Clinical Kidney Journal, 2022, vol. 0, no. 0, 1–10

https://doi.org/10.1093/ckj/sfac247
Advance Access Publication Date: 18 November 2022
Original Article

ORIGINAL ARTICLE

Kidney function before and after acute kidney injury: a nationwide population-based cohort study

Simon Kok Jensen [1,2], Uffe Heide-Jørgensen[1,2], Søren Viborg Vestergaard [1,2], Henrik Gammelager[3], Henrik Birn[4,5], Dorothea Nitsch[6] and Christian Fynbo Christiansen[1,2]

[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark, [2]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, [3]Department of Intensive Care Medicine, Aarhus University Hospital, Aarhus, Denmark, [4]Department of Clinical Medicine and Biomedicine, Aarhus University, Aarhus, Denmark, [5]Department of Renal Medicine, Aarhus University Hospital, Aarhus, Denmark and [6]Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK

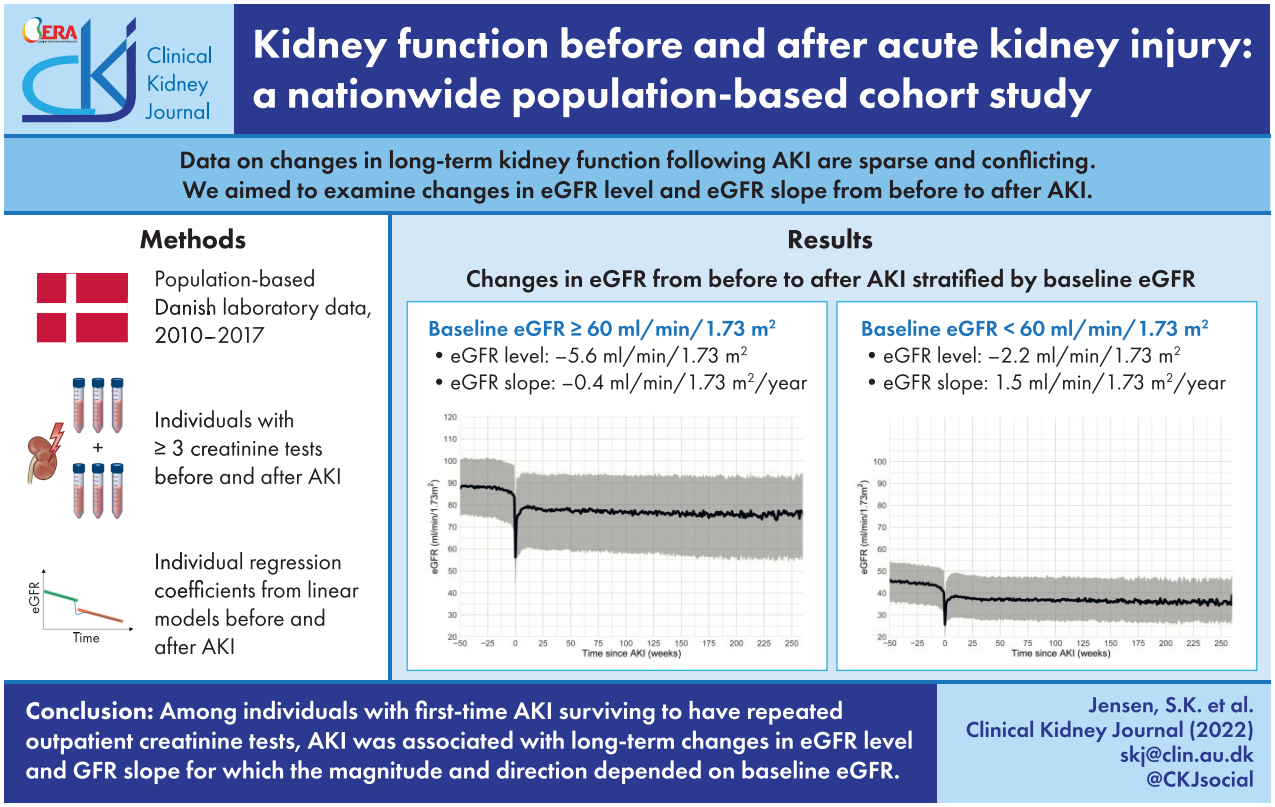
Correspondence to: Simon Kok Jensen; E-mail: skj@clin.au.dk

ABSTRACT

Background. Acute kidney injury (AKI) is a common and serious condition defined by a rapid decline in kidney function. Data on changes in long-term kidney function following AKI are sparse and conflicting. Therefore, we examined the changes in estimated glomerular filtration rate (eGFR) from before to after AKI in a nationwide population-based setting.
Methods. Using Danish laboratory databases, we identified individuals with first-time AKI defined by an acute increase in plasma creatinine (pCr) during 2010 to 2017. Individuals with three or more outpatient pCr measurements before and after AKI were included and cohorts were stratified by baseline eGFR (≥/<60 mL/min/1.73 m^2). Linear regression models were used to estimate and compare individual eGFR slopes and eGFR levels before and after AKI.
Results. Among individuals with a baseline eGFR ≥60 mL/min/1.73 m^2 ($n = 64\,805$), first-time AKI was associated with a median difference in eGFR level of −5.6 mL/min/1.73 m^2 [interquartile range (IQR) −16.1 to 1.8] and a median difference in eGFR slope of −0.4 mL/min/1.73 m^2/year (IQR −5.5 to 4.4). Correspondingly, among individuals with a baseline eGFR <60 mL/min/1.73 m^2 ($n = 33\,267$), first-time AKI was associated with a median difference in eGFR level of −2.2 mL/min/1.73 m^2 (IQR −9.2 to 4.3) and a median difference in eGFR slope of 1.5 mL/min/1.73 m^2/year (IQR −2.9 to 6.5).
Conclusion. Among individuals with first-time AKI surviving to have repeated outpatient pCr measurements, AKI was associated with changes in eGFR level and eGFR slope for which the magnitude and direction depended on baseline eGFR.

Received: 17.2.2022; Editorial decision: 17.10.2022

GRAPHICAL ABSTRACT



Keywords: acute kidney injury, epidemiology, estimated glomerular filtration rate, kidney function, nationwide

INTRODUCTION

Acute kidney injury (AKI) is a common and serious condition defined by a rapid decline in kidney function reflected by a rise in plasma creatinine (pCr) and/or a decrease in urine output [1]. The incidence of AKI has been estimated to be approximately 2–3 per thousand population per year [2, 3], while around 1 in 5 develop AKI during hospitalization [4]. AKI and chronic kidney disease (CKD) are intricately connected conditions, and just as CKD is a well-established risk factor for AKI, AKI is a risk factor for CKD [3, 5, 6]. Intriguingly, even if the estimated glomerular filtration rate (eGFR) recovers to the level prior to AKI, AKI increases the risk of developing CKD [7–10]. This could be a consequence of AKI-induced loss of functioning nephrons, which, however, may stay undetected due to changes in muscle mass, renal reserve and glomerular hyperfiltration [11–13]. Alternatively, an increased risk of CKD following AKI could be due to an accelerated loss of nephrons after AKI, leading to a higher rate of eGFR decline following AKI. Studies describing changes in eGFR from before to after AKI are few and have shown inconsistent results [14–19]. An American cohort study found that AKI was not associated with changes in eGFR level and eGFR slope in individuals with CKD, while individuals without CKD had a drop in eGFR level of around 10% after AKI [14]. Other cohort studies have reported a higher rate of eGFR decline following AKI [15, 17, 18]. However, a lower rate of eGFR decline after AKI among individuals with CKD has also been reported [19]. Similarly, one study reported an increase in eGFR level after AKI among individuals with CKD when combining creatinine samples from both a clinical and research setting [17]. In addition to the relatively small sample sizes [15–19], the transportability of former studies is limited by data stemming from specific patient cohorts or non-population-based databases [14–19], and by primarily addressing eGFR changes in individuals with CKD [14, 15, 17, 19]. Knowledge about changes in kidney function from before to after AKI in an unselected population-based cohort is important for the general understanding of disease mechanisms and to plan follow-up after AKI. Therefore, we examined changes in eGFR level and eGFR slope from before to after first-time AKI in two general population cohorts stratified by baseline eGFR level (≥/<60 mL/min/1.73 m^2) using Danish population-based laboratory databases linked with health and administrative databases.

MATERIALS AND METHODS

Setting

This nationwide cohort study was conducted in Denmark, which had 4.6 million adult residents in 2018 [20]. Denmark has a universal healthcare system allowing for tax-funded access to general practitioners and specialized care, with the latter mainly being provided by hospitals [21]. The unique personal

identification number assigned to all Danish citizens at birth or upon immigration enables individual-level linkage of data across registries [22].

Blood samples performed in general practices, hospitals and other specialized care facilities in Denmark are analyzed at hospital-based laboratories, and test results are recorded in central databases [23, 24]. Information on pCr measurements was obtained from the Clinical Laboratory Information System Research Database (LABKA) [23], which contains laboratory information from blood samples from general practices and hospitals in the North and Central Denmark Regions since the 1990s, and the Register of Laboratory Results for Research (RLRR) [24], which contains nationwide laboratory information from blood samples taken in general practices or hospitals since 2013.

The study was approved by the Danish Data Protection Agency (record number 2015-57-0002) through registration at Aarhus University (record number 2016-051-000001/812). Ethics approval and informed consent are not required for registry-based observational studies in Denmark.

Participants

We identified individuals with a first-time laboratory-recorded AKI (see definition below) among adult Danish individuals with a recorded pCr measurement in LABKA and/or RLRR from 1 April 2010 through 2017. pCr measurements in this period were analyzed using standardized isotope dilution mass spectrometry, ensuring precise measurements with a low level of measurement error and no need for recalibration [25, 26]. We excluded measurements from individuals with kidney failure at the time of testing. Kidney failure was defined as a diagnosis of dependency on dialysis, a procedure code for dialysis due to CKD, previous kidney transplantation or two outpatient eGFR <15 mL/min/1.73 m^2 separated by at least 90 days. To be able to estimate eGFR level and eGFR slope, we restricted the analysis to individuals with three or more outpatient pCr measurements spanning at least 90 days at any time more than 7 days before AKI as well as three or more outpatient pCr measurements spanning at least 90 days from 90 days after AKI and onwards. Furthermore, we required that at least one of the pCr measurements before AKI was performed within a year of AKI as this was used to estimate baseline eGFR (see definition below). Individuals were divided into two main cohorts based on baseline eGFR being ≥/<60 mL/min/1.73 m^2. pCr measurements performed during the first 90 days after AKI were not included as this period is considered the point of transition from an acute to a chronic kidney condition [27].

Acute kidney injury

AKI was defined in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine criteria as: (i) an absolute increase of ≥26.5 μmol/L within 48 h; (ii) a relative increase of ≥1.5 times the lowest pCr within the last 7 days; or (iii) a relative increase of ≥1.5 times baseline. Baseline pCr was defined as the median outpatient pCr within the previous 8–365 days [28]. The urine output criteria for AKI were not incorporated due to a lack of data.

Covariates

We included information on comorbidity at the time of first AKI using information on in- or outpatient diagnoses and treatments within 10 years before AKI from the Danish National Patient Registry [29]. Additionally, we included information on prescriptions filled within 90 days before AKI from the Danish National Prescription Registry [30]. Information on sex and age was obtained from the Danish Civil Registration System [31].

Outcome

Participants were followed from the time of the first pCr measurement until the development of kidney failure, death, censoring or 31 December 2018, whichever came first.

The main outcome was eGFR as a function of time before and after AKI. eGFR was calculated from pCr, age and sex using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation assuming non-Black race [32]. Only outpatient measurements of pCr were included in the calculation of eGFR assuming a steady state, which may not be expected during hospitalization due to acute illness [27, 32].

Statistical analysis

We tabulated characteristics and follow-up information for individuals included and excluded due to insufficient pCr measurements. Characteristics included age, sex, baseline pCr, baseline eGFR, number of outpatient pCr measurements after AKI, follow-up time after AKI, and specific comorbidities and prescriptions at the time of first AKI. These were summarized as medians with interquartile range (IQR) for continuous variables, and as counts with proportions for categorical variables. We used cubic splines to plot median eGFR with IQR against time.

For each individual, we calculated the daily median eGFR if multiple outpatient measurements were performed and modeled eGFR as a function of time since AKI using two linear regression models: one based on measurements >7 days before AKI and one based on measurements >90 days after AKI (Fig. 1). Using the two regression models for each individual, we extrapolated eGFR to the time of AKI and calculated "change in eGFR level," "relative change in eGFR level" and "change in eGFR slope" from before to after AKI. The "change in eGFR level" was defined as the extrapolated eGFR level at the time of AKI (equivalent to the intercept) from the regression using data after AKI minus the extrapolated eGFR level at the time of AKI from the regression using data before AKI. The "relative change in eGFR level" was defined as the "change in eGFR level" divided by the extrapolated eGFR level at the time of AKI from the regression before AKI. The "change in eGFR slope" was defined as the slope of the regression after AKI minus the slope of the regression before AKI. For each cohort and subcohort, estimates were presented as medians with IQR. A "rapid decline in eGFR" was defined as a decline in eGFR of more than 5 mL/min/1.73 m^2/year following AKI in accordance with the KDIGO definition [27].

Additional analyses were conducted to examine the robustness of our findings. First, a sensitivity analysis including patients with two or more pCr tests before and after AKI was conducted. Second, individuals were stratified by age groups (<40, 40–59, 60–79 and ≥80 years) and eGFR category (<45, 45–59, 60–89 and ≥90 mL/min/1.73 m^2). Third, the two main cohorts with baseline eGFR ≥/<60 mL/min/1.73 m^2 were stratified by AKI stage, location, setting and calendar period (2010–13, 2014–15 and 2016–17). The AKI stage was defined in accordance with the KDIGO criteria based on changes in pCr or initiation of renal replacement therapy [33]. AKI was categorized as being: (i) hospital-acquired if the pCr measurement qualifying for AKI was taken during an admission excluding the first day of admission; (ii) community-acquired

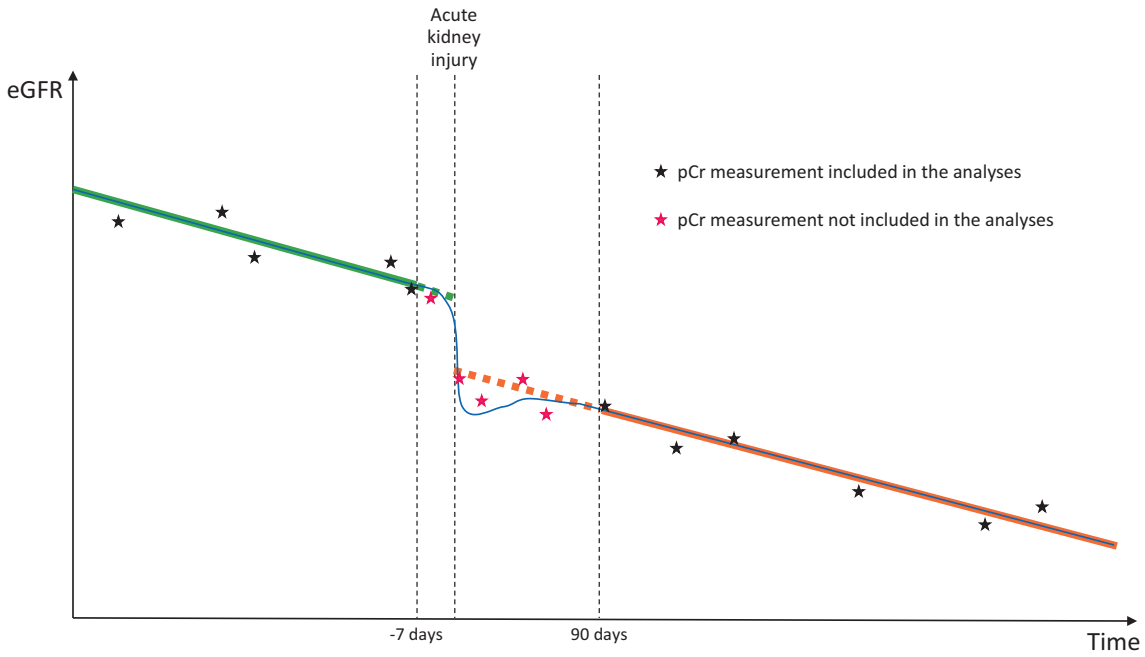


Figure 1: Conceptual model. The blue line represents a hypothetical continuously measured eGFR trajectory. The solid green line represents the eGFR trajectory before AKI and the dotted green line the extrapolated eGFR trajectory from the period before AKI. The solid orange line represents the eGFR trajectory after AKI and the dotted orange line the extrapolated eGFR from the period following AKI.

if the pCr measurement qualifying for AKI was taken on a day without admission or on the first day of admission, since changes at admission most likely would reflect AKI prior to admission; (iii) surgery-related if occurring within 7 days after surgery; and (iv) sepsis-related if occurring during an admission with a diagnosis of sepsis. As groups were not mutually exclusive, each AKI event could be counted in more than one group.

All statistical analyses and visualizations were made using R version 4.0.4 [34] and the data.table [35] and Tidyverse [36] packages.

RESULTS

We identified 265 161 individuals with first-time AKI of whom 98 072 had three or more outpatient pCr measurements before and after AKI, making them eligible for further analyses (Fig. 2 and Supplementary data, Table S1). The included individuals were younger (median ages 71 vs 74 years), had a higher prevalence of most comorbidities, and a higher proportion with stage 1 AKI and a lower proportion with stage 3 AKI compared with those not included (Supplementary data, Table S1). Furthermore, included individuals had a substantially lower 1-year mortality (3% vs 33%) and consequently longer follow-up and more outpatient pCr measurements after AKI. Among included individuals, 64 805 (66%) had a baseline eGFR ≥60 mL/min/1.73 m^2 and 33 267 (34%) had a baseline eGFR <60 mL/min/1.73 m^2 (Fig. 2).

Characteristics

Individuals with a baseline eGFR ≥60 mL/min/1.73 m^2 had a median age of 68 years (IQR 58–77) and one-third were women (Table 1). The median baseline eGFR was 87 mL/min/1.73 m^2 (IQR 74–100). Overall, there was a high prevalence of comorbidities and prescription drug use, with hospital-diagnosed

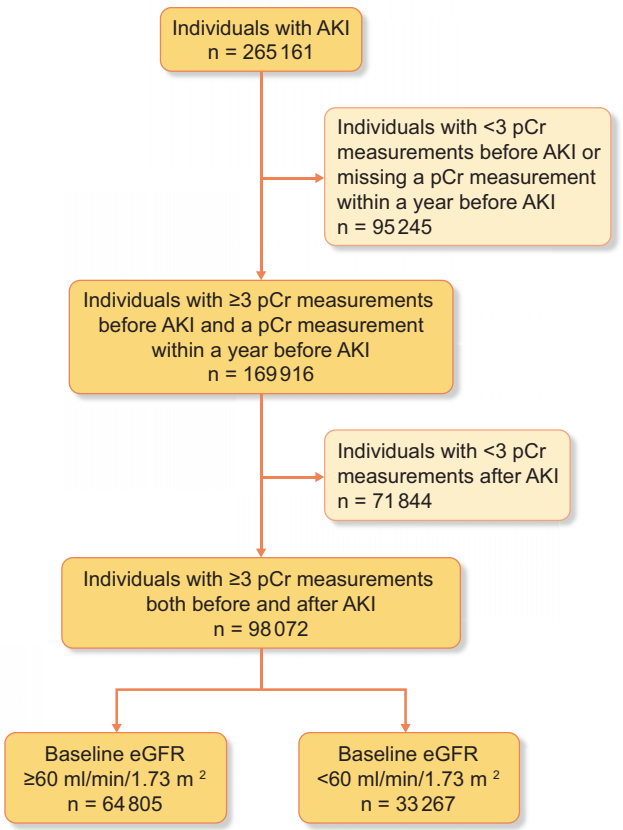


Figure 2: Flow chart of individuals with AKI. Baseline eGFR was defined as the median outpatient eGFR within the previous 8-365 days.

Table 1: Characteristics of individuals with first-time AKI.

	Baseline eGFR ≥60 mL/min/1.73 m^2, *n* (%)	Baseline eGFR <60 mL/min/1.73 m^2, *n* (%)
Number of individuals	64 805	33 267
Female	22 476 (35)	26 009 (78)
Age (years), median (IQR)	68 (58–77)	76 (70–83)
pCr at index (μmol/L), median (IQR)	110 (89–134)	173 (144–216)
Baseline eGFR (mL/min/1.73 m^2), median (IQR)	87 (74–100)	46 (36–53)
No. of outpatient pCr measurements before index, median (IQR)	8 (5–13)	9 (6–16)
AKI stage		
Stage 1	49 927 (77)	26 093 (78)
Stage 2	10 257 (16)	4254 (13)
Stage 3	4621 (7.1)	2920 (8.8)
Comorbidity (within prior 10 years)		
Hospital-diagnosed hypertension	25 517 (39)	17 932 (54)
Atrial fibrillation/flutter	9432 (15)	8999 (27)
Ischemic heart disease	11 749 (18)	10 838 (33)
Heart failure	6737 (10)	7524 (23)
Stroke	5196 (8.0)	3795 (11)
Kidney disease[a]	2647 (4.1)	3988 (12)
Asthma	3110 (4.8)	1096 (3.3)
Chronic obstructive pulmonary disease	8441 (13)	4850 (15)
Chronic liver disease	3087 (4.8)	635 (1.9)
Connective tissue disease	5538 (8.5)	2104 (6.3)
Cancer	15 666 (24)	9050 (27)
Overweight or obesity	6820 (11)	2931 (8.8)
Diabetes[b]	16 725 (26)	11 426 (34)
Prescription drug use (within the prior 90 days)		
ACE-Is/ARBs	26 973 (42)	18 700 (56)
Thiazide or loop diuretics	25 593 (39)	18 525 (56)
Calcium channel blockers	15 508 (24)	10 974 (33)
NSAIDs	10 573 (16)	4438 (13)
Antibiotics	17 586 (27)	9534 (29)
Statins	19 843 (31)	14 133 (42)
Cytostatics	2904 (4.5)	826 (2.5)
Follow-up information		
Duration of follow-up, years, median (IQR)	3.2 (2.1–4.7)	2.8 (1.8–4.3)
No. of outpatient pCr measurements after index, median (IQR)	12 (7–21)	13 (8–22)
Deaths within 1 year after AKI	1731 (2.7)	1326 (4.0)
Deaths within 5 years after AKI	16 754 (26)	13 241 (40)
Kidney failure within 1 year after AKI	30 (0.0)	252 (0.8)
Kidney failure within 5 years after AKI	282 (0.4)	1442 (4.3)

[a]Including diabetic nephropathy, hypertensive kidney disease, glomerular disease, tubulo-interstitial disease and congenital kidney disease
[b]Based on both diagnosis and prescription drug use.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drug.

hypertension and the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers being the most common. The median number of outpatient pCr measurements before first AKI was 8 (IQR 5–13). The median follow-up after first AKI was 3.2 years (IQR 2.1–4.7), and the median number of outpatient pCr measurements was 12 (IQR 7–21).

Individuals with a baseline <60 mL/min/1.73 m^2 had a median age of 76 years (IQR 70–83), and three-quarters were women. The median baseline eGFR was 46 mL/min/1.73 m^2 (IQR 36–53). There was a high prevalence of comorbidities and accordingly a high proportion of prescription drug users. The median number of outpatient pCr measurements before first AKI was 9 (IQR 6–16). The median follow-up after first AKI was 2.8 years (IQR 1.8–4.3), and the median number of outpatient pCr measurements was 13 (IQR 8–22).

Outpatient eGFR level and eGFR slope before and after AKI

In both cohorts, median eGFR decreased in the period before AKI, sharply declined at the time of AKI and subsequently improved, although it did not fully return to the level before AKI (Fig. 3).

In the cohort with baseline eGFR ≥60 mL/min/1.73 m^2, the median difference in absolute eGFR level from before to after AKI was −5.6 mL/min/1.73 m^2 (IQR −16.1 to 1.8), which was equivalent to a median relative change in eGFR level of −6.1% (IQR −18.5 to 2.1) (Fig. 4 and Table 2). The median slope of eGFR was −0.7 mL/min/1.73 m^2/year (IQR −2.9 to 1.5) before AKI and −0.9 mL/min/1.73 m^2/year (IQR −4.2 to 1.9) after AKI, corresponding to a median difference in slope of −0.4 mL/min/1.73 m^2/year (IQR −5.5 to 4.4).

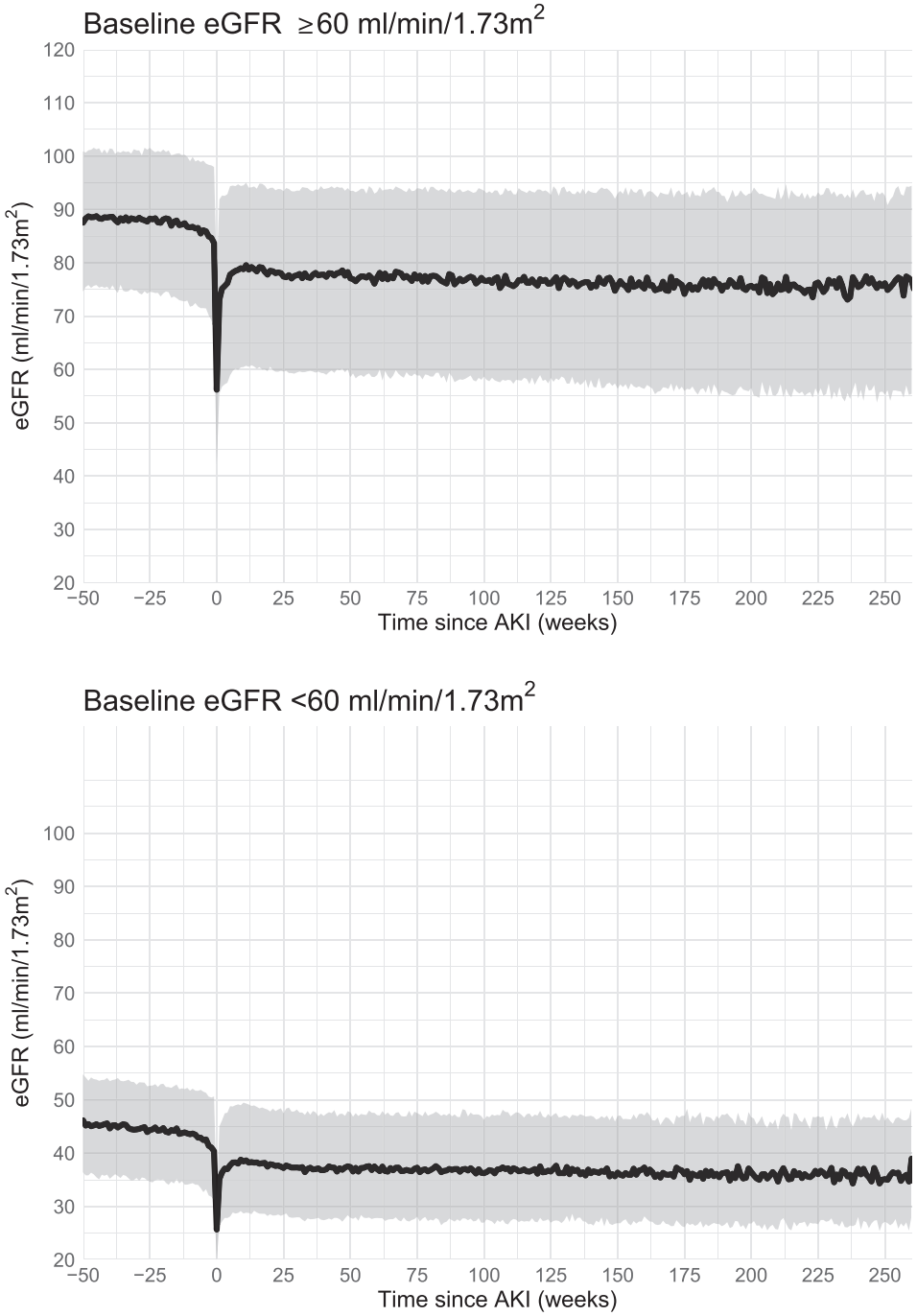


Figure 3: Median eGFR with IQR according to time before and after AKI.

Among individuals with a baseline eGFR <60 mL/min/1.73 m^2, the median difference in absolute eGFR level from before to after AKI was −2.2 mL/min/1.73 m^2 (IQR −9.2 to 4.3), which was equivalent to a median relative change in eGFR level of −5.5% (IQR −21.3 to 11.0), and the median difference in eGFR slope was 1.5 mL/min/1.73 m^2/year (IQR −2.9 to 6.5) (Fig. 4 and Table 2).

Findings from the sensitivity analysis including patients with two or more pCr measurements before and after AKI were similar to the primary analysis (Supplementary data, Tables S2 and S3).

Additional analyses

Stratification by age groups and eGFR category

In the cohort with baseline eGFR ≥60 mL/min/1.73 m^2, we observed consistently lower eGFR levels and faster rates of eGFR decline following AKI across all age groups (Supplementary data, Table S4). Among individuals with a baseline eGFR <60 mL/min/1.73 m^2, changes in eGFR were similar across age groups and comparable to the changes in the overall cohort (Supplementary data, Table S5).

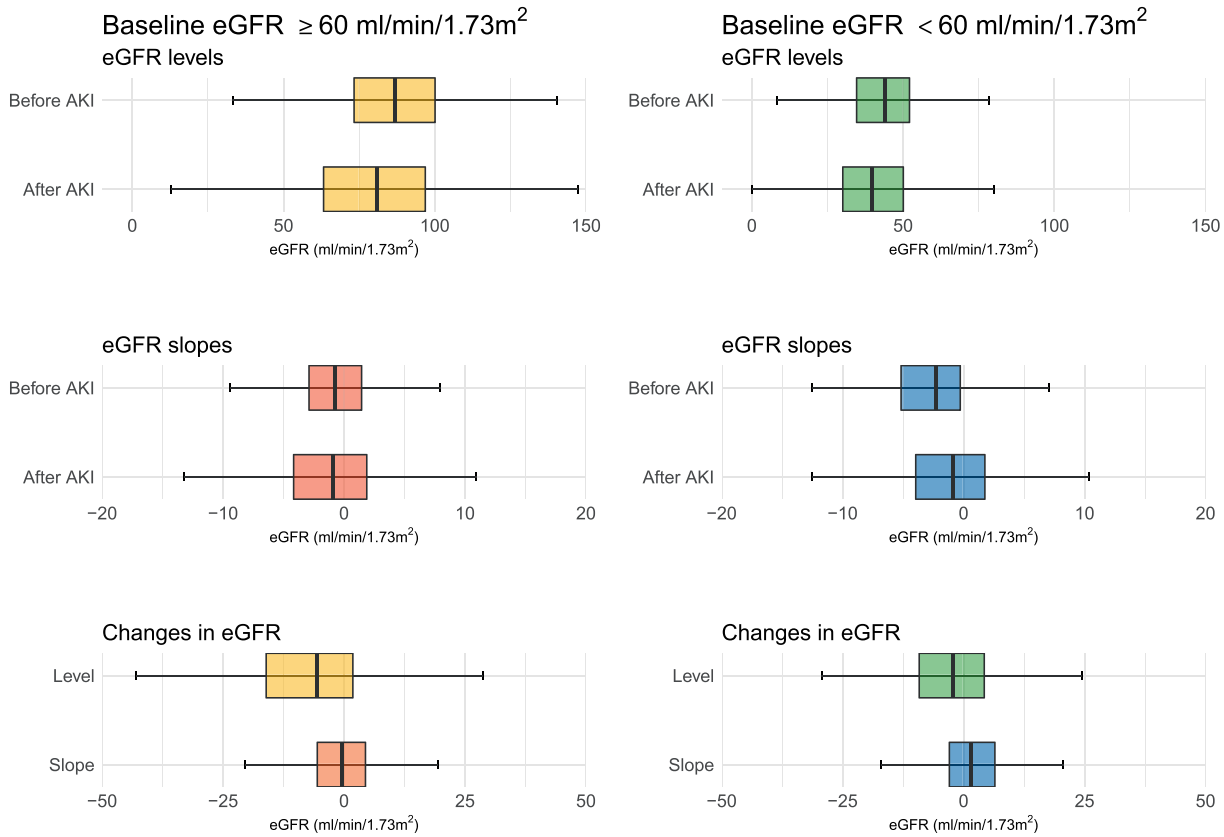


Figure 4: Distribution of extrapolated eGFR levels and eGFR slopes before and after AKI by baseline eGFR.

Table 2: Extrapolated eGFR levels and eGFR slopes before and after AKI by baseline eGFR.

Baseline eGFR ≥60 mL/min/1.73 m^2 (n = 64 805)	
Extrapolated eGFR level at the time of AKI (regression before AKI), mL/min/1.73 m^2, median (IQR)	86.7 (73.3–100.1)
Extrapolated eGFR level at the time of AKI (regression after AKI), mL/min/1.73 m^2, median (IQR)	81.0 (63.2–96.9)
Change in eGFR level, mL/min/1.73 m^2, median (IQR)	−5.6 (−16.1 to 1.8)
Relative change in eGFR level, %, median (IQR)	−6.1 (−18.5 to 2.1)
eGFR slope before AKI, mL/min/1.73 m^2/year, median (IQR)	−0.7 (−2.9 to 1.5)
eGFR slope after AKI, mL/min/1.73 m^2/year, median (IQR)	−0.9 (−4.2 to 1.9)
Change in eGFR slope, mL/min/1.73 m^2/year, median (IQR)	−0.4 (−5.5 to 4.4)
Rapid decline in eGFR before AKI (>5 mL/min/1.73 m^2/year), n (%)	9 396 (14.5)
Rapid decline in eGFR after AKI (>5 mL/min/1.73 m^2/year), n (%)	13 869 (21.4)
Baseline eGFR <60 mL/min/1.73 m^2 (n = 33 267)	
Extrapolated eGFR level at the time of AKI (regression before AKI), mL/min/1.73 m^2, median (IQR)	44.1 (34.6–52.1)
Extrapolated eGFR level at the time of AKI (regression after AKI), mL/min/1.73 m^2, median (IQR)	39.9 (30.1–50.1)
Change in eGFR level, mL/min/1.73 m^2, median (IQR)	−2.2 (−9.2 to 4.3)
Relative change in eGFR level, %, median (IQR)	−5.5 (−21.3 to 11.0)
eGFR slope before AKI, mL/min/1.73 m^2/year, median (IQR)	−2.3 (−5.2 to −0.3)
eGFR slope after AKI, mL/min/1.73 m^2/year, median (IQR)	−0.9 (−4.0 to 1.8)
Change in eGFR slope, mL/min/1.73 m^2/year, median (IQR)	1.5 (−2.9 to 6.5)
Rapid decline in eGFR before AKI (>5 mL/min/1.73 m^2/year), n (%)	8651 (26.0)
Rapid decline in eGFR after AKI (>5 mL/min/1.73 m^2/year), n (%)	6715 (20.2)

When stratifying by baseline eGFR category all four cohorts showed a lower eGFR level following AKI (Supplementary data, Table S6). The cohort with eGFR ≥90 mL/min/1.73 m^2 had a steeper eGFR slope following AKI while the slope from the cohort with eGFR of 60–89 mL/min/1.73 m^2 was unchanged and the cohorts with eGFR 45–59 and <45 mL/min/1.73 m^2 both had an increase in eGFR slope comparable to that of the main cohort with eGFR <60 mL/min/1.73 m^2.

Stratification by AKI stage, location, setting and calendar period

The cohort with a baseline eGFR ≥60 mL/min/1.73 m^2 showed a consistently lower eGFR level following AKI across stage, location and setting (Supplementary data, Table S7). The changes in eGFR levels were −5.5 mL/min/1.73 m^2 (IQR −15.7 to 1.8), −5.4 mL/min/1.73 m^2 (IQR −16.7 to 2.2) and −6.7 mL/min/

1.73 m^2 (IQR −19.0 to 1.6) for stage 1, 2 and 3, respectively. When stratifying by location, community-acquired AKI was associated with a change in eGFR level of −6.2 mL/min/1.73 m^2 (IQR −16.8 to 1.2) and a change in eGFR slope of −0.2 mL/min/1.73 m^2/year (IQR −5.3 to 4.8), while hospital-acquired AKI was associated with a change in eGFR level of −4.3 mL/min/1.73 m^2 (IQR −14.6 to 2.8) and a change in eGFR slope of −0.7 mL/min/1.73 m^2/year (IQR −5.9 to 3.8). Finally, sepsis- and surgery-related AKI were associated with similar changes in in eGFR level and eGFR slope.

In the cohort with a baseline eGFR <60 mL/min/1.73 m^2, stage 1, 2 and 3 AKI were associated with changes in eGFR levels of −2.1 mL/min/1.73 m^2 (IQR −8.8 to 4.3), −3.9 mL/min/1.73 m^2 (IQR −11.7 to 3.6) and −1.5 mL/min/1.73 m^2 (IQR −8.8 to 4.6), respectively (Supplementary data, Table S8). Community- and hospital-acquired AKI were associated with drops in eGFR level of −2.9 mL/min/1.73 m^2 (IQR −10.3 to 3.8) and −1.5 mL/min/1.73 m^2 (IQR −7.8 to 4.7), respectively. Changes in eGFR slope were similar across stages, locations and settings of AKI, with the largest change being associated with community-acquired AKI [2.1 mL/min/1.73 m^2/year (IQR −2.5 to 7.6)].

In both cohorts, the findings were consistent across calendar periods (Supplementary data, Tables S9 and S10).

Individuals with a rapid decline in eGFR after AKI

Individuals with a rapid decline in eGFR following AKI were marginally older, had slightly more comorbidities and had a shorter duration of follow-up, with a larger proportion of individuals developing kidney failure or dying within 1 and 5 years after AKI compared with the overall cohort of individuals with the same baseline eGFR (Supplementary data, Table S11).

DISCUSSION

In this nationwide population-based cohort study of long-term changes in kidney function related to AKI, we found that AKI was consistently associated with a drop in eGFR level when comparing the period after AKI with the period before. The size of the change in absolute eGFR level varied with baseline eGFR and was largest in the cohort with a baseline eGFR ≥60 mL/min/1.73 m^2; however, the relative changes in eGFR level were similar in the cohorts with baseline eGFR ≥/<60 mL/min/1.73 m^2. Moreover, in the cohort with eGFR ≥60 mL/min/1.73 m^2, AKI was associated with a decrease in eGFR slope, while in the cohort with a baseline eGFR <60 mL/min/1.73 m^2, AKI was associated with an increase in eGFR slope.

The high-quality Danish registries with complete follow-up on all Danish residents allowed us to examine this large population-based cohort of individuals with a first-time recorded AKI. However, some limitations need consideration. First, to allow for the estimation of individual-level regressions before and after AKI, we restricted to individuals with three or more outpatient pCr measurements more than 90 days apart before and after AKI. This was reflected by differences in length of follow-up, the number of outpatient pCr measurements following AKI and mortality after AKI when comparing individuals included in the study with those not included (Supplementary data, Table S1). However, findings were consistent when expanding the cohort to individuals with two or more outpatient measurements (Supplementary data, Table S3). Consequently, our findings apply to individuals who survive to have repeated outpatient pCr measurements before and after AKI. Second, we used linear regression to model eGFR before and after AKI. We compared eGFR levels and eGFR slopes before and after AKI from the same individual. Therefore, confounders should be balanced at the time of AKI. Another approach could have been to use a mixed effects model with fixed and random effects. This would have allowed for confounder adjustment in a direct comparison between subcohorts of individuals with AKI. However, a mixed effects model was not applicable as model assumptions were not appropriately fulfilled. Additionally, similar to the linear regression model used, a mixed model would not have accounted for the selection of individuals who survive to have repeated outpatient pCr measurements after AKI. This may vary from subcohort to subcohort and would influence the changes in eGFR from before to after AKI, thus obscuring the comparison. Third, as data on pCr were collected as a part of routine clinical practice, certain conditions or groups of individuals may be overrepresented while others may be underrepresented. This could be the case for young healthy adults without three or more pCr measurements or missing an outpatient baseline pCr measurement at the time of AKI. Finally, in line with current practice in Denmark, we used the CKD-EPI formula for estimating eGFR from pCr. CKD stage classification can be influenced by the choice of formula, which has been shown both when comparing CKD-EPI with the Modification of Diet in Renal Disease and the eGFR equations without race [37–39]. This should be considered when comparing results across settings.

Our study extends the findings from prior smaller studies and contributes new knowledge on the changes in eGFR from before to after AKI in an unselected population-based cohort. We report a drop in eGFR level after AKI in the two main cohorts with baseline eGFR ≥/<60 mL/min/1.73 m^2. These findings are comparable to findings from previous studies [14, 19]. However, discrepancies exist as studies on individuals with CKD found that AKI was not associated with changes in eGFR level [14] or even a rise in eGFR level [17]. In addition to the drop in eGFR level, we found a higher median rate of eGFR decline after AKI compared with before in individuals with a baseline eGFR ≥60 mL/min/1.73 m^2. There is a paucity of studies describing the change in slope from before to after AKI in unselected individuals with eGFR ≥60 mL/min/1.73 m^2. However, our reported decrease in eGFR slope after AKI aligns with the reported higher rate of eGFR decline after AKI in individuals with an eGFR <90 mL/min/1.73 m^2 after coronary angiography [18]. For individuals with baseline eGFR <60 mL/min/1.73 m^2, we found a lower median rate of eGFR decline after AKI compared with before AKI. Similarly, a Belgian study reported a lower rate of eGFR decline in individuals with CKD after AKI [19], while an American study reported a stable eGFR from 1 year before to 5 years after AKI [14]. Other studies on individuals with CKD report a higher rate of eGFR decline following AKI [15, 17]. This discrepancy may be explained by differences in cohorts, causes and definitions of AKI. Prior studies have used research cohorts of individuals with CKD [15, 17], relied on diagnostic coding for AKI identification [14], only included in-hospital AKI [17] or did not require pCr measurements following AKI, and may thereby have incomplete data on changes in eGFR [14, 15, 17]. The increase in eGFR slope after AKI in the cohort with baseline eGFR <60 mL/min/1.73 m^2 might be explained by the exclusion of individuals dying shortly after AKI without having repeated outpatient pCr measurements. Thus, 1-year mortality among individuals included in this study was 3%, while 1-year mortality among all individuals with first-time AKI was 33%. The size of eGFR decline after hospital discharge has been shown to be associated with the risk of death and the requirement for chronic dialysis [16]. Thus, individuals with the most pronounced decline in eGFR might not survive to have repeated outpatient pCr measurements and could therefore be

underrepresented in this study of individuals who survive to have repeated outpatient measurements after AKI.

In conclusion, first-time AKI was associated with changes in eGFR level and eGFR slope in individuals with repeated outpatient pCr measurements before and after AKI. In the cohort with a baseline eGFR ≥60 mL/min/1.73 m^2, first-time AKI was associated with both a drop in eGFR level and a decrease in eGFR slope when comparing the period following AKI with the period before AKI. In individuals with a baseline eGFR <60 mL/min/1.73 m^2, first-time AKI was similarly associated with a drop in eGFR level but also an increase in eGFR slope. Our findings provide new insight into AKI in a population-based setting and emphasize that while AKI might be considered a short-term condition, it is associated with a sustained drop in eGFR level and perhaps also long-term changes in eGFR slope in those who survive to have repeated pCr measurements following AKI. This emphasizes the importance of clinical awareness and continued research in the prevention, treatment and follow-up of individuals with AKI.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

AUTHORS' CONTRIBUTIONS

S.K.J., U.H.-J., S.V.V., H.G., H.B., D.N. and C.F.C. planned and designed the study. All authors participated in the interpretation of the data. S.K.J reviewed the literature, conducted the statistical analyses and wrote the initial manuscript. All authors critically reviewed the manuscript and approved the final version for submission. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

FUNDING

The study was funded by Aarhus University, the A.P. Moller Foundation (grant number 19-L-0332), the Health Research Foundation of Central Denmark Region, the Independent Research Fund Denmark (grant number 0134-00407B) and the Novo Nordisk Foundation (grant number NNF20OC0065973). The funding sources did not influence the study.

DATA AVAILABILITY STATEMENT

The data underlying this article were provided by a third party. Requests to access the databases used in this study from researchers at certified Danish research institutions may be sent to the Danish Health Data Authority by e-mail to forskerservice@sundhedsdata.dk.

CONFLICT OF INTEREST STATEMENT

The authors have no personal conflicts of interest to declare regarding this study. S.K.J., U.H.-J., S.V.V. and C.F.C. have not received any personal fees, grants, travel grants or teaching grants from companies. H.B. has received a research grant from Glaxo Smith Kline and Vifor Pharma (paid to institution) and has received consultancy fees and/or speaker honorarium from Vifor Pharma, AstraZeneca, Galapagos, Alexion, MSD and Novo Nordisk, as well as support for attending meetings by Novartis and AstraZeneca. He serves as a member of a working group established by the Danish Health Authority and the Danish Society of Nephrology. The departments of Clinical Epidemiology, Biomedicine, Renal Medicine and Intensive Care, respectively, are involved in studies with funding from various companies in the form of research grants to (and administered by) Aarhus University or Aarhus University Hospital. None of these grants is related to the present study. D.N. serves as the UK Kidney Association Director of Informatics Research. H.G. has had conference attendance booked and paid for by Baxter A/S.

REFERENCES

1. Kellum JA, Lameire N, Aspelin P *et al*. Notice. *Kidney Int Suppl* 2012;**2**:1–138.
2. Hoste EA, Schurgers M. Epidemiology of acute kidney injury: how big is the problem? *Crit Care Med* 2008;**36**:S146–51. https://doi.org/10.1097/CCM.0b013e318168c590
3. Goldstein SL, Jaber BL, Faubel S *et al*. AKI transition of care: a potential opportunity to detect and prevent CKD. *Clin J Am Soc Nephrol* 2013;**8**:476–83. https://doi.org/10.2215/CJN.12101112
4. Susantitaphong P, Cruz DN, Cerda J *et al*. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol* 2013;**8**:1482–93. https://doi.org/10.2215/CJN.00710113
5. Schiffl H, Fischer R. Five-year outcomes of severe acute kidney injury requiring renal replacement therapy. *Nephrol Dial Transplant* 2008;**23**:2235–41. https://doi.org/10.1093/ndt/gfn182
6. Jones J, Holmen J, De Graauw J *et al*. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am J Kidney Dis* 2012;**60**:402–8. https://doi.org/10.1053/j.ajkd.2012.03.014
7. Patel SS, Palant CE, Mahajan V *et al*. Sequelae of AKI. *Best Pract Res Clin Anaesthesiol* 2017;**31**:415–25. https://doi.org/10.1016/j.bpa.2017.08.004
8. Chawla LS, Eggers PW, Star RA *et al*. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014;**371**:58–66. https://doi.org/10.1056/NEJMra1214243
9. Hsu C-y. Yes, AKI truly leads to CKD. *J Am Soc Nephrol* 2012;**23**:967–9. https://doi.org/10.1681/ASN.2012030222
10. Bucaloiu ID, Kirchner HL, Norfolk ER *et al*. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012;**81**:477–85. https://doi.org/10.1038/ki.2011.405
11. Prowle JR, Kolic I, Purdell-Lewis J *et al*. Serum creatinine changes associated with critical illness and detection of persistent renal dysfunction after AKI. *Clin J Am Soc Nephrol* 2014;**9**:1015–23. https://doi.org/10.2215/CJN.11141113
12. Liu KD, Thompson BT, Ancukiewicz M *et al*. Acute kidney injury in patients with acute lung injury: impact of fluid accumulation on classification of acute kidney injury and associated outcomes. *Crit Care Med* 2011;**39**:2665–71. https://doi.org/10.1097/CCM.0b013e318228234b
13. Thomas DM, Coles GA, Williams JD. What does the renal reserve mean? *Kidney Int* 1994;**45**:411–6. https://doi.org/10.1038/ki.1994.53
14. Amdur RL, Chawla LS, Amodeo S *et al*. Outcomes following diagnosis of acute renal failure in U.S. veterans: focus on acute tubular necrosis. *Kidney Int* 2009;**76**:1089–97. https://doi.org/10.1038/ki.2009.332
15. Asar Ö, Ritchie J, Kalra PA *et al*. Short-term and long-term effects of acute kidney injury in chronic kidney disease patients: a longitudinal analysis. *Biom J* 2016;**58**:1552–66. https://doi.org/10.1002/bimj.201500270

16. Haines RW, Powell-Tuck J, Leonard H *et al*. Long-term kidney function of patients discharged from hospital after an intensive care admission: observational cohort study. *Sci Rep* 2021;**11**:9928. https://doi.org/10.1038/s41598-021-89454-3
17. Hsu RK, Hsu C-y, McCulloch CE *et al*. Research-based versus clinical serum creatinine measurements and the association of acute kidney injury with subsequent kidney function: findings from the Chronic Renal Insufficiency Cohort study. *Clin Kidney J* 2019.
18. James MT, Ghali WA, Tonelli M *et al*. Acute kidney injury following coronary angiography is associated with a long-term decline in kidney function. *Kidney Int* 2010;**78**:803–9. https://doi.org/10.1038/ki.2010.258
19. D'Hoore E, Neirynck N, Schepers E *et al*. Chronic kidney disease progression is mainly associated with non-recovery of acute kidney injury. *J Nephrol* 2015;**28**:709–16. https://doi.org/10.1007/s40620-015-0181-5
20. *Statistics Denmark [homepage on the Internet]. Population figures. Available from*: https://www.dst.dk/da/Statistik/emner/borgere/befolkning/befolkningstal (24 November 2022, date last accessed).
21. Schmidt M, Schmidt SAJ, Adelborg K *et al*. The Danish health care system and epidemiological research: from health care contacts to database records. *Clin Epidemiol* 2019;**11**:563–91. https://doi.org/10.2147/CLEP.S179083
22. Pedersen CB. The Danish Civil Registration system. *Scand J Public Health* 2011;**39**:22–5. https://doi.org/10.1177/1403494810387965
23. Grann AF, Erichsen R, Nielsen AG *et al*. Existing data sources for clinical epidemiology: the clinical laboratory information system (LABKA) research database at Aarhus University, Denmark. *Clin Epidemiol* 2011;**3**:133–8. https://doi.org/10.2147/CLEP.S17901
24. Arendt JFH, Hansen AT, Ladefoged SA *et al*. Existing data sources in clinical epidemiology: laboratory information system databases in Denmark. *Clin Epidemiol* 2020;**12**:469–75. https://doi.org/10.2147/CLEP.S245060
25. Gammelager H. *Prognosis after acute kidney injury among intensive care patients [Dissertation]*. Accra: Aarhus University Department of Clinical Epidemiology, Aarhus University Hospital, Denmark, 2013.
26. Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple! *Nephron* 2017;**136**:302–8. https://doi.org/10.1159/000469669
27. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013;**3**:1–150.
28. Graversen HV, Jensen SK, Vestergaard SV *et al*. Defining baseline creatinine for identification of acute kidney injury in population-based laboratory databases - A Danish nationwide cohort study. *Kidney360* 2021;**3**:232–41 10.34067/KID.0006082021. https://doi.org/10.34067/KID.0006082021
29. Schmidt M, Schmidt SA, Sandegaard JL *et al*. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;**7**:449–90. https://doi.org/10.2147/CLEP.S91125
30. Pottegård A, Schmidt SAJ, Wallach-Kildemoes H *et al*. Data resource profile: the Danish National Prescription Registry. *Int J Epidemiol* 2017;**46**:798–798f.
31. Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;**29**:541–9. https://doi.org/10.1007/s10654-014-9930-3
32. Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006
33. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl* 2012;**2**:1–138.
34. *R: A language and environment for statistical computing [homepage on the Internet]*. R Foundation for Statistical Computing, Vienna, Austria. Available from: https://www.R-project.org/.
35. Dowle M, Srinivasan A. data.table: extension of 'data.frame'. 2022. https://r-datatable.com, https://Rdatatable.gitlab.io/data.table, https://github.com/Rdatatable/data.table (24 November 2022, date last accessed).
36. Wickham H, Averick M, Bryan J *et al*. Welcome to the Tidyverse. *J Open Source Software* 2019;**4**:1686. https://doi.org/10.21105/joss.01686
37. Rocco MV, Chapman A, Chertow GM *et al*. Chronic kidney disease classification in systolic blood pressure intervention trial: comparison using Modification of Diet in Renal Disease and CKD-Epidemiology Collaboration definitions. *Am J Nephrol* 2016;**44**:130–40. https://doi.org/10.1159/000448722
38. Vestergaard SV, Heide-Jørgensen U, Birn H *et al*. Effect of the refitted race-free eGFR formula on the CKD prevalence and mortality in the Danish population. *Clin J Am Soc Nephrol* 2022;**17**:426–8. https://doi.org/10.2215/CJN.14491121
39. Inker LA, Eneanya ND, Coresh J *et al*. New creatinine- and cystatin C-based equations to estimate GFR without race. *N Engl J Med* 2021;**385**:1737–49. https://doi.org/10.1056/NEJMoa2102953