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Environmental heat and acute kidney injury in older adults: A matched case-control study

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Abstract

This matched case-control study examined the association between environmental heat exposure and hospital encounters with acute kidney injury (AKI) among adults, 66 years and older, in the province of Ontario, Canada. We matched 52,913 cases who had an AKI event during the warm seasons (April to September) of 2005 to 2012 with 174,222 controls who did not have an AKI event. We matched cases to controls on date, age, sex, residential status, income, and history of chronic kidney disease using a variable one to four matching ratio. We classified heat periods as three consecutive days where the 95th percentile of area-specific daily maximum temperature was reached or exceeded. We determined associations using conditional logistic regression. Compared to non-heat periods, high heat periods were significantly associated with greater risk of AKI (adjusted odds ratio 1.11, 95% confidence interval 1.00 to 1.23).

Keywords

Acute kidney injury, administrative data, case-control, environmental heat, maximum temperature, Ontario

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List of Abbreviations

ACE = Angiotensin-Converting Enzyme

AKI = Acute Kidney Injury

ARB = Angiotensin II Receptor Blocker

^{o}C = Degrees Celsius

CCI = Canadian Classification of Health Interventions

CCP = Canadian Classification of Diagnostic, Therapeutics, and Surgical Procedures

CDN = Canadian

CI = Confidence Interval

CIHI-DAD = Canadian Institute for Health Information Discharge Abstracts Database

CIHI-NACRS= Canadian Institute for Health Information National Ambulatory Care Reporting System

CKD = Chronic Kidney Disease

DA = Dissemination Area

DLNM = Distributed Lag Non-linear Model

ESRD = End Stage Renal Disease

GEM-SURF = Global Environmental Multiscale Surface System

GFR = Glomerular Filtration Rate

HR = Hazard Ratio

ICD-9 = International Classification of Diseases, Ninth Revision

ICD-10 = International Classification of Diseases, Tenth Revision

ICES = Institute for Clinical Evaluative Sciences

IKN = ICES Key Number

IQR = Interquartile Range

IRR= Incidence Rate Ratio

NSAID = Non-Steroidal Anti-Inflammatory Drug

ODB = Ontario Drug Benefit

ODD = Ontario Diabetes Database

OHIP = Ontario Health Insurance Plan

OR = Odds Ratio

RECORD = REporting of studies Conducted using Observational Routinely-collected health Data

RIW = Resource Intensity Weight

RPDB = Registered Persons Database

RR = Relative Risk

SCr = Serum Creatinine

Chapter 1

1 Introduction

Climatological research strongly indicates that green house gas emissions are contributing to the warming of the Earth's surface.[1] There is near unanimous consensus that climbing temperatures will coincide with more frequent and severe heat waves.[2] This is alarming as the loss of life attributed to heat events is of considerable magnitude.[3] Unmitigated environmental heat has also been repeatedly demonstrated to induce multi-organ morbidity,[4] with the kidneys appearing particularly vulnerable.[5,6] The volume contractions that accompany environmental heat may lead to the short-term loss of kidney function.[7] Acute kidney injury (AKI) is the medical term for this loss of function.[8] AKI is a serious health condition and its occurrence is associated with increased risk of chronic kidney disease, reduced quality of life, and death.[9–12] Older adults may be disproportionately impacted by heat-associated AKI as a result of declining thermoregulatory abilities,[13,14] and age-based declines in kidney function.[15]

In previous studies environmental heat has been shown to consistently and significantly exacerbate the risk of AKI across the United States and Australia.[16–25] However, the generalizability of the association between environmental heat and AKI to more northern latitudes has not been adequately investigated. Moreover existing studies have lacked outcome focus and methodological rigor. To remedy these knowledge gaps, we performed a matched case-control study with the purpose of evaluating the association between environmental heat and hospital encounters with AKI among older adults in Ontario, Canada.

The remainder of this thesis is structured into the following chapters: 2 Literature review, 3 Objectives, 4 Methods, 5 Results, and 6 Discussion. In Chapter 2 we describe what constitutes environmental heat and review effect modifiers of heat health relationships as well as risk factors for heat-related illness. This is followed by an explanation of what constitutes AKI and the salient risk factors for AKI. Finally, we bring the two together to explore what is known of the association between environmental heat and AKI. In

Chapter 3 we explicitly state the objectives of our research project. In Chapter 4 we provide a transparent and detailed summary of our methods. In Chapter 5 we present our written results and accompanying figures and tables. Lastly, in Chapter 6, we discuss our findings, contextualizing them within the current literature and touching briefly on their implications. We also reflect on the strengths and weaknesses of our work and conclude with suggestions for future research.

Chapter 2

2 Literature review

2.1 Environmental heat

Rising ambient temperatures threaten to endanger human health. In conducting this literature review we classified environmental heat as high ambient temperatures originating from natural weather variation experienced at any time of day. This broad definition of environmental heat may at times overlap and be compounded by aspects of occupational heat, which can also originate from natural sources. However, occupational heat is distinct in that it sometimes can stem exclusively from industrial sources and is typically confined to the hours that workers are on the job (e.g. boiler room staff, firefighters).[26]

Environment Canada once provided an official, country-wide definition of a heat wave as three or more consecutive days when the maximum temperature was ≥32^{o}C.[27] However, that definition is no longer in use and has been replaced by region-specific definitions of heat events. Within the province of Ontario, Canada the maximum temperatures for declaring heat alerts range between 29^{o}C to 31^{o}C depending on the location.[28] In many parts of Ontario, the number of days reaching above 30^{o}C between 2021-2040 is predicted to double compared to those observed between 1961-1990.[29] With high heat periods expected to become more frequent, detriments to public health are likely imminent.[30,31]

2.2 Effect modifiers of heat-health relationships and risk factors for heat-related illness

Vulnerability to environmental heat is not uniform. Age, biological sex, comorbidities, medications, residential status, and socioeconomic status may modify heat-health relationships (third level variable) and/or directly alter the risk of heat-related illness (independent variable).

2.2.1 Age

Age is a prominent modifier of the relationship between heat and mortality. In August 2003, a heat wave struck France resulting in roughly 15,000 excess deaths, the majority of which were concentrated among the community-dwelling elderly. [32] Increased age also appears to negatively modify the relationship between heat and morbidity.[14,33] One study out of New South Wales showed that for those aged 75 and older, the risk of all-cause emergency department visits increased by 8% (relative risk [RR] 1.08, 95% confidence interval [CI] 1.04 to 1.11) during heat waves, verses an increase of 1% (RR 1.01, 95% CI 1.00 to 1.02) in the under 75 age group.[14] A formal statistical test for interaction by age group was not performed.[14]

Several risk factors for heat-related mortality occur more frequently with older age as the human body's ability to withstand environmental heat declines.[34] During periods of dehydration, elderly individuals demonstrate impaired thirst recognition as well as diminished conservation of sodium and water.[19] On top of thermoregulatory deficiencies, a lack of mobility may compound heat susceptibility.[35] Being bed-bound (odds ratio [OR] 6.4, 95% CI 4.5 to 9.2), not leaving the home on a daily basis (OR 3.6, 95%CI 1.6 to 6.9) and the inability to administer self care (OR 3.0, 95%CI 1.8 to 4.8) have all been identified as prognostic factors associated with increased odds of death during heat waves.[36]

2.2.2 Biological sex

Evidence for whether biological sex modifies heat-health relationships is conflicting and may be outcome dependent. Some studies have identified increased heat-related morbidity in males,[37–39] explicitly for cardiovascular outcomes such as stroke,[40] and acute myocardial infarction.[41,42] Yet, other studies have identified increased heat-related mortality in females. [32,43–46] Whether biological mechanisms underscore these observed sex differences in morbidity and mortality is poorly understood.[40] It is also possible that the observed sex differences are derived from behavioral discrepancies (e.g. likelihood to engage in outdoor activities).[38] Alternatively, the supposed sex differences may be a statistical byproduct. For instance, the higher suggested heat-related mortality in females

may result from residual confounding. Based on natural age structures and longer life expectancies, older segments of the population are often comprised of greater proportions of females.[43] Moreover in studies that do not control for income, it is possible that age and sex act as proxies for socioeconomic status. Therefore, effect estimates may differ in relation to the specific control variables included within the statistical models of each study.

2.2.3 Comorbidities

The impact of environmental heat on human health should be assessed in accordance with comorbidity status, which can both modify heat-health relationships and serve as a direct risk factor for heat-related illness.

Diabetes has been shown to act as an effect modifier intensifying susceptibility to heat stress. Hallmark features of diabetes such as poor glucose control, changes in insulin kinetics and diabetic neuropathy may adversely impact heat tolerance.[47] In diabetics, the ORs for mortality during episodes of extreme heat, compared to non-heat episodes, range from 1.01 to 1.17.[48,49]

Deaths during heat waves have also been associated with the following risk factors: pre-existing psychiatric illness (OR 3.6, 95% CI 1.3 to 9.8), cardiovascular illness (OR 2.5, 95% CI 1.3 to 4.8), and pulmonary illness (OR 1.6, 95% CI 1.2 to 2.1).[36]

2.2.4 Medications

Certain medications appear to be potent risk factors for morbidity and mortality during heat spells. Medications have the potential to interfere with adaptive heat responses by antagonizing water retention, reducing heart rate, blocking autonomic input, curtailing sweat production, hampering visceral blood flow, and decreasing renal function.[50] Despite the vast potential for harm, there is limited evidence linking medication use to heat-related morbidity and mortality.

Psychotropic drugs seem to be especially hazardous during times of high heat since their actions on neuronal inputs can interfere with heat dissipation.[50] During the Western European August 2003 heat wave, the use of any psychotropic drug was associated with a 29% (95% CI 22% to 37%) increase in risk of death for elderly individuals aged 70 to 100 years.[51] Moreover, there was a significant dose-response relationship between the number of psychotropic drugs and risk of death (adjusted OR for linear trend 1.25, 95% CI 1.21 to 1.29), with the highest effect estimates found for antidepressants (adjusted OR 1.71, 95% CI 1.57 to 1.86), and antipsychotics (adjusted OR 2.09, 95% CI 1.89 to 2.35).[51] Another study that focused on hospital admissions during the same 2003 heat wave yielded analogous main effect estimates.[52] The meta-analysis by Bouchama *et al.* reinforced the dangers, demonstrating that psychotropic drug use during heat waves increased the pooled odds of death almost two-fold (OR 1.9, 95% CI 1.3 to 2.8).[36]

2.2.5 Residential status

The built environment and human activity alter surface temperature conditions. The urban heat island is an example of this, whereby air temperatures in metropolitan regions are elevated in comparison to surrounding non-metropolitan regions.[53] Temperatures in urban centers have been recorded to be between 2^{o}C to 12^{o}C higher than in nearby rural areas.[54] Urban heat islands are the culmination of many factors such as loss of vegetation cover, sparse tree canopies, increased anthropogenic gases, and reduced ventilation.[54,55] Pervasive dark sealed surfaces in urban areas also disrupt energy balances and interfere with nocturnal cooling so that nighttime temperatures stay elevated. Under these conditions, reprieve from the heat is limited. [56,57] Previous studies have found heat-health effect estimates are modified by geographic region with more urban districts showing the largest associations for mortality.[56,58,59]

In addition to having distinct physical landscapes, urban centers also exhibit high settlement densities. Population density is a risk factor for heat stress with greater densities achieved by residents dwelling in closer proximities.[60] Living on the upper floors of high rise apartment buildings has also been demonstrated to aggravate heat-related morbidity.[61,62]

Although not subject to urban heat islands or high settlement densities, rural settings are still vulnerable to environmental heat stress for different reasons. Firstly, the catchment areas for rural hospitals tend to be larger, meaning residents may have to travel further to access care.[63] Secondly, distinct lifestyle differences between urban and rural residents persist. A Canadian study looking at daily time-activity patterns demonstrated that rural seniors (aged 60 and over) spent on average 0.9 more hours outdoors per day compared to urban seniors (p-value<0.001).[64] Overall, rural residents were less likely to have an air conditioner (43.0% vs. 57.2 %, p-value<0.001).[64] Furthermore, 37.8% (95% CI 31.2% to 44.4%) of rural residents reported working in outdoor occupations verses only 23.1% (95%CI 19.0% to 27.2%) of urban residents.[64] Urbanites may be protected in this regard, given that time spent indoors is significantly associated with lower personal heat exposure.[65]

In the past, investigations specific to rural communities have been scarce because meteorological monitors in these locations are usually spaced far apart. A contemporary study used geostatistical kriging to interpolate heat stress and found the average rate of emergency room visits in rural Southern, Ontario (defined as communities of <100,000 population) was 1.11 times higher (95% CI 1.07 to 1.15) during a heat wave than during control periods.[63] As temperature modeling systems continue to improve, it is critical to consider the unique challenges faced by rural communities in juxtaposition to their urban counterparts.

2.2.6 Socioeconomic status

Socioeconomic status has been shown to modify temperature-health relations.[66,67] Lower SES has also been implicated as a risk factor for heat-related illness.[68,69] A study of the 1980 heat wave in St. Louis and Kansas City, United States found age-adjusted rates of heatstroke were six-fold higher in the lowest SES quartile compared to the highest SES quartile.[68] Correspondingly, during the 2009 heat wave in Adelaide, Australia, hospital admissions for heat-related illness more than doubled for individuals in the lowest SES quartile compared to individuals in the other quartiles (OR 2.10, 95% CI 1.09 to 4.04).[69] Poor quality housing and lack of access to air-conditioning are circumstances that are

believed to contribute to the observed increases in heat-related morbidity and mortality in individuals of low SES.[70]

2.3 Acute kidney injury

Acute kidney injury (AKI) was formerly referred to as acute renal failure. In conducting this literature review, AKI was used exclusively and was considered to encompass the more narrowly defined acute renal failure.

AKI is a serious clinical condition characterized by an abrupt decline in kidney function.[71] AKI is classified along a spectrum of pathology, ranging from mild to severe, and occurs over a continuum of time, spanning from hours to days.[72] A cornerstone of AKI is the build-up of serum creatinine (SCr) and other nitrogenous waste products in response to diminishing glomerular filtration rates (GFR).[73] In the majority of patients, the deterioration in kidney function is also followed by a decrease in urine output.[74] Based on the most recent consensus guidelines, AKI can be diagnosed if one of the following criteria is fulfilled: (I) SCr increase $\geq$ 0.3 mg/dl ($\geq$ 26.5 μmol/l) within 48 hours; or (II) a $\geq$1.5-fold SCr increase within seven days (as compared to a known or suspected baseline value); or (III) a reduction in urine output to < 0.5 ml/kg/day for at least 6 hours.[8]

To date, epidemiological research has focused on well-defined cases of hospital-acquired AKI. However, information on the frequency of community-acquired AKI is integral to understanding external risk factors. One study that managed to quantify community-based rates, observed that when comparing 1996-1997 to 2002-2003 the incidence of non-dialysis requiring AKI in the general population rose from 323 (95% CI 317 to 329) to 522 (95%CI 516 to 529) per 100,000 person years; while the incidence of more severe dialysis-requiring AKI rose from 20 (95%CI 18 to 21) to 30 (95%CI 28 to 31) per 100,000 person years.[75] Although AKI-associated mortality has decreased in the last few decades in developed countries, the absolute number dying remains high because of increasing incidence.[76,77]

AKI is estimated to afflict over 13 million people each year, placing a tremendous burden on individual patients and international health-care systems at large.[78] AKI is more

common in the elderly[79] and has been associated with significant mortality, development of end-stage renal disease (ESRD), longer hospital stays, and inflated health care costs.[9,10] There are few proven therapies to reverse the damage of AKI. Acute dialysis is the standard therapeutic option, but is not a direct treatment. Dialysis merely supplants kidney function to allow time for healing. Even if the patient survives, full restitution of kidney function is not guaranteed and depends in part on age, pre-existing disease, and the extent of structural damage.[80,81]

2.4 Risk factors for acute kidney injury

Age, biological sex, chronic kidney disease, diabetes, cardiovascular disease, liver disease, and certain medications have all been identified as risk factors for AKI.

2.4.1 Age

Increasing age is associated with increasing risk of AKI. Older adults are more susceptible to AKI for several reasons; 1) increased prevalence of comorbidities, such as diabetes and heart failure; 2) higher rates of diagnostic procedures and medical interventions;[82] and, 3) increased use of medications that either directly injure the kidneys or indirectly interfere with the kidneys' regulatory capacities.[79]

Further compounding the vulnerability of older adults are anatomical and physiological problems with the kidneys themselves. Age-based structural impairments include decreases in total renal mass, glomerulosclerosis, vessel wall thickening, and tubule loss.[12] Functionally, these impairments translate into natural declines in GFR, usually beginning in the fourth decade of life (30 to 39 years of age).[15,83]

It is probable that the rising incidence rates of AKI are tied to aging population structures.[75,84,85] Community-based incidence rates of AKI have been observed to increase from 815 per 100,000 person-years (95%CI 801 to 828) in those aged 60 to 69, to 1809 per 100,000 person-years (95% CI 1784 to 1835) in those aged 70 to 79, all the way up to 3545 per 100,000 person-years (95%CI 3481 to 3610) in those aged 80 and over.[75]

The high incidence of AKI in older adults is concerning given the poor prognoses for members of this population. In a meta-analysis of 17 studies published between 2000 and 2007, it was shown that 31% of patients with AKI aged 65 and older were unable to return to baseline kidney function or regain independence from renal replacement therapy, compared to 26% of patients under age 65 (pooled RR 1.28, 95% CI 1.06 to 1.55).[80]

2.4.2 Biological sex

Males appear to be more susceptible to AKI than females.[75,84,86] A study investigating community-acquired AKI out of Canada, observed the annual incidence of severe AKI to be 13 per 100,000 in males compared to 9 per 100,000 in females (RR 1.4, 95% CI 1.1 to 1.9).[86] For those aged 65 and older, the sex difference was even greater with 70 per 100,000 males affected verses 32 per 100,000 females (RR 2.2, 95% CI 1.5 to 3.2).[86] Additional work is needed to explain the underpinnings of these reported sex-differences in AKI risk.

2.4.3 Chronic kidney disease

Chronic kidney disease (CKD) is defined by a baseline GFR of <60 ml/min/1.73m^2 persisting for more than 3 months.[87] It is distinguished from AKI by its longevity. Despite having different timescales, the two conditions are closely interrelated.[88]

Research in this area has shown a graded relationship between progressive CKD stages (lower estimated GFR categories) and escalating risk of AKI.[89,90] A study from 1996 to 2003, found the adjusted ORs for dialysis-requiring AKI were 2.0 (95% CI 1.7 to 2.3), 6.5 (95% CI 5.6 to 7.7), 28.5 (95% CI 24.5 to 33.1), and 40.1 (95% CI 33.8 to 47.6) comparing hospitalized adults with respective baseline estimated GFRs of 45-59, 30-44, 15-29, and <15 ml/min/1.73m^2 to a non-CKD referent group with estimated GFRs ≥ 60 ml/min/1.73m^2.[89] An ensuing Canadian study from 2003 to 2006 found congruent results; adjusted ORs for AKI were 2.9 (95% CI 2.7 to 3.1), 6.2 (95% CI 5.7 to 6.8), and 18.3 (95% CI 16.5 to 20.3) comparing hospitalized adults with baseline estimated GFRs of 45-59, 30-44, and <30 ml/min/1.73m^2 to a non-CKD referent group with estimated GFRs ≥60 ml/min/1.73m^2. [90]

2.4.4 Diabetes

Diabetes is a potent risk factor for the development of AKI.[91,92] In diabetes, the inability to produce insulin leads to high blood glucose levels that progressively scar renal vasculature and heighten susceptibility to acute insults. A population-based study of adults in a Health Region of Alberta, Canada estimated the risk of severe community-acquired AKI to be 10.3 times higher in individuals with diabetes compared to those without (RR 10.3, 95% CI 7.7 to 13.6).[86] A case-control study comparing a sample of hospitalized patients also demonstrated an association between hospital-acquired AKI and diabetes, though the effect was dampened (adjusted OR 2.1, 95% CI 1.9 to 2.3).[89]

2.4.5 Cardiovascular disease

There is a reciprocal relationship between heart failure and worsening kidney function. The two adverse outcomes often occur concomitantly with the failing heart accelerating kidney under-perfusion, and vice-versa.[93] A meta-analysis of 80,098 heart failure patients classified 63% as having any renal impairment, with 29% having modest to severe impairment.[94] The adjusted all-cause mortality was significantly elevated in heart failure patients with any renal impairment (hazard ratio [HR] 1.56, 95% CI 1.53 to 1.60) and modest to severe renal impairment (HR 2.31, 95% CI 2.18 to 2.44) compared to heart failure patients without renal impairment.[94]

Beyond heart failure, other cardiovascular conditions may also predispose to AKI. Severe AKI has been found to develop more frequently among individuals with a history of heart disease (RR 24.0, 95% CI 18.5 to 31.2) or stroke (RR 22.0, 95% CI 15.6 to 31.0).[86] AKI requiring dialysis has also been found to develop more frequently among hospitalized adults with diagnosed hypertension.[89]

2.4.6 Liver disease

AKI is a potential sequela of liver disease, occurring in up to 20% of hospitalized patients with cirrhosis.[95] An analysis of intensive care-units in 16 countries found patients with a history of cirrhosis were more than twice as likely to develop AKI than patients without a history of cirrhosis (OR 2.18, 95% CI 1.16 to 4.10). [96] Development of AKI in patients

with compromised liver function is an important prognostic factor, predicting increased morbidity and mortality.[97–100]

2.4.7 Medications

Modulations in renal blood flow may trigger AKI. Three classes of drugs with the capacity to induce AKI through hemodynamically mediated pathways are:
1) diuretics; 2) non-steroidal anti-inflammatory drugs (NSAIDs); and, 3) angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).[101,102]

Diuretics deplete fluid volumes and are known to increase AKI risk.[103,104] A multi-center prospective study identified diuretics as the second-leading cause of drug-induced AKI accounting for 22% of cases.[104]

NSAIDs have also been associated with increased AKI risk.[105] NSAIDs inhibit prostaglandin production, which results in reduced dilation of the afferent arterioles in the kidneys. When renal perfusion is inadequate, the NSAID-invoked limitations on intra-renal blood flow may lead to kidney damage.[101] A meta-analysis of five observational studies found that AKI risk was significantly elevated among traditional NSAID users in comparison to non-users, with the pooled RRs for individual NSAIDs varying between 1.58 and 2.11.[105] The association between NSAIDs and AKI is of concern due to the widespread access and ubiquitous use of these drugs.[106]

Other frequently prescribed drugs that have been associated with increased AKI risk are ACE inhibitors and ARBs. These drugs exert antihypertensive effects by interfering with the production and binding of angiotensin-II. However, by disrupting the renin-angiotensin system, ACE inhibitors and ARBs simultaneously limit the body's ability to compensate for volume losses.[107] An ecological study in England approximated that up to 15% of the escalation in AKI admissions detected from 2007 to 2011 were attributable to increases in ACE inhibitor and ARB prescribing rates.[108]

Diuretics, NSAIDs, and ACE inhibitors or ARBs may be even more dangerous when taken in combination. A nested case-control study followed 487,372 antihypertensive users for a mean of 5.9 years to show that triple therapy was associated with a 31%

increase in AKI risk (RR 1.31, 95% CI 1.12 to 1.53) when compared to use of antihypertensive drugs (diuretics and/or ACEis or ARBs) without NSAIDs.[109] A subsequent nested case control study of 78,379 antihypertensive users, also found that triple therapy was associated with increased AKI risk (adjusted rate ratio 1.64, 95% CI 1.25 to 2.14) when compared to use of antihypertensive drugs without NSAIDs.[110]

2.5 Association between environmental heat and acute kidney injury

We performed a detailed literature search of several bibliographic databases and identified 10 studies that examined the association between environmental heat and AKI. All of the studies (depicted in Table 2-1) found a significant association between various heat indicators and increased risk of AKI.[16–25] However, these studies were limited by outcome measures with unknown or unmentioned validity,[16–19,21–25] exclusive use of coarse weather station data,[16–20,22,24,25] and case-only designs that did not incorporate external controls.[16–25] In addition, the heat indicators were not chosen with the specific etiology of AKI in mind because the majority of these studies set out to explore a plethora of heat-related outcomes.[16,18–21,23–25] Only two of these studies were focused on renal disease.[17,22] Moreover, the effect estimates were consistently small in magnitude. Although small effect sizes are commonplace in environmental epidemiology,[111] in light of the limitations of these studies, it is difficult to discern whether the hypothesized heat and AKI association is a true effect or merely an artifact of uncontrolled confounding.

Furthermore, over half of these studies were confined to California[16,18,19,21,24] and Australia.[22] California is situated along the Pacific coast of the United States, and as a result, has a Mediterranean-like climate with hot, dry summers and mild winters.[112] While in Australia, the temperature threshold for defining heat events tends to be considerably higher than in the northern hemisphere.[113] The relationship between environmental heat and the risk of AKI has not been adequately explored in regions with more fluctuating temperature profiles. This is an important step because these regions have a very different overall temperature experience due to tremendous variation between long cold winters and short summers. For example in Ontario, Canada , winter

temperatures can drop below -40^{o}C; while summer temperatures can exceed 30^{o}C.[114] Although consistent hot temperatures are usually confined to June, July, and August, hot episodes can also occur anomalously in the late spring and early fall months.[115] Taken together, the short summers and anomalous heat events may hinder adaptation thereby altering the relationship between environmental heat and AKI in Ontario compared to other settings.

Table 2-1. Summary of key findings associating environmental heat with AKI

Author, Year	Location, Timeframe	Population (Outcome Definition)	Exposure	Key Findings	Limitations	Quality Score (0-28[1])
Time-Stratified Case-Crossover Studies						
Basu et al., 2012[16]	California, United States, May-September, 2005-2008	21,650 emergency room visits with principal diagnosis of AKI (ICD-9: 584)	Same day mean apparent temperature	- Odds of emergency room visit with AKI increased 15.9% per 5.6^{o}C increase in same day mean apparent temperature (OR 1.159, 95% CI 1.127 to 1.193)	- Ecologic-level exposure data (weather station data, with 10 km radius) - No information on pre-existing illness - Possible deviations from linearity not accounted for	18
Fletcher et al., 2012[17]	New York State, United States, July-August, 1991-2004	12,370 hospitalizations with a principal discharge diagnosis of AKI (ICD-9: 584)	Daily mean, maximum, and minimum values of actual and apparent temperatures, lagged by up to 5 days before admission	- Odds of hospitalization with AKI increased 9% per 2.78^{o}C in mean actual temperature at lag 1 (OR 1.09, 95% CI 1.07 to 1.12) - Lags 0-2 showed significant increases in odds of hospitalization with AKI across all six temperature indicators	- Ecologic-level exposure data (weather stations) - No information on mitigating resources - Failed to capture less severe illness that did not require inpatient admission	18

Green et al., 2010[18]	California, United States, May-September, 1999-2005	17,778 hospital admissions with a primary diagnosis of AKI (ICD-9: 584)	Same day mean apparent temperature	- Odds of hospital admission with AKI increased 7.4% per 5^{o}C increase in same day mean apparent temperature (OR 1.074, 95% CI 1.040 to 1.109)	- Ecologic-level exposure data (weather stations with 10 km radius) - No information on mitigating resources - Do not know validity of coding practices across hospitals and diagnoses	18
Ostro et al., 2010[19]	California, United States, May-September, 1999-2005	34,878 hospital admissions with a primary diagnosis of AKI (ICD-9: 584)	Mean, maximum, and minimum daily apparent temperature	- Odds of hospital admission with AKI increased 10.2% per 5^{o}C increase in same day mean apparent temperature (OR 1.102, 95% CI 1.072 to 1.132)	- Ecologic-level exposure data (weather stations) - Seasonal and long-term effects in exposure series minimized but not eliminated	18
Time-Series Analyses						
Bobb et al., 2014[20]	United States, 1999 to 2010	12,676 hospitalizations with AKI in adults aged 65 years or older, identified by	Heat wave periods defined as at least two consecutive days with average daily	- RR of hospitalizations with AKI increased to 1.14 (95% CI 1.06 to 1.23) on heat-wave days compared to matched non-heat wave days	- Ecologic-level exposure data (weather stations within 35 km from geometric center of county)	20

		clinical classification software algorithm based on ICD-9 codes	temperatures exceeding the 99th percentile of the distribution of daily temperatures for that county	- Absolute risk differences was 0.24 (95%CI 0.09 to 0.39) excess daily hospital admissions with AKI per 100,000 individuals	- Wide variety of outcomes, multiple testing	
Guirguis et al., 2014[21]	California, United States, May-September, 1999-2009	An average of 57 hospitalizations with diagnosis of AKI observed per non-heat day (ICD-9: 584)	Heat events defined as periods where daily maximum temperatures and morbidity were strongly correlated and both metrics showed anomalies	- Average daily excess hospitalizations with AKI increased by a count of 4.5 (95% CI 4.4 to 4.5) when considering the entire span of the heat health event and by a count of 10.1 (95% CI 9.9 to 10.3) at heat wave peak compared to non-heat days	- Ecologic-level exposure data (weather station data interpolated onto a 12 km x 12 km grid)	13
Hansen et al., 2008[22]	Metropolitan Area of Adelaide, Australia, January 1,1995 - December 31, 2006	3579 admissions with discharge diagnosis of AKI (ICD-10: N17)	Heat waves defined as three or more consecutive days with daily maximum temperatures ≥95th percentile	- IRR of hospital admissions with AKI increased to 1.255 (95% CI 1.037 to 1.519) during heat wave periods compared to non-heat wave periods in the warm season	- Ecologic-level exposure data (single weather station) - No information on mitigating resources - Possibility of miscoding - Relatively small	17

			(35°C) of maximum temperature range for study period	(November-March)	number of admissions - No medication histories - Insufficient control of time trends	
Isaksen et al., 2015[23]	King County, Washington, United States, May-September, 1999-2010	- 752,151 unplanned, non-traumatic total hospital admissions - Number of hospital admissions with the specific diagnosis of AKI not specified (ICD-9: 584)	- RR analysis: heat day defined as day average humidex exceeded 99th percentile of all days, January-December (36.2 °C) - Time-series: cut-off defined as 1.2°C above 99th percentile (37.4 °C)	- RR of unplanned, non-traumatic hospitalizations with AKI increased to 1.68 (95% CI 1.41 to 2.01) on a heat day compared to a non-heat day -Time-series: For every 1°C in daily maximum humidex above 37.4°C, hospitalizations with AKI increased by 7.6% (95%CI 3.2% to 12.2%)	- Ecologic-level exposure data (gridded [1/16°] resolution) - No information on mitigating resources - Inappropriate boundary selection - No correction for multiple comparisons	19
Case-Only Analyses						
Knowlton et al., 2009[24]	California, United States, July-August, 2006	- 13,829 hospitalizations with a diagnosis of AKI recorded across any diagnostic field	Heat wave period defined as July 15 to August 1, reference periods defined	- RR of hospitalization with AKI increased to 1.11 (95% CI 1.08 to 1.15) during heat wave periods compared to non-heat wave periods	- Limited to a single heat wave	19

		(ICD-9: 584)	as July 8-14 and August 12-22			
Semenza et al., 1999[25]	Chicago, United States, July 1994, July 1995	- 61 inpatient admissions with a primary discharge diagnosis of AKI observed during heat wave (ICD-9: 584), only 13 admissions were expected	Heat wave period defined as July 13-19 of 1995, expected counts averaged across four referent weeks including July 6-12 of 1995 and July 6-12, 13-19, 20-26 of 1994	- 49 (95% CI: 31 to 66) excess inpatient admissions with a primary discharge diagnosis of AKI during the heat wave compared to reference periods	- Failed to capture less severe illness that did not require inpatient admission - Small sample size	14

Abbreviations: AKI, acute kidney injury; CI, confidence interval; ICD-9 International Classification of Diseases, ninth revision; ICD-10, International Classification of Diseases, tenth revision; IRR, incidence rate ratio; OR, odds ratio; RR, relative risk

[1] We evaluated the quality of individual studies using the Black and Downs quality assessment checklist, which is a list of 27 criteria to evaluate both randomized and non-randomized trials.[116] This scale covers the completeness/clarity of study reporting, external validity, internal validity (e.g. bias and confounding) and power. The tool was modified slightly for our use. Specifically, question 27 was simplified to a choice of awarding either 1 or 0 points depending on whether there was sufficient statistical power to detect a clinically important effect. We gave all included studies a score from 0 to 28, according to the following four quality categories: excellent (26 to 28), good (20 to 25), fair (15 to 19), and poor (less than or equal to 14).

2.6 Conclusion

Environmental heat is recognized as the most common cause of weather-related fatalities in high-income countries.[117] However, the non-fatal effects of environmental heat are underrepresented in the literature.[118] One biologically plausible outcome that mandates further attention is the development of AKI. Knowledge of the heat and AKI association among older adults in Ontario,Canada is imperative because heat exposure is avoidable.[119] Public health action plans, that direct residents to cooling stations and issue heat alerts, may be strengthened by a more thorough understanding of what types of services are needed and for whom.

Chapter 3

3 Objectives

The following objectives pertain to the population of older adults, 66 years and older, residing in Ontario Canada.

3.1 Objective 1 - Costing

To describe the median 30-day government payer health care cost of a hospital encounter with AKI.

3.2 Objective 2 – Impact of heat periods

To evaluate whether heat periods are associated with AKI.
We hypothesize that heat periods will be associated with a higher risk of AKI.

3.3 Objective 3 – Impact of high humidex periods

To evaluate whether high humidex periods are associated with AKI.
We hypothesize that high humidex periods will be associated with a higher risk of AKI.

3.4 Objective 4 – Effect modification by age

a) To evaluate whether the association between heat periods and AKI differs between individuals aged 66 to 79 years versus those over 79 years.
We hypothesize that the association between heat periods and risk of AKI will be elevated in individuals over 79 years compared to individuals aged 66 to 79 years.

b) To evaluate whether the association between high humidex periods and AKI differs between individuals aged 66 to 79 years versus those over 79 years.
We hypothesize that the association between high humidex periods and risk of AKI will be elevated in individuals over 79 years compared to individuals aged 66 to 79 years.

3.5 Objective 5 – Evaluation of methodological approaches

a) To explore whether the association between heat periods and AKI is robust to different methodological approaches.
We hypothesize that the association between heat periods and AKI will be consistent across methodological approaches.

b) To explore whether the association between high humidex periods and AKI is robust to different methodological approaches.
We hypothesize that the association between high humidex periods and AKI will be consistent across methodological approaches.

Chapter 4

4 Methods

4.1 Study design

We conducted a population-based, matched case-control study of older adults, aged 66 years and over, using Ontario's linked health care administrative databases. These datasets were linked using unique encoded identifiers and analyzed at the Institute for Clinical Evaluative Sciences (ICES).

This study was approved by the institutional review board at Sunnybrook Health Sciences Centre, Toronto, Canada. We followed a pre-specified analysis plan and adhered to the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) guidelines.[120]

4.2 Study population

Ontario is Canada's most populous province. As of July 1, 2012, it was estimated that approximately 2 million (15%) of Ontario's roughly 13.5 million residents were aged 65 years and over, while more than 0.5 million (4%) of the total population were over 79 years of age.[121] All Ontario residents' receive universal access to hospital and physician services under a single-payer health care system. However, individuals aged 65 years and over also receive universal outpatient prescription drug coverage. Therefore, we restricted our study to Ontario residents aged 66 years and over to ensure at least one year of complete information on all dispensed drugs was available and could be included in our analysis. Additionally, this age segment mandates specific attention because they are at increased risk of heat illness[34] and AKI.[79]

4.3 Timeframe and setting

The eight accrual periods of this study spanned from April 1st to September 30th of each year from 2005 to 2012. We selected this timeframe because 2005 to 2012 were the only years for which heat exposure data were available across the entire warm seasons. We defined the warm seasons as April 1st to September 30th in order to capture the wide

range of high temperatures experienced across Ontario in a given year. Ontario has a humid continental climate typified by large seasonal variations; it is hallmarked by a general temperature gradient that decreases moving from north to south and is tempered by large bodies of water, especially the Great Lakes.[122] Although June, July, and August tend to be the hottest months with maximum temperatures exceeding 30^{o}C, outlier heat events can occur in the late spring and early fall. As of 2009, over 70% of Ontario households had access to an air conditioning unit.[123]

4.4 Data sources

Administrative databases are compilations of digitized data generated whenever health care is delivered.[124] For instance, the date and time of patient appointments will often be logged in a computerized system, as will any compensation claims made by physicians. This creates digital footprints that can be linked to follow individual patients as they navigate pathways of treatment. Although administrative data are not primarily collected for research purposes, when used appropriately the data provide a fertile ground for performing research.

Our study used a combination of administrative, clinical, survey, and weather data. In total, we used seven databases to ascertain health outcomes, medication use, patient characteristics, temperature exposures, and other covariate information.

1) Registered Persons Database (RPDB)

   RPDB catalogues demographic information and vital statistics for any individual who has been issued a health card number in Ontario. We used RPDB to identify age, sex, and vital status information. RPDB also contains the best-known annual postal code of residence for eligible persons as of July 1st each year. Postal codes are six character strings defined for mailing purposes. At the time of this study, there were over 280,000 postal codes in Ontario.[125]

2) Census

The dissemination area (DA) is the smallest geographic region for which all census data relevant to our study are released; approximately 400 to 700 persons reside within each DA.[126] We retrieved DA-level information on residential status (rural vs. urban) and neighbourhood income quintile. We employed an ICES definition to classify rural areas as those with a community size ≤10,000. Income quintiles were categorized according to fifths of average neighborhood income. These quintiles are constructed separately for each census metropolitan area, census agglomeration, or residual area before being aggregated to the provincial level.[127] Consequently, the exact numerical values defining each quintile vary. We instead used adjectival descriptors for the quintiles with 1 corresponding to the lowest (poorest) quintile and 5 corresponding to the highest (richest) quintile.

3) Global Environmental Multiscale Surface (GEM-SURF) Database

GEM-SURF is an external forecasting system developed by Environment Canada. The system accounts for land cover (e.g. built or natural) to accurately model surface and near-surface meteorological variables with high resolution. In previous studies, GEM-SURF weather predictions were shown to improve upon existing methods.[128–130]

The 2006 census defined 19,177 DAs in Ontario. The GEM-SURF database at ICES has daily weather summaries for 19,094 of these DAs. The missing DAs were removed from GEM-SURF because they either had incomplete daily weather summaries or their central grid points corresponded to bodies of water. For the remaining DAs, we used daily weather summaries expressed as percentiles of maximum temperature and maximum humidex. These percentiles were specific to each DA and were created from the entire timespan of available GEM-SURF data (June 1, 2004 to April 30, 2013).

4) Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD)

   CIHI-DAD contains diagnostic and procedural information for all hospital inpatient admissions in Ontario. Up to 25 diagnostic codes can be attributed by a medical coder to a single hospitalization, while procedural codes are entered as needed. One of the diagnostic codes must be labeled 'M' to indicate the condition that was most responsible for the length of stay and resources used. Prior to 2002, diagnostic codes followed the International Classification of Diseases, Ninth Revision (ICD-9) and procedural codes followed the Canadian Classification of Diagnostic, Therapeutics, and Surgical Procedures (CCP). From 2002 onward, diagnostic codes followed the International Classification of Diseases, Tenth Revision (ICD-10) and were accompanied by a new standard of procedural codes, the Canadian Classification of Health Interventions (CCI). We used diagnostic and procedural codes from these various classification systems to classify comorbidity status using a five-year look back window. Since our accrual period began in 2005, we used ICD-10 codes exclusively to identify cases with AKI. Costing information was also obtained from CIHI-DAD.

5) Canadian Institute for Health Information National Ambulatory Care Reporting System (CIHI-NACRS)

   CIHI-NACRS contains diagnostic and procedural information for all emergency department visits that have occurred in Ontario. Up to 10 diagnostic codes can be attributed by a medical coder to a single emergency department visit. One of the diagnostic codes is referred to as the main diagnosis to indicate the predominant impetus driving the patient's visit and need for treatment. We used CIHI-NACRS to complement CIHI-DAD in identifying cases of AKI. We also obtained costing information from the CIHI-NACRS database.

6) Ontario Drug Benefit (ODB) Database

   All Ontario residents aged 65 and older qualify for coverage under the ODB program. Written claims for outpatient prescription drugs dispensed under this

program are reliably transmitted to the ODB database. Each electronic claim in the ODB database accurately identifies the unique drug dispensed, patient to whom the drug was dispensed to, prescribing physician, date drug was dispensed, number of days supplied, cost, and location of dispensing. The overall error rate for electronic information in the ODB database compared to written prescription information is 0.7% (95% CI 0.5% to 0.9%).[131] We used the ODB database to identify long-term care facility utilization and medication use.

7) Ontario Health Insurance Plan (OHIP) Database

   This database houses information on all health care providers who submit claims under OHIP, and includes data on inpatient and outpatient physician services. We used the claims information captured in OHIP, in addition to diagnostic and procedural information from CIHI-DAD, in identifying comorbidity status. We also obtained costing information from the OHIP database.

These databases, with the exception of GEM-SURF, have been used repeatedly to study the outcome of AKI.[132–135]

4.5 Data linkage and missingness

We linked individual records across datasets using unique, encoded personal identifiers called ICES Key Numbers (IKNs). We then used the Postal Code Conversion File provided by Statistics Canada to convert best annual postal codes of residence, available for each individual record, to the corresponding DA.[136] This allowed us to link geographic attributes (from Census and GEM-SURF) to the IKNs using the assigned DAs as the common element.

We were not able to convert the best annual postal code of residence to the corresponding DA in <0.5% of individuals. Without an identifying DA, we could not link area-level census attributes including residential status and neighbourhood-level income quintile. Instead, we excluded cases and controls missing these attributes prior to matching. Moreover, we were not able to link heat exposure information in <0.5% of individuals because, as stated in Section 4.4, some DAs are missing form the GEM-SURF database.

We excluded cases and controls with missing heat exposures after matching to allow for a complete case analysis. Both of these exclusions are detailed in Figure 4-1 (cases) and Figure 4-2 (controls). Information on all other variables was complete.

4.6 Identification of hospital encounters with acute kidney injury

We defined hospital encounters with AKI by the presence of ICD-10 code N17, across any diagnostic field in either the CIHI-DAD or CIHI-NACRS databases (see Appendix B). In a former validation study, we tested the 'all diagnoses' N17 coding algorithm for the ability to detect a ≥ 2-fold increase in serum creatinine (SCr) concentration from baseline in Ontario's 66 and over population.[137] The sensitivity was found to be 61.6% (95% CI 57.5% to 65.5%) for hospital admissions and 37.4% (95% CI 32.1% to 43.1%) for emergency department visits; however in both of these settings, the specificity was over 95%.[137] For hospital admissions, the median absolute change in SCr was 98 μmol/l (interquartile range [IQR] 43 to 200) in code positive patients and 6μmol/l (IQR -4 to 20) in code negative patients.[137] For emergency department visits, the median absolute change in SCr was 133μmol/l (IQR 62 to 288) in code positive patients and 2 μmol/l (IQR -8 to 14) in code negative patients.[137] Although the incidence of AKI may be underestimated by up to five-fold using the N17 code, the code does clearly distinguish between groups of patients and is more likely to pick up the most severe cases of AKI, as defined by greater elevations in SCr.

4.7 Selection of cases and controls

We selected all Ontario residents who had at least one hospital encounter (hospital admission [CIHI-DAD] or emergency department visit [CIHI-NACRS]) with AKI during the study period from April 1st, 2005 to September 30th, 2012 and who were at least 66 years of age at the time of the encounter. If persons had more than one hospital encounter with AKI during the study period, we restricted our analysis to the first encounter. We selected the first encounter during the study period in an attempt to identify incident AKI cases because it is well established that the initial occurrence of AKI alters the risk of recurrence.[138,139] However, we were not able to rule out AKI encounters that occurred

prior to April 2005. For inpatient admissions we considered the entire hospitalization as one encounter, even if the patient was hospitalized at multiple facilities. We excluded patients whose first encounter with AKI during the study period fell outside of the relevant accrual windows (April 1st to September 30th of each year). For the remaining cases, we designated the date of the hospital encounter as the index date.

We defined potential controls as all individuals who met the eligibility of cases, but did not have a hospital encounter with AKI over the study period. We randomly selected index dates for controls to match the distribution of index dates by cases, so that the relative frequency of every day was equally represented across the two datasets. We eliminated controls who did not meet the age restriction or had died prior to their selected index dates.

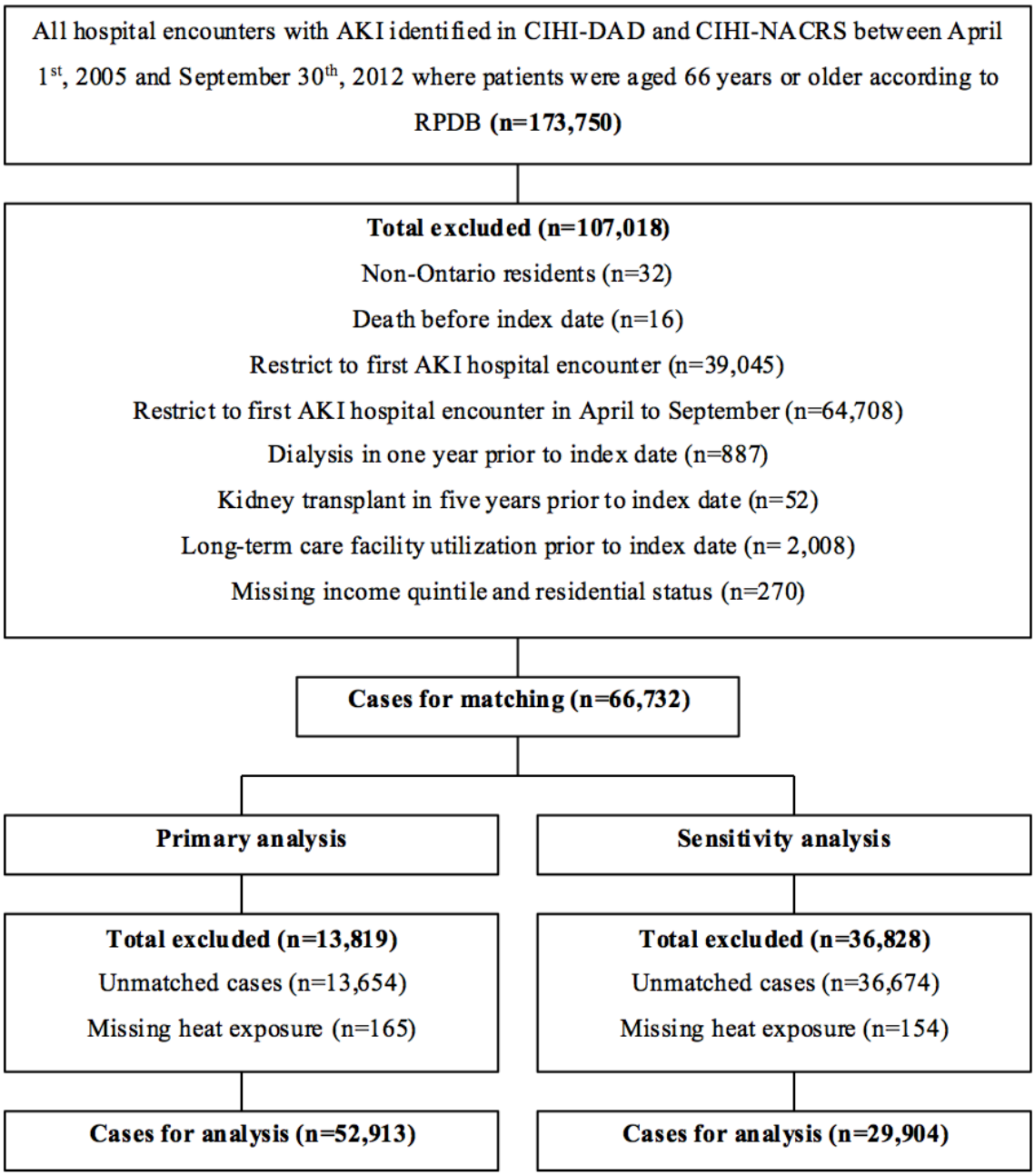
The following exclusions applied to both cases and controls:

1) Receipt of dialysis in the year prior to index date, or, receipt of kidney transplant in the five years prior to index date.
   The development of AKI was not considered relevant in patients whose kidneys were already failing.

2) Long-term care facility utilization prior to index date.
   It was assumed residents' exposures to ambient temperatures would be limited in these climate-controlled facilities.

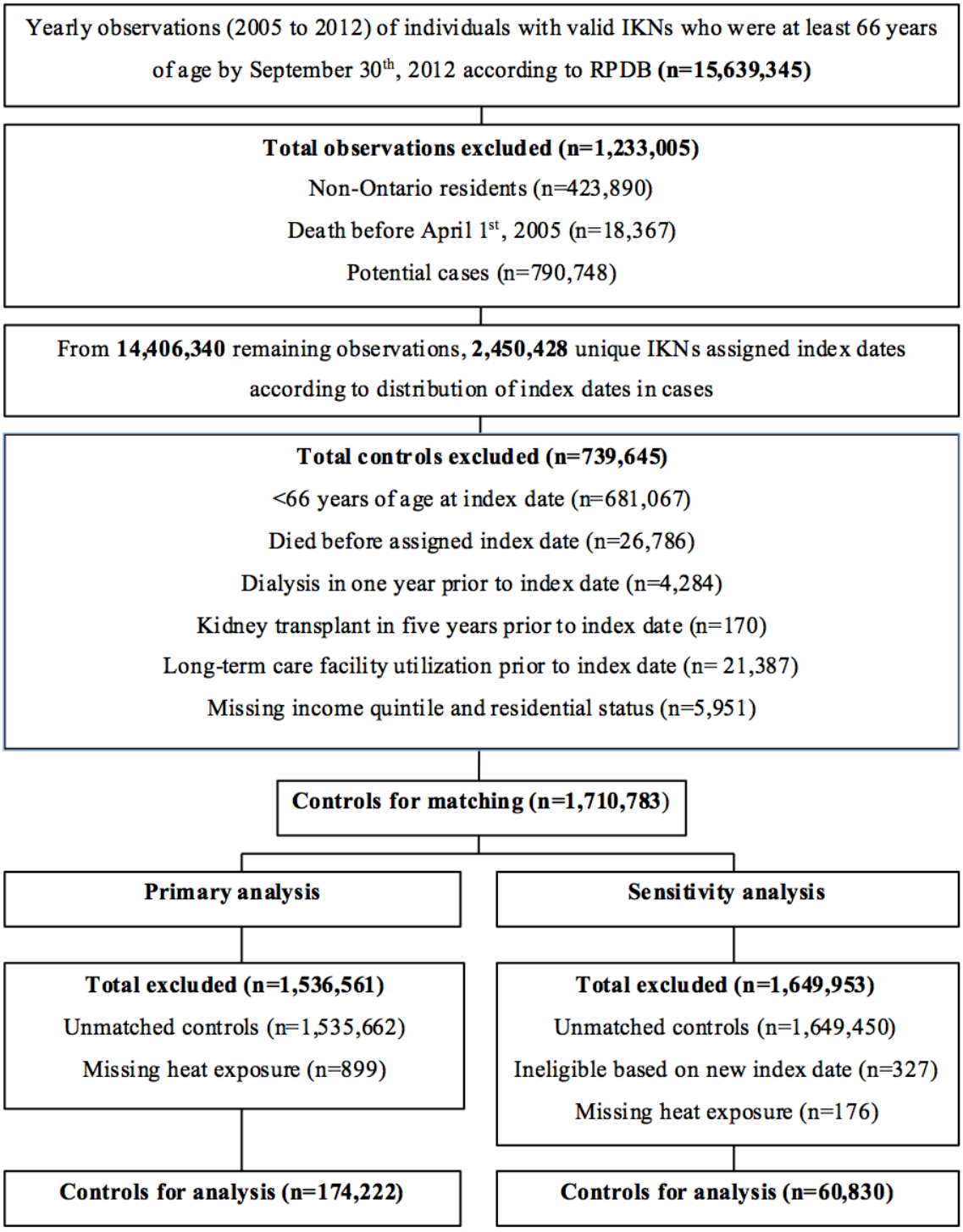
The coding definitions for these exclusions are listed in Appendix A.

Figure 4-1. Selection of cases



Abbreviations: AKI, acute kidney injury; CIHI, Canadian Institute for Health Information; DAD, Discharge Abstract Database; NACRS, National Ambulatory Care Reporting System; n, number; RPDB, Registered Persons Database

Figure 4-2. Selection of controls



Abbreviations: IKN, ICES Key Number; n, number; RPDB, Registered Persons Database

4.8 Matching

There was an abundance of eligible controls in comparison to eligible cases. Hence, we attempted to match up to four controls with each case. We selected four controls wherever possible in an effort to increase statistical power.[140] We chose to use a variable ratio as opposed to a fixed ratio because we planned to match on several factors and we did not want to discard valuable case information if a full set of four controls could not be matched. We used a greedy method of matching without replacement. After a match was made, it was never broken.

We matched on characteristics thought to be associated with heat exposure and/or AKI risk. We matched controls to cases on exact index date, since heat exposure changes over time; age (±2 years), since increased age amplifies AKI risk and may impact likelihood of heat exposure;[79] age group (66 to 79 years, over 79 years), to facilitate a preplanned stratified analysis; sex, since males tend to exhibit greater risk of AKI;[75,86] urban or rural residential status (population, >10,000 or ≤10,000) since residential status may increase risk of AKI and modify heat exposure,[64,65] income (categorized into fifths of average neighborhood income), since lower income may increase risk of heat exposure and AKI,[17,141,142] and history of CKD, since this condition increases risk of AKI.[89,90] We used the cohort of cases and controls produced from this initial methodological approach in conducting all analyses unless explicitly stated otherwise.

4.9 Exposure

There is tremendous heterogeneity in the exposure measures used to examine heat-health relationships. Many studies have used iterations of daily mean actual temperatures[143–148] and maximum actual temperatures[149,150] for their primary analyses. Whereas other studies have used daily mean apparent temperatures[16,18,46] or maximum apparent temperatures.[151] Apparent temperature combines the effects of dry temperature and humidity to serve as an index of human discomfort. [151,152] Overall, no single exposure measure stands out as the best predictor of heat-related mortality across geographic regions and age groups.[152] Rather, the chosen exposure measure tends to reflect practical challenges pertaining to particular investigations.

We chose to use daily maximum actual temperature to define our primary exposure and daily maximum humidex to define our secondary exposure because these indices are easy to interpret. They are also the same measures employed by public health authorities in Ontario when issuing heat alerts. The daily maximum is the highest actual temperature reached in a given DA over a 24-hour period, starting at 12:00 am midnight. Actual temperature is measured independent of the moisture content in the air, and for this reason we chose to explore humidex in a secondary analysis. Humidex was designed by Canadian meteorologists to describe how hot weather feels.[152] Akin to apparent temperature, the humidex is unitless and integrates temperature and dew point to characterize discomfort. A humidex of 30 to 39 is generally associated with some discomfort; a humidex ≥40 is associated with great discomfort.[153]

We expressed daily maximum actual temperatures and daily maximum humidexes as percentiles. We derived each set of percentiles based on the entire ranges of daily temperatures and humidexes recorded in each DA from June 1st, 2004 to April 30th, 2013. We created 19,094 sets of temperature percentiles and 19,094 sets of humidex percentiles corresponding to the 19,094 DAs in the GEM-SURF database. We were driven to use DA-specific percentiles based on the notion of acclimatization. By using percentiles we were able to define environmental heat relative to what individuals were physically accustomed to, a practice that has been substantiated elsewhere.[143,145,154]

Major findings suggest that the impacts of environmental heat on acute health outcomes are quite immediate. In past studies, a consistent three-day lag structure (lag 02) has emerged in the relationship between environmental heat and AKI.[33,113,146,155] The short delay between heat exposure and AKI is physiologically consistent with body water loss over time and disrupted fluid balances from dehydration.[7] Consequently, we chose to implement a three-day lag structure in our study. Day 0 was defined as the index date, day 1 was directly before the index date, and day 2 was two days before the index date.

The relationship between temperature and health outcomes tends to follow a “U”, “V”, or “J”-shape with morbidity rapidly escalating beyond certain thresholds.[46,145,147–150] We

chose to dichotomize our exposures using the 95th percentile as our relative threshold. Our decision to use the 95th percentile as the cut-point was motivated by existing literature.[40,113,156] We chose to dichotomize our exposures rather than model them as continuous moving averages because we did not anticipate that the change in risk would be the same for each stepwise increase in temperature. We also avoided continuous moving averages because our intent was to study sustained high heat without allowing an exceptionally hot day to skew the mean. Although ordinal exposures measures would have allowed examination of non-linearity and possible dose-response relationships, we decided against them because we expected heat effects to be confined to the extreme end of the exposure scale[157] and foresaw small cell sizes in upper percentile categories as a limiting factor.[158]

We defined heat periods as three consecutive days (lag 0 [index], lag 1, and lag 2) where the 95th percentile of daily maximum actual temperature was reached or exceeded. This was our primary measure of environmental heat. We classified cases and controls that did not meet the definition of a heat period as being unexposed.

We defined high humidex periods as three consecutive days (lag 0 [index], lag 1, and lag 2) where the 95th percentile of daily maximum humidex was reached or exceeded. This was our secondary measure of environmental heat. We classified cases and controls that did not meet the definition of high humidex periods as being unexposed.

4.10 Covariate adjustment

We consulted nephrologists and reviewed the literature in order to identify non-intermediary variables believed to be causally associated with AKI. We sought to adjust for these variables in our analysis to correct for different predispositions to AKI among cases and controls. In the five years prior to index date a history of diabetes, congestive heart failure, coronary artery disease excluding angina, stroke, peripheral vascular disease, chronic liver disease, and hypertension were identified for adjustment (Appendix C); in the 120 days prior to index date evidence of prescriptions for angiotensin-converting enzyme (ACE) inhibitors alone, angiotensin II receptor blockers (ARB) alone, ACE inhibitors and ARBs together, potassium-sparing diuretics, nonpotassium-sparing

diuretics, non-steroidal anti-inflammatory drugs (NSAID) excluding aspirin, and psychotropics were identified for adjustment.[36,86,89,93,100,101,109,110,159]

4.11 Costing

We attempted to provide perspective on the potential economic fallout of AKI by determining the government payer health care costs on an individual basis. We tracked government payer health care costs over a 30-day period starting on, and inclusive of, the index date. We aggregated various costing data using only three sources: 1) inpatient hospitalizations from CIHI-DAD, 2) emergency department and dialysis clinic visits from CIHI-NACRS, and, 3) physician billings, non-physician billings and lab claims from OHIP. This was a conservative approach and did not include several cost sources such as same day surgery, medication, rehabilitation, and complex continuing care. CIHI-DAD and CIHI-NACRS attribute resource intensity weights (RIW) to each individual to describe the average amount of hospital resources (administration, staff, supplies, technology, equipment, etc.) used by a patient with a particular condition relative to a reference patient. RIWs are updated annually. To determine the base RIW, individuals are first assigned to a case-mix group according to their most responsible/main diagnoses and interventions received. The case-mix groups are further compartmentalized by age category. After combining the case-mix group with the corresponding age category, each individual's base RIW is then adjusted to incorporate length of stay and comorbidity status.[160] The final RIW is multiplied by the hospital-specific cost-per weighted case to estimate the individual hospitalization costs for that person. In OHIP, RIWs are not applicable. Instead, the unit costs simply represent the fees paid for procedures or consultations. All dollar values were harmonized to 2012.

4.12 Statistical analyses

We expressed continuous variables as medians (IQR) to account for possible skewed distributions and categorical variables as proportions. We used standardized differences to evaluate the distribution of covariates between cases and weighted controls after matching. To calculate the standardized differences, we took the difference in the means of each variable between cases and controls divided by the pooled standard deviation for

that variable. In our study, a standardized difference >10% was considered to represent a meaningful imbalance between cases and controls.[161]

We assigned a weight to controls by dividing the number of cases in a matched set (always one) over the number of matched controls (one, two, three or four).[162] Depending on the number of controls in the matched set, possible weights included 1, 0.5, 0.33, or 0.25. The sum of control weights equaled the case sample size.

To better describe the scope and possible ramifications of AKI in our study, we determined the number of unique hospitals that cases presented to along with the proportion of cases who received acute dialysis during their hospital encounters. We defined receipt of acute dialysis using OHIP feecodes (see Appendix B). We further categorized cases by the top ten most responsible (CIHI-DAD) /main (CIHI-NACRS) diagnoses.

We used several statistics to describe the underlying daily maximum temperatures and daily maximum humidexes represented by the 95th percentiles in our sample of cases and controls. We used ArcGIS software to map the daily maximum actual temperature corresponding to the 95th percentile across all the 19,094 DAs for which GEM-SURF data were available in Ontario.

We performed conditional logistic regression to estimate unadjusted and adjusted ORs along with 95% CIs. We chose conditional logistic regression specifically to account for correlation within matched sets. The adjusted analyses included all variables listed in Section 4.9.

To quantify the effect of our primary analysis in absolute terms, we estimated the population incidence rate of AKI in the absence of heat periods. We restricted our focus to the warm season of 2012 and filtered through individuals DAs to exclude all dates from April 1st, 2012 to September 30th, 2012 that met our definition of a heat period. In other words, we combed through all 19,094 DAs to remove dates where on that day and the two days prior (lag02) the 95th percentile of area-specific maximum temperature was

reached or exceeded. We then linked the list of remaining non-heat dates for each DA to RPDB and obtained the number of older adults, 66 years and over, in each dissemination area on each non-heat date. We summed the number of persons at risk in each of the DAs over all the non-heat period dates to obtain our person-time denominator. Next we identified the number of hospital encounters with AKI that occurred over the same list of non-heat period dates in the 66 and over population to obtain our numerator. We then determined the absolute impact of heat periods on AKI by multiplying our adjusted OR estimate (interpreted as RR) by the population incidence rate. We believe this approximation was appropriate given the low incidence of AKI observed. Although we only sampled controls who remained AKI free at the end of follow-up, rather than sampling controls concurrently with cases, the number of older adults omitted from the control series was relatively small.[163] The rarity of AKI minimized the likelihood of an overestimate.[164]

4.13 Additional analyses

To address our third objective, we conducted an analysis stratified by age groups: 1) those aged 66 to 79 years, and, 2) those over 79 years. We included an interaction term in each model to assess whether the age group-specific odds ratios differed. We expected to see higher OR estimates in the over 79 group because the elderly are known to be vulnerable to environmental heat.[34] We formatted the figure for this analysis using R software.

To address our fourth objective, we examined the robustness of the estimates produced using our initial matching approach by carrying out a subsequent round of matching. The intent of this sensitivity analysis was to control for aspects of location by matching on exact DA (inherently controls for residential status and income quintile), sex, age ± 2 years, age categories (66 to 79 years, over 79 years), and history of CKD. After matching, we randomly reselected a new index date for controls to better account for seasonality, long-term time trends and autocorrelation in the temperature exposure data. For each control, the new index date was on a different date than the matched case, but on the same day of week, within the same month, and year. This is a variant of the time-

stratified method, which has been used extensively for referent selection in previous case-crossover studies.[16–19,33,46,113,144,156,165] We performed exclusions in the control group with respect to the new index dates. We did not need to factor the aforementioned time trends into our primary analysis because cases and controls were compared on the same date. However, we allowed the date to vary in the sensitivity analysis because, otherwise, matching on exact DA and index date would result in cases and controls being assigned identical exposure sequences.

We carried out another sensitivity analysis that was restricted to cases in our primary cohort and looked at the time of presentation to the emergency department or admission to the hospital at lag 0 (index date). The purpose of this analysis was to determine during what time of day hospital encounters with AKI were most frequent and to investigate the validity of temporality assumptions. Although we were able to definitively conclude that daily maximum temperatures at lag 2 and lag 1 preceded the hospital encounters, we did not know whether daily maximum temperatures at lag 0 tended to precede the hospital encounters. We anticipated that daily maximum temperatures would peak, on average, after 12:00 pm. If the majority of cases presented to the hospital after this time we would suggest that, in most instances, heat exposure preceded the outcome.

Lastly, we explored the possibility of overmatching in our primary time-matched analyses. To do so, we reduced matched sets by combining case and control groups with exactly the same matching factors.[166] We then reran the conditional logistic regression analyses.

We conducted all statistical analyses in SAS software version 9.3 (SAS Institute). We interpreted two-sided p-values less than 0.05 as statistically significant.

Chapter 5

5 Results

5.1 Characteristics of cases and controls

Before matching, we isolated 66,732 cases of AKI and 1,710,783 eligible controls. From this population, we matched 53,078 cases to 175,121 controls. After eliminating cases and controls who were missing GEM-SURF temperature information, we ended up with a total of 52,913 cases matched to 174,222 controls (Figure 4-1 and Figure 4-2). We matched 36,424 (69%) cases to four controls, 3,680 (7%) cases to three controls, 4,677 (9%) cases to two controls and 8,132(15%) cases to one control. We created each matched set without any prior knowledge of exposure status.

Characteristics of cases and weighted controls are presented in Table 5-1. Among both cases and controls the median (IQR) age was 80 (74 to 85), 49% were female, 8% were classified as having rural residential status, 24% lived in lowest income quintile neighborhoods, and 16% had a history of CKD. Cases were more likely than matched controls to be diagnosed with diabetes, congestive heart failure, coronary artery disease, stroke, peripheral vascular disease, chronic liver disease, and hypertension. Cases were also more likely than controls to have evidence of prescriptions for ACE inhibitors alone, ARBs alone, both ACE and ARBs together, potassium sparing diuretics, non-potassium sparing diuretics, NSAIDs, and psychotropics. Information for all of these variables was complete.

Cases presented to 180 unique hospitals. In total, 2.7% (n=1440) of AKI cases received acute dialysis during their hospital encounters. The top five most responsible/main diagnoses recorded among cases were acute renal failure (18%), heart failure (6%), other septicaemia (5%), other disorders of urinary system (4%), and acute myocardial infarction (4%) (Appendix D). The median 30-day government payer health care cost among AKI cases was $13,877 (IQR $8,399 to $24,449), compared to a $33 (IQR $0 to $135) among controls.

5.2 Descriptive characteristics of exposures

Summary statistics of the 95th percentile thresholds are presented in Table 5-2. Aggregating the 227,135 case and control observations in our study, the 95th percentiles corresponded to absolute daily maximum actual temperatures as low as 20.1^{o}C and as high as 32.5^{o}C, and to absolute daily maximum humidexes as low as 20.1 and as high as 44.9. The 95th percentiles of daily maximum actual temperatures had an absolute median of 30.2^{o}C (standard deviation 1.3^{o}C). The 95th percentiles of daily maximum humidexes had an absolute median of 41.7 (standard deviation 2.4).

Heat periods did not always coincide with high humidex periods. Overall, heat periods were moderately to strongly correlated with high humidex periods (Pearson correlation coefficient=0.61, p-value<0.0001).

Figure 5-1 is a map of Ontario depicting the absolute daily maximum actual temperature corresponding to the 95th percentile across all of the 19,094 DAs for which data were available.

5.3 Association of acute kidney injury to heat periods and high humidex periods

In our primary analysis, heat periods, compared to non-heat periods, were significantly associated with risk of AKI (adjusted OR 1.11, 95% CI 1.00 to 1.23). In our secondary analysis, high humidex periods were not significantly associated with risk of AKI (adjusted OR 1.04, 95% CI 0.93 to 1.16). The full results from the time-matched cohort are displayed in Table 5-3.

During the 2012 warm season and in the absence of heat periods, we identified 16,071 AKI events over 355,467,493 person-days at risk. This gives a baseline incidence rate of roughly 1,650 cases of AKI per 100,000 person years in the absence of heat periods. Therefore the 11% relative increase in risk of AKI associated with heat periods translates to approximately 182 additional cases of AKI per 100,000 person-years, taking the warm seasons as the time at-risk.

5.4 Additional analyses

We conducted a subgroup analysis to determine whether there was effect modification by age group. Contrary to our expectation, the association between heat periods and hospital encounters with AKI did not differ across age groups (p-value 0.47). However there was a significant difference in the association between high humidex periods and AKI across age groups (p-value 0.01), with the association strengthened in those over 79 years. Results of the age-stratified analysis are presented in Figure 5-2.

In our location-matched sensitivity analysis we ended up with 29,904 cases matched to 60,830 controls (Figure 4-1 and Figure 4-2). The distribution of characteristics for cases and controls can be found in Appendix E. In this location-matched sensitivity analysis, the adjusted OR for AKI was 1.11 (95% CI 1.00 to 1.23) during heat periods, compared to non-heat periods. The adjusted OR for AKI was also elevated during high humidex periods compared to non-high humidex periods (adjusted OR 1.20, 95% CI 1.09 to 1.33). Results of the sensitivity analysis are displayed in Table 5-4.

We performed a subsequent sensitivity analysis to investigate what time of day cases from our initial cohort were most likely to present to the emergency department or be admitted to the hospital with a diagnosis of AKI. We found that on an hourly basis, hospital encounters were most frequent between 4:00 pm and 5:00 pm, with the majority of cases (n=36,515, 69%) presenting to the hospital after 12:00 pm noon. From these results, we would suggest that temporality assumptions were met and that peak heat exposure on the index date (lag 0) tended to precede the AKI events. We would further stipulate that the remaining patients, who presented to the hospital with AKI before peak heat hours (e.g. in the morning), would still have received substantial heat exposure from the culmination of the previous two days (lag 1, lag 2) plus whatever time elapsed prior to their hospital encounter on the index date (lag 0). We believe this is a reasonable conclusion to draw given the high correlation between heat metrics from hour-to-hour. It was necessary to carry out this analysis because temporality is a pre-requisite for causation. Although we were not able to definitively attribute a causal influence of heat

exposure to AKI, the results of this analysis support the possibility of a causal connection.

Collapsing case and control groups to form strata with the same matching criteria did not appreciably alter the OR estimates, indicating that the time-matched analyses were not subject to overmatching.

Table 5-1. Distribution of selected characteristics for AKI cases and controls in time-matched analysis

Variable	AKI cases[1] (N=52,913)	Weighted controls[1] (N=52,913)	Standardized differences[2]
Demographics			
Age (median, IQR)	80 (74-85)	80 (74-85)	0%
Over 79 years of age	27,149 (51.3%)	27,149 (51.3%)	0%
Women	25,688 (48.5%)	25,688 (48.5%)	0%
Rural residential status[3]	4,364 (8.2%)	4,364 (8.2%)	0%
Income quintile[4]			
1, low	12,502 (23.6%)	12,502 (23.6%)	0%
2	11,639 (22.0%)	11,639 (22.0%)	0%
3, middle	9,974 (18.8%)	9,974 (18.8%)	0%
4	9,726 (18.4%)	9,726 (18.4%)	0%
5, high	9,072 (17.1%)	9,072 (17.1%)	0%
Comorbid conditions[5]			
Chronic kidney disease[6]	8,464 (16.0%)	8,464 (16.0%)	0%
Diabetes[7]	23,406 (44.2%)	14,260 (27.0%)	54%
Congestive heart failure	23,894 (45.2%)	6,302 (11.9%)	116%
Coronary artery disease[8]	25,557 (48.3%)	13,489 (25.5%)	71%
Stroke	4,998 (9.4%)	1,490 (2.8%)	41%
Peripheral vascular disease	2,743 (5.2%)	714 (1.3%)	32%
Chronic liver disease	4,755 (9.0%)	1,340 (2.5%)	41%
Hypertension	44,808 (84.7%)	34,862 (65.9%)	65%
Medications[9]			
ACE inhibitors alone	21,772 (41.1%)	14,254 (26.9%)	44%
ARB alone	10,531 (19.9%)	7,943 (15.0%)	19%
ACE inhibitors and	1,907 (3.6%)	847 (1.6%)	18%

ARB use			
Potassium-sparing diuretics	6,727 (12.7%)	2,189 (4.1%)	46%
Nonpotassium-sparing diuretics	31,584 (59.7%)	17,206 (32.5%)	83%
NSAIDs, excluding aspirin	8,407 (15.9%)	5,880 (11.1%)	21%
Psychotropics[10]	11,258 (21.3%)	5,549 (10.5%)	44%

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; IQR, interquartile range; N, number; NSAID, non-steroidal anti-inflammatory drug

[1] Data are presented as number (%) of individuals, unless otherwise stated

[2] Standardized differences were derived by taking the difference in means between cases and weighted controls over the pooled standard deviation. Standardized differences are less sensitive to sample size compared to traditional hypothesis tests. Standardized differences > 10% were considered to represent meaningful imbalances between cases and controls.

[3] All residential areas where the community size was ≤10,000 individuals were classified as rural.

[4] Income was categorized into fifths of average neighborhood income, with 1 indicating the lowest (poorest) quintile and 5 the highest (richest) quintile on a relative scale.

[5] With the exception of diabetes, all other comorbidities were assessed using diagnostic, procedural, and/or fee codes logged in administrative databases in the five years prior to index date.

[6] In Ontario, positive coding algorithm for detecting chronic kidney disease identifies older adults with median (IQR) eGFR of 38 mL/min per 1.73 m^2 (26 to 51); its absence identifies those with a median (IQR) eGFR of 69 mL/min per 1.73 m^2 (56 to 82). [167]

[7] Diabetes was defined using the Ontario Diabetes Database (ODD), which contains records on all Ontario diabetic patients identified since 1991.

[8] Coronary artery disease excluded diagnoses of angina.

[9] Medication use was assessed in the 120 days prior to index date.

[10] Psychotropics included antidepressants (selective-serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors) and antipsychotic medications.

Table 5-2. Descriptive statistics of 95th percentile of daily maximum temperature and humidex among AKI cases and controls

	Minimum	Median (Percentiles 25th, 75th)	Maximum
Daily maximum temperature (^{o}C)	20.1	30.2 (29.3, 30.7)	32.5
Daily maximum humidex[1]	20.1	41.7 (40.8, 42.3)	44.9

Abbreviations: ^{o}C, degrees Celsius

[1]humidex = (air temperature in °C) + h. Where h = (0.5555)(E - 10); E= vapour pressure in hPa (mbar), given by: $e = 6.11*\exp^{[5417.753*((1/273.16)-(1/dewpoint))]}$ with exp = 2.71828. Dewpoint is expressed in kelvins (K) (temperature in K = temperature in °C + 273.16) and 5417.7530 is a rounded constant based on the molecular weight of water, latent heat of evaporation, and the universal gas constant.[168]

Figure 5-1. Map of 95th percentile of daily maximum temperature by dissemination area in Ontario, June 2004 to April 2013

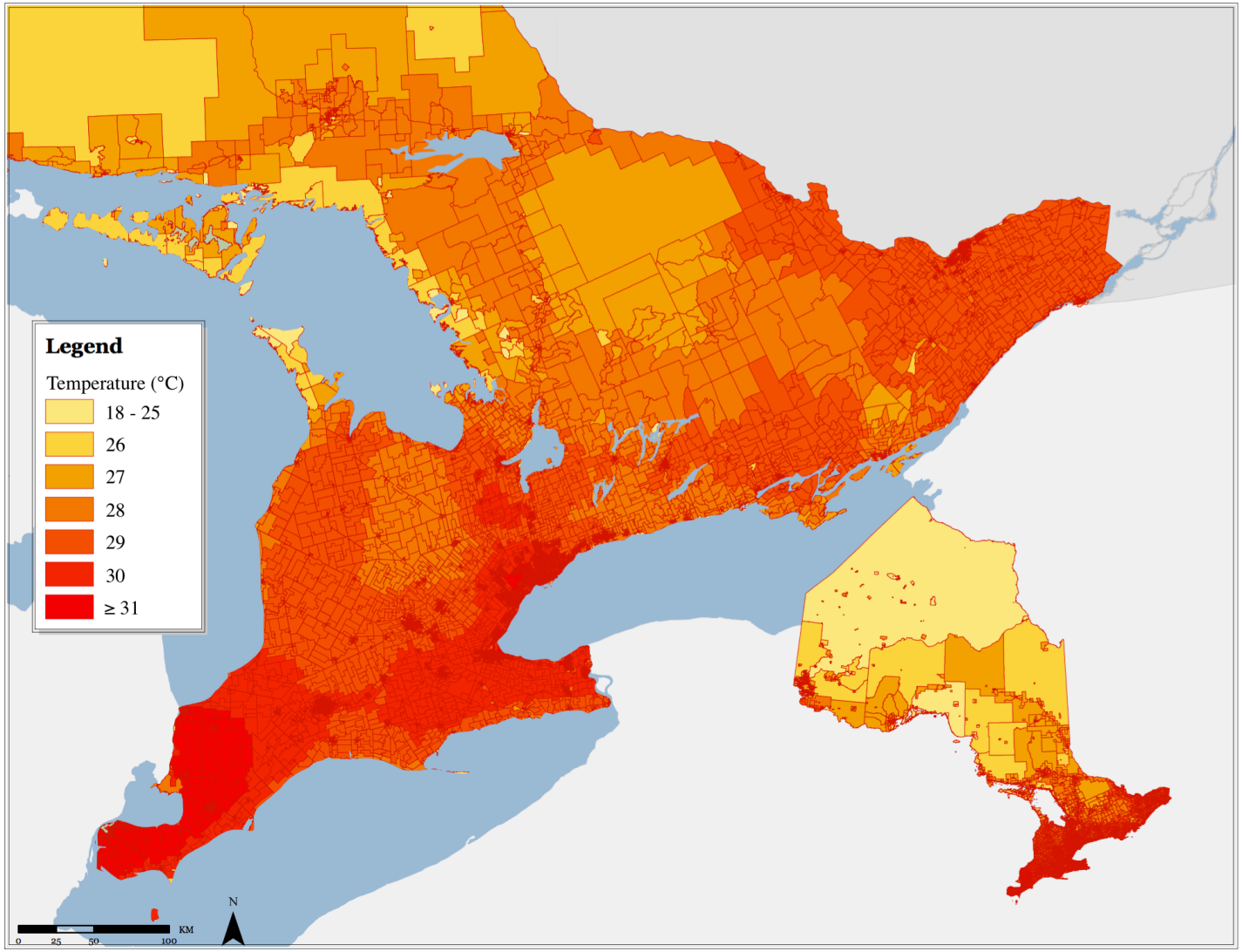


Table 5-3. Association of AKI with exposure to heat periods and high humidex periods in time-matched analysis

Exposure	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[1]
Heat periods[2]	1.07 (0.98, 1.16)	1.11 (1.00, 1.23)
High humidex periods[3]	1.02 (0.93, 1.12)	1.04 (0.93, 1.16)

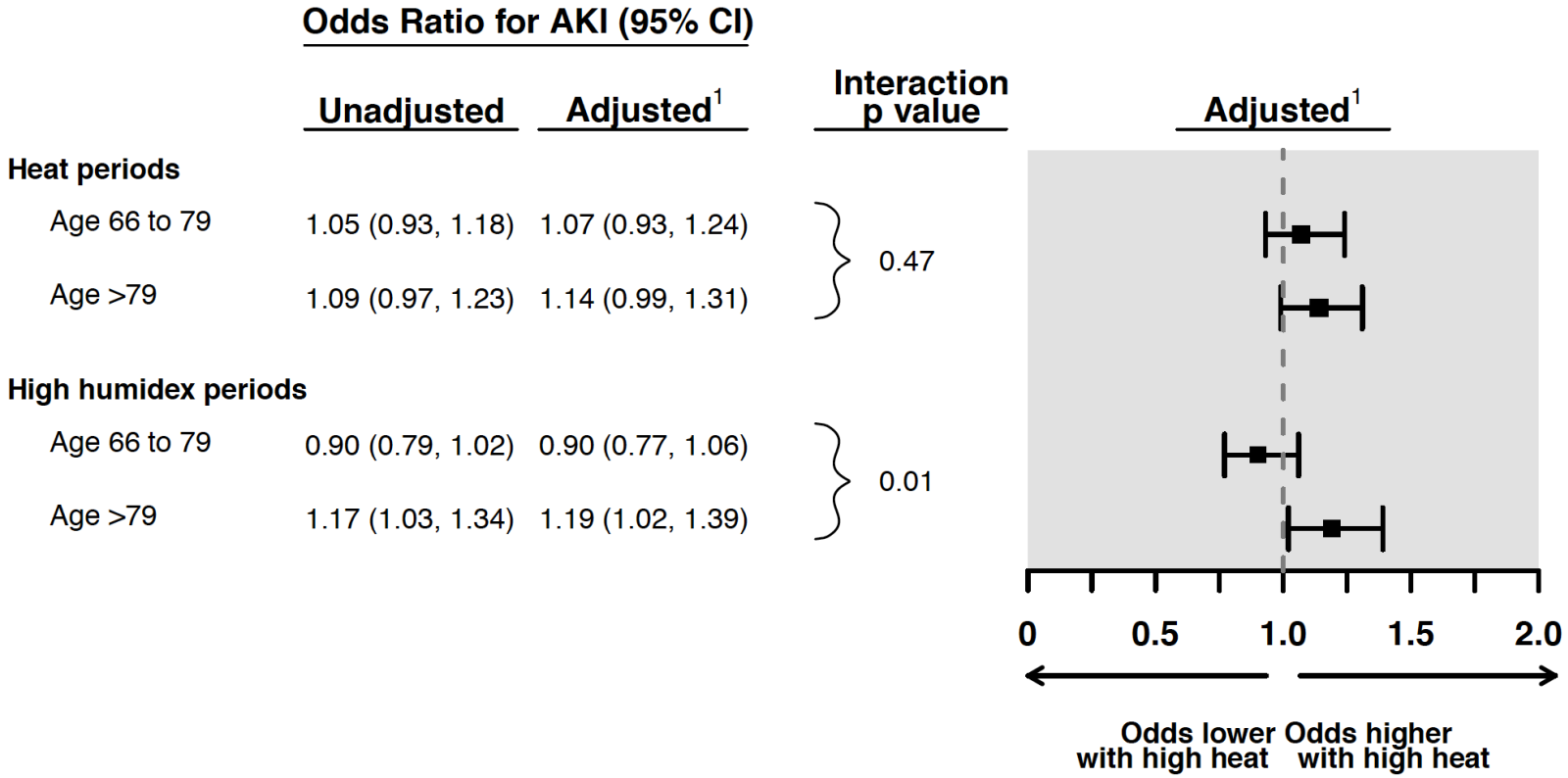
Abbreviations: AKI, acute kidney injury; CI, confidence interval; OR, odds ratio

[1] Adjusted for diabetes, congestive heart failure, coronary artery disease excluding angina, stroke, peripheral vascular disease, chronic liver disease, hypertension, angiotensin-converting enzyme (ACE) inhibitor use alone, angiotensin II receptor blocker (ARB) use alone, ACE inhibitors and ARBs use together, potassium-sparing diuretic use, nonpotassium-sparing diuretic use, non-steroidal anti-inflammatory drugs (NSAIDs) use, and psychotropic use.

[2] Heat periods were defined as 3 consecutive days (lag 02) where area-specific daily maximum actual temperature was $\geq 95^{th}$ percentile, and were compared to all periods that did not meet this definition.

[3] High humidex periods defined as 3 consecutive days (lag 02) where area-specific daily maximum humidex was $\geq 95^{th}$ percentile, and were compared to all periods that did not meet this definition.

Figure 5-2. Age-based subgroup analyses of association between AKI and exposure to heat periods and high humidex periods



Abbreviations: AKI, acute kidney injury; CI, confidence interval

Notes: The vertical lines indicate 95% confidence limits. The squares indicate odds ratios. The size of the squares is proportional to the precision of the estimate (the square is larger when the 95% CI is narrower).

[1] Adjusted for diabetes, congestive heart failure, coronary artery disease excluding angina, stroke, peripheral vascular disease, chronic liver disease, hypertension, angiotensin-converting enzyme (ACE) inhibitor use alone, angiotensin II receptor blocker (ARB) use alone, ACE inhibitors and ARBs use together, potassium-sparing diuretic use, nonpotassium-sparing diuretic use, non-steroidal anti-inflammatory drugs (NSAIDs) use excluding aspirin, and psychotropic use.

Table 5-4. Association of AKI with exposure to heat periods and high humidex periods in location-matched sensitivity analysis

Exposure	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[1]
Heat periods[2]	1.08 (0.99, 1.17)	1.11 (1.00, 1.23)
High humidex periods[3]	1.14 (1.05, 1.24)	1.20 (1.09, 1.33)

Abbreviations: AKI, acute kidney injury; CI, confidence interval; OR, odds ratio

[1] Adjusted for diabetes, congestive heart failure, coronary artery disease excluding angina, stroke, peripheral vascular disease, chronic liver disease, hypertension, angiotensin-converting enzyme (ACE) inhibitor use alone, angiotensin II receptor blocker (ARB) use alone, ACE inhibitors and ARBs use together, potassium-sparing diuretic use, nonpotassium-sparing diuretic use, non-steroidal anti-inflammatory drugs (NSAIDs) use, and psychotropic use.

[2] Heat periods were defined as 3 consecutive days (lag 02) where daily maximum actual temperature was $\geq 95^{th}$ percentile, and were compared to all periods that did not meet this definition.

[3] High humidex periods defined as 3 consecutive days (lag 02) where daily maximum humidex was $\geq 95^{th}$ percentile, and were compared to all periods that did not meet this definition.

Chapter 6

6 Discussion

6.1 Overview of findings

This population-based, matched case-control study adds to the growing body of evidence supporting a link between environmental heat and AKI risk in older adults. To our knowledge, it is one of the first studies to find evidence of this association in Ontario, Canada. Our primary results showed that AKI risk was positively associated with three-day relative heat periods (adjusted OR 1.11, 95% CI 1.00 to 1.23), compared with three-day non-heat periods. As hypothesized, our sensitivity analysis reinforced this estimate (adjusted OR 1.11, 95% CI 1.00 to 1.23). The magnitude of our estimates for heat periods broadly parallel previous findings.[105, 109] Confirmation of this association strengthens our hypothesis that this is a true effect.

The main effect of high humidex periods was more difficult to resolve. Only high humidex periods, and not heat periods, showed a significant interaction effect by age group. Compared to those aged 66 to 79 years, those over 79 years of age were at increased risk of humidex-associated AKI. This is in line with past research documenting impaired heat tolerance in the elderly.[34]

Our decision to define heat periods and high humidex periods by the 95th percentile corresponds well with Environment Canada's thresholds for issuing heat alerts. In Southern Ontario a heat alert may be declared when over two consecutive days the daily maximum temperature is expected to be ≥31^{o}C and nighttime minimum temperature is expected to be ≥20^{o}C, or, when the daily maximum humidex is expected to be ≥40.[28] In Northern Ontario the thresholds are reduced to a daily maximum temperature of ≥29^{o}C and nighttime minimum temperature of ≥16^{o}C, or, a daily maximum humidex ≥36.[28] Extreme heat alerts use the same thresholds sustained over three or more days.[28] In our work, the overall median of the 95th percentile of maximum daily temperature was 30.2^{o}C. The overall median of the 95th percentile of maximum daily humidex was 41.7. This demonstrated that our exposure indicators actually represented high heat.

By using percentiles in our work, we were able to apply a single definition of heat that accounted for the relative experience of temperature across geographic locations in the same way that Environment Canada uses multiple different thresholds for different parts of Ontario. For example, the 95th percentile of daily maximum temperature in a remote northern DA may have represented a raw reading of 28^{o}C. Among individuals living in this northern DA, 28^{o}C would be a manifestation of heat compared to the temperatures they typically experienced. In contrast, the 95th percentile of daily maximum temperature in a more southern DA may have represented a raw reading of 31^{o}C. Since this DA was consistently hotter, it would follow that individuals living there would possess greater adaptive mechanisms for dealing with heat and would be more likely to experience AKI at 31^{o}C than at 28^{o}C. In summary, heat thresholds differed by region as a function of the local climate along with the physiological and behavioral acclimation of residents.

6.2 Implications

The adjusted OR estimates in this study were quite small. However, our method of detecting AKI lacked sensitivity and incidence may have been underestimated by up to five-fold. In absolute terms, we approximated that heat periods associated with an additional 182 cases of AKI per 100,000 person years during the warm seasons. Considering the median 30-day government payer health care costs for a single AKI case was $13,877, the costs of treating 182 cases of AKI may conceivably surpass $2.5 million CDN. With the average yearly temperature in Ontario projected to increase another 2.3^{o}C by the 2020s and as much as 4.1^{o}C by the 2050s,[169] it is probable that more Ontario residents will soon be exposed to heat periods.

Heat-associated AKI can be averted, should the appropriate preventative measures be put in place. To this end, air conditioning is one of the top protective interventions in combatting the effects of environmental heat.[66] During times of extreme heat the provision of sufficient air-conditioned spaces, at community centers and other public institutions, is pertinent.[170] Increased transportation and extended operating hours to these spaces is also recommended to facilitate accessibility. The city of Toronto, Ontario is a good use case for why public cooling stations should be provided. In a survey that included 184 residents, roughly half reported limiting their household use of air

conditioners, citing costly energy bills as a limiting factor.[171] Residents who choose not to run their air conditioners, or who do not have access, may further exacerbate their risk by improper usage of electric fans. Turning on a fan while the windows are closed, and without intermittent air conditioning, simply recirculates hot air. This hinders radiative and conductive heat loss and can hasten the process of dehydration.

Based on past research, the operational costs of running heat alert response programs are minimal relative to the savings gained from effective prevention of heat-related morbidity and mortality.[172] A similar conclusion may be intuited from our results. The dollar values we have reported do not encompass the social and emotional costs of having an AKI event. Therefore coordinating announcements of heat warnings appears to be a promising economic endeavor though more research is needed to confirm cost-effectiveness.

In order to maximize the effectiveness of heat warnings, outreach strategies and messaging should be targeted to vulnerable groups.[173] Taking our findings under consideration, educational content on heat-related AKI may be particularly impactful when framed for community-dwelling seniors. These individuals, who have retained their independence, may be inclined to envisage themselves as resilient to heat despite evidence to the contrary.[174] An interview-based study of subjects aged 72 to 94 found respondents generally recognized the elderly as vulnerable, though they did not perceive themselves as elderly or vulnerable.[175] Interestingly, the behavior of medical caregivers may play into this misperception. An investigation of nursing home patients during the 2003 heat wave in France, demonstrated that the mortality rate in less dependent patients was 8.3 times higher during the heat wave compared to before, but only 3.9 times higher in the most dependent patients.[176] The authors hypothesized that medical staff may have been more prone to administer interventions to the highly dependent patients, thereby preferentially preventing deaths in this group during the heat wave.[176] The impartial focus on the most dependent elderly patients may propagate erroneous beliefs that less dependent elderly patients are immune to the negative impacts of heat. These narratives of independence are persuasive and it is important that attitudes of autonomy and a lack of knowledge regarding heat do not continue to amplify risk in the elderly population.

Moving forward, educating the community-dwelling elderly on relevant heat-coping strategies in a manner that does not undermine their independence should be a priority. The educational content should stress the short-latency period of the proposed heat and AKI association while emphasizing protective measures like air conditioning, increased fluid intake, and avoidance of outdoor physical exertion. It is critical that this educational content also be aimed at caregivers and physicians so that they too understand and can discuss the AKI health risks with their patients.[24,177]

6.3 Implications of the selected study design

Considering our objectives and data constraints, we believe that the case-control design was an efficient choice in comparison to a cohort-design.[178] The case-control design is tailored to explore individual associations between a single outcome and multiple exposures using external controls. Furthermore, the large administrative databases at ICES enabled us to identify a sufficient number of cases to examine associations with precision. However, we do acknowledge that case-control studies are prone to selection bias. We attempted to reduce this bias by selecting cases and controls independent of our exposures of interest.

In the literature, time-series[21,143,145–149,155,165,179] and case-crossover[16–19,33,46,69,113,144,156,165] designs predominate. However, we did not feel that either approach was ideally suited to our purposes.

Contemporary time-series analyses employ distributed lag non-linear models (DLNM). When using the DLMN framework, outcome data are summed into daily-counts which are treated as originating from an overdispersed Poisson distribution.[180] Like the name suggests, DLNMs are ideal for modeling the lagged structure of temperature-health associations. In our study, the temporal delay was not a principal concern as we decided to focus on a fixed three-day lag. The decision to stick with a single lag dimension was guided by clinician expertise and findings from prior investigations.[22,33,113,146] Another reason we chose to forgo the use of DLNMs was because we foresaw numerous problems with model convergence and wished to avoid performing case-only analyses. DLNMs have been designed to be very flexible, with several mutable parameters. As a direct

consequence, the inferences made from DLNMs may be conditional on post-hoc selection of the best model fit. The standard practice has been to use DLNMs to obtain area-specific risk estimates that can then be meta-analyzed to form an overall estimate. Given the sheer number of possible DAs in the GEM-SURF database (19,094) and the small number of cases within each, if applied to our work, this methodology would likely have yielded issues with subjectivity, data suppression, and unreliable estimates.

In the case-crossover design each case serves as its own control. The design is advantageous in that it accounts for all known and unknown confounding factors that do not change with time.[181] However, selecting referent days to compare exposures across the same individual can be problematic. Sampling referents bidirectionally, both before and after case events, achieves substantial reductions in bias from trends in the exposure.[182] Yet, the bidirectional sampling scheme is plagued by the assumption that case events will not be repeated and that having an event will not influence subsequent exposures.[183] We were not prepared to make these assumptions as AKI is a repeatable event and in many circumstances, the occurrence of AKI would likely have modified subsequent behavior of the afflicted individuals. In our sensitivity analysis, we avoided the need to make these assumptions by adapting the time-stratified referent selection strategy of case-crossover studies to a set of external controls. We then used matching techniques and multivariable adjustment to control for inter-individual variation.

6.4 Strengths

One strength of our study was focusing on the single outcome of AKI. We deliberately prespecified our analyses to avoid an inflated type 1 error rate stemming from multiple comparisons.

Another strength of our study was the use of microscale weather data. We capitalized on the granularity of GEM-SURF temperature readings by matching cases and controls on the exact same index date. By comparing matched cases and controls on the same date, our primary analysis controlled for seasonality, long-term trends, and autocorrelation in the exposure series. This circumvented the need for more complicated adjustment approaches that may have introduced error.[111] Matching on index date has not been

possible in the past due to the reliance on weather station data that outputs uniform temperature readings across expansive geographic regions. For example, in prior studies data from the weather station at Pearson International Airport has been extrapolated to cover all of Toronto.

By confining our analysis to the older adult population (66 years and over), we ensured that personal medication histories could be included as control variables in our models. Although this age restriction curtailed generalizability, it strengthened our study because many drugs are known to increase heat-susceptibility and the risk of AKI through alterations in fluid balance.[34,36,184] Previous investigations that provided area-level estimates were unable to incorporate information on personal medication histories.[22,147] While other investigations that used case-crossover designs to provide individual-level estimates also tended to omit information on personal medication histories, implicitly assuming that there was no intra-individual variation. Seeing as medication use does vary with time, this assumption may not have been entirely valid.

6.5 Limitations

The dependence on ecological exposure data is a shared limitation of ambient temperature studies. Traditionally, ecological temperatures were designated to individuals by mapping the individuals' residential postal codes to the nearest weather stations.[16,18,19,113] In an effort to minimize misclassification bias, this process was often extended to create circular buffers with pre-specified radial distances (e.g. 10 kilometers) around each weather station. Only individuals for whom the geographic centroid of their residential postal code fell within the buffers were included. Even with these safeguards in place, it is probable that variable activity patterns introduced exposure error. The same holds true in our study. Although we used GEM-SURF spatial models to provide more targeted exposure data, temperature assignation was still done ecologically at the level of the DA. We had no individual-level data on air conditioning use and work-leisure schedules, both of which may have impacted heat exposure.[19]

To assign DAs, we used residential postal codes as opposed to hospital postal codes because we wanted to apply a uniform technique of converting postal codes to

geographic areas. Both cases and controls had residential postal codes listed in the RPDB database, while only cases had applicable hospital postal codes. Inaccuracies may have resulted from using the residential postal codes, as individuals do not always report changes in addresses and do not always reside full-time at their primary addresses, especially during the summer. The inaccuracies may have been most pronounced in the controls. We would stipulate that controls were more likely than cases to leave their primary dwellings as they were generally in better health. Future studies may benefit from selecting controls with evidence of hospital encounters for conditions unrelated to AKI. This would minimize exposure misclassification by enabling hospital postal codes to be used uniformly for temperature assignation while simultaneously obviating the need to randomly select index dates for the controls series.

Our study may also be limited by inappropriate geographic boundary selection [23] DAs are defined for administrative uses and respect the boundaries of larger geographic units such as census subdivisions and census tracts. They also vary considerably in physical size and tend to be much larger in the north. Differences in temperature recorded between neighboring grid points, or DAs, may be somewhat distorted particularly at the edges where the DAs meet.[185] We did not compensate for the possibility of edge effects.

Another limitation of our study is the heavy reliance on routinely collected administrative data, which are not primarily intended for research purposes. When drawing together information on covariates to adjust for, we were restricted to certain types of data, mainly diagnostic codes, fee codes, and procedural codes. Our retrospective data sources did not contain information on some proposed risk factors for heat-related AKI like exercise-exertion and water intake.

We lost a substantial number of cases during matching. It is possible that the distribution of characteristics in these unmatched cases differs with respect to our matched cases. Thus, the representativeness of our selected population remains in question.

Lastly, we failed to capture AKI events that did not result in a hospital encounter, including out-of-hospital deaths. It is possible that our associations would have been

strengthened had we had individual-level exposure information and more sensitive outcomes measures.

6.6 Conclusion and future directions

AKI is a serious health complication. In accordance with previous work, the results of our study suggest that AKI is positively associated with heat periods among older adults. However, we cannot dismiss the possibility of residual confounding or the influence of unmeasured confounders such as occupation[26] and mental health.[49,186] Up to this point, inconsistent study designs and varied definitions of what comprises heat have inhibited evidence synthesis. Rigorous methods, such as the implementation of percentiles to quantify temperature on a transferable scale, are needed to support cross-investigation comparisons. Whether to select geographic-varying exposures over time-varying exposures as the optimal methodological approach also necessitates further research. The generalizability of the heat and AKI relationship to broader age ranges warrants investigation, as do the specific mechanisms underlying heat-related AKI. Incorporating laboratory information (SCr) may aid in these endeavors by improving identification of AKI events. Randomized controlled trials testing the efficacy of mitigation strategies should also be considered. Knowledge of the types of interventions that are needed (e.g. heat alerts, cooling stations), for whom, and at what regional level is required to inform policy decisions and public health planning.

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Appendices

Appendix A: Definitions of preliminary exclusions

Variable	Database(s)	Code(s)
Dialysis in the year prior to index date. This includes any dialysis modality (e.g. acute, chronic, access creation).	CIHI-DAD	ICD-9: V451, V560, V568, 99673 ICD-10: T824, Y602, Y612, Y622, Y841, Z49, Z992 CCP: 5127, 5142, 5143, 5195, 6698 CCI: 1PZ21, 1OT53DATS, 1OT53HATS, 1OT53LATS, 1SY55LAFT, 7SC59QD, 1KY76, 1KG76MZXXA, 1KG76MZXXN, 1JM76NC, 1JM76NCXXN
	OHIP	OHIP feecodes: R850, G324, G336, G327, G862, G865, G099, R825, R826, R827, R833, R840, R841, R843, R848, R851, R946, R943, R944, R945, R941, R942, Z450, Z451, Z452, G864, R852, R853, R854, R885, G333, H540, H740, R849, G323, G325, G326, G860, G863, G866, G330, G331, G332, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295

Kidney transplant in the five years prior to index date.	CIHI-DAD	CCI: 1PC85
	OHIP	OHIP feecodes: S435, S434
Long-term care facility utilization	ODB	Looked at most recent ODB prescription prior to index date for long-term care flag.

Abbreviations: CCI, Canadian Classification of Health Interventions; CCP Canadian Classification of Diagnostic, Therapeutics, and Surgical Procedures; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; dx, diagnosis; ICD-9 International Classification of Diseases, ninth revision; ICD-10, International Classification of Diseases, tenth revision; ODB, Ontario Drug Benefit database; OHIP, Ontario Health Insurance Plan claims database.

Note: Prior to 2002, diagnostic codes followed ICD-9 and procedural codes followed CCP. From 2002 onward, diagnostic codes followed ICD-10 and procedural codes followed CCI. ICD-9 and ICD-10 were developed by the World Health Organization. CCP and CCI were developed by CIHI.

Appendix B: Definitions of outcomes

Variable	Database(s)	Code(s)
Acute kidney injury	CIHI-DAD, NACRS	ICD-10: N17
Receipt of acute dialysis	OHIP	OHIP feecodes: R849, G323, G866, G330, G331, G093, G095, G294, G295

Abbreviation: CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; ICD-10, International Classification of Diseases, tenth revision; Ontario Health Insurance Plan claims database; NACRS, National Ambulatory Care Reporting System database

Appendix C: Definitions of demographic variables and comorbid conditions

Variable	Database(s)	Code(s)
Age	RPDB	
Sex	RPDB	
Annual postal code of residence	RPDB	Best known postal code for eligible RPDB person on July 1st each year. Drew from previous census data and information collected each time a person makes contact with a health care institution.
Residential status	CENSUS	
Neighbourhood income quintile	CENSUS	
Chronic kidney disease	CIHI-DAD	ICD-9: 4030, 4031, 4039, 4040, 4041, 4049, 585, 586, 5888, 5889, 2504 ICD-10: E102, E112, E132, E142, I12, I13, N08, N18, N19
	OHIP	OHIP dx: 403, 585
Diabetes	ODD	

Congestive heart failure	CIHI-DAD	ICD-9: 425, 5184, 514, 428
		ICD-10: I500, I501, I509, I255, J81
		CCP: 4961, 4962, 4963, 4964
		CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR
	OHIP	OHIP feecodes: R701, R702, Z429
		OHIP dx: 428
Coronary artery disease	CIHI-DAD	ICD-9: 412, 410, 411
		ICD-10: I21, I22, Z955, T822
		CCI: 1IJ50, 1IJ76
		CCP: 4801, 4802, 4803, 4804, 4805, 481, 482, 483
	OHIP	OHIP feecodes: R741, R742, R743, G298, E646, E651, E652, E654, E655, Z434, Z448
		OHIP dx: 410, 412
All stroke	CIHI-DAD	ICD-9: 430, 431, 432, 434, 435, 436, 3623
		ICD-10: I62, I630, I631, I632, I633, I634, I635, I638, I639, I64, H341, I600, I601, I602, I603, I604, I605, I606, I607, I609, I61, G450, G451, G452, G453, G458, G459, H340

Peripheral vascular disease	CIHI-DAD	ICD-9: 4402, 4408, 4409, 5571, 4439, 444 ICD-10: I700, I702, I708, I709, I731, I738, I739, K551 CCP: 5125, 5129, 5014, 5016, 5018, 5028, 5038, 5126, 5159 CCI: 1KA76, 1KA50, 1KE76, 1KG50, 1KG57, 1KG76MI, 1KG87, 1IA87LA, 1IB87LA, 1IC87LA, 1ID87, 1KA87LA, 1KE57
	OHIP	OHIP feecodes: R787, R780, R797, R804, R809, R875, R815, R936, R783, R784,R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649
Chronic liver disease	CIHI-DAD	ICD-9: 4561, 4562, 070, 5722, 5723, 5724, 5728, 573, 7824, V026, 2750, 2751, 7891, 7895, 571 ICD-10: B16, B17, B18, B19, I85, R17, R18, R160, R162, B942, Z225, E831, E830, K70, K713, K714, K715, K717, K721, K729, K73, K74, K753, K754, K758, K759, K76, K77
	OHIP	OHIP dx: 571, 573, 070 OHIP feecodes: Z551, Z554

Hypertension	CIHI-DAD	ICD-9: 401, 402, 403, 404, 405 ICD-10: I10, I11, I12, I13, I15
	OHIP	OHIP dx: 401, 402, 403

Abbreviations: CCI, Canadian Classification of Health Interventions; CCP Canadian Classification of Diagnostic, Therapeutics, and Surgical Procedures; CIHI-DAD, Canadian Institute for Health Information Discharge Abstract Database; dx, diagnosis; ICD-9 International Classification of Diseases, ninth revision; ICD-10, International Classification of Diseases, tenth revision; ODB, Ontario Drug Benefit database; ODD, Ontario Diabetes Database; OHIP, Ontario Health Insurance Plan claims database; RPDB, Registered Persons Database

Note: Prior to 2002, diagnostic codes followed ICD-9 and procedural codes followed CCP. From 2002 onward, diagnostic codes followed ICD-10 and procedural codes followed CCI. ICD-9 and ICD-10 were developed by the World Health Organization. CCP and CCI were developed by CIHI.

Appendix D: Top ten main/most responsible diagnoses among AKI cases

First three characters of ICD-10 code	Description	Number of cases (%)
N17	Acute renal failure	9437 (17.8%)
I50	Heart failure	3299 (6.2%)
A41	Other septicaemia	2664 (5.0%)
N39	Other disorders of urinary system	2093 (4.0%)
I21	Acute myocardial infarction	2083 (3.9%)
J18	Pneumonia, organism unspecified	1943 (3.7%)
J44	Other chronic obstructive pulmonary disease	1790 (3.4%)
Z51	Other medical care	1153 (2.2%)
E11	Type 2 Diabetes mellitus	1138 (2.2%)
E86	Volume depletion	681 (1.3%)

Abbreviations: ICD-10, International Classification of Diseases, tenth revision

Appendix E: Distribution of selected characteristics for AKI cases and controls in location-matched sensitivity analysis

Variable	AKI cases[1] (N=29,904)	Weighted controls[1] (N=29,904)	Standardized differences[2]
Demographics			
Age (median, IQR)	78 (73-84)	78 (73-84)	0%
Over 79 years of age	13,696 (45.8%)	13,682 (45.8%)	0%
Women	15,604 (52.2%)	15,604 (52.2%)	0%
Rural resdience[3]	2,984 (10.0%)	2,984 (10.0%)	0%
Income quintile[4]			
1, low	7,387 (24.7%)	7,387 (24.7%)	0%
2	6,436 (21.5%)	6,436 (21.5%)	0%
3, middle	5,628 (18.8%)	5,628 (18.8%)	0%
4	5,496 (18.4%)	5,496 (18.4%)	0%
5, high	4,957 (16.6%)	4,957 (16.6%)	0%
Comorbid conditions[5]			
Chronic kidney disease[6]	1,554 (5.2%)	1,549 (5.2%)	0%
Diabetes[7]	12,937 (43.3%)	7,564 (25.3%)	47%
Congestive heart failure	12,653 (42.3%)	3,013 (10.1%)	97%
Coronary artery disease[8]	13,902 (46.5%)	7,176 (24.0%)	60%
Stroke	2,738 (9.2%)	847 (2.8%)	33%
Peripheral vascular disease	1,465 (4.9%)	345 (1.2%)	27%
Chronic liver disease	2,761 (9.2%)	728 (2.4%)	36%
Hypertension	25,072 (83.8%)	19,394 (64.9%)	55%
Medications[9]			
ACE inhibitors alone	12,264 (41.0%)	7,843 (26.2%)	39%

ARB alone	5,915 (19.8%)	4,197 (14.0%)	19%
ACE inhibitors and ARB use	1,049 (3.5%)	398 (1.3%)	17%
Potassium-sparing diuretics	3,739 (12.5%)	1,118 (3.7%)	40%
Nonpotassium-sparing diuretics	17,376 (58.1%)	9,257 (31.0%)	70%
NSAIDs, excluding aspirin	5,022 (16.8%)	3,466 (11.6%)	18%
Psychotropics[10]	6,691 (22.4%)	3,581 (12.0%)	34%

Abbreviations: ACE, angiotensin-converting enzyme; AKI, acute kidney injury; ARB, angiotensin II receptor blocker; IQR, interquartile range; N, number; NSAID, non-steroidal anti-inflammatory drug

[1] Data are presented as number (%) of individuals, unless otherwise stated

[2] Standardized differences were derived by taking the difference in means between cases and weighted controls over the pooled standard deviation. Standardized differences are less sensitive to sample size compared to traditional hypothesis tests. Standardized differences >10% were considered to represent meaningful imbalances between cases and controls

[3] All areas where the community size was $\leq$10,000 individuals were classified as rural.

[4] Income was categorized into fifths of average neighborhood income, with 1 indicating the lowest (poorest) quintile and 5 the highest (richest) quintile.

[5] With the exception of diabetes, all other comorbidities were assessed using diagnostic, procedural, and/or fee codes logged in administrative databases in the five years prior to index date.

[6] In Ontario, positive coding algorithm for detecting chronic kidney disease identifies older adults with median (IQR) eGFR of 38 mL/min per 1.73 m^2 (26 to 51); its absence identifies those with a median (IQR) eGFR of 69 mL/min per 1.73 m^2 (56 to 82). [167]

[7] Diabetes was defined using the Ontario Diabetes Database, which contains records on all Ontario diabetic patients identified since 1991.

[8] Coronary artery disease excluded diagnoses of angina.

[9] Medication use was assessed in the 120 days prior to index date.

[10] Psychotropics included antidepressant (selective-serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors) and antipsychotic medication.

Curriculum Vitae

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