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Estimating the Association Between Extreme Heat and Acute Kidney Injury Using Serum Creatinine-Derived Case Definitions

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B.A., Oberlin College, 2016

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Epidemiology
2023

Abstract

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Introduction: Acute kidney injury (AKI) exacts significant morbidity for patients. In addition to well-known clinical risk factors, extreme heat exposure may contribute to the burden of community-acquired AKI. The use of administrative coded data to identify AKI cases has important limitations in estimating the heat-AKI effect. Applying the Kidney Disease: Improving Global Outcomes (KDIGO) criteria instead may improve AKI surveillance while also differentiating hospital-acquired AKI from community-acquired AKI – critical to evaluating risk related to ambient heat.

Methods: We conducted a case-crossover analysis investigating the relationship between daily temperature and AKI-related emergency department (ED) visits in Atlanta, Georgia during consecutive warm seasons between 2016 and 2019. We created six case definitions for AKI using both ICD-coded data and KDIGO-derived equations. KDIGO definitions identified AKI cases by comparing patients' ED serum creatinine values to surrogate measures for baseline renal function. The KDIGO definitions were designed *a priori* to identify community-acquired AKI cases as opposed to hospital-acquired AKI.

Results: 264,415 ED visits across 4 warm seasons were included in our analysis. AKI case numbers ranged from 16,647 events using coded data to 54,320 under the most liberal KDIGO-derived definition. We found positive associations between same-day maximum temperature and ED visits for AKI across six definitions. The strongest heat-AKI effects were observed in the KDIGO definitions derived from the 2021 CKD-EPI equation.

Conclusion: Administrative coded data for AKI may underestimate the incidence of community-acquired AKI as well as its association with extreme heat. Applying the KDIGO criteria represents an alternative approach to better estimate the heat-AKI risk.

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Introduction

Acute kidney injury (AKI) exacts significant morbidity for patients, and its prevalence is increasing nationally.[1] The consequences of severe AKI are well known, but even mild cases are associated with greater risks of de novo chronic kidney disease, progression of CKD, and mortality.[1–3] AKI also comes with immense economic expense. One study estimated costs to exceed $1700 for an inpatient episode of AKI, and more than $11,000 in cases where dialysis was required.[4] Identifying individuals at high risk for AKI, and appropriately managing these patients, is therefore of public health and clinical importance.

The clinical risk factors for developing AKI have been previously documented to include pre-existing renal disease, diabetes mellitus, dehydration and critical illness.[5] Advanced age and female gender are thought to increase one's susceptibility for AKI.[5,6] Prior studies have also observed higher incidence rates of AKI among Black patients compared to White patients. This disparity may stem from multiple causes, including inequities in healthcare access, as well as differences in socioeconomic status and baseline health.[7,8]

In addition to clinical and demographic factors, environmental exposure may play a role in the onset of AKI. Several studies have observed an association between extreme temperatures and the risk of AKI.[9–15] A mechanism explaining this relationship is premised on extreme heat disrupting the kidney's physiologic role in thermoregulation. Acute, sustained heat exposure leads to increases in serum osmolality, vasopressin release and fructokinase generation, with the latter possibly driving tubular inflammation.[16,17] Pre-renal kidney injury may develop under these circumstances without adequate fluid repletion.[16,17]

Understanding the scope of heat-related renal disease is critical in the era of climate change. Human-caused climate change has driven global temperatures to rise 0.8°C to 1.3°C above pre-industrial times.[18] As a result, the proportion of vulnerable populations exposed to extreme heat has increased globally.[19] A cross-sectional study of U.S. counties found extreme heat days were associated with 1,373 excess deaths annually during the summer months between 2008 and 2017.[20] Mortality rates were higher for older adults, males, and non-Hispanic Blacks, underscoring disparities in extreme heat vulnerability.[20] Ambient heat exposure has been linked to higher rates of kidney-related morbidity as well, including renal failure, electrolyte derangements, urolithiasis, and early development of CKD.[16,21–23]

To date, heat and AKI studies have identified cases of acute kidney injury and other manifestations of renal dysfunction using International Classification of Diseases (ICD) diagnosis codes, which are documented by clinicians contemporaneously in the health record. Reliance on ICD-coding is common for AKI surveillance but has several key limitations. Multiple studies have observed low sensitivities for AKI detection using billing codes, ranging from 15 to 81%.[24–28] On the other hand, ICD-coding has a high specificity exceeding 90%.[24–28] Cases of AKI captured by billing code methods also tend to be more severe.[28] The poor sensitivity of ICD-coded data, combined with a propensity for identifying severe cases of AKI, together suggest this method may underestimate the incidence of mild AKI.

Another important consideration in characterizing AKI is the difference between community-acquired AKI (CA-AKI) and hospital-acquired AKI (HA-AKI), which have unique risk factors, etiologies and prognoses.[29,30] HA-AKI frequently arises in the context of severe clinical illness, such as post-operative AKI, cardiac dysfunction, or contrast administration.[31] CA-AKI,

meanwhile, occurs outside the healthcare setting. Individuals at heightened risk include those with pre-existing renal dysfunction, gastrointestinal illness causing pre-renal azotemia, as well as patients using non-steroidal anti-inflammatory medications and diuretics.[29,32] CA-AKI is accompanied by a lower risk of dialysis and in-hospital mortality relative to HA-AKI.[1,33,34] Still, patients with CA-AKI compared to those without any AKI experience longer hospital stays and worse rates of 30-day mortality.[29] ICD-coded billing data cannot distinguish between CA-AKI and HA-AKI because a single code is used to capture all AKI events. The codes are also not time-stamped, which prevents researchers from delineating CA-AKI from HA-AKI based on when the patient presented and when the diagnosis was recorded. Including HA-AKI is problematic for heat-AKI studies because patients who develop AKI while hospitalized are not likely to have been exposed to ambient temperature.

The shortcomings of ICD-coded billing data in terms of underestimating AKI and failing to differentiate CA-AKI from HA-AKI have challenged previous studies of temperature and AKI. An alternative to administrative billing data for AKI identification is the Kidney Disease: Improving Global Outcomes (KDIGO) criteria.[5] The KDIGO definition for AKI relies on laboratory data such as serum creatinine (SCr) or urine output measurements to identify cases of AKI. Two studies comparing the KDIGO criteria with ICD-billing information found better sensitivities with the KDIGO definition.[24,25] The KDIGO criteria improved estimations of CA-AKI incidence as well.[35] With a KDIGO-based approach, researchers can compare an individual's kidney function early in their presentation with a known or presumed baseline value. This method may help delineate CA-AKI from cases of HA-AKI that arise during a patient's subsequent hospital stay. KDIGO-definitions may also identify AKI events missed by ICD diagnosis codes. One barrier to using the KDIGO definition in clinical or research settings, though, is that it requires an accurate estimate of a patient's baseline renal function.[36]

Here, we use detailed electronic medical records to investigate the relationship between ambient heat and AKI in the Atlanta, Georgia metropolitan area, where previous work has shown an association between renal-associated ED visits and heat exposure.[12] To date, no study to our knowledge has applied the KDIGO criteria to investigate the association between ED visits related to AKI and exposure to high ambient temperatures. We hypothesized that KDIGO-based methods may improve estimation of AKI compared to ICD-coded data and help differentiate between cases of CA-AKI and HA-AKI. We conducted a case-crossover analysis investigating the relationship between AKI-related ED visits among adults in Atlanta during the four consecutive warm seasons between 2016 and 2019. Our objectives were to compare estimated effects of heat on ED visits across multiple definitions of AKI, and to identify individual-level factors that may exacerbate this risk, including age, sex, race, CKD, diabetes, and hypertension.

Methods

Clinical Database

De-identified patient information was provided by the Emory University Clinical Data Warehouse (CDW). CDW data comprised clinical and demographic data for patients at four major non-pediatric Atlanta, Georgia-area hospitals: Emory University Hospital, Emory University Midtown Hospital, Emory Saint Joseph's Hospital, and Emory Johns Creek Hospital.

Data for this study was available for the warm seasons (May 1 through September 30) from 2016 to 2019. The CDW provided individual-level data including ED visit date and time of arrival, patient age, sex, race, residential zip code, and primary and secondary diagnosis codes from the International Classification of Diseases, 10th Revision (ICD-10). Clinical variables of importance included all measured serum creatinine values with datetime stamps.

ED visits were defined as any patient seen through the ED as an outpatient and subsequently discharged, or those admitted from the ED to an inpatient service. We excluded patients who were registered to the ED in error, left prior to triage, or whose ED disposition was not recorded in the dataset. Patients residing in a zip code outside of the 10-county Atlanta area were also excluded, as were patients undergoing dialysis (ICD-10 codes N185, N186 or Z992), and individuals younger than 18 years old.

Exposure Data

Outdoor temperature data was obtained from the Daymet meteorological product (https://dayment.ornl.gov/), which provides daily estimates of temperature at a 1 km by 1 km grid resolution. The Daymet data were aggregated to ZIP code tabulation areas (ZCTA) using spatial averaging. Exposures were linked to each individual hospital visit by date and the patient's reported residential address. The *a priori* exposure of interest was same-day maximum temperature, but we also tested minimum temperature in sensitivity analyses. The study was limited to the 10-county Atlanta, Georgia metropolitan area.

AKI Case Definitions

We explored the association of heat and AKI using six distinct case definitions (Table 1). The first AKI definition, "ICD," includes any patient that had an ICD-10 code of N17 as either a principal or secondary diagnosis at any point during their hospital stay. The diagnosis codes were not time stamped, which prevented us from differentiating between CA-AKI and HA-AKI. This case definition reflects the definition used in most prior studies on the association of temperature with AKI.[37–40]

All subsequent definitions used the KDIGO criteria to identify AKI cases, which requires two serum creatinine (SCr) values: a baseline reference and a comparator. Baseline SCr values are ideally estimated using longitudinal outpatient data.[30] However, like in many hospital datasets, outpatient data prior to the patient's ED visit was not available to us. Therefore, we assessed multiple approaches to estimating baseline SCr. In all cases, for the comparator, we used the maximum measured SCr value within 48 hours of a patient's arrival to the ED; a 48 hour cutoff has been previously applied to distinguish cases of CA-AKI from HA-AKI.[30,33,41,42] An AKI case was assigned if the comparator reflected an increase of at least 0.3mg/dL in a patient's SCr above the baseline.[5,35] The different approaches to estimating baseline SCr are described below and in Table 1.

The second AKI definition, "CRUDE," sets a sex-specific baseline equal to the upper limit of the reference values for SCr defined by Emory Healthcare, which is 1.3 mg/dL for males and 1.2 mg/dL for females. Therefore, patients with a maximum SCr within the first 48 hours of their arrival that was greater than or equal to 1.6mg/dL for males, or 1.5mg/dL for females, were classified as having AKI under this definition.

The third definition, "MIN," sets the baseline equal to the minimum SCr measured during a patient's hospitalization.

The final three KDIGO definitions rely on the 2021 CKD-EPI equation to assign a baseline estimate for renal function.[43] The original CKD-EPI equation was developed in 2009 to improve estimation of glomerular filtration rate (GFR) by adjusting for patient age, sex, and race.[44] The CKD-EPI equation improved GFR estimates compared with older GFR-estimating equations, but was found to systematically overestimate GFR in Black individuals.[45] A new 2021 CKD-EPI equation aimed to address this disparity by eliminating the race coefficient from the formula.[46] The modified equation incorporates age, sex, and either cystatin, SCr, or both cystatin and SCr, to estimate GFR. We specifically used the 2021 CKD-EPI creatinine equation to back-calculate estimates of SCr baselines from a set eGFR value because cystatin clearance was not available in the dataset. The ADQI 16 Workgroup recommends using an eGFR value of 75 ml/min/1.73 m^2 for back-calculations when outpatient SCr values are unavailable.[47] An eGFR equal to 75 assumes a population with moderately preserved renal function. We tried to account for individuals with either further reduced or well-preserved renal function by varying our choice of eGFR values in the 2021 CKD-EPI back-calculation. Therefore, we created three case definitions with eGFR set to 60 (Definition 4), 75 (Definition 5) and 90 (Definition 6) ml/min/1.73 m^2. We applied these values along with the patient's age and sex to generate estimates of baseline SCr. Sex-stratified plots reporting the range of baselines back-calculated using the 2021 CKD-EPI equations are included in Supplemental Figures 1-3.

We anticipated advantages and disadvantages for each case definition. The definition derived from billing code information, "ICD," would not distinguish between CA- and HA-AKI. ICD-coding also has low sensitivity for mild AKI, which is a common phenotype for CA-AKI.[48] We expected that the "MIN" definition would be the most flawed definition. Minimum SCr values measured during hospitalization may approach an individual's baseline, but patients are frequently discharged prior to complete resolution in their AKI. This means the observed inpatient minimum SCr value for CA-AKI cases may exceed their true baseline, leading to underestimates of the AKI case incidence.[49] The "CKD-EPI 90" and "CRUDE" case definitions assume a population with preserved renal function. This approach maximizes sensitivity and negative predictive value at the potential expense of specificity and positive predictive value.[50] The poor positive predictive value stems from these definitions' inability to distinguish patients with chronic versus acute elevations in SCr. Patients with CKD but without AKI are therefore vulnerable to misclassification under these case definitions. The "CKD-EPI 75" and "CKD-EPI 60" equation account for patients with reduced renal function to varying degrees, though neither account for patients with a GFR in the CKD range. In contrast, the "ICD" better accounts for a patient's CKD status because this information was available to the billing provider. Overall, we hypothesized that the KDIGO-based definitions would produce a more accurate estimate of the burden of CA-AKI compared to ICD-coded definitions, and ultimately a more robust assessment of the effect of ambient temperature on CA-AKI. In particular, given the distribution of SCr baselines, our *a priori* preferred approach was the "CKD-EPI 75" as it would offer the best estimate of patients with relatively preserved renal function.

Study Design and Statistical Analysis

We employed a case-crossover study design, which is a common approach to evaluate associations between acute health outcomes and an environmental exposure.[51] Individuals in a case-crossover study act as their own control where the day of ED visit is assigned as the case day and control days were defined as the same day of week, month, and year, leading to 3-4 control days for each case. This approach controls for day of week, month, and individual-level factors like age, sex, race, and comorbidities since each individual acts as their own control. Our analysis was limited to the warm season between May 1st and September 30th.

We conducted separate analyses for each of the six AKI case definitions described above to investigate the relationships between short-term heat exposure and CA-AKI incidence. We applied a conditional logistic regression model that included squared and cubic terms to evaluate potential non-linear effects of temperature on hospital visits for AKI. We produced exposure-response functions with 95% confidence intervals for each AKI case definition using a reference value of the median daily maximum temperature. To do so, the median temperature reference was compared to every half-degree temperature increment between 19° C and 36° C, which encompassed the 1st through 99th percentile of daily maximum temperature during the study period. As a straightforward way of comparing results across the AKI definitions, we also calculated odds ratios with 95% confidence intervals contrasting the 95th versus 5th percentiles for daily maximum temperatures at lag 0 days. Finally, we conducted stratified analyses for different sub-groups across each case definition for the 95th versus 5th contrasts. Our stratifying variables were sex (male vs female), race (Black vs non-Black), age ($\geq$65 years old vs $<$65 years old), CKD (yes vs no), Diabetes mellitus (yes vs no), and hypertension (yes vs no).

Finally, we conducted a sensitivity analysis using daily minimum temperature. All analysis was carried out using SAS, Version 9.4, statistical software (SAS Institute, Inc., Cary, North Carolina).

Results

We received individual-level data for 298,628 ED visits during the 4 warm seasons of May through September (n = 612 days). 264,415 ED visits were included in the analysis after excluding visits of individuals younger than 18 years old (n=2031), those undergoing dialysis (n=773), those with erroneous or missing disposition (n=4919), or visits with residential zip codes outside of the 10-county study area (n=26415).

The median daily maximum temperature for the 10-county Atlanta area was 31.37° C (IQR 29.14 - 32.93). A summary of additional meteorological exposure data is provided in Table 2.

Descriptive statistics of the cohort are presented in Table 3. When compared to all hospital visits, individuals with AKI across the case definitions were older, more likely to be male, and experienced higher rates of CKD, hypertension, and diabetes. The proportion of Black patients was lower in the “ICD” cohort compared to the overall population; all other case definitions had a higher proportion of Black patients compared to the population. The average maximum SCr value measured within 48 hours of ED arrival was greater in the case cohorts than the study population across all definitions. “ICD” cases had the lowest maximum SCr values within 48 hours of ED arrival compared to the KDIGO case definitions, which is not

unexpected since it includes both HA-AKI as well as CA-AKI; early SCr values could be normal for HA-AKI cases that developed after the first 48 hours of ED arrival.

Overall, the CKD-EPI 90 definition captured the most AKI cases while the ICD definition captured the fewest (Table 3). The 2021 CKD-EPI-based definitions identified increasing numbers of AKI cases as the assigned baseline GFR increased from 60 to 75 to 90 ml/min/1.73 m^2. We anticipated this result, as a GFR set to 60 ml/min/1.73 m^2 corresponded to a median SCr baseline using the 2021 CKD-EPI equation of 1.12 mg/dL for females, and 1.41 mg/dL for males. An estimated GFR equal to 75 ml/min/1.73 m^2 generated a median SCr baseline of 0.934 mg/dL for females and 1.17 mg/dL among males. The most liberal assigned GFR of 90 ml/min/1.73 m^2 led to median SCr baseline values of 0.802 mg/dL for females and 1.01 mg/dL for males. Applying these distributions to the KDIGO equation meant that lower absolute thresholds were necessary to be assigned a case under CKD-EPI 90, followed by CKD-EPI 75 and lastly CKD-EPI 60.

Table 4 reports the agreement between the case definitions. The CKD-EPI 90 definition identifies the greatest number of AKI cases of all the definitions, and (by definition) it also captures 100% of those under the CKD-EPI 75 and CKD-EPI 60 definitions. CKD-EPI 90 also captured 100% of CRUDE cases. The CKD-EPI 75 definition that we preferred *a priori* illustrates a significant discrepancy compared to the "ICD" definition. The "ICD" definition identifies only 33.1% of CKD-EPI 75 cases. Conversely, the CKD-EPI 75 definition captures 83.4% of ICD cases.

Figure 1 depicts exposure-response functions with 95% confidence intervals for same-day maximum temperature across each case definition. The functions exhibit similar shapes across definitions, with a generally increasing risk as temperatures increase. The effects are summarized further in Figure 2, which compares the risks at the 95th versus the 5th percentile temperatures. Effects were strongest in the definitions that relied on the CKD-EPI equation, with CKD-EPI 75 – our *a priori* definition of choice – showing the highest effect overall (albeit only marginally) with an odds ratio of 1.049 (95% CI 1.007 – 1.093).

Results of the subgroup analysis are summarized in Figure 3. Males were at higher risk than females across all definitions and Black patients similarly experienced increased risk compared to non-Black patients; however, differences across groups were not statistically significant at the 5% level. Individuals without hypertension were at higher risk than those with a diagnosis of hypertension, though these results did not reach statistical significance at the 5% level either. Differences by age and diabetes status were not consistent in direction or magnitude. Individuals with CKD experienced a non-statistically significant increased risk in the ICD, MIN, and CRUDE definitions, but the opposite pattern emerged in the CKD-EPI case definitions.

In our sensitivity analysis, results using daily minimum temperature at lag 0 days were similar to our maximum daily temperature findings (Figure S4).

Discussion

We present an analysis comparing KDIGO-based definitions of AKI with ICD-coded data to estimate the risk of AKI at high ambient temperature exposure. This paper adds to the existing literature of ambient heat exposure and risk of AKI in several key ways. First, it applies KDIGO-based case definitions to a cohort to identify patients with likely CA-AKI, as opposed to

HA-AKI. Second, it uses case definitions that likely capture AKIs that would be excluded by ICD-coding, which is known to under-diagnose AKI.[24,26,28] And third, this is one of a few studies to examine heat-AKI relationships in patients by demographic group and the existence of co-morbidities.

There were notable differences between the sub-cohorts defined by each case definition. The ICD definition assigned 6.3% of all visits to an AKI, which was the smallest percentage across all definitions. The KDIGO-based cohorts ranged from 9.1% to 20.5% of the total hospital visits, possibly reflecting a significant undercount of CA-AKI cases in the ICD cohort. Prior studies have found a 2-3x greater prevalence of CA-AKI compared to HA-AKI, which is supported by our results.[29] Interestingly, the ICD cohort had the lowest maximum SCr in the first 48 hours from ED arrival. This may reflect differences in the timing of CA-AKI and HA-AKI. Patients with CA-AKI present with early elevations in SCr, while HA-AKI can develop at any point during hospitalization; prior studies have reported that SCr values among HA-AKI cases peak between days 4 and 5 of hospitalization.[52] Together, this supports our assessment that the ICD definition likely comprised a greater proportion of HA-AKI than the KDIGO definitions, which is highly relevant to studies of environmental determinants of AKI, including heat. Because HA-AKI patients are not exposed to ambient temperature, including these cases would downward-bias any heat effect.

The agreement between case definitions illustrates a trade-off between sensitivity and specificity in identifying CA-AKI. Lower baseline estimates increase CA-AKI sensitivity. We maximized sensitivity with the CKD-EPI 90 definition. In contrast, the CKD-EPI 60 definition assigned higher baseline SCr estimates and ultimately increased the case definition's specificity. We are unable to calculate positive and negative predictive values for the definitions without longitudinal outpatient measurements to validate baseline estimates.

We decided not to evaluate the other sub-criteria of the KDIGO definition for AKI, which include a 1.5 times increase in SCr within 7 days, or a decrease in urine volume by < 0.5 ml/kg/hour for 6 hours.[5] Urine output was not reliably recorded in our dataset, so this would not have been a reliable measure to identify cases of AKI. An increase in SCr by 1.5 times the baseline within 7 days represents a more specific threshold than an increase of 0.3 mg/dL within 48 hours. However, our focus in this study was evaluating the association of CA-AKI with heat exposure. Comparing SCr values across a 7-day window of hospital data may have increased the proportion of HA-AKI cases in our cohort, and could therefore have increased outcome misclassification. Another important consideration was that CA-AKI are milder in severity compared to HA-AKI, with one meta-analysis noting lower rates of oliguria, ICU admission and mortality.[1,34] Applying a threshold increase of 0.3 mg/dL instead of 1.5 times the baseline would improve our sensitivity for mild cases of AKI.

The exposure response functions revealed a positive effect where the risk of AKI increased at higher temperatures. The shapes of the curves were consistent across case definitions. Stronger effects appeared in the KDIGO case definitions than the ICD definition. This could be explained by the ability of KDIGO definitions to distinguish CA-AKI from HA-AKI. The presence of HA-AKI cases under the ICD definition could have represented outcome misclassification, which, again, may have down-biased results.

Our results add to a body of literature supporting an association between ambient heat exposure and acute renal disease. An analysis of Atlanta area ICD-coded data from 1993 to

2012 found a positive effect for heat on renal-associated ED visits with a slightly larger magnitude than our study.[12] A case-crossover analysis in Seoul, South Korea observed a smaller but statistically significant effect for AKI at high temperatures, again using ICD diagnosis codes.[10] A study analyzing ICD data across multiple South Korean cities found larger, statistically significant effect sizes for acute renal failure risk.[11] A case-control study of older adults in Ontario, Canada between 2004 and 2013 revealed a slightly larger magnitude of AKI risk during extreme heat periods.[37] Another large case-crossover analysis from 2005 to 2013 in New York State revealed an positive association of AKI with extreme heat exposure of similar magnitude to our findings.[40]

These results are supported by a biological mechanism for heat-induced renal injury. Heat stress contributes to dehydration and eventual reductions in intravascular blood volume. A compensatory mechanism allows the kidneys to maintain renal perfusion pressures, but under sufficient stress, these processes may fail and lead to renal hypo-perfusion and injury.[53] Pre-renal azotemia is a common etiology for CA-AKI.[29]

The subgroup analysis revealed several interesting patterns. Males had elevated temperature effects across all case definitions compared to females. A prior study identified male sex as a risk factor for CA-AKI compared to non-AKI controls.[48] Heat-AKI studies have also previously identified non-significant increases in AKI risk among males compared to females, similar to our results.[15,40,54] Our subgroup analysis also found non-significant increases in AKI risk among Black patients compared to non-Black patients. This result is in contrast with a New York-based study, which found higher excess rates of kidney disease related to extreme heat among non-African Americans compared to African Americans.[40] We did not find a consistent signal of age-specific (above/below age 65) effects. Results from other studies overall suggest an elevated effect in the elderly, which is consistent here for the ICD and MIN definitions.[9,10,40,55]

Stratifying our cohorts by CKD allowed us to evaluate if the heat-AKI effect differed depending on CKD status. Only ICD-defined AKI could account for CKD because both CKD and AKI cases under this definition were drawn from diagnosis codes in the medical record. The "ICD" definition suggested a small increase in risk among patients with CKD and those without a CKD diagnosis. This difference did not reach statistical significance at the 5% level.

The CKD subgroup analysis also evaluated potential bias in our outcome ascertainment. In our study, KDIGO-defined AKI could not account for patients with CKD because our baseline estimates assumed normal-range renal function. Odds ratios were higher in the non-CKD group for all three CKD-EPI case definitions. This result suggests there is a heat effect for the risk of CA-AKI among patients with previously normal renal function. It is likely that pre-existing CKD further magnifies this risk given that CKD is a known risk factor for AKI.[56] Future research using KDIGO definitions that can account for CKD-range renal function could further elucidate this relationship.

We acknowledge several limitations of this paper. Access to outpatient SCr measurements would have allowed us to compare the positive and negative predictive values to a gold standard. Unfortunately, access to accurate baseline creatinine values is rare.[47] With partial outpatient data, we could have estimated baseline renal function using a multiple imputation, as has been previously suggested.[57] This method may have improved baseline estimates beyond the eGFR 75 approach that we pursued. However, imputation was

impractical for our dataset given that baselines were missing across all observations. We hope our approach will inform future studies as epidemiologists continue to move towards laboratory-based analyses available through the electronic medical record.

We had access to patient data across a relatively short time period of 4 warm seasons. This contributed to uncertainty in our odds ratio estimates. Our data was also confined to a single metropolitan area, so our results may not be generalizable to other urban or non-urban regions. There are also inherent challenges to estimating disease risk related to ambient heat exposure. Our exposure data summarized daily ambient temperatures across a residential zip code rather than directly measuring individual-level temperature exposure. Therefore, patients who stayed indoors in air-conditioned facilities on warm days would not have experienced our exposure of interest. Area-income could serve as an imperfect proxy for air conditioning utilization to potentially account for this confounder.[58] Using payor information may also help approximate socioeconomic status.[59] This data was not available to us, unfortunately. We also did not control for air pollution or vapor pressure, although a prior Atlanta-based study found that these variables did not substantially impact their results.[12]

Each case definition had unique limitations as well. As previously described, ICD-defined AKI fails to distinguish HA-AKI from CA-AKI. The KDIGO-based definitions relied on imperfect estimates of baseline kidney function because the gold standard for estimating baseline function – outpatient SCr measurements – were unavailable. The CRUDE definition assigned a sex-specific baseline that failed to account for pre-existing renal disease. The MIN-defined AKI assumed the minimum SCr measured during hospitalization approximated the patient's baseline. Patients who were discharged from the hospital prior to complete resolution of their AKI may therefore have had falsely elevated baselines assigned. The 2021 CKD-EPI equations generated age- and sex-specific baselines for three set values of GFR: 60 ml/min/1.73 m^2, 75 ml/min/1.73 m^2, and 90 ml/min/1.73 m^2. Together, these definitions attempted to account for variation in baseline renal function, but they still could not account for patients with pre-existing CKD, which is defined as a GFR less than 60 ml/min/1.73 m^2. However, as we describe above, stratifying by the CKD variable in our subgroup analysis, enabled us to estimate the heat-AKI effect more accurately among individuals with preserved renal function.

Conclusion

In summary, we demonstrate that KDIGO-based AKI definitions are a viable and potentially improved tool to estimate the heat effect on CA-AKI compared to ICD-based definitions. Using KDIGO definitions enables researchers to distinguish HA-AKI from CA-AKI based on the timing of serum creatinine measurements. This is of critical importance to accurately estimate ambient heat-AKI effects. Our results also suggest that KDIGO definitions may capture additional AKI cases that are otherwise missed with ICD-based AKI definitions. Future studies with access to outpatient SCr measurements could build on this research to estimate the risk of AKI superimposed on CKD. This paper has important clinical and public health implications as healthcare providers adapt to health risks from extreme heat related to global warming.

Acknowledgments

I would like to express my gratitude to my co-chairs, Noah Scovronick and Stefanie Ebelt, as well as Rohan D'Souza, Howard Chang, and Ethel J. Weil for their generous help with this project.

Tables and Figures

Table 1: Acute kidney injury (AKI) case definitions

AKI Case	Definition
(1) ICD	ICD-10 classification coding of N17
(2) CRUDE	Maximum SCr value within 48 hours of ED arrival $\geq$ 0.3 + sex-specific baseline: 1.3 mg/dL for males, 1.2 mg/dL for females.
(3) MIN	Maximum SCr value within 48 hours of ED arrival $\geq$ 0.3 + the minimum SCr value measured during a patient's entire hospital stay
(4) CKD-EPI 60	Maximum SCr value within 48 hours of ED arrival $\geq$ 0.3 + baseline back-calculated using the 2021 CKD-EPI equation, where eGFR = **60** ml/min/1.73m^2.
(5) CKD-EPI 75	Maximum SCr value within 48 hours of ED arrival $\geq$ 0.3 + baseline back-calculated using the 2021 CKD-EPI equation, where eGFR = **75** ml/min/1.73m^2.
(6) CKD-EPI 90	Maximum SCr value within 48 hours of ED arrival $\geq$ 0.3 + baseline back-calculated using the 2021 CKD-EPI equation, where eGFR = **90** ml/min/1.73m^2.

Table 2: Daymet temperature data for the 10-county Atlanta, Georgia metropolitan area

10-County Atlanta Temperature	Median (IQR)	95%	5%
Daily Maximum (°C)	31.37 (29.14 – 32.93)	34.78	24.74
Daily Minimum (°C)	19.75 (17.58 – 21.11)	22.45	12.48

Table 3: Demographic and clinical descriptive statistics for all ED visits and sub-cohorts defined by each AKI case definition. (CKD = Chronic Kidney Disease, HTN = Hypertension, DM = Diabetes Mellitus, SCr = Serum Creatinine)

	Cases (% of total)	Mean Age (SD)	Female (%)	Black (%)	CKD (%)	HTN (%)	DM (%)	Mean Maximum SCr within 48 hours (SD)
All visits	264415 (100%)	51.1 (19.8)	58.5	55.6	4.36	43.7	18.7	1.48 mg/dL (2.1)
ICD	16647 (6.3%)	65.4 (17.1)	46.4	51.8	35.0	80.3	43.0	2.23 (1.7)
CRUDE	28205 (10.7%)	63.3 (16.8)	45.9	65.9	27.2	85.6	47.2	4.71 (4.2)
MIN	23979 (9.1%)	63.2 (17.4)	48.4	55.9	24.0	80.7	43.8	3.62 (3.9)
CKD-EPI 60	31484 (12.0%)	65.9 (16.7)	52.4	63.4	27.3	86.4	46.6	4.35 (4.1)
CKD-EPI 75	41938 (15.9%)	66.5 (16.5)	52.2	60.4	23.8	84.0	43.5	3.60 (3.8)
CKD-EPI 90	54320 (20.5%)	66.2 (16.5)	51.7	58.5	19.8	80.8	40.2	3.06 (3.5)

Table 4: Percent Concordance between AKI case definitions

	ICD (n = 16647)	**CRUDE (n = 28205)**	**MIN (n = 23979)**	**CKD-EPI 60 (n = 31484)**	**CKD-EPI 75 (n = 41938)**	**CKD-EPI 90 (n = 54320)**
ICD	100%	36.6%	48.7%	36.2%	33.1%	28.0%
CRUDE	62.1%	100%	62.9%	86.6%	67.2%	51.9%
MIN	70.1%	53.4%	100%	51.0%	44.1%	37.3%
CKD-EPI 60	68.5%	96.7%	67.0%	100%	75.1%	58.0%
CKD-EPI 75	83.4%	99.9%	77.1%	100%	100%	77.2%
CKD-EPI 90	91.4%	100%	84.5%	100%	100%	100%

Figure 1: Exposure-response functions by case definition for the risk of AKI across maximum daily temperature at lag 0 days. (Odds ratios provided with 95% confidence intervals, Red dashed line: Median daily maximum temperature, Green dashed line: 95th and 5th percentile daily maximum temperatures).

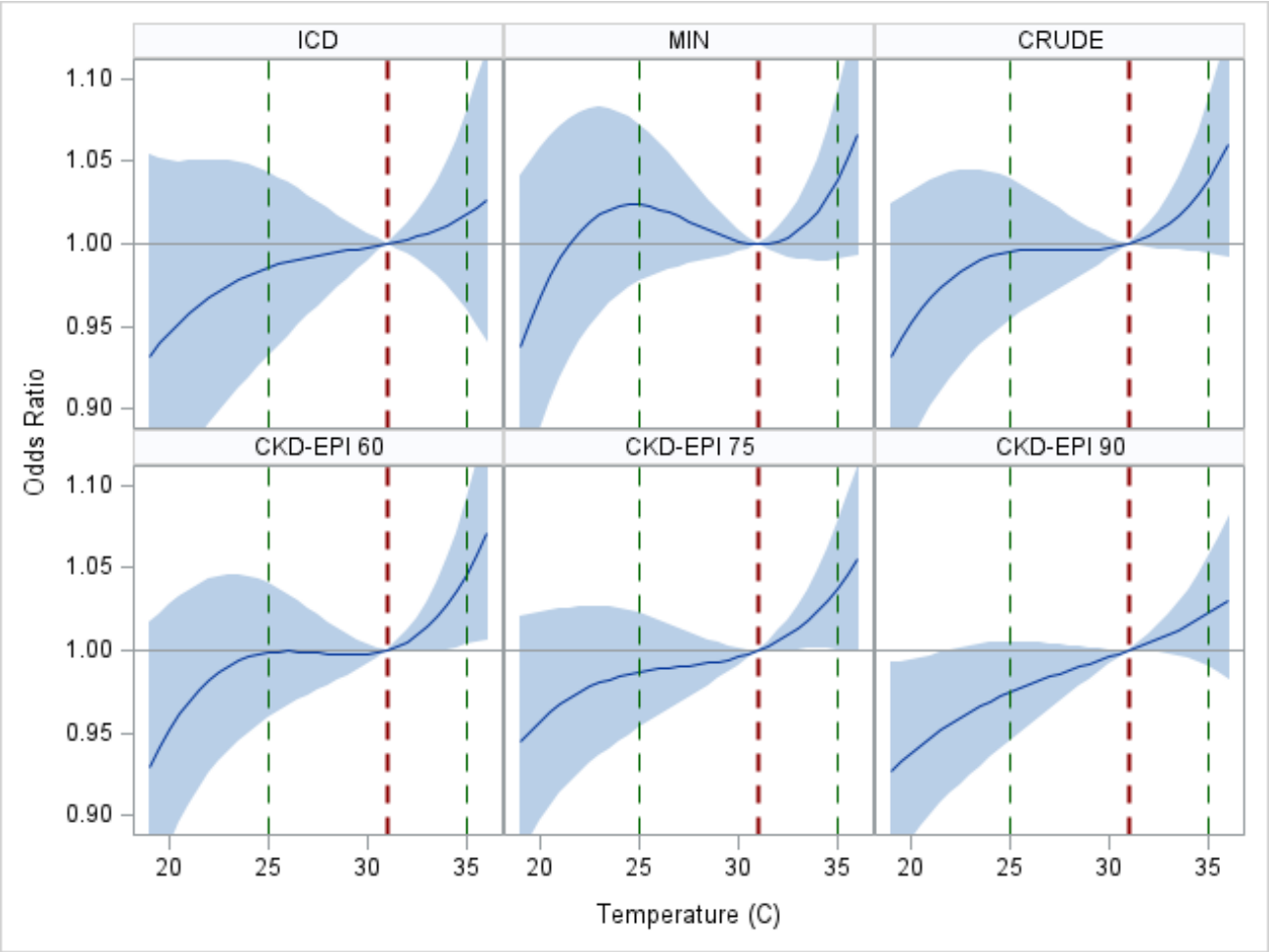


Figure 2: Contrast studies across case definitions for the risk of AKI at the 95th vs 5th percentile for daily maximum temperature. Odds ratios provided with 95% confidence intervals (Red dashed line: null hypothesis).

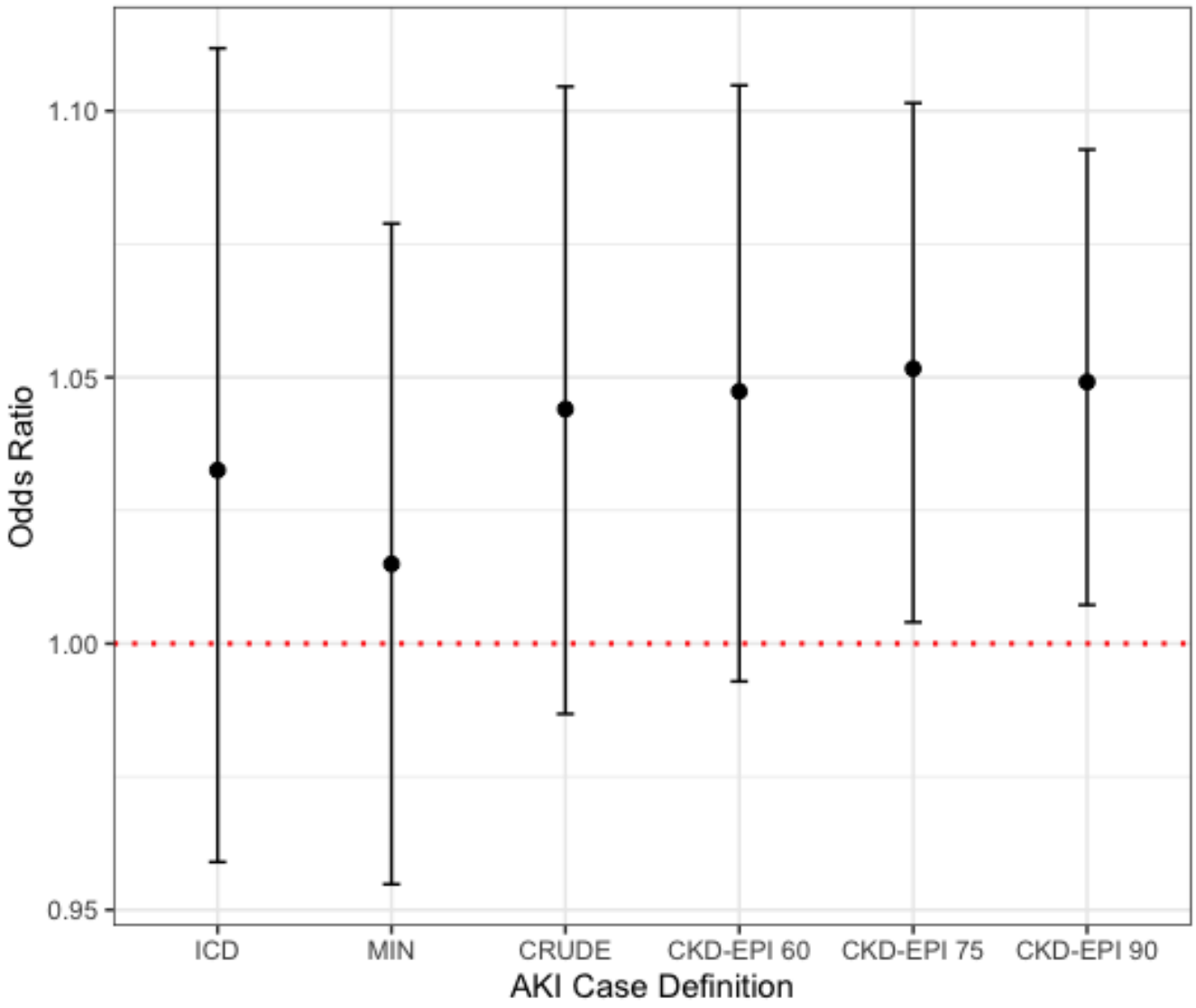
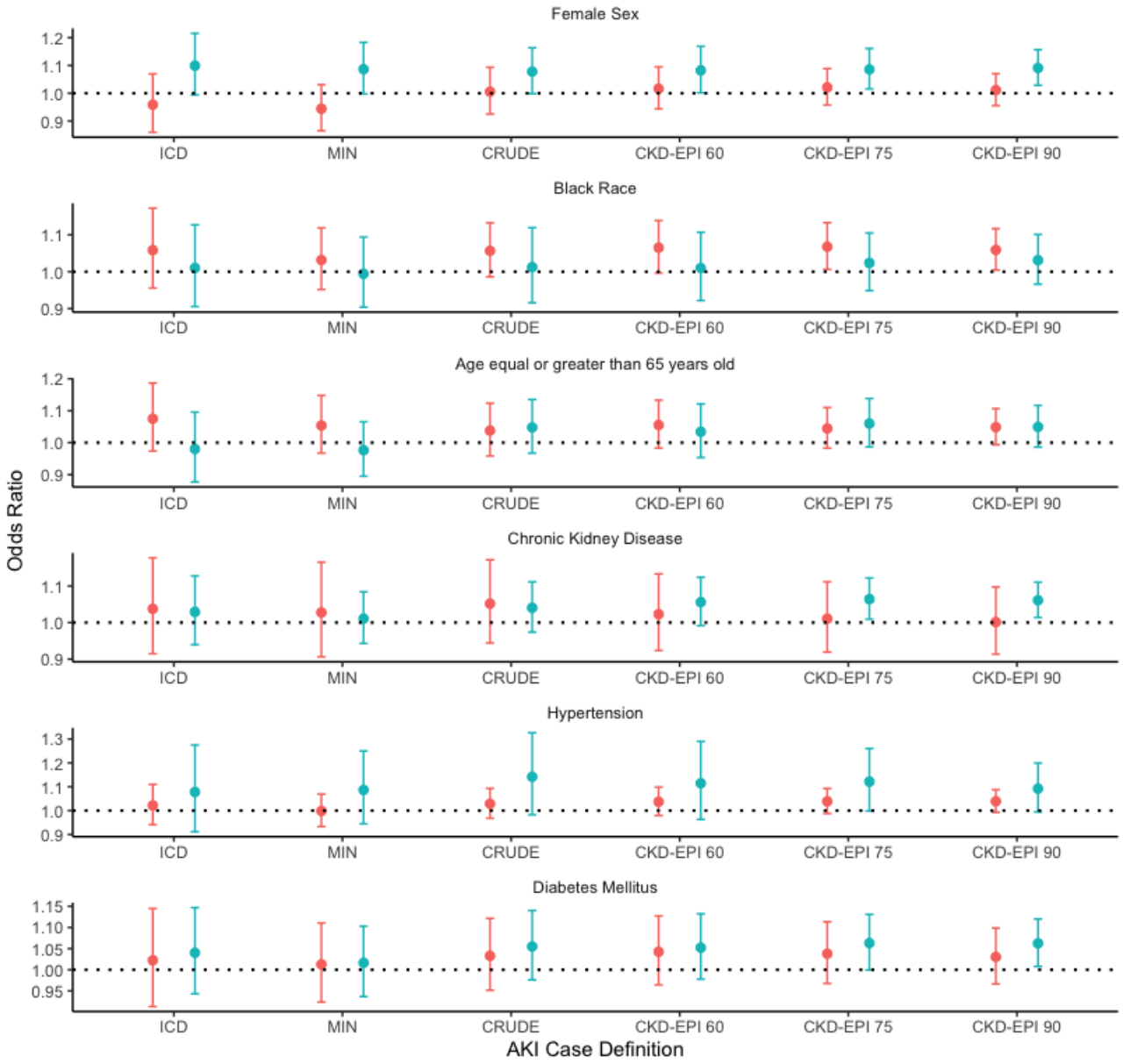
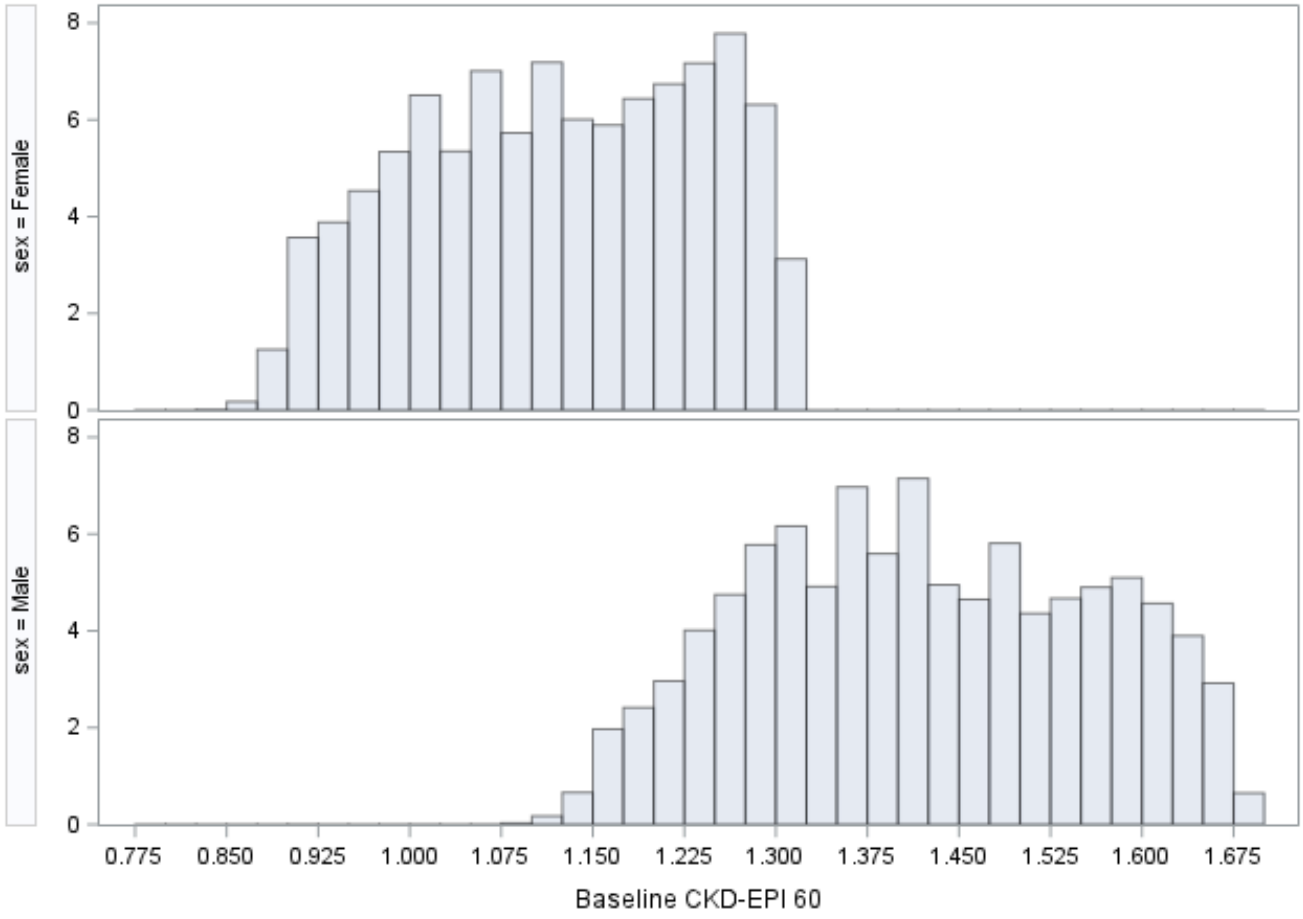


Figure 3: Subgroup analysis across case definitions comparing risk of AKI across the 95th vs 5th percentile for daily maximum temperature. Odds ratios with 95% confidence intervals. (Red = subgroup where stratifying variable = 1, Green = subgroup where stratifying variable = 0).

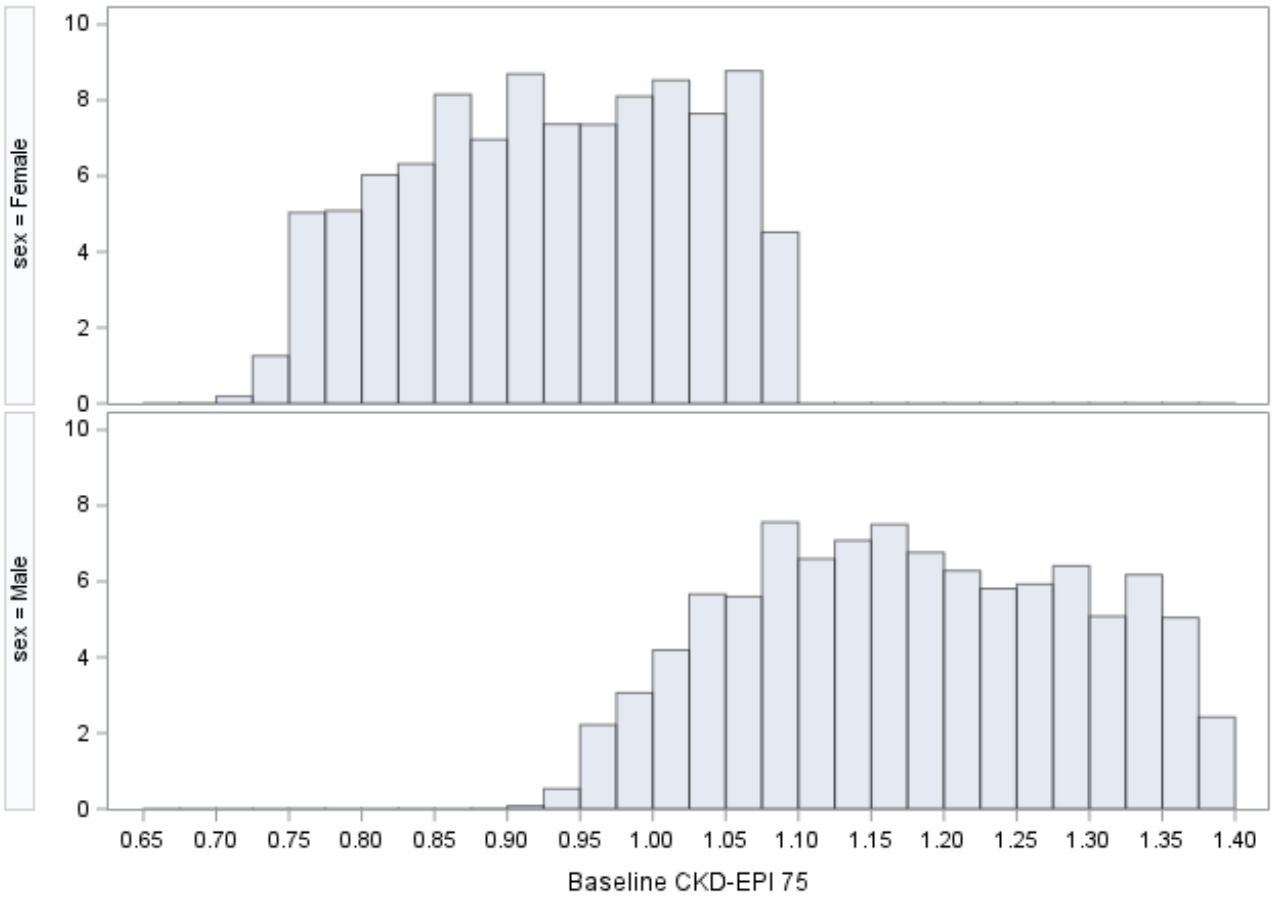


Supplemental Figures

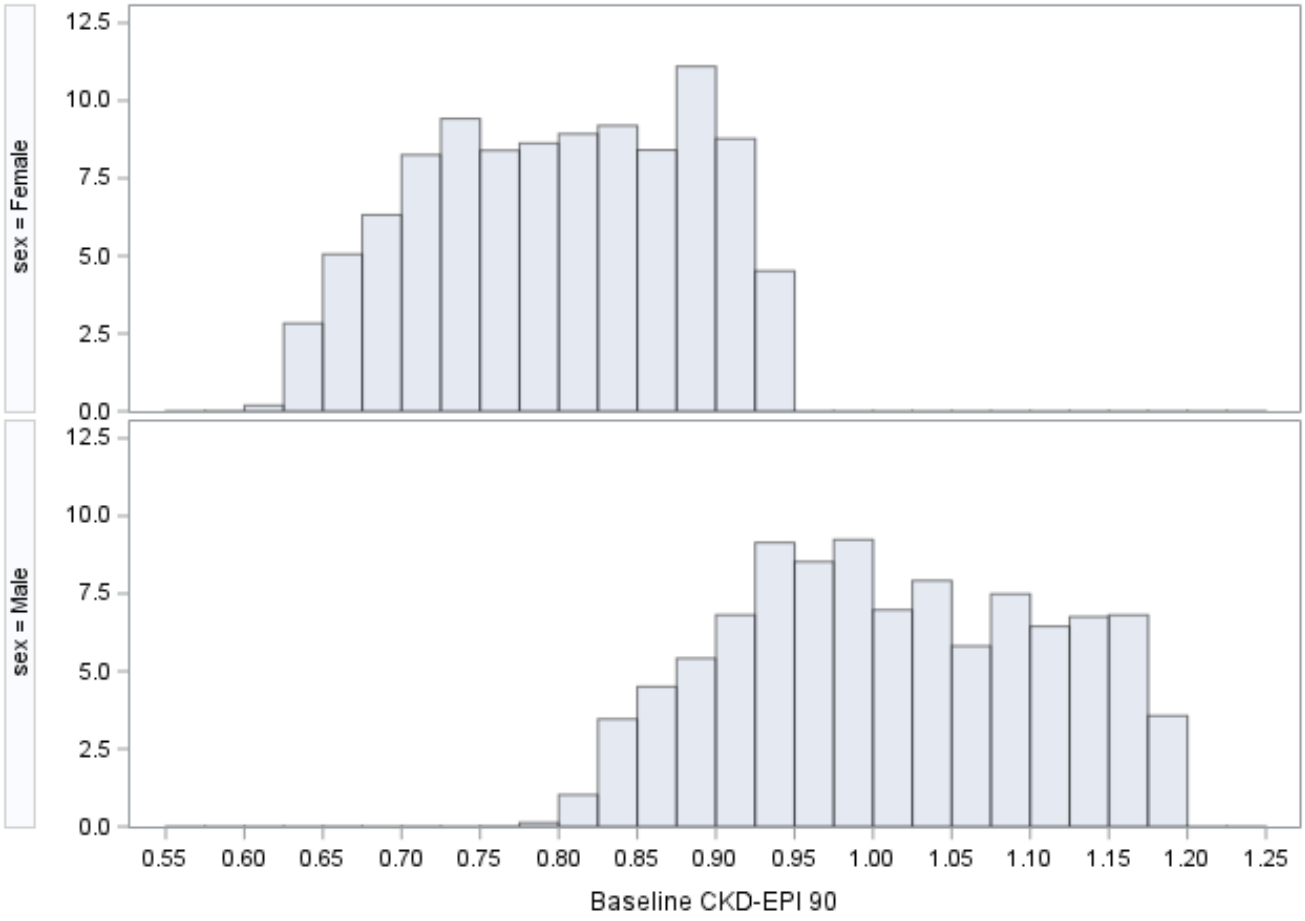
Supplemental Figure 1: Sex-stratified baseline serum creatinine values (md/dL) where 2021 CKD-EPI was back-calculated using a set GFR of 60 ml/min/1.73 m^2 (Above: Female patients; Below: Male patients).



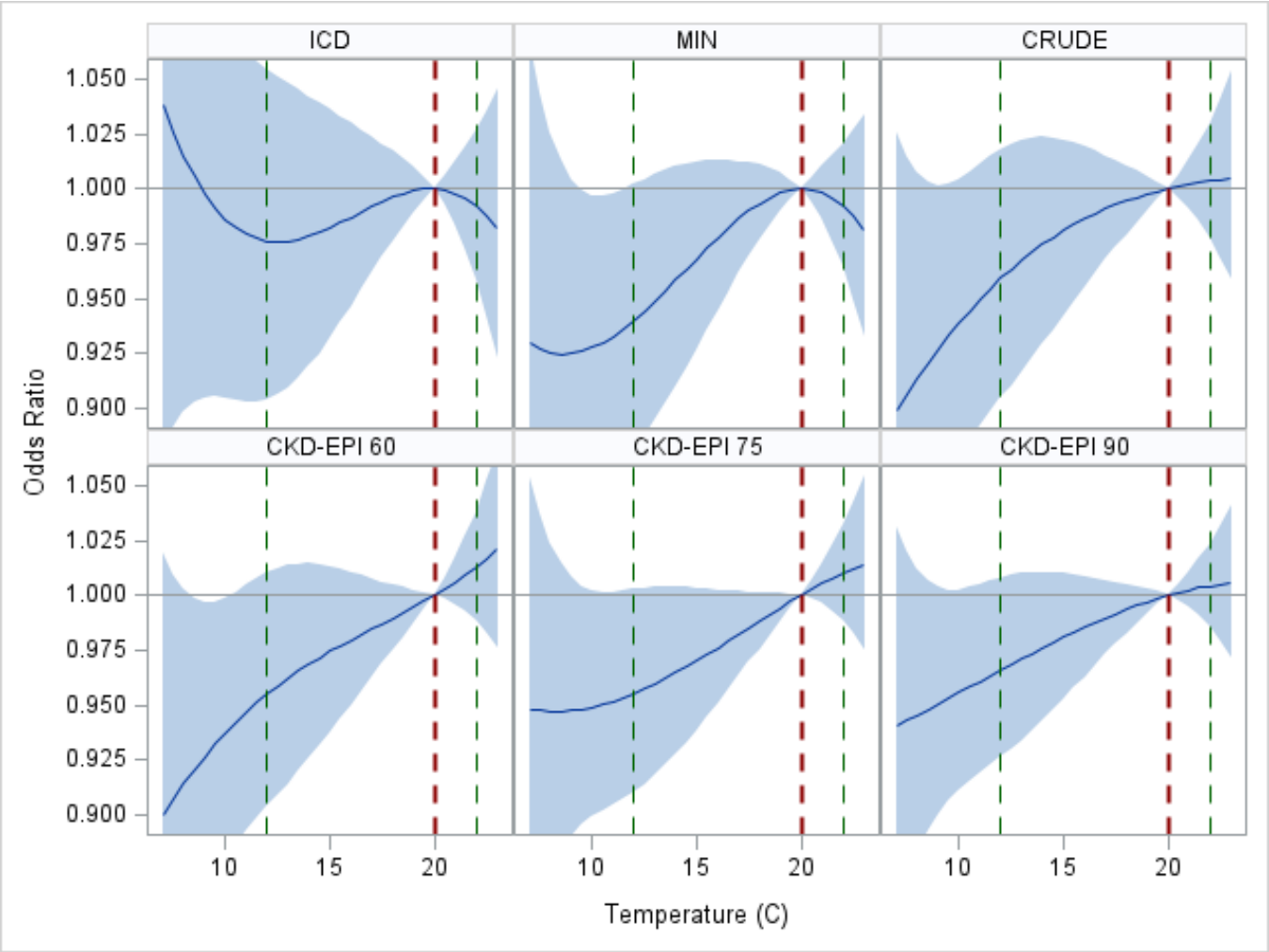
Supplemental Figure 2: Sex-stratified baseline serum creatinine values (md/dL) where 2021 CKD-EPI was back-calculated using a set GFR of 75 ml/min/1.73 m^2 (Above: Female patients; Below: Male patients).



Supplemental Figure 3: Sex-stratified baseline serum creatinine values (md/dL) where 2021 CKD-EPI was back-calculated using a set GFR of 90 ml/min/1.73 m^2 (Above: Female patients; Below: Male patients).



Supplemental Figure 4: Sensitivity analysis with daily minimum temperature. Exposure response functions for the risk of AKI across case definitions by daily minimum temperature. (Odds ratios provided with 95% confidence intervals, Red dashed line: Median daily maximum temperature, Purple dashed line: 25th and 75th percentile daily maximum temperatures, Green dashed line: 95th and 5th percentile daily maximum temperatures).



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