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Potential impact of NICE guidelines on referrals from primary care to nephrology

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Abstract

Background: NICE 2021 guidelines on chronic kidney disease (CKD) recommend the use of the Kidney Failure Risk Equation (KFRE), which includes measurement of albuminuria. The equation to calculate estimated glomerular filtration rate (eGFR) has also been updated.

Aim: To investigate the impact of KFRE and the updated eGFR equation on CKD diagnosis (eGFR<60mL/min/1.73m^2) in primary care and potential referrals to nephrology.

Design/setting: Primary care database (SAIL) and prospective cohort study (UK Biobank).

Method: CKD diagnosis rates were assessed when using the updated eGFR equation. Amongst people with eGFR 30-59mL/min/1.73m^2, we identified those with annual albuminuria testing and those who met nephrology referral criteria by: A) Accelerated eGFR decline or significant albuminuria B) eGFR decline <30mL/min/1.73m^2 only and C) KFRE>5% only. Analyses were stratified by ethnicity in UK Biobank.

Results: Using the updated eGFR equation resulted in a 1.2-fold fall in new CKD diagnoses in the predominantly white population in SAIL, whereas CKD prevalence rose by 1.9-fold amongst black participants in UK Biobank. Rates of albuminuria testing have been consistently below 30% since 2015. In 2019, using KFRE>5% identified 182/61,721 (0.3%) patients at high risk of CKD progression before their eGFR declined and 361 (0.6%) low risk patients who were no longer eligible for referral. Asian and “other” ethnic groups had disproportionately raised KFREs.

Conclusion: Application of KFRE criteria in primary care will lead to referral of more patients at elevated risk of kidney failure (particularly amongst minority ethnic groups) and fewer low-risk patients. Albuminuria testing needs to be expanded to enable wider KFRE implementation.

Keywords: Renal medicine, General practice, Diagnosis, Guidelines, Large database research, Hospital referrals

How this fits in

- A 2021 NICE guideline on chronic kidney disease (CKD) recommended GPs use the kidney failure risk equation (KFRE) to guide referrals to nephrology.
- The equation used for estimating glomerular filtration rate (eGFR) has been updated.
- In a Welsh primary care population, there was a 1.2-fold fall in new CKD diagnoses if laboratories use the updated equation to report eGFR.
- New CKD referral criteria identify patients at high risk of CKD progression before their eGFR falls below 30mL/min/1.73m^2, particularly amongst minority ethnic groups.
- Implementation of KFRE will rely on raising awareness amongst GPs and improved albuminuria testing rates, which are currently low.

Introduction

In 2006, guidelines on chronic kidney disease (CKD) encouraged the use of estimated glomerular filtration rate (eGFR) to identify and categorise CKD.[1,2] Laboratories started routinely reporting eGFR and referral criteria to nephrology were outlined: eGFR less than 30mL/min/1.73m^2, accelerated decline in eGFR, and significant albuminuria. Only 1-4% of people with CKD will progress to kidney failure requiring treatment i.e., dialysis or kidney transplantation.[3,4] If GPs can identify high-risk people and refer them before they progress to this late stage, nephrologists may be able to slow progression to kidney failure and/or prepare for dialysis or transplantation.

In 2021, a National Institute for Health Care Excellence (NICE) guideline made two recommendations which influence CKD diagnosis and referral to nephrology.[5] Although referral criteria based on accelerated eGFR decline and albuminuria were unchanged, using an eGFR threshold of 30mL/min/1.73m^2 was replaced by the Kidney Failure Risk Equation (KFRE).[6] This allows an individual's risk of kidney failure to be defined, permitting referral and management in secondary care to be personalised to their future risk, rather than based on any particularly eGFR value. The KFRE equation takes account of four variables: age, sex, eGFR, and urine albumin-to-creatinine ratio (uACR). GPs are advised to refer to nephrology if the five-year risk of kidney failure is greater than 5%.

The guideline also recommends that laboratories use eGFR equations which do not include ethnicity. The inclusion of ethnicity in these equations has been debated for several years, with many concerned that ethnicity is a social construct rather than a biological one.[7] The updated equation for eGFR calculation (which does not include ethnicity) was released in 2021,[8] shortly after the updated NICE guideline recommended that such equations be used.

We studied a nationally representative primary care cohort, followed by a prospective research cohort to assess the potential impact of these guideline changes on diagnosis of CKD in primary care, potential referral rates to nephrology, and whether there was a differential impact in ethnic groups.

Methods

Data sources

The Secure Anonymised Information Linkage Databank (SAIL) is an electronic health records repository which holds primary care data for 79% of the population of Wales.[9] We studied patients over the age of 18 with serum creatinine values available between 1st January 2013 and 31st December 2020. Values before 2013 were not included because non-validated laboratory analysers may have been in use.[10] Creatinine, uACR values and diagnoses of CKD, diabetes mellitus, and hypertension were taken from GP read codes, as previously described.[11] Ethnicity is not consistently recorded in these records, so it was not used.

UK Biobank is a research cohort which enrolled volunteer participants between 2006 and 2010 as previously described.[12,13] Sociodemographic and medical information were self-reported and blood and urine samples were taken at baseline.[13] The sampling process has been described previously.[14,15,16] In brief, serum and spot urine samples were collected and analysed at an accredited central laboratory. Creatinine was measured using a Beckman Coulter AU5800 analyser and the assay was externally quality controlled. Of 502,536 participants initially recruited, we excluded 76 who withdrew ongoing consent for follow-up, 33,144 participants with missing creatinine values at baseline, 2,201 participants with unknown ethnicity, and 606 with kidney failure requiring replacement therapy at baseline.

Section 1: Albuminuria testing

In SAIL, we first identified patients with prevalent CKD stage G3A/G3B i.e., two eGFR values[8] 30-59mL/min/1.73m^2 at least three months apart with no values >60mL/min/1.73m^2.[17] Prevalence of CKD stage G3A/G3B was described by calendar year from 2013 to 2020. Rates of annual uACR testing were established for these patients. This included patients with previously identified CKD, so long as they were alive throughout the year. We stratified uACR testing by age, sex, eGFR, diabetes mellitus, and hypertension and whether CKD was coded in their medical records. Tested and untested groups were compared using chi-squared tests for categorical variables and analysis of variance tests for continuous variables.

In UK Biobank, participants were labelled with CKD stage G3A/G3B if the single baseline eGFR available was 30-59mL/min/1.73m^2.

Section 2: Patients meeting referral criteria to nephrology

From the group of patients with CKD stage G3A/G3B, we identified those eligible for nephrology referral by three criteria:

1. Accelerated eGFR decline or albuminuria:

   eGFR decline by ≥25% or ≥15mL/min/1.73m^2 within 12 months, sustained for ≥3 months with no values rising above the threshold; or uACR≥70mg/mmol. Two sensitivity analyses were performed:

   A. Patients with known diabetic nephropathy are not to be referred with this albuminuria threshold. We therefore studied whether patients with diabetes would only be referred if they had heavy to nephrotic-range proteinuria (uACR>200mg/mmol).
   B. Haematuria criteria were not included because information on haematuria was not available. We therefore studied impact on referrals when using a lower uACR threshold of 30mg/mmol instead of 70mg/mmol, which would warrant nephrology referral if accompanied by haematuria.

2. eGFR<30 only

   Incident eGFR <30mL/min/1.73m^2 sustained for ≥3 months with no values rising above 30.

3. KFRE>5% only

   Five-year KFRE of >5%.[5,6,18] For patients with several measurements of eGFR and uACR, we selected the highest KFRE result, given GPs are likely to act on an elevated result when it becomes available.

We discounted those currently or previously under nephrology follow-up, assuming that patients discharged back to primary care had already been assessed. We compared the patients eligible for referral based on eGFR<30 only and KFRE>5% only using analysis of variance tests for age and chi-squared tests for sex (excluding those eligible by both criteria).

In UK Biobank, we identified participants with five-year KFRE>5% and stratified the results, first by ethnicity and then by ethnicity and diabetes mellitus status.

Section 3: CKD prevalence according to eGFR equation

We estimated CKD prevalence in SAIL using different eGFR equations and stratified this by ethnicity in UK Biobank. The approach is detailed in the supplementary file.

Statistical analyses were conducted using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, AUT).

Results

We studied 1,845,040 patients in SAIL and 466,561 participants in UK Biobank (Table 1). Figure S1 is a consort diagram showing the people included in the analysis.

		SAIL	UK Biobank
N		1,845,040	466,561
Female sex: n (%)		1,015,078 (55.0)	253,258 (54.3)
Age (years): median (IQI)		53 (37-67)	58 (50-63)
Ethnicity*: n (%)	**White**	-	441,848 (94.7)
	Black	-	8,241 (1.8)
	Asian	-	11,293 (2.4)
	Mixed	-	1,013 (0.2)
	Other	-	4,166 (0.9)
Diabetes mellitus: n (%)		310,352 (16.8)	24,241 (5.2)
Hypertension: n (%)		569,918 (30.9)	111,475 (23.9)

Table 1. Summary of baseline characteristics by cohort. IQI, interquartile interval

*Ethnicity was not consistently recorded in SAIL. The Welsh population is approximately 95.0% white[19]

Section 1: Albuminuria testing

In SAIL, the prevalence of CKD stage G3A/G3B amongst those with a creatinine measurement was 55,193/752,517 (7.3%) in 2013 and 61,721/850,394 (7.3%) in 2019 (Figure 1A). In 2020, spanning the Covid-19 pandemic, this figure was 53,406/659,740 (8.1%). In UK Biobank, there were 6,739 participants with CKD stage G3A/G3B (1.4%).

Amongst patients with prevalent CKD stage G3A/G3B in SAIL, the rate of annual uACR testing fell from 46.3% in 2013 to 25.3% in 2019 (Figure 1A). eGFR and uACR testing were reduced further in 2020 during the Covid-19 pandemic. The demographics of patients with coded and biochemical CKD G3A/G3B (56.1% female, median age 82 years: IQI 76-88) were similar to patients with biochemical CKD but not coded (55.1% female, median age 81 years: IQI 75-87). Of the patients with CKD G3A/G3B at any time, factors associated with higher rates of uACR testing were male sex, young age, coded CKD, diabetes mellitus, hypertension, and low eGFR (Table S2, Figures S2 and S3).

Section 2: Patients meeting referral criteria to nephrology

Patients meeting referral criteria based on accelerated eGFR decline or albuminuria

In SAIL, between 883 and 1240 people per year had accelerated eGFR decline or significant albuminuria (Figure 1B). Referral of these people are unaffected by the guideline change. Using a uACR threshold of 200mg/mmol for patients with diabetes led to a reduction of patients eligible for referral by these criteria (Figure S4). Using a uACR threshold of 30mg/mmol instead of 70mg/mmol led to an increase in patients eligible for referral by these criteria, assuming these patients also had evidence of haematuria (Figure S5).

Patients meeting referral criteria based on eGFR<30 only

In SAIL, between 265 and 456 people per year developed CKD G4-5 without accelerated eGFR decline or significant albuminuria (0.5% to 0.8% of those with CKD stage G3A/G3B: Figure 1B). In 2019 (the last year before the Covid-19 pandemic), this figure was 361 (0.6%). Using the 2021 NICE guideline, these patients would no longer necessarily be eligible for referral.

Patients meeting referral criteria based on KFRE>5% only

In SAIL, KFRE consistently identified a substantial number of patients who should be referred to nephrology who did not meet other criteria (Figure 1B). In 2019 (the last year before the Covid-19 pandemic), 182/61,721 (0.3%) patients with CKD stage G3A/G3B met referral criteria by KFRE only. In the same year, 802 of 17,332 (4.6%) of patients with CKD stage G3A/G3B and uACR measured had KFRE>5% (this figure includes those already under nephrology follow-up). Importantly, patients eligible for referral only by KFRE criteria were a median of five years younger and more likely to be men than those eligible by eGFR<30 only (Table S1: $p<0.001$ for both variables).

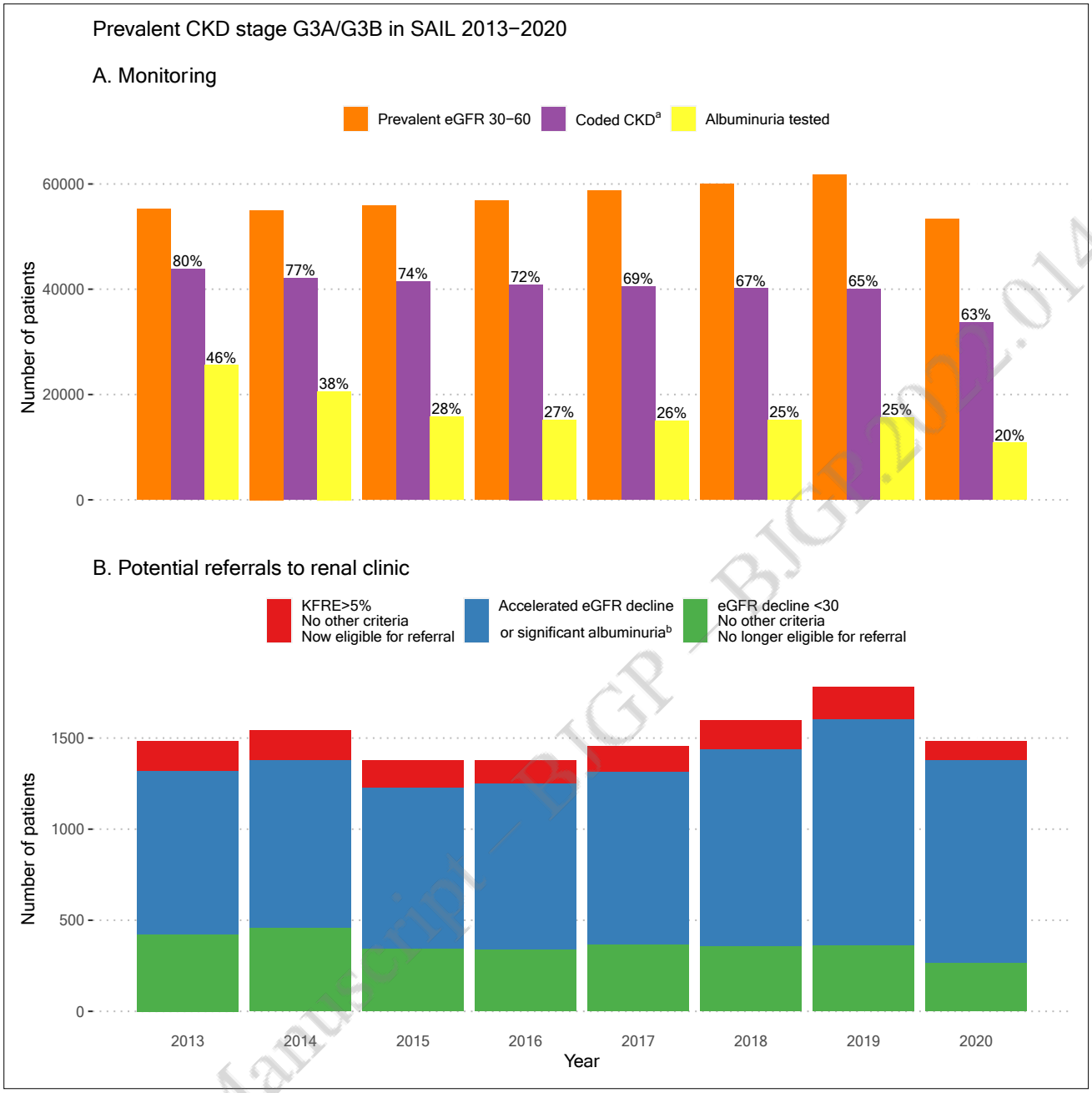

Figure 1. Prevalent CKD stage G3A/G3B in SAIL 2013-2020. [a]In the UK, GPs are expected to add a CKD code as an entry to the patient diagnosis list. The denominator for percentages in panel A are those with prevalent eGFR 30-60. [b] Some of these patients also have KFRE>5% or eGFR decline <30, but their identification is unchanged by the guideline change

In UK Biobank, 150 of 6,739 (2.2%) participants with eGFR 30-59mL/min/1.73m^2 had a five-year KFRE>5%. The proportion of participants with KFRE>5% was highest in those of Asian and other ethnicity (Figure 2). In both cohorts and in all ethnic groups, the proportion of participants with elevated KFRE was higher amongst those with diabetes mellitus compared to those without diabetes mellitus (Figure S6).

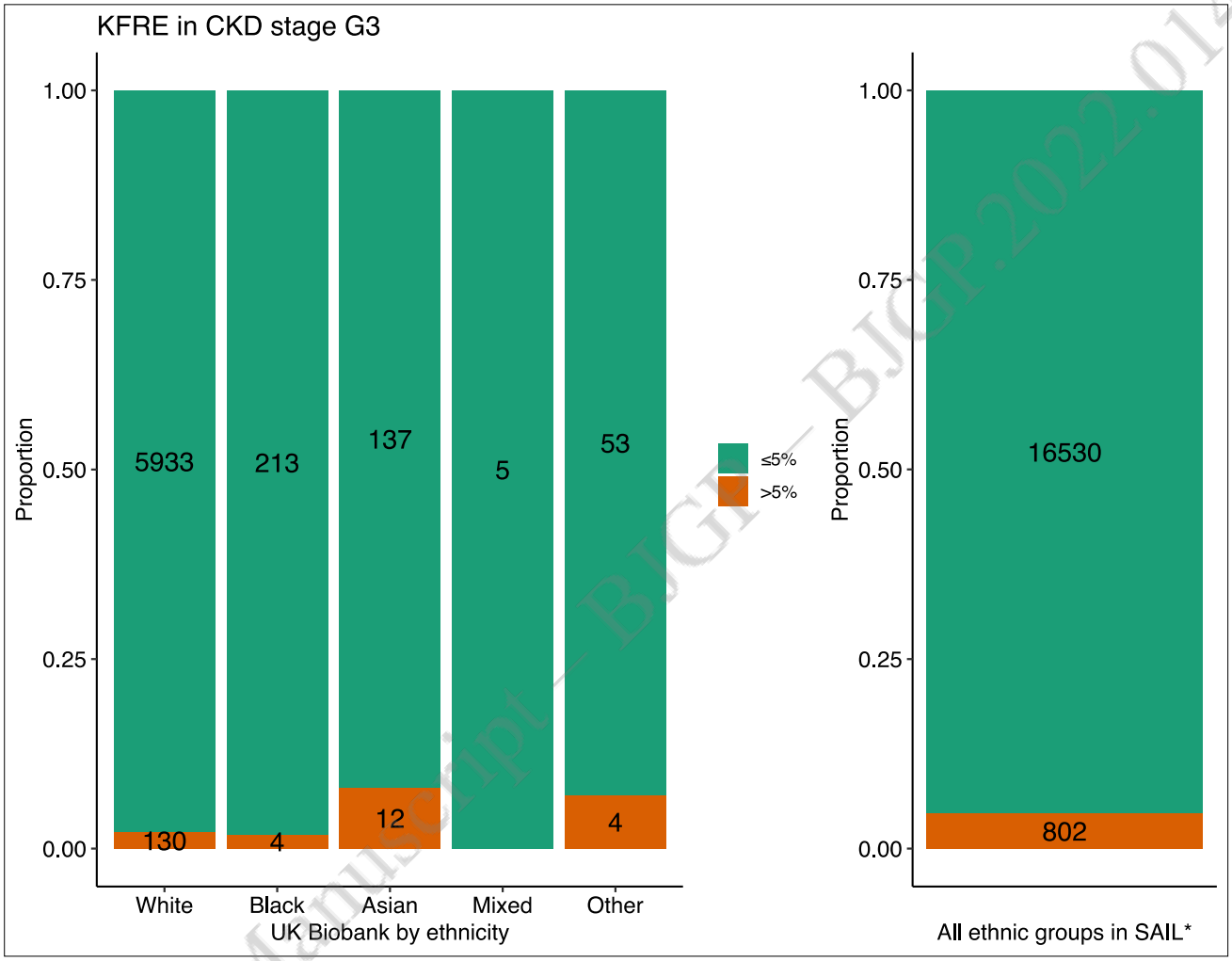

Figure 2. Kidney failure risk by ethnicity in UK Biobank and overall in SAIL. *Ethnicity is not consistently recorded in SAIL

Section 3: CKD prevalence according to eGFR equation

eGFR was lowest using the $eGFR_{MDRD}$ equation and highest using the $eGFR_{2021}$ equation (Figure S7). Amongst patients in SAIL with CKD G3-5, a switch to using $eGFR_{2021}$ from $eGFR_{MDRD}$ would be associated with an average increase in reported eGFR by 2.7mL/min/1.73m^2 (IQI 1.2-4.5).

In practice, this change to laboratory reporting from $eGFR_{MDRD}$ to $eGFR_{2021}$ would result in a 1.2-fold reduction in people diagnosed with CKD Stage G3-5 and a 1.1-fold reduction in CKD G4-5. The number of patients in SAIL with incident CKD Stage G3-5 or incident CKD Stage G4-5 was lowest using the updated $eGFR_{2021}$ equation (Figure 3).

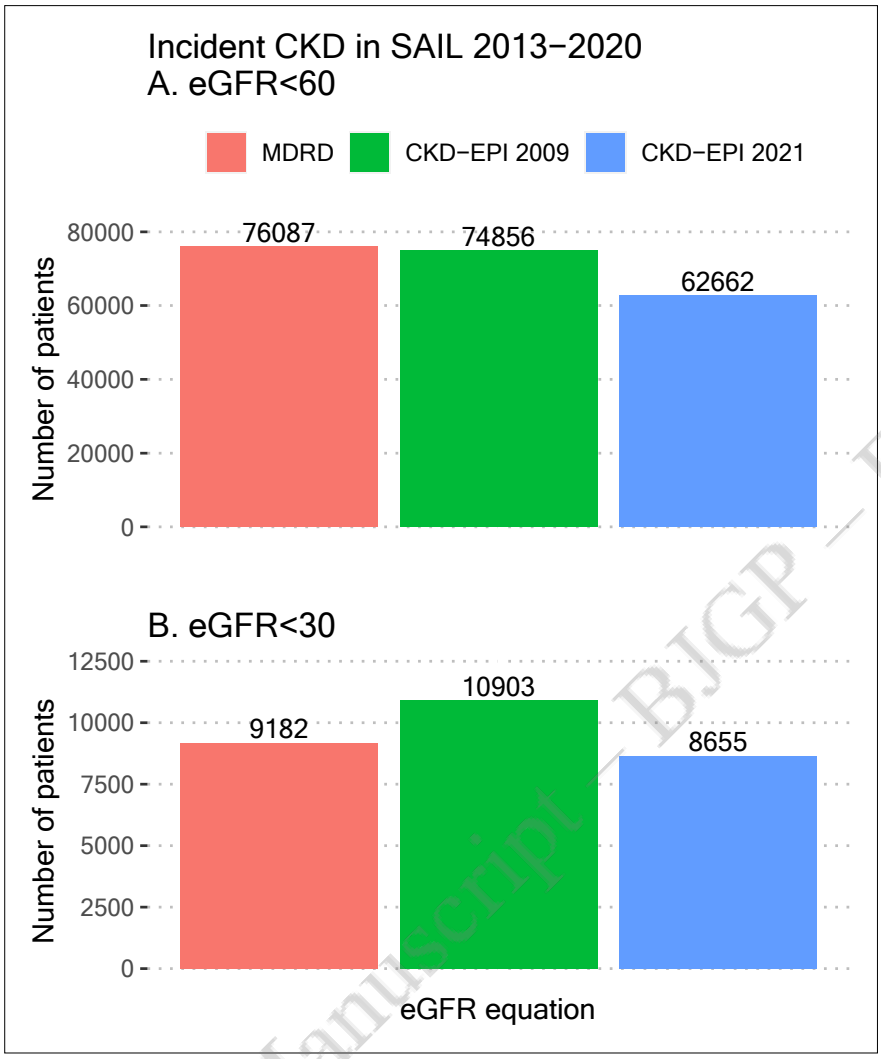

Figure 3. Numbers of patients with incident CKD in SAIL using different eGFR equations between 2013 and 2020

In general, a change in laboratory reporting of $eGFR_{MDRD}$ to $eGFR_{2021}$ is more likely to de-classify older women from a CKD diagnosis (Table S2).

In UK Biobank, the changes in eGFR values and thus categorisation of CKD using different equations were similar amongst non-black participants (Figure S8, Table S4). If laboratories reported $eGFR_{2021}$ instead of $eGFR_{MDRD}$, the number of black participants meeting criteria for CKD G3-5 diagnosis would increase from 124 to 237 (a 1.9-fold increase). This would be offset by 3,463 (33.9%) fewer non-black participants classified as having CKD G3-5 if making

this same reporting change. If $eGFR_{2021}$ was used to calculate KFRE instead of $eGFR_{MDRD}$, the number of black participants with a KFRE over 5% would increase from three to four.

Discussion

Summary

Implementation of KFRE in primary care can help GPs identify a small proportion of additional patients with previously unrecognised elevated risk who may be referred to nephrology before their eGFR declines below 30mL/min/1.73m^2. This will be offset by reductions in referrals for patients with slow declines in eGFR. Regular uACR testing is required for all CKD patients for KFRE calculation, but annual uACR testing is not consistently performed in all people with CKD. Optimal referrals to nephrology will therefore depend on increases in uACR testing and awareness amongst GPs of KFRE.

Implications for research and/or practice

In stage G3A/G3B CKD, only a small proportion of patients are at high risk of CKD progression. These patients can be readily identified using KFRE; however, KFRE will only report elevated five-year risk of kidney failure if there is at least moderate, detected albuminuria i.e., uACR>3mg/mmol. We observed low uACR testing rates (consistently less than 30%) in primary care from 2015 onwards, and particularly low rates in 2020, probably because much routine disease monitoring stopped during the Covid-19 pandemic. We reported annual albuminuria testing rates, although Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend more frequent testing: four- or six-monthly in those with eGFR 30-44mL/min/1.73m^2 and in those with uACR>3mg/mmol.[17] We may therefore have over-estimated the proportion of individuals with albuminuria testing appropriate for their stage of CKD.

Several factors may explain the suboptimal rates of albuminuria testing that we observed in these populations with CKD. Many people with CKD are unaware of the diagnosis (10-59%[20,21]), perhaps because most of them are asymptomatic. By raising patient awareness of CKD and the importance of albuminuria testing, patients may engage better with CKD management, e.g., by encouraging home blood pressure monitoring and proactively providing urine samples for albuminuria testing. We observed higher rates of albuminuria testing in people with coded compared to biochemical CKD. As clinical and laboratory records are predominantly electronic, there may be a role for automating KFRE calculation or indeed entry onto CKD registers, which has been associated with improved albuminuria testing.[22]

Comparison with existing literature

Reduced rates of laboratory testing in primary care in the UK have been reported before in association with changes in the Quality and Outcomes Framework (QOF).[23] The incentivisation of annual uACR testing for people with diabetes mellitus was removed from the GP contract in April 2014.[24] The 2017 National CKD audit in England and Wales reported that 31.1% of people with CKD had an annual uACR test.[25] In 2017, we found the rate to be 25.5%, which may have been lower because the CKD audit reports on stages G3-5, whereas our study was limited to stage G3A/G3B. In keeping with the findings of the National CKD audit, our study suggests that improvements in albuminuria testing particularly need to be targeted in patients with non-diabetic CKD.

By improving uACR testing and using KFRE, GPs will identify patients at high risk of kidney failure at a younger age and an earlier stage of CKD. The lifetime risk of kidney failure is higher at younger age and patients are more likely to live long enough to require dialysis or kidney transplantation compared to older adults. However, CKD is associated with broader risks, primarily cardiovascular disease. Greater recognition of patients at risk of progressive CKD will also identify people at higher risk of cardiovascular disease[26,27] and provide earlier opportunities for primary prevention interventions such as statins and SGLT2-inhibitors.[28,29] A study using five-year KFRE>3% to guide nephrology referrals similarly found that using KFRE to guide referrals instead of an eGFR threshold of 30mL/min/1.73m^2 would reallocate patients between primary and secondary care.[30]

Importantly, KFRE was more likely to be elevated in non-white ethnic groups, in keeping with the previous literature suggesting that non-white people are at the greatest risk of CKD progression.[31] We did not find high rates of elevated KFRE in black participants, which may reflect low levels of albuminuria, Caucasian predominance and healthy volunteer bias in UK Biobank.[32] Nevertheless, we show that implementation of KFRE can identify those at the highest risk and may go some way to attenuating healthcare inequalities in CKD management in non-white ethnic groups. Although the UK population is predominantly non-black, our study confirms that amongst people of black ethnicity, the rates of CKD will rise significantly if laboratories start to report eGFR using the 2021 CKD-EPI equation.

Strengths and limitations

Our study has some limitations. First, we have not reported the rates of observed kidney failure events. Neither SAIL nor UK Biobank are linked to national renal registry records, which most accurately record kidney failure events. However, KFRE has already been validated extensively,[6,33] and is now recommended as a tool to guide risk assessment, nephrology referral, and aid with risk reduction strategies. Second, the lack of ethnicity data in SAIL means we could not report this key information. Though we could report ethnicity differences in KFRE in UK Biobank, diagnosis of CKD here was based on a single baseline measure of kidney function, and we could not use two confirmatory measurements at least three months apart, as recommended in clinical guidelines.[17] Given the relatively healthy and predominantly white population in UK Biobank,[32] and lower rate of CKD and heavy albuminuria than observed than in the general population, it is likely that KFRE underestimated risk of kidney failure in this population. Finally, we used a uACR of >200mg/mmol as an equivalent to nephrotic-range proteinuria (i.e., urine protein to creatinine ratio (uPCR) of >300mg/mmol). Although uACR 200mg/mmol is approximately equivalent to uPCR 300mg/mmol,[34] it would have been preferable if uPCR data had been available to identify patients with nephrotic-range proteinuria.[35]

Conclusion

In summary, use of KFRE in general practice will identify more CKD patients at risk of kidney failure and needing nephrology referral, particularly amongst minority ethnic groups. Fewer patients will be referred with eGFR declining slowly to less than 30mL/min/1.73m^2 with no markers of elevated risk. However, KFRE use will be dependent on universal and regular uACR testing, particularly amongst older adults and those without diabetes mellitus. Overall, updated eGFR equations, if used by UK laboratories, will reduce the numbers of patients categorised as having CKD.

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Ethical approval

SAIL: Swansea University's Health Information Research Unit Information Governance Review Panel granted ethical approval for this study as part of project 0830. UK Biobank: Ethical approval was obtained from the North West Multi-Centre Research Ethics Committee (REC reference 11/NW/03820). The study was conducted under UK Biobank project 69891.

Data availability

The data that support the findings of this study are available from UK Biobank and SAIL, subject to successful registration and application process. Further details can be found at ukbiobank.ac.uk and saildatabank.com.

Competing interests

Outside the submitted work, JSL has received personal honoraria from Pfizer, Bristol Myers Squibb and Astra Zeneca. PBM reports lecture fees and travel to meetings support from Vifor, AstraZeneca, Pharmacosmos, Napp, Astellas, lecture fees from Novartis, Astellas and grants from Boehringer Ingelheim outside the submitted work.

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