabetes, hypertension, GFR type markers, albumin type markers and economic evaluations. For the updated review in 2020, the original search strategies from 2015 were checked for changes to subject heading such as MeSH. The strategies for CINAHL, MEDLINE and PsycInfo remained the same. Additional subject headings for CKD were found and added to the EMBASE strategies (CKD-mineral and bone disorder/and renal osteodystrophy/). The 2015 search strategy used in EconLit was a copy of the

CINAHL strategy and used CINAHL headings that are not recognised in EconLit – a new search strategy was therefore devised for EconLit in the update review, based on the original search but without CINAHL subject headings applied. The HTA database stopped having new content added to it in March 2018, and in February 2020 (when the update searches were run) HTA database records were only available via searching the Centre for Reviews and Dissemination (CRD) database platform and limiting results to 'HTA'. It was therefore not possible to replicate the original HTA search which identified records having both a relevant MeSH and a relevant text word in any field; instead, a more sensitive strategy was adopted in 2020, to search for relevant text words in any fields, without limiting results to those containing specified MeSH.

All searches were limited to English-only studies. The original February 2015 searches were not limited by date. The updated February 2020 searches were limited to studies published from 2014 onwards, to ensure that any studies from 2014 or 2015 that were added to the databases after February 2015 would be identified. For the HTA database, the updated search was run from 2014 to 31 March 2018, since new content stopped being added to that database in March 2018. The full search strategies are provided in *Economic evaluation review search strategies*.

The results of the database searches were stored and de-duplicated in an EndNote library. Further relevant studies were sought by hand-searching of the bibliographies of the included studies.

Inclusion criteria

The review inclusion and exclusion criteria are outlined in *Table 42*. Studies were included if they reported a peer-reviewed, de novo, model-based economic evaluation, which included test-based strategies (using albuminuria and/or eGFR tests), on patients with possible or confirmed CKD, and reported an incremental cost-effectiveness ratio. Studies were excluded if they: reported on non-CKD cohorts or patients with end-stage kidney disease (ESKD) only; did not report a full cost-effectiveness evaluation (e.g. focused on costs alone); did not use a decision-analytic model (e.g. clinical trial-based analyses); were not primary research (i.e. reviews or opinion pieces); or were published as a conference proceeding only (i.e. abstracts or posters).

TABLE 42 Systematic review of model-based economic evaluations: inclusion and exclusion criteria

Component	Inclusion criteria	Exclusion criteria
Population	Patients at risk of, or with confirmed, CKD, including: • General populations • Hypertensive populations • Diabetic populations • CKD populations (GFR ≥ 15 ml/minute/1.73 m^2)	Patients with ESKD only (GFR < 15 ml/minute/1.73 m^2)
Intervention	Albuminuria and/or eGFR-based testing	
Comparator	Any	
Outcomes	ICER	
Study methods/design	Model-based economic evaluation, including a CEA, CUA or CBA	Trial-based economic evaluation; or not a full economic evaluation (e.g. cost-minimisation analysis)
Research type	Primary research (i.e. de novo economic model)	Literature reviews, editorials, letters, opinion pieces
Manuscript type	Full peer-reviewed text available	Conference proceeding (abstract or poster)
Language	English only	Non-English language

CBA, cost–benefit analysis; CEA, cost-effectiveness analysis; CUA, cost–utility analysis; ICER, incremental cost-effectiveness ratio.

A two-stage screening process was undertaken to determine which studies should be included in the review. First, records were screened by title and abstract and were included if they were considered to possibly meet the above inclusion criteria. Second, the full-text reports for records were retrieved, and final inclusions were determined based on a full review of the study report. Each screening stage was undertaken in duplicate by two independent reviewers: in the original review, Andrew Sutton and Katie Breheny conducted the screening, while in the updated review, Bethany Shinkins (BS) and Alison Smith (AFS) completed the screening. Any disagreements were resolved via discussion.

Data extraction and quality assessment

For each study included in the review, data extraction was conducted by a single reviewer (AFS) to collate information on the study characteristics and methodology. The data extraction form is provided in *Economic evaluation review data extraction form*. In particular, data extraction focused on addressing the following research questions:

- ***How was test diagnostic accuracy considered in the analysis?*** Was the accuracy of each test defined, justified and incorporated in the analysis? How was the accuracy of any repeated-testing scenarios characterised? Were the parameters that define the test accuracy subjected to sensitivity analysis? How did test accuracy (e.g. FP and/or FN results) impact on patient outcomes in the model?
- ***What approach was used to model disease progression?*** What type of model was used (e.g. Markov, decision tree)? How was progression of the chronic nature of CKD described in the analysis? Were any additional clinical events, risks, or treatment side effects captured in the model?
- ***Were the impacts of any delays on the testing and treatment pathway considered?*** Were patient outcomes in the model impacted by delays in testing, diagnosis and/or treatment? Did the analysis explore the impact of changing the timing of testing, decision-making or treatment on patient outcomes?
- ***Which testing resources and costs were captured in the analyses and how?*** How were the testing costs derived, and what elements of resource use (e.g. test kit, laboratory personnel, GP/physician visits, confirmatory tests) were captured in the cost? Were the costs incurred by the patients (societal costs) along the testing pathway incorporated into the analysis?

Any uncertainties regarding the data extraction were discussed and checked with the second reviewer (BS). Due to the change in reviewers completing the initial versus updated review, all items in the data extraction table produced from the initial review were subsequently double checked by the primary reviewer in the updated review (AFS), to ensure consistency in the data extraction and reporting. All findings were narratively synthesised.

The methodological quality of each paper was also assessed using the 10-item checklist originally proposed by Drummond *et al.*[193,194] The aim of this systematic review was to examine the methods used in describing testing and diagnostic pathways in economic evaluations in this field and not to comment regarding the results and conclusions drawn from these studies. Consequently, no studies were excluded from this review due to issues regarding quality.

Results

Study selection

Figures 32 and *33* summarise the initial and update review findings respectively. For clarity, the findings of the original and updated review are shown separately.

The initial search strategy of the databases conducted in February 2015 identified 2671 records, of which 908 were duplicate records. Based on title and abstract screening, 74 reports were selected for full-text review, of which 20 studies were included (reported across 21 reports). One further study was identified via citation checking, giving a total of 21 studies reported across 22 reports.

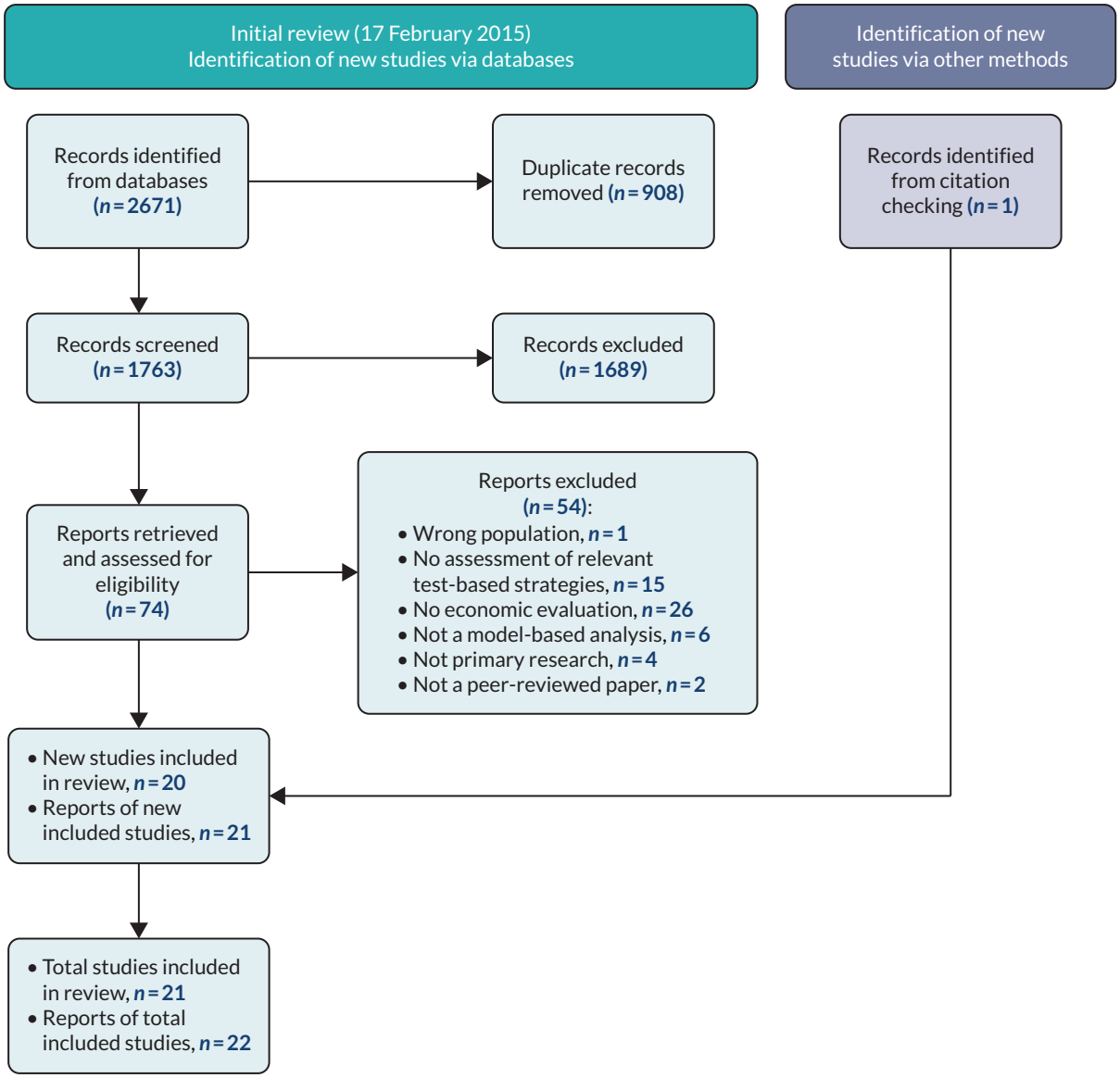


FIGURE 32 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of studies included in the initial systematic review of model-based economic evaluations.

The updated search strategy conducted in February 2020 identified 1357 records, of which 342 were duplicate studies. Based on title and abstract screening, 12 reports were selected for full-text review, of which 7 studies (reported across 7 reports) were included. No studies were identified via citation checking in the update review. In total, across the initial and updated searches, 28 studies were included in the review, reported across 29 reports.

Study characteristics

A summary of the included studies is provided in *Table 43*. Nine studies originated from USA, four studies were from Canada, three from the Netherlands, two from China, and one each from Australia, Europe, France, Germany, Iran, Japan, Korea, UK, Switzerland and Thailand.

The majority of studies (*n* = 24) considered proteinuria or albuminuria tests: 8 specified the evaluated test(s) as reagent strip (or 'dipstick') tests;[195–202] 11 referred to urine albumin excretion, urine albumin concentration or urinary albumin-to-creatinine ratio tests;[203–214] and 5 evaluated both dipstick and standard albuminuria tests.[215–219] Six studies meanwhile evaluated eGFR testing: two of which

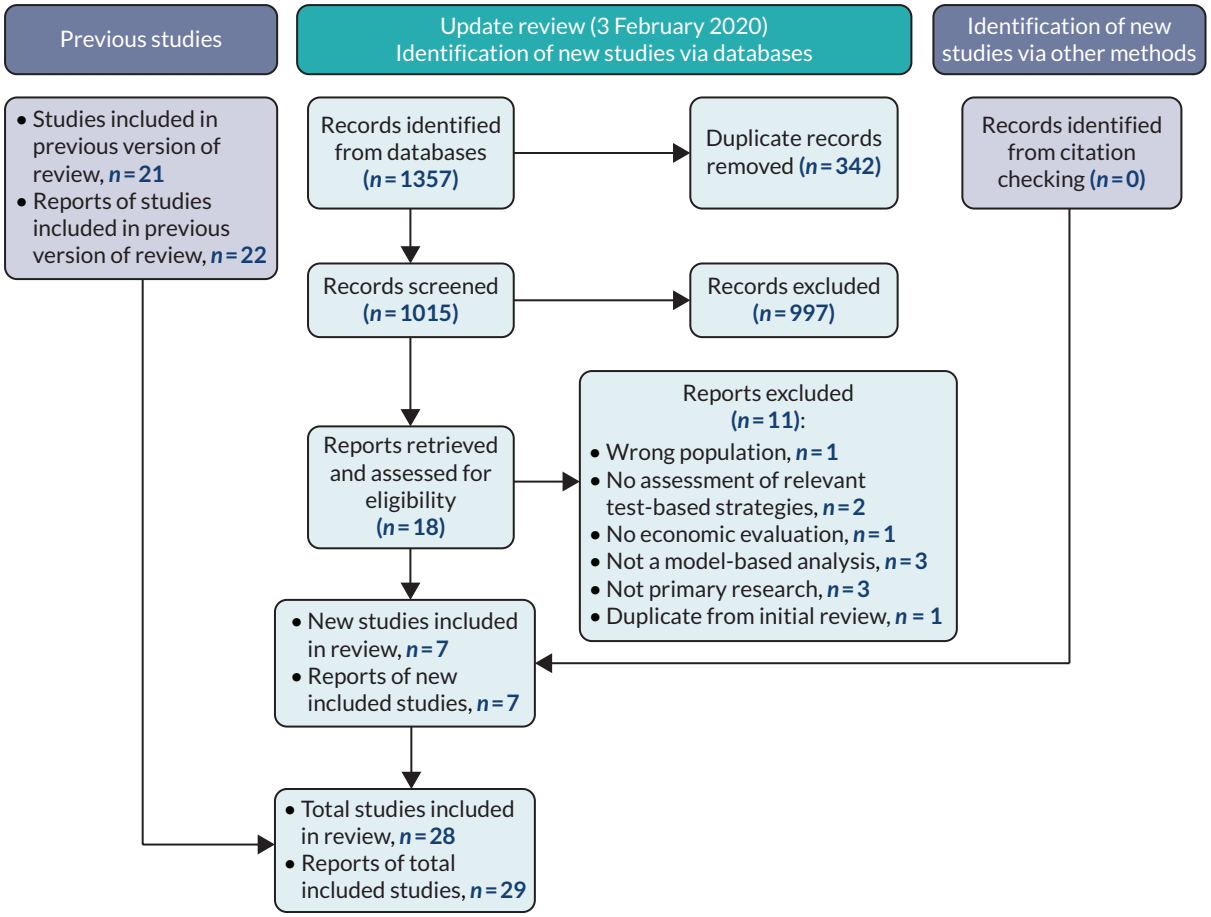


FIGURE 33 Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram of studies included via the updated review.

incorporated both dipstick and eGFR tests; and one of which incorporated both albuminuria and eGFR tests.[200,202,211,220–222] Of those studies evaluating eGFR-based strategies, four specified the equation underpinning the eGFR calculation: three used the MDRD equation, while one used the CKD-EPI equation. A final study evaluated a novel biomarker for CKD – described as a capillary electrophoresis–mass spectrometry-based urinary peptide classifier (CKD273).[223]

All of the identified studies evaluated screening strategies in at-risk groups or general populations not currently diagnosed with CKD. No studies were identified which assessed test-based monitoring strategies for patients with known CKD (i.e. matching the role of monitoring being considered in this HTA). Half of the studies (*n* = 14) focused on screening strategies for patients with diabetes[195,201,203,204,210,215–219] or patients with diabetes and/or hypertension[197,212,214,223] (both known risk-factors for CKD). Note in the initial 2015 review, these screening studies (conducted in diabetic and hypertensive populations) were listed as monitoring studies. In the updated review, it was decided that for clarity these studies should be listed as screening studies. Although repeated screening within high-risk populations can be classified as a type of early-stage monitoring for disease *onset*, in the context of this report (where the focus is on monitoring within patients already known to have CKD), we believe it is more appropriate to identify such studies as 'screening' studies. This terminology also aligns with that used by the original study authors. The other half focused on screening strategies in the general population,[196,198,200,202,205–209,213,220–222] with one study considering school children,[199] and a further study focusing on screening within a rural indigenous population.[211] Of those studies focusing on population-based screening strategies, several also included subgroups or scenario analyses restricting screening to patients with diabetes and/or hypertension.[196,198,202,207,209,221] Testing was most often administered in

TABLE 43 Summary table of studies included in the systematic review of model-based economic evaluations

Study	Population	Objective	Type and timing of testing	Testing strategies	Comparator(s)	Health outcome	Model type	Perspective	Cost-effectiveness conclusions
Adarkwah *et al.* (2010) Germany[218]	Patients with newly diagnosed T2D, aged 50	Assess the best time to start an ACE inhibitor (or A2RB therapy in the event of cough)	Annual screening	(1) Micro-albuminuria (HPLC; UAE > 30 mg/day); or (2) Macro-albuminuria (dipstick test; > 300 mg/day)	(1) No screening and no treatment (standard care); (2) Treat all immediately with an ACE inhibitor or A2RB	LYG/QALY	Cohort Markov model	Statutory health insurance provider	Immediately treating all patients with newly diagnosed diabetes is the most cost-effective strategy
Adarkwah *et al.* (2011) Netherlands[219]	Patients with newly diagnosed T2D, aged 50	Assess the best time to start an ACE inhibitor treatment	Annual screening	(1) Micro-albuminuria (HPLC or immune-turbidimetric; UAE > 30 mg/day); or (2) Macro-albuminuria (dipstick test; > 300 mg/day)	(1) No screening and no treatment (standard care); or (2) Treat all with an ACE inhibitor	LYG/QALY	Cohort Markov model	Statutory health insurance provider	Immediately treating all patients with newly diagnosed diabetes is the most cost-effective strategy
Boersma *et al.* (2010) Netherlands[205]	General population aged 28–75	Assess the cost-effectiveness of population screening for albuminuria	One-off screening	Micro-albuminuria (UAC ≥ 20 mg/l) with confirmatory test (24-hour UAE ≥ 30 mg/day). Treat with an ACE inhibitor	No screening and no treatment	LYG	Cohort Markov model	Healthcare provider	One-off population screening is potentially cost-effective (depends on screening age and test thresholds)
Boulware *et al.* (2003) USA[196]	General population aged 50, (1) without HT or diabetes; and (2) with HT	Assess the cost-effectiveness of screening for the early detection of urine protein	Annual screening	Proteinuria (dipstick). Confirmatory ACR and eGFR testing (< 90 ml/minute/1.73 m^2) (equation N/R). Treat with ACE inhibitor or A2RB therapy	No screening (but included annual opportunity for incidental testing or symptomatic presentation)	QALY	Cohort Markov model	Societal	Population screening is not cost-effective unless targeted towards at-risk groups (older or HT persons)
Critselis *et al.* (2018) Europe[223]	Patients with T2D, aged 50	Assess the cost-effectiveness of screening for CKD progression with the CKD273 classifier	Annual screening	A urinary peptide classifier (CKD273), + UAE testing (test cut-offs N/R). Treat with standard anti-HT or intensified therapy depending on albuminuria and screening status	Screen for micro-albuminuria (UEA) only (test cut-off N/R)	QALY	Cohort Markov model	European healthcare system	CKD273 screening is cost-effective in diabetic patients and high-risk patients, but not in low-risk patients

TABLE 43 Summary table of studies included in the systematic review of model-based economic evaluations (*continued*)

Study	Population	Objective	Type and timing of testing	Testing strategies	Comparator(s)	Health outcome	Model type	Perspective	Cost-effectiveness conclusions
Den Hartog *et al.* (2009) USA[220]	General population, aged 60	Assess whether routine reporting of eGFR is cost-effective for identifying CKD	Annual screening	eGFR (MDRD equation) (< 60 ml/minute/1.73 m^2) + serum creatinine. Treat with an ACE inhibitor and BP control	Serum creatinine (accuracy drawn from papers using a range of thresholds: 1.06–1.36 mg/dl)	QALY	Cohort Markov model	Healthcare provider	eGFR is cost-effective, but not when assuming a > 2% quality-of-life decrement for FP cases
Farmer *et al.* (2014) UK[210]	Patients with: (1) T1D (mean age 27); or (2) T2D (mean age 63)	Assess the cost-effectiveness of screening for early kidney disease	Screening every 1–10 years [starting at age ≥ 12 (T1D), or from diagnosis (T2D)]	Micro-albuminuria (UACR > 2.5 mg/mmol for men and > 3.5 mg/mmol for women). Treat with ACE inhibitor or A2RB therapy	Various screening strategies evaluated, altering the screening interval from 1 to 10 years	QALY	Individual based simulation model	Healthcare provider	Annual ACR screening is cost-effective for patients with T1D and T2D compared to using longer screening intervals (supporting UK screening guidance)
Ferguson *et al.* (2017) Canada[211]	Manitoba's rural indigenous peoples, aged 18 +	Assess the cost–utility of screening for CKD in rural indigenous adults	One-off screening	(1) eGFR (≤ 30 ml/minute/1.73 m^2) (CKD-EPI equation), or (2) Urine ACR (≥ 300 mg/g, or 30 mg/mmol and eGFR 30–45 mg/minute/1.73 m^2). Treat with ACE inhibitor or A2RB therapy	Usual care (no screening)	QALY	Cohort Markov model	Public health-care payer	Screening for CKD in rural indigenous adults is cost-effective, particularly in remote air access-only communities with higher risks of disease
Go *et al.* (2019) Korea[202]	General population, modelled from age 20	Estimate the cost–utility of the NHSP for CKD in Korea	Screening every 2 years, starting age 40	Proteinuria (dipstick) and eGFR (serum creatinine; MDRD formula). Different tests, population, intervals and ages explored. Treat with ACE inhibitors	No screening	QALY	Cohort Markov model	Societal	National screening for CKD is more cost-effective for patients with diabetes or HT than the general population
Golan *et al.* (1999) USA[203]	Patients with newly T2D, aged 50	Assess the cost-effectiveness of treat all vs. screening strategies	Annual screening	(1) Micro-albuminuria (UAE 30–300 mg/day); or (2) Gross proteinuria (UAE > 300 mg/day). Treat with an ACE inhibitor	Treat all with an ACE inhibitor	LYG/QALY	Cohort Markov model	Societal	The 'treat all' strategy is most cost-effective, but the results depend on patients' quality of life with treatment

continued

TABLE 43 Summary table of studies included in the systematic review of model-based economic evaluations (*continued*)

Study	Population	Objective	Type and timing of testing	Testing strategies	Comparator(s)	Health outcome	Model type	Perspective	Cost-effectiveness conclusions
Hoerger *et al.* (2010) USA[206,207]	General population, aged 50 (including diabetic and HT subgroups)	Assess the cost-effectiveness of micro-albuminuria screening strategies	Screening every 1, 2. 5, or 10 years, or one-off screening	Micro-albuminuria (ACR 30–299 mg/day). Treat with ACE inhibitor or A2RB therapy	(1) No screening; (2) Usual care (including low annual screening rates for persons with diabetes and/or HT)	QALY	Micro-simulation Markov model	Healthcare provider	Screening is cost-effective for diabetic or HT patients, but not for the general pop. unless using longer intervals or as part of existing clinician visits
Hoerger *et al.* (2012) USA[208]	African or non-African Americans, aged ≥ 50 (including diabetic and HT subgroups)	Assess the cost-effectiveness of micro-albuminuria screening	Screening at 1-, 2-, 5- or 10-year intervals	Micro-albuminuria (ACR 30–299 mg/g). Treat with ACE inhibitor or A2RB therapy	Usual care (including low annual screening rates for patients with diabetes and HT)	QALY	Micro-simulation Markov model	Healthcare provider	Screening African or non-African Americans with diabetes or HT at 5- or 10-year intervals respectively is cost-effective
Howard *et al.* (2010) Australia[198]	Asymptomatic 50- to 69-year-olds	Assess the cost-effectiveness of strategies to prevent ESKD	Annual screening	Proteinuria (dipstick, ≥ 1 +) + confirmatory spot UPCR (> 20 mg/mg). Treat with an ACE inhibitor. Other tests used to identify diabetes and HT	Current practice, which included the opportunity for opportunistic clinical diagnosis	QALY	Cohort Markov model	Healthcare provider	Primary care screening and treatment for diabetes, HT and proteinuria are likely to be cost-effective
Kessler *et al.* (2012) Switzerland[209]	General population, aged ≥ 50 (including. subgroups with diabetes or HT)	Assess the cost-effectiveness of screening in different populations	Screening every 1, 2, 5, or 10 years	Micro-albuminuria (ACR 30–299 mg/g). Treat with ACE inhibitor or A2RB therapy	(1) No screening; (2) Usual care (including low annual screening rates for patients with diabetes ± HT)	QALY	Micro-simulation Markov model	Healthcare provider	Screening is cost-effective at 2-, 5- or 10-year intervals in diabetic, HT or general populations, respectively
Kiberd *et al.* (1995) Canada[216]	Patients with insulin-dependent diabetes mellitus for 5 years	Examine the conditions necessary to make screening cost-effective	Annual screening	Micro-albuminuria alone (UAE > 20 µg/minute on two out of three tests). Treat with an ACE inhibitor	Treat patients with HT and/or macro-albuminuria (dipstick > 0.3 g/l or positive Albustix confirmed with > 300 mg/day or > 200 µg/minute)	QALY	Cohort Markov model	Third party and government	Micro-albuminuria surveillance is cost-effective, but the results are sensitive to key parameters including test accuracy

TABLE 43 Summary table of studies included in the systematic review of model-based economic evaluations (*continued*)

Study	Population	Objective	Type and timing of testing	Testing strategies	Comparator(s)	Health outcome	Model type	Perspective	Cost-effectiveness conclusions
Kiberd *et al.* (1998) Canada[217]	Patients with insulin-dependent diabetes mellitus for 5 years	Determine how effective ACE inhibitors must be in preventing diabetic nephropathy to warrant routine administration	Annual screening	(1) Micro-albuminuria (UAE > 20 µg/minute or 30 mg ACR on two out of three tests); or (2) Treat all high-risk patients (ACE inhibitor) and screen low risk for HT and macro-albuminuria (dipstick > 0.3 g/l or positive Albustix with > 300 mg/day or 200 µg/minute proteinuria)	Treat all patients with an ACE inhibitor	LYG/ QALY	Cohort Markov model	Third party and government	Routine ACE inhibitor therapy for patients with diabetes is expected to be cost-effective, especially if treatment can be targeted to high-risk individuals
Kiberd *et al.* (1999) USA[204]	Pima Indians with T2D, at the point of diagnosis	Determine how effective ACE inhibitors must be to warrant early routine therapy	Annual screening	Micro-albuminuria (UACR: > 3 mg/1 mmol or > 30 mg/1 g on two of three morning urine samples), starting 1 year after diabetes diagnosis	Treat all with ACE inhibitor 1 year after diagnosis of diabetes	LYG	Cohort Markov model	Third party and government	Routine ACE inhibitor therapy in Pima Indians with T2D could be cost-effective compared micro-albuminuria screening
Kondo *et al.* (2012) Japan[200]	General population, aged 40–74	Assess the cost-effectiveness of population screening for CKD	One-off screening	(1) Proteinuria (dipstick, ≥ 1); (2) eGFR (based on serum creatinine; ≥ stage 3); or (3) Dipstick test + eGFR (≥ 1 or ≥ stage 3). Treat with ACE inhibitors	(1) Do nothing; (2) Status quo (40% receive dipstick test; 60% dipstick + serum creatinine)	QALY	Cohort Markov model	Societal	Population-based screening using the dipstick test and/or serum creatinine is cost-effective
Le Floch *et al.* (1994) France[215]	Patients with T1D and T2D (mean age = 53)	Examine the cost-effectiveness of screening for albuminuria in diabetic patients	Annual screening	Semiquantitative dipstick (UAE > 20 µg/minute on ≥ 1 of two separate tests on same sample), + standard test for albuminuria for positive dipstick results. Treatments not assessed	Standard test for albuminuria using immuno-turbidimetry (micro-albuminuria if > 20 µg/minute; macro-albuminuria if > 200 µg/minute)	QALY	Cohort Markov model	Healthcare provider	Dipstick pre-screening results in a cost saving of £6600 per QALY lost. The authors concluded that this may be considered cost-effective

continued

TABLE 43 Summary table of studies included in the systematic review of model-based economic evaluations (*continued*)

Study	Population	Objective	Type and timing of testing	Testing strategies	Comparator(s)	Health outcome	Model type	Perspective	Cost-effectiveness conclusions
Manns *et al.* (2010) Canada[221]	General population (incl. age < 65 vs. > 65, diabetic, ± HT subgroups)	Assess the cost-effectiveness of one-off population screening for CKD	One-off screening	eGFR testing (MDRD equation) (< 60 ml/minute/1.73 m^2). Treat with an ACE inhibitor or A2RB therapy	No screening	QALY	Cohort Markov model	Healthcare provider	Population screening is not cost-effective in the general public, but it is likely to be cost-effective in patients with diabetes
Palmer *et al.* (2008) USA[197]	Patients with T2D and HT	Assess the cost-effectiveness of screening for nephropathy	Annual screening	Micro-albuminuria (semiquantitative urine dipsticks) (UAE 20–199 µg/minute). Treat with an A2RB + other HT agents	No screening (BP control achieved with conventional medications alone)	QALY	Cohort Markov model	US third-party health insurance payer	Micro-albuminuria screening in patients with T2D and HT is expected to be cost-effective
Ravaghi *et al.* (2019) Iran[222]	General adult population (age N/R)	Explore the cost-effectiveness of screening for CKD among adults	One-off screening	eGFR (including blood creatinine + urine creatinine and volume; equation N/R), with kidney ultrasound if indicated. Treatments not specified	No screening	QALY	Cohort Markov model	Social insurance organisations	Based on the high prevalence of CKD in Iran, population-based screening is cost-effective in this setting
Sekhar *et al.* (2010) USA[199]	School children aged 8–15	Assess the cost-effectiveness of dipstick uranalysis for the detection of CKD in children	One-off screening	Proteinuria/haematuria (dipstick), + repeat test for elevated results (abnormal if: ≥ 1 proteinuria and ≥ 1 haematuria). Treatments not considered	No screening	Cases of CKD diagnosed	Decision tree	Healthcare provider	Screening for CKD using dipstick uranalysis amongst school children is not cost effective
Siegel *et al.* (1992) USA[195]	Patients with newly diagnosed insulin-dependent diabetes, aged 15	Examine the effects of screening and early ACE inhibitor treatment programs	Twice-yearly screening	(1) Proteinuria (≥ 300 µg/minute on two out of three dipstick tests); (2) Sign. micro-albuminuria (≥ 100 µg/minute in two out of three urinalyses); or (3) Micro-albuminuria (≥ 20 µg/minute in two of three tests). Treat with an ACE inhibitor	Standard therapy: annual testing for proteinuria, with ACE inhibitor treatment for HT patients only	LYG	Cohort Markov model	Healthcare provider	Early treatment with ACE inhibitors is likely to be cost-effective. Screening for micro-albuminuria and then initiation of treatment is the most cost-effective option

TABLE 43 Summary table of studies included in the systematic review of model-based economic evaluations (*continued*)

Study	Population	Objective	Type and timing of testing	Testing strategies	Comparator(s)	Health outcome	Model type	Perspective	Cost-effectiveness conclusions
Srisubat *et al.* (2014) Thailand[201]	45 years old patients with T2D and normotension	Assess the cost-effectiveness of micro-albuminuria screening	Annual screening	Micro-albuminuria (urine dipstick). Treat with an ACE inhibitor	Do nothing scenario (patients receive ACE inhibitor at discovery of macro-albuminuria and ESKD)	QALY	Cohort Markov model	Societal	Micro-albuminuria screening using urine dipsticks in patients with T2D is highly cost-effective
Wang *et al.* (2017) China[212]	Hospital outpatients aged 45+, with HT, diabetes or CHD, and previously elevated ACR	Identify a feasible and cost-effective strategy for the identification of persistent albuminuria	One-off screening	Micro-albuminuria (UACR > 30 mg/g creatinine); different combinations of repeated testing strategies (over 3-month period) evaluated	Different combinations of repeated testing strategies (over 3-month period) were evaluated	QALY	Decision tree + cohort Markov model	Societal	Screening using two first morning urine samples and one randomised spot urine sample over 2 consecutive days is most cost-effective
Wu *et al.* (2018) China[214]	Patients with newly diagnosed T2D (mean age = 51)	Assess the cost-effectiveness of preventing CKD in patients with newly diagnosed T2D	Annual screening	Micro-albuminuria (immuno-nephelometric method) (UAE ≥ 30 mg/day). Treat with ACE inhibitor/A2RB if test positive or if patient is HT	(1) No testing and no treatment; (2) No testing and treat all (ACE inhibitor/A2RB therapy)	QALY	Decision tree + cohort Markov model	Healthcare provider	Screening for micro-albuminuria in patients with T2D is cost-effective
Yarnoff *et al.* (2017) USA[213]	General population (age N/R)	Assess the cost-effectiveness of screening for early-stage CKD using published CKD risk scores	Initial screen + follow-up at 1-, 2- or 5-year intervals	Initial risk assessment (two published CKD risk scores) + albuminuria screening (ACR ≥ 30 mg/g), with follow-up screening for test negative cases. Treat with ACE inhibitors or A2RBs	No screening	QALY	Micro-simulation Markov model	Healthcare perspective (insurer payments + patient out of pocket payments)	Population screening incorporating an initial risk assessment and using a 2-year follow-up interval is cost-effective

CHD, coronary heart disease; HT, hypertensive; HPLC, high-performance liquid chromatography; LYG, life year gained; NHSP, National Health Screening Program; N/R, not reported; QALY, quality-adjusted life-year; T1D, type 1 diabetes; T2D, type 2 diabetes; UACR, urinary albumin-to-creatinine ratio; UAE, urine albumin excretion; UPCR, urine protein creatinine ratio.

primary care,[195–197,199,203,205,207–210,218,219] or had no clearly-defined setting.[200,202,204,213,214,216,217,220,221,223] Less commonly explored settings included community care and secondary care settings.

The time horizons adopted in these studies were based either on the final age of the patient population or on a specific period of time. The vast majority of studies adopted long-term time horizons to capture downstream cost and health outcomes: 5 studies adopted a lifetime horizon until all the patients had died;[195,202,203,210,221] 10 studies ran the model analysis until the patient population had reached 90 years old or more;[198,200,207–209,213,214,218,219,223] 2 studies ran the analysis until the patient population had reached age 75 years;[196,201] 3 studies adopted a time horizon of 45–60 years;[211,216,217] and 5 studies adopted a 25- to 30-year time horizon.[197,204,210,212,215] Only two studies implemented time horizons of < 20 years.[205,220] A further study did not incorporate a time horizon – this study adopted a decision tree approach and considered the cost-per-case of CKD detected for urine dipsticks targeting school-aged children.[199] One final study failed to report the time horizon.[222]

Study methods

How was test diagnostic accuracy considered in the analysis?

Eight studies did not incorporate any measure of diagnostic accuracy into the model, despite evaluating test-based strategies.[195,200,203,204,211,214,221,222] Of these, most did not mention or discuss the topic of accuracy at all. Only one explicitly reported their assumptions: in their analysis of annual screening for albuminuria in patients with type 2 diabetes, Golan and colleagues explained that the evaluated test for micro-albuminuria was assumed to have perfect diagnostic sensitivity in the model (which would favour the testing arm compared to the 'treat all' comparator), and that the outcomes for any FP cases resulting from testing were assumed to be captured within clinical trial data used to inform subsequent CKD progression rates within the model.[203]

Table 44 summarises the methods employed across the 20 studies that did explicitly incorporate diagnostic accuracy into their models. Fourteen studies incorporated the possibility of both FP and FN test results (typically using diagnostic sensitivity and specificity metrics).[196,197,201,202,207,209,210,212,213,215,220,223] Six studies meanwhile only considered the possibility of FP test results (mostly modelled using either PPV or diagnostic specificity metrics);[199,205,216–219] of those, three studies explained that FN test results were not considered since the evaluated test was assumed to have perfect diagnostic sensitivity[218,219] or NPV,[199] without providing any justification for this assumption, while two studies did not mention or discuss the possibility of FN results.[216,217] A final study indirectly captured FPs by calculating the number of subjects needed to be screened and tested to identify and treat 1000 subjects with confirmed albuminuria.[205]

In the majority of studies, diagnostic accuracy values were informed by a single published study;[197–199,201,207–209,213,218,219,223] in two cases, the cited study was a systematic review.[218,219] Two studies cited multiple publications informing the diagnostic accuracy estimates,[196,220] one of which reported taking averages of the published values to derive the model diagnostic accuracy parameters.[220] No studies reported conducting a formal literature review or meta-analysis to inform the model diagnostic accuracy values. Two studies derived accuracy values from a primary diagnostic accuracy study,[212,215] and a further study derived values from insurance claims data.[202] One study utilised individual-level data from available data sets of repeated test values, to construct linear random-effects models of longitudinal log-ACR values (for patients with type 1 and type 2 diabetes) incorporating: (1) between-subject variation in baseline ACR (i.e. the intercept); (2) the average change in ACR over time; and (3) the difference between observed ACR and the underlying 'true' ACR for an individual, described as the within-person variability in ACR measurement arising from assay variability and short-term biological variability.[210] The FP and FN rates in this case were then calculated based on classification errors resulting in differences between the true and measured ACR values over different time points, based on the regression simulation models. Two final studies failed to report any source for the reported accuracy values.[216,217]

TABLE 44 Summary of approaches to incorporating test diagnostic accuracy for studies included in the systematic review of model-based economic evaluations

Study	Type and timing of testing	Tests evaluated	Diagnostic accuracy measures modelled	Source for diagnostic accuracy data	Consequences for FP and FN results in the model	SA conducted and key results
Adarkwah *et al.* (2010) Germany[218]	Annual screening	(1) Micro-albuminuria; (2) macro-albuminuria	(1) Micro-albuminuria: assumed perfect accuracy in base case; 81% specificity applied in SA. (2) Macro-albuminuria: accuracy not discussed	Published systematic review (details N/R)	FPs: not considered. FNs: consequences unclear	Micro-albuminuria: 81% specificity applied in one-way SA. Specificity was not included in the list of parameters stated to have the greatest impact on the results
Adarkwah *et al.* (2011) The Netherlands[219]	Annual screening	As above	As above	As above	As above	As above
Boersma *et al.* (2010) The Netherlands[205]	One-off screening	Micro-albuminuria (UAC) + confirmatory test (UAE)	Number of subjects needed to be screened to identify 1000 subjects with albuminuria (reported 373 identified with micro-albuminuria per 10,000 screened)	PREVEND trial study data (n = 8592)	FPs: incurred cost of confirmatory testing (assumed to be perfect, thus no unnecessary treatment). FNs: not considered	Different test thresholds were explored (accuracy values N/R). Higher thresholds improved the cost-effectiveness but reduced the overall health gains achieved
Boulware *et al.* (2003) USA[196]	Annual screening	Proteinuria (dipstick). Confirmatory ACR and eGFR	Proteinuria dipstick test: sensitivity (76%) and specificity (79%)	Four published studies (N/R if/how values were synthesised)	FPs: all assumed to be identified at confirmatory testing. FNs: remained in untreated states until further screening, subject to higher risk of mortality and CKD progression	In one-way SA, dipstick sensitivity and specificity values were among those parameters found to have the highest impact on the model results
Critselis *et al.* (2018) Europe[223]	Annual screening	A urinary peptide classifier (CKD273) + UAE	CKD273: sensitivity (94.6%) and specificity (97.1%). UAE test: sensitivity (70%) and specificity (71%)	Two published studies	FPs: received unnecessary treatment (unclear if/when treatment would be stopped). FNs: remain untreated, and appeared to be subject to higher risk of CKD progression (full details N/R)	All variables were stated to be explored in one-way SA. No diagnostic accuracy values were included in the results (only those parameters with the highest impact were shown)
Den Hartog *et al.* (2009) USA[220]	Annual screening	eGFR + serum creatinine	eGFR: sensitivity (92.4%) and specificity (83.5%). Serum creatinine: sensitivity (55.9%) and specificity (95.0%)	Averages taken across n = 2 (eGFR) and n = 3 (serum creatinine) published studies	FPs: incurred one-time cost of confirmatory testing by a nephrologist, then return to a 'true negative' state. FNs: remain untreated with higher risks of progression to ESKD	One-way SA showed that increasing the sensitivity of serum creatinine led to that strategy becoming superior to eGFR

continued

TABLE 44 Summary of approaches to incorporating test diagnostic accuracy for studies included in the systematic review of model-based economic evaluations (*continued*)

Study	Type and timing of testing	Tests evaluated	Diagnostic accuracy measures modelled	Source for diagnostic accuracy data	Consequences for FP and FN results in the model	SA conducted and key results
Farmer *et al.* (2014) UK[210]	Screening every 1–10 years	Micro-albuminuria (UACR)	FP and FN rates over time were derived from random-effects linear regression models of log-ACR, which incorporated within-patient biological variation	Regression models constructed using individual patient-level data sets (ORPS and CARDS)	FPs: lead to additional testing and unnecessary treatment. FNs: remain untreated and subject to higher risks of progression (and mortality in the case of T2D)	No SA conducted on diagnostic accuracy
Go *et al.* (2019) Korea[202]	Screening every 2 years, starting age 40	Proteinuria (urine dipstick) and eGFR	Dipstick: sensitivity (range: 31–36%) and specificity (95–98%). eGFR: sensitivity (69–74%) and specificity (88–96%). Different values listed for diabetic, HT, or 'neither' populations	Estimated based on NHIS claims data (2013)	FPs: unclear (not discussed). FNs: remain untreated, with higher risks of progression, CVD events and mortality	Diagnostic accuracy ranged from −20% to 1 in one-way SA. Diagnostic accuracy was not included in the list of parameters stated to have the most influential impact on the results
Hoerger *et al.* (2010), USA[206,207]	Screening every 1, 2, 5 or 10 years	Micro-albuminuria (ACR)	Sensitivity (76%) and specificity (96%).	Single published study of 165 patients	FPs: receive confirmatory ACR test, with all FPs assumed to be identified at this stage. FNs: remain untreated and subject to higher risks of progression and mortality	Sensitivity of ACR test varied by ±25% in one-way SA. Compared to other parameters, the test sensitivity did not have a large impact on the results
Hoerger *et al.* (2012), USA[208]	As above	As above	As above	As above	As above	No SA conducted on diagnostic accuracy
Howard *et al.* (2010) Australia[198]	Annual screening	Proteinuria (urine dipstick) + confirmatory spot UPCR	Protein dipstick: sensitivity (89%) and specificity (94%)	Single published study + expert opinion	FPs: unclear (not discussed). FNs: remain untreated, with higher risks of progression, CVD events and death	No SA conducted on diagnostic accuracy
Kessler *et al.* (2012) Switzerland[209]	Screening every 1, 2, 5 or 10 years	Micro-albuminuria (ACR)	As in Hoerger *et al.* (2010)	As in Hoerger *et al.* (2010)	As in Hoerger *et al.* (2010)	No SA conducted on diagnostic accuracy
Kiberd *et al.* (1995) Canada[216]	Annual screening	(1) Micro-albuminuria (UAE); (2) macro-albuminuria (dipstick)	Micro-albuminuria: PPV (80%). Macro-albuminuria: N/R	No source provided	FPs: for micro-albuminuria screening, FPs appeared to receive unnecessary treatment (details N/R). FNs: not considered	One-way SA lowering the PPV showed that the results were sensitive to this parameter
Kiberd *et al.* (1998) Canada[217]	Annual screening	(1) Micro-albuminuria (UAE); (2) macro-albuminuria (dipstick)	Micro-albuminuria: PPV (80%). Macro-albuminuria: N/R	No source provided	FPs: for micro-albuminuria screening, FPs appeared to receive unnecessary treatment (details N/R). FNs: not considered	No SA conducted on diagnostic accuracy

TABLE 44 Summary of approaches to incorporating test diagnostic accuracy for studies included in the systematic review of model-based economic evaluations (*continued*)

Study	Type and timing of testing	Tests evaluated	Diagnostic accuracy measures modelled	Source for diagnostic accuracy data	Consequences for FP and FN results in the model	SA conducted and key results
Le Floch *et al.* (1994) France[215]	Annual screening	Semiquantitative dipstick (UAE) + standard albuminuria test for positive dipstick results	Pre-screen dipstick: sensitivity (90.8%) and specificity (80.1%)	Primary diagnostic test accuracy study (*n* = 506)	FPs: assumed to all be identified at confirmatory testing. FNs: days of life lost in perfect health for delays in diagnosis (1–5 years) were estimated based on an expert elicitation exercise with 30 physicians	The frequency of FN results was found to have a significant effect on the results in one-way SA
Palmer *et al.* (2008) USA[197]	Annual screening	Micro-albuminuria (semiquantitative urine dipstick) (UAE)	Sensitivity (range 70–97%) and specificity (range 71–98%) reported for urine test strips	Single published study	FPs: received unnecessary treatment (unclear if/when treatment would be corrected). FNs: remain untreated and subject to higher risks of CKD progression	Test accuracy included in PSA only
Sekhar *et al.* (2010) USA[199]	One-off screening	Proteinuria/ haematuria (urine dipstick), + repeat test for elevated results	NPV assumed to be 100%. Reported data relating to PPV: of 8954 tested, 1264 had an initially raised result, 319 had a persistent abnormality, and 11 had a final diagnosis of CKD	Previously published study including *n* = 8954 children	FPs: assumed to all be identified at confirmatory testing. FNs: not considered	No SA conducted on diagnostic accuracy
Srisubat *et al.* (2014) Thailand[201]	Annual screening	Micro-albuminuria (urine dipstick)	Sensitivity (95.2%) and specificity (84.7%)	Single published cost-effectiveness study	FPs: receive unnecessary treatment (unclear if/when treatment would be corrected). FNs: remain untreated and subject to higher risks of CKD progression	The PPV was found to have the largest impact on the ICER result in one-way SA
Wang *et al.* (2017) China[212]	One-off screening	Micro-albuminuria (UACR)	Sensitivity (range: 93.9–100%) and specificity (46.7–81.3%) reported for different combinations of sequential testing strategies	Primary diagnostic accuracy cohort study (*n* = 160)	FPs: receive unnecessary treatment, with the possibility of reverting to a Negative Urine Test state. FNs: remain untreated and subject to higher risk of mortality	The FN and TP rate of different strategies were stated to have the highest impact on the cost-effectiveness results in one-way SA (full results N/R)
Yarnoff *et al.* (2017) USA[213]	Initial screen + follow-up every 1, 2 or 5 years	Risk assessment + albuminuria testing (ACR)	ACR: sensitivity (73%) and specificity (96%)	Single published study	FPs: appeared to all be identified at second ACR confirmatory test. FNs: remain untreated and subject to higher risks of progression and mortality	No SA conducted on diagnostic accuracy

CARDS, Collaborative Atorvastatin Diabetes; HT, hypertensive; HPLC, high-performance liquid chromatography; NHIS, National Health Insurance Service; N/R, not reported; ORPS, Oxford Regional Prospective Diabetes Study; PSA, probabilistic sensitivity analysis; SA, sensitivity analysis; UAC, urinary albumin concentration; UACR, urinary ACR; UAE, urinary albumin excretion; UPCR, urine protein creatinine ratio;

In terms of modelling the impact of test inaccuracies, patients with FN results were assumed to remain in 'untreated' health states, and thereby could not benefit from treatment for CKD (typically corresponding to ACE inhibitor or A2RB therapy) until future screening rounds. Most often the consequence of missed treatment was modelled as higher risks of progression to later CKD stages (which in turn could be associated with higher mortality risks and lower health-related quality of life values);[196–198,201,202,207–210,213,220,223] two studies also included higher risks of cardiovascular disease (CVD) events for patients with FN results.[198,202] One of the earlier studies identified quantified the impact of FN results in terms of patient lost 'quality of life days', based on an expert elicitation exercise conducted with 30 physicians.[215]

In the case of FP results, the most common consequence modelled was the unnecessary cost of additional/confirmatory testing.[196,199,205,207–210,213,215,220] In most cases, confirmatory testing was assumed to have perfect accuracy, thus removing all FP cases at this stage (although this was typically not clearly reported). In several studies, FP cases were stated to undergo unnecessary treatment.[197,201,210,212,216,217,223] However, in general it was not clear how long patients were assumed to remain on unnecessary treatment. In two studies, the consequences for FP cases were not reported.[198,202]

Of those studies that evaluated repeated testing scenarios and explicitly accounted for diagnostic accuracy in the model, the majority assumed that the same diagnostic accuracy values would apply over time.[196–198,201,202,207–209,213,215–220,223] While no study explicitly stated this assumption, it may be inferred from the fact that single values of diagnostic accuracy were reported, and that no considerations concerning accuracy over repeated tests were discussed. Two studies meanwhile did attempt to account for changes in test diagnostic accuracy that could result from sampling at different time points.[210,212] The study conducted by Wang and colleagues included a primary diagnostic accuracy study, in which the impact of within-patient biological variability and assay variability was explored by evaluating different repeated-sampling strategies over a 3-month period – consisting of different combinations of five samples taken at the first day ante meridiem of each month (labelled DAY-1, MONTH-2, MONTH-3), the second day in the first month (DAY-2) and a random spot urine sample taken in the afternoon of the first day (RANDOM-1).[212] Farmer and colleagues meanwhile constructed random-effects linear regression models to simulate the trajectory of log-ACR values over time for two separate populations (type 1 and type 2 diabetes), which accounted for errors in measured ACR values resulting from within-patient biological variation and assay imprecision.[210] Using these simulation models, the authors were able to model changing rates of FP and FN values over time.

What approach was used to model disease progression?

The majority of studies used a cohort Markov model approach to model disease progression. Four studies applied a microsimulation approach to a Markov model structure.[207–209,213] This means that the model followed patients individually as they passed through different states of the Markov model rather than monitoring the average probability of events for a representative cohort of patients. An additional study, which included two separate cost-effectiveness models (one for each of type 1 and type 2 diabetes), utilised an individual based model structure in which a series of risk equations were run within each model cycle (dependant on individual patient characteristics), to predict the timing of a series of cardiovascular and mortality events, in addition to renal failure.[210] Only one study did not model disease progression and instead used a decision tree approach to establish the cost-effectiveness of identifying cases of CKD amongst school children.[199]

Amongst those studies that described the progression of CKD (prior to ESKD), this was implemented through the use of progressive albuminuria[195,201,203,204,210,214–219,223] or GFR states.[202,222] In addition, four studies modelled CKD progression based on both albuminuria and GFR states:[207–209,213] all of these were based on the 'CKD Health Policy Model', originally published by Hoerger and colleagues in 2010.[206,207] Of those studies that tracked progression via albuminuria levels, health states were typically divided into 'normal albuminuria', 'microalbuminuria' and 'macroalbuminuria', before progression to end-stage disease states. Of those studies that tracked progression according to GFR levels, the stages of CKD were most

often split into five GFR levels. Most studies assumed a step-by-step process of disease progression (i.e. patients could only move up one health state in the ladder of progression per model cycle), and only a minority explicitly allowed for the possibility of the reversibility in CKD severity.[201,205,211]

For the later stages of disease, the majority of studies included a single health state for ESKD, followed by death. Several others delineated this stage of disease, most often including states for ESKD with and without renal replacement therapy; and before and after kidney transplantation. In addition, beyond the modelled CKD health states, several studies also captured cardiovascular complications associated with CKD (including events such as 'heart attack', 'stroke', 'cardiovascular disease' and 'coronary artery disease') either in the form of separate health states or additional risks applied to CKD health states.[195,198,202,205,207–210,213,223] One study also captured additional outcomes for patients with diabetes (blindness and amputation).[210]

Were the impacts of any delays on the testing and treatment pathway considered?

Since the focus of the included studies was on screening, the most common type of delay considered was in correctly identifying disease positive patients. The most frequently evaluated screening strategy involved annual screening.[196–198,201,203,204,207–210,213–220,223] Several studies also explored increasing the screening interval beyond 1 year up to a maximum of 10 years, thereby implying that a patient who becomes eligible may have to wait up to 10 years before diagnosis and treatment is offered (although several studies allowed for the possibility of clinical presentations and diagnoses, or opportunistic screening, between scheduled screening intervals).[207–210,213] Interestingly, only one study considered the possibility of a screening interval of < 1 year.[195] It is noted that among the studies included in this review, screening interventions tended to be cost-effective among patients with diabetes and/or hypertension but were typically not cost-effective within general populations unless restricted to higher-risk groups or adopting a longer screening interval.

No studies considered the possibility of a delay in receiving results following testing. While it is acknowledged that for the modern healthcare systems considered in this review, these delays will be minimal, delays in the communication of abnormal test results to patients can still occur. In addition, receiving immediate treatment following a confirmed positive test seems to have been an implicit assumption made in all of the studies where testing and treatment were considered.

Which testing costs were captured in the analyses and how?

The cost of testing related to screening activities captured in the included studies was typically limited to the unit cost of the screening test alone.[195,198,199,201–205,208,212,214–219,223] Eight studies also included the cost of a physician/GP visit associated with the initial screening test(s) undertaken.[196,197,207,209–211,213,221] One study included additional screening costs (including transportation of equipment and personnel, advertisement, human resources and dissemination) related to undertaking screening within a remote indigenous population.[211] One study provided no specific details regarding screening test costs,[222] while another assumed that no screening costs would be incurred due to the fact that the tests evaluated were assumed to already be reported routinely in standard care.[220] One study applied the cost of a physician visit only, without explicitly including the cost of the screening test.[213]

Of those studies that provided information on the included screening costs, the most commonly cited sources related to national costing tariffs such as the Medicare and Medicaid fee schedule or reimbursement rates in the USA,[196,203,207,208,213,220] and similar costing resources across other jurisdictions.[198,212,218,221] Two studies reported that the test costs were based on a 'recommended retail price'[223] or 'notified fee'[202] but did not provide specific sources for these costs. Four studies meanwhile reported that they based screening costs on local institution (e.g. hospital)[199,204,214] or national[215] cost data, but failed to provide specific details. Of the remaining studies, five based the costs on previous studies including cost-effectiveness models,[205,209–211,219] while one derived costs from a survey of health service providers, based on the respondents quoted prices to add the evaluated screening test to standard care (specific details about what this cost was assumed to include were not reported).[200] Five

studies failed to provide a source for the included test costs,[197,201,216,217,222] while one study stated that the reported test costs were based on assumed values.[195]

Six studies reported adopting a societal perspective,[196,200–203,212] with the remainder using a healthcare provider/insurer perspective. Of those studies stating that a societal perspective was adopted, half of them did not provide any specific details.[200,203,212] One study included societal costs relating to lost wages alone: Boulware *et al.* incorporated lost wages resulting from patients aged < 65 years unable to work in the ESKD health state.[196] The two remaining studies captured additional elements of societal costs. Srisubat *et al.* included nonmedical costs relating to food and travel expenditure in addition to lost earnings, based on a cross-sectional survey of patients with normoalbuminuria, microalbuminuria, macroalbuminuria and ESKD;[201] Go and colleagues based their model health state costs on a previously published costing study, which captured productivity loss, transportation and caregiver costs associated with hospital inpatient and outpatient visits.[202] None of the identified studies specifically discussed societal costs resulting from having to attend testing (and re-testing) – rather the focus tended to be on societal costs associated with long-term treatment of disease.

Study quality

The most common issue apparent from the study quality assessment concerned a failure of all but four studies to discuss all the issues relevant to users, which in this case meant that studies did not include any discussion regarding the impact of testing diagnostic accuracy on the modelled outcomes, or the impact of testing from the patient perspective (e.g. costs incurred, anxiety, etc.).

In terms of determining the validity of the models, the most common approach was to address the cross-validity of the model results, by comparing them to results obtained from other, similar studies within the study discussion sections.[196,198–201,205,207,210,211,214,218,219,221] Seven studies took a more formal approach to model validation, and assessed the external validity of their models by comparing key model outcomes (most commonly, mortality) against external data not used in the model itself.[196,202,206,207,210,211,216,223] Only one study reported having conducted internal validation checks of the model coding.[223] Ten studies did not appear to conduct any validation exercises.[195,203,208,209,212,215–217,220,222]

Economic evaluation review search strategies

All searches were conducted on 4 February 2020.

CINAHL (EBSCO) 1981–present

S23 S13 AND S16 AND S20 Limiters – Published Date: 20140101 150
S22 S13 AND S16 AND S20 Limiters – Language: English 353
S21 S13 AND S16 AND S20 356
S20 S17 OR S18 OR S19 306,573
S19 ((MH 'Renal Insufficiency, Chronic') OR (MH 'Kidney Failure, Chronic')) OR 'Chronic kidney disease' 31,469
S18 (MH 'Diabetes Mellitus+') OR 'diabetes' OR (MH 'Diabetes Mellitus, Type 1+') OR (MH 'Diabetes Mellitus, Type 2') 201,556
S17 (MH 'Hypertension, Renal+') OR (MH 'Hypertension+') OR 'hypertension' OR (MH 'Masked Hypertension') OR (MH 'Hypertension, Renovascular') 105,989
S16 S14 OR S15 32,022
S15 AB glomerular filtration rate or gfr or egfr or microalbuminuria or macroalbuminuria or albuminuria or proteinuria or urine albumin electrolyte or UAE or albumin creatinine ratio or ACR or Modification of Diet in Renal Disease or MDRD or dipstick or serum creatinine or Cystatin C or Chronic Kidney Disease Epidemiology Collaboration equation or CKD-EPI 27,306

S14 TI glomerular filtration rate or gfr or egfr or microalbuminuria or macroalbuminuria or albuminuria or proteinuria or urine albumin electrolyte or UAE or albumin creatinine ratio or ACR or Modification of Diet in Renal Disease or MDRD or dipstick or serum creatinine or Cystatin C or Chronic Kidney Disease Epidemiology Collaboration equation or CKD-EPI 9247
S13 s7 not s12 256,118
S12 S8 OR S9 OR S10 OR S11 711,380
S11 (MH 'Animals+') not (MH 'Human') 77,363
S10 PT commentary 264,411
S9 PT letter 278,709
S8 PT editorial 263,811
S7 S3 OR S4 OR S5 OR S6 274,668
S6 TI (cost or costs or economic* or pharmacoeconomic* or price* or pricing*) OR AB (cost or costs or economic* or pharmacoeconomic* or price* or pricing*) 206,333
S5 (MH 'Health Resource Utilization') 16,908
S4 (MH 'Health Resource Allocation') 8503
S3 S1 not S2 95,952
S2 (MH 'Financial Management+') OR (MH 'Financial Support+') OR (MH 'Financing, Organized+') OR (MH 'Business+') 766,422
S1 (MH 'Economics+') 770,281

CRD Database (University of York)

Search ALL FIELDS: (glomerular filtration rate or gfr or egfr or microalbuminuria or macroalbuminuria or albuminuria or proteinuria or urine albumin electrolyte or UAE or albumin creatinine ratio or ACR or Modification of Diet in Renal Disease or MDRD or dipstick or serum creatinine or Cystatin C or Chronic Kidney Disease Epidemiology Collaboration equation or CKD-EPI)

Limit to: HTA

Limit to: 2014 TO 2020

29 records

EconLit (EBSCO) 1886–present

S3 S1 AND S29
S2 TX (kidney or renal) OR TX diabetes OR TX hypertension1030
S1 TX glomerular filtration rate or gfr or egfr or microalbuminuria or macroalbuminuria or albuminuria or proteinuria or urine albumin electrolyte or UAE or albumin creatinine ratio or ACR or Modification of Diet in Renal Disease or MDRD or dipstick or serum creatinine or Cystatin C or Chronic Kidney Disease Epidemiology Collaboration equation or CKD-EPI3192

EMBASE Classic + EMBASE (Ovid) 1947 to 3 February 2020

1 exp chronic kidney failure/ (96540)
2 testing.mp. (877236)
3 test.mp. (3158854)
4 1 or 2 or 3 (3794963)
5 (glomerular filtration rate or gfr or egfr or microalbuminuria or macroalbuminuria or albuminuria or proteinuria or urine albumin electrolyte or UAE or albumin creatinine ratio or ACR or Modification of Diet in Renal Disease or MDRD or dipstick or serum creatinine or Cystatin C or Chronic Kidney Disease Epidemiology Collaboration equation or CKD-EPI).mp. (357113)
6 health economics/ (37526)

7 exp economic evaluation/ (302308)
8 exp Health Care Cost/ (290317)
9 pharmacoeconomics/ (7284)
10 6 or 7 or 8 or 9 (537767)
11 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (1057908)
12 (expenditure$ not energy).ti,ab. (40339)
13 (value adj2 money).ti,ab. (2413)
14 budget$.ti,ab. (38477)
15 11 or 12 or 13 or 14 (1094602)
16 10 or 15 [Economic Evaluations] (1323184)
17 letter.pt. (1106184)
18 editorial.pt. (642779)
19 note.pt. (792819)
20 17 or 18 or 19 (2541782)
21 16 not 20 (1219885)
22 (metabolic adj cost).ti,ab. (1523)
23 ((energy or oxygen) adj cost).ti,ab. (4565)
24 ((energy or oxygen) adj expenditure).ti,ab. (31751)
25 22 or 23 or 24 (36709)
26 21 not 25 (1212209)
27 animal/ (1946633)
28 exp animal experiment/ (2501074)
29 nonhuman/ (6063266)
30 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (6490855)
31 27 or 28 or 29 or 30 (9609463)
32 exp human/ (21886995)
33 human experiment/ (484426)
34 32 or 33 (21888608)
35 31 not (31 and 34) (7168250)
36 26 not 35 (1101886)
37 conference abstract.pt. (3694392)
38 36 not 37 [Econ Evaluations with exclusions removed] (906391)
39 4 and 5 and 38 [(Chronic Kidney Failure or test) and CKF marker and Economic Evaluation] (1671)
40 limit 39 to english language (1557)
41 limit 40 to yr='2014 -Current' (727)

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process and Other Non-Indexed Citations and Daily 1946 to February 03, 2020

1 chronic kidney disease.mp. or Renal Insufficiency, Chronic/ (55137)
2 Diabetes Mellitus, Type 1/ or diabetes.mp. or Diabetes Mellitus, Type 2/ or Diabetes Mellitus/ (603783)
3 Hypertension, Renal/ or Hypertension/ or hypertension.mp. (478207)
4 1 or 2 or 3 (1037198)
5 (glomerular filtration rate or gfr or egfr or microalbuminuria or macroalbuminuria or albuminuria or proteinuria or urine albumin electrolyte or UAE or albumin creatinine ratio or ACR or Modification of Diet in Renal Disease or MDRD or dipstick or serum creatinine or Cystatin C or Chronic Kidney Disease Epidemiology Collaboration equation or CKD-EPI).mp. (210479)
6 Economics/ (27127)
7 exp 'costs and cost analysis'/ (232285)
8 Economics, Dental/ (1910)

9 exp economics, hospital/ (24201)
10 Economics, Medical/ (9054)
11 Economics, Nursing/ (3996)
12 Economics, Pharmaceutical/ (2913)
13 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (766016)
14 (expenditure$ not energy).ti,ab. (28921)
15 value for money.ti,ab. (1643)
16 budget$.ti,ab. (28480)
17 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 (916045)
18 ((energy or oxygen) adj cost).ti,ab. (4028)
19 (metabolic adj cost).ti,ab. (1375)
20 ((energy or oxygen) adj expenditure).ti,ab. (24472)
21 18 or 19 or 20 (28903)
22 17 not 21 (909395)
23 letter.pt. (1060967)
24 editorial.pt. (516776)
25 historical article.pt. (356566)
26 23 or 24 or 25 (1915078)
27 22 not 26 (873818)
28 exp animals/ not humans/ (4669954)
29 27 not 28 (818401)
30 4 and 5 and 29 (1269)
31 limit 30 to english language (1180)
32 limit 31 to yr='2014 -Current' (440)

PsycInfo (Ovid) 1806 to January Week 4 2020

1 chronic kidney disease.mp. (829)
2 exp Diabetes Insipidus/ or diabetes.mp. or exp Diabetes/ or exp Diabetes Mellitus/ (30318)
3 exp Hypertension/ or exp Essential Hypertension/ or hypertension.mp. (17966)
4 1 or 2 or 3 (44050)
5 (glomerular filtration rate or gfr or egfr or microalbuminuria or macroalbuminuria or albuminuria or proteinuria or urine albumin electrolyte or UAE or albumin creatinine ratio or ACR or Modification of Diet in Renal Disease or MDRD or dipstick or serum creatinine or Cystatin C or Chronic Kidney Disease Epidemiology Collaboration equation or CKD-EPI).mp. (2044)
6 'costs and cost analysis'/ (16418)
7 'Cost Containment'/ (588)
8 (economic adj2 evaluation$).ti,ab. (1668)
9 (economic adj2 analy$).ti,ab. (1519)
10 (economic adj2 (study or studies)).ti,ab. (788)
11 (cost adj2 evaluation$).ti,ab. (333)
12 (cost adj2 analy$).ti,ab. (3638)
13 (cost adj2 (study or studies)).ti,ab. (862)
14 (cost adj2 effective$).ti,ab. (15030)
15 (cost adj2 benefit$).ti,ab. (3438)
16 (cost adj2 utili$).ti,ab. (1241)
17 (cost adj2 minimi$).ti,ab. (366)
18 (cost adj2 consequence$).ti,ab. (115)
19 (cost adj2 comparison$).ti,ab. (186)
20 (cost adj2 identificat$).ti,ab. (26)
21 (pharmacoeconomic$ or pharmaco-economic$).ti,ab. (314)
22 or/6-21 (34293)

23 (task adj2 cost$).ti,ab,id. (625)
24 (switch$ adj2 cost$).ti,ab,id. (1309)
25 (metabolic adj cost).ti,ab,id. (100)
26 ((energy or oxygen) adj cost).ti,ab,id. (285)
27 ((energy or oxygen) adj expenditure).ti,ab,id. (2686)
28 23 or 24 or 25 or 26 or 27 (4720)
29 (animal or animals or rat or rats or mouse or mice or hamster or hamsters or dog or dogs or cat or cats or bovine or sheep or ovine or pig or pigs).ab,ti,id,de. (350338)
30 editorial.dt. (43579)
31 letter.dt. (21932)
32 dissertation abstract.pt. (487548)
33 29 or 30 or 31 or 32 (881656)
34 22 not (28 or 33) (29682)
35 4 and 5 and 34 (6)
36 limit 35 to english language (6)
37 limit 36 to yr='2014 -Current' (2)

Economic evaluation review data extraction form

For those papers included in this systematic review, information was extracted using the following form, copied into an Excel spreadsheet.

Study information
Authors
Title
Year
Location
Study objective
Type of testing (e.g. monitoring/screening)
Timing of test (e.g. annually, one-off, etc.)
Testing strategies evaluated
Comparators evaluated
Specific patient group
Type of economic evaluation (cost-utility, cost-effectiveness etc.)
Source of data to parameterise model
Setting (e.g. primary care, secondary care)
Modelling methodology
What type of model is used (e.g. Markov model, decision tree)?
How is the progression of CKD described in the analysis?
Does the model allow for reversibility (i.e. disease regression)?
What model structures have been used to describe the different model states?
Time horizon
Test accuracy

Study information
Is test accuracy considered in the analysis?
How is the accuracy of repeated testing captured?
Is the possibility of inaccurate (e.g. TN/FP, incorrect prognosis), indeterminate or test failure considered in the analysis?
What was the impact of FP test results in the model?
What was the impact of FN test results in the model?
Is the test accuracy subjected to any sensitivity analysis?
Was confirmatory testing conducted follow test positives?
Patient outcomes
What patient outcomes are considered in the analysis (clinical events, quality of life, etc.)?
Can patient outcomes be influenced by time delay as a result of patients not receiving prompt treatment?
Can patient outcomes be influenced by the timing of testing, decision-making and treatment?
Economic outcomes
Perspective (healthcare provider, societal)
If societal, what societal costs are incorporated in the analysis?
What/how were test costs captured?
What/how were CKD treatment costs captured?
What/how were other costs captured? (e.g. cardiovascular events)
What was concluded from the analysis with respect to the cost-effectiveness of the tests?

Economic evaluation review quality assessment criteria

The following criteria were used in the systematic review of model-based economic evaluations, to assess the quality of the included economic evaluations.

Criteria for quality assessment of economic evaluations	
1	Was a well-defined question posed in an answerable form?
2	Was a comprehensive description of the competing alternatives given?
3	Was the effectiveness of the programmes of services established?
4	Were all the important and relevant costs and consequences for each alternative established?
5	Were costs and consequences measured accurately in appropriate physical units?
6	Were costs and consequences valued credibly?
7	Were costs and consequences adjusted for differential timing?
8	Was an incremental analysis of costs and consequences of alternatives performed?
9	Was allowance made for uncertainty in the estimates of costs and consequences?
10	Did the presentation and discussion of study results include all issues of concern to users?

EME
HSDR
HTA
PGfAR
PHR

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