

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056806
Article Type:	Original research
Date Submitted by the Author:	26-Aug-2021
Complete List of Authors:	Majeed, Haris; University of Toronto Floras, John; Department of Medicine
Keywords:	Cardiology < INTERNAL MEDICINE, PUBLIC HEALTH, Cardiac Epidemiology < CARDIOLOGY

SCHOLARONE™  
Manuscripts



I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3  
4 **Warmer summer nocturnal surface air temperatures and cardiovascular disease death risk: a population-**  
5 **based study**  
6  
7  
8  
9

10 Haris Majeed<sup>1\*</sup> & John S Floras<sup>1,2</sup>  
11  
12  
13

14  
15 <sup>1</sup> Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada  
16

17  
18 <sup>2</sup> University Health Network and Sinai Health Division of Cardiology, Department of Medicine, University of  
19 Toronto, Toronto, Ontario, Canada  
20  
21  
22  
23  
24

25 \*Corresponding Author:

26 Haris Majeed, HBSc, MSc

27 University of Toronto

28 Toronto, ON

29 Canada M5S 1A8

30 Email: [haris.majeed@utoronto.ca](mailto:haris.majeed@utoronto.ca)

31 Phone: +1 (416) 946-8286  
32  
33  
34  
35

36 Word Count: 2810  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

August 25, 2021

## 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

1  
2 29 **Strengths and limitations of this study:**  
3

- 4 30 • Ecological study of a large population advantaged by rigorous national mortality and meteorological  
5  
6 31 data.  
7  
8 32 • Replication of principal finding in a climatically similar but geographically distinct region.  
9  
10 33 • General rather than granular (e.g., urban versus rural) outcome and exposure data.  
11  
12 34 • This observational study design cannot exclude residual confounding by other cardiovascular risk  
13 35 factors.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## Background

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

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

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<sup>21</sup>) 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<sup>22</sup>, 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

1  
2 83 prevalence of residential air conditioning<sup>23</sup>. These two jurisdictions also were selected because of their large  
3  
4 84 populaces, of whom the majority (~90%) resides in urban or semi-urban 'heat-islands', readily accessible  
5  
6 85 statistics, and data affirming that over this time-span both regions witnessed greater increases in nighttime than  
7  
8 86 daytime SAT<sup>15</sup>.  
9

## 14 89 **Methods**

### 16 90 *Climatological Exposure Data*

17 90  
18  
19 91 Mid- to high-latitude regions, such as England and Wales and the State of Washington experience similar  
20  
21 92 seasonal cycles, in which diurnal and nocturnal SAT are such higher in summer than winter<sup>24</sup>. Guided by  
22  
23 93 previous observations of positive associations between summer nocturnal SAT and mortality<sup>5,16</sup>, we ascertained,  
24  
25 94 for June and July, minimum SAT for England and Wales (collectively) and King County, Washington, US from  
26  
27 95 the Meteorology Office UK: [https://www.metoffice.gov.uk/research/climate/maps-and-data/uk-and-regional-](https://www.metoffice.gov.uk/research/climate/maps-and-data/uk-and-regional-series)  
28  
29 96 [series](https://www.metoffice.gov.uk/research/climate/maps-and-data/uk-and-regional-series) and the National Oceanic and Atmospheric Administration (NOAA):  
30  
31 97 <https://www.ncdc.noaa.gov/cag/county/time-series>, respectively. Minimum SAT was used as a proxy for  
32  
33 98 nocturnal SAT<sup>15</sup>. Since air pollution (i.e. through particulate matter 2.5 [PM2.5]) can influence local CVD  
34  
35 99 events<sup>25</sup>, we included United States Environmental Protection Agency (EPA): [https://www.epa.gov/outdoor-air-](https://www.epa.gov/outdoor-air-quality-data/download-daily-data)  
36  
37 100 [quality-data/download-daily-data](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  
38  
39 101 smaller region of King County.  
40  
41  
42 102  
43

### 44 103 *Cardiovascular Disease Mortality Data*

45  
46 104 For England and Wales sex- and age-specific deaths attributed to CVD and mental and behavioural  
47  
48 105 disorders occurring in June and July (in Europe, mental and behavioural disorders are an established strong risk  
49  
50 106 factor for CVD death among adults over 60 years of age<sup>25</sup>) for the years 2001-2015 were extracted from Office  
51  
52 107 for National Statistics (ONS, reference #: 007957) data:  
53  
54 108 <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deaths>  
55  
56 109 [bymonthofoccurrenceaged60andoverbysingleyearofagesexandspecifiedcausesenglandandwales2001to2015](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deaths). For  
57  
58  
59  
60



1  
2 110 King County, sex- and age-specific CVD mortality for June and July for the years 2001-2015 were extracted  
3  
4 111 from Centers for Disease Control and Prevention (CDC) WONDER data<sup>23</sup>. CVD death was defined as per the  
5  
6 112 International Classification of Diseases (ICD), tenth revision (ICD-10: I00-I99) criteria, whereas deaths due to  
7  
8 113 mental and behavioural disorders were defined as ICD-10: F00-F99.  
9

10  
11 114 Sex-specific analyses were partitioned into two age groups: 60-64 years and 65-69 years. We elected to  
12  
13 115 exclude from analysis both younger adults, due to their lower CVD event rates and older adults, whose higher  
14  
15 116 prevalence of co-morbid conditions has been shown in English data to risk cause of death misclassification<sup>26</sup>.  
16  
17 117 Numerators of region-specific CVD deaths were based on the presence of one or more ICD-10 codes listed on  
18  
19 118 each death record in a given month of the year, with denominators established on mid-year annual population  
20  
21 119 estimates for the sum of England plus Wales and similarly for King County. Data were stratified by sex and age  
22  
23 120 group. Monthly summer CVD and mental and behavioural mortality rates were computed by region- sex- and  
24  
25 121 age-specific deaths occurring each month of the year and were reported as the number of male and female  
26  
27 122 deaths per 100,000 persons.  
28

### 29 123 30 124 31 124 *Statistical Analysis*

32  
33 125 Since atmospheric systems act on long time-scales, our primary exposures (June and July) nocturnal  
34  
35 126 SAT were standardized as monthly anomalies from a reference period<sup>21</sup>. For the purpose of the present analysis,  
36  
37 127 SAT anomalies were defined as deviations from a 30-year (1981-2010) baseline average<sup>21</sup>. For each year of the  
38  
39 128 exposure period (2001-2015), June and July nocturnal SAT anomalies were computed separately for England  
40  
41 129 and Wales and for King County by subtracting the monthly averages for these regions from their respective  
42  
43 130 1981-2010 average nocturnal SAT.  
44  
45

46 131 CVD mortality rates were found to be auto-correlated (i.e. rates in the prior and subsequent years were  
47  
48 132 significantly correlated) and the outcome variable's variance was considerably greater than its mean, leading to  
49  
50 133 over-dispersion of data<sup>21,27</sup>. In addition, the incidence of mental health and behavioural distress in England and  
51  
52 134 Wales has been shown to increase over time and identified as a strong risk factor for associations between  
53  
54 135 diurnal SAT and cause-specific adult mortality<sup>13</sup>. To address these issues in our models, we used negative  
55  
56 136 binomial regression with auto-correlated residuals of order one<sup>21</sup> to assess the association between sex- and age-

1  
2 137 specific CVD mortality rates to summer nocturnal SAT for England and Wales from 2001-2015, while  
3  
4 138 controlling for mental health and behaviour mortality rates, the trend, and the summer month as our covariates.  
5  
6 139 For King County, we used quasi-Poisson to assess all associations, while controlling for PM2.5, the trend, and  
7  
8 140 the summer month as our covariates. Findings are reported as incidence rate ratios (RR) and interpreted as  
9  
10 141 change for one-unit increase of the exposure variable<sup>21,27</sup>. Confidence intervals (CI) were evaluated at 95%,  
11  
12 142 along with Student's two-sided *t*-tests. Microsoft Excel (version 2013), RStudio (version 4.1.1), and STATA  
13  
14 143 (version 15) were used for computation, analyses, and figure composition.  
15  
16  
17 144  
18  
19 145

## 21 146 **Results**

22  
23 147 Within the selected cohorts, over the years 2001-2015, there were 39,912 (68.9% men) CVD deaths  
24  
25 148 recorded in England and Wales and 488 male CVD deaths (54.1% in the group aged 65-69 years) in King  
26  
27 149 County. Over this time period, CVD rates declined substantially in both regions (Table 1).  
28

29 150 For England and Wales, CVD mortality rates, categorized by sex, age, and month, are illustrated in  
30  
31 151 Figure 1A. The older (65-69 years) men and women exhibited higher CVD mortality rates than during both  
32  
33 152 summer months. CVD mortality rates were consistently higher amongst men than women. Summer nocturnal  
34  
35 153 SAT anomalies are plotted in Figure 1B. June anomalies ranged from -0.63°C (2015) to 1.17°C (2003-  
36  
37 154 corresponding to a protracted western European heatwave). July anomalies ranged from -1.37°C (2011) to  
38  
39 155 1.73°C (2006).  
40  
41

42 156 After adjusting for covariates, associations between exposure (a 1-unit increase in summer nocturnal  
43  
44 157 SAT<sup>27</sup>) and CVD mortality rates, stratified by sex and age appear in Figure 2. As shown in Figure 2A, a +1°C  
45  
46 158 anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality  
47  
48 159 rates among men aged 60-64 [adjusted RR 1.031; 95% CI, 1.003-1.059] but not in those aged 65-69 years  
49  
50 160 [adjusted RR 0.999; 95% CI, 0.976-1.021], nor in adult women in either age group (Figure 2B).  
51

52 161 For King County, summer CVD mortality rates were also higher within the older male cohort (Figure  
53  
54 162 3A). Summer nocturnal SAT anomalies are plotted in Figure 3B. June SAT anomalies ranged from -1.4°C  
55  
56 163 (2008) to 2.49° (2015, a year when western North America recorded a record number of heatwaves and forest  
57  
58  
59

1  
2 164 fires in the context of a strong El Niño event<sup>21</sup>). July anomalies ranged from -1.25°C (2011) to 1.92°C (also in  
3  
4 165 2015). The smaller land mass of King County permits integration of PM2.5 into these models. In general, King  
5  
6 166 County PM2.5 levels generally were higher in July than in June, 2001-2015. After adjusting for covariates, a  
7  
8 167 +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD  
9  
10 168 mortality rates among men aged 60-64 [adjusted RR 1.049; 95% CI, 1.017-1.081] but not in those aged 65-69  
11  
12 169 [adjusted RR 1.014; 95% CI, 0.996-1.032] (Figure 4).  
13  
14  
15 170  
16  
17 171  
18

## 19 172 **Discussion**

20  
21 173 CVD mortality rates in both England and Wales and in King County, Washington State declined  
22  
23 174 substantially between 2001 and 2015 (Table 1) in parallel with greater population uptake of effective primary  
24  
25 175 and secondary preventive therapies. Nonetheless, considerable residual risk persists, and in England and Wales,  
26  
27 176 event rates remain >50% higher in adults aged 65-69 than in those aged 60-64 years.

28  
29 177 High summer nocturnal SAT may be a source of such risk<sup>6</sup>. Such high summer SAT has been associated  
30  
31 178 with increased cause-specific adult mortality in various high-income regions<sup>3-8,10,13,16,17</sup>. Importantly, in recent  
32  
33 179 years populous mid- to high-latitude regions have experienced a proportionately rise in nocturnal than in  
34  
35 180 daytime summer heat intensity<sup>15</sup>. The present work is one of few investigating potential associations between  
36  
37 181 summer nocturnal SAT and CVD mortality rates. Our finding of significant associations, in men aged 60-64  
38  
39 182 residing in England and Wales or in King County, Washington State, US, between +1°C summer nocturnal SAT  
40  
41 183 anomalies and summer CVD mortality rates, support this concept.  
42  
43

44 184 An association between summer nocturnal SAT and CVD mortality is biologically plausible hypothesis.  
45  
46 185 The incidence and severity of CVD events can be exacerbated by temporal dys-synchrony between  
47  
48 186 cardiovascular circadian clock gene rhythms and exogenous or endogenous homeostatic stresses<sup>28</sup>. One such  
49  
50 187 stress is warmer nocturnal SAT, which also amplifies self-reported sleep-deprivation, itself a risk factor for adult  
51  
52 188 heart disease mortality<sup>20</sup>. Waking itself, whether concordant with normal cardiovascular circadian rhythms or  
53  
54 189 due to interrupted sleep, triggers increases in heart rate, vascular resistance, and blood pressure and predisposes  
55  
56 190 to thrombosis<sup>29</sup>.  
57  
58  
59

1  
2 191 No significant association was detected in English and Welsh women, but their event rates were <50%  
3  
4 192 of males of comparable age (Table 1). Thus, there may have been insufficient statistical power to appreciate a  
5  
6 193 qualitatively similar association in women, if present. On the other hand, their generally larger sweat gland  
7  
8 194 volume<sup>30</sup> predisposes men exposed to heat to greater insensible fluid loss and intra-vascular volume depletion.  
9  
10 195 Additionally, the authors of a recent systematic review of 36 studies attributed the greater male susceptibility to  
11  
12 196 heat-attributable illnesses to their psychology and behavior<sup>31</sup>.

14 197 Several studies<sup>4,15-17</sup> report a positive association between summer nocturnal SAT and either all-cause,  
15  
16 198 heat-related, or CVD mortality. In one focusing on London, UK, nighttime temperatures had a more potent  
17  
18 199 influence than daytime exposure on all-cause mortality, ischemic heart disease events, and stroke, particularly in  
19  
20 200 those  $\leq 64$  years of age; sex-specific risk was not reported<sup>16</sup>. Other European studies also noted significant  
21  
22 201 positive relationships between average/diurnal SAT and all-cause/CVD mortality in men <65 years or in  
23  
24 202 working-age or middle-aged men<sup>10-12</sup>. An Australian group documented a significant association between  
25  
26 203 ambient temperature in Queensland and the relative risk of CVD hospitalization over a comparable time period  
27  
28 204 (1995-2016); risk was greater in men than in women and in adults <70 years of age when compared with those  
29  
30 205 70 years and older<sup>32</sup>.

33 206 The non-significant trends observed for the older men in the present analysis and in these previous  
34  
35 207 reports may reflect resilient survivor bias or signal the exponential accretion of coronary and peripheral vascular  
36  
37 208 disease with age, resulting in more conventional than anomalous temperature-triggered cardiovascular events.  
38  
39 209 Conversely, younger men may be more susceptible to increased summer nocturnal SAT. It has been noted<sup>32</sup> that  
40  
41 210 endogenous testosterone, which declines with age, is in mice an heat-stress susceptibility factor<sup>33</sup>.

44 211 Nearly a third of United Kingdom's population resides in southeast England<sup>15</sup>. This region's  
45  
46 212 employment opportunities attract young and middle-aged men<sup>34</sup>. Urban design is also an important parameter,  
47  
48 213 because majority of daytime summer heat is absorbed, then radiates locally at night<sup>15</sup>. Residential air  
49  
50 214 conditioning is less common in both England and Wales and in Seattle, Washington, relative to other high-  
51  
52 215 income mid- to high-latitude nations such as the United States or Canada<sup>14</sup>. If uncomfortable warmth obliges  
53  
54 216 individuals to open their bedroom windows, this action, in turn might increase CVD event risk by exposing  
55  
56 217 sleepers to more intense outside nocturnal heat, atmospheric pollutants<sup>35</sup>, and road and aircraft noise<sup>26</sup>, which in

1  
2 218 adult men increases the risk of developing hypertension<sup>16,36</sup>. Nighttime noise-related stress<sup>36</sup> and warmer  
3  
4 219 summer SAT also disrupt sleep, especially among vulnerable populations with lower socioeconomic status<sup>20</sup>.  
5  
6 220 Sleep deprivation, in turn can increased central sympathetic outflow<sup>37</sup>, which over time can increase blood  
7  
8 221 pressure and induce insulin resistance<sup>38</sup>. Dry air can exacerbate snoring<sup>39</sup>; in middle-aged men snoring is  
9  
10 222 common, as is obstructive sleep apnea, which can trigger nocturnal CVD events<sup>40</sup>.  
11

12  
13 223 Although we cannot infer causality from our models, our age- and sex-specific analyses nonetheless  
14  
15 224 represent a novel contribution to the present literature. The principal strengths of this ecological study accrue  
16  
17 225 from the large population sampled, its linkage with rigorous national mortality and meteorological data, and the  
18  
19 226 replication of the principal observation concerning the effect and direction of summer nocturnal SAT on CVD  
20  
21 227 mortality among men aged 60-64 years in a geographically distinct region with similar climate. The main  
22  
23 228 limitations are lack of access to 15-year sex- and age-specific granular monthly/weekly data (i.e. district or city  
24  
25 229 level) outcome and exposure data, which might have identified stronger associations between nighttime summer  
26  
27 230 heat and CVD mortality in populous urban regions, where ~90% of citizens are projected to reside within a few  
28  
29 231 decades<sup>15</sup>. The anxieties/mental health of men in their early sixties anticipating retirement and reduced income  
30  
31 232 or benefits may have increased their risk for CVD death, as posited by a British study<sup>13</sup>, but this potential was  
32  
33 233 adjusted for, in our models. Lastly, we are not able to adjust for potential confounding factors such as local  
34  
35 234 public health initiatives, or in secular trends in the discovery and implementation of effective primary and  
36  
37 235 secondary CVD risk prevention strategies, cause of death misclassification, or ICD coding error.  
38  
39  
40 236  
41  
42 237  
43

## 44 238 **Conclusion**

45  
46 239 Our observation of an association between warm summer nighttime conditions and CVD mortality risk amongst  
47  
48 240 men aged 60-64 year residing in England and Wales was replicated in our analysis of comparable American data  
49  
50 241 from King County, Washington State. The present findings should stimulate similar investigation of exposure  
51  
52 242 and event rates in other populous mid- to high-latitude regions. Considering the growing likelihood of extreme  
53  
54 243 summers in Western United States and United Kingdom<sup>22</sup>, our results invite preventive population health  
55  
56 244 initiatives and novel urban policies aimed at reducing future risk of CVD events.  
57  
58  
59

1  
2 245  
3  
4 246  
5 247 **Contributors:** HM and JSF contributed to the conception or design of the work. HM and JSF contributed to the  
6  
7 248 acquisition, analysis, or interpretation of data for the work. HM drafted the initial manuscript. JSF critically  
8  
9 249 revised the manuscript. Both authors gave final approval and agree to be accountable for all aspects of work  
10 250 ensuring integrity and accuracy.

11 251  
12  
13 252 **Funding:** The authors have not declared a specific grant for this research from any funding agency in the  
14  
15 253 public, commercial or not-for-profit sectors.

16 254  
17  
18 255 **Competing interests:** None declared.

19  
20 256  
21  
22 257 **Patient and public involvement:** Patients and/or the public were not involved in the design, or conduct, or  
23  
24 258 reporting, or dissemination plans of this research.

25  
26 259  
27  
28 260 **Patient consent for publication:** Not required.

29  
30 261  
31  
32 262 **Provenance and peer review:** Not commissioned; externally peer reviewed.

33  
34 263  
35  
36  
37 264 **Data availability statement:** All data has been provided within the manuscript as weblinks. Further data  
38  
39 265 inquires are available upon reasonable request.

## References

1. Timmis A, Townsend N, Gale C, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. *Eur Heart J* 2018; 39: 508–579.
2. Schwartz J, Samet JM, Patz JA. Hospital Admissions for Heart Disease: The Effects of Temperature and Humidity. *Epidemiology* 2004; 15: 755–761.
3. Michelozzi P, Accetta G, De Sario M, et al. High Temperature and Hospitalizations for Cardiovascular and Respiratory Causes in 12 European Cities. *Am J Respir Crit Care Med* 2009; 179: 383–389.
4. D'Ippoliti D, Michelozzi P, Marino C, et al. The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project. *Environ Health* 2010; 9: 37.
5. Achebak H, Devolder D, Ballester J. Trends in temperature-related age-specific and sex-specific mortality from cardiovascular diseases in Spain: a national time-series analysis. *Lancet Planet Health* 2019; 3: e297–e306.
6. Son J-Y, Liu JC, Bell ML. Temperature-related mortality: a systematic review and investigation of effect modifiers. *Environ Res Lett* 2019; 14: 073004.
7. Saucy A, Ragettli MS, Vienneau D, et al. The role of extreme temperature in cause-specific acute cardiovascular mortality in Switzerland: A case-crossover study. *Sci Total Environ* 2021; 790: 147958.
8. van Steen Y, Ntarladima A-M, Grobbee R, et al. Sex differences in mortality after heat waves: are elderly women at higher risk? *Int Arch Occup Environ Health* 2019; 92: 37–48.
9. Mari-Dell'Olmo M, Tobías A, Gómez-Gutiérrez A, et al. Social inequalities in the association between temperature and mortality in a South European context. *Int J Public Health* 2019; 64: 27–37.
10. Näyhä S. Environmental temperature and mortality. *Int J Circumpolar Health* 2005; 64: 451–458.
11. Rowland ST, Boehme AK, Rush J, et al. Can ultra short-term changes in ambient temperature trigger myocardial infarction? *Environ Int* 2020; 143: 105910.
12. Rocklöv J, Forsberg B, Ebi K, et al. Susceptibility to mortality related to temperature and heat and cold wave duration in the population of Stockholm County, Sweden. *Glob Health Action* 2014; 7: 10.3402/gha.v7.22737.
13. Gasparrini A, Armstrong B, Kovats S, et al. The effect of high temperatures on cause-specific mortality in England and Wales. *Occup Environ Med* 2012; 69: 56–61.
14. Arbuthnott KG, Hajat S. The health effects of hotter summers and heat waves in the population of the United Kingdom: a review of the evidence. *Environ Health* 2017; 16: 119.
15. Eunice Lo YT, Mitchell DM, Bohnenstengel SI, et al. U.K. Climate Projections: Summer Daytime and Nighttime Urban Heat Island Changes in England's Major Cities. *J Clim* 2020; 33: 9015–9030.
16. Murage P, Hajat S, Kovats RS. Effect of night-time temperatures on cause and age-specific mortality in London. *Environ Epidemiol* 2017; 1: e005.
17. Laaidi K, Zeghnoun A, Dousset B, et al. The Impact of Heat Islands on Mortality in Paris during the August 2003 Heat Wave. *Environ Health Perspect* 2012; 120: 254–259.

18. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. *Am J Physiol - Heart Circ Physiol* 2015; 309: H1793–H1812.
19. Obradovich N, Fowler JH. Climate change may alter human physical activity patterns. *Nat Hum Behav* 2017; 1: 1–7.
20. Obradovich N, Migliorini R, Mednick SC, et al. Nighttime temperature and human sleep loss in a changing climate. *Sci Adv* 2017; 3: e1601555.
21. Majeed H, Moineddin R, Booth GL. Sea surface temperature variability and ischemic heart disease outcomes among older adults. *Sci Rep* 2021; 11: 3402.
22. Christidis N, McCarthy M, Stott PA. The increasing likelihood of temperatures above 30 to 40 °C in the United Kingdom. *Nat Commun* 2020; 11: 3093.
23. Calkins MM, Isaksen TB, Stubbs BA, et al. Impacts of extreme heat on emergency medical service calls in King County, Washington, 2007–2012: relative risk and time series analyses of basic and advanced life support. *Environ Health* 2016; 15: 13.
24. Staddon PL, Montgomery HE, Depledge MH. Climate warming will not decrease winter mortality. *Nat Clim Change* 2014; 4: 190–194.
25. Analitis A, Michelozzi P, D'Ippoliti D, et al. Effects of heat waves on mortality: effect modification and confounding by air pollutants. *Epidemiol Camb Mass* 2014; 25: 15–22.
26. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* 2017; 16: 163–180.
27. Halonen JI, Hansell AL, Gulliver J, et al. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur Heart J* 2015; 36: 2653–2661.
28. Mohammad MA, Koul S, Rylance R, et al. Association of Weather With Day-to-Day Incidence of Myocardial Infarction: A SWEDEHEART Nationwide Observational Study. *JAMA Cardiol* 2018; 3: 1081–1089.
29. Durgan DJ, Young ME. The cardiomyocyte circadian clock: emerging roles in health and disease. *Circ Res* 2010; 106: 647–658.
30. Tofler Geoffrey H., Muller James E. Triggering of Acute Cardiovascular Disease and Potential Preventive Strategies. *Circulation* 2006; 114: 1863–1872.
31. Iyoho AE, Ng LJ, MacFadden L. Modeling of Gender Differences in Thermoregulation. *Mil Med* 2017; 182: 295–303.
32. Gifford RM, Todisco T, Stacey M, et al. Risk of heat illness in men and women: A systematic review and meta-analysis. *Environ Res* 2019; 171: 24–35.
33. Lu P, Xia G, Zhao Q, et al. Temporal trends of the association between ambient temperature and hospitalisations for cardiovascular diseases in Queensland, Australia from 1995 to 2016: A time-stratified case-crossover study. *PLOS Med* 2020; 17: e1003176.
34. Chen Y, Yu T. Testosterone mediates hyperthermic response of mice to heat exposure. *Life Sci* 2018; 214: 34–40.



- 1  
2 35. Andrew M, Meen G. Population structure and location choice: A study of London and South East  
3 England\*. *Pap Reg Sci* 2006; 85: 401–419.  
4  
5 36. Jarup L, Babisch W, Houthuijs D, et al. Hypertension and Exposure to Noise Near Airports: the HYENA  
6 Study. *Environ Health Perspect* 2008; 116: 329–333.  
7  
8 37. Taylor KS, Kucyi A, Millar PJ, et al. Association between resting-state brain functional connectivity and  
9 muscle sympathetic burst incidence. *J Neurophysiol* 2016; 115: 662–673.  
10  
11 38. Ayas NT, White DP, Manson JE, et al. A Prospective Study of Sleep Duration and Coronary Heart  
12 Disease in Women. *Arch Intern Med* 2003; 163: 205–209.  
13  
14 39. Lappharat S, Taneepanichskul N, Reutrakul S, et al. Effects of Bedroom Environmental Conditions on the  
15 Severity of Obstructive Sleep Apnea. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med* 2018; 14:  
16 565–573.  
17  
18 40. Lee SA, Amis TC, Byth K, et al. Heavy Snoring as a Cause of Carotid Artery Atherosclerosis. *Sleep* 2008;  
19 31: 1207–1213.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

**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

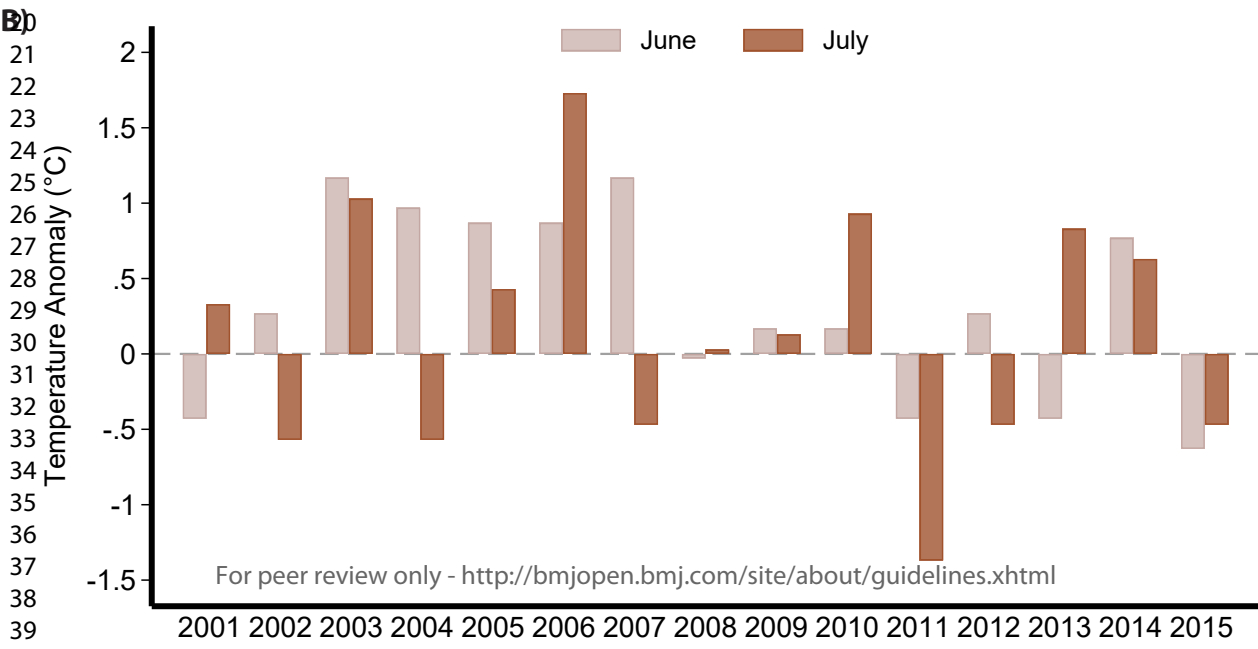
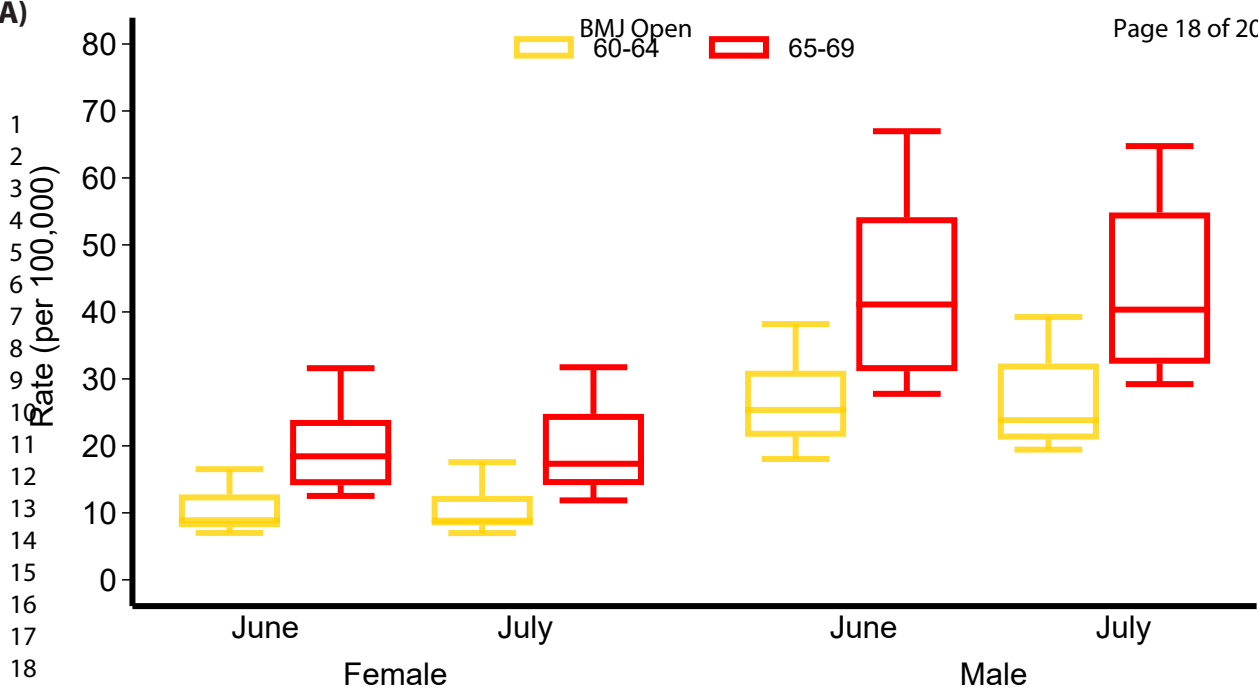
## **Figure Legends:**

**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.

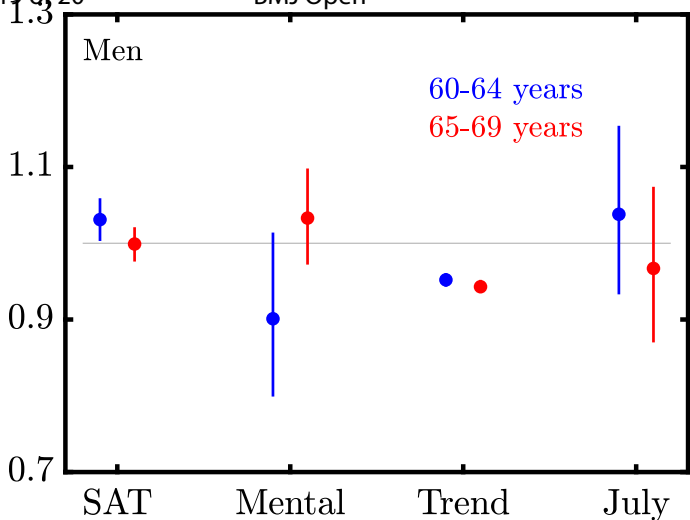
**Figure 2.** **A)** Forest plot depicting the association between summer CVD mortality rates and nocturnal SAT anomalies for middle- and older-aged men in England & Wales from 2001-2015. **B)** Forest plot depicting the association between summer CVD mortality rates and nocturnal SAT anomalies for middle- 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.

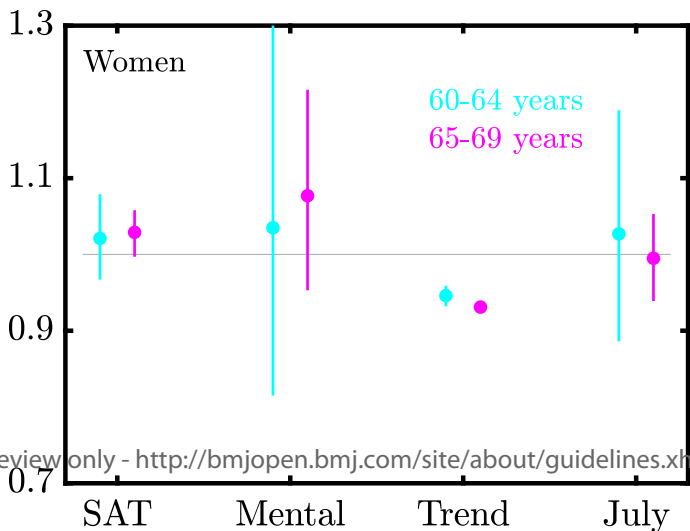
**Figure 4.** Forest plot depicting the association between summer CVD mortality rates and nocturnal SAT anomalies for middle- and older-aged men in King County, Washington United States from 2001-2015. Covariates includes PM2.5, trend, and month (reference to June).



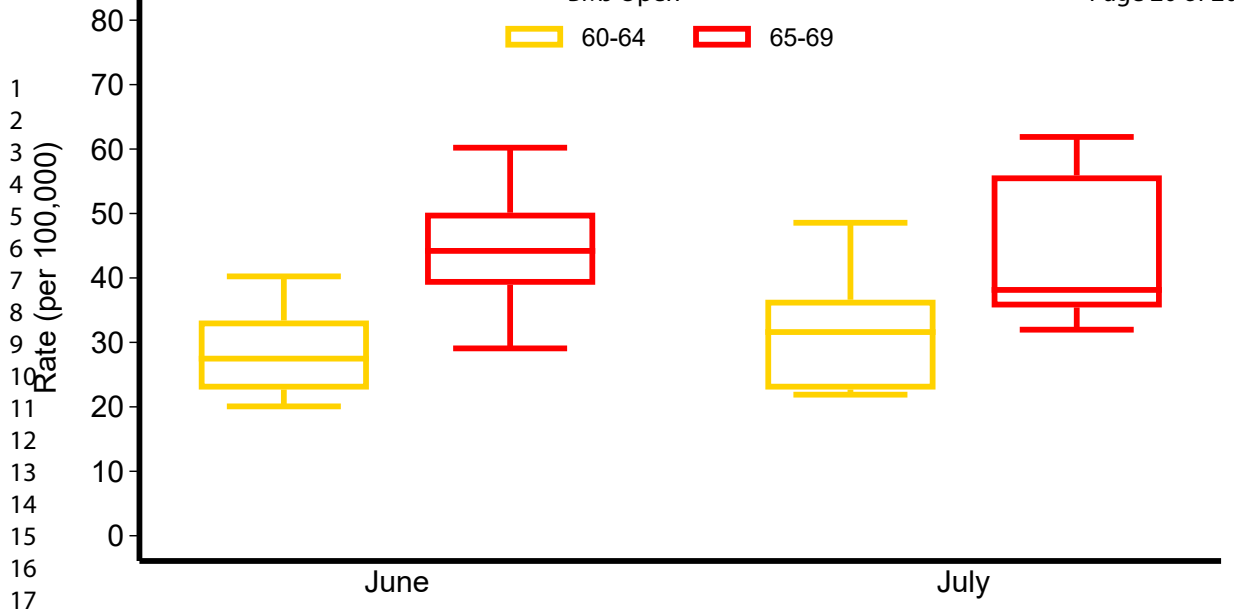
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15



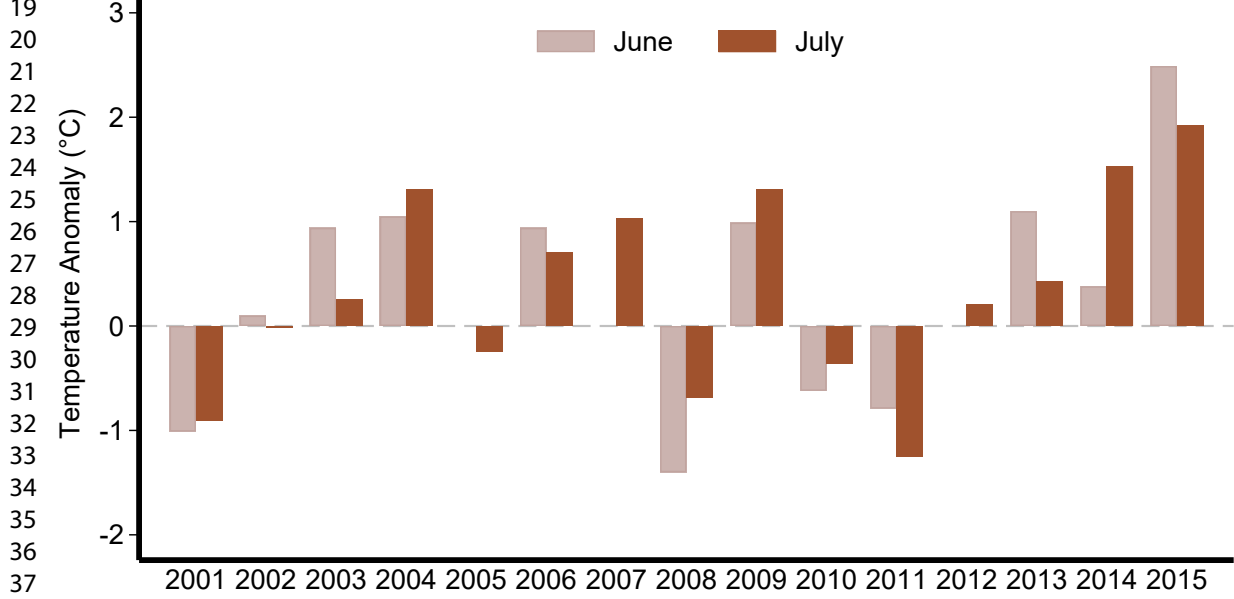
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33



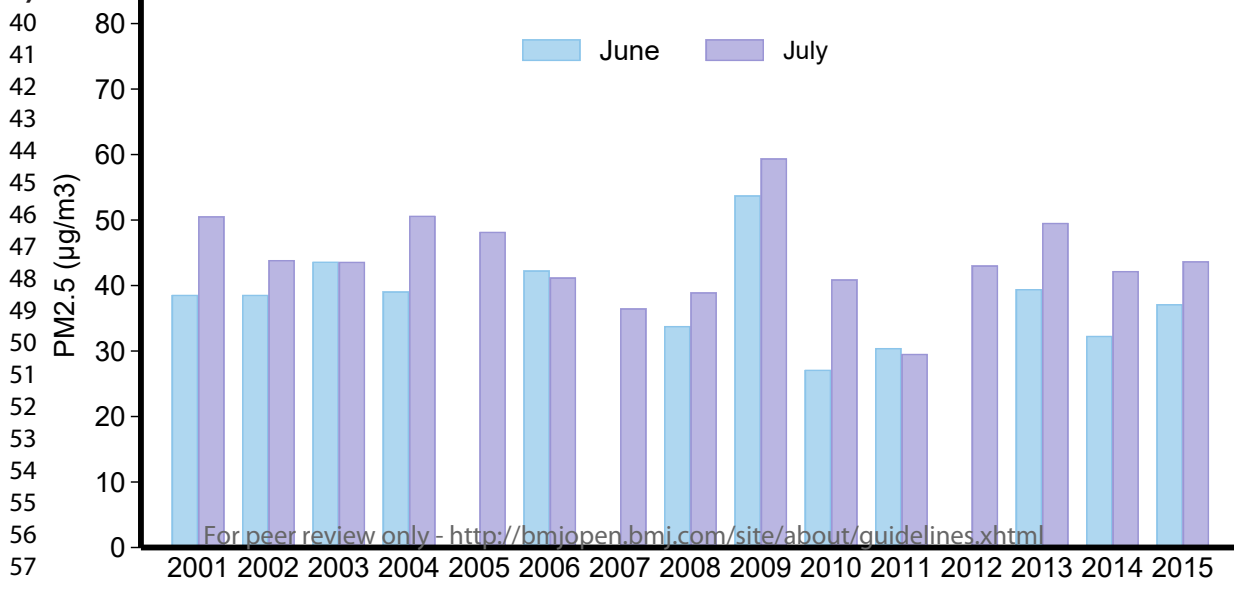
A)

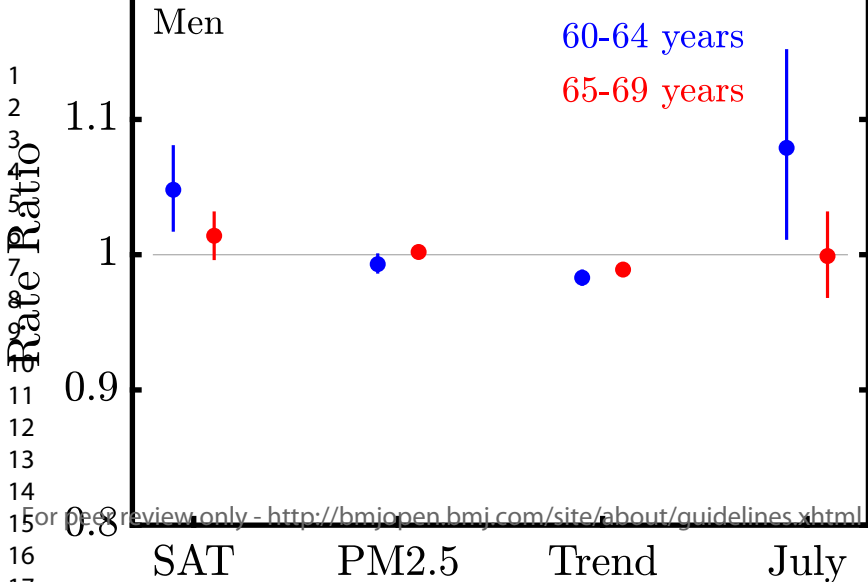


B)



C)





# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056806.R1
Article Type:	Original research
Date Submitted by the Author:	27-Dec-2021
Complete List of Authors:	Majeed, Haris; University of Toronto Floras, John; University of Toronto Temerty Faculty of Medicine, Department of Medicine
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Epidemiology, Global health, Health services research, Cardiovascular medicine
Keywords:	Cardiology < INTERNAL MEDICINE, PUBLIC HEALTH, Cardiac Epidemiology < CARDIOLOGY

SCHOLARONE™  
Manuscripts





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3  
4 **Warmer summer nocturnal surface air temperatures and cardiovascular disease death risk: a population-**  
5 **based study**  
6  
7  
8  
9

10 Haris Majeed<sup>1\*</sup> & John S Floras<sup>1,2</sup>  
11  
12  
13

14  
15 <sup>1</sup> Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada  
16

17  
18 <sup>2</sup> University Health Network and Sinai Health Division of Cardiology, Department of Medicine, University of  
19 Toronto, Toronto, Ontario, Canada  
20  
21  
22  
23  
24

25 \*Corresponding Author:

26 Haris Majeed, HBSc, MSc

27 University of Toronto

28 Toronto, ON

29 Canada M5S 1A8

30 Email: [haris.majeed@utoronto.ca](mailto:haris.majeed@utoronto.ca)

31 Phone: +1 (416) 946-8286  
32  
33  
34  
35

36 Word Count: 3125  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

December 18, 2021

## 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 autocorrelative 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<sup>1</sup>. With warm spells of extreme or sustained elevation in average summer surface air temperatures (SAT) occasioning surges in deaths and hospitalisations<sup>2-5</sup>, their potential contribution to cardiovascular events has been a focus of vigorous recent research<sup>6</sup>. Findings thus far, with respect to age and sex, have been inconsistent<sup>6</sup>. 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 ( $\geq 65$  years) women than men<sup>5,7-9</sup>. Other European studies report the opposite, with men more at risk of an acute CVD event during periods of extreme summer SAT<sup>10,11</sup>. Some have also identified a significant effect of summer average/diurnal SAT on CVD mortality amongst men aged  $< 65$  years<sup>11-13</sup>. Social determinants, including the low prevalence of residential air-conditioning in Europe, may contribute to such variance<sup>9,14</sup>.

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

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<sup>22</sup>) 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<sup>23</sup>, 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<sup>24</sup>. 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<sup>15</sup>.

## 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<sup>25</sup>. Guided by previous observations of positive associations between summer nocturnal SAT and mortality<sup>5,16</sup>, 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/country/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<sup>26</sup>.

Minimum SAT was used as a proxy for nocturnal SAT<sup>15</sup>. Since air pollution (i.e. through particulate matter 2.5 [PM<sub>2.5</sub>]) can influence local CVD events<sup>27</sup>, we included United States Environmental Protection Agency (EPA): <https://www.epa.gov/outdoor-air-quality-data/download-daily-data>. PM<sub>2.5</sub> 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

1  
2 110 factor for CVD death among adults over 60 years of age<sup>28</sup>) for the years 2001-2015 were extracted from Office  
3  
4 111 for National Statistics (ONS, reference #: 007957) data:  
5  
6 112 <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deaths>  
7  
8 113 [bymonthofoccurrenceaged60andoverbysingleyearofagesexandspecifiedcausesenglandandwales2001to2015](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deaths/bymonthofoccurrenceaged60andoverbysingleyearofagesexandspecifiedcausesenglandandwales2001to2015) we  
9  
10 114 extracted 2001-2015. CVD death was defined as per the International Classification of Diseases (ICD), tenth  
11  
12 115 revision (ICD-10: I00-I99) criteria, whereas deaths due to ‘mental and behavioural disorders’ were defined as  
13  
14 116 ICD-10: F00-F99. For King County, sex- and age-specific CVD mortality for June and July for the years 2001-  
15  
16 117 2015 were extracted from Centers for Disease Control and Prevention (CDC) WONDER data<sup>24</sup>.  
18

19 118 Sex-specific analyses were partitioned into two age groups: 60-64 years and 65-69 years. We elected to  
20  
21 119 exclude from analysis younger adults, due to their lower CVD event rates and older adults, since in England the  
22  
23 120 cause of death of individuals  $\geq 75$  years of age is likely to be misclassified, due to their higher prevalence of  
24  
25 121 comorbid conditions<sup>29</sup>. Numerators of region-specific CVD deaths were based on the presence of one or more  
26  
27 122 ICD-10 codes listed on each death record in a given month of the year, with denominators established on mid-  
28  
29 123 year annual population estimates for the sum of England plus Wales and similarly for King County. Data were  
30  
31 124 stratified by sex and age group. Monthly summer CVD and mental and behavioural mortality rates were  
32  
33 125 computed by region- sex- and age-specific deaths occurring each month of the year and were reported as the  
34  
35 126 number of men and women deaths per 100,000 persons.  
36  
37  
38 127  
39

#### 40 128 *Statistical Analysis*

41  
42 129 Since atmospheric systems act on long time-scales, our primary exposures (June and July) nocturnal  
43  
44 130 SAT were standardized as monthly anomalies from a reference period<sup>22</sup>. For the purpose of the present analysis,  
45  
46 131 SAT anomalies were defined as deviations from a 30-year (1981-2010) baseline average<sup>22</sup>. For each year of the  
47  
48 132 exposure period (2001-2015), June and July nocturnal SAT anomalies were computed separately for England  
49  
50 133 and Wales and for King County by subtracting these regions’ months’ averages from their respective 1981-2010  
51  
52 134 average nocturnal SAT.  
53

54  
55 135 CVD mortality rates were found to be auto-correlated (i.e. rates in the prior and subsequent years were  
56  
57 136 significantly correlated). Additionally, the outcome variable’s variance was much greater than its mean, leading  
58  
59  
60

1  
2 137 to over-dispersion of data<sup>22,30</sup>. Moreover, a previous study showed that the incidence of mental health and  
3  
4 138 behavioural distress in England and Wales has both increased over time and been identified as a strong risk  
5  
6 139 factor for associations between diurnal SAT and cause-specific adult mortality<sup>13</sup>. To address these issues in our  
7  
8 140 models, we used negative binomial regression with auto-correlated residuals of order one<sup>22</sup> to assess the  
9  
10 141 association between sex- and age-specific CVD mortality rates to summer nocturnal SAT for England and  
11  
12 142 Wales from 2001-2015, while controlling for each of mental health and behaviour mortality rates, an increase or  
13  
14 143 decrease in CVD mortality rates with respect to the annual calendar year (i.e. trend), and the summer month as  
15  
16 144 our covariates. For King County, we used quasi-Poisson to assess all associations, while controlling for each of  
17  
18 145 PM<sub>2.5</sub>, an increase or decrease in CVD mortality rates with respect to the annual calendar year (i.e. trend), and  
19  
20 146 the summer month as our covariates. Findings are reported as incidence rate ratios (RR) and interpreted as  
21  
22 147 change for one-unit increase of the exposure variable<sup>22,30</sup>. Confidence intervals (CI) were evaluated at 95%,  
23  
24 148 along with Student's two-sided *t*-tests. Microsoft Excel (version 2013), RStudio (version 4.1.1), and STATA  
25  
26 149 (version 15) were used for computation, analyses, and figure composition.  
27  
28  
29  
30  
31  
32  
33  
34  
35

## 36 153 **Results**

37  
38 154 Within the selected cohorts, over the years 2001-2015, there were 39,912 (68.9% men) CVD deaths  
39  
40 155 recorded in England and Wales and 488 male CVD deaths (54.1% in the group aged 65-69 years) in King  
41  
42 156 County. Over this time period, CVD rates declined substantially in both regions annually (Table 1), and notably  
43  
44 157 over the summer months (Supplementary Figure 1).  
45

46 158 For England and Wales, CVD mortality rates, categorized by sex, age, and month, are illustrated in  
47  
48 159 Figure 1A. The older (65-69 years) men and women exhibited higher CVD mortality rates than during both  
49  
50 160 summer months. CVD mortality rates were consistently higher amongst men than women. Summer nocturnal  
51  
52 161 SAT anomalies are plotted in Figure 1B. June anomalies ranged from -0.63°C (2015) to 1.17°C (2003-  
53  
54 162 corresponding to the notable western European heatwave). July anomalies ranged from -1.37°C (2011) to  
55  
56 163 1.73°C (2006).  
57  
58  
59  
60



1  
2 164 After adjusting for covariates, associations between exposure (a 1-unit increase in summer nocturnal  
3  
4 165 SAT<sup>30</sup>) and CVD mortality rates, stratified by sex and age appear in Figure 2. As shown in Figure 2A, a +1°C  
5  
6 166 anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality  
7  
8 167 rates among men aged 60-64 [adjusted RR 1.031; 95% CI, 1.003-1.059] but not in those aged 65-69 years  
9  
10 168 [adjusted RR 0.999; 95% CI, 0.976-1.021], nor in adult women in either age group (Figure 2B). There were no  
11  
12 169 such associations with anomalous summer diurnal SAT as exposures in men or women of either age group (not  
13  
14 170 shown).

15  
16  
17 171 For King County, summer CVD mortality rates were also higher within the older male cohort (Figure  
18  
19 172 3A). Summer nocturnal SAT anomalies are plotted in Figure 3B and Figure 3C. June SAT anomalies ranged  
20  
21 173 from -1.4°C (2008) to 2.49° (2015, a year when western North America recorded a record number of heatwaves  
22  
23 174 and forest fires attributed to a strong El Niño event<sup>22</sup>). July anomalies ranged from -1.25°C (2011) to 1.92°C  
24  
25 175 (also in 2015). The smaller land mass of King County permits integration of PM<sub>2.5</sub> into these models. In general,  
26  
27 176 King County PM<sub>2.5</sub> levels generally were higher in July than in June, 2001-2015. After adjusting for covariates,  
28  
29 177 a +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD  
30  
31 178 mortality rates among men aged 60-64 [adjusted RR 1.049; 95% CI, 1.017-1.081] but not in those aged 65-69  
32  
33 179 [adjusted RR 1.014; 95% CI, 0.996-1.032] (Figure 4).  
34  
35  
36 180  
37  
38 181  
39

## 40 182 Discussion

41  
42 183 CVD mortality rates in both England and Wales and in King County, Washington State declined  
43  
44 184 substantially between 2001 and 2015 (Table 1) in parallel with greater population uptake of effective primary  
45  
46 185 and secondary preventive therapies. Nonetheless, considerable residual risk persists, and in England and Wales,  
47  
48 186 event rates remain >50% higher in adults aged 65-69 than in those aged 60-64 years.

49  
50 187 High summer nocturnal SAT may be a source of such risk<sup>6</sup>. Such high summer SAT has been associated  
51  
52 188 with increased cause-specific adult mortality in various high-income regions<sup>3-8,10,13,16,18</sup>. Importantly, in recent  
53  
54 189 years populous mid- to high-latitude regions have experienced a proportionately rise in nocturnal than in  
55  
56 190 daytime summer heat intensity<sup>15</sup>. The present work is one of few investigating potential associations between  
57  
58  
59

1  
2 191 summer nocturnal SAT and CVD mortality rates. Our finding of significant associations, in men aged 60-64  
3  
4 192 residing in England and Wales or in King County, Washington, United States, between +1°C summer nocturnal  
5  
6 193 SAT anomalies and summer CVD mortality rates, support this concept.

8 194 An association between summer nocturnal SAT and CVD mortality is biologically plausible hypothesis.  
9  
10 195 The incidence and severity of CVD events can be exacerbated by temporal dys-synchrony between  
11  
12 196 cardiovascular circadian clock gene rhythms and exogenous or endogenous homeostatic stresses<sup>31</sup>. One such  
13  
14 197 stress is warmer nocturnal SAT, which also amplifies self-reported sleep-deprivation, itself a risk factor for adult  
15  
16 198 heart disease mortality<sup>21</sup>. Waking itself, whether concordant with normal cardiovascular circadian rhythms or  
17  
18 199 due to interrupted sleep, triggers increases in heart rate, vascular resistance, and blood pressure and predisposes  
19  
20 200 to thrombosis<sup>32</sup>.

23 201 No significant association was detected in English and Welsh women, but their event rates were <50%  
24  
25 202 of males of comparable age (Table 1). Thus, there may have been insufficient statistical power to appreciate a  
26  
27 203 qualitatively similar association in women, if present. On the other hand, their generally larger sweat gland  
28  
29 204 volume<sup>33</sup> predisposes men exposed to heat to greater insensible fluid loss and intra-vascular volume depletion.  
30  
31 205 However, the authors of a recent systematic review of 36 studies attributed the greater male susceptibility to  
32  
33 206 heat-attributable illnesses to their psychology and behavior rather than to any physiological dimorphism<sup>34</sup>.

35 207 Several studies<sup>4,15-18</sup> report a positive association between summer nocturnal SAT and either all-cause,  
36  
37 208 heat-related, or CVD mortality. In one focusing on London, United Kingdom, nighttime temperatures had a  
38  
39 209 more potent influence than daytime exposure on all-cause mortality, ischemic heart disease events, and stroke,  
40  
41 210 particularly in those  $\leq 64$  years of age; sex-specific risk was not reported<sup>16</sup>. A recent investigation of  
42  
43 211 approximately 10 years' data for 11 southern European cities reported associations between the relative risk of  
44  
45 212 cause-specific mortality and the magnitude and duration of nocturnal SAT exceeding 20°C, where four of these  
46  
47 213 cities, yielded a significant association with CVD event rates<sup>17</sup>. However, sex- and age- specific associations  
48  
49 214 were not reported, and our work, in contrast, considered monthly anomalies relative to a 30-year reference  
50  
51 215 period as the thermal exposure of interest.

54 216 Other European studies also noted significant positive relationships between average/diurnal SAT and  
55  
56 217 all-cause/CVD mortality in men <65 years or in working-age or middle-aged men<sup>10-12</sup>. An Australian group

1  
2 218 documented a significant association between ambient temperature in Queensland and the relative risk of CVD  
3  
4 219 hospitalization over a comparable time period (1995-2016); risk was greater in men than in women and in  
5  
6 220 adults <70 years of age when compared with those 70 years and older<sup>35</sup>.  
7

8 221 The non-significant trends observed for the older men in the present analysis and in these previous  
9  
10 222 reports may reflect resilient survivor bias or signal the exponential accretion of coronary and peripheral vascular  
11  
12 223 disease with age, resulting in more conventional than anomalous temperature-triggered cardiovascular events.  
13  
14 224 Conversely, younger men may be more susceptible to increased summer nocturnal SAT. It has been noted<sup>35</sup> that  
15  
16 225 endogenous testosterone, which declines with age, is in mice an heat-stress susceptibility factor<sup>36</sup>.  
17

18 226 Nearly a third of United Kingdom's population resides in southeast England<sup>15</sup>. This region's  
19  
20 227 employment opportunities attract young and middle-aged men<sup>37</sup>. Urban design is also an important parameter,  
21  
22 228 because majority of daytime summer heat is absorbed, then radiates locally at night<sup>15</sup>. Residential air  
23  
24 229 conditioning is less common in both England and Wales and in Seattle, Washington, relative to other high-  
25  
26 230 income mid- to high-latitude nations such as the United States or Canada<sup>14</sup>. If uncomfortable warmth obliges  
27  
28 231 individuals to open their bedroom windows, this action, in turn might increase CVD event risk by exposing  
29  
30 232 sleepers to more intense outside nocturnal heat, atmospheric pollutants<sup>27</sup>, and road and aircraft noise<sup>29</sup>, which in  
31  
32 233 adult men increases the risk of developing hypertension<sup>16,38</sup>. Nighttime noise-related stress<sup>38</sup> and warmer  
33  
34 234 summer SAT also disrupt sleep, especially among vulnerable populations with lower socioeconomic status<sup>21</sup>.  
35  
36 235 Sleep deprivation, in turn can increased central sympathetic outflow<sup>39</sup>, which over time can increase blood  
37  
38 236 pressure and induce insulin resistance<sup>40</sup>. Dry air can exacerbate snoring<sup>41</sup>; in middle-aged men snoring is  
39  
40 237 common, as is obstructive sleep apnea, which can trigger nocturnal CVD events<sup>42</sup>.  
41  
42  
43

44 238 Although we cannot infer causality from our models, our age- and sex-specific analyses nonetheless  
45  
46 239 represent a novel contribution to the present literature. The principal strengths of this ecological study accrue  
47  
48 240 from the large population sampled and its linkage with rigorous national mortality and meteorological data. The  
49  
50 241 principal limitations are lack of access to 15-year sex- and age-specific granular monthly/weekly data (i.e.  
51  
52 242 district or city level) outcome and exposure data. The latter might have identified stronger associations between  
53  
54 243 nighttime summer heat and CVD mortality in populous urban regions, where ~90% of citizens are projected to  
55  
56 244 reside within a few decades<sup>15</sup>. Nonetheless, in our supplementary analysis of King County, the effect and  
57  
58  
59

1  
2 245 direction of summer nocturnal SAT on CVD mortality among men aged 60-64 years were consistent with our  
3  
4 246 primary analysis. The majority of adult men in England and Washington State retire at age 65. It is conceivable  
5  
6 247 that the anxieties/mental health of men in their early sixties anticipating retirement and reduced income or  
7  
8 248 benefits added to their risk for CVD death, as posited by a British study<sup>13</sup>, but this potential confounder was  
9  
10 249 adjusted for, in our models. Lastly, we are not able to adjust for potential confounding factors such as local  
11  
12 250 public health initiatives, or in secular trends in the discovery and implementation of effective primary and  
13  
14 251 secondary CVD risk prevention strategies, cause of death misclassification, or ICD coding error.  
15  
16  
17 252  
18

## 19 253 **Conclusion**

20  
21 254 Our observation of an association between warm summer nighttime conditions and CVD mortality risk amongst  
22  
23 255 men aged 60-64 year residing in England and Wales was replicated in our analysis of comparable American data  
24  
25 256 from King County, Washington State. The present findings should stimulate similar investigation of exposure  
26  
27 257 and event rates in other populous mid- to high-latitude regions. Considering the growing likelihood of extreme  
28  
29 258 summers in Western United States and United Kingdom<sup>23</sup>, our results invite preventive population health  
30  
31 259 initiatives and novel urban policies aimed at reducing future risk of CVD events.  
32  
33  
34 260

## 35 261 **Author contributions**

36  
37 262 HM and JSF contributed to the conception or design of the work. HM and JSF contributed to the acquisition,  
38  
39 263 analysis, or interpretation of data for the work. HM drafted the initial manuscript. JSF critically revised the  
40  
41 264 manuscript. Both authors gave final approval and agree to be accountable for all aspects of work ensuring  
42  
43 265 integrity and accuracy.  
43  
44 266

## 45 267 **Declaration of conflicting interests**

46 268 The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication  
47  
48 269 of this article.  
49  
50 270

## 52 271 **Funding**

53  
54 272 The authors received no financial support for the research, authorship and/or publication of this article.  
55  
56  
57 273  
58  
59  
60

1  
2 274 **Data sharing statement**

3  
4 275 All data related to this study has been provided as weblinks in the 'Methods' section.  
5

6 276

7  
8 277 **Ethics approval statement**

9  
10 278 No ethics approval was needed to conduct this study.  
11

12 279

13  
14 280 **Patient and public involvement**

15  
16 281 Patients were not involved in the design, or conduct, or reporting, or dissemination plans of this research study.  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## References

1. Timmis A, Townsend N, Gale C, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. *Eur Heart J* 2018; 39: 508–579.
2. Schwartz J, Samet JM, Patz JA. Hospital Admissions for Heart Disease: The Effects of Temperature and Humidity. *Epidemiology* 2004; 15: 755–761.
3. Michelozzi P, Accetta G, De Sario M, et al. High Temperature and Hospitalizations for Cardiovascular and Respiratory Causes in 12 European Cities. *Am J Respir Crit Care Med* 2009; 179: 383–389.
4. D'Ippoliti D, Michelozzi P, Marino C, et al. The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project. *Environ Health* 2010; 9: 37.
5. Achebak H, Devolder D, Ballester J. Trends in temperature-related age-specific and sex-specific mortality from cardiovascular diseases in Spain: a national time-series analysis. *Lancet Planet Health* 2019; 3: e297–e306.
6. Son J-Y, Liu JC, Bell ML. Temperature-related mortality: a systematic review and investigation of effect modifiers. *Environ Res Lett* 2019; 14: 073004.
7. Saucy A, Ragetti MS, Vienneau D, et al. The role of extreme temperature in cause-specific acute cardiovascular mortality in Switzerland: A case-crossover study. *Sci Total Environ* 2021; 790: 147958.
8. van Steen Y, Ntarladima A-M, Grobbee R, et al. Sex differences in mortality after heat waves: are elderly women at higher risk? *Int Arch Occup Environ Health* 2019; 92: 37–48.
9. Mari-Dell'Olmo M, Tobías A, Gómez-Gutiérrez A, et al. Social inequalities in the association between temperature and mortality in a South European context. *Int J Public Health* 2019; 64: 27–37.
10. Näyhä S. Environmental temperature and mortality. *Int J Circumpolar Health* 2005; 64: 451–458.
11. Rowland ST, Boehme AK, Rush J, et al. Can ultra short-term changes in ambient temperature trigger myocardial infarction? *Environ Int* 2020; 143: 105910.
12. Rocklöv J, Forsberg B, Ebi K, et al. Susceptibility to mortality related to temperature and heat and cold wave duration in the population of Stockholm County, Sweden. *Glob Health Action* 2014; 7: 10.3402/gha.v7.22737.
13. Gasparrini A, Armstrong B, Kovats S, et al. The effect of high temperatures on cause-specific mortality in England and Wales. *Occup Environ Med* 2012; 69: 56–61.
14. Arbuthnott KG, Hajat S. The health effects of hotter summers and heat waves in the population of the United Kingdom: a review of the evidence. *Environ Health* 2017; 16: 119.
15. Eunice Lo YT, Mitchell DM, Bohnenstengel SI, et al. U.K. Climate Projections: Summer Daytime and Nighttime Urban Heat Island Changes in England's Major Cities. *J Clim* 2020; 33: 9015–9030.
16. Murage P, Hajat S, Kovats RS. Effect of night-time temperatures on cause and age-specific mortality in London. *Environ Epidemiol* 2017; 1: e005.
17. Royé D, Sera F, Tobías A, et al. Effects of Hot Nights on Mortality in Southern Europe. *Epidemiol Camb Mass* 2021; 32: 487–498.

18. Laaidi K, Zeghnoun A, Dousset B, et al. The Impact of Heat Islands on Mortality in Paris during the August 2003 Heat Wave. *Environ Health Perspect* 2012; 120: 254–259.
19. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. *Am J Physiol - Heart Circ Physiol* 2015; 309: H1793–H1812.
20. Obradovich N, Fowler JH. Climate change may alter human physical activity patterns. *Nat Hum Behav* 2017; 1: 1–7.
21. Obradovich N, Migliorini R, Mednick SC, et al. Nighttime temperature and human sleep loss in a changing climate. *Sci Adv* 2017; 3: e1601555.
22. Majeed H, Moineddin R, Booth GL. Sea surface temperature variability and ischemic heart disease outcomes among older adults. *Sci Rep* 2021; 11: 3402.
23. Christidis N, McCarthy M, Stott PA. The increasing likelihood of temperatures above 30 to 40 °C in the United Kingdom. *Nat Commun* 2020; 11: 3093.
24. Calkins MM, Isaksen TB, Stubbs BA, et al. Impacts of extreme heat on emergency medical service calls in King County, Washington, 2007–2012: relative risk and time series analyses of basic and advanced life support. *Environ Health* 2016; 15: 13.
25. Staddon PL, Montgomery HE, Depledge MH. Climate warming will not decrease winter mortality. *Nat Clim Change* 2014; 4: 190–194.
26. Hollis D, McCarthy M, Kendon M, et al. HadUK-Grid—A new UK dataset of gridded climate observations. *Geosci Data J* 2019; 6: 151–159.
27. Analitis A, Michelozzi P, D'Ippoliti D, et al. Effects of heat waves on mortality: effect modification and confounding by air pollutants. *Epidemiol Camb Mass* 2014; 25: 15–22.
28. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* 2017; 16: 163–180.
29. Halonen JI, Hansell AL, Gulliver J, et al. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur Heart J* 2015; 36: 2653–2661.
30. Mohammad MA, Koul S, Rylance R, et al. Association of Weather With Day-to-Day Incidence of Myocardial Infarction: A SWEDEHEART Nationwide Observational Study. *JAMA Cardiol* 2018; 3: 1081–1089.
31. Durgan DJ, Young ME. The cardiomyocyte circadian clock: emerging roles in health and disease. *Circ Res* 2010; 106: 647–658.
32. Tofler Geoffrey H., Muller James E. Triggering of Acute Cardiovascular Disease and Potential Preventive Strategies. *Circulation* 2006; 114: 1863–1872.
33. Iyoho AE, Ng LJ, MacFadden L. Modeling of Gender Differences in Thermoregulation. *Mil Med* 2017; 182: 295–303.
34. Gifford RM, Todisco T, Stacey M, et al. Risk of heat illness in men and women: A systematic review and meta-analysis. *Environ Res* 2019; 171: 24–35.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
35. Lu P, Xia G, Zhao Q, et al. Temporal trends of the association between ambient temperature and hospitalisations for cardiovascular diseases in Queensland, Australia from 1995 to 2016: A time-stratified case-crossover study. *PLOS Med* 2020; 17: e1003176.
  36. Chen Y, Yu T. Testosterone mediates hyperthermic response of mice to heat exposure. *Life Sci* 2018; 214: 34–40.
  37. Andrew M, Meen G. Population structure and location choice: A study of London and South East England\*. *Pap Reg Sci* 2006; 85: 401–419.
  38. Jarup L, Babisch W, Houthuijs D, et al. Hypertension and Exposure to Noise Near Airports: the HYENA Study. *Environ Health Perspect* 2008; 116: 329–333.
  39. Taylor KS, Kucyi A, Millar PJ, et al. Association between resting-state brain functional connectivity and muscle sympathetic burst incidence. *J Neurophysiol* 2016; 115: 662–673.
  40. Ayas NT, White DP, Manson JE, et al. A Prospective Study of Sleep Duration and Coronary Heart Disease in Women. *Arch Intern Med* 2003; 163: 205–209.
  41. Lappharat S, Taneepanichskul N, Reutrakul S, et al. Effects of Bedroom Environmental Conditions on the Severity of Obstructive Sleep Apnea. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med* 2018; 14: 565–573.
  42. Lee SA, Amis TC, Byth K, et al. Heavy Snoring as a Cause of Carotid Artery Atherosclerosis. *Sleep* 2008; 31: 1207–1213.



**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:**

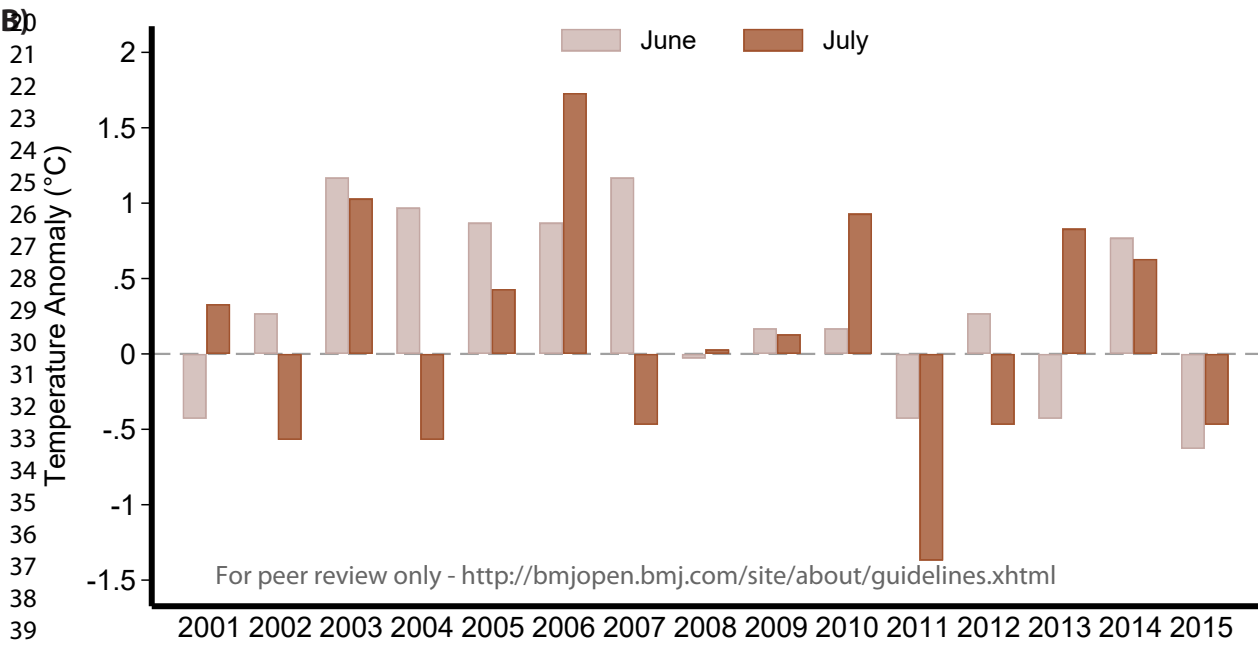
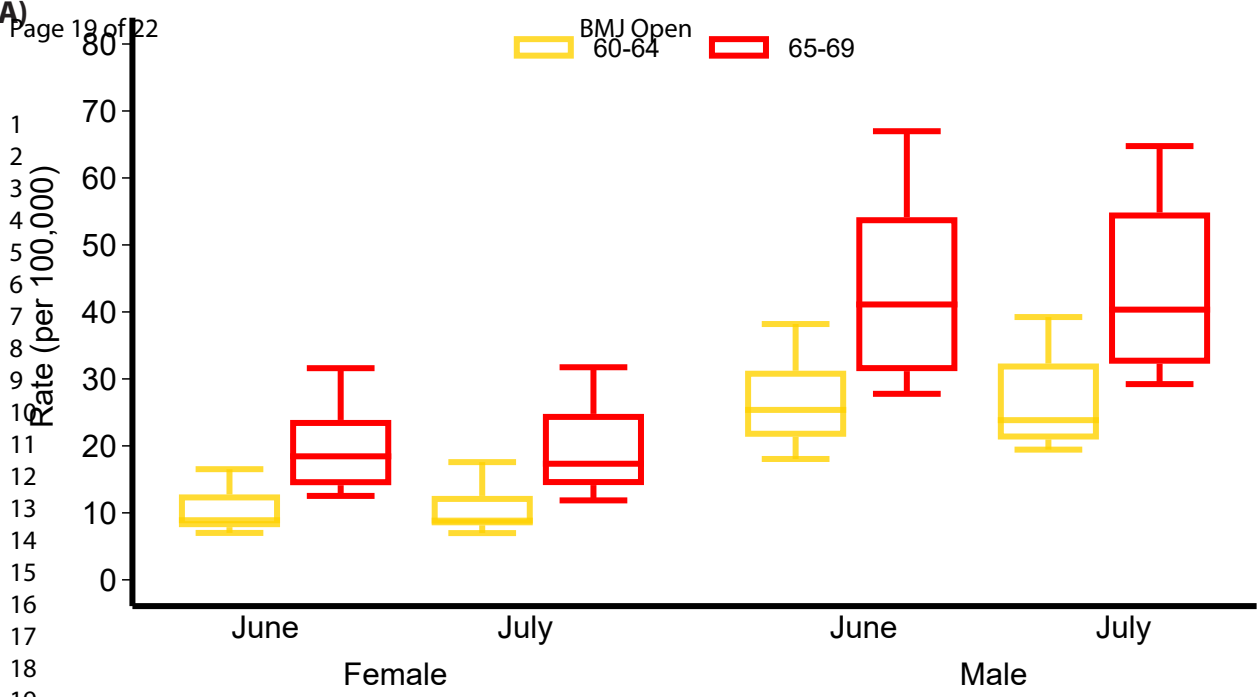
**Figure 1:** **A)** Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in England & Wales from 2001-2015. **B)** Month-specific summer (June-July) nocturnal SAT anomalies (based on deviations from the baseline period of 1981-2010) in England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

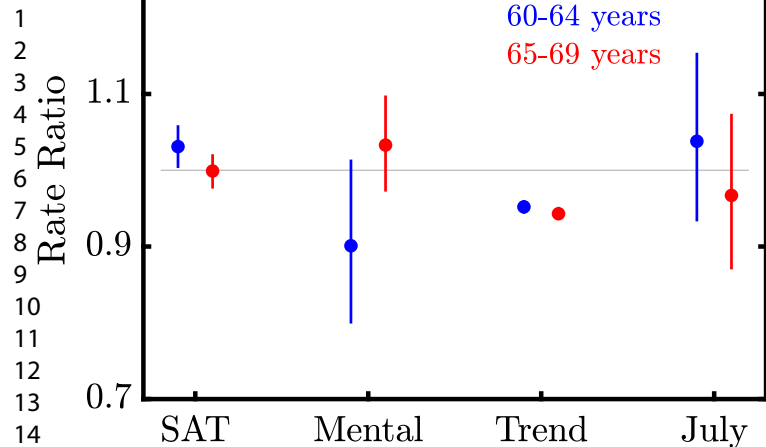
**Figure 3:** **A)** Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in King County, Washington, United States from 2001-2015. **B)** Month-specific summer (June-July) night SAT anomalies (based on deviations from the baseline period of 1981-2010) in King County. **C)** Month-specific summer (June-July) PM<sub>2.5</sub> 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<sub>2.5</sub>, trend, and month (reference to June).

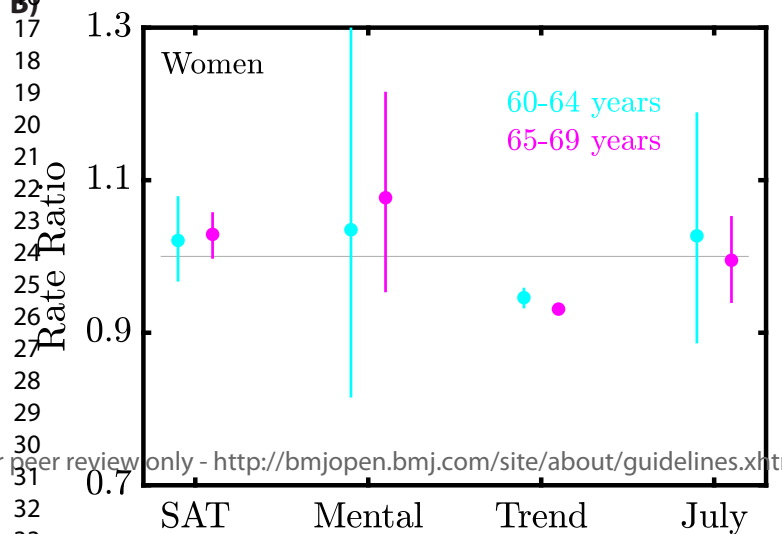
**Supplementary Figure 1:** Monthly summer (6=June, 7=July) cardiovascular mortality trends by age-groups among (A) men and (B) women from 2001-2015 in England and Wales.

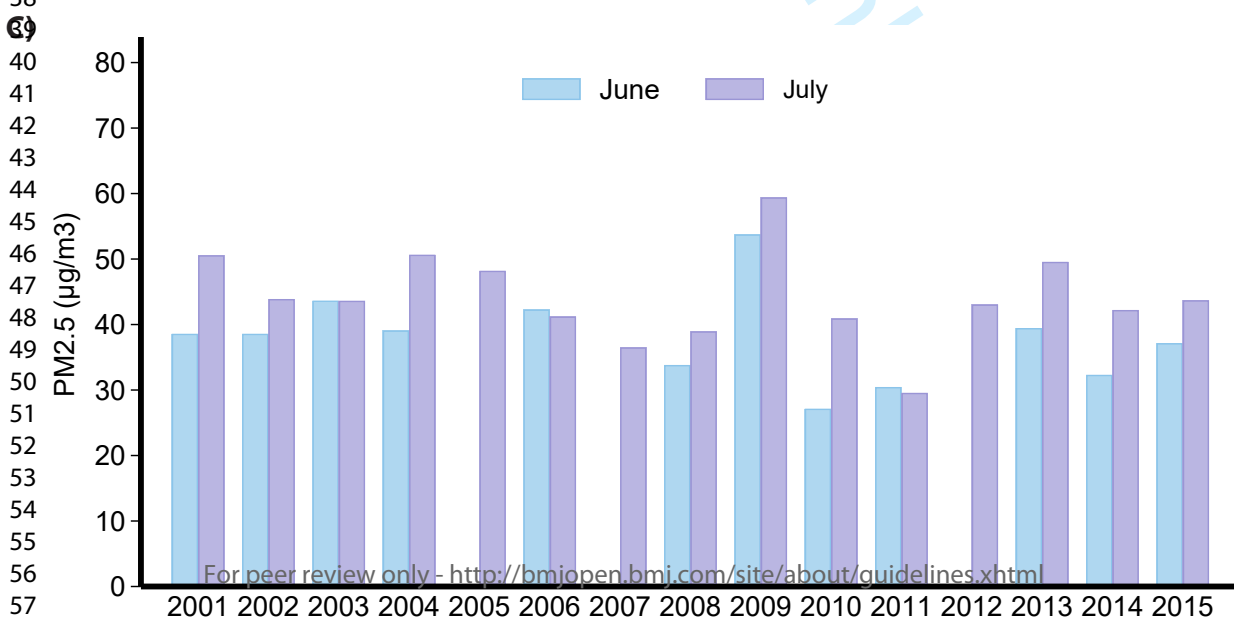
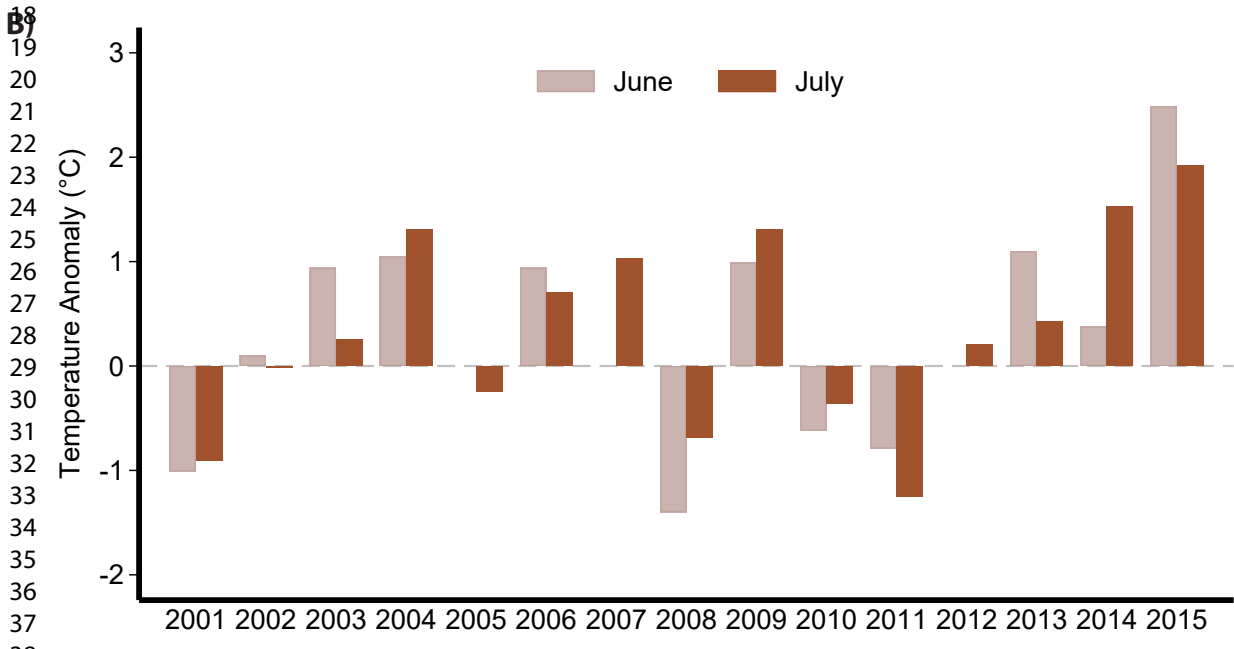
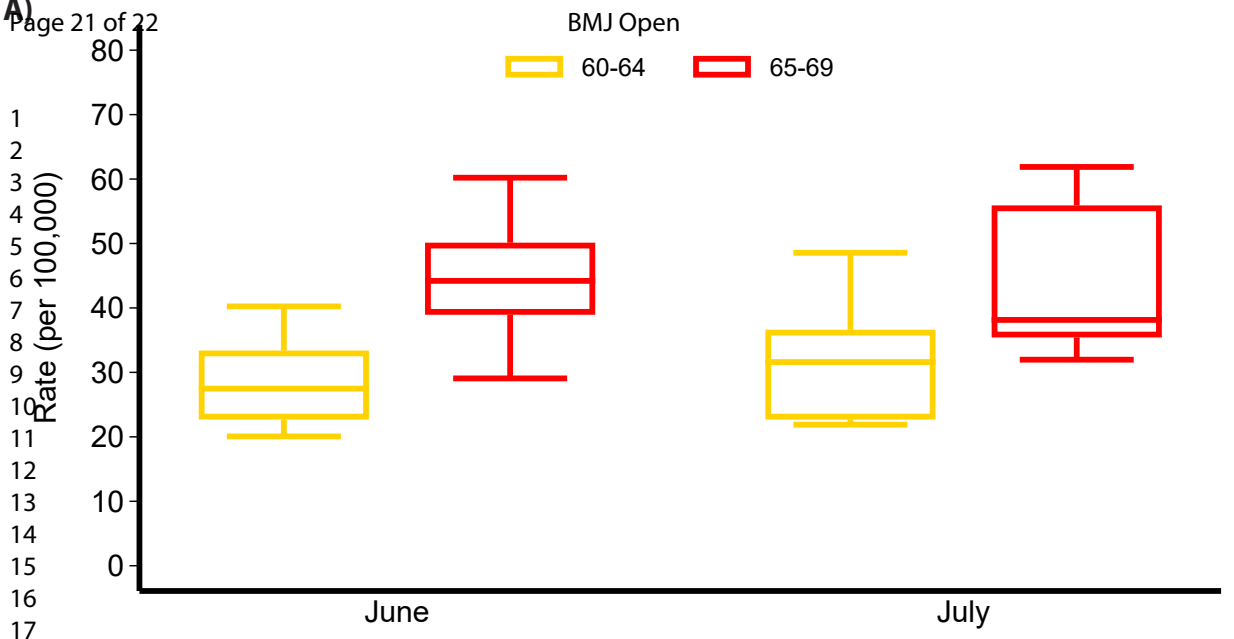


A)



B)





Men

60-64 years

65-69 years

Rate Ratio

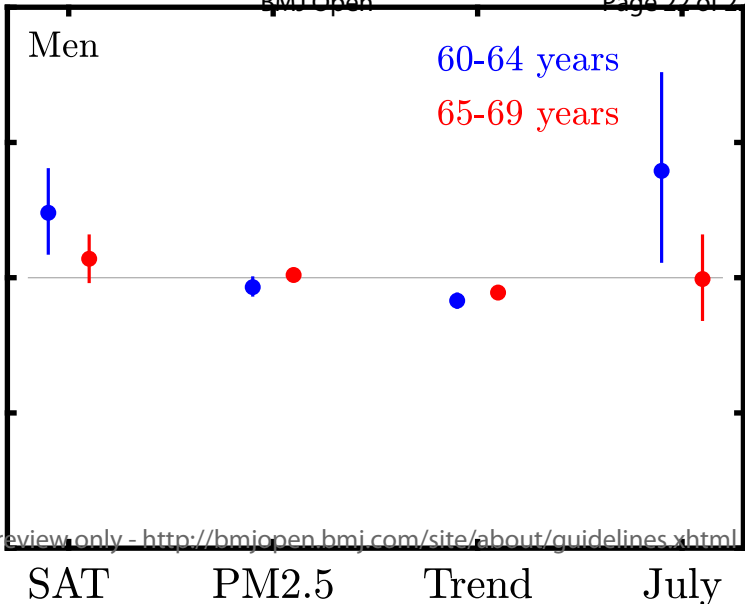
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
171.2  
1.1  
1  
0.9  
0.8

SAT

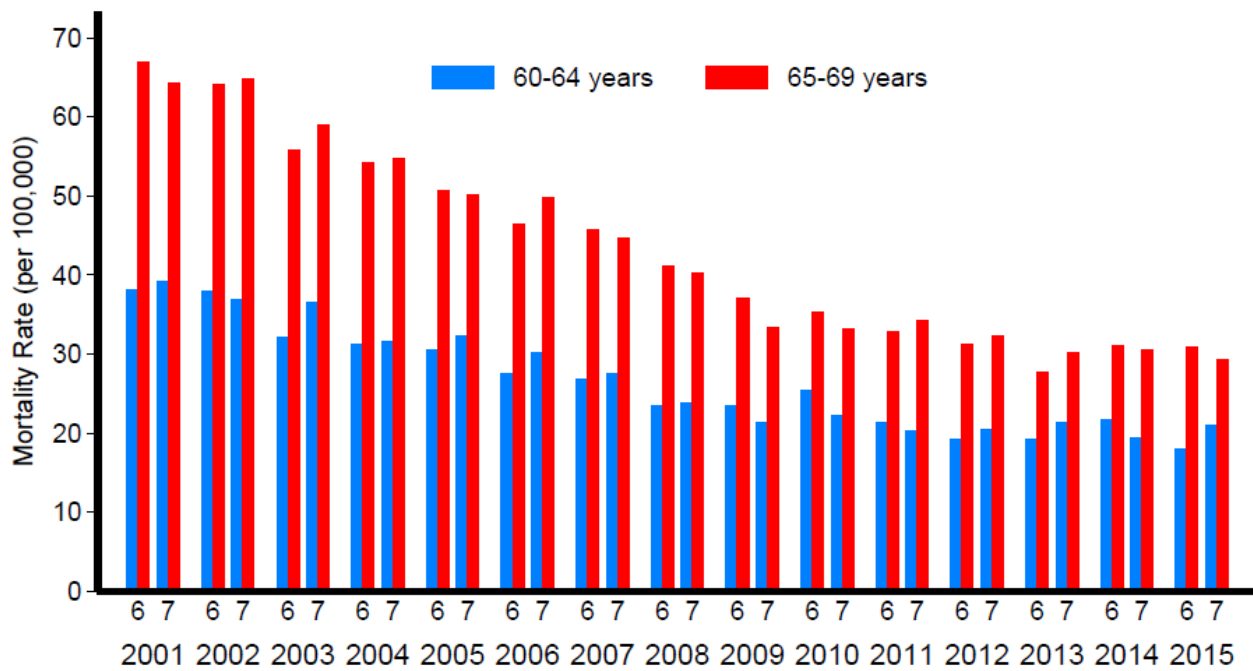
PM2.5

Trend

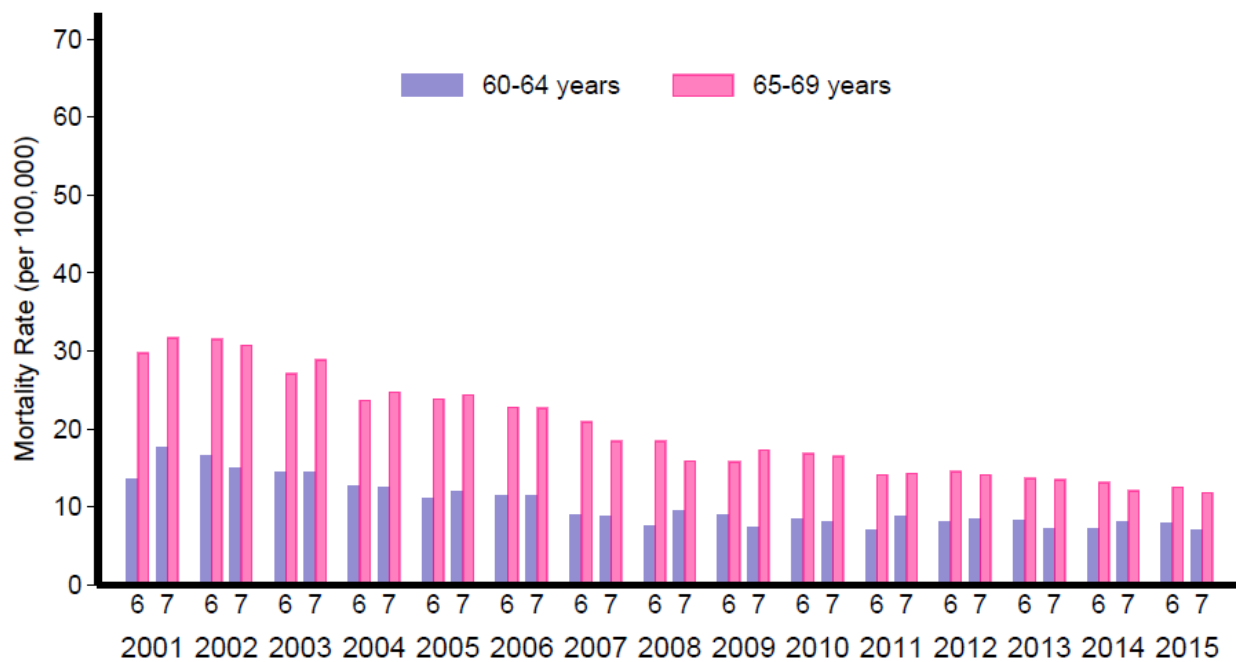
July

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

## 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.

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-056806.R2
Article Type:	Original research
Date Submitted by the Author:	16-Jan-2022
Complete List of Authors:	Majeed, Haris; University of Toronto Floras, John; University of Toronto Temerty Faculty of Medicine, Department of Medicine
<b>Primary Subject Heading</b>:	Public health
Secondary Subject Heading:	Epidemiology, Global health, Health services research, Cardiovascular medicine
Keywords:	Cardiology < INTERNAL MEDICINE, PUBLIC HEALTH, Cardiac Epidemiology < CARDIOLOGY

SCHOLARONE™  
Manuscripts





I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our [licence](#).

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which [Creative Commons](#) licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

1  
2  
3  
4 **Warmer summer nocturnal surface air temperatures and cardiovascular disease death risk: a population-**  
5 **based study**  
6  
7  
8  
9

10 Haris Majeed<sup>1\*</sup> & John S Floras<sup>1,2</sup>  
11  
12  
13

14  
15 <sup>1</sup> Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada  
16

17  
18 <sup>2</sup> University Health Network and Sinai Health Division of Cardiology, Department of Medicine, University of  
19 Toronto, Toronto, Ontario, Canada  
20  
21  
22  
23  
24

25 \*Corresponding Author:

26 Haris Majeed, HBSc, MSc

27 University of Toronto

28 Toronto, ON

29 Canada M5S 1A8

30 Email: [haris.majeed@utoronto.ca](mailto:haris.majeed@utoronto.ca)

31 Phone: +1 (416) 946-8286  
32  
33  
34  
35

36 Word Count: 3116  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

January 16, 2022

## 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 autocorrelative 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<sup>1</sup>. With warm spells of extreme or sustained elevation in average summer surface air temperatures (SAT) occasioning surges in deaths and hospitalisations<sup>2-5</sup>, their potential contribution to cardiovascular events has been a focus of vigorous recent research<sup>6</sup>. Findings thus far, with respect to age and sex, have been inconsistent<sup>6</sup>. 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 ( $\geq 65$  years) women than men<sup>5,7-9</sup>. Other European studies report the opposite, with men more at risk of an acute CVD event during periods of extreme summer SAT<sup>10,11</sup>. Some have also identified a significant effect of summer average/diurnal SAT on CVD mortality amongst men aged  $< 65$  years<sup>11-13</sup>. Social determinants, including the low prevalence of residential air-conditioning in Europe, may contribute to such variance<sup>9,14</sup>.

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

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<sup>22</sup>) 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<sup>23</sup>, 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<sup>24</sup>. 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<sup>15</sup>.

## 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<sup>25</sup>. Guided by previous observations of positive associations between summer nocturnal SAT and mortality<sup>5,16</sup>, 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/country/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<sup>26</sup>.

Minimum SAT was used as a proxy for nocturnal SAT<sup>15</sup>. Since air pollution (i.e. through particulate matter 2.5 [PM<sub>2.5</sub>]) can influence local CVD events<sup>27</sup>, we included United States Environmental Protection Agency (EPA): <https://www.epa.gov/outdoor-air-quality-data/download-daily-data>. PM<sub>2.5</sub> 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

1  
2 110 established strong risk factor for CVD death among adults over 60 years of age<sup>28</sup>) for the years 2001-2015 were  
3  
4 111 extracted from Office for National Statistics (ONS, reference #: 007957) data:  
5  
6 112 <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deaths>  
7  
8 113 [bymonthofoccurrenceaged60andoverbysingleyearofagesexandspecifiedcausesenglandandwales2001to2015](https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/adhocs/007957deaths/bymonthofoccurrenceaged60andoverbysingleyearofagesexandspecifiedcausesenglandandwales2001to2015) we  
9  
10 114 extracted 2001-2015. CVD death was defined as per the International Classification of Diseases (ICD), tenth  
11  
12 115 revision (ICD-10: I00-I99) criteria, whereas deaths due to ‘mental and behavioural disorders’ were defined as  
13  
14 116 ICD-10: F00-F99. For King County, sex- and age-specific CVD mortality for June and July for the years 2001-  
15  
16 117 2015 were extracted from Centers for Disease Control and Prevention (CDC) WONDER data<sup>24</sup>.

18  
19 118 Sex-specific analyses were partitioned into two age groups: 60-64 years and 65-69 years. We elected to  
20  
21 119 exclude from analysis younger adults, due to their lower CVD event rates and older adults, since in England the  
22  
23 120 cause of death of individuals  $\geq 75$  years of age is likely to be misclassified, due to their higher prevalence of  
24  
25 121 comorbid conditions<sup>29</sup>. Numerators of region-specific CVD deaths were based on the presence of one or more  
26  
27 122 ICD-10 codes listed on each death record in a given month of the year, with denominators established on mid-  
28  
29 123 year annual population estimates for the sum of England plus Wales and similarly for King County. Data were  
30  
31 124 stratified by sex and age group. Monthly summer CVD and mental and behavioural mortality rates were  
32  
33 125 computed by region- sex- and age-specific deaths occurring each month of the year and were reported as the  
34  
35 126 number of men and women deaths per 100,000 persons.

### 40 128 *Statistical Analysis*

41  
42 129 Since atmospheric systems act on long time-scales, our primary exposures (June and July) nocturnal  
43  
44 130 SAT were standardized as monthly anomalies from a reference period<sup>22</sup>. For the purpose of the present analysis,  
45  
46 131 SAT anomalies were defined as deviations from a 30-year (1981-2010) baseline average<sup>22</sup>. For each year of the  
47  
48 132 exposure period (2001-2015), June and July nocturnal SAT anomalies were computed separately for England  
49  
50 133 and Wales and for King County by subtracting these regions’ months’ averages from their respective 1981-2010  
51  
52 134 average nocturnal SAT.

53  
54  
55 135 CVD mortality rates were found to be auto-correlated (i.e. rates in the prior and subsequent years were  
56  
57 136 significantly correlated). Additionally, the outcome variable’s variance was much greater than its mean, leading

1  
2 137 to over-dispersion of data<sup>22,30</sup>. Moreover, a previous study showed that the incidence of mental health and  
3  
4 138 behavioural distress in England and Wales has both increased over time and been identified as a strong risk  
5  
6 139 factor for associations between diurnal SAT and cause-specific adult mortality<sup>13</sup>. To address these issues in our  
7  
8 140 models, we used negative binomial regression with auto-correlated residuals of order one<sup>22</sup> to assess the  
9  
10 141 association between sex- and age-specific CVD mortality rates to summer nocturnal SAT for England and  
11  
12 142 Wales from 2001-2015, while controlling for each of mental health and behaviour mortality rates, an increase or  
13  
14 143 decrease in CVD mortality rates with respect to the annual calendar year (i.e. trend), and the summer month as  
15  
16 144 our covariates. For King County, we used quasi-Poisson to assess all associations, while controlling for each of  
17  
18 145 PM<sub>2.5</sub>, an increase or decrease in CVD mortality rates with respect to the annual calendar year (i.e. trend), and  
19  
20 146 the summer month as our covariates. Findings are reported as incidence rate ratios (RR) and interpreted as  
21  
22 147 change for one-unit increase of the exposure variable<sup>22,30</sup>. Confidence intervals (CI) were evaluated at 95%,  
23  
24 148 along with Student's two-sided *t*-tests. Microsoft Excel (version 2013), RStudio (version 4.1.1), and STATA  
25  
26 149 (version 15) were used for computation, analyses, and figure composition.  
27  
28  
29  
30  
31  
32  
33  
34

## 35 153 **Results**

36 154 Within the selected cohorts, over the years 2001-2015, there were 39,912 (68.9% men) CVD deaths  
37  
38 155 recorded in England and Wales and 488 male CVD deaths (54.1% in the group aged 65-69 years) in King  
39  
40 156 County. Over this time period, CVD rates declined substantially in both regions annually (Table 1), and notably  
41  
42 157 over the summer months (Supplementary Figure 1).  
43  
44  
45

46 158 For England and Wales, CVD mortality rates, categorized by sex, age, and month, are illustrated in  
47  
48 159 Figure 1A. The older (65-69 years) men and women exhibited higher CVD mortality rates than during both  
49  
50 160 summer months. CVD mortality rates were consistently higher amongst men than women. Summer nocturnal  
51  
52 161 SAT anomalies are plotted in Figure 1B. June anomalies ranged from -0.63°C (2015) to 1.17°C (2003-  
53  
54 162 corresponding to the notable western European heatwave). July anomalies ranged from -1.37°C (2011) to  
55  
56 163 1.73°C (2006).  
57  
58  
59  
60



1  
2 164 After adjusting for covariates, associations between exposure (a 1-unit increase in summer nocturnal  
3  
4 165 SAT<sup>30</sup>) and CVD mortality rates, stratified by sex and age appear in Figure 2. As shown in Figure 2A, a +1°C  
5  
6 166 anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD mortality  
7  
8 167 rates among men aged 60-64 [adjusted RR 1.031; 95% CI, 1.003-1.059] but not in those aged 65-69 years  
9  
10 168 [adjusted RR 0.999; 95% CI, 0.976-1.021], nor in adult women in either age group (Figure 2B). There were no  
11  
12 169 such associations with anomalous summer diurnal SAT as exposures in men or women of either age group (not  
13  
14 170 shown).

15  
16  
17 171 For King County, summer CVD mortality rates were also higher within the older male cohort (Figure  
18  
19 172 3A). Summer nocturnal SAT anomalies are plotted in Figure 3B and Figure 3C. June SAT anomalies ranged  
20  
21 173 from -1.4°C (2008) to 2.49° (2015, a year when western North America recorded a record number of heatwaves  
22  
23 174 and forest fires attributed to a strong El Niño event<sup>22</sup>). July anomalies ranged from -1.25°C (2011) to 1.92°C  
24  
25 175 (also in 2015). The smaller land mass of King County permits integration of PM<sub>2.5</sub> into these models. In general,  
26  
27 176 King County PM<sub>2.5</sub> levels generally were higher in July than in June, 2001-2015. After adjusting for covariates,  
28  
29 177 a +1°C anomalous summer nocturnal SAT associated significantly with an increased risk of summer CVD  
30  
31 178 mortality rates among men aged 60-64 [adjusted RR 1.049; 95% CI, 1.017-1.081] but not in those aged 65-69  
32  
33 179 [adjusted RR 1.014; 95% CI, 0.996-1.032] (Figure 4).  
34  
35  
36 180  
37  
38 181

## 40 182 Discussion

41  
42 183 CVD mortality rates in both England and Wales and in King County, Washington State declined  
43  
44 184 substantially between 2001 and 2015 (Table 1) in parallel with greater population uptake of effective primary  
45  
46 185 and secondary preventive therapies. Nonetheless, considerable residual risk persists, and in England and Wales,  
47  
48 186 event rates remain >50% higher in adults aged 65-69 than in those aged 60-64 years.

49  
50 187 High summer nocturnal SAT may be a source of such risk<sup>6</sup>. Such high summer SAT has been associated  
51  
52 188 with increased cause-specific adult mortality in various high-income regions<sup>3-8,10,13,16,18</sup>. Importantly, in recent  
53  
54 189 years populous mid- to high-latitude regions have experienced a proportionately rise in nocturnal than in  
55  
56 190 daytime summer heat intensity<sup>15</sup>. The present work is one of few investigating potential associations between  
57  
58  
59

1  
2 191 summer nocturnal SAT and CVD mortality rates. Our finding of significant associations, in men aged 60-64  
3  
4 192 residing in England and Wales or in King County, Washington, United States, between +1°C summer nocturnal  
5  
6 193 SAT anomalies and summer CVD mortality rates, support this concept.  
7

8 194 An association between summer nocturnal SAT and CVD mortality is biologically plausible hypothesis.  
9  
10 195 The incidence and severity of CVD events can be exacerbated by temporal dys-synchrony between  
11  
12 196 cardiovascular circadian clock gene rhythms and exogenous or endogenous homeostatic stresses<sup>31</sup>. One such  
13  
14 197 stress is warmer nocturnal SAT, which also amplifies self-reported sleep-deprivation, itself a risk factor for adult  
15  
16 198 heart disease mortality<sup>21</sup>. Waking itself, whether concordant with normal cardiovascular circadian rhythms or  
17  
18 199 due to interrupted sleep, triggers increases in heart rate, vascular resistance, and blood pressure and predisposes  
19  
20 200 to thrombosis<sup>32</sup>.  
21  
22

23 201 No significant association was detected in English and Welsh women, but their event rates were <50%  
24  
25 202 of males of comparable age (Table 1). Thus, there may have been insufficient statistical power to appreciate a  
26  
27 203 qualitatively similar association in women, if present. On the other hand, their generally larger sweat gland  
28  
29 204 volume<sup>33</sup> predisposes men exposed to heat to greater insensible fluid loss and intra-vascular volume depletion.  
30  
31 205 However, the authors of a recent systematic review of 36 studies attributed the greater male susceptibility to  
32  
33 206 heat-attributable illnesses to their psychology and behavior rather than to any physiological dimorphism<sup>34</sup>.  
34  
35

36 207 Several studies<sup>4,15-18</sup> report a positive association between summer nocturnal SAT and either all-cause,  
37  
38 208 heat-related, or CVD mortality. In one focusing on London, United Kingdom, nighttime temperatures had a  
39  
40 209 more potent influence than daytime exposure on all-cause mortality, ischemic heart disease events, and stroke,  
41  
42 210 particularly in those  $\leq 64$  years of age; sex-specific risk was not reported<sup>16</sup>. A recent investigation of  
43  
44 211 approximately 10 years' data for 11 southern European cities reported associations between the relative risk of  
45  
46 212 cause-specific mortality and the magnitude and duration of nocturnal SAT exceeding 20°C<sup>17</sup>. Significant  
47  
48 213 associations with CVD event rates were identified for Madrid, Lisbon, Porto, and Rome<sup>17</sup>. However, sex- and  
49  
50 214 age- specific associations were not reported, and our work, in contrast, considered monthly anomalies relative to  
51  
52 215 a 30-year reference period as the thermal exposure of interest.  
53  
54

55 216 Other European studies also noted significant positive relationships between average/diurnal SAT and  
56  
57 217 all-cause/CVD mortality in men <65 years or in working-age or middle-aged men<sup>10-12</sup>. An Australian group  
58  
59

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<sup>35</sup>.

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<sup>35</sup> that endogenous testosterone, which declines with age, is in mice an heat-stress susceptibility factor<sup>36</sup>.

Nearly a third of United Kingdom's population resides in southeast England<sup>15</sup>. This region's employment opportunities attract young and middle-aged men<sup>37</sup>. Urban design is also an important parameter, because majority of daytime summer heat is absorbed, then radiates locally at night<sup>15</sup>. 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<sup>14</sup>. 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<sup>27</sup>, and road and aircraft noise<sup>29</sup>, which in adult men increases the risk of developing hypertension<sup>16,38</sup>. Nighttime noise-related stress<sup>38</sup> and warmer summer SAT also disrupt sleep, especially among vulnerable populations with lower socioeconomic status<sup>21</sup>. Sleep deprivation, in turn can increase central sympathetic outflow<sup>39</sup>, which over time can increase blood pressure and induce insulin resistance<sup>40</sup>. Dry air can exacerbate snoring<sup>41</sup>; in middle-aged men snoring is common, as is obstructive sleep apnea, which can trigger nocturnal CVD events<sup>42</sup>.

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<sup>15</sup>. Nonetheless, in our supplementary analysis of King County, the effect and

1  
2 245 direction of summer nocturnal SAT on CVD mortality among men aged 60-64 years were consistent with our  
3  
4 246 primary analysis. The majority of adult men in England and Washington State retire at age 65. It is conceivable  
5  
6 247 that the anxieties/mental health of men in their early sixties anticipating retirement and reduced income or  
7  
8 248 benefits added to their risk for CVD death, as posited by a British study<sup>13</sup>, but this potential confounder was  
9  
10 249 adjusted for, in our models. Lastly, we are not able to adjust for potential confounding factors such as local  
11  
12 250 public health initiatives, or in secular trends in the discovery and implementation of effective primary and  
13  
14 251 secondary CVD risk prevention strategies, cause of death misclassification, or ICD coding error.  
15  
16  
17 252  
18

## 19 253 **Conclusion**

20  
21 254 Our observation of an association between warm summer nighttime conditions and CVD mortality risk amongst  
22  
23 255 men aged 60-64 year residing in England and Wales was replicated in our analysis of comparable American data  
24  
25 256 from King County, Washington State. The present findings should stimulate similar investigation of exposure  
26  
27 257 and event rates in other populous mid- to high-latitude regions. Considering the growing likelihood of extreme  
28  
29 258 summers in Western United States and United Kingdom<sup>23</sup>, our results invite preventive population health  
30  
31 259 initiatives and novel urban policies aimed at reducing future risk of CVD events.  
32  
33  
34 260

## 35 261 **Author contributions**

36  
37 262 HM and JSF contributed to the conception or design of the work. HM and JSF contributed to the acquisition,  
38  
39 263 analysis, or interpretation of data for the work. HM drafted the initial manuscript. JSF critically revised the  
40  
41 264 manuscript. Both authors gave final approval and agree to be accountable for all aspects of work ensuring  
42  
43 265 integrity and accuracy.  
43  
44 266

## 45 267 **Declaration of conflicting interests**

46 268 The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication  
47  
48 269 of this article.  
49  
50  
51 270  
52  
53 271  
54  
55 272  
56  
57 273  
58  
59

1  
2 274 **Funding**

3  
4 275 The authors received no financial support for the research, authorship and/or publication of this article.  
5  
6 276

7  
8 277 **Data sharing statement**

9  
10 278 All data related to this study has been provided as weblinks in the 'Methods' section.  
11  
12 279

13  
14 280 **Ethics approval statement**

15  
16 281 No ethics approval was needed to conduct this study.  
17  
18 282

19  
20 283 **Patient and public involvement**

21  
22 284 Patients were not involved in the design, or conduct, or reporting, or dissemination plans of this research study.  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## References

1. Timmis A, Townsend N, Gale C, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. *Eur Heart J* 2018; 39: 508–79.
2. Schwartz J, Samet JM, Patz JA. Hospital Admissions for Heart Disease: The Effects of Temperature and Humidity. *Epidemiology* 2004; 15: 755–61.
3. Michelozzi P, Accetta G, De Sario M, et al. High Temperature and Hospitalizations for Cardiovascular and Respiratory Causes in 12 European Cities. *Am J Respir Crit Care Med* 2009; 179: 383–89.
4. D'Ippoliti D, Michelozzi P, Marino C, et al. The impact of heat waves on mortality in 9 European cities: results from the EuroHEAT project. *Environ Health* 2010; 9: 37.
5. Achebak H, Devolder D, Ballester J. Trends in temperature-related age-specific and sex-specific mortality from cardiovascular diseases in Spain: a national time-series analysis. *Lancet Planet Health* 2019; 3: e297–e306.
6. Son J-Y, Liu JC, Bell ML. Temperature-related mortality: a systematic review and investigation of effect modifiers. *Environ Res Lett* 2019; 14: 073004.
7. Saucy A, Ragettli MS, Vienneau D, et al. The role of extreme temperature in cause-specific acute cardiovascular mortality in Switzerland: A case-crossover study. *Sci Total Environ* 2021; 790: 147958.
8. van Steen Y, Ntarladima A-M, Grobbee R, et al. Sex differences in mortality after heat waves: are elderly women at higher risk? *Int Arch Occup Environ Health* 2019; 92: 37–48.
9. Mari-Dell'Olmo M, Tobías A, Gómez-Gutiérrez A, et al. Social inequalities in the association between temperature and mortality in a South European context. *Int J Public Health* 2019; 64: 27–37.
10. Näyhä S. Environmental temperature and mortality. *Int J Circumpolar Health* 2005; 64: 451–58.
11. Rowland ST, Boehme AK, Rush J, et al. Can ultra short-term changes in ambient temperature trigger myocardial infarction? *Environ Int* 2020; 143: 105910.
12. Rocklöv J, Forsberg B, Ebi K, et al. Susceptibility to mortality related to temperature and heat and cold wave duration in the population of Stockholm County, Sweden. *Glob Health Action* 2014; 7: 10.3402/gha.v7.22737.
13. Gasparrini A, Armstrong B, Kovats S, et al. The effect of high temperatures on cause-specific mortality in England and Wales. *Occup Environ Med* 2012; 69: 56–61.
14. Arbuthnott KG, Hajat S. The health effects of hotter summers and heat waves in the population of the United Kingdom: a review of the evidence. *Environ Health* 2017; 16: 119.
15. Eunice Lo YT, Mitchell DM, Bohnenstengel SI, et al. U.K. Climate Projections: Summer Daytime and Nighttime Urban Heat Island Changes in England's Major Cities. *J Clim* 2020; 33: 9015–30.
16. Murage P, Hajat S, Kovats RS. Effect of night-time temperatures on cause and age-specific mortality in London. *Environ Epidemiol* 2017; 1: e005.
17. Royé D, Sera F, Tobías A, et al. Effects of Hot Nights on Mortality in Southern Europe. *Epidemiology* 2021; 32: 487–98.

18. Laaidi K, Zeghnoun A, Dousset B, et al. The Impact of Heat Islands on Mortality in Paris during the August 2003 Heat Wave. *Environ Health Perspect* 2012; 120: 254–59.
19. Liu C, Yavar Z, Sun Q. Cardiovascular response to thermoregulatory challenges. *Am J Physiol - Heart Circ Physiol* 2015; 309: H1793–H1812.
20. Obradovich N, Fowler JH. Climate change may alter human physical activity patterns. *Nat Hum Behav* 2017; 1: 1–7.
21. Obradovich N, Migliorini R, Mednick SC, et al. Nighttime temperature and human sleep loss in a changing climate. *Sci Adv* 2017; 3: e1601555.
22. Majeed H, Moineddin R, Booth GL. Sea surface temperature variability and ischemic heart disease outcomes among older adults. *Sci Rep* 2021; 11: 3402.
23. Christidis N, McCarthy M, Stott PA. The increasing likelihood of temperatures above 30 to 40 °C in the United Kingdom. *Nat Commun* 2020; 11: 3093.
24. Calkins MM, Isaksen TB, Stubbs BA, et al. Impacts of extreme heat on emergency medical service calls in King County, Washington, 2007–2012: relative risk and time series analyses of basic and advanced life support. *Environ Health* 2016; 15: 13.
25. Staddon PL, Montgomery HE, Depledge MH. Climate warming will not decrease winter mortality. *Nat Clim Change* 2014; 4: 190–94.
26. Hollis D, McCarthy M, Kendon M, et al. HadUK-Grid—A new UK dataset of gridded climate observations. *Geosci Data J* 2019; 6: 151–59.
27. Analitis A, Michelozzi P, D'Ippoliti D, et al. Effects of heat waves on mortality: effect modification and confounding by air pollutants. *Epidemiol Camb Mass* 2014; 25: 15–22.
28. Correll CU, Solmi M, Veronese N, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry* 2017; 16: 163–180.
29. Halonen JI, Hansell AL, Gulliver J, et al. Road traffic noise is associated with increased cardiovascular morbidity and mortality and all-cause mortality in London. *Eur Heart J* 2015; 36: 2653–61.
30. Mohammad MA, Koul S, Rylance R, et al. Association of Weather With Day-to-Day Incidence of Myocardial Infarction: A SWEDEHEART Nationwide Observational Study. *JAMA Cardiol* 2018; 3: 1081–89.
31. Durgan DJ, Young ME. The cardiomyocyte circadian clock: emerging roles in health and disease. *Circ Res* 2010; 106: 647–58.
32. Tofler Geoffrey H., Muller James E. Triggering of Acute Cardiovascular Disease and Potential Preventive Strategies. *Circulation* 2006; 114: 1863–72.
33. Iyoho AE, Ng LJ, MacFadden L. Modeling of Gender Differences in Thermoregulation. *Mil Med* 2017; 182: 295–303.
34. Gifford RM, Todisco T, Stacey M, et al. Risk of heat illness in men and women: A systematic review and meta-analysis. *Environ Res* 2019; 171: 24–35.

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
35. Lu P, Xia G, Zhao Q, et al. Temporal trends of the association between ambient temperature and hospitalisations for cardiovascular diseases in Queensland, Australia from 1995 to 2016: A time-stratified case-crossover study. *PLOS Med* 2020; 17: e1003176.
  36. Chen Y, Yu T. Testosterone mediates hyperthermic response of mice to heat exposure. *Life Sci* 2018; 214: 34–40.
  37. Andrew M, Meen G. Population structure and location choice: A study of London and South East England\*. *Pap Reg Sci* 2006; 85: 401–19.
  38. Jarup L, Babisch W, Houthuijs D, et al. Hypertension and Exposure to Noise Near Airports: the HYENA Study. *Environ Health Perspect* 2008; 116: 329–33.
  39. Taylor KS, Kucyi A, Millar PJ, et al. Association between resting-state brain functional connectivity and muscle sympathetic burst incidence. *J Neurophysiol* 2016; 115: 662–73.
  40. Ayas NT, White DP, Manson JE, et al. A Prospective Study of Sleep Duration and Coronary Heart Disease in Women. *Arch Intern Med* 2003; 163: 205–9.
  41. Lappharat S, Taneepanichskul N, Reutrakul S, et al. Effects of Bedroom Environmental Conditions on the Severity of Obstructive Sleep Apnea. *J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med* 2018; 14: 565–73.
  42. Lee SA, Amis TC, Byth K, et al. Heavy Snoring as a Cause of Carotid Artery Atherosclerosis. *Sleep* 2008; 31: 1207–13.



**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:**

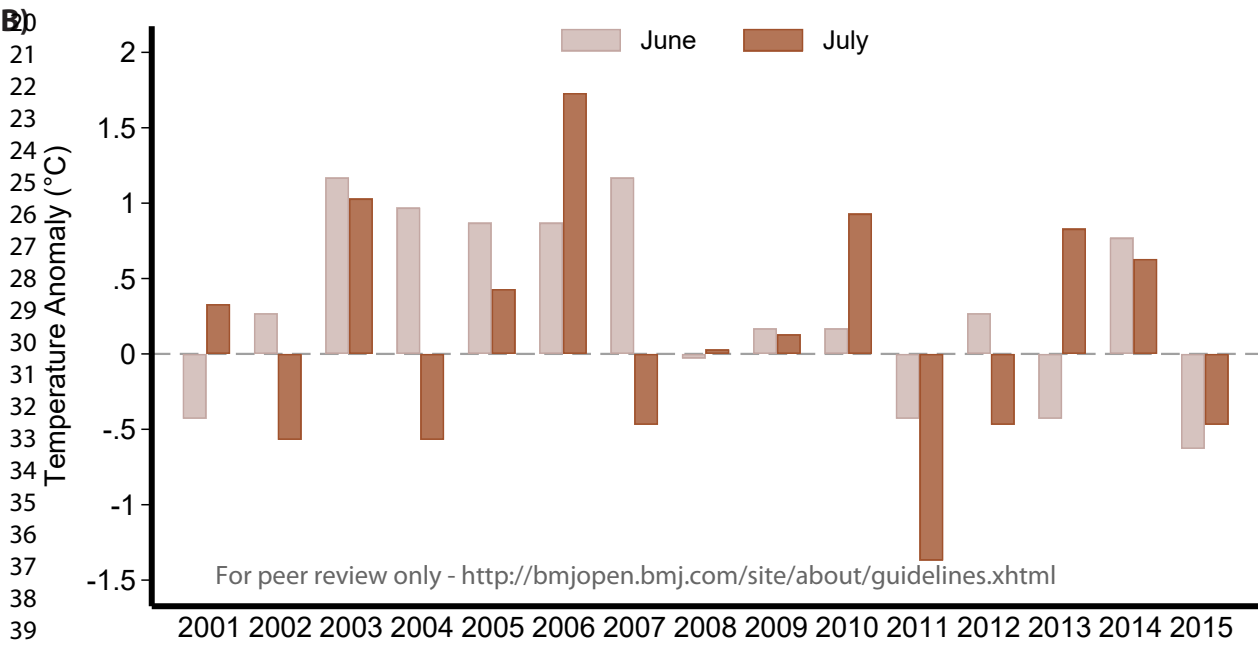
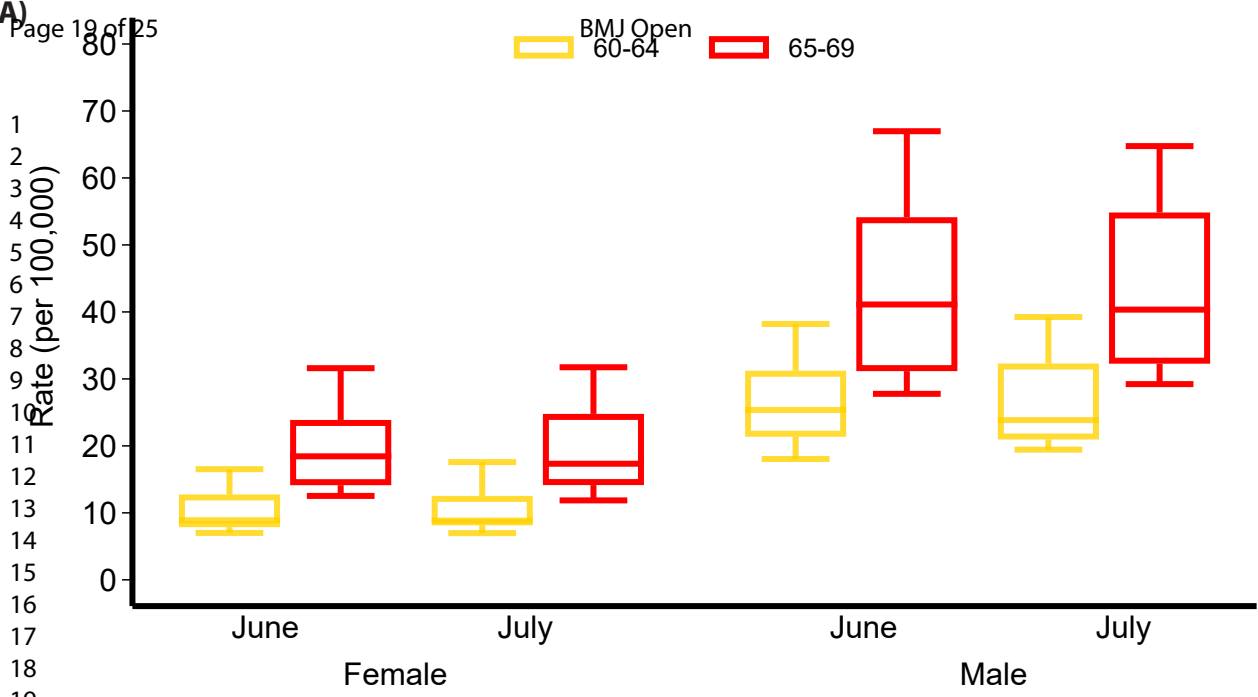
**Figure 1:** **A)** Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in England & Wales from 2001-2015. **B)** Month-specific summer (June-July) nocturnal SAT anomalies (based on deviations from the baseline period of 1981-2010) in England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

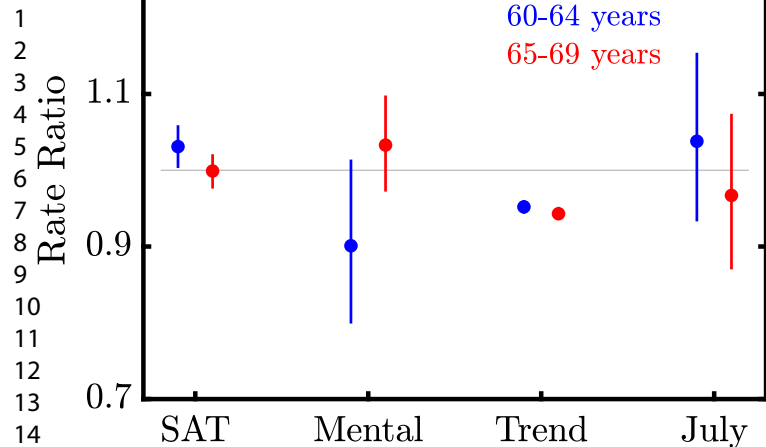
**Figure 3:** **A)** Data spread for sex-specific monthly summer (June-July) CVD mortality rates among middle- and older-aged adults in King County, Washington, United States from 2001-2015. **B)** Month-specific summer (June-July) night SAT anomalies (based on deviations from the baseline period of 1981-2010) in King County. **C)** Month-specific summer (June-July) PM<sub>2.5</sub> 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<sub>2.5</sub>, trend, and month (reference to June).

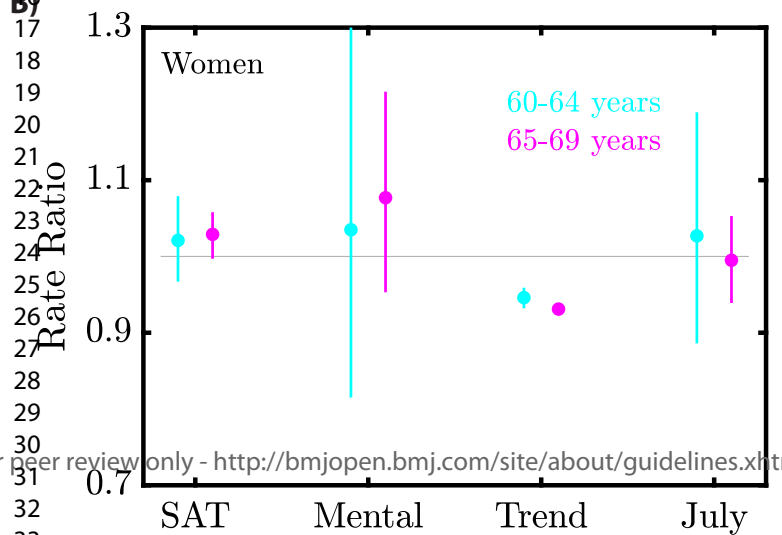
**Supplementary Figure 1:** Monthly summer (6=June, 7=July) cardiovascular mortality trends by age-groups among (A) men and (B) women from 2001-2015 in England and Wales.

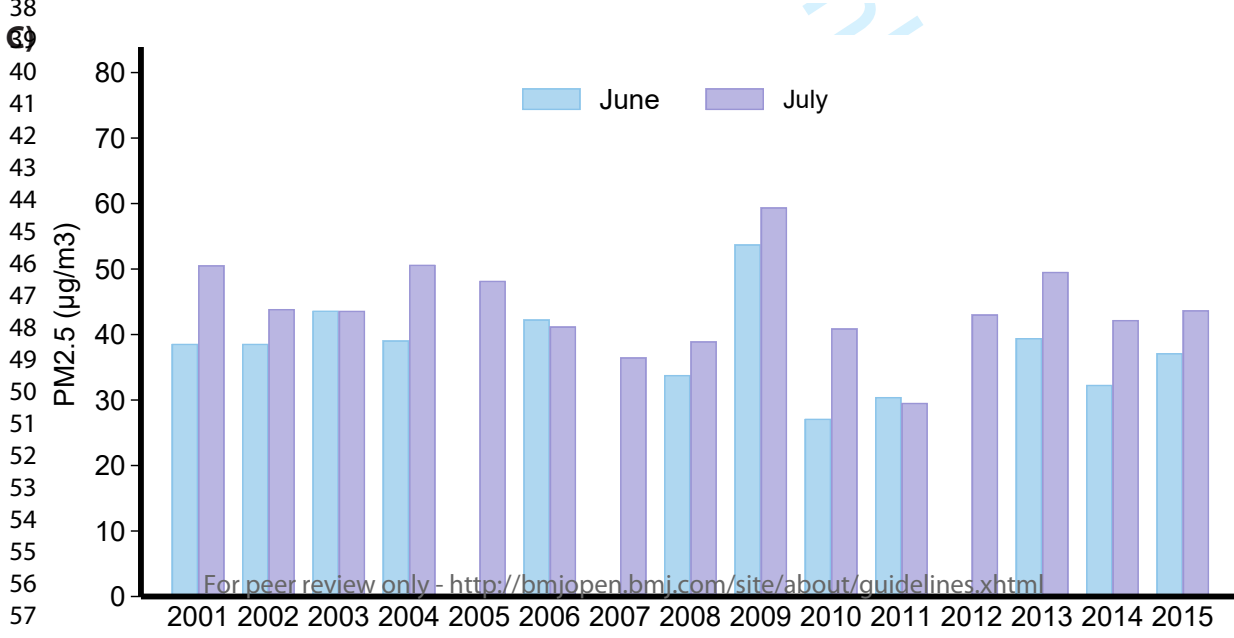
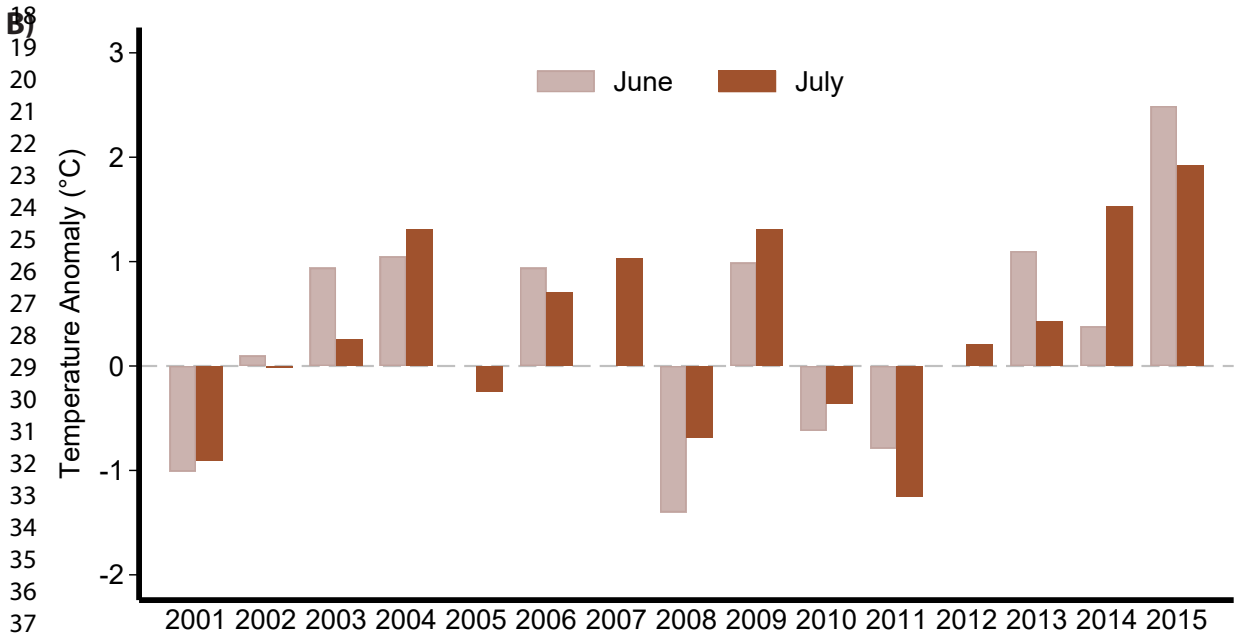
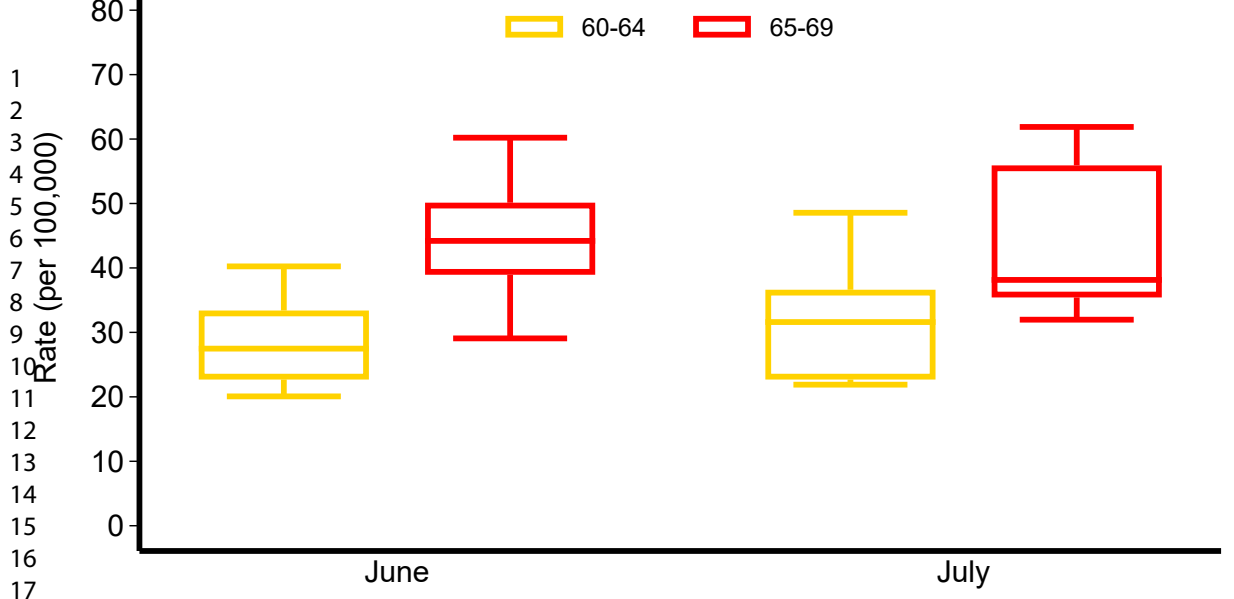


A)



B)





Men

60-64 years

65-69 years

Rate Ratio

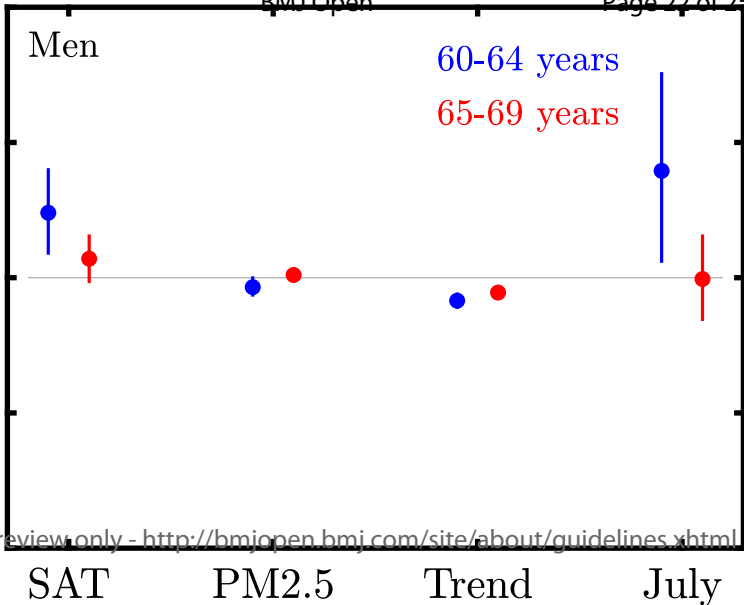
1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
171.2  
1.1  
1  
0.9  
0.8

SAT

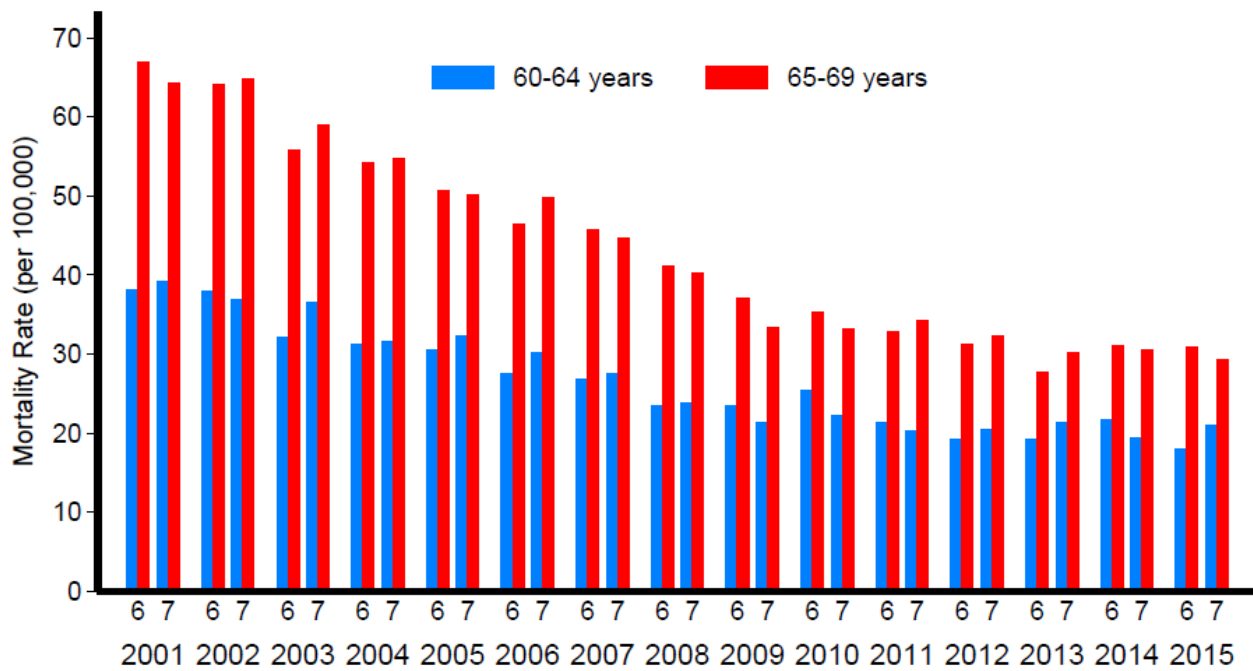
PM2.5

Trend

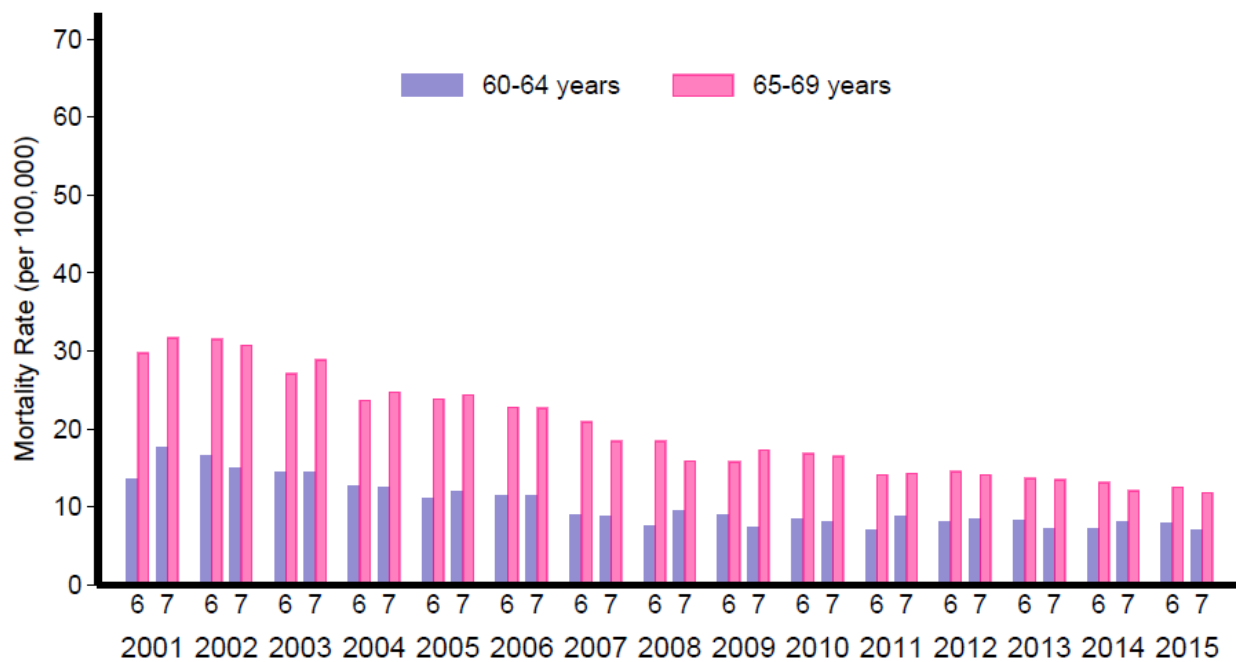
July

For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>

## 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
<b>Title and abstract</b>	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	
<b>Introduction</b>				
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	
<b>Methods</b>				
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6	
		<i>Case-control study</i> —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		
		<b>Cross-sectional study</b> —Give the eligibility criteria, and the sources and methods of selection of participants		
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed		
		<i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy		
		(e) Describe any sensitivity analyses	6	
<b>Results</b>				
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)		
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time		
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure		
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).