High Ambient Temperature and Mortality: A Review of Epidemiological Studies from 2001 to 2008~~A Review of the Epidemiologic Evidence of High Ambient Temperature and Mortality Accounting for Air Pollutants and Identifying Vulnerable Subgroups~~

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~~Abstract~~

~~Background:~~ ~~This review examines recent evidence on mortality from elevated ambient temperature for studies published from January 2001 to September 2008.~~

~~Methods:~~ ~~Pub Med was used to search for the following keywords: temperature, apparent temperature, heat, heat index, and mortality. The search was limited to the English language and epidemiologic studies. Studies that reported mortality counts or excess deaths following heat waves were excluded so that the focus remained on general ambient temperature exposure in a variety of locations. Studies focusing on cold temperature effects were also excluded.~~

~~Results:~~ ~~Thirty-eight total studies were presented in three tables: 1) elevated ambient temperature and mortality; 2) air pollutants as confounders and/or effect modifiers of the elevated ambient temperature and mortality association; and 3) vulnerable subgroups of the elevated ambient temperature-mortality association. The evidence suggests that particulate matter with less than 10um in aerodynamic diameter and ozone are both confounders, while ozone was also found to be an effect modifier in the warmer months in some studies. Elevated temperature was associated with increased risk for those dying from cardiovascular, respiratory, cerebrovascular, and some specific cardiovascular diseases, such as ischemic heart disease, congestive heart failure, and myocardial infarction. Vulnerable subgroups also included: Black racial/ethnic group, women, those with lower socioeconomic status, and several age groups, particularly the elderly over 65 years of age as well as infants and young children.~~

~~Conclusions:~~ ~~Many of these outcomes and vulnerable subgroups have not been identified previously and were dependent on the location and study population. Thus,~~

~~region-specific policies, especially in urban areas, are vital to the mitigation of heat-related deaths.~~

Background

In 2002, a comprehensive epidemiologic review by Basu and Samet [1] summarized the findings from studies examining mortality from elevated ambient temperature and heat waves. Most of the evidence at that time was based on studies following heat waves. Several studies have been conducted more recently using modern statistical approaches, consisting primarily of the time-series ~~approach~~ and ~~the time-stratified~~ case-crossover approaches ~~design~~. While other reviews have been conducted more recently on heat and mortality, the focus has been on methodological issues and approaches [2] and on climatology [3], leaving a number of important epidemiologic ~~issues~~ studies excluded~~largely unaddressed~~. Many studies of~~included in the previous review of~~ ambient temperature and mortality did not account for air pollutants, and in the previous review [1], it was not clear from the few studies conducted whether air pollutants acted as confounders, effect modifiers, or both. It is critical to separate the independent effects of both ambient temperature and air pollutants, since they may often influence each other on a daily basis. Thus, ~~only after accounting for pollutants in the models with ambient temperature,~~ the actual association between ambient temperature and mortality can be observed, only after accounting for pollutants in the models with ambient temperature. Furthermore, demographic characteristics, such as poverty and age, can modify the severity of heat effects through various physiological and behavioral pathways. Thus, certain subgroups may be particularly vulnerable to heat effects, and identifying them for specific locations would be beneficial for targeting public health interventions.

Here, the epidemiologic evidence from ~~January~~ the past decade~~2001 to September 2008~~ of high ambient temperature and mortality is summarized, with a closer examination of studies of the potential effect of air pollution on the temperature-mortality association ~~as a confounder and/or effect modifier~~, as well as~~nd~~ vulnerable subgroups ~~of the temperature-mortality association~~. A general discussion of ~~harvesting~~ mortality displacement on the association between temperature and mortality is also included. Mortality displacement (also known as harvesting) refers to the phenomena suggesting that observed deaths from some environmental exposure, such as ambient temperature, occur in the most frail individuals whose deaths have only been brought forward by a few days.

Methodological issues

Inclusion/exclusion criteria

All studies included in this review were published in peer-reviewed journals between January 2001 and December 2008. Pub Med was used to search for the following keywords: temperature, apparent temperature, heat, heat index, and mortality. In addition, Tables 2 and 3 had the keyword "air pollutants," "ozone," and "particulate matter" added, and Table 4 and 5 had "vulnerable", "susceptible subgroups/groups" added. The search was limited to the English language and epidemiologic studies. The review focused primarily on quantitative studies of ambient temperature, consisting of studies using the time-series and/or case-crossover methods. The outcomes from these studies reported a regression coefficient, relative risk, odds ratio, or percent change in mortality, along with corresponding standard errors or confidence intervals. Studies that reported mortality counts or excess deaths following heat waves were excluded so that the focus remained on general ambient temperature exposure~~ in a variety of locations~~, rather than on short time periods. Review articles or s~~S~~tudies focusing on cold temperature effects ~~-~~were also excluded. ~~Thirty-eight~~ Thirty-six studies published in peer-reviewed journals were selected for this epidemiologic review, with 57~~64~~ total studies in the references that included a general discussion of temperature and mortality.

Exposure assessment

Temperature data are often measured near airport monitoring stations, and analyzed at the city or county level. Thus, misclassification of exposure may occur, especially for larger geographic areas. Also, measuring ambient temperature outside of urban areas may artificially reduce the temperature measurement, since urban areas often have higher temperatures than suburban or surrounding areas because of heat absorbed by buildings and roadways (known as the urban heat-island effect). However, since the bias should be non-differential (i.e,, not different by county or other unit of analysis), the bias in the estimate would be toward the null, where the results would be underestimated. Misclassification of exposure may be reduced in future studies by using smaller buffer zones, such as five or ten kilometers around each monitor, if sufficient data are available.

Exposure to ambient temperature is often defined as some combined metric of temperature and relative humidity or dew point temperature, such as heat index, humidex, or apparent temperature, depending on the study location and author’s preference. In addition, other variables, such as day of the week, time trend, and barometric pressure, are often added to the model. In some studies, air pollutants have been assessed as confounders or effect modifiers in an attempt to tease apart the independent effect of temperature. A monitor or an average of monitors is often used to characterize exposure for a county, or a given distance from the home address using geospatial coding. Many investigators relied on mean daily average to classify exposure, although others used maximum or minimum temperature to capture daytime and nighttime exposures, respectively, since those have also been shown to play a role in heat-related mortality. Because the effect of temperature has been found to be immediate (i.e., same lagged day), exposure can be characterized by the place of death.

Case selection

H~~Since h~~eat-related mortality is~~ still~~ often underestimated, and since a systematic definition still does not exist, it may only be indicated when heat waves occur, resulting in ~~(~~a signal detection bias~~)~~. Thus,~~,~~ investigators often use all-cause mortality excluding mortality due to accidents, or other related outcome, such as mortality from cardiovascular or respiratory diseases in epidemiologic studies of heat or elevated ambient temperature. The underlying cause of death is usually used for epidemiologic studies and should be sufficient for characterizing the temperature-mortality association, although associated causes of death can also be used~~, although the immediate cause of death may be more useful since the effect of heat is imminent~~.

The studies to date are often limited by information provided by the death certificate data. For example, information on income level, poverty, or air conditioning use is not offered on the individual level, so it is difficult to examine socioeconomic status. Thus, gathering data on individual characteristics, as has been done in a previous study [4], would be informative. In addition, medication use, time-activity patterns, and biologic mechanisms could be further understood.

Study design

Most of the studies conducted in the past decade rely on the time-series or case-crossover study designs, with the exception of the studies of the 2003 European heat wave, which are not included in this review. Regardless of the method chosen, the time-series and case-crossover study designs should yield similar results, as has been shown in some temperature-mortality studies [5-7]~~[4-6]~~.

The time-series is a widely accepted approach in both air pollution and temperature studies~~, while the case-crossover design has been employed more recently~~. The time-series study generally encompasses large populations in multiple geographic areas over a given time period.~~,~~ Mortality ~~where mortality~~ counts or rates are compared to exposure measurements collected at regular time intervals (e.g., daily, weekly)~~, usually daily~~. Seasonality and other confounding factors that fluctuate over time are accounted for by adding the covariates to the model (i.e., day of the week, air pollutants) and using smoothing functions to the model using specified degrees of freedom.

The case-crossover design has been employed more recently, gaining widespread popularity for studying air pollution and temperature in the past decade. This~~case-crossover~~ study design is similar to a matched case-control study; however, each case in the case-crossover study serves as his/her own control. Thus, biases due to measured and unmeasured confounders, such as genetics, health behaviors, and physiologic differences, are~~-~~ controlled for by study design. The case-crossover study design has been refined since its introduction in 1991, from the unidirectional, to the bidirectional, and most recently~~currently~~, to the time-stratified approach. The time-stratified approach limits the bias from selecting control periods only previously to the case period (unidirectional), or from not selecting control periods at random from the time at which the case occurred (bidirectional). Most commonly, control periods are selected within the same month and the same year that the case period occurred in the time-stratified approach to inherently minimize biases that may occur from time trends. Day of the week is also matched for by study design by choosing control periods every seven days, or may be added to the model as an indicator variable, especially if data are sparse (e.g., if using particulate matter in the model, data are often collected every third day, and thus, would warrant control periods to be selected every third day). ~~.~~ In the studies listed in the following tables, all case-crossover studies used the time-stratified approach.

Multi-city analyses are preferred, since bias from a single city analysis may result and the findings from multiple areas may be more generalizable [6]. Thus, city or county-level estimates are usually combined into one overall estimate using meta-analytic techniques using a random effects model.

Mortality displacement

In epidemiologic studies of temperature or air pollution and mortality or morbidity, mortality displacement/harvesting has been addressed in several different ways [8-13]. Among the more intuitive approaches, one can examine very long cumulative averages (i.e., 20 to 40 days of exposure) to determine whether a positive association found over the first few days is offset by a negative association over subsequent days. This would suggest that a pool of frail individuals was the only or major subgroup that was impacted by the exposure. However, if harvesting is not found, then the exposure under study is a real public health issue.

In studies of temperature and mortality, very few studies have addressed the harvesting issue; a few are summarized here. Braga et al. [8, 11] considered the effect of temperature on various causes of mortality, and reported a harvesting effect on very hot days, but not on cold days. Schwartz et al. [14] reached a similar conclusion in their study of temperature and hospitalizations for myocardial infarction. In another study, a similar effect was found in Sofia, but for both cold and hot temperatures, and less of a harvesting effect was observed at high temperatures in London [15] and Dublin [16]. In a study of Sao Paulo, Delhi and London, Hajat et al. [17] reported mixed results. Short-term mortality displacement was apparent in London, but in both Delhi and Sao Paolo, the risk for mortality remained high at comparatively longer lag periods. This finding could be partially explained by the different temperature patterns in the cities as well as a larger impact on infants and children in Delhi and Sao Paolo. Among the several studies following the 2003 European heat wave, Le Tertre et al. [18] examined the possibility of harvesting in 9 French cities, and concluded that the harvesting effect was not found, and thus, could not solely explain the excess mortality (determined by the number of observed cases subtracted from the number of expected cases based on previous years). Toulemon and Barbieri [19] reported a modest harvesting effect following the 2003 heat wave and attributed most of the deaths in the elderly to other factors, such as social isolation. In Germany, harvesting did not play a role for all-cause or respiratory mortality, but have impacted deaths due to neoplasms [20].

Thus, the evidence is mixed and may depend on: (1) whether one is examining heat waves versus a more general rise in temperature; (2) the study design and lag structure used for temperature effects; (3) the potential interactions with air pollution; (4) the baseline health status of the population; (5) the population at risk; and (6) other local factors that might determine vulnerability.

Summary of Studies~~Results~~

Fourteen studies were epidemiologic studies of ambient temperature and mortality, while 14 other studies considered air pollutants as potential confounders/effect modifiers, and six considered vulnerable subgroups. Most of these studies used either the time-series method (n = 29), while fewer used the case-crossover approach (n = 10). Eleven studies were conducted in the US. Ten studies were published using European data, three in Latin America, three in Australia, two in Canada, and elsewhere. The studies are all summarized in the following Tables 1 to 5 by year of publication, with the most recent studies first, followed by alphabetical order of the first author's last name. Since some studies included an examination of general ambient temperature and mortality, accounted for air pollutants, and/or identified vulnerable subgroups, the same study may be listed in multiple tables with the relevant results.

General Ambient Temperature and Mortality

In Table 1, the recent studies of high ambient temperature and mortality are summarized. To focus on the effects of warmer temperatures, most investigators limited their data above a threshold value~~ around 29C (equivalent to 85F)~~, or have compared ~~the~~ effect estimates from temperatures above a threshold value to another lower value~~those effects from lower temperatures (i.e., 1st or 5th percentile)~~. The threshold value is often~~established a priori or~~ based on some percentile of the data (i.e., 90th or 95th percentile), after visual inspection of the exposure-response curves or by mathematical (i.e., through derivatives) or statistical (i.e., by maximum likelihood) methods. The data are often limited to the summer months or warm season to establish heat effects. Limiting the data to summer months or the warm season is also employed to exclude possible (negative or positive) effects from cold temperatures on mortality in the attempt to estimate the actual risk from heat effects. Because of these several classifications of temperature exposure, it is difficult to directly compare the values resulting from these studies. However, few comparisons can be made. For example, in Europe and Korea, where different levels of temperature and humidity ~~levels~~ were experienced~~, and therefore, different acclimatization patterns exist~~, the mortality estimates above a threshold of (23.3C to 29.7C) resulted in different effect estimates [12, 21]~~[7]~~. With similar threshold values in the Mediterranean (29.4C) and Korea (27-29.7C), a 1C increase of apparent temperature corresponded to a 3.12% increase in daily mortality in Mediterranean cities, and a much higher effect in Korea (6.73%-16.3% in 6 cities) for a similar time period. Two recent studies conducted by Basu et al. [6, 22]~~[5, 8]~~ and Zanobetti and Schwartz [7]~~[6]~~ using identical methods suggested that the effect estimates throughout California and other parts of the US are similar, even with different ranges of apparent temperature. They both found approximately a 2% increase in mortality associated with a 10F increase in apparent temperature.

Air Pollutants as Confounders/Effect Modifiers

Tables 2 and 3 includes recent studies that have evaluated air pollutants as a potential confounder and/or effect modifier of the high ambient temperature and mortality association. The pollutants that have been examined include ozone (O_3~~O3~~), particulate matter less than 10 ug/m3 in aerodynamic diameter (PM_{10}), fine particulate matter ($PM_{2.5}$~~PM2.5~~), carbon monoxide (CO), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2). Most investigators who considered pollutants evaluated PM and O_3~~O3~~, since these pollutants have been found to be associated with mortality and are often correlated with high temperature. Table 2a and 2b list the studies of O_3, while Tables 3a and 3b list studies of particulate matter (PM). In addition, the studies are also separated by study design: Tables 2a and 3a summarize time-series studies, and Tables 2b and 3b summarize case-crossover studies. If an investigator used both study designs and/or examined O_3 and PM, then a study may be more than once in the respective tables. ~~The results remain mixed, with some investigators reporting air pollutants as confounders or effect modifiers while others reported no significant confounding or effect modification in their studies.~~

Although the effect estimates changed with pollutants in the model, no significant confounding [23]~~[9]~~ or effect modification by pollution on the association between temperature and mortality was reported in some recent studies conducted in the US [6, 7]~~[5, 6]~~. The studies conducted by Bell et al. and Zanobetti and Schwartz considered PM_{10} (as well as $PM_{2.5}$~~PM2.5~~ in the Zanobetti and Schwartz study) and O_3~~O3~~, while the study by Basu et al. considered O_3~~O3~~, $PM_{2.5}$~~PM2.5~~, PM_{10}, NO_2, CO, and SO_2. Stafoggia [24] and Rainham and Smoyer-Tomic [25] also reported no confounding by O_3 in Italy and Canada, respectively, and Pattenden did not find confounding by markers of PM in both Sofia (total suspended in particulates) and London (black smoke). However, PM_{10} was found to be confounder in Monterrey, Mexico [26]~~[10]~~, Sydney, Australia [27], and in regions throughout the United States, especially in the summer [5]~~[4]~~. Ren and Tong~~, and an effect modifier in Australia~~ [28]~~[11]~~ also observed PM10 to modify the association in their study conducted in Brisbane, Australia. O_3~~O3~~ was found to be a confounder especially on hot days [26, 29]~~[10, 12]~~, a~~ but not in another Italian study [13], a~~nd ~~three~~ other investigators~~studies~~ also showed O_3~~O3~~ to be a positive effect modifier of temperature and mortality, at least in some study locations ~~[14-16]~~ [30, 31].

The results for confounding and/or effect modification by air pollutants on the temperature-mortality association remain mixed; as stated, some investigators reported air pollutants as confounders or effect modifiers while others found no significant confounding or effect modification in their studies.

Cause-specific Outcomes and Vulnerable Subgroups

Much of the focus of epidemiologic studies has been identifying cause-specific outcomes and vulnerable subgroups of mortality from high ambient temperature (Tables 4 and 5~~3~~). Table 4 specifically focuses on studies using the time-series analysis, while

Table 5 summarizes studies using the case-crossover study design. ~~Some investigators have examined specific diseases as outcomes, such as cardiovascular (CVD), respiratory, cerebrovascular, and diabetes. Education, gender, racial/ethnic group, and indicators for socioeconomic status have also been examined in fewer studies.~~

Some investigators have reported greater risks for deaths from cardiovascular (CVD)~~CVD~~ [5, 22, 32]~~[4, 8, 17]~~, respiratory [5, 32, 33]~~[4, 17, 18]~~, cerebrovascular [24]~~[13]~~, diabetes [34, 35]~~[19, 20]~~, or pre-existing psychiatric disorders [24, 36, 37]~~[13, 21, 22]~~. Other studies also showed elevated risk from mortality subcategories of CVD diseases, such as myocardial infarction [8, 22, 38]~~[8, 23, 24]~~, ischemic heart disease [22]~~[8]~~, and congestive heart failure [22, 37, 39]~~[8, 22, 25]~~,

Age has been found to modify the association between ambient temperature and mortality. The elderly have been~~were~~ reported to be at greater risk from mortality following heat waves, as well as ambient temperature. In addition to the elderly who were at least 70 years [38]~~[23]~~ or 65 years [5, 22, 23, 32, 33, 40]~~[4, 8, 9, 17, 18, 26]~~ of age, children under 15 years [26, 40]~~[10, 26]~~, children five years and younger [22]~~[8]~~, and infants one year of age and under [22, 41]~~[8, 27]~~ have been identified to be at increased risk for mortality from high ambient temperature. One investigator also reported 15 to 64 years of age to be at a significantly increased risk, although still lower than the elderly or young children [40]~~[26]~~.

Modifications by gender has also been studied, and some investigators reported no difference by gender [22]~~[8]~~, while others found men in Santiago and Sao Paolo [23]~~[9]~~ specifically for circulatory causes [41]~~[27]~~ or women in various locations [23-25, 32, 42]~~[9, 13, 17, 28, 29]~~ to be at higher risk for mortality.

Other recent epidemiologic studies also reported Black racial ethnic group [22, 43]~~[8, 30]~~ and non-Whites [35]~~[20]~~ to be at greater risk than Whites in the US. Hispanic subgroups, however, have not been identified as being at greater risk in one study, partially explained by more social networking among this ethnic group [22]~~[8]~~.

Other factors that provoked greater risk included indicators for lower socioeconomic status, including the less educated, persons living in lower income areas [24]~~[13]~~ and dying out of the hospital [22, 34, 44]~~[8, 19, 31]~~. However, lower socioeconomic status [40]~~[26]~~ and education level were not found to be a risk factor in all studies [22]~~[8]~~.

~~***Harvesting***~~

~~Harvesting refers to the phenomena suggesting that observed deaths from some environmental exposure occur in the most frail individuals whose deaths have only been brought forward by a few days. In epidemiologic studies of temperature or air pollution and mortality, harvesting has been addressed in several different ways~~ [7, 8]~~[32, 33]. Among the more intuitive approaches, one can examine very long cumulative averages~~

~~(i.e., 20 to 40 days of exposure) to determine whether a positive association found over the first few days is more than offset by a negative association over subsequent days. This would suggest that a pool of frail individuals was the only (or major) group that was impacted by the exposure. Such a phenomenon would have important consequences for attempts to apply economic valuation to this outcome since it would indicate that the lost of life was on the order of a few days, rather than several years.~~

~~In studies of temperature and mortality, very few studies have addressed the harvesting issue. Braga et al. ~~[9, 10]~~[24, 34] considered the effect of temperature on various causes of mortality, and reported a harvesting effect on very hot days, but not on cold days. Schwartz et al. ~~[11]~~[35] reached a similar conclusion in their study of temperature and hospitalizations for myocardial infarction. In another study, a similar effect was found in Sofia, but for both cold and hot temperatures, and less of a harvesting effect was observed at high temperatures in London ~~[12]~~[36] and Dublin ~~[13]~~[37]. In a study of Sao Paulo, Delhi and London, Hajat et al. ~~[14]~~[38] reported mixed results. Short-term mortality displacement was apparent in London, but in both Delhi and Sao Paolo, the risk for mortality remained high at comparatively longer lag periods, partially due to the larger impact on infants and children. Among the several studies following the 2003 European heat wave, Le Tertre et al. ~~[15]~~[39] examined the possibility of harvesting in 9 French cities, and concluded that the harvesting effect was not found, and thus, could not solely explain the excess mortality (determined by the number of observed cases subtracted from the number of expected cases based on previous years). Toulemon and Barbieri ~~[16]~~[40] reported a modest harvesting effect following the 2003 heat wave~~

~~and attributed most of the deaths in the elderly to other factors, such as social isolation. In Germany, harvesting did not play a role for all-cause or respiratory mortality, but have impacted deaths due to neoplasms~~ [17]~~[41].~~

~~Thus, the evidence is mixed and may depend on: (1) whether one is examining heat waves versus a more general rise in temperature; (2) the study design and lag structure used for temperature effects; (3) the potential interactions with air pollution; (4) the baseline health status of the population; (5) the population at risk; and (6) other local factors that might determine vulnerability.~~

Conclusions~~Discussion~~

In the past few years, several epidemiologic studies have been conducted in various locations to characterize temperature and mortality. In the US, similar effects were found in nine~~9~~ counties in California and in nine~~9~~ counties outside of California in two separate studies using the same methods [6, 7]~~[5, 6]~~. In Europe and Korea, however, the effect estimates were larger [12, 21]~~[7, 42]~~, further supporting the need to conduct temperature-mortality studies for specific areas. The results from future studies can be more readily compared if estimates are reported per degree Celsius or Fahrenheit per unit change in temperature (assuming linearity), or if a regression coefficient is given, rather than selecting a threshold value for temperature. In addition, investigators should consider accounting for air pollutants and identifying vulnerable subgroups in their epidemiologic studies.

The recent epidemiologic evidence suggests that PM and O_3~~O3~~ may be~~are both~~ confounders, and some studies also found O_3~~O3~~ to be an effect modifier in the warmer months. In other words, the association between temperature and mortality is partially a result of the effect of~~confounding by~~ PM and O_3~~O3~~. Others have reported that temperature has a greater effect on mortality with higher levels of O_3~~O3~~ (i.e., synergism). Some of the conflicting evidence for confounding and effect modification by air pollutants may be due to different sources, chemistry, size distribution of particles, compositions and patterns of exposure [45]~~[43]~~ of gases and particles. Although O_3~~O3~~ generally peaks in the summer throughout the US, particulate matter peaks in the winter in California and in the summer on the East Coast. Thus, there would more likely be an impact of PM on elevated ambient temperature and health outcomes on the East Coast. Acclimatization may also play a critical role in the temperature-mortality association. People who live in areas where high ambient temperatures or heat waves are typically experienced may be less affected than people who reside in areas where high ambient temperatures are less commonly observed. Thus, even if there is effect modification between ambient temperature and a pollutant, such as O_3~~O3~~, the influence on mortality may be minimal, but synergistic in areas where heat waves are uncommon.

Several vulnerable subgroups have been identified. Many of these outcomes and vulnerable subgroups have not been identified in previous epidemiologic studies of ambient temperature and were dependent on the location and study population. Thus, region-specific policies, especially in urban areas, are vital to the mitigation of heat-related deaths. Specifically, t~~T~~hose dying from cardiovascular, respiratory, and some specific cardiovascular diseases, such as ischemic heart disease, congestive heart failure, and myocardial infarction were at greater risk for heat-related mortality. Other vulnerable subgroups included: Black racial/ethnic group, women, those with lower socioeconomic status, and all age groups, particularly the elderly over 65 years of age as well as infants and young children.

Infants,~~ and~~ young children, and the elderly should be specifically targeted in future studies to prevent heat-related mortality. With the elderly increasing in urban environments, an important research goal is the identification of clinical patterns of chronic diseases that increase the susceptibility to heat. Furthermore, vulnerable subgroups need to be further identified by cause-specific outcomes or demographics, such as racial/ethnic group. Furthermore, adverse birth outcomes have been found to be associated with air pollutants in previous studies, but have not been investigated, specifically for ambient temperature. Although previous studies of air pollution and birth outcomes have not accounted for temperature, some investigators have suggested seasonal associations, implying that temperature could also play a role with adverse birth outcomes and warrants further investigation.

~~There is less known about morbidity associated with temperature, and because few of the outcomes examined have enough overlap across studies, it is difficult to come up with a consensus of the results. Following the Chicago heat wave in July 1995,~~

~~Semenza et al. [44] found an excess risk of dehydration and heat stroke as primary diagnoses and CVD, renal disease and diabetes as underlying causes. Hansen et al. [45] also found an association with renal disease and mental health [46] in Australia. Other investigators also reported increased associations with other CVD outcomes, such as acute myocardial infarction [20, 35, 47], congestive heart failure [47], and coronary atherosclerosis [47]. Ischemic, but not hemorraghic [48] stroke, and pulmonary heart disease [47] were also found to have elevated associations in Glasgow, Scotland and Denver, Colorado, respectively. Further research of morbidity can be assessed by examining emergency room/urgent care visits and hospitalizations.~~

Although many studies of temperature have been conducted in other disciplines such as climatology, they have received greater attention in epidemiology in the past five years. Several biological mechanisms have been postulated for susceptible populations to heat-related mortality, particularly the elderly [46]~~[49]~~. When body temperatures rise, blood flow generally shifts from the vital organs to underneath the skin's surface in an effort to cool down. The body's ability to regulate its temperature (also known as thermoregulation) may be impeded when too much blood is diverted, putting increased stress on the heart and lungs. Increased blood viscosity, elevated cholesterol levels associated with higher temperatures, and higher sweating threshold may also trigger heat-related mortality [47]~~[50]~~. The body's ability to adapt to high ambient temperature can be influenced by acclimatization. People who live in areas where high ambient temperatures are not generally experienced are more likely to be affected by a heat wave. The synergistic impact of high ambient temperature along with high levels of air pollutants, such as O_3 and PM, may also play a role in increasing the mortality effect. Furthermore, heat waves occurring earlier in the year may have a greater impact on mortality since the population has not had the chance to adapt to hotter temperatures.

~~The studies to date are often limited by information provided by the death certificate data. For example, information on income level, poverty, or air conditioning use is not offered on the individual level, so it is difficult to examine socioeconomic status. Gathering data on individual characteristics, as has been done in a previous study [51], would be informative. In addition, medication use, time-activity patterns, and biologic mechanisms could be further understood. Since temperature has often been examined on the county level in most studies, misclassification of exposure may occur, especially for larger counties. However, since the bias should be non-differential (i.e, not different by county or unit of analysis), the bias in the estimate would be toward the null, where the results would be underestimated.~~

This review is timely as climate change receives more global attention, and more epidemiologic studies have been recently conducted. It, however, has several limitations. While it includes the most recent epidemiologic studies using time-series and case-crossover methods, it does not include studies of heat waves or studies using other approaches in an effort to focus on general ambient temperature over longer time periods. Both methods rely on ecologic exposure variables for temperature, and the time-series analysis also uses aggregated counts of mortality. Thus, an advantage of the case-crossover study is that differences by individual-level characteristics such as age, race/ethnic group, gender can be analyzed. Although the methods used across studies were similar, it was still often difficult to compare estimates between studies because of the analysis type (e.g., different threshold values). There were also not a sufficient number of studies to conduct a meta-analysis of the results, or other more substantial quantification. Finally, there may be some publication bias in the studies that were chosen, but by using PubMed, the bias may be limited, as it includes most scientific journals.

Further studies need to be conducted in more urban locations so that policies can be implemented for specific areas rather than for an entire geographic area. These studies would be helpful to the National Weather Service, health care institutions, and governmental agencies to implement policies to prevent heat-related mortality and also create a better heat warning system based on current studies. They will also be helpful to establish policy guidelines for the U.S. Environmental Protection Agency (personal communication), and could be used for economic analyses. Although no formal evaluation of heat-health watch warning systems has been performed to date, s~~S~~ome city-based heat-health watch warning systems~~ that~~ have already been implemented appear to be successful in greatly reducing mortality following heat waves [48]~~[52]~~.~~.~~ For example, the 2003 heat wave in Western Europe resulted in 35,000 deaths, but a warning system is being developed by the World Health Organization so that subsequent heat waves do not ~~in more recent years did~~ produce ~~not produce~~ such devastating~~etrimental~~ results.~~effects.~~ However, heat-health watch warning systems are not able to reduce heat-related mortality without a prevention plan targeting vulnerable subgroups, such as the one being developed by the World Health Organization on Health Health Action Plans (http://www.euro.who.int/Document/E91350.pdf). ~~Since many of these deaths occurred in the elderly in urban areas, the diminished mortality can be partially attributed to the loss of the susceptible population, but also to better heat warning systems especially in the affected areas, such as Western Europe [39, 53, 54].~~

~~Conclusions~~

~~There appears to be confounding/effect modification by particulate matter and/or ozone in some studies. Elevated temperature was associated with increased risk for those dying from cardiovascular, respiratory, cerebrovascular, and some specific cardiovascular diseases, such as ischemic heart disease, congestive heart failure, and myocardial infarction. Vulnerable subgroups also included: Black racial/ethnic group, women, those with lower socioeconomic status, and all age groups, particularly the elderly over 65 years of age as well as infants and young children. Many of these outcomes and vulnerable subgroups have not been identified previously and were dependent on the location and study population. Thus, region-specific policies, especially in urban areas, are vital to the mitigation of heat-related deaths.~~

List of abbreviations

CO carbon monoxide
NO_2 nitrogen dioxide
O_3 ozone
PM particulate matter
SO_2 sulfur dioxide
C Celsius
F Fahrenheit
CI confidence interval

Competing interests

The author declares no competing interests.

~~The opinions expressed in this article are solely those of the author and do not represent the policy or position of the State of California or the California Environmental Protection Agency.~~

Author's contributions

R~~upa ~~B~~asu~~ conducted the literature search for this review, specified the inclusion and exclusion criteria, constructed the tables, and drafted and revised the manuscript for consideration for publication.

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~~R~~REFERENCES

1. Basu R, Samet JM: **Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence.** *Epidemiol Rev* 2002, **24:**190-202.
2. Kinney P, O'Neill M. S., Bell M. L., Schwartz J.: **Approaches for estimating effects of climate change on heat-related deaths: challenges and opportunities.** *Environmental Science & Policy* 2008, **11:**87-96.
3. Gosling SN, McGregor GR, Paldy A: **Climate change and heat-related mortality in six cities part 1: model construction and validation.** *Int J Biometeorol* 2007, **51:**525-540.
4. Basu R, Samet JM: **An exposure assessment study of ambient heat exposure in an elderly population in Baltimore, Maryland.** *Environ Health Perspect* 2002, **110:**1219-1224.
5. Basu R, Dominici F, Samet JM: **Temperature and mortality among the elderly in the United States: a comparison of epidemiologic methods.** *Epidemiology* 2005, **16:**58-66.
6. Basu R, Feng WY, Ostro BD: **Characterizing Temperature and Mortality in Nine California Counties.** *Epidemiology* 2008, **19:**138-145.
7. Zanobetti A, Schwartz J: **Temperature and mortality in nine US cities.** *Epidemiology* 2008, **19:**563-570.
8. Braga AL, Zanobetti A, Schwartz J: **The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities.** *Environ Health Perspect* 2002, **110:**859-863.
9. Zeger SL, Dominici F, Samet J: **Harvesting-resistant estimates of air pollution effects on mortality.** *Epidemiology* 1999, **10:**171-175.
10. Schwartz J: **Harvesting and long term exposure effects in the relation between air pollution and mortality.** *Am J Epidemiol* 2000, **151:**440-448.
11. Braga AL, Zanobetti A, Schwartz J: **The time course of weather-related deaths.** *Epidemiology* 2001, **12:**662-667.
12. Baccini M, Biggeri A, Accetta G, Kosatsky T, Katsouyanni K, Analitis A, Anderson HR, Bisanti L, D'Ippoliti D, Danova J, et al: **Heat effects on mortality in 15 European cities.** *Epidemiology* 2008, **19:**711-719.
13. Hajat S, Kovats RS, Atkinson RW, Haines A: **Impact of hot temperatures on death in London: a time series approach.** *J Epidemiol Community Health* 2002, **56:**367-372.
14. Schwartz J, Samet JM, Patz JA: **Hospital admissions for heart disease: the effects of temperature and humidity.** *Epidemiology* 2004, **15:**755-761.
15. Pattenden S: **Mortality and temperature in Sofia and London.** 2003.
16. Goodman PG, Dockery DW, Clancy L: **Cause-specific mortality and the extended effects of particulate pollution and temperature exposure.** *Environ Health Perspect* 2004, **112:**179-185.
17. Hajat SA, Ben G.; Gouveia, Nelson; Wilkinson, Paul: **Mortality Displacement of Heat-Related Deaths: A Comparison of Delhi, Sao Paulo, and London.** *Epidemiology* 2005, **16:**613.

18. Le Tertre AL, Agnes; Eilstein, Daniel; Declercq, Christophe; Medina, Sylvia; Blanchard, Myriam; Chardon, BenoOEt; Fabre, Pascal; Filleul, Laurent; Jusot, Jean-Francois; Pascal, Laurence; Prouvost, Helene; Cassadou, Sylvie; Ledrans, Martine: **Impact of the 2003 Heatwave on All-Cause Mortality in 9 French Cities.** *Epidemiology* 2006, **17:**15.

19. Toulemon L, Barbieri M: **The mortality impact of the August 2003 heat wave in France: investigating the 'harvesting' effect and other long-term consequences.** *Popul Stud (Camb)* 2008, **62:**39-53.

20. Hoffmann B, Hertel S, Boes T, Weiland D, Jockel KH: **Increased cause-specific mortality associated with 2003 heat wave in Essen, Germany.** *J Toxicol Environ Health A* 2008, **71:**759-765.

21. Kim H, Ha JS, Park J: **High temperature, heat index, and mortality in 6 major cities in South Korea.** *Arch Environ Occup Health* 2006, **61:**265-270.

22. Basu R, Ostro BD: **A multicounty analysis identifying the populations vulnerable to mortality associated with high ambient temperature in California.** *Am J Epidemiol* 2008, **168:**632-637.

23. Bell ML, O'Neill MS, Ranjit N, Borja-Aburto VH, Cifuentes LA, Gouveia NC: **Vulnerability to heat-related mortality in Latin America: a case-crossover study in Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico.** *Int J Epidemiol* 2008, **37:**796-804.

24. Stafoggia M, Forastiere F, Agostini D, Biggeri A, Bisanti L, Cadum E, Caranci N, de' Donato F, De Lisio S, De Maria M, et al: **Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis.** *Epidemiology* 2006, **17:**315-323.

25. Rainham DG, Smoyer-Tomic KE: **The role of air pollution in the relationship between a heat stress index and human mortality in Toronto.** *Environ Res* 2003, **93:**9-19.

26. O'Neill MS, Hajat S, Zanobetti A, Ramirez-Aguilar M, Schwartz J: **Impact of control for air pollution and respiratory epidemics on the estimated associations of temperature and daily mortality.** *Int J Biometeorol* 2005, **50:**121-129.

27. Vaneckova P, Beggs PJ, de Dear RJ, McCracken KW: **Effect of temperature on mortality during the six warmer months in Sydney, Australia, between 1993 and 2004.** *Environ Res* 2008a, **108:**361-369.

28. Ren C, Tong S: **Temperature modifies the health effects of particulate matter in Brisbane, Australia.** *Int J Biometeorol* 2006, **51:**87-96.

29. Medina-Ramon M, Schwartz J: **Temperature, Temperature Extremes, and Mortality: A Study of Acclimatization and Effect Modification in 50 United States Cities.** *Occup Environ Med* 2007.

30. Ren C, Williams GM, Morawska L, Mengersen K, Tong S: **Ozone modifies associations between temperature and cardiovascular mortality: analysis of the NMMAPS data.** *Occup Environ Med* 2008, **65:**255-260.

31. Filleul L, Cassadou S, Medina S, Fabres P, Lefranc A, Eilstein D, Le Tertre A, Pascal L, Chardon B, Blanchard M, et al: **The relation between temperature, ozone, and mortality in nine French cities during the heat wave of 2003.** *Environ Health Perspect* 2006, **114:**1344-1347.

32. Ishigami A, Hajat S, Kovats RS, Bisanti L, Rognoni M, Russo A, Paldy A: **An ecological time-series study of heat-related mortality in three European cities.** *Environ Health* 2008, **7:**5.

33. Hajat S, Kovats RS, Lachowycz K: **Heat-related and cold-related deaths in England and Wales: who is at risk?** *Occup Environ Med* 2007, **64:**93-100.

34. Medina-Ramón M, Antonella Zanobetti, David Paul Cavanagh, and Joel Schwartz: **Extreme Temperatures and Mortality: Assessing Effect Modification by Personal Characteristics and Specific Cause of Death in a Multi-City Case-Only Analysis.** *Environ Health Perspect* 2006, **114:**1331.

35. Schwartz J: **Who is sensitive to extremes of temperature?: A case-only analysis.** *Epidemiology* 2005, **16:**67-72.

36. Stafoggia M, Schwartz J, Forastiere F, Perucci CA: **Does Temperature Modify the Association between Air Pollution and Mortality? A Multicity Case-Crossover Analysis in Italy.** *Am J Epidemiol* 2008, **167**.

37. Stafoggia M, Forastiere F, Agostini D, Caranci N, de'Donato F, Demaria M, Michelozzi P, Miglio R, Rognoni M, Russo A, Perucci CA: **Factors affecting in-hospital heat-related mortality: a multi-city case-crossover analysis.** *J Epidemiol Community Health* 2008, **62:**209-215.

38. Dilaveris P, Synetos A, Giannopoulos G, Gialafos E, Pantazis A, Stefanadis C: **CLimate Impacts on Myocardial infarction deaths in the Athens TErritory: the CLIMATE study.** *Heart* 2006, **92:**1747-1751.

39. Kolb S, Radon K, Valois MF, Heguy L, Goldberg MS: **The short-term influence of weather on daily mortality in congestive heart failure.** *Arch Environ Occup Health* 2007, **62:**169-176.

40. Gouveia N, Hajat S, Armstrong B: **Socioeconomic differentials in the temperature-mortality relationship in Sao Paulo, Brazil.** *Int J Epidemiol* 2003, **32:**390-397.

41. Diaz J, Linares C, Tobias A: **Impact of extreme temperatures on daily mortality in Madrid (Spain) among the 45-64 age-group.** *Int J Biometeorol* 2006, **50:**342-348.

42. Hajat S, Armstrong B, Baccini M, Biggeri A, Bisanti L, Russo A, Paldy A, Menne B, Kosatsky T: **Impact of High Temperatures on Mortality: Is There an Added Heat Wave Effect?** *Epidemiology* 2006, **17:**632-638.

43. O'Neill MS, Zanobetti A, Schwartz J: **Disparities by race in heat-related mortality in four US cities: the role of air conditioning prevalence.** *J Urban Health* 2005, **82:**191-197.

44. O'Neill MS, Zanobetti A, Schwartz J: **Modifiers of the temperature and mortality association in seven US cities.** *Am J Epidemiol* 2003, **157:**1074-1082.

45. Blanchard C: **Spatial and Temporal Characterization of Particulate Matter.** In *Particulate Matter Science for Policy Makers: A NARSTO Assessment.* Edited by McMurry PH, Shepherd MF, Vickery JS. Cambridge: Cambridge University Press; 2003: Chapter 6

46. Bouchama A, Knochel JP: **Heat stroke.** *N Engl J Med* 2002, **346:**1978-1988.

47. Astrand P-O, Rodahl K, Dahl HA, Stromme SB: *Textbook of Work Physiology: Physiological Bases of Exercise.* 4th edn. Canada: McGraw-Hill; 2003.

48. Smoyer KE, Rainham DG, Hewko JN: **Heat-stress-related mortality in five cities in Southern Ontario: 1980-1996.** *Int J Biometeorol* 2000, **44:**190-197.

49. McMichael AJ, Wilkinson P, Kovats RS, Pattenden S, Hajat S, Armstrong B, Vajanapoom N, Niciu EM, Mahomed H, Kingkeow C, et al: **International study of temperature, heat and urban mortality: the 'ISOTHURM' project.** *Int J Epidemiol* 2008, **37:**1121-1131.

50. Vaneckova P, Hart MA, Beggs PJ, de Dear RJ: **Synoptic analysis of heat-related mortality in Sydney, Australia, 1993-2001.** *Int J Biometeorol* 2008b, **52:**439-451.

51. Barnett AG: **Temperature and cardiovascular deaths in the US elderly: changes over time.** *Epidemiology* 2007, **18:**369-372.

52. Michelozzi P, De Sario M, Accetta G, de'Donato F, Kirchmayer U, D'Ovidio M, Perucci CA: **Temperature and summer mortality: geographical and temporal variations in four Italian cities.** *J Epidemiol Community Health* 2006, **60:**417-423.

53. El-Zein A, Tewtel-Salem M, Nehme G: **A time-series analysis of mortality and air temperature in Greater Beirut.** *Sci Total Environ* 2004, **330:**71-80.

54. Curriero FC, Heiner KS, Samet JM, Zeger SL, Strug L, Patz JA: **Temperature and mortality in 11 cities of the eastern United States.** *Am J Epidemiol* 2002, **155:**80-87.

55. Braga AL, Zanobetti A, Schwartz J: **The lag structure between particulate air pollution and respiratory and cardiovascular deaths in 10 US cities.** *J Occup Environ Med* 2001, **43:**927-933.

56. Ren C, Williams GM, Tong S: **Does particulate matter modify the association between temperature and cardiorespiratory diseases?** *Environ Health Perspect* 2006, **114:**1690-1696.

57. Yip FY, Flanders WD, Wolkin A, Engelthaler D, Humble W, Neri A, Lewis L, Backer L, Rubin C: **The impact of excess heat events in Maricopa County, Arizona: 2000-2005.** *Int J Biometeorol* 2008, **52:**765-772.

~~eferences~~

~~1. Basu R, Samet JM: **Relation between elevated ambient temperature and mortality: a review of the epidemiologic evidence.** *Epidemiol Rev* 2002, **24:**190-202.~~

~~2. Kinney P: **Approaches for estimating effects of climate change on heat-related deaths: challenges and opportunities.** 2008.~~

~~3. Gosling SN, McGregor GR, Paldy A: **Climate change and heat-related mortality in six cities part 1: model construction and validation.** *Int J Biometeorol* 2007, **51:**525-540.~~

~~4. Basu R, Dominici F, Samet JM: **Temperature and mortality among the elderly in the United States: a comparison of epidemiologic methods.** *Epidemiology* 2005, **16:**58-66.~~

~~5. Basu R, Feng WY, Ostro BD: **Characterizing Temperature and Mortality in Nine California Counties.** *Epidemiology* 2008, **19:**138-145.~~

~~6. Zanobetti A, Schwartz J: **Temperature and mortality in nine US cities.** *Epidemiology* 2008, **19:**563-570.~~

~~7. Baccini M, Biggeri A, Accetta G, Kosatsky T, Katsouyanni K, Analitis A, Anderson HR, Bisanti L, D'Ippoliti D, Danova J, et al: **Heat effects on mortality in 15 European cities.** *Epidemiology* 2008, **19:**711-719.~~

~~8. Basu R, Ostro BD: **A multicounty analysis identifying the populations vulnerable to mortality associated with high ambient temperature in California.** *Am J Epidemiol* 2008, **168:**632-637.~~

~~9. Bell ML, O'Neill MS, Ranjit N, Borja-Aburto VH, Cifuentes LA, Gouveia NC: **Vulnerability to heat-related mortality in Latin America: a case-crossover study in Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico.** *Int J Epidemiol* 2008, **37:**796-804.~~

~~10. O'Neill MS, Hajat S, Zanobetti A, Ramirez-Aguilar M, Schwartz J: **Impact of control for air pollution and respiratory epidemics on the estimated associations of temperature and daily mortality.** *Int J Biometeorol* 2005, **50:**121-129.~~

~~11. Ren C, Tong S: **Temperature modifies the health effects of particulate matter in Brisbane, Australia.** *Int J Biometeorol* 2006, **51:**87-96.~~

~~12. Medina-Ramon M, Schwartz J: **Temperature, Temperature Extremes, and Mortality: A Study of Acclimatization and Effect Modification in 50 United States Cities.** *Occup Environ Med* 2007.~~

~~13. Stafoggia M, Forastiere F, Agostini D, Biggeri A, Bisanti L, Cadum E, Caranci N, de' Donato F, De Lisio S, De Maria M, et al: **Vulnerability to heat-related mortality: a multicity, population-based, case-crossover analysis.** *Epidemiology* 2006, **17:**315-323.~~

~~14. Filleul L, Cassadou S, Medina S, Fabres P, Lefranc A, Eilstein D, Le Tertre A, Pascal L, Chardon B, Blanchard M, et al: **The relation between temperature, ozone, and mortality in nine French cities during the heat wave of 2003.** *Environ Health Perspect* 2006, **114:**1344-1347.~~

~~15. Ren C, Williams GM, Morawska L, Mengersen K, Tong S: **Ozone modifies associations between temperature and cardiovascular mortality: analysis of the NMMAPS data.** *Occup Environ Med* 2008, **65:**255-260.~~

~~16. Dear K, Ranmuthugala G, Kjellstrom T, Skinner C, Hanigan I: **Effects of temperature and ozone on daily mortality during the August 2003 heat wave in France.** *Arch Environ Occup Health* 2005, **60:**205-212.~~

~~17. Ishigami A, Hajat S, Kovats RS, Bisanti L, Rognoni M, Russo A, Paldy A: **An ecological time-series study of heat-related mortality in three European cities.** *Environ Health* 2008, **7:**5.~~

~~18. Hajat S, Kovats RS, Lachowycz K: **Heat-related and cold-related deaths in England and Wales: who is at risk?** *Occup Environ Med* 2007, **64:**93-100.~~

~~19. Medina-Ramón M, Antonella Zanobetti, David Paul Cavanagh, and Joel Schwartz: **Extreme Temperatures and Mortality: Assessing Effect Modification by Personal Characteristics and Specific Cause of Death in a Multi-City Case-Only Analysis.** *Environ Health Perspect* 2006, **114:**1331.~~

~~20. Schwartz J: **Who is sensitive to extremes of temperature?: A case-only analysis.** *Epidemiology* 2005, **16:**67-72.~~

~~21. Stafoggia M, Schwartz J, Forastiere F, Perucci CA: **Does Temperature Modify the Association between Air Pollution and Mortality? A Multicity Case-Crossover Analysis in Italy.** *Am J Epidemiol* 2008, **167**.~~

~~22. Stafoggia M, Forastiere F, Agostini D, Caranci N, de'Donato F, Demaria M, Michelozzi P, Miglio R, Rognoni M, Russo A, Perucci CA: **Factors affecting in-hospital heat-related mortality: a multi-city case-crossover analysis.** *J Epidemiol Community Health* 2008, **62:**209-215.~~

~~23. Dilaveris P, Synetos A, Giannopoulos G, Gialafos E, Pantazis A, Stefanadis C: **CLimate Impacts on Myocardial infarction deaths in the Athens TErritory: the CLIMATE study.** *Heart* 2006, **92:**1747-1751.~~

~~24. Braga AL, Zanobetti A, Schwartz J: **The effect of weather on respiratory and cardiovascular deaths in 12 U.S. cities.** *Environ Health Perspect* 2002, **110:**859-863.~~

~~25. Kolb S, Radon K, Valois MF, Heguy L, Goldberg MS: **The short-term influence of weather on daily mortality in congestive heart failure.** *Arch Environ Occup Health* 2007, **62:**169-176.~~

~~26. Gouveia N, Hajat S, Armstrong B: **Socioeconomic differentials in the temperature-mortality relationship in Sao Paulo, Brazil.** *Int J Epidemiol* 2003, **32:**390-397.~~

~~27. Diaz J, Linares C, Tobias A: **Impact of extreme temperatures on daily mortality in Madrid (Spain) among the 45-64 age-group.** *Int J Biometeorol* 2006, **50:**342-348.~~

~~28. Hajat S, Armstrong B, Baccini M, Biggeri A, Bisanti L, Russo A, Paldy A, Menne B, Kosatsky T: **Impact of High Temperatures on Mortality: Is There an Added Heat Wave Effect?** *Epidemiology* 2006, **17:**632-638.~~

~~29. Rainham DG, Smoyer-Tomic KE: **The role of air pollution in the relationship between a heat stress index and human mortality in Toronto.** *Environ Res* 2003, **93:**9-19.~~

~~30. O'Neill MS, Zanobetti A, Schwartz J: **Disparities by race in heat-related mortality in four US cities: the role of air conditioning prevalence.** *J Urban Health* 2005, **82:**191-197.~~

~~31. O'Neill MS, Zanobetti A, Schwartz J: **Modifiers of the temperature and mortality association in seven US cities.** *Am J Epidemiol* 2003, **157:**1074-1082.~~

~~32. Zeger SL, Dominici F, Samet J: **Harvesting-resistant estimates of air pollution effects on mortality.** *Epidemiology* 1999, **10:**171-175.~~

~~33. Schwartz J: **Harvesting and long term exposure effects in the relation between air pollution and mortality.** *Am J Epidemiol* 2000, **151:**440-448.~~

~~34. Braga AL, Zanobetti A, Schwartz J: **The time course of weather-related deaths.** *Epidemiology* 2001, **12:**662-667.~~

~~35. Schwartz J, Samet JM, Patz JA: **Hospital admissions for heart disease: the effects of temperature and humidity.** *Epidemiology* 2004, **15:**755-761.~~

~~36. Pattenden S: **Mortality and temperature in Sofia and London.** 2008.~~

~~37. Goodman PG, Dockery DW, Clancy L: **Cause-specific mortality and the extended effects of particulate pollution and temperature exposure.** *Environ Health Perspect* 2004, **112:**179-185.~~

~~38. Hajat SA, Ben G.; Gouveia, Nelson; Wilkinson, Paul: **Mortality Displacement of Heat-Related Deaths: A Comparison of Delhi, Sao Paulo, and London.** *Epidemiology* 2005, **16:**613.~~

~~39. Le Tertre AL, Agnes; Eilstein, Daniel; Declercq, Christophe; Medina, Sylvia; Blanchard, Myriam; Chardon, BenoOEt; Fabre, Pascal; Filleul, Laurent; Jusot, Jean-Francois; Pascal, Laurence; Prouvost, Helene; Cassadou, Sylvie; Ledrans, Martine: **Impact of the 2003 Heatwave on All-Cause Mortality in 9 French Cities.** *Epidemiology* 2006, **17:**15.~~

~~40. Toulemon L, Barbieri M: **The mortality impact of the August 2003 heat wave in France: investigating the 'harvesting' effect and other long-term consequences.** *Popul Stud (Camb)* 2008, **62:**39-53.~~

~~41. Hoffmann B, Hertel S, Boes T, Weiland D, Jockel KH: **Increased cause-specific mortality associated with 2003 heat wave in Essen, Germany.** *J Toxicol Environ Health A* 2008, **71:**759-765.~~

~~42. Kim H, Ha JS, Park J: **High temperature, heat index, and mortality in 6 major cities in South Korea.** *Arch Environ Occup Health* 2006, **61:**265-270.~~

~~43. Blanchard C: **Spatial and Temporal Characterization of Particulate Matter.** In *Particulate Matter Science for Policy Makers: A NARSTO Assessment.* Edited by McMurry PH, Shepherd MF, Vickery JS. Cambridge: Cambridge University Press; 2003: Chapter 6~~

~~44. Semenza JC, McCullough JE, Flanders WD, McGeehin MA, Lumpkin JR: **Excess hospital admissions during the July 1995 heat wave in Chicago.** *Am J Prev Med* 1999, **16:**269-277.~~

~~45. Hansen AL, Bi P, Ryan P, Nitschke M, Pisaniello D, Tucker G: **The effect of heat waves on hospital admissions for renal disease in a temperate city of Australia.** *Int J Epidemiol* 2008, **37:**1359-1365; discussion 1365-1356.~~

~~46. Hansen A, Bi P, Nitschke M, Ryan P, Pisaniello D, Tucker G: **The effect of heat waves on mental health in a temperate Australian city.** *Environ Health Perspect* 2008, **116:**1369-1375.~~

~~47. Koken PJ, Piver WT, Ye F, Elixhauser A, Olsen LM, Portier CJ: **Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver.** *Environ Health Perspect* 2003, **111:**1312-1317.~~

~~48. Dawson J, Weir C, Wright F, Bryden C, Aslanyan S, Lees K, Bird W, Walters M: **Associations between meteorological variables and acute stroke hospital admissions in the west of Scotland.** *Acta Neurol Scand* 2008, **117:**85-89.~~

~~49. Bouchama A, Knochel JP: **Heat stroke.** *N Engl J Med* 2002, **346:**1978-1988.~~

~~50. Astrand P-O, Rodahl K, Dahl HA, Stromme SB: *Textbook of Work Physiology: Physiological Bases of Exercise.* 4th edn. Canada: McGraw-Hill; 2003.~~

~~51. Basu R, Samet JM: **An exposure assessment study of ambient heat exposure in an elderly population in Baltimore, Maryland.** *Environ Health Perspect* 2002, **110:**1219-1224.~~

~~52. Smoyer KE, Rainham DG, Hewko JN: **Heat-stress-related mortality in five cities in Southern Ontario: 1980-1996.** *Int J Biometeorol* 2000, **44:**190-197.~~

~~53. Grize L, Huss A, Thommen O, Schindler C, Braun-Fahrlander C: **Heat wave 2003 and mortality in Switzerland.** *Swiss Med Wkly* 2005, **135:**200-205.~~

~~54. Conti S, Meli P, Minelli G, Solimini R, Toccaceli V, Vichi M, Beltrano C, Perini L: **Epidemiologic study of mortality during the Summer 2003 heat wave in Italy.** *Environ Res* 2005, **98:**390-399.~~

~~55. McMichael AJ, Wilkinson P, Kovats RS, Pattenden S, Hajat S, Armstrong B, Vajanapoom N, Niciu EM, Mahomed H, Kingkeow C, et al: **International study of temperature, heat and urban mortality: the 'ISOTHURM' project.** *Int J Epidemiol* 2008, **37:**1121-1131.~~

~~56. Michelozzi P, De Sario M, Accetta G, de'Donato F, Kirchmayer U, D'Ovidio M, Perucci CA: **Temperature and summer mortality: geographical and temporal variations in four Italian cities.** *J Epidemiol Community Health* 2006, **60:**417-423.~~

~~57. Davis RE, Knappenberger PC, Michaels PJ, Novicoff WM: **Changing heat-related mortality in the United States.** *Environ Health Perspect* 2003, **111:**1712-1718.~~

~~58. Curriero FC, Heiner KS, Samet JM, Zeger SL, Strug L, Patz JA: **Temperature and mortality in 11 cities of the eastern United States.** *Am J Epidemiol* 2002, **155:**80-87.~~

~~59. Braga AL, Zanobetti A, Schwartz J: **The lag structure between particulate air pollution and respiratory and cardiovascular deaths in 10 US cities.** *J Occup Environ Med* 2001, **43:**927-933.~~

~~60. Ren C, Williams GM, Tong S: **Does particulate matter modify the association between temperature and cardiorespiratory diseases?** *Environ Health Perspect* 2006, **114:**1690-1696.~~

~~61. Yip FY, Flanders WD, Wolkin A, Engelthaler D, Humble W, Neri A, Lewis L, Backer L, Rubin C: **The impact of excess heat events in Maricopa County, Arizona: 2000-2005.** *Int J Biometeorol* 2008, **52:**765-772.~~

Table 1: Recent Studies of High Ambient Temperature and Daily* Mortality

Reference	Study location	Method	Exposure	Result
Baccini 2008 [12]~~[7]~~	15 European cities, June-August 1990-2000 (5-11 years depending on data availability for city)	Time-series	Maximum apparent temperature (threshold 29.4C Mediterranean cities and 23.3C north-continental cities)	1C increase above threshold 3.12% (0.60-5.72%) in Mediterranean and 1.84% (0.06-3.64%) in north-continental region
Basu 2008 [6]~~[5]~~	9 California counties, May to September 1999-2003	Time-series and case-crossover	Daily apparent temperature (minimum, mean, maximum); daily mean ~~O3~~O_3, $PM_{2.5}$, PM_{10}, NO_2, CO, SO_2	2.3% (1.0-3.6%) per 10F increase in mean apparent temperature; similar results for minimum and maximum and between methods; lag 0 best fit and strongest effect estimates
McMichael 2008 [49]~~[55]~~	Delhi, Monterrey, Mexico City, Chiang Mai, Bangkok, Salvador, Sao Paulo, Santiago, Cape Town, Ljubljana, Bucharest, Sofia, 2 to 5-year series (1991-1999)	Time-series ~~(Poisson models with season, humidity, pollution, day of the week and holidays)~~	Daily maximum, minimum temperature, relative humidity, precipitation data, PM_{10}, BS, or TSP	Increasing death rates with increasing heat in all cities except Chiang Mai and Cape Town; threshold 16C-31C, generally higher in cities with warmer climates (also cold effects, unrelated to climate)
Vaneckova 2008a [50]	Sydney, Australia, October to March 1993-2001	Time-series	Temporal Synoptic Index (TSI)	Hot, dry (rare) and warm, humid (more frequent) TSIs highest rates; elderly, women more vulnerable; O_3 on warm, humid days and PM_{10} on hot, dry days found at high concentrations, but impact unclear
Zanobetti and Schwartz 2008 [7]~~[6]~~	9 U.S. counties, May to September 1999-2002	Time-series and case-crossover	Daily apparent temperature (minimum, mean, maximum); daily mean O_3, $PM_{2.5}$, PM_{10}	1.8% (1.09-2.5%) case-crossover and 2.7% (2-3.5%) time-series per 10F increase in mean apparent temperature; similar results for minimum and maximum temperature; lag 0 best fit and strongest effect estimates
Barnett 2007 [51]	107 U.S cities using data from the National Morbidity and Mortality Study, 1987-2000	Case-crossover	Daily temperature	Summer 1987 average increase in cardiovascular deaths was 4.7% per 10F. By summer 2000, the risk with higher temperature had disappeared (-0.4%), possibly due to air conditioning use.
Carson 2006 [52]	London, England, 1900-1910, 1927-1937, 1954-1964, 1986-1996	Time-series	Daily mean temperature	Ratio of winter deaths higher than non-winter deaths in four time periods; heat deaths diminished over the century
Kim 2006 [21]~~[42]~~	6 cities in South Korea, summer 1994-2006	Time-series	Temperature thresholds (27-29.7C)	16.3% (14.2, 18.4), 9.10% (5.12, 13.2), 7.01% (4.42, 9.66), 6.73% (2.47, 11.2) for Seoul, Daegu, Incheon and Gwangiu,

				respectively, for daily mean temperature 1C above threshold
~~Le Tertre 2006 [15][39]~~	~~9 French cities, August 2003 heat wave~~	~~Time-series~~	~~Temperature terms with added heat wave term~~	~~3,096 excess deaths; RR for excess deaths ranged from 1.16 to 5.00~~
Michelozzi 2006 [52]~~[56]~~	4 Italian cities, June to September 2003 & 2004 and reference period (Roma, Torino, Milano: 1995-2002 and Bologna: 1996-2002)	Time-series	Daily maximum apparent temperature	Greatest variation in mortality in 2003 for all cities; increase also at 26-28C for Torino and Roma
~~Conti 2005 [54]~~	~~21 capitals of Italian regions, June to August 2003~~	~~Comparison of mortality counts to 2002~~	~~Humidex~~	~~3,134 excess deaths; greatest increase among elderly and NW cities~~
~~Grize 2005 [53]~~	~~Switzerland, January 1990-December 2003~~	~~Excess mortality from 2003 heat wave~~	~~Daily mean, minimum, maximum temperature, mean/maximum PM10, O3, NO2~~	~~7% increase June to August 2003; mostly in region north of Alps with combination of day temperature above 35C and night temperature above 20C~~
~~Davis 2003 [57]~~	~~28 US metropolitan areas, 1964-1998~~	~~Annual excess mortality~~	~~Threshold for apparent temperature~~	~~41.0 (SE 4.8) per million in the 1960s and 70s, 17.3 (2.7) in the 80s and 10.5 (2.0) in the 90s in combined analysis~~
El-Zein 2004 [53]	Greater Beirut, Lebanon, 1997-1999	Time-series	Mean daily temperature, mean daily humidity	Relatively high minimum mortality temperature (TMM) = 27.5 C; 12.3% (5.7, 19.4%) increase in annual mortality above TMM
Goodman 2004 [16]	Dublin, Ireland, April 1980 to December 1996	Time-series	Mean daily minimum temperature (same-day up to 40 days after exposure), daily mean relative humidity	0.4% increase in total mortality per 1C increase, and 2.5% in mortality in the following days; immediate cardiovascular effects, delayed respiratory effects; all death rates age-standardized
Pattenden 2003 [15]	Sofia, Bulgaria (1996-1999) and London, England (1993-1996)	Time-series	Daily weather (2-day mean) and PM (black smoke for London and total suspended particulates for Sofia)	For every C increase above the 95th %, mortality increased by 1.9% (1.4 to 2.4) in London, and 3.5% (2.2 to 4.8) in Sofia.
Curriero 2002 [54]~~[58]~~	11 Eastern US cities, 1973-1994	Time-series	Models using temperature, dew point temperature	J-shaped curve, lag01 most predictive, variations by latitude, socioeconomic~~SES~~ factors
Braga 2001 [55]~~[59]~~	12 US cities. 1986-1993	Time-series	Temperature, humidity (% increase relative to 30C)	Hot temperature effect primarily harvesting effect; neither hot or cold temperatures had much effect in hot cities

*** exceptions: El-Zein 2004 (annual), Carson 2006 (weekly)~~Table 2: Recent Studies of High Ambient Temperature and Mortality Examining Air Pollution as a Potential Confounder and/or Effect Modifier~~**

Table 2a: Recent Time-series Studies of High Ambient Temperature and Mortality Examining Ozone as a Potential Confounder and/or Effect Modifier

Reference	Study location	Exposure	Outcome	Result
Basu 2008 [6]	9 California counties, May to September 1999-2003	Mean daily apparent temperature; daily mean O_3, also PM2.5, PM_{10}, NO_2, CO, SO_2	All-cause mortality	O_3 not significant confounder or effect modifier
Ren 2008 [30]	US 95 NMMAPS counties, June to September 1987-2000	Daily maximum temperature (same-day, lag 1), maximum hourly O_3	CVD mortality	O_3 positive effect modifier in some cities; 10C increase in same-day temperature 1.17% and 8.31% increase in mortality for lowest and highest quartile O_3
Vaneckova 2008b [27]	Sydney, Australia, October to March 1993-2004	Daily maximum temperature, maximum O_3	Underlying and associated causes of death	Per 10C increase, 4.5% to 12.1% change with O_3 and PM_{10} in the model (% changed by -1.1% to 0.9% without pollutants), confounding present
Zanobetti and Schwartz 2008 [7]	9 U.S. counties, May to September 1999-2002	Daily apparent temperature (minimum, mean, maximum); daily mean O_3	All-cause mortality	O_3 not significant confounder or effect modifier
Filleul 2006 [31]	9 French cities, all year and heat wave August 2003	Minimum and maximum temperature, 8-hour maximum O_3	Daily mortality	O_3 different impact with temperature by city
Basu 2005 [5]	20 US metropolitan areas, seasonal analysis 1992	Mean daily temperature per 10F adjusted for dew point temperature; daily O_3	Individual and daily cardiorespiratory mortality	O_3 not confounder
O'Neill 2005 [26]	Mexico City (1996-98) and Monterrey (1996-99)	% change for heat (35-36C for Monterrey), mean temperature (25C Monterrey, 15C Mexico City), daily O_3	Daily mortality	Monterrey: adjusted heat effect=18.7% (11.7, 26.1); elevated risk persisted even with O_3; on hot days, O_3 negative confounder
Rainham and Smoyer-Tomic 2003 [25]	Toronto, May 1 to September 30, 1980-1996	Humidex, O_3, also CO, NO_2, SO_2	Daily mortality	Total RR=1.061 (1.045, 1.077) for 50-95% and 1.004 (significant) per 1C; O_3 not confounder

Table 2b: Recent Case-crossover Studies of High Ambient Temperature and Mortality Examining Ozone as a Potential Confounder and/or Effect Modifier

Reference	Study location	Exposure	Outcome	Result
Basu 2008 [6]	9 California counties, May to September 1999-2003	Mean daily apparent temperature; daily mean O_3	All-cause mortality	O_3 not significant confounder or effect modifier
Bell 2008 [23]	Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico, 1998-2002	Same day apparent temperature, O_3	All-cause daily mortality	Among those 65+ years, 2.69% (-2.06, 7.88) for Santiago, 6.51% (3.57, 9.52) for Sao Paulo and 3.22% (0.93, 5.57) for Mexico City; estimates lowered although still positive after adjusting for ozone
Zanobetti and Schwartz 2008 [7]	9 U.S. counties, May to September 1999-2002	Daily apparent temperature (minimum, mean, maximum); daily mean O_3	All-cause mortality	O_3 not significant confounder or effect modifier
Medina-Ramon 2007 [29]	50 US cities in cold (November to March) and warm (May to September) seasons	Binary variable as extreme temperature and continuous; O_3	All-cause and CVD mortality	Adjustment for ozone reduced effect of extreme heat and linear hot temperature by 15% and 16%, respectively
Stafoggia 2006 [24]	Bologna, Milan, Rome, Turin, 1997-2003	30C mean apparent temperature (lag01) relative to 20C	All-cause mortality and previous hospitalization	Overall OR=1.34 (1.27, 1.42); city-specific summer O_3 not confounder
Basu 2005 [5]	20 US metropolitan areas, seasonal analysis 1992	Mean daily temperature per 10F adjusted for dew point temperature; daily O_3	Individual and daily cardiorespiratory mortality	O_3 not confounder

~~Reference~~	~~Study location~~	~~Method~~	~~Exposure~~	~~Outcome~~	~~Result~~
~~Basu 2008 [5]~~	~~9 California counties, May to September 1999-2003~~	~~Time-series and case-crossover~~	~~Mean daily apparent temperature; daily mean O3, PM$_{2.5}$, PM10, NO2, CO, SO2~~	~~All-cause mortality~~	~~No pollutant examined confounder or effect modifier~~
~~Bell 2008 [9]~~	~~Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico, 1998-2002~~	~~Case-crossover~~	~~Same day apparent temperature~~	~~All-cause daily mortality~~	~~Among those 65+ years, 2.69% (-2.06, 7.88) for Santiago, 6.51% (3.57, 9.52) for Sao Paulo and 3.22% (0.93, 5.57) for Mexico City; estimates lowered although still positive after adjusting for ozone or PM10~~
~~Ren 2008 [15]~~	~~US 95 NMMAPS counties, June to September 1987-2000~~	~~Time-series~~	~~Daily maximum temperature (same-day, lag 1), maximum hourly ozone~~	~~CVD mortality~~	~~Ozone positive effect modifier in some cities; 10C increase in same-day temperature 1.17% and 8.31% increase in mortality for lowest and highest quartile ozone~~
~~Zanobetti and Schwartz 2008 [6]~~	~~9 U.S. counties, May to September 1999-2002~~	~~Time-series and case-crossover~~	~~Daily apparent temperature (minimum, mean, maximum); daily mean O3, PM2.5, PM10~~	~~All-cause mortality~~	~~No pollutant examined confounder or effect modifier; lag 0 best fit and strongest effect estimates~~
~~Medina-Ramon 2007 [12]~~	~~50 US cities in cold (November to March) and warm (May to September) seasons~~	~~Case-crossover~~	~~Binary variable as extreme temperature and continuous; ozone~~	~~All-cause and CVD mortality~~	~~Adjustment for ozone reduced effect of extreme heat and linear hot temperature by 15% and 16%, respectively~~
~~Filleul 2006 [14]~~	~~9 French cities, all year and heat wave~~	~~Time-series~~	~~Minimum and maximum temperature,~~	~~Daily mortality~~	~~Ozone different impact with temperature by~~

	~~August 2003~~		~~8-hour maximum ozone~~		~~city~~
~~Ren 2006 [60]~~	~~Brisbane, Australia (all year January 1996 to December 2001)~~	~~Time-series~~	~~Minimum temperature, daily PM10 as modifier~~	~~Cardiorespiratory morbidity and mortality~~	~~PM10 significantly modified temperature and all-cause mortality and CVD mortality~~
~~Stafoggia 2006 [13]~~	~~Bologna, Milan, Rome, Turin, 1997-2003~~	~~Case-crossover~~	~~30C mean apparent temperature (lag01) relative to 20C~~	~~All-cause mortality and previous hospitalization~~	~~Overall OR=1.34 (1.27, 1.42); city-specific summer ozone not confounder~~
~~Basu 2005 [4]~~	~~20 US metropolitan areas, seasonal analysis 1992~~	~~Case-crossover and time-series~~	~~Mean daily temperature per 10F adjusted for dew point temperature; also PM10 and ozone~~	~~Individual and daily cardiorespiratory mortality~~	~~Strongest associations for summer in SW, SE, NW, NE; both methods similar results; PM10 confounder in summer, not ozone~~
~~Dear 2005 [16]~~	~~12 French cities, June 25-August 23, 2003~~	~~Polynomial distributed lag model~~	~~Maximum, minimum daily temperature, peak ozone level, humidity, rainfall, wind speed~~	~~Mortality~~	~~Minimum, maximum temperature and ozone all associated, also had significant interactions~~
~~O'Neill 2005 [10]~~	~~Mexico City (1996-98) and Monterrey (1996-99)~~	~~Time-series~~	~~% change for heat (35-36C for Monterrey), mean temperature (25C Monterrey, 15C Mexico City), daily ozone and PM10~~	~~Daily mortality~~	~~Monterrey: adjusted heat effect=18.7% (11.7, 26.1); elevated risk persisted even with PM10 and ozone; on hot days, ozone and PM10 negative confounders, with larger PM10 effect~~
~~Rainham and Smoyer-Tomic 2003 [29]~~	~~Toronto, May 1 to September 30, 1980-1996~~	~~Time-series~~	~~Humidex, CO, O3, NO2, SO2~~	~~Daily mortality~~	~~Total RR=1.061 (1.045, 1.077) for 50-95% and 1.004 (significant) per 1C; pollution not confounder~~

Table 3a: Recent Time-series Studies of High Ambient Temperature and Mortality Examining Particulate Matter as a Potential Confounder and/or Effect Modifier

Reference	Study location	Exposure	Outcome	Result
Basu 2008 [6]	9 California counties, May to September 1999-2003	Mean daily apparent temperature; daily mean $PM_{2.5}$, PM_{10}	All-cause daily mortality	$PM_{2.5}$ or PM_{10} not significant confounder or effect modifier
Bell 2008 [23]	Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico, 1998-2002	Same day apparent temperature, PM_{10}	All-cause daily mortality	Among those 65+ years, 2.69% (-2.06, 7.88) for Santiago, 6.51% (3.57, 9.52) for Sao Paulo and 3.22% (0.93, 5.57) for Mexico City; estimates lowered although still positive after adjusting for PM_{10}
Vaneckova 2008b [27]	Sydney, Australia, October to March 1993-2004	Daily maximum temperature, maximum O_3	Underlying and associated causes of death	Per 10C increase, 4.5% to 12.1% change with O_3 and PM_{10} in the model (% changed by -1.1% to 0.9% without pollutants), confounding present
Ren 2006 [56]	Brisbane, Australia (all year January 1996 to December 2001)	Minimum temperature, daily PM_{10} as modifier	Cardiorespiratory morbidity and mortality	PM_{10} significantly modified temperature and all-cause mortality and CVD mortality
Basu 2005 [5]	20 US metropolitan areas, seasonal analysis 1992	Mean daily temperature per 10F adjusted for dew point temperature; daily PM_{10}	Individual and daily cardiorespiratory mortality	Strongest associations for summer in SW, SE, NW, NE; both methods similar results; PM_{10} confounder in summer
O'Neill 2005 [26]	Mexico City (1996-98) and Monterrey (1996-99)	% change for heat (35-36C for Monterrey), mean temperature (25C Monterrey, 15C Mexico City), daily PM_{10}	Daily mortality	Monterrey: adjusted heat effect=18.7% (11.7, 26.1); elevated risk persisted even with PM_{10}; on hot days, PM_{10} negative confounder, larger PM_{10} effect
Pattenden 2003 [15]	Sofia, Bulgaria (1996-1999) and London, England (1993-1996)	Daily weather (2-day mean) and PM (black smoke for London and total suspended particulates for Sofia)	Daily mortality	PM not found to be a significant confounder in either location during hot days

Table 3b: Recent Case-crossover Studies of High Ambient Temperature and Mortality Examining Particulate Matter as a Potential Confounder and/or Effect Modifier

Reference	Study location	Exposure	Outcome	Result
Basu 2008 [6]	9 California counties, May to September 1999-2003	Mean daily apparent temperature; daily mean PM$_{2.5}$, PM$_{10}$	All-cause mortality	PM$_{2.5}$ or PM$_{10}$ not significant confounder or effect modifier
Bell 2008 [23]	Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico, 1998-2002	Same day apparent temperature, PM$_{10}$	All-cause daily mortality	Among those 65+ years, 2.69% (-2.06, 7.88) for Santiago, 6.51% (3.57, 9.52) for Sao Paulo and 3.22% (0.93, 5.57) for Mexico City; estimates lowered although still positive after adjusting for PM$_{10}$
Basu 2005 [5]	20 US metropolitan areas, seasonal analysis 1992	Mean daily temperature per 10F adjusted for dew point temperature; daily PM$_{10}$	Individual and daily cardiorespiratory mortality	Strongest associations for summer in SW, SE, NW, NE; both methods similar results; PM$_{10}$ confounder in summer

1

Table 4~~3~~: Recent Time-series Studies Identifying Vulnerable Subgroups of Mortality from High Ambient Temperature

Reference	Study location	Exposure	Outcome	Result
Ishigami 2008 [32]	Budapest, London and Milan, 2003	Mean daily temperature (lag0 and lag1), PM_{10} (TSP in Budapest), ozone	Daily mortality	Increased risk with age, female years greater risk in London an and non-elderly adults in Milan; from external causes and respi CVD disease at higher tempera
Yip 2008 [57]	Maricopa County, Arizona, June to September 2000-2005	Heat index	Heat-related deaths	182% increase in 2005 compar 2000-2004, same demographic 56 years, young and old outdoo more elderly found indoors)
Hajat 2007 [33]	England and Wales, 1993-2003	Heat (>95th %) and cold (<5th %) thresholds	Mortality	Elderly, those in nursing care h vulnerable, great risk for heat-re mortality for respiratory and ext causes, women and in London, modified by deprivation
Diaz 2006 [41]	Madrid, January 1986-December 1997	T(hwave)=Tmax-36.5C if Tmax>36.5C; 5th % to 95th % temperature, NO_2	AR=(RR-1)/RR for daily mortality	AR=13.3% for circulatory cause males 45-64 years
Hajat 2005 [17]	Delhi, Sao Paulo, London, January 1991-December 1994	Daily temperature (lag 0,1) greater than 20C	Daily mortality	Delhi: 3 weeks after exposure; days after exposure; Sao Paulo intermediate; up to 4 weeks for deaths in SP and London and Delhi
O'Neill, Zanobetti and Schwartz 2005 [43]	Chicago, Detroit, Minneapolis, Pittsburgh, 1988-1993 for Chicago and 1986-1993 for other cities	Percent change daily mean temperature 29C relative to 15C (lag0), barometric pressure, day of the week, PM_{10}	Mortality, prevalence of air conditioner (AC)	Deaths among Blacks (9%; 5.3 greater than Whites (3.7%; 1.9, prevalence among Blacks less that among Whites in combined
O'Neill 2005 [26]	Mexico City (1996-1998) and Monterrey (1996-1999)	% change for heat (35-36C for Monterrey), mean temperature (25C Monterrey, 15C Mexico City)	Daily mortality	Monterrey: adjusted heat effect (11.7, 26.1); lower effect among
Gouveia 2003 [40]	Sao Paulo, Brazil, 1991-1994	Daily mean temperature (lag01), SO_2, PM_{10}, CO, O_3, NO_2, day of the week, season, humidity	Daily mortality, excluding violent deaths	For each 1C above 20C, 2.5% for 65+years, 2.6% (1.6, 3.6) fo years, 1.5% (1.1, 1.8) 15-64 yea cause; similar CVD effect for el respiratory effect for adults and modification by SES
O'Neill 2003 [44]	7 US cities, 1986-1993	Mean daily apparent temperature (% change 29C and -5C), PM_{10}	Daily mortality, looking at effect modification by demographics & other variables	More deaths among Blacks co Whites, less educated, and outs hospital more strongly associate and cold temperatures
Rainham and Smoyer-Tomic 2003 [42]	Toronto, May 1 to September 30, 1980-1996	Humidex, CO, O_3, NO_2, SO_2	Daily mortality	Total RR=1.061 (1.045, 1.077) and 1.004 (significant) per 1C; pronounced in females

Table 5: Recent Case-crossover Studies Identifying Vulnerable Subgroups of Mortality from High Ambient Temperature

Reference	Study location	Exposure	Outcome	Result
Basu and Ostro 2008 [22]~~[8]~~	9 California counties, May to September 1999-2003	Daily apparent temperature	Cause-specific mortality; all-cause mortality by age, race/ ethnicity, gender, education level	Increased risk for: CVD, IHD, MI, and CHF, ≤1 yr, ≤5 yrs, elderly, Black race, out of hospital death; no elevated risks for cerebrovascular, diabetes, respiratory; no difference by gender or high school graduation
Bell 2008 [23]~~[9]~~	Sao Paulo, Brazil, Santiago, Chile and Mexico City, Mexico, 1998-2002	Same day apparent temperature	All-cause daily mortality	Among those 65+ years, 2.69% (-2.06, 7.88) for Santiago, 6.51% (3.57, 9.52) for Sao Paulo and 3.22% (0.93, 5.57) for Mexico City; higher risk for women in Mexico City, but higher for men in Santiago and Sao Paulo, less educated greater risk in Sao Paulo
~~Ishigami 2008~~ [28]~~[17]~~	~~Budapest, London and Milan, 2003~~	~~Mean daily temperature (lag0 and lag1), PM10 (TSP in Budapest), ozone~~	~~Daily mortality~~	~~Increased risk with age, females 65+ years greater risk in London and Milan and non-elderly adults in Milan; mortality from external causes and respiratory and CVD disease at higher temperatures~~
Stafoggia 2008 [37]~~[22]~~	4 Italian cities, 1997-2004	Apparent temperature 30C compared to 20C	Deaths in hospitals for those with 2+ days in hospital	Overall OR=1.32 (1.25, 1.39); age, marital status and hospital ward risk indicators; greater risk for general medicine than high and intensive care units, for those with history of psychiatric disorders and cerebrovascular diseases, and heart failure, stroke, chronic pulmonary diseases
~~Yip 2008 [61]~~	~~Maricopa County, Arizona, June to September 2000-2005~~	~~Heat index~~	~~Heat-related deaths~~	~~182% increase in 2005 compared to 2000-2004, same demographics (mean 56 years, young and old outdoors, but more elderly found indoors)~~
~~Hajat 2007~~ [29]~~[18]~~	~~England and Wales, 1993-2003~~	~~Heat (>95th %) and cold (<5th %) thresholds~~	~~Mortality~~	~~Elderly, those in nursing care homes most vulnerable, great risk for heat-related mortality for respiratory and external causes, women and in London, not modified by deprivation~~
Kolb 2007 [39]~~[25]~~	Montreal, Canada 1984-1993	Mean daily and maximum temperature, barometric pressure, relative humidity, adjusted for ozone and both NO_2 and O_3 ~~ozone~~	Daily mortality from congestive heart failure among 65+ years	Strong nonlinear association with maximum temperature in the warmer months, with a threshold at 25C; no association after lag 3 days
Medina-Ramon	50 US cities in	Binary variable	All-cause and CVD	Extreme heat (5.74%, 95% CI: 3.38,

2007 [29]~~[12]~~	cold (November to March) and warm (May to September) seasons	as extreme temperature and continuous; ozone	mortality	8.15); largest effects in cities with milder summers, less air conditioning and higher population density
~~Diaz 2006 [37][27]~~	~~Madrid, January 1986-December 1997~~	~~T(hwave)=Tmax-36.5C if Tmax>36.5C; 5th % to 95th % temperature, NO2~~	~~AR=(RR-1)/RR for daily mortality~~	~~AR=13.3% for circulatory causes for males 45-64 years~~
~~Dilaveris 2006 [34][23]~~	~~Athens, 2001~~	~~7-day average temperature, barometric pressure, relative humidity~~	~~Daily and monthly acute myocardial infarction mortality~~	~~More winter deaths, more pronounced in over 70 years of age; humidity indicator of monthly deaths~~
~~Medina-Ramon 2006 [30][19]~~	~~50 US cities, 1989-2000~~	~~>=99th % for heat (May to September) and <=1st % for cold (November to March)~~	~~Daily all-cause and CVD mortality~~	~~Older age, diabetics, dying outside hospital increased risk for heat mortality~~
Stafoggia 2006 [24]~~[13]~~	Bologna, Milan, Rome, Turin, 1997-2003	30C mean apparent temperature (lag01) relative to 20C	All-cause mortality and previous hospitalization	Overall OR=1.34 (1.27, 1.42); increased with age and greater for women, widows and widowers, psychiatric disorders, depression, heart and circulatory disorders

~~Hajat 2005 [14][38]~~	~~Delhi, Sao Paulo, London, January 1991-December 1994~~	~~Time-series~~	~~Daily temperature (lag 0,1) greater than 20C~~	~~Daily mortality~~	~~Delhi: 3 weeks after exposure; London: 2 days after exposure; Sao Paulo: intermediate; up to 4 weeks for respiratory deaths in SP and London and children in Delhi~~
~~O’Neill, Zanobetti and Schwartz 2005 [40][30]~~	~~Chicago, Detroit, Minneapolis, Pittsburgh, 1988-1993 for Chicago and 1986-1993 for other cities~~	~~Time-series~~	~~Percent change daily mean temperature 29C relative to 15C (lag0), barometric pressure, day of the week, PM10~~	~~Mortality, prevalence of air conditioner (AC)~~	~~Deaths among Blacks (9%; 5.3, 12.8) greater than Whites (3.7%; 1.9, 5.4); AC prevalence among Blacks less than half that among Whites in combined estimate~~
~~O’Neill 2005 [21][10]~~	~~Mexico City (1996-1998) and Monterrey (1996-1999)~~	~~Time-series~~	~~% change for heat (35-36C for Monterrey), mean temperature (25C~~	~~Daily mortality~~	~~Monterrey: adjusted heat effect=18.7% (11.7, 26.1); lower effect among~~

			~~Monterrey, 15C Mexico City)~~		~~children~~
~~Schwartz 2005 [31][20]~~	~~Medicare patients with previous hospital admission for heart or lung disease, Michigan~~	~~Case-only~~	~~99th% hot days (also analyzed cold days as 1%)~~	~~Mortality~~	~~Diabetics (1.17; 1.04, 1.32) higher risk on hot days. Nonwhites greater risks on both hot (1.22; 1.09-1.37) and cold (1.25; 1.12-1.40) days~~
~~Gouveia 2003 [36][26]~~	~~Sao Paulo, Brazil, 1991-1994~~	~~Time-series~~	~~Daily mean temperature (lag01), SO2, PM10, CO, O3, NO2, day of the week, season, humidity~~	~~Daily mortality, excluding violent deaths~~	~~For each 1C above 20C, 2.5% (2.1, 2.8) for 65+years, 2.6% (1.6, 3.6) for <15 years, 1.5% (1.1, 1.8) 15-64 years for all-cause; similar CVD effect for elderly and respiratory effect for adults and elderly; no modification by SES~~
~~O'Neill 2003 [31]~~	~~7 US cities, 1986-1993~~	~~Time-series~~	~~Mean daily apparent temperature (% change 29C and -5C), PM10~~	~~Daily mortality, looking at effect modification by demographics & other variables~~	~~More deaths among Blacks compared to Whites, less educated, and outside hospital more strongly associated with hot and cold temperatures~~
~~Rainham and Smoyer-Tomic 2003 [29, 52]~~	~~Toronto, May 1 to September 30, 1980-1996~~	~~Time-series~~	~~Humidex, CO, O3, NO2, SO2~~	~~Daily mortality~~	~~Total RR=1.061 (1.045, 1.077) for 50-95% and 1.004 (significant) per 1C; more pronounced in females~~