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Title: Ambient temperature and cardiorespiratory morbidity: A systematic review and meta-analysis

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Abstract

Background:

Evaluating the impact of temperature on morbidity has received less attention than mortality. As the effect of extreme temperature has become an increasing public health concern, this meta-analysis attempted to quantify the exposure–response relationship between ambient temperatures and morbidity.

Methods:

We performed a systematic literature review and extracted quantitative estimates of the effects of hot temperatures on cardiorespiratory morbidity. There were too few studies on cold effects to warrant a summary. Pooled estimates of hot effects were calculated using a Bayesian hierarchical approach that allowed for the inclusion of multiple results from the same study, particularly different latitudes and lagged effects.

Results:

Twenty-one studies were included in the final meta-analysis. The pooled results show that a 1 °C increase on hot days was related to a statistically non-significant increase of 3.2% (95% Posterior Interval (PI): –3.2%, 10.1%) in respiratory morbidity, and also no apparent association was observed for cardiovascular morbidity (–0.5%, 95% PI: –3.0%, 2.1%). The length of lags had mixed effects on the risk of respiratory and cardiovascular morbidity, while latitude had little effect on either morbidity type.

Conclusions:

In this meta-analysis, we found that the effects of temperature on cardiorespiratory morbidity appeared to be smaller and more variable than previous findings related to mortality.

Importantly, the effect of hot temperatures on respiratory and cardiovascular morbidity appears to differ.

Introduction

Systemic environmental changes and their effect on human health have become an increasing public concern.[1–3] Temperature-related health effects have received much attention,[4–6] particularly since projected climate change scenarios point to increasing and more varied temperatures throughout the world.[7] Increasing ambient temperatures mean that heat effects are of particular importance from a public health perspective.[8,9]

The ability to measure the effects of temperature on human health is vital for a number of reasons. Firstly, it improves understanding of how temperature affects morbidity and mortality in different populations, which increases knowledge of how climate change will influence human health. Secondly, it may contribute to effective public health interventions that can better target vulnerable groups within the population.[10] Finally, it may also assist in the development of strategies for reducing both the social and economic burden associated with major chronic diseases such as cardiovascular and respiratory diseases.[11]

Most research to date has concentrated on examining the relation between temperature and mortality.[12–18] In terms of the effects of temperature on morbidity, only three types have been primarily examined in the literature: total hospital admissions; hospitalizations for respiratory disease;[19–21] and cardiovascular (CV) disease which includes myocardial infarction (MI), acute coronary syndrome (ACS) and stroke.[19,22–29] Particular attention has been given to some methodological issues such as distributed lagged effects and harvesting, particularly when examining the effects of sustained periods of extreme weather in time series studies.

Distributed lagged effects (including both short term and cumulative lagged effects) have been examined in a number of studies.[30–32] In particular, it has been observed that short term lags are important for heat-related effects.[33] Mortality displacement or harvesting[16,34] occurs when the deaths of particularly frail individuals are brought forward by extreme temperatures, leading to a decrease in effect estimates for longer lag periods.

Non-linear exposure–response relationships have also been reported,[35–37] below and above which the effect on health outcomes significantly increases.[18] This common 'U' or 'V' relationship is often modelled by a piecewise function, which for the former is specified by a 'comfort zone' of no effect between hot and cold thresholds. Other non-linear splines using more complex bases have also been used to describe the general nature of the exposure–response relationship.[35] However, in some studies the non-linear effect of temperature has been found to be weak or even nonexistent, leading to the use of a linear model across all temperatures.[22,38,39] These modelling differences may be explained in part by the temperature range of the particular studies, and also by population acclimatization. For this reason, acclimatization has often been incorporated into studies of multiple locations, most commonly by including the latitude of the population as a proxy for climate.[18,32,40]

Compared with studies examining temperature effects on mortality, less attention has been paid to the effects of temperature on morbidity.[41–46] Among a relatively small number of temperature–morbidity studies, most have focused on the effects of hot temperatures. Our study therefore aims to identify and quantify the relationship between hot temperatures and morbidity through a systematic review and meta-analysis.

Methods

Data extraction

We used a systematic search to identify all relevant studies investigating the association between temperature and morbidity. The search used the databases: PubMed, Web of Science, Science Direct and Scopus, and was conducted during October 2010 and January

2012 with no limitations on search criteria. The specific search terms used for each database differed slightly (see Supplemental Material). Additional articles were obtained by manually scanning the reference lists of each publication.

Filtering procedure

The title and abstract were first used to filter studies not related to the research question. The remaining results were merged into an Endnote library and duplicates were removed. Studies that contained no quantitative results were removed next. Studies related to periods of extreme temperature such as heatwaves were also excluded, because of the different methods used to examine heatwaves.

The full texts of the remaining studies were then thoroughly reviewed against selection criteria. Studies were required to be of time series, case–control or case–crossover design. To examine the short-term effects of changes in temperature on morbidity, each study had to contain an outcome measure related to hospitalization for either all-causes, cardiovascular (including myocardial infarction or stroke) or respiratory diseases. As the exposure–response relationship was of interest, the outcome measure was the change in the number of hospitalizations for a unit change in temperature, reported over a daily timescale. This resulted in the exclusion of studies reporting only non-linear temperature–morbidity curves, since while their effect values could be estimated from the plots, it was not possible to derive associated standard errors which are required for inclusion in the meta-analysis. All temperature measures were allowed, following recent evidence that the magnitude of temperature effects on mortality does not vary significantly with the exposure measure used.[17,47,48] The effect estimates had to be presented as a Poisson or negative binomial regression coefficient, percentage change, relative risk or odds ratio.

All effect size results with confidence intervals or standard errors were collected. Additional data collected were the number of lagged days used and the study latitude, along with an associated threshold temperature, when reported.

Statistical methods

All effect estimates were converted to a relative risk (RR) reflecting a change in hospitalizations due to a 1 °C increase in temperature. For some studies this was the increase in temperature above a threshold. Standard errors for relative risks were derived from associated confidence intervals. All results were converted to the log scale for the meta-analysis.

We combined the studies in the meta-analysis, using a random effects model to incorporate heterogeneity both within and between studies. As a number of studies reported multiple estimates for different lags and latitudes, we used a two-stage Bayesian hierarchical model.[49] The hierarchical modelling approach assumes in the first stage that individual results (Y_{ij}) in each study are distributed around a study-level effect mean (θ_i). In the second stage, the study means are distributed around an overall effect mean (θ), with the model producing estimates for the pooled mean effects at both study and overall levels. The model took the following form:

$$
\begin{aligned}
&Y_{ij} \sim N\left(\delta_{ij}, \sigma_{ij}^2\right), \\
&\delta_{ij} \sim N\left(\theta_{ij}, \varphi_i^2\right), \\
&\theta_i \sim N\left(\theta, \tau^2\right), \quad i = 1, \ldots N_j, \quad j = 1, \ldots M,
\end{aligned}
$$

where σ_{ij}^2, φ_i^2 and τ^2 are the result, study and between-study variances, respectively calculated over N_j results taken from M studies.

In order to model both lagged effects and absolute latitude of the population, the effect specific mean (δ_{ij}) was related to each study mean (θ_i), lag (Lag_{ij}) and latitude (Lat_{ij}) via the following regression equation:

$$\theta_{ij} = \theta_i + \beta_0 Lag_{ij} + \beta_1 Lat_{ij},$$

the unit of the lag term being days, while absolute latitude was standardised to a 5 degree increase. The pooled study mean effect sizes (θ_i) corresponded to the baseline state of 0 days lag and the mean latitude of the included studies. The latitude effect (β_1) was assumed to be linear, while the lag effect (β_0) was specified in two forms using linear and polynomial expressions, both based on the distributed lag model approach.[50,51] These two specifications for the lag effect were compared in separate analyses using the deviance information criterion (DIC). We found that using a polynomial model for the lag effect did not perform better, and therefore a linear term was used.

We implemented the meta-analyses using WinBUGS.[52] Sampling used a burn-in of 20,000 Markov chain Monte Carlo iterations followed by a sample of 80,000 iterations. All pooled results for the study effect estimates (θ_i) were transformed to percent changes for presentation, and estimates for lag and latitude were converted to represent the percentage change in relative risk due to a one day or 5 degree increase, respectively. For comparison, the analyses were also re-run, replacing each location's latitude with Average Summer Temperature (AST).

Separate analyses were performed on studies related to respiratory and cardiovascular morbidities. We hypothesized that studies assuming a linear temperature relationship over all data would underestimate a heat effect due to the mixing of data from hot and cold periods. To account for this, analyses were also conducted on those studies that used either a non-linear temperature relationship or restricted analyses to warm seasons only to specifically examine a heat effect. This was achieved by removing studies assuming a linear temperature relationship across all temperatures. Sufficient numbers of results were obtained to allow for further analyses of results related to stroke, ACS/MI and asthma.

Sensitivity analyses were performed on different sub-groups based on temperature measures, age groups and study design. As hot temperatures have been observed to have an immediate and short term effect on respiratory and cardiovascular diseases, these sensitivity analyses were performed on same day effect results only. The I^2 statistic[53] was used to examine heterogeneity between studies, where increasing values (from 0 to 100%) denote increasing heterogeneity between the studies.

Results

In total, 2527 articles were identified by the systematic search. Through an examination of titles, abstracts and full text, 2489 of these studies were excluded. The results of the search strategy are shown in Figure 1.

[Figure 1 here]

From the remaining 38 studies, 4 studies reported population-standardised relative risks.[33,54–56] Five studies provided effect estimates that were based on grouped temperature exposure levels rather than a unit change in temperature,[36,57–60] and one study aggregated daily data over multiple days.[31] Seven studies only reported correlations of hospital admissions with temperature.[61–67] The remaining 21 studies were included in the meta-analysis. Table 1 shows descriptive information of these studies.

[Table 1 here]

Among the included studies, 12 provided effect estimates for respiratory morbidity, while 17 provided results for cardiovascular morbidity, with some studies examining both. Respiratory studies included both total respiratory admissions and admissions for asthma, while cardiovascular morbidity included total cardiovascular admissions, and admissions for MI, ACS and stroke. The populations were from a variety of climate zones, ranging from temperate to tropical (see Supplemental Material for a map). All age groups were examined, including the young[75] and elderly.[32,77]

Only three studies specifically examined cold effects on morbidity, [28,68,83] and therefore our meta-analyses only examined heat effects. The majority of studies applied a time series design using either generalised linear models (GLM) or generalised additive models (GAM), although some studies used a case–crossover design.[68,81–83] Confounding variables were considered, such as air pollution, humidity and/or atmospheric pressure, and seasons.[73,74,76] The most commonly used temperature definitions were daily mean and maximum temperatures, although minimum and apparent temperatures were also used. Lagged effects were considered in most studies, with lags ranging from 1 to 28 days, with one study finding that effects weakened considerably for lags longer than 7 and 13 days, respectively.[39,84]

Several approaches were used to model the relationship between temperature and morbidity. Eleven studies examined heat effects using either a non-linear relationship incorporating a particular threshold or a linear relationship over summer data only.[28,68,81–83] For those specifying a threshold, values were identified using different techniques.[70,79,84] In the absence of a derived threshold, several studies used a specific percentile of temperature to test for the presence of a heat effect.[73,77,80] From those studies where explicit threshold values were provided, temperatures associated with heat effect estimates ranged from 19.3 °C (minimum temperature) to 41.5 °C (maximum temperature).

Eleven studies assumed a linear temperature effect over all temperatures. These included 3 studies[75,76,78] that did not consider a non-linear temperature effect in their respective analyses at all, along with a further 7 studies[38,39,69,71,72,74,84] that did test for the presence of non-linear effects, but found none that were statistically significant. One study[32] applied a non-linear effect model but reported linear effect estimates. These studies proposed several reasons for the lack of non-linearity, including the weak effect of hot temperatures observed on MI or stroke, the temperate environments in which the studies were based, and population adaptation. The results extracted from each study are presented in Table 2.

[Table 2 here]

Figure 2 shows the meta-analysis results for studies of respiratory morbidity. The pooled effect estimate for all studies was that respiratory morbidity increased by 2.0% (95% PI: –1.4%, 5.5%) for a 1 °C increase in temperature. After removing four studies that assumed a linear relationship between temperature and respiratory morbidity, the pooled effect estimate increased to 3.2% (95% PI: –3.2%, 10.1%).

[Figure 2 here]

The results for cardiovascular morbidities (Figure 3) show that no temperature effect was observed when all studies were included (–0.1%, 95% PI: –1.8%, 1.6%), or after removing eight studies that assumed a linear relationship between temperature and cardiovascular morbidity (–0.5%, 95% PI: –3.0%, 2.1%).

[Figure 3 here]

The effect of both latitude and lag varied across both morbidity subgroups, although these effects were not statistically significant (Table 3). The results showed a decreasing effect (–0.47, 95% PI: –1.71, 0.78) on the risk of respiratory morbidity for increasing lag, while lag had an increasing effect (0.29, 95% PI: –0.46, 1.04) on the risk of cardiovascular morbidity. An increase of 5 degrees above the mean latitude for each group had little effect on the risk of either respiratory morbidity (0.03, 95% PI: –2.19, 2.31) or cardiovascular morbidity (0.13, 95% PI: –0.91, 1.17). When the analysis was performed using AST to replace the latitude for each study, it was found that AST had little effect on respiratory (0.16, 95% PI: –0.76, 1.08) or cardiovascular (–0.03, 95% PI: –0.54, 0.48) morbidities. The analyses were also run using AST in place of latitude to compare the effect. The results (not shown here) were found to be almost identical to those obtained when incorporating latitude.

[Table 3 here]

Analyses were performed on sub-groups relating to stroke, ACS/MI and asthma (Figure 4). The pooled results for stroke (–1.0%, 95% PI: –11.3%, 10.5%) and ACS/MI (1.0%, 95% PI: –7.0%, 9.7%) showed similar effects to those found for cardiovascular morbidity as a whole. No effect was observed for asthma (0.3%, 95% PI: –11.8%, 14.1%), for which four studies were available.

[Figure 4 here]

Table 4 shows the pooled results for different subgroups examined in the additional sensitivity analyses. The findings for the same day heat effect for respiratory morbidity (3.3%, 95% PI: –2.7%, 9.6%) and cardiovascular morbidity (–0.3%, 95% PI: –2.8%, 2.4%) did not differ substantially from the pooled results incorporating lagged effects. An analysis of only those studies that used mean and maximum temperatures resulted in a slight increase in respiratory morbidity risk (4.4%, 95% PI: –3.1%, 12.5%).

[Table 4 here]

An increase in risk was observed when studies that applied a case–crossover study design were removed (5.1%, 95% PI: –5.9%, 17.3%). The risk was reduced after excluding studies of the elderly (1.3%, 95% PI: –2.7%, 5.5%).

The sensitivity analyses performed on same day effect results for cardiovascular morbidity showed no difference to the results incorporating lagged effects.

In both respiratory and cardiovascular morbidity groups, I^2 values were mostly of the order of 88% to 100%, indicating a large between study heterogeneity and supporting the use of random effects models.

Discussion

To our knowledge, this is the first meta-analysis to assess available literature reporting quantitative estimates of ambient temperature effects on morbidity. This analysis reveals inconsistencies in the pooled effect estimates of temperature on cardiorespiratory morbidity. The results show a statistically non-significant increase of respiratory hospitalizations associated with a 1 °C increase in ambient temperature. There was no apparent association found for cardiovascular morbidity, with a mean percent change of close to zero indicating no change in morbidity.

The difference in heat effect on cardiovascular and respiratory morbidities observed in this study is consistent with previous findings. While a heat effect has been found for respiratory hospital admissions,[70,85] other studies[22,24,39,86] have suggested that hot temperatures have a smaller effect on cardiovascular morbidity than cold temperatures. Cold effects are often due to potential complications associated with decreased cardiovascular performance and effects of respiratory infections which are more common in winter, a combination that is less prevalent in the warmer months of the year. One large study[80] from the European Union noted similar differences in temperature effects on respiratory and cardiovascular morbidities, suggesting that an increase in out-of-hospital deaths prior to medical treatment for acute cardiovascular events could explain this difference. The observation that vulnerable people die instead of being admitted to hospital has been made elsewhere[45] and is a potential explanation for the smaller morbidity effect of heat observed in this study compared with previously reported mortality impacts.[87,88] Furthermore, previous research[89] has shown little evidence of a specific heat effect for myocardial infarction which may also explain the weak cardiovascular results.

It has been found[33,90] that heat effects are generally immediate and short-term. Our results for respiratory morbidity support these observations, with the lag coefficient for the heat effect showing a reduced effect on morbidity as lag increased. The positive lag coefficient found for cardiovascular morbidity does not agree with the respiratory results; however it should be noted that only short lags were included in the meta-analysis, and therefore extrapolation to longer lags may be problematic.

An increase in latitude was found to have little effect on both respiratory and cardiovascular morbidity, although the direction of effect for cardiovascular morbidity was consistent with findings elsewhere;[18,35,91] that is, the effect of heat increases at higher latitudes (colder climates). The adaptive capability of specific populations has been cited as a primary reason as to why people in colder climates are affected more by warmer temperatures. In general, such populations are less acclimatized to high temperatures, live in houses that are unsuitable in dealing with hot weather, and lack adaptive methods such as air conditioning.

The variability between individual study results, along with heterogeneity observed in the sensitivity analyses, may be related to a number of different factors. While the location of the different studies would be expected to contribute to this heterogeneity, the fact that most of the studies were performed in temperate regions, and that the effect of latitude was non-significant, supports the pooling of the studies. Other factors including different study periods, demographics of each population and other socioeconomic conditions may also contribute to the observed heterogeneity. For example, such differences can be seen in studies that take account of adaptive factors such as air-conditioning usage.[82] Differences in both the design and modelling methods applied in each study, including different sets of confounding variables, may also have contributed to between-study heterogeneity.

The review has a number of strengths. Firstly, it is the first time that a meta-analysis approach has been used to assess the available literature related to the effects of hot temperatures on morbidity. Secondly, through the implementation of a Bayesian hierarchical model multiple results from individual studies were able to be included in the same meta-analysis. Additionally, the modelling approach provided a convenient method to directly incorporate and assess effects of both lags and latitude of each study on the pooled estimates. Finally, the extensive nature of the search strategy covered multiple literature sources and so hopefully reduced any potential publication bias. While any non-significant results that have not been published would not be included in this study, the overall non-significant results found here would indicate that publication bias was not a major issue in our study.

The study also has some limitations. Firstly, the results are based on a small number of studies, particularly once separated according to type of morbidity. The studies cover limited geographical areas and therefore a limited range of climatic conditions. It is important to exercise caution when generalising the pooled results. Secondly, the meta-analysis excluded studies reporting only non-linear splines as there was no way to estimate the standard error of the heat slope; however the number of such studies was small since most studies reported parametric heat effect estimates with standard errors or confidence intervals. Thirdly, the lack of cold effect studies and the difficulty assessing both cold and heat effects simultaneously meant that consideration of the complete temperature effect curve[36,59] was not possible. Important variables such as the use of air conditioning and socioeconomic and demographic factors were also lacking in most of the studies.[16,82] Finally, given that the included studies generally did not report for lags longer than 4 days, it is difficult to interpret the estimates of delayed effects for longer lag periods. This had minimal impact, however, given the short-term, immediate nature of heat effects that were observed.

There are a number of directions we feel are valuable for further research. While the focus here was purely on hospitalization, analysis of General Practitioner consultations[92] may be worthwhile, particularly as a means to developing strategies for the early detection of temperature-related morbidity. Studies of this type would also help to pick up those health effects of temperature that were not sufficiently serious to cause hospitalization, but still cause important morbidity. Extended periods of heat were not examined here, as it has been proposed[85,93,94] that the effect of heatwaves plays a stronger role in heat-related health effects than do extremes in ambient temperature. Finally, further research is required into quantifying the effect of cold and hot temperatures on morbidity, particularly those related to cardiorespiratory diseases.

This study examined the effect of temperature on morbidity using a meta-analysis that incorporated a Bayesian hierarchical modelling approach. We found a potential heat effect on respiratory morbidity, though there was no apparent effect on cardiovascular morbidity. Additionally, it was found that lagged effects differed in direction between respiratory and cardiovascular morbidity. This study adds to the current research on temperature effects on cardiorespiratory morbidity, particularly in relation to potential differences in effect between respiratory and cardiovascular morbidity. It is important that such effects are more thoroughly understood, to ensure that public health strategies are effectively designed and implemented to minimise and prevent heat-related morbidity.

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List of Figures:

Figure 1: Procedure of literature search

Figure 2: Meta-analysis (study-specific and overall, ordered by latitude of study) of heat effects (1 °C increase in temperature) on respiratory morbidity. Estimates are for baseline of 0 lag days and mean latitude of included studies. Each central square is proportional to the study's weight in the meta-analysis

Figure 3: Meta-analysis (study-specific and overall, ordered by latitude of study) of heat effects (1 °C increase in temperature) on cardiovascular morbidity. Estimates are for baseline of 0 lag days and mean latitude of included studies. Each central square is proportional to the study's weight in the meta-analysis

Figure 4: Meta-analysis (study-specific and overall, ordered by latitude of study) of heat effects (1 °C increase in temperature) on morbidity related to stroke, ACS/MI and asthma. Estimates are for baseline of 0 lag days and mean latitude of included studies. Each central square is proportional to the study's weight in the meta-analysis

Figure 1

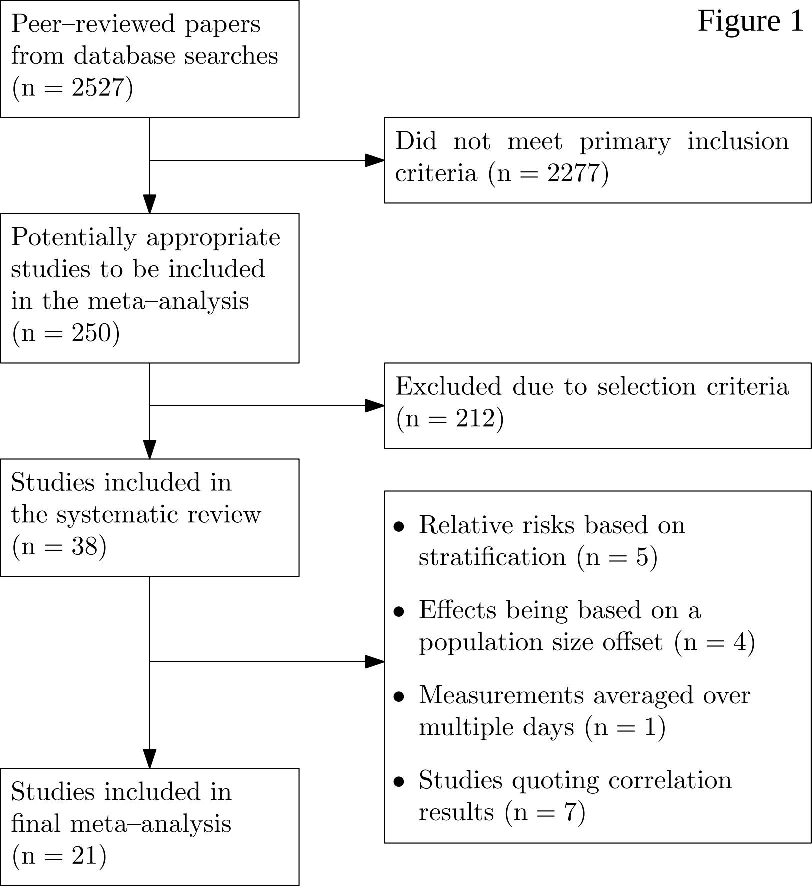

Peer–reviewed papers from database searches (n = 2527)
Did not meet primary inclusion criteria (n = 2277)
Potentially appropriate studies to be included in the meta–analysis (n = 250)
Excluded due to selection criteria (n = 212)
Studies included in the systematic review (n = 38)
• Relative risks based on stratification (n = 5)
• Effects being based on a population size offset (n = 4)
• Measurements averaged over multiple days (n = 1)
• Studies quoting correlation results (n = 7)
Studies included in final meta–analysis (n = 21)

Figure 2

Subgroup	Study	RR (95% PI)
All Studies	Pudpong & Hajat 2011[84]	1.028 (0.970, 1.089)
	Ren et al. 2006[73] / Ren & Tong 2006[74]	0.994 (0.969, 1.019)
	Green et al. 2010[81] / Ostro et al. 2010[82]	1.006 (0.982, 1.030)
	Nastos et al. 2008[78]	0.991 (0.958, 1.026)
	Babin et al. 2007[75]	1.010 (0.977, 1.044)
	Linares et al. 2008[77]	1.095 (0.985, 1.217)
	Lin et al. 2009[79]	1.015 (0.986, 1.045)
	Michelozzi et al. 2009[80]	1.015 (0.978, 1.053)
	Kovats et al. 2004[70]	1.040 (0.985, 1.099)
	Wichmann et al. 2011[83]	1.007 (0.954, 1.063)
	Pooled effect (I^2 = 92%)	**1.020 (0.986, 1.055)**
Heat effect studies only	Ren et al. 2006[73]	0.993 (0.944, 1.044)
	Green et al. 2010[81] / Ostro et al. 2010[82]	1.006 (0.976, 1.037)
	Linares et al. 2008[77]	1.139 (1.001, 1.296)
	Lin et al. 2009[79]	1.018 (0.983, 1.055)
	Michelozzi et al. 2009[80]	1.017 (0.967, 1.070)
	Kovats et al. 2004[70]	1.048 (0.972, 1.130)
	Wichmann et al. 2011[83]	1.011 (0.931, 1.098)
	Pooled effect (I^2 = 91%)	**1.032 (0.968, 1.101)**

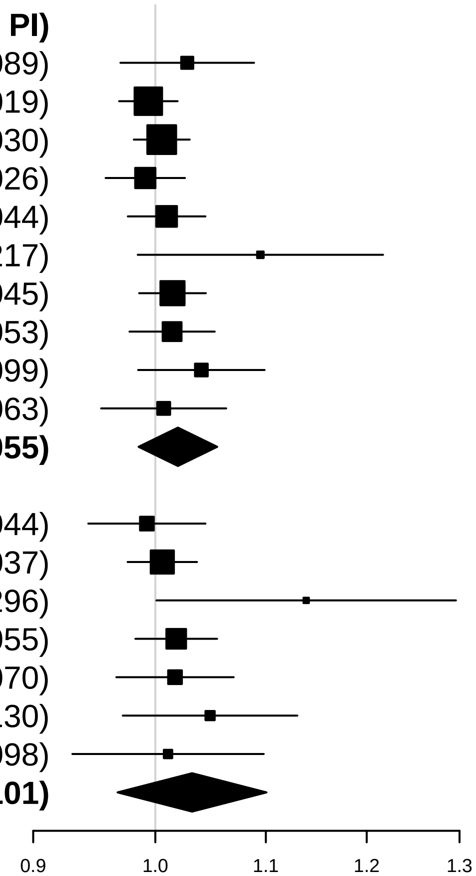
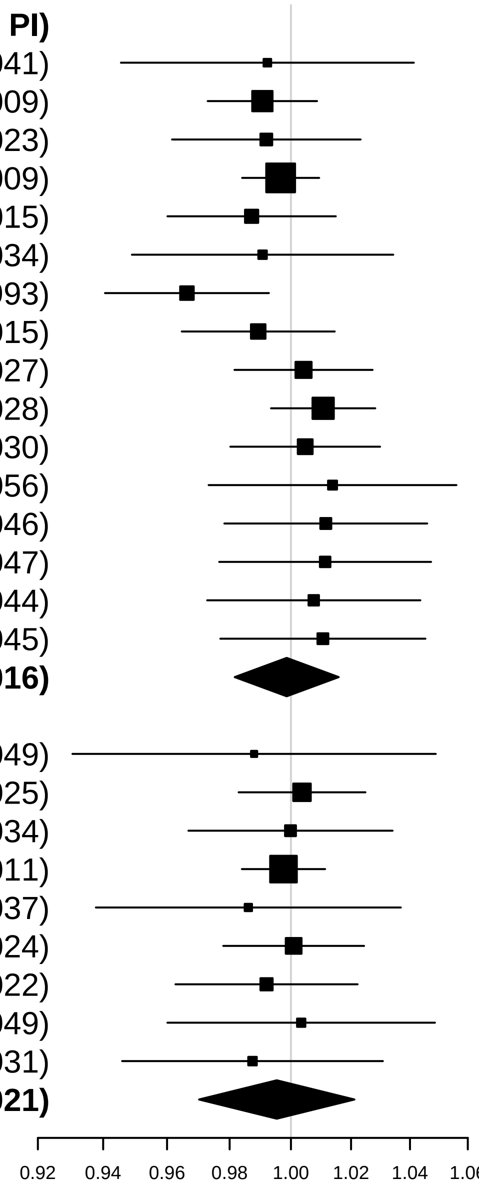
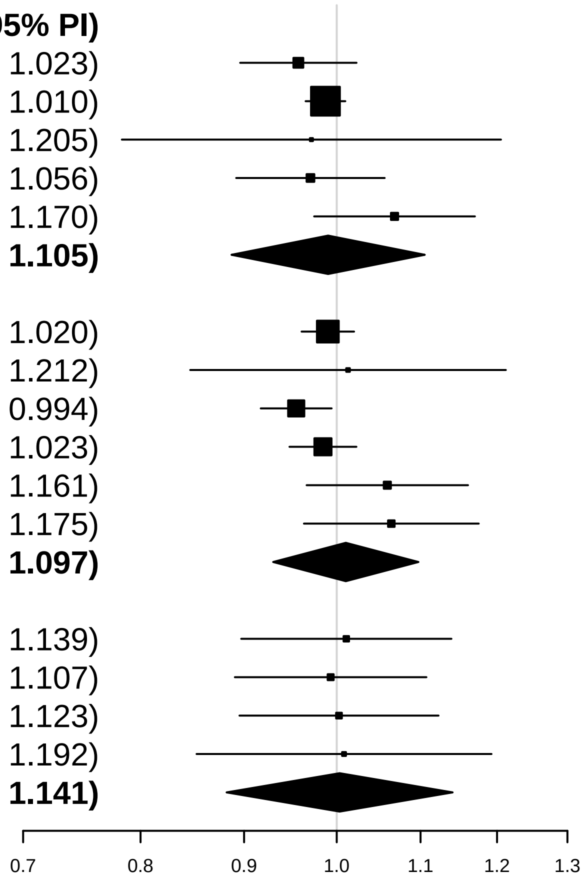


Figure 3

Subgroup	Study	RR (95% PI)
All studies	Pudpong & Hajat 2011[84]	0.992 (0.946, 1.041)
	Ren et al. 2006[73] / Ren & Tong 2006[74]	0.991 (0.973, 1.009)
	Wang et al. 2009[28]	0.992 (0.962, 1.023)
	Green et al. 2010[81] / Ostro et al. 2010[82]	0.997 (0.984, 1.009)
	Ebi et al. 2004[69]	0.987 (0.960, 1.015)
	Hong et al. 2003[68]	0.991 (0.949, 1.034)
	Panagiotakos et al. 2004[71]	0.966 (0.941, 0.993)
	Misailidou et al. 2006[72]	0.989 (0.965, 1.015)
	Schwartz et al. 2004[32]	1.004 (0.982, 1.027)
	Lin et al. 2009[79]	1.011 (0.993, 1.028)
	Michelozzi et al. 2009[80]	1.005 (0.980, 1.030)
	Kovats et al. 2004[70]	1.014 (0.973, 1.056)
	Bhaskaran et al. 2010[39]	1.012 (0.978, 1.046)
	Wolf et al. 2009[38]	1.011 (0.977, 1.047)
	Wichmann et al. 2011[83]	1.008 (0.973, 1.044)
	Dawson et al. 2008[76]	1.011 (0.977, 1.045)
	Pooled effect (I^2 = 99%)	**0.999 (0.982, 1.016)**
Heat effect studies only	Pudpong & Hajat 2011[84]	0.988 (0.931, 1.049)
	Ren et al. 2006[73]	1.004 (0.983, 1.025)
	Wang et al. 2009[28]	1.000 (0.967, 1.034)
	Green et al. 2010[81] / Ostro et al. 2010[82]	0.998 (0.984, 1.011)
	Hong et al. 2003[68]	0.986 (0.938, 1.037)
	Lin et al. 2009[79]	1.001 (0.978, 1.024)
	Michelozzi et al. 2009[80]	0.992 (0.963, 1.022)
	Kovats et al. 2004[70]	1.003 (0.960, 1.049)
	Wichmann et al. 2011[83]	0.987 (0.946, 1.031)
	Pooled effect (I^2 = 89%)	**0.995 (0.970, 1.021)**



Subgroup	Study	RR (95% PI)
Stroke	Wang et al. 2009[28]	0.957 (0.896, 1.023)
	Green et al. 2010[81] / Ostro et al. 2010[82]	0.987 (0.965, 1.010)
	Ebi et al. 2004[69]	0.972 (0.783, 1.205)
	Hong et al. 2003[68]	0.971 (0.892, 1.056)
	Dawson et al. 2008[76]	1.068 (0.975, 1.170)
	Pooled effect (I^2 = 100%)	**0.990 (0.887, 1.105)**
ACS / MI	Green et al. 2010[81] / Ostro et al. 2010[82]	0.990 (0.961, 1.020)
	Ebi et al. 2004[69]	1.013 (0.847, 1.212)
	Panagiotakos et al. 2004[71]	0.955 (0.917, 0.994)
	Misailidou et al. 2006[72]	0.984 (0.948, 1.023)
	Bhaskaran et al. 2010[39]	1.059 (0.966, 1.161)
	Wolf et al. 2009[38]	1.064 (0.963, 1.175)
	Pooled effect (I^2 = 99%)	**1.010 (0.930, 1.097)**
Asthma	Green et al. 2010[81] / Ostro et al. 2010[82]	1.011 (0.897, 1.139)
	Nastos et al. 2008[78]	0.993 (0.891, 1.107)
	Babin et al. 2007[75]	1.003 (0.895, 1.123)
	Lin et al. 2009[79]	1.008 (0.853, 1.192)
	Pooled effect (I^2 = 92%)	**1.003 (0.882, 1.141)**



eAppendix

Electronic literature search terms

PubMed:

("environmental temperature change" [all] OR hot temperature/adverse effects [mh] OR cold temperature/adverse effects [mh] OR extreme heat OR extreme cold [tw] OR "heat wave" [tw]) AND (morbidity OR "heat stress" OR hospitalisation OR emergency admission OR myocardial infarction OR respiratory disease OR cardiorespiratory disease OR ischemic heart disease OR cardiovascular disease OR heart failure OR stroke OR dehydration OR cerebrovascular disease OR heat stroke OR pneumonia OR asthma OR bronchitis OR emphysema) AND (environment [all] OR climate [all] OR weather [all])

Web of Science:

Topic=(temperature OR "heat wave" OR "cold spell" OR "extreme heat" OR "extreme cold" OR "hot temperature" OR "cold temperature") AND Topic=(morbidity OR "heat stress" OR hospitalisation OR "emergency admission*" OR "hospital admission*" OR "myocardial infarction" OR "respiratory disease" OR "cardiorespiratory disease" OR "ischemic heart disease" OR "cardiovascular disease" OR "heart failure" OR stroke OR dehydration OR "cerebrovascular disease" OR "heat stroke" OR pneumonia OR asthma OR bronchitis OR emphysema)

Science direct:

("environmental temperature change" OR temperature OR (extreme heat) OR (extreme cold) OR "heat wave") AND (morbidity OR "heat stress" OR hospitalisation OR emergency admission OR myocardial infarction OR respiratory disease OR cardiorespiratory disease OR ischemic heart disease OR cardiovascular disease OR heart failure OR stroke OR dehydration OR cerebrovascular disease OR heat stroke OR pneumonia OR asthma OR bronchitis OR emphysema) AND (environment OR climate OR weather)

Scopus:

("environmental temperature change" OR hot temperature OR cold temperature OR extreme heat OR extreme cold OR "heat wave") AND (morbidity OR "heat stress" OR hospitalisation OR emergency admission OR myocardial infarction OR respiratory disease OR cardiorespiratory disease OR ischemic heart disease OR cardiovascular disease OR heart failure OR stroke OR dehydration OR cerebrovascular disease OR heat stroke OR pneumonia OR asthma OR bronchitis OR emphysema) AND (environment OR climate OR weather) e figure: Map showing the locations of included studies (marked by black triangles).