Vulnerability to Heat-related Mortality: A Systematic Review, Meta-analysis, and Meta-regression Analysis

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Abstract

Background: Addressing vulnerability to heat-related mortality is a necessary step in the development of specific policies dictated by heat action plans. Epidemiologic studies can be used to orient such policies. The aim of this study was to provide a systematic assessment of the epidemiologic evidence regarding vulnerability to heat-related mortality.

Methods: Studies published between January 1980 and August 2014 were identified through PubMed and Elsevier Embase on the Ovid SP portal and in Web of Science. Studies assessing the association between high ambient temperature or heat-waves and mortality among different subgroups were selected. Estimates of association for all the included subgroups were extracted. We assessed the presence of heterogeneous effects between subgroups conducting Cochran Q tests. We then conducted random effect meta-analyses of ratios of relative risks (RRR) for high ambient temperature studies. Finally, we performed random effects meta-regression analyses to investigate factors associated with the magnitude of the RRR.

Results: Overall 61 studies were included in the review. Using the Cochran Q test we consistently found evidence of vulnerability for the elderly aged more than 85 years. We then found a pooled RRR of 0.99 (95% CI: 0.97, 1.01) for male sex, 1.02 (95% CI: 1.01, 1.03) for age>65 years, 1.04 (95% CI: 1.02, 1.07) for age>75 years, 1.03 (95% CI: 1.01, 1.05) for low individual socioeconomic status (SES) and 1.01 (95% CI: 0.99, 1.02) for low ecological socioeconomic status (SES). We found contrast definition use to be a determinant of heterogeneity in the pooled RRR.

Conclusions: We found strongest evidence of heat-related vulnerability for the elderly aged more than 65 years and more than 75 years and low SES groups (measured at the individual level). Further studies are needed to clarify if other subgroups like children or people living alone are also vulnerable to heat in order to inform public health programs.

Keywords: Vulnerability, heat, population health, temperature, temperature related mortality, climate change, meta-analysis.

Introduction

Rising temperatures, and their impact on human mortality, are a primary public health concern in the context of climate change. Studies of heat and mortality have increased during the last two decades, particularly with the documentation of prominent events including heat waves in Chicago in 1995 [1] and in Western Europe in 2003 [2]. In the heat-related mortality literature, it is typical to distinguish two types of heat exposures: first, increases in ambient temperatures which can be defined as periods of high temperatures over single days, associated with mortality, and second, consecutive days of high heat also known as heat wave days, where population mortality is greater than on non-heat wave days. Many literature reviews [3-8] have examined the evidence for associations of mortality with elevated ambient temperatures, focusing on the variation of heat effect thresholds or heat slopes, as a measure of effect size [7].

In epidemiologic studies of heat-related mortality, various subgroups have been identified as being more severely impacted, and are therefore defined as "vulnerable" [9,10]. Vulnerability is often used synonymously with susceptibility, although they are sometimes used to refer to separate processes related to whether the impacts are from external factors or intrinsic [11]. Vulnerability can thus be defined as "the condition of having one or more interacting causes already and therefore being susceptible to the effect of the other" [11] or as "a greater likelihood of an adverse outcome given a specific exposure, compared with the general population; including both host (individual) and environmental (contextual) factors" [12]. Factors that mark greater vulnerability are modifiers of the association between an exposure and mortality, whenever the causal effect of the exposure of interest differs across levels of the modifying factor. Thus, there would be greater vulnerability in some subgroup whenever the causal effect of heat on mortality across two or more strata is heterogeneous.

Several individual or contextual subgroup characteristics marking greater vulnerability have been documented in the past decade of epidemiologic research. Individual vulnerability factors include age (elderly, children) [3,13], sex, and socio economic factors (education, ethnicity, income, or social isolation)[4]. Contextual vulnerability factors include urban design (micro heat islands, population density), neighborhood (or ecologic) socioeconomic and community factors, and material conditions (air conditioning). These subgroups have mostly been identified in studies on the relationship between temperature, or heat waves, and mortality, using stratified analyses.

Addressing vulnerability to heat-related mortality is a necessary step in the development of heat action plans [14], to orient specific actions towards sensible subgroups [15,16]. The need to consider vulnerable populations in heat action plans and other related policies is well recognized [9,17,18]. The international epidemiologic literature can provide insights to orient policies dictated by heat action plans.

Yet, no study to date has systematically assessed the epidemiologic evidence concerning the characterization of vulnerable subgroups in the peer-reviewed heat-related mortality literature. The aim of this review is thus to systematically assess heterogeneity in the heat mortality associations with respect to individual and contextual population characteristics.

Methods

Search Strategy

We identified peer-reviewed epidemiologic studies investigating potential heterogeneity in the associations between either high ambient temperature, or heat waves, and mortality, published between January 1980 and August 2014 in English. The search was conducted in September 2013 with an update in January 2015. The strategy used to conduct this review, in accordance with the PRISMA guidelines [19], consisted of grouping keywords representing three categories: heat, mortality, and vulnerability (or heterogeneity). Keywords, titles, and abstracts were searched in PubMed and Elsevier Embase on the Ovid SP portal and in Web of Science as well. No restriction was put on the geographical location. The keywords used for this review were: (Heat OR climate OR environmental change OR heat stress OR hot weather OR high temperature OR heat effect OR hot effect OR hot temperature OR extreme temperature OR temperature) AND (Mortality OR health OR risk OR deaths) AND (vulnerability OR modif* OR interaction OR susceptibility OR stratification OR differ* OR hetero*), where * indicates any combination of subsequent letters.

Selection of studies

First, we screened manually the abstracts of all studies selected in the literature search according to the following exclusion criteria:

- Studies without estimation of an association between mortality and heat.
- Studies reporting associations between mortality and heat only for the entire population and not for subgroups constituting vulnerability (as described in the introduction).
- Studies not performed on human populations.
- Commentaries, editorials, or review articles.

We examined remaining articles from the previous step in full. In this second step, we further screened studies or assessments within studies (i.e. by vulnerability subgroups) based on the following exclusion criteria:

- Studies or vulnerability subgroups (within a study) with either no comparison group or no reference group. If a study assessed only one of the strata for a given vulnerability factor, it was not possible to assess heterogeneity, thus such estimates were not considered. For instance, if a study assessed the association among individuals of 65 years and older, without giving the corresponding association for the 0-64 years age group, this study was excluded.
- Studies not reporting a non-heat wave reference period (i.e. when the heat-exposure did not differ) were also excluded. These studies were excluded because they were not estimating a heat-wave effect, by comparing heat-wave days with non-heat wave days across different subgroups, but rather assocations across different subgroups during heat-wave periods solely.
- When the vulnerability subgroups considered were assessed only once in all of the final set of selected papers without distinguishing ambient temperature and heat-waves studies (e.g. body mass index in Xu et al. [20], depression in Stafoggia et al. [10], smoking in Madrigano et al. [21]).
- When subcategories of outcomes, such as cause of death or place of death, were considered as vulnerability factors. We excluded these subgroups as, based on the definition of vulnerability we use, they cannot logically modify the associations between heat and mortality.

In addition, the reference sections of studies identified as described above were searched, and pertinent references not initially identified were thus added. Where published literature reviews on heat-related health effects were cited in these reference lists, we additionally searched their references: the reference lists of eight reviews on temperature effects in children [13,22], the elderly [3] and general population [4,5,7,8,23] were thus searched by hand.

We separated the articles finally selected into two categories: 1) studies investigating associations of high ambient temperature with mortality and 2) studies investigating associations of heat waves with mortality.

Data extraction

From the selected studies, we extracted the estimates of association (e.g. RR, IRR or OR) for all the included subpopulations. The estimates were obtained from the published tables, figures (when it was possible to precisely determine the estimates of association from the published material), through text descriptions, supplemental material, and when accessible from the original data. When different lag effects were presented, we systematically used estimates of association between heat and mortality for the shortest lag effects presented. We then documented the location of the studies, their time period, study design, the temperature exposure variable and the following vulnerability factors (see details in supplemental material: Table 1S): i) sex; ii) age: elderly and children; iii) individual and ecological socioeconomic status; iv) urban design and housing: intra-urban heat variations, air conditioning, and population density; v) marital status.

Heterogeneity assessment using the Cochran Q test

To assess whether there was a heterogeneous association with high temperatures between subgroups, we conducted a Cochran Q test (see supplemental material: Appendix 1S for details). We considered the presence of heterogeneity at the 10% level of significance [24,25]. When estimates for all groups combined were not reported, we calculated them as described in the supplemental material (Appendix 1S) (for example, if a study presented estimates for men and women without presenting the estimate for both sexes combined). When analyses were conducted in the same study for different cities or for different time periods (e.g. different heat waves), we assessed the heterogeneity between different subgroups separately; for this reason, the number of strata comparisons is greater than the number of studies finally included. When more than two strata were presented, we compared only the two extreme groups. For example, if the heat associations were presented by quintiles of socioeconomic status (SES), we compared the least deprived group (first quintile) to the most deprived group (fifth quintile). For ethnic groups, we only compared White persons to Black persons or to Non-White persons and we did not include Hispanic persons in the comparisons (as this group was only assessed in one study [26]). In one study [27], many employment status categories were presented, and we only compared unemployed to white collar.

Heterogeneity assessment using a meta-analysis

In parallel to the heterogeneity assessment described above, we conducted a meta-analysis. We included only high ambient temperature studies. We did not conduct a meta-analysis for heat wave studies since the study designs and methods were not comparable to one another. The minimum number of studies required to conduct a meta-analysis was fixed at 10 [28,29]. We considered sex, age (more than 65 and more than 75), and SES (individual and ecological definitions separately) subgroups.

In order to compare subgroups within selected studies, we used the natural logarithm of the ratio of RR values (RRR) (or analogous estimates of association) for the two compared subgroups (e.g. RR_{men}/RR_{women}) as described by Altman et al. [30] or Bassler et al. [31]. The formula used to calculate the standard errors of the ratios is presented in the Supplemental Material (Appendix 1S). Moreover, for the studies that reported contrast definition by comparing two percentiles of temperature distributions, the highest percentile was always above the 95th percentile. We used random-effects models to account for heterogeneity between studies. To assess heterogeneity of the ln(RRR)s across individual studies, we used the I^2 statistic (I^2 >50% was used as a threshold) [29,32]. Publication bias was assessed with funnel plots and Egger's regression model [33].

Meta-regression analysis

To investigate factors associated with the magnitude of the RRR, we performed random effects meta-regression analyses in which the dependent variable was the ln(RRR) and independent variables were: study design (i.e. case-crossover or time series), continent (i.e. Europe, America, Asia and Australia) and contrast definition (i.e. percentage increase comparing two percentiles of the temperature distribution or percent changes associated with degree units increases above a city specific threshold) for sex and age >65 years; the continent and the contrast definition for age >75 years; study design, continent, and contrast definition for SES. We also investigated in all meta-regression analysis the separate associations with the following variables: local temperature, using the yearly summer temperature average for single cities, and when multiple cities were assessed simultaneously, the average for all the cities was considered; latitude, creating four groups of latitude positions: i) 60 °N to 30 °N; ii) 30 °N to equator; iii) equator to 30 °S; iv) 30 °S to 60 °S); study period, including the median year of study period (as indicated in Table 1) as indicator of change of heat associations over time.

We conducted a meta-regression for each variable separately. We estimated from these meta-regressions the regression coefficients (betas and 95% CI), the *P* Value, the R^2 statistic (which represents the proportion of between-study variance explained by the covariate), the residual I^2 (which represents after adjustment for the predictors, a measure of the percentage of the residual variation that is attributable to between-study heterogeneity), and the adjusted pooled RRR (and 95% CI).

Results

Selection of studies

Altogether the abstracts of 299 articles were assessed and 111 underwent in-depth review, with 61 studies fulfilling the inclusion criteria. **Figure 1** presents the inclusion and exclusion of studies. Among the 111 articles retained based on the first exclusion criteria with abstract screening, 43 studies were excluded entirely because they did not report a comparison group. Among them, three studies [34-36] were excluded because they used a case-only design that did not permit the comparison of different subgroups, and seven studies were excluded because they only assessed the spatial variability of heat-related mortality. Eight studies were excluded because they showed variation only according to cities or regions. Among the 61 remaining studies, seven were identified through reference searching. Two studies were excluded because it was impossible to precisely determine the estimates of association from the published material.

Description of selected studies

The characteristics of the included studies are presented in **Table 1** and **Table 2**. All the studies were published between 1998 and 2014. Twenty-four studies were conducted in Europe, 12 in North America, 19 in Asia, seven in Australia, one in Africa, and two studies that assessed multiple regions.

Fortyone studies retained assessed the association of high ambient temperature (**Table 1**) with mortality. Among these studies, 35 used a time-series design and six used a case-crossover design. Various contrast definitions between mortality and high ambient temperature were reported: 27 studies assessed the relationship by reporting percent changes or RR (or IRR) associated with degree unit increases (1°C, 3°C, 10°C, 10°F) above a city-specific threshold, and 14 reported percent increase or RR or odds ratios (OR) comparing two percentiles of temperature distributions.

Twenty of the retained studies assessed the association of heat waves (**Table 2**) with mortality. The definitions were very different from one study to another [3,4] as described in Table 2. Two types of definition have been used: one criterion requires 2 or 3 consecutive days with a specific temperature threshold, whereas the other criterion is based on single days above a temperature threshold. Among these studies, ten used a descriptive design in which observed mortality rates during heat-wave days were compared to mortality rates during non-heat-wave days across different subgroups. Seven studies used a time-series design, and three used a case-crossover design (see **Table 2**). Various contrast definitions between mortality and heat waves were reported. Seven studies reported this relationship by a percent increase on heat wave days compared to non-heat-wave days, and 13 with RR, IRR or excess mortality rates for heat-wave days compared with non-heat-wave days.

Heterogeneity findings

We systematically compared all the included subgroup estimates of association between heat and mortality, separately for high ambient temperature (**Table 3**) and for heat wave studies (**Table 4**). A description of the stratified estimates included in the review is presented in supplemental Table 6S for high ambient temperature studies and Table 7S for heat-waves studies. For studies of the association between high ambient temperature and mortality, we consistently found evidence of vulnerability for one subgroup: populations living in areas characterized by a low percentage of households having central air conditioning. For studies on the association between heat waves and mortality, we consistently found evidence of vulnerability for the following three subgroups: elderly persons above 85 years of age, populations living in hot places, and individuals who were not married (used as a proxy for social isolation [37]). Heterogeneity was not always found for other subgroups studied, such as SES subgroups or children.

Nonetheless when heterogeneity was found from studies on the association between temperature and mortality, the following subgroups were always identified as vulnerable: elderly persons by every age cut-point examined, low individual SES groups, populations living in high density areas, and unmarried individuals. The comparison of heterogeneity findings between high ambient temperature and heat waves studies is presented in Supplemental **Table 2S**.

Meta-analysis results

We conducted meta-analyses of the ln(RRR) for sex, age (more than 65 and more than 75 years) and SES (individual and ecologic separately) only on studies of high ambient temperature. We found that the pooled RRR for male sex was 0.99 (95% CI: 0.97, 1.01) (**Figure 2**). We found that the pooled ratio of RRs for individuals aged > 65 years, compared to adults aged between 15 and 64 years was 1.02 (95% CI: 1.01, 1.03) (**Figure 3**), and that the pooled ratio of RRs for those aged >75 years, compared to adults aged between 15 and 74 years was 1.04 (95% CI: 1.02, 1.07) (**Figure 4**). For SES measured at the individual level, we found that the pooled RRR for low SES compared to high SES groups was 1.03 (95% CI: 1.01, 1.05) (**Figure 5**). For SES measured at the ecologic level, we found that the pooled RRR for low SES compared to high SES groups was 1.01 (95% CI: 0.99, 1.02) (**Figure 6**). Evidence of bias (assessed with Egger's test) was apparent for studies that assessed sex and age > 75 years as vulnerable factors, but not for age > 65 years and SES (see Supplemental Figures 1S to 4S).

Meta-regression results

The large heterogeneity (all $I^2 > 50\%$) found in the pooled RRR suggests the existence of study characteristics influencing this variability. We conducted meta-regression analyses to assess the influence of different study characteristics on meta-analysis heterogeneity.

Of the study characteristics assessed for articles exploring age > 75 years, only the contrast definition was a significant factor in explaining heterogeneity in the pooled RRR, such that the use of a percentage increase comparing two percentiles of the temperature distribution was associated with a higher vulnerability for the elderly. This suggests that when studies used a percentage increase as the contrast definition they were more likely to find vulnerability differences by age as compared to using the comparison of two percentiles of the temperature distribution. For individual SES studies, contrast definition was also related to the heterogeneity in the pooled RRR. Similarly to older age, the use of a percentage increase as the contrast was associated with higher vulnerability for low individual SES groups. Finally, we did not find that local temperature, latitude or study period were related to the heterogeneity in the pooled RRR in any of the meta-regression conducted (see Tables 5, 6; see supplemental material for sex, aged > 65 years and aged > 75 years). The pooled estimate for the ratios for age > 75 years vs. younger age groups, adjusted for the contrast definition, was 1.11 (95% CI: 1.05, 1.17). The pooled ratio for low vs. high SES measured at the individual level, adjusted for measures of associations, was 1.05 (95% CI: 1.03, 1.07). It is interesting to note that for individual SES, adjustment for the contrast definition decreased the I^2 to 50%, which we define as a low degree of heterogeneity in the pooled RRR. The meta-regression results for individual SES and ecologic SES are respectively presented in **Tables 5** and **6** and other meta-regression results for sex, age > 65 years and > 75 years are presented in Supplemental Tables 3S to 5S.

Discussion

Summary of results

In this systematic review we assessed the published evidence supporting the presence of subgroups vulnerable to heat-related mortality. Using Cochran's Q test we found evidence of particular vulnerability for the most elderly and for populations living in areas characterized by a low percentage of households having central air conditioning. Vulnerability was also noted, in heat wave studies, for populations living in hot places and for unmarried people, and in high ambient temperature studies, for people living in areas with a low percentage of households with central air conditioning, although very few assessments were available. On the other hand, results of the meta-analyses, focusing on high ambient temperature studies only, showed that elderly persons 65+ and 75+ and low individual SES groups were more vulnerable than their respective counterparts using the pooled estimate (RRR).

Comparison of the results with current knowledge

The results of the present study can be compared to factors of vulnerability reported in various institutional guidelines, aimed at informing interventions for the prevention of heat-related mortality such as the WHO heat action plan [38,39]. Heat action plans include heat warning systems during heat waves, plans for emergency measures, as well as actions aimed at reducing high ambient temperatures over the long term (e.g. greening activities).

In the European WHO heat health action plan [38], the vulnerable subgroups identified are the elderly, infants, and children, people with chronic diseases, people taking particular medications, people with low SES, and people in specific occupations. The identification of elderly people and those from low SES subgroups as being of particular vulnerability is concordant with our results.

Lowe et al.[40] , in assessing the content of 12 European heat health action plans, also reported that in 11 out of 12 plans, the elderly, children, the chronically ill, and those on medication were considered vulnerable subgroups. Thus, it appears that some subgroups identified as vulnerable in both the heat action plans and in guidelines for planning were not assessed, or not reported as having heterogeneous associations with mortality, in the present study. Other reviews addressed heat-related vulnerability. Bouchama et al. [41] conducted a meta-analysis of 6 case-control studies on heat wave-related mortality, and found that both not leaving home daily and having a pre-existing illness were associated with higher risk, while greater social contact and having air conditioning were protective.

Limitations of the review

This review has some limitations. First, we excluded a number of studies because the statistical heterogeneity test could not be performed.

In epidemiologic studies addressing inequalities in the health effects of heat, such as those included in this review, the relative scale (e.g. risk ratio, incidence rate ratio, odds ratio...) is most often used and the absolute scale (e.g. risk difference, incidence rate difference ...) is generally ignored [42]. However, baseline risks can differ considerably across different subgroups, as for elderly compared to younger adults. Using absolute measures when addressing vulnerabilities reflects not only differences in health impacts across different subgroups, but can be a more useful public health strategy, as risk difference corresponds directly to attributable cases [43,44]. Moreover, absolute measures will often highlight different patterns of inequalities between subgroups than relative measures [43,45].

We conducted meta-analyses only for high ambient temperature studies to minimize the differences between study designs and methods of analysis.

Still, we found considerable heterogeneity between studies (all $I^2 > 50\%$), which makes complicates the interpretation of a single summary estimate [28,46]. Hence, we conducted meta-regression analyses to investigate factors associated with the magnitude of the RRR, and found that only the inclusion of contrast definition reduced the I^2 estimate to 50% for the individual SES meta-analysis. However, other study-related factors that were not assessed in this review, such as population age and sex structures, presence of local heat action plans or population's resilience facing hot temperatures [7], could explain some of the residual heterogeneity. We also did not assess the influence of lag effects on modification effects. Yet, mortality displacement could be heterogeneous because of subgroups in different populations. Further studies may address this matter. Finally, it is worth noting that in addition to the previous factors that can affect heterogeneity between studies, the differences between two subgroups within a study's population can impact heterogeneity between studies as well. For instance, the magnitude of socio-economic inequalities can differ widely between two cities over the world, so that the comparison of the lowest to highest groups can reflect completely different degrees of disparity.

We assessed socioeconomic vulnerability to heat, considering together income, education, immigration status, deprivation composite indexes, and other ecologic or individual characteristics, assuming that they represent the comparable measures of social hierarchy. However, the various individual and/or ecologic socioeconomic measures may not represent the same social dimension [47-50]. For example, education may influence the understanding of preventive messages, while income may limit access to air conditioning.

We considered vulnerability factors independently as assessed in the majority of the studies since many of the factors considered are highly correlated. Yet, when assessing vulnerability according to sex, for example, it is possible that sex differences in age distribution could explain some of this heterogeneity.

Finally, as many vulnerability definitions exist, the one adopted in our study could be disputed [51,52]. We chose an epidemiologic definition (i.e. effect measure modification) to identify factors of vulnerability to heat, but vulnerability can encompass other dimensions beyond this definition, such as the notion of social trajectory [52]. Also, in the literature reviewed in this paper, vulnerability factors were considered separately, but it is reasonable to think that several modifying factors might interact synergistically in the heat-related mortality relationship.

Recommendations for studies on the relationship between heat and death

We noted some limitations in the selected studies of our review, so here we present recommendations to guide further research on heat-related mortality vulnerability. As noted above, the absolute scale is rarely used in this context; therefore we encourage integrating risk differences in case-crossover designs for example. To do so, we recommend that future studies estimate risk differences directly from logistic regressions. The use of novel inequality measures in time-series analyses is also encouraged, such as use of the Index of Disparity [53], or simple measurement of differences in daily death counts between two subgroups as outcomes [45,54].

We excluded both cause of death and place of death as modifying factors as they are subcategories of the mortality outcome. In the studies reviewed, causes of death for instance were used as proxies for existing cardiovascular or respiratory diseases. We argue that this is an inappropriate proxy as these factors are themselves due to heat (i.e. stratification for factors affected by exposure). Even if association estimates across these strata are observed to be heterogeneous, they do not constitute a modifying factor in the same sense. This point should be further explored using appropriately designed studies with prospective data, in which the diagnosis of a pre-existing illness is used, as was undertaken in a recent paper on elderly persons [55].

Some effect modifiers were difficult to assess in the present study due to the lack of published examples. These include marital status or living in hot places (e.g. micro heat islands), and could be addressed in the future studies.

We found that contrast definition can influence the heterogeneity between studies. Further studies may assess effect modification using different contrast definitions, as sensitivity analyses.

The causal pathways linking vulnerability factors (i.e. modifying factors) are complex and need further consideration. More effort is needed toward the inclusion of causal inference methods to properly consider the role of measured individual or contextual determinants in the heat-related mortality studies, and their synergic influence. Using directed acyclic graphs can be useful for identifying inappropriate practices in causal structures investigating vulnerable subgroups to heat-related mortality [56,57], as illustrated with respect to confounding in two recent papers [58,59]. Methodologic developments are also required since the distinction between individual and contextual factors remains unclear, and methods used to date do not permit one to elucidate the association of place characteristics with individual outcomes while accounting for non-independence of observations [60,61].

Conclusions

While the link between excess heat and mortality is well established, the needed fundamental evidence on heat-vulnerable subgroups remains incomplete. Knowledge about vulnerable subgroups is essential for the success of public health programs [15,16,62], and is necessary for the application of blended intervention strategies, such as proportionate universalism and targeting within universalism [63,64]. Where specific interventions are planned to reduce health impacts in vulnerable populations or territories, such as adapted campaigns or urban modifications, misclassification of vulnerability status may challenge intervention effectiveness and implementation success.

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Figure Legends

Figure 1: Flowchart outlining study selection. NB: 2 studies [89, 100] investigated both ambient temperature and heat waves.

Figure 2: Meta-analysis of the ratio of the RRs according to sex (RR_{men}/RR_{women}); ES: Effect Size; n=39 studies

Figure 3: Meta-analysis of the ratio of the RRs according to age 65+ (individuals aged > 65 years, compared to adults aged between 15 and 64 years) (RR_{65+}/RR_{15-64}); ES: Effect Size; n=39 studies

Figure 4: Meta-analysis of the ratio of the RRs according to age 75+ (individuals aged > 75 years, compared to adults aged between 15 and 74 years) (RR_{75+}/RR_{15-74}); ES: Effect Size; n=13 studies

Figure 5: Meta-analysis of the ratio of the RRs according to individual SES ($RR_{lowSES}/RR_{highSES}$); ES: Effect Size; n=15 studies

Figure 6: Meta-analysis of the ratio of the RRs according to ecologic SES ($RR_{lowSES}/RR_{highSES}$); ES: Effect Size; n=12 studies