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Modification of the effects of air pollutants on mortality by temperature: A systematic review and meta-analysis

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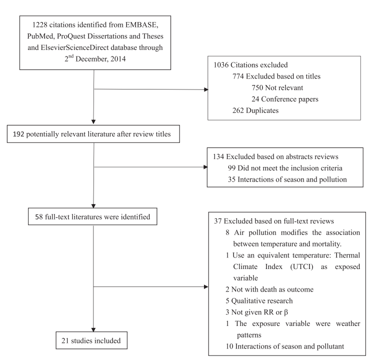
HIGHLIGHTS

- This is the first review and meta-analysis on the modification of pollutants' effects on mortality by temperature.
- We found temperature extremes modify the effects of PM_{10} and O_3 on both non-accidental and cardiovascular mortality.
- There may be value in promoting use of early warning systems on extremely hot or cold days that are also heavily polluted.

GRAPHICAL ABSTRACT



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ABSTRACT

Temperature extremes and air pollution both pose significant threats to human health, but it remains uncertain whether pollutants' effects on mortality are modified by temperature levels. In this review, we summarized epidemiologic evidence on the modification by temperature of the acute effects of air pollutants on non-accidental and cardiovascular mortality. The EMBASE, PubMed, ProQuest Dissertations and Theses, and Elsevier Science Direct databases were used to identify papers published up to 2nd December 2014. Studies with appropriate design, exposures and outcome indicators, quantitative estimates and high/intermediate quality were included. Twenty-one studies met the inclusion criteria, of which 12 reported the effects of PM_{10} on mortality modified by temperature, 10 studied O_3, and the rest examined NO_2, SO_2, $PM_{2.5}$, $PM_{10-2.5}$, CO and black smoke. We divided temperature into low, medium, and high categories as defined in each study. In high temperature days, a 10 μg/m^3 increment in PM_{10} concentration corresponded to pooled estimates of 0.78% (95% CI: 0.44%,

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Systematic review
Meta-analysis

1.11%) and 1.28% (0.66%, 1.91%) increase in non-accidental and cardiovascular mortality, both statistically significantly higher than the estimates in medium temperature stratum. Pooled effects of O_3 on non-accidental mortality on low and high temperature days were increases of 0.48% (0.28%, 0.69%) and 0.47% (0.32%, 0.63%) respectively, for 10 $\mu g/m^3$ increase in exposure, both significantly higher than the increase of 0.20% (0.07%, 0.34%) on medium temperature days. The effect of O_3 on cardiovascular mortality was strongest on high temperature days with pooled estimate of 1.63% (1.14%, 2.13%). No significant interactions between SO_2/NO_2 and temperature were detected by meta-analysis. Other pollutants were not analyzed due to the lack of suitable studies. In summary, we observed interactions between high temperature and PM_{10} and O_3 in the effects on non-accidental and cardiovascular mortality. Low temperature modified the effects of air pollutants but not in a consistent fashion: the effect of PM_{10} oncardiovascular mortality was diminished but the association between O_3 and non-accidental mortality was strengthened.

1. Introduction

Climate change, it has been suggested, is the biggest global health threat (Costello et al., 2009) and therefore tackling climate change could be the greatest global health opportunity of the 21st century (Watts et al., 2015). The average global mean surface temperature is expected to rise by a further 0.3 °C to 0.7 °C by 2035 (Stocker et al., 2013). The frequency of very hot days is projected to increase rapidly (Christidis et al., 2015). The health impacts of temperature extremes associated with global climate change is a relatively new topic within the field of environmental health (Myers et al., 2013). Typically, a “J”, “V” or “U” shaped relationship between temperature and daily mortality is observed, with increased mortality during both low and high temperature days (Kunst et al., 1993; Touloumi et al., 1994). Elevated temperature is associated with increased mortality risk for those dying from respiratory, cerebrovascular diseases and specific cardiovascular diseases, such as ischemic heart disease, congestive heart failure and myocardial infarction (Basu, 2009). Cold, on the other hand, is associated with increased non-accidental, cardiovascular, respiratory, and cerebrovascular deaths (Analitis et al., 2008).

With accelerated industrialization and urbanization, outdoor air pollution has become a worldwide environmental health problem that threatens people in both developed and developing countries. The most important air pollutants are particulate matter (PM), ozone (O_3), nitrogen oxides (NO_x), sulfur oxides (SO_x) and carbon monoxide (CO). At least one fourth of the world's population is exposed to unhealthy concentrations of ambient air pollutants (WHO, 2006). In 2014, the World Health Organization (WHO) declared air pollution as the world's single largest environmental health risk. Globally, pollution is linked to one in eight deaths (Organization, 2015). Both case-crossover and time series analyses have demonstrated that short-term exposure of air pollutants (PM_{10}, $PM_{2.5}$, O_3, SO_2, NO_2) is associated with adverse health outcomes including hypertension (Cai et al., 2016), raised pulse pressure and systolic blood pressure (Tsai et al., 2015), increased risk of hospitalizations for Parkinson's disease and diabetes (Zanobetti et al., 2014), and all-cause, respiratory (Filleul et al., 2001) and cardiovascular mortality (Bhaskaran et al., 2009) as well as deaths from specific diseases such as myocardial infarction (Mustafic et al., 2012), stroke (Yang et al., 2014), heart failure (Shah et al., 2013), and coronary heart disease (Li et al., 2015a, 2015b).

Traditionally, studies of health effects of air pollution have controlled for ambient temperature as a confounder, and vice versa. However, interest has grown recently in whether pollutants' effects on mortality are modified by temperature levels. The evidence so far is mixed. For example, a study in North America (Roberts, 2004) reported that PM_{10} has the largest effect on non-accidental mortality on hot days, whereas a study of Shanghai (Cheng and Kan, 2012) found only a statistically significant interaction between PM_{10} and extreme low temperatures for non-accidental mortality. In five Indian cities (Dholakia et al., 2014), there was no significant interaction effect between temperature and PM_{10} on non-external mortality. Given the heterogeneity in results of different studies, we have conducted a systematic review and meta-analysis with the aim of summarizing what is known about the influence of temperature on mortality related to air pollutants. If temperature does indeed multiply health risks due to air pollution, there may be significant implications for mitigation policies, adaptation measures and risk assessment.

2. Materials and methods

2.1. Literature search

We searched all studies on human subjects published in English up to the December 2nd 2014 using EMBASE, PubMed, ProQuest Dissertations and Theses, and Elsevier Science Direct database. The following search terms were used: “Temperature”, “weather”, “meteorology”, “heat”, “cold”, “season”, “pollution”, “ambient particulate matter”, “particulate matter”, “particles”, “sulfur dioxide”, “SO_2”, “nitrogen dioxide”, “NO_2”, “ozone”, “O_3”, “carbon monoxide”, “CO”, “PM_{10}”, “$PM_{2.5}$”, “modify”, “interaction”, “interactive”, “interact”, “mortality”, “death”, “deaths”, “health effect”, “health effects”. We also sought additional relevant articles from the references of studies identified in the search process. The full search strategy is included in Appendix I.

2.2. Inclusion criteria

We have included publications that:

1. Reported epidemiological studies on the interaction between daily outdoor air pollution and temperature on cause-specific mortality. Case reports, conference papers, and literature review were excluded.
2. Included measures of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, SO_2, NO_2 or CO and temperature (not season or weather patterns).
3. Specified mortality as an outcome (not morbidity, hospital admissions or emergency room visits).
4. Used outdoor ambient temperature and air quality (not indoor, occupational or accidental exposures).
5. Provided as measures of effect odds ratio (OR), relative risk (RR), the regression coefficients or percent change with their 95% confidence interval (CI) or standard error.
6. Examined the effect of specific air pollutants across strata of temperature.

2.3. Data extraction

After developing a data extraction form, two researchers (JL and JHG) independently extracted data from the literature guided by the agreed eligibility criteria. If necessary, disagreements were settled by consulting a third investigator (QYL). The following items were extracted: reference (the first author's name and years of publication), region and period, main method of analysis, cut-off points and thresholds, outcome variables and results, potential confounders, conclusion and relevant comments.

In order to quantify the influence of temperature on the association between air pollutants and mortality, temperatures were grouped into three categories: "low", "medium" and "high". This was done study by study, using the groupings that were reported on each occasion. If papers reported >3 levels, we defined the lowest layer as "low", the highest one as "high", others as "medium". For studies that reported two levels, we defined the lower one as "low", the other as "high". For multi-city studies, we used city-specific data where possible.

We did not attempt to set common specific cut-off points for the three temperature levels, since the range of exposures varied greatly between the studies. For example, the cut-off points for low and medium temperature level varied from −14 °C to 32.6 °C; and the cut-off points for medium and high temperature level varied from 17.6 °C to 37.9 °C.

2.4. Quality assessment

To our knowledge, no validated scales have been developed to gauge the quality of time-series and case-crossover studies. We drew on the New Castle Ottawa Scale, the Cochrane risk of bias tool and other instruments (Deeks et al., 2003; Higgins et al., 2011; Moher et al., 2000; Wells et al., 2000), as applied in previous studies (Mustafic et al., 2012; Yang et al., 2014).

We assessed studies on four aspects:

1. The quality of temperature and air pollution data (0–2 points):
   Studies with at least 75% of daily temperature and air pollution data available received two points;
   studies with at least 75% of either daily temperature or air pollution data available received one point;
   studies with fewer than 75% of daily temperature and air pollution data available received zero points.
2. The quality of mortality data (0–1 point):
   One point was assigned to studies with causes of mortality coded according to the International Classification of Disease, Revision 9 (ICD-9) or Revision 10 (ICD-10), whereas no points were given for studies that did not satisfy the above criterion.
3. Adjustments for potential confounders (0–3 points):
   Three points were given to studies that controlled for influenza epidemics, relative humidity/barometric pressure, day of week, holiday and time trend or seasonality;
   two points were given to studies that controlled for all of the above confounders except for influenza epidemics;
   one point was given to studies that only controlled for time trend or seasonality;
   no points were given to studies that did not control for any of the aforementioned confounder.
   Studies that obtained the full score for all three components were regarded as high quality, those that obtained a zero score in any of the three components were regarded as low-quality, while others were regarded as intermediate quality.

2.5. Meta-analysis

The most commonly used study design in assessing the effects of temperature and air pollution on mortality was time-series analysis. Case-crossover studies typically report their findings in the form of odds ratios (OR), which are broadly comparable to the relative risks (RR) generated by time-series analysis (Fung et al., 2003; Shah et al., 2013). Therefore, we used RR as the common effect measure, and expressed this as percentage change per 10 μg/m^3 increase in concentration of PM_{10}, $PM_{2.5}$, $PM_{10-2.5}$, O_3, SO_2, NO_2 or CO. We selected 10 μg/m^3 because this was the most frequently used increment in the literature. Most of the studies included used generalized additive models (GAM) based on a linear relationship between air pollutants and mortality (Li et al., 2014; Li et al., 2012; Qian et al., 2008), so we used the below formula to convert the study RR to a standardized RR with a 10 μg/m^{3}increment:

$$RR_{standardized} = e^{\left(\frac{10\ln RR_{origin}}{increment_{origin}}\right)}$$

where ln refers to the log to base e.

The combined RR in each temperature stratum was calculated from the inverse variance weighted average of RR from individual studies. The statistical significance of the effect estimates for low and high temperature strata compared to medium temperature was tested by calculating the 95% confidence interval (95% CI). The formula $(\widehat{Q_1}-\widehat{Q_2}) \pm 1.96\sqrt{(\widehat{SE_1})^2+(\widehat{SE_2})^2}$ was used, where $\widehat{Q_1}, \widehat{Q_2}$ were the estimates of the two categories, $\widehat{SE_1}, \widehat{SE_2}$were their respective standard errors (Zeka et al., 2006).

Many studies estimated the effect size of air pollutants on mortality in different temperature strata on various lag days. We chose the most commonly used lags in the selected studies, which were lags in day 0 and 1 (lag0, lag1 or lag0–1). When there was more than one article on the same population with the same research objectives, we chose the most recently published paper, unless there was an earlier, higher quality publication. For multi-city studies, the authors were contacted and the related estimates of individual city were requested. We focus on non-accidental and cardiovascular mortality as these were the cause of death categories most commonly reported.

2.6. Heterogeneity and publication bias

Heterogeneity between the studies was assessed using the I^2 statistic (Higgins et al., 2003). We estimated combined RRs and 95% CIs using a random effects model if I^2 was >50% or the p-value of heterogeneity was <0.05. Otherwise we used a fixed effects model. Funnel plots with Egger's test and Begg's test were used to identify publication bias (Begg and Mazumdar, 1994; Egger et al., 1997). Trim and fill methods were applied to adjust for publication bias (Mavridis and Salanti, 2014).

2.7. Sensitivity analysis

Sensitivity analyses were performed by combining multi- and single-city studies. We also tested the effects of combining studies with the same cut-off points [(P_{25}, P_{75}) or (P_5, P_{95})]of temperature and the same lag day (lag0–1). Further sensitivity analyses were conducted to estimate the effect sizes in different geographic locations (Europe, Asia). All statistical analyses were performed with STATA/SE 12.0. All tests were 2-sided and statistical significance was defined as $P < 0.05$.

3. Results

3.1. Study characteristics

After searching the electronic databases and subsequent references, we identified 1228 articles of which 29 met the inclusion criteria (Table 1). The steps in the search strategy are shown in Fig. 1

Twelve studies measured the influence of temperature on the association between PM_{10} and non-accidental mortality, ten studies examined PM_{10} and cardiovascular mortality. Nine studies reported the modification of pollutants' effects on non-accidental mortality by temperature levels, seven on cardiovascular mortality. The number of

Table 1
Summary of pooled effects of PM_{10}, O_3, SO_2 and NO_2 on cause-specific mortalities at different temperature strata (excess risk per 10 μg/m³).

	Number of studies	Number of effect estimates	% change in risk (95% CI) in mortality per 10 μg/m³	I^2 (p for heterogeneity)	Publication bias (P value) Begg's test	Publication bias (P value) Egger's test
PM_{10} and non-accidental						
Low	9	26	0.19 (−0.01, 0.40)	62.20% (0.00)	0.07	0.26
Normal	8	40	0.31 (0.21, 0.42)	42.10% (0.00)	0.32	0.32
High	9	26	0.78 (0.44, 1.11)[a]	78.40% (0.00)	0.88	0.01
High[c]		34	0.60 (0.30, 0.90)	–	–	–
PM_{10} and cardiovascular						
Low	7	19	0.17 (−0.01, 0.35)[a]	0.00% (0.79)	0.81	0.71
Normal	7	28	0.40 (0.31, 0.49)	8.00% (0.34)	0.51	0.60
High	7	19	1.28 (0.66, 1.91)[a]	71.20% (0.00)	0.70	0.07
O_3 and non-accidental						
Low	7	112	0.48 (0.28, 0.69)[a]	0.00% (0.72)	0.30	0.06
Normal	7	121	0.20 (0.07, 0.34)	5.00% (0.33)	1.00	0.40
High	7	112	0.47 (0.32, 0.63)[a]	3.00% (0.40)	0.21	0.04
High[c]		112	0.50 (0.30, 0.60)	–	–	–
O_3 and cardiovascular						
Low	6	108	0.59 (0.27, 0.92)[b]	0.00% (0.96)	0.43	0.01
Normal	6	117	0.27 (0.03, 0.51)	21.80% (0.02)	0.23	0.90
High	6	108	1.63 (1.14, 2.13)[a]	64.20% (0.00)	0.10	0.44
SO_2 and non-accidental						
Low	3	3	1.22 (0.80, 1.64)	16.00% (0.30)	0.60	0.70
Normal	3	3	1.05 (0.71, 1.40)	0.00% (0.79)	0.60	0.26
High	3	3	0.94 (0.29, 1.59)	0.00% (0.79)	0.12	0.56
SO_2 and cardiovascular						
Low	3	3	1.44 (0.83, 2.06)	56.90%(0.10)	0.60	0.49
Normal	3	3	1.28 (0.78, 1.79)	36.90%(0.03)	0.60	0.14
High	3	3	0.44 (−0.54, 1.42)	0.00%(0.63)	0.12	0.46
NO_2 and non-accidental						
Low	3	3	1.08 (0.67, 1.60)	60.10% (0.08)	0.60	0.79
Normal	3	3	1.07 (0.04, 2.12)	78.40% (0.01)	0.60	0.84
High	3	3	0.90 (0.39, 1.42)	26.40% (0.26)	0.60	1.00
NO_2 and cardiovascular						
Low	3	3	1.46 (0.87,2.06)	0.00% (0.91)	0.60	0.78
Normal	3	3	1.48 (0.98,1.98)	0.00% (0.59)	0.60	0.90
High	3	3	0.90 (0.13,1.68)	0.00% (0.65)	0.12	0.50

Note: All the effect estimates were evaluated at lag0, lag1 or lag0–1. Low: low temperature strata. Normal: normal temperature strata. High: high temperature strata.
[a] The difference was significant ($P < 0.05$) when comparing with the normal temperature days.
[b] The difference might be significant ($P < 0.10$) when comparing with the normal temperature days.
[c] The estimates adjusted through the trim and fill methods only when the *P* value of Egger's test or Begg's test were less than 0.05.

studies for NO_2, SO_2, $PM_{2.5}$, $PM_{10-2.5}$, CO and black smoke were three, four, two, one, one and two, respectively.

Of all the included studies, six studies were conducted in Europe (Carder et al., 2008; Pascal et al., 2014; Pascal et al., 2012; Pattenden et al., 2010; Sartor et al., 1995; Stafoggia et al., 2008); eleven were in Asia (ten of them were in China (Chen et al., 2013; Cheng and Kan, 2012; Li et al., 2011; Li et al., 2012; Li et al., 2015a, 2015b; Li et al., 2013; Lin and Liao, 2009; Liu et al., 2013; Meng et al., 2012; Qian et al., 2008), and one was in India (Dholakia et al., 2014)). Four studies were carried out in North America (Jhun et al., 2014; Ren et al., 2008a; Ren et al., 2009; Roberts, 2004), and one took place in Oceania (Ren and Tong, 2006) (Fig. 2). Eleven were multi-city studies (Carder et al., 2008; Dholakia et al., 2014; Jhun et al., 2014; Meng et al., 2012; Pascal et al., 2014; Pascal et al., 2012; Pattenden et al., 2010; Ren et al., 2008a; Ren et al., 2009; Roberts, 2004; Stafoggia et al., 2008), 11 were single city studies. Among the single city studies, 9 were carried out in China (Chen et al., 2013; Cheng and Kan, 2012; Li et al., 2011; Li et al., 2012; Li et al., 2015a, 2015b; Li et al., 2013; Lin and Liao, 2009; Liu et al., 2013; Qian et al., 2008), one was in Australia (Ren and Tong, 2006), and one was in Belgium (Sartor et al., 1995). Twenty-one studies were classified as high or intermediate quality according to the quality assessment scale (Appendix II).

3.2. The short term effects of PM_{10} on non-accidental and cardiovascular mortality in different temperature levels

Twelve studies investigated the effect of pollutants' effects on non-accidental mortality according to temperature levels. Five found a statistically significant interaction between high temperature and PM_{10} on non-accidental mortality (Li et al., 2012; Pascal et al., 2014; Qian et al., 2008; Ren and Tong, 2006; Roberts, 2004); five detected no statistically significant interaction (Dholakia et al., 2014; Li et al., 2014; Li et al., 2011; Lin and Liao, 2009; Stafoggia et al., 2008); one reported a significant interaction between low temperature and PM_{10} (Cheng and Kan, 2012). A study from China reported a statistically significant interaction between high temperature and PM_{10} in southern Chinese cities, but not in northern Chinese cities (Meng et al., 2012).

Ten studies examined PM_{10} and cardiovascular mortality using a temperature-stratified model (Cheng and Kan, 2012; Li et al., 2014; Li et al., 2011; Li et al., 2012; Lin and Liao, 2009; Meng et al., 2012; Pascal et al., 2014; Qian et al., 2008; Ren and Tong, 2006; Stafoggia et al., 2008). Four found a greater effect of PM_{10} on cardiovascular mortality on high temperature days (Li et al., 2011; Li et al., 2012; Qian et al., 2008; Ren and Tong, 2006); one only found this effect in cities in southern China (Meng et al., 2012); one reported a stronger PM_{10} effect on

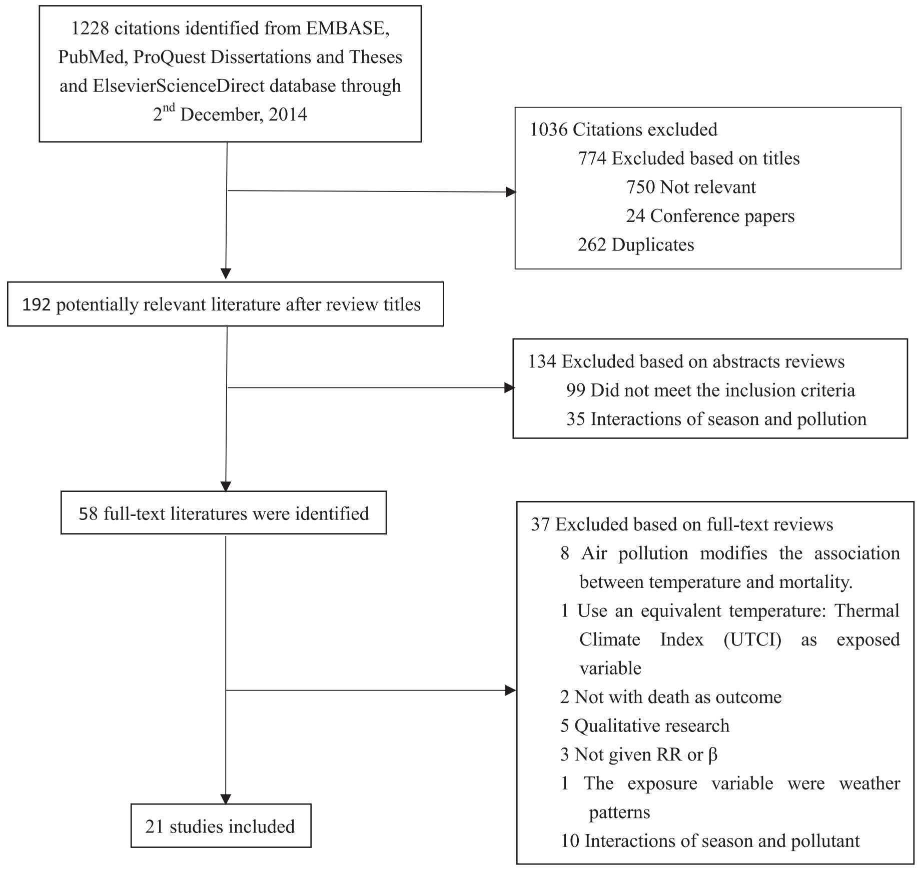

Fig. 1. Flow chart of literature search.

low temperature days only (Cheng and Kan, 2012) and four found no interaction (Li et al., 2014; Lin and Liao, 2009; Pascal et al., 2014; Stafoggia et al., 2008).

All the studies quantified interactive effects by dividing temperature into several levels, two in Wuhan, China (Meng et al., 2012; Qian et al., 2008), three in Tianjin, China (Li et al., 2011; Li et al., 2012; Meng et al., 2012), two in Guangzhou, China (Li et al., 2014; Meng et al., 2012), two in Shanghai, China (Cheng and Kan, 2012; Meng et al., 2012). To avoid over-representation, we selected the latest and highest quality publications from studies of the same city (Li et al., 2014; Li et al., 2012; Meng et al., 2012; Qian et al., 2008). Single city estimates could not be obtained from two multi-city studies (Pascal et al., 2014; Stafoggia et al., 2008). Finally, only nine studies met the inclusion criteria of the meta-analysis. Seven studies applied a single-pollutant model, the other two used two-pollutant or multi-pollutant models.

Table 1 shows the pooled effect estimates of PM_{10} on mortality in specified temperature strata. A 10 μg/m^3 increment in PM_{10} was associated with a 0.19% (−0.01%,0.40%), a 0.31% (0.21%,0.42%) and a 0.78% (0.44%,1.11%) increase in non-accidental mortality in low, normal and high temperature strata, respectively; the corresponding effect estimates in each stratum for cardiovascular mortality were 0.17% (−0.01%,0.35%), 0.40% (0.31%,0.49%) and1.28% (0.66%,1.91%). The PM_{10} effect on non-accidental mortality was greater on high temperature days than on normal temperature days ($P < 0.05$). The PM_{10} effect on cardiovascular mortality was stronger at both high and low temperatures than in the normal temperature stratum.

There was significant between-study heterogeneity in the effects of PM_{10} on non-accidental mortality at all temperature levels ($I^2 > 50\%$ or $P < 0.05$), whilst significant heterogeneity was only found for CVD in the high temperature stratum (see in Table 1).

We found evidence of potential publication bias only for studies of PM_{10} on non-accidental mortality in the high temperature stratum. The estimate adjusted according to the trim and fill methods was 0.60% (0.30%, 0.90%), which was similar to pre-adjusted result.

Similar trends were observed in the sensitivity analysis, when combining the estimates from multi-city studies with individual city results, and when grouping studies with the same lag day, the same geographic locations and the same cut-off points of temperature (P_{25}, P_{75} or P_5, P_{95}) (see in Table 2).

3.3. The short term effects of O_3 on non-accidental and cardiovascular mortality in different temperature levels

Of the nine studies that stratified the effect of ozone by temperature (Chen et al., 2013; Cheng and Kan, 2012; Jhun et al., 2014; Lin and Liao, 2009; Liu et al., 2013; Pascal et al., 2012; Pattenden et al., 2010; Qian et al., 2008; Ren et al., 2008a), two found a significant interaction between ozone and high temperature; two detected similar results only in some of the study cities but not others (Pattenden et al., 2010; Ren et al., 2008a); one found a negative association between non-accidental mortality rate and O_3 level on warm days (Lin and Liao, 2009); three found significant interaction between ozone and low temperature (Chen et al., 2013; Cheng and Kan, 2012; Liu et al., 2013); and one found no interaction between O_3 and temperature (Jhun et al., 2014).

An interaction between O_3 and high temperature acting on cardiovascular mortality was observed in only one of the seven studies that measured the effects of O_3 in strata of temperature (Qian et al., 2008). Two studies (Lin and Liao, 2009; Ren et al., 2009) reported a negative association between cardiovascular mortality rate and O_3 level on warm days. Cheng and Kan (2012) and Chen et al. (2013) detected statistically significantly interactive effects between O_3 and low temperature, whilst two other studies showed no interaction between O_3 and temperature. At last, only seven studies were included in the meta-analysis, and four

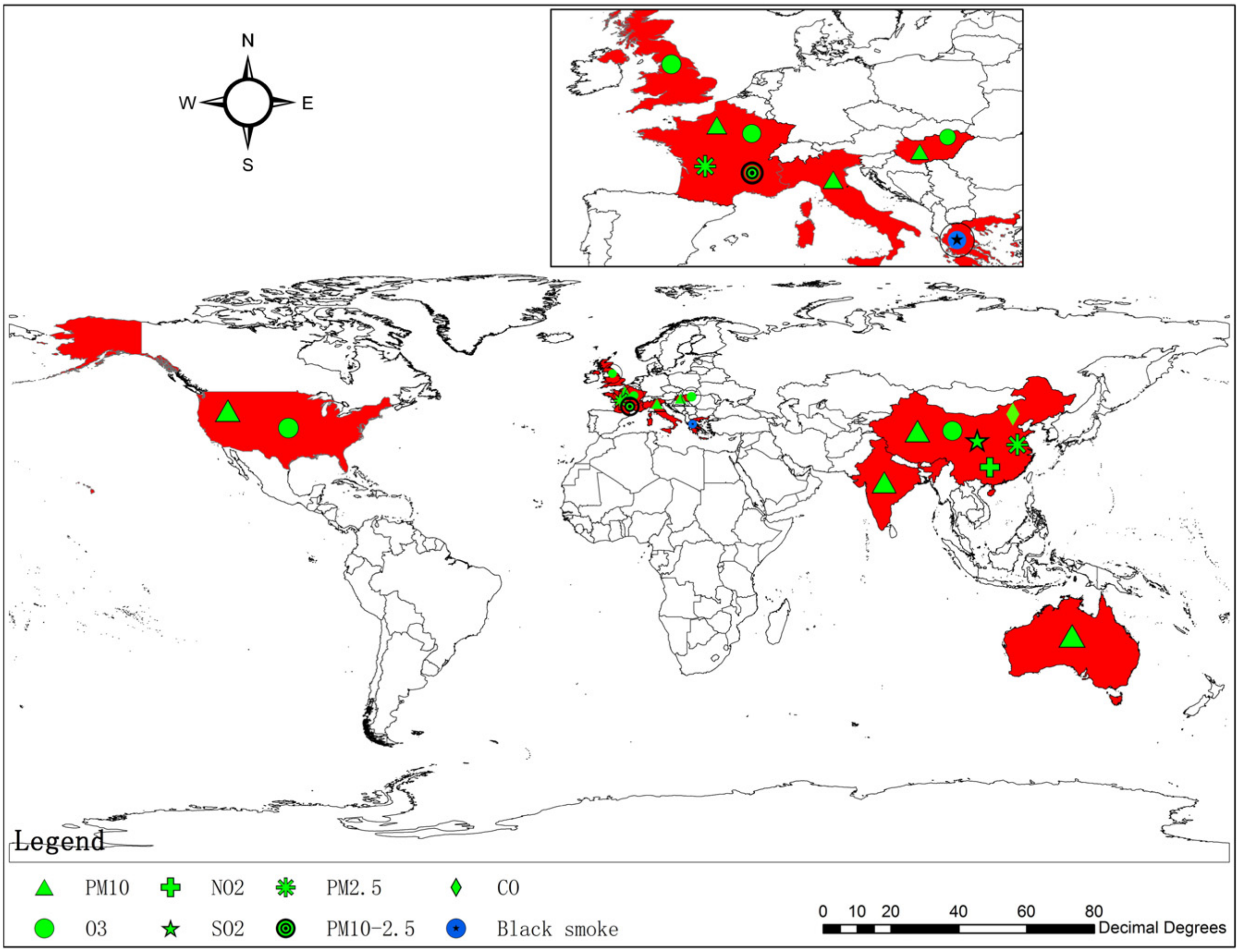

Fig. 2. The cities included in the systematic review and meta-analysis.

studies included used one-pollutant model, the next three used two-pollutant or multi-pollutant model. The combined results were in Table 1.

The meta-analysis found a statistically significant greater effect of O_3 on non-accidental mortality in both low and high temperature strata. The pooled results were 0.48% (0.28%, 0.69%) and 0.47% (0.32%, 0.63%) respectively. The pooled effect of O_3 on CVD was greatest on high temperature days (pooled estimate 1.63% (1.14%, 2.13%)) and significantly higher than on normal temperature days ($P < 0.05$) (see in Table 1).

Heterogeneity between studies was low, except for those that reported on CVD in the high temperature strata ($I^2 = 64.2\%$, $P = 0.000$). Egger's test for heterogeneity suggested possible publication bias of O_3 effect on non-accidental mortality at high temperature strata ($P = 0.036$), however the effect size did not change after adjusting with the trim and fill methods. Considering the studies in Asia alone, the O_3 effect on non-accidental mortality was higher on low but not high temperature days (see in Table 1).

The results of the sensitivity analysis showed similar trends and the interaction between O_3 and temperature on cardiovascular mortality was present in all but Asian cities (see in Table 2).

3.4. The short term effects of SO_2 on non-accidental and cardiovascular mortality in different temperature levels

Of the four studies (Cheng and Kan, 2012; Katsouyanni et al., 1993; Lin and Liao, 2009; Qian et al., 2008) on the interaction between SO_2 and temperature on mortality, one was deemed of low quality (Katsouyanni et al., 1993). One study found significant interaction between high temperature and SO_2 on non-accidental and cardiovascular mortality (Qian et al., 2008), whereas two found no such interaction.

The effects of SO_2 were highest in the low temperature stratum (non-accidental mortality: 1.22% (0.80%, 1.64%); cardiovascular: 1.44% (0.83%, 2.06%)), lower in the medium temperature stratum (non-accidental:1.05% (0.71%, 1.40%); cardiovascular: 1.28% (0.78%, 1.79%)), and the lowest in the high temperature stratum (non-accidental:0.94% (0.29%, 1.59%); cardiovascular: 0.44% (−0.54%, 1.42%)). However, overall no statistically significant interaction was detected (see in Table 1).

Heterogeneity among estimates was low, except for the estimates for SO_2 and cardiovascular mortality in the low temperature stratum ($I^2 = 56.9\%$, $P = 0.098$). Publication bias was not detected (see in Table 2).

3.5. The short term effects of NO_2 on non-accidental and cardiovascular mortality in different temperature levels

Three single city studies in China (Cheng and Kan, 2012; Lin and Liao, 2009; Qian et al., 2008) found no substantial variation in effects of NO_2 on non-accidental and cardiovascular mortality in different temperature strata. The combined estimates for non-accidental mortality based on meta-analysis were 1.08% (0.67%, 1.60%), 1.07% (0.04%, 2.12%) and 0.90% (0.39%, 1.42%) on low, normal, high temperature days, respectively, and for cardiovascular mortality, they were 1.46% (0.87%, 2.06%), 1.48% (0.98%, 1.98%) and 0.90% (0.13%, 1.68%) (see in Table 1).

Heterogeneity among studies ranged widely but was mostly low with the exception of the effects of NO_2 on non-accidental mortality

Table 2
Summary of pooled effects of PM_{10}/O_3 on non-accidental and cardiovascular mortality in different subgroups (sensitivity analysis).

	Number of studies	Number of effect estimates	% change in risk (95% CI) in mortality per 10 μg/m^3	I^2 (p for heterogeneity)	Publication bias (*P* value) Begg's test	Publication bias (*P* value) Egger's test
PM_{10} and non-accidental mortality						
Lag0–1						
Low	5	10	0.30 (0.09, 0.51)	63.60% (0.00)	0.70	0.61
Normal	5	12	0.39 (0.34, 0.45)	0.00% (0.50)	0.22	0.36
High	6	11	1.01 (0.64, 1.38)[a]	83.10% (0.00)	0.48	0.26
Asia						
Low	6	14	0.29 (0.07, 0.51)	77.10% (0.00)	0.87	0.01
Normal	5	10	0.30 (0.20, 0.40)	51.50% (0.00)	0.19	0.09
High	6	14	0.65 (0.30, 1.01)[b]	89.40% (0.00)	0.70	0.14
Europe						
Low	2	10	0.16 (−0.04, 0.36)[a]	6.20% (0.38)	0.87	0.01
Normal	2	19	1.28 (0.39, 2.17)	28.00% (0.13)	0.33	0.87
High	2	10	2.78 (2.01, 3.57)[a]	0.00% (0.91)	0.25	0.08
Cut-off points (P_{25}, P_{75})						
Low	5	17	0.05 (−0.16, 0.27)	27.70% (0.14)	0.32	0.63
Normal	6	33	0.26 (0.32, 0.49)	47.30% (0.00)	0.25	0.19
High	6	18	0.91 (0.40, 1.43)[a]	80.80% (0.00)	0.79	0.01
Cut-off points (P_5, P_{95})						
Low	3	8	0.32 (−0.02, 0.66)	73.00% (0.00)	0.81	0.83
Normal	3	8	0.40 (0.34, 0.46)	0.00% (0.84)	1.00	0.94
High	3	8	0.82 (0.39, 1.24)[b]	83.50% (0.00)	0.81	0.71
Combine the multi-city and single city results						
Low	10	27	0.20 (0.01, 0.38)	62.90% (0.00)	0.06	0.25
Normal	9	41	0.33 (0.22, 0.44)	45.90% (0.00)	0.32	0.60
High	10	27	0.88 (0.54, 1.22)[a]	84.90% (0.00)	0.92	0.01
High[c]		35	0.70 (0.40, 1.00)	0.000		
PM_{10} and cardiovascular mortality						
Lag0–1						
Low	5	17	0.17 (−0.01, 0.35)[a]	0.00% (0.82)	1.00	0.82
Normal	5	27	0.40 (0.31, 0.49)	11.20% (0.30)	0.48	0.51
High	5	17	1.21 (0.58, 1.83)[a]	72.60% (0.00)	0.68	0.41
Asia						
Low	5	9	0.18 (0.00, 0.36)[a]	0.00% (0.77)	0.68	0.92
Normal	5	10	0.40 (0.31, 0.49)	0.00% (0.95)	0.72	0.30
High	5	9	0.85 (0.65, 1.05)[a]	80.50% (0.00)	0.68	0.41
Cut-off points (P_{25}, P_{75})						
Low	4	12	0.03 (−0.26, 0.33)[a]	0.00% (0.47)	0.60	0.91
Normal	4	22	0.39 (0.22, 0.55)	19.40% (0.20)	0.55	0.46
High	4	12	2.64 (0.65, 4.66)[a]	48.80% (0.03)	0.58	0.08
Cut-off points (P_5, P_{95})						
Low	2	6	0.25 (0.02, 0.47)	0.00% (0.99)	0.57	0.90
Normal	2	6	0.41 (0.30, 0.51)	0.00% (0.66)	1.00	0.54
High	2	6	0.93 (0.17, 1.70)	85.3% (0.000)	0.573	0.606
Combine the multi-city and single city results						
Low	8	20	0.21 (0.05, 0.36)[a]	0.00% (0.80)	0.85	0.60
Normal	8	29	0.41 (0.32, 0.49)	16.50% (0.22)	0.46	0.37
High	8	20	1.41 (0.79, 2.03)[a]	72.10% (0.00)	0.66	0.25
O_3 and non-accidental mortality						
Asia						
Low	5	5	1.39 (0.90, 1.88)[a]	0.00% (0.68)	0.33	0.91
Normal	5	5	0.13 (−0.39, 0.65)	58.40% (0.05)	1.00	0.40
High	5	5	0.42 (−0.34, 1.18)	58.80% (0.05)	0.33	0.83
Combine the multi-city and single city results						
Low	7	112	0.48 (0.28, 0.69)[a]	0.00% (0.72)	0.30	0.06
Normal	8	122	0.20 (0.09, 0.32)	4.30% (0.35)	0.66	0.16
High	8	113	0.49 (0.35, 0.64)[a]	2.40% (0.41)	0.19	0.03
High[c]		113	0.49 (0.35, 0.64)[a]			
O_3 and cardiovascular mortality						
Asia						
Low	4	4	0.56 (−0.89, 2.03)	66.30% (0.03)	1.00	0.88
Normal	4	4	0.20 (−1.10, 1.51)	84.70% (0.00)	0.50	0.99
High	4	4	0.56 (−0.89, 2.03)	66.30% (0.03)	1.00	0.88
Combine the multi-city and single city results						
Low[&]	6	108	0.59 (0.27, 0.92)[b]	0.00% (0.96)	0.43	0.01
Normal	7	118	0.22 (0.02, 0.42)	21.50% (0.03)	0.24	0.83
High	7	109	1.62 (1.14, 2.10)[a]	65.20% (0.00)	0.09	0.99

Note: All the effect estimates were evaluated at lag0, lag1 or lag0–1. Low: low temperature strata. Normal: normal temperature strata. High: high temperature strata.
[a] The difference was significant ($P < 0.05$) when comparing with the normal temperature days.
[b] The difference might be significant ($P < 0.10$) when comparing with the normal temperature days.
[c] The estimates adjusted through the trim and fill methods only when the P value of Egger's test or Begg's test were less than 0.05.

($I^2 = 60.1\%$, $P = 0.082$; $I^2 = 78.4\%$, $P = 0.010$ respectively for low and normal temperature days) and the effects of NO_2 on respiratory mortality ($I^2 = 80.5\%$, $P = 0.024$). Evidence of publication bias was not observed (see in Table 2).

3.6. Other air pollutants

There were very few studies of the interactive effects of other air pollutants and temperature on mortality. Therefore, we did not conduct a meta-analysis in this area.

4. Discussion

Most of the publications included here were multi-city studies conducted in developed countries. The studies in developing countries were based mostly on single city studies. Our systematic review and meta-analysis found a statistically significant interaction between PM_{10} or O_3 and high temperature acting on non-accidental and CVD mortality. At low temperature, the effect of PM_{10} on cardiovascular mortality was reduced, whereas that of O_3 on non-accidental mortality was increased. The pooled effect sizes of PM_{10} or O_3 on mortality in each temperature strata differed between countries in Asia and in Europe. The meta-analysis found no interactive effects between SO_2 or NO_2 and extreme temperature on either non-accidental or cardiovascular mortality.

The mechanisms that explain a synergistic association between temperature and air pollutants on mortality are likely to be complex and are not yet clearly defined. However, there are several ways in which the two exposures may interact.

Personal exposure to air pollutants may be greater in warmer conditions because people tend to open windows more and go outdoors more (Michelozzi et al., 1998). This could lead to indoor levels of PM_{10}, O_3, SO_2 and NO_2 that were closer to the ambient air pollutant concentrations measured at monitoring sites. Also, the thermoregulatory system responds to heat stress by increasing sweating, minute ventilation and cardiac output, all of which tend to increase the uptake and distribution of air pollutants in the human body (Gordon, 2003).

There are several possible explanations for the combination between high temperature and PM_{10} acting specifically on non-accidental and cardiovascular mortality. The source and composition of PM may vary with ambient temperature with a greater fraction of more toxic forms of PM present at higher temperature (Analitis et al., 2014; Andrady et al., 2006; Peng et al., 2005). PM_{10} and high temperature may have synergistic effects because they act on common pathophysiological pathways. For example, PM is associated with systemic inflammation and increased risk of clotting by increasing blood levels of C-reactive protein (Bartoli et al., 2009; Peters et al., 2001a; Peters et al., 2001b) and fibrinogen (Huang et al., 2003) level. Heat may promote thrombosis through increasing blood viscosity and cholesterol levels secondary to dehydration and salt depletion (Bouchama and Knochel, 2002; McGeehin and Mirabelli, 2001). Similarly, the weaker effects of PM_{10} on cardiovascular mortality on low temperature days may result from slower physiological functions at lower temperature attenuating the toxicity of environmental pollutants (Gordon et al., 1988; Watkinson et al., 2003).

We found a non-monotonic effect of ozone with increasing temperature, that is, both extreme high and low temperature enhanced the effect of O_3 on non-accidental and cardiovascular mortality. It may be that residents were more susceptible to the effect of O_3 when they experienced a marked change in temperature (Noyes et al., 2009). Ozone causes inflammation of airways and increased permeability, and impairs host defense functioning (I., 1998; Paige and Plopper, 1999) making people more vulnerable perhaps to the stresses of temperature variability (Gordon, 2003).

We did not find interactions between SO_2 or NO_2 and low temperature acting on mortality, inconsistent with some other reports (Anderson et al., 1996; Bell et al., 2005; Bremner et al., 1999; Ito et al., 2005; Ostro et al., 1996). We note the small number of studies on SO_2 and NO_2 in our meta-analysis, and the wide confidence intervals for risk estimates.

4.1. Source of heterogeneity and possible bias

We observed substantial heterogeneity in the pooled effect sizes of PM_{10} and O_3 on mortality in each temperature stratum between different regions – especially between Asia and Europe. For example, on high temperature days, the effect size of PM_{10} on non-accidental mortality was 2.78% (2.01%, 3.57%) in Europe, nearly four times the PM_{10} effect seen in Asia, which was 0.65% (0.30%, 1.01%). There are several possible explanations. Firstly, there is great spatial variation in the chemical compositions of particulate matter (PM). PM is comprised of dust, pollens, soot and aerosols from combustion activities in the air, each element poses different degrees of threat to human health (Lambert et al., 1998), and the overall effect depends on the mix. Secondly, the use of heating systems and air-conditioning influences personal exposures and is likely to vary by city. For example, in China, residents living south of the line of Huai River and Qin Mountains near the latitude of 33° north do not have access to central heating in winter, while north of this line, central heating is provided (Yang et al., 2016). As a result, residents of northern Chinese cities may be exposed to cold temperatures less frequently than in those living in cities without well-heated homes, and the potential interactive effects between air pollution and low temperature may not be expressed. We note another study (Jhun et al., 2014) that reported the influence of high temperature on the relation between ozone and mortality is attenuated by high air-conditioning prevalence. Thirdly, climatic features of study cities differ in ways that may be relevant. Ren et al. (2009) conjectured that cities with high humidity, frequent precipitation and many cloudy days in summer generate less ozone, so that days with both high temperature and high ozone are few and far between, diluting the power to detect a significant interactive effect. High precipitation during high temperature days could also force residents to stay indoors thereby reducing their personal exposure to air pollutants during high temperature (Yang et al., 2012). Fourthly, latitude may be important. Individuals seem to be more vulnerable to higher temperatures in higher-latitude areas and to colder temperatures in lower-latitude areas (Analitis et al., 2008; Baccini et al., 2008; Bai et al., 2014; Yu et al., 2012) reflecting increased susceptibility to less common environments. It is well-known that the threshold for adverse effects of heat is higher in residents accustomed to high temperature (Hajat and Kosatky, 2010; Yu et al., 2012). In a similar vein, populations in regions with high levels of ozone and high temperature seem to be less sensitive to day-to-day variations in ozone concentration and temperature (Ren et al., 2009) due possibly to physiological adaptation (Folinsbee et al., 1994).

4.2. Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis examining the modification of the effects of air pollutants on acute non-accidental and cardiovascular mortality by temperature. We managed the difficulties of combining single and multi-city study results by obtaining the single city results from authors of multi-city studies. The cut-off points defining low-, medium-, and high-level temperature varied widely from study to study. However our use of study-specific cut points acknowledges the fact that populations tend to adapt to local conditions, and optimal temperatures for health differ depending on the prevailing climate. Most of the studies were sited in urban areas, so caution is required when generalizing the results to other settings. The studies included in this report were all ecologic in design. This means there may be misclassification of personal exposures to air pollution and temperatures, and no account can be taken of potential individual-level confounders such as smoking habits, social-economic status and preexisting health conditions. This study did not include eligible articles in languages other than English.

4.3. Implications

The findings of this systematic review and meta-analysis bring several important implications. Early warning systems should highlight extremely hot or cold days that are also heavily polluted and encourage adaptive and preventive measures to avoid exposures to both air pollution and extreme temperature. The interaction between temperature and air pollution should also be taken into account in health risk assessments, such as estimates of the health burden attributable to climate change. We note that climate change will lead not only to higher temperature and more frequent extremes of temperature but may also intensify air pollution in some regions. For all these reasons, policymakers should be encouraged to take actions to mitigate both air pollution and extreme temperature from climate change since the two have common sources, particularly the combustion of fossil fuels.

4.4. Research needs

Further research is needed to identify subgroups most vulnerable to interactive effects as defined by sex, age, occupation, social economic status, etc. It would be also valuable to look into variations in the interactive effects on different lag days and in different climatic zones. In our view, there should be a stronger focus on $PM_{2.5}$, $PM_{10-2.5}$ and CO, since these pollutants are particularly damaging for health but few studies have investigated interactions with temperature. In addition, it is important to verify whether interactive effects between O_3 and low temperature exist and which causes of mortality could be affected. We believe that there would be value in exploring the use of alternative exposure metrics that are more representative of personal exposure, and it would worthwhile also to examine the mechanisms which lie behind this interaction, such as window opening behaviors and pathophysiological pathways.

5. Conclusions

This systematic review and meta-analysis of 21 studies on the modification of pollutants' effects on mortality by temperature levels found a statistically significant interactive effect between temperature and levels of PM_{10} and O_3 acting on both non-accidental and cardiovascular mortality. Extreme high temperature significantly increased the effect of PM_{10} and O_3 on non-accidental and cardiovascular mortality, whereas the effect of PM_{10} on cardiovascular mortality was decreased during low temperature days. Our meta-analysis also found a significant synergistic effect between low temperature and O_3 acting on non-accidental mortality. We did not observe an interaction between SO_2 and NO_2 with either high or low temperature and this may be due to the small number of studies on these pollutants. Further research is needed to better understand the interactive effects between temperature and $PM_{2.5}$, $PM_{10-2.5}$ and CO, and to investigate different exposure lags and vulnerable populations.

Abbreviations

PM	particulate matter
NO_2	nitrogen dioxide
SO_2	sulfur dioxide
O_3	ozone
$PM_{2.5}$	particles smaller than 2.5 μm
PM_{10}	particles smaller than 10 μm
$PM_{10-2.5}$	particles between 2.5 μm and 10 μm
CO	carbon monoxide
CI	confidence interval
SE	standard error
OR	odds ratio
RR	relative risk
ICD-9	International Classification of Disease, Revision 9
ICD-10	International Classification of Disease, Revision 10
GAM	generalized additive model
CVD	cardiovascular mortality
VOCs	volatile organic compounds

Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

JL and JY defined the standard of stratifying the temperature into three levels. JL and JHG abstracted data from the articles. JY organized panel discussions to settle disagreement. JL wrote the manuscript. RQ helped to send emails to obtain single city results and to modify the first draft of the paper. AJW made substantial contributions to design and interpretation of data, and drafted the paper. XYH, TZ, JLZ, HB, JL, SHG, LX and XBL gave important comments, read and approved the final manuscript.

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Appendix I. The search strategies used in our literature review

The search strategy of Pubmed:

((((((((temperature[Title/Abstract]) OR weather[Title/Abstract]) OR meteorolog*[Title/Abstract]) OR heat[Title/Abstract]) OR cold[Title/Abstract]) OR season[Title/Abstract])) AND (((((((((((((pollution[Title/Abstract]) OR "ambient particulate matter"[Title/Abstract]) OR "particulate matter" [Title/Abstract]) OR particles[Title/Abstract]) OR "sulfur dioxide"[Title/Abstract]) OR "SO2"[Title/Abstract]) OR "nitrogen dioxide"[Title/Abstract]) OR "NO2"[Title/Abstract]) OR "ozone"[Title/Abstract]) OR "O3"[Title/Abstract]) OR "carbon monoxide"[Title/Abstract]) OR "CO"[Title/Abstract]) OR "PM10"[Title/Abstract]) OR "PM2.5"[Title/Abstract])) AND ((modif*[Title/Abstract]) OR interact*[Title/Abstract])) AND (((mortality[Title/Abstract]) OR death*
[Title/Abstract])OR "health effect*"[Title/Abstract]).

The search strategy of **Elsevier Science Direct**:

tak((temperature OR weather OR heat OR cold OR meteorolog* OR season) AND (pollution OR {ambient particulate matter} OR particle OR {particulate matter} OR { sulfur dioxide } OR { nitrogen dioxide } OR { ozone } OR { carbon monoxide } OR {SO2} OR {NO2} OR {O3} OR {CO} OR {PM10} OR {PM2.5}) AND (modif* OR interact* OR influence) AND ({health effects} OR {health effect} OR death* OR mortality))

The search strategy of ProQuest Dissertations and Theses ((ti(pollution) OR ti((“ambient particulate matter” OR “particulate matter”)) OR ti((particle OR “sulfur dioxide”)) OR ti((“nitrogen dioxide” OR ozone)) OR ti((“carbon monoxide” OR SO2)) OR ti((NO2 OR O3)) OR ti((CO OR PM2.5)) OR ti(PM10)) OR (ab(pollution) OR ab((“ambient particulate matter” OR “particulate matter”)) OR ab((particle OR “sulfur dioxide”)) OR ab((“nitrogen dioxide” OR ozone)) OR ab((“carbon monoxide” OR SO2)) OR ab((NO2 OR O3)) OR ab((CO OR PM2.5)) OR ab(PM10))) AND (ti(temperature) OR ti((weather OR season)) OR ti((cold OR heat)) OR ti(meteorology*) OR ab((temperature OR weather)) OR ab((season OR cold)) OR ab((heat OR meteorology*))) AND (ti(modify*) OR ti(interact*) OR ab((interact* OR modify*))) AND (ti(death*) OR ti((mortality OR “health effect*”)) OR ab((“health effect*” OR = mortality)) OR ab(death*))

Appendix Table 1
EMBASE search strategy

Search strategy no.	Search terms
#1	Season*:ab,ti AND [humans]/lim
#2	‘cold’/exp. OR cold: ab,ti AND [humans]/lim
#3	‘heat’/exp. OR heat: ab,ti AND [humans]/lim
#4	‘meteorology’/exp. OR meteorology: ab,ti AND [humans]/lim
#5	‘weather’/exp. OR weather: ab,ti AND [humans]/lim
#6	‘temperature’/exp. OR temperature: ab,ti AND [humans]/lim
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
#8	‘pollution’/exp. OR ‘pollution’: ab,ti AND [humans]/lim
#9	‘ambient particulate matter’: ab,ti AND [humans]/lim
#10	‘particulate matter’: ab,ti AND [humans]/lim
#11	particle* OR particle*: ab,ti AND [humans]/lim
#12	‘sulfur dioxide’: ab,ti AND [humans]/lim
#13	‘nitrogen dioxide’: ab,ti AND [humans]/lim
#14	‘ozone’: ab,ti AND [humans]/lim
#15	‘carbon monoxide’: ab,ti AND [humans]/lim
#16	‘pm10’: ab,ti AND [humans]/lim
#17	‘pm2.5’: ab,ti AND [humans]/lim
#18	‘so2’: ab,ti AND [humans]/lim
#19	‘no2’: ab,ti AND [humans]/lim
#20	‘o3’: ab,ti AND [humans]/lim
#21	‘co’: ab,ti AND [humans]/lim
#22	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	modif* OR modif*: ab,ti AND [humans]/lim
#24	interact* OR interact*: ab,ti AND [humans]/lim
#25	‘influence’ OR influence: ab,ti AND [humans]/lim
#26	#23 OR #24 OR #25
#27	‘death’/exp. OR death: ab,ti AND [humans]/lim
#28	‘mortality’/exp. OR mortality: ab,ti AND [humans]/lim
#29	‘health effects’ OR health AND effect: ab,ti AND [humans]/lim
#30	#27 R #28 R #29
#31	#7 AND #22 AND #30

Appendix II. Details of studies included in this article

Reference	Region and period	Methods	Cut-off points and threshold	Outcome	Potential confounder included	Conclusion	Comments
PM_{10}							
Roberts (2004)	Cook County and Allegheny County, America/1987–1994	GAM GLM	Stratified by temperature 10th (NA),90th (NA)	Non-accidental mortality	Long-term trend, DOW, dew point temperature	There is an interaction between PM_{10} and temperature. PM_{10} has the largest effect on mortality on hot days.	The results were less sensitive to the estimation method used-GAM or GLM.
Pascal et al. (2014)	Nine French urban areas: Bordeaux, Le Havre, Lille, Lyon, Marseille, Paris, Rouen, Strasbourg and Toulouse/2000–2006	GAM	Stratified by temperature, warm days: 97.5th (NA)	Non accidental, CVD, cardiac, IHD, cerebrovascular, and respiratory mortality	Long-term and seasonal trends, DOW, holiday	There is a significant interaction between warm days and PM_{10}	August 2003 was excluded from the analysis, due to the very unusual mortality during the heat wave.
Li et al. (2013)	Tianjin (11 urban and suburban districts), China/2006–2009	GAM	Stratified by temperature 25th (NA), 50th (NA), 75th (NA)	Non-accidental, CVD, respiratory, cardiopulmonary, IHD and stroke mortality	Days of calendar time, DOW, relative humidity, holidays	Temperature modify the adverse effect of PM_{10} and the effects of PM_{10} on causes specific mortalities were strongest for high temperature days.	Influenza (J09–11) was excluded from respiratory diseases.
Li et al. (2014)	Guangzhou (8 districts), China/2005–2009	GA	Stratified by temperature 5th (NA), 95th (NA)	Non-accidental, CVD, respiratory, and cardiopulmonary mortality	Days of calendar time, DOW, relative humidity, holidays	High temperature enhanced the effect of PM10 on non-accidental and CVD mortality, while the interactive effects were	Influenza (J09–11) was excluded from respiratory diseases. The effects of PM_{10} on mortality decreased after adding SO_2 and

(continued on next page)

Appendix II *(continued)*

Reference	Region and period	Methods	Cut-off points and threshold	Outcome	Potential confounder included	Conclusion	Comments
						not statistically significant.	NO_2 into the model
Ren and Tong (2006)	Brisbane, Australia/1996–2001	GAM	Stratified by maximum temperature 50th (25.25 °C)	Non-accidental and CVD mortality	Seasonality, DOW, influenza, rainfall, relative humidity, O_3 and NO_2	There existed a statistically significantly interaction between PM_{10} and temperature on mortality at various lags. PM_{10} exhibited more adverse health effects on warm days than cold days.	
Li et al. (2011)	Tianjin, China/2007–2009	GAM	Stratified by temperature; based on dose-response relationship (20 °C)	Non-accidental, CVD, respiratory, cardiopulmonary, stroke and IHD mortality	Seasonal, DOW, relative humidity, holidays	PM_{10} effects were stronger on high temperature level days. The interactions between PM_{10} and temperature were statistically significant on CVD, cardiopulmonary, and IHD mortalities	In two-pollutant models, the interaction effects between PM_{10} and temperature on mortality did not alter much after adding SO_2; however, when adding NO_2, the effects on non-accidental mortality became significant.
Meng et al. (2012)	Eight Chinese cities include Guangzhou/2007–2008; Hangzhou/2002–2004; Shanghai/2001–2008; Shenyang, Suzhou, Tianjin/2005–2008; Taiyuan/2004–2008; Wuhan/2003–2005	GAM	Stratified by temperature Guangzhou (5th:11.7 °C, 95th:31.2 °C); Hangzhou (4.2, 30.7 °C); Shanghai (4 °C,30.7 °C); Shenyang (−14 °C, 25 °C); Suzhou (2 °C, 30.2 °C); Taiyuan (−6.1 °C, 26.1 °C); Tianjin (−4.3 °C, 28.3 °C); Wuhan (2.7 °C,31.9 °C)	Non-accidental, CVD and respiratory mortality	Time trend, DOW, humidity	Extreme high temperature significantly increased the associations of PM_{10} with non-external and CVD mortality. The effect was statistically significant in southern Chinese cities, but not in northern Chinese cities.	This study used a GAM with thin-plate spline to fit a response surface model without assuming linearity.
Cheng and Kan (2011)	Shanghai (9 urban districts), China/2001–2004	GAM	Stratified by temperature 15th (NA), 85th (NA)	Non-accidental, CVD and respiratory mortality	time trend, DOW, humidity	We found a statistically significant interaction between PM_{10} and extreme low temperatures for both total non- accidental and cause-specific mortality.	–
Stafoggia et al. (2008)	Nine Italian cities/1997–2004	Case crossover design	Stratified by temperature. Bologna (50th: 13 °C, 75th: 22 °C); Florence (15 °C, 22 °C); Mestre (15 °C, 24 °C); Milan (13 °C, 22 °C); Palermo (18 °C, 26 °C); Pisa (14 °C, 22 °C); Rome (16 °C, 23 °C); Taranto (16 °C,23 °C); Turin (11 °C, 20 °C)	Non-accidental, CVD, respiratory and other causes of death	Population, DOW, holidays, pressure, influenza epidemics	Analysis of the interaction between PM_{10} and temperature within temperature strata resulted in positive but, in most cases, no statistically significant coefficients. The authors found much higher PM_{10} effects on mortality during warmer days.	Influenza epidemics (defined as the annual 3-week period of maximum incidence of flulike illness based on estimates of weekly influenza incidence, as reported by the Italian National Health Service).
Qian et al. (2008)	Wuhan, China/2000.7.1–2004.6.30	GAM	Stratified by temperature 5th (3.6 °C), 95th (31.7 °C)	Non-accidental, CVD, stroke, cardiac, respiratory and cardiopulmonary mortality	Relative humidity, time trend, DOW, seasonal and extreme weather indicators	There were synergistic effects of PM_{10} and high temperatures on daily non-accidental, cardiovascular, and cardiopulmonary mortality.	We added a factor variable for the three periods [sum03 (28 July–3 August 2003), win03 (1 December–31 December 2003), and others] ns methods were parametric-based regression splines.
Lin and Liao (2009)	Taiwan (Kaohsiung), China/1995–1999	GAM, the geographic information system and mapping software	stratified by temperature 25th (19.7 °C), 50th (24.8 °C), 75th (27.6 °C)	Non-accidental and CVD mortality	Relative humidity, time trend	No significant interaction effect between temperature and PM_{10}	Subjects who resided in districts over 4 km (km) from the nearest air quality monitoring stations were excluded
Dholakia et al. (2014)	Five Indian cities (Ahmedabad, Bangalore, Hyderabad, Mumbai,	Poisson regression models	Stratified by temperature, Ahmedabad (25th:	Total death	Time trend, DOW, humidity,	No significant interaction effect between temperature	Put "βPM10i, j-1" and "αTij*PM10ij" in the same model may cause

Appendix II *(continued)*

Reference	Region and period	Methods	Cut-off points and threshold	Outcome	Potential confounder included	Conclusion	Comments
	Shimla)/2005–2012		31 °C, 50th: 34 °C, 75th: 37.2 °C); Bangalore (27.5 °C, 29.3 °C, 30.7 °C); Hyderabad (30.7 °C, 33.1 °C, 35.9 °C); Mumbai (30.8 °C, 32.5 °C, 34 °C); Shimla (17 °C, 21 °C, 23.4 °C)		holiday	and pollution on mortality was observed	collinearity.
O_3							
Cheng et al. (2011)	Shanghai (9 urban districts), China/2001–2004	GAM	Stratified by temperature 15th (NA), 85th (NA)	Non-accidental, CVD and respiratory mortality	Time trend, DOW, humidity	We found a statistically significant interaction between O_3 and extreme low temperatures for both total non-accidental and cause-specific mortality.	It used a GAM to fit a response surface model without assuming linearity.
Liu et al. (2013)	Guangzhou (YueXiu and Li Wan), China/2006–2008	DLM GAM	Stratified by temperature 25th (18.6 °C), 75th (27.7 °C)	Non-accidental mortality	Time trend, DOW, humidity, SO_2, NO_2, PM_{10}	There is significant interaction between low temperature and ozone. The lower temperature, the higher the risk of ozone concentration on total non-accidental mortality.	The cubic regression spline function is used to fit the nonlinear relationship between temperature and ozone.
Qian et al. (2008)	Wuhan, China/2000–2004	GAM	Stratified by temperature 25th (NA), 75th (NA)	Non-accidental, CVD, stroke, cardiac, respiratory and cardiopulmonary mortality	Relative humidity, time trend, DOW and extreme weather indicators	There was statistically significant interaction between O_3 and extreme high temperature on non-accidental mortality.	We added a factor variable for the three periods [sum03 (28 July–3 August 2003), win03 (1 December–31 December 2003), and others] ns methods were parametric-based regression splines.
Jhun et al. (2014)	97 communities in US/1987–2000 (May to September)	GLM	Stratified by temperature 25th, 75th	Non-accidental deaths	Long-term patterns and seasonality, DOW, dew point temperature	The interaction between ozone and temperature was not statistically significant.	At the high temperature category, the air conditioning prevalence mitigated mortality risk associated with ozone exposure.
Ren et al. (2009)	95 large US cities/1987–2000 (May to September)	GAM, GLM, Bayesian meta-analyses	Stratified by temperature 33.3th (NA), 66.7th (NA)	CVD mortality	Long-term patterns and seasonality, DOW, dew point temperature, age	Temperature modified effects of ozone, particularly in the northern regions.	Excluding 10% extreme mean value of ozone to reduce the influence of outliers.
Lin and Liao (2009)	Kaohsiung, Taiwan, China/1995–1999	GAM, The geographic information system and mapping software	Stratified by temperature. 25th (mean temperature: 19.7 °C), 50th (24.8 °C), 75th (27.6 °C)	Non-accidental and CVD mortality	Relative humidity, time trend	A negative association between mortality rate and O_3 level on warm days.	Subjects who resided in districts over 4 km (km) from the nearest air quality monitoring stations were excluded.
Pattenden et al. (2010)	Fifteen conurbations in England and Wales (5–9, 1993–2003).	GLM	Stratified by temperature, 'hot' days: ≥95th of all 0–1 daily mean temperature (17.6 °C–19.9 °C)	Non-accidental, respiratory and CVD mortality	Seasonal, long-term time trends, PM_{10}, DOW, holiday	On daily mean temperature ozone-heat interaction was significant in London only. On substituting maximum for mean temperature, the overall ozone effect reduced to null	'Hot days' were defined as days on which the 2-day average temperature exceeded the 95th percentile of all 2-day averages.
Ren et al. (2008a, 2008b)	34 communities in the northeast of US and 26 in the southeast of US/1987–2000 (April 1st and October 31st)	GAM	Stratified by temperature 25th (NA), 75th (NA)	Non-accidental mortality.	Seasonal, long-term trends, DOW, dew point temperature	Temperature synergistically modified the ozone-mortality association in the northeast region, but not in the southeast region.	A two-stage hierarchical model was used to estimate the ozone effects on mortality across temperature levels and the regions.
Pascal et al. (2012)	French (Bordeaux, Le Havre, Lille, Lyon,	Time stratified case-crossover	stratified by temperature, 25th (NA),	Non-accidental, CVD, cardia,	DOW, month	Associations between ozone and	Temperature at lag 0 was not included

(continued on next page)

Appendix II *(continued)*

Reference	Region and period	Methods	Cut-off points and threshold	Outcome	Potential confounder included	Conclusion	Comments
	Marseille, Paris, Rouen, Strasbourg and Toulouse)/1998–2006	model	50th (NA), 75th (NA)	cerebrovascular, IHD and respiratory mortality		non-accidental, cardiac and cardiovascular mortality were stronger in the warmest temperature strata	
Chen et al. (2013)	Suzhou/2008–2009	GAM	Stratified by temperature, 25th (8.75 °C), 75th (25.0 °C)	Non-accidental and CVD mortality	Time trend, DOW, humidity	O_3 effects were stronger in cold season and low temperature days.	The 1-h maximum, the maximum 8-h average, and the 24-h average O_3 concentrations were used.
SO_2							
Cheng et al. (2011)	Shanghai (9 urban districts), China/2001–2004	GAM	stratified by temperature: 15th (NA), 85th (NA)	Non-accidental, CVD and respiratory mortality	Time trend, DOW, humidity	There is no interaction between SO_2 and temperatures for mortality.	It used a GAM to fit a response surface model without assuming linearity.
Qian et al. (2008)	Wuhan, China/2000–2004	GAM	Stratified by temperature 5th (3.6 °C); 95th (31.7 °C)	Non-accidental, CVD, stroke, cardiac, respiratory and cardiopulmonary mortality	Relative humidity, time trend, DOW, and extreme weather indicators	There was no statistically significant interaction between SO_2 and temperature on mortality.	We added a factor variable for the three periods [sum03 (28 July–3 August 2003), win03 (1 December–31 December 2003), and others] ns methods were parametric-based regression splines.
Lin and Liao (2009)	Kaohsiung, Taiwan/1995–1999	GAM, The geographic information system and mapping software	Stratified by temperature. 25th (19.7 °C), 50th (24.8 °C), 75th (27.6 °C).	Non-accidental and CVD mortality	Relative humidity, time trend	There is no interaction between SO_2 and temperatures for mortality.	Subjects who resided in districts over 4 km (km) from the nearest air quality monitoring stations were excluded.
Katsouyanni et al. (1993)	Athens, Greece/1983–1987 in summer (March 22to September 21)	Multiple linear regression equation	High SO2: ≥80 μg/m^3, high temperature: ≥ 30 °C, medium temperature: ≥25 °C and <30 °C	Total mortality	DOW, month, long term trends, holiday and humidity	The interaction between high levels of SO_2 and high temperature are statistically significant ($P < 0.05$).	The discomfort index (DI) is based on the air temperature measured by dry (Td) and wet (Tw) thermometers. DI = 0.4 (Td + Tw) + 4.8.
NO_2							
Cheng et al. (2011)	Shanghai (9 urban districts), China/2001–2004	GAM	Stratified by temperature 15th (NA), 85th (NA)	Non-accidental, CVD and respiratory mortality	Time trend, DOW, humidity	There is no interaction between NO_2 and temperatures for mortality.	It used a GAM to fit a response surface model without assuming linearity.
Qian et al. (2008)	Wuhan/2000–2004	GAM	Stratified by temperature 5th (3.6 °C); 95th (31.7 °C)	Non-accidental, CVD, stroke, cardiac, respiratory and cardiopulmonary mortality	Relative humidity, time trend, DOW, and extreme weather indicators	There is no interaction between NO_2 and temperatures for mortality.	We added a factor variable for the three periods [sum03 (28 July–3 August 2003), win03 (1 December–31 December 2003), and others] ns methods were parametric-based regression splines.
Lin and Liao (2009)	Kaohsiung, Taiwan/1995–1999	GAM, The geographic information system and mapping software	Stratified by temperature. 25th (19.7 °C), 50th (24.8 °C), 75th (27.6 °C)	Non-accidental, and CVD mortality	Relative humidity, time trend	There is no interaction between NO_2 and temperatures for mortality.	Subjects who resided in districts over 4 km (km) from the nearest air quality monitoring stations were excluded
$PM_{2.5}$							
Li et al. (2013)	Beijing, China/2004–2009	GAM	Stratified by temperature (5th, 10th, 15th, 20th, 25th, 30th, 35th, 40th, 45th percentile) at the lag of 3 days	Respiratory mortality	Time trend, season, holiday, relative humidity, DOW	We found that extremely low temperature elevated the mortality risk of $PM_{2.5}$ remarkably.	
Pascal et al. (2014)	Nine French urban areas: Bordeaux, Le Havre, Lille, Lyon, Marseille, Paris, Rouen, Strasbourg and Toulouse/2000–2006	GAM	Stratified by temperature, warm days: 97.5th (NA)	Non accidental, CVD, cardiac, IHD, cerebrovascular, and respiratory mortality	Long-term and seasonal trends, DOW, holiday	$PM_{2.5}$ have larger impacts on mortality during extreme temperature episodes	August 2003 was excluded from the analysis, due to the very unusual mortality during the heat wave.
$PM_{10-2.5}$							
Pascal et al. (2014)	Nine French urban areas: Bordeaux, Le Havre, Lille,	GAM	Stratified by temperature, warm	Non-accidental, CVD, cardiac, IHD,	Long-term and seasonal	$PM_{10-2.5}$ have larger impacts on mortality	August 2003 was excluded from the

Appendix II *(continued)*

Reference	Region and period	Methods	Cut-off points and threshold	Outcome	Potential confounder included	Conclusion	Comments
	Lyon, Marseille, Paris, Rouen, Strasbourg and Toulouse/2000–2006		days: 97.5th (NA)	cerebrovascular, and respiratory mortality	trends, DOW and holiday	during extreme temperature episodes.	analysis, due to the very unusual mortality during the heat wave.
CO							
Lin and Liao (2009)	Kaohsiung, Taiwan, China/1995–1999	GAM, The geographic information system and mapping software	Stratified by temperature. 25th (19.7 °C), 50th (24.8 °C), 75th (27.6 °C)	Non-accidental and CVD mortality	Relative humidity, time trend	A statistically significant interaction between CO and temperature, with non-accidental mortality increasing with a warm climate and cardiovascular mortality increasing with a cold climate.	Subjects who resided in districts over 4 km (km) from the nearest air quality monitoring stations were excluded.
Black smoke							
Carder et al. (2008)	Three largest Scottish cities (Glasgow, Edinburgh, Aberdeen)/1981–2001	GLMs	Five-range temperature model (≤1 °C, 1–6 °C, 6–11 °C, 11–16 °C, ≥ 16 °C)	Non-accidental, CVD, respiratory and non-cardiorespiratory mortality	Time trend and DOW	For all-cause and non-cardiorespiratory mortality there was a suggestion for interaction between temperature and black smoke.	
Katsouyanni et al. (1993)	Athens, Greece/1983–1987 (March 22 to September 21)	Multiple linear regression equation	High black smoke: ≥ 125 μg/m^3, high temperature: ≥30 °C, medium temperature: ≥ 25 °C and <30 °C	Total mortality	DOW, month, long term trends, holiday, and Humidity	The interaction between high levels of black smoke and high temperature are suggestive ($P < 0.20$).	The discomfort index (DI) is based on the air temperature measured by dry (Td) and wet (Tw) thermometers. DI = 0.4 (Td + Tw) + 4.8.

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