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Warmer summer nocturnal surface air temperatures and cardiovascular disease death risk: a population-based study

Haris Majeed[1]* & John S Floras[1,2]

[1] Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada

[2] University Health Network and Sinai Health Division of Cardiology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

*Corresponding Author:
Haris Majeed, HBSc, MSc
University of Toronto
Toronto, ON
Canada M5S 1A8
Email: haris.majeed@utoronto.ca
Phone: +1 (416) 946-8286

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Abstract

Objective: In recent summers, some populous mid- to high-latitude regions have experienced greater heat intensity, more at night than by day. Such warming has been associated with increased cause-specific adult mortality. The objective was to determine whether summer nocturnal surface air temperatures (SAT) relate to cardiovascular disease (CVD) deaths in England and Wales.

Methods: A time series analysis was performed on English and Welsh sex-specific data concerning CVD deaths of adults aged 60-64 and 65-69 years during the months of June and July, 2001-2015. Associations between summer (June-July) nocturnal SAT anomalies (primary exposure) and CVD death rates (outcome) were computed using negative binomial regression with autocorrelative residuals, controlling for key covariates. To assess external validity, similar associations with respect to CVD death in King County, Washington, US, also were calculated for men aged 60-64 and 65-69 years. Results are reported as incidence rate ratios (RR).

Results: From 2001-2015, within these specific cohorts, 39,912 CVD deaths (68.9% men) were recorded in England and Wales and 488 CVD deaths in King County. In England and Wales, after controlling for covariates, a 1°C rise in anomalous summer nocturnal SAT associated significantly with a 3.1% (95% CI, 0.3-5.9%) increased risk of CVD mortality amongst men aged 60-64, but not older men or either women age-groups. In King County, after controlling for covariates, a 1°C rise associated significantly with a 4.8% (95% CI, 1.7-8.1%) increased risk of CVD mortality amongst those <65 years but not older men.

Conclusion: In two mid-latitude regions, warmer summer nights are accompanied by an increased risk of death from CVD amongst men aged 60-64.

Keywords: cardiovascular disease, mortality, nocturnal, surface air temperatures

Strengths and limitations of this study:

- Ecological study of a large population advantaged by rigorous national mortality and meteorological data.
- Replication of principal finding in a climatically similar but geographically distinct region.
- General rather than granular (e.g., urban versus rural) outcome and exposure data.
- This observational study design cannot exclude residual confounding by other cardiovascular risk factors.

Background

Cardiovascular disease (CVD) is a principal cause of death among adult men and women habiting high-income nations[1]. With warm spells of extreme or sustained elevation in average summer surface air temperatures (SAT) occasioning surges in deaths and hospitalisations[2–5], their potential contribution to cardiovascular events has been a focus of vigorous recent research[6]. Findings thus far, with respect to age and sex, have been inconsistent[6]. Some European studies, focusing principally on daytime recordings, report that extreme summer average and/or diurnal SAT increase the risks of all-cause, heat-related, and CVD mortality to a greater extent in older (≥65 years) women than men[5,7–9]. Other European studies report the opposite, with men more at risk of an acute CVD event during periods of extreme summer SAT[10,11]. Some have also identified a significant effect of summer average/diurnal SAT on CVD mortality amongst men aged <65 years[11–13]. Social determinants, including the low prevalence of residential air-conditioning in Europe, may contribute to such variance[9,14].

In recent summers, some populous mid- to high latitude regions have experienced greater intensification of nocturnal than daytime heat[15], with consequent adverse effects on human health[4,15,16]. Anomalously high death rates in the elderly coincident with the 2003 French heatwave were attributed specifically to elevated nocturnal SAT[17]. Older individuals are generally more vulnerable intra-vascular volume depletion when exposed to heat[18], with consequent hypotension, thrombocytosis, and hyperlipidemia[3,18]. Such maladaptation, often exacerbated by more sedentary behaviour[19] and by disrupted or insufficient sleep[20], may render men more vulnerable than women to CVD events when exposed to anomalously high average summer SAT[3,5,18].

There are few present age- or sex- specific data concerning associations between summer nocturnal SAT and CVD mortality. We posited that summer nocturnal SAT anomalies (defined as deviations from 30-year [1981-2010] baseline averages[21]) associate with increased CVD mortality amongst men and women between the ages of 60 and 69 years. To test this hypothesis, we acquired English and Welsh population-based data encompassing the years 2001-2015. Because heatwaves in the United Kingdom are most frequent and intense during June and July[22], we acquired exposure data specific to these two months. To assess external validity, we secured corresponding information for King County, Washington State, US, a likewise sea-facing region, at parallel latitude to England and Wales, with comparable land-ocean atmospheric properties and similarly low prevalence of residential air conditioning[23]. These two jurisdictions also were selected because of their large populaces, of whom the majority (~90%) resides in urban or semi-urban 'heat-islands', readily accessible statistics, and data affirming that over this time-span both regions witnessed greater increases in nighttime than daytime SAT[15].

Methods

Climatological Exposure Data

Mid- to high-latitude regions, such as England and Wales and the State of Washington experience similar seasonal cycles, in which diurnal and nocturnal SAT are such higher in summer than winter[24]. Guided by previous observations of positive associations between summer nocturnal SAT and mortality[5,16], we ascertained, for June and July, minimum SAT for England and Wales (collectively) and King County, Washington, US from the Meteorology Office UK: https://www.metoffice.gov.uk/research/climate/maps-and-data/uk-and-regional-series and the National Oceanic and Atmospheric Administration (NOAA): https://www.ncdc.noaa.gov/cag/county/time-series , respectively. Minimum SAT was used as a proxy for nocturnal SAT[15]. Since air pollution (i.e. through particulate matter 2.5 [PM2.5]) can influence local CVD events[25], we included United States Environmental Protection Agency (EPA): https://www.epa.gov/outdoor-air-quality-data/download-daily-data. PM2.5 data averaged for June and July of each year in our models for the smaller region of King County.

Cardiovascular Disease Mortality Data

For England and Wales sex- and age-specific deaths attributed to CVD and mental and behavioural disorders occurring in June and July (in Europe, mental and behavioural disorders are an established strong risk factor for CVD death among adults over 60 years of age[25]) for the years 2001-2015 were extracted from Office for National Statistics (ONS, reference #: 007957) data: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deathsbymonthofoccurrenceaged60andoverbysingleyearofagesexandspecifiedcausesenglandandwales2001to2015. For

King County, sex- and age-specific CVD mortality for June and July for the years 2001-2015 were extracted from Centers for Disease Control and Prevention (CDC) WONDER data[23]. CVD death was defined as per the International Classification of Diseases (ICD), tenth revision (ICD-10: I00-I99) criteria, whereas deaths due to mental and behavioural disorders were defined as ICD-10: F00-F99.

Sex-specific analyses were partitioned into two age groups: 60-64 years and 65-69 years. We elected to exclude from analysis both younger adults, due to their lower CVD event rates and older adults, whose higher prevalence of co-morbid conditions has been shown in English data to risk cause of death misclassification[26]. Numerators of region-specific CVD deaths were based on the presence of one or more ICD-10 codes listed on each death record in a given month of the year, with denominators established on mid-year annual population estimates for the sum of England plus Wales and similarly for King County. Data were stratified by sex and age group. Monthly summer CVD and mental and behavioural mortality rates were computed by region- sex- and age-specific deaths occurring each month of the year and were reported as the number of male and female deaths per 100,000 persons.

Statistical Analysis

Since atmospheric systems act on long time-scales, our primary exposures (June and July) nocturnal SAT were standardized as monthly anomalies from a reference period[21]. For the purpose of the present analysis, SAT anomalies were defined as deviations from a 30-year (1981-2010) baseline average[21]. For each year of the exposure period (2001-2015), June and July nocturnal SAT anomalies were computed separately for England and Wales and for King County by subtracting the monthly averages for these regions from their respective 1981-2010 average nocturnal SAT.

CVD mortality rates were found to be auto-correlated (i.e. rates in the prior and subsequent years were significantly correlated) and the outcome variable's variance was considerably greater than its mean, leading to over-dispersion of data[21,27]. In addition, the incidence of mental health and behavioural distress in England and Wales has been shown to increase over time and identified as a strong risk factor for associations between diurnal SAT and cause-specific adult mortality[13]. To address these issues in our models, we used negative binomial regression with auto-correlated residuals of order one[21] to assess the association between sex- and age-specific CVD mortality rates to summer nocturnal SAT for England and Wales from 2001-2015, while controlling for mental health and behaviour mortality rates, the trend, and the summer month as our covariates. For King County, we used quasi-Poisson to assess all associations, while controlling for PM2.5, the trend, and the summer month as our covariates. Findings are reported as incidence rate ratios (RR) and interpreted as change for one-unit increase of the exposure variable[21,27]. Confidence intervals (CI) were evaluated at 95%, along with Student's two-sided *t*-tests. Microsoft Excel (version 2013), RStudio (version 4.1.1), and STATA (version 15) were used for computation, analyses, and figure composition.

Results

Within the selected cohorts, over the years 2001-2015, there were 39,912 (68.9% men) CVD deaths recorded in England and Wales and 488 male CVD deaths (54.1% in the group aged 65-69 years) in King County. Over this time period, CVD rates declined substantially in both regions (Table 1).

For England and Wales, CVD mortality rates, categorized by sex, age, and month, are illustrated in Figure 1A. The older (65-69 years) men and women exhibited higher CVD mortality rates than during both summer months. CVD mortality rates were consistently higher amongst men than women. Summer nocturnal SAT anomalies are plotted in Figure 1B. June anomalies ranged from -0.63°C (2015) to 1.17°C (2003- corresponding to a protracted western European heatwave). July anomalies ranged from -1.37°C (2011) to 1.73°C (2006).

After adjusting for covariates, associations between exposure (a 1-unit increase in summer nocturnal SAT[27]) and CVD mortality rates, stratified by sex and age appear in Figure 2. As shown in Figure 2A, a +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality rates among men aged 60-64 [adjusted RR 1.031; 95% CI, 1.003-1.059] but not in those aged 65-69 years [adjusted RR 0.999; 95% CI, 0.976-1.021], nor in adult women in either age group (Figure 2B).

For King County, summer CVD mortality rates were also higher within the older male cohort (Figure 3A). Summer nocturnal SAT anomalies are plotted in Figure 3B. June SAT anomalies ranged from -1.4°C (2008) to 2.49° (2015, a year when western North America recorded a record number of heatwaves and forest fires in the context of a strong El Niño event[21]). July anomalies ranged from -1.25°C (2011) to 1.92°C (also in 2015). The smaller land mass of King County permits integration of PM2.5 into these models. In general, King County PM2.5 levels generally were higher in July than in June, 2001-2015. After adjusting for covariates, a +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality rates among men aged 60-64 [adjusted RR 1.049; 95% CI, 1.017-1.081] but not in those aged 65-69 [adjusted RR 1.014; 95% CI, 0.996-1.032] (Figure 4).

Discussion

CVD mortality rates in both England and Wales and in King County, Washington State declined substantially between 2001 and 2015 (Table 1) in parallel with greater population uptake of effective primary and secondary preventive therapies. Nonetheless, considerable residual risk persists, and in England and Wales, event rates remain >50% higher in adults aged 65-69 than in those aged 60-64 years.

High summer nocturnal SAT may be a source of such risk[6]. Such high summer SAT has been associated with increased cause-specific adult mortality in various high-income regions[3–8,10,13,16,17]. Importantly, in recent years populous mid- to high-latitude regions have experienced a proportionately rise in nocturnal than in daytime summer heat intensity[15]. The present work is one of few investigating potential associations between summer nocturnal SAT and CVD mortality rates. Our finding of significant associations, in men aged 60-64 residing in England and Wales or in King County, Washington State, US, between +1°C summer nocturnal SAT anomalies and summer CVD mortality rates, support this concept.

An association between summer nocturnal SAT and CVD mortality is biologically plausible hypothesis. The incidence and severity of CVD events can be exacerbated by temporal dys-synchrony between cardiovascular circadian clock gene rhythms and exogenous or endogenous homeostatic stresses[28]. One such stress is warmer nocturnal SAT, which also amplifies self-reported sleep-deprivation, itself a risk factor for adult heart disease mortality[20]. Waking itself, whether concordant with normal cardiovascular circadian rhythms or due to interrupted sleep, triggers increases in heart rate, vascular resistance, and blood pressure and predisposes to thrombosis[29].

No significant association was detected in English and Welsh women, but their event rates were <50% of males of comparable age (Table 1). Thus, there may have been insufficient statistical power to appreciate a qualitatively similar association in women, if present. On the other hand, their generally larger sweat gland volume[30] predisposes men exposed to heat to greater insensible fluid loss and intra-vascular volume depletion. Additionally, the authors of a recent systematic review of 36 studies attributed the greater male susceptibility to heat-attributable illnesses to their psychology and behavior[31].

Several studies[4,15–17] report a positive association between summer nocturnal SAT and either all-cause, heat-related, or CVD mortality. In one focusing on London, UK, nighttime temperatures had a more potent influence than daytime exposure on all-cause mortality, ischemic heart disease events, and stroke, particularly in those ≤64 years of age; sex-specific risk was not reported[16]. Other European studies also noted significant positive relationships between average/diurnal SAT and all-cause/CVD mortality in men <65 years or in working-age or middle-aged men[10–12]. An Australian group documented a significant association between ambient temperature in Queensland and the relative risk of CVD hospitalization over a comparable time period (1995-2016); risk was greater in men than in women and in adults <70 years of age when compared with those 70 years and older[32].

The non-significant trends observed for the older men in the present analysis and in these previous reports may reflect resilient survivor bias or signal the exponential accretion of coronary and peripheral vascular disease with age, resulting in more conventional than anomalous temperature-triggered cardiovascular events. Conversely, younger men may be more susceptible to increased summer nocturnal SAT. It has been noted[32] that endogenous testosterone, which declines with age, is in mice an heat-stress susceptibility factor[33].

Nearly a third of United Kingdom's population resides in southeast England[15]. This region's employment opportunities attract young and middle-aged men[34]. Urban design is also an important parameter, because majority of daytime summer heat is absorbed, then radiates locally at night[15]. Residential air conditioning is less common in both England and Wales and in Seattle, Washington, relative to other high-income mid- to high-latitude nations such as the United States or Canada[14]. If uncomfortable warmth obliges individuals to open their bedroom windows, this action, in turn might increase CVD event risk by exposing sleepers to more intense outside nocturnal heat, atmospheric pollutants[35], and road and aircraft noise[26], which in adult men increases the risk of developing hypertension[16,36]. Nighttime noise-related stress[36] and warmer summer SAT also disrupt sleep, especially among vulnerable populations with lower socioeconomic status[20]. Sleep deprivation, in turn can increased central sympathetic outflow[37], which over time can increase blood pressure and induce insulin resistance[38]. Dry air can exacerbate snoring[39]; in middle-aged men snoring is common, as is obstructive sleep apnea, which can trigger nocturnal CVD events[40].

Although we cannot infer causality from our models, our age- and sex-specific analyses nonetheless represent a novel contribution to the present literature. The principal strengths of this ecological study accrue from the large population sampled, its linkage with rigorous national mortality and meteorological data, and the replication of the principal observation concerning the effect and direction of summer nocturnal SAT on CVD morality among men aged 60-64 years in a geographically distinct region with similar climate. The main limitations are lack of access to 15-year sex- and age-specific granular monthly/weekly data (i.e. district or city level) outcome and exposure data, which might have identified stronger associations between nighttime summer heat and CVD mortality in populous urban regions, where ~90% of citizens are projected to reside within a few decades[15]. The anxieties/mental health of men in their early sixties anticipating retirement and reduced income or benefits may have increased their risk for CVD death, as posited by a British study[13], but this potential was adjusted for, in our models. Lastly, we are not able to adjust for potential confounding factors such as local public health initiatives, or in secular trends in the discovery and implementation of effective primary and secondary CVD risk prevention strategies, cause of death misclassification, or ICD coding error.

Conclusion

Our observation of an association between warm summer nighttime conditions and CVD mortality risk amongst men aged 60-64 year residing in England and Wales was replicated in our analysis of comparable American data from King County, Washington State. The present findings should stimulate similar investigation of exposure and event rates in other populous mid- to high-latitude regions. Considering the growing likelihood of extreme summers in Western United States and United Kingdom[22], our results invite preventive population health initiatives and novel urban policies aimed at reducing future risk of CVD events.

Contributors: HM and JSF contributed to the conception or design of the work. HM and JSF contributed to the acquisition, analysis, or interpretation of data for the work. HM drafted the initial manuscript. JSF critically revised the manuscript. Both authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

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Data availability statement: All data has been provided within the manuscript as weblinks. Further data inquires are available upon reasonable request.

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Table 1. Total summer (June-July) sex- and age-specific cardiovascular disease deaths and its corresponding rates by British and United States region for the years 2001 and 2015.

Region	**Group**	**2001**			**2015**		
		No. Deaths	Population	Rate (per 100,000)	No. Deaths	Population	Rate (per 100,000)
England and Wales	Men						
	60-64	969	1,251,730	77.4	590	1,512,948	39.0
	65-69	1,451	1,104,859	131.3	938	1,560,546	60.1
	Women						
	60-64	403	1,297,331	31.1	234	1,576,695	14.8
	65-69	735	1,194,005	61.6	403	1,652,275	24.4
King County, Washington US	Men						
	60-64	27	29,824	90.5	37	58,227	63.5
	65-69	24	21,944	109.4	17	44,574	38.1

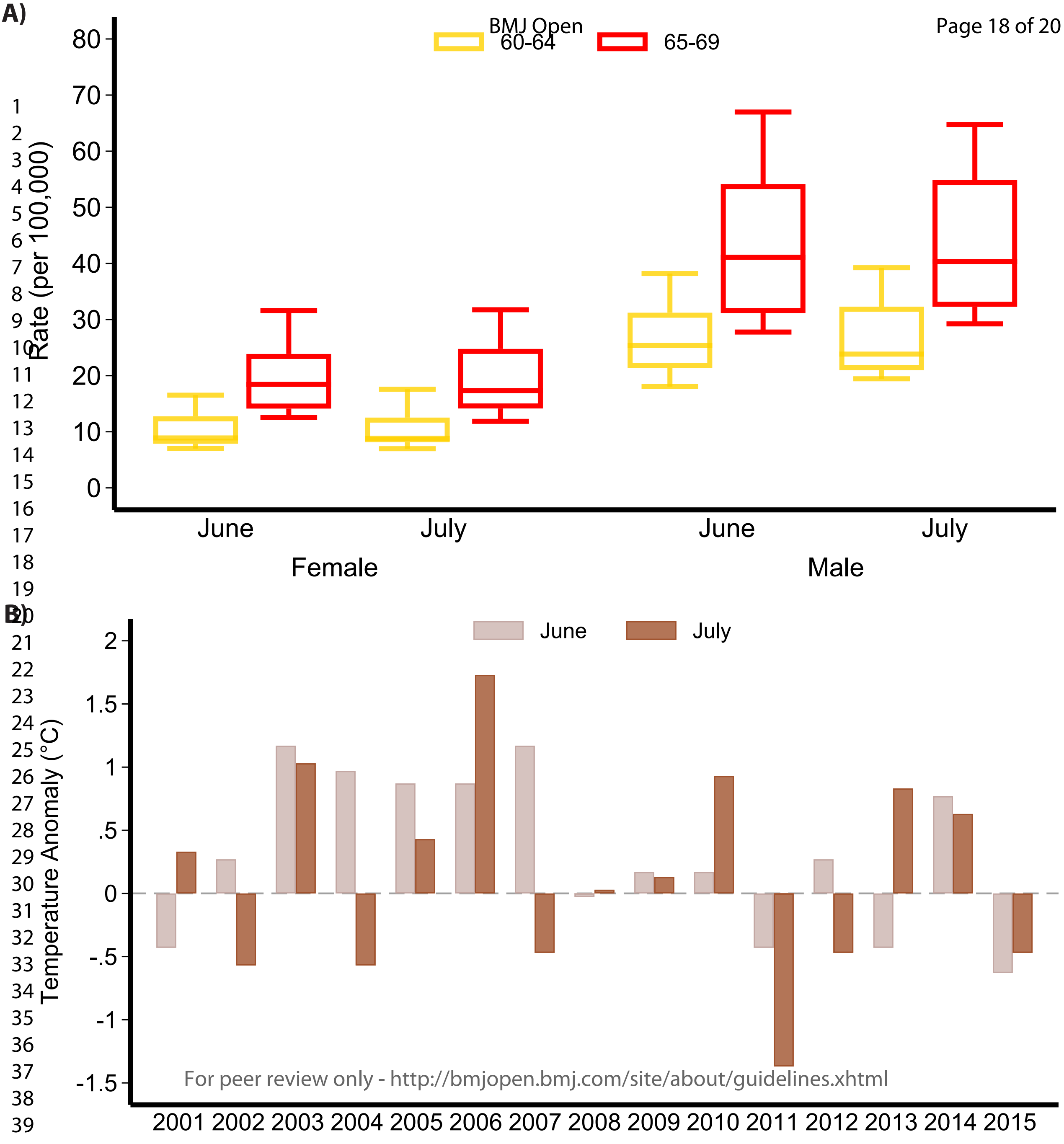
Figure Legends:

Figure 1. **A**) Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in England & Wales from 2001-2015. **B**) Month-specific summer (June-July) nocturnal SAT anomalies (based on deviations from the baseline period of 1981-2010) in England & Wales.

Figure 2. **A**) Forest plot depicting the association between summer CVD mortality rates and nocturnal SAT anomalies for middle- and older-aged men in England & Wales from 2001-2015. **B**) Forest plot depicting the association between summer CVD mortality rates and nocturnal SAT anomalies for middle- and older-aged women in England & Wales from 2001-2015. Covariates includes mental and behavioural mortality rates, trend, and month (reference to June).

Figure 3. **A**) Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in King County, Washington United States from 2001-2015. **B**) Month-specific summer (June-July) nocturnal SAT anomalies (based on deviations from the baseline period of 1981-2010) in King County. **C**) Month-specific summer (June-July) PM2.5 values in King County.

Figure 4. Forest plot depicting the association between summer CVD mortality rates and nocturnal SAT anomalies for middle- and older-aged men in King County, Washington United States from 2001-2015. Covariates includes PM2.5, trend, and month (reference to June).


A)
60-64
65-69
Rate (per 100,000)
0
10
20
30
40
50
60
70
80
June
July
June
July
Female
Male
B)
June
July
Temperature Anomaly (°C)
-1.5
-1
-.5
0
.5
1
1.5
2
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
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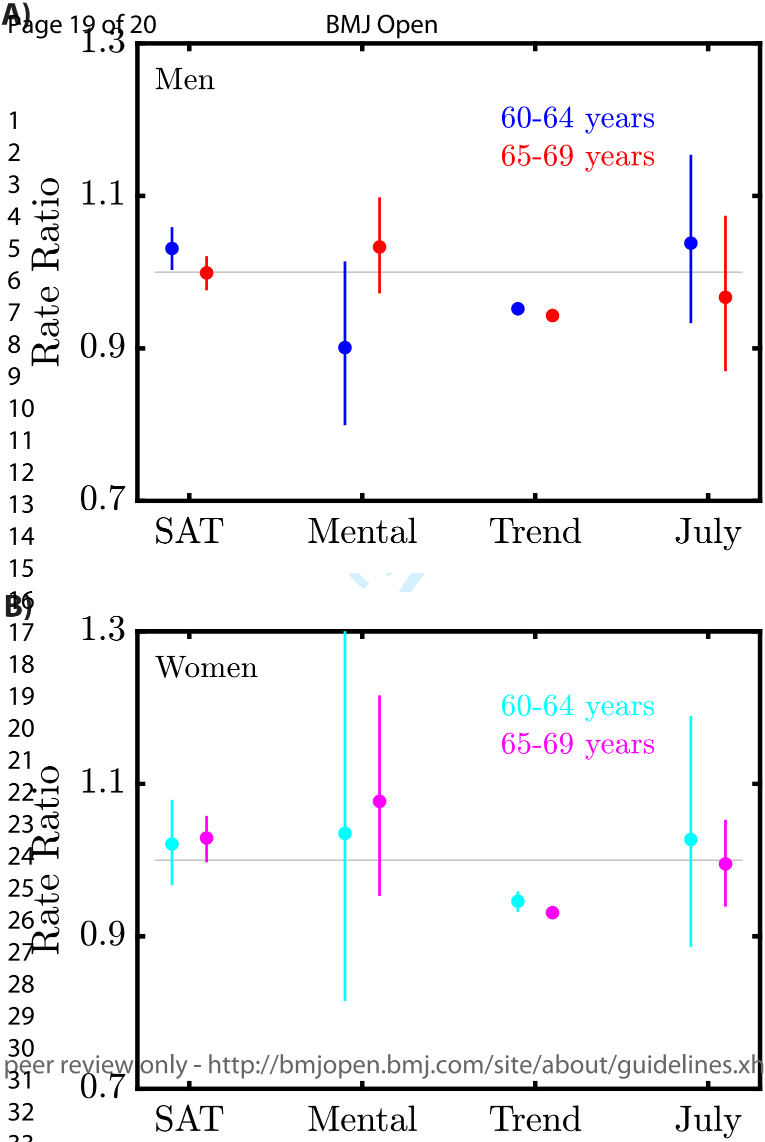
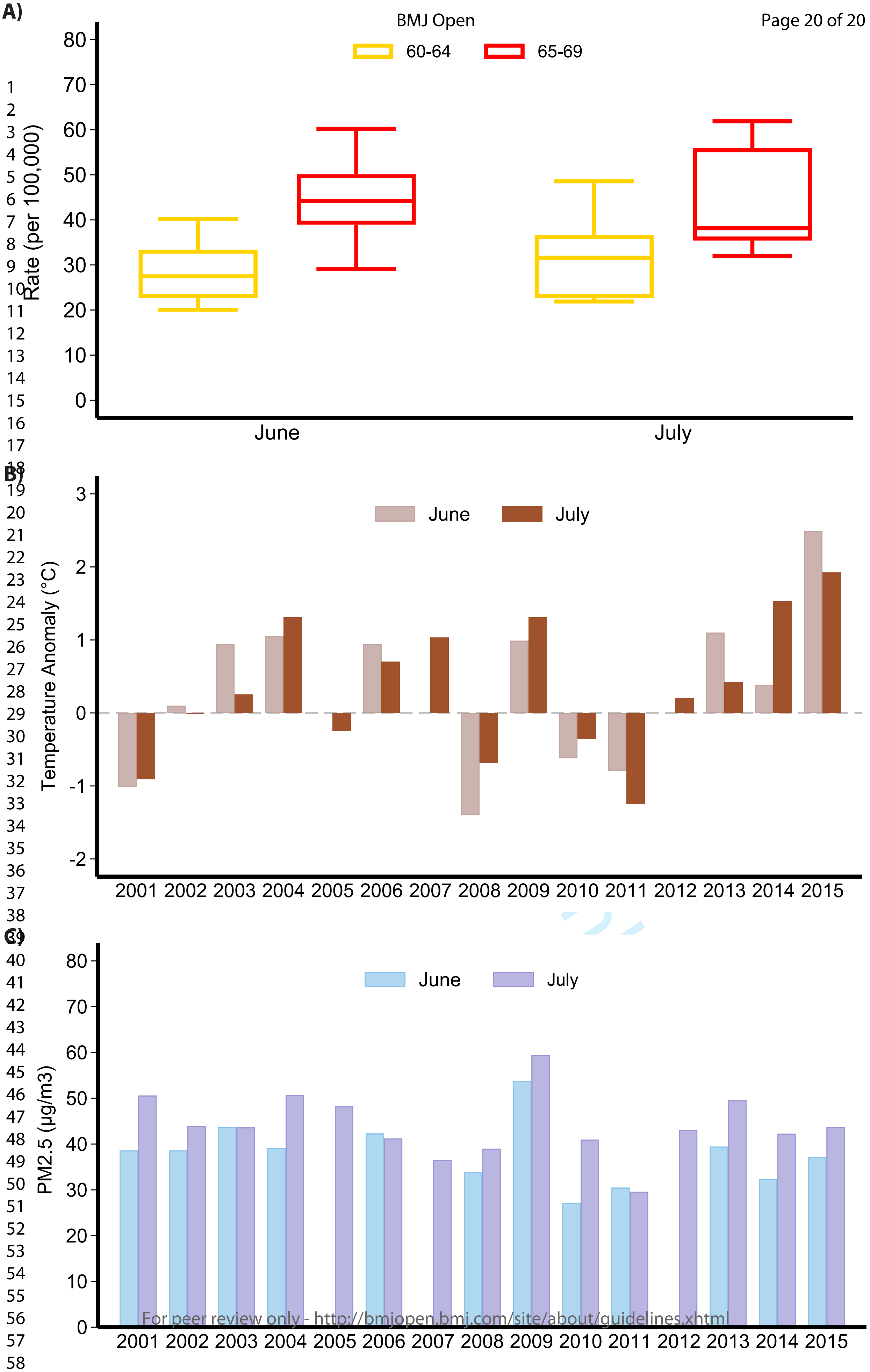
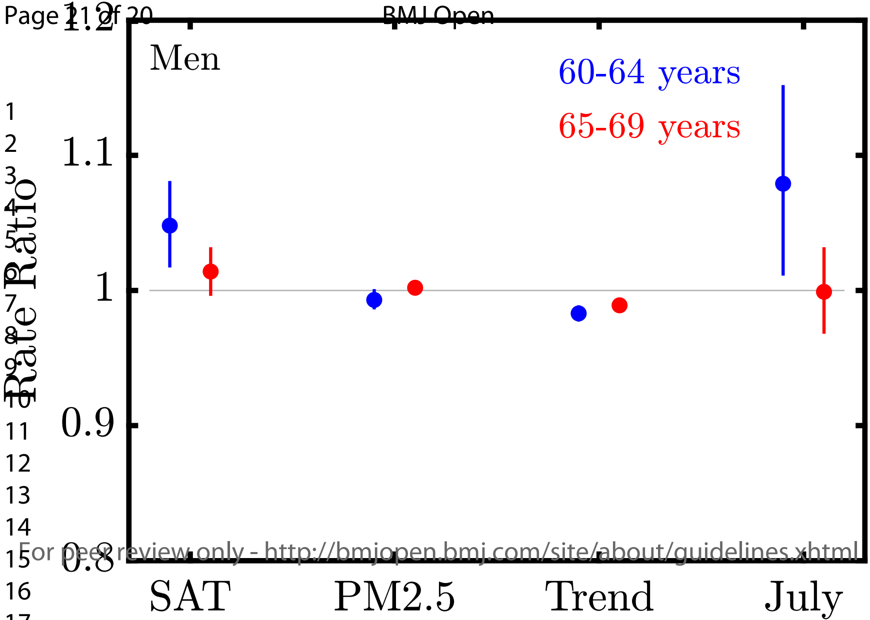
2014
2015


A)
Men
60-64 years
65-69 years
Rate Ratio
1.3
1.1
0.9
0.7
SAT
Mental
Trend
July
B)
Women
60-64 years
65-69 years
Rate Ratio
1.3
1.1
0.9
0.7
SAT
Mental
Trend
July


A)
60-64
65-69
Rate (per 100,000)
80
70
60
50
40
30
20
10
0
June
July
B)
June
July
Temperature Anomaly (°C)
3
2
1
0
-1
-2
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
C)
June
July
PM2.5 (µg/m3)
80
70
60
50
40
30
20
10
0
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015


Men
60-64 years
65-69 years
Rate Ratio
1.2
1.1
1
0.9
0.8
SAT
PM2.5
Trend
July

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Warmer summer nocturnal surface air temperatures and cardiovascular disease death risk: a population-based study

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Warmer summer nocturnal surface air temperatures and cardiovascular disease death risk: a population-based study

Haris Majeed[1]* & John S Floras[1,2]

[1] Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada

[2] University Health Network and Sinai Health Division of Cardiology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

*Corresponding Author:
Haris Majeed, HBSc, MSc
University of Toronto
Toronto, ON
Canada M5S 1A8
Email: haris.majeed@utoronto.ca
Phone: +1 (416) 946-8286

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Abstract

Background/Objective: In recent summers, some populous mid- to high-latitude regions have experienced greater heat intensity, more at night than by day. Such warming has been associated with increased cause-specific adult mortality. Sex- and age-specific associations between summer nocturnal surface air temperatures (SAT) and cardiovascular disease (CVD) deaths have yet to be established.

Methods: A monthly time series analysis (June-July, 2001-2015) was performed on sex-specific CVD deaths in England and Wales of adults aged 60-64 and 65-69 years. Using negative binomial regression with auto-correlative residuals, associations between summer (June-July) nocturnal SAT anomalies (primary exposure) and CVD death rates (outcome) were computed, controlling for key covariates. To explore external validity, similar associations with respect to CVD death in King County, Washington, US, also were calculated, but only for men aged 60-64 and 65-69 years. Results are reported as incidence rate ratios (RR).

Results: From 2001-2015, within these specific cohorts, 39,912 CVD deaths (68.9% men) were recorded in England and Wales and 488 deaths in King County. In England and Wales, after controlling for covariates, a 1°C rise in anomalous summer nocturnal SAT associated significantly with a 3.1% (95% CI, 0.3-5.9%) increased risk of CVD mortality amongst men aged 60-64, but not older men or either women age-groups. In King County, after controlling for covariates, a 1°C rise associated significantly with a 4.8% (95% CI, 1.7-8.1%) increased risk of CVD mortality amongst those <65 years but not older men.

Conclusion: In two mid-latitude regions, warmer summer nights are accompanied by an increased risk of death from CVD amongst men aged 60-64 years.

Keywords: cardiovascular disease, mortality, nocturnal, surface air temperatures

Strengths and limitations of this study

- Previous population-based studies have shown that summer nighttime ambient temperatures are associated with increased risk for either all-cause, heat-related, or cardiovascular mortality.
- Sex- and age-specific associations between variations in summer nighttime air temperatures and cardiovascular disease mortality have not been reported.
- From 2001-2015, warmer summer nocturnal (but not diurnal) surface air temperatures (SAT) were associated with significantly increased risk of cardiovascular mortality amongst men aged 60-64 in both England and Wales and King County, Washington, United States.
- There was no association, in either group, between summer nocturnal SAT and cardiovascular mortality in English and Welsh women.
- These findings should prompt preventive policy initiatives to mitigate the potential population-level cardiovascular impact of more frequent or extreme future summer nocturnal SAT.

Background

Cardiovascular disease (CVD) is a principal cause of death among adult men and women habiting high-income nations[1]. With warm spells of extreme or sustained elevation in average summer surface air temperatures (SAT) occasioning surges in deaths and hospitalisations[2–5], their potential contribution to cardiovascular events has been a focus of vigorous recent research[6]. Findings thus far, with respect to age and sex, have been inconsistent[6]. Some European studies, focusing principally on daytime recordings, report that extreme summer average and/or diurnal SAT increase the risks of all-cause, heat-related, and CVD mortality to a greater extent in older (≥65 years) women than men[5,7–9]. Other European studies report the opposite, with men more at risk of an acute CVD event during periods of extreme summer SAT[10,11]. Some have also identified a significant effect of summer average/diurnal SAT on CVD mortality amongst men aged <65 years[11–13]. Social determinants, including the low prevalence of residential air-conditioning in Europe, may contribute to such variance[9,14].

In recent summers, some populous mid- to high latitude regions have experienced greater intensification of nocturnal than daytime heat[15], with consequent adverse effects on human health[4,15–17]. Anomalously high death rates in the elderly coincident with the 2003 French heatwave were attributed specifically to elevated nocturnal SAT[18], and more recently, the magnitude and duration of nocturnal thermal excess was linked to several southern European cities' CVD and respiratory mortality rates[17]. Middle- to older-aged populations are generally more vulnerable intra-vascular volume depletion when exposed to heat[19], with consequent hypotension, thrombocytosis, and hyperlipidemia[3,19]. Such maladaptation, often exacerbated by more sedentary behaviour[20] and by disrupted or insufficient sleep[21], may render men more vulnerable than women to CVD events when exposed to anomalously high average summer SAT[3,5,19].

There are few present age- or sex- specific data concerning associations between summer nocturnal SAT and CVD mortality. We posited that summer nocturnal SAT anomalies (defined as deviations from 30-year [1981-2010] baseline averages[22]) associate with increased CVD mortality amongst men and women between the ages of 60 and 69 years. To test this hypothesis, we acquired English and Welsh population-based data encompassing the years 2001-2015. Because heatwaves in the United Kingdom are most frequent and intense during June and July[23], we acquired exposure data specific to these two months. To assess external validity, we secured corresponding information for King County, Washington, United States, a likewise sea-facing region, at parallel latitude to England and Wales, with comparable land-ocean atmospheric properties and similarly low prevalence of residential air conditioning[24]. These two jurisdictions also were selected because of their large populaces, of whom the majority (~90%) resides in urban or semi-urban 'heat-islands', readily accessible statistics, and data affirming that over this time-span both regions witnessed greater increases in nighttime than daytime SAT[15].

Methods

Climatological Exposure Data

Mid- to high-latitude regions, such as England and Wales and the State of Washington experience similar seasonal cycles, in which diurnal and nocturnal SAT are such higher in summer than winter[25]. Guided by previous observations of positive associations between summer nocturnal SAT and mortality[5,16], we ascertained, for June and July, minimum SAT for England and Wales (collectively) and King County, Washington, United States from the Meteorology (Met) Office United Kingdom: https://www.metoffice.gov.uk/research/climate/maps-and-data/uk-and-regional-series and the National Oceanic and Atmospheric Administration (NOAA): https://www.ncdc.noaa.gov/cag/county/time-series , respectively. The Met Office provides the most accurate and reliable providers of this information in the United Kingdom, with a geospatial resolution of 1km × 1km[26].

Minimum SAT was used as a proxy for nocturnal SAT[15]. Since air pollution (i.e. through particulate matter 2.5 [$PM_{2.5}$]) can influence local CVD events[27], we included United States Environmental Protection Agency (EPA): https://www.epa.gov/outdoor-air-quality-data/download-daily-data. $PM_{2.5}$ data averaged for June and July of each year in our models for the smaller region of King County.

Cardiovascular Disease Mortality Data

For England and Wales sex- and age-specific deaths attributed to CVD and mental and behavioural disorders occurring in June and July (in Europe, mental and behavioural disorders are an established strong risk factor for CVD death among adults over 60 years of age[28]) for the years 2001-2015 were extracted from Office for National Statistics (ONS, reference #: 007957) data: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deathsbymonthofoccurrenceaged60andoverbysingleyearofagesexandspecifiedcausesenglandandwales2001to2015 we extracted 2001-2015. CVD death was defined as per the International Classification of Diseases (ICD), tenth revision (ICD-10: I00-I99) criteria, whereas deaths due to ‘mental and behavioural disorders’ were defined as ICD-10: F00-F99. For King County, sex- and age-specific CVD mortality for June and July for the years 2001-2015 were extracted from Centers for Disease Control and Prevention (CDC) WONDER data[24].

Sex-specific analyses were partitioned into two age groups: 60-64 years and 65-69 years. We elected to exclude from analysis younger adults, due to their lower CVD event rates and older adults, since in England the cause of death of individuals ≥75 years of age is likely to be misclassified, due to their higher prevalence of comorbid conditions[29]. Numerators of region-specific CVD deaths were based on the presence of one or more ICD-10 codes listed on each death record in a given month of the year, with denominators established on mid-year annual population estimates for the sum of England plus Wales and similarly for King County. Data were stratified by sex and age group. Monthly summer CVD and mental and behavioural mortality rates were computed by region- sex- and age-specific deaths occurring each month of the year and were reported as the number of men and women deaths per 100,000 persons.

Statistical Analysis

Since atmospheric systems act on long time-scales, our primary exposures (June and July) nocturnal SAT were standardized as monthly anomalies from a reference period[22]. For the purpose of the present analysis, SAT anomalies were defined as deviations from a 30-year (1981-2010) baseline average[22]. For each year of the exposure period (2001-2015), June and July nocturnal SAT anomalies were computed separately for England and Wales and for King County by subtracting these regions’ months’ averages from their respective 1981-2010 average nocturnal SAT.

CVD mortality rates were found to be auto-correlated (i.e. rates in the prior and subsequent years were significantly correlated). Additionally, the outcome variable’s variance was much greater than its mean, leading to over-dispersion of data[22,30]. Moreover, a previous study showed that the incidence of mental health and behavioural distress in England and Wales has both increased over time and been identified as a strong risk factor for associations between diurnal SAT and cause-specific adult mortality[13]. To address these issues in our models, we used negative binomial regression with auto-correlated residuals of order one[22] to assess the association between sex- and age-specific CVD mortality rates to summer nocturnal SAT for England and Wales from 2001-2015, while controlling for each of mental health and behaviour mortality rates, an increase or decrease in CVD mortality rates with respect to the annual calendar year (i.e. trend), and the summer month as our covariates. For King County, we used quasi-Poisson to assess all associations, while controlling for each of $PM_{2.5}$, an increase or decrease in CVD mortality rates with respect to the annual calendar year (i.e. trend), and the summer month as our covariates. Findings are reported as incidence rate ratios (RR) and interpreted as change for one-unit increase of the exposure variable[22,30]. Confidence intervals (CI) were evaluated at 95%, along with Student's two-sided *t*-tests. Microsoft Excel (version 2013), RStudio (version 4.1.1), and STATA (version 15) were used for computation, analyses, and figure composition.

Results

Within the selected cohorts, over the years 2001-2015, there were 39,912 (68.9% men) CVD deaths recorded in England and Wales and 488 male CVD deaths (54.1% in the group aged 65-69 years) in King County. Over this time period, CVD rates declined substantially in both regions annually (Table 1), and notably over the summer months (Supplementary Figure 1).

For England and Wales, CVD mortality rates, categorized by sex, age, and month, are illustrated in Figure 1A. The older (65-69 years) men and women exhibited higher CVD mortality rates than during both summer months. CVD mortality rates were consistently higher amongst men than women. Summer nocturnal SAT anomalies are plotted in Figure 1B. June anomalies ranged from -0.63°C (2015) to 1.17°C (2003- corresponding to the notable western European heatwave). July anomalies ranged from -1.37°C (2011) to 1.73°C (2006).

After adjusting for covariates, associations between exposure (a 1-unit increase in summer nocturnal SAT[30]) and CVD mortality rates, stratified by sex and age appear in Figure 2. As shown in Figure 2A, a +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality rates among men aged 60-64 [adjusted RR 1.031; 95% CI, 1.003-1.059] but not in those aged 65-69 years [adjusted RR 0.999; 95% CI, 0.976-1.021], nor in adult women in either age group (Figure 2B). There were no such associations with anomalous summer diurnal SAT as exposures in men or women of either age group (not shown).

For King County, summer CVD mortality rates were also higher within the older male cohort (Figure 3A). Summer nocturnal SAT anomalies are plotted in Figure 3B and Figure 3C. June SAT anomalies ranged from -1.4°C (2008) to 2.49° (2015, a year when western North America recorded a record number of heatwaves and forest fires attributed to a strong El Niño event[22]). July anomalies ranged from -1.25°C (2011) to 1.92°C (also in 2015). The smaller land mass of King County permits integration of $PM_{2.5}$ into these models. In general, King County $PM_{2.5}$ levels generally were higher in July than in June, 2001-2015. After adjusting for covariates, a +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality rates among men aged 60-64 [adjusted RR 1.049; 95% CI, 1.017-1.081] but not in those aged 65-69 [adjusted RR 1.014; 95% CI, 0.996-1.032] (Figure 4).

Discussion

CVD mortality rates in both England and Wales and in King County, Washington State declined substantially between 2001 and 2015 (Table 1) in parallel with greater population uptake of effective primary and secondary preventive therapies. Nonetheless, considerable residual risk persists, and in England and Wales, event rates remain >50% higher in adults aged 65-69 than in those aged 60-64 years.

High summer nocturnal SAT may be a source of such risk[6]. Such high summer SAT has been associated with increased cause-specific adult mortality in various high-income regions[3–8,10,13,16,18]. Importantly, in recent years populous mid- to high-latitude regions have experienced a proportionately rise in nocturnal than in daytime summer heat intensity[15]. The present work is one of few investigating potential associations between summer nocturnal SAT and CVD mortality rates. Our finding of significant associations, in men aged 60-64 residing in England and Wales or in King County, Washington, United States, between +1°C summer nocturnal SAT anomalies and summer CVD mortality rates, support this concept.

An association between summer nocturnal SAT and CVD mortality is biologically plausible hypothesis. The incidence and severity of CVD events can be exacerbated by temporal dys-synchrony between cardiovascular circadian clock gene rhythms and exogenous or endogenous homeostatic stresses[31]. One such stress is warmer nocturnal SAT, which also amplifies self-reported sleep-deprivation, itself a risk factor for adult heart disease mortality[21]. Waking itself, whether concordant with normal cardiovascular circadian rhythms or due to interrupted sleep, triggers increases in heart rate, vascular resistance, and blood pressure and predisposes to thrombosis[32].

No significant association was detected in English and Welsh women, but their event rates were <50% of males of comparable age (Table 1). Thus, there may have been insufficient statistical power to appreciate a qualitatively similar association in women, if present. On the other hand, their generally larger sweat gland volume[33] predisposes men exposed to heat to greater insensible fluid loss and intra-vascular volume depletion. However, the authors of a recent systematic review of 36 studies attributed the greater male susceptibility to heat-attributable illnesses to their psychology and behavior rather than to any physiological dimorphism[34].

Several studies[4,15–18] report a positive association between summer nocturnal SAT and either all-cause, heat-related, or CVD mortality. In one focusing on London, United Kingdom, nighttime temperatures had a more potent influence than daytime exposure on all-cause mortality, ischemic heart disease events, and stroke, particularly in those ≤64 years of age; sex-specific risk was not reported[16]. A recent investigation of approximately 10 years' data for 11 southern European cities reported associations between the relative risk of cause-specific mortality and the magnitude and duration of nocturnal SAT exceeding 20℃, where four of these cities, yielded a significant association with CVD event rates[17]. However, sex- and age- specific associations were not reported, and our work, in contrast, considered monthly anomalies relative to a 30-year reference period as the thermal exposure of interest.

Other European studies also noted significant positive relationships between average/diurnal SAT and all-cause/CVD mortality in men <65 years or in working-age or middle-aged men[10–12]. An Australian group documented a significant association between ambient temperature in Queensland and the relative risk of CVD hospitalization over a comparable time period (1995-2016); risk was greater in men than in women and in adults <70 years of age when compared with those 70 years and older[35].

The non-significant trends observed for the older men in the present analysis and in these previous reports may reflect resilient survivor bias or signal the exponential accretion of coronary and peripheral vascular disease with age, resulting in more conventional than anomalous temperature-triggered cardiovascular events. Conversely, younger men may be more susceptible to increased summer nocturnal SAT. It has been noted[35] that endogenous testosterone, which declines with age, is in mice an heat-stress susceptibility factor[36].

Nearly a third of United Kingdom's population resides in southeast England[15]. This region's employment opportunities attract young and middle-aged men[37]. Urban design is also an important parameter, because majority of daytime summer heat is absorbed, then radiates locally at night[15]. Residential air conditioning is less common in both England and Wales and in Seattle, Washington, relative to other high-income mid- to high-latitude nations such as the United States or Canada[14]. If uncomfortable warmth obliges individuals to open their bedroom windows, this action, in turn might increase CVD event risk by exposing sleepers to more intense outside nocturnal heat, atmospheric pollutants[27], and road and aircraft noise[29], which in adult men increases the risk of developing hypertension[16,38]. Nighttime noise-related stress[38] and warmer summer SAT also disrupt sleep, especially among vulnerable populations with lower socioeconomic status[21]. Sleep deprivation, in turn can increased central sympathetic outflow[39], which over time can increase blood pressure and induce insulin resistance[40]. Dry air can exacerbate snoring[41]; in middle-aged men snoring is common, as is obstructive sleep apnea, which can trigger nocturnal CVD events[42].

Although we cannot infer causality from our models, our age- and sex-specific analyses nonetheless represent a novel contribution to the present literature. The principal strengths of this ecological study accrue from the large population sampled and its linkage with rigorous national mortality and meteorological data. The principal limitations are lack of access to 15-year sex- and age-specific granular monthly/weekly data (i.e. district or city level) outcome and exposure data. The latter might have identified stronger associations between nighttime summer heat and CVD mortality in populous urban regions, where ~90% of citizens are projected to reside within a few decades[15]. Nonetheless, in our supplementary analysis of King County, the effect and direction of summer nocturnal SAT on CVD morality among men aged 60-64 years were consistent with our primary analysis. The majority of adult men in England and Washington State retire at age 65. It is conceivable that the anxieties/mental health of men in their early sixties anticipating retirement and reduced income or benefits added to their risk for CVD death, as posited by a British study[13], but this potential confounder was adjusted for, in our models. Lastly, we are not able to adjust for potential confounding factors such as local public health initiatives, or in secular trends in the discovery and implementation of effective primary and secondary CVD risk prevention strategies, cause of death misclassification, or ICD coding error.

Conclusion

Our observation of an association between warm summer nighttime conditions and CVD mortality risk amongst men aged 60-64 year residing in England and Wales was replicated in our analysis of comparable American data from King County, Washington State. The present findings should stimulate similar investigation of exposure and event rates in other populous mid- to high-latitude regions. Considering the growing likelihood of extreme summers in Western United States and United Kingdom[23], our results invite preventive population health initiatives and novel urban policies aimed at reducing future risk of CVD events.

Author contributions

HM and JSF contributed to the conception or design of the work. HM and JSF contributed to the acquisition, analysis, or interpretation of data for the work. HM drafted the initial manuscript. JSF critically revised the manuscript. Both authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data sharing statement

All data related to this study has been provided as weblinks in the ‘Methods’ section.

Ethics approval statement

No ethics approval was needed to conduct this study.

Patient and public involvement

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of this research study.

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Table 1. Total summer (June-July) sex- and age-specific cardiovascular disease deaths and its corresponding rates by British and United States region for the years 2001 and 2015.

Region	Group	2001			2015		
		No. Deaths	Population	Rate (per 100,000)	No. Deaths	Population	Rate (per 100,000)
England and Wales	Men						
	60-64	969	1,251,730	77.4	590	1,512,948	39.0
	65-69	1,451	1,104,859	131.3	938	1,560,546	60.1
	Women						
	60-64	403	1,297,331	31.1	234	1,576,695	14.8
	65-69	735	1,194,005	61.6	403	1,652,275	24.4
King County, Washington United States	Men						
	60-64	27	29,824	90.5	37	58,227	63.5
	65-69	24	21,944	109.4	17	44,574	38.1

Figure Legends:

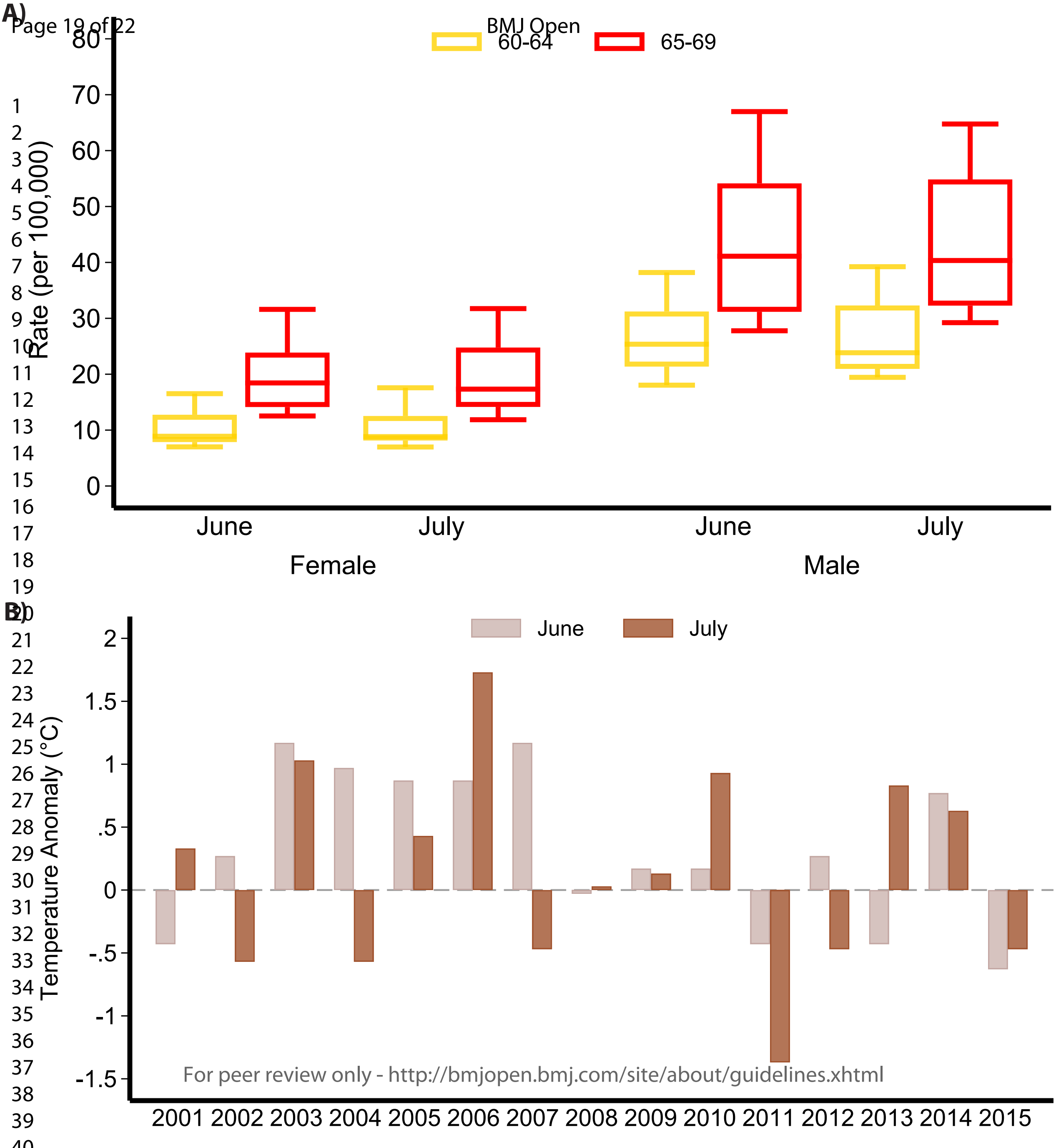
Figure 1: **A**) Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in England & Wales from 2001-2015. **B**) Month-specific summer (June-July) nocturnal SAT anomalies (based on deviations from the baseline period of 1981-2010) in England & Wales.

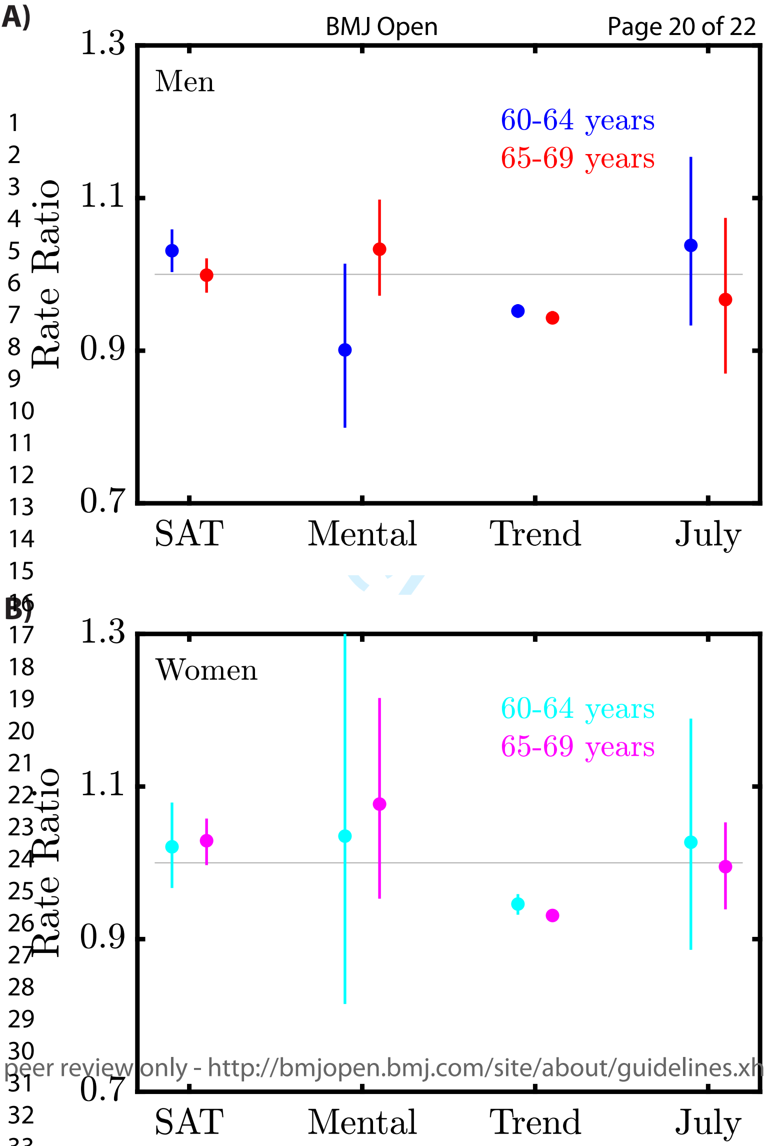
Figure 2: **A**) Plot depicting the association between summer CVD mortality rates and night SAT anomalies for middle- and older-aged men in England & Wales from 2001-2015. **B**) Plot depicting the association between summer CVD mortality rates and night SAT anomalies for middle- and older-aged women in England & Wales from 2001-2015. Covariates includes mental and behavioural mortality rates, trend, and month (reference to June).

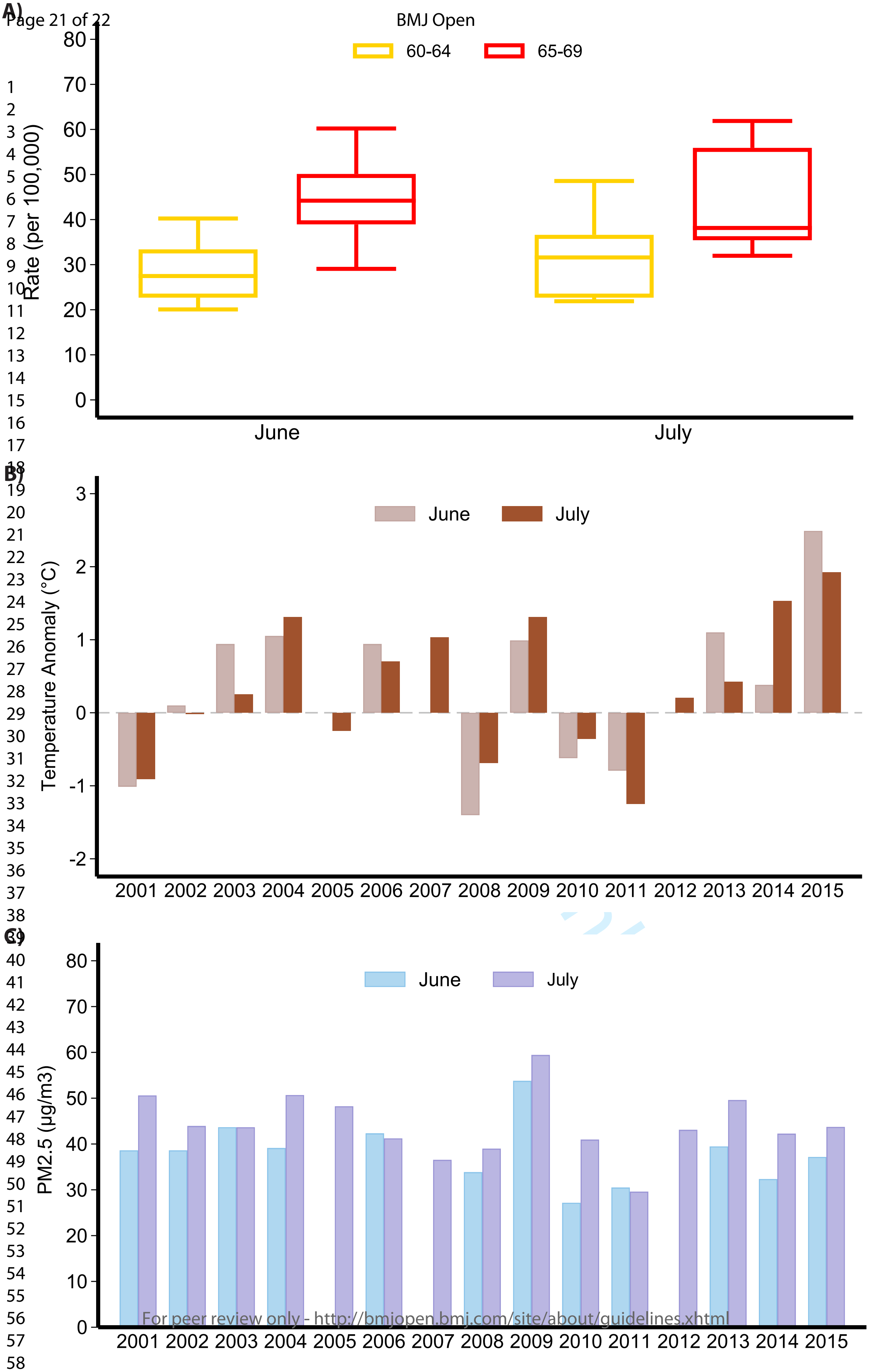
Figure 3: **A**) Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in King County, Washington, United States from 2001-2015. **B**) Month-specific summer (June-July) night SAT anomalies (based on deviations from the baseline period of 1981-2010) in King County. **C**) Month-specific summer (June-July) $PM_{2.5}$ values in King County.

Figure 4: Plot depicting the association between summer CVD mortality rates and nocturnal SAT anomalies for middle- and older-aged men in King County, Washington, United States from 2001-2015. Covariates includes $PM_{2.5}$, trend, and month (reference to June).

Supplementary Figure 1: Monthly summer (6=June, 7=July) cardiovascular mortality trends by age-groups among (A) men and (B) women from 2001-2015 in England and Wales.


A)
60-64
65-69
Rate (per 100,000)
0
10
20
30
40
50
60
70
80
June
July
June
July
Female
Male
B)
June
July
Temperature Anomaly (°C)
2
1.5
1
.5
0
-.5
-1
-1.5
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015


A)
1.3
1.1
0.9
0.7
Rate Ratio
Men
60-64 years
65-69 years
SAT
Mental
Trend
July
B)
1.3
1.1
0.9
0.7
Rate Ratio
Women
60-64 years
65-69 years
SAT
Mental
Trend
July


A)
60-64
65-69
Rate (per 100,000)
80
70
60
50
40
30
20
10
0
June
July
B)
June
July
Temperature Anomaly (°C)
3
2
1
0
-1
-2
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
C)
June
July
PM2.5 (μg/m3)
80
70
60
50
40
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0
2001
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2003
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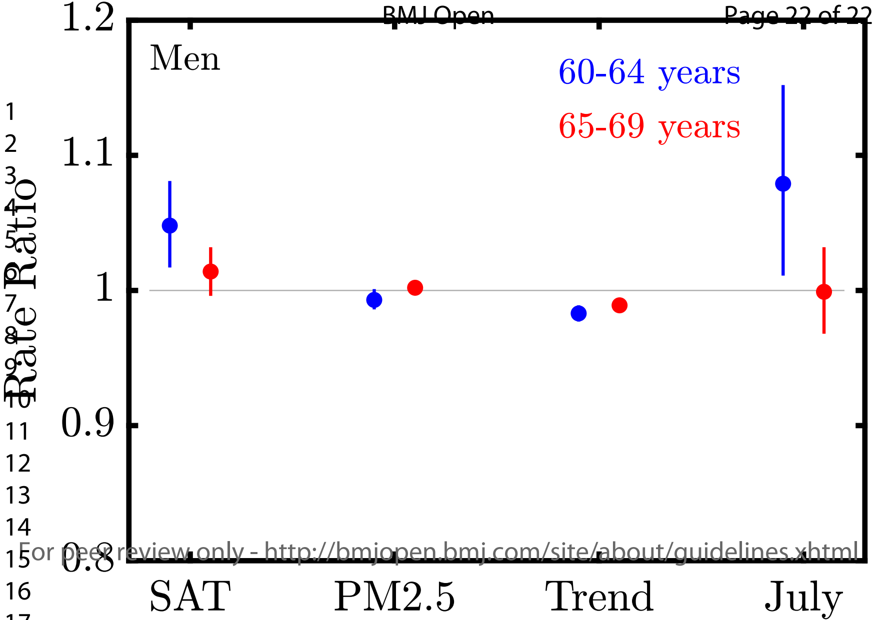
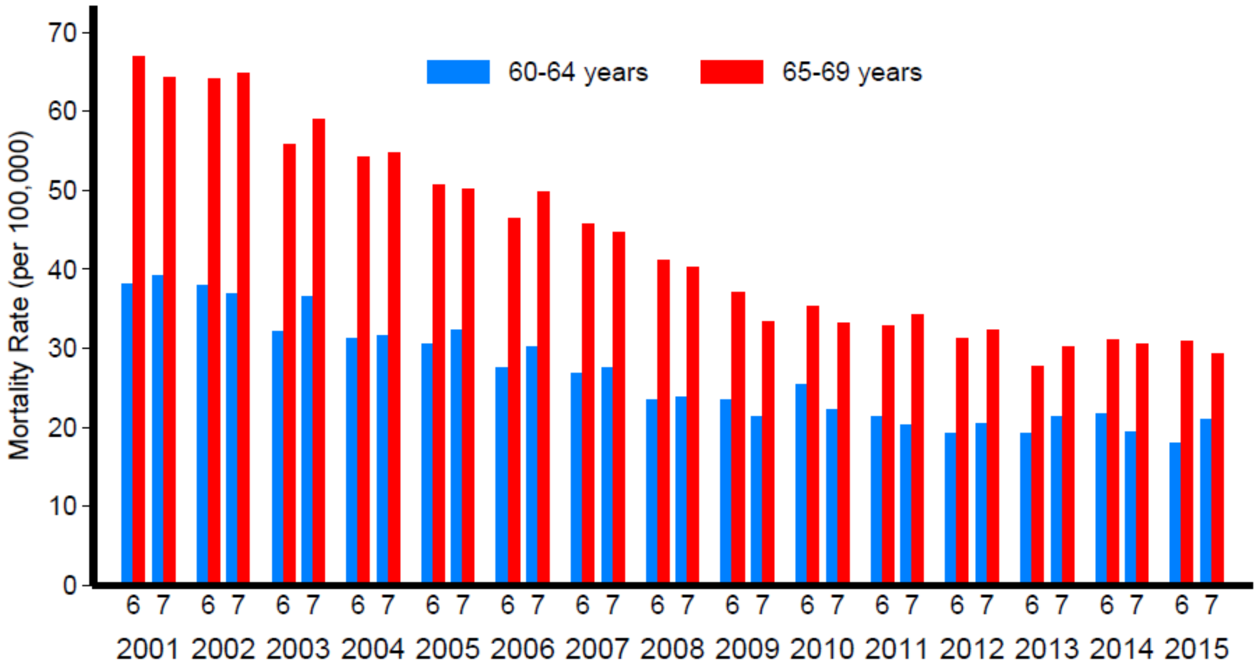
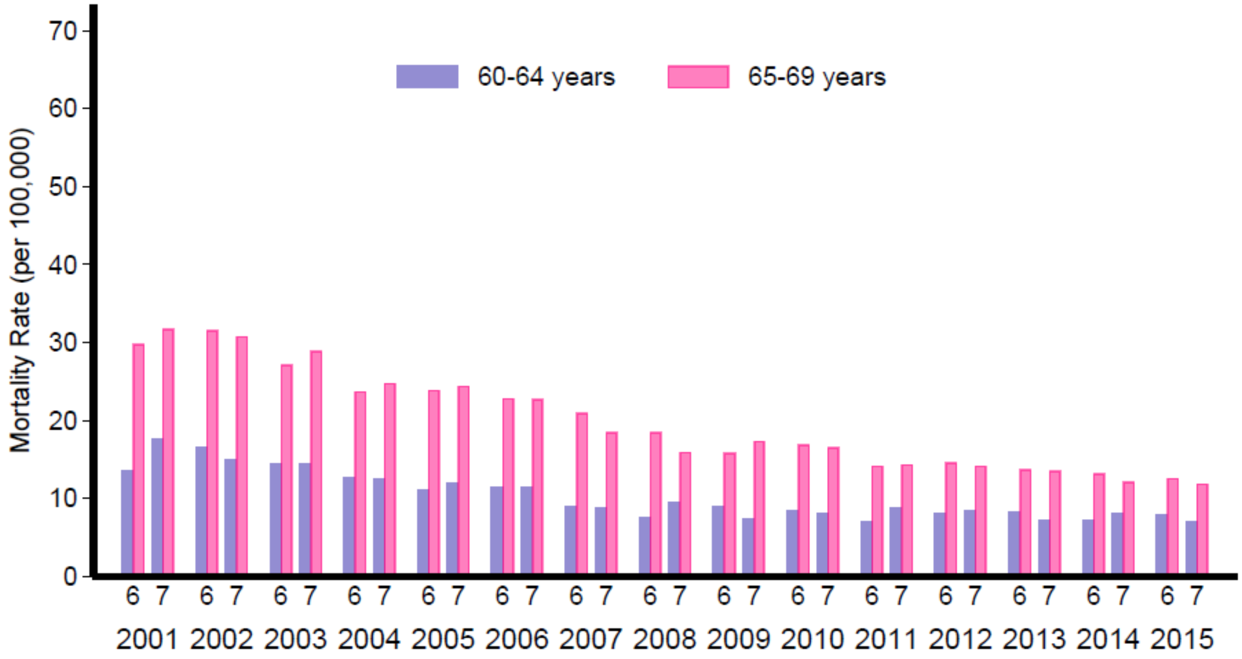
2011
2012
2013
2014
2015


Men
60-64 years
65-69 years
Rate Ratio
1.2
1.1
1
0.9
0.8
SAT
PM2.5
Trend
July

A) Men



B) Women



Supplementary Figure 1: Monthly summer (6=June, 7=July) cardiovascular mortality trends by age-groups among (A) men and (B) women from 2001-2015 in England and Wales.

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Warmer summer nocturnal surface air temperatures and cardiovascular disease death risk: a population-based study

Haris Majeed[1]* & John S Floras[1,2]

[1] Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada

[2] University Health Network and Sinai Health Division of Cardiology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada

*Corresponding Author:
Haris Majeed, HBSc, MSc
University of Toronto
Toronto, ON
Canada M5S 1A8
Email: haris.majeed@utoronto.ca
Phone: +1 (416) 946-8286

Word Count: 3116

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Abstract

Background/Objective: In recent summers, some populous mid- to high-latitude regions have experienced greater heat intensity, more at night than by day. Such warming has been associated with increased cause-specific adult mortality. Sex- and age-specific associations between summer nocturnal surface air temperatures (SAT) and cardiovascular disease (CVD) deaths have yet to be established.

Methods: A monthly time series analysis (June-July, 2001-2015) was performed on sex-specific CVD deaths in England and Wales of adults aged 60-64 and 65-69 years. Using negative binomial regression with auto-correlative residuals, associations between summer (June-July) nocturnal SAT anomalies (primary exposure) and CVD death rates (outcome) were computed, controlling for key covariates. To explore external validity, similar associations with respect to CVD death in King County, Washington, US, also were calculated, but only for men aged 60-64 and 65-69 years. Results are reported as incidence rate ratios (RR).

Results: From 2001-2015, within these specific cohorts, 39,912 CVD deaths (68.9% men) were recorded in England and Wales and 488 deaths in King County. In England and Wales, after controlling for covariates, a 1°C rise in anomalous summer nocturnal SAT associated significantly with a 3.1% (95% CI, 0.3-5.9%) increased risk of CVD mortality amongst men aged 60-64, but not older men or either women age-groups. In King County, after controlling for covariates, a 1°C rise associated significantly with a 4.8% (95% CI, 1.7-8.1%) increased risk of CVD mortality amongst those <65 years but not older men.

Conclusion: In two mid-latitude regions, warmer summer nights are accompanied by an increased risk of death from CVD amongst men aged 60-64 years.

Keywords: cardiovascular disease, mortality, nocturnal, surface air temperatures

Strengths and limitations of this study

- Previous population-based studies have shown that summer nighttime ambient temperatures are associated with increased risk for either all-cause, heat-related, or cardiovascular mortality.
- Sex- and age-specific associations between variations in summer nighttime air temperatures and cardiovascular disease mortality have not been reported.
- From 2001-2015, warmer summer nocturnal (but not diurnal) surface air temperatures (SAT) were associated with significantly increased risk of cardiovascular mortality amongst men aged 60-64 in both England and Wales and King County, Washington, United States.
- There was no association, in either group, between summer nocturnal SAT and cardiovascular mortality in English and Welsh women.
- These findings should prompt preventive policy initiatives to mitigate the potential population-level cardiovascular impact of more frequent or extreme future summer nocturnal SAT.

Background

Cardiovascular disease (CVD) is a principal cause of death among adult men and women habiting high-income nations[1]. With warm spells of extreme or sustained elevation in average summer surface air temperatures (SAT) occasioning surges in deaths and hospitalisations[2–5], their potential contribution to cardiovascular events has been a focus of vigorous recent research[6]. Findings thus far, with respect to age and sex, have been inconsistent[6]. Some European studies, focusing principally on daytime recordings, report that extreme summer average and/or diurnal SAT increase the risks of all-cause, heat-related, and CVD mortality to a greater extent in older (≥65 years) women than men[5,7–9]. Other European studies report the opposite, with men more at risk of an acute CVD event during periods of extreme summer SAT[10,11]. Some have also identified a significant effect of summer average/diurnal SAT on CVD mortality amongst men aged <65 years[11–13]. Social determinants, including the low prevalence of residential air-conditioning in Europe, may contribute to such variance[9,14].

In recent summers, some populous mid- to high latitude regions have experienced greater intensification of nocturnal than daytime heat[15], with consequent adverse effects on human health[4,15–17]. Anomalously high death rates in the elderly coincident with the 2003 French heatwave were attributed specifically to elevated nocturnal SAT[18], and more recently, the magnitude and duration of nocturnal thermal excess was linked to several southern European cities' CVD and respiratory mortality rates[17]. Middle- to older-aged populations are generally more vulnerable intra-vascular volume depletion when exposed to heat[19], with consequent hypotension, thrombocytosis, and hyperlipidemia[3,19]. Such maladaptation, often exacerbated by more sedentary behaviour[20] and by disrupted or insufficient sleep[21], may render men more vulnerable than women to CVD events when exposed to anomalously high average summer SAT[3,5,19].

There are few present age- or sex- specific data concerning associations between summer nocturnal SAT and CVD mortality. We posited that summer nocturnal SAT anomalies (defined as deviations from 30-year [1981-2010] baseline averages[22]) associate with increased CVD mortality amongst men and women between the ages of 60 and 69 years. To test this hypothesis, we acquired English and Welsh population-based data encompassing the years 2001-2015. Because heatwaves in the United Kingdom are most frequent and intense during June and July[23], we acquired exposure data specific to these two months. To assess external validity, we secured corresponding information for King County, Washington, United States, a likewise sea-facing region, at parallel latitude to England and Wales, with comparable land-ocean atmospheric properties and similarly low prevalence of residential air conditioning[24]. These two jurisdictions also were selected because of their large populaces, of whom the majority (~90%) resides in urban or semi-urban 'heat-islands', readily accessible statistics, and data affirming that over this time-span both regions witnessed greater increases in nighttime than daytime SAT[15].

Methods

Climatological Exposure Data

Mid- to high-latitude regions, such as England and Wales and the State of Washington experience similar seasonal cycles, in which diurnal and nocturnal SAT are such higher in summer than winter[25]. Guided by previous observations of positive associations between summer nocturnal SAT and mortality[5,16], we ascertained, for June and July, minimum SAT for England and Wales (collectively) and King County, Washington, United States from the Meteorology (Met) Office United Kingdom: https://www.metoffice.gov.uk/research/climate/maps-and-data/uk-and-regional-series and the National Oceanic and Atmospheric Administration (NOAA): https://www.ncdc.noaa.gov/cag/county/time-series , respectively. The Met Office provides the most accurate and reliable providers of this information in the United Kingdom, with a geospatial resolution of 1km × 1km[26].

Minimum SAT was used as a proxy for nocturnal SAT[15]. Since air pollution (i.e. through particulate matter 2.5 [$PM_{2.5}$]) can influence local CVD events[27], we included United States Environmental Protection Agency (EPA): https://www.epa.gov/outdoor-air-quality-data/download-daily-data. $PM_{2.5}$ data averaged for June and July of each year in our models for the smaller region of King County.

Cardiovascular Disease Mortality Data

In this population-based study, England and Wales sex- and age-specific deaths attributed to CVD and mental and behavioural disorders occurring in June and July (in Europe, mental and behavioural disorders are an established strong risk factor for CVD death among adults over 60 years of age[28]) for the years 2001-2015 were extracted from Office for National Statistics (ONS, reference #: 007957) data: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deathsbymonthofoccurrenceaged60andoverbysingleyearofagesexandspecifiedcausesenglandandwales2001to2015 we extracted 2001-2015. CVD death was defined as per the International Classification of Diseases (ICD), tenth revision (ICD-10: I00-I99) criteria, whereas deaths due to ‘mental and behavioural disorders’ were defined as ICD-10: F00-F99. For King County, sex- and age-specific CVD mortality for June and July for the years 2001-2015 were extracted from Centers for Disease Control and Prevention (CDC) WONDER data[24].

Sex-specific analyses were partitioned into two age groups: 60-64 years and 65-69 years. We elected to exclude from analysis younger adults, due to their lower CVD event rates and older adults, since in England the cause of death of individuals ≥75 years of age is likely to be misclassified, due to their higher prevalence of comorbid conditions[29]. Numerators of region-specific CVD deaths were based on the presence of one or more ICD-10 codes listed on each death record in a given month of the year, with denominators established on mid-year annual population estimates for the sum of England plus Wales and similarly for King County. Data were stratified by sex and age group. Monthly summer CVD and mental and behavioural mortality rates were computed by region- sex- and age-specific deaths occurring each month of the year and were reported as the number of men and women deaths per 100,000 persons.

Statistical Analysis

Since atmospheric systems act on long time-scales, our primary exposures (June and July) nocturnal SAT were standardized as monthly anomalies from a reference period[22]. For the purpose of the present analysis, SAT anomalies were defined as deviations from a 30-year (1981-2010) baseline average[22]. For each year of the exposure period (2001-2015), June and July nocturnal SAT anomalies were computed separately for England and Wales and for King County by subtracting these regions’ months’ averages from their respective 1981-2010 average nocturnal SAT.

CVD mortality rates were found to be auto-correlated (i.e. rates in the prior and subsequent years were significantly correlated). Additionally, the outcome variable’s variance was much greater than its mean, leading to over-dispersion of data[22,30]. Moreover, a previous study showed that the incidence of mental health and behavioural distress in England and Wales has both increased over time and been identified as a strong risk factor for associations between diurnal SAT and cause-specific adult mortality[13]. To address these issues in our models, we used negative binomial regression with auto-correlated residuals of order one[22] to assess the association between sex- and age-specific CVD mortality rates to summer nocturnal SAT for England and Wales from 2001-2015, while controlling for each of mental health and behaviour mortality rates, an increase or decrease in CVD mortality rates with respect to the annual calendar year (i.e. trend), and the summer month as our covariates. For King County, we used quasi-Poisson to assess all associations, while controlling for each of $PM_{2.5}$, an increase or decrease in CVD mortality rates with respect to the annual calendar year (i.e. trend), and the summer month as our covariates. Findings are reported as incidence rate ratios (RR) and interpreted as change for one-unit increase of the exposure variable[22,30]. Confidence intervals (CI) were evaluated at 95%, along with Student's two-sided *t*-tests. Microsoft Excel (version 2013), RStudio (version 4.1.1), and STATA (version 15) were used for computation, analyses, and figure composition.

Results

Within the selected cohorts, over the years 2001-2015, there were 39,912 (68.9% men) CVD deaths recorded in England and Wales and 488 male CVD deaths (54.1% in the group aged 65-69 years) in King County. Over this time period, CVD rates declined substantially in both regions annually (Table 1), and notably over the summer months (Supplementary Figure 1).

For England and Wales, CVD mortality rates, categorized by sex, age, and month, are illustrated in Figure 1A. The older (65-69 years) men and women exhibited higher CVD mortality rates than during both summer months. CVD mortality rates were consistently higher amongst men than women. Summer nocturnal SAT anomalies are plotted in Figure 1B. June anomalies ranged from -0.63°C (2015) to 1.17°C (2003- corresponding to the notable western European heatwave). July anomalies ranged from -1.37°C (2011) to 1.73°C (2006).

After adjusting for covariates, associations between exposure (a 1-unit increase in summer nocturnal SAT[30]) and CVD mortality rates, stratified by sex and age appear in Figure 2. As shown in Figure 2A, a +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality rates among men aged 60-64 [adjusted RR 1.031; 95% CI, 1.003-1.059] but not in those aged 65-69 years [adjusted RR 0.999; 95% CI, 0.976-1.021], nor in adult women in either age group (Figure 2B). There were no such associations with anomalous summer diurnal SAT as exposures in men or women of either age group (not shown).

For King County, summer CVD mortality rates were also higher within the older male cohort (Figure 3A). Summer nocturnal SAT anomalies are plotted in Figure 3B and Figure 3C. June SAT anomalies ranged from -1.4°C (2008) to 2.49° (2015, a year when western North America recorded a record number of heatwaves and forest fires attributed to a strong El Niño event[22]). July anomalies ranged from -1.25°C (2011) to 1.92°C (also in 2015). The smaller land mass of King County permits integration of $PM_{2.5}$ into these models. In general, King County $PM_{2.5}$ levels generally were higher in July than in June, 2001-2015. After adjusting for covariates, a +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality rates among men aged 60-64 [adjusted RR 1.049; 95% CI, 1.017-1.081] but not in those aged 65-69 [adjusted RR 1.014; 95% CI, 0.996-1.032] (Figure 4).

Discussion

CVD mortality rates in both England and Wales and in King County, Washington State declined substantially between 2001 and 2015 (Table 1) in parallel with greater population uptake of effective primary and secondary preventive therapies. Nonetheless, considerable residual risk persists, and in England and Wales, event rates remain >50% higher in adults aged 65-69 than in those aged 60-64 years.

High summer nocturnal SAT may be a source of such risk[6]. Such high summer SAT has been associated with increased cause-specific adult mortality in various high-income regions[3–8,10,13,16,18]. Importantly, in recent years populous mid- to high-latitude regions have experienced a proportionately rise in nocturnal than in daytime summer heat intensity[15]. The present work is one of few investigating potential associations between summer nocturnal SAT and CVD mortality rates. Our finding of significant associations, in men aged 60-64 residing in England and Wales or in King County, Washington, United States, between +1°C summer nocturnal SAT anomalies and summer CVD mortality rates, support this concept.

An association between summer nocturnal SAT and CVD mortality is biologically plausible hypothesis. The incidence and severity of CVD events can be exacerbated by temporal dys-synchrony between cardiovascular circadian clock gene rhythms and exogenous or endogenous homeostatic stresses[31]. One such stress is warmer nocturnal SAT, which also amplifies self-reported sleep-deprivation, itself a risk factor for adult heart disease mortality[21]. Waking itself, whether concordant with normal cardiovascular circadian rhythms or due to interrupted sleep, triggers increases in heart rate, vascular resistance, and blood pressure and predisposes to thrombosis[32].

No significant association was detected in English and Welsh women, but their event rates were <50% of males of comparable age (Table 1). Thus, there may have been insufficient statistical power to appreciate a qualitatively similar association in women, if present. On the other hand, their generally larger sweat gland volume[33] predisposes men exposed to heat to greater insensible fluid loss and intra-vascular volume depletion. However, the authors of a recent systematic review of 36 studies attributed the greater male susceptibility to heat-attributable illnesses to their psychology and behavior rather than to any physiological dimorphism[34].

Several studies[4,15–18] report a positive association between summer nocturnal SAT and either all-cause, heat-related, or CVD mortality. In one focusing on London, United Kingdom, nighttime temperatures had a more potent influence than daytime exposure on all-cause mortality, ischemic heart disease events, and stroke, particularly in those ≤64 years of age; sex-specific risk was not reported[16]. A recent investigation of approximately 10 years' data for 11 southern European cities reported associations between the relative risk of cause-specific mortality and the magnitude and duration of nocturnal SAT exceeding 20°C[17]. Significant associations with CVD event rates were identified for Madrid, Lisbon, Porto, and Rome[17]. However, sex- and age- specific associations were not reported, and our work, in contrast, considered monthly anomalies relative to a 30-year reference period as the thermal exposure of interest.

Other European studies also noted significant positive relationships between average/diurnal SAT and all-cause/CVD mortality in men <65 years or in working-age or middle-aged men[10–12]. An Australian group documented a significant association between ambient temperature in Queensland and the relative risk of CVD hospitalization over a comparable time period (1995-2016); risk was greater in men than in women and in adults <70 years of age when compared with those 70 years and older[35].

The non-significant trends observed for the older men in the present analysis and in these previous reports may reflect resilient survivor bias or signal the exponential accretion of coronary and peripheral vascular disease with age, resulting in more conventional than anomalous temperature-triggered cardiovascular events. Conversely, younger men may be more susceptible to increased summer nocturnal SAT. It has been noted[35] that endogenous testosterone, which declines with age, is in mice an heat-stress susceptibility factor[36].

Nearly a third of United Kingdom's population resides in southeast England[15]. This region's employment opportunities attract young and middle-aged men[37]. Urban design is also an important parameter, because majority of daytime summer heat is absorbed, then radiates locally at night[15]. Residential air conditioning is less common in both England and Wales and in Seattle, Washington, relative to other high-income mid- to high-latitude nations such as the United States or Canada[14]. If uncomfortable warmth obliges individuals to open their bedroom windows, this action, in turn might increase CVD event risk by exposing sleepers to more intense outside nocturnal heat, atmospheric pollutants[27], and road and aircraft noise[29], which in adult men increases the risk of developing hypertension[16,38]. Nighttime noise-related stress[38] and warmer summer SAT also disrupt sleep, especially among vulnerable populations with lower socioeconomic status[21]. Sleep deprivation, in turn can increased central sympathetic outflow[39], which over time can increase blood pressure and induce insulin resistance[40]. Dry air can exacerbate snoring[41]; in middle-aged men snoring is common, as is obstructive sleep apnea, which can trigger nocturnal CVD events[42].

Although we cannot infer causality from our models, our age- and sex-specific analyses nonetheless represent a novel contribution to the present literature. The principal strengths of this ecological study accrue from the large population sampled and its linkage with rigorous national mortality and meteorological data. The principal limitations are lack of access to 15-year sex- and age-specific granular monthly/weekly data (i.e. district or city level) outcome and exposure data. The latter might have identified stronger associations between nighttime summer heat and CVD mortality in populous urban regions, where ~90% of citizens are projected to reside within a few decades[15]. Nonetheless, in our supplementary analysis of King County, the effect and direction of summer nocturnal SAT on CVD morality among men aged 60-64 years were consistent with our primary analysis. The majority of adult men in England and Washington State retire at age 65. It is conceivable that the anxieties/mental health of men in their early sixties anticipating retirement and reduced income or benefits added to their risk for CVD death, as posited by a British study[13], but this potential confounder was adjusted for, in our models. Lastly, we are not able to adjust for potential confounding factors such as local public health initiatives, or in secular trends in the discovery and implementation of effective primary and secondary CVD risk prevention strategies, cause of death misclassification, or ICD coding error.

Conclusion

Our observation of an association between warm summer nighttime conditions and CVD mortality risk amongst men aged 60-64 year residing in England and Wales was replicated in our analysis of comparable American data from King County, Washington State. The present findings should stimulate similar investigation of exposure and event rates in other populous mid- to high-latitude regions. Considering the growing likelihood of extreme summers in Western United States and United Kingdom[23], our results invite preventive population health initiatives and novel urban policies aimed at reducing future risk of CVD events.

Author contributions

HM and JSF contributed to the conception or design of the work. HM and JSF contributed to the acquisition, analysis, or interpretation of data for the work. HM drafted the initial manuscript. JSF critically revised the manuscript. Both authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Data sharing statement

All data related to this study has been provided as weblinks in the ‘Methods’ section.

Ethics approval statement

No ethics approval was needed to conduct this study.

Patient and public involvement

Patients were not involved in the design, or conduct, or reporting, or dissemination plans of this research study.

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Table 1. Total summer (June-July) sex- and age-specific cardiovascular disease deaths and its corresponding rates by British and United States region for the years 2001 and 2015.

Region	Group	2001			2015		
		No. Deaths	Population	Rate (per 100,000)	No. Deaths	Population	Rate (per 100,000)
England and Wales	Men						
	60-64	969	1,251,730	77.4	590	1,512,948	39.0
	65-69	1,451	1,104,859	131.3	938	1,560,546	60.1
	Women						
	60-64	403	1,297,331	31.1	234	1,576,695	14.8
	65-69	735	1,194,005	61.6	403	1,652,275	24.4
King County, Washington United States	Men						
	60-64	27	29,824	90.5	37	58,227	63.5
	65-69	24	21,944	109.4	17	44,574	38.1

Figure Legends:

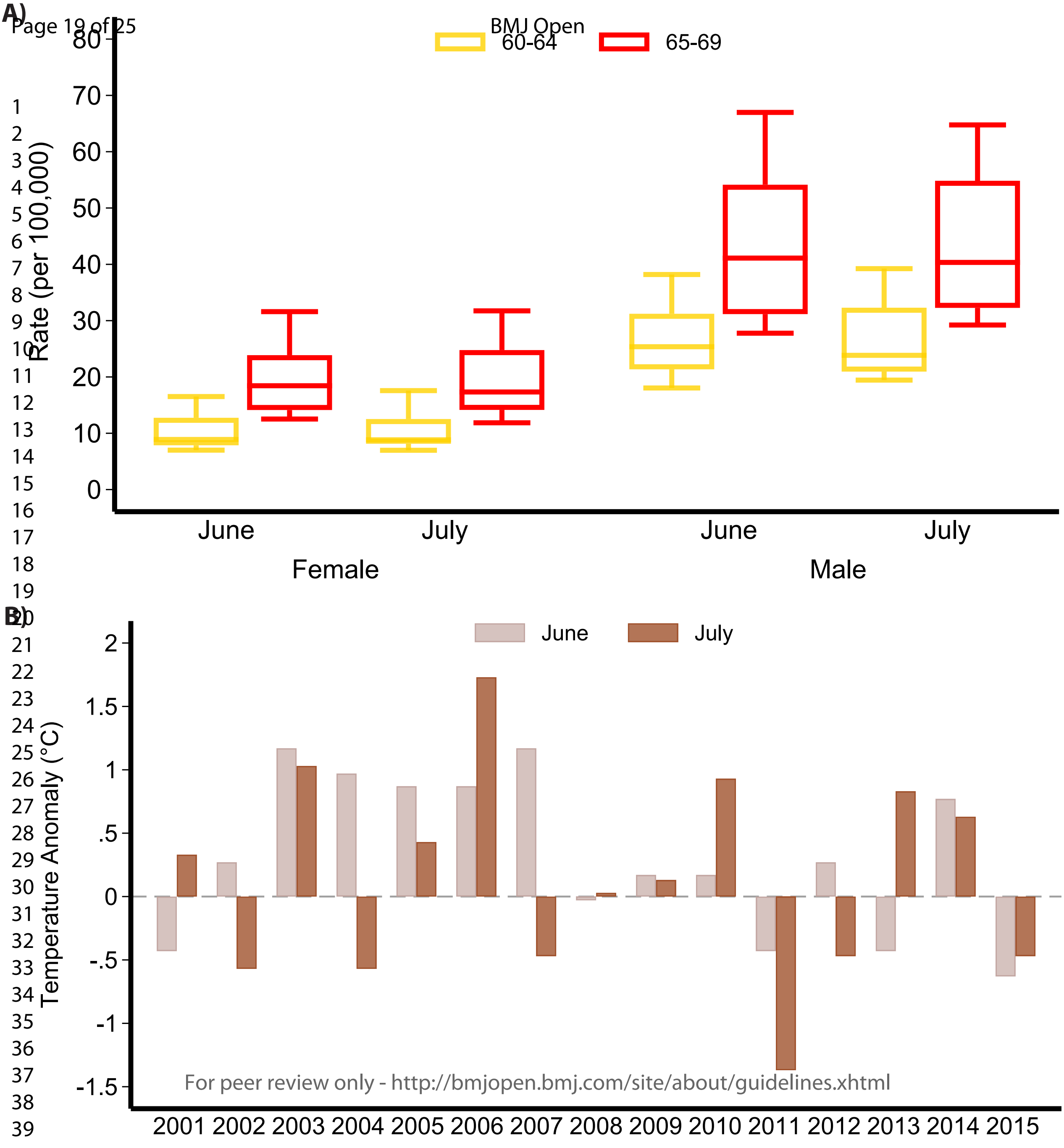
Figure 1: **A**) Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in England & Wales from 2001-2015. **B**) Month-specific summer (June-July) nocturnal SAT anomalies (based on deviations from the baseline period of 1981-2010) in England & Wales.

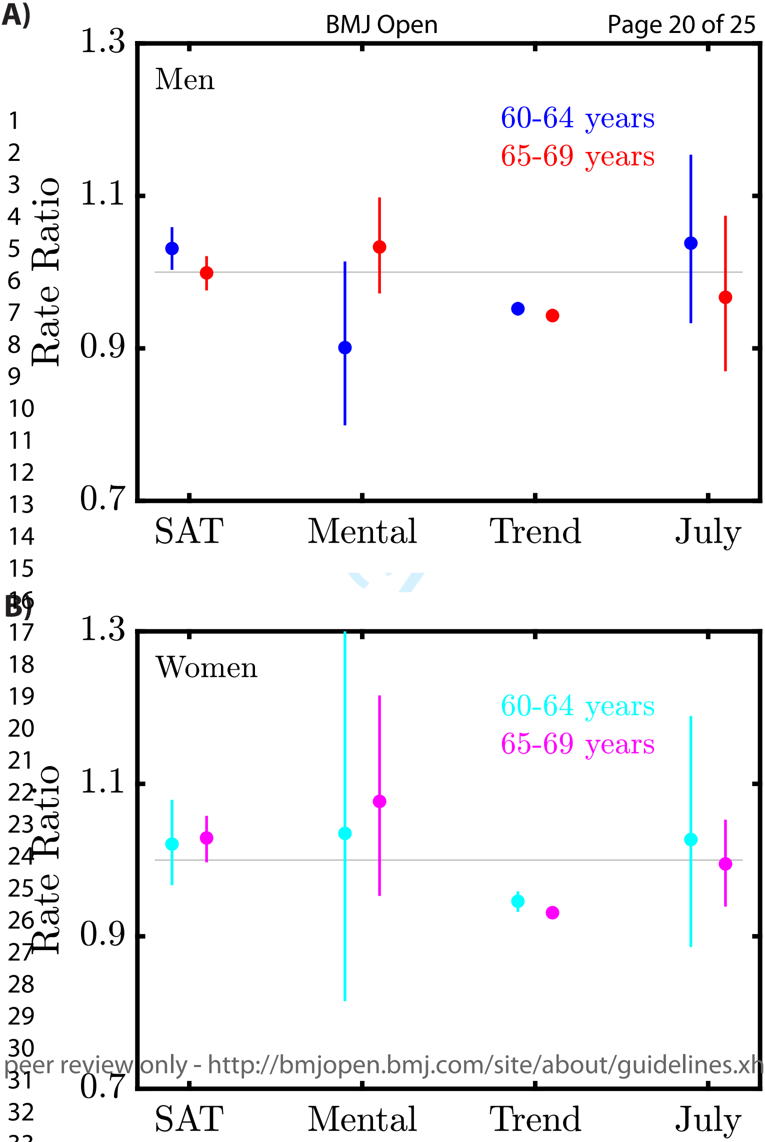
Figure 2: **A**) Plot depicting the association between summer CVD mortality rates and night SAT anomalies for middle- and older-aged men in England & Wales from 2001-2015. **B**) Plot depicting the association between summer CVD mortality rates and night SAT anomalies for middle- and older-aged women in England & Wales from 2001-2015. Covariates includes mental and behavioural mortality rates, trend, and month (reference to June).

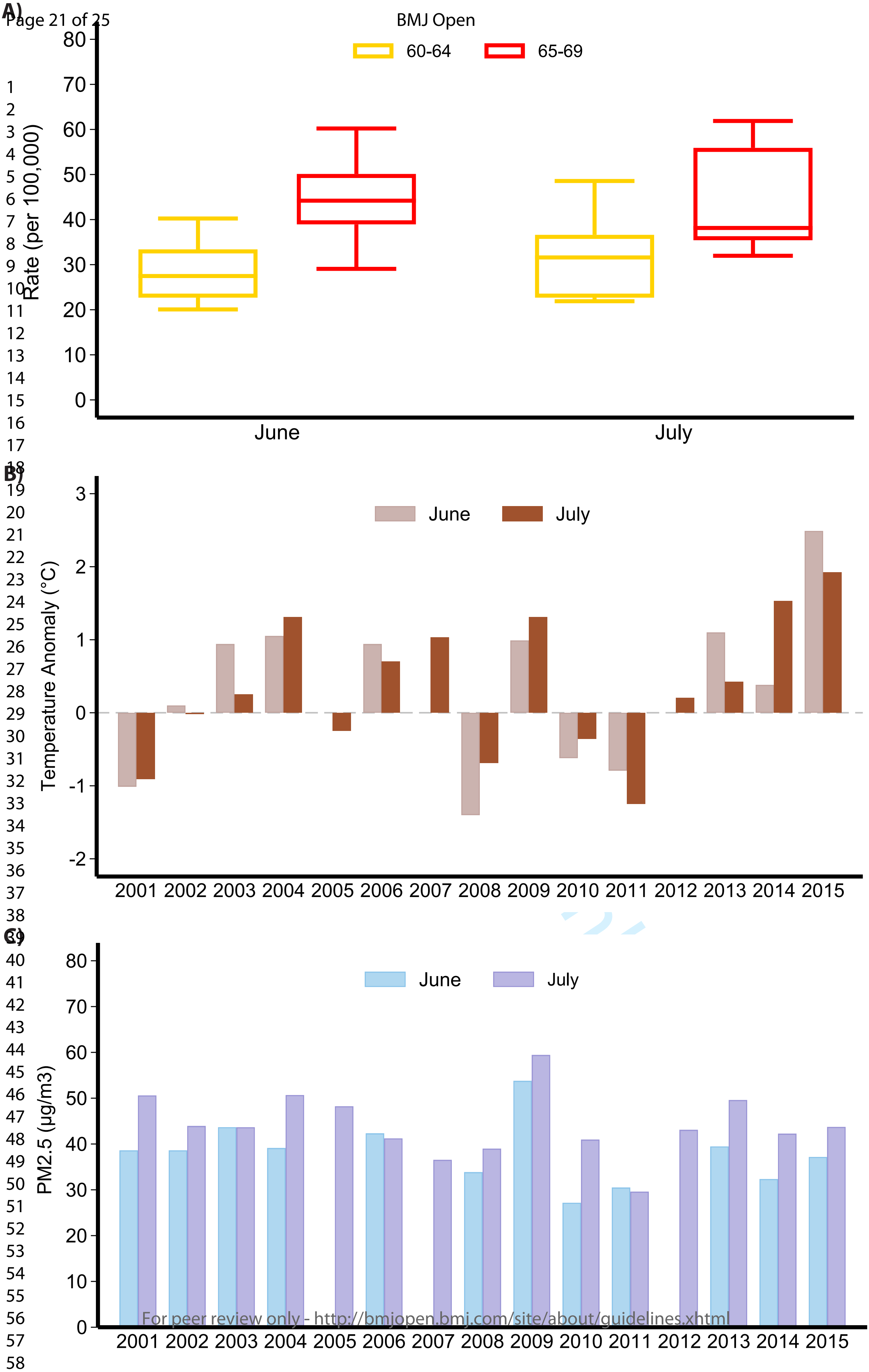
Figure 3: **A**) Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in King County, Washington, United States from 2001-2015. **B**) Month-specific summer (June-July) night SAT anomalies (based on deviations from the baseline period of 1981-2010) in King County. **C**) Month-specific summer (June-July) $PM_{2.5}$ values in King County.

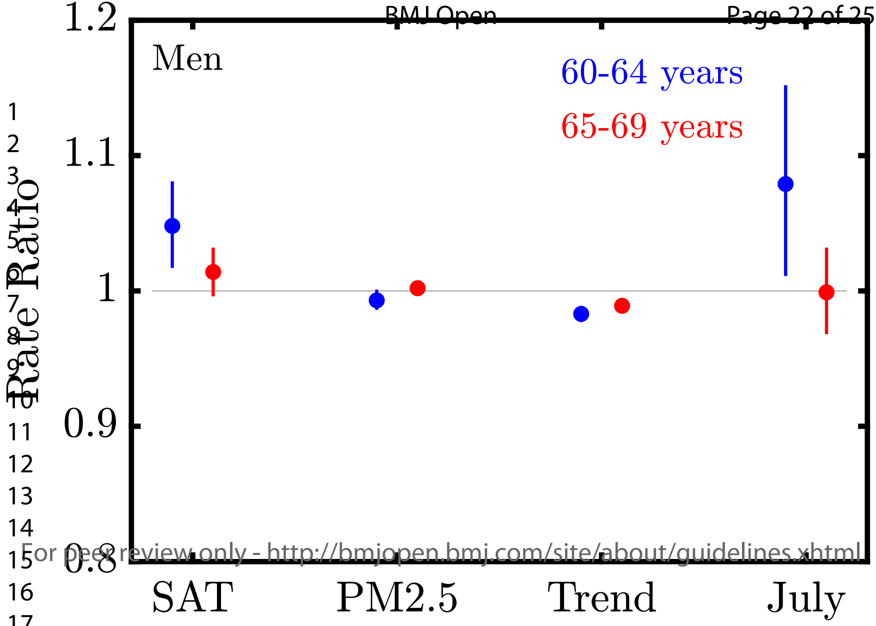
Figure 4: Plot depicting the association between summer CVD mortality rates and nocturnal SAT anomalies for middle- and older-aged men in King County, Washington, United States from 2001-2015. Covariates includes $PM_{2.5}$, trend, and month (reference to June).

Supplementary Figure 1: Monthly summer (6=June, 7=July) cardiovascular mortality trends by age-groups among (A) men and (B) women from 2001-2015 in England and Wales.

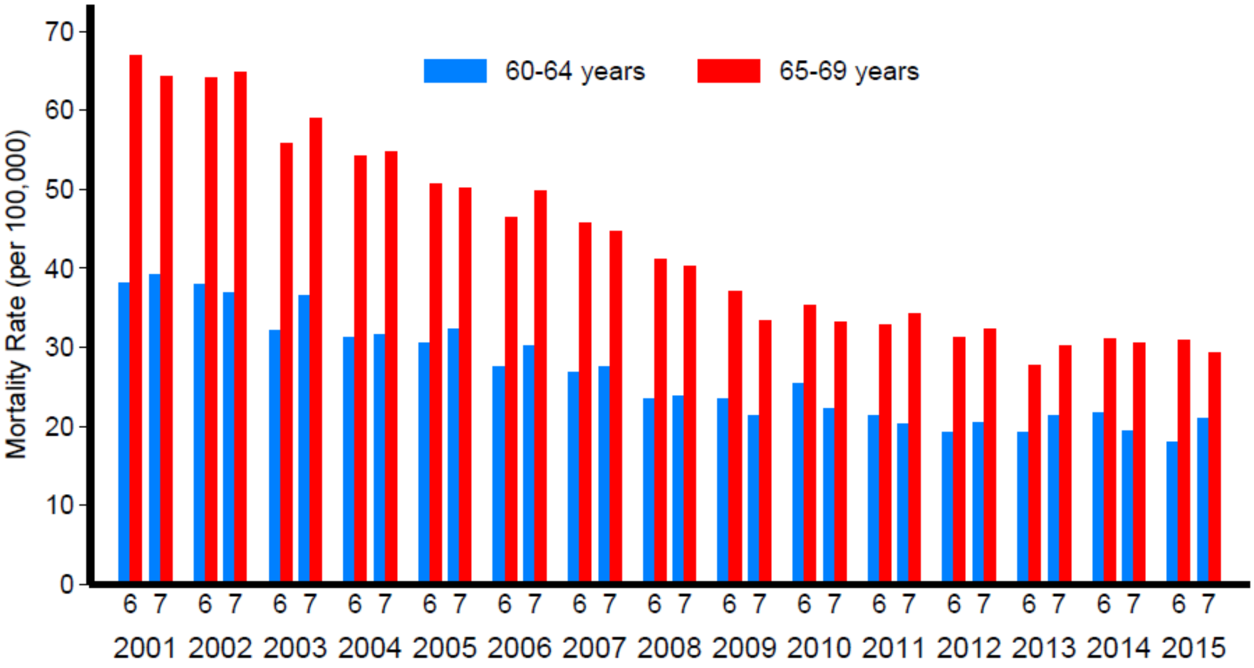

A)
60-64
65-69
Rate (per 100,000)
0
10
20
30
40
50
60
70
80
June
July
June
July
Female
Male
B)
June
July
Temperature Anomaly (°C)
2
1.5
1
.5
0
-.5
-1
-1.5
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015


A)
1.3
1.1
0.9
0.7
Rate Ratio
Men
60-64 years
65-69 years
SAT
Mental
Trend
July
B)
1.3
1.1
0.9
0.7
Rate Ratio
Women
60-64 years
65-69 years
SAT
Mental
Trend
July


A)
60-64
65-69
Rate (per 100,000)
0
10
20
30
40
50
60
70
80
June
July
B)
June
July
Temperature Anomaly (°C)
-2
-1
0
1
2
3
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015
C)
June
July
PM2.5 (μg/m3)
0
10
20
30
40
50
60
70
80
2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015


Men
60-64 years
65-69 years
Rate Ratio
1.2
1.1
1
0.9
0.8
SAT
PM2.5
Trend
July

A) Men



B) Women

Supplementary Figure 1: Monthly summer (6=June, 7=July) cardiovascular mortality trends by age-groups among (A) men and (B) women from 2001-2015 in England and Wales.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	
Objectives	3	State specific objectives, including any prespecified hypotheses	5	
Methods				
Study design	4	Present key elements of study design early in the paper	5	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls ***Cross-sectional study***—Give the eligibility criteria, and the sources and methods of selection of participants	6	
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5	
Bias	9	Describe any efforts to address potential sources of bias	6	
Study size	10	Explain how the study size was arrived at	6	

Continued on next page

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6	Findings are reported as incidence rate ratios (RR) and interpreted as change for one-unit increase of the exposure variable
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7	
		(*b*) Describe any methods used to examine subgroups and interactions	7	
		(*c*) Explain how missing data were addressed		
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy		
		(*e*) Describe any sensitivity analyses	6	
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7	
		(b) Give reasons for non-participation at each stage		
		(c) Consider use of a flow diagram		
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	8	
		(b) Indicate number of participants with missing data for each variable of interest		
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time		
		Case-control study—Report numbers in each exposure category, or summary measures of exposure		
		Cross-sectional study—Report numbers of outcome events or summary measures	7	Included as well in Table 1
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8	
		(*b*) Report category boundaries when continuous variables were categorized	8	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	8	

Continued on next page

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.