Associations with age and glomerular filtration rate in a referred population with chronic kidney disease: methods and baseline data from a UK multicentre cohort study (NURTuRE-CKD)

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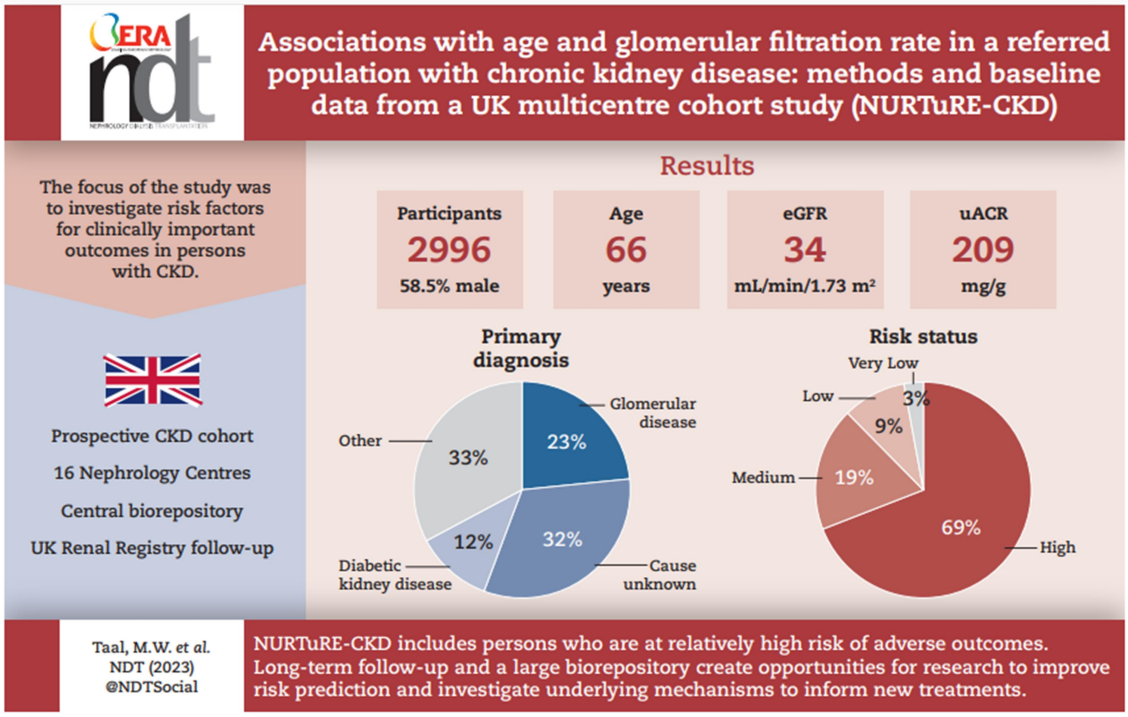
Running title: NURTuRE-CKD, a UK cohort study

GRAPHICAL ABSTRACT



ABSTRACT

Background. Chronic kidney disease (CKD) is common but heterogenous and is associated with multiple adverse outcomes. The National Unified Renal Translational Research Enterprise (NURTuRE)-CKD cohort was established to investigate risk factors for clinically important outcomes in persons with CKD referred to secondary care.

Methods. Eligible participants with CKD stages G3-4 or stages G1-2 plus albuminuria > 30 mg/mmol were enrolled from 16 nephrology centres in England, Scotland and Wales from 2017 to 2019. Baseline assessment included demographic data, routine laboratory data and research samples. Clinical outcomes are being collected over 15 years by the UK Renal Registry using established data linkage. Baseline data are presented with subgroup analysis by age, sex and estimated GFR (eGFR).

Results. 2996 participants were enrolled. Median (interquartile range) age was 66 (54 to 74) years, 58.5% were male, eGFR 33.8 (24.0 to 46.6) ml/min/1.73m^2 and UACR 209 (33 to 926) mg/g. 1883 participants (69.1%) were in high-risk CKD categories. Primary renal diagnosis was CKD of unknown cause in 32.3%, glomerular disease in 23.4% and diabetic kidney disease in 11.5%. Older participants and those with lower eGFR had higher systolic blood pressure and were less likely to be treated with renin-angiotensin system inhibitors (RASi) but were more likely to receive a statin. Female participants were less likely to receive a RASi or statin.

Conclusions. NURTuRE-CKD is a prospective cohort of persons who are at relatively high risk of adverse outcomes. Long-term follow-up and a large biorepository create opportunities for research to improve risk prediction and investigate underlying mechanisms to inform new treatment development.

KEY LEARNING POINTS

What was known:

1. Chronic kidney disease is common and associated with increased risk of multiple adverse outcomes including end-stage kidney disease, all-cause mortality, cardiovascular events, and acute kidney injury.

This study adds:

2. Nevertheless, chronic kidney disease is heterogeneous with respect to clinical characteristics and the risk of adverse outcomes is variable.

Potential impact:

3. Cohort studies are valuable to improve understanding of risk factors for adverse outcomes associated with chronic kidney disease, improve risk prediction to allow patient stratification, and identify novel therapeutic targets.

Keywords: albuminuria, chronic kidney disease, cohort study, risk profile

INTRODUCTION

Chronic kidney disease (CKD) is prevalent in 10 to 15% of the adult population in most countries [1] resulting in an estimated ≥840 million persons affected globally [2] and is associated with increased risk of multiple adverse outcomes including kidney failure (KF), all-cause mortality, cardiovascular events (CVE) and acute kidney injury (AKI) [3, 4]. However, the risk profile associated with CKD is heterogeneous with outcomes varying even within the same primary renal disease. There is therefore a need to better predict adverse clinical outcomes in individuals with CKD, so that interventions to reduce risk can be targeted to those most likely to benefit. The Kidney Failure Risk Equation (KFRE) has been validated as a useful tool to estimate the likelihood of progression to kidney failure treated by dialysis or transplantation [5], but better characterisation of individual risk may be required to facilitate personalised medicine.

Prospective cohort studies have been established in several countries and have made substantial contributions to the understanding of the epidemiology of CKD and associated risk factors [3, 4, 6, 7] but multiple questions remain unanswered. The National Unified Renal Translational Research Enterprise (NURTuRE) – CKD study was therefore established as a multicentre cohort study to investigate risk factors for clinically important adverse outcomes in persons with CKD in the United Kingdom (UK).

The prevalence of CKD rises sharply with age [8] and further exploration of the relationship between age, clinical characteristics and treatment therefore remains a research priority. Recent focus on the impact of sex differences on CKD progression motivates further research on this topic. Additionally, CKD encompasses a wide

range of GFR values and improved understanding of how clinical characteristics and treatment vary with GFR will assist in the development of personalised medicine.

In this paper we present baseline data that characterise the NURTuRE-CKD cohort in relation to other international cohorts, and furthermore, explore the impact of age, sex and eGFR values on participant characteristics..

MATERIALS AND METHODS

Study Design

This prospective, multi-centre cohort study is a collaborative project between independent academic investigators, a leading kidney research charity and multiple industry partners, to establish a large national cohort of adults with CKD with a linked biorepository and long-term outcome data collection in the UK. The main aim of the study is to investigate risk factors for clinically important adverse outcomes in persons with CKD. Secondary aims include identification and validation of biomarkers that predict clinically important outcomes, and investigation of the mechanisms that may link CKD to these adverse outcomes. Performance of previously published risk scores for CKD will be assessed. Finally, factors that impact health-related quality of life (HRQoL) in persons with CKD at different stages of severity will be assessed along with their use of health care resources, thus allowing assessment of the associated healthcare costs.

Enrolment and Eligibility

Enrolment commenced in July 2017 and continued until September 2019 at 16 secondary care Nephrology centres in England, Wales, and Scotland (Supplementary Table1). Participants were eligible if they were ≥18 years old, had

been seen at least once in a Nephrology clinic, had an estimated GFR (eGFR) 15-59 ml/min/1.73m^2 or eGFR ≥60ml/min/1.73m^2 with urine albumin to creatinine ratio (UACR) more than 30mg/mmol, were willing and able to participate in two study visits and able to give informed consent. Participants were excluded if they were solid organ transplant recipients, on dialysis, had an expected survival of less than 1 year, had AKI or a major cardiovascular event within three months of recruitment, or were receiving chemotherapy for the treatment of cancer. Patients with idiopathic nephrotic syndrome (primary focal and segmental glomerulosclerosis or idiopathic minimal change disease) were excluded because they were enrolled in the NURTuRE Nephrotic Syndrome cohort study.

All participants provided written informed consent. The study was approved by the South Central - Berkshire Research Ethics Committee, abides by the principles of the Declaration of Helsinki and is registered at Clinical Trials.gov (NCT04084145).

Baseline visits

At baseline, information was collected by interview, questionnaire and from medical records. Information on socio-demographics, past medical history, family history, medication history, prior laboratory results and vaccination status were recorded. Health-Related Quality of Life (HRQoL) was assessed by completion of the EQ-5D-5L questionnaire [9] and functional status by the Karnofsky score [10], symptoms, health literacy, cognition and anxiety and depression were measured by validated scores and questionnaires [11-13].

Anthropometric measurements were taken according to standard operating procedures (SOPs) by trained research practitioners and urine dipstick testing was performed (standard multisticks) to detect haematuria. Blood pressure (BP) was

measured in the seated position after 5 minutes of rest using an oscillometric device according to a standard operating procedure. Three measurements that differed by <10% were recorded and the mean value was used for analysis. Blood and urine samples were obtained and were sent to local NHS chemical pathology laboratories for routine biochemical analysis and full blood count. Baseline data items collected and disease definitions are presented in Supplementary Table 2.

Participants who had undergone a kidney biopsy as part of their clinical care were invited to consent for access to processed histology slides and any surplus biopsy tissue to be utilised for a sub-study. Primary renal diagnosis was obtained from medical records and verified against renal biopsy reports.

Sample storage and Processing

In addition to samples for routine laboratory tests, 10 ml of plasma (30 ml whole blood), 10 ml of serum (30 ml whole blood), 2x3 ml of whole blood for DNA extraction, 2.5 ml whole blood for RNA extraction and up to 100 ml urine were obtained from each participant. Detailed SOPs were developed for sample collection and handling to ensure standardisation across sites. Samples were separated into multiple aliquots (up to 42 aliquots of plasma, 51 aliquots of serum and 36 aliquots of urine per participant) and stored locally at -20^{o}C within 2 hours of collection before being transferred to -80^{o}C within 72 hours. Batched frozen samples were transferred on dry ice by courier from each site to the NIHR National Biosample Centre in Milton Keynes. Whole blood stored at the National Biosample Centre will be used for DNA extraction and future analysis.

Kidney biopsy samples from 451 participants (diagnostic slides and residual tissue blocks) were transported to the Human Tissue Authority (HTA) licensed Human

Biomaterials Resource Centre (HBRC) at University of Birmingham for digital scanning and further analysis, including immunohistochemistry, RNA extraction and analysis of gene expression.

Laboratory Analyses

Routine biochemistry analyses and full blood counts were performed in local hospital laboratories. Serum creatinine and C reactive protein (CRP) and urine albumin to creatinine ratio (UACR) were measured centrally on stored samples collected at the baseline visit at Geneva University Hospitals, Switzerland. These analyses were performed on routine Roche Cobas 8000/c702/c502 chemistry analyzers under ISO 15189 certification. Creatinine was measured using an isotope dilution mass spectrometry traceable Jaffé-kinetic picric acid method on the c702 module. CRP and urine albumin was measured using an immunoturbidimetric method on the c502 module. Glomerular filtration rate was estimated using the 2009 CKD-EPI equation without the ethnicity variable as recommended by the National Institute for Health and Care Excellence in 2021 [14].

Follow-up

The assessments and procedures at baseline are being repeated at a single follow up visit at least 12 months after baseline, along with a health utilisation questionnaire to detail hospital admissions, primary care visits and medication changes since recruitment. Additional follow-up by questionnaire only is also planned. Participants are registered with the United Kingdom Renal Registry (UKRR: https://ukkidney.org/about-us/who-we-are/uk-renal-registry) to enable the collection of all results from routine blood sampling performed by local laboratories for the duration of follow-up, planned to be for up to 15 years. The UKRR will also provide

data regarding initiation of kidney replacement therapy (KRT) and death. Data from death certificates and coding details for all hospital admissions will be requested from NHS Digital (https://digital.nhs.uk).

Study Outcomes

The co-primary endpoints are: 1) Progression of CKD (defined by 50% decline in eGFR, sustained decrease to <15 mL/min/1.73m^2 or initiation of renal replacement therapy) and 2) Major Acute Cardiovascular Events (MACE), defined as cardiac death, non-fatal myocardial infarction, cerebral infarction, intracerebral haemorrhage or arterial revascularisation. Secondary endpoints include death from any cause, less severe progression of CKD (KDIGO definition: decrease in estimated GFR of >25% and progression to a more advanced category of CKD), KF (eGFR<15 mL/min/1.73m^2 or initiation of KRT), AKI, hospitilisation for cardiac failure, unplanned hospital admission, infections requiring hospital admission, a new diagnosis of cancer and hip fracture.

Data management

Data are entered into a central database held by the UKRR using an electronic case report form. The UKRR will obtain all past and future routine laboratory data direct from electronic patient records at each participating site. Data are stored on a secure server by the UKRR and managed in compliance with the general data protection regulation (GDPR).

Statistical Analysis

Standard descriptive statistics are used to describe the study population at baseline. Normality of data distributions was assessed by Kolmogorov-Smirnov or Shapiro-Wilk tests, as appropriate. Continuous data are presented as mean ± SD for

normally distributed variables and median (interquartile range - IQR) otherwise; categorical data are presented as frequency (percent). Missing values were excluded from analysis. Group differences were assessed using T-tests, Mann-Whitney U-tests and Chi-squared tests as appropriate. Differences across multiple groups were tested with analysis of variance (ANOVA). The slope of change in eGFR over time was estimated using linear regression on each individual's local laboratory eGFR values prior to baseline. Slopes were only estimated for participants with at least 3 eGFR values and at least 6 months between first and last eGFR value. The median (IQR) number of eGFR values was 11 (9-24) at a median (IQR) rate of 6.2 (4.0-10.1) eGFR values per year.

Study management structure and funding

NURTuRE is a collaborative project with multiple academic and commercial partners listed in Supplementary Table 3 and is governed by a formal collaboration agreement. The NURTuRE collaboration is currently running two cohort studies, the study described in this manuscript (the CKD cohort), and another study recruiting people with idiopathic nephrotic syndrome. The project is coordinated by a Joint Steering Committee which is chaired by a Director from Kidney Research UK and includes representatives from all partners. Funding is provided by the commercial partners. All funds are paid to Kidney Research UK and awarded to the investigators as a research grant. The CKD study is led by an academic steering group comprised of MWT, PC, PR, SDSF, DCW and PAK.

RESULTS

Whole Cohort Data

A total of 3004 participants was enrolled but 8 were found not to meet the inclusion criteria after recruitment and were therefore excluded, resulting in a final cohort of 2996. A summary of baseline data is presented in Table 1. Over half of participants were 65 years or older, 58.5% were males and the majority were of white ethnicity (84.2%). At baseline, median eGFR was 33.8 (IQR 24.0 to 46.6) ml/min/1.73 m^2 and 2087 of 2726 (76.6%) of participants with UACR values had albuminuria. Median eGFR slope was -1.4 ml/min/year prior to the baseline visit in 2029 participants. The distribution of participants in risk categories according to the Kidney Disease Improving Global Outcomes (KDIGO) classification system is shown in Figure 1. Overall, 79 (2.9%) participants were in very low risk, 259 (9.5%) in low risk, 505 (18.5%) in moderate risk and 1883 (69.1%) in high-risk categories. The prevalence of different primary renal diagnoses is presented in Table 2. The most common specific primary renal diagnosis was glomerular disease (23.4) but the largest diagnostic category was miscellaneous renal disorders (32.3%). Diabetic kidney disease was present in 11.5%.

Subgroup analysis by age

Comparison of data in participants <65 years versus ≥65 years is shown in Table 1. A greater proportion of male and white participants was observed in those ≥65 years. Older participants were less likely to drink alcohol, be current smokers or have an educational qualification. Those ≥65 years were more likely to have diabetes, a history of atherosclerotic cardiovascular disease and/or atrial fibrillation. Regarding treatment, older participants were less likely to be receiving a renin angiotensin

system inhibitor (RASi) but more likely to be on a statin. Mean systolic BP was higher in those ≥65 years but mean diastolic BP was lower. Older participants had a lower median eGFR and mean haemoglobin but higher CRP concentration. The prevalence and magnitude of albuminuria was lower in older participants. Older participants were less likely to have had a kidney biopsy. Primary renal diagnoses of miscellaneous renal disorders, diabetic kidney disease and hypertension/renal vascular disease were more common in older participants whereas glomerular disease, and familial/hereditary nephropathies were less common (Table 2).

Subgroup analysis by sex

Data for male versus female participants are presented in Tables 1 and 2. When compared with males, female participants were younger, less likely to have a history of diabetes or atherosclerotic cardiovascular disease, less likely to drink alcohol or to have smoked in the past, less likely to be on a RASi or statin, evidenced lower systolic BP and UACR, higher eGFR and a lower predicted risk of KRT. Distribution of primary renal diagnosis categories was similar, though females tended to have a higher proportion of hereditary nephropathy and tubulointerstitial disease.

Subgroup analysis by eGFR

Baseline data in eGFR categories of 10 ml/min/1.73 m^2 are presented in Table 3. Median age, proportion of males and proportion of white ethnicity all tended to be higher in lower eGFR categories. Diabetes tended to be more prevalent in those with lower eGFR but there was no difference in mean BMI across eGFR categories. Participants with lower eGFR were less likely to be receiving a RASi but more likely to be receiving a statin. Correspondingly, total cholesterol concentration was lower with lower eGFR. Mean systolic BP tended to be higher at lower eGFR but diastolic

BP tended to be lower. Serum potassium and phosphate as well as CRP concentrations tended to be higher in those with lower eGFR whereas serum bicarbonate and haemoglobin concentrations were lower. Serum sodium concentration was lower in the highest and lowest eGFR categories. The prevalence and magnitude of albuminuria tended to increase with decreasing eGFR except that the highest eGFR category also had the highest median UACR, likely reflecting a group with nephrotic syndrome. The median slope of eGFR prior to enrolment was negative in all eGFR categories, but the magnitude tended to be greater at lower baseline eGFR.

DISCUSSION

Analysis of baseline data shows that the NURTuRE-CKD cohort is comprised of persons who are predominantly older, male and of white ethnicity. The median eGFR was relatively low (33.8 ml/min/1.73m^2) and 76.6% had albuminuria. As a result, 69.1% were in KDIGO classification high-risk categories. These data are broadly similar to previously published single-centre cohort studies in England (Supplementary Table 4), though participants in the Salford Kidney Study tended to have more severe proteinuria and a higher proportion of white ethnicity [7, 15].

Comparison with large national cohort studies from other countries including the Chronic Renal Insufficiency Cohort (CRIC) from the United States [16], Chronic Kidney Disease Japan Cohort (CKD-JAC) [17], Canadian study of prediction of death, dialysis and interim cardiovascular events (CanPREDDICT) [18], German Chronic Kidney Disease cohort (GCKD) [19], Chinese cohort study of chronic kidney disease (C-STRIDE) [20], French Chronic Kidney Disease–Renal Epidemiology and Information Network study (CKD-REIN) [21] and Indian CKD (ICKD) study [22] reveals some important differences in study design (Table 4). Our approach to enrolment was to have as few exclusion criteria as possible. We therefore did not exclude persons with Autosomal Dominant Polycystic Kidney Disease (as done in CRIC, C-STRIDE and CKD-JAC), on immunosuppression (as done in CRIC, CanPREDDICT, C-STRIDE and ICKD) or on the basis of ethnicity (as done in

GCKD). Nevertheless, baseline characteristics were similar to other national cohorts, though median age was higher than in CRIC, CKD-JAC, C-STRIDE, GCKD and ICKD. Baseline eGFR was lower than in CRIC, C-STRIDE ,GCKD and ICKD. Overall, baseline characteristics most closely matched those for CKD-REIN and CanPREDDICT. Our results are therefore likely to be broadly comparable with those from other national cohort studies though important differences should be borne in mind.

Subgroup analysis by age

Persons 65 years or older comprised 52.6% of the population and our analysis shows important differences between older and younger participants. Mean systolic BP was higher but diastolic BP was lower, likely reflecting greater arterial stiffness with older age. Our analysis indicates that older persons with CKD carry a high burden of cardiovascular comorbidity and tended to have more advanced CKD than younger persons, putting them at higher risk for adverse outcomes, yet were less likely to be treated with a RAS inhibitor, achieve adequate blood pressure control, or have had a kidney biopsy. Similar trends have been reported in other cohort studies. In the Berlin Initiative Study, a cohort of persons with CKD aged ≥70 years, mean systolic blood pressure was 145.5±21.8 mmHg, indicating that the majority had poorly controlled hypertension [23]. In a cohort of predominantly older persons with CKD category G3 in primary care, age >60 years was independently associated with a lower likelihood of achieving a range of blood pressure targets [24]. The reasons for this age-related difference are unclear. Interestingly, few major CKD cohort studies have published data on age subgroups, though one did report decreased use of RASi and statins in older participants [25]. Since the prevalence of CKD rises steeply with age, it is clear that further research is warranted to investigate optimal care in older people.

Subgroup analysis by sex

We observed significant differences between male and female participants, with females having a lower risk profile overall but also less likely to receive treatment with a RASi or statin. A similar finding was reported in a recent population-based study [26]. There is renewed interest in sex-related differences in CKD prevalence and progression as well as potential treatment disparities [27, 28].

Subgroup analysis by eGFR

Our analysis demonstrates heterogeneity in a population with CKD and important associations between lower eGFR and other biochemical as well as physiological variables. Though none of these associations are unexpected, they highlight the importance of an individualised approach to CKD management. Participants with lower eGFR also had higher UACR levels reflecting a higher risk of adverse outcomes. However, the proportion on RAS inhibitor treatment decreased progressively at lower levels of eGFR, possibly reflecting concern about the increasing risk of hyperkalaemia and possible doubt regarding the benefit of RAS inhibitor treatment. However, in a previous trial, treatment with ramipril provided kidney protection in participants with serum creatinine 1.5-3.0 mg/dL [29] and a recent trial reported no benefit from RAS inhibitor withdrawal in persons with eGFR<30 ml/min/1.73m^2 [30]. Additionally, our data show a progressive increase in achieved systolic BP with lower eGFR. This may reflect increasing resistance to antihypertensive therapy but also indicates that this modifiable risk factor is not being optimised in persons with the lowest eGFR values, who are also at highest risk of adverse outcomes.

Strengths and limitations

Strengths of our study include recruitment across England, Wales and Scotland, detailed baseline assessment, a robust electronic data collection platform, linkage to the UK Renal Registry for robust long-term outcome data and a large biorepository of samples collected using standard operating procedures. Some weaknesses should also be considered. Participants were volunteers and there may therefore have been a degree of selection bias, favouring those who are more engaged with their healthcare. However, similarities with other UK and international cohorts suggests no severe bias. Second, we relied on local laboratory results for some baseline investigations though importantly, baseline serum creatinine, UACR and CRP were measured in a central laboratory. Possible variation between laboratories in the UK is mitigated by the National External Quality Assessment Service (NEQAS) which seeks to standardise laboratory assays across the national health service (NHS).

CONCLUSION

NURTuRE-CKD is a prospective cohort of participants who are at relatively high risk of adverse outcomes. Long-term follow-up of routine biochemical data and outcomes via the UK Renal Registry and a large biorepository will create opportunities for research to improve risk prediction and investigate underlying mechanisms of CKD progression to inform the development of novel therapies. Stored biosamples will also be made available to external investigators via an independent access committee to the maximise the potential for future research.

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CONFLICT OF INTEREST STATEMENT

MWT reports consulting fees from Boehringer Ingelheim, honoraria from Bayer and support to attend conferences from Bayer and a leadership role in the International Society of Nephrology; **BL** reports grant funding from the National Institute for Health Research; **PC** reports a leadership position in the UK Kidney Association; **DCW** reports grant funding from Kidney Research UK, consultancy fees from Astellas, AstraZenca, Bayer, Boehringer Ingelheim, GlaxoSmithKline, Gilead, Janssen, ProKidney and Tricida, honoraria from Amgen, Mundipharma, Merck Sharp and Dohme and Zydus; support for attending meetings from Astellas and AstraZeneca; participation in the data safety monitoring board for the following studies: ProKidney; Galderma; Eledon and a leadership role in the International Society of Nephrology; **MAS** reports consulting fees from Travere, Dimerix and Pfizer, honoraria from American Society of Nephrology and American Society of Paediatric Nephrology, patents in AAV gene therapy, participation in the data safety monitoring board for the ECUSTEC study, and stock options in Purespring Therapeutics; **SDSF** reports grant funding from Kidney Research UK; **REB** reports grant funding and a patent with Randox Laboratories; **TJ** reports previous salary from UCB Biopharma, consulting fees from UCB Pharma and stock in UCB Pharma; **LJH** reports salary from and stock in UCB Pharma; **RU** reports stock in AstraZeneca BioPharmaceuticals and a leadership position in the Faculty of Pharmaceutical Medicine, Royal College of Physicians (London); **DP** reports salary support from the UK Kidney Association and support to attend conferences from Travere Therapeutics Inc; **MN** reports grant funding from AstraZeneca BioPharmaceuticals and Gore Medical; **PAK** reports grant funding from Vifor and Astellas, consulting fees from Astra Zeneca, Vifor, Unicyte

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The other authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

MWT, PR, PC, DCW, MAS, TJ, UA, PS, NV, FR, EC, FB, ED, MN and PAK contributed to conception and design of the study. MB (Evotec), RD, FR, EC, FB and MB (Nottingham) contributed to data acquisition and cleaning. Data analysis was performed by DP and interpretation by MWT, BL, PR, PC, DCW, MAS, SDSF, REB, TJ, LJH, UA, PS, MB (Evotec), RU, NV and PAK. MWT and BL drafted the manuscript which was reviewed and revised by all co-authors. The final version was approved for publication by all co-authors.

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DATA AVAILABILITY STATEMENT

Anonymised participant level data will be made available to external investigators upon successful application to the independent data access committee.

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Table 1: Summary of baseline demographic and biological variables in 2996 participants.

Variable	n=missing	Value[b]	Age <65 years (n=1419)	Age ≥65 years (n=1577)	Male (n=1753)	Female (n=1243)
Age (years)	0	66 (54 to 74)	53 (44 to 59)	74* (70 to 79)	64±14	61±15†
Male	0	1753 (58.5)	764 (53.8)	989* (62.7)		
Ethnicity	4					
White		2523 (84.2)	1091 (76.9)	1432* (90.8)	1480 (84.6)	1042(83.9)
Asian		159 (5.3)	114 (8.0)	45 (2.9)	100 (5.7)	59 (4.8)
Black		81 (2.7)	53 (3.7)	28 (1.8)	45 (2.6)	36 (2.9)
Other		229 (7.5)	157 (11.1)	72 (4.6)	124 (7.1)	105 (8.5)
Diabetes	59	922 (31.4)	306 (22.2)	616* (39.5)	594 (34.5)	328 (27.0)†
Atherosclerotic CVD	59	504 (17.2)	121 (8.8)	383* (24.6)	367 (21.3)	137 (11.3)†
Smoking status	41					
Never		1483 (50.2)	790 (56.8)	693* (44.3)	802 (46.3)	681 (55.7)†
Previous		1209 (40.9)	428 (30.8)	781 (49.9)	779 (45.0)	430 (35.2)
Current		263 (8.9)	172 (12.4)	91 (5.8)	152 (8.8)	111 (9.1)
Alcohol consumption	59	1567 (53.4)	770 (55.7)	797* (51.2)	1052 (61.0)	515 (42.5)†
Renal Biopsy	79	923 (31.6)	533 (38.9)	390* (25.2)	564 (32.9)	359 (33.2)
Educational level	50					
Higher Degree (>16y)		298 (10.1)	168 (12.1)	130* (8.3)	182 (10.6)	116 (9.5)†
First degree (16y)		485 (16.5)	294 (21.2)	191 (12.3)	304 (17.7)	181 (14.8)
A Level (13y)		221 (7.5)	118 (8.5)	103 (6.6)	136 (7.9)	85 (7.0)
NVQ (11-16y)		407 (13.8)	260 (18.8)	147 (9.4)	228 (13.2)	179 (14.6)
GCSE (11y)		723 (24.5)	382 (27.5)	341 (21.9)	395 (22.9)	328 (26.8)
None		793 (26.9)	159 (11.5)	634 (40.7)	463 (26.9)	330 (27.0)
Other		19 (0.6)	6 (0.4)	13 (0.8)	15 (0.9)	4 (0.3)
RAAS inhibitor	44	1982 (67.1)	1047 (75.4)	935* (59.8)	1208 (69.9)	774 (63.2)†
Statin	44	1740 (58.9)	685 (49.3)	1055* (67.5)	1091(63.1)	649 (53.1)†
SBP (mmHg)	4	139±20	136±19	143±21*	140±20	138±21†

DBP (mmHg)	4	80±12	84±12	76±12*	80±13	80±12
BMI (kg/m^2)	81	29.6±6.3	29.5±6.6	29.6±5.9	29.5±5.8	29.6±6.9
Haemoglobin (g/L)	200	127±18	130±18	124±17*	130±19	122±15†
CRP (mg/L)	67	2.6 (1.1 to 5.7)	2.1 (0.9 to 5.0)	2.9* (1.3 to 6.5)	2.5 (1.1 to 5.8)	2.7 (1.1 to 5.6)
Serum Creatinine (μmol/L)	0	163 (125 to 215)	155 (116 to 205)	170 * (133 to 222)	183 (143 to 240)	137 † (107 to 177)
Baseline eGFR (ml/min/1.73m^2)	-0	33.8 (24.0 to 46.6)	39.2 (27.4 to 53.9)	30.0* (22.1 to 40.1)	33.0 (22.9 to 44.5)	35.4 † (25.4 to 49.3)
UACR (mg/g)	270	209 (33 to 926)	307 (43 to 1195)	148* (27 to 692)	288 (47 to 1041)	105 † (21 to 647)
Albuminuria categories						
A1		639 (23.4)	268 (20.2)	371 * (26.5)	305 (18.9)	334(30.0)†
A2		894 (32.8)	391 (29.5)	503 (36.0)	515 (31.9)	379 (34.1)
A3		1193 (43.8)	668 (50.3)	525 (37.5)	793 (49.2)	400(35.9)
GFR slope(ml/min/year)[e]	967	-1.4 (-4.1 to 0.8)	-1.8 (-4.7 to 0.4)	-1.1* (-3.3 to 1.2)	-1.6 (-4.2 to 0.6)	-1.2 (-3.9 to 1.0)
KFRE 5 yr risk of KRT (%)	270	8.1% (1.6 to 28.8)	7.1 (0.9 to 31.3)	9.1 (2.5 to 27.8)	11.1 (2.5 to 35.4)	5.0 † (0.9 to 19.3)

[a] number of participants with available data

[b] number (percentage), median (interquartile range) or mean±standard deviation

[c] Age <65 versus ≥65 years

[d] current alcohol consumption

[e]GFR slope prior to enrolment

Abbreviations: BMI – body mass index, DBP diastolic blood pressure, CVD– cardiovascular disease, eGFR – estimated glomerular filtration rate, GCSE – general certificate of secondary education, KFRE – kidney failure risk equation, KRT – kidney replacement therapy, NVQ – national vocational qualification, RAAS – renin angiotensin aldosterone system, SBP – systolic blood pressure, UACR – urine albumin to creatinine ratio,

* denotes statistical significance between age subgroups

† denotes statistical significance between sex subgroups

Table 2: Distribution of Primary Renal Diagnoses by ERA code in the whole study population age and sex subgroups.

Primary Renal Diagnosis	Whole Cohort	Age <65 years (n=1419)	Age ≥65 years (n=1577)	Male (n=1753)	Female (n=1243)
Miscellaneous renal disorders	968 (32.3)	339 (23.8)	629 (39.9)	564 (32.2)	404 (32.5)
Glomerular Disease	700 (23.4)	396 (27.9)	304 (19.3)	425 (24.2)	275 (22.1)
Diabetes Mellitus	344 (11.5)	141 (9.9)	203 (12.9)	222 (12.7)	122 (9.8)
Family/hereditary nephropathies	327 (10.9)	255 (18.0)	72 (4.6)	154 (8.8)	173 (13.9)
Hypertension/ Renal vascular disease	268 (8.9)	85 (6.0)	183 (11.6)	183 (10.4)	85 (6.8)
Tubulointerstitial Disease	325 (10.8)	175 (12.3)	150 (9.5)	167 (9.5)	158 (12.7)
Other Systemic Diseases	64 (2.1)	28 (2.0)	36 (2.3)	38 (2.2)	26 (2.1)

Table 3: Baseline variables analysed in subgroups according to baseline GFR.

Variable	eGFR (ml/min/1.73m2) <20 (n=418)	20-29 (n=783)	30-39 (n=707)	40-49 (n=490)	50-59 (n=293)	60-69 (n=174)	≥70 (n=131)	P-value[a]
Age (years)	71 (60 - 79)	70 (60 - 77)	67 (55 - 74)	64 (53 - 72)	59 48 - 69)	55 (47 - 64)	45 (35 - 56)	<0.001
Male	266 (63.6)	468 (59.8)	440 (62.2)	277 (56.5)	142 (48.5)	97 (55.8)	63 (48.1)	<0.001
White ethnicity	359 (85.9)	675 (86.2)	607 (85.9)	414 (84.5)	242 (82.6)	138 (79.3)	88 (67.2)	<0.001
Diabetes	157 (38.0)	298 (38.3)	237 (34.0)	127 (26.7)	52 (18.3)	24 (14.3)	27 (22.5)	<0.001
Smoking status								0.005
Never	183 (44.4)	377 (48.8)	351 (50.7)	246 (51.0)	158 (54.3)	97 (55.8)	71 (54.2)	
Previous	194 (47.1)	340 (44.4)	277 (40.0)	194 (40.3)	107 (36.8)	56 (32.2)	41 (31.3)	
Current	35 (8.5)	55 (7.1)	65 (9.4)	42 (8.7)	26 (8.9)	21 (12.1)	19 (14.5)	
RAAS inhibitor	228 (54.7)	510 (65.5)	487 (69.9)	335 (69.8)	205 (71.7)	117 (69.6)	100 (80)	<0.001
Statin	279 (66.9)	504 (64.7)	440 (63.1)	260 (54.2)	133 (46.5)	70 (41.7)	54 (43.2)	<0.001
SBP (mmHg)	142±21	141±21	140±21	140±21	136±18	136±19	132±18	<0.001
DBP (mmHg)	77±12	78±13	80±12	81±13	82±10	84±12	84±12	<0.001
BMI (kg/m^2)	29.4±6.2	29.8±6.5	30.0±6.4	29.0±5.7	29.2±5.9	29.7±6.9	28.9±6.4	0.08
Serum albumin (g/L)	41 (38 - 44)	41 (37 - 44)	41 (37 - 45)	41 (37 - 44)	42 (38 - 45)	42 (39 - 46)	39 34 - 43)	<0.001
Total cholesterol (mmol/L)	4.3 (3.5 - 5.3)	4.4 (3.7 – 5.3)	4.5 (3.8 – 5.5)	4.6 (3.8 – 5.5)	4.8 (4.0 – 5.6)	5.0 (4.3 – 5.9)	5.3 (4.6 – 6.3)	<0.001
Triglycerides (mmol/L)	1.7 (1.2 - 2.5)	1.7 (1.2 – 2.6)	1.7 (1.2 – 2.5)	1.6 (1.1 – 2.3)	1.5 (1.1 – 2.2)	1.6 (1.2 – 2.5)	1.7 (1.1 – 2.8)	0.04
Serum sodium (mmol/L)	139±3	140±3	140±3	140±3	140±3	140±3	139±3	<0.001
Serum potassium (mmol/L)	4.8±0.6	4.7±0.6	4.7±0.5	4.6±0.5	4.4±0.4	4.4±0.5	4.4±0.6	<0.001
Serum bicarbonate (mmol/L)	23.3±3.4	23.9±3.4	24.8±3.3	25.3±3.1	25.7±2.9	26.1±2.8	25.1±3.2	<0.001
Serum phosphate	1.26±0.23	1.16±0.21	1.09±0.20	1.06±0.19	1.05±0.23	1.03±0.18	1.05±0.20	<0.001

(mmol/L)								
Haemoglobin (g/L)	116±16	122±16	127±17	132±18	134±16	139±16	138±17	<0.001
CRP (mg/L)	3.4 (1.4 – 7.9)	2.7 (1.2 – 6.1)	2.8 (1.3 – 5.7)	2.2 (1.0 – 5.0)	1.8 (0.8 – 4.3)	2.0 (0.8 – 4.9)	1.8 (0.7 – 4.3)	<0.001
UACR (mg/g)	576 (133-1625)	241 (54-926)	189 (32-783)	102 (19-609)	62 (15-589)	79 (16-464)	742 (124-1787)	<0.001
Albuminuria categories								
A1	33 (8.8)	116 (16.7)	144 (22.3)	141 (30.6)	98 (36.4)	52 (32.1)	17 (14.2)	<0.001
A2	104 (27.7)	248 (35.8)	218 (33.8)	144 (31.2)	81 (30.1)	57 (35.2)	22 (18.3)	
A3	238 (63.5)	329 (47.5)	284 (44.0)	176 (38.2)	90 (33.5)	53 (32.7)	81 (67.5)	
GFR slope (ml/min/year)*	-2.2 (-4.5 to -0.8)	-1.7 (-4.0 to 0.2)	-1.5 (-4.6 to 0.8)	-0.3 (-2.4 to 2.4)	-0.5 (-3.2 to 2.4)	-1.0 (-4.8 to 2.5)	-0.6 (-3.9 to 2.8)	<0.001

[a] P-value for trend

Abbreviations: ACR – albumin to creatinine ratio, BMI – body mass index, DBP – diastolic blood pressure; ESKD – end stage kidney disease, eGFR – estimated glomerular filtration rate, KFRE – kidney failure risk equation, RAAS – renin angiotensin aldosterone system, SBP – systolic blood pressure

*GFR slope prior to enrolment

Table 4: Summary baseline data from major national chronic kidney disease cohort studies versus NURTuRE-CKD.

	CRIC (USA)	CKD-JAC (Japan)	CanPREDDICT (Canada)	GCKD (Germany)	C-STRIDE (China)	CKD-REIN (France)	ICKD (India)	NURTuRE-CKD (UK)
n	3612	2977	2402	5217	3168	3033	4056	2996
Age	58.2±11.0	60.8±11.6	68.1±12.7	60.1±12.0	48.2±13.7	69 (60-76)	50.3±11.8	66 (54-74)
Female (%)	46	38	37	40	41	35	32.8	42
White (%)	45	0	89	100	0	96†	0	84
Diabetes (%)	47	38	48	35	22	43	37.5	31
SBP (mmHg)	127.7±21.9	131.7±18.6	134.3±20*	139.5±20.4	129.3±17.5	142±20	130 (120 to144)	139±20
DBP (mmHg)	71.4±12.8	76.3±11.8	70.8±11.9*	79.3±11.7	80.9±11.7	78±12	80 (78 to 90)	80±12
BMI (kg/m^2)	32.1±7.9	23.5±3.8	28.7 (25.1-33.2)*	29.8±6.0	24.5±3.6	29±6	24.4 (21.6 to 27.4)	29.6±6.3
eGFR (ml/min/1.73m^2)	43.4±13.5	28.7±12.2	27.9±9.0	47.1±16.7	50.7±30.0	33±12	40.5 (33.7 to 50.8)	34 (24 to47)
Proteinuria (g/d)	0.17 (0.07-0.81)	0.68 (0.21 to 1.68)			0.94 (0.34 to2.3)			
UACR (mg/g)		481.3 (120.2 to 1298.2)	142 (27 to779)	50.9 (8.9 to391.7)		120 (24 to 535) †	29 (11 to 304)	209 (33 to 926)
Started	2003	2007	2008	2010	2011	2013	2016	2017
Recruitment	5 years	20 months	18 months	2 years	4.3 years	3 years	4 years	2 years
Follow-up	Life	4 years	5 years	10 years	≥ 5 years	5 years	5 years	15 years
Exclusions	ADPKD IS HIV Cirrhosis NYHA III-IV Myeloma	APKD HIV Cirrhosis Cancer	IS	Non-white NYHA IV	Hereditary CKD IS AI disease NYHA III or IV HIV Cirrhosis		IS Survival <1 year Malignancy	Idiopathic NS Chemotherapy Survival <1 year

Abbreviations: ADPKD – autosomal dominant polycystic kidney disease, AI – autoimmune, BMI – body mass index, DBP – diastolic blood pressure; eGFR – estimated glomerular filtration rate (ml/min/1.73m^2), HIV – human immunovirus infection, IS – immunosuppression, NYHA – New York Heart Association class, SBP – systolic blood pressure, UACR – urine albumin to creatinine ratio

*Data obtained from Alencar de Pinho et al. [6] when not reported in original paper.

†Data provided by personal communication by the authors

Figure 1. Number and proportion of participants in KDIGO CKD categories

	A1 UACR <30 mg/g	A2 UACR 30-300 mg/g	A3 UACR >300 mg/g	Total
G1 (GFR >90)	5 (0.2%)	10 (0.4%)	37 (1.4%)	52 (1.9%)
G2 (GFR 60-89)	74 (2.7%)	75 (2.8%)	91 (3.3%)	240 (8.8%)
G3a (GFR 45-59)	174 (6.4%)	146 (5.4%)	166 (6.1%)	486 (17.8%)
G3b (GFR 30-44)	231 (8.5%)	314 (11.5%)	371 (13.6%)	916 (33.6%)
G4 (GFR 15-29)	148 (5.4%)	336 (12.3%)	486 (17.8%)	970 (35.6%)
G5 (GFR <15)	7 (0.3%)	13 (0.5%)	42 (1.5%)	62 (2.3%)
Total	639 (23.4%)	894 (32.8%)	1193 (43.8%)	2726

Abbreviations: GFR – glomerular filtration rate in ml/min/1.73m^2; UACR – urine albumin to creatinine ratio