Population Epidemiology of Hyperkalemia – Cardiac and Kidney Long Term Health Outcomes.

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Epidemiology of hyperkalemia

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Abstract:

Rationale & Objective

The population burden and long-term implications of hyperkalemia have not been comprehensively studied. We studied how often and where hyperkalemia occurs as well as its independent association with survival and long-term cardiac and kidney health.

Study Design

Population-based cohort study of adults residents of Grampian, UK (adult population 468,594).

Setting and Participants

Among the 468,594 adult residents, 2012-2014, 302,630 people with at least one blood test were followed until 2019.

Exposures

Hyperkalemia was defined as serum potassium ≥5.5 mmol/L. Adjustment for comorbidities, demographics, KDIGO measures of acute and chronic kidney function, and medications prescribed prior to measurement of serum potassium.

Outcomes

All-cause mortality, cardiac events and kidney failure.

Analytical Approach

Description of the annual incidence of hyperkalemia and the characteristics associated with its occurrence. Adjusted Cox proportional hazards (PH) analysis to evaluate the independent long-term association of hyperkalemia with all-cause mortality among people who survived ≥90-days after blood testing. Cause-specific PH models were fit to evaluate the association of HK with cardiac events/death, non-cardiac death, and kidney failure. Effect modification by level of eGFR at the time of blood testing was explored.

Results

The annual population incidence of HK was 0.96 per 100 person-years. This represented 2.3%, 2.1%, and 1.9% of people with at least one blood test in 2012, 2013 and 2014, respectively. Two-thirds of episodes of hyperkalemia occurred in the community. The HK rate was two-fold higher for each 10-year greater age. Those with HK were 20 times more likely to have concurrent AKI, and 17 times more likely to have eGFR <30 ml/min/1.73m^2. Throughout five years of follow-up (2,483,452 person-years), hyperkalemia was associated with poorer health outcomes. This association held across all levels of kidney function and was irrespective of concurrent AKI, but was stronger among those with baseline eGFR ≥60 ml/min/1.73m^2 (p for interaction <0.001). The adjusted hazard ratios (HR) (hyperkalemia vs no hyperkalemia) and 95% confidence intervals for people with eGFR ≥60 ml/min/1.73m^2 and eGFR<30 ml/min/1.73m^2 were 2.3 (2.2-2.5) and 1.5 (1.3-1.6) for mortality; 1.8 (1.6-1.9) and 1.4 (1.2-1.6) for cardiac events; and 17.0 (9.3-31.1) and 2.0 (1.5-2.8) for kidney failure, respectively.

Limitations

The observational nature of this study limits evaluation of causal relationships.

Conclusions

There is a substantial burden of hyperkalemia in the general population. Hyperkalemia is associated with poorer long-term health outcomes, especially kidney outcomes, that are independent of other established risk factors.

Summary

Epidemiology of hyperkalemia

Severe hyperkalemia is a recognized clinical emergency but the burden of more moderate hyperkalemia and its clinical implications are not well known. This study describes the burden and health outcomes associated with hyperkalemia episodes in a completely captured population in Scotland over a three-year period.

Hyperkalemia occurred in one in one-hundred persons per year. Hyperkalemia was much more common among the elderly, as well as those with advanced chronic kidney disease or acute kidney injury. People without chronic kidney disease who developed hyperkalemia were twice as likely to die, twice as likely to have a cardiac event, and 17 times more likely to develop kidney failure.

These findings indicate that hyperkalemia signals diminished kidney function and lasting subsequent risk to kidney health.

Introduction

The emergency management of hyperkalaemia (HK) is well outlined in best practice guidelines, but the true population burden remains unclear [1-3]. Existing studies have focused on selected patient subsets [4-8], or have incomplete capture of the population and laboratory tests [9,10], and as a result, may have limited generalisability for health policy and planning. Thresholds for defining HK are inconsistent, and absent from the Kidney Diseases Improving Global Outcomes (KDIGO) guidelines [11,12]. Guidelines from the UK Renal Association (2020) and the European Resuscitation Council have placed serum potassium thresholds for HK at mild (≥5.5 mmol/L), moderate (≥6.0 mmol/L) and severe (≥6.5 mmol/L) levels [1,13]. In current guidelines, HK at extreme levels (potassium ≥6.5 mmol/L) represents a clear-cut clinical emergency, whereas milder HK (≥5.5 mmol/L) may prompt a review of contributory factors (e.g. new drugs), but may lead to little further investigation [1]. This contrasts with a recent meta-analysis with individual person data which found an adverse prognosis even when baseline potassium is only slightly elevated within the normal range [14], but the lasting implications of an acute HK event remain unclear within a wider context of kidney function assessment including acute kidney injury. Accordingly, there is a need to understand not just how often hyperkalaemia occurs, but also where it occurs, why it has developed, and whether there are lasting considerations beyond the immediate phase of management.

HK is associated with both chronic (CKD) and acute kidney diseases (AKD) – conditions that have already undergone a paradigm shift in care and understanding over the past decade [11,12]. With emerging new therapeutic options for HK, a similar shift may also now be due [15-17]. Previously, acute kidney injury (AKI) was once considered an urgent transient problem of little long term

relevance, but is now understood to be associated with serious long term poor health within a broader umbrella of AKD [11,18]. Similarly, HK has been described in guidelines as a serious but transient problem solved by stopping drugs (e.g. Renin Angiotensin Aldosterone System [RAAS] blockers) even when of proven clinical benefit for heart failure, diabetes and kidney disease [19-25]. However, if an episode of HK worsens kidney and cardiac outcomes independent of AKI and CKD, it may represent a powerful additional risk stratification tool for evaluation of kidney reserve, need for monitoring and long term decision making. While such an independent association of HK with poorer kidney and cardiac outcomes would not causally confirm HK as a marker of low kidney functional reserve, it would imply such a relationship, and the need for further monitoring. Accordingly, it may now be necessary to reconsider long term strategies in HK, informed by population real-world evidence and new potential treatment strategies.

In this long term population study, we have used electronic health data covering a complete health jurisdiction in North Scotland (adult population 468,594) capable of following all laboratory, health episode and prescribing data for all adult residents irrespective of how they transition through health care across the community and hospital divide [26-28]. We wished to determine the full population burden of HK: to establish how often HK occurs, where it occurs, the long-term implications for mortality, cardiac and kidney health, and how hyperkalaemia fits within existing kidney paradigms of AKI, AKD and CKD. We hypothesised that, controlling for AKI and CKD, mild episodes of hyperkalaemia may be a complementary marker of diminished kidney or physiological reserve even when standard metrics of kidney function (such as eGFR) are otherwise normal. Thus, in prognostic analysis, we assessed whether mild episodes of HK (≥5.5mmol/L) were associated with an excess of poor outcomes even into the long term,

independent of level of kidney function (AKI and CKD), with a particular focus on cardiac events and kidney failure.

Methods

We reported this study according to the STROBE guidelines [29]. Permissions for the use of unconsented, pseudonymised, routinely collected health data were provided by North of Scotland Research Ethics Committee (18/NS/0051), Grampian Caldicott guardian, and NHS Research and Development.

Data sources

The Grampian Laboratory Outcomes Morbidity and Mortality Study (GLOMMS) covers linked biochemistry and haematology laboratory data all processed in a single department for the whole Grampian region (covering all tests from both national health service and private clinics), linked to all hospital admissions, outpatient care, and community prescribing over a 10-year period. A strength of the laboratory data is the pre-transit centrifugation of all samples in community general practices since 2011 to minimise the potential for spurious HK secondary to haemolysis during transit for analysis [30]. Linkage to the Grampian kidney information management system enables the identification of people receiving renal replacement therapy (RRT).

Population

All adult (aged 18 years or over) Grampian residents with at least one laboratory serum potassium test in 2012-2014 were included. Results for people were excluded if they were already receiving long term RRT at the time of test.

Exposure and comparator

The exposure of interest was the first instance of HK for Grampian residents within each year of interest (2012, 2013 and 2014), defined in the main analysis as a serum potassium ≥5.5 mmol/L. Hence, a person with HK could present more than once if they had blood tests in multiple years. In sensitivity analyses, we also described HK at alternative potassium thresholds of ≥5.0, ≥6.0 and ≥6.5 mmol/L (i.e. thresholds not mutually exclusive). For non-HK comparators, we identified people who had at least one blood test during the year of interest (2012, 2013, or 2014) but did not meet a definition of HK in that year. The absence of HK in a given year was confirmed if no blood tests met HK in that year, and the last blood test in the year was taken as the start date for survival analyses. We used the last test to ensure that every person in the comparator group had an opportunity for monitoring for development of HK and to avoid bias in favour of the non-HK comparators that would otherwise occur (if the first test were used) due to pre-empting no subsequent HK episodes through the remainder of the calendar year after the first test.

Outcomes

The primary outcome was all-cause mortality followed up for at least 5 years to the end of 2019. We also assessed the outcome of cardiovascular events (fatal or non-fatal myocardial infarction, heart failure or stroke), and long term RRT (dialysis or kidney transplant). Follow up was through linkage to national registers. Migration to beyond the capture of these registers was negligible

for the age-mix of the cohort [31]. Those not registered as dead during follow up were assumed to be still alive.

Covariates of interest

These included age, sex, kidney function, medications, and comorbidities. Kidney function metrics included the presence of concurrent AKI within 7 days before or after the index presentation blood test and baseline estimated glomerular filtration rate (eGFR) at the time of the index blood test. AKI and eGFR were determined using a previously described and validated KDIGO based definition described in detail in previous studies [27,28]. To calculate eGFR we used the CKD-EPI equation [32]. Medications of interest were RAAS blockers, aldosterone antagonists, non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim containing antibiotics, loop diuretics, and thiazide diuretics used in the 90 days prior to presentation. Comorbidities were previous diagnoses of coronary heart disease, diabetes, heart failure, atrial fibrillation, peripheral arterial disease, hypertension, cancer, chronic pulmonary disease, and chronic liver disease using international classification of disease 10 (ICD-10) codes from hospital episodes in the previous 5 years [26,27].

To understand the context of presentation characteristics we recorded four groups describing the location and timing of the index blood test at the start of follow up: [1] Presentation in the community, which did not lead to hospital admission; [2] Presentation in the community and leading to an admission within 7 days; [3] Presentation within 24 hours of a hospital admission; and [4] Presentation that subsequently developed during a hospital admission.

Statistical analyses

We reported both the annual incidence of HK, and health outcomes after HK comparing those with and without HK.

We expressed the annual incidence in two ways, first we counted those with HK each year and used the whole adult Grampian population as the denominator; second we calculated the proportion of people HK among those with at least one blood test in a given year.

For health outcomes (mortality, cardiac and kidney failure), we compared those with HK, to those with at least one blood test in the same calendar year who did not have hyperkalemia. Since a person could contribute up to three records across multiple calendar years of the study we used robust variance estimation to account for instances of multiple records per person.

Annual incidence of HK

We determined the crude annual incidence rate of new HK episodes per 100 person-years using the published mid-year adult resident population of Grampian as the denominator. We determined rates overall, within ten-year bands of age, and for hyperkalaemia defined by thresholds at 5.0, 5.5, 6.0 and 6.5 mmol/L respectively. As we captured all population blood tests (including the negligible number of tests in private clinics outside of the NHS), and a denominator covering the full reference population overall, and within age-groups, the incidence rates represent the full burden of HK within the population. We also expressed the burden of HK as the proportion of those who received a blood test.

Characteristics of HK presentation

We described characteristics of presentations with and without hyperkalaemia by pooling first presentations across 2012, 2013 and 2014 and summarising covariates of interest both for the main analysis threshold 5.5 mmol/L, and at each alternative HK threshold (5.5, 6.0 and 6.5 mmol/L). We included as a comparator group, people who had a blood test but did not meet the main analysis hyperkalaemia definition.

Mortality and cardiac outcomes

A priori, we anticipated that any excess risk may change over time, particularly when stratifying by AKI. As our interest was in long term outcomes, in main analyses we excluded outcomes in the first 90 days after the presentation, but provided the outcomes of the first 90 days as an additional analysis in the supplementary material [27,33]. First, to assess if HK episodes were associated with all-cause mortality in both people with and without AKI, we plotted cumulative incidence of mortality (1 – Kaplan-Meier) stratified by HK and concurrent AKI status.

In a sensitivity analysis around HK definition threshold, we evaluated cumulative incidence of mortality according to the thresholds for the HK definition of (≥5.0, ≥5.5, ≥6.0 and ≥6.5 mmol/L); and for HK within a community context, by excluding any HK occurring within or leading to a hospital admission. Second, we plotted the separate cumulative incidences of the competing events of fatal/non-fatal cardiac event and non-cardiac death. Competing risks non-parametric cumulative plots were done using "stcompet" in Stata version 16 [34].

Adjusted long term mortality, cardiac and kidney outcomes

To evaluate the association of HK on the long-term mortality and cardiac outcome controlling for other covariates, we analysed the data using two statistical models. First, over a follow up of 5

years (to end 2019), we developed a Cox proportional hazard regression models (restricted to 90-day survivors) to assess the long term risk of all-cause mortality after HK compared to those receiving blood tests who did not have HK. As HK is recognised to be associated with CKD and may have different prognostic relevance depending on the level of kidney function, we tested an interaction term to examine whether the association between HK (adjusted for all covariates outlined above) and mortality differed between different levels of baseline eGFR category [35,36]. Second, to explore if HK was associated with both cardiac and non-cardiac outcomes we fitted cause-specific Cox proportional hazard regression models for cardiac events/death and the outcome of non-cardiac death, again with interaction term with baseline eGFR (<30, 30-44, 45-59, >=60 ml/min/1.73m^2) and adjusted for all covariates. We also fitted a cause-specific Cox regression model for long term RRT, censoring subjects at time of death and end of follow-up. As we were interested in the association between HK and outcomes, we considered the cause-specific model for this study as opposed to a Fine and Gray model for sub-distribution hazard ratios. We used the vce(cluster) option in Stata for robust variance estimation to account for instances of multiple records per person [37].

Sensitivity analyses

In the main analysis we focused on long term outcomes among people who had already survived 90 days. In a sensitivity analysis we also reported short term outcomes limited to the first 90 days, including everyone from day zero, with censoring at 90 days.

As diabetes and diabetes control could also influence HK incidence and outcome, we also tested for additional interaction between diabetes control (suboptimal if HbA1c >58 mmol/mol or 7.5%) and HK to determine the consistency of the findings across the presence and control of diabetes.

To avoid introducing bias from differences in calendar date of follow up of those with and without HK, we compared those presenting with HK with those with blood tests and no HK during the same calendar year. As a sensitivity analysis, to ensure that population specification did not materially influence results, we also specified a cohort with only unique patients comparing the first HK blood test presentation across the case ascertainment window 2012-2014 with those with blood tests and no HK across the whole window.

As a final sensitivity analysis we repeated the main analyses using time-varying Cox regression. We treated HK status as a time-varying exposure following unique patients from the first blood after 1st January 2012, updating HK and AKI exposure statuses when the HK definition was satisfied. Note that unlike the main analysis, this sensitivity analysis was not limited to the long term outcomes of 90-day survivors.

All analyses were formed using Stata SE 16 [37-40].

Results

Annual incidence of HK

Over a three-year period of monitoring adults at risk within the Grampian population, we identified 13482 people with a first HK event at a threshold of potassium ≥5.5 mmol/L (table 1). Using alternative HK thresholds there were 59571 first HK events at ≥5.0 mmol/L, 4491 at ≥6.0 mmol/L; and 2016 at ≥6.5 mmol/L. These definitions corresponded to respective annual

incidence rates per 100 person years (95% confidence interval) of 0.96 (0.94-0.98) at ≥5.5 mmol/L, vs 4.24 (4.20-4.27) at ≥5.0 mmol/L, 0.32 (0.31-0.33) at ≥6.0 mmol/L and 0.14 (0.14-0.15) at ≥6.5 mmol/L (table S1). Figure 1 (on the log scale) shows that annual rates of hyperkalaemia increased exponentially for any given HK threshold, with approximately a doubling of the HK incidence rate with each 10-year increase from age 40 years. A full breakdown of incidence rates at different HK thresholds and age groups is in table S1.

Alternatively, expressing HK as a proportion of people with blood tests (302630 unique people over the three years), HK represented 4099/182135 (2.3%), 4044/188539 (2.1%) and 3769/193407 (1.9%) of people with at least one blood test in 2012, 2013 and 2014 respectively.

Characteristics of people presenting with HK

Table 1 describes the characteristics of people presenting with HK, compared to all other people with at least one blood test. Alternative HK thresholds are provided in table S2. Most people with HK presented in the community and were not admitted to hospital, although the proportion requiring admission increased when restricting to only the most severe HK episodes ≥6.5mmol/L. More than half of those with HK had normal baseline kidney function and fewer than 20% had concurrent AKI, even among those with severe HK. Nevertheless, compared to people with blood tests who did not have HK, those with HK were 20 times more likely (unadjusted) to have had concurrent AKI, or a baseline estimated glomerular filtration rate (eGFR) <30ml/min/1.73m^2. Unadjusted, those with HK were also more likely to have diabetes (five-fold), heart failure (five-fold) and peripheral arterial disease (four-fold). Those with HK had greater prior use of RAAS

blockers, aldosterone antagonists and trimethoprim containing antibiotics, but less prior use of thiazide diuretics.

Clinical outcomes after HK accounting for the presence of AKI

Figures 2-3 and figures S1-S2 show cumulative incidence plots for all-cause mortality after HK. As shown in figure 2, even a mild threshold for HK (potassium ≥5.5mmol/L) was associated with a substantial increased long-term mortality, although excess mortality was less pronounced if the threshold for HK was 5.0 mmol/L. Figure S1 shows that excess all-cause mortality was associated with HK after accounting for AKI. Notably, whereas AKI was associated with substantial short-term mortality, HK was associated with greater long-term mortality as shown by the intersection of cumulative incidence plots. After excluding outcomes prior to 90 days (figure 3), a persistent long-term excess risk independent of AKI was evident up to five years, even when restricting the cohort only to people who remained in the community (figure S2). Figure 4 contrasts cumulative incidence for cardiac events (figure 4A) vs non-cardiac death (figure 4B). There was an excess of both cardiac and non-cardiac outcomes for those with HK, irrespective of AKI status. This is also represented as a stacked cumulative incidence plot in figure S3.

Adjusted long term outcomes after HK according to baseline eGFR

Table 2 provides the estimated long-term all-cause mortality for HK (vs no HK) among 90-day survivors at each level of baseline eGFR, adjusted for age-sex, and then adjusted for all listed covariates. Similarly, table 3 provides estimated cause-specific (cardiac and non-cardiac; RRT and non-RRT) hazard ratios. An interaction term between HK and eGFR group was significant, and therefore, retained in all models ($p<0.001$). Controlling for the baseline eGFR, outcomes from all models (Cox model for all-cause hazard ratios, table 2; Cox model for cause-specific hazard

ratios, table 3) demonstrated that hyperkalaemia was associated with long term excess overall mortality, and both cardiac events and non-cardiac death.

Table 3 also shows that excess event rates after HK also extend to the kidney outcome of renal replacement therapy (RRT). HK was particularly associated with an increased relative hazard of future RRT among those with otherwise preserved baseline kidney function, however we note wide confidence intervals due to the small number of events among those without HK (hazard ratio 17.0, 95% confidence interval 9.3-31.1).

In sensitivity analysis we reported outcomes of the first 90 days separately in table S3. These were excluded from the main analysis of long term outcomes, but the sensitivity analysis confirmed increased short term mortality among those with HK. Additional sensitivity analyses demonstrated a significant interaction between the presence of diabetes / diabetes control and HK ($p<0.001$). The results are presented separately in table S4, and all are consistent with the main results. We also repeated the main analysis, respecifying the cohort population so that non-HK comparators were only selected if there were no HK blood tests over the whole three year case ascertainment period. These findings were also comparable to the main analysis although the proportion of people within each calendar year of study was different (table S5 and table S6). Finally, respecifying the cohort with each person included once, followed from the first blood test from 2012 onwards, and HK as a time-varying exposure also showed materially similar results for all of the main analyses (table S7 and table S8).

Discussion

Although HK is a recognised clinical emergency, the full population burden, context and long-term implications of HK have not been comprehensively studied. In this full regional population with complete capture of all blood potassium values, clinical contexts and health outcomes, this analysis provides evidence of a greater burden related to HK than reported in previous literature. By capturing laboratory measures of HK in all settings (hospital and community), the annual incidence of potassium levels ≥5.5 mmol/L was 1 per 100 person years, increasing exponentially with age. This contrasts with a previous UK population estimate of 0.25 per 100 person years for the subset of people with HK ≥5.5 mmol/L based on an analysis limited to primary care records [9].

Our analysis shows that HK is associated with a lasting increased rate of poor outcomes even in mild cases. Previous pooled analyses have consistent findings [14], and this analysis now extends these findings showing they hold in the largest general population dataset to date, even among 90-day survivors, and even after accounting for baseline levels of kidney function and concurrent AKI. Crucially this excess event rate is present for all-cause mortality, cardiac events, kidney failure as well as non-cardiac and non-kidney health outcomes. An increase in kidney failure after HK among those with preserved baseline kidney function is particularly notable and implies a mechanism of reduced kidney reserve may be contributing to the poorer outcomes. Thus, “mild” HK is a novel predictor of lasting poor health outcomes that is independent of conventional kidney excretory function metrics. HK should not be considered solely an acute or transient problem, but a red flag indicator of diminished kidney reserve, and of lasting future health risk.

The most recent clarifications of acute kidney disease (AKD) as a diagnostic category have suggested its use as a term that encompasses more than just creatinine change measures of kidney excretory function, but also broader metrics of kidney structure and function [11,18]. The pattern and timing of health outcomes after HK in this analysis is notable, providing three reasons to support the inclusion of HK as an additional prognostic measure within this framework: First, the excess event rate following HK was independent of both AKI and baseline eGFR (table 2). Second, HK was associated with all health outcomes, but the association was particularly strong for kidney failure (table 3). Third, with respect to the timing of outcomes, whereas the excess event rate after AKI diminished over time, the excess event rate after HK followed a different pattern remaining consistently high over five years of follow-up (figure 4).

Strengths of this analysis include coverage of a complete population irrespective of where care was received, to enable a more accurate estimation of the full burden of HK. Centrifugation of community blood samples will have minimised the proportion of artefactual cases of HK related haemolysis. The long duration of follow up, and consideration of existing metrics of acute and chronic kidney excretory function demonstrate the clinical importance of HK as a long-term health outcome predictor. In particular, the separation of HK as a prognostic marker distinct from both AKI and CKD in one analysis is novel and of clinical significance.

A limitation is that this analysis cannot and should not be used to justify a putative causal relationship between HK and poor outcomes, or the extent to which the care or prevention of HK could lead to beneficial health outcomes. For many episodes, a causal relationship would be doubtful given the late timing of outcomes that were neither cardiac nor kidney related. It is more plausible that HK in this context represents a failed response to a “stressful challenge”. We

also acknowledge that an acute illness episode severe enough to cause hyperkalemia may have lasting health consequences that are not related to kidney functional reserve, but other factors related to the acute insult (e.g. damage to other organs). Nevertheless, the particularly high excess rate of kidney failure among those with normal baseline eGFR, and the lasting excess mortality rate after excluding the first 90 days both imply a need for ongoing kidney monitoring. Finally, these results do not suggest that an HK triggered cessation or dose reduction of RAAS blockers can explain this poorer prognosis because only 43% of people with HK were taking RAAS blockers prior to presentation, only 12% of people with HK had an established diagnosis of heart failure, and cardiac and non-cardiac outcomes were equally common after HK. Future work, therefore, should now dissect further current clinical care after HK, including existing patterns of monitoring, the risk of recurrent hyperkalaemia, and mediators of excess risk after hyperkalemia (e.g. recurrent AKI, recurrent cardiac events, or cardiac medication discontinuation).

In conclusion, this analysis reports a greater incidence of hyperkalaemia than has been possible to determine in previous studies. The analysis also demonstrates poorer long-term health outcomes after hyperkalaemia, especially kidney outcomes, that are complementary to and not explained by existing metrics of acute and chronic kidney excretory function. Clinicians should note that even minor episodes of hyperkalaemia are prognostically relevant, important to communicate, and worthy of consideration in the planning of ongoing care, monitoring and expectations for future health.

Supplementary Material

Figure S1. Cumulative all-cause mortality for the combination of hyperkalemia and AKI (including follow up of the first 90 days)

Figure S2. Cumulative all-cause mortality among 90-day survivors treated only in the community for the combination of hyperkalemia and acute kidney injury (AKI)

Figure S3. Stacked cumulative incidence of fatal / non-fatal cardiac events (solid line) and non-cardiac death (dashed line) among 90-day survivors for the combination of hyperkalemia and acute kidney injury (AKI)

Table S1. Annual incidence rate of hyperkalemia by age, based on different hyperkalemia definition thresholds

Table S2. Characteristics of people with and without hyperkalemia comparing the main analysis threshold (5.5) with alternative thresholds (5.0, 6.0 and 6.5 mmol/L)

Table S3. Short term mortality within the first 90 days after presenting with and without hyperkalemia at different levels of baseline kidney function (note the first 90 days were excluded from the main analysis of long term outcomes)

Table S4. Mortality among 90-day survivors after presenting with and without hyperkalemia at different levels of baseline kidney function and status of diabetes control

Table S5. Long term mortality among 90-day survivors after presenting with and without hyperkalemia at different levels of baseline kidney function, using the sensitivity analysis cohort population definition

Table S6. Counts of people within each year of the analysis period within the main analysis cohort, and the cohort developed for sensitivity analyses

Table S7. Long term mortality of people with at least one blood test in Grampian at different levels of baseline kidney function, with follow up from first blood test and hyperkalemia as a time varying exposure

Table S8. Long term cardiac events / cardiac death, renal replacement therapy, and non-cardiac death, with follow up from first blood test and hyperkalemia as a time varying exposure

Article Information

Author Contributions: Research idea and study design: AM, SS; data acquisition: SS; data analysis / interpretation: AM, MN, SS; statistical analysis: SS; supervision or mentorship: SS. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author

was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate.

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Table 1. Characteristics of people with and without hyperkalemia

	No HK (n = 550599)		HK ≥5.5 (n = 13482)		Overall (n = 564081)	
	n	%	n	%	n	%
Demographics						
mean age (SD)	57.2	(18.5)	67.9	(17.0)	57.5	(18.5)
female sex	304551	(55.3)	6215	(46.1)	310766	(55.1)
deprived	37023	(6.7)	992	(7.4)	38015	(6.7)
Presentation context						
community, not admitted	493519	(89.6)	8110	(60.2)	501629	(88.9)
community, subsequently admitted	5809	(1.1)	833	(6.2)	6642	(1.2)
presented at time of hospital admission	27374	(5.0)	2099	(15.6)	29473	(5.2)
presented during hospital admission	23897	(4.3)	2440	(18.1)	26337	(4.7)
Concurrent AKI of any stage						
Overall	3293	(0.6)	1645	(12.2)	4938	(0.9)
AKI stage 1	2482	(0.45)	816	(6.1)	3298	(0.6)
AKI stage 2	548	(0.1)	416	(3.1)	964	(0.2)
AKI stage 3	263	(0.05)	413	(3.1)	676	(0.1)
Baseline eGFR						
>=60	493642	(89.7)	7523	(55.8)	501165	(88.8)
45-59	37254	(6.8)	2032	(15.1)	39286	(7.0)
30-44	15402	(2.8)	2120	(15.7)	17522	(3.1)
<30	4301	(0.8)	1807	(13.4)	6108	(1.1)
Comorbidity						
diabetes mellitus	35864	(6.5)	3398	(25.2)	39082	(6.9)
suboptimal diabetes control (HbA1c >58)	18371	(3.3)	1973	(14.6)	20344	(3.6)
coronary heart disease	29934	(5.4)	2215	(16.4)	32149	(5.7)
heart failure	14965	(2.7)	1678	(12.4)	16643	(3.0)
hypertension	98811	(17.9)	5322	(39.5)	104133	(18.5)
stroke	17100	(3.1)	1123	(8.3)	18223	(3.2)
peripheral arterial disease	12600	(2.3)	1227	(9.1)	13827	(2.5)
atrial fibrillation	23514	(4.3)	1779	(13.2)	25293	(4.5)
chronic liver disease	8510	(1.5)	609	(4.5)	9119	(1.6)
cancer	32620	(5.9)	2136	(15.8)	34756	(6.2)
chronic pulmonary disease	46381	(8.4)	2170	(16.1)	48551	(8.6)
Medication in 90 days prior to HK						
renin angiotensin system blocker	136386	(24.8)	5810	(43.1)	142196	(25.2)
aldosterone antagonist	1942	(0.4)	87	(0.6)	2029	(0.4)
non-steroidal anti-inflammatory	55636	(10.1)	1417	(10.5)	57053	(10.1)
trimethoprim containing drug	19762	(3.6)	1135	(8.4)	20897	(3.7)
loop diuretic	28771	(5.2)	2479	(18.4)	31250	(5.5)
thiazide diuretic	65550	(11.9)	4453	(7.5)	66638	(11.8)

Abbreviations:

eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; n/a, not applicable (no milder form of HK); SD, standard deviation

Table 2. Long term mortality among 90-day survivors after presenting with and without hyperkalemia at different levels of baseline kidney function

	group	n subjects	n events	event rate (person years)	mean follow up (years)	All cause mortality HR (95% CI) (age-sex)	All cause mortality HR (95% CI) (fully adjusted)
HK vs no HK, eGFR>=60	no HK	486932	35553	0.016	4.6	2.90 (2.74-3.08)	2.33 (2.19-2.48)
	HK	6656	1603	0.059	4.1		
HK vs no HK, eGFR 45-59	no HK	35695	9660	0.066	4.1	2.17 (2.00-2.37)	1.70 (1.55-1.86)
	HK	1705	739	0.123	3.5		
HK vs no HK, eGFR 30-44	no HK	14154	5850	0.111	3.7	1.94 (1.78-2.11)	1.63 (1.49-1.78)
	HK	1754	952	0.171	3.2		
HK vs no HK, eGFR <30	no HK	3267	1827	0.175	3.2	1.65 (1.48-1.84)	1.46 (1.30-1.63)
	HK	1386	840	0.204	3.0		

Abbreviations:

CI, confidence interval (robust variance estimation to account for multiple records per person); eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; HR, hazard ratio; ref, reference group

Notes:

Full adjustment includes age, sex, acute kidney injury, eGFR, medications (RAAS blockers, aldosterone antagonists, non-steroidal anti-inflammatory drugs [NSAIDs], trimethoprim containing antibiotics, loop diuretics, and thiazide diuretics), and comorbidities (coronary heart disease, diabetes, heart failure, atrial fibrillation, peripheral arterial disease, hypertension, cancer, chronic pulmonary disease, and chronic liver disease). P-value for two-way interaction with eGFR <0.001.

Table 3. Long term cardiac events / cardiac death, renal replacement therapy, and non-cardiac death among 90-day survivors after presenting with and without hyperkalemia at different levels of baseline kidney function

	Cardiac events / cardiac death							Non-cardiac death							RRT						
eGFR category	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)
eGFR >=60	no HK	485189	30809	4.5	0.014	1.75	(1.62-1.89)	no HK	485189	22257	4.5	0.010	2.42	(2.24-2.62)	no HK	486930	79	4.6	0.00004	16.99	(9.29-31.07)
	HK	6438	1048	3.8	0.043			HK	6438	897	3.8	0.036			HK	6651	16	4.1	0.00059		
eGFR 45-59	no HK	35252	7505	3.8	0.056	1.37	(1.22-1.55)	no HK	35252	4921	3.8	0.037	1.87	(1.66-2.11)	no HK	35695	37	4.1	0.00025	4.66	(2.18-9.96)
	HK	1586	511	3.1	0.105			HK	1586	347	3.1	0.071			HK	1703	11	3.5	0.00184		
eGFR 30-44	no HK	13926	4264	3.3	0.092	1.46	(1.32-1.63)	no HK	13926	2699	3.3	0.058	1.65	(1.44-1.90)	no HK	14154	57	3.7	0.00109	4.33	(2.77-6.78)
	HK	1614	637	2.7	0.144			HK	1614	390	2.7	0.088			HK	1751	48	3.1	0.00877		
eGFR <30	no HK	3176	1209	2.8	0.133	1.37	(1.20-1.56)	no HK	3176	776	2.8	0.086	1.63	(1.39-1.91)	no HK	3249	153	3.1	0.01523	2.03	(1.48-2.77)
	HK	1261	498	2.5	0.155			HK	1261	369	2.5	0.115			HK	1333	173	2.6	0.05068		

Abbreviations:

CI, confidence interval (robust variance estimation to account for multiple records per person); eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; HR, hazard ratio; ref, reference group

Notes:

Cause specific models of HK vs no HK with censoring at the end of follow up, or the alternative outcome (i.e. censoring at non-cardiac death for the outcome of cardiac events, at any cardiac event for the outcome of non-cardiac death, and at death for the outcome of RRT). Cardiac event includes death of cardiac cause. Full adjustment includes age, sex, acute kidney injury, eGFR, medications (RAAS blockers, aldosterone antagonists, non-steroidal anti-inflammatory drugs [NSAIDs], trimethoprim containing antibiotics, loop diuretics, and thiazide diuretics), and comorbidities (coronary heart disease, diabetes, heart failure, atrial fibrillation, peripheral arterial disease, hypertension, cancer, chronic pulmonary disease, and chronic liver disease). P-value for two-way interactions with eGFR for each model all <0.0001.

Figures

Population epidemiology of hyperkalemia – Cause, context, cardiac and kidney long term health outcomes.

Supplementary material

Tables

Figures

Table S1. Annual incidence rate of hyperkalemia by age, based on different hyperkalemia definition thresholds

Age group in years	Grampian population	K >=5.0 rate per 100 person years (95% CI)		K >=5.5 rate per 100 person years (95% CI)		K >=6.0 rate per 100 person years (95% CI)		K >=6.5 rate per 100 person years (95% CI)	
>=80	24908	17.36	(17.06-17.66)	4.91	(4.75-5.07)	1.61	(1.52-1.70)	0.67	(0.61-0.73)
70-79	40996	11.44	(11.25-11.63)	2.71	(2.62-2.81)	0.87	(0.82-0.92)	0.34	(0.31-0.38)
60-69	64865	6.71	(6.59-6.82)	1.42	(1.37-1.48)	0.43	(0.40-0.46)	0.18	(0.17-0.20)
50-59	78759	3.83	(3.76-3.91)	0.72	(0.69-0.76)	0.23	(0.21-0.25)	0.11	(0.09-0.12)
40-49	84247	2.08	(2.02-2.14)	0.35	(0.33-0.37)	0.12	(0.11-0.14)	0.06	(0.06-0.08)
30-39	75827	1.28	(1.24-1.33)	0.25	(0.23-0.28)	0.11	(0.09-0.12)	0.06	(0.05-0.07)
18-29	98992	0.76	(0.72-0.79)	0.18	(0.16-0.20)	0.09	(0.08-0.11)	0.06	(0.05-0.07)
Overall	468594	4.24	(4.20-4.27)	0.96	(0.94-0.98)	0.32	(0.31-0.33)	0.14	(0.14-0.15)

Abbreviations:

CI, confidence interval; K, serum potassium threshold

Table S2. Characteristics of people with and without hyperkalemia comparing the main analysis threshold (5.5) with alternative thresholds (5.0, 6.0 and 6.5 mmol/L)

	HK ≥5.0 (n = 59571)		HK ≥5.5 (n = 13482)		HK ≥6.0 (n = 4491)		HK ≥6.5 (n = 2016)	
	n	%	n	%	n	%	n	%
Demographics								
mean age (SD)	65.8	(16.8)	67.9	(17.0)	66.5	(18.6)	64	(20.0)
female sex	27837	(46.7)	6215	(46.1)	2093	(46.6)	980	(48.6)
deprived	4412	(7.4)	992	(7.4)	352	(7.8)	156	(7.7)
Presentation context								
community, not admitted	45129	(75.8)	8110	(60.2)	2219	(49.4)	932	(46.2)
community, subsequently admitted	2394	(4.0)	833	(6.2)	365	(8.1)	190	(9.4)
presented at time of hospital admission	5734	(9.6)	2099	(15.6)	973	(21.7)	496	(24.6)
presented during hospital admission	6314	(10.6)	2440	(18.1)	934	(20.8)	398	(19.7)
Concurrent AKI of any stage								
Overall	3232	(5.4)	1645	(12.2)	787	(17.5)	369	(18.3)
AKI stage 1	1900	(3.2)	816	(6.1)	334	(7.4)	132	(6.5)
AKI stage 2	763	(1.3)	416	(3.1)	197	(4.4)	102	(5.1)
AKI stage 3	569	(1.0)	413	(3.1)	256	(5.7)	135	(6.7)
Baseline eGFR								
>=60	41995	(70.5)	7523	(55.8)	2285	(50.9)	1119	(55.5)
45-59	8210	(13.8)	2032	(15.1)	622	(13.8)	235	(11.7)
30-44	6102	(10.2)	2120	(15.7)	712	(15.9)	277	(13.7)
<30	3264	(5.5)	1807	(13.4)	872	(19.4)	385	(19.1)
Comorbidity								
diabetes mellitus	10515	(17.7)	3398	(25.2)	1240	(27.6)	520	(25.8)
suboptimal diabetes control (HbA1c >58)	5929	(10.0)	1973	(14.6)	763	(17.0)	316	(15.7)
coronary heart disease	7554	(12.7)	2215	(16.4)	747	(16.6)	276	(13.7)
heart failure	4639	(7.8)	1678	(12.4)	636	(14.2)	263	(13.0)
hypertension	18290	(30.7)	5322	(39.5)	1824	(40.6)	755	(37.5)
stroke	3641	(6.1)	1123	(8.3)	395	(8.8)	167	(8.3)
peripheral arterial disease	3605	(6.1)	1227	(9.1)	449	(10.0)	197	(9.8)
atrial fibrillation	5689	(9.5)	1779	(13.2)	628	(14.0)	277	(13.7)
chronic liver disease	1729	(2.9)	609	(4.5)	241	(5.4)	99	(4.9)
cancer	6850	(11.5)	2136	(15.8)	787	(17.5)	362	(18.0)
chronic pulmonary disease	7905	(13.3)	2170	(16.1)	763	(17.0)	334	(16.6)
Medication in 90 days prior to HK								
renin angiotensin system blocker	23048	(38.7)	5810	(43.1)	1816	(40.4)	721	(35.8)
aldosterone antagonist	303	(0.5)	87	(0.6)	29	(0.6)	14	(0.7)
non-steroidal anti-inflammatory	7066	(11.9)	1417	(10.5)	396	(8.8)	164	(8.1)
trimethoprim containing drug	3640	(6.1)	1135	(8.4)	446	(9.9)	208	(10.3)
loop diuretic	7142	(12.0)	2479	(18.4)	925	(20.6)	408	(20.2)
thiazide diuretic	1088	(8.1)	4453	(7.5)	352	(7.8)	158	(7.8)

Abbreviations:

eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; n/a, not applicable (no milder form of HK); SD, standard deviation

Notes:

Alternative HK thresholds are non-mutually exclusive alternative definitions, rather than mutually exclusive categories.

Table S3. Short term mortality within the first 90 days after presenting with and without hyperkalemia at different levels of baseline kidney function (note the first 90 days were excluded from the main analysis of long term outcomes)

	group	n subjects	n events	mean follow up (days)	event rate (person days)	All cause mortality HR (95% CI) (age-sex)	All cause mortality HR (95% CI) (fully adjusted)
HK vs no HK, eGFR>=60	no HK	492950	6018	89.2	0.00014	6.43 (5.94-6.95)	3.11 (2.84-3.43)
	HK	7447	791	83.0	0.00128		
HK vs no HK, eGFR 45-59	no HK	37074	1379	87.6	0.00042	4.32 (3.80-4.91)	2.03 (1.73-2.37)
	HK	1994	289	80.5	0.00180		
HK vs no HK, eGFR 30-44	no HK	15225	1071	85.2	0.00083	2.69 (2.37-3.05)	1.44 (1.24-1.68)
	HK	2083	329	80.3	0.00197		
HK vs no HK, eGFR <30	no HK	4110	843	74.9	0.00274	1.30 (1.14-1.48)	0.80 (0.67-0.93)
	HK	1773	387	75.6	0.00289		

Abbreviations:

CI, confidence interval (robust variance estimation to account for multiple records per person); eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; HR, hazard ratio; ref, reference group

Notes:

Full adjustment includes age, sex, acute kidney injury, eGFR, medications (RAAS blockers, aldosterone antagonists, non-steroidal anti-inflammatory drugs [NSAIDs], trimethoprim containing antibiotics, loop diuretics, and thiazide diuretics), and comorbidities (coronary heart disease, diabetes, heart failure, atrial fibrillation, peripheral arterial disease, hypertension, cancer, chronic pulmonary disease, and chronic liver disease). P-value for two-way interaction with eGFR <0.001.

Table S4. Mortality among 90-day survivors after presenting with and without hyperkalemia at different levels of baseline kidney function and status of diabetes control

	No diabetes							Diabetes without suboptimal control							Diabetes with suboptimal control (last HbA1c >58)						
eGFR category	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)
eGFR >=60	no HK	460106	30780	4.6	0.015	2.44	(2.28-2.61)	no HK	12344	2616	4.2	0.050	1.81	(1.50-2.20)	no HK	14482	2157	4.4	0.034	2.18	(1.87-2.55)
	HK	5373	1140	4.1	0.051			HK	457	179	3.7	0.107			HK	826	284	3.8	0.090		
eGFR 45-59	no HK	31603	8114	4.1	0.062	1.85	(1.67-2.05)	no HK	2370	918	3.8	0.102	1.43	(1.13-1.82)	no HK	1722	628	3.9	0.094	1.46	(1.16-1.84)
	HK	1130	491	3.5	0.124			HK	247	108	3.5	0.126			HK	328	140	3.6	0.012		
eGFR 30-44	no HK	11822	4738	3.7	0.107	1.61	(1.45-1.79)	no HK	1256	603	3.5	0.138	1.62	(1.28-2.06)	no HK	1076	509	3.6	0.133	1.72	(1.36-2.17)
	HK	1176	627	3.2	0.166			HK	256	148	2.8	0.190			HK	322	177	3.2	0.174		
eGFR <30	no HK	2528	1373	3.3	0.166	1.39	(1.21-1.59)	no HK	370	236	2.9	0.217	1.86	(1.40-2.47)	no HK	369	218	3.1	0.191	1.44	(1.10-1.87)
	HK	925	534	3.0	0.190			HK	202	137	2.8	0.239			HK	259	169	2.8	0.230		

Abbreviations:

CI, confidence interval (robust variance estimation to account for multiple records per person); eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; HR, hazard ratio; ref, reference group; RRT, renal replacement therapy

Notes:

Full adjustment includes age, sex, acute kidney injury, eGFR, medications (RAAS blockers, aldosterone antagonists, non-steroidal anti-inflammatory drugs [NSAIDs], trimethoprim containing antibiotics, loop diuretics, and thiazide diuretics), and comorbidities (coronary heart disease, diabetes, heart failure, atrial fibrillation, peripheral arterial disease, hypertension, cancer, chronic pulmonary disease, and chronic liver disease). P-value for adding diabetes control as interaction tern into the model <0.0001.

Table S5. Long term mortality among 90-day survivors after presenting with and without hyperkalemia at different levels of baseline kidney function, using the sensitivity analysis cohort population definition.

	group	n subjects	n events	mean follow up (years)	event rate (person years)	All cause mortality HR (95% CI) (age-sex)	All cause mortality HR (95% CI) (fully adjusted)
HK vs no HK, eGFR>=60	no HK	259106	15311	4.6	0.014	2.85 (2.70-3.01)	2.30 (2.17-2.43)
	HK	6023	1386	4.1	0.053		
HK vs no HK, eGFR 45-59	no HK	14708	4070	4.0	0.067	2.05 (1.88-2.23)	1.63 (1.49-1.77)
	HK	1374	611	3.5	0.118		
HK vs no HK, eGFR 30-44	no HK	5903	2595	3.5	0.120	1.66 (1.53-1.81)	1.44 (1.32-1.56)
	HK	1316	706	3.2	0.156		
HK vs no HK, eGFR <30	no HK	1530	862	3.0	0.173	1.45 (1.30-1.61)	1.33 (1.19-1.47)
	HK	926	573	2.9	0.194		

Abbreviations:

CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; HR, hazard ratio; ref, reference group

Notes:

Full adjustment includes age, sex, acute kidney injury, eGFR, medications (RAAS blockers, aldosterone antagonists, non-steroidal anti-inflammatory drugs [NSAIDs], trimethoprim containing antibiotics, loop diuretics, and thiazide diuretics), and comorbidities (coronary heart disease, diabetes, heart failure, atrial fibrillation, peripheral arterial disease, hypertension, cancer, chronic pulmonary disease, and chronic liver disease). P-value for two-way interaction with eGFR <0.001. Sensitivity analysis cohort refers to cohort population in which cases and comparators are collected across all calendar years, rather than collected within the same calendar year and then pooled across years (with multiple records for some people).

Table S6. Counts of people within each year of the analysis period within the main analysis cohort, and the cohort developed for sensitivity analyses

Year of presentation	Number of people in main analysis cohort				Number of people in sensitivity analysis cohort			
	No HK (%)		HK (%)		No HK (%)		HK (%)	
2012	177517	(32.2)	4618	(34.3)	38708	(13.3)	4618	(40.5)
2013	183950	(33.4)	4589	(34.0)	63394	(21.8)	3721	(32.7)
2014	189132	(34.3)	4275	(31.7)	189132	(64.9)	3057	(26.8)

Abbreviations: HK, hyperkalemia

Notes: Sensitivity analysis cohort refers to cohort population in which cases and comparators are collected across all calendar years, rather than collected within the same calendar year and then pooled across years (with multiple records for some people).

Table S7. Long term mortality of people with at least one blood test in Grampian at different levels of baseline kidney function, with follow up from first blood test and hyperkalemia as a time varying exposure

	group	n subjects	n events	mean follow up (years)	event rate (person years)	All cause mortality HR (95% CI) (age-sex)	All cause mortality HR (95% CI) (fully adjusted)
HK vs no HK, eGFR>=60	no HK	264745	20950	4.7	0.017	2.56 (2.41-2.71)	2.10 (1.98-2.23)
	HK	6751	2114	3.9	0.081		
HK vs no HK, eGFR 45-59	no HK	16005	5367	3.9	0.086	1.79 (1.63-1.97)	1.42 (1.29-1.56)
	HK	1632	869	3.1	0.169		
HK vs no HK, eGFR 30-44	no HK	6918	3610	3.2	0.161	1.49 (1.36-1.63)	1.32 (1.20-1.44)
	HK	1601	991	2.8	0.218		
HK vs no HK, eGFR <30	no HK	2337	1669	2.2	0.330	1.44 (1.30-1.60)	1.34 (1.21-1.48)
	HK	1241	888	2.4	0.299		

Abbreviations:

CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; HR, hazard ratio; ref, reference group

Notes:

Cohort developed by identifying unique individuals with follow up from time of first blood test. Full adjustment includes age, sex, acute kidney injury, eGFR, medications (RAAS blockers, aldosterone antagonists, non-steroidal anti-inflammatory drugs [NSAIDs], trimethoprim containing antibiotics, loop diuretics, and thiazide diuretics), and comorbidities (coronary heart disease, diabetes, heart failure, atrial fibrillation, peripheral arterial disease, hypertension, cancer, chronic pulmonary disease, and chronic liver disease). Hyperkalemia status, concurrent AKI and eGFR included as time varying covariates. P-value for two-way interaction with eGFR <0.001.

Table S8. Long term cardiac events / cardiac death, renal replacement therapy, and non-cardiac death, with follow up from first blood test and hyperkalemia as a time varying exposure

	Cardiac events / cardiac death							Non-cardiac death							RRT						
eGFR category	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)	group	n subjects	n events	mean follow up (years)	event rate (person years)	HR	(95% CI)
eGFR >=60	no HK	265378	11199	4.8	0.009	2.17	(2.03-2.32)	no HK	265378	11623	4.8	0.009	4.42	(4.12-4.75)	no HK	265378	34	4.8	0.00002	17.42	(10.94-27.75)
	HK	6818	1188	3.9	0.045			HK	6818	1332	3.9	0.050			HK	6818	18	4.1	0.00064		
eGFR 45-59	no HK	16175	2922	4.2	0.043	1.46	(1.32-1.62)	no HK	16175	2359	4.2	0.034	3.12	(2.77-3.52)	no HK	16175	13	4.4	0.00018	3.41	(1.63-7.16)
	HK	1665	563	3.2	0.106			HK	1665	452	3.2	0.085			HK	1665	9	3.6	0.00150		
eGFR 30-44	no HK	7087	1926	3.8	0.072	1.35	(1.22-1.49)	no HK	7087	1597	3.8	0.060	2.76	(2.42-3.14)	no HK	7087	16	3.9	0.00058	3.70	(2.27-6.04)
	HK	1636	660	2.9	0.137			HK	1636	459	2.9	0.095			HK	1636	31	3.3	0.00570		
eGFR <30	no HK	2519	902	2.9	0.122	1.39	(1.22-1.59)	no HK	2519	895	2.9	0.121	2.78	(2.37-3.25)	no HK	2519	88	3.0	0.01157	3.55	(2.57-4.90)
	HK	1269	562	2.5	0.174			HK	1269	421	2.5	0.130			HK	1268	127	2.7	0.03705		

Abbreviations:

CI, confidence interval; eGFR, estimated glomerular filtration rate (ml/min/1.73m^2); HK, hyperkalemia; HR, hazard ratio; ref, reference group

Notes:

Cause specific models of HK vs no HK with censoring at the end of follow up, or the alternative outcome (i.e. censoring at non-cardiac death for the outcome of cardiac events, at any cardiac event for the outcome of non-cardiac death, and at death for the outcome of RRT). Cardiac events include death of cardiac cause. Cohort developed by identifying unique individuals with follow up from time of first blood test. Full adjustment includes age, sex, acute kidney injury, eGFR, medications (RAAS blockers, aldosterone antagonists, non-steroidal anti-inflammatory drugs [NSAIDs], trimethoprim containing antibiotics, loop diuretics, and thiazide diuretics), and comorbidities (coronary heart disease, diabetes, heart failure, atrial fibrillation, peripheral arterial disease, hypertension, cancer, chronic pulmonary disease, and chronic liver disease). Hyperkalemia status, concurrent AKI and eGFR included as time varying covariates. P-value for two-way interaction with eGFR <0.001.

Figure S1. Cumulative all-cause mortality for the combination of hyperkalemia and AKI (including follow up of the first 90 days)

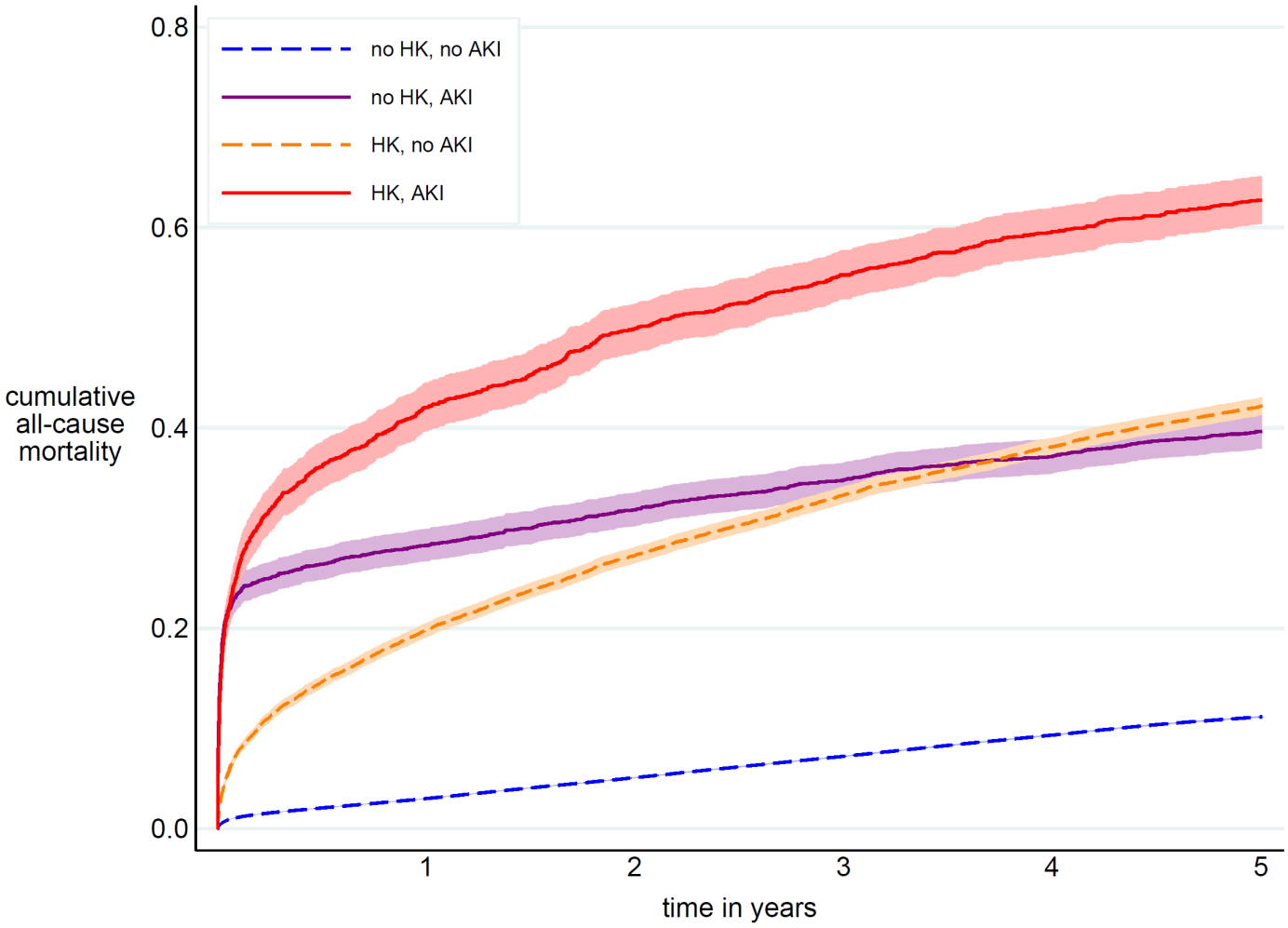


Figure S2. Cumulative all-cause mortality among 90-day survivors treated only in the community for the combination of hyperkalemia and acute kidney injury (AKI)

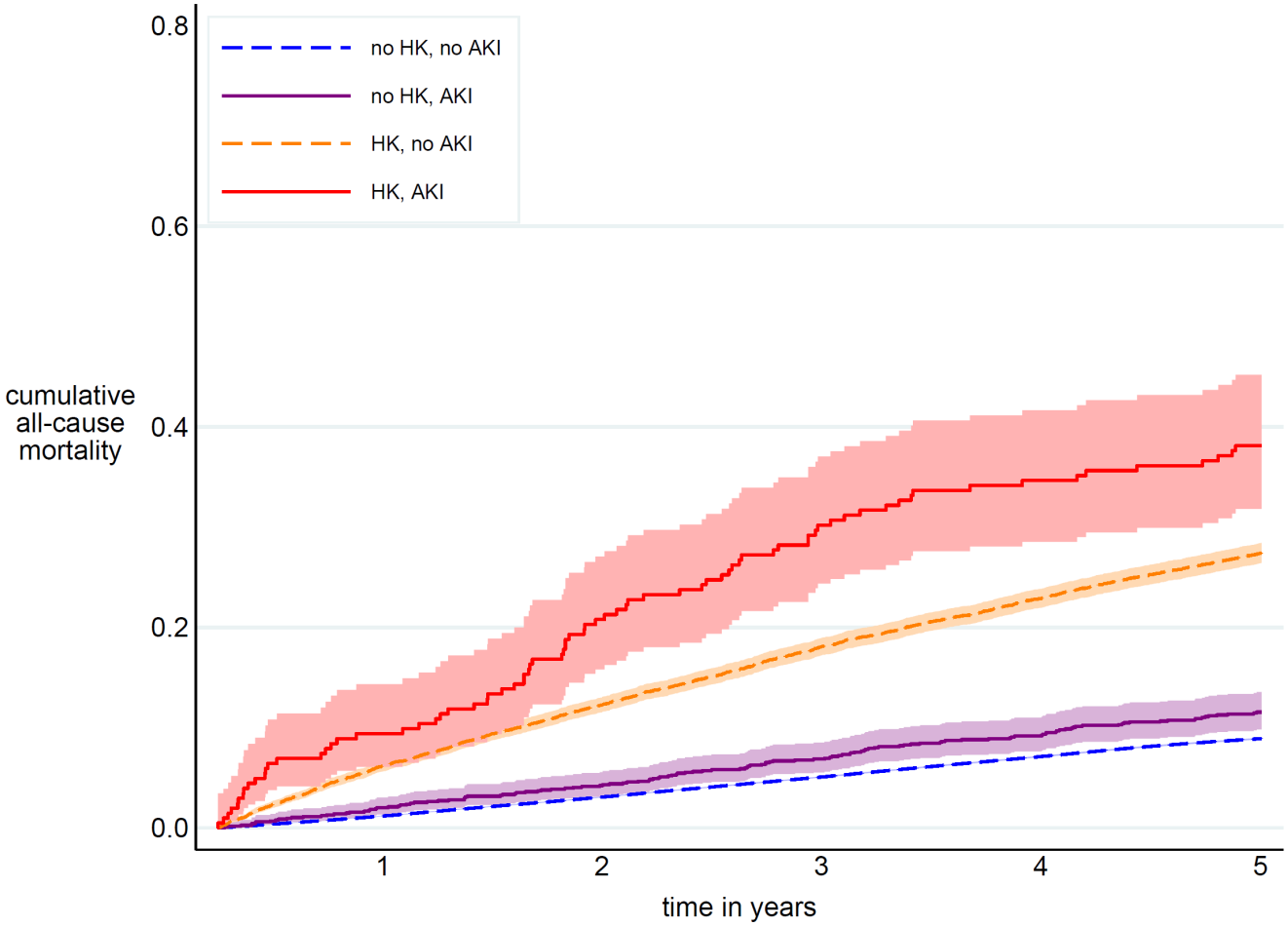
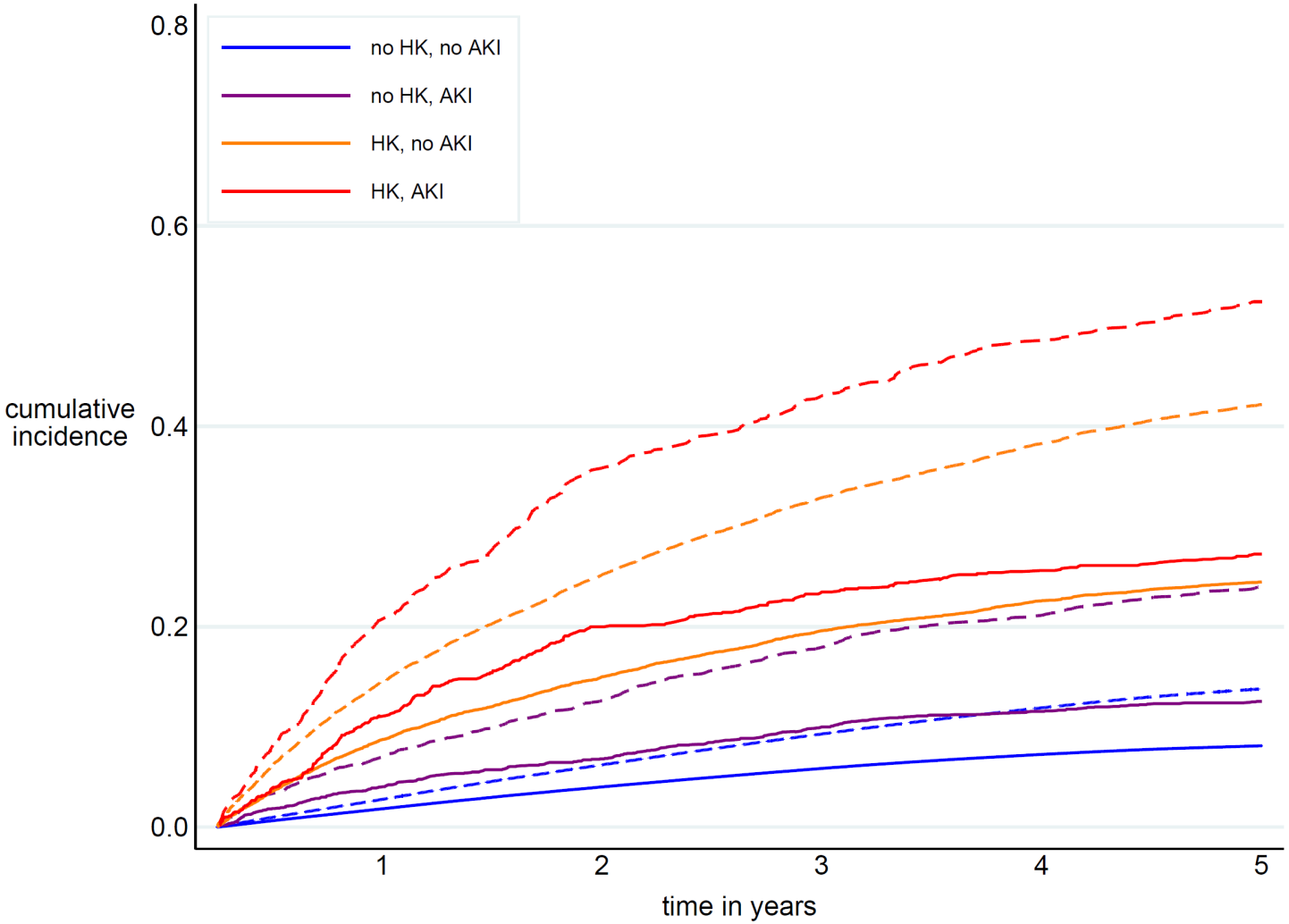


Figure S3. Stacked cumulative incidence of fatal / non-fatal cardiac events (solid line) and non-cardiac death (dashed line) among 90-day survivors for the combination of hyperkalemia and acute kidney injury (AKI)



Population Epidemiology of Hyperkalemia

Population

Scottish population (2012-2014)
1 HK episode / 100 person years

66% present in the community

18% on initial hospitalization

15% during admission

Characteristics

Serum potassium ≥5.5 associated with:

Heart Failure	**x 5**
AKI	**x 20**
CKD G4	**x 17**
Diabetes	**x 5**

Long Term Health Outcomes

Cox models for HK vs no HK
HRs at different eGFR levels:

MACE	eGFR ≥ 60 = **1.8** eGFR < 30 = **1.5**
Kidney failure	eGFR ≥ 60 = **17** eGFR < 30 = **4.3**
Mortality	eGFR ≥ 60 = **2.4** eGFR < 30 = **1.7**

CONCLUSION: A substantial population burden of hyperkalemia exists, and is associated with poorer long-term health outcomes, particularly kidney failure.

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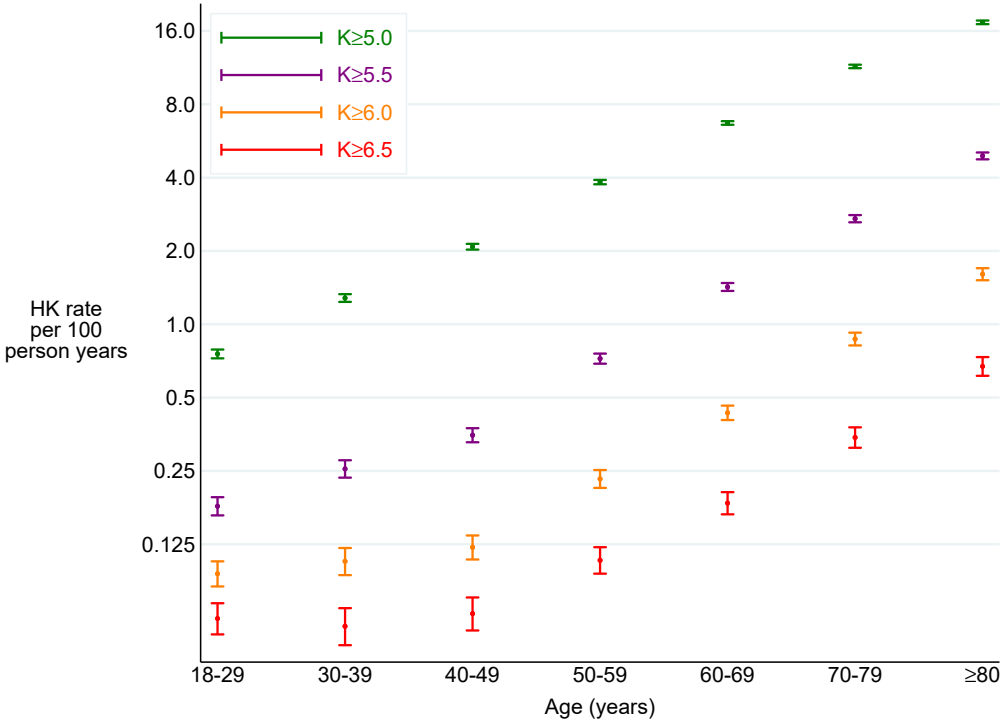
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K≥5.5
K≥6.0
K≥6.5
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8.0
4.0
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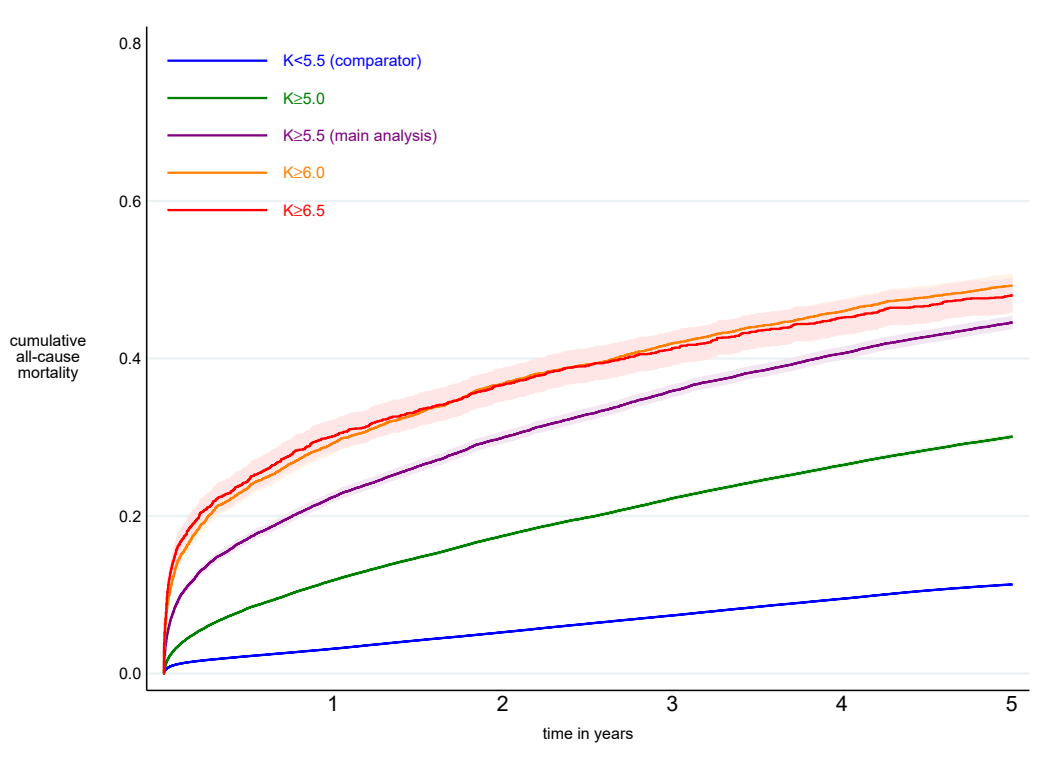
1.0
0.5
0.25
0.125
HK rate per 100 person years
18-29
30-39
40-49
50-59
60-69
70-79
≥80
Age (years)


K<5.5 (comparator)
K≥5.0
K≥5.5 (main analysis)
K≥6.0
K≥6.5
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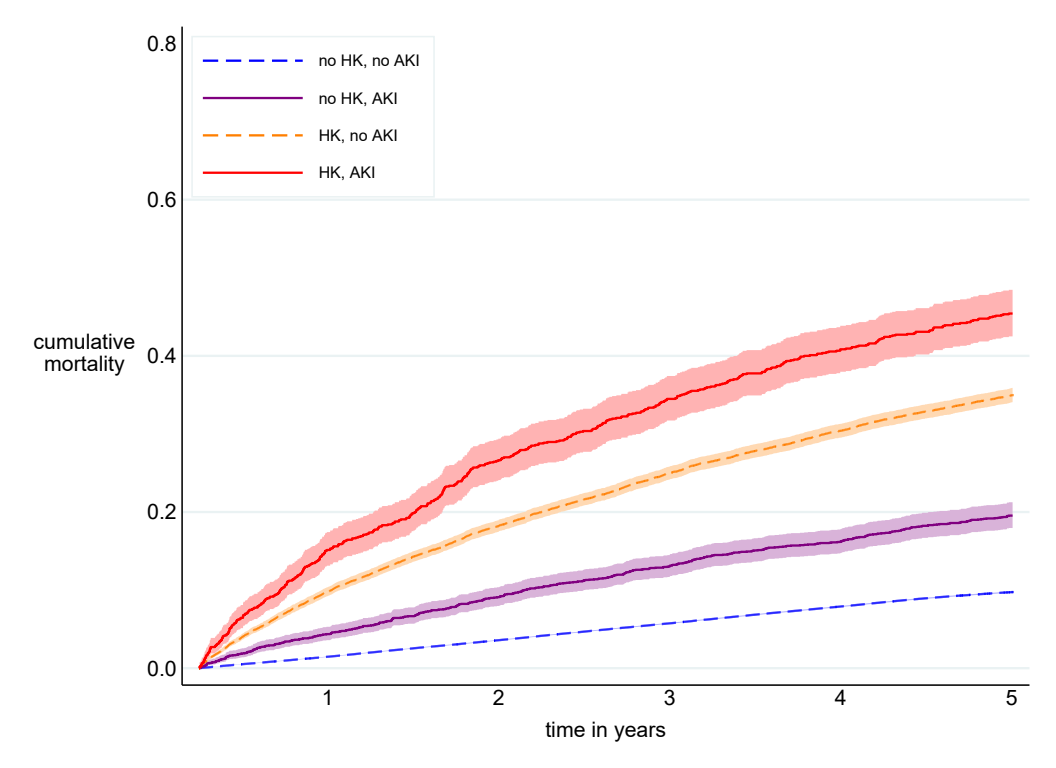
0.4
0.6
0.8
1
2
3
4
5
time in years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HK, no AKI
HK, AKI
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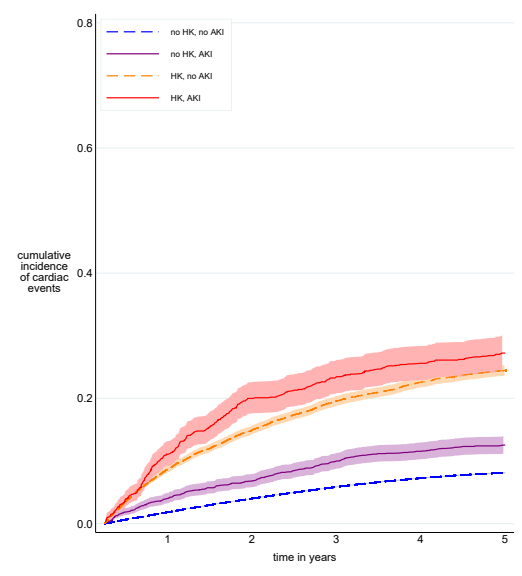
time in years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HK, no AKI
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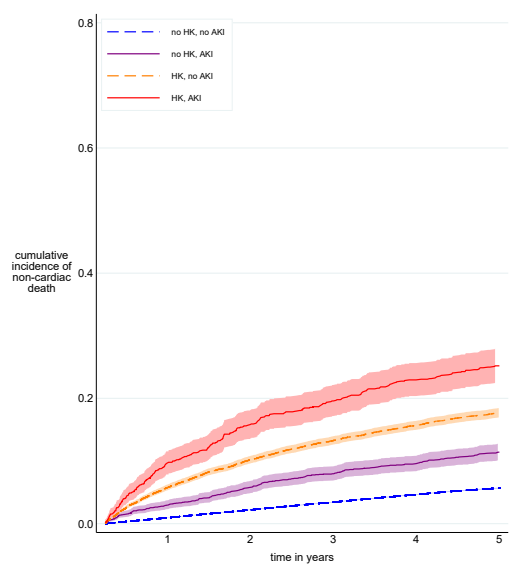
time in years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HK, AKI
cumulative incidence of non-cardiac death
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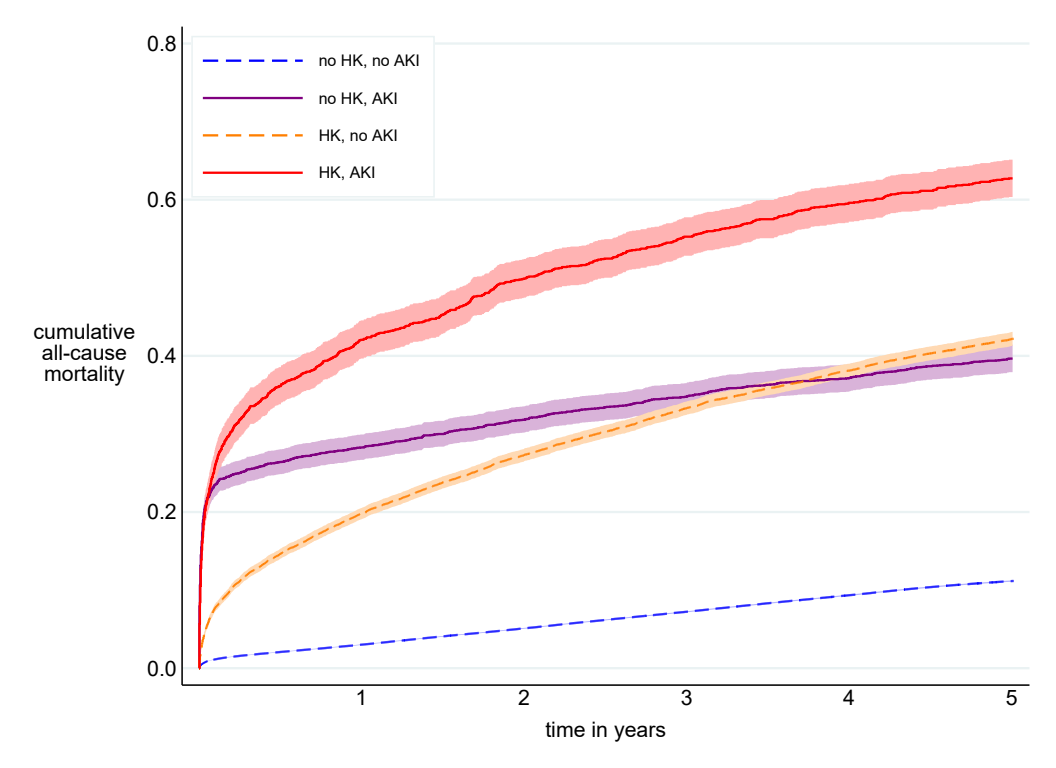
time in years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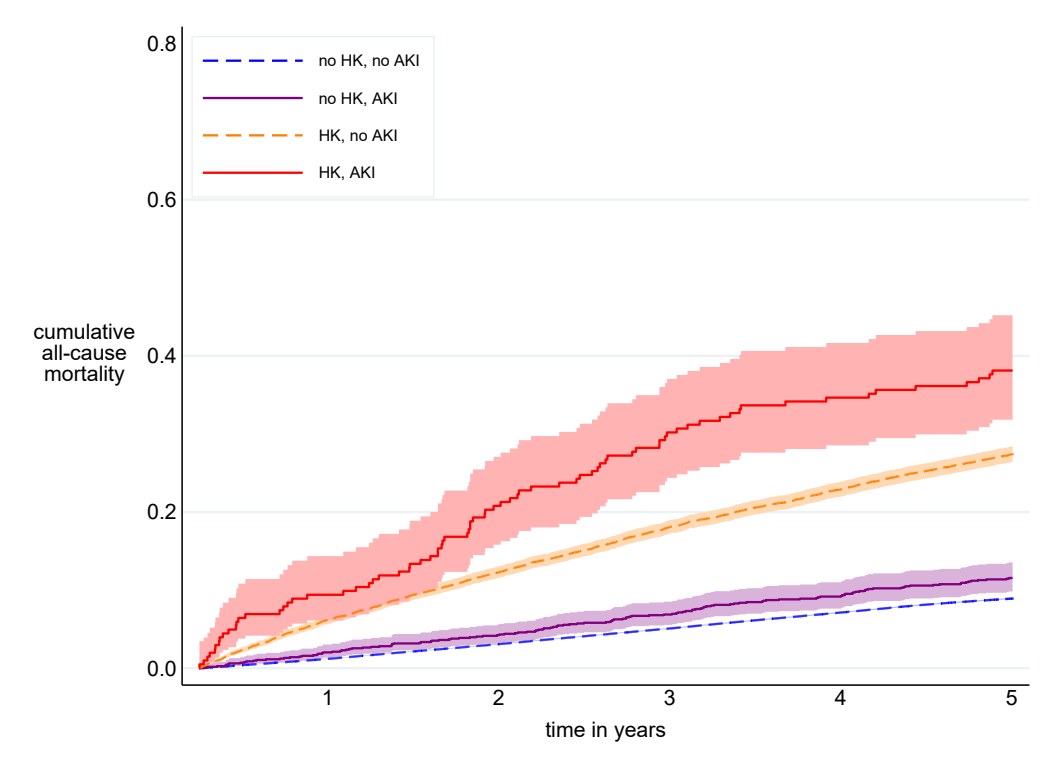
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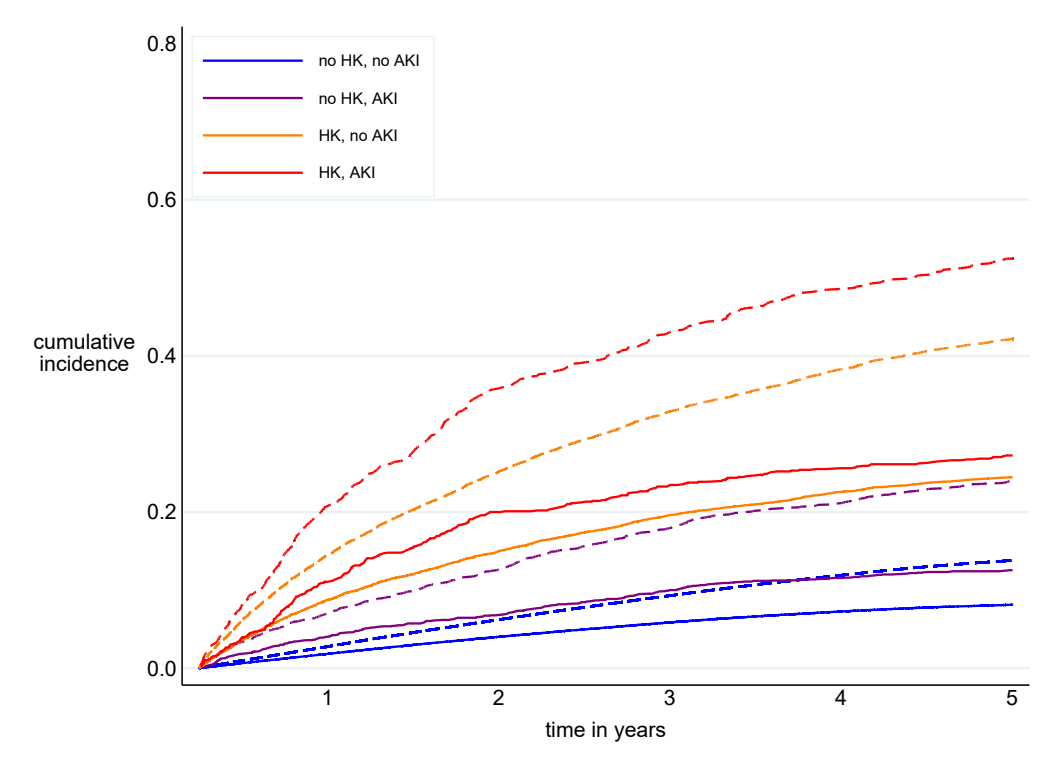
time in years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HK, AKI
cumulative incidence
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0.2
0.4
0.6
0.8
1
2
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4
5
time in years