Ambient heat and acute kidney injury: case-crossover analysis of 1 354 675 automated e-alert episodes linked to high-resolution climate data

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Summary

Background As global temperatures continue to rise, the effects of ambient heat on acute kidney injury (AKI) are of growing concern. We used a novel nationwide electronic alert (e-alert) system to detect increases in AKI risk associated with high temperatures.

Methods We used a case-crossover design to link 1 354 675 AKI episodes occurring in England between April and September in years 2017–2021 to daily maximum temperature data at postcode sector level. AKI episode data were obtained from the UK Renal Registry. There were no further inclusion or exclusion criteria. Conditional logistic regression employing distributed lag non-linear models was used to assess odds of AKI episode on case days compared with day-of-week matched control days. Effects during heatwaves were also assessed using heat-episode analysis.

Findings There were strongly increased odds of AKI episode associated with high temperatures, with odds ratio (OR) 1·623 (95% CI 1·319–1·997) on a day of temperature 32°C compared with one of 17°C, the effects being strongest on a lag of 1 day. There was an OR of 1·020 (1·019–1·020) per 1°C increase in temperature above 17°C. The odds of a heat-related AKI episode were similar between AKI stages 1 and 2, but considerably lower for stage 3 events. A 7-day heatwave in July 2021 was associated with a 28·6% increase in AKI counts (95% CI 26·5–30·7).

Interpretation Heat-related AKI is a growing public health challenge. As even small changes in renal function can affect patient outcomes, susceptible individuals should be advised to take preventive measures whenever hot weather is forecast. Use of an e-alert system allows effects in milder cases that do not require secondary care to also be detected.

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Introduction

As global temperatures continue to rise, the health risks associated with the renal system are of particular concern.[1] As well as playing a critical role in thermoregulation and in preventing dehydration during hot weather, the kidney is a key organ where heat-related diseases might manifest.[2] Occupational health studies have shown that regular strenuous physical activity in hot environments without adequate rest and rehydration can lead to reduced kidney function and even the development of acute and chronic kidney diseases in workers.[3] However, increased heat extremes as well as greater water insecurity in various parts of the world mean that this is also a growing concern for public health.

Acute kidney injury (AKI), previously known as acute renal failure, is a heterogeneous group of conditions characterised by a sudden decline in kidney function, with incidence increasing worldwide. Susantitaphong and colleagues[4] estimated global AKI incidence rates of 21·6% in adults and 33·7% in children, although with large regional variations. AKI can be acquired either in the community or in hospital, in the ratio of about 2:1

in the UK, and occurs in approximately 15% of patients in hospital and up to 60% of adults receiving intensive care.[5] Data from England in 2018 found that 18% of people with an AKI episode died within 30 days, and this rises to 24% for those with hospital-acquired AKI.[6] AKI is also a common manifestation in people presenting with heatstroke.[2] One study observed AKI in 91% of cases of exertional heatstroke.[7] Milder heat-related illnesses, such as heat exhaustion, heat syncope, and heat cramps, can also result in electrolyte abnormalities and AKI.[8]

Given these connections, epidemiological studies have unsurprisingly reported associations between heat and various kidney disease outcomes,[9] although these are often based on a low number of events.[10] Moreover, morbidity effects are assessed using hospital data, which could lead to an underestimation of temperature effects as milder cases are missed. Furthermore, there is currently very little evidence of heat effects on AKI in the UK setting, despite AKI being associated with 100 000 deaths in UK hospitals each year[11] and AKI inpatient costs accounting for 1% of the UK National Health Service budget.[12] The few existing UK studies of AKI and heat are

Research in context

Evidence before this study

Epidemiological studies have reported associations between heat and various kidney disease outcomes, including acute kidney injury (AKI). A search in PubMed between Jan 1, 1990, and May 26, 2023, for studies published in English, including the search terms "acute kidney injury", "acute renal failure", "climate", "temperature", and "heat", returned two previous systematic literature reviews of studies conducted in non-occupational health settings. These showed that all studies to date on morbidity effects are based on hospital data, which could lead to an underestimation of temperature effects as milder cases are missed.

Added value of this study

To the best of our knowledge, this study provides the first use of a novel nationwide electronic alert (e-alert) system to detect ambient heat effects on AKI. Because every laboratory in England contributes data, even milder cases that do not require secondary care are captured. As well as providing a larger

number of AKI events than in previous studies, detailed information on the location of each episode allows linkage to spatially resolved climate data to enable individual exposures to be characterised. Our results show a clear increase in AKI episodes associated with heatwaves and high temperatures, with effects being far greater than those estimated in the 2021 meta-analysis by Liu and colleagues.

Implications of all the available evidence

Our findings have important implications for the identification and management of AKI, especially for mild cases in the community setting where monitoring and clinical intervention might be less likely. AKI e-alert data in England could be used as a syndromic surveillance tool in heat action plans to monitor effects on public health in real time during heat alerts. More broadly, kidney health can be a global risk indicator and therapeutic target for actions that address climate change adaptation and mitigation.

either limited to a single region using regional-level weather exposures[13] or only model seasonal patterns in AKI without direct attribution to environmental factors.[14] Therefore, ambient temperature as a risk factor for AKI in the UK remains poorly understood.

Since 2015, an automated real-time electronic alert (e-alert) system has been operating across all areas of the National Health Service in England to detect AKI episodes in both hospital and community settings. For each patient, alerts are automatically triggered whenever there is a change in serum creatinine level compared with their own baseline, with the resulting data being sent to the UK Renal Registry (UKRR).[15] Because every laboratory in England contributes data, even milder cases that do not require secondary care are captured. Furthermore, detailed information on the date and location of each alert as well as AKI stage is held by UKRR and, as such, provides a unique opportunity to link to spatially resolved weather data in order to identify the ambient temperature conditions that might trigger AKI events.

In this study, we link AKI episodes across England held by the UKRR to gridded daily temperature data to characterise associations between ambient heat and AKI risk and assess modification of temperature effects by AKI stage and by region. To the best of our knowledge, this study provides the first use of an e-alert system to detect climate effects on AKI.

Methods

Participant data

AKI episodes occurring during warm months (April–September) in years 2017–2021 were obtained from the UKRR. AKI is determined through routine blood tests taken in any hospital setting. An individual's

current serum creatinine level is compared with their previous blood tests using a standardised algorithm to determine the presence and severity of AKI. AKI diagnosis and staging is based on the Kidney Disease Improving Global Outcomes classification system.[16] When a blood creatinine test fulfils AKI criteria, health staff are alerted to a worsening of kidney function and a record of the alert is sent to UKRR by the testing laboratories. Following the protocol of Savino and colleagues,[15] we defined an AKI episode in an individual as one or more e-alerts separated by no more than 30 days; ie, if more than one alert was present, all alerts following the first were considered part of the same episode unless a 30-day alert-free period had elapsed. This ensured that the temperature data were not linked to multiple related alerts. Each episode contained information on the date of alert, postcode sector of patient's residence, and AKI severity stage (defined as stage 1: 1·5–1·9 times baseline or ≥0·3 mg/dL increase in serum creatinine; stage 2: 2·0–2·9 times baseline; and stage 3: 3·0 times baseline).[16] A postcode sector in the UK typically consists of about 3000 addresses. To preserve patient anonymity, data on age and sex were not available. Children were included in our data; however, they constitute only 2·3% of cases because they are infrequently tested for kidney function in routine care and an alert is only triggered if there is a significant change in creatinine compared with a value taken within the same year.

Each AKI episode was linked to localised daily maximum temperature using the HadUK-Grid dataset from the Met Office, which provides climate data at 1 km grid resolution for the UK based on regression and interpolation of observed measurements from meteorological stations, taking into account latitude and

longitude, altitude and terrain shape, coastal influence, and urban land use. Postcode sectors were georeferenced and daily maximum temperature values were extracted and interpolated from the values of the four nearest raster (grid) cells using the bilinear function in R (version 4.2.1). This resulted in a composite series for each postcode sector to allow linkage to the AKI data (figure 1). Permissions and approval were obtained via the UKRR Integrated Research Application System.

Statistical analysis

We assessed two different aspects of heat exposure: effects during individual heatwave periods using heat-episode analyses of daily counts of AKI episodes, and effects associated with general heat exposure across the full study period using a case-crossover design and assigning individual exposure to each AKI record.

To assess effects during individual heatwaves, the observed number of AKI counts during identified hot periods was compared with a baseline representing the expected number of counts. This baseline was derived by averaging counts during the same time period as each heatwave period from other years in the dataset. For example, counts observed during a heatwave period in 2021 were compared with expected counts derived from the same time period in years 2018–2020. The year 2017 was excluded from all baseline calculations because the number of AKI events in 2017 was markedly lower than in later years due to an incomplete number of laboratories contributing data. Because the number of AKI counts varied by day of the week, a 7-day moving average of both the observed and expected series was used in comparisons. The percentage excess in AKI counts during heatwaves was estimated based on the difference between observed and expected counts, with calculation of CIs obtained by assuming a Poisson distribution.

A bidirectional, time-stratified case-crossover design was used to assess acute associations between temperature and AKI episodes occurring throughout the warm months.[17] Each AKI episode was linked to temperature measures corresponding to its postcode sector to characterise individual exposure. With the case-crossover design, each case is represented by temperatures on and around the day of the AKI episode, and controls by temperatures on nearby days. Therefore, confounding factors that are time invariant are implicitly controlled for. Control days were time stratified, in this case restricted to the same calendar month as the case day, and bidirectional, meaning that they could occur either before or after the case day. Control days were also matched to case days by day of the week to allow for the daily variation in AKI counts. This meant up to four control days were available for each case.

Conditional logistic regression was then used to assess odds of AKI episodes during case day temperatures compared with control day temperatures. Distributed lag
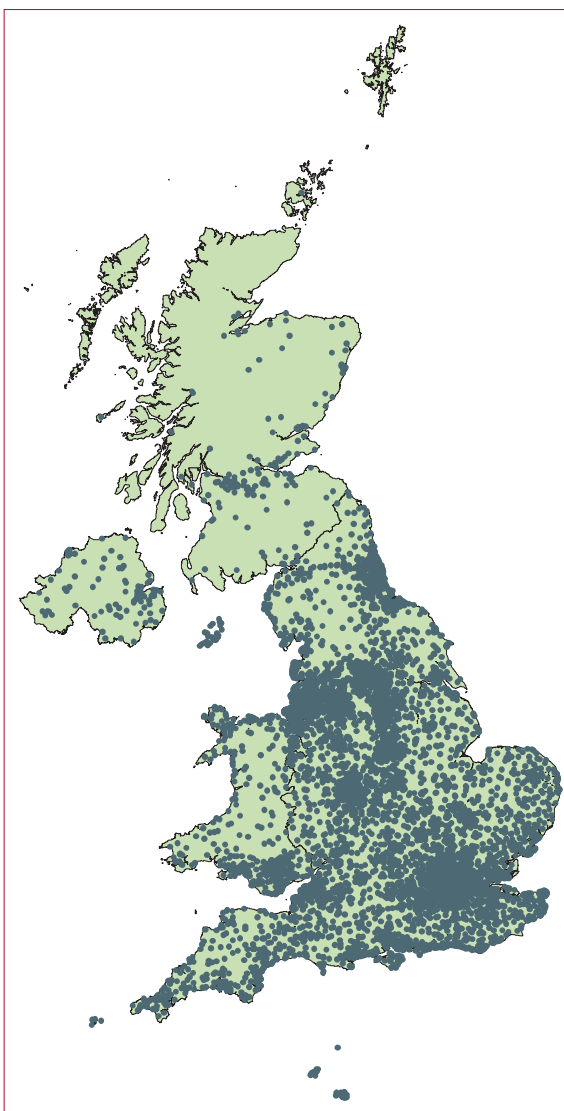

Figure 1: Geocoded postcode sectors of patients with acute kidney injury

non-linear models employing crossbasis functions were used to flexibly model potential non-linear and delayed effects of temperature on the triggering of AKI using previously developed code (appendix).[18] Spline functions were used to model both temperature and lag domains in the distributed lag non-linear models, with five degrees of freedom for the temperature splines and a maximum lag of 6 days before the day of AKI alert. Heat effects on AKI are known to be mostly immediate, and a maximum of 6 days lag avoids any overlap in exposures between case and (day-of-week matched) control days.[19] We identified the minimum morbidity temperature (MMT), which is defined as the value of temperature at which odds of AKI are lowest. Odds ratios (ORs) are presented as comparisons between the MMT and higher temperature values, and the fraction of all AKI episodes attributable to high temperatures was also estimated. To
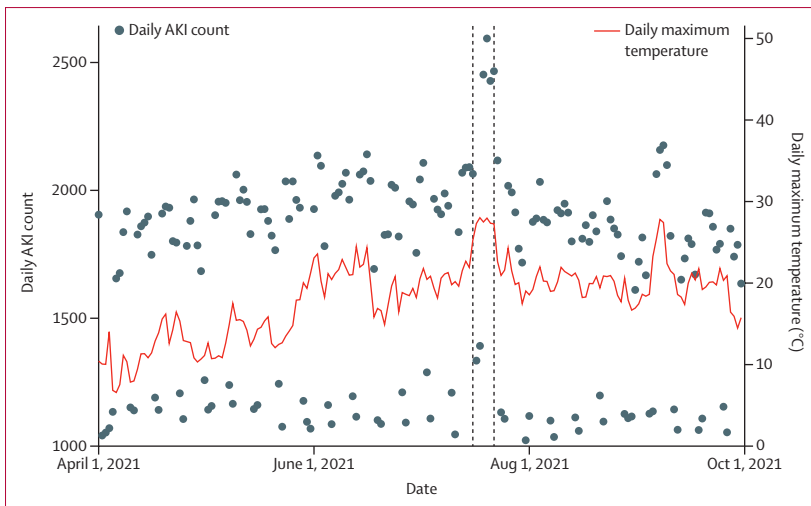
See **Online** for appendix

Figure 2: Daily national AKI episode counts and daily maximum temperature during summer, 2021
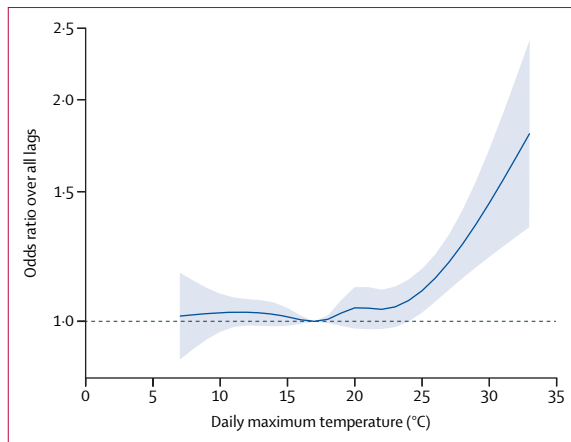AKI=acute kidney injury.

Figure 3: Relationship between daily maximum temperature and acute kidney injury episode up to 6 days lag

allow comparison with other studies, we also estimated heat effects based on a linear-threshold model, assuming a linear increase in OR per 1°C rise in temperature above the MMT, and no risk below the MMT. The linear effect was also estimated using a higher heat threshold fixed at the 90th percentile of the temperature distribution based on initial visual assessment of the temperature–AKI relationship. Stratified analysis was conducted by AKI severity stage, by year and month of AKI episode, and by government region of patient residence. Analyses were conducted in STATA 17. Linkage of AKI episodes to the gridded temperature data was conducted using the high-powered computing facilities at the London School of Hygiene & Tropical Medicine.

Role of the funding source
The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results
Between April and September in the years 2017–2021, 1354675 AKI episodes occurred that were linked to localised temperature data. A further 273 episodes with Guernsey or Jersey postcode sectors were not successfully linked to temperature data and were excluded from analyses. The numbers of AKI episodes between April and September were 204777 (15·1% of all episodes during the 5-year study period) in 2017, 280388 (20·7%) in 2018, 296953 (21·9%) in 2019, 266186 (19·6%) in 2020, and 306371 (22·6%) in 2021. The mean daily count of AKI episodes during 2017–2021 was 1481 (range 650–2594). A majority of 1070661 (79·0%) AKI episodes were of stage 1 severity, with 172004 (12·7%) stage 2 and 112010 (8·3%) stage 3. AKI episode counts varied by day of week: 129455 (9·6%) were recorded as occurring on Sundays, 212484 (15·7%) on Mondays, 222213 (16·4%) on Tuesdays, 224415 (16·6%) on Wednesdays, 222419 (16·4%) on Thursdays, 208903 (15·4%) on Fridays, and 134786 (10·0%) on Saturdays.

Figure 2 shows daily national counts of AKI episodes and daily maximum temperature in the summer of 2021. The separate banding of AKI counts is due to differences between weekdays and weekends. There was a clear spike in AKI episodes coinciding with periods of high temperature. For example, a 7-day heatwave during July 16–22, 2021 (represented by the dashed vertical lines in figure 2), was associated with a 28·6% excess in AKI counts (95% CI 26·5–30·7) compared with expected levels. The later hot period during Sept 5–9 was associated with a 15·7% excess in AKI counts (13·3–18·1). In other years, a heatwave on Aug 10–14, 2020, was associated with a 13·9% excess (11·5–16·3) and one on July 22–26, 2019, showed a 23·6% excess (21·1–26·1).

Figure 3 shows the temperature–AKI relationship across the full study period from the distributed lag non-linear model using lagged exposures of up to 6 days. An increased risk of AKI is observed with high temperatures, particularly once daily maximum temperatures rise above 25°C (approximately the 90th percentile of temperature). The temperature value at which AKI risk was lowest was 17°C, and 3·5% of all AKI episodes were attributable to temperatures above this value. The OR of an AKI episode at 32°C compared with at 17°C was 1·623 (95% CI 1·319–1·997). From a linear-threshold model, the OR of an AKI episode per 1°C increase in maximum temperature above 17°C was 1·020 (1·019–1·020). A 1°C increase in temperature above the 90th percentile of 25°C resulted in an OR of 1·049 (1·047–1·051). The heat effect was strongest on a lag of 1 day, with the next strongest effect associated with exposures on the same day as the AKI episode (lag 0).

Figure 4 shows the OR of an AKI episode per 1°C increase in daily maximum temperature above 17°C for all cases and by AKI stage. The odds of a heat-related AKI episode were similar between stages 1 and 2 but noticeably lower for stage 3 events, with an estimated OR of 1·018 (1·015–1·020) per 1°C increase.
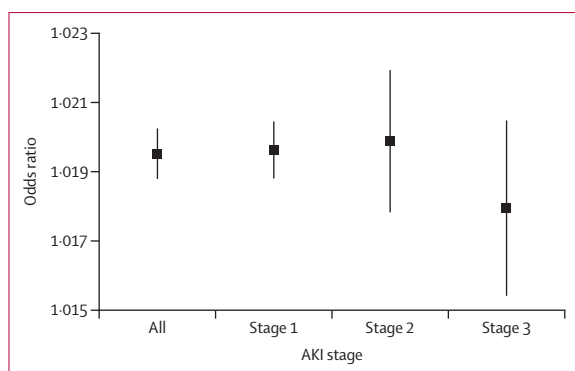
Figure 4: Odds ratio of AKI episode per 1°C increase in daily maximum temperature, by AKI stage
Bars denote 95% CIs. AKI=acute kidney injury.

Figure 5 shows the OR of an AKI episode per 1°C increase in daily maximum temperature above 17°C by year and by month. Heat-related odds were lowest in 2019, but the two most recent years were associated with the highest odds despite not being the hottest summers. The average temperature between April and September was 18·7°C in 2017, 20·1°C in 2018, 19·1°C in 2019, 19·7°C in 2020, and 18·6°C in 2021. Heat effects on AKI peaked in July and were present in all months except April.

Figure 6 shows the OR of an AKI episode per 1°C increase in temperature above the 90th percentile for all cases, and separately by region based on the 90th percentile specific to each region. Differences were not statistically significant, but heat effects were generally higher in the southern and Midlands regions and lower in the cooler northern regions. The North East region had the lowest OR.

Discussion

Our results show a clear increase in AKI episodes associated with high temperatures and heatwaves, with 62·3% increased odds of AKI on a day of 32°C maximum temperature compared with at 17°C. Many studies of heat-related AKI focus on extreme temperature conditions in outdoor occupational settings,[10] but we show that effects are also evident in England in everyday settings. We estimated a 2% increase in AKI odds per 1°C increase above the MMT, which is almost double the effect size of 1·012 estimated in a 2021 meta-analysis of 25 AKI studies based on either emergency department or hospital admissions data.[9] Furthermore, effects were more than four times greater when considering a higher heat threshold. The greater effects observed in our study might be because the e-alert system also captures milder cases that do not require secondary care, thus providing a more complete assessment of heat burdens on AKI morbidity. However, much of the increase we observed was driven by the years 2020 and 2021, when the combined OR was 1·023 (95% CI 1·022–1·024) per 1°C
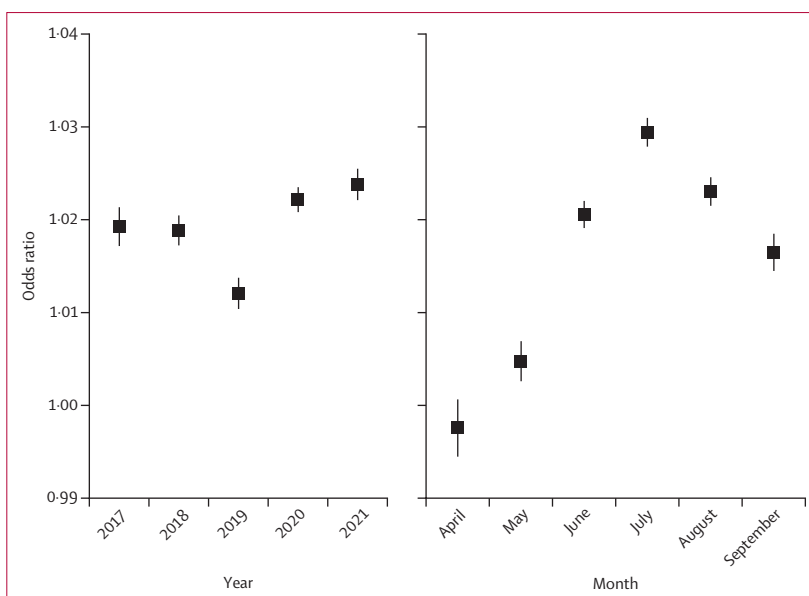

Figure 5: Odds ratio of acute kidney injury episode per 1°C increase in daily maximum temperature above 17°C, by year and month
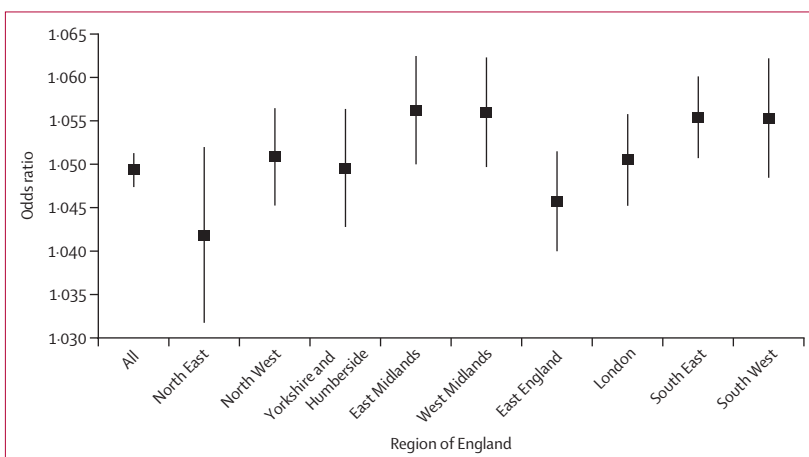Bars denote 95% CIs.

Figure 6: Odds ratio of acute kidney injury episode per 1°C increase in daily maximum temperature above 90th percentile, by region
Bars denote 95% CIs.

change above 17°C, which is significantly higher than the OR of 1·016 (1·015–1·017) for the years 2017–2019. This increase in the later years could be related to the COVID-19 pandemic. AKI rates were heavily affected by the pandemic because the cancellation of elective surgeries meant that only the most unwell people would have contracted AKI in hospitals and fewer people in the community would have been tested and had access to treatments.

In our study, heat effects were greatest in the hottest months, which is in contrast to a recent US study on hospital emergency department visits for kidney disease where effects were strongest in the transitional months of May and September.[19] Unlike in England, individuals

in the USA are likely to have been living in air-conditioned homes, which might explain the lower risks in the height of summer. We observed variation in AKI counts by day of the week, which is likely to be an artifact of data recording as the generation of e-alerts by laboratories is less likely to happen at weekends. There was lower heat risk associated with stage 3 AKI compared with the less severe stages 1 and 2, possibly because individuals with stage 3 AKI are likely to already be in hospital care and therefore less affected by environmental exposures. The reduced odds at stage 3 could also reflect better recognition and management of severe AKI, especially among individuals with community-acquired AKI who might be more likely than those with hospital-acquired AKI to be referred directly to nephrology wards.[5] In addition, Johnson and colleagues[2] draw a distinction between two types of AKI associated with either classical or exertional heatstroke, with the former more likely to be associated with normal or mildly elevated creatinine phosphokinase levels. They report that this is likely to manifest as an acute interstitial nephritis resulting from ischaemia, temperature-induced oxidative stress, and decreasing intracellular energy stores.[2] Dehydration can lead to high urine concentrations, which reduces the filtration rate of the glomerulus, leading to increased risk of AKI.[20] In addition, intense physical exercise can increase biomarkers of AKI, especially in serum urea nitrogen and serum creatinine kinase, even within 1 h of activity.[21] Experimental evidence suggests that both dehydration and hyperthermia independently contribute to the increased risk of AKI during hot weather, and that the location of injury is likely to be in the renal proximal tubules.[22]

A key strength of our study is the novel use of an automated e-alert system for the whole country, which provides a large number of AKI episodes to analyse that was far higher than the number of events in previous studies on kidney disease morbidity reviewed by Lee and colleagues.[10] Unlike in previous studies, the use of an e-alert system allows effects in primary as well as secondary care to be captured. Exposure information was also characterised for each individual patient at postcode sector level, within which ambient temperature measures are fairly homogeneous, thus limiting exposure measurement error. In terms of study limitations, we did not draw a distinction between hospital-acquired and community-acquired AKI, which could have yielded differential temperature effects. Moreover, although the e-alert algorithm has been validated with a high degree of sensitivity and specificity in different hospital settings,[23] alerts to UKRR will not be flagged when baseline creatine values are not available and so this might also affect AKI rates, which in turn could have attenuated heat effects. Heat effects could also have been modified by age, sex, comorbidities, and medication use, which we were unable to assess. In addition, although the case-crossover design controls for known and unknown time-invariant

confounding factors, we did not control for air pollution, which is a known risk factor for AKI.[24] However, the need to control for air pollution in epidemiological studies of weather and health has been questioned,[25] and any role of air pollution might be clearer in assessments of low-temperature effects on AKI.[26] A similar analysis of our data could be used to assess air pollution effects in future work, as well as the potential effects of low temperatures and other weather factors such as relative humidity.

Our findings have important implications for the identification and management of AKI, especially for mild cases in the community setting where careful monitoring and clinical intervention might be less likely. Existing AKI risk stratification tools could be adapted for heat vulnerability, including potentially important comorbidities such as diabetes and heart failure, and use of certain medications such as diuretics.[27] As even small changes in renal function can affect patient outcomes, susceptible patients should be advised to take preventive measures whenever hot weather is forecast, such as increasing fluid intake and avoiding diuretics.[28] Soft drinks could increase the risk of AKI and so targeted messaging regarding this might be required.[29] Given the clear spikes in AKI counts observed during heatwaves in our data, there is scope for the incorporation of AKI e-alert data into syndromic surveillance tools used as part of heat action plans to monitor effects on public health in real time during heat alerts. Additionally, although AKI can occur in people with or without underlying chronic kidney disease, incomplete recovery might increase the risk of developing subsequent chronic kidney disease. Therefore timely interventions can also help to reduce the global burden of chronic kidney disease, epidemics of which are now said to be occurring across the world where heat stress nephropathy might be a contributor.[30] This is of particular concern in low-income countries where underdevelopment and insufficient availability of kidney replacement therapy add considerably to existing renal burdens.[20] In such settings, other planetary health processes, such as water depletion and reducing biodiversity, might also affect kidney disease.[31] Conversely, nephrology practices, especially in high-income settings, can also be a major contributor to global environmental changes, with haemodialysis associated with high energy and water usage and accounting for one-third of all clinical medicine-related waste.[32] Bharati and colleagues[31] therefore argue that, given its sensitivity and contribution to environmental degradation, kidney health can be a global risk indicator and therapeutic target for actions that address climate change adaptation and mitigation.

In conclusion, we show strong associations between ambient heat exposure and AKI risk in a temperate high-income country. Such effects are likely to be even greater in parts of the world that experience hotter climates and where safe drinking water is not readily available. As the

climate continues to change, heat-related AKI will become a growing public health challenge in England and elsewhere.

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