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Temperature-Mortality Relationship in North Carolina, USA: Regional and Urban-Rural Differences

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Abstract

Background—Health disparities exist between urban and rural populations, yet research on rural-urban disparities in temperature-mortality relationships is limited. As inequality in the United States increases, understanding urban-rural and regional differences in temperature-mortality association is crucial.

Objective—We examined regional and urban-rural difference of the temperature-mortality association in North Carolina (NC), USA, and investigated potential effect modifiers.

Methods—We applied time-series models allowing nonlinear temperature-mortality associations for 17 years (2000–2016) to generate heat and cold county-specific estimates. We used second-stage analysis to quantify the overall effects. We also explored potential effect modifiers (e.g. social associations, greenness) using stratified analysis. Analysis considered relative effects (comparing risks at 99th to 90th temperature percentiles based on county-specific temperature distributions for heat, and 1st to 10th percentiles for cold) and absolute effects (comparing risks at specific temperatures).

Results—We found null effects for heat-related mortality (relative effect: 1.001 (95% CI: 0.995–1.007)). Overall cold-mortality risk for relative effects was 1.019 (1.015–1.023). All three regions had statistically significant cold-related mortality risks for relative and absolute effects (relative effect: 1.019 (1.010–1.027) for Coastal Plains, 1.021 (1.015–1.027) for Piedmont, 1.014 (1.006–1.023) for Mountains). The heat mortality risk was not statistically significant, whereas the cold mortality risk was statistically significant, showing higher cold-mortality risks in urban areas than rural areas (relative effect for heat: 1.006 (0.997–1.016) for urban, 1.002 (0.988–1.017) for rural areas; relative effect for cold: 1.023 (1.017–1.030) for urban, 1.012 (1.001–1.023) for rural areas). Findings are suggestive of higher relative cold risks in counties with less social association, higher population density, less green-space, higher $PM_{2.5,}$ lower education level, higher residential

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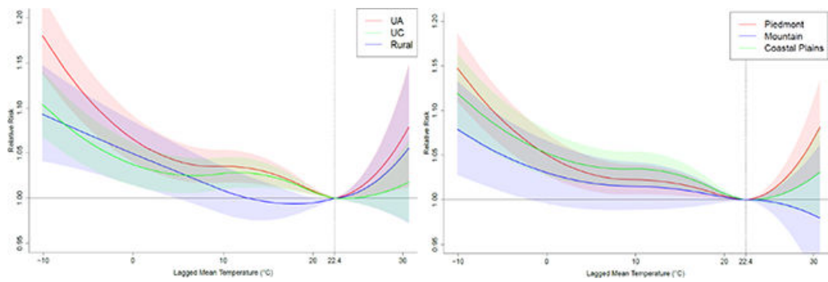
Credit Author Statement
HMC and MLB conceptualized the study and developed methodology. CC and JYS aided in methodological design. HMC performed analysis. HMC wrote the original draft paper. All authors aided in review and editing of the paper and in interpretation of results.

Conflict Interest
The authors declare they have no actual or potential competing financial interests.

segregation, higher income inequality, and higher income (e.g., Ratio of Relative Risks 1.72 (0.68, 4.35) comparing low to high education).

Conclusion—Results indicate cold-mortality risks in NC, with potential differences by regional, urban-rural areas, and community characteristics.

Graphical Abstract



Keywords

Temperature; Mortality; Region; Urban; Effect modification; USA

Introduction

Nearly 60 million people in the US live in rural areas (Census 2016). This represents 20% of the US total population, and rural populations experience significant health disparities (HRSA 2019). The mortality risk difference between urban and rural regions has increased from 1999 through 2015 for all-cause age-adjusted mortality (Singh and Siahpush 2014, HRSA 2019). In the US, nonmetropolitan areas had a higher percentage of excess deaths for the 5 leading causes of death than did metropolitan areas (HRSA 2019). Life expectancy in rural nonmetropolitan areas is 3 years less than in large metropolitan areas, and the disparity is growing (Singh and Siahpush 2014, Singh, Daus et al. 2017). Reducing the growing inequalities in urban-rural health is a critical national health initiative goal for the US (DHHS 2010). Scientific evidence on disparities for temperature and health associations has been highlighted as an area of needed research (Gronlund 2014, Vargo, Stone et al. 2016, Marí-Dell’Olmo, Tobías et al. 2019, Son, Liu et al. 2019).

Many studies have examined the association between extreme temperature (e.g., heat and cold) and risk of mortality (Medina-Ramón, Zanobetti et al. 2006, Anderson and Bell 2009, Lee, Choi et al. 2018). The temperature-mortality risk may vary by region, population characteristics, air quality, green space, climatic conditions, population density, air conditioning, and healthcare facilities (Stafoggia, Forastiere et al. 2006, Schifano, Leone et al. 2012, Hondula, Davis et al. 2015, Ingole, Kovats et al. 2017). However, most studies have been conducted in urban areas (e.g., cities) or overlook the heterogeneity within a region by aggregating across large areas (Curriero, Heiner et al. 2002, Lee, Nordio et al. 2014, Kinney 2018). Few studies focused on rural areas or on regional differences within a region that included non-urban areas (Sheridan and Dolney 2003, Hashizume, Wagatsuma et al. 2009, Henderson, Wan et al. 2013, Wang, Zhang et al. 2018). Also, most studies assumed the same exposure-response relationship for the entire population (Ballester, Robine et al. 2011, Huang, Barnett et al. 2011), which could obscure differences in the mortality-temperature association by subpopulations, including by region, urban/rural differences, race/ethnicity, socio-economic status, etc.

The association between temperature and mortality can vary by location as the population experiences different climates and can have different demographics (Baccini, Biggeri et al. 2008, Gasparrini, Guo et al. 2015, Heo, Lee et al. 2016). The association between cold and mortality is higher in decreasing latitude or mild winter climate region, whereas heat-related mortality is higher in higher latitudes (Curriero, Heiner et al. 2002, Ma, Chen et al. 2014). The spatial heterogeneity in temperature-mortality risk indicates that a single exposure-response relationship may not apply across a large region such as a state (Iñiguez, Ballester et al. 2010, Armstrong, Chalabi et al. 2011, Li, Cheng et al. 2014, Chen, Li et al. 2017). Also, these findings suggest different adaptations of the community with local weather conditions (Curriero, Heiner et al. 2002, Turner, Barnett et al. 2012). This could relate to different housing conditions, behaviors, or other factors.

The few studies on temperature-health relationships in rural areas showed a higher mortality risk for rural settings than in the urban areas (Lippmann, Fuhrmann et al. 2013, Berko, Ingram et al. 2014, Heaviside, Macintyre et al. 2017, Dang, Van et al. 2018, Adeyeye, Insaf et al. 2019). The rural population is vulnerable to extreme temperatures, and the risk needs to be evaluated and characterized (Hashizume, Wagatsuma et al. 2009, Loughnan, Nicholls et al. 2010, Henderson, Wan et al. 2013). While many factors are relevant, such urban-rural disparities in temperature-health relationships may contribute to the lower life expectancies in US non-metropolitan areas, compared to metropolitan areas, when stratified by gender, race, and income (Singh and Siahpush 2014). The inequality between rural and urban populations is increasing over time in the US (Singh and Siahpush 2006). These trends in health differences relate to different characteristics in rural settings, such as the lack of access to health care and public services, differences in environmental factors such as air quality and population characteristics (Mirabelli and Richardson 2005).

Although analysis is limited, a few studies have compared the temperature-mortality or temperature-morbidity relationship among subregions within a large region such as a state or have considered differences in urban-rural areas (Henderson, Wan et al. 2013, Lippmann, Fuhrmann et al. 2013, Madrigano, Jack et al. 2015, Sugg, Konrad et al. 2016, Dang, Van et al. 2018). In British Columbia, Canada, the heat-related attributable mortality was higher in the Mountain region, which has a cooler climate zone, compared to the Dry Plateau region with a higher mean temperature (Henderson, Wan et al. 2013). In California, US, the northern part of the state had the lowest heat-mortality risk compared to the other climate zones (e.g., Coastal and Dry Plateau), which have higher temperatures (Joe, Hoshiko et al. 2016). The risk of emergency department visits from heat-related illness in North Carolina was significantly higher in the Coastal Plain than in the Piedmont and Mountain regions (Sugg, Konrad et al. 2016). In another study assessing the incidence rate ratio of heat-related illness emergency department visits in North Carolina, the rates were highest for the Coastal Plain and Mountain regions (Lippmann, Fuhrmann et al. 2013). These studies compared differences in heat risk by region but did not analyze the cold mortality risk in those regions. In the northeastern US, urban counties had a higher mortality risk from heat than did non-urban counties (for temperature increase from 21.2°C to 32.2°C) for urban: 8.88%, 95% PI: 7.38–10.41; non-urban: 8.08%, 95% PI: 6.16–10.05) (Madrigano, Jack et al. 2015). On the other hand, some studies suggested that the less urban areas were more susceptible to extreme temperature than are urban areas (Lippmann, Fuhrmann et al. 2013, Bai, Cirendunzhu et al. 2014, Chen, Zhou et al. 2016, Lee, Shi et al. 2016). Of the existing studies that compared weather-related mortality risk in urban and rural areas, most used binary urban-rural classifications.

Most studies on the temperature-mortality association focused on heat. However, of the studies that did investigate cold, most found cold to be associated with a higher risk of mortality than heat (Huynen, Martens et al. 2001, Dixon, Brommer et al. 2005, Gasparrini, Guo et al. 2015). Also, many temperature-mortality studies assessed temperature using data from monitoring sites (Curriero, Heiner et al. 2002, Dang, Van et al. 2018), which has benefits of using actual measurements, but also could result in exposure measurement errors for locations further from monitors even though temperature is relatively homogenous across nearby communities.

Many studies have reported that individual factors such as age, sex, income, and education modify temperature's effect on mortality and morbidity (Stafoggia, Forastiere et al. 2006, Harlan, Declet-Barreto et al. 2013, Benmarhnia, Deguen et al. 2015, Kovach, Konrad et al. 2015, Shi, Liu et al. 2016, O'Lenick, Winquist et al. 2017). A study of Italian cities found that the heat mortality risk increased with age and was higher for women than men (Stafoggia, Forastiere et al. 2006). Similarly, the association for emergency department visits from heatstroke in North Carolina increased among elderly patients during the June heat event in 2007 to 2011 (Fuhrmann, Sugg et al. 2016). A study in China found suggestive evidence of increased heat mortality risks in communities with low socioeconomic status (Huang, Lin et al. 2015), and in Worcester, Massachusetts, the association between extreme heat and acute myocardial infarction was higher for people below the poverty line (Madrigano, Mittleman et al. 2013). In North Carolina, heat-related illness rates were higher for those living below the poverty line and in areas with less forested land (Kovach, Konrad et al. 2015). In Germany, ozone but not PM_{10} was an effect modifier for the temperature-mortality relationship (Breitner, Wolf et al. 2014). Urban green space had a protective effect on heat-related mortality in the elderly population in Lisbon (Burkart, Meier et al. 2016). There was no evidence of effect modification related to the social connectivity of the community.

The temperature-related mortality risk varies by geographical region, socio-economic conditions, and urbanization (Luber and McGeehin 2008, Wang, Liu et al. 2016). Heat-related mortality risk vary widely between cities within the same country due to differences in summer heat intensity (Michelozzi, De Sario et al. 2006, Iñiguez, Ballester et al. 2010). Cities with warmer climates tended to have lower mortality risk, suggesting that populations that are more exposed to heat may be better able to cope with heat (Chung, Honda et al. 2009, Morabito, Crisci et al. 2012, Li, Cheng et al. 2014). However, most studies focus on the risk of heat-related mortality between regions with different climates, and less information is known on the differences in cold-mortality relationship and on the differences in temperature-mortality associations by socioeconomic and urbanization factors.

In this study, we address these research gaps for the state of North Carolina, US, which has different climatic regions and rural-urban heterogeneity. We used temperature estimates with a high spatial resolution to assess the entire state, which allows investigation of regional and urban-rural differences in mortality risks for both heat and cold. We further consider effect modification by social association, a measure of connectivity in communities; greenness; air pollution; education; residential segregation; income inequality; and income.

Methods

Study Site

North Carolina is located in the southeastern region of the US, with more than 10.4 million residents at about 80.6 people/km^2 in 2019 (Census 2019). North Carolina's 100 counties are mostly in the humid subtropical climate zone, experiencing hot and humid summers and cold to mild winters. However, the western side of North Carolina lies in the subtropical highland climate, with mountainous areas experiencing cool summers.

We selected this state for several reasons. First, the state has a large population and is rapidly growing (top 10 US states for population size and population growth). Second, due to North Carolina's various land cover characteristics, this region allows the investigation of multiple important research questions for this study. The three principal regions of North Carolina are the Mountain, Piedmont, and Coastal Plain (from west to east) (Sayemuzzaman and Jha 2014). The diversity of North Carolina in terms of regional characteristics allows the study of the possible health disparities that might relate to heat- and cold-related mortality risks. Finally, the study area has demographic diversity allowing the study of effect modification of heat and cold mortality associations.

Data

Mortality dataset—We obtained individual-level mortality data for North Carolina from 2000 to 2016 from the North Carolina State Center for Health Statistics, Vital Statistics Department. For each participant, mortality data included date of death and residential county. We categorized mortality data as total deaths for all causes of death excluding external causes (International Classification of Diseases, ICD-10, A00-R99). We excluded participants with incomplete data for any variable.

Meteorological dataset—Due to the lack of measured daily weather data at all study locations, we used estimated gridded weather data to provide coverage for the entire state and then converted that data to the county level. The gridded weather data using Parameter-elevation Regressions on Independent Slopes Model (PRISM) interpolation method are reported for daily estimates and at high spatial resolution (4×4km grid) (PRISM Climate Group). The algorithms and further details are described elsewhere (Daly, Halbleib et al. 2008, Thornton, Thornton et al. 2014). A previous study showed good agreement between measured and gridded weather data (Mourtzinis, Rattalino Edreira et al. 2017). We used daily estimates of temperature and dew point temperature at the county level. County-level values were calculated as the average of values for all grid cells with centroids within each county. For sensitivity analysis, data on daily relative humidity for weather stations across

North Carolina were analyzed. Data on daily relative humidity from 172 weather stations were averaged to generate estimates for each county.

Urbanization and Regional dataset—Data on the designations of urbanicity were obtained from the Census Bureau, which classified urbanization into three types: urbanized areas, urban clusters, and rural. Urbanized Areas are areas with 50,000 or more people, Urban Clusters are areas with at least 2,500 but fewer than 50,000 people and rural areas have less than 2,500 people in a census block (Ratcliffe, Burd et al. 2016). In this study, we used the US Census dataset containing the urbanization classification at the county level (Census 2010).

List of potential effect modifiers—To assess potential disparities in the temperature-mortality relationship, we included several county-level environmental and socio-economic factors based on the previous literature (Son, Lane et al. 2020). We considered county-level regional characteristics: 1) social associations, 2) population density (persons/km^2); 3) greenness, as measured by Normalized Difference Vegetation Index (NDVI); 4) particulate matter with aerodynamic diameter no larger than 2.5m ($PM_{2.5}$); 5) education level, measured as the percentage of people with a high school degree; 6) residential segregation, assessed as the dissimilarity index between non-White and White residents; 7) income inequality, calculated as the ratio of the household income at the 80th percentile to the income at the 20th percentile, and 8) income, computed as the median household income for each county. We stratified variables for effect modification by the median value; this approach has been used in previous studies of temperature-mortality effect modification (Goggins, Chan et al. 2012, Luo, Li et al. 2017). We used the mean value of the effect modification instead of the median as sensitivity analysis.

1) Social Associations: We considered social associations, which is the number of membership associations per 10,000 population. This variable reflects social or community support, which relates to social connectedness. Social association data for each county were obtained from the County Health Rankings (CHR), created by the University of Wisconsin Population Health Institute and the Robert Wood Johnson Foundation (CHR&R 2021). CHR has been used in identifying the relationship between various factors and health outcomes (Anderson, Saman et al. 2015, Hood, Gennuso et al. 2016). We used the average values of social associations by county from 2000 to 2016. We categorized the social association for each county as above or below the median across counties (≥12.8 associations/10,000 persons or <12.8 associations/10,000 persons).

2) Population Density: Population density (persons/km^2) data were obtained from US Census Bureau and were averaged at the county level based on available Census data (for the year 2000, and for the year 2010, represents the years 2006 to 2016). We classified the population density by county using the median value to distinguish the high population density group (≥43.46 people/km^2) and low group (<43.46 people/km^2).

3) Normalized Difference Vegetation Index (NDVI): Greenspace was assessed as vegetation using NDVI derived from the Moderate Resolution Imaging Spectroradiometer (MODIS) sensor aboard the Terra satellite image from NASA's Earth Observing System for years 2000 to 2016. We used the global MODIS product MOD13Q1 version 6, which has been corrected for atmospheric contamination from water, clouds, and aerosols. This product is a 16-day composite at a spatial resolution of 250 m. We calculated the average of NDVI for each county by averaging pixel values across the remote sensing image files of NDVI through all 16-day composites from January 1, 2000 to December 19, 2016. The gridded data were converted into points using ArcGIS and then spatially joined at the county level for the study period. NDVI values range from 0 to1 with higher values reflecting higher levels of vegetation. We calculated the median NDVI and categorized the greenness as above or below (≥0.61 or <0.61).

4) Particulate matter with aerodynamic diameter no larger than 2.5μm ($PM_{2.5}$): Ambient daily $PM_{2.5}$ concentrations (μg/m^3) for North Carolina by county were obtained for 2002 to 2016 from the downscaler output from the US Environmental Protection Agency (EPA) at 12×12 km grid cell resolution (Son, Lane et al. 2020). Long-term averages were generated for each county by averaging values from 2002 to 2016 and converting the gridded estimates to county values using area-weighted averaging. The overall median value of $PM_{2.5}$ for North Carolina was used to categorize counties (<10.3 μg/m^3 or ≥10.3 μg/m^3). O_3 was also examined as a potential effect modifier for air pollution. The daily 8-hour maximum O_3 concentrations (ppb) were also obtained from the downscaler output from the US Environmental Protection Agency (EPA) at 12×12 km grid cell resolution (Son, Lane et al. 2020), and the daily average values for each county were calculated based on these estimates in the same manner as $PM_{2.5}$. The overall median value of O_3 for North Carolina was used to categorize counties (<41.1 ppb or ≥41.4 ppb).

5) Education Level: The overall education level for each county was assessed as the percentage of people with at least a high school degree. The education level data were obtained from the County Health Rankings (CHR) (CHR&R 2021). Values were averaged for each county for the period 2000 to 2016. The education level for each county was categorized as above or below the median value across counties (≥86 percent or <86 percent).

6) Residential Segregation: We obtained the dissimilarity index between non-White and White county residents as residential segregation. A higher value represents greater residential segregation between non-White and White county residents. The residential segregation index values were obtained from the County Health Rankings (CHR) (CHR&R 2021) and were averaged for the period 2010 to 2014. The overall median value of the residential segregation was used to categorize counties (<30 or ≥30).

7) Income Inequality: Income inequality was defined as the ratio of the household income at the 80^{th} percentile to the income at the 20^{th} percentile. A higher value indicates greater division between the highest and the lowest income range within a county. Income inequality was assessed from the County Health Rankings (CHR) (CHR&R 2021) and was averaged for the period 2012 to 2016 for each county. Counties were divided into two categories by the median value for income inequality (<4.6 or ≥4.6).

8) Income: The median annual household income ($) was examined for each county and was averaged during the study period (2000–2016) for each county. Income data were obtained from the County Health Rankings (CHR) (CHR&R 2021). The overall median annual income was used to categorize the counties into two groups above or below the median value (<$41,701 or ≥$41,701).

Statistical Analysis

Two-stage hierarchical time-series analyses—We excluded counties with less than 10,000 total population based on the average value of 2000 and 2010 US Census, due to potential convergence issues; this excluded 6 counties, leaving a total of 94 counties for analysis. Sensitivity analysis was conducted including all 100 counties.

We applied a two-stage hierarchical model. In the first stage, we used a time-series quasi-Poisson generalized additive model (GAM) to link daily mortality with daily average temperature, producing an overall exposure–response curve for each county. The model allows a nonlinear relationship between temperature and risk of mortality. We adjusted for day of the week, daily dew point temperature, and temporal trends accounting for long-term and seasonal trends. The model structure is:

$$\log\left(Y_t^c\right) \sim \beta_0^c + \beta_1 * ns\left(T_{lag}^c, 3\right) + \beta_2 * \ \mathrm{ns}\left(time_t, 7/year\right) + \beta_3 * \mathrm{DOW}_t + \beta_4 * \mathrm{ns}\left(D_t^c, 3\right), \tag{1}$$

where Y_t^c= expected mortality rate for county c on day t; β_0^c= model intercept for county c; $\mathrm{ns}(T_{lag}^c)$= natural cubic spline of a temperature metric for county c for a specific lag from day t, with 3 degrees of freedom (df) and knots at quantiles; ns ($time_t$)= natural cubic spline of time, with 7 df per year; DOW_t= categorical variable for the day of the week for day t; $\mathrm{ns}(D_t^c)$ = natural cubic spline of adjusted dew point temperature for county c on day t, with 3 df.

Equation 1 provides an estimate of a nonlinear association between temperature and risk of mortality for each county. To compare the effects across counties, we estimated the effect of relative and absolute temperature changes from the temperature-mortality response curves by county. Relative temperature change compares risk effect estimates at two temperatures based on percentiles, allowing these percentile-based temperatures to differ by community. Absolute temperature change compares risk effect estimates at two specific temperatures using the same specific temperatures across all counties (Anderson and Bell 2009). The effects of relative temperature change were calculated by comparing risks at the 1st and 10th percentiles (cold effect) and 99th and 90th percentiles (hot effect) of each county's temperature distribution (i.e., allowing different percentile-based temperatures by county). The effects of absolute temperature change were calculated by comparing risks at 28.2°C and 25.5°C (heat effect) and −3.7°C and 2.9°C (cold effect) for all counties with temperature data available in this range (83 counties for heat effect and 94 counties for cold effect). These temperatures (−3.7°C, 2.9°C, 25.5°C, and 28.2°C) are the approximate average for the 1st, 10th, 90th, and 99th percentiles of mean daily temperature across counties. Effects based on absolute temperatures compare risks at the same temperature across counties, whereas effects based on relative temperatures compare risks at temperatures relative to each county's temperature distribution and weather conditions.

In the second stage of the analysis, we pooled the county-specific estimates of absolute and relative heat and cold effects, and estimates of their uncertainty, for overall, regional, and urban-rural categories using Bayesian hierarchical modeling with Two-Level Normal independent sampling estimation (TLNise) (Everson and Morris 2000). This statistical analysis has been widely used in studies of temperature and health (Anderson and Bell 2009, Son, Bell et al. 2014). Sensitivity analyses were performed using a variable for relative humidity instead of the dew point temperature, and another model was run excluding the variable for the day of week.

Different lag days for heat and cold: Previous studies showed that mortality risk at low temperatures (i.e., cold effect) persists for a longer time, with more lag days than does mortality risk at high temperatures (i.e., heat effect) (Anderson and Bell 2009, Huang, Wang et al. 2014). We modeled the heat and cold effects separately, using lag 0–1 days (same day and previous day) for heat and lag 0–25 days for cold. This lag selection for heat and cold has been used in other temperature-mortality US studies (Anderson and Bell 2009, Chen, Du et al. 2019).

Effect modification analysis and statistical significance: We examined whether county characteristics modify the temperature-mortality associations, based on social association, population density, greenness, particulate matter, education level, residential segregation, income inequality, and income. We performed stratified analyses by county-level factors and then tested the statistical significance of the differences between the effect estimates of each potential effect modifier strata (low and high) by calculating the 95% confidence interval as $(\mathrm{Q1} - \mathrm{Q2}) \pm 1.96\sqrt{SE_1^2 + SE_2^2}$, where Q1 and Q2 are the estimates for the two strata of the potential effect modifier (e.g., low $PM_{2.5}$ and high $PM_{2.5}$ group) and SE_1 and SE_2 are their respective standard errors. For effect modification, we tested dividing counties by the mean rather than median as sensitivity analysis. The correlations between potential effect modifiers are provided in Table S1. All analyses were conducted using SAS (9.4, SAS Institute, Cary, NC, US) and R (version 3.5.1, R Core Team).

Results

Descriptive characteristics

Table 1 shows summary statistics of daily meteorological variables and daily mortality counts for all the counties, by region and urban-rural categories in North Carolina. The Coastal region has more counties than other regions at 37 counties. Within the state, 53 counties were categorized as Urban Cluster. The average daily mean temperature was highest in the Coastal region and lowest in the Mountain region (16.43°C and 12.62°C, respectively). Urban Area counties' average temperature was 1.39°C higher than that of Rural counties. The dataset includes a total of 1,208,766 deaths (all non-accidental causes), with 659,594 in the Piedmont, and 631,905 in Urban Area counties (Table 1). Figure 1 represents the geographic distribution of the mean temperature for each county and region

(Mountain, Piedmont, Coastal Plain). The mean temperature increases from the Mountain region to the Coastal Plain. The distribution of the urban-rural categories within the same region was fairly evenly distributed.

Exposure-response curve and temperature histogram

Figure 2 provides the overall non-linear association between temperature and risk of mortality across the state; this figure displays the estimated relative risk for a given temperature compared with the minimum mortality temperature (MMT), which is 22.4°C. This figure shows both cold and heat impacts for the state. Figure 2 also provides a histogram of the 1st, 10th, 90th, and 99th temperature distributions among the 94 counties, which indicate variation in the temperature distributions across counties.

Relative and Absolute effect of temperature-mortality relationship

Slopes of the exposure-response curves for heat and cold were summarized by comparing the risk of relative and absolute temperature changes (Table 2). The estimated relative effect of mortality risk was 1.001 (95% CI: 0.995–1.007) comparing the 99th and 90th percentiles for T_{lag0-1} (relative heat effect). The overall estimated relative effect for mortality risk comparing the 1st and 10th percentiles of $T_{lag0-25}$ (relative cold effect) was 1.019 (95% CI: 1.015–1.023). The estimated relative risk for mortality was 0.998 (95% CI: 0.993–1.004) at 28.2°C compared to 25.5°C for T_{lag0-1} (absolute heat effect) and 1.018 (95% CI: 1.013–1.022) comparing −3.7°C to 2.9°C for $T_{lag0-25}$ (absolute cold effect). Figure S1 shows the forest plot of relative and absolute cold and heat effects for each county, showing the range of estimates across counties. Sensitivity analysis including the additional 6 counties that were excluded in the original analysis provided similar results (Table S2). Also, the overall results were similar when a variable for relative humidity was included in the model instead of dew point temperature (Table S3). The model without a variable for day of week also resulted in similar relative and absolute heat and cold effects (Table S4).

Regional Disparity in Temperature-Mortality Relationships—Table 2 provides the estimated relative and absolute effects for heat and cold by region. The Coastal Plain region had the lowest heat effect for both relative and absolute temperature; results for this region did not suggest an association between heat and mortality. The Piedmont region had the highest heat relative risk and the Mountain region the highest heat absolute risk, although neither were statistically significant. The cold relative and absolute effect risks were statistically significant in all three regions. The cold relative and absolute effects were higher in the warm regions (Piedmont and Coastal Plain) and lowest in the coldest region (Mountain region). The pooled regional temperature-mortality curves for heat and cold risk by different regions are shown in Figure S2. Sensitivity analysis showed that the relative and absolute effects for each region were similar when including the 6 previously excluded counties (Table S2).

The geographic distributions of heat and cold effects of each county for relative (comparing risk across each county’s temperature percentile) and absolute (comparing risk at specific temperatures) effects are mapped in Figures 3 and 4. The estimated relative and absolute heat effects were statistically significant in two counties, which were located in the

Piedmont and Coastal regions (Anson and Martin), with lower mortality risk with heat(Figure 3). There were no counties with a statistically significant risk of higher mortality risk from heat (Figure 3). On the other hand, several counties had statistically significant estimated effects for the relative and absolute cold effects, with higher mortality risk with cold (Figure4).

Urban-Rural Disparity in Temperature-Mortality Relationships—When we examined the temperature-mortality association by urbanization (Table 2), Urban Area counties had the highest relative and absolute heat effects, although neither was statistically significant. All three levels of urbanization had statistically significant associations for cold for relative and absolute effects, both of which were highest for Urban Area counties. Figure S3 shows the pooled temperature-mortality curves for heat and cold risk by urban-rural categories. Sensitivity analysis found similar results when the remaining 6 counties were included (Table S2).

Potential Effect Modification of Temperature-Mortality Relationships—We assessed whether the temperature-mortality association differed by county-level characteristics of social associations, greenness, particulate matter, education level, residential segregation, income inequality, or income. Summary statistics of these potential effect modifiers are shown in Table S5. The correlations between potential effect modifiers were low, with the highest for population density and $PM_{2.5}$ (0.45) (Table S1). Stratified analyses showed that associations between relative heat and mortality were statistically higher in counties with low social association and low NDVI (below the median compared to counties with social association or NDVI above the median) (Figure 5, Table 3). Most estimated relative heat and cold effects were not statistically different between regional and urban-rural categories, and the mortality risk showed a similar pattern among regional and urban-rural categories for heat and cold effects (Figure 5). We found higher estimated relative heat mortality risk in counties with higher population density, lower education level, and higher residential segregation, although estimates were not statistically different. The relative cold effect estimates were statistically higher for counties with higher population density, higher $PM_{2.5}$, lower education level, higher residential segregation, higher income inequality, and higher income value overall across the counties.

Population density groups were statistically different for total, Urban Cluster, and Coastal relative cold effects. The estimated risk for both the high NDVI group and the low NDVI group were statistically different for total, Urban Cluster, and Coastal heat effects. The high and low $PM_{2.5}$ groups had statistically different estimated relative cold effects overall (all North Carolina) and the Coastal region. Results for potential effect modifiers were similar when dividing into groups based on the mean value rather than the median (Table S6). The sensitivity analyses for O_3 were conducted for state overall and separately the three different regions (Table S7). Results showed a different trend among different regions for the heat relative risk. The heat relative risk was higher in groups with higher ozone levels in the urban areas, although results were not statistically different. The cold relative risk was higher in groups with lower ozone levels among the different regions, although results were not statistically different.

Discussion

Our results suggest both regional and urban-rural disparities for cold temperature-mortality risks. The Coastal Plain had significant associations for cold-related mortality. We also found that the urban areas had a higher central estimate for the estimated mortality risk associated with cold, compared to the rural areas. Lower population density, lower $PM_{2.5}$, higher education level, lower residential segregation, lower income inequality, and lower income level was associated with a lower central estimate for the cold relative effect.

Our results are consistent with other temperature-mortality studies conducted in various climate conditions (Henderson, Wan et al. 2013, Joe, Hoshiko et al. 2016). Although results were not statistically significant, the central estimate of the absolute heat effect was highest in the Mountain region, where the overall temperature is low compared to the other regions. On the other hand, the Coastal Plain, which had the highest mean temperature, had a lower central estimate for heat-mortality risk. This pattern is consistent with cold effects. The central estimates for the relative and absolute cold effects were higher in the Piedmont and Coastal Plain, which have high mean temperature, and the cold-mortality risk was lower in the Mountain region, which has a cooler climate. This suggests that the populations living in hot or cold conditions adapt to those temperatures to some degree. Furthermore, the estimated absolute cold and heat effect esitmates differed among counties indicating that the populations' responses differ for a given temperature.

Previous findings on the urban-rural difference in temperature-mortality relationships vary across studies. Our result is consistent with studies conducted in Ho Chi Minh City, Vietnam (Dang, Van et al. 2018), the northeastern part of the US (Madrigano, Jack et al. 2015), the United Kingdom (Hajat, Kovats et al. 2007), Germany (Gabriel and Endlicher 2011), and Greece (Katsouyanni, Pantazopoulou et al. 1993). In Ho Chi Minh City, the estimated heat mortality risk was higher in the central area than in the outer area (Dang, Van et al. 2018). In the northeastern part of the US, urban counties had a higher estimated percent increase in mortality in relation to heat than did non-urban counties (Madrigano, Jack et al. 2015). However, in Zhejiang Province, the urban areas had a lower estimated heat-mortality risk than rural areas (Hu, Guo et al. 2018). Furthermore, a nationwide US study reported that the urban-rural temperature-mortality risk differs by region (Berko, Ingram et al. 2014). The inconsistency of previous results suggests that the heat effect of urban-rural categories varies by region and nation, and likely by population. For these reasons, although general conclusions can be drawn, the estimates of weather and mortality in one area may not be generalizable to another. In particular, our findings indicate that urban and rural areas may require different analysis.

The urban-rural difference for cold effects is not well studied. Our results suggest differences in the urban-rural mortality risk for cold (relative effects of 1.023 (95% CI: 1.017, 1.03) and 1.012 (95% CI: 1.001, 1.023) for urban and rural areas, respectively), which were higher than the heat effects (relative effects of 1.006 (95% CI: 0.997, 1.016) and 1.002 (95% CI: 0.988, 1.017), for urban and rural areas, respectively). This result is consistent with a previous study in Zhejiang Province, China (Hu, Guo et al. 2019). This could relate to high temperatures in urban areas during wintertime, which may expand the urban-rural difference in heat-mortality risk, whereas the low vulnerability for high temperatures in the summer could decrease the risk gap between urban and rural.

We found evidence of adaptation in high-temperature counties; however, we did not observe adaptation to cold-related mortality risk in colder counties. For instance, even though the urban cluster counties had a high mean temperature, they had a lower heat effect and a higher cold effect (0.996 (95% CI: 0.987, 1.004), 1.017 (95% CI: 1.011, 1.023) for relative temperature effect for heat and cold, respectively). In addition, we did not observe statistically significant estimated effects for heat risk, whereas cold-related mortality risks were statistically significant. These findings support the various study findings that urban areas are more adjusted to heat effects than cold effects (Rocklöv, Forsberg et al. 2014, Arbuthnott, Hajat et al. 2016, Martínez-Solanas and Basagaña 2019).

Counties with lower social association and lower NDVI had a higher estimated mortality risk from heat than did other counties. For the cold effect, counties with higher population density, higher $PM_{2.5}$ value, lower education level, higher residential segregation index, higher income inequality, and higher income value were associated with increased mortality risk. We conclude that social and environmental factors affect the temperature-mortality relationship, which is consistent with results in prior studies. A previous study found that increases in green space are expected to prevent attributable deaths related to heat (Dang, Van et al. 2018). In Korea, higher social isolation was associated with increased heat risk for the elderly living in an urban environment (Kim, Lee et al. 2020). Social isolation is a risk factor that could increase mortality (House 2001), whereas populations in areas with high social connections are more likely to have improved health (Kawachi, Kennedy et al. 1999). Estimated heat effects were higher in more densely populated cities (Medina-Ramón and Schwartz 2007), and a decrease in $PM_{2.5}$ levels was associated with lower mortality risk (Wu, Braun et al. 2020). A study in the US found that heat-related mortality risk decreases as the education level increases (Lee, Shi et al. 2016). Also, higher residential segregation was associated with higher heat risk-related land cover (Jesdale, Morello-Frosch et al. 2013) and urban heat risk index (Mitchell and Chakraborty 2018) in the US. A study of 14 European countries found a significant association between the cold effect and elderly mortality with poverty, income inequality, and deprivation rate (Healy 2003). In 50 US states, the median income was negatively associated with mortality in people aged 25 to 64 (Backlund, Rowe et al. 2007). Similarly, a study in US found higher heat effects in higher income communities (Anderson and Bell 2009). These previous study results are consistent with our study results. There are few studies on effect modification by community-level factors, and most of them focus on heat effect (Son, Liu et al. 2019). Our study results provide evidence of effect modifications on both heat and cold mortality risk.

The Healthy People 2020 initiative has identified goals to improve community health over the next decade (DHHS 2010). This includes goals to attain high-quality and longer lives, achieve health equity and eliminate disparities, and improve the health of all persons (DHHS 2010). These goals pose a challenge to North Carolina (Mansfield, Kirk et al. 2001) since the average life expectancy in this state is 77.86 years, which is 1.22 years lower than the average life span in the US (UW 2014). To extend life expectancy in North Carolina, efforts are needed to identify a way to bridge the health gap and achieve health equity for all populations (Dwyer-Lindgren, Bertozzi-Villa et al. 2017).

While mortality rates have declined in the US (Woolf and Schoomaker 2019), populations living in rural areas have maintained higher mortality rates than metropolitan areas for more than 10 years (Singh and Siahpush 2014, Gong, Phillips et al. 2019). Rural areas in North Carolina have higher rates of years of life lost, injury, uninsured patients, and preventable hospitalizations (HRSA 2016, Holmes 2018). However, social association, which measures social capital, was higher in rural regions than metropolitan areas in North Carolina (Julie L. Marshall 2017, Holmes 2018). Health outcomes can be improved by identifying North Carolina’s existing urban and rural gaps in various population health indicators (Gong, Phillips et al. 2019).

Assessment of the temperature-mortality risk in rural and isolated areas is challenging due to the small population and data availability limitations. In this study, we examined the temperature-mortality risk within those populations and specified different ecoregions (e.g., Mountain, Piedmont, and Coastal Plain) and urban-rural categories. We explored North Carolina, which consists of diverse microclimate conditions and urban-rural populations. This approach could be applied to other states in the US and other areas with different climate conditions and with various population distributions.

This study had several limitations. First, we analyzed at the county level, which could obscure heterogeneities within counties. Second, exposure measurement error may occur, as in all environmental epidemiological studies (Zeger, Thomas et al. 2000). Also, this study was conducted in one state in the US, and the most rural counties with a population of less than 10,000 were excluded from the analysis. Further areas need to be investigated, including urban-rural and regional disparities. Analysis at the sub-county level examining neighborhood-level and individual-level characteristics would further elucidate how temperature impacts mortality. Lastly, effect modifiers analyzed in this study should be interpreted and applied in the light of wider research. Additional factors, not addressed here, may also modify the temperature-mortality relationship.

We found suggestive evidence that higher social association and high NDVI values were associated with lower heat relative effect. The greenspace metric used (NDVI) does not fully characterize the complex pathways through which greenspace could influence the temperature-mortality relationship. Tree canopy cover, land cover characteristics, different types of vegetation, and Enhanced Vegetation Index (EVI) could be explored (Ziter, Pedersen et al. 2019, Fong, Mehta et al. 2020). EVI is also used to measure high-density vegetation (Chen, Fedosejevs et al. 2006), but NDVI is primarily used to compare green areas (Son, Lane et al. 2016). Future work could investigate different aspects of green space such as EVI as well as different types of vegetation, access to green space, seasonal patterns, etc.

The socio-economic effect modifiers analyzed in this study warrant careful interpretation, and other factors relating to socioeconomic status should be further studied in the future. In future analysis, social cohesion or social networks could be considered in characterizing social interaction, with more detail regarding which types of social networks are most impactful. In this study, education level was defined as the percentage of people with high school degrees. Education attainment could be defined in other ways (e.g., completed college), and actual socioeconomic status relates to income, history of income, socioeconomic status during childhood, and other factors. We analyzed race/ethnicity and analyzed residential segregation, however, further distinctions of race/ethnicity examining additional categories of populations of color are needed. Similarly, further analysis for economic effect modifiers (e.g., poverty ratio, gross domestic product (GDP), and unemployment rates) could be examined. In addition, other factors such as population change should be discussed further, considering the temporal trend of the effect modifier. In the study, we investigated several metrics of social or environmental justice (income, income inequality, residential segregation, education), however there exist a wide array of other metrics. The variables we selected reflect different aspects of socio-economic position and demographic patterns and are related in complex ways. For example, we used the percentage of people with a high school diploma as an indicator of educational attainment. Previous studies have found that lack of high school education is associated with lack of health insurance and working in high-risk jobs (Muller 2002). Lack of high school education may also indicate a lifelong impact of socioeconomic deprivation. There exists no gold standard for what social or environmental justice metric is most appropriate, and they each represent different aspects of complex and interrelated social, cultural, political, and environmental systems. Future research could investigate other metrics such as a direct measure of income, other measures of race/ethnicity, etc., which may reflect different underlying pathways through which the association between weather and risk of mortality could differ by subpopulation.

Despite these limitations, this study identified regional and urban-rural differences in the mortality risk for cold. The estimated cold effect was higher for high-temperature regions than the cooler region. Urban counties had higher central estimates for heat and cold mortality risk than did the rural counties of North Carolina. Also, this study suggests that higher social connectedness, higher green space, lower population density, lower air pollution level, higher education level, lower residential segregation, lower income inequality, and low income are associated with lower temperature-mortality risk. Previous temperature-mortality studies primarily focused on hot temperatures and few explored rural settings. In conclusion, future temperature-mortality studies should account for regional and urban-rural differences in mortality risk. Our findings suggest that local health plans and implementations to address heat and cold would be most effective if they account for regional and urban-rural differences. Furthermore, the social and environmental factors we identified as effect modifiers could be used to diminish the health burden from heat or cold.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

NDVI	Normalized Difference Vegetation Index
$PM_{2.5}$	particulate matter with aerodynamic diameter no larger than 2.5μm

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Highlights

- Results suggest potential regional and urban-rural disparities for high and low temperature-mortality risks in North Carolina, USA.
- The Piedmont region had the highest cold-mortality risks, whereas the Mountain region had the lowest cold mortality risks.
- Although not statistically different from rural temperature-mortality risks, urban areas had higher estimated mortality risk associated with both heat and cold.
- Findings suggest that high social association and high NDVI value were associated with lower heat relative effects, and that low population density, low $PM_{2.5}$, higher education level, lower residential segregation, and lower income inequality were associated with a low cold relative effect.

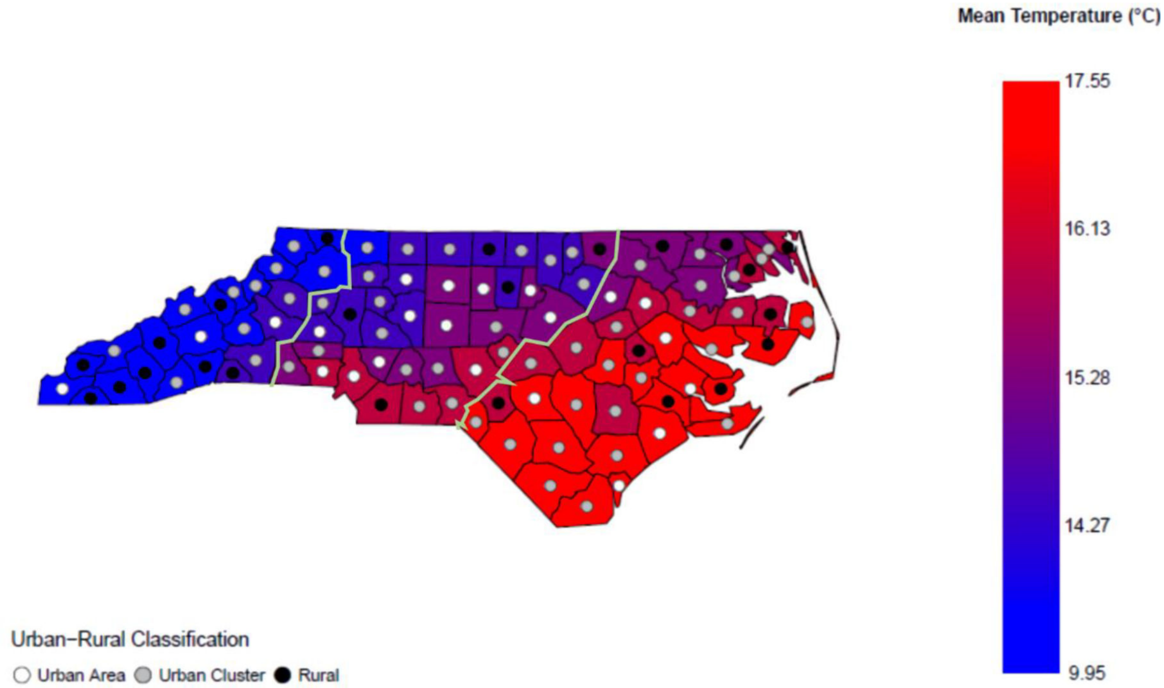

Figure 1.

Geographic temperature distribution by county. Note: The green lines divide the state into three regions: Mountain, Piedmont, Coastal Plain (left to right), and the dot in each county indicates Urban Area (White), Urban Cluster (Grey), and Rural (Black).

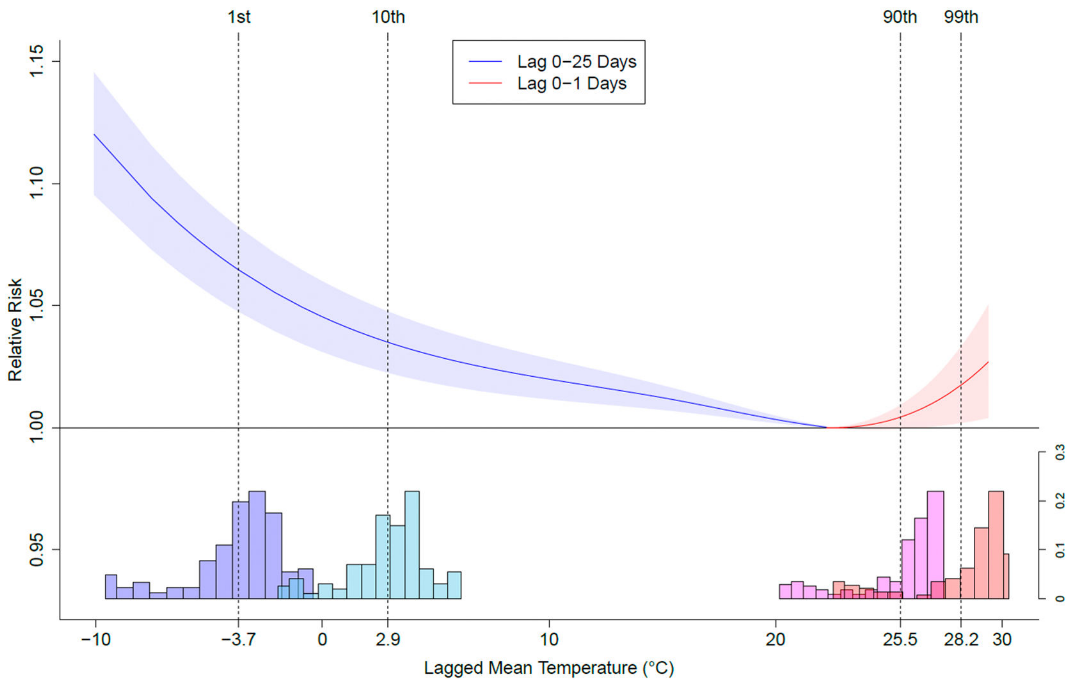

Figure 2.

Cold and heat exposure-response curve: estimated relative risk for a given temperature compared to the minimum mortality temperature (MMT). Note: Each histogram displays the temperature distribution for 94 counties at the 1st, 10th, 90th, and 99th (left to right) percentiles. Dotted vertical line indicate the mean across counties for temperature value for each percentile (−3.7°C, 2.9°C, 25.5°C and 28.2°C).

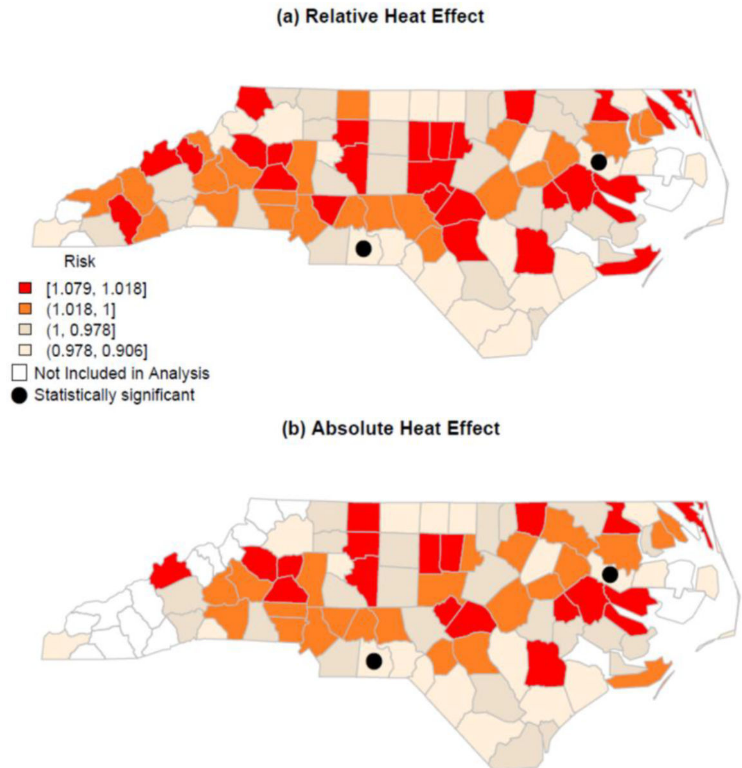

Figure 3.
Geographic distribution of the estimated relative heat effect (a) and absolute heat effect (b) by county

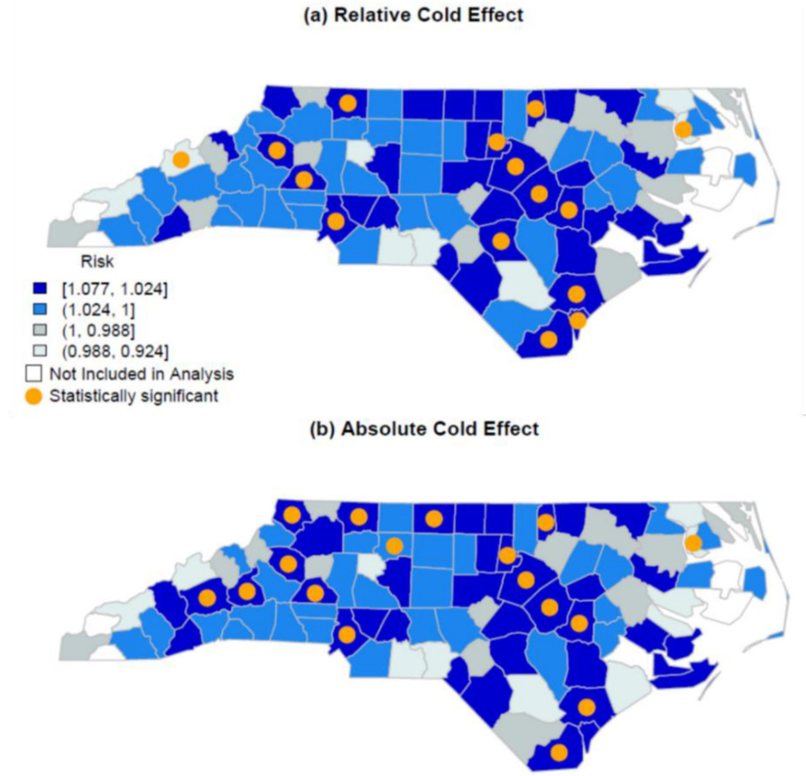

Figure 4.

Geographic distribution of the estimated relative cold effect (a) and absolute cold effect (b) by county

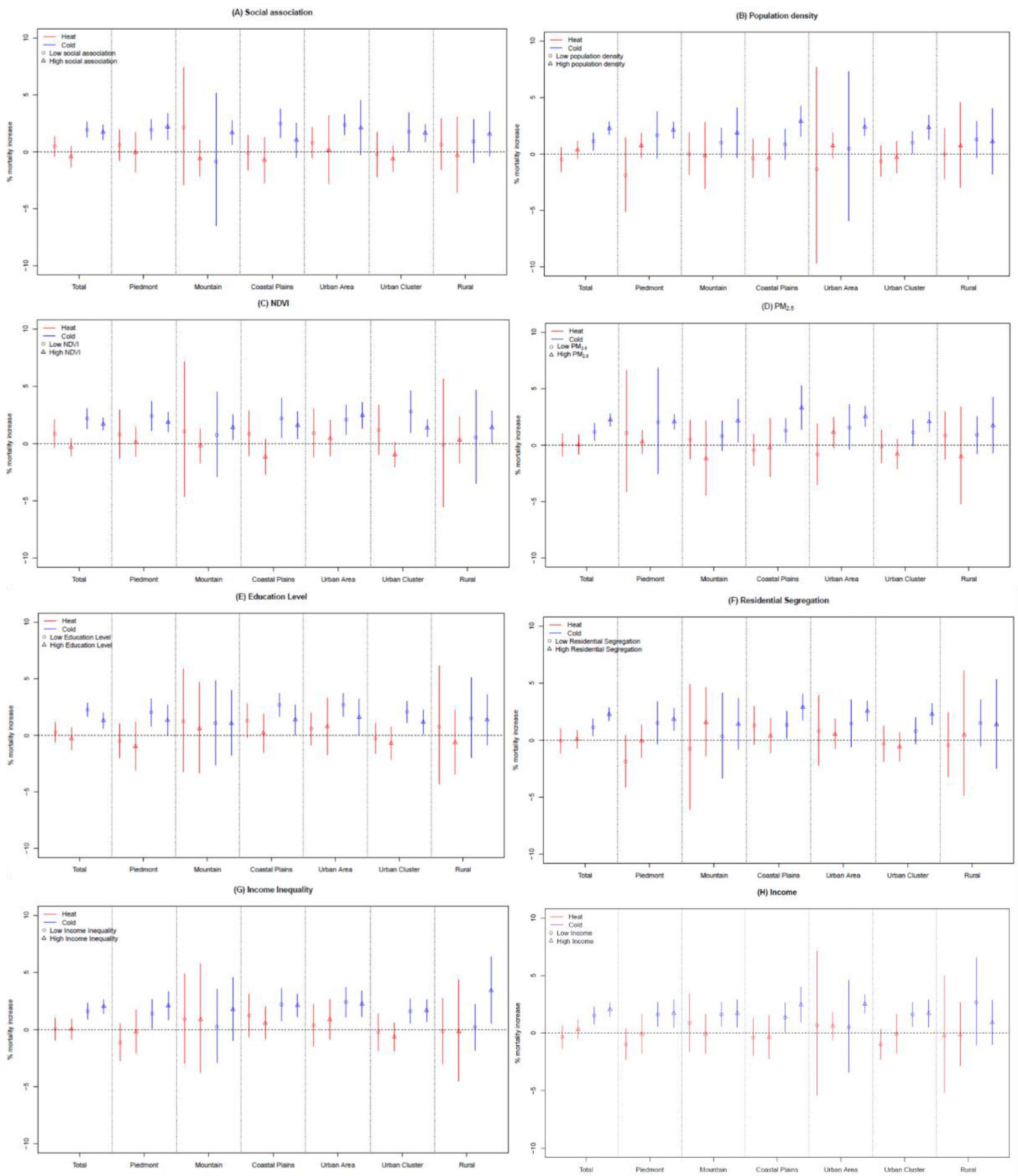

Figure 5.

Estimated mortality increases due to the relative effect for heat and cold by: (A): social association, (B) population density, (C) NDVI, (D) $PM_{2.5}$, (E) education level, (F) residential segregation, (G) income inequality, and (H) income. Note: Low and high levels represent counties above and below median values.

Table 1.

Average temperature and mortality count by region and urban-rural categories (2000–2016).

Variables	Total	Region			Urban/Rural classification		
		Piedmont	Mountain	Coastal Plain	Urban Area	Urban Cluster	Rural
Total number of counties	94	34	23	37	22	53	19
Total mortality count	1,208,766	659,594	192,731	356,441	631,905	452,993	123,868
Mortalities/day [mean (SD)]	2.95 (2.72)	3.89 (3.54)	2.21 (1.71)	2.33 (1.63)	4.96 (3.75)	2.05 (1.29)	2.04 (1.44)
Mean temperature °C [mean (SD)]	15.11 (8.76)	15.2 (8.79)	12.62 (8.47)	16.43 (8.59)	15.5 (8.72)	15.16 (8.78)	14.11 (8.7)
Dew point temperature °C [mean (SD)]	8.64 (9.8)	8.27 (9.88)	6.49 (9.73)	10.27 (9.47)	8.86 (9.78)	8.73 (9.81)	7.84 (9.78)

Note: Urban Area= Urbanized areas with 50,000 or more people, Urban Cluster= Urban clusters with at least 2,500 but fewer than 50,000 people, and Rural= rural areas with less than 2,500 people

Table 2.

Estimated relative risk for the relative and absolute heat and cold effect for different regions and urban/rural categories

		Heat (lag 0–1 days)		Cold (lag 0–25 days)	
		Relative	**Absolute**	**Relative**	**Absolute**
Temperature comparison		99^{th} to 90^{th} percentiles	28.2°C to 25.5°C	1^{st} to 10^{th} percentiles	−3.7°C to 2.9°C
Overall		1.001 (0.995, 1.007)	0.998 (0.993, 1.004)	1.019 (1.015, 1.023)	1.018 (1.013, 1.022)
Region	Piedmont	1.004 (0.995, 1.012)	1.001 (0.993, 1.009)	1.021 (1.015, 1.027)	1.021 (1.015, 1.027)
	Mountain	1.000 (0.988, 1.012)	1.014 (0.988, 1.041)	1.014 (1.006, 1.023)	1.012 (1.005, 1.020)
	Coastal Plain	0.997 (0.987, 1.007)	0.996 (0.987, 1.004)	1.019 (1.010, 1.027)	1.018 (1.009, 1.027)
Urbanization	Urban Area	1.006 (0.997, 1.016)	1.004 (0.995, 1.013)	1.023 (1.017, 1.030)	1.023 (1.016, 1.030)
	Urban Cluster	0.996 (0.987, 1.004)	0.993 (0.985, 1.001)	1.017 (1.011, 1.023)	1.016 (1.009, 1.022)
	Rural	1.002 (0.988, 1.017)	0.999 (0.984, 1.014)	1.012 (1.001, 1.023)	1.011 (1.002, 1.021)

Table 3.

The relative effect using stratified analysis for potential effect modification of the temperature-mortality association, overall (all North Carolina) and for groups with the most counties (Urban Cluster for urbanization category and Coastal Plain for region)

	Total		Urban Cluster		Coastal Plain	
	Heat	**Cold**	**Heat**	**Cold**	**Heat**	**Cold**
Social association						
<12.8 associations/10,000 persons	0.47 (−0.42, 1.36)*	1.95 (1.28, 2.62)	−0.24 (−2.18, 1.73)	1.74 (0.07, 3.44)	−0.11 (−1.64, 1.43)	2.48 (1.21, 3.76)
≥12.8 associations/10,000 persons	−0.42 (−1.34, 0.5)*	1.73 (1.1, 2.37)	−0.61 (−1.73, 0.53)	1.65 (0.88, 2.44)	−0.73 (−2.72, 1.31)	1.03 (−0.46, 2.55)
Population Density						
<43.46 persons/km^2	−0.47 (−1.54, 0.61)	1.1 (0.34, 1.86)*	−0.65 (−2.01, 0.73)	1.03 (0.07, 2)*	−0.39 (−2.12, 1.36)	0.86 (−0.47, 2.2)*
≥43.46 persons/km^2	0.35 (−0.44, 1.15)	2.27 (1.71, 2.83)*	−0.3 (−1.69, 1.11)	2.36 (1.31, 3.42)*	−0.34 (−2.06, 1.41)	2.9 (1.54, 4.27)*
NDVI						
<0.61	0.87 (−0.35, 2.1)*	2.19 (1.31, 3.08)	1.18 (−0.99, 3.4)*	2.79 (0.98, 4.64)	0.87 (−1.09, 2.86)*	2.2 (0.46, 3.98)*
≥0.61	−0.31 (−1.06, 0.45)*	1.7 (1.16, 2.24)	−0.97 (−2.03, 0.1)*	1.36 (0.61, 2.12)	−1.17 (−2.69, 0.38)*	1.59 (0.43, 2.77)*
$PM_{2.5}$						
<10.3 μg/m^3	0.02 (−0.97, 1.01)	1.17 (0.41, 1.93)*	−0.1 (−1.54, 1.35)	1.1 (−0.07, 2.28)	−0.43 (−1.82, 0.98)	1.3 (0.21, 2.39)*
≥10.3 μg/m^3	0.04 (−0.81, 0.89)	2.25 (1.69, 2.82)*	−0.79 (−2.1, 0.54)	2.07 (1.18, 2.97)	−0.23 (−2.79, 2.39)	3.3 (1.38, 5.27)*
Education Level						
<86	0.28 (−0.57, 1.13)	2.24 (1.65, 2.84)*	−0.28 (−1.6, 1.05)	2.06 (1.11, 3.02)*	1.28 (−0.23, 2.81)	2.67 (1.66, 3.68)
≥86	−0.29 (−1.27, 0.71)	1.3 (0.59, 2.01)*	−0.7 (−2.15, 0.76)	1.17 (0.09, 2.27)*	0.19 (−1.49, 1.9)	1.38 (0.07, 2.7)
Residential Segregation						
<30	−0.05 (−1.11, 1.03)	1.11 (0.35, 1.88)*	−0.34 (−1.89, 1.23)	0.82 (−0.3, 1.96)*	1.27 (−0.37, 2.94)	1.33 (0.18, 2.5)*
≥30	0.08 (−0.72, 0.88)	2.27 (1.71, 2.83)*	−0.59 (−1.83, 0.67)	2.28 (1.36, 3.2)*	0.38 (−1.15, 1.94)	2.89 (1.78, 4.01)*
Income Inequality						
<4.6	0.04 (0.91, 1)	1.6 (0.91, 2.3)*	−0.24 (−1.83, 1.37)	1.6 (0.51, 2.7)	1.22 (−0.66, 3.13)	2.17 (0.74, 3.62)*
≥4.6	0.03 (−0.84, 0.9)	2.03 (1.42, 2.64)*	−0.64 (−1.87, 0.59)	1.67 (0.69, 2.65)	0.56 (−0.83, 1.97)	2.11 (1.13, 3.1)*
Income						

	Total		Urban Cluster		Coastal Plain	
	Heat	Cold	Heat	Cold	Heat	Cold
<41,701	−0.33 (−1.33, 0.67)	1.52 (0.79, 2.26)*	−0.99 (−2.3, 0.33)	1.62 (0.58, 2.66)	−0.37 (−1.98, 1.27)	1.36 (0.1, 2.64)
≥41,701	0.31 (−0.52, 1.15)	2.05 (1.47, 2.64)*	−0.08 (−1.76, 1.64)	1.71 (0.52, 2.91)	−0.37 (−2.22, 1.52)	2.46 (0.95, 4)

* The difference of estimated effects between the low and high groups is statistically significant (p-value < 0.05)