# Acute kidney injury in the UK: A replication cohort study of the variation across three regional populations

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Acute kidney injury in the UK: A replication cohort study of the variation across three regional populations

Short title:

Variation in acute kidney injury in the UK

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Abstract

Objectives

A rapid growth in the reported rates of acute kidney injury (AKI) has led to calls for greater attention and resources for improving care. However, the reported incidence of acute kidney injury (AKI) also varies more than tenfold between previous studies. Some of this variation is likely to stem from methodological heterogeneity. This study explores the extent of cross-population variation in AKI incidence after minimising heterogeneity.

Design

Population-based cohort study analysing data from electronic health records from three regions in the UK through shared analysis code and harmonised methodology.

Setting


Participants

All residents in each region, aged 15 years or older.

Main outcome measures

Population incidence of AKI, and AKI phenotype (severity, recovery, recurrence). Determined using shared biochemistry-based AKI episode code and standardised by age and sex.

Results

Respectively, crude AKI rates (per 10,000/year) were: 131, 138, 139, 151 and 124 (p value = 0.095); and after standardisation for age and sex: 147, 151, 146, 146 and 142 (p value = 0.257) for Grampian
2003, 2007, 2012; Swansea 2007; and Salford 2012. The pattern of variation in crude rates was robust to any modifications of the AKI definition. Across all populations and time periods AKI rates increased substantially with age from ~20 to ~550 per 10,000/year among those aged <40 and ≥70 years.

Conclusion

When harmonised methods are used and age and sex differences are accounted for, a similar high burden of AKI is consistently observed across different populations and time periods (~150 per 10,000/year). There are particularly high rates of AKI among older people. Policy-makers should be careful not draw simplistic assumptions about variation in AKI rates based on comparisons that are not rigorous in methodological terms.

Strengths and limitations

- Previous studies have reported substantial variation in the incidence of AKI between regions and over time, but have involved heterogeneous methods that limit comparability. To our best knowledge, this is the first cross-population study of AKI incidence within one study, with minimised methodological heterogeneity by sharing analysis code across regions.

- By using consistent methods, and real-life, routinely collected health care data, we provide new evidence that the rates of AKI in the UK are similar across different regions and time periods: ~150 events per 10,000/year (1.5% of the population).

- These findings may not be generalisable outside of the regions of the UK in the study. However to enable researchers to replicate this work, we have made publically available our analysis code for identifying and characterising AKI episodes.
Introduction

The reported outcomes following acute kidney injury (AKI) are consistently poor[1]. Reports of a growth in rates of AKI have led to calls for greater attention and resources for improving care[2], but there is a more than tenfold variation between studies in the reported population incidence of AKI[3-7]. Population based estimates of AKI incidence range from 18 per 10,000/year[3] to 250 per 10,000/year[5] based on changes in serum creatinine over time, and from 3 to 40 per 10,000/year based on hospital episode codes for “non-dialysis requiring AKI”[8,9]. This wide variation is difficult to fully explain[10], but is likely to be due in part to a changing clinical landscape with evolving international AKI criteria[11-14], and different pragmatic interpretations of AKI criteria in research[5,15]. These reasons for variation are all potential sources of bias in clinical studies of AKI (figure 1). Without a clearer understanding of why populations differ, it is challenging (and potentially misleading) to interpret clinical research in context, to make comparisons across populations or over time, or to make informed public health recommendations.

Worldwide, health services are undertaking quality initiatives to increase clinical awareness and improve treatment of AKI[16-19] in order to achieve the International Society of Nephrology (ISN) target of eliminating avoidable deaths from AKI by 2025[20]. To evaluate the effectiveness of these initiatives, it is vital that there is a harmonisation of approaches to clinical research. This means minimising methodological heterogeneity so that the findings of future research are more comparable, and maximising transparency so that trends in disease incidence and outcomes can be understood. Methodological heterogeneity can arise when researchers extract data from different data infrastructures, make different assumptions, and adopt different criteria for identifying events. These steps are particularly important in AKI, because of the recognised challenges of AKI research: it occurs unpredictably, in different clinical locations[21], may be transient[22], and relies on trends rather than absolute values[12-14]. Small differences in how these challenges are handled can alter both the reported incidence and prognosis of AKI[5,15,21,23]. Despite its importance, this information is
often undocumented or described in insufficient detail for research to be reproduced\textsuperscript{24}. We have described these reasons for variation in AKI rates in a conceptual model (figure 1).

Algorithms using blood test data from electronic health records (EHR), offer the potential of an objective common language for observing common diseases in clinical practice, audit and research\textsuperscript{25}. In previous work, we developed an extended version of a widely used NHS algorithm for detecting AKI in blood tests\textsuperscript{26} which not only flags individual “AKI” blood tests, but also applies phenotyping methods to combine AKI flagged blood tests into clinically meaningful AKI illness episodes grouped by severity, duration, recovery and recurrence\textsuperscript{27,28}. Sharing this algorithm between researchers working with different populations provides an opportunity to develop a harmonised approach to clinical research, robustly comparing the burden of AKI across different populations and over time, even when patient-level data cannot be shared. We used this to study of variation in the incidence of AKI across three populations from England, Scotland and Wales. The analysis spans a decade of change in the clinical awareness of AKI\textsuperscript{16}, change in international AKI criteria\textsuperscript{12-14} and change in the emphasis on community surveillance of people with chronic diseases\textsuperscript{29-31}. Our aim was to explore the extent of cross-population variation in AKI incidence using real-life data, while minimising heterogeneity through harmonised methods.

Materials and Methods

Population profiles

This study compares datasets created using linked EHR data from primary and secondary care for three UK regions with different “index” years from 2003-2014: Grampian 2003, 2007 and 2012; Abertawe Bro Morgannwg University Health Board (ABMU, referred to in this article as Swansea) 2007; and Salford 2012 (supplemental figure 1). Each dataset involves health data from the UK NHS and includes complete primary and secondary care biochemistry capture for the region. A fourth
region initially considered for this analysis (from South England) was excluded because initial
inspection of the data characteristics revealed that the population capture of the data source was
incomplete and might have led to bias in the estimation of AKI. All regions provide public healthcare,
free at the point of use.

NHS Grampian, a health authority in Scotland, is served primarily by one large tertiary hospital and
another district general hospital. All biochemistry for the dataset was extracted from a single
biochemistry department covering the entire regional population\textsuperscript{[5]}. The Grampian dataset was
linked with the Scottish Renal Registry to exclude those already receiving chronic renal replacement
therapy (RRT), to avoid misclassification of RRT as AKI. Similarly, Salford (North England) represents
one borough of Greater Manchester, served by a single NHS hospital and biochemistry laboratory\textsuperscript{[32]}.  
Read codes (version 2) were used to extract biochemistry information and exclude records from
people receiving chronic RRT. In contrast, ABMU (Swansea, Wales) in 2007 covered a region served
by four district general hospitals and four laboratories using two information management
systems\textsuperscript{[33,34]}. Those receiving chronic RRT could not be directly determined from a register but could
be excluded based on the hospital location marked on the blood tests.

To provide further contextual description of these populations we collected information on
population mortality and relevant morbidities (renal and vascular) from the Office of National
Statistics, UK Renal Registry, and Quality Outcomes Framework (QOF) data entered by GP practices
(table 1). Importantly, QOF data represent incentivised recording by GPs of people with a given
condition (e.g. chronic kidney disease), rather than actual population prevalences. This means that
small differences in prevalence on the disease registers may represent recording practice as well as
actual disease prevalence, and should be interpreted with caution.
Conceptual framework

In figure 1, we provide a conceptual framework for understanding the sources of variation in AKI revealed by our analysis. We sought to minimise “artefactual” methodological differences in AKI episode rates by utilising only datasets where complete data capture (from both hospital and community settings) was possible; by harmonising data preparation and cleaning; and by standardising code sets for identifying AKI episodes. We also accounted for “real” potential sources of variation in AKI rates by performing age and sex standardisation, stratification by baseline eGFR for case-mix differences, and comparing the number of people with blood tests in rapid succession as a surrogate for presence of an acute illness.

Data extraction and processing

This study used a distributed analysis approach to protect the confidentiality of patient-level data. Data were analysed by on-site researchers working from the same code. Non-disclosive summary statistics were aggregated into a single dataset, which was analysed centrally. This ensured that patient-level data were never brought together in a single physical location. All serum creatinine results for each individual were extracted. Creatinine values that were missing, were a non-value (e.g. “sample inadequate”, “sample error”), or were lower than the limit for detection of the analyser were excluded. The “Modification of Diet in Renal Disease” (MDRD) study estimated glomerular filtration rate (eGFR) was calculated using the abbreviated 4 variable equation\[^{35}\]. Finally, to avoid a non-chronological evaluation of samples from different locations, where multiple samples were available for the same individual on a given day, the sample with the highest creatinine value was retained for analysis.

AKI identification and phenotyping

A challenge of AKI clinical research is the operationalisation of precise international AKI criteria in “real-life” data where people do not receive blood tests in a protocolised fashion. Blood tests may
not have been done at the necessary times to directly observe an acute rise in creatinine from a previous baseline, and assumptions based on available data are required. We identified differences in assumptions for determining AKI as an important potential methodological reason for observed variation in AKI rates (figure 1) and therefore used the exact same definition and analysis code in each region. Kidney Disease Improving Global Outcomes (KDIGO)-based AKI detection and phenotyping algorithm code was applied by separate analysts working locally on each dataset[14]. As summarised in supplemental table 1, these criteria compare each blood test with previous “baseline” results within the last 365 days (“the look-back period”) to determine if a recent change has occurred[27]. Where AKI occurred, a “look-forward period” of 90 days was used to follow and phenotype the whole AKI episode. In supplemental figure 2, these look-back and look-forward time periods are illustrated for a single hypothetical patient with respect to a moment of developing AKI within the index year. For those without AKI, the first eGFR of the index year was used as the baseline eGFR. For convenience we used a baseline eGFR <60 ml/min/1.72m² as an indicator of chronic kidney disease. Shared Stata code provided the following outputs: number of blood tests consistent with AKI, number of AKI episodes, baseline eGFR, AKI episode severity stage, progression of AKI severity from a lower to higher stage, recovery to baseline within 90 days, and presence of prior AKI episodes in the past three years (i.e. making the episode a recurrent AKI episode).

We also analysed data using more parsimonious versions of the KDIGO criteria: a “narrow interpretation” in which blood tests were only compared if they were no more than a week apart (i.e. restricted to criteria 2 and 3), and a “very narrow interpretation” comparing only tests no more than two days apart (i.e. restricted to criterion 3). If variation was due to a lack of robustness of AKI criteria in the face of estimating baseline from less recent data, these narrower interpretations would be expected to lead to less variation in AKI incidence.
To ensure uniformity of the application and interpretation of AKI code, a mock dataset of 40 hypothetical patients was developed. This mock dataset deliberately contained unformatted variables and a variety of creatinine trend patterns to represent a full range of data cleaning steps, AKI phenotypes, blood test intervals and interpretation issues. Each analyst used the same code on the test dataset and reproduced the same results before progressing to analysing regional data. We have made the algorithm code, mock dataset, and instructions for their optimal use in Stata freely available from https://github.com/RenalHDRUK.

Statistical analysis

Analyses included the description of baseline characteristics, comparison of both crude and age-sex standardised rates of AKI, and phenotypes of AKI episodes. We also compared AKI rates in subgroups of baseline eGFR (as described above) and individual components of AKI criteria to determine if variations in rate were robust to changes in the AKI definition (table 2). AKI can only be identified when sufficient blood tests have been performed to detect a change. Therefore, to evaluate reasons for residual variation, we described the patterns of blood testing in each region, including the frequency of blood tests, the regularity (e.g. blood tests no more than 2 and 7 days apart) and blood test location (hospital and outpatient/community).

Baseline characteristics included age, sex, the number of people with evidence of renal impairment (eGFR < 60 ml/min/1.73m²) on their first test in the index year, the number of people with blood tests sufficiently close together for it to be possible to detect an "AKI" result if present (two tests no more than 365 days apart).

We compared population rates of AKI episodes across each region and index year. We compared AKI episode rates using national statistics mid-year population estimates for each region, and then standardised to the England population for 2012[36], a reference population selected as two of the
three regions provided 2012 data. All AKI episodes in the index year counted towards the overall AKI episode rate. One way ANOVA followed by Tukey's post-hoc test (in the event of significant differences) was used to identify pairwise significant differences in population level AKI episode rates.

For people with sufficient blood tests to potentially detect an episode of AKI (at least two tests no more than 365 days apart), we compared rates within eGFR strata (<30, 30-44, 45-59 and ≥60 ml/min/1.73m²). The proportion of the population with at least one AKI result based on AKI criteria 1, 2, or 3 (table 2), and the proportion of the population with at least one AKI result based on narrower interpretations of KDIGO criteria (restricting to criteria 2 & 3, or criterion 3 alone) were also recorded. To evaluate the impact of incomplete biochemistry capture, we also recalculated AKI rates using only tests taken from people in hospital. Of note a distinction between hospital inpatient and outpatient results was not possible in Salford.

To evaluate potential sources of residual variation in AKI rates after harmonised analysis we compared patterns of blood testing (number, frequency and location).

Patient involvement
No patients were involved in development of the research question or the design of the study. There are no plans to disseminate the results of the research to study participants.

Results
Populations and baseline characteristics
As described in table 1, populations ranged in size from 193,882 (Salford 2012) to 482,444 people (Grampian 2012) (table 3). Crude reported population mortality rates were higher in Swansea than
Grampian and Salford, as was the incidence of people starting long term RRT. The recognition of diabetes and cardiovascular diseases in incentivised GP registers was similar across the populations.

Table 2 shows the baseline characteristics of extracted datasets after harmonised data cleaning. The percentage of people with at least two tests no more than 365 days apart varied from 17 – 25% with the fewest in the earliest dataset (Grampian 2003). There was a greater proportion of people tested with renal impairment (estimated glomerular filtration rate, eGFR <60 ml/min/1.73m²) in 2007 compared to the other years of study.

**Incidence of AKI episodes**

Table 3 and figure 2 show the differences in crude and standardised rates of AKI episodes for each dataset. A minority of people had more than one AKI episode in the index year. For reporting AKI episode rates (table 3) all episodes are included, whereas for reporting phenotypes of people with an AKI episode, the first episode is described (bottom of table 3 and table 4). Crude AKI rates varied with the lowest in Salford 2012 and highest rate in Swansea 2007 (124-151 per 10,000/year, p value = 0.095). Standardisation by age and sex accounted for residual differences (142-151 per 10,000/year, p value = 0.257), with 95% confidence intervals overlapping in all instances. Age and sex standardised AKI rates varied little between Grampian 2003, 2007 and 2012 (146-151 per 10,000/year). Table 3 also shows that the majority of people developing AKI could be identified using hospital tests alone, and just over half could be identified in each region using a rigid interpretation of KDIGO AKI criteria. Finally, across all populations, the proportion of people developing AKI in the index year increased substantially with increasing age and lower eGFR.

As shown in figure 3, the pattern of variation in crude AKI rates was the same when narrower interpretations of KDIGO AKI criteria were used, comparing only blood tests in the prior 2 and 7
days. Table 4 shows this pattern was also similar when analysis was limited to each individual component of the AKI criteria, or within strata of baseline eGFR.

AKI phenotypes

Table 4 describes the first AKI episode for people with an AKI episode during the index year. As well as having the highest crude AKI rate, a greater proportion of those with AKI in Swansea were older, had baseline eGFR <60 ml/min/1.73m² (37.6%), had a severe AKI episode (15.4% stage 3) had non-recovery at 90 days (45.1%). In Grampian between 2003 and 2012 there was a steady improvement in the proportion of people with renal recovery 90 days after AKI from 42% to 49%.

Further sources of variation

In addition to assessing for age, sex and case-mix differences, we evaluated the blood testing patterns and clinical location contexts of each dataset (figure 4). Figure 4A shows the frequency of blood tests taken grouped by location: hospital inpatient or outpatient/community. Figure 4B shows the proportion of people with blood tests in close succession. In Grampian from 2003 to 2012, community blood testing increased over time but the frequency of hospital inpatient testing remained unchanged. Test location was not available in Salford, but the proportions of people with two blood tests no more than 2 and 7 days apart was lower than in Grampian and Swansea. Figure 1 shows the conceptual framework for understanding these sources of variation.

Discussion

To our knowledge, this is the first multicentre study to systematically evaluate the extent of and reasons for regional and temporal variation in population rates of AKI, using a harmonised methodological approach. There were differences in the crude rates of AKI between datasets, but after accounting for age and sex, standardised rates were strikingly similar (at 140-150 episodes per
10,000/year, or ~1.5% of the population). The consistently high proportion of people aged over 70
developing AKI was also striking (>5%), and has implications for the planning the future health care
requirements of an aging population. This analysis shows the importance of both harmonised
methods and standardisation for case-mix prior to any between centre comparisons for description
of variation in AKI.

Our analysis provides additional insight into previous reports of a rising AKI incidence in studies
based on hospital episode codes or differing AKI definitions. Applying the same KDIGO-based AKI
definition to data from the same region, over a ten-year span (2003-2012), the standardised AKI
rates in Grampian changed little. Notably, this stability was in spite of an increasing frequency of
outpatient/community testing in Grampian (whereas the frequency of hospital inpatient testing
changed little over the same period). In addition, our analysis showed similar (albeit reduced) AKI
rates across the regions when only hospital blood samples were analysed, or when the AKI definition
was limited on only blood tests within the past week. Our analysis also showed a pattern of AKI
phenotypes that was consistent with case-mix differences between regions. Swansea, which had the
highest all-cause population mortality, also had the highest proportion of AKI phenotypes for
severity, AKI progression, and non-recovery.

Between population variation in the prevalence of kidney disease has previously been described for
CKD in Ireland, Germany, and Taiwan, as have variation between European countries. In
our analysis, we have now shown that much of the regional variation in AKI between UK regions can
be eliminated by harmonising methods, definitions and correcting for age and sex differences. The
stability we report in the AKI incidence over multiple time points in a ten year period is contrary to
previous studies from the UK and North America. Given the precautions that we took to minimise
heterogeneity, it is possible that some differences reported in previous studies represent a
methodological artefact (e.g. data capture or case-mix). Consistent with our findings, a recent study
of hospital based AKI among people admitted to the Mayo Clinic also found no significant change in
AKI rates between 2006-2014 using a consistent creatinine change AKI definition across each year
and stratifying by age and sex[41]. Furthermore, in our analysis the pattern of differences in crude AKI
rates was robust to modifications of KDIGO criteria using shorter look-back periods.

Our study has caveats common to observational studies, which we have highlighted in a conceptual
model that explains the reasons for observed variation in AKI rates (figure 1). In particular, even
though we utilised data from three regions with the same social healthcare system (the UK National
Health Service), we encountered incomplete population data capture that led to the exclusion of a
fourth region from the study. As we note in figure 1, differences in population capture arising out of
incomplete data extraction are not necessarily visible to researchers analysing anonymised large
datasets. This serves as a critical caution for researchers and policy-makers to avoid making
simplistic assumptions that data from different regions are necessarily comparable when they are
derived from different sources. We note that while we have used data from GP registers to provide
contextual information on the populations, these data need to be interpreted carefully as they also
reflect recording practices in primary care rather than solely disease burden. We would also like to
remind readers that while we have applied AKI criteria consistently with the same code in each
region, where sparse data exist there still may have been bidirectional misclassification between AKI
and CKD. Similarly, where AKI has occurred in the context of critical illness, falsely low creatinine
values from loss of muscle mass may imply a renal recovery that has not occurred. This is a challenge
for all observational studies using routine blood test data. Nevertheless a strength of our analysis is
that we have used the same pragmatic approach to this challenge across each of the populations
and time periods in the study. Finally, we note that only data from three UK regions were available
for inclusion in our study. This is insufficient to describe variation for the whole of the UK and other
countries. This article represents a first step towards more harmonised comparisons of AKI across
populations. We have shared our code with this article (https://github.com/RenalHDRUK) and now invite researchers working with population datasets in other regions to add to our experience.

In conclusion, our analysis shows the need for a robust methodological approach and recognition of case-mix differences when evaluating between-centre and temporal trends in AKI. The sharing of code is key to this approach and we have made our code from this article available for researchers to use. Using this approach we show strikingly similar rates of AKI across different populations from England, Scotland and Wales over a ten year period. A consistently high burden of AKI is apparent with an estimated 1.5% of the UK population experiencing AKI each year, rising to more than 5% per year in the elderly. Current quality initiatives should adopt these methods or similar methods when evaluating the impact of changes in practice on the burden of AKI.

Contributors

CB, SF, SS and SV conceived the study. AM, GD, HR, HH, MJ, SS and TS contributed to collection of the data. AM, CB, HH, HR, JC, NP, PF, PR, SS, SV, TS and SF contributed to analysis of the data. AM, CB, DN, EMH, GD, HH, HR, JC, MJ, NH, NP, PF, PR, RL, SS, SV, TS and SF contributed to interpretation of the data. SS and SF drafted the manuscript with input from AM, CB, DN, EMH, GD, HH, HR, JC, MJ, NH, NP, PF, PR, RL, SV and TS. All authors approved the final version.

Acknowledgements

We would like to acknowledge all the data providers who make anonymised data available for research. This study makes use of anonymised data held in the Secure Anonymised Information Linkage (SAIL) system, which is part of the national e-health records research infrastructure for Wales. We thank the Salford Integrated Record (SIR) board for providing us with the 2014 release of the SIR used in this study.
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Competing Interests

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coiDisclosure.pdf and declare: DN reports grants from Informatica, for analyses of the National CKD Audit which was tendered by HQIP (funding from NHS Wales and NHS England), outside the submitted work. SS is supported by a research training fellowship from the Wellcome Trust to study the outcomes of acute kidney injury (WT102729/Z/13/Z). No other support from any organisation for the submitted work; no other financial relationships with any organisations that might have an interest in the submitted
work in the previous three years; no other relationships or activities that could appear to have
influenced the submitted work.

**Ethical Approval**

Permission for the use of Grampian biochemistry data using routine biochemistry to identify AKI was
provided by University of Aberdeen Sponsor, NHS Grampian Caldicott, respective data custodians,
NHS Privacy Advisory Committee (ref PAC 33/14), NHS Research and Development Office (project
no. 2014RM003) and National Research Ethics Service (reference 14/NW/1371). Permission to
analyse SIR data was granted to North West eHealth via the SIR approval board in 2012, which
incorporates the appropriate information governance. Further ethical approval was not required,
due to the anonymised nature of the data. We thank the SIR board for providing us with the 2014
release of the SIR used in this study. Permissions for using the SAIL databank were gained through
application for the SAIL 0505 project, looking at acute kidney injury in Wales. This was reviewed by
the Information governance review panel (IGRP) which contains members of the British Medical
Association (BMA), National Research Ethics Service (NRES), public health Wales, NHS Wales
informatics service (NWIS) and consumer panel.

**Data Sharing**

No additional data available. Analysis code is freely available from https://github.com/RenalHDRUK.

**Transparency declaration**

The lead author (SS) affirms that the manuscript is an honest, accurate, and transparent account of
the study being reported; that no important aspects of the study have been omitted; and that any
discrepancies from the study as planned have been explained.
References


## Tables and Figures

### Table 1 – Contextual information on the populations in this study

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<tr>
<td><strong>Mid-year regional population (all ages) during index year¹</strong></td>
<td>529,360</td>
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<td><strong>Percentage of population in urban settlements of &gt; 10,000 people²</strong></td>
<td>49.3%</td>
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<td><strong>Regional crude all-cause mortality rate ages 15+ (index year/100,000)¹</strong></td>
<td>1192</td>
<td>1154</td>
<td>1093</td>
<td>1334</td>
<td>1135</td>
</tr>
<tr>
<td><strong>Crude adult incidence of chronic RRT per million population (UKRR)³</strong></td>
<td>98</td>
<td>102</td>
<td>93</td>
<td>167</td>
<td>85</td>
</tr>
<tr>
<td><strong>Prevalence of chronic kidney disease per 100 people (QOF)⁴</strong></td>
<td>n/a²</td>
<td>2.8</td>
<td>3.3</td>
<td>1.6</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Prevalence of coronary heart disease per 100 people (QOF)⁴</strong></td>
<td>4.1</td>
<td>4.0</td>
<td>3.9</td>
<td>4.1</td>
<td>3.9</td>
</tr>
<tr>
<td><strong>Prevalence of diabetes registration per 100 people (QOF)⁴</strong></td>
<td>3.0</td>
<td>3.3</td>
<td>4.2</td>
<td>4.3</td>
<td>4.5</td>
</tr>
<tr>
<td><strong>Prevalence of heart failure registration per 100 people (QOF)⁴</strong></td>
<td>n/a²</td>
<td>0.8</td>
<td>0.8</td>
<td>1.0</td>
<td>0.9</td>
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<tr>
<td><strong>Prevalence of hypertension registration per 100 people (QOF)⁴</strong></td>
<td>11.0</td>
<td>11.7</td>
<td>13.2</td>
<td>12.5</td>
<td>13.8</td>
</tr>
<tr>
<td><strong>Prevalence of stroke &amp; TIA registration per 100 people (QOF)⁴</strong></td>
<td>1.6</td>
<td>1.7</td>
<td>1.9</td>
<td>2.1</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Number of biochemistry departments for whole region</strong></td>
<td>One department covers in and outpatient, community and private tests</td>
<td>One department covers in and outpatient, community and private tests</td>
<td>One department covers in and outpatient, community and private tests</td>
<td>Four departments cover in and outpatient, community and private tests</td>
<td>One department covers in and outpatient and community tests. Privately obtained samples unavailable</td>
</tr>
<tr>
<td><strong>Means of excluding samples belonging to people on long term RRT from dataset</strong></td>
<td>Link to Scottish Renal Registry</td>
<td>Link to Scottish Renal Registry</td>
<td>Link to Scottish Renal Registry</td>
<td>Removing samples from locations where renal replacement is performed, including intensive care unit</td>
<td>Read code screening</td>
</tr>
<tr>
<td><strong>IDMS aligned creatinine assay</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>From 2007</td>
<td>Yes</td>
</tr>
</tbody>
</table>

¹ From the Office of National Statistics  
² From the 2011 National Census in England and Wales and Scottish Government Urban Rural Classification  
³ From the UK Renal Registry (UKRR) annual reports  
⁴ Quality Outcomes Framework (QOF) data is incentivised information entered by GP practices. Not recorded in Grampian in 2003, for which 2004 data is provided where available.  
⁵ Data not available
<table>
<thead>
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<tbody>
<tr>
<td>Patient total (%)</td>
<td>438332</td>
<td>458900</td>
<td>482444</td>
<td>415500</td>
<td>193882</td>
</tr>
<tr>
<td><strong>Population ascertainment of renal impairment (eGFR &lt; 60 ml/min/1.73m²)</strong> in index year</td>
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<tr>
<td>No tests during index year</td>
<td>311922 (71.2)</td>
<td>303673 (66.2)</td>
<td>301992 (62.6)</td>
<td>253531 (61.0)</td>
<td>116977 (60.3)</td>
</tr>
<tr>
<td>eGFR ≥60 ²</td>
<td>101595 (23.2)</td>
<td>120854 (26.3)</td>
<td>158736 (32.9)</td>
<td>129959 (31.3)</td>
<td>66890 (34.5)</td>
</tr>
<tr>
<td>eGFR &lt;60 ²</td>
<td>24805 (5.7)</td>
<td>34373 (11.3)</td>
<td>21716 (4.5)</td>
<td>32010 (7.7)</td>
<td>10015 (5.2)</td>
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<tr>
<td><strong>Sufficiency of tests to enable AKI detection</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>People with no tests during index year</td>
<td>311922 (71.2)</td>
<td>303673 (66.2)</td>
<td>301992 (62.6)</td>
<td>253531 (61.0)</td>
<td>116977 (60.3)</td>
</tr>
<tr>
<td>People with insufficient tests</td>
<td>52602 (12.0)</td>
<td>57788 (12.6)</td>
<td>69239 (14.4)</td>
<td>59839 (14.4)</td>
<td>31467 (16.2)</td>
</tr>
<tr>
<td>People with ≥2 tests within 365 days</td>
<td>73808 (16.8)</td>
<td>97439 (21.2)</td>
<td>111213 (23.1)</td>
<td>102130 (24.6)</td>
<td>45438 (23.4)</td>
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<tr>
<td><strong>Characteristics of people with ≥2 tests within 365 days</strong></td>
<td></td>
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</tr>
<tr>
<td>Proportion female</td>
<td>40413 (54.8)</td>
<td>53061 (54.5)</td>
<td>60330 (54.2)</td>
<td>55685 (54.5)</td>
<td>24723 (54.4)</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>63 (48-74)</td>
<td>63 (50-75)</td>
<td>63 (49-74)</td>
<td>64 (51-75)</td>
<td>63 (49-74)</td>
</tr>
<tr>
<td>eGFR &lt;60 ²</td>
<td>18573 (25.2)</td>
<td>28274 (29.0)</td>
<td>18679 (20.2)</td>
<td>25952 (25.4)</td>
<td>8541 (18.8)</td>
</tr>
</tbody>
</table>

1 Expressed as a percentage of total residents unless specified otherwise
2 First estimated glomerular filtration rate in index year (ml/min/1.73m²)
3 Expressed as a percentage of people with ≥2 tests within 365 days
Table 3 – Crude and standardised rates of AKI episodes, and components of AKI criteria

<table>
<thead>
<tr>
<th></th>
<th>Grampian 2003 (Rate per 10,000)</th>
<th>Grampian 2007 (Rate per 10,000)</th>
<th>Grampian 2012 (Rate per 10,000)</th>
<th>Swansea 2007 (Rate per 10,000)</th>
<th>Salford 2012 (Rate per 10,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adult resident population</strong></td>
<td>438332</td>
<td>458900</td>
<td>482444</td>
<td>415500</td>
<td>193882</td>
</tr>
<tr>
<td><strong>AKI incidence rates</strong></td>
<td></td>
<td></td>
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<tr>
<td>Crude AKI incidence (95% CI)</td>
<td>131.2 (127.7-134.7)</td>
<td>138.3 (134.9-141.7)</td>
<td>139.1 (135.8-142.4)</td>
<td>151.1 (147.4-154.8)</td>
<td>124.3 (118.8-129.8)</td>
</tr>
<tr>
<td>Age-sex standardised AKI incidence (95% CI)</td>
<td>147.2 (143.3-151.1)</td>
<td>150.6 (146.9-154.3)</td>
<td>146.3 (142.8-149.8)</td>
<td>145.6 (142.0-149.2)</td>
<td>141.8 (136.2-147.4)</td>
</tr>
<tr>
<td>Total AKI episodes</td>
<td>5749 (131)</td>
<td>6346 (138)</td>
<td>6711 (139)</td>
<td>6266 (151)</td>
<td>2399 (124)</td>
</tr>
<tr>
<td>People with AKI</td>
<td>5362 (122)</td>
<td>5930 (129)</td>
<td>6277 (130)</td>
<td>5847 (141)</td>
<td>2208 (114)</td>
</tr>
<tr>
<td><strong>Subgroups of people with AKI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKI using hospital tests only</td>
<td>4386 (100)</td>
<td>4739 (103)</td>
<td>4492 (93)</td>
<td>4432 (107)</td>
<td>n/a</td>
</tr>
<tr>
<td>Rigid KDIGO criteria</td>
<td>3436 (78)</td>
<td>3803 (83)</td>
<td>3617 (75)</td>
<td>3469 (83)</td>
<td>1114 (57)</td>
</tr>
<tr>
<td>People meeting 2d criterion</td>
<td>2486 (57)</td>
<td>2831 (62)</td>
<td>2714 (56)</td>
<td>2424 (58)</td>
<td>741 (38)</td>
</tr>
<tr>
<td>People meeting 7d criterion</td>
<td>2488 (57)</td>
<td>2696 (56)</td>
<td>2664 (55)</td>
<td>2611 (63)</td>
<td>821 (42)</td>
</tr>
<tr>
<td>People meeting 8-90d criterion</td>
<td>2619 (60)</td>
<td>2830 (59)</td>
<td>3351 (69)</td>
<td>3287 (79)</td>
<td>1163 (60)</td>
</tr>
<tr>
<td>People meeting 91-365d criterion</td>
<td>1408 (32)</td>
<td>1528 (32)</td>
<td>1850 (38)</td>
<td>1591 (38)</td>
<td>737 (38)</td>
</tr>
<tr>
<td><strong>People with AKI in age strata</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70 years</td>
<td>3205 (562)</td>
<td>3561 (587)</td>
<td>3705 (572)</td>
<td>3785 (584)</td>
<td>1299 (544)</td>
</tr>
<tr>
<td>40-69 years</td>
<td>1765 (88)</td>
<td>1903 (89)</td>
<td>2021 (89)</td>
<td>1699 (89)</td>
<td>740 (92)</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>392 (22)</td>
<td>466 (25)</td>
<td>551 (29)</td>
<td>363 (23)</td>
<td>169 (19)</td>
</tr>
<tr>
<td><strong>People with AKI in eGFR strata among people with at least two tests within 365 days (rates expressed within strata of tested individuals at risk)</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Baseline eGFR ≥60</td>
<td>3612 (654)</td>
<td>3874 (560)</td>
<td>4419 (478)</td>
<td>3648 (479)</td>
<td>1512 (410)</td>
</tr>
<tr>
<td>Baseline eGFR 45-59</td>
<td>809 (673)</td>
<td>940 (496)</td>
<td>894 (756)</td>
<td>1044 (618)</td>
<td>323 (607)</td>
</tr>
<tr>
<td>Baseline eGFR 30-44</td>
<td>597 (1222)</td>
<td>723 (1000)</td>
<td>661 (1282)</td>
<td>732 (1097)</td>
<td>202 (867)</td>
</tr>
<tr>
<td>Baseline eGFR &lt;30</td>
<td>344 (2064)</td>
<td>393 (1861)</td>
<td>303 (1781)</td>
<td>423 (1778)</td>
<td>171 (1921)</td>
</tr>
</tbody>
</table>

1 Rate expressed per 10,000 residents unless specified otherwise
2 Location data not available

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Table 4 – Phenotype of AKI episodes

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (%) people</td>
<td>Total (%) people</td>
<td>Total (%) people</td>
<td>Total (%) people</td>
<td>Total (%) people</td>
</tr>
<tr>
<td>People with AKI</td>
<td>5362</td>
<td>5930</td>
<td>6277</td>
<td>5847</td>
<td>2208</td>
</tr>
<tr>
<td>Proportion female</td>
<td>2899 (54.1)</td>
<td>3256 (54.9)</td>
<td>3443 (54.9)</td>
<td>3195 (54.6)</td>
<td>1250 (56.6)</td>
</tr>
<tr>
<td>Median age (IQR)</td>
<td>73 (61-81)</td>
<td>74 (61-82)</td>
<td>74 (60-82)</td>
<td>76 (64-84)</td>
<td>74 (61-83)</td>
</tr>
<tr>
<td>Peak AKI severity stage for first episode</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>stage 1</td>
<td>3720 (69.4)</td>
<td>4211 (71.0)</td>
<td>4389 (69.9)</td>
<td>3720 (63.6)</td>
<td>1435 (65.0)</td>
</tr>
<tr>
<td>stage 2</td>
<td>1014 (18.9)</td>
<td>1063 (17.9)</td>
<td>1174 (18.7)</td>
<td>1224 (20.9)</td>
<td>451 (20.4)</td>
</tr>
<tr>
<td>stage 3</td>
<td>628 (11.7)</td>
<td>656 (11.1)</td>
<td>714 (11.4)</td>
<td>903 (15.4)</td>
<td>322 (14.6)</td>
</tr>
<tr>
<td>AKI stage progression</td>
<td>817 (15.2)</td>
<td>792 (13.4)</td>
<td>850 (13.5)</td>
<td>900 (15.4)</td>
<td>300 (13.6)</td>
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<tr>
<td>Baseline eGFR for first episode (ml/min/1.73m²)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥60</td>
<td>3612 (67.4)</td>
<td>3874 (65.3)</td>
<td>4419 (70.4)</td>
<td>3648 (62.4)</td>
<td>1512 (68.5)</td>
</tr>
<tr>
<td>45-59</td>
<td>809 (15.1)</td>
<td>940 (15.9)</td>
<td>894 (14.2)</td>
<td>1044 (17.9)</td>
<td>323 (14.6)</td>
</tr>
<tr>
<td>30-44</td>
<td>597 (11.1)</td>
<td>723 (12.2)</td>
<td>661 (10.5)</td>
<td>732 (12.5)</td>
<td>202 (9.1)</td>
</tr>
<tr>
<td>&lt;30</td>
<td>344 (6.4)</td>
<td>393 (6.6)</td>
<td>303 (4.8)</td>
<td>423 (7.2)</td>
<td>171 (7.7)</td>
</tr>
<tr>
<td>Prior AKI episodes detected in last 3 years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior episodes</td>
<td>4415 (82.3)</td>
<td>4847 (81.7)</td>
<td>5052 (80.5)</td>
<td>4824 (82.5)</td>
<td>1708 (77.4)</td>
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<tr>
<td>1 prior episode</td>
<td>723 (13.5)</td>
<td>833 (14.0)</td>
<td>897 (14.3)</td>
<td>784 (13.4)</td>
<td>349 (15.8)</td>
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<tr>
<td>2 or more prior episodes</td>
<td>224 (4.2)</td>
<td>250 (4.2)</td>
<td>328 (5.2)</td>
<td>239 (4.1)</td>
<td>151 (6.8)</td>
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<tr>
<td>Prior AKI within 1 year</td>
<td>414 (7.7)</td>
<td>459 (7.7)</td>
<td>492 (7.8)</td>
<td>488 (8.3)</td>
<td>216 (9.8)</td>
</tr>
<tr>
<td>Renal recovery to within 20% of baseline</td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Renal recovery</td>
<td>2239 (41.8)</td>
<td>2588 (43.6)</td>
<td>3077 (49.0)</td>
<td>2156 (36.9)</td>
<td>970 (43.9)</td>
</tr>
<tr>
<td>Renal non-recovery</td>
<td>2203 (41.1)</td>
<td>2387 (40.3)</td>
<td>2245 (35.8)</td>
<td>2635 (45.1)</td>
<td>820 (37.1)</td>
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<tr>
<td>Repeat samples not available</td>
<td>920 (17.2)</td>
<td>955 (16.1)</td>
<td>955 (15.2)</td>
<td>1056 (18.1)</td>
<td>418 (18.9)</td>
</tr>
</tbody>
</table>

1Expressed as a percentage of people with at least one AKI episode
2Insufficient biochemistry data available to report on the previous 3 years
Figure 1 – Conceptual framework for the reasons for cross-population differences in AKI rates

Figure 2 – Crude and age-sex standardised rate of AKI episodes

Figure 3 – Crude AKI rates using different interpretations of the KDIGO-based AKI definition

Figure 4 – Patterns of blood testing by clinical location (4A), and by test regularity (4B)
Conceptual framework for the reasons for cross-population differences in AKI rates

181x205mm (300 x 300 DPI)
Crude and age-sex standardised rate of AKI episodes

75x25mm (300 x 300 DPI)
Crude AKI rates using different interpretations of the KDIGO-based AKI definition

73x26mm (300 x 300 DPI)
Patterns of blood testing by clinical location (4A), and by test regularity (4B)

155x111mm (300 x 300 DPI)
Supplemental table 1 – AKI definition and phenotype criteria for this study

<table>
<thead>
<tr>
<th>AKI Criteria</th>
<th>AKI definition</th>
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<tbody>
<tr>
<td>Criterion 1</td>
<td>Serum creatinine ≥1.5 times higher than the median of all creatinine values 8-90 days ago, or 91-365 days ago if no tests between 8-90 days</td>
</tr>
<tr>
<td>Criterion 2</td>
<td>Serum creatinine ≥1.5 times higher than the lowest creatinine within 7 days</td>
</tr>
<tr>
<td>Criterion 3</td>
<td>Serum creatinine &gt;26 µmol/L, higher than the lowest creatinine within 48 hours</td>
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</table>

AKI severity | Staging definition (based on peak creatinine within 90 days of diagnosis) |
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Stage 1</td>
<td>Rise in creatinine of &gt;26 µmol/L, or index/baseline ratio ≥1.5 and &lt;2</td>
</tr>
<tr>
<td>Stage 2</td>
<td>Index/baseline ratio ≥2 and &lt;3</td>
</tr>
<tr>
<td>Stage 3</td>
<td>Index/baseline ratio ≥3, or ≥1.5 and index creatinine &gt;354 µmol/L</td>
</tr>
</tbody>
</table>

Prior AKI episodes | Prior AKI definition |
<table>
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</thead>
<tbody>
<tr>
<td>No prior AKI</td>
<td>AKI episode not preceded by any previous AKI episodes in the prior 3 years</td>
</tr>
<tr>
<td>Prior AKI</td>
<td>AKI episode preceded by at least one previous AKI episode in the prior 3 years</td>
</tr>
<tr>
<td>Recent prior AKI</td>
<td>AKI episode preceded by at least one previous AKI episode in the prior 1 year</td>
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</tbody>
</table>

90 day AKI recovery | Recovery definition |
<table>
<thead>
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</thead>
<tbody>
<tr>
<td>Recovery</td>
<td>Last creatinine within 90 days of AKI &lt;1.2 times higher than the baseline creatinine at diagnosis</td>
</tr>
<tr>
<td>Non-recovery</td>
<td>Last creatinine within 90 days of AKI ≥1.2 times higher than the baseline creatinine at diagnosis, or still receiving acute RRT</td>
</tr>
<tr>
<td>“Untested”</td>
<td>No repeat blood tests taken within 90 days of AKI diagnosis</td>
</tr>
</tbody>
</table>

Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy
Supplementary figure 1 – Map of the UK populations in this analysis
Supplemental figure 2 – Hypothetical patient illustrating look-back (for baseline) and look-forward (for AKI episode phenotyping) time periods from the start of an AKI episode.
STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

<table>
<thead>
<tr>
<th>Item No</th>
<th>Recommendation</th>
<th>Pages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td><em>(a)</em> Indicate the study’s design with a commonly used term in the title or the abstract. <em>(b)</em> Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>3</td>
</tr>
<tr>
<td><strong>Introduction</strong></td>
<td>Explain the scientific background and rationale for the investigation being reported.</td>
<td>5</td>
</tr>
<tr>
<td><strong>Objectives</strong></td>
<td>State specific objectives, including any prespecified hypotheses.</td>
<td>6</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Present key elements of study design early in the paper.</td>
<td>6</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.</td>
<td>6</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td><em>(a)</em> Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. <em>(b)</em> For matched studies, give matching criteria and number of exposed and unexposed.</td>
<td>7, 8, n/a</td>
</tr>
<tr>
<td><strong>Variables</strong></td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.</td>
<td>9, 10</td>
</tr>
<tr>
<td><strong>Data sources/ measurement</strong></td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.</td>
<td>8-10</td>
</tr>
<tr>
<td><strong>Bias</strong></td>
<td>Describe any efforts to address potential sources of bias.</td>
<td>9</td>
</tr>
<tr>
<td><strong>Study size</strong></td>
<td>Explain how the study size was arrived at.</td>
<td>6, 11, table 1</td>
</tr>
<tr>
<td><strong>Quantitative variables</strong></td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.</td>
<td>10, 11</td>
</tr>
<tr>
<td><strong>Statistical methods</strong></td>
<td><em>(a)</em> Describe all statistical methods, including those used to control for confounding. <em>(b)</em> Describe any methods used to examine subgroups and interactions. <em>(c)</em> Explain how missing data were addressed. <em>(d)</em> If applicable, explain how loss to follow-up was addressed. <em>(e)</em> Describe any sensitivity analyses.</td>
<td>10, 11, n/a, n/a, n/a, 11</td>
</tr>
<tr>
<td><strong>Results</strong></td>
<td><em>(a)</em> Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. <em>(b)</em> Give reasons for non-participation at each stage. <em>(c)</em> Consider use of a flow diagram.</td>
<td>11, tables 1 &amp; 2, 7, n/a</td>
</tr>
<tr>
<td><strong>Descriptive data</strong></td>
<td><em>(a)</em> Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. <em>(b)</em> Indicate number of participants with missing data for each variable of interest. <em>(c)</em> Summarise follow-up time (eg, average and total amount).</td>
<td>Tables 1 and 2, n/a, n/a</td>
</tr>
<tr>
<td><strong>Outcome data</strong></td>
<td>Report numbers of outcome events or summary measures over time.</td>
<td>12, 13, table 3</td>
</tr>
</tbody>
</table>
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(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included 12, 13, table 3

(b) Report category boundaries when continuous variables were categorized Table 3

(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period n/a

Other analyses 17

Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Tables 3 & 4

Discussion

Key results 18

Summarise key results with reference to study objectives 13, 14

Limitations 19

Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias 15

Interpretation 20

Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence 16

Generalisability 21

Discuss the generalisability (external validity) of the study results 15

Other information

Funding 22

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based 17

*Give information separately for exposed and unexposed groups.