Major cardiovascular events and subsequent risk of kidney failure with replacement therapy- a CKD Prognosis Consortium study

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Abstract

Background and Aims: Chronic kidney disease (CKD) increases risk of cardiovascular disease (CVD). Less is known about how CVD associates with future risk of kidney failure with replacement therapy (KFRT).

Methods: The study included 25,903,761 individuals from the CKD Prognosis Consortium with known baseline eGFR and evaluated the impact of prevalent and incident coronary heart disease (CHD), stroke, heart failure (HF), and atrial fibrillation (AF) events as time-varying exposures on KFRT outcomes.

Results: Mean age was 53 years (SD 17) and mean estimated glomerular filtration rate (eGFR) was 89 ml/min/1.73m^2, 15% had diabetes and 8.4% had urinary albumin-to-creatinine ratio (ACR) available (median 13 mg/g); 9.5% had prevalent CHD, 3.2% prior stroke, 3.3% HF and 4.4% prior AF. During follow-up there were 269,142 CHD, 311,021 stroke, 712,556 HF, and 605,596 AF incident events and 101,044 (0.4%) patients experienced KFRT. Both prevalent and incident CVD were associated with subsequent KFRT with adjusted hazard ratios (HR) of 3.1 (95% CI 2.9-3.3), 2.0 (1.9-2.1), 4.5 (4.2-4.9), 2.8 (2.7-3.1) after incident CHD, stroke, HF and AF, respectively. HRs were highest in first three months post CVD incidence declining to baseline after three years. Incident HF hospitalisations showed the strongest association with KFRT (HR 46 (95% CI 43-49) within 3 months) after adjustment for other CVD subtype incidence.

Conclusions: Incident CVD events strongly and independently associate with future KFRT risk, most notably after HF, then CHD, stroke, and AF. Optimal strategies for addressing the dramatic risk of KFRT following CVD events are needed.

Background

It is well established that chronic kidney disease (CKD) is a risk factor for developing cardiovascular disease (CVD)[1,2]. However, whether CVD is a risk factor for CKD progression and subsequent kidney failure with replacement therapy (KFRT, i.e. dialysis or kidney transplant) is less clear. Such bidirectional association is plausible and consistent with the hypotheses postulated in the cardiorenal syndrome[3,4]. Many consequences of CVD, including inflammation[5,6], oxidative stress[7], haemodynamic changes (e.g. renal congestion, neurohormonal activation)[8], and medical interventions (e.g. use of loop diuretics, radiocontrast agents)[9] may negatively impact kidney function.

Epidemiological data exploring CVD as a cause of CKD is scarce, and potentially limited by small sample sizes, single-center studies, the timing of the CVD event and varying definitions of CKD outcomes mostly focused on relative declines of estimated glomerular filtration rate (eGFR). Early reports disclosed that patients with *prevalent* CVD were at higher risk of receiving a diagnosis of CKD or having a more rapid eGFR decline[10-12]. More recently, *incident* major CVD events, particularly heart failure (HF) have been associated with a faster eGFR decline[13] and KFRT [14,15].

A comprehensive analysis evaluating the robustness and consistency of this association is lacking, perhaps because the outcome of KFRT is rare and requires large sample sizes with long follow-up. Using data from the multinational CKD-Prognosis Consortium, we sought to quantify the association of CVD incidence, prevalence and subtypes on subsequent risk of KFRT. We hypothesized that incident CVD events would be associated with increased risk of KFRT.

Methods

This study was approved for use of de-identified data by the institutional review board at the Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA (#IRB00003324). The need for informed consent was waived by the institutional review board.

Populations

We included cohorts in the CKD-PC with available data for the present study. The details of CKD-PC are described elsewhere[16], but in brief, this consortium included both research cohorts and health system datasets, with participants from 41 countries from North America, Europe, the Middle East, Asia, and Australia. These cohorts included general population (screening cohorts and health systems), high-risk (specifically selected for clinical conditions, such as diabetes), and CKD (exclusively enrolling individuals with CKD) cohorts. For the present study, cohorts were required to have data on at least one CVD subtype and subsequent follow-up for KFRT as the outcome. Cohorts also needed to have baseline information on eGFR and some albuminuria data. In total, 81 cohorts had adequate data and agreed to participate. Further information on cohorts is available in Appendix 1. Individual patient data (IPD) level analysis was performed in two stages. First the analysis was conducted within each cohort and then the results were meta-analyzed. This permits IPD analysis of cohorts where the data must reside on a separate server (e.g., VA and OLDW).

Exposures: CVD types of interest

We explored the risk associated with prevalent and incident non-fatal coronary heart disease (CHD), stroke, HF, and atrial fibrillation (AF) events on the outcome of KFRT. Prevalent CHD was defined as positive history of myocardial infarction (MI), bypass grafting, or percutaneous coronary intervention. Incidence of CHD was defined as the occurrence of a *de novo* MI. Most cohorts did not have information on HF type, so we analyzed overall HF (see Appendix 1.4 for details and ICD codes).

Outcomes

The main outcome of interest was KFRT defined as initiation of chronic dialysis or transplant. Information on outcome ascertainment is provided in Appendix 1. The secondary outcome was the combined end point of kidney failure defined as KFRT or having a follow-up eGFR <15 ml/min/1.73m^2. We also considered mortality as a competing outcome.

Covariables

Demographic variables included age, sex, and race. Body mass index was modelled as linear spline with knot at 30 kg/m^2. Smoking status was recoded as current smoking, former smoking versus never smoking. eGFR was estimated by the CKD-EPI equation using age, sex, race, and serum creatinine[17]. eGFR was modelled as linear spline with knot at 60. Albuminuria was recorded as the urinary albumin-to-creatinine ratio (ACR) or protein-to-creatinine ratio and converted to ACR as done previously[18]. If these measurements were not available, we used dipstick proteinuria information and converted to ACR[18]. When albuminuria was missing more than 25% in a single study, a missing indicator was used (a value of 10 mg/g was used to anchor the missing ACR category); this occurred in health systems where the missing ACR indicator reflects existing clinical practice. Hyperlipidaemia status was controlled for with information on total cholesterol, HDL cholesterol and use of lipid lowering medication. Diabetes mellitus was defined as the use of glucose lowering drugs, a fasting glucose ≥7.0 mmol/L or non-fasting glucose ≥ 11.1 mmol/L, hemoglobin A1c ≥6.5%, or self-reported diabetes. Hypertension was modelled as continuous systolic blood pressure and antihypertensive medication use. These variables were imputed to the sample mean if less than 50% missing in a single study, otherwise the variables were excluded from the model.

Statistical Analyses

Descriptive data are presented as mean and standard deviation (SD) or median and inter quartile interval (IQI). Time to event analysis was analyzed for each CVD event separately with follow-up from baseline as the time scale. Baseline was selected on the first serum creatinine measurement 12 months after start date in health system cohorts to allow adequate information for determining prevalent CVD. Incident CVD was modelled as a time dependent exposure. Hazard ratios and 95% confidence intervals were obtained from Cox regression models in each cohort, adjusted for all available covariables. Estimates were meta-analyzed using a random effects meta-analysis to conservatively incorporate any between cohort variance. Following analysis of each CVD event type separately, we analyzed all four CVD subtypes in a single model adjusting for each other. The latter analysis was limited to cohorts that had data on all CVD subtypes. Timing of excess risk and absolute risk after CVD were estimated in the Optum Labs Data Warehouse (OLDW) cohorts only due to their large sample size and representativeness of health system data. The OLDW is a longitudinal, real-world data asset with de-identified administrative claims and electronic health record (EHR) data.[19] Time after incidence of CVD was modelled in three month categories to quantify a priori hypothesized higher risk proximal to the CVD event. Baseline absolute risk was estimated from a Fine and Gray model with mortality as a competing outcome for each CVD type[20]. Risks were expressed across categories of eGFR and ACR and adjusted to age 70 and 50% male to facilitate comparisons across CVD events. Absolute risk was not included for times without CVD since the focus of this risk analysis was time after an event and a comparison of absolute risk across CVD subtypes. In models adjusting for all subtypes of CVD, each was modelled as a time-varying covariate in a single model with all the CVD subtypes, censoring only for KFRT, death, and administrative censoring. As a result, risk is attributed to each of the CVD subtypes when each of multiple events occur. We only model the first CVD event of each subtype to avoid intractable model complexity in the setting of multiple hospitalisations.

Missingness in covariates was modelled with a missing indicator variable (see eAppendix 1). The variable most often missing was albuminuria, which reflects clinical practice. Sensitivity analyses adjusted for the last eGFR before the CVD event to conservatively remove the part of the risk associated with eGFR decline prior to the event. Analyses were done in Stata version 16 (StataCorp). Statistical significance was determined using a 2-sided test.

Results

Baseline characteristics

Across 25,903,761 patients from 81 cohorts, the mean age was 53 (SD 17), 52% were female, the mean baseline eGFR was 89 ml/min/1.73m^2 (SD 23), 8.8% were black, 15% had diabetes and 8.4% had ACR available (median 13 mg/g, IQI 6-36); 2,450,902 (9.5%) had prevalent CHD, 824,717 (3.2%) prior stroke, 848,609 (3.3%) HF and 1,071,615 (4.4%) a history of AF (**Table 1** and **Tables S1-S3**).

Incidence of CVD and KFRT

During a mean follow up of 4.2 years 269,142 (1.0%) participants experienced CHD, 311,021 (1.2%) stroke, 712,556 (2.8%) HF and 605,596 (2.5%) AF incident events. Respective mean (SD) age for these incident events were 69 (13), 71 (13), 72 (12) and 73 (11) years, with details in **Table S3**. In this follow-up period, 101,044 participants developed KFRT in the overall population, whilst 221,659 participants developed the combined end point of KFRT or eGFR <15 ml/min/1.73m^2 in the subpopulation with repeated eGFR available after the index eGFR (**Table S4**). Among participants who developed KFRT, 53% experienced CVD events (including both prevalent and incident cases) prior to KFRT, compared to only 17% experiencing CVD events among participants who did not develop KFRT. **Figure 1** shows the distribution of CVD events by occurrence of KFRT during follow-up.

Prevalent and incident CVD and subsequent risk of KFRT

Patients with prevalent CHD, stroke, HF, and AF at cohort entry were at higher risk of future KFRT with adjusted hazard ratios of 1.21 (95% CI 1.17, 1.26), 1.14 (1.10, 1.18), 1.41 (1.34, 1.49), and 1.12 (1.07, 1.18) respectively (**Table 2; Table S5** shows further details of progressive adjustment and sex stratified analyses). Incident CVD during follow-up was strongly associated with subsequent risk of KFRT with hazard ratios ranging from 1.99 for stroke to 4.50 for HF; Forest plots show the meta-analysis results were supported by the majority of the cohorts (Figure S1). Analysis of each CVD event adjusted for all the other CVD events in 55 cohorts showed that the largest hazard ratio for KFRT was associated with HF. Among prevalent events, the hazard ratios were 1.12 (1.08, 1.15), 1.07 (1.03, 1.11), 1.37 (1.31, 1.44), and 0.98 (0.94, 1.02) for CHD, stroke, HF, and AF adjusted for each other. For incident events, the hazard ratios were 1.49 (1.38, 1.61), 1.33 (1.22, 1.45), 3.69 (3.36, 4.04), and 1.39 (1.28, 1.52) for CHD, stroke, HF, and AF adjusted for each other.

The excess risk was highest in the months following the CVD events, persisted for two years and returned to baseline three years after CVD among those who survived (**Figure 2, Table S6**). This analysis was limited to the OLDW cohorts since their large sample size (greater than 19 million) allowed for a detailed examination of the change in hazard ratio of KFRT for each quarter year. This revealed adjusted relative hazards of KFRT ranging from 45 (95% CI 41, 49) for stroke to 106 (102, 110) for HF in the first 3 months following the CVD event. The risks declined progressively until three years after each event. An analysis adjusting each incident CVD event for the other events showed very high risk persisting for HF with an adjusted hazard ratio of 46 (95%CI 43, 50) in the first months after HF incidence. In contrast, adjusted for HF and the other CVD events, the adjusted hazard ratio for CHD, stroke and AF

declined markedly with remaining short term risks ranging from 2.1 to 3.6 which declined to less than two-fold after 3 months but stayed statistically significant for over a year.

Sensitivity analyses showed that the excess risk associated with CVD remained, even after adjustment for the most recent eGFR recorded prior to the CVD event (**Table S7**). Results were consistent if shorter follow-up time after the CVD event was considered (**Table S8**) as well as for the secondary broader outcome including eGFR <15 ml/min/1.73m^2 during follow-up (**Table S9**). Interaction models showed that the hazard ratios of KFRT after CVD incidence were somewhat smaller at lower eGFR and higher albuminuria (**Table S7 and S8**).

Absolute risk of KFRT

The 2-year risk of KFRT following CVD events was higher at lower eGFR and elevated ACR with highest absolute risk in HF compared to other CVD subtypes. The 2-year risk of KFRT in eGFR 15-29 and ACR 300+ was 21.1%, 17.9%, 25.6%, and 19.1% for CHD, stroke, HF, and AF adjusted to age 70 and half male population after taking death into account as a competing outcome (**Table 3**). The risk of death after CVD events was substantial and higher with lower eGFR and higher ACR (**Table S10**). Among those with eGFR above 60 ml/min/1.73m^2, the risk of KFRT was higher among younger individuals with diabetes (**Table S11**).

Discussion

In this large multinational individual participant meta-analysis, we observed strong associations between major CVD events and subsequent risk of KFRT. The risk of KFRT was strikingly elevated after incident HF, but also after CHD, stroke and AF. Excess risk was present for prevalent CVD events but much higher for incident CVD events, particularly HF with consistent results across subgroups and a wide range of sensitivity analyses. Given the poor clinical and patient-reported outcomes as well as the excessive healthcare costs of KFRT[21-23], our results have implications on need of detection and monitoring of kidney disease measures, including eGFR and albuminuria, as well as on need of therapeutic strategies to delay KFRT after CVD events.

Previous smaller studies have shown prevalent or 'baseline' CVD to be associated with subsequent accelerated decline in eGFR[10-12]. However, studies of prevalent CVD and future eGFR decline are biased by their inability to take into account the decline in eGFR that occurs between the CVD event and subsequent entry into the cohort studied. Hence these analyses give limited insight into the degree of risk directly attributable to the CVD event. Our results are in agreement with analyses of the Atherosclerosis Risk in Communities (ARIC) study, which examined the impact of incident CVD and future KFRT, in both degree of risk and effect of each of the CVD subtypes[14]. However, the number of KFRT events in ARIC was small (n=210), and was limited to US participants. In the Stockholm CREAtinine Measurements (SCREAM) project, incident CVD was associated with an acceleration in decline in eGFR over the subsequent two years post CVD event[13]. This was most marked for HF events, with lesser magnitude of acceleration in eGFR decline observed following CHD events. However, quantification of pre-post eGFR slopes depended on testing and on surviving two years post CVD event.

The complex mechanisms underlying the increased risk of KFRT in patients with CVD in general and with HF in particular are outlined in Figure S2. On one hand, both conditions share common risks factors, such as hypertension, diabetes, smoking, obesity and physical inactivity[1,24], so these could be thought of as confounders. Conversely, both conditions share mediating pathophysiological mechanisms, often inducing a 'vicious cycle' of dysregulated homeostasis including neurohormonal activation, anaemia, endothelial dysfunction, arterial calcification and fibrotic responses leading to kidney disease[25]. We are unable to attribute causality, or clearly distinguish confounding from mediation, in these associations. However, the observed greater than 50-fold relative hazard within months of HF incidence, which diminishes nearly all the way to baseline three years later, demonstrating an extremely strong temporal association.

The bidirectional, inter-dependent interaction between HF and kidney dysfunction is well acknowledged, with worsening HF being a risk factor for decline in kidney function, whilst lower eGFR predicts adverse outcomes, including mortality, in patients with HF[26]. The relationship between evidence-based medicines for treatment of HF (e.g. renin angiotensin-aldosterone system inhibition) and decline in kidney function is controversial with much evidence coming from observational data which is susceptible to indication bias[27] as they may be prone to indication bias. We did not have access to prescribing information for the duration of follow up in all cohorts to evaluate this. For other CVD subtypes, acute kidney injury is common in the setting of atherothrombotic CVD events such as stroke or CHD. Subsequent KFRT risk may reflect loss of eGFR after an episode of AKI or *de novo* accelerated eGFR decline as suggested previously[28,29].

Our findings have clinical implications on risk stratification and informing decisions around therapeutic interventions, intensity of monitoring kidney disease measures, and planning for long term KFRT. eGFR monitoring is already emphasized by cardiology guidelines[30], and creatinine is included in some risk calculators for predicting survival of patients with HF[31]. Albuminuria testing is an additional, inexpensive early sign of kidney damage to add to routine secondary CVD prevention workup, hence informing KFRT risk and CVD prognostication simultaneously[32-34]. Our results evidence the need for preventing KFRT through established therapies including renin angiotensin system inhibition[35-37], sodium glucose transport 2 (SGLT2) inhibition[38] and finerenone[39,40]. These agents have demonstrated efficacy in both reducing albuminuria and delaying eGFR decline with additional cardiovascular benefits. Prudent use of diuretics to ensure 'decongestion' has a role in both treatment of HF and maintenance of kidney function[27]. Routine care data and clinical trials shows suboptimal use of guideline based cardio- and nephroprotection with opportunities for improvement[41,42].

Collaboration between nephrology and cardiology is crucial in personalizing preparation for KFRT. For example: creation of an arteriovenous fistula for haemodialysis risks exacerbating pre-existing HF[43]; Management of CKD- related complications such as anaemia, acidosis and mineral bone disorders; Long-term planning to consider dialysis modality and/or consider whether kidney transplantation is feasible. Indeed, workup of kidney transplant candidates with cardiovascular disease is controversial and requires advance planning[44]. Patients at highest risk of CKD progression are likely to benefit from additional management efforts, including avoidance of nephrotoxins like non-steroidal anti-inflammatory drugs, proton-pump inhibitors, warfarin or certain antibiotics.

Strengths of this study include the large sample sizes of the study populations; the clinical and geographic diversity of the participants in both general population and high cardiovascular risk cohorts; and the rigorous analytical approach. However, limitations also exist. Misclassification is amplified by any heterogeneity in how CVD subtypes were determined or defined across cohorts as well as baseline eGFR and albuminuria measurement at a single visit. Consistency of our findings despite this inevitable heterogeneity favors, however, true and generalizable associations. We lack data on a number of important variables such as inflammation, socioeconomic status, complete medication history and exposure to radiocontrast, and some covariates were not present in all cohorts. Whilst CHD, HF and stroke are likely to represent cardiovascular events with a definitive date of occurrence, the incidence and timing of atrial fibrillation diagnosis may be prone to acquisition bias[45]. Some cohorts rely on health record coding for outcomes, and lack detailed phenotyping of CVD subtypes, such as ejection fraction by echocardiography in HF or distinction between ischaemic/haemorrhagic strokes. Inherent to observational studies, residual confounding may exist, and we are unable to separate the effect that incident CVD has *per se* on KFRT risk from that of CVD-management, nor did we evaluate acute kidney injury risks and mediation of KFRT risk. Understanding best management strategies within secondary CVD prevention that may alter CKD progression warrants further study and may serve to individualize treatment pathways. Finally, absolute risk estimates and the time dependent analysis of risk after CVD had to be limited to the OLDW cohorts, due to their large sample size, availability of all four CVD subtypes, and representativeness of health care systems.

In summary, we show evidence that incident CVD events are strongly and independently associated with risk for KFRT, with greatest risk in the first year following HF, then CHD, stroke, and AF. Patients, clinicians and healthcare systems engaged with the management of

major CVD should be aware of this risk to optimize long-term care and ensure that those at highest risk receive appropriate evaluation, counselling, therapy, and referral for management of progressive CKD.

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Data Availability Statement: Under agreement with the participating cohorts, CKD-PC cannot share individual data with third parties. Inquiries regarding specific analyses should be made to ckdpc@jhmi.edu. Investigators may approach the original cohorts regarding their own policies for data sharing (e.g., https://sites.cscc.unc.edu/aric/distribution-agreements for the Atherosclerosis Risk in Communities Study).

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FIGURE TITLES AND LEGENDS

Figure 1. CVD events distribution by occurrence of KFRT during follow-up. Both prevalent and incident CVD events are included. Among individuals who developed KFRT events are limited to CVD prior to KFRT while among individuals without KFRT all events during follow-up are included

Figure 2. Adjusted hazard ratios and 95% confidence intervals of kidney failure replacement therapy (KFRT) associated with different cardiovascular (CVD) events modelled (A) separately or (B) simultaneously adjusted for each other by timing after the incident CVD event in OLDW

Dots show the hazard ratio and whiskers are the 95% confidence intervals. The dots are plotted in the center of 3 month windows (e.g., for 0-3 months, the dot is at 1.5 months or 0.125 years).

Structured Graphical abstract. Hazard ratios (and 95% confidence intervals) for the risk of kidney failure with replacement therapy (KFRT) associated to developing heart failure (HF), myocardial infarction (MI), atrial fibrillation (AF) or stroke, across 81 global cohorts and graphically depicted using the OLDW database.

Supplementary Material

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eAppendix 1. Data analysis overview and analytic notes for some individual cohorts

1.1 Overview:

As previously described,[1] the collaborating cohorts were asked to compile a dataset with approximately 25 variables (main exposure [serum creatinine to estimate GFR, albuminuria, age, sex, race/ethnicity, history of CVD, smoking, diabetes, systolic blood pressure, antihypertensive medications, total cholesterol, HDL cholesterol], outcome [cardiovascular mortality, fatal coronary heart disease, fatal stroke, myocardial infarction, ischemic stroke, hemorrhagic stroke]). To be consistent across cohorts, the CKD-PC Data Coordinating Center sent definitions for those variables to participating cohorts. We instructed studies not to impute any variables.

The CKD-PC data request and processing procedures are as follows. After obtaining opt-in preferences from cohorts for the topics for each phase, the Data Coordinating Center (DCC) requests de-identified data using a specific data request document describing the variables and preferred definitions needed for the current phase of the CKD-PC. Cohorts work with the DCC on any data use agreements, IRB approvals, and other logistic issues for de-identified data transfer. The DCC also advises on any differences in definitions or questions on data formatting. Cohorts then provide de-identified data (in whatever program format, e.g., Stata, SAS, csv) via a secure data transfer provided or their own secure transfer program/platform. Data is stored on a secure password protected network server that is only accessed by limited faculty and staff (<10). All those faculty and staff have completed HIPAA and CITI certification and have signed internal data use agreements to not use the data for any other than stated purposed and to not remove the data from that network drive. The CKD-PC does not share data with any external parties. Once data is received and stored in the network drive, the DCC programmer reviews the data and the data dictionary provided by the cohort to check for any missing information, outliers, and potentials issues with variable units, dates, etc. Any questions are sent to the cohort representatives for data checking and cleaning. Further data checking is done throughout the analysis process for each CKD-PC paper, including a review from a cohort representative of all tables and figures to confirm their cohort representation.

For 75 of the 81 cohorts in this specific study, the DCC at Johns Hopkins University conducted the analysis; the remainder ran the standard code written in Stata by the DCC and shared the output with the DCC. As in the data processing procedures above, the DCC works with the cohort to confirm the variable definitions and data formatting to prepare for the code. The standard code was designed to automatically save all estimates and variance-covariance matrices needed for the meta-analysis. Then the DCC meta-analyzed the estimates across cohorts using Stata.

As detailed in our previous reports,[2,3] each cohort was instructed to standardize their serum creatinine and report its method when available. The reported creatinine standardization allows grouping studies into studies that reported using a standard IDMS traceable method or conducted some serum creatinine standardization to IDMS traceable methods (ARIC, CanPREDDICT, CRIC, GCKD, Geisinger, GLOMMS, GoDARTS, Gubbio, ICES-KDT, LCC, Maccabi, MASTERPLAN, MMKD, NephroTest, RCAV, REGARDS, SCREAM, SEED, SRR-CKD, UK Biobank, West of Scotland CKD, UK Biobank) and studies where the creatinine standardization was not done (ADVANCE CRIB, MDRD, Nefrona, PSP-CKD, RENAAL, SHARP, SKS, SMART, Sunnybrook). For those cohorts without standardization, the creatinine levels were reduced by 5%, the calibration factor used to adjust non-standardized MDRD Study samples to IDMS.[2,4]. We did not adjust creatinine levels in those studies with unknown standardization status (CARE FOR HOMe, Hongkong CKD, Nanjing-CKD, Mt Sinai BioMe, OLDW all cohorts, and YWSCC).

We calculated eGFR using the CKD-EPI equation: $eGFR_{CKD\text{-}EPI} = 141 \times (\text{minimum of standardized serum creatinine [mg/dL]}/\kappa \text{ or } 1)^{\alpha} \times (\text{maximum of standardized serum creatinine [mg/dL]}/\kappa \text{ or } 1)^{-1.209} \times 0.993^{age} \times (1.018 \text{ if female}) \times (1.159 \text{ if black})$, where κ is 0.7 if female and 0.9 if male and α is -0.329 if female and -0.411 if male.[5] The selection of knots for eGFR and urine albumin-to-creatinine ratio was based on clinical thresholds.[6] Baseline for each study was considered first available creatinine unless otherwise noted. Other variables were taken either on baseline date or within one year before baseline date.

1.2 Notes for individual cohorts:

ADVANCE: This study is a clinical trial which includes participants with diabetes only. Only Statin use was available as lipid lowering medication.

ARIC: Only Statin use was available as lipid lowering medication. Visit 4 was used as the baseline.

CanPREDDICT: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing. Only Statin use was available as lipid lowering medication.

CRIB: Only Statin use was available as lipid lowering medication.

CRIC: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing.

Geisinger: Urine albumin-to-creatinine ratio measures were imputed by PCR measures and then dipstick measurements when missing. Baseline was considered first available creatinine starting from Jan 1, 2008, and at least one year after entering the health system.

GLOMMS: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing. Baseline was considered first available creatinine at least one year after entering the health system.

GoDARTS: Baseline was considered first available creatinine at least one year after entering the local health board authority area.

Hongkong CKD: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing.

ICES-KDT: Urine albumin-to-creatinine ratio measures were imputed by PCR measures and then dipstick measurements when missing. Baseline was considered first available creatinine at least one year after entering the health system.

LCC: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing. Only Statin use was available as lipid lowering medication.

Maccabi: Urine albumin-to-creatinine ratio measures above 300 were imputed by PCR measures. Baseline was considered first available creatinine starting from June 1, 2008, and at least one year after entering the health system.

MASTERPLAN: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing.

MDRD: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing.

MMKD: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing.

Mt Sinai BioMe: Urine albumin-to-creatinine ratio measures were imputed by PCR measures and then dipstick measurements when missing. Baseline was considered first available creatinine starting from Jan 1, 2008, and at least one year after entering the health system. Only Statin use was available as lipid lowering medication.

Nanjing-CKD: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing.

Nefrona: Participants free from previous cardiovascular disease at baseline.

NephroTest: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing. Only Statin use was available as lipid lowering medication.

OLDW: This study used de-identified electronic health record (EHR) data from the Optum Labs Data Warehouse (OLDW). The database contains longitudinal health information on enrollees and patients, representing a mixture of ages, ethnicities and geographical regions across the United States. The EHR-derived data includes a subset of EHR data that has been normalized and standardized into a single database.[7] Cohort inclusion criteria was more than 50 events of KFRT before excluding missing values of main exposure variables and more than 4-year of 90th percentile of follow-up in events. Baseline was considered first available creatinine starting from Jan 1, 2012, and at least one year after entering the health system. Smoking status might be under measured in this study. Urine albumin-to-

creatinine ratio measures were imputed by PCR measures and then dipstick measurements when missing. We validated separately in each cohort in this study.

PSP-CKD: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing. Only Statin use was available as lipid lowering medication. Baseline was considered first available creatinine after enrollment.

RCAV: Urine albumin-to-creatinine ratio measures were imputed by PCR measures and then dipstick measurements when missing. Baseline was considered first available creatinine at least one year after entering the health system.

REGARDS: Only Statin use was available as lipid lowering medication.

SCREAM: Urine albumin-to-creatinine ratio measures were imputed by dipstick measurements when missing. Baseline was considered first available creatinine starting from Jan 1, 2008, and at least one year after entering the health system.

SRR-CKD: Only Statin use was available as lipid lowering medication.

SKS: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing.

Sunnybrook: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing. Baseline was considered first available creatinine starting from Jan 1, 2001, and at least one year after entering the health system.

West of Scotland: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing. Baseline was considered first available creatinine after enrollment.

YWSCC: Urine albumin-to-creatinine ratio measures were imputed by PCR measures when missing.

1.3 Missing exposure variables, %

Cohort	N	Covariates												
		History of CHD	History of stroke	History of HF	History of AF	smoking	DM	HTN	SBP	Anti-HTN	cholesterol	HDL-C	lipid	BMI
ADVANCE	11091	0	0	0	100	0.50	0	0	0.0090	0	0.018	0.13	0	0.027
ARIC	11527	2.0	0.22	1.7	1.3	0.62	0.49	0.41	<0.1	0	0	0	0.29	0.19
CanPREDDICT	1894	0	0	0	100	100	0	0	1.7	0.11	50	53	0.11	100
CARE FOR HOMe	541	0	0	100	100	0	0	0	0.37	0	0	100	0	0
CRIB	264	0	0	100	100	0	0	0	1.5	0	4.2	19	0	0.76
CRIC	5494	0	0	0	0	0	0	0	0.073	0.75	29	29	0.75	0.56
GCKD	5128	0.039	1.1	5.1	2.6	0.29	0	0.059	0.60	0.70	0.14	0.21	0.70	1.0
Geisinger	366016	0	0	0	0	0	0	0	9.9	0	40	40	0	17
GLOMMS	329977	0	0	0	0	100	0	0	100	0	56	56	0	100
Go-DARTs	17821	0	0	0	0	0	0	0	92	0	50	58	0	88
Gubbio	4597	0	0	0	0	0.24	0	0	0.15	0	0.044	0.022	0	1.5
Hongkong CKD	245	0	100	100	100	0	0	100	0	0	0.41	0.41	100	2.0
ICES-KDT	1017530	0	0	0	0	100	0	0	100	0	25	25	0	100
LCC	17132	0	0	0	0	0	0	0	0.61	0	4.4	7.0	0	5.0
Maccabi	1440372	0	0	0	100	0	0	0	30	0	16	17	0	35
MASTERPLAN	650	6.5	6.5	100	100	1.2	0	100	0	0	0.15	0.46	0	0
MDRD	1618	0	0	100	100	0.25	0.62	0	0	51	0.062	0.12	100	0.62
MMKD	172	0	0	100	100	0	0	0	0	0	0	0	0	0
Mt Sinai BioMe	17446	0	0	0	100	0	0	0	5.2	0	32	34	0	14
Nanjing CKD	1275	5.9	6.7	100	100	19	2.4	1.6	23	2.9	19	50	100	72
Nefrona	1471	0	0	0	0	0	0	0	0	0	1.1	11	0	0
NephroTest	1757	0	0	0	100	0	0	0.17	3.5	0.11	1.5	4.3	0.11	0
OLDW cohort 1	317354	0	0	0	0	0	0	40	36	10	7.2	0	0	0
OLDW cohort 2	88380	0	0	0	0	0	0	58	55	80	71	0	0	0
OLDW cohort 3	110002	0	0	0	0	0	0	41	37	99	95	0	0	0
OLDW cohort 4	304007	0	0	0	0	0	0	45	41	11	18	0	0	0
OLDW cohort 5	175556	0	0	0	0	0	0	47	43	38	36	0	0	0

OLDW cohort 6	165729	0	0	0	0	0	0	48	45	6.4	10	0	0	0
OLDW cohort 7	121413	0	0	0	0	0	0	46	42	3.9	2.9	0	0	0
OLDW cohort 8	266591	0	0	0	0	0	0	34	30	23	22	0	0	0
OLDW cohort 9	1473923	0	0	0	0	0	0	45	41	24	21	0	0	0
OLDW cohort 10	1305648	0	0	0	0	0	0	46	42	10	8.0	0	0	0
OLDW cohort 11	176874	0	0	0	0	0	0	54	50	69	66	0	0	0
OLDW cohort 12	385105	0	0	0	0	0	0	29	24	10	9.1	0	0	0
OLDW cohort 13	849173	0	0	0	0	0	0	39	36	15	25	0	0	0
OLDW cohort 14	133785	0	0	0	0	0	0	45	43	13	10	0	0	0
OLDW cohort 15	81203	0	0	0	0	0	0	39	35	96	95	0	0	0
OLDW cohort 16	231809	0	0	0	0	0	0	49	46	99	97	0	0	0
OLDW cohort 17	153560	0	0	0	0	0	0	34	30	3.8	2.1	0	0	0
OLDW cohort 18	278097	0	0	0	0	0	0	43	40	96	92	0	0	0
OLDW cohort 19	308518	0	0	0	0	0	0	44	41	32	28	0	0	0
OLDW cohort 20	669837	0	0	0	0	0	0	48	44	14	14	0	0	0
OLDW cohort 21	181418	0	0	0	0	0	0	48	44	13	14	0	0	0
OLDW cohort 22	836079	0	0	0	0	0	0	41	37	14	11	0	0	0
OLDW cohort 23	365414	0	0	0	0	0	0	58	56	86	85	0	0	0
OLDW cohort 24	543380	0	0	0	0	0	0	48	46	49	41	0	0	0
OLDW cohort 25	537225	0	0	0	0	0	0	42	39	24	15	0	0	0
OLDW cohort 26	1141213	0	0	0	0	0	0	51	49	21	20	0	0	0
OLDW cohort 27	40674	0	0	0	0	0	0	37	33	65	63	0	0	0
OLDW cohort 28	330566	0	0	0	0	0	0	56	53	19	18	0	0	0
OLDW cohort 29	747255	0	0	0	0	0	0	52	49	19	18	0	0	0
OLDW cohort 30	366530	0	0	0	0	0	0	54	51	35	33	0	0	0
OLDW cohort 31	363900	0	0	0	0	0	0	46	42	45	43	0	0	0
OLDW cohort 32	216369	0	0	0	0	0	0	58	56	33	28	0	0	0
OLDW cohort 33	244814	0	0	0	0	0	0	48	44	17	15	0	0	0
OLDW cohort 34	131205	0	0	0	0	0	0	43	39	28	23	0	0	0
OLDW cohort 35	148535	0	0	0	0	0	0	45	42	6.6	6.1	0	0	0
OLDW cohort 36	175418	0	0	0	0	0	0	51	48	8.4	8.7	0	0	0

OLDW cohort 37	367461	0	0	0	0	0	0	54	51	56	52	0	0	0
OLDW cohort 38	224879	0	0	0	0	0	0	52	50	13	14	0	0	0
OLDW cohort 39	51457	0	0	0	0	0	0	54	50	47	47	0	0	0
OLDW cohort 40	204235	0	0	0	0	0	0	38	34	12	12	0	0	0
OLDW cohort 41	518142	0	0	0	0	0	0	50	47	52	46	0	0	0
OLDW cohort 42	420302	0	0	0	0	0	0	44	38	13	16	0	0	0
OLDW cohort 43	68240	0	0	0	0	0	0	33	30	2.9	2.1	0	0	0
OLDW cohort 44	199070	0	0	0	0	0	0	31	27	9.1	9.0	0	0	0
OLDW cohort 45	3136664	0	0	0	0	0	0	45	41	47	43	0	0	0
PSP-CKD	26072	0	0	0	100	0	0	0	15	0	26	82	0	26
RCAV	2237948	0	0	0	0	0	0	0	3.7	0	46	34	0	13
REGARDS	28689	100	0.31	100	100	0.37	0.52	0.25	0.25	0	0	0.52	0	0.32
RENAAL	1510	0	0	0	100	0.26	0	0	0	0	0.99	1.5	100	2.3
SCREAM	696881	0	0	0	0	100	0	0	100	0	49	100	0	100
SEED	9512	0.17	0.13	100	100	0.14	1.3	0.28	0.042	0.94	0	0	100	0.49
SHARP	4790	0	0	100	100	0	0	0	0.17	0.17	11	11	0	2.0
SKS	2395	0	0	0	100	0	0	100	0	0	7.3	24	100	17
SMART	13010	0.20	0.22	0	100	0.0077	0.47	0	2.2	0.16	0	0.23	0.38	0
SRR-CKD	2559	2559	0	0	0	100	100	0	0.039	3.8	0	61	100	0
Sunnybrook	2524	2575	0	0	0	100	0	0	0	22	100	58	62	100
UK Biobank	463563	463563	0	0	0	0	0	0	0	6.5	0	0.030	8	0
West of Scotland	2412	2412	0	0	0	0	100	0	0	98	0	54	63	0
YWSCC	869	869	0	0.23	0	0	28	0	0.12	0.23	100	0.69	2.5	100

AF: atrial fibrillation, BMI: body mass index, CHD: congestive heart failure; DM: diabetes mellitus, HDL-C: high-density lipoprotein cholesterol, HF: heart failure, HTN: hypertension, SBP: systolic blood pressure.

1.4 CVD subtype and KFRT ascertainment

1.4.1 ICD codes used to define CVD events if not specified

Outcome	ICD-9 codes	ICD-10 codes
Myocardial infarction (MI)	410	I21, I22
Hemorrhagic stroke	431, 432	I61, I62
Ischemic stroke	433.?1, 434.?1	I63
Heart failure (HF)	428	I50
Atrial fibrillation (AF)	427.3	I48

1.4.2 Details of individual cohorts

	Cardiovascular disease ascertainment type	KFRT ascertainment type
ADVANCE	• By ICD codes from hospital discharge	• Active
ARIC	• Adjudicated by a physician panel	• Linkage to the United States Renal Data System[8]
CanPREDDICT	• Adjudicated by a physician panel and linkage to BC Renal database via comorbidity reporting	• Active
CARE FOR HOMe	• By medical chart review (adjudicated by a physician panel)	• Active (with adjudicated by a physician panel)
CRIB	• By medical chart review	• By medical chart review
CRIC	• Adjudicated by a physician panel	• Active (with confirmation), Linkage
GCKD	• By medical chart review (adjudicated by a physician panel)	• Active (with adjudicated by a physician panel)
Geisinger	• By ICD codes from hospital discharge	• Linkage
GLOMMS	• By ICD codes from hospital discharge	• Linkage
GoDARTS	• Electronic health records -ICD codes	• Linkage
Gubbio	• By medical chart review	• Linkage
Hong Kong CKD	• By medical chart review and ICD codes from hospital discharge	• Active (with confirmation), Linkage
ICES-KDT	• By ICD codes from hospital discharge	• Linkage, Codes
LCC	• By ICD codes from hospital discharge and primary care records	• Codes
Maccabi	• By ICD codes from hospital discharge	• Active
MASTERPLAN	• Adjudicated by a physician panel	• Active
MDRD	• By medical chart review	• Active, Linkage
MMKD	• By medical chart review	• By medical chart review
Mt Sinai BioMe	• By ICD codes from hospital discharge	• Codes
Nanjing CKD	• By ICD codes from hospital discharge	• Electronic medical records

Nefrona	• By ICD codes from referring physicians	• Linkage
NephroTest	• By medical chart review and ICD codes from the national death registry	• Linkage to the national REIN registry
OLDW cohorts	• By ICD codes from hospital discharge	• Codes
PSP-CKD	• Primary care records	• Codes
RCAV	• By ICD codes from hospital discharge	• Linkage
REGARDS	• Adjudicated by a physician panel	• Linkage to the United States Renal Data System[8]
RENAAL	• Adjudicated by a physician panel	• Active (with adjudication)
SCREAM	• By ICD codes from hospital discharge	• Linkage
SEED	• By ICD codes from hospital discharge	• Linkage
SHARP	• Active, followed by physician panel adjudication; AFwas active direct follow-up for serious atrial fibrillation (i.e.; hospitalisation or death)	• Active (followed by physician panel adjudication)
SKS	• Adjudicated by a physician panel	• Active
SMART	• Adjudicated by a physician panel	• Active (with adjudication)
SRR-CKD	• Linkage	• Active, Linkage
Sunnybrook	• Linkage to provincial data	• Linkage
UK Biobank	• By ICD codes from hospital discharge	• Linkage (Hospital Episode Statistics data managed by NHS Digital for England, NHS Wales Informatics Service's Information Services Division for Wales, and Information Services Division Scotland part of NHS National Services Scotland for Scotland)
West of Scotland	• By ICD codes from hospital discharge, supplemented with labs and imaging.	• Active (pulled from electronic medical records)
YWSCC	• By ICD codes from hospital discharge	• Linkage

Active: self-report usually without specific chart validation. **Linkage**: linkage to a registry or database for the outcome. **Codes**: death certificate or registry coded cause or International Classification of Disease codes.

eAppendix 2. Acronyms or abbreviations for cohorts included in the current study and their key references linked to the Web references

ADVANCE	The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial[9]
ARIC	Atherosclerosis Risk in Communities Study[10]
CanPREDDICT	Canadian Study of Prediction of Death, Dialysis and Interim Cardiovascular Events[11]
CARE FOR HOMe	The Cardiovascular and Renal Outcome in CKD 2-4 Patients—The Fourth Homburg evaluation
CRIB	Chronic Renal Impairment in Birmingham[12]
CRIC	Chronic Renal Insufficiency Cohort Study[13]
GCKD	German Chronic Kidney Disease Study[14]
Geisinger	Geisinger Health System[15]
GLOMMS	Grampian Laboratory Outcomes, Morbidity and Mortality Studies[16]
GoDARTS	Genetics of Diabetes Audit and Research in Tayside Scotland[17]
Gubbio	Gubbio Study[18]
Hong Kong CKD	Hong Kong CKD Studies[19]
ICES-KDT	Institute for Clinical Evaluative Sciences, Provincial Kidney, Dialysis and Transplantation program (ICES KDT)[20]
LCC	The Leicester City and County Chronic Kidney Disease Cohort[21]
Maccabi	Maccabi Health System[22]
MASTERPLAN	Multifactorial Approach and Superior Treatment Efficacy in Renal Patients with the Aid of a Nurse Practitioner[23]
MDRD	Modification of Diet in Renal Disease Study[24]
MMKD	Mild to Moderate Kidney Disease Study[25]
Mt Sinai BioMe	Mount Sinai BioMe Biobank Platform[26]
Nanjing CKD	Nanjing CKD Network Cohort
Nefrona	Observatorio Nacional de Aterosclerosis en Nefrologia[27]
NephroTest	NephroTest Study[28]
OLDW	Optum Labs Data Warehouse
PSP-CKD	Primary-Secondary Care Partnership to Prevent Adverse Outcomes in Chronic Kidney Disease[29]
RCAV	Racial and Cardiovascular Risk Anomalies in CKD Cohort[30]
REGARDS	Reasons for Geographic And Racial Differences in Stroke Study[31]
RENAAL	Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan[32]
SCREAM	Stockholm CREAtinine Measurements Cohort[33]
SEED	Singapore Epidemiology of Eye Diseases[34]
SHARP	Study of Heart and Renal Protection
SKS	Salford Kidney Study[35]
SMART	Second Manifestations of ARTerial Disease Study
SRR-CKD	Swedish Renal Registry CKD Cohort[36]
Sunnybrook	Sunnybrook Cohort[37]
UK Biobank	The United Kingdom Biobank Study[38]
West of Scotland	West of Scotland study[39]
YWSCC	Yonsei Wonju Severance CKD Cohort

eAppendix 3. Acknowledgements and funding for collaborating cohorts

Cohort	List of sponsors
ADVANCE	National Health and Medical Research Council (NHMRC) of Australia program grants 358395, 571281, 1052555 and 1149987 and project grant 211086 and research grants from Servier International
ARIC	The Atherosclerosis Risk in Communities study has been funded in whole or in part with Federal funds from the National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, under Contract nos. (HHSN268201700001I, HHSN268201700003I, HHSN268201700005I, HHSN268201700004I, HHSN2682017000021). The authors thank the staff and participants of the ARIC study for their important contributions.
CanPREDDICT	
CARE FOR HOMe	Supported by the Else Kröner-Fresenius Stiftung
CRIB	British Renal Society Project Grant Award British Heart Foundation Project Grant Award.
CRIC	Funding for the CRIC Study was obtained under a cooperative agreement from National Institute of Diabetes and Digestive and Kidney Diseases (*U01DK060990, U01DK060984, U01DK061022, U01DK061021, U01DK061028, U01DK060980, U01DK060963, U01DK060902 and U24DK060990*). In addition, this work was supported in part by: the Perelman School of Medicine at the University of Pennsylvania Clinical and Translational Science Award NIH/NCATS *UL1TR000003*, Johns Hopkins University *UL1 TR-000424*, University of Maryland *GCRC M01 RR-16500*, Clinical and Translational Science Collaborative of Cleveland, *UL1TR000439* from the National Center for Advancing Translational Sciences (NCATS) component of the National Institutes of Health and NIH roadmap for Medical Research, Michigan Institute for Clinical and Health Research (MICHR) *UL1TR000433*, University of Illinois at Chicago CTSA *UL1RR029879*, Tulane COBRE for Clinical and Translational Research in Cardiometabolic Diseases *P20 GM109036*, Kaiser Permanente NIH/NCRR *UCSF-CTSI UL1 RR-024131*, Department of Internal Medicine, University of New Mexico School of Medicine Albuquerque, *NM R01DK119199*.
GCKD	The GCKD study is supported by grants from the Federal Ministry of Education and Research (Bundesministerium für Bildung und Forschung; www.bmbf.de), FKZ 01ER 0804, 01ER 0818, 01ER 0819, 01ER 0820, 01ER 0821, and 01ER 0822, and the Foundation for Preventive Medicine of the KfH (Kuratorium für Heimdialyse und Nierentransplantation e.V. – Stiftung Präventivmedizin; www.kfh-stiftung-praeventivmedizin.de) and corporate partners (for a list see www.gckd.org). The GCKD investigators gratefully acknowledge the expert support of all members of study staff, the dedicated contribution of all collaborating nephrologists (for a list of contributors and the 169 study sites, see www.gckd.org) and the support of patients participating in the study.
Geisinger	Geisinger Clinic; NIDDK R01DK100446
GLOMMS	GLOMMS was initially funded, in first version, by a grant from Chief Scientist Office CZH/4/656. GLOMMS was subsequently expanded with support from a starter grant from the Academy of Medical Sciences, Wellcome Trust; Medical Research Council, British Heart Foundation; Arthritis Research UK; the Royal College of Physicians; and Diabetes UK [SGL020\1076]; and a research training fellowship from the Wellcome Trust [102729/Z/13/Z]. The GLOMMS study also acknowledges support from the Grampian Data Safe Haven (DaSH) facility within the Aberdeen Centre for Health Data Science and the associated financial support of the University of Aberdeen, and National Health Service (NHS) Research Scotland (through NHS Grampian investment in DaSH). More

	information is available at the DaSH website: http://www.abdn.ac.uk/iahs/facilities/grampian-data-safe-haven.php.
GoDARTS	GoDARTS is funded and supported by the Wellcome Trust Type 2 Diabetes Case Control Collection (072960/Z/03/Z, 084726/Z/08/Z, 084727/Z/08/Z, 085475/Z/ 08/Z, 085475/B/08/Z) and as part of the EU IMI-SUMMIT programme). Tenovus Scotland and Diabetes UK grants.
Gubbio	Municipal and Health Authorities of Gubbio, Italy; Center of Gubbio Epidemiological Studies, Gubbio, Italy; University of Naples "Federico II", Naples, Italy.
Hong Kong CKD	This study was supported by the Hong Kong Health Service Research Funds and Fund support from Sanofi Renal.
ICES-KDT	This study was conducted at the Institute for Clinical Evaluative Sciences (ICES) Western Site. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-Term Care. ICES Western is funded by an operating grant from the Academic Medical Organization of Southwestern Ontario. This project was conducted with members of the provincial ICES Kidney, Dialysis and Transplantation Research Program (www.ices.on.ca/kdt), which receives programmatic grant funding from the Canadian Institutes of Health Research. Dr. Amit Garg is supported by the Dr. Adam Linton Chair in Kidney Health Analytics. Research personnel who worked on this project were supported by the Lilibeth Caberto Kidney Clinical Research Unit. We thank Gamma-Dynacare for the linked laboratory values used in this analysis.
LCC	Funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East Midlands and Kidney Research UK (Grant TF2/2015)
Maccabi	
MASTERPLAN	The MASTERPLAN study is a clinical trial with trial registration ISRCTN registry: 73187232. Sources of funding: The MASTERPLAN Study was supported by grants from the Dutch Kidney Foundation (Nierstichting Nederland, number PV 01), and the Netherlands Heart Foundation (Nederlandse Hartstichting, number 2003 B261). Unrestricted grants were provided by Amgen, Genzyme, Pfizer and Sanofi-Aventis.
MDRD	NIDDK UO1 DK35073 and K23 DK67303, K23 DK02904
MMKD	The MMKD study was funded by the Austrian Heart Fund and by the Innsbruck Medical University.
Mt Sinai BioMe	
Nanjing CKD	
Nefrona	The Nefrona study was funded by research grants from Abvie, and Instituto de Salud Carlos III (PI16/01354, PI18/00610, RD16/0009/0011 (Co-funded by European Regional Development Fund "A way to make Europe").
NephroTest	The NephroTest CKD cohort study is supported by grants from: Inserm GIS-IReSP AO 8113LS TGIR; French Ministry of Health AOM 09114 and AOM 10245; Inserm AO 8022LS; Agence de la Biomédecine R0 8156LL, AURA, and Roche 2009-152-447G. The Nephrotest initiative was also sponsored by unrestricted grants from F.Hoffman-La Roche Ltd. The authors thank the collaborators and the staff of the NephroTest Study: François Vrtovsnik, Eric Daugas, Martin Flamant, Emmanuelle Vidal-Petiot (Bichat Hospital); Alexandre Karras, Eric Thervet, P. Houillier, M. Courbebaisse, D. Eladari (European Georges Pompidou Hospital); Jean-Jacques Boffa, Pierre Ronco, H. Fessi, Eric Rondeau, Emmanuel Letavernier, Jean Philippe Haymann (Tenon Hospital); Marie Metzger, Pablo Urena-Torres
OLDW	

PSP-CKD	The PSP-CKD study was funded by the National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care (CLAHRC) East Midlands. Ongoing support for the study is funded by NIHR CLAHRC East Midlands and Kidney Research UK (Grant TF2/2015).
RCAV	This study was supported by grant R01DK096920 from NIH-NIDDK and is the result of work supported with resources and the use of facilities at the Memphis VA Medical Center and the Long Beach VA Medical Center. Support for VA/CMS data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Health Services Research and Development, VA Information Resource Center (project numbers SDR 02-237 and 98-004).
REGARDS	This research project is supported by cooperative agreement U01 NS041588 co-funded by the National Institute of Neurological Disorders and Stroke (NINDS) and the National Institute on Aging (NIA), National Institutes of Health, Department of Health and Human Service. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NINDS or the NIA. Representatives of the NINDS were involved in the review of the manuscript but were not directly involved in the collection, management, analysis or interpretation of the data. The authors thank the other investigators, the staff, and the participants of the REGARDS study for their valuable contributions. A full list of participating REGARDS investigators and institutions can be found at: https://www.uab.edu/soph/regardsstudy/
RENAAL	This study was supported by Merck and Company.
SCREAM	This study was supported by Stockholm County Council and the Swedish Heart and Lung Foundation.
SEED	This study was supported by grants from the Singapore Ministry of Health's National Medical Research Council (NMRC), NMRC/STaR/0003/2008, NMRC/0796/2003, NMRC/1249/2010, NMRC/TA/0008/2012, NMRC CIRG/1371/2013, NMRC/STaR/016/2013/ and NMRC/OFLCG/001/2017.
SHARP	SHARP was funded by Merck/Schering-Plough Pharmaceuticals (North Wales, PA), with additional support from the Australian National Health and Medical Research Council, the British Heart Foundation, and the UK Medical Research Council. SHARP was initiated, conducted, and interpreted independently of the principal study funder (Merck & Co. and Schering Plough Corp., which merged in 2009). The authors thank the participants in the SHARP trials, as well as the local clinical center staff, regional and national coordinators, steering committees, and data monitoring committees.
SKS	Support received from the local LCRN and funded by Investigator-Initiated (IIT) grants from Vifor, Astellas, Bergen Bio and EVOTEC
SMART	Funded by the University Medical Center Utrecht.
SRR-CKD	The SRR-CKD is a national health care quality register funded by The Swedish Association of Local Authorities and Regions, which is an organisation that represents and advocates for local government in Sweden. All of Sweden's municipalities, county councils and regions are members.
Sunnybrook	
UK Biobank	The UK Biobank was supported by the Medical Research Council, the Wellcome Trust, the UK Department of Health, the British Heart Foundation, Cancer Research UK, the US National Institute for Health Research, the Scottish Government, the North West Development Agency, Diabetes UK, and the Welsh Government (grants are listed here https://www.ukbiobank.ac.uk/wp-content/uploads/2018/10/Funding-UK-Biobank-summary.pdf).
West of Scotland	No Sponsors. Data collected as part of routine patient care.

YWSCC	No sponsors. Data collected as part of CKD outpatient clinic

Table S1. Baseline characteristics, general covariates

Cohort	N	Age, years	Female	Black	Smoker		DM	HTN	SBP, mmHg	HTN meds	Total chol, mM	HDLC, mM	Lipid lowering meds€	BMI, kg/m^2
					Current	Former								
Overall	**25,903,761**	**53 (17)**	**52%**	**8.8%**	**7.8%**	**10%**	**15%**	**36%**	**126 (17)**	**18%**	**4.7 (1.0)**	**1.3 (0.4)**	**13%**	**30 (7)**
ADVANCE	11091	66 (6)	42%	0.34%	15%	27%	100%	83%	145 (22)	75%	5.2 (1.2)	1.3 (0.4)	28%	28 (5)
ARIC	11527	63 (6)	56%	22%	15%	44%	17%	48%	128 (19)	44%	5.2 (1.0)	1.3 (0.4)	11%	29 (6)
CanPREDDICT	1894	68 (13)	37%	1.5%	NA	NA	51%	98%	134 (20)	92%	4.2 (1.2)	1.2 (0.4)	68%	NA
CARE FOR HOMe	541	65 (12)	41%	0.4%	11%	49%	38%	99%	152 (24)	96%	5.0 (1.1)	NA	51%	30 (5)
CRIB	264	61 (15)	32%	4.9%	13%	51%	15%	92%	151 (23)	80%	5.7 (1.3)	1.3 (0.4)	17%	27 (5)
CRIC	5494	60 (11)	44%	44%	13%	41%	51%	88%	128 (21)	92%	4.8 (1.2)	1.2 (0.4)	62%	32 (8)
GCKD	5128	61 (12)	40%	0%	16%	43%	36%	96%	139 (20)	95%	5.5 (1.4)	1.3 (0.5)	52%	30 (6)
Geisinger	366016	54 (18)	57%	2.5%	21%	29%	15%	41%	125 (17)	45%	4.9 (1.1)	1.3 (0.4)	30%	31 (7)
GLOMMS	329977	54 (18)	56%	0.0%	NA	NA	3%	10%	NA	13%	5.0 (1.1)	1.4 (0.4)	8%	NA
Go-DARTs	17821	58 (12)	47%	0.0%	15%	39%	30%	41%	134 (19)	31%	5.4 (1.1)	1.4 (0.4)	11%	27 (5)
Gubbio	4597	50 (18)	55%	0%	30%	23%	5%	34%	128 (20)	17%	5.6 (1.1)	1.3 (0.3)	4%	27 (4)
Hongkong CKD	245	60 (11)	41%	0%	13%	23%	43%	NA	136 (19)	97%	4.8 (1.2)	1.2 (0.4)	NA	26 (5)
ICES-KDT	1017530	60 (15)	50%	0%	NA	NA	55%	71%	NA	29%	4.6 (1.1)	1.3 (0.4)	23%	NA
LCC	17132	77 (10)	60%	0.81%	8.2%	36%	32%	94%	135 (16)	89%	4.6 (1.1)	1.4 (0.4)	64%	28 (6)
Maccabi	1440372	42 (17)	55%	0.00%	24%	5.8%	6.7%	18%	122 (16)	21%	4.9 (1.0)	1.3 (0.3)	11%	27 (5)
MASTERPLAN	650	61 (13)	31%	0%	16%	79%	24%	NA	139 (21)	94%	4.8 (1.1)	1.3 (0.4)	68%	27 (4)
MDRD	1618	51 (13)	39%	13%	12%	0%	6.2%	60%	132 (18)	76%	5.6 (1.2)	1.0 (0.4)	NA	27 (5)
MMKD	172	46 (12)	30%	0%	20%	25%	0%	88%	138 (21)	80%	5.8 (1.5)	1.2 (0.4)	20%	25 (4)
Mt Sinai BioMe	17446	53 (15)	62%	28%	15%	14%	26%	55%	126 (19)	44%	4.8 (1.1)	1.4 (0.5)	21%	29 (7)
Nanjing CKD	1275	46 (14)	43%	0%	0.49%	17%	22%	77%	141 (22)	78%	5.6 (1.9)	1.2 (0.5)	NA	24 (4)
Nefrona	1471	60 (12)	38%	0.20%	20%	36%	31%	96%	144 (21)	92%	4.8 (1.0)	1.3 (0.4)	68%	29 (5)
NephroTest	1757	59 (15)	32%	13%	14%	33%	30%	91%	136 (20)	89%	4.9 (1.2)	1.3 (0.8)	44%	27 (5)
OLDW cohort 1	317354	53 (17)	60%	13%	6.9%	17%	16%	43%	126 (18)	26%	4.7 (0.9)	1.3 (0.4)	15%	31 (8)
OLDW cohort 2	88380	51 (18)	56%	2%	5.7%	13%	10%	30%	122 (16)	13%	4.7 (0.9)	1.4 (0.4)	6.6%	29 (7)
OLDW cohort 3	110002	56 (16)	58%	10%	4.8%	16%	20%	51%	128 (17)	31%	4.6 (0.9)	1.3 (0.4)	17%	31 (7)
OLDW cohort 4	304007	56 (17)	55%	1%	8.2%	20%	16%	48%	125 (17)	32%	4.7 (0.9)	1.4 (0.4)	18%	31 (7)
OLDW cohort 5	175556	54 (17)	58%	0%	10.5%	9.0%	11%	31%	126 (18)	16%	4.8 (0.9)	1.4 (0.4)	7.2%	30 (7)
OLDW cohort 6	165729	56 (17)	60%	22%	5.3%	14%	18%	50%	129 (18)	26%	4.7 (0.9)	1.4 (0.4)	14%	30 (7)
OLDW cohort 7	121413	50 (16)	60%	10%	4.0%	11%	14%	38%	126 (16)	24%	4.7 (0.8)	1.3 (0.4)	12%	30 (7)
OLDW cohort 8	266591	49 (18)	58%	3%	1.4%	5%	10%	26%	120 (15)	15%	4.7 (0.8)	1.5 (0.4)	10%	28 (6)
OLDW cohort 9	1473923	53 (17)	58%	13%	0.9%	2%	7.0%	21%	125 (17)	13%	4.7 (0.9)	1.4 (0.4)	7.8%	30 (7)
OLDW cohort 10	1305648	50 (17)	58%	5%	6.0%	13%	13%	36%	126 (17)	22%	4.7 (0.9)	1.3 (0.4)	10%	30 (7)
OLDW cohort 11	176874	57 (17)	56%	4%	12%	12%	13%	41%	122 (17)	17%	4.8 (0.9)	1.3 (0.4)	9.9%	29 (7)
OLDW cohort 12	385105	47 (15)	57%	12%	4.1%	8.7%	12%	34%	122 (15)	22%	4.7 (0.8)	1.4 (0.4)	12%	30 (7)

OLDW cohort 13	849173	51 (17)	58%	18%	6.8%	10%	16%	43%	125 (17)	22%	4.7 (0.9)	1.4 (0.4)	12%	29 (7)
OLDW cohort 14	133785	47 (15)	58%	8%	10%	5.9%	25%	43%	130 (20)	21%	4.5 (0.9)	1.2 (0.4)	8.7%	31 (8)
OLDW cohort 15	81203	49 (17)	59%	10%	9.5%	9.6%	14%	33%	125 (17)	19%	4.7 (0.9)	1.3 (0.4)	9.9%	29 (7)
OLDW cohort 16	231809	53 (17)	58%	5%	12%	17%	14%	41%	126 (17)	25%	4.7 (0.9)	1.3 (0.4)	13%	31 (8)
OLDW cohort 17	153560	54 (18)	57%	6%	3.2%	10%	17%	41%	130 (18)	29%	4.6 (0.9)	1.3 (0.4)	18%	30 (7)
OLDW cohort 18	278097	54 (17)	58%	2%	4.7%	11%	10%	33%	130 (18)	18%	4.7 (0.9)	1.5 (0.5)	10%	28 (6)
OLDW cohort 19	308518	51 (18)	58%	6%	4.2%	7.6%	11%	27%	125 (16)	12%	4.6 (0.9)	1.3 (0.4)	6.1%	30 (7)
OLDW cohort 20	669837	53 (17)	57%	10%	5.7%	14%	14%	37%	126 (17)	22%	4.7 (0.9)	1.3 (0.4)	12%	30 (8)
OLDW cohort 21	181418	52 (17)	55%	7%	7.2%	15.9%	12%	38%	125 (17)	26%	4.7 (0.9)	1.4 (0.4)	14%	30 (7)
OLDW cohort 22	836079	53 (18)	59%	10%	2.3%	6.2%	11%	30%	124 (17)	17%	4.7 (0.9)	1.5 (0.5)	10%	28 (6)
OLDW cohort 23	365414	50 (18)	56%	6%	1.5%	2.4%	3.9%	9.4%	126 (18)	2.5%	4.7 (0.9)	1.3 (0.4)	1.3%	29 (7)
OLDW cohort 24	543380	50 (18)	56%	5%	4.3%	7.8%	8.2%	23%	126 (17)	12%	4.7 (0.9)	1.4 (0.4)	7.2%	29 (7)
OLDW cohort 25	537225	51 (17)	57%	21%	3.4%	6.9%	11%	28%	125 (18)	17%	4.7 (0.9)	1.4 (0.4)	8.3%	30 (7)
OLDW cohort 26	1141213	51 (17)	57%	13%	5.0%	11%	9.9%	27%	126 (18)	16%	4.7 (0.9)	1.4 (0.4)	8.2%	29 (7)
OLDW cohort 27	40674	57 (17)	57%	12%	4.7%	10%	15%	46%	128 (19)	27%	4.7 (0.9)	1.4 (0.4)	15%	30 (7)
OLDW cohort 28	330566	54 (18)	55%	5%	6.6%	14%	14%	37%	129 (18)	13%	4.7 (0.9)	1.3 (0.4)	6.0%	30 (8)
OLDW cohort 29	747255	50 (17)	56%	4%	4.2%	8%	10%	29%	124 (16)	10%	4.7 (0.9)	1.3 (0.4)	4.2%	31 (8)
OLDW cohort 30	366530	54 (17)	58%	2%	4.68%	8.3%	10%	26%	125 (17)	14%	4.7 (0.9)	1.4 (0.4)	6.6%	29 (7)
OLDW cohort 31	363900	49 (17)	54%	2%	1.4%	2.7%	3%	10%	125 (17)	5%	4.8 (0.8)	1.4 (0.4)	2.7%	29 (6)
OLDW cohort 32	216369	53 (17)	57%	14%	3.5%	6.3%	13%	32%	127 (18)	12%	4.7 (0.9)	1.4 (0.4)	5.6%	30 (7)
OLDW cohort 33	244814	51 (16)	59%	6%	7.9%	11%	14%	34%	125 (17)	19%	4.8 (0.9)	1.4 (0.4)	9.3%	30 (8)
OLDW cohort 34	131205	52 (17)	57%	1%	31%	10%	10%	27%	123 (16)	10%	4.7 (0.9)	1.4 (0.4)	4.9%	29 (7)
OLDW cohort 35	148535	48 (16)	56%	6%	9.2%	14%	10%	25%	123 (17)	18%	4.8 (0.9)	1.3 (0.4)	10%	29 (7)
OLDW cohort 36	175418	52 (18)	58%	5%	2.8%	7.0%	14%	34%	128 (18)	23%	4.6 (0.9)	1.3 (0.4)	12%	31 (8)
OLDW cohort 37	367461	50 (17)	59%	8%	1.9%	3.1%	5%	12%	126 (16)	4.2%	4.6 (0.9)	1.3 (0.4)	1.8%	31 (8)
OLDW cohort 38	224879	53 (17)	58%	29%	5.0%	6.5%	15%	36%	127 (18)	18%	4.6 (0.9)	1.4 (0.4)	9.8%	30 (8)
OLDW cohort 39	51457	58 (17)	56%	0%	5.1%	6.1%	13%	40%	127 (17)	15%	4.8 (0.9)	1.4 (0.5)	6.5%	30 (7)
OLDW cohort 40	204235	48 (17)	56%	4%	7.5%	6.6%	11%	30%	123 (17)	17%	4.7 (0.9)	1.4 (0.4)	10%	29 (7)
OLDW cohort 41	518142	50 (17)	58%	11%	1.6%	3.7%	8.6%	23%	128 (18)	9%	4.7 (0.9)	1.4 (0.4)	4%	31 (8)
OLDW cohort 42	420302	50 (17)	55%	2%	2.9%	5.8%	8.8%	25%	123 (16)	15%	4.9 (0.9)	1.4 (0.4)	8%	29 (7)
OLDW cohort 43	68240	51 (17)	67%	8%	2.1%	4.3%	13%	34%	125 (15)	29%	4.7 (0.8)	1.4 (0.4)	17%	30 (7)
OLDW cohort 44	199070	55 (17)	55%	6%	2.6%	5.4%	17%	44%	127 (16)	37%	4.7 (0.9)	1.3 (0.4)	23%	31 (7)
OLDW cohort 45	3136664	53 (17)	58%	14%	4.8%	6.9%	16%	42%	126 (18)	19%	4.7 (0.9)	1.4 (0.4)	11%	30 (8)
PSP-CKD	26072	75 (11)	62%	0.78%	9.6%	24%	21%	70%	134 (16)	23%	4.4 (1.3)	1.5 (0.5)	23%	29 (6)
RCAV	2237948	63 (13)	6.1%	17%	20%	19%	30%	71%	131 (17)	5.2%	4.6 (1.0)	1.1 (0.4)	36%	29 (6)
REGARDS	28689	65 (9)	55%	41%	15%	40%	21%	59%	128 (17)	59%	5.0 (1.0)	1.3 (0.4)	31%	29 (10)
RENAAL	1510	60 (7)	37%	15%	18%	NA	100%	100%	153 (19)	88%	5.9 (1.4)	1.2 (0.4)	NA	30 (6)
SCREAM	696881	57 (18)	55%	0%	NA	NA	5.3%	9%	NA	37%	5.3 (1.1)	1.4 (0.4)	15%	NA
SEED	9512	59 (10)	50%	0%	16%	14%	30.0%	61%	140 (22)	34%	5.4 (1.1)	1.2 (0.4)	NA	25 (5)
SHARP	4790	63 (12)	35%	2.1%	13%	37%	24%	85%	139 (21)	88%	5.1 (1.1)	1.1 (0.3)	0.042%*	28 (5)

SKS	2395	64 (15)	38%	1.0%	12%	54%	32%	NA	138 (27)	90%	4.6 (1.3)	1.4 (0.5)	NA	28 (9)
SMART	13010	57 (12)	35%	0%	28%	43%	18%	56%	141 (22)	66%	5.1 (1.4)	1.3 (0.4)	55%	27 (4)
SRR-CKD	2559	68 (15)	32%	0%	NA	NA	38%	97%	140 (22)	92%	5.1 (1.5)	NA	44%	28 (5)
Sunnybrook	2524	63 (17)	45%	0%	10%	15%	46%	86%	130 (20)	NA	4.7 (1.2)	1.3 (0.4)	NA	30 (22)
UK Biobank	463563	57 (8)	54%	2%	10%	35%	5%	50%	140 (20)	10%	5.7 (1.1)	1.4 (0.4)	0.1792788	27 (5)
West of Scotland	2412	70 (12)	55%	0%	NA	NA	30%	44%	150 (28)	99%	4.6 (1.3)	1.2 (0.4)	99%	28 (6)
YWSCC	869	68 (12)	29%	0%	3.4%	18%	57%	86%	130 (33)	NA	4.1 (1.6)	1.2 (0.5)	NA	27 (11)

Numbers provided are mean (SD) or percent unless otherwise stated.

€ Only statin use was available in ADVANCE, ARIC, CanPREDDICT, CRIB, LCC, Mt Sinai BioMe, NephroTest, PSP-CKD, REGARDS, SRR-CKD

*Pre-randomization value

BMI: body mass index, DM: diabetes mellitus, HDLC: high-density lipoprotein cholesterol, HTN: hypertension, SBP: systolic blood pressure, SD: standard deviation.

Table S2. Baseline characteristics, kidney function/kidney damage covariates

Cohort	N	eGFR (SD), ml	ACR £		Dipstick				
			N	Median (IQI), mg/g	N	trace	+	++	>++
Overall	**25,903,761**	**89 (23)**	**2178788**	**13 (6-36)**	**5605219**	**8.9%**	**6.8%**	**2.9%**	**0.90%**
ADVANCE	11091	78 (17)	10592	15 (7-40)					
ARIC	11527	86 (16)	11417	4 (2-8)					
CanPREDDICT	1894	28 (9)	1828	136 (26-723)	411	3.6%	3.2%	14.4%	25.8%
CARE FOR HOMe	541	48 (18)	503	42 (11-213)					
CRIB	264	27 (9)	216	284 (50-1029)	254		34.3%	22.4%	6.3%
CRIC	5494	49 (16)	5205	46 (8-368)					
GCKD	5128	49 (18)	5055	51 (10-387)					
Geisinger	366016	88 (23)	17455	8 (4-26)					
GLOMMS	329977	91 (22)	2590	9 (9-22)					
GoDARTS	17821	83 (19)	1369	106 (71-222)					
Gubbio	4597	86 (17)	1674	9 (4-14)					
Hongkong CKD	245	23 (4)	245	18 (5-67)					
ICES-KDT	1017530	84 (22)	339906	18 (7-29)	413310	4.0%	0.9%	0.1%	0.6%
LCC	17132	52 (13)	9242	70 (27-243)					
Maccabi	1440372	104 (20)	46250	10 (7-21)					
MASTERPLAN	650	38 (14)	597	97 (24-355)					
MDRD	1618	44 (20)	1573	60 (8-585)					
MMKD	172	53 (28)	169	2 (1-3)					
Mt Sinai BioMe	17446	83 (24)	1980	14 (6-78)					
Nanjing CKD	1275	24 (4)	936	1156 (574-2361)	708	9.3%	21.2%	45.6%	16.7%
Nefrona	1471	36 (15)	994	93 (14-423)					
NephroTest	1757	46 (22)	1738	72 (14-421)					
OLDW cohort 1	317354	86 (22)	22138	14 (6-35)	83688	9.2%	5.9%	2.5%	1.1%
OLDW cohort 2	88380	88 (23)	393	30 (17-98)	22237	7.3%	8.3%	4.8%	1.9%
OLDW cohort 3	110002	84 (23)	2878	30 (26-30)	40310	7.4%	5.2%	2.7%	1.0%
OLDW cohort 4	304007	85 (23)	18895	13 (6-37)	78411	8.1%	7.6%	3.7%	1.1%

OLDW cohort 5	175556	84 (22)	8653	20 (9-57)	33697	9.9%	6.7%	4.1%	1.6%
OLDW cohort 6	165729	86 (25)	9892	13 (6-39)	57644	9.3%	7.1%	3.4%	1.2%
OLDW cohort 7	121413	91 (22)	6395	10 (5-27)	29107	8.4%	5.6%	3.0%	1.2%
OLDW cohort 8	266591	93 (21)	19726	9 (4-24)	139825	10.7%	7.4%	1.7%	0.3%
OLDW cohort 9	1473923	88 (24)	117412	16 (8-48)	430832	6.8%	8.9%	4.3%	1.1%
OLDW cohort 10	1305648	89 (23)	57148	15 (6-46)	297563	9.9%	7.7%	3.1%	1.3%
OLDW cohort 11	176874	84 (22)	4822	20 (8-69)	25805	10.4%	8.0%	4.1%	1.5%
OLDW cohort 12	385105	92 (21)	30066	9 (4-26)	166654	7.3%	4.1%	1.4%	0.5%
OLDW cohort 13	849173	90 (24)	45824	18 (7-50)	274211	9.1%	6.9%	3.1%	0.5%
OLDW cohort 14	133785	98 (24)	17478	15 (7-58)	27938	8.0%	6.1%	5.0%	1.9%
OLDW cohort 15	81203	93 (23)	1510	11 (5-32)	25135	8.2%	5.9%	2.3%	0.7%
OLDW cohort 16	231809	87 (23)	10926	14 (7-45)	81732	12.7%	8.2%	3.0%	0.9%
OLDW cohort 17	153560	84 (23)	9774	12 (6-36)	77924	10.9%	5.5%	2.0%	0.5%
OLDW cohort 18	278097	95 (23)	10476	37 (19-103)	98929	5.8%	3.5%	2.0%	0.5%
OLDW cohort 19	308518	90 (24)	14501	16 (7-49)	67715	10.7%	8.9%	2.3%	1.1%
OLDW cohort 20	669837	88 (23)	39282	12 (6-36)	159887	10.5%	6.6%	2.8%	0.9%
OLDW cohort 21	181418	85 (23)	12922	26 (10-93)	51610	6.9%	6.0%	3.6%	1.2%
OLDW cohort 22	836079	89 (22)	57933	13 (6-41)	331500	6.3%	5.0%	2.3%	0.4%
OLDW cohort 23	365414	94 (24)	15132	12 (6-37)	125154	7.9%	9.2%	3.9%	0.7%
OLDW cohort 24	543380	90 (23)	15749	15 (7-41)	158466	4.7%	9.0%	4.3%	0.6%
OLDW cohort 25	537225	98 (25)	32633	15 (7-48)	135182	10.2%	9.8%	3.4%	0.9%
OLDW cohort 26	1141213	90 (23)	51174	15 (6-48)	303108	11.3%	8.7%	3.6%	1.1%
OLDW cohort 27	40674	85 (24)	2271	8 (4-25)	16329	7.4%	4.0%	1.8%	0.5%
OLDW cohort 28	330566	87 (24)	21695	17 (7-45)	74945	10.5%	7.3%	3.4%	1.3%
OLDW cohort 29	747255	90 (23)	28924	17 (8-52)	135828	8.8%	7.1%	3.5%	1.2%
OLDW cohort 30	366530	84 (22)	12907	17 (7-55)	61312	11.8%	6.6%	2.8%	1.0%
OLDW cohort 31	363900	89 (21)	18097	13 (6-39)	83506	9.9%	7.4%	1.4%	0.7%
OLDW cohort 32	216369	87 (23)	6864	10 (4-30)	58929	9.5%	6.4%	2.9%	1.1%
OLDW cohort 33	244814	91 (22)	16045	14 (5-47)	46742	10.3%	8.1%	3.7%	1.3%
OLDW cohort 34	131205	90 (22)	4306	15 (8-42)	21696	21.0%	9.9%	2.9%	1.1%
OLDW cohort 35	148535	90 (22)	7406	10 (5-34)	48907	21.2%	11.0%	3.4%	1.1%

OLDW cohort 36	175418	90 (24)	7115	30 (9-98)	28088	9.8%	7.5%	1.1%	0.3%
OLDW cohort 37	367461	90 (24)	19495	11 (5-31)	91909	12.3%	7.5%	4.1%	1.2%
OLDW cohort 38	224879	90 (25)	14731	12 (5-42)	45990	11.9%	7.8%	4.0%	2.3%
OLDW cohort 39	51457	86 (22)	779	21 (10-54)	8645	6.2%	7.0%	3.6%	1.3%
OLDW cohort 40	204235	91 (22)	15597	12 (5-38)	54628	10.7%	8.2%	3.6%	1.2%
OLDW cohort 41	518142	94 (24)	29663	13 (6-38)	83159	5.9%	9.8%	4.0%	0.7%
OLDW cohort 42	420302	92 (21)	24600	12 (5-39)	76026	13.0%	6.4%	3.4%	1.3%
OLDW cohort 43	68240	89 (23)	8803	13 (6-37)	11855	6.1%	4.3%	1.4%	0.5%
OLDW cohort 44	199070	85 (21)	5304	23 (11-67)	20271	8.2%	6.1%	2.8%	0.9%
OLDW cohort 45	3136664	88 (23)	172026	13 (6-39)	807468	10.0%	7.1%	2.7%	0.9%
PSP-CKD	26072	55 (14)	5998	18 (11-47)	6325	8.8%	9.2%	4.8%	3.3%
RCAV	2237948	80 (17)	142892	13 (5-44)					
REGARDS	28689	85 (20)	27598	7 (5-16)					
RENAAL	1510	39 (12)	1510	1242 (557-2545)					
SCREAM	696881	89 (21)	14892	9 (4-24)	82652	10.7%	4.1%	1.8%	
SEED	9512	84 (19)	6819	13 (7-28)					
SHARP	4790	30 (11)	3909	147 (32-625)					
SKS	2395	35 (15)	1580	55 (17-342)					
SMART	13010	84 (19)	6999	9 (5-23)					
SRR-CKD	2559	27 (11)	2556	171 (34-838)					
Sunnybrook	2524	54 (29)	920	76 (17-333)	198	5.1%	21.2%	13.1%	8.1%
UK Biobank	463563	91 (13)	450454	6 (4-10)					
West of Scotland	2412	41 (11)	338	4 (2-15)	29	13.8%	10.3%	13.8%	17.2%
YWSCC	869	39 (16)	429	131 (33-589)	835	1.2%	23.2%	15.4%	8.7%

Numbers provided are mean (SD) or percent unless otherwise stated.

£ PCR was converted to ACR when ACR was not available in CanPREDDICT, CRIC, Geisinger, Hongkong CKD, LCC, MASTERPLAN, MDRD, MMKD, Mt Sinai BioMe, Nanjing CKD, Nefrona, NephroTest, OLDW all cohorts, PSP-CKD, SKS, Sunnybrook, YWSCC

Table S3. Number of participants with a history of CVD events and incident CVD events.

Cohort	N	Coronary Heart Disease				Stroke				Heart Failure				Atrial fibrillation			
		Hx	Hx < 1y	Inc	Age (SD)	Hx	Hx < 1y	Inc	Age (SD)	Hx	Hx < 1y	Inc	Age (SD)	Hx	Hx < 1y	Inc	Age (SD)
Overall	**25,903,761**	**2,450,902**	**697234**	**269,142**	**69 (13)**	**824717**	**299769**	**311021**	**71 (13)**	**848609**	**313975**	**712556**	**72 (12)**	**1071615**	**326720**	**605596**	**73 (11)**
ADVANCE	11091	1769	NA	470	72 (7)	1019	NA	724	73 (7)	355	NA	305	73 (7)	NA	NA	NA	NA
ARIC	11527	971	51	963	74 (8)	262	26	905	76 (7)	629	90	2059	77 (8)	288	94	2412	76 (7)
CanPREDDICT	1894	493	NA	63	73 (13)	169	NA	47	74 (10)	250	NA	105	75 (10)	NA	NA	NA	NA
CARE FOR HOMe	541	118	NA	5	71 (9)	52	NA	16	72 (9)	NA	NA	39	75 (8)	NA	NA	NA	NA
CRIB	264	56	NA	NA	NA	18	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CRIC	5494	1185	NA	228	65 (10)	572	NA	155	66 (9)	535	NA	555	66 (10)	942	NA	365	69 (8)
GCKD	5128	1020	NA	131	68 (9)	421	NA	153	69 (8)	911	NA	199	71 (8)	1041	NA	182	71 (7)
Geisinger	366016	44093	7819	4148	70 (14)	14445	4054	3928	73 (13)	14462	3993	13730	75 (13)	17411	4188	12519	74 (12)
GLOMMS	329977	10816	2054	196	78 (10)	6226	1245	8675	76 (12)	4953	1165	7654	77 (12)	8209	1699	11863	77 (11)
GoDARTS	17821	2209	345	NA	NA	240	71	NA	NA	109	35	NA	NA	293	98	NA	NA
Gubbio	4597	117	NA	NA	NA	39	NA	NA	NA	122	NA	NA	NA	32	NA	NA	NA
Hongkong CKD	245	53	NA	NA	NA	NA	NA	12	67 (9)	NA	NA	NA	NA	NA	NA	13	72 (7)
ICES-KDT	1017530	89760	6998	26068	73 (13)	17672	2086	20456	76 (11)	92517	10001	35194	77 (11)	203066	15569	26567	76 (10)
LCC	17132	4354	NA	383	82 (9)	2109	NA	790	84 (8)	1669	NA	NA	NA	921	NA	NA	NA
Maccabi	1440372	44639	5987	8438	67 (14)	7026	1575	11536	72 (14)	6904	1507	15004	76 (13)	NA	NA	NA	NA
MASTERPLAN	650	121	NA	6	67 (10)	42	NA	9	71 (14)	NA	NA	26	71 (7)	NA	NA	NA	NA
MDRD	1618	136	NA	NA	NA	41	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MMKD	172	11	NA	4	60 (6)	10	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Mt Sinai BioMe	17446	709	110	422	65 (11)	766	175	590	66 (13)	1494	314	931	64 (13)	NA	NA	NA	NA
Nanjing CKD	1275	68	NA	6	61 (13)	50	NA	10	58 (13)	23	NA	14	54 (19)	NA	NA	NA	NA
Nefrona	1471	NA	NA	NA	NA	NA	NA	NA	NA	35	NA	NA	NA	41	NA	NA	NA
NephroTest	1757	255	NA	NA	NA	89	NA	NA	NA	72	NA	NA	NA	NA	NA	NA	NA
OLDW cohort 1	317354	34673	11891	3281	67 (13)	15572	5428	4235	69 (13)	13177	6056	11550	71 (12)	13006	4862	9147	72 (11)
OLDW cohort 2	88380	7805	3121	670	67 (13)	4241	1662	794	69 (13)	2626	1355	2009	72 (12)	3994	1770	1914	72 (11)
OLDW cohort 3	110002	13024	3007	452	70 (11)	7573	1839	447	72 (11)	3813	1431	1388	74 (9)	6668	1940	1268	74 (9)
OLDW cohort 4	304007	40112	8223	3325	71 (12)	18996	4731	3969	72 (12)	16988	5246	11427	74 (10)	19709	5011	9060	74 (10)
OLDW cohort 5	175556	15467	4682	1683	69 (12)	6682	2461	2287	71 (13)	8807	3729	5523	72 (12)	7344	2672	5048	73 (10)
OLDW cohort 6	165729	18058	4020	1238	70 (12)	9011	2934	2234	72 (11)	7139	2621	4618	73 (11)	9299	2643	3658	74 (10)
OLDW cohort 7	121413	8519	2275	520	68 (13)	3988	1571	622	68 (13)	2385	966	1293	72 (11)	3424	1054	1172	72 (11)
OLDW cohort 8	266591	13634	3964	802	73 (12)	10081	2745	967	73 (12)	2940	1044	2327	77 (9)	6610	2115	2402	75 (10)
OLDW cohort 9	1473923	65335	28429	10368	69 (12)	22876	10303	17341	70 (13)	18624	10018	32165	73 (12)	27952	13508	31263	73 (11)
OLDW cohort 10	1305648	106778	34944	12275	66 (13)	49969	17966	15751	69 (13)	41687	18280	34595	71 (12)	45616	16692	30662	72 (11)
OLDW cohort 11	176874	16319	3690	1089	70 (12)	8741	2285	1973	73 (11)	7686	3107	4206	74 (11)	11190	3201	3628	74 (10)
OLDW cohort 12	385105	22053	7220	1039	62 (12)	8716	3506	1427	64 (13)	6808	3018	2796	67 (13)	9040	3339	2858	67 (12)
OLDW cohort 13	849173	86503	26687	5912	66 (13)	43760	16694	11614	68 (13)	33251	13391	21763	70 (12)	35620	11896	19206	71 (11)
OLDW cohort 14	133785	9427	2881	670	58 (12)	4181	1380	867	58 (12)	3566	1280	1644	60 (12)	2044	714	1191	64 (12)
OLDW cohort 15	81203	4080	1426	306	67 (12)	2060	738	534	70 (13)	1170	506	1084	72 (12)	1833	674	1194	73 (10)
OLDW cohort 16	231809	18982	7132	2323	69 (13)	8868	3287	2379	72 (12)	5021	2490	5177	74 (11)	8033	3179	5586	74 (10)
OLDW cohort 17	153560	14036	4878	2415	72 (11)	5653	2570	3248	74 (11)	3434	1741	6152	76 (9)	6700	2363	6474	75 (9)
OLDW cohort 18	278097	22333	8938	1749	73 (11)	9516	4364	2336	74 (10)	7336	3636	5448	76 (9)	14028	5529	5067	75 (9)
OLDW cohort 19	308518	21955	10212	4172	68 (14)	9947	4319	4261	70 (13)	8383	4958	10242	73 (12)	11344	5645	8922	73 (12)
OLDW cohort 20	669837	56983	20607	6613	68 (13)	25423	9601	7976	70 (13)	20803	9810	18872	72 (12)	25207	9468	16121	72 (11)
OLDW cohort 21	181418	13162	4469	1564	68 (13)	6092	2206	1793	71 (12)	4977	2263	3903	73 (12)	7072	2611	3516	73 (11)

OLDW cohort 22	836079	80445	30522	6856	71 (13)	28038	11733	3873	71 (14)	19888	9478	11244	75 (11)	34517	13404	9902	74 (11)
OLDW cohort 23	365414	8510	4453	6562	69 (14)	3088	1538	5344	68 (14)	3425	2271	10720	73 (12)	4466	2464	10855	73 (12)
OLDW cohort 24	543380	29788	15742	2898	66 (13)	11220	5688	4368	70 (13)	8448	5558	10752	72 (12)	14167	8425	10397	71 (11)
OLDW cohort 25	537225	33329	14851	12712	69 (13)	11646	5825	9551	70 (13)	13159	6522	23215	72 (12)	12945	6942	19468	73 (11)
OLDW cohort 26	1141213	80464	34212	10363	66 (13)	35196	15283	12886	67 (14)	31877	17152	32317	70 (13)	41920	19077	28663	71 (12)
OLDW cohort 27	40674	6597	2515	445	73 (12)	2003	905	491	73 (12)	2538	1239	1428	76 (10)	3950	1495	1100	75 (10)
OLDW cohort 28	330566	41110	19840	7250	70 (12)	16006	7129	9066	71 (13)	12257	7049	20524	73 (12)	15297	7622	17798	73 (11)
OLDW cohort 29	747255	44897	19370	7979	67 (13)	19124	7442	8149	69 (14)	16046	9557	21577	72 (12)	22424	11190	18037	72 (12)
OLDW cohort 30	366530	29258	14423	4393	70 (12)	9629	4896	5574	72 (12)	10583	6063	15036	73 (11)	14600	7616	14288	74 (10)
OLDW cohort 31	363900	8712	3676	3023	69 (14)	3581	1681	2629	70 (14)	2283	1304	6717	73 (12)	5527	2530	7534	73 (12)
OLDW cohort 32	216369	18587	8644	1381	67 (13)	6833	3208	1783	68 (13)	8041	4126	6197	70 (12)	8846	4591	5226	71 (12)
OLDW cohort 33	244814	16169	7214	2709	67 (13)	7160	3202	1915	68 (13)	7461	4044	5738	68 (13)	8736	3967	4307	70 (12)
OLDW cohort 34	131205	7435	2810	1358	69 (13)	3669	1369	1613	70 (13)	2647	1540	3570	73 (11)	4573	1898	3114	73 (11)
OLDW cohort 35	148535	7432	2210	1584	65 (14)	3396	968	1000	64 (15)	3187	1156	2082	67 (14)	3693	1098	1715	68 (12)
OLDW cohort 36	175418	16010	5447	2350	68 (13)	6041	2484	2644	69 (13)	5155	2638	6590	71 (12)	6951	2875	5783	72 (12)
OLDW cohort 37	367461	10624	4701	4990	67 (14)	3257	1643	4535	68 (14)	3723	2099	13351	71 (13)	4598	2355	12811	72 (12)
OLDW cohort 38	224879	21207	9920	4352	67 (13)	8112	4210	4146	68 (13)	8174	4428	9845	69 (13)	8410	4419	7540	71 (12)
OLDW cohort 39	51457	6670	1696	305	69 (11)	2086	659	392	74 (11)	1907	747	1039	74 (10)	3637	926	908	74 (10)
OLDW cohort 40	204235	12358	2281	1959	67 (14)	5885	1223	2420	70 (14)	4289	1225	5384	74 (12)	6739	1487	4754	74 (11)
OLDW cohort 41	518142	28493	13247	7612	65 (14)	11240	5196	6015	67 (14)	9748	5545	16347	69 (13)	13041	6384	13978	70 (12)
OLDW cohort 42	420302	18617	4958	2035	67 (12)	7652	2438	969	71 (12)	5920	2593	2880	72 (12)	10806	3714	2893	73 (10)
OLDW cohort 43	68240	3249	1874	175	72 (12)	1190	680	235	76 (11)	1319	889	337	77 (12)	1898	1273	352	77 (10)
OLDW cohort 44	199070	12892	5106	993	68 (13)	4936	1668	927	71 (13)	3108	1511	2522	73 (12)	5673	2577	2161	73 (11)
OLDW cohort 45	3136664	471788	180594	36005	69 (13)	189108	78693	45965	70 (13)	138248	63995	118138	72 (12)	140855	57484	101488	73 (11)
PSP-CKD	26072	6002	1001	701	78 (10)	3388	501	920	81 (9)	1984	541	1159	82 (9)	NA	NA	NA	NA
RCAV	2237948	567343	55573	17487	67 (11)	53243	14172	19567	69 (11)	156228	32697	76806	70 (11)	118438	22297	54172	72 (10)
REGARDS	28689	NA	NA	1726	74 (9)	1773	NA	1379	75 (9)	NA	NA	NA	NA	NA	NA	NA	NA
RENAAL	1510	242	NA	75	63 (6)	130	NA	68	64 (7)	81	NA	183	63 (7)	NA	NA	NA	NA
SCREAM	696881	26988	4217	9152	76 (12)	22275	3473	12746	78 (12)	19680	3877	20379	81 (11)	39197	6054	17212	78 (11)
SEED	9512	607	NA	632	69 (11)	238	NA	376	72 (10)	NA	NA	NA	NA	NA	NA	NA	NA
SHARP	4790	166	NA	114	72 (11)	354	NA	107	72 (11)	NA	NA	NA	NA	NA	NA	95	72 (9)
SKS	2395	372	2	40	69 (12)	191	1	37	72 (12)	410	3	14	78 (9)	NA	NA	NA	NA
SMART	13010	5131	NA	250	67 (11)	2499	NA	310	69 (10)	NA	NA	96	73 (11)	175	NA	NA	NA
SRR-CKD	2559	233	NA	147	75 (9)	218	NA	103	77 (10)	398	NA	348	77 (9)	NA	NA	NA	NA
Sunnybrook	2524	156	38	85	76 (11)	82	23	57	79 (11)	186	52	178	78 (11)	NA	NA	NA	NA
UK Biobank	463563	16240	NA	4347	65 (7)	6776	NA	3712	67 (7)	317	NA	1725	68 (6)	7343	NA	5607	67 (7)
West of Scotland	2412	368	29	104	74 (10)	112	10	81	75 (10)	95	13	101	74 (8)	150	14	173	77 (8)
YWSCC	869	222	8	17	74 (10)	128	6	16	70 (16)	138	12	20	73 (9)	66	8	8	79 (4)

Hx: history; Inc: incidence. Incidence was defined with free history unless information of history was not available.

£ PCR was converted to ACR when ACR was not available in CanPREDDICT, CRIC, Geisinger, Hongkong CKD, LCC, MASTERPLAN, MDRD, MMKD, Mt Sinai BioMe, Nanjing CKD, Nefrona, NephroTest, OLDW all cohorts, PSP-CKD, SKS, Sunnybrook, YWSCC

€ Only statin use was available in ADVANCE, ARIC, CanPREDDICT, CRIB, LCC, Mt Sinai BioMe, NephroTest, PSP-CKD, REGARDS, SRR-CKD

Table S4. Number of KFRT and KF events during follow-up within each cohort

Cohort	N	KFRT		KFRT+eGFR<15
		n	Follow-up	n
Overall	25,903,761	101,044	4.2 (2.9)	221659
ADVANCE	11091	81	8.6 (2.9)	127
ARIC	11527	243	21.2 (1.9)	NA
CanPREDDICT	1894	375	3.5 (1.6)	729
CARE FOR HOMe	541	67	4.7 (2.2)	72
CRIB	264	90	5.3 (3.0)	NA
CRIC	5494	1213	7.0 (4.4)	1337
GCKD	5128	498	6.0 (1.8)	NA
Geisinger	366016	1958	6.0 (3.6)	5945
GLOMMS	329977	392	5.8 (3.0)	2700
Go-DARTs	17821	171	14.5 (5.6)	1297
Gubbio	4597	51	16.0 (4.1)	NA
Hongkong CKD	245	125	5.8 (3.5)	NA
ICES-KDT	1017530	6963	6.0 (1.9)	19521
LCC	17132	123	4.0 (1.5)	NA
Maccabi	1440372	1909	7.5 (3.4)	6853
MASTERPLAN	650	116	5.9 (1.2)	163
MDRD	1618	996	10.2 (7.1)	NA
MMKD	172	45	4.4 (1.5)	NA
Mt Sinai BioMe	17446	264	3.8 (2.3)	487
Nanjing CKD	1275	733	4.4 (3.4)	1028
Nefrona	1471	113	3.8 (1.1)	NA
NephroTest	1757	354	5.6 (3.1)	NA
OLDW cohort 1	317354	1717	4.5 (2.5)	2865
OLDW cohort 2	88380	335	4.4 (2.8)	784
OLDW cohort 3	110002	231	2.9 (1.8)	536
OLDW cohort 4	304007	1604	3.2 (1.9)	2938
OLDW cohort 5	175556	679	3.7 (2.6)	1622
OLDW cohort 6	165729	738	3.1 (1.8)	1690
OLDW cohort 7	121413	226	3.3 (2.2)	419
OLDW cohort 8	266591	428	4.1 (2.5)	914
OLDW cohort 9	1473923	4717	3.8 (2.5)	13055
OLDW cohort 10	1305648	3688	4.3 (3.0)	8393
OLDW cohort 11	176874	508	2.7 (2.0)	1375
OLDW cohort 12	385105	666	2.5 (1.9)	998
OLDW cohort 13	849173	5713	3.5 (2.2)	8798
OLDW cohort 14	133785	1774	2.7 (2.3)	2238
OLDW cohort 15	81203	149	5.0 (3.1)	408
OLDW cohort 16	231809	1106	4.3 (2.4)	2153
OLDW cohort 17	153560	594	5.1 (3.1)	1562
OLDW cohort 18	278097	873	2.4 (1.7)	1337
OLDW cohort 19	308518	1202	3.6 (2.9)	2907
OLDW cohort 20	669837	2723	3.7 (2.4)	5069
OLDW cohort 21	181418	719	3.8 (2.6)	1919
OLDW cohort 22	836079	1967	2.7 (2.3)	4133
OLDW cohort 23	365414	882	4.2 (3.0)	3452
OLDW cohort 24	543380	1043	3.2 (2.0)	4622
OLDW cohort 25	537225	2914	4.2 (2.6)	4868
OLDW cohort 26	1141213	5789	4.2 (2.8)	12052
OLDW cohort 27	40674	170	2.7 (1.9)	268

OLDW cohort 28	330566	2890	4.9 (3.1)	5122
OLDW cohort 29	747255	2077	4.5 (2.7)	4904
OLDW cohort 30	366530	1445	3.8 (2.6)	2785
OLDW cohort 31	363900	580	4.5 (2.8)	2311
OLDW cohort 32	216369	1501	2.8 (2.3)	2168
OLDW cohort 33	244814	606	2.8 (2.1)	1094
OLDW cohort 34	131205	376	4.6 (2.9)	1058
OLDW cohort 35	148535	1418	4.1 (3.0)	1798
OLDW cohort 36	175418	853	3.5 (2.6)	1396
OLDW cohort 37	367461	1132	4.2 (2.6)	3528
OLDW cohort 38	224879	1614	4.2 (2.9)	3304
OLDW cohort 39	51457	142	2.1 (1.2)	273
OLDW cohort 40	204235	505	5.4 (3.1)	1527
OLDW cohort 41	518142	1473	3.7 (2.6)	3549
OLDW cohort 42	420302	909	4.3 (3.0)	2400
OLDW cohort 43	68240	95	2.1 (1.5)	188
OLDW cohort 44	199070	286	3.2 (1.7)	851
OLDW cohort 45	3136664	14232	4.0 (2.9)	28139
PSP-CKD	26072	137	3.8 (1.5)	357
RCAV	2237948	4311	2.6 (1.1)	16629
REGARDS	28689	590	11.4 (3.4)	NA
RENAAL	1510	338	2.9 (0.9)	533
SCREAM	696881	539	3.5 (1.2)	1634
SEED	9512	139	10.1 (2.7)	141
SHARP	4790	1058	4.0 (1.5)	1840
SKS	2395	384	5.0 (3.5)	897
SMART	13010	81	8.8 (5.4)	NA
SRR-CKD	2559	522	2.9 (1.6)	NA
Sunnybrook	2524	179	3.3 (2.1)	293
UK Biobank	463563	362	8.1 (1.1)	NA
West of Scotland	2412	158	7.0 (3.0)	1168
YWSCC	869	77	2.7 (0.5)	138

Table S5. Unadjusted, minimally adjusted, and fully adjusted hazard ratios of kidney failure replacement therapy (KFRT) after different cardiovascular events, by prevalence and incidence (with baseline adjustment or time dependent covariates), modelled separately and simultaneously adjusted for each other, in the Optum Labs Data Warehouse (OLDW) cohorts

	Cardiovascular event types modelled separately				**Cardiovascular event types adjusted for each other**			
N = 19,150,075	**CHD**	**Stroke**	**HF**	**Atrial fibrillation**	**CHD**	**Stroke**	**HF**	**Atrial fibrillation**
Baseline covariates	**HRs (95% CI) of KFRT after Baseline Prevalent CVD**				**HRs (95% CI) of KFRT after Baseline Prevalent CVD**			
Unadjusted	**4.13 (3.84, 4.44)**	**3.41 (3.17, 3.67)**	**9.32 (8.49, 10.2)**	**3.13 (2.87, 3.42)**	**2.34 (2.20, 2.50)**	**1.90 (1.80, 2.00)**	**5.11 (4.79, 5.44)**	**1.08 (1.02, 1.15)**
Age and sex adjusted	**2.59 (2.47, 2.71)**	**2.22 (2.10, 2.35)**	**5.94 (5.60, 6.29)**	**1.78 (1.67, 1.89)**	**1.70 (1.63, 1.77)**	**1.64 (1.56, 1.71)**	**4.59 (4.36, 4.84)**	**0.87 (0.83, 0.91)**
Age, sex, eGFR, ACR, missing ACR adj.	**1.51, 1.44, 1.60)**	**1.37 (1.30, 1.45)**	**1.85 (1.74, 1.97)**	**1.20 (1.12, 1.28)**	**1.28 (1.23, 1.33)**	**1.19 (1.14, 1.24)**	**1.70 (1.62, 1.78)**	**0.91 (0.87, 0.96)**
Fully adjusted	**1.26 (1.21, 1.30)**	**1.16 (1.12, 1.20)**	**1.47 (1.40, 1.53)**	**1.14 (1.08, 1.20)**	**1.13 (1.10, 1.17)**	**1.09 (1.05, 1.13)**	**1.40 (1.35, 1.46)**	0.99 (0.95, 1.04)
Fully adjusted in male	**1.22 (1.18, 1.27)**	**1.14 (1.09, 1.18)**	**1.44 (1.36, 1.52)**	**1.13 (1.06, 1.20)**	**1.11 (1.07, 1.15)**	**1.08 (1.03, 1.13)**	**1.38 (1.30, 1.45)**	1.00 (0.94, 1.05)
Fully adjusted in female	**1.27 (1.22, 1.33)**	**1.20 (1.14, 1.27)**	**1.51 (1.42, 1.60)**	**1.18 (1.12, 1.24)**	**1.14 (1.09, 1.18)**	**1.12 (1.05, 1.19)**	**1.45 (1.38, 1.53)**	0.99 (0.93, 1.06)
Baseline covariates	**HRs (95% CI) of KFRT after Incident CVD During Follow-up**				**HRs (95% CI) of KFRT after Incident CVD During Follow-up**			
Unadjusted	**9.37 (8.64, 10.2)**	**5.81 (5.21, 6.47)**	**18.9 (17.0, 21.0)**	**7.96 (7.15, 8.86)**	**1.69 (1.57, 1.83)**	**1.99 (1.80, 2.19)**	**14.4 (12.9, 16.2)**	**1.26 (1.14, 1.40)**
Age and sex adjusted	**6.43 (6.00, 6.88)**	**3.87 (3.54, 4.24)**	**12.9 (11.9, 13.9)**	**4.81 (4.42, 5.23)**	**1.58 (1.47, 1.69)**	**1.74 (1.59, 1.91)**	**10.6 (9.68, 11.7)**	1.00 (0.91, 1.10)
Age, sex, eGFR, ACR, missing ACR adj.	**3.77 (3.48, 4.08)**	**2.48 (2.28, 2.69)**	**5.10 (4.74, 5.49)**	**3.02 (2.79, 3.28)**	**1.55 (1.42, 1.69)**	**1.50 (1.37, 1.65)**	**4.12 (3.78, 4.49)**	**1.20 (1.09, 1.32)**
Fully adjusted	**3.37 (3.17, 3.59)**	**2.13 (1.96, 2.31)**	**4.47 (4.17, 4.80)**	**2.93 (2.70, 3.18)**	**1.50 (1.39, 1.61)**	**1.36 (1.25, 1.49)**	**3.57 (3.27, 3.89)**	**1.37 (1.24, 1.50)**
Fully adjusted in male	**3.27 (3.09, 3.47)**	**2.16 (1.96, 2.38)**	**4.33 (3.96, 4.74)**	**2.94 (2.70, 3.21)**	**1.52 (1.39, 1.67)**	**1.37 (1.21, 1.54)**	**3.46 (3.14, 3.82)**	**1.40 (1.27, 1.55)**
Fully adjusted in female	**3.62 (3.34, 3.93)**	**2.16 (1.96, 2.39)**	**4.77 (4.45, 5.11)**	**2.96 (2.71, 3.23)**	**1.53 (1.37, 1.71)**	**1.40 (1.22, 1.61)**	**3.91 (3.55, 4.31)**	**1.30 (1.16, 1.46)**
Time dependent covariates	**HRs (95% CI) of KFRT after Incident CVD During Follow-up**				**HRs (95% CI) of KFRT after Incident CVD During Follow-up**			
Unadjusted	**9.37 (8.64, 10.2)**	**5.81 (5.21, 6.47)**	**18.9 (17.0, 21.0)**	**7.96 (7.15, 8.86)**	**1.69 (1.57, 1.83)**	**1.99 (1.80, 2.19)**	**14.4 (12.9, 16.2)**	**1.26 (1.14, 1.40)**
Age and sex adjusted	**5.93 (5.53, 6.36)**	**3.57 (3.26, 3.91)**	**12.2 (11.3, 13.1)**	**4.48 (4.12, 4.87)**	**1.55 (1.44, 1.66)**	**1.69 (1.54, 1.85)**	**10.0 (9.14, 11.0)**	0.98 (0.89, 1.07)
Age, sex, eGFR, ACR, missing ACR adj.	**1.65 (1.51, 1.80)**	**1.28 (1.15, 1.43)**	**2.39 (2.16, 2.64)**	**1.63 (1.47, 1.81)**	**1.14 (1.05, 1.23)**	**1.12 (1.03, 1.21)**	**1.90 (1.72, 2.11)**	1.08 (0.99, 1.18)
Fully adjusted	**1.60 (1.43, 1.79)**	**1.20 (1.05, 1.37)**	**2.15 (1.92, 2.42)**	**1.59 (1.41, 1.81)**	**1.09 (1.01, 1.15)**	1.00 (0.91, 1.10)	**1.58 (1.43, 1.76)**	**1.15 (1.06, 1.25)**
Fully adjusted in male	**1.72 (1.54, 1.92)**	**1.16 (1.01, 1.32)**	**2.12 (1.83, 2.45)**	**1.57 (1.35, 1.82)**	**1.13 (1.03, 1.14)**	0.99 (0.87, 1.14)	**1.54 (1.36, 1.75)**	**1.16 (1.06, 1.25)**
Fully adjusted in female	**1.51 (1.26, 1.81)**	**1.36 (1.10, 1.69)**	**2.28 (2.04, 2.55)**	**1.72 (1.49, 1.97)**	1.06 (0.94, 1.20)	1.05 (0.93, 1.18)	**1.65 (1.50, 1.82)**	**1.19 (1.07, 1.33)**

ACR: urine albumin-to-creatinine ratio; CHD: coronary heart disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; HF: heart failure; KFRT: kidney failure replacement therapy

Fully adjusted model includes age, sex, black race, eGFR, smoking status, diabetes mellitus, systolic blood pressure and antihypertensive medication use, total cholesterol, HDL cholesterol and use of lipid lowering medication use, body mass, missing indicator of ACR and log-transformed ACR.

Table S6. Adjusted hazard ratios of kidney failure replacement therapy (KFRT) associated with incidence of different cardiovascular events, adjusting for most recent eGFR with shorter follow-up, in Optum Labs Data Warehouse (OLDW) cohorts, N = 19,157,009

First incident event of each CVD subtype in separate models, regardless of the other three CVD types		**Coronary Heart Disease**	**Stroke**	**Heart Failure**	**Atrial fibrillation**
		KFRT			
Adjusted for baseline eGFR	Incident < 3 month	**79.33 (73.86, 85.20)**	**44.90 (41.11, 49.04)**	**106.06 (101.91, 110.38)**	**78.35 (74.68, 82.20)**
	Incident 4 - 6 month	**15.14 (13.41, 17.10)**	**10.27 (8.82, 11.95)**	**24.07 (22.68, 25.54)**	**14.91 (13.69, 16.23)**
	Incident 7 - 9 month	**7.90 (6.80, 9.19)**	**6.38 (5.44, 7.47)**	**14.02 (13.11, 15.00)**	**8.99 (8.16, 9.91)**
	Incident 10 - 12 month	**7.78 (6.71, 9.03)**	**4.05 (3.41, 4.81)**	**9.70 (9.01, 10.45)**	**6.49 (5.83, 7.21)**
	Incident 13 - 15 month	**5.66 (4.82, 6.64)**	**4.62 (3.91, 5.45)**	**8.41 (7.79, 9.08)**	**5.05 (4.51, 5.66)**
	Incident 16 - 18 month	**3.82 (3.22, 4.53)**	**3.19 (2.65, 3.83)**	**5.57 (5.10, 6.08)**	**3.45 (3.03, 3.94)**
	Incident 19 - 21 month	**3.35 (2.74, 4.09)**	**2.69 (2.21, 3.27)**	**4.98 (4.55, 5.45)**	**3.06 (2.68, 3.50)**
	Incident 22 - 24 month	**2.66 (2.16, 3.28)**	**2.18 (1.76, 2.71)**	**3.99 (3.62, 4.40)**	**2.72 (2.36, 3.12)**
	Incident 25 - 27 month	**2.48 (1.99, 3.08)**	**1.94 (1.56, 2.42)**	**3.53 (3.19, 3.91)**	**2.06 (1.76, 2.41)**
	Incident 28 - 30 month	**2.16 (1.70, 2.74)**	**1.97 (1.58, 2.47)**	**2.85 (2.55, 3.19)**	**1.92 (1.65, 2.25)**
	Incident 31 - 33 month	**1.52 (1.16, 1.99)**	**1.92 (1.56, 2.35)**	**2.50 (2.22, 2.81)**	**1.62 (1.37, 1.92)**
	Incident 34 - 36 month	**2.13 (1.67, 2.72)**	**1.44 (1.12, 1.85)**	**2.33 (2.05, 2.63)**	**1.48 (1.24, 1.77)**
	Incident 3y+	**0.61 (0.54, 0.69)**	**0.54 (0.48, 0.61)**	**0.94 (0.88, 0.99)**	**0.58 (0.53, 0.63)**
First incident event of each CVD subtype in one model, adjusted for the other three CVD types		**Coronary Heart Disease**	**Stroke**	**Heart Failure**	**Atrial fibrillation**
		KFRT			
Adjusted for baseline eGFR	Incident < 3 month	**2.13 (1.94, 2.34)**	**2.46 (2.18, 2.78)**	**46.45 (43.21, 49.94)**	**3.61 (3.31, 3.93)**
	Incident 4 - 6 month	**1.64 (1.41, 1.91)**	**1.76 (1.43, 2.16)**	**15.53 (14.20, 16.99)**	**1.94 (1.71, 2.21)**
	Incident 7 - 9 month	**1.25 (1.04, 1.51)**	**1.91 (1.56, 2.35)**	**9.40 (8.50, 10.40)**	**1.85 (1.60, 2.15)**
	Incident 10 - 12 month	**1.77 (1.49, 2.12)**	**1.74 (1.40, 2.17)**	**7.07 (6.35, 7.88)**	**1.46 (1.24, 1.72)**
	Incident 13 - 15 month	**1.56 (1.29, 1.89)**	**1.56 (1.26, 1.94)**	**6.64 (5.97, 7.39)**	**1.23 (1.03, 1.46)**
	Incident 16 - 18 month	**1.30 (1.06, 1.60)**	**1.59 (1.25, 2.04)**	**4.41 (3.88, 5.01)**	**1.24 (1.03, 1.51)**
	Incident 19 - 21 month	**1.42 (1.13, 1.78)**	**1.88 (1.47, 2.40)**	**3.97 (3.49, 4.52)**	1.20 (0.98, 1.46)
	Incident 22 - 24 month	1.18 (0.93, 1.51)	**1.61 (1.24, 2.08)**	**3.65 (3.20, 4.18)**	0.98 (0.80, 1.22)

	Incident 25 - 27 month	1.29 (0.99, 1.68)	**1.50 (1.15, 1.95)**	**3.07 (2.66, 3.54)**	0.98 (0.78, 1.22)
	Incident 28 - 30 month	1.26 (0.96, 1.66)	**1.57 (1.19, 2.08)**	**2.64 (2.27, 3.07)**	1.09 (0.88, 1.37)
	Incident 31 - 33 month	1.03 (0.76, 1.38)	**1.55 (1.19, 2.02)**	**2.15 (1.82, 2.53)**	1.04 (0.82, 1.31)
	Incident 34 - 36 month	1.29 (0.96, 1.73)	1.10 (0.80, 1.51)	**2.14 (1.80, 2.54)**	0.90 (0.70, 1.17)
	Incident 3y+	**0.67 (0.58, 0.77)**	**0.58 (0.50, 0.68)**	0.97 (0.90, 1.04)	**0.56 (0.50, 0.62)**

Table S7. Adjusted hazard ratios of kidney failure replacement therapy (KFRT) associated with incidence of different cardiovascular events, adjusting for most recent eGFR with shorter follow-up and interaction analyses

	Myocardial Infarction	**Stroke**	**Heart Failure**	**Atrial fibrillation**
N overall	25,902,290	25,902,290	25,858,471	24,353,175
KFRT events overall	100,931	100,931	98,001	93,600
Incident CVD event, N	269,142	311,021	712,556	605,596
Adjusted for most recent eGFR – KFRT events within shorter windows after CVD event				
Incident overall	1.55 (1.39, 1.73)	1.03 (0.79, 1.34)	2.03 (1.62, 2.53)	1.37 (1.05, 1.77)
Incident overall†	1.73 (1.48, 2.03)	1.02 (0.72, 1.44)	1.81 (1.41, 2.33)	1.44 (1.06, 1.96)
Incident < 1y	7.91 (6.35, 9.86)	4.49 (3.43, 5.89)	10.15 (7.95, 12.96)	7.52 (5.62, 10.06)
Incident 1-2y	1.63 (1.30, 2.05)	1.40 (1.07, 1.84)	2.37 (1.89, 2.98)	1.57 (1.21, 2.03)
Incident 2y+	0.56 (0.49, 0.64)	0.52 (0.39, 0.70)	0.71 (0.57, 0.88)	0.44 (0.34, 0.57)
Incident < 30d	86.12 (69.87, 106.16)	49.49 (37.95, 64.55)	120.27 (95.05, 152.18)	86.00 (67.49, 109.58)
Incident 30d-1y	4.03 (3.39, 4.80)	2.69 (2.19, 3.30)	6.58 (5.14, 8.41)	3.90 (3.07, 4.95)
Incident 1-2y	1.45 (1.20, 1.75)	1.26 (1.07, 1.49)	2.33 (1.85, 2.92)	1.41 (1.12, 1.77)
Incident 2y+	0.54 (0.47, 0.62)	0.47 (0.39, 0.55)	0.71 (0.57, 0.87)	0.42 (0.32, 0.54)
Incident < 90d	37.56 (28.61, 49.31)	20.51 (14.34, 29.32)	42.67 (33.77, 53.91)	33.05 (24.82, 44.02)
Incident 90d-1y	3.85 (3.03, 4.90)	2.59 (1.89, 3.53)	5.50 (4.27, 7.08)	3.54 (2.60, 4.83)
Incident 1-2y	1.66 (1.32, 2.08)	1.54 (1.11, 2.12)	2.39 (1.90, 3.01)	1.58 (1.23, 2.02)
Incident 2y+	0.55 (0.48, 0.63)	0.51 (0.38, 0.70)	0.72 (0.58, 0.89)	0.43 (0.33, 0.56)
Adjusted for most recent eGFR -- interaction model				
Incident overall at eGFR 60 ACR 10	2.86 (2.41, 3.39)	1.93 (1.60, 2.33)	4.98 (4.30, 5.77)	3.01 (2.59, 3.50)
Incident overall * eGFR <60 /-15ml	0.80 (0.74, 0.86)	0.76 (0.70, 0.82)	0.71 (0.66, 0.76)	0.77 (0.73, 0.82)
Incident overall * eGFR 60+ /-15ml	0.71 (0.65, 0.77)	0.62 (0.57, 0.67)	0.61 (0.57, 0.65)	0.62 (0.58, 0.66)
Incident overall * logACR /8 fold	0.82 (0.78, 0.87)	0.96 (0.90, 1.01)	0.82 (0.78, 0.86)	0.81 (0.76, 0.86)

† Incident free of history of all 4 subtypes. eGFR updated to the most recent value prior to the onset of CVD.

Table S8. Adjusted hazard ratios of kidney failure replacement therapy (KFRT) associated with incidence of different cardiovascular events, adjusting for baseline eGFR with shorter follow-up and interaction analyses

	Myocardial Infarction	**Stroke**	**Heart Failure**	**Atrial fibrillation**
N overall	25,902,290	25,902,290	25,858,471	24,353,175
KFRT events overall	100,931	100,931	98,001	93,600
Incident CVD event, N	269,142	311,021	712,556	605,596
Adjusted for baseline eGFR – KFRT events within shorter windows after CVD event				
Incident < 30d	268.16 (228.79, 314.31)	137.07 (109.12, 172.17)	361.39 (311.57, 419.16)	262.87 (223.84, 308.70)
Incident 30d-1y	13.46 (12.11, 14.96)	7.77 (6.88, 8.77)	18.59 (15.93, 21.68)	11.72 (10.56, 13.02)
Incident 1-2y	3.52 (3.02, 4.11)	2.99 (2.61, 3.42)	5.39 (4.74, 6.13)	3.41 (3.10, 3.76)
Incident 2y+	0.95 (0.88, 1.03)	0.79 (0.71, 0.88)	1.26 (1.16, 1.38)	0.85 (0.78, 0.93)
Incident < 90d	106.32 (91.22, 123.91)	51.17 (42.48, 61.65)	122.83 (106.58, 141.57)	94.55 (78.99, 113.17)
Incident 90d-1y	11.67 (10.07, 13.53)	6.70 (5.91, 7.59)	15.21 (13.11, 17.65)	10.50 (9.02, 12.23)
Incident 1-2y	3.84 (3.29, 4.47)	3.28 (2.85, 3.78)	5.47 (4.81, 6.21)	3.76 (3.29, 4.29)
Incident 2y+	0.94 (0.86, 1.04)	0.81 (0.74, 0.90)	1.28 (1.18, 1.40)	0.86 (0.79, 0.94)
Adjusted for baseline eGFR -- interaction model				
Incident overall at eGFR 60 ACR 10	4.86 (4.31, 5.49)	2.81 (2.41, 3.26)	9.74 (8.72, 10.88)	4.89 (4.32, 5.53)
Incident overall * eGFR <60 /-15ml	0.69 (0.64, 0.74)	0.71 (0.65, 0.78)	0.58 (0.55, 0.61)	0.66 (0.62, 0.70)
Incident overall * eGFR 60+ /-15ml	0.69 (0.65, 0.74)	0.63 (0.58, 0.67)	0.62 (0.59, 0.66)	0.66 (0.62, 0.70)
Incident overall * logACR /8 fold	0.97 (0.93, 1.02)	1.08 (1.02, 1.14)	0.91 (0.87, 0.96)	0.93 (0.88, 0.98)
Incident < 1y at eGFR 60 ACR 10	65.73 (54.31, 79.54)	26.92 (21.82, 33.22)	96.32 (82.17, 112.92)	54.73 (44.65, 67.08)
Incident 1-2y at eGFR 60 ACR 10	8.45 (3.95, 18.05)	2.02 (0.47, 8.67)	15.88 (13.55, 18.62)	6.32 (4.61, 8.66)
Incident 2y+ at eGFR 60 ACR 10	1.67 (1.39, 2.01)	1.51 (1.22, 1.89)	3.21 (2.80, 3.69)	1.59 (1.36, 1.86)
Incident < 1y * eGFR <60 /-15ml	0.54 (0.50, 0.59)	0.57 (0.51, 0.63)	0.48 (0.46, 0.51)	0.51 (0.47, 0.55)
Incident 1-2y * eGFR <60 /-15ml	0.61 (0.27, 1.40)	1.08 (0.48, 2.46)	0.51 (0.48, 0.54)	0.66 (0.56, 0.77)
Incident 2y+ * eGFR <60 /-15ml	0.63 (0.57, 0.71)	0.60 (0.53, 0.67)	0.51 (0.47, 0.56)	0.60 (0.55, 0.66)
Incident < 1y * eGFR 60+ /-15ml	0.65 (0.60, 0.72)	0.55 (0.50, 0.61)	0.58 (0.55, 0.61)	0.62 (0.57, 0.66)

Incident 1-2y * eGFR 60+ /-15ml	0.63 (0.41, 0.97)	0.47 (0.26, 0.83)	0.62 (0.57, 0.68)	0.62 (0.54, 0.72)
Incident 2y+ * eGFR 60+ /-15ml	0.78 (0.70, 0.87)	0.69 (0.62, 0.77)	0.69 (0.64, 0.73)	0.73 (0.66, 0.82)
Incident < 1y * logACR /8 fold	0.81 (0.75, 0.87)	0.96 (0.87, 1.06)	0.80 (0.76, 0.85)	0.85 (0.79, 0.90)
Incident 1-2y * logACR /8 fold	0.90 (0.62, 1.31)	2.13 (0.94, 4.85)	0.88 (0.84, 0.93)	0.93 (0.84, 1.02)
Incident 2y+ * logACR /8 fold	1.06 (0.97, 1.16)	1.16 (1.05, 1.29)	0.96 (0.91, 1.02)	1.08 (0.99, 1.18)

Table S9. Adjusted hazard ratios of kidney failure replacement therapy (KFRT) or eGFR <15 associated with prevalence and incidence of different cardiovascular events considered separately

	Myocardial Infarction	**Stroke**	**Heart Failure**	**Atrial fibrillation**
N overall	**25,352,029**	**25,352,029**	**25,337,727**	**23,836,747**
KFRT events overall	**221,659**	**221,659**	**219,678**	**209,979**
Prevalent CVD event, N	**2,422,325**	**810,462**	**844,456**	**1,061,774**
Prevalent overall	1.13 (1.10, 1.17)	1.12 (1.09, 1.16)	1.39 (1.33, 1.46)	1.12 (1.08, 1.16)
Incident CVD events, N	**261,191**	**303,657**	**708,129**	**597,382**
Incident overall	3.53 (3.24, 3.86)	2.55 (2.40, 2.71)	5.11 (4.79, 5.44)	3.70 (3.47, 3.95)
Incident overall†	4.03 (3.74, 4.33)	2.83 (2.65, 3.03)	5.86 (5.54, 6.20)	3.93 (3.69, 4.18)
Incident < 1y	12.63 (10.94, 14.58)	9.63 (8.63, 10.74)	17.24 (15.25, 19.48)	14.26 (13.02, 15.61)
Incident 1-2y	3.39 (3.10, 3.71)	2.59 (2.34, 2.86)	4.39 (4.01, 4.81)	3.01 (2.78, 3.26)
Incident 2y+	0.96 (0.89, 1.02)	0.79 (0.73, 0.85)	1.26 (1.17, 1.36)	0.88 (0.83, 0.94)
Incident < 30d	16.52 (13.01, 20.97)	12.82 (10.59, 15.52)	21.31 (17.80, 25.51)	19.97 (16.84, 23.68)
Incident 30d-1y	11.37 (10.25, 12.62)	8.00 (7.29, 8.79)	15.06 (13.67, 16.60)	10.86 (10.03, 11.75)
Incident 1-2y	3.39 (3.11, 3.70)	2.59 (2.34, 2.87)	4.32 (3.95, 4.73)	2.99 (2.77, 3.22)
Incident 2y+	0.96 (0.90, 1.03)	0.78 (0.72, 0.84)	1.24 (1.14, 1.33)	0.87 (0.82, 0.93)
Incident < 90d	16.99 (13.65, 21.16)	13.53 (11.41, 16.04)	22.87 (19.33, 27.05)	20.14 (17.54, 23.13)
Incident 90d-1y	8.96 (8.11, 9.89)	6.33 (5.77, 6.94)	11.72 (10.64, 12.91)	8.44 (7.78, 9.15)
Incident 1-2y	3.41 (3.13, 3.72)	2.57 (2.31, 2.86)	4.32 (3.95, 4.73)	3.00 (2.77, 3.24)
Incident 2y+	0.95 (0.89, 1.02)	0.78 (0.72, 0.84)	1.23 (1.14, 1.33)	0.87 (0.82, 0.93)

† Incident free of history of all 4 subtypes. Adjusted for baseline eGFR.

Table S10. Absolute 2-year risk of death after incident CVD in the Optum Labs Data Warehouse (OLDW) by eGFR and ACR category

	eGFR	Regardless of ACR				ACR <30 or missing				ACR 30-299				ACR 300+			
		MI	Stroke	HF	Afib	MI	Stroke	HF	Afib	MI	Stroke	HF	Afib	MI	Stroke	HF	Afib
N	90+	45609	48397	88507	77038	42767	45313	82029	50390	2104	2297	4559	3402	738	787	1919	791
	60-89	82966	99212	215338	211302	77830	92808	200269	160355	3636	4655	10784	11327	1500	1749	4285	2442
	45-59	32789	41675	111743	96564	29735	37936	101483	79123	2059	2575	6863	6956	995	1164	3397	1879
	30-44	21201	24691	80702	62272	18286	21450	69905	50666	1824	2046	6737	5897	1091	1195	4060	1995
	15-29	10190	9570	39442	27253	7977	7614	31274	20076	1010	950	3834	2997	1203	1006	4334	1746
Age and sex adjusted risk of death without KFRT	90+	28.1%	30.0%	33.8%	30.3%	28.0%	29.9%	33.9%	30.1%	26.8%	29.3%	32.4%	33.4%	37.8%	33.6%	36.3%	39.9%
	60-89	21.8%	23.8%	26.6%	21.6%	21.3%	23.4%	26.3%	21.1%	26.7%	26.7%	29.3%	27.3%	32.6%	34.7%	33.8%	32.2%
	45-59	27.7%	28.3%	29.2%	26.6%	27.1%	27.8%	28.9%	26.1%	30.9%	29.9%	29.5%	27.9%	34.5%	36.0%	35.4%	36.9%
	30-44	36.6%	36.3%	35.0%	35.7%	36.4%	36.5%	35.0%	35.5%	35.3%	34.3%	33.5%	33.9%	42.0%	37.8%	37.6%	42.5%
	15-29	47.8%	47.7%	42.9%	48.1%	48.8%	48.5%	43.5%	48.5%	46.5%	43.5%	42.3%	47.2%	45.1%	46.9%	41.2%	47.2%

Risk of death is age and sex adjusted to age 70 and half male to allow comparisons across the CVD subtypes

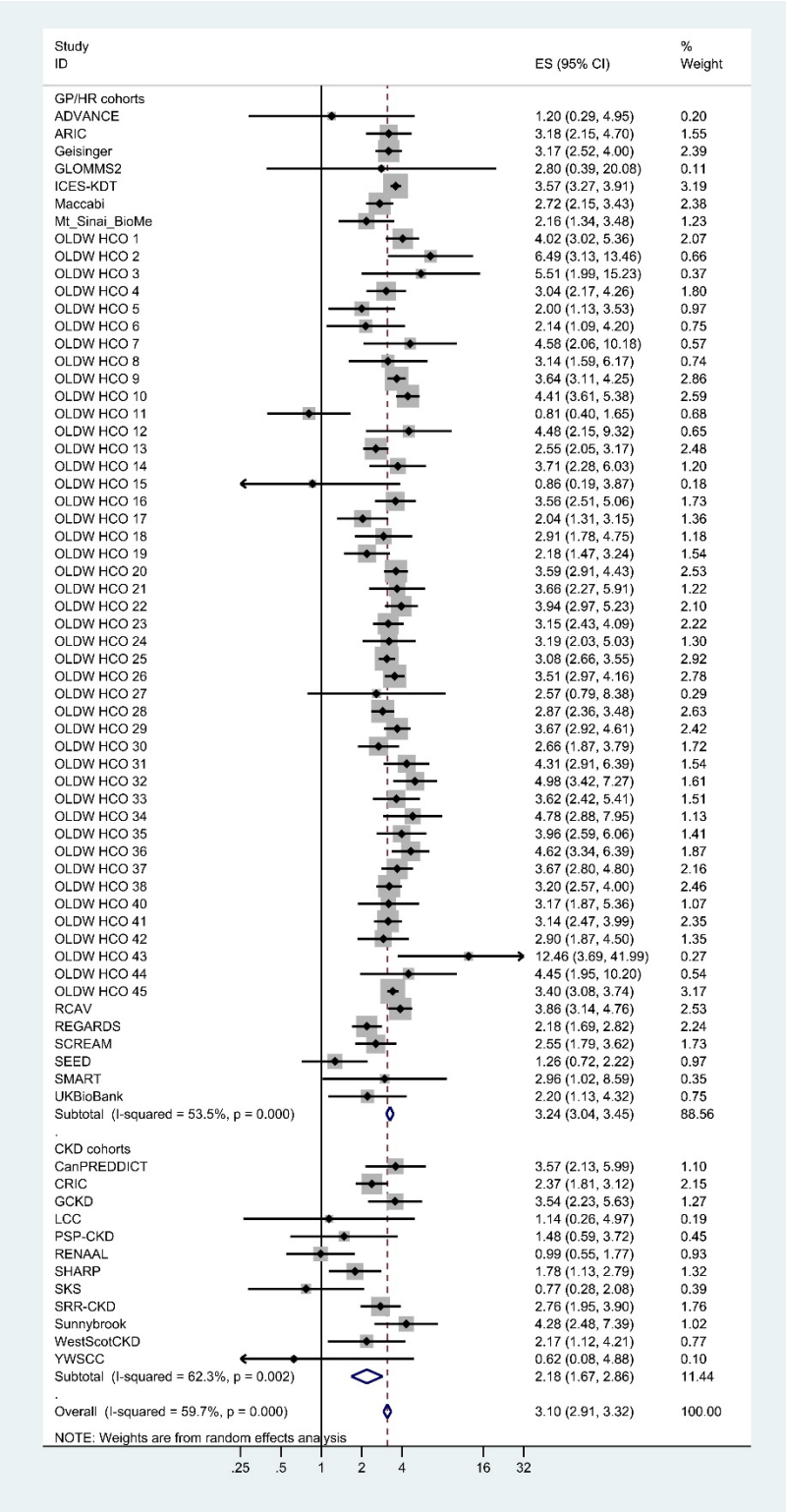
Table S11. Absolute 2-year risk of KFRT, death, and KFRT with a competing risk of death after incident CVD in the Optum Labs Data Warehouse (OLDW) by eGFR and ACR category in those with eGFR 60+ with differing risk factors

eGFR 60+		MI	Stroke	HF	Afib
N	No DM, Age <65	41541	41152	62771	62587
	No DM, Age 65+	40420	52692	116039	128108
	DM, Age <65	23256	23030	49547	32271
	DM, Age 65+	23358	30735	75488	65374
Unadjusted risk of KFRT	No DM, Age <65	0.2%	0.2%	0.5%	0.3%
	No DM, Age 65+	0.1%	0.1%	0.2%	0.2%
	DM, Age <65	0.9%	0.8%	1.5%	0.8%
	DM, Age 65+	0.5%	0.3%	0.4%	0.4%
Unadjusted risk of death without KFRT	No DM, Age <65	11.1%	15.6%	17.8%	14.0%
	No DM, Age 65+	30.8%	32.4%	37.6%	30.9%
	DM, Age <65	14.0%	16.4%	18.1%	18.1%
	DM, Age 65+	33.2%	32.9%	35.6%	33.6%
Unadjusted risk of KFRT accounting for death as a competing risk	No DM, Age <65	0.2%	0.2%	0.5%	0.3%
	No DM, Age 65+	0.1%	0.1%	0.2%	0.2%
	DM, Age <65	0.8%	0.7%	1.3%	0.7%
	DM, Age 65+	0.4%	0.2%	0.4%	0.3%

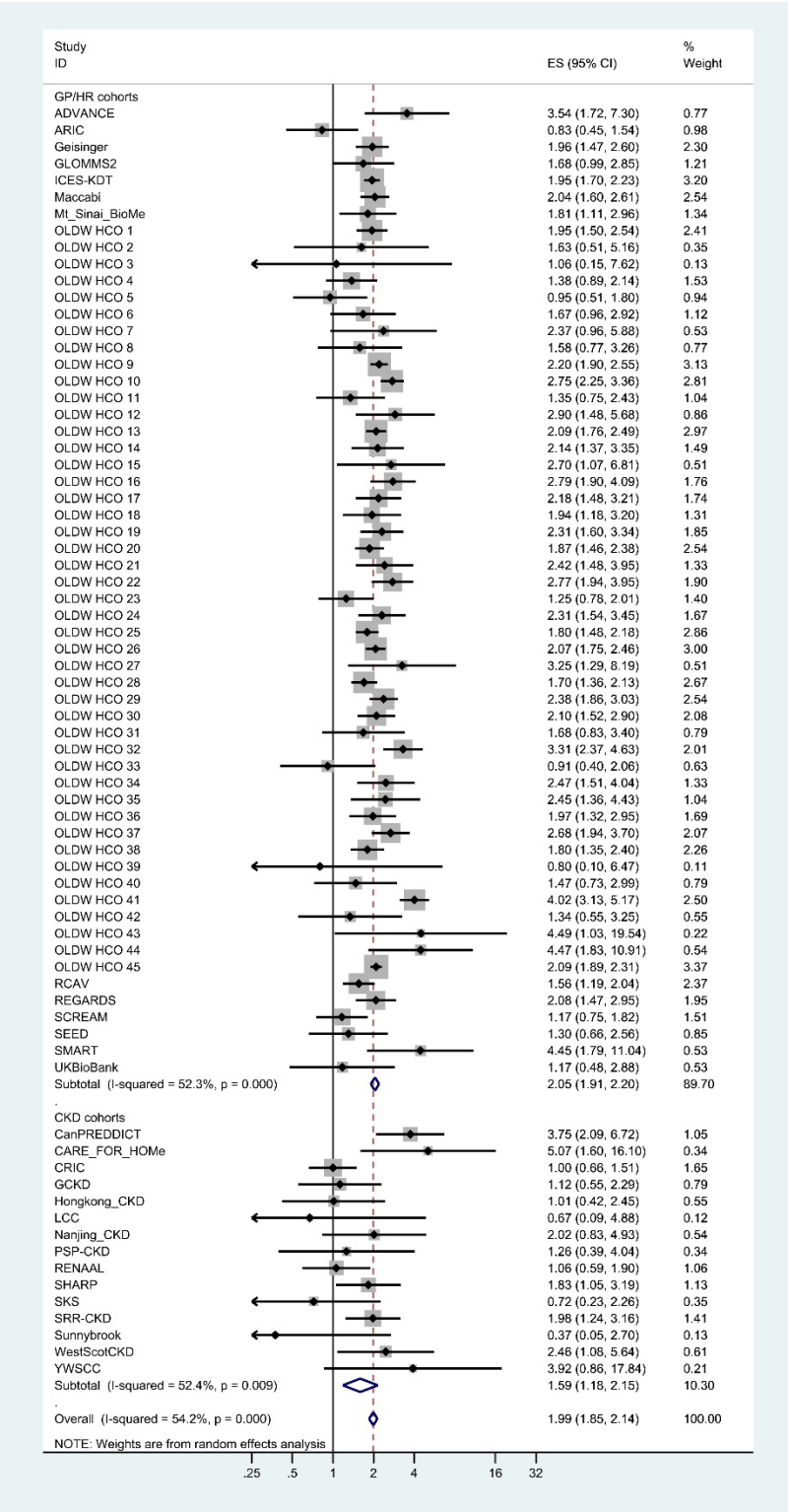
DM: diabetes mellitus

Figure S1. Forest plots of the adjusted hazard ratios of kidney failure replacement therapy (KFRT) associated with incidence of different cardiovascular events within each cohort

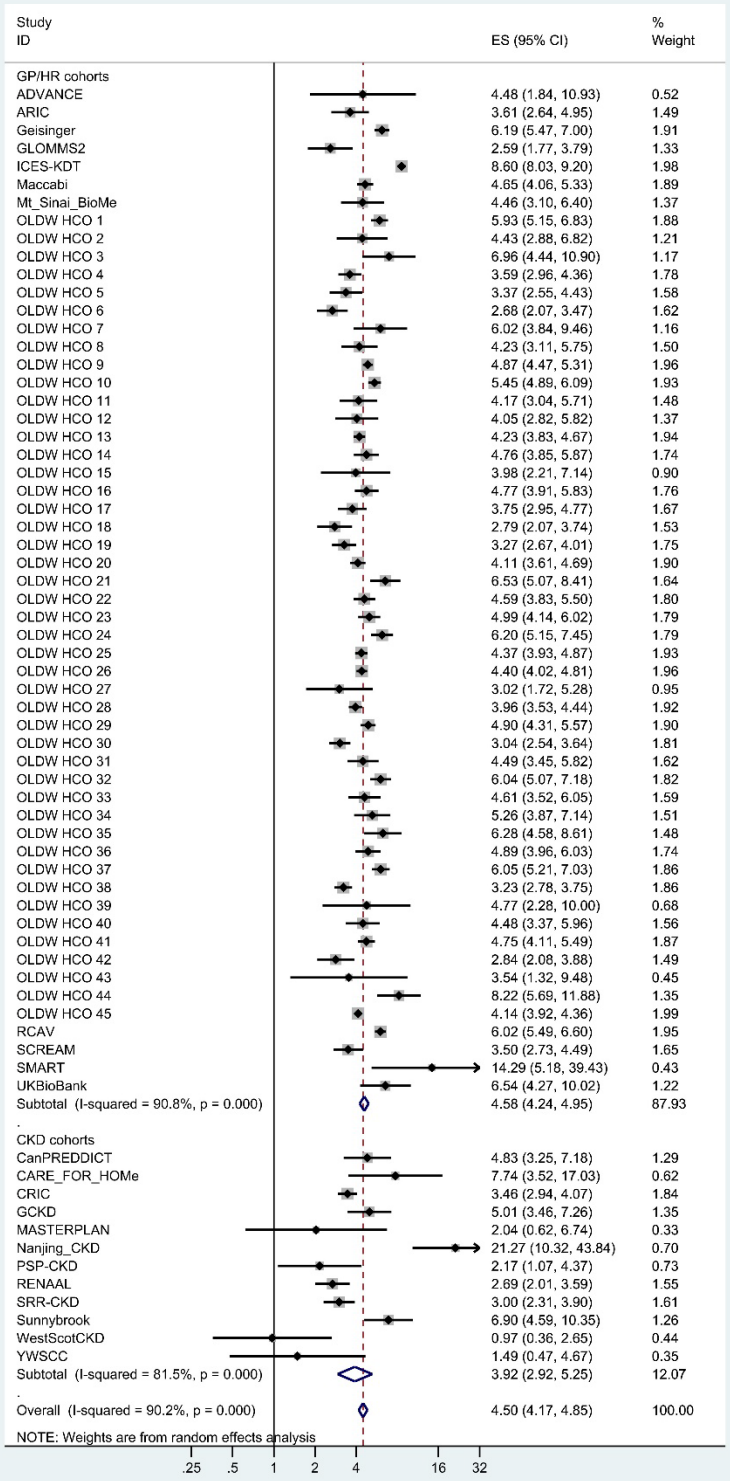
A. Myocardial infarction



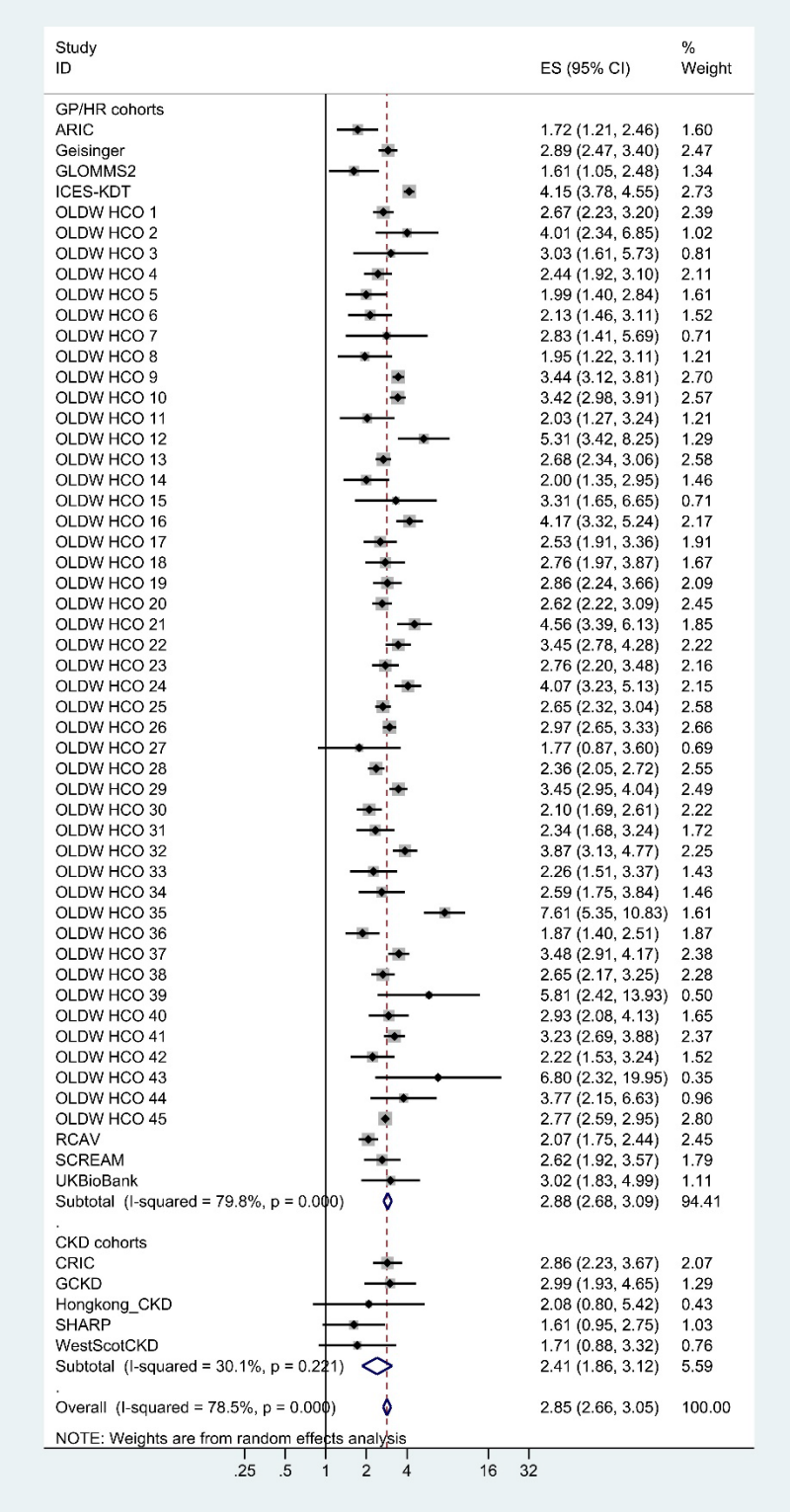
B. Stroke


Study
ID
ES (95% CI)
%
Weight
GP/HR cohorts
ADVANCE 3.54 (1.72, 7.30) 0.77
ARIC 0.83 (0.45, 1.54) 0.98
Geisinger 1.96 (1.47, 2.60) 2.30
GLOMMS2 1.68 (0.99, 2.85) 1.21
ICES-KDT 1.95 (1.70, 2.23) 3.20
Maccabi 2.04 (1.60, 2.61) 2.54
Mt_Sinai_BioMe 1.81 (1.11, 2.96) 1.34
OLDW HCO 1 1.95 (1.50, 2.54) 2.41
OLDW HCO 2 1.63 (0.51, 5.16) 0.35
OLDW HCO 3 1.06 (0.15, 7.62) 0.13
OLDW HCO 4 1.38 (0.89, 2.14) 1.53
OLDW HCO 5 0.95 (0.51, 1.80) 0.94
OLDW HCO 6 1.67 (0.96, 2.92) 1.12
OLDW HCO 7 2.37 (0.96, 5.88) 0.53
OLDW HCO 8 1.58 (0.77, 3.26) 0.77
OLDW HCO 9 2.20 (1.90, 2.55) 3.13
OLDW HCO 10 2.75 (2.25, 3.36) 2.81
OLDW HCO 11 1.35 (0.75, 2.43) 1.04
OLDW HCO 12 2.90 (1.48, 5.68) 0.86
OLDW HCO 13 2.09 (1.76, 2.49) 2.97
OLDW HCO 14 2.14 (1.37, 3.35) 1.49
OLDW HCO 15 2.70 (1.07, 6.81) 0.51
OLDW HCO 16 2.79 (1.90, 4.09) 1.76
OLDW HCO 17 2.18 (1.48, 3.21) 1.74
OLDW HCO 18 1.94 (1.18, 3.20) 1.31
OLDW HCO 19 2.31 (1.60, 3.34) 1.85
OLDW HCO 20 1.87 (1.46, 2.38) 2.54
OLDW HCO 21 2.42 (1.48, 3.95) 1.33
OLDW HCO 22 2.77 (1.94, 3.95) 1.90
OLDW HCO 23 1.25 (0.78, 2.01) 1.40
OLDW HCO 24 2.31 (1.54, 3.45) 1.67
OLDW HCO 25 1.80 (1.48, 2.18) 2.86
OLDW HCO 26 2.07 (1.75, 2.46) 3.00
OLDW HCO 27 3.25 (1.29, 8.19) 0.51
OLDW HCO 28 1.70 (1.36, 2.13) 2.67
OLDW HCO 29 2.38 (1.86, 3.03) 2.54
OLDW HCO 30 2.10 (1.52, 2.90) 2.08
OLDW HCO 31 1.68 (0.83, 3.40) 0.79
OLDW HCO 32 3.31 (2.37, 4.63) 2.01
OLDW HCO 33 0.91 (0.40, 2.06) 0.63
OLDW HCO 34 2.47 (1.51, 4.04) 1.33
OLDW HCO 35 2.45 (1.36, 4.43) 1.04
OLDW HCO 36 1.97 (1.32, 2.95) 1.69
OLDW HCO 37 2.68 (1.94, 3.70) 2.07
OLDW HCO 38 1.80 (1.35, 2.40) 2.26
OLDW HCO 39 0.80 (0.10, 6.47) 0.11
OLDW HCO 40 1.47 (0.73, 2.99) 0.79
OLDW HCO 41 4.02 (3.13, 5.17) 2.50
OLDW HCO 42 1.34 (0.55, 3.25) 0.55
OLDW HCO 43 4.49 (1.03, 19.54) 0.22
OLDW HCO 44 4.47 (1.83, 10.91) 0.54
OLDW HCO 45 2.09 (1.89, 2.31) 3.37
RCAV 1.56 (1.19, 2.04) 2.37
REGARDS 2.08 (1.47, 2.95) 1.95
SCREAM 1.17 (0.75, 1.82) 1.51
SEED 1.30 (0.66, 2.56) 0.85
SMART 4.45 (1.79, 11.04) 0.53
UKBioBank 1.17 (0.48, 2.88) 0.53
Subtotal (I-squared = 52.3%, p = 0.000) 2.05 (1.91, 2.20) 89.70
.
CKD cohorts
CanPREDDICT 3.75 (2.09, 6.72) 1.05
CARE_FOR_HOMe 5.07 (1.60, 16.10) 0.34
CRIC 1.00 (0.66, 1.51) 1.65
GCKD 1.12 (0.55, 2.29) 0.79
Hongkong_CKD 1.01 (0.42, 2.45) 0.55
LCC 0.67 (0.09, 4.88) 0.12
Nanjing_CKD 2.02 (0.83, 4.93) 0.54
PSP-CKD 1.26 (0.39, 4.04) 0.34
RENAAL 1.06 (0.59, 1.90) 1.06
SHARP 1.83 (1.05, 3.19) 1.13
SKS 0.72 (0.23, 2.26) 0.35
SRR-CKD 1.98 (1.24, 3.16) 1.41
Sunnybrook 0.37 (0.05, 2.70) 0.13
WestScotCKD 2.46 (1.08, 5.64) 0.61
YWSCC 3.92 (0.86, 17.84) 0.21
Subtotal (I-squared = 52.4%, p = 0.009) 1.59 (1.18, 2.15) 10.30
.
Overall (I-squared = 54.2%, p = 0.000) 1.99 (1.85, 2.14) 100.00
NOTE: Weights are from random effects analysis
.25
.5
1
2
4
16
32

C. Heart failure

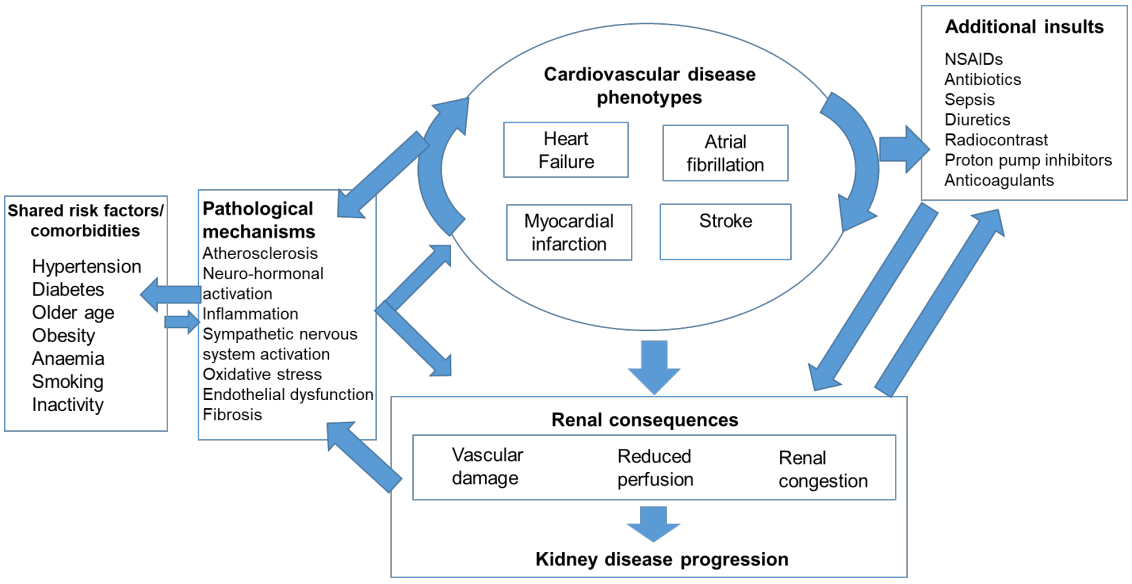


D. Atrial fibrillation



Models adjusted to age, sex, black race, eGFR, smoking status, diabetes mellitus, systolic blood pressure and antihypertensive medication use, total cholesterol, HDL cholesterol and use of lipid lowering medication use, body mass, missing indicator of ACR and log-transformed ACR.

Figure S2. Proposed pathways linking CVD events with kidney disease progression.



Shared risk factors between heart failure and kidney disease (e.g. hypertension, diabetes) contribute to the gradual progression of both heart and kidney disease. In addition, comorbidity-driven inflammatory state surrounding heart and kidney disease may accelerate tissue fibrosis, endothelial dysfunction, microvascular ischaemia, and oxidative stress. These conditions are manifested as heart failure, stroke, atrial fibrillation, and myocardial infarction. Additional pathways linking kidney disease to heart disease exist as well but are not the focus of this figure as they are less relevant for kidney disease incidence.

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