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# Recovery of kidney function after acute kidney disease—a multi-cohort analysis

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## ABSTRACT

**Background.** There are no consensus definitions for evaluating kidney function recovery after acute kidney injury (AKI) and acute kidney disease (AKD), nor is it clear how recovery varies across populations and clinical subsets. We present a federated analysis of four population-based cohorts from Canada, Denmark and Scotland, 2011–18.

**Methods.** We identified incident AKD defined by serum creatinine changes within 48 h, 7 days and 90 days based on KDIGO AKI and AKD criteria. Separately, we applied changes up to 365 days to address widely used e-alert implementations that extend beyond the KDIGO AKI and AKD timeframes. Kidney recovery was based on resolution of AKD and a subsequent creatinine measurement below 1.2× baseline. We evaluated transitions between non-recovery, recovery and death up to 1 year; within age, sex and comorbidity subgroups; between subset AKD definitions; and across cohorts.

**Results.** There were 464 868 incident cases, median age 67–75 years. At 1 year, results were consistent across cohorts, with pooled mortalities for creatinine changes within 48 h, 7 days, 90 days and 365 days (and 95% confidence interval) of 40% (34%–45%), 40% (34%–46%), 37% (31%–42%) and 22% (16%–29%) respectively, and non-recovery of kidney function of 19% (15%–23%), 30% (24%–35%), 25% (21%–29%) and 37% (30%–43%), respectively. Recovery by 14 and 90 days was frequently not sustained at 1 year. Older males and those with heart failure or cancer were more likely to die than to experience sustained non-recovery, whereas the converse was true for younger females and those with diabetes.

**Conclusion.** Consistently across multiple cohorts, based on 1-year mortality and non-recovery, KDIGO AKD (up to 90 days) is at least prognostically similar to KDIGO AKI (7 days), and covers more people. Outcomes associated with AKD vary by age, sex and comorbidities such that older males are more likely to die, and younger females are less likely to recover.

**Keywords:** AKI, CKD, epidemiology, prognosis, recovery

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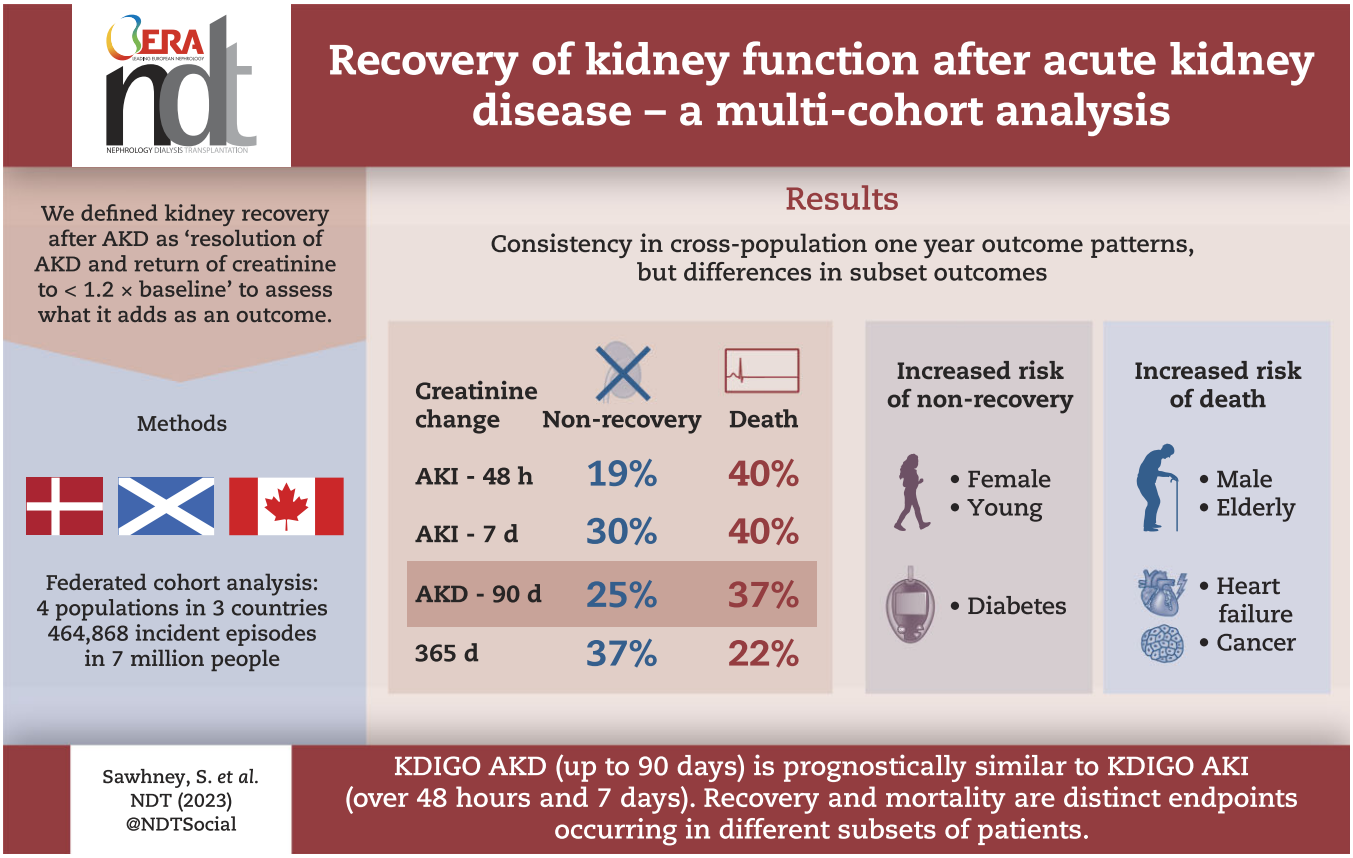
## GRAPHICAL ABSTRACT




## KEY LEARNING POINTS

**What was known:**

- There are no consensus definitions for evaluating kidney function recovery after KDIGO acute kidney injury (AKI) and acute kidney disease (AKD), nor is it clear what recovery assessment adds as an outcome for clinical evaluation.
- Implementation of AKI and AKD is variable in clinical practice and research, and widespread 'AKI' e-alerts are pragmatically extended beyond both the AKI (7 days) and AKD (90 days) timeframes.
- KDIGO have called for large-scale population-level studies to reconcile the use of these definitions and characterize kidney recovery to address this knowledge gap.

**This study adds:**

- This multi-cohort study rigorously applied KDIGO AKI, AKD and e-alert implementations across a population of 7 million to identify 464 868 incident cases. It characterized both recovery and mortality outcomes across cohorts, clinical subsets and definitions (which rarely overlapped).
- Non-recovery and mortality were both common, but occurred in different clinical subgroups such that older males and those with heart failure or cancer were more likely to die than experience sustained non-recovery, whereas the converse was true for younger females and those with diabetes.
- In every population and subset, the KDIGO definition of AKD was at least as prognostically important as KDIGO AKI for both mortality and recovery, so long as it as strictly interpreted as creatinine changes up to and not beyond 90 days.

**Potential impact:**

- With consistency across populations and clinical subsets, this analysis supports the notion of KDIGO AKD being a condition at least as prognostically important as KDIGO AKI and that would not be served by a focus on AKI alone.
- E-alert implementations should consider aligning with KDIGO AKD by restricting to creatinine changes with 90 days.
- Mortality and non-recovery typically happen in different subsets of patients. The recovery endpoint introduced and evaluated in this study should be considered in future clinical outcome evaluations.

## INTRODUCTION

Over 20 years since introduction of the term acute kidney injury (AKI), and 10 years since the KDIGO AKI clinical practice guidelines were published [1], clinical research has consistently demonstrated associations between AKI and adverse outcomes, including mortality, development and progression of chronic kidney disease (CKD), and cardiovascular events [2]. In many jurisdictions, AKI is now identified in clinical settings using e-alerts to facilitate and monitor improvement work [3, 4]. The 2012 KDIGO guideline also described AKI as a condition within a broader group of disorders termed acute kidney diseases and disorders (AKD). As reaffirmed by KDIGO in 2022, AKD includes not only AKI episodes of longer duration up to 90 days [5], but more broadly encompasses changes in serum creatinine identified within a period of 90 days, with AKI being a disorder nested within AKD, and AKD occurring even in the absence of AKI [6]. However, as noted in a recent KDIGO consensus conference, further work has been called for to reconcile the use of these definitions for clinicians and researchers, and to provide a common understanding of disease definitions for comparisons of the burden and outcomes of AKI and AKD across time, patient subgroups and clinical settings. In particular, little research has characterized the prognosis for recovery of kidney function after AKI and AKD, even though this may represent an important and common outcome for survivors.

Federated analyses, using shared code and harmonized curation of study populations, provide an opportunity to evaluate the consistency of measures of disease burden and outcomes [7]. While the concepts of kidney recovery and non-recovery may seem clinically intuitive, examination of the consistency of these measurements at the population level is important to ensure meaningful comparisons of outcomes across groups, for evaluating interventions to optimize kidney recovery and to recognize people who may be more vulnerable to adverse outcomes [8, 9].

In this study we applied a common analytical approach to data from four cohorts with complete population laboratory test capture to evaluate kidney function recovery trajectories over the first year after AKD. We used this approach to determine the timing, extent and persistence of recovery over the first year after AKD, and the consistency across subset AKD definitions, population cohorts, and demographic and disease subgroups. Our purpose was to; (i) characterize kidney function recovery according to contemporary definitions of AKD, (ii) determine whether recovery profiles were consistent across geographically distinct clinical populations and (iii) identify potential differences in recovery according to age, sex or comorbidities.

## MATERIALS AND METHODS

### Data sources

Complete population community and hospital laboratory data were extracted from 2009 to 2019 from four regions with a combined population of 7 million inhabitants: Alberta (Canada), North and Central Denmark, Grampian (UK) and Tayside (UK) [7, 10–18]. These populations, served by universal healthcare systems, were selected for their ability to provide integrated data on isotope-dilution mass spectrometry–calibrated creatinine measurements for all residents within their source population, irrespective of clinical setting (hospital inpatient, outpatient specialty, community). Ethical and other approvals for use of unconsented routine health data were provided by research ethics boards and/or other relevant authorities for each region as summarized in the Supplementary data.

### Data processing and harmonization

Datasets for each region were prepared using a common analytical protocol and statistical code for both data preparation and analysis (the code and instructions for use are provided in the Supplementary data to allow replication of these methods in other cohorts). All creatinine results for each individual within each cohort were used for analyses. Creatinine values that were recorded as a non-value (e.g. 'sample inadequate', 'sample error'), or were outside the limits for detection of the analyser were excluded. To avoid privacy risks associated with movement of individual-level patient data between regions, the analytical code was designed for each centre to produce output files of aggregated data only, which were then sent to the coordinating centre (University of Aberdeen) for pooling and final reporting.

### Study population

All adult (age ≥18 years) residents within each population region with at least one serum creatinine test during 2009–18 were included. Creatinine tests taken after initiation of long-term kidney replacement therapy (KRT) (dialysis or transplant) for established kidney failure were excluded, as established by KRT registry data for each site and performed previously [7].

The first instance of AKD occurring between 2011 and 2018 was identified for each participant based on KDIGO serum creatinine criteria. Those meeting criteria for AKD in 2009 and 2010 were excluded to ensure only patients with incident AKD were included and to avoid inclusion of prevalent/recurrent episodes (prevalent pool effect).

### Exposure—AKD subsets

Four definition subsets based on serum creatinine change were evaluated (Fig. 1). The 48-h and 7-day subsets followed the existing KDIGO AKI criteria, and an 8- to 90-day subset followed the KDIGO AKD criteria. A separate final group covered those with creatinine changes up to 365 days if no blood tests were available within 8–90 days. This was to understand the implications of using longer creatinine intervals beyond 90 days, as adopted in existing e-alert systems [19]. Additional detail is available in our previous work [7], with accompanying code in the Supplementary data.

Because the subset definitions of AKD can co-occur, occur in isolation or occur sequentially in a patient, in the main analysis we assessed the extent to which individual patients 'overlapped' in the presenting subsets of an AKD episode if they met multiple subset criteria within 1 week of first AKD onset. In a secondary analysis this definition of overlap was restricted to co-presentation of subsets only if they occurred on the first day of AKD onset in a given patient.

For analyses of characteristics and outcomes in the main analysis, each of the four AKD subsets were reported separately, while in a secondary analysis only the characteristics of those who presented with one subset exclusively (e.g. 48-h subset without being in the 7-, 90- or 365-day subsets) were reported. In this secondary analysis, outcomes for the exclusive 90-day subset can be understood to represent outcomes of those who have 'AKD without AKI'.

### Covariates

Additional variables collected included age, sex, comorbidities, hospital context (whether the participant was in hospital at time of AKD onset) and baseline level of kidney function. Baseline kidney function was determined from the reference creatinine measurement that served as baseline for the AKD episode (Fig. 1), which was used to calculate estimated glomerular filtration rate

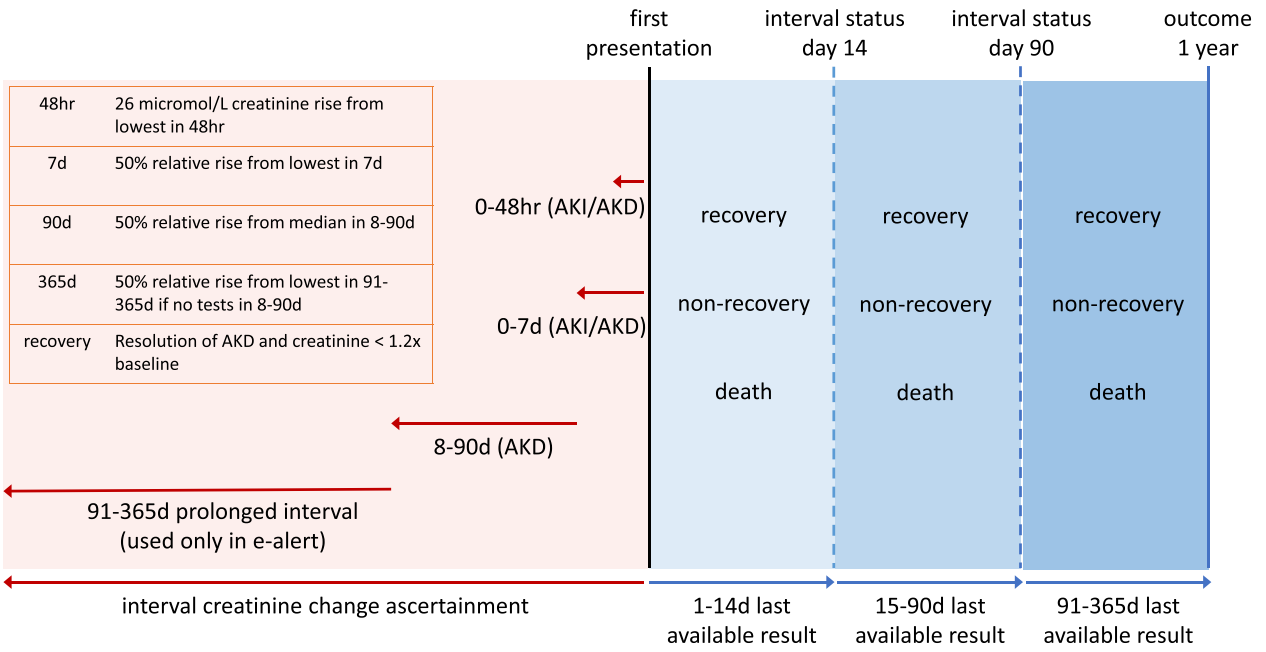



**Figure 1:** Visual overview of the study. Red shading represents study definitions of AKD subsets up to 90 days and the extension to address e-alert implementations beyond 90 days (adapted from Sawhney *et al.* [7]). Blue shading represents follow-up of the clinical course with status updated in three periods up to 1 year based on the most recently available clinical information.

(eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation excluding the coefficient for race (2009 version) in the main analysis, and the CKD-EPI equation 2021 version in a secondary analysis [20, 21]. The coefficient for race was excluded in line with current clinical practice in each of the populations of study.

Comorbidities, including diabetes, cancer, coronary heart disease, heart failure, stroke and peripheral arterial disease, were identified using validated coding approaches [International Classification of Diseases (ICD)-10 codes] applied to hospital discharge abstract records within 2 years prior to AKD onset date. In the Alberta cohort, comorbidities were also extracted from physicians' claims from hospital and community settings, using ICD-9-CM codes (see Supplementary data) [18, 22, 23].

## Outcomes

Subsequent kidney function trajectories were characterized based on absolute and relative changes (vs baseline) moving forward from the date of AKD onset to the peak serum creatinine (and the corresponding eGFR) within 7 days, and the latest recorded subsequent measures at 14, 90 and 365 days following AKD (subset definition) onset (Fig. 1).

Kidney function recovery was operationalized by a subsequent return of serum creatinine to within 1.2× of the baseline value for all participants meeting any AKD subset criteria [11, 24]. Of note, those meeting a 48-h absolute creatinine change of 0.3 mg/dL (26 µmol/L) as per the KDIGO AKI definition may not exceed the threshold of a 1.2× increase from baseline. Accordingly, for consistency, our operationalized definition of recovery required both a fall in creatinine to within 1.2× baseline and resolution of the serum creatinine based AKD/AKI criteria.

Mortality and date of death were determined by linkage to national or regional vital statistics for each region as in previous work [7].

## Statistical analyses

Descriptive statistics and outcomes were reported for each cohort separately according to participants meeting each AKD subset definition, and also with pooling of the 1-year outcomes across regions using random effects proportional meta-analysis. One-year outcomes were also reported within subgroups by age (</≥70 years), sex and comorbidities (cancer, diabetes and heart failure).

The proportions of participants who were identified according to each combination of AKD subset definition met within 1 week of AKD onset (to capture patterns of overlap of individuals who met multiple subset definitions but on different days during the same episode) (primary analysis), as well as those identified only on the day of first AKD onset (secondary analysis), were reported using Euler diagrams to illustrate the degree of overlap of patients co-presenting with multiple AKD subset definitions.

For those who survived 1 year after AKD onset, distributions of serum creatinine and eGFR at baseline, peak within 0–7 days of AKD onset, and during follow-up to 14, 90 and 365 days were determined. In addition, for all people, trajectories of kidney function and recovery were reported using Sankey plots to visualize the flow over time in the proportion of participants with statuses of kidney function recovery, non-recovery and death at 14, 90 and 365 days. Because blood testing in routine practice is non-protocolized, follow-up was considered an 'informative observation' and missing data on a given day 'missing not at random' (i.e. fewer tests occur among patients who have become stable). Accordingly, multiple imputation was deemed inappropriate. In the main analysis, the most recent available result for participants was carried forward when a creatinine measurement was missing from any follow-up interval. A secondary analysis was also performed that categorized those missing a measurement within each time period in a separate 'untested' group. Cohort preparation was conducted in Stata SE 16, with Sankey and Euler plots produced in R [25, 26].

# RESULTS

## Cohort characteristics

There were 464 868 patients with incident AKD from the four cohorts, with median age ranging from 67 to 75 years and 50%–54% females across the cohorts (Table 1). The proportions of patients presenting with each AKD subset criterion were similar across cohorts, with the greatest number of patients presenting with AKD in the 90-day subset. Across the cohorts, 93%–96% of patients in the 48-h subset were identified in a hospital setting, whereas 47%–58% of patients with 365-day subset were identified in a community setting. Comorbidities of diabetes, cancer, heart failure and cardiovascular diseases were most common among those in the 48-h subset, and least common among those in the 90- and 365-day subsets. When the cohort was restricted to patients meeting only one of the AKD subset criteria exclusively, similar differences in baseline characteristics were observed between the groups (Supplementary data, Table S1).

## Frequency and overlap according to AKD subset criteria

The scaled proportions and overlap of people based on all combinations of subset criteria met within 1 week of AKD onset are illustrated in Fig. 2, and combinations of co-presentation on the same day of first AKD onset are provided in Supplementary data, Fig. S1. Overall, 71% (330 305/464 868) of people met only one of the AKD subset criteria during their episode, and 80% (370 545/464 868) of people met only one of the AKD subset criteria if co-presentation was restricted to the same day of first onset.

## Trajectories of kidney function

Among people surviving 1 year, the distributions of serum creatinine at baseline, AKD onset, and 14, 90 and 365 days after onset of AKD, according to each AKD subset criterion are illustrated in Fig. 3 and the clinical course of creatinine, ratio vs baseline, and eGFR are elaborated in Supplementary data, Table S2. The patterns were similar across the four cohorts, and illustrate a positive (right) shift of distributions from baseline to peak creatinine within the first 7 days of AKD onset. Patients identified based on changes within 48 h had a larger positive shift in distribution of serum creatinine at the onset of AKI, with the distributions returning closer to that at baseline by 14 days and beyond. In contrast, the distributions of serum creatinine for those identified based on other definitions showed positive shifts that did not return as close to the baseline by 14, 90 or 365 days. Similar findings were observed when kidney function was evaluated based on eGFR or based on the ratio of creatinine concentration at each time point relative to baseline (Supplementary data, Table S2). These differences in the pattern of distribution were even more apparent when restricted to those exclusively meeting each subset criterion in isolation (e.g. those with AKD based on interval changes within 90 days but in no other subset) (Supplementary data, Fig. S2).

## Mortality and recovery of kidney function

Overall, at 1 year, patients meeting the 48-h, 7-day and 90-day AKD criteria, and 365-day (i.e. e-alert) interval changes had pooled mortalities (95% confidence intervals) of 40% (34%–45%), 40% (34%–46%), 37% (31%–42%) and 22% (16%–29%), respectively, and non-recovery of kidney function of 19% (15%–23%), 30% (24%–35%), 25% (21%–29%) and 37% (30%–43%), respectively. This pattern of lower mortality for people with 365-day interval changes, and

**Table 1:** Description of AKD subsets for each cohort.

| | Alberta | | | | Denmark | | | | Grampian | | | | Tayside | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days |
| N | 100 278 | 101 075 | 136 465 | 93 640 | 57 659 | 56 043 | 77 254 | 37 240 | 18 620 | 18 524 | 22 767 | 13 252 | 24 932 | 24 441 | 31 696 | 18 011 |
| Age, median (IQR) | 72 (60–83) | 69 (56–81) | 69 (55–81) | 63 (46–78) | 75 (65–83) | 72 (63–81) | 72 (62–81) | 72 (59–81) | 75 (64–83) | 73 (62–82) | 73 (61–82) | 72 (57–82) | 75 (68–85) | 76 (65–84) | 76 (65–84) | 74 (61–83) |
| Female % | 42.8 | 51.5 | 53.1 | 59.5 | 51.4 | 48.7 | 49.6 | 54.4 | 45.4 | 52.6 | 53.4 | 58.3 | 47.7 | 55 | 54 | 57.7 |
| Inpatient % | 96.0 | 91.7 | 74.0 | 58.2 | 96.7 | 91.6 | 71.3 | 53.4 | 93.8 | 88.7 | 66.7 | 46.5 | 96.4 | 93.2 | 74.2 | 55.2 |
| Reference eGFR, median (IQR) | 63 (40–89) | 89 (62–106) | 84 (59–102) | 93 (70–111) | 62 (40–87) | 86 (60–101) | 83 (59–98) | 86 (64–101) | 66 (43–90) | 88 (63–102) | 84 (60–100) | 88 (66–104) | 59 (38–85) | 85 (58–99) | 80 (56–96) | 84 (61–100) |
| Reference Cr, median (IQR) | 97 (73–139) | 70 (51–98) | 76 (59–100) | 69 (54–89) | 99 (74–140) | 73 (54–100) | 77 (61–101) | 73 (58–93) | 93 (70–131) | 69 (52–95) | 74 (58–97) | 71 (55–90) | 99 (73–142) | 72 (53–99) | 77 (60–101) | 74 (57–94) |
| Comorbidities (%) | | | | | | | | | | | | | | | | |
| Diabetes | 16.3 | 14.9 | 13.5 | 12.2 | 18.7 | 16.6 | 16.8 | 13.7 | 22.5 | 20.3 | 20.5 | 17.0 | 23.5 | 20.7 | 19.7 | 15.3 |
| Cancer | 18.3 | 18.7 | 16.8 | 9.6 | 25.8 | 28.7 | 27.5 | 10.3 | 23.8 | 25.6 | 24.1 | 11.0 | 22.2 | 24.4 | 22.2 | 9.3 |
| Coronary heart disease | 26.1 | 23.0 | 19.1 | 12.8 | 23.6 | 20.5 | 17.9 | 13.0 | 33.0 | 29.2 | 27.0 | 21.5 | 27.1 | 24.2 | 21.9 | 17.3 |
| Heart failure | 20.6 | 18.4 | 14.8 | 8.7 | 16.0 | 13.8 | 12.3 | 8.4 | 17.9 | 15.1 | 14.0 | 8.9 | 18.0 | 15.2 | 13.4 | 8.5 |
| Stroke | 15.8 | 15.4 | 13.6 | 9.9 | 13.6 | 13.5 | 12.2 | 10.9 | 12.3 | 12.3 | 10.2 | 8.6 | 11.4 | 11.6 | 9.8 | 7.9 |
| Peripheral arterial disease | 12.1 | 11.2 | 9.7 | 6.6 | 11.8 | 10.9 | 9.6 | 7.1 | 12.3 | 11.0 | 9.6 | 7.0 | 10.3 | 9.5 | 7.8 | 5.6 |

Cr, creatinine; IQR, inter-quartile range.

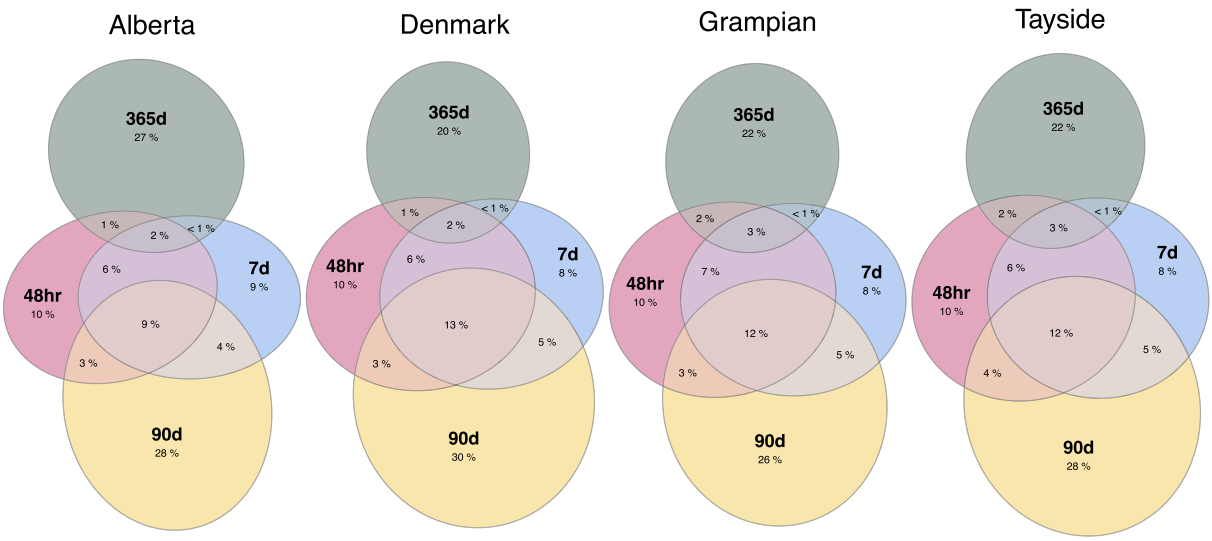



**Figure 2:** Proportions and overlap of people meeting each combination of AKD criteria in each cohort (co-presenting within 1 week of first AKD onset).

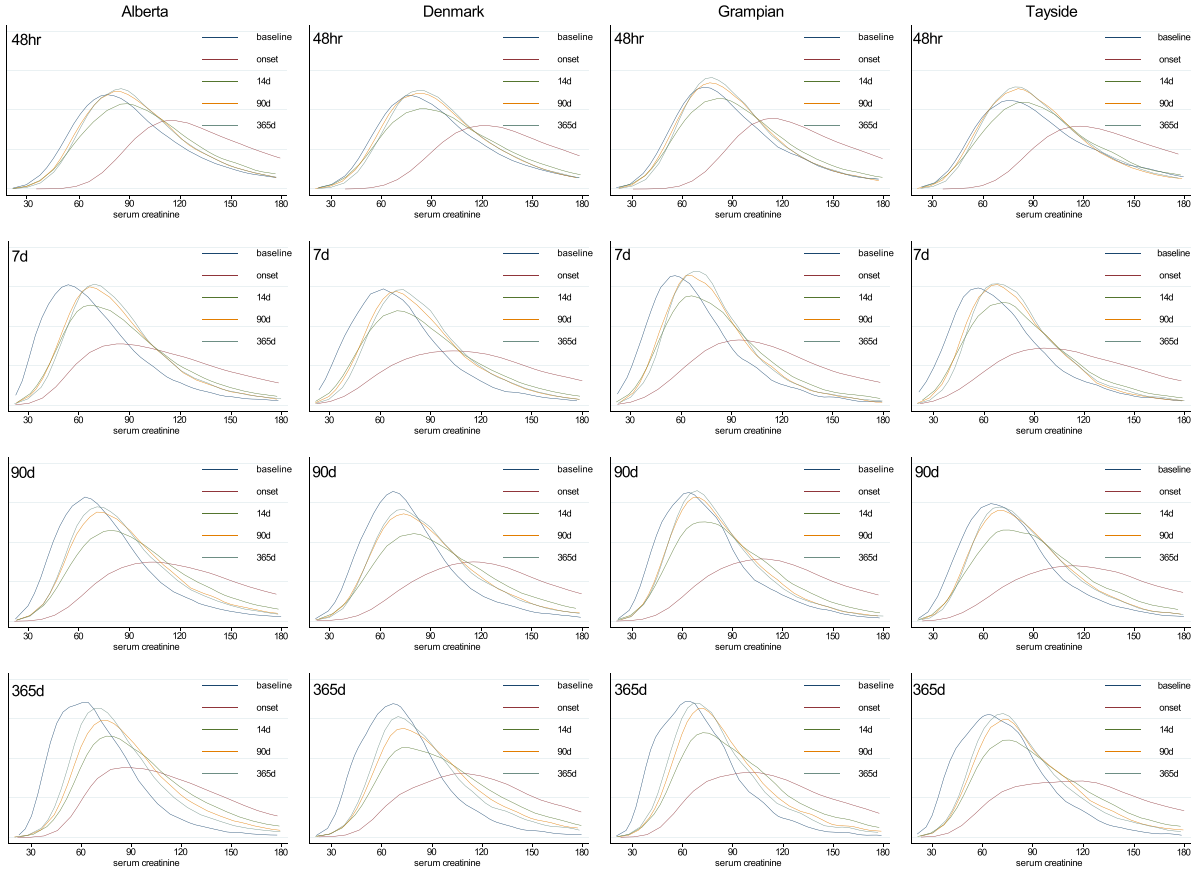



**Figure 3:** Distribution of creatinine over the course of 1 year according to each AKD subset definition and cohort.

more recovery among those within a 48-h change was consistent across all cohorts (Table 2); and across age, sex and disease subgroups (Table 3) although notably those of male sex, older age and with cancer had higher mortality, whereas female sex, young age and diabetes more frequently experienced non-recovery. Further sensitivity analysis identified consistent findings when patients without creatinine test results in a follow-up window were included in a separate 'untested' category, consistent when the analysis was restricted to those meeting exclusively one subset definition in isolation (Supplementary data, Table S3) and when

**Table 2:** One-year outcome percentages of AKD subsets for each cohort.

| | Alberta | | | | Denmark | | | | Grampian | | | | Tayside | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days |
| N | 100 278 | 101 075 | 136 465 | 93 640 | 57 659 | 56 043 | 77 254 | 37 240 | 18 620 | 18 524 | 22 767 | 13 252 | 24 932 | 24 441 | 31 696 | 18 011 |
| Dead | 33.7 | 33.4 | 29.9 | 15.4 | 42.0 | 41.9 | 37.0 | 23.8 | 39.3 | 39.8 | 38.1 | 23.4 | 44.2 | 44.9 | 41.8 | 27.4 |
| (95% CI) | (33.4–34.0) | (33.1–33.7) | (29.7–30.1) | (15.2–15.6) | (41.6–42.4) | (41.5–42.3) | (36.7–37.3) | (23.4–24.2) | (38.6–40.0) | (39.1–40.5) | (37.5–38.7) | (22.7–24.1) | (43.6–44.8) | (44.3–45.5) | (41.3–42.3) | (26.7–28.1) |
| Non-recovery | 23.6 | 36.6 | 30.3 | 45.0 | 19.4 | 29.8 | 26.0 | 36.8 | 17.5 | 27.0 | 22.0 | 33.1 | 15.7 | 25.4 | 21.8 | 32.0 |
| (95% CI) | (23.3–23.9) | (36.3–36.9) | (30.1–30.5) | (44.7–45.3) | (19.1–19.7) | (29.4–30.2) | (25.7–26.3) | (36.3–37.3) | (16.9–18.1) | (26.4–276) | (21.5–22.5) | (32.3–33.9) | (15.2–16.2) | (24.9–26.0) | (21.3–22.3) | (31.3–32.7) |
| Recovery | 42.7 | 30.0 | 39.8 | 39.6 | 38.6 | 28.3 | 37.0 | 39.3 | 43.3 | 33.2 | 29.9 | 43.5 | 40.1 | 29.6 | 36.4 | 40.5 |
| (95% CI) | (42.4–43.0) | (29.7–30.3) | (39.5–40.1) | (39.3–40.0) | (38.2–39.0) | (27.9–28.7) | (36.7–37.3) | (38.8–39.8) | (42.6–44.0) | (32.5–33.9) | (29.3–30.5) | (42.7–44.4) | (39.5–40.7) | (29.0–30.2) | (35.9–36.9) | (39.8–41.2) |

Percentages may not add to exactly 100% due to rounding.
CI, confidence interval.

further broken down by combinations of AKD subset definitions met during the AKD episode (Supplementary data, Table S4).

The proportions of people with recovery of kidney function, non-recovery and death at 14, 90 and 365 days after AKD, according to AKD subset definitions, are shown in Fig. 4. The proportion of people with non-recovery decreased over time from 14 to 365 days, with the largest proportion with recovery among those within the 48-h subset. Across all subsets, a substantial proportion of people with evidence of recovery at 14 and 90 days subsequently deteriorated to a state of non-recovery or death. Overall, non-recovery deteriorations occurred in 44% and 30% of people who had apparent recovery at 14 and 90 days, respectively. These findings were similar when earlier creatinine values were not carried forward for those without tests in each time period, with the exception of those with 365-day interval change where a larger proportion of people did not have available repeat creatinine tests (Table 2, Supplementary data, Fig. S3). When the cohort was restricted to patients meeting only one of the AKD subset criteria, a similar pattern of differences in recovery between subset definitions was observed (Supplementary data, Table S2).

## DISCUSSION

This study used a harmonized analytical approach to measure kidney recovery after AKD across four population-based cohorts from three high-income countries with universal health coverage. There were consistent findings across all cohorts, age, sex and comorbidity subgroups underlining the transportability and reproducibility both of AKD as an exposure, and kidney recovery (defined as a resolution of AKD and a fall in creatinine to within 1.2× baseline) as a reliable outcome measurement. Using this replicable method, there were two key findings. First, both non-recovery and mortality at 1 year were common outcomes for people within each AKD subset encompassing interval creatinine changes within but not beyond 90 days, with changes over longer intervals than 90 days (i.e. not AKD) associated with lower mortality. This is consistent with the current scope of AKD encompassing all creatinine changes within 90 days whether with or without AKI, and indeed 90-day creatinine change intervals were as serious for both kidney non-recovery and mortality prognosis as AKI identified by shorter creatinine change intervals. In contrast, these findings do not reconcile with the design of existing e-alert systems, suggesting consideration should be given to limiting the algorithms that underpin such systems to 90 days where they currently span longer intervals. Secondly, across all populations, we found consistent patterns of the balance between mortality and non-recovery across subsets, including higher mortality among males and at older ages, and higher rates of non-recovery among females and at younger ages. This underlines the clinical importance to consider both mortality and non-recovery as separate outcomes experienced by different people for whom priorities may also differ: for instance younger individuals may benefit from greater focus on strategies to maximize kidney recovery after AKD, whereas elderly individuals may benefit more from strategies to minimize the risk of recurrent acute illnesses and to ensure advance care plans are accurately updated.

It is notable that kidney recovery was more frequent and rapid when creatinine changes were over a short interval (48 h), and persistent non-recovery was more common when creatinine changes were over longer intervals. This is clinically intuitive and likely reflects an arbitrary distinction between AKI, AKD and CKD across the spectrum of progression of kidney diseases over time. Also notably, the 48-h subset had a lower eGFR at baseline. Possible

**Table 3:** One-year outcome percentages of AKD subsets for each cohort across age, sex and morbidity subgroups.

| | Alberta | | | | Denmark | | | | Grampian | | | | Tayside | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days | 48 h | 7 days | 90 days | 365 days |
| *N* | 100 278 | 101 075 | 136 465 | 93 640 | 57 659 | 56 043 | 77 254 | 37 240 | 18 620 | 18 524 | 22 767 | 13 252 | 24 932 | 24 441 | 31 696 | 18 011 |
| Diabetes (*N*) | 15 849 | 13 523 | 18 668 | 10 026 | 12 019 | 10 380 | 14 863 | 6181 | 4195 | 3761 | 4666 | 2255 | 5853 | 5052 | 6235 | 2757 |
| Dead | 36.3 | 38.5 | 34.3 | 23.0 | 41.6 | 43.2 | 35.7 | 24.1 | 40.0 | 41.7 | 39.5 | 26.5 | 43.6 | 46.7 | 42.8 | 30.3 |
| Non-recovery | 24.3 | 32.1 | 27.0 | 39.1 | 19.6 | 27.0 | 24.8 | 36.1 | 17.3 | 23.2 | 19.1 | 28.2 | 15.4 | 22.8 | 20.1 | 28.8 |
| Recovery | 39.4 | 29.4 | 38.7 | 37.9 | 38.8 | 29.8 | 39.5 | 39.9 | 42.7 | 35.2 | 41.4 | 45.4 | 41.0 | 30.6 | 37.1 | 40.9 |
| Cancer (*N*) | 6879 | 6734 | 9399 | 4203 | 17 535 | 18 494 | 24 644 | 5591 | 4428 | 4738 | 5497 | 1452 | 5525 | 5972 | 7048 | 1670 |
| Dead | 48.1 | 50.6 | 47.1 | 29.9 | 54.1 | 54.9 | 52.3 | 35.3 | 56.0 | 59.1 | 58.0 | 39.7 | 62.3 | 64.4 | 62.9 | 48.0 |
| Non-recovery | 17.9 | 26.8 | 21.0 | 33.0 | 16.3 | 24.6 | 20.7 | 32.6 | 15.1 | 20.9 | 16.9 | 27.2 | 12.8 | 19.4 | 17.0 | 27.0 |
| Recovery | 34.0 | 22.6 | 31.9 | 37.1 | 29.6 | 20.5 | 27.0 | 32.1 | 29.0 | 20.0 | 25.1 | 33.1 | 24.9 | 16.2 | 20.1 | 25.0 |
| Heart failure (*N*) | 7227 | 5976 | 7894 | 3258 | 11 026 | 9158 | 11 556 | 4120 | 3329 | 2801 | 3181 | 1186 | 4489 | 3723 | 4244 | 1523 |
| Dead | 48.4 | 50.9 | 48.1 | 39.0 | 51.1 | 52.1 | 45.8 | 38.4 | 55.4 | 57.8 | 56.0 | 45.4 | 60.5 | 62.3 | 58.2 | 45.1 |
| Non-recovery | 18.1 | 23.8 | 19.7 | 29.1 | 16.9 | 23.5 | 23.4 | 29.7 | 12.6 | 17.1 | 14.4 | 22.3 | 12.1 | 16.9 | 16.0 | 23.7 |
| Recovery | 33.5 | 25.3 | 32.2 | 31.9 | 32.0 | 24.4 | 30.8 | 31.9 | 32.0 | 25.1 | 29.6 | 32.3 | 27.4 | 20.8 | 25.8 | 31.2 |
| Female (*N*) | 42 872 | 52 053 | 72 409 | 55 693 | 23 858 | 27 300 | 38 320 | 20 266 | 8448 | 9750 | 12 165 | 7723 | 11 885 | 13 440 | 17 121 | 10 397 |
| Dead | 34.7 | 31.2 | 26.8 | 13.0 | 43.2 | 40.4 | 34.8 | 22.3 | 38.8 | 37.1 | 35.0 | 20.6 | 43.7 | 42.1 | 38.9 | 25.2 |
| Non-recovery | 24.0 | 39.9 | 33.6 | 50.0 | 19.9 | 33.1 | 28.7 | 40.4 | 17.4 | 29.2 | 24.4 | 36.7 | 16.3 | 28.3 | 24.2 | 35.6 |
| Recovery | 41.2 | 28.9 | 39.5 | 37.0 | 36.9 | 26.5 | 36.5 | 37.3 | 43.7 | 33.7 | 40.7 | 42.8 | 40.1 | 29.6 | 36.8 | 39.2 |
| Male (*N*) | 57 406 | 49 022 | 64 056 | 37 947 | 33 801 | 28 743 | 38 934 | 16 974 | 10 172 | 8774 | 10 602 | 5529 | 13 047 | 11 001 | 14 575 | 7614 |
| Dead | 33.0 | 35.8 | 33.3 | 19.0 | 41.1 | 43.4 | 39.2 | 25.7 | 39.6 | 42.8 | 41.7 | 27.3 | 44.6 | 48.4 | 45.2 | 30.5 |
| Non-recovery | 23.3 | 33.0 | 26.6 | 37.5 | 19.0 | 26.6 | 23.4 | 32.5 | 17.5 | 24.6 | 19.2 | 28.1 | 15.3 | 22.0 | 18.9 | 27.2 |
| Recovery | 43.7 | 31.1 | 40.1 | 43.5 | 39.9 | 30.0 | 37.4 | 41.8 | 42.9 | 32.6 | 39.1 | 44.6 | 40.1 | 29.6 | 35.9 | 42.4 |
| Age ≥70 years (*N*) | 54 779 | 49 157 | 64 007 | 35 090 | 36 997 | 32 659 | 45 036 | 20 618 | 11 762 | 10 774 | 13 161 | 7135 | 17 528 | 15 973 | 20 256 | 10 784 |
| Dead | 42.3 | 44.4 | 42.3 | 30.0 | 49.2 | 50.6 | 46.0 | 34.7 | 46.3 | 48.2 | 47.7 | 34.4 | 49.3 | 51.4 | 49.3 | 37.1 |
| Non-recovery | 20.2 | 29.2 | 22.3 | 32.5 | 17.1 | 25.0 | 21.6 | 30.9 | 14.4 | 20.8 | 16.0 | 23.5 | 13.9 | 21.0 | 16.9 | 24.0 |
| Recovery | 37.5 | 26.5 | 35.4 | 37.5 | 33.7 | 24.5 | 32.4 | 34.4 | 39.3 | 30.9 | 36.2 | 42.1 | 36.8 | 27.6 | 33.8 | 38.9 |
| Age <70 years (*N*) | 45 499 | 51 918 | 72 458 | 58 550 | 22 221 | 24 991 | 34 354 | 17 507 | 6858 | 7750 | 9606 | 6117 | 7404 | 8468 | 11 440 | 7227 |
| Dead | 23.4 | 23.1 | 18.9 | 6.7 | 29.6 | 30.5 | 25.2 | 10.8 | 27.2 | 28.1 | 24.9 | 10.5 | 31.9 | 32.7 | 28.6 | 13.0 |
| Non-recovery | 27.8 | 43.5 | 37.4 | 52.4 | 23.3 | 36.1 | 31.8 | 43.7 | 22.7 | 35.6 | 30.1 | 44.2 | 20.1 | 33.9 | 30.3 | 44.0 |
| Recovery | 48.9 | 33.3 | 43.7 | 40.9 | 47.1 | 33.4 | 43.0 | 45.5 | 50.1 | 36.3 | 45.0 | 45.3 | 48.0 | 33.4 | 41.1 | 43.0 |

Percentages may not add to exactly 100% due to rounding.

explanations could either be a later presentation of AKI, or a tendency for transient absolute creatinine rises to occur more frequently among those with CKD. As recovery was more frequent and rapid in this subset, we favour the latter explanation. Nevertheless, as mortality was high across all three AKD subsets (48 h, 7 days, 90 days; ~40% at 1 year), this analysis suggests that all forms of AKD merit clinical attention. Collectively, these findings suggest that AKD (either with or without AKI) cannot be viewed conceptually as a 'milder' form of AKI, but as a syndrome of similar prognostic importance with respect to both mortality and non-recovery. Moreover, those who had AKD without AKI more commonly presented in the community and therefore could be less visible within the health system despite the clinical importance and potential urgency.

A final consideration relates to the transition between states of kidney recovery, non-recovery and death over the course of 1 year after AKD. Among people in our analysis who initially appeared to recover kidney function within 14 or 90 days after onset, it was commonplace to subsequently deteriorate. Thus, while current KDIGO AKI guidelines suggest following people until 90 days for assessment of recovery or *de novo* CKD, future guidelines should consider that this needs to be tailored to each individual, approached with caution and with the assurance of safety nets, such as a clarity on the responsibility and frequency of primary care (or non-specialist) surveillance and measures to avoid recurrence/relapse. In addition, differences in the relative frequencies of non-recovery and mortality outcomes for different subgroups (i.e. males, old age, cancer and heart failure had higher frequencies of death, and females, young age and diabetes had higher frequencies of non-recovery) indicate that the priorities and considerations within follow-up also require individualization beyond a single assessment for *de novo* CKD.

A limited number of prior studies have assessed recovery of kidney function following either AKI or AKD, although variable populations, definitions and timeframes for identification of kidney recovery makes comparisons between studies challenging [27]. A systematic review found that transient AKI (occurring and recovering within 48 h) was associated with lower mortality than AKI that persisted for >7 days, and that AKI that persisted at hospital discharge carried the poorest long-term prognosis [28]. Heung *et al.* reported increasing time to recovery up to 10 days from AKI onset was associated with greater risk of developing CKD 1 year later [29]. Among patients hospitalized with AKI in Canada, age, sex, AKI stage, prehospitalization serum creatinine level, albuminuria and discharge serum creatinine were identified as predictors for developing *de novo* advanced CKD stage G4 or greater [30]. More recently, a population-based study by Wang *et al.* [24] reported complete recovery in 35% of patients at 7 days after AKI onset and 49% of patient at 90 days, with risk factors for lack of recovery within 7 days including greater AKI severity, pre-existing cancer or heart failure, and recent use of loop diuretics. Our study extends this knowledge about kidney recovery by assessing differences in kidney recovery, persistence of recovery and mortality across AKI/AKD subset criteria, populations and subgroups, and provides tools to allow replication of these methods in a consistent manner in other cohorts.

Strengths of this study include the use of four large population-based cohorts from three different countries that capture all blood tests for all residents, accompanied by the consistency of findings across these cohorts. There are also important limitations. First, in this analysis we restricted the definition of AKD to functional creatinine change criteria within 90 days. Structural changes such as proteinuria were not assessed. Secondly, our study was dependent on the complete capture of blood test data within four

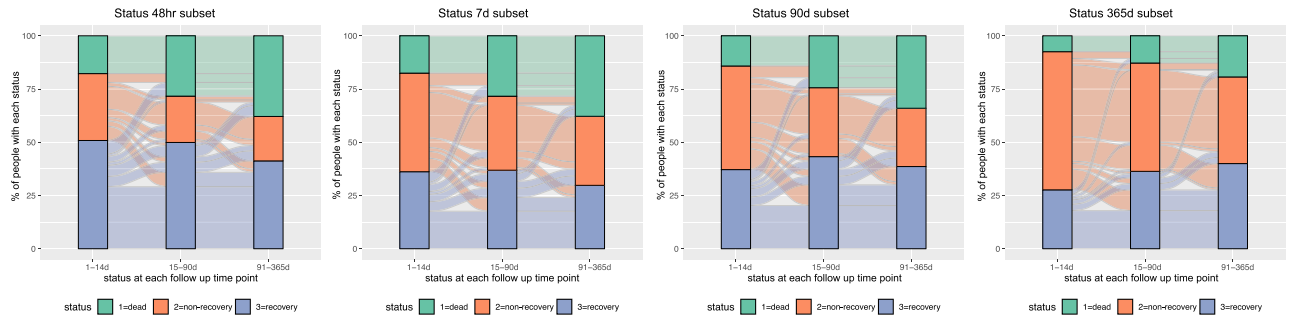



**Figure 4:** Proportions of patients with kidney function recovery status over the first year according to each AKD subset definition and cohort.

populations from high-income countries, both for initial identification of AKD, and for following the outcomes of non-recovery and death. Decision making is dependent on good quality data, but unfortunately such completeness is not possible in countries where access to blood tests to identify AKD is limited, care is not integrated across clinical locations, or surveillance systems and infrastructure are insufficient. Thirdly, in this analysis we focused on new (incident) presentations of AKD. Elsewhere we have shown that 20% of people with AKI have had prior events within the past year and have more vascular morbidities than those presenting for the first time [22]. This association is plausible across all subsets of AKI/AKD discussed here and may influence kidney recovery. Future work should evaluate how these recurrent presentations differ with respect to recovery and how this interacts with underlying cause. Finally, we did not have granular information on detailed attributed causative factors for each presentation, but we did find that recovery differed with the presence of comorbidities of cancer, diabetes and heart failure. Further steps are also now warranted to apply these operationalized definitions of AKD, subsets and kidney recovery, to examine the prognostic implications of combining them with other clinical and biological information to predict patient outcomes or develop clinical phenotypes that warrant different clinical approaches.

In summary, this study applied and shared the tools to replicate a harmonized approach to study AKD across geographically distinct populations and operationalize kidney recovery as an outcome. It demonstrated, consistently across populations, that while the case-mix and setting may vary between subsets of AKD (over intervals of 48 h, 7 days and 90 days), all subsets of AKD confer a high mortality and non-recovery at 1 year. The relative balance between mortality and non-recovery rates differs according to age and case-mix, which reinforces the need for a personalized approach to post-AKI care. Irrespectively, across populations, age, sex and comorbidity subgroups, AKD covering an interval up to but not beyond 90 days represents a clinical syndrome of at least similar prognostic importance to AKI with respect to both mortality and sustained non-recovery.

## SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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## DATA AVAILABILITY STATEMENT

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

## CONFLICT OF INTEREST STATEMENT

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 express any opinion in relation to this study. All authors declared no competing interests.

(See related article by Faguer and Schanstra. Acute kidney injury or acute kidney disease: is it time to change endpoints in studies relying on intensive nephrology care? *Nephrol Dial Transplant* 2024; 39: 385–386)

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**Multi-cohort analysis of recovery of kidney function after acute kidney disease**

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| **Supplementary material** | **Page** |
|---|---|

Supplementary table S1 – Description of AKD subsets for each cohort when limited only to people presenting after meeting one subset criterion exclusively

| | Alberta | | | | Denmark | | | | Grampian | | | | Tayside | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 48hr | 7d | 90d | 365d | 48hr | 7d | 90d | 365d | 48hr | 7d | 90d | 365d | 48hr | 7d | 90d | 365d |
| N | 30832 | 24785 | 75674 | 71385 | 16378 | 11299 | 41504 | 26656 | 5256 | 3988 | 11771 | 9549 | 6893 | 5096 | 16703 | 12776 |
| age median/IQR | 75 (62-84) | 65 (51-78) | 66 (52-79) | 61 (43-75) | 77 (68-84) | 69 (58-79) | 72 (61-81) | 70 (56-81) | 78 (68-85) | 70 (57-81) | 72 (59-82) | 70 (53-81) | 80 (71-86) | 74 (61-83) | 74 (63-83) | 73 (59-82) |
| female % | 32.6 | 60.6 | 56.4 | 61.5 | 32.1 | 59.9 | 53.2 | 56.4 | 36.1 | 62.8 | 57.2 | 60.4 | 40.0 | 64.3 | 55.8 | 58.8 |
| inpatient % | 95.3 | 88.7 | 65.3 | 53.1 | 96.5 | 85.8 | 59.0 | 46.4 | 94.0 | 85.0 | 51.8 | 36.9 | 95.9 | 90.4 | 61.7 | 47.1 |
| ref eGFR median/IQR | 57 (38-79) | 105 (92-119) | 89 (66-106) | 96 (75-114) | 55 (37-76) | 102 (91-115) | 86 (64-100) | 89 (67-103) | 56 (39-77) | 102 (90-115) | 88 (65-102) | 90 (69-107) | 53 (36-74) | 99 (88-112) | 84 (61-99) | 86 (64-102) |
| ref Cr median/IQR | 106 (84-145) | 48 (38-62) | 72 (56-92) | 67 (52-85) | 109 (85-148) | 49 (38-63) | 73 (58-94) | 71 (56-90) | 105 (84-143) | 49 (39-63) | 71 (55-91) | 68 (53-86) | 109 (85-147) | 49 (38-65) | 74 (58-95) | 71 (56-91) |
| Comorbidities (%) | | | | | | | | | | | | | | | | |
| diabetes | 15.4 | 11.2 | 11.5 | 11.5 | 19.0 | 11.9 | 15.4 | 11.8 | 23.8 | 13.6 | 17.8 | 14.6 | 24.1 | 14.1 | 16.2 | 11.9 |
| cancer | 14.5 | 17.0 | 14.2 | 7.8 | 20.1 | 27.9 | 24.5 | 8.2 | 18.9 | 24.1 | 21.1 | 8.9 | 17.5 | 25.3 | 19.1 | 7.1 |
| coronary heart disease | 27.0 | 15.8 | 13.7 | 9.2 | 28.5 | 14.6 | 13.9 | 9.8 | 38.7 | 21.1 | 22.3 | 17.4 | 29.6 | 17.8 | 18.0 | 13.0 |
| heart failure | 20.2 | 11.3 | 9.4 | 5.6 | 18.2 | 8.2 | 9.2 | 5.5 | 21.0 | 8.1 | 9.9 | 6.2 | 19.6 | 8.6 | 9.4 | 5.5 |
| stroke | 15.0 | 13.3 | 10.7 | 7.3 | 13.8 | 13.7 | 10.9 | 9.0 | 13.3 | 12.1 | 8.4 | 6.6 | 11.8 | 11.7 | 7.7 | 6.0 |
| peripheral arterial disease | 11.6 | 7.8 | 7.0 | 4.6 | 12.1 | 7.7 | 7.4 | 5.4 | 13.8 | 7.7 | 7.0 | 4.6 | 11.3 | 7.1 | 5.4 | 4.0 |

Abbreviations: AKD, acute kidney disease; Cr, creatinine; d, day; eGFR, estimated glomerular filtration rate; hr, hour; IQR, inter-quartile range

Supplementary table S2 (part a) – Kidney function over the first year after presentation for each subset of AKD

| | Alberta | | | | | | | | Denmark | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 48hr | | 7d | | 90d | | 365d | | 48hr | | 7d | | 90d | | 365d | |
| **Serum Creatinine** | | | | | | | | | | | | | | | | |
| ref median | 94 | (72-129) | 67 | (50-91) | 73 | (57-96) | 67 | (52-86) | 94 | (73-130) | 70 | (53-93) | 75 | (60-96) | 71 | (56-89) |
| presentation median | 137 | (110-184) | 115 | (82-165) | 130 | (97-182) | 116 | (87-158) | 140 | (112-187) | 123 | (89-170) | 134 | (102-183) | 125 | (95-170) |
| peak median | 145 | (114-202) | 120 | (85-176) | 133 | (98-190) | 117 | (87-162) | 150 | (117-210) | 129 | (92-188) | 138 | (104-195) | 127 | (96-175) |
| d14 median | 104 | (80-140) | 84 | (64-114) | 95 | (72-128) | 93 | (73-123) | 103 | (78-142) | 86 | (65-118) | 96 | (72-129) | 96 | (73-128) |
| d90 median | 97 | (76-127) | 80 | (63-104) | 86 | (68-113) | 86 | (69-111) | 96 | (75-128) | 81 | (64-106) | 87 | (68-114) | 88 | (69-115) |
| d365 median | 98 | (77-130) | 81 | (65-106) | 84 | (67-110) | 81 | (65-104) | 98 | (77-130) | 83 | (66-108) | 86 | (68-112) | 84 | (67-109) |
| **Ratio vs baseline** | | | | | | | | | | | | | | | | |
| ratio onset median | 1.41 | (1.29-1.59) | 1.63 | (1.55-1.80) | 1.66 | (1.56-1.89) | 1.65 | (1.56-1.86) | 1.42 | (1.29-1.62) | 1.64 | (1.55-1.84) | 1.67 | (1.56-1.91) | 1.66 | (1.56-1.89) |
| ratio 7d median | 1.47 | (1.33-1.71) | 1.69 | (1.57-1.96) | 1.69 | (1.57-1.98) | 1.66 | (1.56-1.90) | 1.50 | 1.34-1.78) | 1.72 | (1.58-2.04) | 1.71 | (1.58-2.04) | 1.68 | (1.56-1.96) |
| ratio 14d median | 1.10 | (0.91-1.33) | 1.30 | (1.05-1.57) | 1.35 | (1.04-1.60) | 1.53 | (1.19-1.67) | 1.08 | (0.90-1.31) | 1.26 | (1.02-1.54) | 1.29 | (1.03-1.58) | 1.51 | (1.11-1.64) |
| d90 median | 1.05 | (0.87-1.26) | 1.22 | (1.00-1.50) | 1.16 | (0.98-1.50) | 1.40 | (1.07-1.60) | 1.03 | (0.86-1.23) | 1.18 | (0.99-1.45) | 1.14 | (0.98-1.41) | 1.26 | (1.04-1.56) |
| d365 median | 1.07 | (0.88-1.29) | 1.24 | (1.02-1.52) | 1.15 | (0.98-1.39) | 1.23 | (1.04-1.52) | 1.06 | (0.88-1.27) | 1.21 | (1.01-1.47) | 1.14 | (0.99-1.36) | 1.19 | (1.02-1.48) |
| **CKD EPI 2009** | | | | | | | | | | | | | | | | |
| ref median | 64 | (42-87) | 89 | (65-108) | 84 | (60-103) | 92 | (70-112) | 62 | (41-86) | 86 | (63-101) | 81 | (59-97) | 85 | (64-101) |
| presentation median | 40 | (27-54) | 50 | (31-75) | 43 | (28-62) | 50 | (33-73) | 38 | (27-52) | 45 | (30-67) | 41 | (27-57) | 44 | (30-62) |
| peak median | 37 | (24-52) | 47 | (29-72) | 41 | (26-61) | 49 | (32-72) | 35 | (23-49) | 42 | (27-64) | 39 | (25-56) | 43 | (28-62) |
| d14 median | 57 | (38-79) | 72 | (49-94) | 62 | (43-87) | 65 | (45-89) | 56 | (37-80) | 69 | (47-92) | 61 | (42-85) | 61 | (41-85) |
| d90 median | 62 | (43-84) | 77 | (54-96) | 70 | (49-92) | 72 | (51-93) | 61 | (42-84) | 75 | (53-93) | 69 | (48-09) | 68 | (47-90) |
| d365 median | 61 | 42-83 | 76 | (53-95) | 73 | (51-94) | 78 | (55-98) | 60 | (41-82) | 73 | (52-92) | 69 | (49-90) | 72 | (50-93) |
| **CKD EPI 2021** | | | | | | | | | | | | | | | | |
| ref median | 68 | (45-92) | 93 | (69-109) | 89 | (64-106) | 96 | (75-114) | 67 | (44-90) | 90 | (67-104) | 86 | (63-101) | 90 | (69-104) |
| presentation median | 42 | (29-57) | 53 | (34-79) | 46 | (30-66) | 53 | (35-76) | 41 | (29-55) | 48 | (32-71) | 43 | (29-60) | 47 | (32-66) |
| peak median | 40 | (27-55) | 50 | (31-76) | 44 | (28-64) | 52 | (34-75) | 38 | (25-52) | 45 | (29-68) | 42 | (27-59) | 46 | (30-65) |
| d14 median | 60 | (41-84) | 76 | (52-98) | 66 | (46-91) | 68 | (48-92) | 60 | (40-85) | 74 | (50-96) | 65 | (44-90) | 64 | (44-90) |
| d90 median | 65 | (46-88) | 81 | (58-100) | 74 | (53-96) | 75 | (54-97) | 65 | (45-88) | 79 | (56-97) | 73 | (52-94) | 72 | (50-94) |
| d365 median | 65 | (45-87) | 80 | (57-99) | 77 | (54-89) | 82 | (59-101) | 64 | (44-87) | 77 | (55-96) | 73 | (52-94) | 76 | (53-97) |

Abbreviations: AKD, acute kidney disease; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration Equation; Cr, creatinine; d, day; hr, hour

Supplementary table S2 (part b) – Kidney function over the first year after presentation for each subset of AKD

| | Grampian | | | | | | | | Tayside | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 48hr | | 7d | | 90d | | 365d | | 48hr | | 7d | | 90d | | 365d | |
| **Serum Creatinine** | | | | | | | | | | | | | | | | |
| ref median | 88 | (68-122) | 66 | (51-88) | 71 | (56-92) | 68 | (53-86) | 94 | (71-132) | 69 | (51-92) | 74 | (58-96) | 71 | (55-90) |
| presentation median | 134 | (108-176) | 115 | (86-160) | 126 | (95-173) | 120 | (90-163) | 141 | (111-188) | 120 | (87-169) | 134 | (100-185) | 128 | (94-175) |
| peak median | 141 | (111-194) | 120 | (88-173) | 129 | (97-182) | 121 | (90-168) | 149 | (115-206) | 126 | (90-182) | 139 | (103-196) | 130 | (95-181) |
| d14 median | 95 | (73-127) | 80 | (62-106) | 87 | (67-116) | 89 | (70-117) | 99 | (76-134) | 82 | (63-109) | 91 | (69-121) | 91 | (70-122) |
| d90 median | 89 | (70-116) | 76 | (60-97) | 80 | (63-103) | 82 | (66-104) | 92 | (72-120) | 77 | (61-100) | 83 | (66-109) | 84 | (67-110) |
| d365 median | 90 | (72-117) | 77 | (62-97) | 79 | (63-102) | 78 | (63-100) | 93 | (73-123) | 79 | (63-102) | 83 | (66-108) | 81 | (66-106) |
| **Ratio vs baseline** | | | | | | | | | | | | | | | | |
| ratio onset median | 1.44 | (1.31-1.65) | 1.63 | (1.55-1.83) | 1.66 | (1.56-1.89) | 1.66 | (1.56-1.90) | 1.42 | (1.30-1.61) | 1.65 | (1.56-1.86) | 1.67 | (1.57-1.93) | 1.67 | (1.57-1.94) |
| ratio 7d median | 1.51 | (1.35-1.78) | 1.70 | (1.57-2.00) | 1.69 | (1.57-1.99) | 1.68 | (1.56-1.96) | 1.48 | (1.33-1.75) | 1.72 | (1.58-2.02) | 1.72 | (1.58-2.05) | 1.70 | (1.58-2.00) |
| ratio 14d median | 1.07 | (0.89-1.29) | 1.21 | (1.00-1.51) | 1.21 | (1.00-1.54) | 1.48 | (1.08-1.61) | 1.05 | (0.87-1.26) | 1.20 | (1.00-1.51) | 1.21 | (1.00-1.54) | 1.39 | (1.06-1.61) |
| d90 median | 1.01 | (0.85-1.20) | 1.14 | (0.96-1.38) | 1.10 | (0.95-1.34) | 1.20 | (1.01-1.54) | 1.00 | (0.83-1.19) | 1.14 | (0.95-1.39) | 1.10 | (0.95-1.35) | 1.19 | (1.00-1.53) |
| d365 median | 1.04 | (0.87-1.22) | 1.16 | (0.98-1.40) | 1.10 | (0.97-1.30) | 1.15 | (1.00-1.42) | 1.03 | (0.84-1.22) | 1.17 | (0.98-1.43) | 1.11 | (0.97-1.32) | 1.16 | (1.00-1.43) |
| **CKD EPI 2009** | | | | | | | | | | | | | | | | |
| ref median | 67 | (44-88) | 87 | (65-103) | 84 | (61-100) | 86 | (66-106) | 60 | (39-83) | 84 | (60-100) | 79 | (56-96) | 82 | (61-101) |
| presentation median | 40 | (28-53) | 48 | (31-70) | 43 | (28-62) | 46 | (30-67) | 37 | (25-50) | 44 | (29-66) | 39 | (26-57) | 42 | (28-62) |
| peak median | 37 | (25-51) | 46 | (29-67) | 42 | (27-60) | 45 | (29-66) | 34 | (23-48) | 41 | (26-63) | 37 | (24-55) | 41 | (27-61) |
| d14 median | 61 | (42-83) | 74 | (52-94) | 67 | (47-90) | 65 | (46-89) | 57 | (39-79) | 70 | (49-91) | 62 | (43-86) | 62 | (43-87) |
| d90 median | 66 | (47-86) | 79 | (58-96) | 75 | (54-94) | 73 | (53-93) | 61 | (43-93) | 76 | (55-93) | 69 | (50-90) | 68 | (49-90) |
| d365 median | 66 | (46-86) | 78 | (58-95) | 76 | (55-94) | 77 | (55-97) | 60 | (42-82) | 74 | (53-91) | 70 | (49-90) | 71 | (51-92) |
| **CKD EPI 2021** | | | | | | | | | | | | | | | | |
| ref median | 71 | (48-93) | 91 | (70-106) | 89 | (65-104) | 91 | (71-108) | 64 | (42-88) | 88 | (64-102) | 84 | (60-100) | 87 | (66-104) |
| presentation median | 43 | (30-57) | 51 | (34-74) | 46 | (31-65) | 49 | (33-71) | 39 | (27-53) | 47 | (31-70) | 42 | (28-60) | 44 | (30-65) |
| peak median | 40 | (27-55) | 49 | (31-71) | 44 | (29-64) | 48 | (31-70) | 37 | (24-51) | 44 | (28-67) | 40 | (26-58) | 43 | (29-64) |
| d14 median | 65 | (45-88) | 79 | (56-98) | 71 | (50-94) | 69 | (49-93) | 60 | (42-84) | 75 | (52-95) | 66 | (46-90) | 66 | (46-91) |
| d90 median | 70 | (50-91) | 84 | (62-99) | 79 | (57-98) | 77 | (56-97) | 65 | (47-88) | 80 | (58-97) | 74 | (53-94) | 73 | (53-94) |
| d365 median | 70 | (50-90) | 83 | (62-99) | 80 | (58-98) | 81 | (58-100) | 65 | (45-87) | 78 | (57-95) | 74 | (53-94) | 76 | (54-96) |

Abbreviations: AKD, acute kidney disease; CKD EPI, Chronic Kidney Disease Epidemiology Collaboration Equation; Cr, creatinine; d, day; hr, hour

Supplementary table S3 – One year outcomes for each subset of AKD

| | Alberta | | | | Denmark | | | | Grampian | | | | Tayside | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 48hr | 7d | 90d | 365d | 48hr | 7d | 90d | 365d | 48hr | 7d | 90d | 365d | 48hr | 7d | 90d | 365d |
| **Outcomes of all people who meet a subset definition either in combination or exclusively** | | | | | | | | | | | | | | | | |
| N | 100278 | 101075 | 136465 | 93640 | 57659 | 56043 | 77254 | 37240 | 18620 | 18524 | 22767 | 13252 | 24932 | 24441 | 31696 | 18011 |
| **Status at 1year (%) blood tests not carried forward if missing** | | | | | | | | | | | | | | | | |
| dead | 33.7 | 33.4 | 29.9 | 15.4 | 42.0 | 41.9 | 37.0 | 23.8 | 39.3 | 39.8 | 38.1 | 23.4 | 44.2 | 44.9 | 41.8 | 27.4 |
| non-recovery | 20.0 | 30.2 | 24.3 | 28.9 | 17.1 | 25.8 | 22.4 | 27.1 | 14.6 | 22.3 | 17.6 | 23.2 | 13.4 | 21.3 | 17.9 | 23.5 |
| recovery | 36.3 | 25.4 | 35.2 | 33.1 | 33.6 | 24.5 | 33.1 | 33.3 | 36.8 | 27.9 | 35.6 | 36.7 | 34.7 | 25.3 | 32.3 | 34.3 |
| untested at 91-365d | 10.0 | 10.9 | 10.6 | 22.6 | 7.2 | 7.7 | 7.5 | 15.8 | 9.3 | 10.0 | 8.7 | 16.7 | 7.8 | 8.5 | 7.9 | 14.7 |
| **Status at 1year (%) blood tests carried forward if missing** | | | | | | | | | | | | | | | | |
| dead | 33.7 | 33.4 | 29.9 | 15.4 | 42.0 | 41.9 | 37.0 | 23.8 | 39.3 | 39.8 | 38.1 | 23.4 | 44.2 | 44.9 | 41.8 | 27.4 |
| non-recovery | 23.6 | 36.6 | 30.3 | 45.0 | 19.4 | 29.8 | 26.0 | 36.8 | 17.5 | 27.0 | 22.0 | 33.1 | 15.7 | 25.4 | 21.8 | 32.0 |
| recovery | 42.7 | 30.0 | 39.8 | 39.6 | 38.6 | 28.3 | 37.0 | 39.3 | 43.3 | 33.2 | 29.9 | 43.5 | 40.1 | 29.6 | 36.4 | 40.5 |
| **Outcomes limited only to only those presenting with one subset definition exclusively** | | | | | | | | | | | | | | | | |
| N | 30832 | 24785 | 75674 | 71385 | 16378 | 11299 | 41504 | 26656 | 5256 | 3988 | 11771 | 9549 | 6893 | 5096 | 16703 | 12776 |
| **Status at 1year (%) blood tests not carried forward if missing** | | | | | | | | | | | | | | | | |
| dead | 25.4 | 23.7 | 23.8 | 12.4 | 33.6 | 33.2 | 31.6 | 20.3 | 31.8 | 32.3 | 32.8 | 20.0 | 36.2 | 36.8 | 36.2 | 24.4 |
| non-recovery | 23.6 | 45.6 | 25.9 | 28.9 | 21.3 | 42.2 | 23.9 | 27.5 | 17.3 | 37.2 | 19.3 | 24.4 | 17.3 | 35.9 | 20.0 | 24.7 |
| recovery | 38.7 | 14.8 | 37.1 | 32.8 | 36.6 | 13.9 | 35.6 | 34.2 | 40.9 | 17.8 | 37.7 | 36.3 | 38.1 | 15.7 | 34.3 | 34.1 |
| untested at 91-365d | 12.4 | 15.8 | 13.3 | 25.9 | 8.5 | 10.8 | 8.9 | 18.0 | 10.0 | 12.6 | 10.2 | 19.3 | 8.4 | 11.6 | 9.5 | 16.8 |
| **Status at 1year (%) blood tests carried forward if missing** | | | | | | | | | | | | | | | | |
| dead | 25.4 | 23.7 | 23.8 | 12.4 | 33.6 | 33.2 | 31.6 | 20.3 | 31.8 | 32.3 | 32.8 | 20.0 | 36.2 | 36.8 | 36.2 | 24.4 |
| non-recovery | 28.1 | 57.7 | 34.1 | 48.0 | 23.8 | 50.0 | 28.6 | 39.0 | 20.0 | 46.3 | 25.1 | 36.6 | 19.5 | 43.5 | 25.0 | 34.9 |
| recovery | 46.6 | 18.6 | 42.1 | 39.6 | 42.7 | 16.9 | 39.8 | 40.7 | 48.2 | 21.4 | 42.1 | 43.4 | 44.4 | 19.7 | 38.8 | 40.7 |

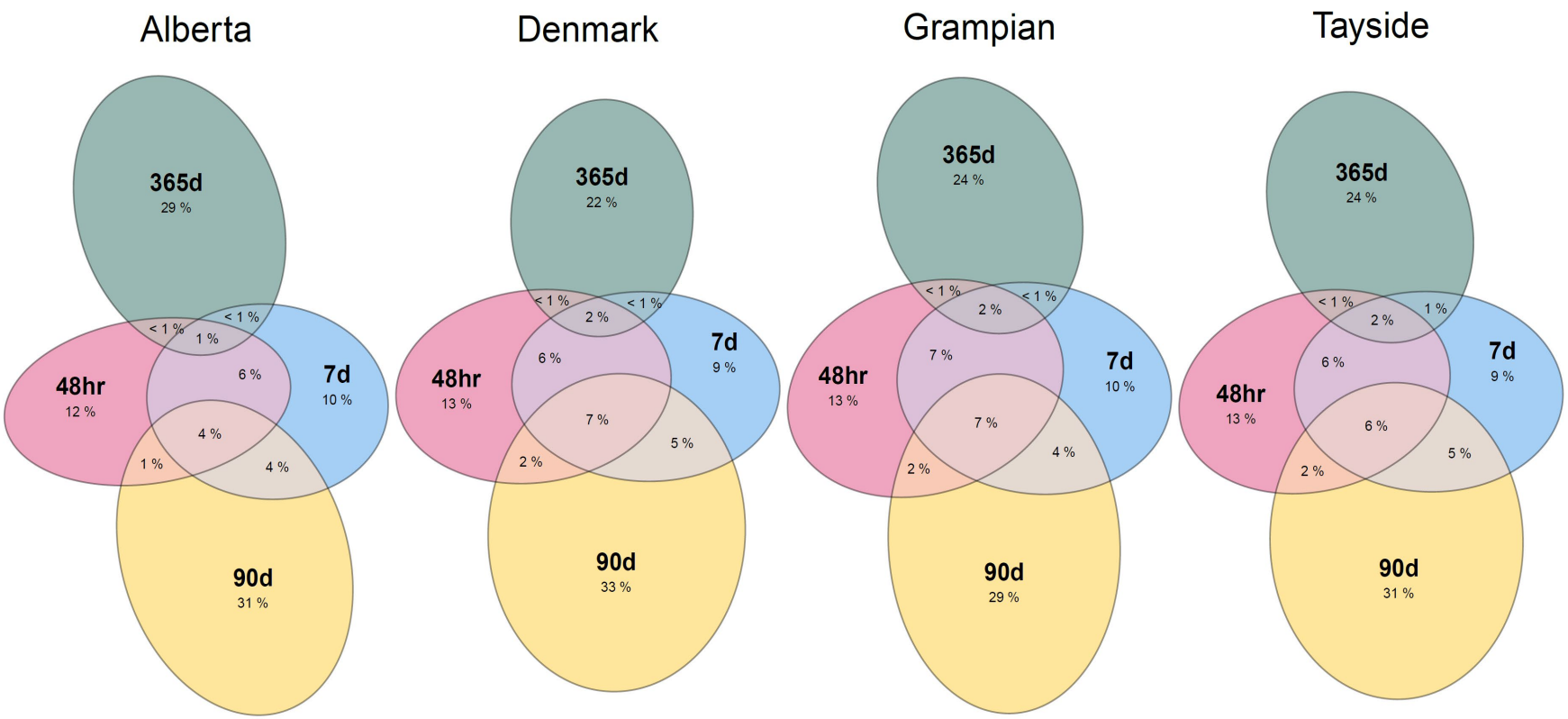
Abbreviations: AKD, acute kidney disease; d, day; hr, hour

Supplementary table S4 – Combinations of subset definitions met during each AKD episode and one year outcomes

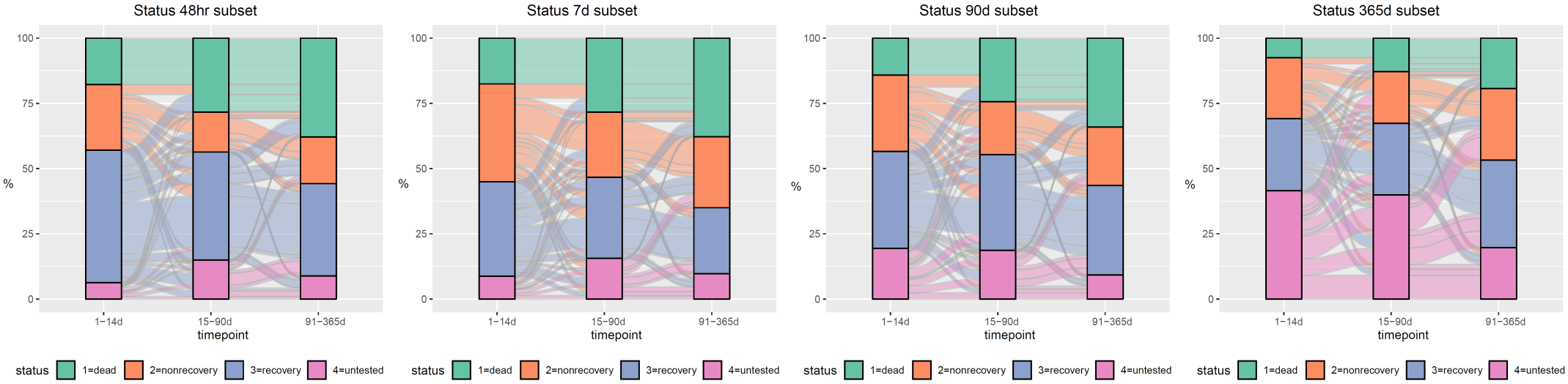
| | | | | N | Status at 1 year | | |
|---|---|---|---|---|---|---|---|
| 48hr | 7d | 90d | 365d | | dead | non-recovery | recovery |
| 1 | 0 | 0 | 0 | 46804 | 26.1 | 25.4 | 48.5 |
| 1 | 1 | 0 | 0 | 28179 | 30.0 | 36.8 | 33.2 |
| 1 | 0 | 1 | 0 | 13529 | 42.6 | 20.5 | 36.9 |
| 1 | 0 | 0 | 1 | 6821 | 34.4 | 25.2 | 40.4 |
| 1 | 1 | 1 | 0 | 49474 | 44.4 | 26.6 | 29.0 |
| 1 | 1 | 0 | 1 | 10995 | 36.0 | 23.6 | 40.4 |
| 0 | 1 | 0 | 0 | 38311 | 26.0 | 54.8 | 19.2 |
| 0 | 1 | 1 | 0 | 22000 | 36.6 | 32.8 | 30.6 |
| 0 | 1 | 0 | 1 | 3565 | 22.8 | 27.6 | 49.6 |
| 0 | 0 | 1 | 0 | 132262 | 25.8 | 31.8 | 42.4 |
| 0 | 0 | 0 | 1 | 112928 | 14.3 | 44.9 | 40.8 |
| Any combination (overall) | | | | 464868 | 26.6 | 35.4 | 38.0 |

Abbreviations: AKD, acute kidney disease; d, day; hr, hour

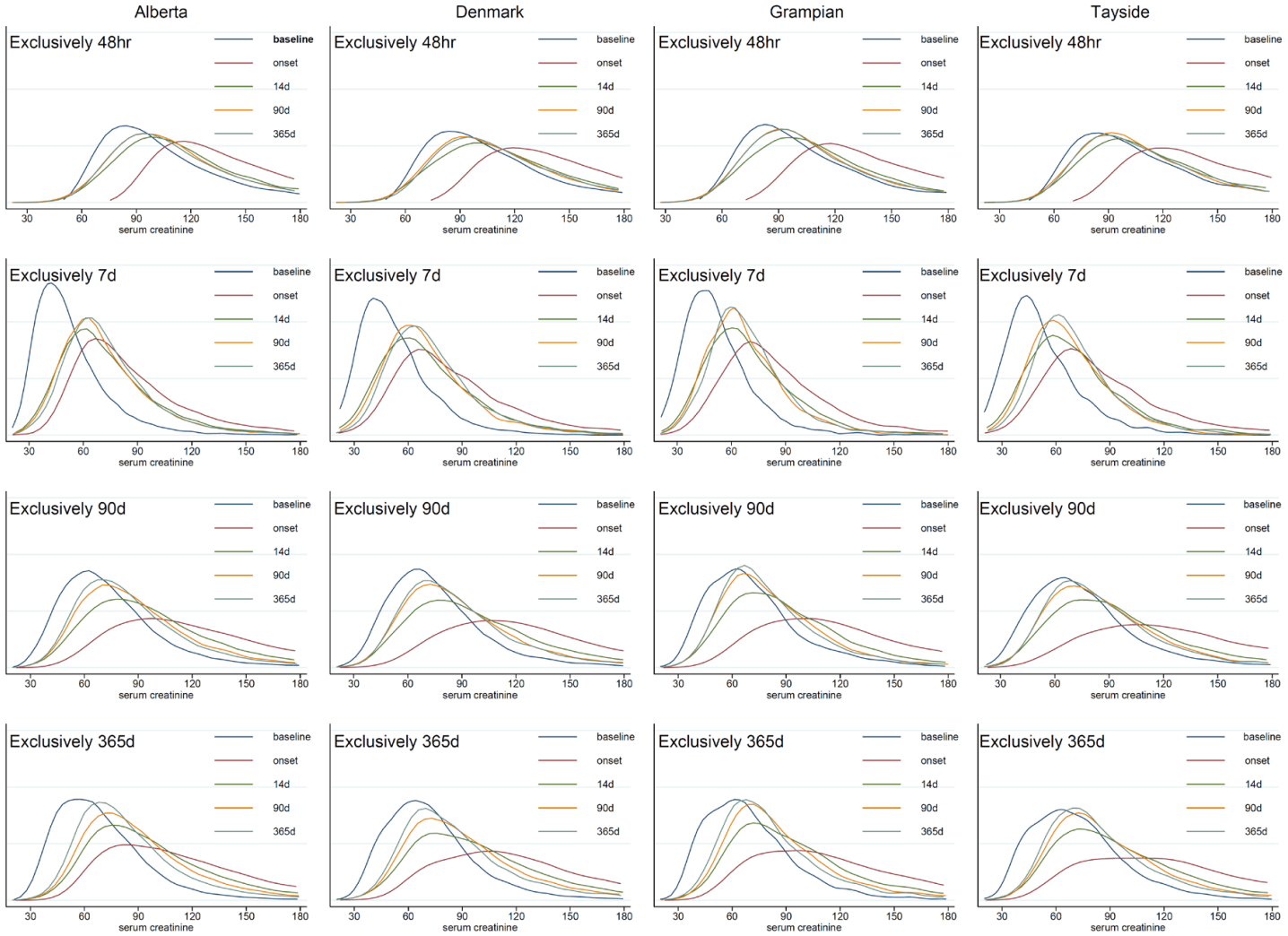
Supplementary figure S1 – Proportions and overlap of people meeting each combination of AKD criteria in each cohort (co-presenting on the same day as first AKD onset)



Supplementary figure S2 – Distribution of creatinine over the course of one year according to each AKD subset definition and cohort when limited only to people presenting after meeting one subset criterion exclusively



Supplementary figure S3 – Proportions of patients with kidney function recovery status over the first year for each AKD subset when those without bloods tests during an interval are included as a separate group



**Protocol: Multi-cohort analysis of recovery of kidney function after acute kidney disease**

Aim:

To determine the feasibility of comparing AKD epidemiology across geographically different populations, evaluate subsets of AKD criteria, and the consistency of a definition of kidney recovery

Objective:

Evaluate one year kidney function (both absolute and relative to baseline) by cohort population, over time, and definition subset criterion to inform definitions of AKI, AKD, and kidney recovery.

Population:

Population laboratory dataset constructed from all people in the population with IDMS aligned serum creatinine blood tests between 1st Jan 2009 and 31st Dec 2019.

Exclude from the dataset any blood tests (note not people) in instances where the test was done on a person aged <18, or where the test was done on a person receiving long term renal replacement therapy (i.e. cannot develop AKD as already have established kidney failure).

Exposure:

The first instance of AKD between 2011-2018 (two year run in to avoid the prevalent pool) based on changes in serum creatinine using a subsets of KDIGO based AKI/AKD criteria. This will involve use of the Aberdeen AKI definition that loops through blood tests meeting narrow and broad interpretations of KDIGO criteria and arranges into 90d episodes.

1. 26 micromol/l change in creatinine in 48 hrs
2. 1.5x rise in creatinine compared to lowest in last 7 d.
3. Ascertained reference creatinine from median 8-90 d if available
4. Ascertained reference creatinine from median 91 – 365 if 8-90d value not available.

Each of these subsets will be characterised in combination, separately in parallel, and in mutually exclusive subsets. Event start will be the date on which the respective definition was met, and severity onset based on the peak creatinine within 7d of day of onset vs the reference creatinine determined day of onset.

Characteristics:

Age, sex, blood test pattern, comorbidities (see table), context of presentation (hospitalised or not).

Outcomes:

Kidney function at 14d, 90d and 365d (as creatinine and eGFR), and recovery relative to baseline reference value. Recovery will be determined by a fall in creatinine to within 1.2x baseline for all, and both within 1.2 x baseline and < 26.5micromol/L above baseline for those in definition subset 1.

Analyses:

The analysis will report the total number of people meeting each subset definition, and the total with at least one AKD episode based on any definition. For the first AKD presentation by any definition, the analysis will report the combination of overlapping subset definitions in Euler 4 set diagrams (note a Euler diagram because the 90d and 365d rules cannot co-occur).

For combinations of subset definitions tables will be produced for characteristics, and 1 year outcomes. Characteristics reported for each subset combination will be age, sex, morbidities, kidney function at reference and onset, and context of presentation.

For outcomes within each definition subset, both absolute kidney function and recovery status relative to baseline: recovered, unrecovered, no tests, dead. These will be reported at reference, AKD peak (between days 0-7), 14d, 90d, 365d. A table will provide medians and IQRs, and if feasible (pending disclosure assessment), kdensity plots of absolute function among one year survivors. Overlaid kdensity plots for absolute eGFR distribution at each time point will use "last-value-carried-forward" approach. We note methodological issues with both eGFRs (issue that the 14d result is problematic as non-steady state) or creatinines (less meaningful at 90d and one year). Accordingly, both can be reported.

The results will populate Sankey plots of flow of kidney function recovery status at 14d, 90d, 365d between states of recovered, impaired, dead assuming "last value carried forward" in main analysis, and with/without "untested" as a separate category (sensitivity analysis).

**Preparation:**

This is a distributed analysis. The same Stata "do" file ("p2_replicationcode.do" attached in supplementary material) applies for each site for the population study. For the do-file to work, a lab data file will need to be prepared and saved as instructed below. A second data file will contain dates of death and date on which the person started kidney replacement therapy for end-stage kidney failure for all people in the population.

Once these files are ready provide update the file-path in the do file to run in Stata and prepare the AKD episodes and characterisation. The analysis will loop through all blood tests, collapse to first presentations, and link in the morbidities. A log output file and table frames will be generated to send back for sense checking. Figures will be generated in R.

**File 1:**

File name – "labdata_p2.dta"
File path – "C:\AKIstudy\p2\" (if different, you will need to amend the path in the coding file)
Structure – long format (multiple lab entries per individual, each date/lab result on a different row)

Variables and cleaning instructions

| | | |
|---|---|---|
| studyid | numeric | Pseudonymised ID. Please ensure the index is retained so that morbidity and other event data can be merged in in the future. Note only include results for people who are aged ≥18 years on the date of sample. Note the supplied code will remove observations in people who have already developed kidney failure on the date of the result. |
| dos | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the sample was received by the laboratory. While there may be multiple lab entries on the same day in the dataset you provide, the AKD code will select only the highest creatinine on a given day and drop the rest. Samples should be all creatinines in population 01jan2009-31dec2019 with those samples after a date of long term dialysis excluded as per above. |
| stcreat | numeric | IDMS aligned serum creatinine. Please check that instances of truncation e.g. "<10" are retained by converting to numeric "10" rather than removing. |
| age | numeric | Age in years on the date of sample |
| inpatient | numeric, binary | 1 = yes, 0 = no, applies to the location of that particular serum creatinine test result. For consistency across datasets, this includes any acute hospital setting including inpatient wards, admission/triage assessment units, emergency department. |
| femalesex | numeric, binary | 1 = female, 0 = male |

**File 2:**

File name – "patientdata_p2.dta"
File path – "C:\AKIstudy\p2" (must be the same directory as for labdata_p2.dta)
Structure – wide format (one entry per individual, each morbidity date in a different column)

Variables and cleaning instructions

| | | |
|---|---|---|
| studyid | numeric | Pseudonymised id. Please ensure the index is retained so that morbidity and other event data can be merged in in the future. |
| dod | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the person died. Blank if not dead. |

| | | |
|---|---|---|
| RRTdate | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the person started RRT for end-stage kidney failure (long term dialysis or kidney transplant). Blank if has not occurred. |
| CAdate | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the person first had a hospital based diagnosis, admin, or claim code for cancer. Blank if has not occurred.<br><br>ICD-10: C00-C96, except for C44<br><br>ICD-09 (Alberta): 140-165, 170-176, 179-208, 2386 |
| CHDdate | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the person first had a hospital based diagnosis, admin, or claim code for coronary heart disease. Blank if has not occurred.<br><br>ICD-10: I20, I21, I22, I23, I24, I25<br><br>ICD-09 (Alberta): 414, 410 |
| CHFdate | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the person first had a hospital based diagnosis, admin, or claim code for heart failure. Blank if has not occurred.<br><br>ICD-10: I09.9, I25.5, I42.0, I42.5–I42.9, I43, I50<br><br>ICD-09 (Alberta): 39891, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493, 4254, 4255, 4257, 4258, 4259, 428 |
| CVAdate | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the person first had a hospital based diagnosis, admin, or claim code for stroke. Blank if has not occurred.<br><br>ICD-10: G45, G46, H34.0, I6<br><br>ICD-09 (Alberta): 36234, 430-438 |
| DMdate | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the person first had a hospital based diagnosis, admin, or claim code for diabetes mellitus. Blank if has not occurred.<br><br>ICD-10: E10-E14<br><br>ICD-09 (Alberta): 250 |

| | | |
|---|---|---|
| PADdate | stata dofc date format e.g. 17898 = 01jan2009 | Date on which the person first had a hospital based diagnosis, admin, or claim code for peripheral arterial disease. Blank if has not occurred.<br><br>ICD-10: I70, I71, I731, I738, I739, I771, I790, I792, K551, K558, K559, Z958, Z959<br><br>ICD-09 (Alberta): 0930, 4373, 440, 441, 4431, 4432, 4438, 4439, 4471, 5571, 5579, V434 |

**Running the code file to generate outputs**

File name – "p2_replicationcode.do"
File path – "C:\AKIstudy\p2"

Please open the file in Stata, and check and confirm the file path at the beginning of the document (line that begins "cd… *filepath*"). To run the entire code, select all code (CTRL A) and run the do file (CTRL + D, rather than cutting and pasting into the console). Any potential errors should flag red in the console window, and the analysis should terminate (assume you ran by CTRL+D).

The code file will generate the files listed below. If acceptable with your local disclosure control policy and ethics permissions, please send them to me by email. In populations of ~1 million people, we do not anticipate any counts<5.

**Output files**

descriptives_p2.xlsx
distributions_p2.csv
euler_p2.xlsx
flow_cf.csv
flow_ncf.csv
function_p2.xlsx

There is also an option at the end of the code of producing the kdensity plots.

**Ethics permissions**

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 the 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 anonymised data performed in an ISO27001 and Scottish Government accredited secure safe haven. HIC Standard Operating Procedures have been reviewed and approved by the NHS East of Scotland Research Ethics Service and consent for this study was obtained from the NHS Fife Caldicott Guardian. Use of Grampian unconsented,

pseudonymised, routinely collected health data were provided by North West Research Ethics Committee (19/NW/0552), Grampian Caldicott guardian, and NHS Research and Development.