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Change in GFR over time in the Oxford Renal Cohort Study

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How this fits in

The prevalence of chronic kidney disease (CKD) increases with age and some people are unaware that they have CKD. We know that some people with CKD will go on to develop adverse health outcomes and understanding what makes this more (or less) likely is important in primary care.

We report the number of people with CKD who experience a rapid deterioration of kidney function measured as a decline in estimated glomerular filtration rate. This work identifies factors associated with a rapid decline in kidney function and describes the number of people who enter and leave CKD remission during follow-up.

Abstract: Max 250 words

Background

Decline in kidney function can result in adverse health outcomes. The OxREN study has detailed baseline assessments from 884 participants ≥60 years.

Aim

To determine the proportion of participants with decline in estimated glomerular filtration rate (eGFR), identify determinants of decline and determine proportions with chronic kidney disease (CKD) remission.

Design and setting

Observational cohort study in UK primary care.

Methods

Data were used from baseline and annual follow-up assessments to monitor change in kidney function. Rapid eGFR decline was defined as eGFR decrease >5 ml/min/1.73m^2/year, improvement as eGFR increase >5ml/min/1.73m^2/year and remission in those with CKD at baseline and eGFR>60 ml/min/1.73m^2 during follow-up. Cox proportional hazard models were used to identify factors associated with eGFR decline.

Results

In 686 participants with a median follow-up of 2.1 years, 164 (24%) evidenced rapid GFR decline, 185 (27%) experienced eGFR improvement and 82 of 394 (21%) meeting CKD stage 1-4 at baseline experienced remission. In the multivariable analysis, smoking status, higher systolic blood pressure and being known to have CKD at cohort entry were associated with rapid GFR decline. Those with CKD stage 3 at baseline were less likely to exhibit GFR decline compared with normal kidney function.

Conclusions

This study established that 24% of people evidenced rapid GFR decline whereas 21% evidenced remission of CKD. People at risk of rapid GFR decline may benefit from closer monitoring and appropriate treatment to minimise risks of adverse outcomes, though only a small proportion meet the NICE criteria for referral to secondary care.

Background

Chronic kidney disease (CKD) is defined as decreased estimated glomerular filtration rate (eGFR) or markers of renal damage of at least 3 months duration.(1) Early stages of CKD are asymptomatic, but over time eGFR may decline and increase risk of cardiovascular disease(2, 3) kidney failure(4) and premature mortality.(2, 5) A sustained decline in eGFR of >5 ml/min/year is the accepted definition of rapid decline in eGFR(1) and factors associated with a decline in eGFR and progression of CKD include poor blood pressure control, diabetes,(6) and obesity.(7) Variability in eGFR itself is also associated with poor health outcomes including end stage kidney disease,(8) cardiovascular events(9) and mortality(10) and may therefore indicate reduced kidney resilience. Data from UK primary care indicates that many people with a diagnosis of CKD experience 'remission' of their CKD as they move back and forth across the 60 ml/min/1.73m^2 eGFR threshold over time.(11)

The prevalence of CKD increases with age(12, 13) and many people live with undiagnosed CKD.(14, 15). It is not well understood whether people with unidentified CKD are at similar risk of adverse health outcomes to those known to have CKD. The Oxford Renal cohort study (OxREN) was established in 2013 to screen an older population in UK primary care for all stages of CKD.(16) The baseline characteristics of the study established that 56% of people with confirmed CKD were already known to have the condition at recruitment to the study, whereas 44% were diagnosed through screening.(15) Some OxREN participants now have over five years' follow-up data allowing us to explore the changes in eGFR over time and identify risk factors associated with eGFR decline. We used follow-up data to determine the proportion of participants who experienced rapid eGFR decline, describe numbers of people moving in and out of remission, and identify determinants of rapid GFR decline and remission.

Methods

The OxREN study was approved by South Central Oxfordshire Research Ethics Committee B Reference 13/SC/0020.

Study population and laboratory methods

Participants aged 60 years or over in UK primary care were screened for CKD by determining albumin-creatinine ratio (ACR) and the Modification of Diet in Renal Disease (MDRD) eGFR.(17) Briefly, participants were screened to identify those who had a CKD diagnosis confirmed by two positive tests a minimum of 90 days apart and those who did not have a CKD diagnosis, but had a single test with either a decreased eGFR (<60 ml/min/1.73m^2) or a raised urinary ACR (>3 mg/mmol). Participants with existing CKD or those with a positive screening test based on eGFR and ACR were invited to a baseline assessment. All laboratory measurements were performed in a single laboratory and those with existing CKD or a positive screening test based on eGFR and ACR attended a baseline assessment. Those who had a baseline assessment by December 2019 (n=884) were included in the analysis. Full details of OxREN have been reported elsewhere.(15) Data management decisions on laboratory test results made prior to analysis are detailed in the Supplementary data (Box S1).

Outcomes

Potential CKD progression was calculated in participants who had two or more eGFR measurements at least 12 weeks apart.(18) In the primary analysis, rapid GFR decline was defined as a decrease in eGFR of at least 5ml/min/1.73m^2 per year in line with the Kidney Disease Improving Global Outcomes

(KDIGO) definition.(1) Numbers who met different definitions of CKD progression were also reported, including a decline in eGFR of at least 15ml/min/1.73m^2 per year, a 25% decline in eGFR combined with progression to the next CKD stage, (indications for referral to a nephrology service)(1) and a decline in the slope of at least 5ml/min/1.73m^2 per year through regression of three or more readings.

We defined improvement both as an increase in eGFR of at least 5ml/min/1.73m^2 per year and remission as eGFR>60ml/min/1.73m^2 and ACR<3 mg/mmol.(11) Progression and remission of CKD in 403 people with full baseline and two-year follow-up results were presented in a flow chart to show the proportions that enter and leave remission at each visit. Movement between each stage of CKD at baseline and at year 2 were presented in a table.

Statistical analysis

All analyses were performed using Stata SE16 (Statacorp, Tx). Descriptive data on eGFR and numbers who progressed were presented in tables, bar charts and graphs as mean and standard deviation (SD) of eGFR at baseline and each year of follow-up. Covariates used in the primary analysis included demographic data, anthropometric measurements and history of CKD (Supplementary Table S1). An extended analysis was conducted, which included history of comorbidities collected at participant's baseline assessment.

The primary analysis was conducted using univariable and multivariable Cox proportional hazards regression analyses to estimate hazard ratio (HR) and 95% confidence intervals (95%CI) for the association of covariates with time to progression or censoring at the end of follow-up (December 2019). The dependent variable was time to first GFR that was >5ml/min/1.73m^2 per year lower than the baseline value. The index date was the date of the participant's baseline eGFR test. Assumption of proportional hazards was verified and no violations were observed for any of the predictors. Because of skewed data, urinary ACR was logarithmically transformed and alcohol consumption was dichotomised to no alcohol use or any alcohol use prior to analysis. Improvement in eGFR was analysed using the same covariates using Cox regression. All covariates were included in the multivariable analysis.

To determine whether eGFR variability was associated with rapid eGFR decline, participants' laboratory eGFR results before and up to their baseline assessment date were used to calculate variability. Variability independent of the mean (VIM)(9, 19, 20) was calculated using the following equation: 100 x standard deviation/mean$^{\beta}$. Where β was the regression coefficient, calculated from a simple linear regression of the natural logarithm of the standard deviation against the natural logarithm of the mean within-individual eGFR. The VIM was classified into four quartiles, the highest quartile representing the participants with the highest eGFR variability,(9) which were used as categorical variables in the analysis. Because this method has not been widely used, sensitivity analyses were performed using mean eGFR and standard deviation,(10, 21) and the CV(10, 19) to ensure that the choice of methods had not affected the outcome.

Results

Description of data

In 884 people with baseline data: 291 (33%) had CKD at cohort entry, 375 (42%) were diagnosed with CKD on screening and 218 (25%) had only a single test above diagnostic thresholds, and thus did not meet the full KDIGO criteria for CKD. Mean±SD age was 74.3±6.7 years, 46% were women and the majority of people exhibited either normal renal function (eGFR>60ml/min/1.73m^2 and ACR<3 mg/mmol) (n=296, 33%) or CKD stage 3a (n=279, 32%) at baseline (Table 1). There were 547

people (62%) who had a follow-up eGFR measurement 1 year from baseline; 377 (43%) 2 years from baseline; 211 (24%) 3 years from baseline; 65 (7%) 4 years from baseline and 28 (3%) with an eGFR 5 years from their baseline visit (Figure 1). Median follow-up time was 2.1 years. Mean(SE) eGFR for the population at baseline and years 1, 2, 3, 4 and 5 was 63.9(0.53), 61.4(0.65), 60.4(0.79), 60.7(1.06), 56.6(1.94) and 57.3(2.95) ml/min/1.73m^2, respectively (Figure 2).

In total, 686 participants had two or more eGFR measurements during follow-up and were included in the analysis of CKD progression. Mean age and sex were similar to the full cohort (Table 1). Of these, 164 people (24%) experienced rapid GFR decline (>5ml/min/1.73m^2 eGFR decrease per year), 27 people (4%) experienced progression of ≥15ml/min/1.73m^2/year, 48 people (7%) experienced a 25% decrease in eGFR combined with progression to the next stage and 30 people (7%) experienced a sustained decline in the slope from at least three eGFR measurements of >5ml/min/1.73m^2. Additionally, 185 (27%) people experienced improvement in eGFR of at least 5ml/min/1.73m^2/year and 82 (21%) of 394 people who fell into CKD stages 1-4 at the baseline visit, experienced remission of their CKD at some point during follow-up. These data and numbers of participants with known CKD, CKD identified by screening and without CKD who progressed are shown in Table 2. During follow-up, there were 224 withdrawals in the full cohort (n=884) and 27 deaths, and for those with two or more eGFR measurements (n=686), there were 122 withdrawals and 17 deaths.

Regression models

The univariate Cox model revealed significant associations of rapid eGFR decline with being a former smoker, higher systolic and diastolic blood pressure, higher eGFR and higher log ACR at baseline. In the multivariable analysis, being a former smoker (HR 1.457, 95%CI 1.033 - 2.054) higher systolic blood pressure (HR 1.013, 95%CI 1.004 - 1.022) and being known to have CKD at cohort entry (HR 1.670, 95% CI 1.140 - 2.446) were associated with rapid GFR decline (Table 3). Those with CKD stages 3a or 3b at baseline were less likely to evidence rapid GFR decline, compared to those with normal kidney function. Extending the model to include history of comorbidities at baseline did not identify any other factors to be significantly associated with rapid eGFR decline (Table S2 – Supplementary data).

There were no associations between variability in eGFR prior to the baseline visit and rapid eGFR decline. Including eGFR variability in the multivariable analysis resulted in female sex, having higher BMI, being a former smoker and having stage 3a CKD at baseline being significantly associated with progression of CKD. Results did not change substantially when variability was defined as mean and SD or CV of eGFR in place of VIM (Table S3- Supplementary data).

Lower systolic blood pressure and lower log ACR were significantly associated with CKD improvement in the univariable analysis. Only lower systolic blood pressure remained significant in the multivariable analysis (Table S4-Supplementary data). Those with lower ACR were more likely to experience remission and those with known CKD were less likely to experience remission in the univariable analysis. Only lower ACR remained significant in the multivariable analysis (Table S4- Supplementary data).

Figure 3 shows that people move across the CKD diagnostic threshold over a two-year follow-up in both directions, with 30-40% of the cohort falling below the eGFR/ACR threshold for CKD at any one time and 139 participants remained below CKD diagnostic thresholds over the entire follow-up. When we mapped CKD stage changes between baseline and year 2, we found that whilst 59% of people remained in the same stage, 41% had changed stage (Table S5- Supplementary data). Of participants who were classified as having CKD at baseline, 83% were also classified as having CKD at their 2-year follow-up, but 17%, fell into the non-CKD range after 2 years. Of those with CKD at baseline, 8% of

people moved to a less advanced CKD stage and 18% moved to a more advanced CKD stage after 2 years.

Discussion

Summary

In this older primary care population with early stage CKD or some renal impairment, we have determined that 24% of people experienced rapid eGFR decline of at least 5ml/min/1.73m^2/year. We have also identified that having a higher BMI, being a smoker, having a higher systolic blood pressure and being known to have CKD at cohort entry were all associated with rapid GFR decline in this population. In addition to eGFR and CKD progression, we have determined that 27% of people experience an improvement in eGFR, and that having a lower systolic blood pressure showed the strongest association with this improvement. Those who experienced remission, were most likely to have a lower ACR. During two years of follow-up, at any one time, approximately 30% of people were in remission, despite many of them meeting the definition of CKD at some point.

Strengths and limitations

This work provides reliable, prospectively collected data from an observational study that will help clinicians to prioritise those at greatest need of closer monitoring or medication reviews. Although eGFR decline is indicative of deterioration in kidney function and CKD, our data demonstrate that, in some instances, it may be a temporary decrease, such as an episode of acute kidney injury following which kidney function recovers. This and other potential reasons for a temporary decline in kidney function include biological and analytical variability, which are outlined in Table S7 in the supplementary data. The KDIGO guidelines(1) state that confidence in the precision of the decline increases with an increasing number of serum creatinine tests and duration of follow-up. We explored the impact of a larger number of eGFR results on our analysis, but fewer events meant that we were unable to conduct a full analysis. Furthermore, those with a more advanced stage of CKD at baseline were less likely to experience eGFR progression which represent “regression to the mean.” This has been noted in other studies,(22, 23) and arises when day-to-day biological variations and imprecision in the measurement result in some people by chance having a spuriously high eGFR at their baseline assessment, meaning they may be more likely to meet the definition of progression in subsequent measurements. We have recognised this by also reporting numbers of participants who meet different definitions of progression and sustained progression. In addition, we have reported the numbers of people whose eGFR improves and the number who experienced remission in those who met the definition of having CKD. The follow-up time for this cohort is relatively short, which may have impacted on the numbers of people who experienced progression. Whereas the proportion of participants experiencing a short-term rapid decline in GFR was relatively high (24%), the proportion with GFR decline sufficient to prompt referral to secondary care was low (7%).

This analysis has found that those who were already known to have CKD may be more likely to experience rapid eGFR decline than those who were identified to have CKD on screening but, depending on the statistical method used, this was not consistent, which may result from a lack of statistical power. However, characteristics of the OxREN baseline population have already been reported and those with existing CKD had lower eGFR than those who were diagnosed through screening,(15) so may have been living longer with CKD.

Comparison with existing literature

A previous study reported that 18% of people experienced CKD progression over five years when defining progression as a 25% decline in eGFR combined with moving to a higher CKD stage.(11) Using this definition, we found that only 7% of our cohort progressed over a shorter follow-up time. Furthermore, if the slope of three or more eGFR measurements was used to define progression, only 7% of the OxREN cohort progressed, suggesting that some of those with rapid decline may have had more variability in their eGFR measurements. Other studies reported progression in 15% to 20% of participants,(24, 25) with higher rates of progression in those with the most severe CKD.(24) The proportion who experienced an improvement in eGFR was similar to other studies, ranging from 12% to 27%, depending on stage of CKD.(11, 24, 25)

We have observed that kidney function fluctuated during follow-up as people move back and forth across the 60 ml/min/1.73m^2 eGFR threshold over time and, therefore, that a substantial minority of participants evidenced "remission" of their CKD. This type of variability in eGFR has been described previously,(24, 25) with one study in UK primary care reporting a similar observation,(11) such that over 25% of participants were 'in remission' at any one time. We found a slightly higher proportion (30-40%) demonstrating remission after one and two years' follow-up, but some people in our cohort had an earlier stage of CKD, or did not fully meet the definition for CKD on cohort entry. Many of these fluctuations will result from normal biological variability and measurement error in people who were near measurement thresholds. However, those who remain in remission at baseline and year one have lower mortality (3.2%) compared with those who meet criteria for CKD at both visits (15.7%).(11) The issue of CKD "remission" and the associated clinical implications warrants further investigation.

However, regardless of individuals who cycle back and forth between CKD and "remission", the overall outcome during two years of follow-up was an overall trend towards a lower eGFR over a 2-year period. Whether those with rapid GFR decline in this study go on to develop adverse health outcomes is yet to be determined. With continued follow up of this cohort, data on long term health and mortality can be evaluated in relation to CKD progression.

In our analysis of variability in eGFR prior to entering the cohort, we did not find any association with subsequent eGFR decline. To our knowledge, only one study has carried out similar analyses which found that eGFR variability was associated with increased mortality.(10)

Implications for practice

This work adds to existing knowledge of CKD progression and GFR decline as well as tools that can be used to identify risk of progression. The findings will help clinicians identify patients who may be at greatest risk of deteriorating renal function to prioritise closer monitoring or medication reviews to reduce cardiovascular risk including blood pressure management and lifestyle interventions.(1) Particular attention should perhaps be directed towards overweight women with a history of smoking. Nevertheless, it should also be appreciated that GFR may fluctuate over time and that only a small proportion of people with a sustained and large GFR decline warrant referral to a nephrology service.

In the OxRen cohort, those known to have CKD on cohort entry were more likely to experience rapid GFR decline than those who were only found to have CKD on screening and those who did not meet the KDIGO criteria for CKD at their baseline assessment. This preliminary analysis casts some doubt on the value of screening for CKD in older populations since those at highest risk may be those already known to have CKD.

Overall conclusion

This work has improved our understanding of how eGFR fluctuates over time and will help clinicians identify those who may benefit most from closer monitoring and appropriate treatment to minimise risks of adverse outcomes.

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Contribution statement

JH contributed to the data collection, carried out the analysis and wrote the first draft. COC, MT, SF and RM helped design the work, contributed to the interpretation, revised the manuscript and approved the final version. JOM contributed to the analysis and interpretation, revised the manuscript and approved the final version, CT contributed to the design and interpretation, revised the manuscript and approved the final version, YY contributed to the interpretation, revised the manuscript and approved the final version, EE contributed to the data collection, revised the manuscript and approved the final version FDRH conceived the study, gained funding for OxREN, designed the work, contributed to the interpretation, revised the manuscript and approved the final version.

Figure 1 – Number of participants with eGFR tests at their baseline visit and subsequent eGFR tests for each year after entering the cohort

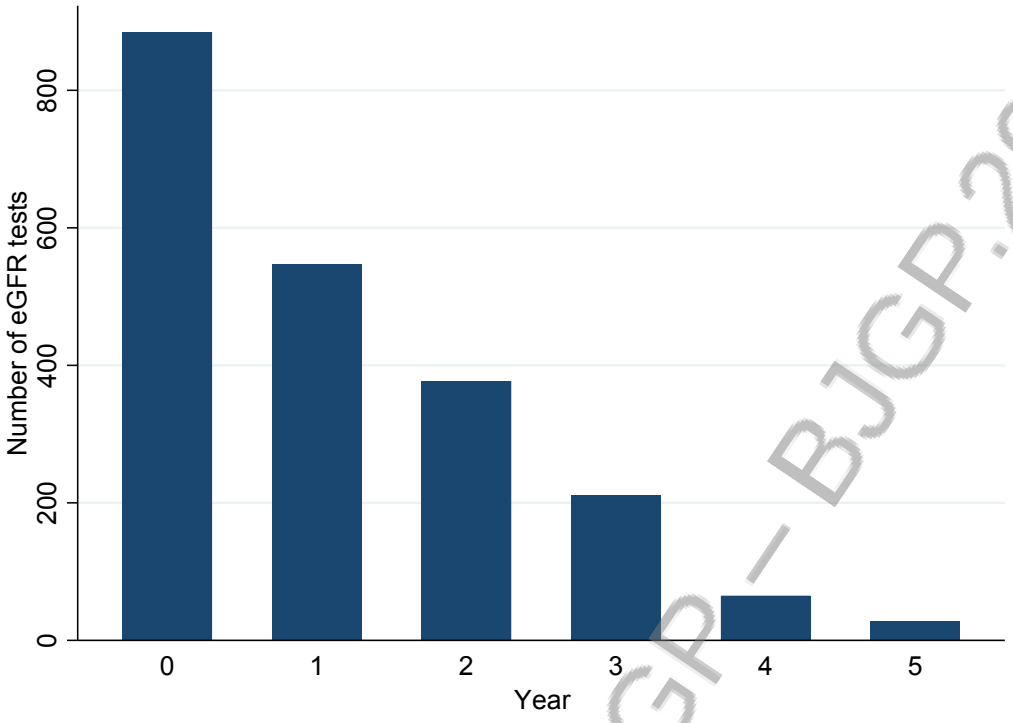


Figure 2 – Mean eGFR for people with up to five eGFR tests (n=884)

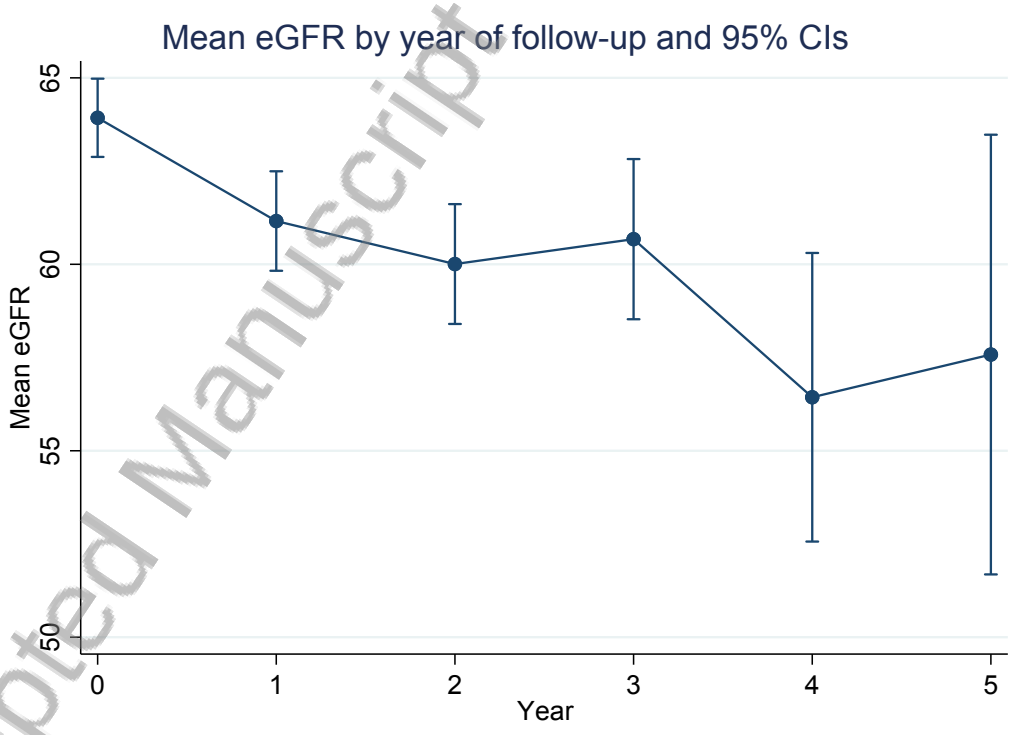


Table 1 Baseline characteristics of the cohort

	All participants	CKD at baseline	Newly diagnosed CKD	No CKD*
Full cohort				
N	884	291	375	218
Mean±SD Age (years)	74.3±6.7	75.1±6.8	74.1±6.4	73.7±7.1
% women	54%	56%	50%	58%
Mean±SD eGFR (ml/min/1.73m^2)	63.9±15.8	55.9±13.8	68.3±15.3	67.1±15.2
Stage of CKD, N (%)				
Normal kidney function‡	296 (33%)	70 (24%)	135 (36%)	91 (42%)
1	34 (4%)	0	24 (6%)	10 (5%)
2	114 (13%)	17 (6%)	77 (21%)	20 (9%)
3a	279 (32%)	120 (41%)	93 (25%)	66 (30%)
3b	88 (10%)	60 (21%)	18 (5%)	10 (5%)
4	5 (1%)	5 (2%)	0	0
Missing	68 (8%)	19 (7%)	28 (7%)	21 (10%)
Included in progression analysis				
N	686	238	268	180
Mean±SD Age (years)	74.0±6.7	74.9±6.6	73.8±6.5	73.1±7.0
% women	54%	55%	51%	58%
Mean±SD eGFR (ml/min/1.73m^2)	62.9±15.3	55.5±13.2	67.2±15.2	66.4±14.4
Stage of CKD				
Normal kidney function‡	214 (31%)	53 (22%)	89 (33%)	72 (40%)
1	23 (3%)	0	16 (6%)	7 (4%)
2	82 (12%)	13 (5%)	54 (20%)	15 (8%)
3a	215 (31%)	96 (40%)	65 (24%)	54 (30%)
3b	69 (10%)	49 (21%)	12 (4%)	8 (4%)
4	5 (1%)	5 (2%)	0	0
Missing	78 (11%)	22 (9%)	32 (12%)	24 (13%)

*Participants had one eGFR or ACR suggestive of CKD, but did not meet the full KDIGO/NICE criteria
‡ normal kidney function: those with eGFR>60ml/min/1.73m^2 and ACR<3mg/mmol

Table 2 - Progression of eGFR in participants with more than one eGFR test result.

	All participants (n=686)	Mean (SD) time to progression (days)	CKD at baseline (n=238)	Newly diagnosed CKD (n=268)	No CKD* (n=180)
Number GFR decline >5ml/min/1.73 m²/year, N (%)	164 (24%)	457±160	58 (35%)	73 (45%)	33 (20%)
Number who progressed >15ml/min/1.73 m²/year, N (%)	27 (4%)	418±82	5 (19%)	17 (63%)	5 (19%)
Numbers of people who progressed one CKD stage and 25% decline compared to baseline, N (%)	48 (7%)	543±275	21 (44%)	20 (42%)	7 (15%)
Number who progressed >5ml/min/1.73 m²/year based on regression of 3 or more measurements (N=423), N (%)	30 (7%)	428±188	9 (30%)	17 (57%)	4 (13%)
Number whose eGFR improved by ≥5ml/min/1.73 m²/year, N (%)	185 (27%)	456±188	44 (24%)	59 (32%)	49 (26%)
Of 394 people with an eGFR or ACR stage 1-4 at baseline:					
Number with remission (eGFR>60 5ml/min/1.73m² and ACR<3 mg/mmol), N(%)	82 (21%)	593±292	22 (27%)	36 (44%)	24 (29%)

*Participants with "no CKD" at baseline had one eGFR or ACR suggestive of CKD, but did not meet the full KDIGO/NICE criteria

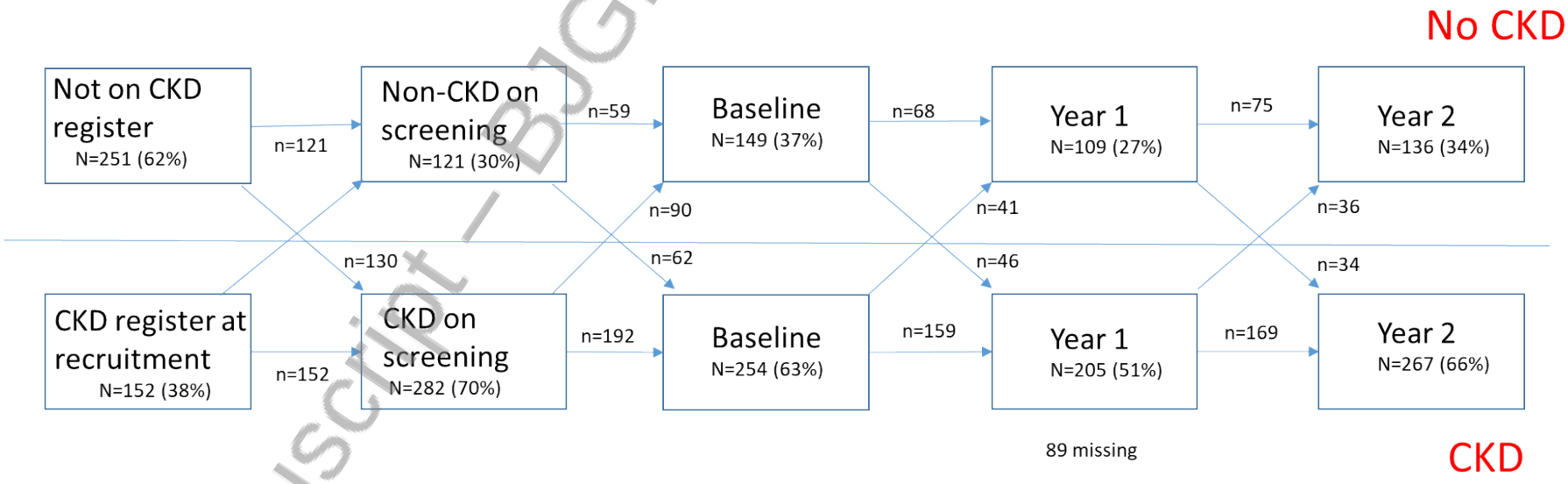
Table 3 - Predictors of rapid decline in eGFR (>5ml/min/1.73 m^2/year from baseline) using Cox proportional hazards

Covariate	Univariable analysis, HR and 95% CI	p-value	Multivariable analysis, HR and 95% CI (N=568)	p-value
Age (years)	1.005 (0.983 - 1.028)	0.663	1.012 (0.985 - 1.040)	0.389
Sex (male compared to female)	0.887 (0.653 - 1.204)	0.443	0.753 (0.518 - 1.096)	0.139
BMI (kg/m^2)	1.025 (0.997 - 1.054)	0.083	1.030 (0.998 - 1.062)	0.068
Smoking status (compared to never smoker)				
- Current smoker	0.761 (0.280 - 2.076)	0.594	0.858 (0.304 - 2.424)	0.773
- Former smoker	1.388* (1.021 - 1.887)	0.037	1.457* (1.033 - 2.054)	0.032
Alcohol use compared to no alcohol	0.833 (0.602 - 1.152)	0.270	0.740 (0.508 - 1.076)	0.115
Level of education (higher education compared to secondary)	1.098 (0.782 - 1.542)	0.590	1.419 (0.953 - 2.112)	0.085
Systolic blood pressure (mg Hg)	1.017* (1.009 - 1.025)	<0.0001	1.013* (1.004 - 1.022)	0.006
Diastolic blood pressure (mg Hg)	1.014* (1.001 - 1.028)	0.041		
Ethnicity (White compared to non-white)	0.582 (0.216 - 1.570)	0.285	0.550 (0.169 - 1.792)	0.321
Waist:Hip ratio	1.743 (0.374 - 8.120)	0.479		
Waist circumference	1.010 (0.999 – 1.020)	0.050		
CKD stage at baseline compared with normal kidney function‡				
1	1.695 (0.918 - 3.130)	0.092	1.521 (0.722 - 3.206)	0.270
2	1.191 (0.790 - 1.796)	0.405	0.993 (0.596 - 1.654)	0.987
3a	0.351* (0.229 - 0.540)	<0.0001	0.218* (0.129 - 0.368)	<0.0001
3b	0.332* (0.166 - 0.666)	0.002	0.267* (0.127 - 0.563)	0.001
Log ACR	1.174* (1.033 - 1.334)	0.014	1.116 (0.935 - 1.332)	0.224
Known CKD at baseline (Yes vs. No)	1.017 (0.741 - 1.394)	0.919	1.670* (1.140 - 2.446)	0.008

* Statistical significance at 5% (p≤0.05)

‡ normal kidney function: those with eGFR>60ml/min/1.73m^2 and ACR<3mg/mmol

Figure 3 - Flowchart showing people moving across the diagnostic threshold for CKD for those with complete baseline and year 2 follow-up (n=403)



139 participants (55%) who were CKD at baseline remained below the CKD threshold throughout follow-up at both year 1 and year 2

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