Original Research Article

Temperature-mortality associations by age and cause: a multi-country multi-city study

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Running Head: Temperature-mortality risks by age and cause

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ABSTRACT

Background: Heterogeneity in temperature-mortality relationships across locations may partly result from differences in the demographic structure of populations, and their cause-specific vulnerabilities. Here we conduct the largest epidemiological study to date on the association between ambient temperature and mortality by age and cause using data from 532 cities in 33 countries.

Methods: We collected daily temperature and mortality data from each country. Mortality data was provided as daily death counts within age groups from all, cardiovascular, respiratory or non-cardiorespiratory causes. We first fit quasi-Poisson regression models to estimate location-specific associations for each age-by-cause group. For each cause, we then pooled location-specific results in a dose-response multivariate meta-regression model that enabled us to estimate overall temperature-mortality curves at any age. The age analysis was limited to adults.

Results: We observed high temperature effects on mortality from both cardiovascular and respiratory causes compared to non-cardiorespiratory causes, with the highest cold-related risks from cardiovascular causes and the highest heat-related risks from respiratory causes. Risks generally increased with age, a pattern most consistent for cold and for non-respiratory causes. For every cause group, risks at both temperature extremes were strongest at the oldest age (age 85). Excess mortality fractions were highest for cold at the oldest ages.

Conclusions: There is a differential pattern of risk associated with heat and cold by cause and age; cardiorespiratory causes show stronger effects than non-cardiorespiratory causes, and older adults have higher risks than younger adults.

WHAT THIS STUDY ADDS

This is the largest epidemiological study to date on the association between ambient temperature and mortality by age and cause. Using data from 532 cities in 33 countries, we find higher temperature effects from cardiorespiratory causes compared to non-cardiorespiratory causes, with the highest cold-related risks from cardiovascular causes and the highest heat-related risks from respiratory causes. The results can be used to inform burden of disease analyses – which are currently based on data from fewer countries – and can enhance future projections of temperature-related mortality, which will depend in part on evolving demographic and health characteristics of the study population.

INTRODUCTION

Over the past several years, there has been enormous growth in the number of studies investigating associations between ambient temperature and mortality.[1-8] These studies have reported associations for dozens of countries from every inhabited continent. A consistent feature of the findings is that the temperature-mortality relationship differs across locations, including in the magnitude of the heat and cold effects, in the shape of the relationship, and in the 'optimal' (minimum mortality) temperature.[8-13] Acclimatization may explain part of the heterogeneity, as temperature associations appear to be related, in part, to local climate.[10-15] Population characteristics, such as the age structure, may also play an important role; prior studies indicate that risks are highest in children and the elderly.[1,2,4,11] Rates of underlying disease may be another factor, as evidence suggests that temperature has a relatively strong effect on cardiorespiratory causes compared to many other types of disease.[1,2,4,11,16]

Nevertheless, these prior studies have mostly come from investigations with limited geographical scope and used disparate epidemiological designs. As a result, evidence is still needed to understand how temperature-mortality relationships differ by age and cause of death.

In this study, we use data from 532 cities in 33 countries to explore temperature-mortality associations by age and cause using state-of-the-art epidemiological and statistical methods. The analysis can serve multiple purposes: (1) it can help explain observed differences in temperature effects across locations, (2) shed light on potential biological mechanisms underlying the effect, and (3) identify at-risk populations, thus aiding in the design and targeting of heat-health interventions. In addition, robust estimates of temperature risks by age and cause can improve burden of disease assessments and projections of future mortality under climate change, as many populations are aging and/or transitioning towards different causes of death.[17,18]

METHODS

Data collection

We obtained mortality and temperature data from the database of the Multi-Country, Multi-City (MCC) Collaborative Research Network, which has been described previously.[9,19,20] The current analysis was limited to locations that had available mortality data by age or cause, with the latter analysis focusing on cardiovascular causes (ICD-10 codes I00-I99), respiratory causes (ICD-10 codes J00-J99), and non-cardiorespiratory causes (other ICD odes). All mortality and temperature data were obtained from local authorities in each country (Supplementary Table 1). In total, we included 532 locations from 33 countries (Figure 1, Supplementary Tables 1 and 2).

The mortality data was supplied as daily counts for each location, although with heterogeneous age groupings. For the countries with available age-specific data, the number of age groups differed and ranged from two to six groups, comprised of different age ranges (Supplementary Table 2). For example, some countries provided data only as above or below 65, while others had much finer age stratification. Because temperature risks may differ substantially in children compared to adults[3,21,22], and considering the limited availability and small counts at the youngest ages, we decided to limit the age analysis to adults and therefore removed any age group that included children younger than 15. Still, some adult age groups included a small number of total or cause-specific deaths, which can cause problems for model convergence. Therefore, if any age-by-cause group had fewer than 450 deaths total in the series, we combined it with the next oldest age group in that location; 450 deaths was the minimum number that resulted in adequate model convergence in preliminary analyses. Histograms of the final age-by-cause groups are reported in Supplementary Figure 1.

Statistical analysis

We applied an extended two-stage time-series design that allows for a flexible specification of temperature-mortality risks and the simultaneous modelling of multiple estimates from the same location. Specifically, in the first stage, we estimated the temperature-mortality association for each location for all adults for each cause and for the age-by-cause groups using quasi-Poisson regression with distributed lag non-linear models.[9,23,24] This modelling technique captures the non-linear and lagged features of the temperature-mortality association. We modelled the cross-basis function of daily mean temperature with a natural cubic spline for the temperature dimension, with three internal knots at the 10th, 75th, and 90th percentiles of the location-specific temperature distribution. The 21-day lag-mortality curve – which captures the delayed effect of cold as well as the more immediate effect of heat – was modelled using a natural cubic spline with an intercept and three internal knots equally spaced on the logarithmic scale. The model also included an indicator for day of the week and a natural cubic spline of time with eight degrees of freedom per year to control for seasonal variations and long-term trends. The model selection was based on previous work using an overlapping dataset.[9]

In the second-stage, for each cause, we derived reduced estimates of age-specific overall cumulative exposure-response associations, representing the net effects summed across lags, and we pooled them using a novel dose-response multivariate meta-regression.[25] This model was defined using a mixed-effects meta-analytical framework that allows specification of continuous age-varying risks using multiple unit-level estimates. The meta-regression models included random effects for each location (city) nested within a country-by-climate zone grouping, in addition to a fixed effect for age as a continuous term (with a spline parameterization). Specifically, for each age group in each location, we assigned an average age of death, using 5-year mortality estimates from the Global Burden of Disease project for 2008.

The estimated coefficients from the multilevel multivariate meta-regression model can be used to estimate pooled temperature-mortality curves at any age from any of the causes. In preliminary analyses, we explored the structure of the age effect by modeling age as (1) a linear function, (2) a natural spline with a single knot at age 65, and (3) a natural spline with two internal knots at age 50 and 75. The latter approach generally performed best according to the Akaike Information Criteria (Supplementary Table 3), so all results use the 2-knot model. Effect summaries are defined as pooled overall cumulative exposure-response curves of relative risks predicted at specific ages for each cause.

In secondary analyses, we tested for interactions using multivariate Wald tests, including whether all-age results differed by cause and whether cause-specific results differed by age.

Finally, we quantified the fraction of excess deaths attributable to heat and cold by age and cause, with associated empirical confidence intervals, using methods described previously.[9,26] Briefly, the approach entails using the best linear unbiased prediction of the overall cumulative exposure-response association in each location to compute the number of cold- and heat-related deaths by summing the daily mortality contributions when the temperature on a specific day was higher or lower than the location-specific reference temperature (the "minimum mortality temperature"). The minimum mortality temperatures were estimated from the best linear unbiased prediction and, based on prior studies, were restricted to be between the 25th and 99th percentile of the temperature distribution.[9] The ratio of cold- and heat-related deaths with the total number of corresponding age- and cause-specific deaths provides the excess mortality fraction. We calculated the excess deaths for each age-by-cause group in each location and then aggregated the estimates across all locations for the following age categories based on the average age at death in each group: 30-44, 45-59, 60-74 and 75-100.

RESULTS

A total of 88,483,994 deaths were analyzed in 532 locations from 33 countries (Figure 1), with an average time series of 18 years (Supplementary Table 2). The dataset included both high-income (n=18) and middle-income (n=15) countries. Twenty-one countries included age-specific data by cause of death, eight countries included age-specific data only for all-cause mortality, and four countries had cause-specific but not age-specific data. Average mean temperature ranged widely across locations both between and within countries (Figure 1). For example, locations in Greece, Italy, Kuwait and the USA recorded daily mean temperatures above 36 ˚C, whereas locations in Canada, Estonia, Norway and the USA recorded days below -25 ˚C (Supplementary Table 2).

Figure 2 reports the pooled overall relative risks by cause for all ages and predicted at ages 40, 55, 70 and 85 (see Supplementary Figures 2 and 3 for associated 95% CIs). The left panel indicates strong evidence of differences in the risk curves for all ages by cause of death (p-value of the multivariate Wald test <0.01). Specifically, we found elevated mortality risks for cardiorespiratory causes compared to other causes, and in particular, relatively high cold effects for cardiovascular causes and high heat effects for respiratory causes. For example, the relative risk of death from cold at the first temperature percentile compared to the optimal temperature was 1.34 (95% CI 1.29,1.39) for cardiovascular causes and 1.27 (95% CI 1.21,1.34) for respiratory causes, both higher than the 1.14 (95% CI 1.12,1.17) for non-cardiorespiratory causes and 1.22 (95% CI 1.18,1.25) from all causes combined. The corresponding risks for extreme heat – defined as the 99th temperature percentile compared to the optimal temperature – were 1.13 (95% CI 1.10,1.17), 1.22 (95% CI 1.15,1.29), 1.09 (95% CI 1.07,1.12) and 1.11 (95% 1.09,1.14) for cardiovascular, respiratory, non-cardiorespiratory, and all causes, respectively. In all cases, the average minimum mortality temperature percentile was at the warm end of the temperature distribution, between the 84th and 87th percentile (also see Supplementary Table 4).

The right four panels of Figure 2 report age-specific results by cause. As with the all-age results, the age-by-cause groups displayed the characteristic U-shape indicative of both cold and heat effects, with relatively high minimum mortality temperatures. Two exceptions were evident, both in the youngest age; non-cardiorespiratory causes showed little evidence of a cold effect, and cardiovascular causes showed little evidence of a heat effect.

Variations in temperature-mortality associations by age were significant in every cause group ($p<0.01$). For all-causes and cardiovascular causes, risks increased with age along much of the temperature distribution for both heat and cold. Cold effects also increased with age for non-cardiorespiratory causes, but heat effects were similar for the three younger ages. There was not as clear of an age trend for respiratory causes, but as with the other three causes, mortality risks at the temperature extremes were highest at the oldest age (age 85) and lower at the youngest age (age 40). In general, risks often increased rapidly at the temperature extremes. Minimum mortality temperatures and relative risks at the temperature extremes for each age-by-cause group are reported in Supplementary Tables 4 and 5, respectively.

For all age groups and causes, excess mortality fractions were higher for cold than heat, sometimes by an order of magnitude (Figure 3). The highest cold-related excess mortality fractions were for cardiovascular causes, which were 9-13% in all age groups (see Supplementary Table 6 for exact values). The highest heat-related excess mortality fractions were from respiratory causes, except for the youngest age group where it was from non-cardiorespiratory mortality. Total (all-cause) excess mortality increased with age for cold, but was more variable for heat, though still highest in the oldest age group.

DISCUSSION

This study represents the largest epidemiological assessment to date on the association between ambient temperature and mortality by age and cause. Our results provide evidence that: (1) cardiorespiratory causes generally exhibit higher heat and cold-effects than non-cardiorespiratory causes; (2) risks often (but not always) increase with age, particularly at the colder end of the temperature distribution; and (3) it is not only the elderly that are vulnerable to ambient temperature, as demonstrated by the ‘U’-shaped relative risk curves seen for cardiorespiratory causes in younger adults.

The elevated mortality risks found for cardiorespiratory causes have been reported in a number of other, smaller studies and in systematic reviews. For example, a 2016 systematic review and meta-analysis of nine estimates reported stronger associations with cold for cardiorespiratory compared to all causes.[4] In that study, respiratory diseases had the highest risk, followed by cardiovascular and then all causes, which differs somewhat from our results in that we found the highest cold effects for cardiovascular causes. Reviews of hot temperatures and heat waves also report elevated mortality risks from cardiorespiratory causes,[1,16,27] including a meta-analysis which estimated relatively higher cardiovascular compared to respiratory effects, albeit with overlapping confidence intervals.[16] Many single-country studies of cause-specific mortality provide additional evidence of elevated cardiorespiratory risks, and support the finding of strong associations with cardiovascular causes during colder temperatures and/or respiratory causes during warmer temperatures.[28-30] A systematic review of studies on long-term exposure to ambient temperature reported similar findings.[6] Despite these similarities, it is difficult to directly compare existing studies due in part to differences in study design, which this study avoids through the use of uniform methods across all locations.

The high risks we identified for cardiorespiratory causes is also supported by plausible biological mechanisms, which have been discussed elsewhere.[1,3,21,29,31-34] Briefly, exposure to hot and cold temperatures can trigger a cascade of pathophysiological effects which include increases in respiratory rate and heart rate, as well as changes to blood viscosity, blood pressure, coagulability, cholesterol levels and vasoconstriction. Thermoregulation may also divert blood away from vital organs and towards the body's surface. Inflammatory responses have also been described.[35]

Higher mortality risks from ambient temperature in older age groups has also been reported in other studies[1,4,11,16,36], and is not surprising considering that the body's thermoregulatory processes become compromised with age.[37] Aging is also associated with other risk factors for temperature vulnerability including certain medication use and living with co-morbid conditions.[3,38] Older people are also less likely to notice they are becoming dehydrated at higher temperatures. An advantage of our approach over prior studies investigating age effects is the use of novel, state-of-the-art meta-analytical methods that, coupled with largest health database collected so far, which allowed us to explore temperature-mortality associations across the age distribution; most prior studies on the topic have investigated temperature effects for specific age ranges, which are often large, especially for those aged under 65. Here we generally found evidence of increasing risks with age, a pattern most pronounced at the colder end of the temperature distribution; heat effects on hot days were more similar across ages, but still highest in the oldest age group.

An important feature of our results is that for nearly every age and cause group we investigated, the relative risk curves exhibited the classic 'U'-shaped pattern, indicating vulnerability to both heat and cold, even in younger adults (e.g. at age 40). One key exception was for non-cardiorespiratory causes, where younger adults did not exhibit increased risks at cold temperatures. This finding requires further investigation, but a lack of a cold effect has been reported in studies of several specific non-cardiorespiratory causes of death that are relatively more common in younger compared to older adults (e.g. violence, self-harm, and certain unintentional injuries).[7,39-42] However, cold effects have been reported for other types of non-cardiorespiratory causes (e.g. traffic accidents) that would presumably affect younger adults.[42,43]

In terms of mortality burdens, the fraction of deaths attributable to non-optimal temperature were much higher for cold than for heat, a result reported in other multi-location studies.[7,9,28,44,45] Overall, the differences in excess mortality fractions roughly corresponded to the relative risk curves in that the oldest age group almost universally had higher heat and cold burdens compared to the youngest. However, the excess mortality fractions did not always monotonically increase by age. Excess mortality fractions can be heavily influenced by the ordering of risks at relatively moderate temperatures, which occur more frequently, but where risks were less differentiated by age compared to more extreme temperatures. The minimum mortality temperatures – which are subject to uncertainty[46] – also differed somewhat by age, which contributes to the excess mortality calculation. As a point of comparison, disease burdens attributable to non-optimal temperatures were recently included for the first time in the Global Burden of Disease exercise based on data from eight countries (nine in a follow-up study), extrapolated globally.[7,15] The study reported mortality burdens of about two million deaths per year, also primarily due to cardiorespiratory diseases. Burdens were higher at older ages.

The results of this study have several potential policy applications. For one, our findings support the need to protect older populations, in particular, from exposure to hot and cold temperatures. Examples may include targeted warning systems, interventions to help heat or cool homes, and neighbor outreach programs.[47] However, we find risks across the adult age distribution, meaning that younger populations are also vulnerable. In addition, our study can help inform burden of disease analyses, which are currently based on data from a smaller number of countries.[7,15] And finally, our findings suggest that future projections of temperature-related mortality should account for shifting demographic and health characteristics of the study population. An obvious example is in estimating health burdens under future climate change, which require projections with long time horizons during which population demographics and health status will evolve.[48] Recent evidence indicates that the effect on mortality from temperature exposure is likely to be a dominant type of climate change impact, and therefore accurate estimates of future burdens are necessary to set policy, including the social cost of carbon.[27,49-51]

Our findings should be interpreted in light of the study's limitations. One key limitation is that despite our extensive dataset – representing 532 locations in 33 countries – there are still large parts of the world that we were not able to include because of lack of data, including much of Africa and south and central Asia. In addition, for some of the countries we did include, the data was only available for coarse age groupings. We recommend future work that includes other locations and more specific causes and age groupings, as data becomes available. Future work could also assess temporal changes in temperature-mortality associations by age and cause, as prior MCC work based on all-cause mortality (or all non-external causes) identified evidence of changes over time.[52] (However, we note that that although we do not look at temporal changes over time, the time periods are identical within countries when comparing age groups and/or causes, so differences across countries would not affect the difference in estimates across ages/causes.) We also have not included differences by sex and have excluded children in our age analysis, as children may exhibit markedly different risk patterns from temperature compared to adults;[3,21,22] we expect to explore temperature effects in children in future research. And finally, although we investigated different causes of death, we did not have information on whether the individuals had pre-existing disease.

CONCLUSIONS

This study, based on data from 33 countries, indicates that ambient temperature is associated with mortality across the adult age range, and tends to increase as people get older, particularly for cold. The highest risks were evident for cardiorespiratory causes of death, with especially high cold effects for cardiovascular causes and high heat effects for respiratory causes. Mortality burdens attributable to temperature are non-trivial even amongst younger adults. These results can help inform interventions aiming to protect populations against temperature-related mortality and improve burden of disease assessments and projections of health impacts from climate change.

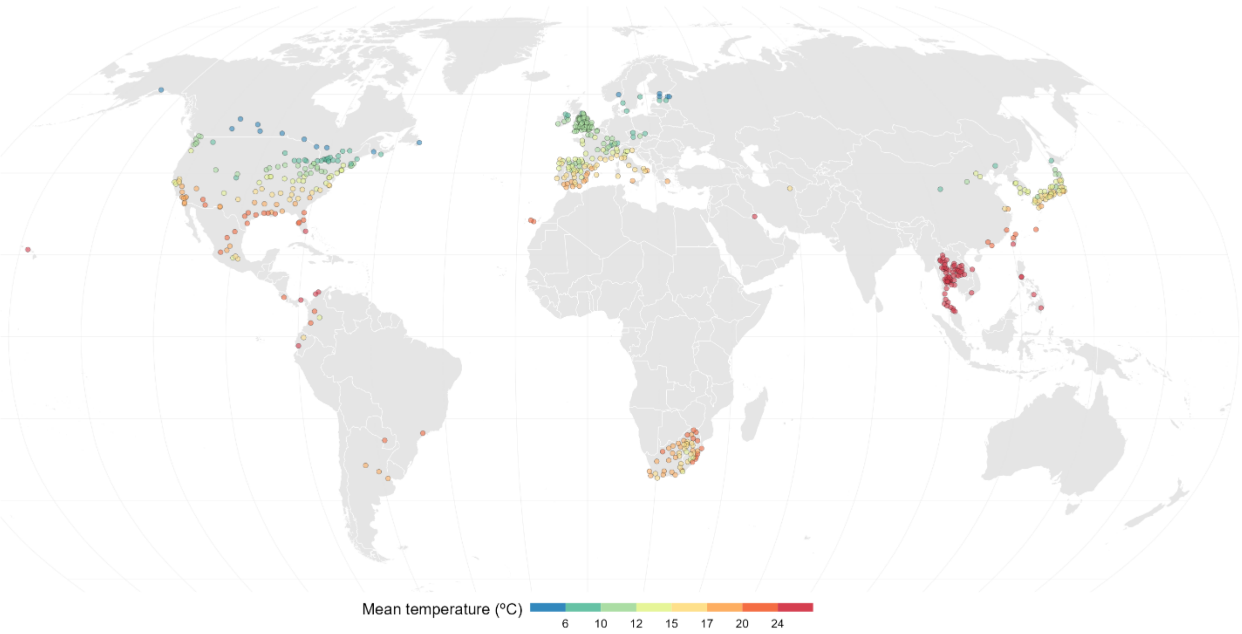

Figure 1. Geographic distribution and mean daily temperature of all locations included in this study.

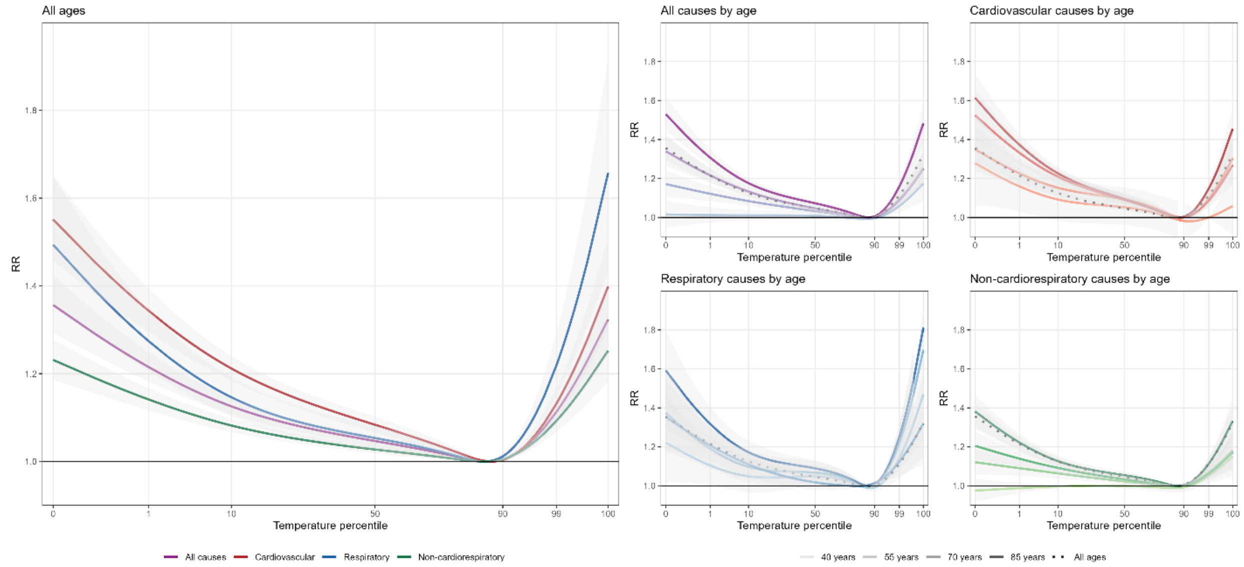

Figure 2. Overall cumulative relative risk curves by age for different cause groupings. Temperatures are represented on a relative scale, expressed as percentiles of the average temperature distribution; dotted vertical lines show the 1st and 99th percentile temperatures. All 95% confidence intervals are presented in Supplementary Figures 2 and 3. The dotted lines on the age-specific plots reproduce the all-age results from the top panel for comparison.

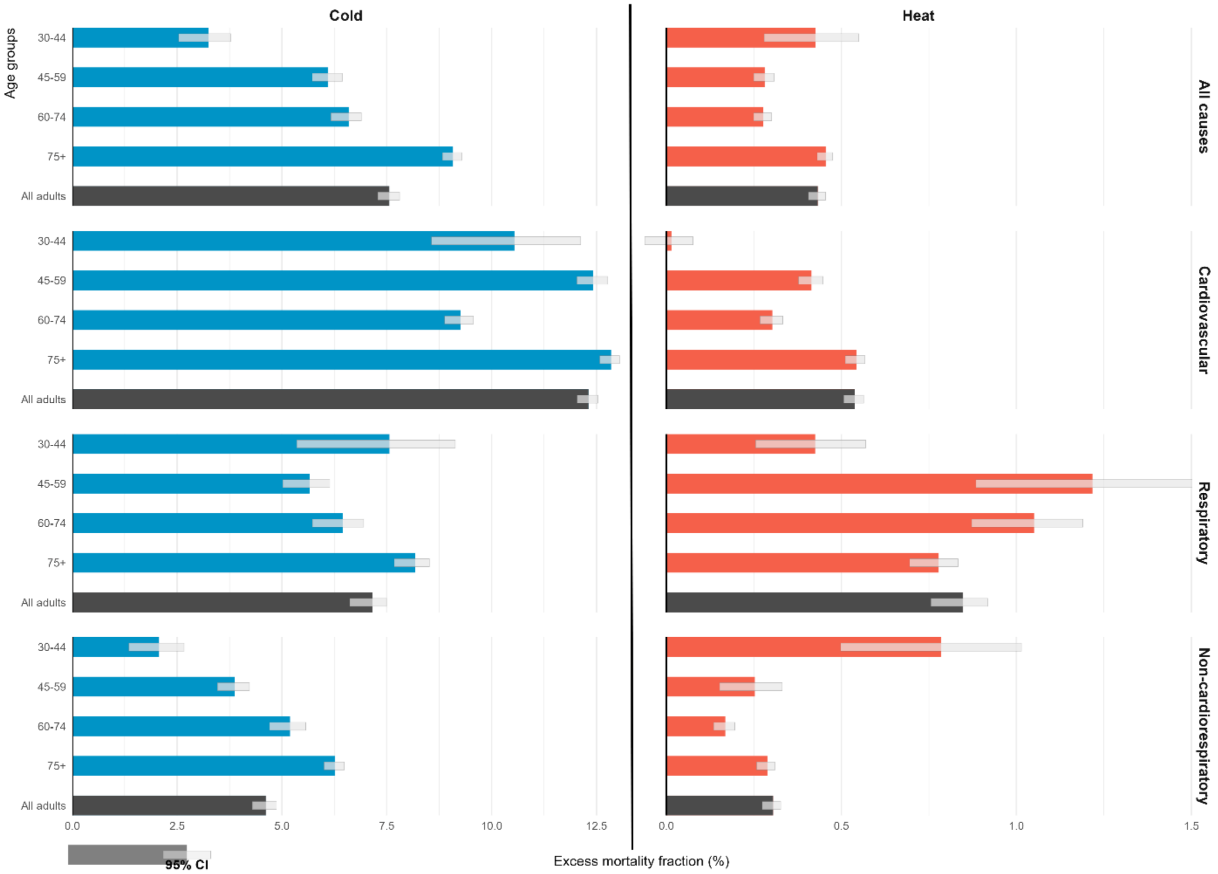

Figure 3. Excess mortality fractions by age group for cold (left) and heat (right).

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