Harmonization of epidemiology of acute kidney injury and acute kidney disease produces comparable findings across four geographic populations

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There is substantial variability in the reported incidence and outcomes of acute kidney injury (AKI). The extent to which this is attributable to differences in source populations versus methodological differences between studies is uncertain. We used 4 population-based datasets from Canada, Denmark, and the United Kingdom to measure the annual incidence and prognosis of AKI and acute kidney disease (AKD), using a homogenous analytical approach that incorporated KDIGO creatinine-based definitions and subsets of the AKI/AKD criteria. The cohorts included 7 million adults ≥18 years of age between 2011 and 2014; median age 59-68 years, 51.9-54.4% female sex. Age- and sex-standardised incidence rates for AKI or AKD were similar between regions and years; range 134.3-162.4 events/10,000 person years. Among patients who met either KDIGO 48-hour or 7-day AKI creatinine criteria, the standardised 1-year mortality was similar (30.4%-38.5%) across the cohorts, which was comparable to standardised 1-year mortality among patients who met AKI/AKD criteria using a baseline creatinine within 8-90 days prior (32.0%-37.4%). Standardised 1-year mortality was lower (21.0%-25.5% across cohorts) among patients with AKI/AKD ascertained using a baseline creatinine >90 days prior. These findings illustrate that the incidence and prognosis of AKI and AKD based on KDIGO criteria are consistent across 3 high-income countries when capture of laboratory tests is complete, creatinine-based definitions are implemented consistently within but not beyond a 90-day period, and adjustment is made for population age and sex. These approaches should be consistently applied to improve the generalizability and comparability of AKI research and clinical reporting.

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Over the past decade, significant progress has been made in the understanding of the epidemiology of acute kidney injury (AKI), including its incidence and outcomes.[1–4] An important facilitator of this process has been the uptake of consensus criteria for defining AKI, most recently using the Kidney Disease: Improving Global Outcomes (KDIGO) definitions.[5] The KDIGO criteria have increased care provider awareness, research, and public appreciation of AKI as a global health problem. Consensus reports of the Acute Dialysis Quality Initiative (ADQI) have further led to recognition of the importance of acute kidney disease (AKD), based on changes in kidney function developing over 90 days, to bridge the conceptual models of AKI and chronic kidney disease (CKD).[6,7]

Despite this progress, uncertainty remains about fundamental elements of AKI and AKD epidemiology. Several challenges to applying the KDIGO AKI and AKD criteria for epidemiologic research, and in clinical applications such as e-alert systems, are well recognized.[8,9] These include the following: the selection of timeframes and measures for establishing an individual's baseline kidney function; the question of whether small absolute changes in creatinine level (0.3 mg/dl) over 48 hours should be considered equivalent to larger relative changes (1.5-fold) over 7 days; and the implications of including changes in kidney function detected over 90 days, as represented by the AKD criteria. Meta-analysis of studies in which the KDIGO definition was applied

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demonstrated very high heterogeneity in estimates of the burden of AKI, with marked differences in incidence ranging from <10% to >40% across hospital-based cohorts,[1] and mortality rates for AKI based on the KDIGO definition that vary more than 3-fold across studies.[1,2] What remains unclear is the extent to which the variability in reported incidence and outcome of AKI relates to differences in the source populations of cohorts versus methodological differences among studies, including the application of KDIGO definitions. These uncertainties currently undermine the ability to make generalizable conclusions about the current clinical burden of AKI/AKD and to develop standardized recommendations about how AKI/AKD identification should be operationalized in research and clinical practice. A recent KDIGO controversies conference acknowledged these issues, calling for further work to reconcile these uncertainties and enhance our understanding of the epidemiology of AKD, including AKI.[10]

In this study, we used whole-population data covering 7 million residents in Canada, Denmark, and the UK to measure the incidence and prognosis of AKI and AKD using a homogenous analytical approach incorporating KDIGO definitions. We sought to determine whether harmonized analytical approaches would produce comparable findings for AKI incidence and mortality across 4 independent cohorts from high-income countries with universal access to care and complete population ascertainment of kidney function measurements.

METHODS

Data sources

Complete population community and hospital laboratory data were extracted from a 5-year period (2010–2014) from 4 regions with a combined population of 7 million inhabitants: Alberta (Canada), northern Denmark, Grampian (UK), and Tayside (UK). These populations, served by socialized health systems, were selected for their ability to provide integrated data on isotope-dilution mass spectrometry (IDMS) calibrated creatinine measurements for all residents within their source population, irrespective of clinical setting (hospital inpatient, outpatient specialty, community). Waivers of consent were provided by research ethics boards for use of health data for each region. Use of Alberta data was approved by the Conjoint Health Research Ethics Board (CHREB) of the University of Calgary (ID# REB20-0970)—including waiver of consent for use of previously collected health data in accordance with Alberta Health Information Act. Use of data from northern Denmark (the north and central regions in Denmark) was reported to the Danish Data Protection Agency through registration at Aarhus University (record number 2016-051-000001/812). According to Danish legislation, no ethical approval was required. For Tayside, data provision and linkage were carried out by the University of Dundee Health Informatics Centre (HIC, https://www.dundee.ac.uk/hic), with analysis of anonymized data performed in an ISO27001 and Scottish Government accredited secure safe haven. HIC standard operating procedures have been reviewed and approved by the National Health Service East of Scotland Research Ethics Service, and consent for this study was obtained from the National Health Service Fife Caldicott Guardian. Use of Grampian unconsented, pseudonymized, routinely collected health data were provided by North West Research Ethics Committee (19/NW/0552), Grampian Caldicott Guardian, and National Health Service Research and Development. All cohorts have been used in previous epidemiologic research on kidney disease, with additional details provided in previous publications.[11–19]

Data processing and harmonization

Datasets for each region were prepared using a common analytical protocol and statistical code for both data preparation and analysis (available in the Supplementary Stata Analysis Code). The code was applied for analysis within each region. To avoid privacy risks associated with movement of individual-level patient data between regions, the analytical code was designed for each center to produce output files of aggregated data only, which were then sent to the coordinating center (University of Aberdeen) for pooling and final reporting. All creatinine results for each individual within each underlying population were extracted for analyses. Creatinine values that were recorded as missing or as a non-value (e.g., "sample inadequate," "sample error"), or were outside the limits for detection of the analyser, were excluded.

Study population

All adult (age ≥ 18 years) residents within each population region with at least one creatinine test during 2009–2014 were included. Creatinine tests taken after initiation of long-term kidney replacement therapy (dialysis or transplant) for established kidney failure were excluded, as established by kidney replacement therapy registry data for each site.

Identification of AKI and AKD subsets

Shared statistical code was used to determine the subsets of patients that had AKI/AKD, based on KDIGO criteria (the Aberdeen definition). This code has been validated previously and used in AKI studies and is provided in the Supplementary Stata Analysis Code.[17,20] Four definition subsets (Box 1) of AKI/AKD were evaluated, alone and in combination. Subsets (1) and (2) comprise patients whose fulfillment of KDIGO AKI criteria could be ascertained directly from existing blood tests within the timeframes specified by the KDIGO AKI definition; subsets (3) and (4) comprise patients who fulfilled KDIGO criteria for AKD *without* observed AKI, or with *presumed* AKI, based on ascertainment using longer periods of time from the baseline creatinine measurement.[10]

AKI/AKD were further categorized based on the following considerations: (i) the highest KDIGO AKI stage obtained over 90 days from AKI onset; (ii) kidney recovery (to within 50% of baseline by 90 days from onset); and (iii) presence of prior AKI within the previous year.

Box 1 | Definitions of AKI and AKD subsets

Subsets 1 and 2: direct ascertainment of AKI according to KDIGO creatinine criteria:
1. 50% relative rise in creatinine from the lowest level within preceding 7 d
2. 0.3 mg/dl (26 micromol/l) absolute rise in creatinine from the lowest level within preceding 48 h

Subsets 3 and 4: AKD according to KDIGO criteria without observed AKI, or with AKI that is presumed based on longer periods of time since baseline creatinine measurement:
3. 50% rise in creatinine from median creatinine value in preceding 8–90 d
4. 50% rise in creatinine from median creatinine value in preceding 91–365 d if no tests within preceding 8–90 d

AKD, acute kidney disease; AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.

Covariates

Additional variables collected included age, sex, and baseline level of kidney function. Baseline kidney function was derived from the reference creatinine measurement that served as a baseline for that AKI/AKD episode, and was based on the estimated glomerular filtration rate (eGFR), determined using the Chronic Kidney Disease–Epidemiology Collaboration (CKD-EPI) equation, excluding the coefficient for Black race.[21] AKI/AKD associated with hospitalization was defined by a creatinine test from a hospital location within 7 days of onset of an AKI/AKD event.

Outcome

The incidence of AKI/AKD was determined for each cohort overall, and according to AKI/AKD subset definitions. Mortality from any cause, at 30 days and 1 year after onset of AKI/AKD, was also reported. All cohorts included linkages to national or regional vital statistics repositories to ensure comprehensive ascertainment of vital status in their regions.

Statistical analyses

Results were reported for the years 2011, 2012, 2013, and 2014. Data from 2009 and 2010 were used for estimation of baseline kidney function and assessment of prior AKI. Incidence rates were standardized for age and sex to a UK population from 2012. Mid-year population denominators were obtained from population census reports for each region stratified by age and sex to calculate age- and sex-standardized incidence rates (per 10,000 person-years [py]).[22–24]

Characteristics were reported by region and year, including population size, total number of adults with at least one blood test in the period, overall number of blood tests, mean/median number of blood tests, and mean/median value of creatinine results. Further characteristics of AKI/AKD included the following: number of people with at least one AKI/AKD episode overall and within definition subsets; AKI/AKD by stage; AKI/AKD associated with hospitalization, recovery, and prior AKI; and the proportion of people with AKI/AKD who progressed from stage 1 to stage 2 or 3.

Annual AKI/AKD incidence rates were based on the first presentation of each person within a given year, expressed as the number of people first presenting with AKI/AKD per 10,000 py. Rates were reported stratified by age (in 10-year groups) and sex. For comparisons by sex, we reported those aged ≥40 versus <40 years separately, in recognition of the potential for artefactually increased rates of AKI/AKD due to physiological changes during pregnancy.

Mortality was reported within each region at 30 days, 1 year, and by cumulative incidence plots for AKI/AKD overall and within each definition subset. To assess the implications of including each subset within the overall definition, both incidence and mortality were also assessed in groups created by sequentially removing AKI/AKD subcriteria from the definition (i.e., we assessed the number and outcomes of those people who could be identified by only one definition subset and would no longer be included among cases of AKI/AKD if that definition subset were to be removed). The purpose of this process was to assess the impact of including incrementally longer lookback periods beyond 7 days (to 90 days, or 1 year) for ascertaining baseline creatinine measurements when laboratory capture is complete across community and hospital settings. To additionally account for age and sex differences among AKI/AKD cohorts, mortalities were standardized for age and sex compared to the Grampian AKI/AKD population. All analyses were performed in Stata/SE 16 (StataCorp, release 16).

RESULTS

Cohort characteristics

Table 1 describes the characteristics of the study cohorts by geographic region and year. Of 7 million inhabitants included across all regions, 5.2–5.5 million adults were included annually. In each year, the number of people with at least one creatinine test increased from approximately 2.2 million in 2011 to 2.5 million in 2014, amounting to approximately 40% of the population from each region. The median creatinine level was similar among regions (range: 0.83–0.88 mg/dl). For 3 of the 4 geographic cohorts, the median creatinine level was stable across the years; however, an isolated increase was observed in the Tayside cohort in 2011, following a change in creatinine assay for the region during that year. The median age of people with a creatinine test in Alberta was lower (59 years) than that in northern Denmark, Grampian, and Tayside (65–68 years). Sex distributions were similar (range: 51.9%–54.4% female).

Overall AKI/AKD incidence

Table 2 and Figure 1 describe the incidence of AKI/AKD. The majority of events were first episodes during the study period; 53.2% occurred in female patients, and 75.4%–79.7% were associated with hospitalization. Crude incidence rates varied among regions: crude incidence rates of AKI/AKD ranged from 114.5 (Alberta) to 174.0 (Tayside) per 10,000 py. After standardizing for age and sex, the standardized rates were similar across regions and years, ranging from 134.3 to 162.4 per 10,000 py (Figure 1). Figure 2 shows the age-stratified annual incidence of AKI/AKD, illustrating a consistent pattern of doubling of incidence with every 10-year increase in age across all regions and years, so that 8% of those aged >80 years had at least one AKI/AKD episode in a given year. AKI/AKD rates also had a consistent pattern across regions by sex, with greater age-standardized AKI incidence rates among male patients than among female patients aged >40 years, and substantially lower AKI/AKD incidence among male patients than among female patients aged <40 years (Figures 3 and 4).

AKI/AKD incidence by subset definitions, stages, and recovery

AKI/AKD incidence by subset definitions is reported in Table 2. Of those with AKI/AKD, 23%–31% met the KDIGO AKI definition based on 7-day relative increase in creatinine; 23%–33% met the definition based on a 48-hour absolute increase in creatinine; and 38%–42% met the definition based on an 8–365-day relative increase in creatinine, with consistent proportions across regions. Excluding those with AKI/AKD identified based only on a creatinine baseline lookback >90 days led to removal of 19%–25% of people contributing to the overall AKI/AKD incidence. The incidences of AKI/AKD stages, AKI/AKD progression, AKI recovery, and proportion with a prior AKI/AKD episode were similar across all regions and years (Table 2).

Table 1 | Population characteristics of people with versus without blood-test monitoring (continued)

	Alberta, Canada				Denmark			
	2011	2012	2013	2014	2011	2012	2013	2014
Population	3,789,030	3,874,548	3,981,011	4,083,648	1,842,528	1,847,738	1,853,678	1,860,807
Population age ≥18 yr	2,945,556	3,013,627	3,098,198	3,179,467	1,436,104	1,445,442	1,456,622	1,468,340
Total number of blood tests	3,001,983	3,155,388	3,302,643	3,506,829	1,890,616	1,977,443	2,066,721	2,121,404
People monitored with ≥1 test in year	1,277,503	1,324,261	1,381,273	1,466,432	599,266	622,352	638,402	659,094
People monitored as % of population	43.4	43.9	44.6	46.1	41.7	43.1	43.8	44.9
Mean no. tests per monitored person	2.3	2.4	2.4	2.4	3.2	3.2	3.2	3.2
Mean age of people tested, yr	58.8	58.9	58.9	58.8	62.2	62.5	62.6	62.5
Median age of people tested, yr	59.5	59.7	59.7	59.7	65.0	65.0	65.0	65.0
% of people tested, female	53.4	53.5	53.3	53.1	52.0	52.0	51.9	51.9
Median creatinine level, mg/dl	0.88	0.87	0.87	0.87	0.85	0.85	0.87	0.87

AKI/AKD mortality

Supplementary Table S1 reports the unadjusted mortalities for those with AKI/AKD overall, and within AKI/AKD definition subsets for each year of study. Table 3 reports mortalities pooled across years and standardized for age and sex differences. People with AKI/AKD in Alberta had a lower unadjusted mortality than those in the other regions at 30 days and 1 year (Supplementary Table S1), although this difference was attenuated by accounting for age and sex differences. Respective standardized 30-day and 1-year mortalities were 13.1% and 27.8% for Alberta; 16.5% and 23.8% in northern Denmark; 15.7% and 32.1% in Tayside; and 15.9% and 32.6% in Grampian (Table 3). Associations with mortality were similar for AKI/AKD subset definitions across years and regions (Figure 5), with similar mortality for those with AKI

Table 2 | Population rate and annual incidence of AKI and AKD overall and within definition subsets (continued)

	Alberta, Canada				Denmark			
	2011	2012	2013	2014	2011	2012	2013	2014
AKI/AKD rates								
Total number of episodes	36,578	40,180	42,298	44,377	21,304	22,216	22,390	21,796
Incident episodes	33,726	37,014	39,031	40,949	19,501	20,303	20,549	19,941
Crude incidence, per 10,000 per yr	114.5	122.8	126.0	128.8	135.8	140.5	141.1	135.8
(95% CI)	(113.2–115.7)	(121.6–124.1)	(124.7–127.2)	(127.5–130.0)	(133.9–137.7)	(148.5–142.3)	(139.2–143.0)	(133.9–137.7)
Age–sex standardized incidence, per 10,000 py	149.1	157.9	160.3	162.4	138.1	141.6	141.5	134.3
(95% CI)	(147.5–150.7)	(156.3–159.5)	(158.7–161.9)	(160.8–164.0)	(136.2–140.0)	(139.7–143.5)	(139.6–143.4)	(132.5–136.2)
AKI/AKD subset definitions, %								
Meets criterion of changes within 7 d	24.5	24.3	23.7	23.4	26.3	25.8	25.0	25.4
48 h	25.3	23.8	24.0	24.5	30.6	29.2	29.9	30.4
8–90 d	39.3	39.1	38.3	38.0	40.9	41.8	41.8	42.4
91–365 d	25.5	26.9	27.9	27.8	21.9	22.2	22.0	20.4
Exclusively only meets criterion of changes within 7-d criterion	9.5	9.6	9.2	9.1	8.1	7.9	7.8	7.8
48 h	12.7	11.7	11.8	12.4	14.9	13.8	14.8	15.1
8–90 d	29.9	29.8	29.4	29.2	29.0	30.0	30.0	30.6
91–365 d	22.9	24.3	25.3	25.1	19.0	19.4	19.4	17.7
AKI/AKD phenotype, %								
Stage 1	69.2	69.5	70.4	71.2	65.1	65.6	66.8	67.4
Stage 2	18.6	18.5	17.8	17.4	19.7	19.5	19.0	18.3
Stage 3	12.2	12.0	11.8	11.5	15.1	14.8	14.2	14.2
AKI/AKD in hospital	77.3	75.8	75.7	77.5	77.5	75.4	75.9	77.3
Progression from stage 1 to 2/3	14.6	13.8	13.5	12.9	18.1	17.5	17.0	16.3
Without recovery to within 1.5× baseline	33.8	34.9	35.3	36.0	32.6	32.8	31.2	32.1
Prior AKI/AKD episode in the past year	8.8	9.0	8.8	9.3	9.3	9.2	9.5	9.8

AKD, acute kidney disease; AKI, acute kidney injury; CI, confidence interval; na, not available; py, person-year.

Table 1 | (Continued)

Grampian, UK				Tayside, UK			
2011	2012	2013	2014	2011	2012	2013	2014
569,580	573,400	579,200	584,220	410,250	411,740	412,160	413,800
459,439	463,114	468,594	473,815	331,515	333,457	334,164	336,098
515,709	534,608	541,527	563,180	444,012	451,672	464,562	475,969
171,534	177,688	183,154	187,057	140,720	143,527	146,215	147,757
37.3	38.4	39.1	39.5	42.4	43.0	43.8	44.0
3.0	3.0	3.0	3.0	3.2	3.1	3.2	3.2
62.0	62.0	61.7	61.9	65.5	65.6	65.6	65.9
65.0	65.0	65.0	65.0	68.0	68.0	68.0	68.0
54.2	54.0	53.8	54.0	54.4	54.4	54.3	54.2
0.84	0.83	0.83	0.83	0.88	0.83	0.81	0.81

based on 7-day, 48-hour, and 90-day baseline lookback periods (Box 1, subset definitions 1, 2, and 3, respectively), but lower mortality among those with AKI/AKD when based on only a baseline ascertained between 91and 365 days prior (Box 1, subset definition 4). Those meeting presumed AKI/AKD criteria based exclusively on a baseline measure >90 days (Box 1, subset definition 4) had substantially lower mortality than those meeting AKI/AKD criteria under any other subset definition (Supplementary Table S1). For example, in Alberta in 2014, the 30-day and 1-year mortalities were 6.2% and 14.5% for those with AKI/AKD, based only on a baseline creatinine measurement beyond 90 days (Box 1, subset definition 4), compared with overall 30-day and 1-year mortalities of 11.2% and 24.1%, respectively, for those with AKI/AKD defined by any criteria (Box 1, subset

Table 2 | (Continued)

Grampian, UK				Tayside, UK			
2011	2012	2013	2014	2011	2012	2013	2014
6406	6619	6505	6777	6239	5518	5721	5727
5955	6190	6099	6261	5769	5148	5375	5314
129.6	133.7	130.2	132.1	174.0	154.4	160.8	158.1
(126.3–132.9)	(130.4–137.0)	(126.9–133.5)	(129.2–135.7)	(169.6–178.6)	(150.2–158.7)	(156.6–165.2)	(153.9–162.4)
137.0	140.1	135.8	137.3	162.3	142.3	147.9	143.9
(133.6–140.4)	(136.7–143.5)	(132.5–139.1)	(134.0–140.7)	(158.3–166.4)	(138.6–146.3)	(144.0–151.8)	(140.1–147.8)
29.1	28.5	28.6	27.6	28.8	31.4	29.3	28.2
31.4	29.4	28.7	29.1	28.6	32.7	28.6	30.3
39.2	40.0	40.1	40.4	37.7	39.7	40.9	40.3
23.2	26.3	25.9	25.4	24.2	20.7	24.4	22.7
9.9	9.2	9.8	8.4	11.0	11.0	10.0	9.8
14.0	12.1	12.2	12.5	13.2	15.2	12.2	14.0
27.2	27.1	28.2	28.2	26.5	26.6	29.0	28.7
19.9	22.8	22.2	21.8	21.4	17.4	21.1	19.4
68.2	70.0	69.2	70.6	69.6	67.7	68.3	68.9
19.3	18.8	19.0	18.9	18.5	19.1	19.6	18.7
12.4	11.3	11.8	10.5	11.9	13.2	12.1	12.4
79.7	78.2	77.2	75.6	na	na	na	na
15.3	14.2	14.0	12.6	14.3	15.2	14.4	14.4
30.7	29.6	29.9	30.3	31.9	30.0	28.7	31.2
9.2	7.6	7.8	7.6	8.4	8.4	7.2	8.6

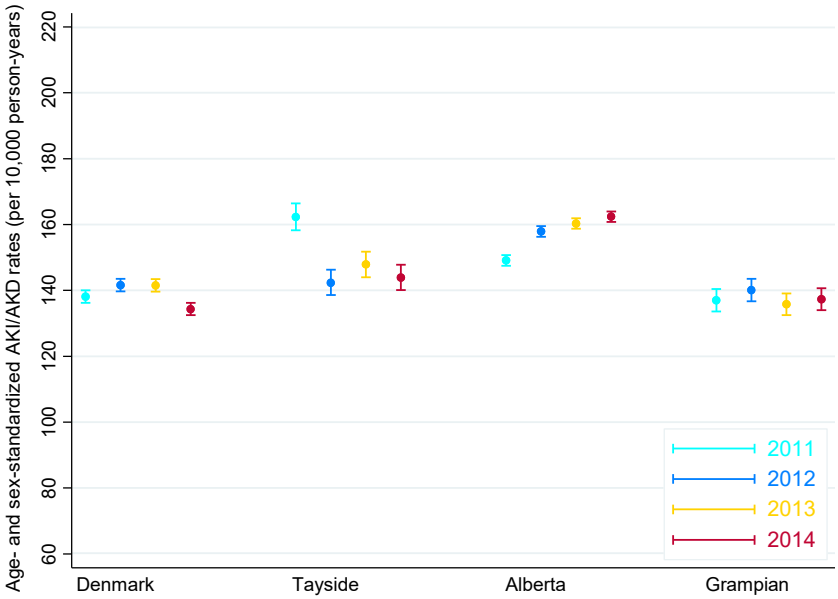

Figure 1 | Age- and sex-standardized rates of acute kidney injury (AKI) and acute kidney disease (AKD) across populations and time periods (Denmark; Tayside, UK; Alberta, Canada; Grampian, UK).

definitions 1–4). The patterns of 30-day and 1-year mortality across definition subsets were similar when restricted to only those with AKI/AKD associated with hospitalization (Supplementary Table S2).

DISCUSSION

In this large multinational study, we used a homogenous analytical approach applied identically across 4 regional populations to characterize incidence and prognosis of AKI and AKD using KDIGO definitions. Unlike previous attempts that reported significant differences in AKI epidemiology from studies with differences in sampling and AKI ascertainment methods,[1,9] we report substantial consistency across 4 geographic population-based cohorts from 3 high-income countries and time periods with an age–sex standardized annual incidence of AKI/AKD ranging between 134.3 and 162.4 per 10,000 py. We found that both components of KDIGO AKI criteria (small absolute creatinine changes in 48 hours, and large relative changes over 7 days) were associated with similar mortality risk in all cohorts. Further, we found that AKI/AKD based on a baseline creatinine measurement ascertained *within* 8–90 days was associated with a similar prognosis; however, AKI/AKD based on a baseline creatinine measurement ascertained *beyond* 90 days carried a different prognosis, with substantially lower mortality, even after accounting for age and sex differences.

This consistency across 4 separate regional populations demonstrates the robustness and replicability of estimates of AKI/AKD incidence and prognosis in high-income countries based on KDIGO criteria, when capture of laboratory tests is complete, creatinine-based definitions are implemented consistently, and adjustment is made for differences in age and sex. Furthermore, the association of 3 subset definitions for AKI with similar 1-year mortality provides clarification of the prognostic consistency based on creatinine changes within 48 hours and 7 days from routinely collected laboratory data (in line with current AKI criteria), as well as with use of creatinine changes from a baseline within 90 days (in line with current KDIGO AKD criteria). The significantly lower mortality we observed among patients with AKI/AKD based on changes from a baseline beyond 90 days is noteworthy and could be explained only partially by age and sex differences. This finding implies that attempts to extend the ascertainment period for baseline creatinine measurements up to 1 year, as suggested as an acceptable approach in other studies,[25] identifies a prognostically distinct subpopulation of patients. This subset, representing just over 20% of all people identified with AKI/AKD, may include people with AKI, AKD, or progressive CKD, for whom different approaches may be warranted for identification and reporting in research and clinical practice. Our findings support using AKI/AKD detection algorithms that distinguish patients with serum creatinine increases from a baseline creatinine ascertainment more than 90 days prior. Use of such algorithms is in keeping with a stricter interpretation of the existing KDIGO AKI guidelines and enables more intuitive reconciliation with KDIGO CKD criteria (involving persistence for at least 90 days).

Notably, half (47.1%–54.7%) of all people with AKI/AKD in our cohorts could be identified based on creatinine changes within 7 days. This finding is relevant when comparing AKI incidence between health systems and studies in which capture of all inpatient and community

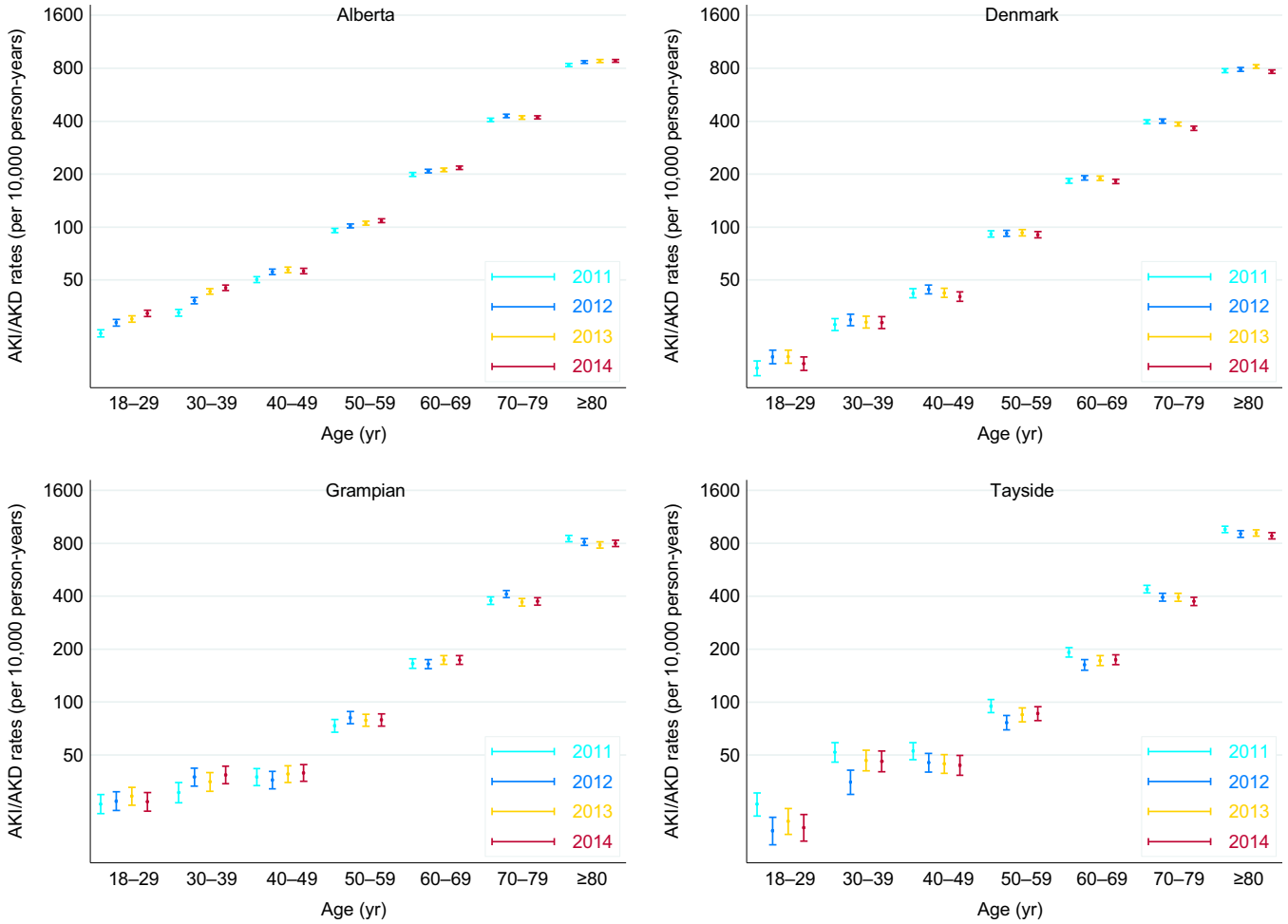

Figure 2 | Population incidence rates of acute kidney injury (AKI) and acute kidney disease (AKD) per 10,000 person-years within age groups (Denmark; Tayside, UK; Alberta, Canada; Grampian, UK).

blood-test data has been versus has not been possible. In places where all test results are not available, half of AKI/AKD cases can be identified based on recent results if preadmission data are unavailable; however, efforts to enhance integration of health records from all sources within the preceding 90 days would improve identification of AKI/AKD cases with similar mortality rates. We also noted a higher age-standardized rate of AKI/AKD among male patients, compared to that among female patients. Prior literature provides conflicting information on sex differences in the risk of AKI/AKD, which also may relate to differences in study populations and methods, but it is plausible that female patients experience slower creatinine generation during acute illness.[26,27] Further investigation is warranted to investigate sex differences in AKI/AKD incidence and outcomes and is necessary to ensure that guidelines for AKI/AKD are equitable.

Other studies that have attempted to measure the population-based incidence of AKI have reported variable incidence rates of AKI based on serum creatinine changes that were lower than those we observed across regions in our study.[28] One study from the US reported an incidence of AKI that increased between 1996 and 2003, from 32.3 to 52.2 per 10,000 py.[29] A more recent study from the US reported an incidence of AKI of 28.7 to 31.7 per 10,000 py between 2006 and 2014, without a significant change in the annual incidence after adjustment for age and sex.[30] The higher incidence of AKI and consistency between regions in our study are likely due to the fact that we ascertained AKI based on increases in serum creatinine measured in outpatient as well as inpatient settings, whereas these previous studies ascertained AKI in only hospitalized patients. Admission to the hospital represents a clinical decision driven by both clinical and health system factors. Thus, the likelihood of hospital admission may vary by region and over time, which may affect comparisons of observed rates of AKI incidence in past studies, independent of the actual AKI incidence per population. Differences in population sample selection may also contribute to the significant variation seen among regions in CKD prevalence estimates from Europe and North America, whereas age and sex estimates for

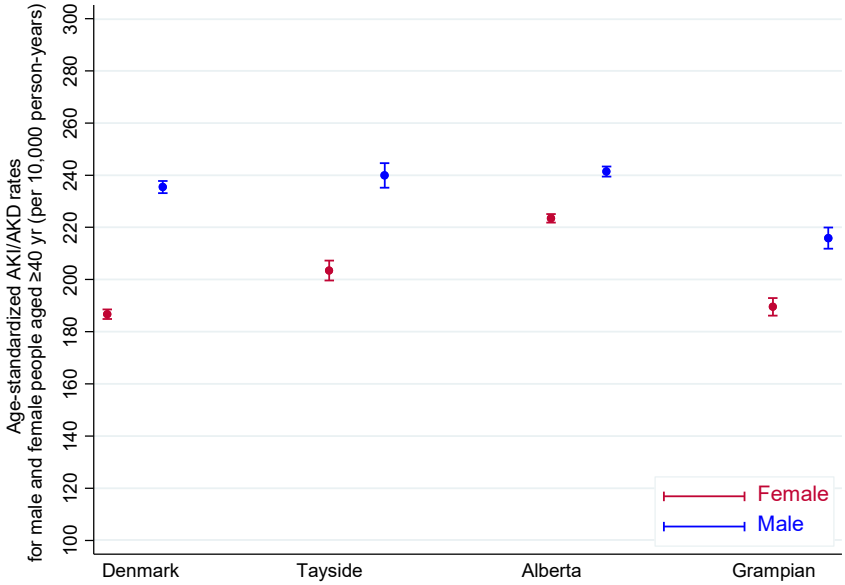

Figure 3 | Age- and sex-standardized rates of acute kidney injury (AKI) and acute kidney disease (AKD) for male and female people aged ≥40 years (Denmark; Tayside, UK; Alberta, Canada; Grampian, UK).

AKI/AKD incidence in our study were similar among regions when whole-population data were used.[31,32]

Strengths of this study include the large multinational population-based design, with complete data capture of all kidney laboratory measurements across community and acute care settings in each geographic region. We used a standardized analytical approach to remove the variability in how KDIGO definitions can be interpreted and applied to existing health data, thereby reducing methodological differences that have affected other comparisons of AKI epidemiology among regions. Limitations include the fact that these findings may not be generalizable to other health systems in which full-population laboratory data capture is not possible, or in which access to laboratory testing may be reduced due to availability or cost. Future studies should explore the implications of adopting these criteria in other settings, particularly given the increasing emphasis on use of artificial intelligence techniques in clinical research, which may be sensitive to variation in data quality and completeness. Although we have focused on prognosis based on mortality, our study did not distinguish among

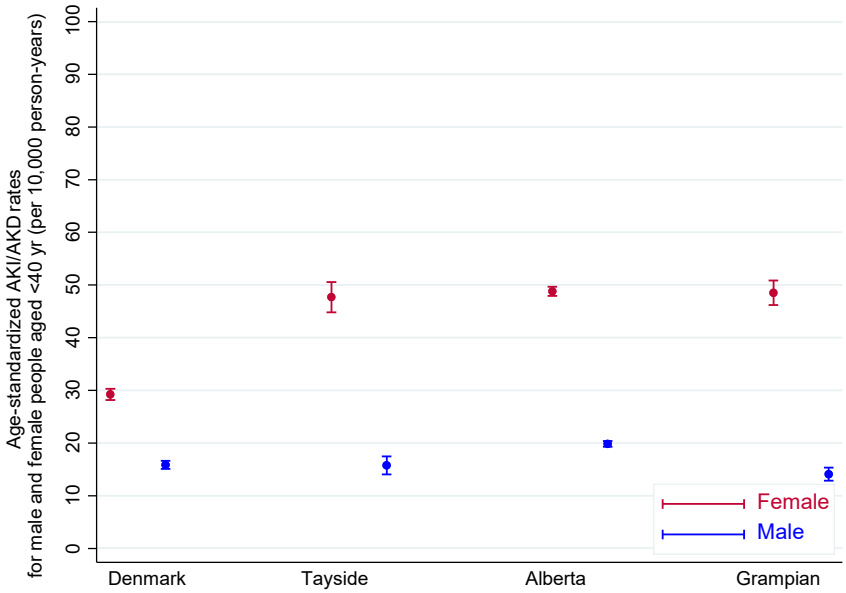

Figure 4 | Age- and sex-standardized rates of acute kidney injury (AKI) and acute kidney disease (AKD) for male and female people aged <40 years (Denmark; Tayside, UK; Alberta, Canada; Grampian, UK).

Table 3 | Age- and sex-standardized mortality of people with acute kidney injury and acute kidney disease overall and within definition subsets

Mortality	Alberta, Canada	Denmark	Grampian, UK	Tayside, UK
Overall				
30-d	13.1 (12.9–13.2)	16.5 (16.2–16.7)	15.9 (15.4–16.3)	15.7 (15.2–16.2)
1-yr	27.8 (27.6–28.0)	32.8 (32.5–33.1)	32.6 (32.0–33.1)	32.1 (31.6–32.7)
30-d in subsets, by criterion				
7-d	17.2 (16.8–17.6)	22.5 (21.9–23.0)	20.4 (19.5–21.3)	20.3 (19.3–21.2)
48-h	15.4 (15.1–15.8)	19.4 (18.9–19.8)	17.1 (16.3–17.9)	18.6 (17.7–19.5)
8–90-d	15.9 (15.6–16.2)	18.7 (18.3–19.1)	19.2 (18.5–20.0)	18.1 (17.3–18.8)
91–365-d	9.8 (9.5–10.2)	11.6 (11.1–12.0)	11.7 (11.0–12.5)	11.7 (10.9–12.6)
1-yr in subsets, by criterion				
7-d	32.9 (32.4–33.3)	38.5 (37.8–39.1)	37.4 (36.4–38.5)	36.5 (35.4–37.6)
48-h	30.4 (29.9–30.8)	35.2 (34.7–35.8)	33.1 (32.1–34.1)	33.9 (32.8–35.0)
8–90-d	32.0 (31.6–32.3)	36.3 (35.9–36.8)	37.4 (36.6–38.4)	35.4 (35.4–37.6)
91–365-d	21.0 (20.6–21.4)	24.4 (23.8–25.0)	24.6 (23.6–25.6)	25.5 (24.3–26.6)

Values are % (95% confidence interval).

outcomes according to different causes of AKI/AKD, or by comorbidities, which may modify the survival of individual patients with AKI/AKD. Further, kidney recovery and progression may differ among AKI/AKD definition subsets, or across geographic populations, warranting further research.

Our findings show the value of applying consistent analytical methods within population-based studies, to enhance the comparability of AKI/AKD research conducted in different settings. We have provided our analytical code in the Supplementary Stata Analysis Code, to aid in the implementation of these methods and promote consistency in

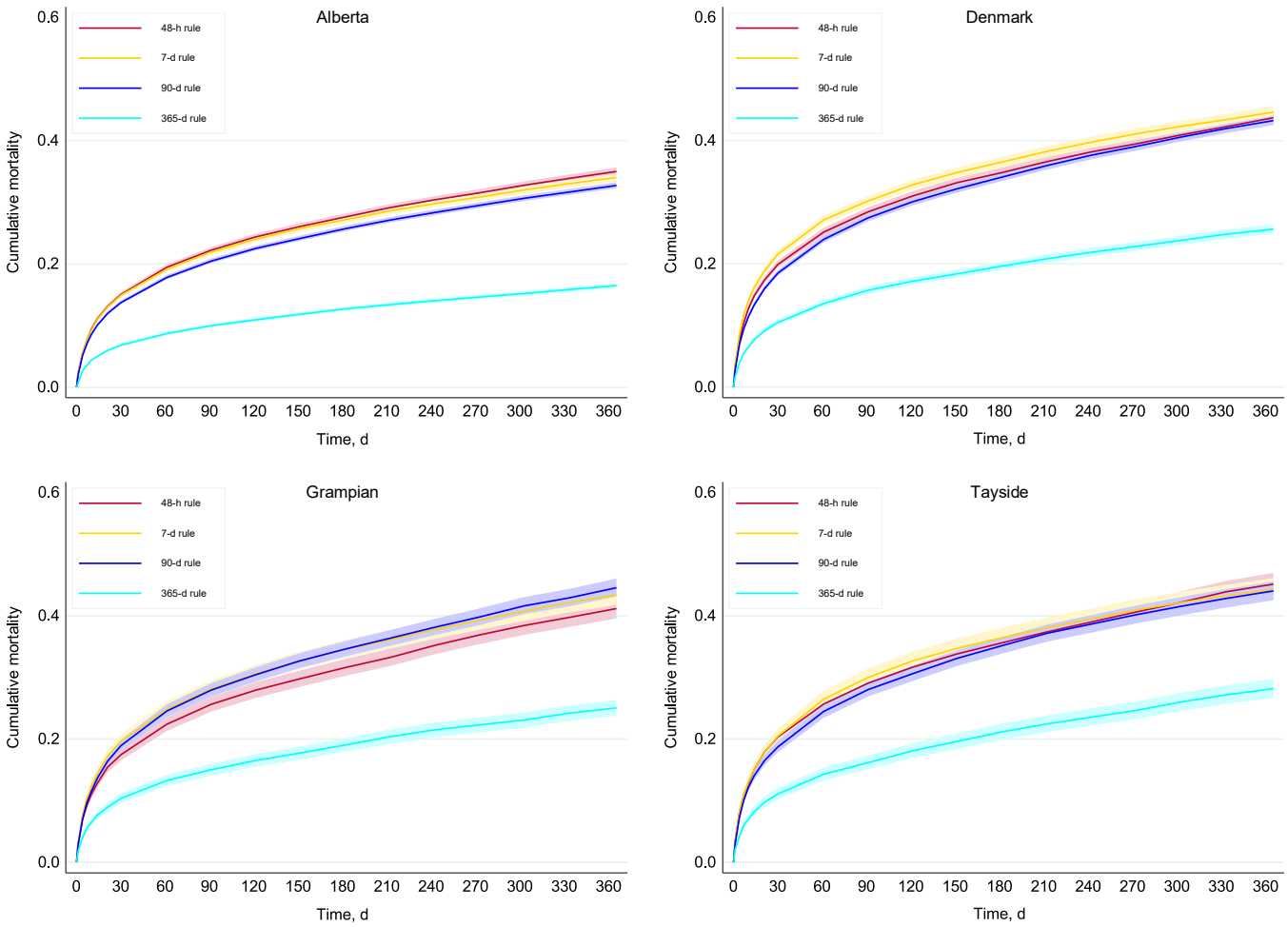

Figure 5 | Cumulative mortality for incident presentations of acute kidney injury and acute kidney disease based on different subset definitions (Denmark; Tayside, UK; Alberta, Canada; Grampian, UK).

future AKI/AKD research studies. Our findings also have implications for AKI surveillance and reporting systems (e.g., AKI e-alerts), many of which use algorithms that report AKI based on up to 1-year lookback periods for baseline creatinine measurements.[33]

In conclusion, with a standardized analytical approach, a consistent burden of AKI and AKD can be demonstrated across 3 high-income countries with integrated healthcare systems. Subsets of AKI and AKD defined using lookbacks for baseline creatinine measurements within 90 days are associated with equivalent short- and long-term mortality. These findings resolve questions related to between-study variability in incidence and prognosis identified in past epidemiologic studies of AKI and suggest that existing consensus criteria for AKI and AKD confined to a 90-day period can be consistently operationalized across regions. These approaches should be used consistently to improve the generalizability and comparability of AKI/AKD identification in clinical practice and research, in alignment with existing KDIGO definitions for AKI, AKD, and CKD.

DISCLOSURE

This study is based in part on data provided by Alberta Health and Alberta Health Services. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views of the Government of Alberta or Alberta Health Services. Neither the Government of Alberta, nor Alberta Health or Alberta Health Services expresses any opinion in relation to this study. MTJ was the principal investigator on an investigator-initiated grant from Amgen Canada, outside the submitted work. All the other authors declared no competing interests.

DATA STATEMENT

Datasets cannot be made available to other researchers due to contractual arrangements with government agencies that are the data custodians. Information on how researchers may make requests to obtain similar datasets from health research dataset custodians may be provided upon request.

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SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Instruction Files. Replication instructions, replication data dictionary. Code files are for dataset preparation, acute kidney injury (AKI)/acute kidney disease (AKD) identification, and summary statistics for the study. Instructions file for prerequisite preparation of data files prior to analysis to enable replication.

Supplementary Stata Analysis Code. Replication_AKIpopulation.do and Replication_population_summary.do.

Table S1. Unadjusted mortality of people with acute kidney injury (AKI) and acute kidney disease (AKD), overall and within definition subsets.

Table S2 Age- and sex-standardized mortality restricted to acute kidney injury (AKI) and acute kidney disease (AKD) events associated with hospitalization, overall and within definition subsets

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