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The association of socioeconomic status with incidence and outcomes of acute kidney injury

Hilda O. Hounkpatin[1], Simon D.S. Fraser [2], Matthew J. Johnson[3], Scott Harris[2], Mark Uniacke[4] and Paul J. Roderick[2]

[1]National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care (NIHR CLAHRC) Wessex, School of Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Southampton, UK, [2]School of Primary Care and Population Sciences, Faculty of Medicine, University of Southampton, Southampton, UK, [3]Medical Research Council Lifecourse Epidemiology Unit, University of Southampton, Southampton, UK and [4]Queen Alexandra Hospital, Portsmouth, UK

Correspondence and offprint requests to: Simon D.S. Fraser; E-mail: s.fraser@soton.ac.uk

ABSTRACT

Background. Acute kidney injury (AKI) is common and is associated with significant morbidity and mortality. Socioeconomic status may be negatively associated with AKI as some risk factors for AKI such as chronic kidney disease, diabetes and heart failure are socially distributed. This study explored the socioeconomic gradient of the incidence and mortality of AKI, after adjusting for important mediators such as comorbidities.

Methods. Linked primary care and laboratory data from two large acute hospitals in the south of England, sourced from the Care and Health Information Analytics database, were used to identify AKI cases over a 1-year period (2017–18) from a population of 580 940 adults. AKI was diagnosed from serum creatinine patterns using a Kidney Disease: Improving Global Outcomes-based definition. Multivariable logistic regression and Cox proportional hazard models adjusting for age, sex, comorbidities and prescribed medication (in incidence analyses) and AKI severity (in mortality analyses), were used to assess the association of area deprivation (using Index of Multiple Deprivation for place of residence) with AKI risk and all-cause mortality over a median (interquartile range) of 234 days (119–356).

Results. Annual incidence rate of first AKI was 1726/100 000 (1.7%). The risk of AKI was higher in the most deprived compared with the least deprived areas [adjusted odds ratio = 1.79, 95% confidence interval (CI) 1.59–2.01 and 1.33, 95% CI 1.03–1.72 for <65 and >65 year old, respectively] after controlling for age, sex, comorbidities and prescribed medication. Adjusted risk of mortality post first AKI was higher in the most deprived areas (adjusted hazard ratio = 1.20, 95% CI 1.07–1.36).

Conclusions. Social deprivation was associated with higher incidence of AKI and poorer survival even after adjusting for the higher presence of comorbidities. Such social inequity should be considered when devising strategies to prevent AKI and improve care for AKI patients.

Keywords: age, AKI, creatinine, epidemiology, survival analysis

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INTRODUCTION

Acute kidney injury (AKI) is now widely classified using the Kidney Disease: Improving Global Outcomes (KDIGO) creatinine change criteria. Early recognition and management of AKI are necessary to minimize preventable harm [1] , mortality [2] and healthcare costs [3]. The International Society of Nephrology 0by25 initiative aims to prevent all avoidable deaths from AKI worldwide by 2025 [4, 5]. In the UK, the National Health Service (NHS England) has mandated national implementation of an AKI detection algorithm, based on KDIGO criteria, which generates electronic alerts ('e-alerts') for clinicians to facilitate earlier identification [6].

AKI is a heterogeneous condition that can occur in any clinical setting. A better understanding of risk factors for AKI could help prevent avoidable deaths. Older age, comorbidities such as cardiovascular disease, heart failure, chronic kidney disease (CKD) and diabetes, severe infections and nephrotoxic drugs have been found to be associated with AKI [7–10]. Many of these factors have higher frequency in lower socioeconomic groups [11, 12]. However, relatively little work has focused on the link between socioeconomic status and AKI in high-income countries. In the UK, a study using data from general practices covering ∼7% of the UK population found little evidence for an association between lower socioeconomic status (indicated by area deprivation) and risk of AKI in older patients who had diabetes and pneumonia [13]. However, studies using data from over 57 000 patients in the Welsh national electronic AKI reporting system reported that area deprivation was associated with higher incidence of AKI [14] and age-adjusted mortality following AKI [15]. Phillips *et al.* [14] suggested that higher incidence of AKI in deprived areas may be attributed to higher incidence of comorbidities in these areas, but incorporation of comorbidities was limited. To our knowledge, no previous study has assessed whether an association between area deprivation and AKI persists after adjusting for the presence of comorbidities that may mediate any association. In order to appropriately develop AKI prevention and management policy, a better understanding of the nature of the relationship between socioeconomic status and AKI is needed.

Using linked routinely collected primary care and hospital laboratory data across a large population in southern England, we aimed to describe the association of deprivation with incidence and outcomes of AKI, before and after adjusting for comorbidities.

MATERIALS AND METHODS

Study population

The Care and Health Information Analytics database (CHIA) was used to assess the incidence and severity stage of AKI alerts by applying the NHS England e-alert algorithm to a 1-year period (1 October 2017 to 30 September 2018). The CHIA is an anonymized electronic database containing linked primary care data for approximately 1.4 million patients across Hampshire (UK) and clinical biochemistry data (including creatinine data) from two large hospital laboratories (University Hospital Southampton NHS Foundation Trust and Portsmouth Hospitals NHS Trust). Our study used data from individuals aged ≥18 years for whom complete biochemical data were available for the duration of the study (1 October 2017 to 30 September 2018) plus a 'look-back' period of 1 year (1 October 2016 to 30 September 2017) to establish baseline creatinine according to KDIGO AKI criteria [16]. The baseline creatinine was either (i) the lowest creatinine value within 0–7 days prior to the index creatinine value, (ii) the median creatinine value within 8–365 days prior to the index creatinine value or (iii) a creatinine value taken up to 48 h prior to the index creatinine that is ≥26 μmol/L lower than the index creatinine. The study denominator ($n = 581\,650$) was defined by the number of adults who remained within practices that consistently sent all laboratory data to one of two large hospitals in Hampshire (Southampton and Portsmouth) for the duration of the study and look-back period. Individuals registered with general practitioner practices with biochemical testing rates that fell below a pre-defined threshold [calculated as the lower quartile less 1.5 times the interquartile range (IQR)] were excluded from the study. Further details have been published elsewhere [17]. Ethical approval for the study was obtained from the University of Southampton Faculty of Medicine Research Ethics Committee (Submission ID: 15753).

Table 1. AKI criteria based on the rise in creatinine from reference creatinine

AKI criteria	Description
Criterion 1	Index creatinine >26 μmol/L rise higher than lowest creatinine in previous 48 h
Criterion 2	Index creatinine >1.5 times higher than lowest creatinine in previous 7 days
Criterion 3	Index creatinine >1.5 times higher than median of all creatinine tests in previous 8–365 days
AKI stage	**Rise in serum creatinine**
1	>26 μmol/L within 48 h or index creatinine ≥1.5 and <2 times higher than reference creatinine
2	Index creatinine ≥2 and <3 times higher than reference creatinine
3	Index creatinine ≥3 times higher or ≥1.5 times and >354 μmol/L higher than reference creatinine

NHS England e-alert algorithm

The NHS England e-alert algorithm is shown in Supplementary data, Figure S1. It compares each new (index) creatinine to a reference (baseline) creatinine and generates an alert, with corresponding AKI stage, if one of three criteria in Table 1 is satisfied. The NHS England e-alert algorithm has been shown to perform well as a diagnostic tool for AKI [18, 19]. Urine output was not used to define AKI as this was not recorded in CHIA. We did not impute data for those with missing creatinine tests.

Baseline characteristics

Patients were characterized by age, sex and ethnicity (Caucasian, Indian/Bangladeshi/Pakistani, African/Caribbean, Mixed and other). Socioeconomic status was defined using the 2015 Index of Multiple Deprivation (IMD) quintiles [20]. The IMD is a small-area measure of socioeconomic status, ranked nationally, and comprises seven domains: income, employment, education/skills/training, health and disability, crime, barriers to housing and services, and living environment [20]. Baseline comorbidity and dialysis and/or kidney transplant were defined from a set of standard Read codes (used to record primary care diagnoses) agreed between two clinicians (including S.D.S.F., available upon request from the authors) [21]. The comorbidities included were those found in previous literature to be most

strongly associated with AKI, namely CKD, hypertension, diabetes, cardiovascular disease and heart failure [1]. Individuals were considered to have a comorbidity if they were diagnosed as having the comorbidity at the start of the study period. Prescribed medication data were obtained from the primary care record within the dataset. Medications of interest were those most strongly associated with AKI in previous studies: diuretics, renin–angiotensin aldosterone system inhibitors (RAASi) and non-steroidal anti-inflammatory drugs (NSAIDs) [1, 22]. Individuals were considered to be exposed to a specific medication if they received a prescription for the medication: (i) throughout the study period or during the 6 months prior to the study period and the first 6 months of the study period (for those who did not develop an AKI alert), or (ii) early on in the study period (during the first 6 months of the index period) and for the following 6 months (for those who did not alert), or (iii) early on in the study period and continued during the period they alerted (for those who alerted). A detailed classification of drug exposure is available in Supplementary data, Table S1.

Repeat blood tests, repeat alerts, AKI progression and recovery of kidney function assessed by serum creatinine fall

The number of repeat alerts and median time (and IQR) between the first and subsequent alert were calculated. Peak AKI stage within 7 days of the first alert was determined using the NHS England e-alert algorithm [7]. Progression of AKI alert severity stage (progressed, did not progress) within 7 days was defined as progressing from Stages 1 to 2 or 3 or from Stages 2 to 3. Creatinine recovery was identified at Days 90 and 180 and described in three categories: full recovery, partial recovery and no recovery at 90 and 180 days. It was assessed by comparing the lowest creatinine value within 90 and 180 days, respectively, to the baseline creatinine at the time of the alert, for individuals with at least 90 and 180 days of follow-up, respectively, during 2017–18. Full creatinine recovery was defined as a return to $\leq$1.2 times the baseline creatinine, partial creatinine recovery was defined as a return to >1.2 and <1.5 times the baseline creatinine and no recovery was defined as creatinine remaining $\geq$1.5 times the baseline creatinine [23]. The proportion of individuals having repeat blood tests was also explored for a more comprehensive assessment of creatinine recovery, and as an indicator of potential differences in care across deprivation levels.

Statistical analyses

All analyses excluded dialysis and transplant patients ($n = 710$). Descriptive statistics were used to compare baseline characteristics for people with at least one AKI alert (AKI group) and those who did not have an alert (no AKI group). A series of regression models based on the whole study sample were fitted to assess the association of deprivation (using IMD quintiles) with generating at least one AKI alert (versus not generating an AKI alert), before and after adjusting for potential confounders or mediators: (i) univariate; (ii) age- and sex-adjusted; (iii) age-, sex- and comorbidity-adjusted; and (iv) fully adjusted: age-, sex-, comorbidity- and prescribed medication-adjusted logistic regression models. Similar models were used to assess socioeconomic differences in the proportion of people with repeat blood tests, peak AKI stage, AKI stage progression within 7 days and full creatinine recovery. A series of univariate and multivariable-adjusted Cox proportional hazards models were also fitted to assess associations between IMD quintiles and all-cause mortality over a median (IQR) period of 234 days (119–356) post first AKI. These models were: (i) univariate; (ii) age- and sex-adjusted; (iii) age-, sex- and comorbidity-adjusted; and (iv) fully adjusted: age-, sex-, comorbidity- and AKI severity stage-adjusted models. Multivariable regression models additionally containing an interaction term between age (<65, $\geq$65 years) and IMD quintiles were fitted to assess the effect of age on the association of IMD quintiles with AKI and all-cause mortality [15, 24]. Proportional hazards assumptions were checked visually using plots of Schoenfeld residuals. All analyses were performed using StataSE 14 [25].

RESULTS

Population characteristics

Our final study population consisted of 580 940 individuals (Figure 1). AKI status could be assessed for 235 962 (40.6%) individuals who had had two or more creatinine tests between 1 October 2016 and 30 September 2018 (with at least one test between 1 October 2017 and 30 September 2018); 72 693 (12.5%) individuals had only one creatinine test between 1 October 2016 and 30 September 2018 and 272 285 (46.9%) individuals did not have any creatinine tests between 1 October 2017 and 30 September 2018. Of the final study population of 580 940 individuals, 10 028 (1.7%) generated at least one AKI alert between 1 October 2017 and 30 September 2018—an overall incidence of first alerts of 1726 per 100 000 adults per year (Figure 1).

Table 2 shows the characteristics of individuals who generated an AKI alert and those who did not. A higher proportion of those who generated an alert were older, had comorbidities or were prescribed diuretics, RAASi or NSAIDs than individuals who did not. A higher proportion of individuals who generated an alert were Caucasian compared with those who did not alert. A slightly higher proportion of individuals who generated an alert were living in the most deprived areas compared with those who did not alert.

Associations with incident AKI

Univariate analysis showed that older age, female sex, lower IMD quintile (indicating greater deprivation), hypertension, diabetes, CKD, heart failure, cardiovascular disease and being prescribed NSAIDs, RAASi or diuretics were all associated with greater likelihood of generating an AKI alert (Table 3). Greater deprivation was associated with higher risk of generating an AKI alert, even after adjusting for age, sex, comorbidities and prescribed medication [odds ratio (OR) = 1.97, 95% confidence interval (CI) 1.85–2.11 and OR = 1.61, 95% CI 1.50–1.72 in age- and sex-adjusted models and fully adjusted models, respectively]. There was a significant interaction effect between age and deprivation, such that the negative association of deprivation with AKI was stronger for individuals aged <65 years in multivariable models. The fully adjusted OR for generating an AKI alert was 1.79 (95% CI 1.59–2.01) and 1.33 (95% CI 1.03–1.72) for individuals aged <65 and >65 years, respectively, in the most compared with least deprived groups.

Repeat blood tests, repeat alerts, AKI progression and creatinine recovery

About 48.2% (4832/10 028) of people who had an AKI alert in our study had a second alert between 1 October 2017 and 30 September 2018, with 3056 (30.5%) people having more than two alerts. Median (IQR) time between first and second alert was 2

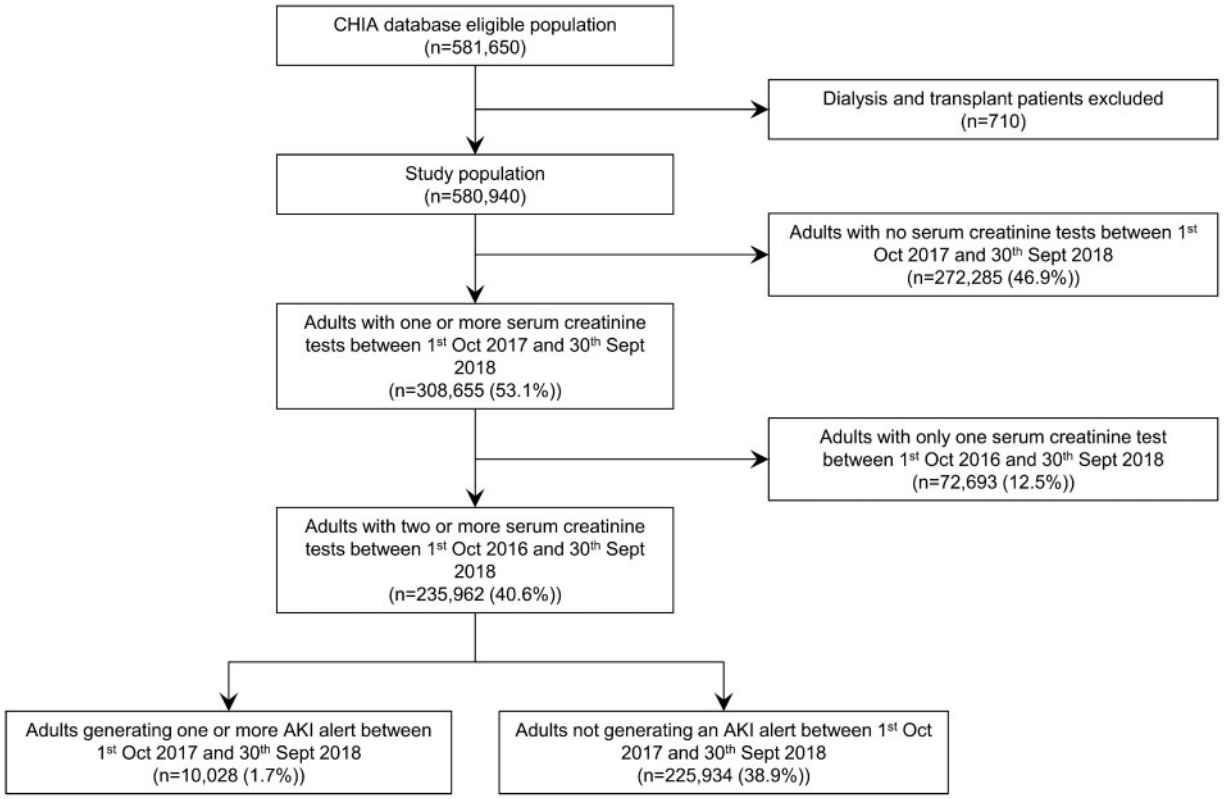

FIGURE 1: Flow diagram of the study population.

days (1–10 days), suggesting a high likelihood that they were part of the same clinical episode.

A high proportion of individuals had repeat blood tests at 90 and 180 days (89.8 and 93.5%, respectively). There were no significant differences in testing by deprivation (data not shown). Peak AKI stage, AKI stage progression (observed for 7.2% of individuals) and creatinine recovery (at 90 and 180 days) were also not associated with deprivation.

Mortality

Of the 10 028 individuals who generated an AKI alert, 3029 (30.2%) died. The age- and sex-adjusted hazard ratio (HR) of mortality was 1.21 (95% CI 1.07–1.45) for the most compared with the least deprived IMD quintile and the respective fully adjusted HR was 1.20 (95% CI 1.07–1.36). There was no interaction between deprivation (IMD quintiles) and age (Table 4) .

DISCUSSION

In a population-based study using routine serum creatinine data, we showed that deprivation was positively associated with risk of AKI, especially in people aged <65 years old, and with poorer survival in age- and sex-adjusted models. These associations were reduced but persisted after adjusting for comorbidity (and medication use in incidence analyses and AKI severity in mortality analyses). This is one of the few existing large population-based studies to assess within-country socioeconomic differences in incidence and outcomes of AKI and is in line with recent recommendations to improve our understanding of how deprivation is linked to poor outcomes for AKI [26]. The results of the study are generalizable to high-income countries with similar health systems.

The incident rate of 1.7% for first AKI in 1 year is higher than Sawhney *et al.*'s Grampian study [18, 27] using the NHS England e-alert algorithm, but considerably lower than that reported in studies not using a KDIGO-based algorithm to identify AKI [28–30]. Differences in incidence rate between our study and Sawhney *et al.* [31] may be due to case-mix differences around baseline estimated glomerular filtration rate, age and sex population differences and availability of repeat blood tests.

Our findings are consistent with those from a Welsh study [14, 15], and extends them by adjusting for comorbidities that may mediate the association between socioeconomic status and AKI, and exploring related effect moderation. Furthermore, we adjusted for AKI severity and pre-existing CKD in our analyses exploring the link between socioeconomic status and mortality, as these have been associated with excess mortality in socially deprived areas [15]. Further studies that replicate these findings and explore other potential confounders or mediators linking socioeconomic status, for example obesity and health behaviours such as alcohol misuse and smoking that are causally linked to other comorbidities (e.g. chronic obstructive pulmonary disease) and increase risk of AKI, may help improve understanding of the influence of socioeconomic status on AKI [32, 33]. Other factors that may contribute to the association between socioeconomic status and AKI include timely access and/or presentation to health services or the effects of environment or factors that may predispose to AKI [34].

We observed an age–deprivation interaction effect on the risk of AKI. This is consistent with a study showing a declining association between risk factors (such as atrial fibrillation and hypertension) and AKI for older age groups and a separate study

Table 2. Characteristics of individuals, overall and by AKI group

Characteristic	Total population ($n = 580\,940$)	AKI group		P-value
		No AKI	AKI	
N (%)	580 940 (100.0)	570 912 (98.3)	10 028 (1.7)	–
Mean age (standard deviation), years	53.2 (18.9)	52.9 (18.7)	70.2 (17.4)	<0.001
Median age (IQR), years	54 (38–68)	53 (38–68)	74 (61–83)	<0.001
Female, *n* (%)	324 486 (55.9)	319 073 (55.9)	5413 (54.0)	<0.001
Ethnicity[a], *n* (%)				
British/Mixed British/Irish	368 920 (87.3)	361 989 (87.2)	6504 (91.9)	<0.001
Mixed	1979 (0.5)	1962 (0.5)	15 (0.2)	
Indian/Bangladeshi/Pakistani	7873 (1.9)	7769 (1.9)	85 (1.2)	
African/Caribbean	3254 (0.8)	3214 (0.8)	34 (0.5)	
Other	40 764 (9.6)	40 293 (9.7)	443 (6.2)	
Socioeconomic status[a], *n* (%)				
Index of Multiple Deprivation quintile 1 (most deprived)	75 404 (13.1)	73 906 (13.1)	1498 (15.1)	<0.001
Index of Multiple Deprivation quintile 2	107 922 (18.7)	105 916 (18.7)	2006 (20.2)	
Index of Multiple Deprivation quintile 3	103 106 (17.9)	101 399 (17.9)	1707 (17.2)	
Index of Multiple Deprivation quintile 4	122 838 (21.3)	120 761 (21.3)	2077 (20.9)	
Index of Multiple Deprivation quintile 5 (least deprived)	166 999 (29.0)	164 341 (29.0)	2658 (26.7)	
Health conditions (as of start of index year)[a], *n* (%)				
CKD	35 770 (6.2)	32 997 (5.8)	2773 (27.7)	<0.001
Hypertension	145 768 (25.1)	140 102 (24.6)	5666 (56.8)	<0.001
Diabetes	61 200 (10.5)	58 352 (10.2)	2848 (28.5)	<0.001
Cardiovascular disease[b]	56 568 (9.7)	53 155 (9.3)	3413 (34.0)	<0.001
Heart failure	12 728 (2.2)	11 195 (2.0)	1533 (15.3)	<0.001
Prescribed medication[c], *n* (%)	50 666 (8.7)	46 385 (8.1)	4281 (42.7)	<0.001
Diuretics				
Renin–angiotensin aldosterone system inhibitors	34 840 (6.0)	33 294 (5.8)	1546 (15.4)	<0.001
NSAIDs	25 078 (4.3)	24 114 (4.2)	964 (9.6)	<0.001
Initial AKI stage at first detection, *n* (%)	–	–	–	–
1	–	–	7887 (78.7)	–
2	–	–	1328 (13.2)	–
3	–	–	813 (8.1)	–

[a]Ethnicity data were available for 422 308 individuals only, Index of Multiple Deprivation data was known for 576 269 patients, CKD, hypertension, diabetes and heart failure status was available for 580 839, 580 259, 580 439 and 580 940 patients, respectively.
[b]Comprising ischaemic, cerebrovascular and peripheral vascular disease.
[c]Those prescribed medication as described in Supplementary Material. P-value comparing 'no AKI' and 'AKI' groups.

reporting a complex interaction of age with socioeconomic status on the prevalence of CKD [35, 36]. As the risk of AKI is higher in older age, this may blunt the socioeconomic gradient in older age groups, although the absolute risk of AKI is greater among older people.

Strengths and limitations

The strengths of the study include the availability of all serum creatinine tests as well as data on medication and comorbidities for a large defined population. The richness and size of the dataset enabled us to apply the NHS England e-alert algorithm to individuals, and explore associations at the different deprivation quintiles using place of residence. However, several limitations must be considered. First, the NHS England e-alert algorithm uses only blood tests, although the diagnosis of AKI is essentially clinical and there were no data on urine output, which is part of the KDIGO definition [11]. As with most studies using routine data, it was not possible to undertake clinical verification when identifying AKI. It is unlikely that all alerts would be considered to represent a clinically relevant AKI episode. Individuals with baseline CKD may also have been misclassified as having AKI due to variation in their serum creatinine or infrequent testing [22, 37]. We did not have data on the date of the creatinine tests taken during the look-back period to explore which criteria triggered the AKI alert for most individuals. This may have helped us identify which patients had pre-existing CKD. A subset analysis of 1381 (13.8%) AKI individuals who did not have any creatinine tests during the look-back period (i.e. individuals for whom we have full creatinine data), showed that 30, 31 and 61% of alerts were generated by criteria 1, 2 and 3, respectively (some alerts were generated by more than one criterion). Compared with those whose alert was triggered by criterion 1 or 2, a smaller proportion of individuals who alerted due to criterion 3 progressed in AKI severity (9.4–9.8% versus 5.8%) or had full creatinine recovery within 90 or 180 days (70.2–73.6% versus 63.8%) and (67.5–70.8% versus 62.8%), respectively. This may suggest a large proportion of individuals who alerted may have had pre-existing CKD. However, it is possible that these individuals are systematically different from those who have had creatinine tests during the look-back period as well as the index year. Nevertheless, even mild and transient increases in serum creatinine are associated with poorer outcomes [38, 39]. There may also be some under ascertainment of CKD as we used Read-coded CKD rather than biochemical (as more

Table 3. Unadjusted and adjusted associations of having an AKI alert with socioeconomic status (using Index of Multiple Deprivation quintiles as a proxy for socioeconomic status)

Characteristic	Unadjusted OR (95% CI)	Age- and sex-adjusted OR (95% CI)	Age-, sex- and comorbidity-adjusted OR (95% CI)	Age-, sex-, comorbidity and medication-adjusted OR (95% CI)
Index of Multiple Deprivation (versus 5, least deprived)[a] for <65s				
1	**1.25 (1.17–1.33)**	**1.98 (1.76–2.22)**	**1.87 (1.67–2.1)**	**1.79 (1.59–2.01)**
2	**1.17 (1.10–1.24)**	**1.67 (1.49 (1.86)**	**1.63 (1.46–1.82)**	**1.59 (1.42–1.77)**
3	1.04 (0.98–1.11)	**1.25 (1.11–1.42)**	**1.24 (1.09–1.4)**	**1.21 (1.07–1.37)**
4	1.06 (1.00–1.12	**1.17 (1.04–1.32**	**1.16 (1.03–1.31**	**1.15 (1.02–1.30**
Index of Multiple Deprivation (versus 5, least deprived)[a] for >65s				
1	**1.25 (1.17–1.33)**	**1.68 (1.3–2.16)**	**1.38 (1.07–1.78)**	**1.33 (1.03–1.72)**
2	**1.17 (1.10–1.24)**	**1.43 (1.12–1.82)**	1.26 (0.99–1.61)	1.23 (0.96–1.57)
3	1.04 (0.98–1.11)	1.2 (0.92–1.56)	1.11 (0.85–1.45)	1.09 (0.84–1.42)
4	1.06 (1.00–1.12)	1.12 (0.86–1.44)	1.08 (0.83–1.4)	1.07 (0.82–1.38)
Age [>65 years (versus <65)]	**5.41 (5.18–5.65)**	**6.23 (5.67–6.84)**	**3.26 (2.95–3.59)**	**2.87 (2.60–3.17)**
Female	**0.92 (0.89–0.96)**	**0.95 (0.91–0.99)**	1.05 (1–1.09)	0.99 (0.95–1.03)
Has hypertension	**4.04 (3.88–4.21)**		**1.59 (1.51–1.66)**	**1.15 (1.09–1.21)**
Has diabetes	**3.48 (3.33–3.64)**		**1.74 (1.66–1.83)**	**1.64 (1.56–1.72)**
Has CKD	**6.23 (5.95–6.52)**		**2.00 (1.90–2.11)**	**1.89 (1.79–1.99)**
Has heart failure	**9.04 (8.53–9.58)**		**2.84 (2.67–3.03)**	**1.84 (1.72–1.97)**
Has cardiovascular disease	**5.01 (4.80–5.22)**		**1.69 (1.61–1.77)**	**1.69 (1.61–1.78)**
Prescribed diuretics	**8.42 (8.08–8.78)**			**3.29 (3.12–3.46)**
Prescribed renin–angiotensin aldosterone system inhibitors	**2.93 (2.77–3.10)**			1.01 (0.95–1.07)
Prescribed NSAIDs	**2.42 (2.26–2.59)**			**2.58 (2.40–2.77)**

All (n = 575 017).
[a]Index of Multiple Deprivation quintile 1 = most deprived.
Bold font = statistically significant (P < 0.05).

Table 4. Cox regression models for mortality with adjustment for sociodemographic factors, comorbidities and prescribed medication

Characteristic	Unadjusted HR 95% CI	Age- and sex-adjusted HR 95% CI	Age-, sex- and comorbidity-adjusted HR 95% CI	Age-, sex-, comorbidity and medication- adjusted HR 95% CI
Index of Multiple Deprivation (versus 5)[a]				
1	0.88 (0.78–0.99)	**1.21 (1.07–1.36)**	**1.21 (1.07–1.45)**	**1.20 (1.07–1.36)**
2	0.98 (0.88–1.09)	**1.17 (1.05–1.31)**	**1.16 (1.05–1.36)**	**1.17 (1.05–1.30)**
3	1.03 (0.93–1.16)	**1.14 (1.02–1.27)**	**1.13 (1.01–1.33)**	**1.14 (1.03–1.27)**
4	1.07 (0.96–1.18)	**1.10 (1.00–1.22)**	**1.10 (0.99–1.22)**	**1.10 (1.00–1.22)**
Age (continuous)	**1.04 (1.04–1.04)**	**1.04 (1.04–1.04)**	**1.04 (1.04–1.04)**	**1.04 (1.04–1.04)**
Female	**0.78 (0.73–0.84)**	**0.78 (0.72–0.84)**	**0.79 (0.73–0.84)**	**0.81 (0.75–0.87)**
Has hypertension	**1.30 (1.20–1.40)**		**0.84 (0.78–0.91)**	**0.83 (0.77–0.90)**
Has diabetes	1.02 (0.94–1.11)		0.99 (0.91–1.07)	0.98 (0.91–1.07)
Has CKD	**1.42 (1.32–1.53)**		0.99 (0.91–1.07)	0.97 (0.89–1.05)
Has heart failure	**1.57 (1.44–1.71)**		1.19 (1.09–1.31)	**1.21 (1.10–1.33)**
Has cardiovascular disease	**1.49 (1.38–1.60)**		1.03 (0.95–1.11)	1.04 (0.97–1.13)
Initial AKI stage 1 (reference)				
2	**1.57 (1.42–1.73)**			**1.60 (1.45–1.76)**
3	**1.80 (1.60–2.02)**			**1.88 (1.67–2.11)**

[a]Index of Multiple Deprivation quintile 1 = most deprived.
Bold font = statistically significant (P < 0.05).

clinically applicable and to be consistent with other comorbidities), which may lead to some residual mediation of socioeconomic status and AKI and mortality.

A second limitation of the study is that a large proportion of the source population had no or only one serum creatinine test, and was excluded from the analysis. It is, therefore, possible that the number of AKI episodes may have been underestimated as those who are not tested or tested only once would not have been captured [40]. Given the known high proportion of AKI that occurs in the community, it is possible that this proportion with undetected AKI is considerable [27]. We did not impute data for those with missing creatinine tests as this represented a large proportion of individuals and it is unlikely that such data would be missing at random. Thirdly, socioeconomic status was assessed by deprivation based on place of residence rather than using an individual-level measure of

socioeconomic status, which may lead to some misclassification of socioeconomic status causing a bias of the ORs towards the null. Fourthly, we used selected comorbidities. We were not able to control for some comorbidities such as chronic liver disease and chronic obstructive pulmonary disease, nor for the severity of CKD or heart failure, all of which may vary by socioeconomic status. Similarly, we did not adjust for ethnicity, which is closely linked to socioeconomic status, as this was less well recorded and there is only a small ethnic minority population in the study area (Table 2) [41]. Fifthly, it was also not possible to identify people who were taking 'over-the counter' (purchased and not-prescribed) NSAIDs. Furthermore, our categorization of drug exposure was limited to specific periods of time (those on the relevant drugs prior to, early or late in the index year). This may have misclassified some individuals' exposure status. Sixthly, we did not have access to secondary care data such as hospitalization data, which meant we could not distinguish between community and hospital-acquired AKI and could not exclude maternity-related AKI alerts. Ideally, maternity-related alerts would be excluded as the normal rise in serum creatinine to pre-pregnancy levels following delivery may result in a false alert [42]. We also did not have complete data on albuminuria (due to under-testing and under-recording in routine data), and presence of albuminuria is a key component of risk prediction in CKD as well as AKI [43–45]. It is possible that albuminuria may mediate part of the association between socioeconomic status and AKI as albuminuria has been linked to low socioeconomic status in a national population-representative study in England [46]. Finally, we described the epidemiology of first alerts in a defining year. However, some alerts at the beginning of this period may be repeat alerts of an AKI episode in the previous period rather than a first alert, particularly for hospitalized patients.

Implications

This study suggests social inequity in the occurrence and outcomes of AKI. These findings would benefit from further replication and a better understanding of the impact of clinical setting (community versus hospital-acquired) of the AKI alert trigger. Despite its limitations, this study suggests that socioeconomic status needs to be taken into account in strategies for AKI prevention, prediction and management. Clinical prediction tools [47] can help identify high-risk individuals in primary care who may benefit from targeted prevention such as medication review, and recognition of risk during inter-current illness with consideration of temporary medication withdrawal at times of illness. Further study is justified to explore how socioeconomic status adds to such tools.

CONCLUSION

Incidence of AKI and risk of all-cause mortality within a median of 234 days post first AKI was higher among more deprived groups compared with less deprived, with no socioeconomic variation seen in AKI severity. Prevention efforts should prioritize areas of socioeconomic deprivation. Early recognition, monitoring of blood tests and subsequent attention to modifiable risk factors may help reduce incidence, progression and outcomes of AKI in these groups.

SUPPLEMENTARY DATA

Supplementary data are available at ckj online.

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AUTHORS' CONTRIBUTIONS

This study was devised by S.D.S.F., H.O.H. and P.J.R. Data were extracted by M.J.J. M.U. provided nephrological expertise. H.O.H. conducted the analyses and S.H. and M.J.J. provided statistical expertise.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Stewart J, Findlay G, Smith N *et al*. *Adding Insult to Injury: A Review of the Care of Patients who Died in Hospital with a Primary Diagnosis of Acute Kidney Injury*. London: National Confidential Inquiry into Patient Outcome and Death, 2009 https://www.ncepod.org.uk/2009report1/Downloads/AKI_report.pdf (12 August 2019, date last accessed)
2. Scott RA, Austin AS, Kolhe NV *et al*. Acute kidney injury is independently associated with death in patients with cirrhosis. *Frontline Gastroenterol* 2013; 4: 191–197
3. Bedford M, Stevens PE, Wheeler TW *et al*. What is the real impact of acute kidney injury? *BMC Nephrol* 2014; 15: 95
4. International Society of Nephrology. *Acute Kidney Injury (AKI) is Preventable and Treatable*. 2019. https://www.theisn.org/all-articles/616-0by25 (12 August 2019, date last accessed)
5. Remuzzi G, Horton R. Acute renal failure: an unacceptable death sentence globally. *Lancet* 2013; 382: 2041–2042
6. NHS England. *Acute Kidney Injury (AKI) Algorithm*. 2014. https://www.england.nhs.uk/patientsafety/akiprogramme/aki-algorithm/ (12 August 2019, date last accessed)
7. Talabani B, Zouwail S, Pyart RD *et al*. Epidemiology and outcome of community-acquired acute kidney injury. *Nephrology* 2014; 19: 282–287
8. Leblanc M, Kellum JA, Gibney RT *et al*. Risk factors for acute renal failure: inherent and modifiable risks. *Curr Opin Crit Care* 2005; 11: 533–536
9. Hsu CY, Ordonez JD, Chertow GM *et al*. The risk of acute renal failure in patients with chronic kidney disease. *Kidney Int* 2008; 74: 101–107
10. Wonnacott A, Meran S, Amphlett B *et al*. Epidemiology and outcomes in community-acquired versus hospital-acquired AKI. *Clin J Am Soc Nephrol* 2014; 9: 1007–1014

11. Bello AK, Peters J, Rigby J *et al*. Socioeconomic status and chronic kidney disease at presentation to a renal service in the United Kingdom. *Clin J Am Soc Nephrol* 2008; 3: 1316–1323
12. Zeng X, Liu J, Tao S *et al*. Associations between socioeconomic status and chronic kidney disease: a meta-analysis. *J Epidemiol Community Health* 2018; 72: 270–279
13. Jain A, McDonald HI, Nitsch D *et al*. Risk factors for developing acute kidney injury in older people with diabetes and community-acquired pneumonia: a population-based UK cohort study. *BMC Nephrol* 2017; 18: 142
14. Phillips D, Holmes J, Davies R *et al*. The influence of socioeconomic status on presentation and outcome of acute kidney injury. *QJM* 2018; 111: 849–857
15. Holmes J, Rainer T, Geen J *et al*. Acute kidney injury, age, and socioeconomic deprivation: evaluation of a national data set. *Kidney Int Rep* 2019; 4: 824–832
16. Kidney Disease: Improving Global Outcomes (KDIGO) Acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int* 2012; 2: 1–138
17. Johnson M, Hounkpatin H, Fraser S *et al*. Using a linked database for epidemiology across the primary and secondary care divide: acute kidney injury. *BMC Med Inform Decis Mak* 2017; 17: 106
18. Sawhney S, Fluck N, Marks A *et al*. Acute kidney injury – how does automated detection perform? *Nephrol Dial Transplant* 2015; 30: 1853–1861
19. Sawhney S, Marks A, Ali T *et al*. Maximising acute kidney injury alerts – A cross-sectional comparison with clinical diagnosis. *PLoS One* 2015; 10: e0131909
20. Department for Communities and Local Government. *English Indices of Deprivation*. 2015. https://www.gov.uk/government/statistics/english-indices-of-deprivation-2015 (12 August 2019, date last accessed)
21. NHS Digital. *Read Codes*. https://digital.nhs.uk/services/terminology-and-classifications/read-codes (12 August 2019, date last accessed)
22. Abdel-Kader A, Palevsky P. Acute kidney injury in the elderly. *Clin Geriatr Med* 2009; 25: 331–358
23. Lewington A, Kanagasundaram S. *Renal Association Clinical Practice Guidelines on Acute Kidney Injury*. 5th edn. Hampshire, UK: UK Renal Association, 2011
24. Caskey FJ, Roderick P, Steenkamp R *et al*. Social deprivation and survival on renal replacement therapy in England and Wales. *Kidney Int* 2006; 70: 2134–2140
25. StataCorp. *Stata statistical software: release 14*. College Station, TX: StataCorp LP, 2015
26. Kidney Research UK. *Kidney Health Inequalities in the United Kingdom: Reflecting on the Past, Reducing in the Future*. https://www.kidneyresearchuk.org/file/research/health_inequalities_report.pdf (12 August 2019, date last accessed)
27. Sawhney S, Fluck N, Fraser SD *et al*. KDIGO-based acute kidney injury criteria operate differently in hospitals and the community—findings from a large population cohort. *Nephrol Dial Transplant* 2016; 31: 922–929
28. Bedford M, Hobbs H, Irving J *et al*. Does acute kidney injury managed entirely in the community have similar mortality outcomes to hospital acquired acute kidney injury? *Nephrol Dial Transplant* 2012; 27: ii21
29. Hobbs H, Bassett P, Wheeler T *et al*. Do acute elevations of serum creatinine in primary care engender an increased mortality risk? *BMC Nephrol* 2014; 15: 206
30. Xu G, Player P, Shepherd D, Brunskill NJ. Identifying acute kidney injury in the community – a novel informatics approach. *J Nephrol* 2016; 29: 93–98
31. Sawhney S, Robinson HA, van der Veer S *et al*. Acute kidney injury in the UK: a replication cohort study of the variation across three regional populations. *BMJ Open* 2018; 8: e019435
32. Danziger J, Chen K, Lee J *et al*. Obesity, acute kidney injury, and mortality in critical illness. *Crit Care Med* 2016; 44: 328–334
33. Varga ZV, Matyas C, Paloczi J *et al*. Alcohol misuse and kidney injury: epidemiological evidence and potential mechanisms. *Alcohol Res* 2017; 38: 283–288
34. National Clinical Guideline Centre. National Institute for Health and Clinical Excellence: Guidance. *Acute Kidney Injury: Prevention, Detection and Management up to the Point of Renal Replacement Therapy*. London: Royal College of Physicians, 2013
35. Chao CT, Wang J, Wu HY *et al*. Age modifies the risk factor profiles for acute kidney injury among recently diagnosed type 2 diabetic patients: a population-based study. *GeroScience* 2018; 40: 201–217
36. So BH, Methven S, Hair MD *et al*. Socio-economic status influences chronic kidney disease prevalence in primary care: a community-based cross-sectional analysis. *Nephrol Dial Transplant* 2015; 30: 1010–1017
37. Lin J, Fernandez H, Shashaty MGS *et al*. False-positive rate of AKI using consensus creatinine-based criteria. *Clin J Am Soc Nephrol* 2015; 10: 1723–1731
38. Chertow GM, Burdick E, Honour M *et al*. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol* 2005; 16: 3365–3370
39. Goldberg A, Kogan E, Hammerman H *et al*. The impact of transient and persistent acute kidney injury on long-term outcomes after acute myocardial infarction. *Kidney Int* 2009; 76: 900–906
40. Susantitaphong P, Cruz DN, Cerda J *et al*. Acute kidney injury advisory group of the American society of nephrology: world incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol* 2013; 8: 1482–1493
41. Grams ME, Matsushita K, Sang Y *et al*. Explaining the racial difference in AKI incidence. *J Am Soc Nephrol* 2014; 25: 1834–1841
42. Cheung KL, Lafayette RA. Renal physiology of pregnancy. *Adv Chronic Kidney Dis* 2013; 20: 209–214
43. Matsushita K, Ballew SH, Astor BC *et al*. Cohort profile: the chronic kidney disease prognosis consortium. *Int J Epidemiol* 2013; 42: 1660–1668
44. Grams ME, Sang Y, Ballew SH *et al*. A meta-analysis of the association of estimated GFR, albuminuria, age, race, and sex with acute kidney injury. *Am J Kidney Dis* 2015; 66: 591–601
45. Fraser SDS, Parkes J, Culliford D *et al*. Timeliness in chronic kidney disease and albuminuria identification: a retrospective cohort study. *BMC Fam Pract* 2015; 16: 18
46. Fraser SD, Roderick PJ, Aitken G *et al*. Chronic kidney disease, albuminuria and socioeconomic status in the Health Surveys for England 2009 and 2010. *J Public Health (Oxf)* 2014; 36: 577–586
47. Think Kidneys Risk Workstream. Communities at Risk of Developing Acute Kidney Injury. 2015. https://www.thinkkidneys.nhs.uk/wp-content/uploads/2015/07/Communities-at-risk-of-developing-AKI-Think-Kidneys-010715.pdf (12 August 2019, date last accessed)