Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas

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Abstract

Background: Although epidemiological studies have reported associations between mortality and both ambient air pollution and air temperature, it remains uncertain whether the mortality effects of air pollution are modified by temperature and vice versa. Moreover, little is known on the interactions between ultrafine particles (diameter ≤ 100 nm, UFP) and temperature.

Objective: We investigated whether the short-term associations of particle number concentration (PNC in the ultrafine range (≤ 100 nm) or total PNC ≤3000 nm, as a proxy for UFP), particulate matter ≤ 2.5 μm ($PM_{2.5}$) and ≤ 10 μm (PM_{10}), and ozone with daily total natural and cardiovascular mortality were modified by air temperature and whether air pollution levels affected the temperature-mortality associations in eight European urban areas during 1999-2013.

Methods: We first analyzed air temperature-stratified associations between air pollution and total natural (nonaccidental) and cardiovascular mortality as well as air pollution-stratified temperature-mortality associations using city-specific over-dispersed Poisson additive models with a distributed lag nonlinear temperature term in each city. All models were adjusted for long-term and seasonal trend, day of the week, influenza epidemics, and population dynamics due to summer vacation and holidays. City-specific effect estimates were then pooled using random-effects meta-analysis.

Results: Pooled associations between air pollutants and total and cardiovascular mortality were overall positive and generally stronger at high relatively compared to low air temperatures. For example, on days with high air temperatures (>75^{th} percentile), an increase of 10,000 particles/cm^3 in PNC corresponded to a 2.51% (95% CI: 0.39%, 4.67%) increase in cardiovascular mortality, which was significantly higher than that on days with low air temperatures (<25th percentile) [-0.18% (95% CI: -0.97%, 0.62%)]. On days with high air pollution (>50th percentile), both heat- and cold-related mortality risks increased.

Conclusion: Our findings showed that high temperature could modify the effects of air pollution on daily mortality and high air pollution might enhance the air temperature effects.

Keywords:

Ultrafine particles; particulate matter; ozone; air temperature; mortality; effect modification

Highlights:

- High air temperature enhanced the mortality effects of UFP, $PM_{2.5}$, PM_{10}, and O_3
- Heat-related mortality risks were higher at high levels of $PM_{2.5}$, PM_{10}, and O_3
- Cold effects on mortality were stronger when PNC was high
- First study to investigate the interaction between UFP and temperature on mortality

1. Introduction

Exposure to ambient air pollution has been identified as a leading contributor to the global disease burden which caused 4.5 million deaths in 2015 (Cohen et al. 2017). Meanwhile, a large number of epidemiological studies has shown adverse impacts of exposure to both high and low ambient air temperatures on mortality (Basu and Samet 2002; Curriero et al. 2002; Guo et al. 2014; Ma et al. 2014). Given the increasing concern regarding the health impacts of climate change, interest has grown recently in estimating the joint effects of air pollution and air temperature on health. However, little is known about the potential interaction between air temperature and air pollution, which is crucial for estimating their joint health effects.

Meteorological conditions affect surface air quality by influencing emissions, atmospheric chemistry, and pollutant transport (Fiore et al. 2015). Especially, ground-level ozone (O_3) is formed by chemical reactions between nitrogen oxides and volatile organic compounds in the presence of sunlight and high temperature (Crutzen 1974; Sillman 1999). Thus, air pollution can be influenced by air temperature. In studies assessing air pollution health effects, air temperature is usually controlled for as a confounder rather than a modifier (Chen et al. 2013; Li et al. 2017). The potential effect modification of air pollution on mortality by air temperature has been largely neglected, until recently, in epidemiological studies (Stafoggia et al. 2008). On the other hand, air pollution may amplify people's vulnerability to the adverse effects of temperature (Gordon 2003) and could act as an effect modifier in the short-term effects of air temperature on mortality (Breitner et al. 2014; Ren et al. 2006). This effect modification of temperature health effects by air pollution may be of great importance to public health benefits because air temperature is expected to continue to rise over the 21st century under all emission scenarios (IPCC 2013), whereas air pollution can be reduced in a few decades to yield measurable improvements in public health (Breitner et al. 2009; Pope III et al. 2009). Thus, both directions of effect modification, hence the two-way effect modifications, matter for public health under a warming climate and changing air quality.

Although a few studies have examined the modifying effect by air temperature on particulate matter (PM)- and O_3-associated mortality, results are inconsistent regarding: (1) the direction of the interaction: most studies reported stronger PM or O_3 effects on days with high air temperatures (Jhun et al. 2014; Kim et al. 2015; Li et al. 2011; Qian et al. 2008; Ren et al. 2008a; Stafoggia et al. 2008), whereas few also reported stronger air pollution effects on days with low air temperatures (Chen et al. 2013; Cheng and Kan 2012; Sun et al. 2015); (2) the significance of interaction: among 12 studies of PM effects on daily total nonaccidental mortality, only six found statistically significant interactions, five observed nonsignificant interactions, and one reported significance only in Southern Chinese cities (Li et al. 2017; Meng et al. 2012). In contrast, only a limited number of studies have evaluated the modifying effect of air pollution on air temperature-related mortality (Breitner et al. 2014; Li et al. 2015; Ren et al. 2006). PM was found as a significant effect modifier in the association between temperature and total and cardiovascular mortality in Brisbane, Australia (Ren et al. 2006) and Guangzhou, China (Li et al. 2015), but not in three cities of Bavaria, Germany (Breitner et al. 2014). However, these studies have important limitations in characterizing the complex interaction between air temperature and air pollution: first, their analyses were based on a single city analysis; second, they assumed a linear effect, a single lag, or a moving average lag structure for temperature, therefore simplifying to a great extent the nonlinear and delayed temperature-mortality dependencies (Gasparrini et al. 2015b).

Epidemiological evidence on whether air temperature modifies the effect of ultrafine particles (UFP) and vice versa is lacking, mostly due to the unavailability of routinely collected relevant data. UFP are hypothesized to have a high and independent toxic potential due to their small size (<100nm), large active surface area, and their ability to penetrate into the pulmonary alveoli and to translocate in the circulation (Brook et al. 2010; HEI Review Panel on Ultrafine Particles 2013). Few epidemiological studies have reported a (weak) positive association between short-term UFP exposure and mortality (Atkinson et al. 2010; Breitner et al. 2011; Breitner et al. 2009; Lanzinger et al. 2016; Stafoggia et al. 2017).

In the present study, we aimed to investigate the two-way effect modifications of air pollution (UFP, PM, and O_3) and air temperature on total (nonaccidental) and cardiovascular mortality in eight European urban areas. This study is the result of a collaborative effort among the Ultrafine Particles and Health (UF&HEALTH) Study Group in Europe (Stafoggia et al. 2017). The UF&HEALTH Study aimed to gather available data on UFP measures and mortality over a relatively long time period from cities across Europe to enlarge statistical power to detect weak associations (Samoli et al. 2016).

2. Methods

2.1 Data collection

Daily mortality, air pollution, and air temperature data during 1999-2013 were collected from eight European urban areas: Athens (Greece), Augsburg (Germany), Barcelona (Spain), Copenhagen (Denmark), Helsinki (Finland), Rome (Italy), Ruhr area (three adjacent cities including Essen, Mülheim, and Oberhausen, Germany), and Stockholm (Sweden) (Supplemental Information, Fig.S1). Detailed description of the study areas, including main sources of air pollution, are reported in the Supplemental Information, Text S1.

Daily death counts of urban residents were provided by each participating center of the UF&HEALTH Study Group. Mortality data were classified into the following categories using the International Classification of Diseases, 9th revision (ICD-9) and the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10): deaths from total natural (ICD-9 1-799 and ICD-10 A00-R99) and cardiovascular (ICD-9

390-459 and ICD-10 I00-I99) causes. Respiratory mortality was not investigated because our previous study did not found associations of UFP and PM with respiratory mortality (Stafoggia et al. 2017). For total natural mortality, daily counts were also stratified by sex and age (0-74 years and 75 and above years). The two age groups (nonelderly vs. elderly) were used for analysis as previous studies suggested that the elderly are more vulnerable to the mortality risks of air pollution and air temperature (Anderson and Bell 2009; Bell et al. 2005; Hajat et al. 2007; Samoli et al. 2008).

Daily mean particle number concentration (PNC, as a surrogate for UFP (HEI Review Panel on Ultrafine Particles 2013)) was obtained from independent monitoring campaigns in each city. In all cities, one urban or suburban background PNC monitoring site was used, except for a traffic site in Rome. Due to different monitoring instruments used in different cities, PNC was measured in slightly different size ranges (Supplemental Information, Table S1). For Athens, Copenhagen, and Helsinki, PNC was available in the ultrafine range (≤100 nm), in the other cities total PNC (≤3000 nm) was used as it is often assumed that particles in the ultrafine range dominated PNC (HEI Review Panel on Ultrafine Particles 2013). In each city, we further collected daily 24-h average PM with an aerodynamic diameter ≤ 2.5 µm ($PM_{2.5}$) and ≤ 10 µm (PM_{10}) and daily maximum 8-h average O_3 concentrations from multiple stations of the local air quality monitoring networks. Daily concentrations were averaged from all valid monitoring stations in each city, which had at least 75% of the daily data for the study period. For details with regard to air pollution data collection we refer to the preceding publication (Stafoggia et al. 2017). As in previous studies, daily mean air temperature was used as the metric for temperature (Chen et al. 2016; Gasparrini et al. 2015b). Data on daily mean air temperature were collected from local meteorological services or airport meteorological networks. Relative humidity was not collected since previous studies showed robust air temperature effects on daily mortality when additionally adjusting for relative humidity (Breitner et al. 2014; Gasparrini et al. 2015b; Guo et al. 2014). Influenza epidemics (a dummy variable denoting days with particularly high influenza episodes) were identified from national surveillance systems and hospitalization records.

2.2 Statistical Analysis.

2.2.1 Basic confounder model

We used Poisson additive models with over-dispersion to estimate the city-specific associations between mortality and air pollutants or air temperature. Several confounders were included in the city-specific models: (1) natural cubic spline with eight degrees of freedom (*df*) per year to control for long-term and seasonal trend, (2) indicator variables for day of the week, (3) an indicator variable for influenza epidemics, (4) an indicator variable for population dynamics due to summer vacation and holidays (Stafoggia et al. 2017), and (5) a penalized distributed lag nonlinear temperature term using marginal P-spline smoothers with dimension 7 for both exposure and lag spaces and a maximum lag of 21 days. The penalized distributed lag nonlinear temperature term was characterized as a cross-basis matrix, which had 42 (7×6) parameters for the bi-dimensional space of the exposure and lags. Penalization was implemented through a double varying penalty with a second-order difference penalty and a ridge penalty (Gasparrini et al. 2017). Because of the different lag periods for heat effect (within a few days) and cold effect (up to 3 or 4 weeks) (Anderson and Bell 2009; Gasparrini et al. 2015b), we applied a maximum of 21 lag days for temperature.

2.2.2 Air pollution effects stratified by air temperature

To examine effect modification by air temperature in each city, we categorized air temperature into three levels: high (>75th city-specific percentile), medium (25^{th}-75^{th} city-specific percentile), and low (<25th city-specific percentile). Consistent with prior studies (Chen et al. 2013; Jhun et al. 2014; Ren et al. 2008a), the 25^{th} and 75^{th} percentiles were used as temperature cut-offs. In addition, compared with other percentile cut-offs (5^{th} and 95^{th}, 10^{th}

and 90th, 15th and 95th, 20th and 80th), this percentile cut-offs could yield similar estimates but with narrower confidence intervals due to increased sample size in the low and high temperature levels (Chen et al. 2013; Jhun et al. 2014). After defining the basic confounder model, we introduced the interaction terms between air pollutant (PNC, $PM_{2.5}$, PM_{10}, and O_3 in turn) and categorized air temperature at the same lag structure. Due to the multiple missing data in many of the air pollution series (Supplemental Information, Table S2), we could not compute averages over multiple days for air pollution. Based on our previous analysis (Stafoggia et al. 2017), we chose lag 6 for PNC and lag 1 for other pollutants. Heterogeneity among city-specific air pollution effects was assessed by the I^2 statistic from Cochran's Q test. Heterogeneity was considered to be significant if $I^2 > 0.5$, moderately significant if $0.25 < I^2 \leq 0.5$, and nonsignificant if $I^2 \leq 0.25$ (Higgins et al. 2003).

2.2.3 Air temperature effects stratified by air pollution concentrations

For each city, we introduced an interaction term between the above mentioned penalized distributed lag nonlinear temperature term and an air pollutant strata indicator in the basic confounder model. To examine effect modification by air pollutants, we divided the air pollutants (PNC at lag 6, $PM_{2.5}$, PM_{10}, and O_3 at lag 1) into two levels: high (> city-specific median value) and low (≤ city-specific median value). Air pollution was categorized into two levels rather than three levels in order to ensure enough statistical power for the parameters in the cross-basis matrix of temperature and its interaction term with air pollution strata indicator. As the short-term effects of air pollutants are generally within several days (Bell et al. 2005; Samoli et al. 2008), we did not used the same cumulative lag structure (lag0-21) for air pollution and air pollution categories. To adjust for potential residual confounding, the air pollutant was also included as a linear continuous term in the model. The overall cumulative exposure-response curves for temperature and mortality were estimated along percentiles of the average temperature distribution in the eight European urban areas under study, with a minimum mortality temperature percentile between the first and the 99th percentiles as the reference temperature (Gasparrini et al. 2015b). Relative, city-specific temperature percentiles were used to characterize differences in temperature distributions and population acclimatization to temperature changes in cities with different climate conditions (Guo et al. 2014; Jhun et al. 2014). Because the average temperature distributions were similar in different strata of PNC and PM but different in different strata of O_3 (Supplemental Information, Table S3), we constructed overall cumulative exposure-response relationships for each strata of air pollutants and represented these curves on a relative scale, along percentiles of the overall average temperature distribution. In addition, we calculated heat effects as cumulative mortality risk at the 99th percentile relative to the 90th percentile and cold effects as cumulative mortality risk at the 1st percentile relative to the 10th percentile. Since the 99th percentile (25.6 °C) is larger than the maximum value of temperature in low ozone levels, we calculated the heat effects in low ozone levels by comparing its maximum value (24.4 °C) with the 90th percentile (21.5 °C). The overall lag-response relationships for heat and cold effects across the lag period (0-21) were estimated separately.

City-specific effect estimates were pooled using univariate random-effects meta-analyses (Gasparrini et al. 2012). For temperature effects, city-specific coefficients for the cross-basis term were first pooled and then the pooled coefficients were used to reconstruct overall cumulative exposure-response associations on a relative scale using average temperature distribution percentiles (Gasparrini et al. 2015a). We tested the statistical significance of differences between the pooled estimates of the temperature or air pollutant strata by calculating the 95% confidence interval (CI) as $(\hat{Q}_1 - \hat{Q}_2) \pm 1.96\sqrt{(S\hat{E}_1)^2 + (S\hat{E}_2)^2}$, where $\hat{Q}_1$and $\hat{Q}_2$ are the estimates, and $S\hat{E}_1$and $S\hat{E}_2$ are their respective standard errors (Zeka et al. 2006). We also tested the statistical significance of differences between the overall temperature-mortality associations at low and high air pollution levels using a multivariate

Wald test based on the pooled reduced coefficients of the cross-basis matrix of temperature (Gasparrini et al. 2015a).

2.3 Sensitivity analyses

We performed several sensitivity analyses by changing the *df* (6-10 per year) for time trend and using alternative maximum lag days for temperature (14 and 28 days). In addition, when analyzing modifications of the air pollution effects by air temperature, different cutoffs ($20^{th}/80^{th}$, $15^{th}/85^{th}$, and $10^{th}/90^{th}$) and lag days (lag 0 to lag 6) for temperature categories were also explored. Moreover, we fitted two-pollutant models by adding other co-pollutants one at a time to account for potential confounding from multiple exposures. Additionally, we explored whether differences in city-specific characteristics such as average temperature, temperature range, average air pollution level, and total number of population were associated with the estimated temperature-stratified air pollution effects. Using potential city-specific characteristics as additional meta-predictors, we then performed sensitivity analyses to pool the city-specific results using multivariate meta-regression models (Gasparrini et al. 2012). Furthermore, we tested effect modification by sex and age group performing gender- and age-specific subgroup analyses. Besides, we compared the results of using UFP (3-100 nm) with using total PNC (10-2000 nm) in Augsburg during 2004-2009. Finally, as Rome was previously found to dominate the pooled effects of PNC on mortality (Stafoggia et al. 2017), we also checked the influence of Rome on the modification of air pollution effects by air temperature through removing it from the meta-analyses.

All analyses were performed with R software, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria), using the packages mgcv (Wood 2011), dlnm (Gasparrini 2011), and mvmeta (Gasparrini et al. 2012).

3. Results

3.1. Descriptive statistics

Table 1 summarizes daily mortality counts and cutoffs for air pollution and temperature strata in the eight European cities. Different research periods with available data on UFP measurements and mortality were investigated across different cities. During the study period, there were overall 742,526 total natural deaths in the eight cities, among which 39.3% were cardiovascular deaths. Daily total and cardiovascular mortality were highest in Athens and lowest in Augsburg. Median values of daily PNC ranged from 4,685 particles/cm^3 in Copenhagen to 29,168 particles/cm^3 in Rome. Cutoffs for both air pollutants and air temperature were generally higher in the Southern cities. The correlations of PNC with PM, ozone, and air temperature, and correlations between PM and temperature were weak to moderate in each city (Supplemental Information, Fig.S2). On the contrary, ozone was moderately to strongly positively correlated with air temperature.

3.2. Air pollution effects modified by temperature

Table 2 shows that the pooled effects of PNC, PM, and ozone on daily mortality varied by temperature levels. Associations between increases in air pollutants and mortality were generally stronger at high compared to low air temperatures. For example, a 10,000 particles/cm^3 increase in PNC at lag 6 was associated with percent increases in cardiovascular mortality of -0.18% (95% CI: -0.97%, 0.62%), 0.81% (95% CI: -1.92%, 0.32%), and 2.51% (95% CI: 0.39%, 4.67%) at low, medium, and high air temperatures, respectively. The corresponding effect estimates on total mortality at each temperature level for a 10 $\mu g/m^3$ increase in $PM_{2.5}$ were -0.46% (95% CI: -1.02%, 0.12%), 0.84% (95% CI: 0.05%, 1.63%), and 2.36% (95% CI: 0.11%, 4.65%). Nonsignificant or moderately significant heterogeneity ($I^2 \leq 0.5$) across different cities was observed for associations between mortality and PNC, PM_{10}, and O_3, whereas significant heterogeneity ($I^2 > 0.5$) was found for associations between mortality and $PM_{2.5}$ at high temperatures (Table 2 and Supplemental Information, Fig.S3-S6).

3.3. Air temperature effects modified by air pollutants

In the basic confounder model, the pooled air temperature-mortality associations were U-shaped and significant for both total natural and cardiovascular mortality (Fig.1). The lag-response relationships showed that heat effects were limited within the first week while cold effects lasted two to three weeks. No harvesting effect (deaths advanced by a few days) or mortality displacement was observed for both heat and cold effects.

Fig.2 shows the pooled estimates of the exposure-response relationship between air temperature and total and cardiovascular mortality at low and high air pollution levels. Associations between high temperatures and mortality were generally stronger at high PNC, PM, and O_3 levels. Estimates for low temperatures and mortality were much stronger at high PNC levels compared to low PNC levels, while were similar at PM and O_3 strata, with overlapping CIs. The results of the multivariate Wald test indicated evidence ($p < 0.05$) of significant differences in the exposure-response curves for total natural mortality stratified by PM and O_3 levels.

Table 3 reports the overall cumulative mortality risk of heat exposure (99^{th} percentile relative to 90^{th} percentile of air temperature) and cold exposure (1^{st} percentile relative to 10^{th} percentile of air temperature) by air pollutant strata. In general, both heat and cold effects on total and cardiovascular mortality were stronger at high air pollution levels. For example, heat exposure was associated with an increase in cardiovascular mortality by 19.02% (95% CI: -13.24%, 46.68%) at high PNC levels and 3.75% (95% CI: 0.29%, 7.33%) at low PNC levels. Cold-related cardiovascular mortality risk was also higher at high PNC levels (16.23%; 95% CI: 3.80%, 30.14%), compared to low PNC levels (2.00%; 95% CI: 0.16%, 3.88%).

3.4. Subgroup and sensitivity analyses

In population subgroup analyses, we did not find substantially different interactions between air temperature and PNC, PM, and O_3 on total natural mortality across age groups and sex (data not shown). Sensitivity analyses indicated that our results were robust when we changed *df* for time-trend (Supplemental Information, Fig.S7 and Fig.S8), used different percentile cutoffs of air temperature categories, and different lag periods for the air temperature effect (data not shown). Choosing different lag days for air temperature categories did not materially change the temperature-stratified air pollution effects on mortality (Supplemental Information, Fig.S9). After adjustment for co-pollutants, the pattern of effect modification on air pollution-related mortality by air temperature did not change substantially (Supplemental Information, Fig.S10). The effects of PNC on mortality across air temperature levels decreased after adjustment for $PM_{2.5}$ but remained similar when controlling for PM_{10} and ozone. Estimates of PM-related mortality across air temperature levels were robust when we controlled for PNC and ozone. Effect modification of ozone-related mortality by air temperature persisted after adjustment for PNC and PM. When we considered potential predictors (average temperature, temperature range, and population) of the city-specific risk estimates (Supplemental Information, Fig.S11), we found similar temperature-stratified air pollution effects (Supplemental Information, Fig.S12) and air pollution-stratified temperature effects (Supplemental Information, Fig.S13). Using UFP instead of total PNC generated similar results in Augsburg (Supplemental Information, Fig.S14). When we excluded Rome from the meta-analyses, the pooled effect modification of PNC- and PM-related cardiovascular mortality risks by high temperatures became nonsignificant, whereas effect modification of $PM_{2.5}$-related total natural mortality by high temperatures remained statistically significant (data not shown).

4. Discussion

To the best of our knowledge, this is the first time-series study to examine the interactions between UFP and air temperature on total natural and cardiovascular mortality. Our multi-city analyses in eight European urban areas showed that high temperatures could significantly enhance the effect of PNC on cardiovascular mortality, the effects of $PM_{2.5}$ and PM_{10} on total natural and cardiovascular mortality, and the effects of O_3 on total natural mortality. Furthermore, our results showed that the air temperature effects on mortality were greater at high air pollution levels. Significant effect modification was found on heat-related total natural mortality by $PM_{2.5}$, PM_{10}, and O_3, and on cold-related total natural and cardiovascular mortality by PNC.

4.1 Effect modification of air pollution effects by temperature

We found stronger PM effects on mortality on days with high air temperatures. Similarly, high temperatures were found to enhance the acute effect of PM on mortality in Australia (Ren and Tong 2006), China (Li et al. 2011; Meng et al. 2012; Qian et al. 2008; Qin et al. 2017), South Korea (Kim et al. 2015), and Europe (Katsouyanni et al. 2001; Pascal et al. 2014; Shaposhnikov et al. 2014; Stafoggia et al. 2008). In the present analysis, an increase of 10 $\mu g/m^3$ in PM_{10} was associated with 0.03% (95% CI: -0.32%, 0.38%), 0.28% (95% CI: 0.01%, 0.55%), and 0.93% (95% CI: 0.31%, 1.55%) increase of total natural mortality at low, medium, and high temperatures. Our results were consistent with a recent meta-analysis, which reported a 0.19% (95% CI: −0.01%, 0.40%), 0.31% (95% CI: 0.21%, 0.42%) and 0.78% (95% CI: 0.44%, 1.11%) increase in total natural mortality per 10 $\mu g/m^3$ increase in PM_{10} at study-specific low, medium, and high temperatures (Li et al. 2017). Moreover, in our study we observed a high heterogeneity of the $PM_{2.5}$ effects between the cities and therefore our results should be regarded with caution.

In accordance with our PM analysis, we also found stronger UFP effects on daily mortality on days with high temperatures. However, the effect modification was only significant for cardiovascular mortality. Evidence from very few studies on the seasonal association between PNC and mortality indicate that UFP effects may be larger in the warm season (Meng et al. 2013; Stafoggia et al. 2017), which provides support for our findings.

Effect estimates were robust after adjustment for PM_{10} and O_3, but weaker after adjustment for $PM_{2.5}$. In contrast, the temperature-stratified $PM_{2.5}$ effects on mortality remained robust after adjustment of co-pollutants, which suggests independent effects of $PM_{2.5}$. This contrasting effects indicates some residual confounding in PNC effects due to co-exposure to $PM_{2.5}$. However, the contrasting results between PNC and $PM_{2.5}$ should be interpreted with caution due to different size fractions of PNC measured in different cities. Except for Athens, Copenhagen, and Helsinki, total PNC (≤ 3000 nm) rather than PNC at ultrafine range (≤ 100 nm) was measured (Supplemental Information, Table S1). In previous studies measuring UFP at ultrafine range (≤ 100 nm), the mortality effects of UFP remained similar when adjusting for $PM_{2.5}$ (Lanzinger et al. 2016) or mass concentration metrics (Breitner et al. 2011).

City-specific effect modification of PNC effects by temperature showed different patterns, where largest effects occurring at high temperatures were observed in Athens, Augsburg, Barcelona, Helsinki, and Rome, but not in Copenhagen, Ruhr area, and Stockholm (Supplemental Information, Fig.S3). This difference may be due to different source contributions to UFP in different cities. A previous study evidenced that in Northern and Central EU cities PNC and black carbon (BC) had a similar hourly pattern, whereas in Southern EU cities, maximum PNC occurred at midday with minimum BC levels due to midday nucleation episodes (Reche et al. 2011). To quantify the sources and processes contributing to UFP, it can be segregated into two components based on the high correlation between BC and PNC: N1, the primary emission of vehicle exhaust, and N2, the newly formed secondary origin from mostly nucleation processes and other low BC-bearing UFPs from different sources (Brines et al. 2015; Cheung et al. 2011; Rodríguez and Cuevas 2007). Short-term effects of UFP on daily mortality are affected by different origins of UFP. A recent study in three Spanish cities found an association of daily mortality with N1 but not with N2 in Barcelona and Santa Cruz de Tenerife, which were influenced by traffic emissions, whereas an association with N2 was observed in an industrial city Huelva (Tobías et al. 2018). Thus, different source contributions of UFP in our eight EU cities may lead to different effects of PNC on daily mortality. Further studies with both PNC and BC measurements are need to differentiate modification effects of primary and secondary UFP on health by air temperature. Furthermore, city-specific modified PNC effects by temperature on total mortality were not fully explained by those effects on cardiovascular mortality. This suggests that PNC may have effects on other causes of deaths.

A small number of studies have examined the modifying effect of air temperature on ozone-related mortality and the results are inconsistent (Li et al. 2017). In line with our findings, significant effect modifications of the association between O_3 and mortality with stronger effects on warmer days were found in the U.S. (Jhun et al. 2014; Ren et al. 2008a) and France (Pascal et al. 2012). On the contrary, stronger O_3 effects on colder days were observed in several cities in China (Chen et al. 2013; Cheng and Kan 2012; Liu et al. 2013). This difference may be likely due to inadequate control of cold effects in these studies by using short lags for temperature in the ozone-mortality association. A previous study in 21 East Asia cities demonstrated that adjusting only for short lags of temperature could result in higher ozone effect estimates in winter than in summer (Chen et al. 2014).

4.2 Effect modification of temperature effects by air pollution

Effect modification by air pollution on air temperature-mortality relationships has been barely investigated. We observed higher heat- and cold-related mortality risks at high air pollution levels, with significant effect modification by $PM_{2.5}$, PM_{10}, and O_3 on heat-related mortality risks and by PNC on cold-related mortality risks (Table 3). Similar findings on PM_{10} and O_3 were obtained by time-series studies conducted in Guangdong, China (Li et al. 2015), Brisbane, Australia (Ren et al. 2006), 95 U.S. communities (Ren et al. 2008b), Berlin, Germany, and Lisbon, Portugal (Burkart et al. 2013), and three cities of Bavaria, Germany

(Breitner et al. 2014). Another study using a case-crossover design also reported larger heat effects on mortality at high PM_{10} concentrations in Rotterdam, The Netherlands (Willers et al. 2016). No prior investigations have assessed the modifying effect of short-term exposure to PNC and $PM_{2.5}$ on temperature-mortality associations.

4.3 Plausible biological mechanism

Although the underlying biological mechanism of effect modification of air pollution and temperature on mortality is not fully understood, several hypotheses have been proposed. Firstly, PM, O_3, and air temperature may have synergistic effects on cardiovascular system as they have common pathophysiological pathways. Air temperature changes (higher or lower) are associated with increased blood viscosity and coagulability, elevated cholesterol levels, and inflammatory responses (Keatinge et al. 1986; Schneider et al. 2008). Increased UFP and PM can also cause increased blood pressure and platelet aggregation, systemic oxidative stress and inflammation (Brook et al. 2010; Rückerl et al. 2011). In addition, both airborne particles and temperature were associated with changes in heart rate and repolarization parameters among myocardial infarction survivors (Hampel et al. 2010). On the other hand, ozone at high temperatures may impair fibrinolysis, thus reducing the efficiency of preventing clot formation and clearance (Kahle et al. 2015). Second, high temperatures could increase thermoregulatory stress and alter the physiological response to toxicants, leading to a higher susceptibility to air pollution effects (Gordon 2003). Third, population exposures to air pollution might increase during the warm season (Meng et al. 2013) as people tend to go more outside and to keep windows open and at the same time the chemical composition of UFP (Kim et al. 2002) and PM (Bell et al. 2007) could vary by season. In addition, secondary UFPs formed from mostly nucleation events contributed as a major component of UFP in Australian and European cities (Brines et al. 2015; Salma et al. 2014). Because nucleation events generally occurred at midday with high temperature and low levels of nitrogen oxides

(Brines et al. 2015), source contribution of UFP may greatly differ at low and high temperatures. Seasonal variations in both chemical composition and source contribution of UFP may affect its toxicity, which was observed to be higher in the summer (Baldauf et al. 2016).

4.4 Strengths and limitations

The eight European cities with PNC measurements offer advantages for the study of the interactions between UFP and air temperature on daily mortality for the first time to our knowledge. Furthermore, this study benefits from analyses on different particle sizes (UFP, $PM_{2.5}$, and PM_{10}) and the potential synergistic role of temperatures. Another main strength of this study is the multi-city design with standardized protocols for health data collection covering a wide range of locations in Europe with different climates, which can provide robust results and may avoid potential publication bias that commonly occur in single-city studies. Moreover, disentangling interactions between the air pollution and air temperature on health is challenging in part because of their different lag structures and a different shape of their exposure-response functions (Zanobetti and Peters 2015). In the present analysis on effect modification by air pollutant, rather than using a linear, single lagged or moving averaged temperature term, we applied a distributed lag nonlinear temperature term, which captures the complex non-linear and lagged dependencies in both the exposure-response and lag-response associations (Gasparrini et al. 2015b). In the interaction term, this distributed lag nonlinear temperature term was added together with a linear single lagged air pollution strata. Thus, our models characterizing interactions with different lag structures and different exposure-response functions may better assess the complex interplay between air pollutants and air temperature on daily mortality.

Several limitations should be acknowledged in this study. First, there were potential exposure measurement errors because we used measured air pollution and air temperature at fixed outdoor monitoring stations. This measurement error may be especially relevant to UFP as it is known to have a high spatial variation within cities (HEI Review Panel on Ultrafine Particles 2013). However, this concern was lessened to some extent as we analyzed the temporal variations in time-series models and the temporal correlations across different sites within a city were generally high (Cyrys et al. 2008). Second, different air pollution measurement instruments were used and slightly different size fractions of PNC were collected in different cities (Stafoggia et al. 2017), which might limit the direct comparison among cities and introduce differential exposure measurement errors. Third, the UFP measurements in Rome were influenced by traffic and had much higher particle number concentrations, which may increase the statistical power and lead to the dominating role of Rome in the pooled PNC effects (Stafoggia et al. 2017). Moreover, the multiple missing data in air pollution measurements prevented us from conducting a sensitivity analysis using the same cumulative lag structure for air temperature and air pollutants in assessing their interactions. Furthermore, due to power issue we did not examine whether the observed effect modifications varied by season. Further study is warranted to investigate the seasonal interactions between air pollution and air temperature. Another limitation is that by testing multiple air pollutants, temperature, and total and cardiovascular mortality, the possibility that some of the observed significant effect modifications might occur by chance cannot be fully excluded. In addition, our results might not be generalized to health impact assessments in another region with different basic health status and air pollution compositions (Krzyzanowski et al. 2002).

5. Conclusion

Overall, our findings showed that the association between daily total natural and cardiovascular mortality and air pollution (UFP, $PM_{2.5}$, PM_{10}, and ozone) was modified by air temperature and vice versa. Results therefore suggest that interactions between air pollution and air temperature should be considered to assess their joint health effects. Our findings point to the importance of understanding and reducing the health burdens attributable to ambient air pollution and air temperature in the context of climate change. Further studies are needed to investigate the effect modification of air pollution and air temperature using morbidity data (i.e. hospitalization, emergency room visits) to get a more comprehensive knowledge of the air temperature-pollution interaction.

Founding

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Conflict of interest

The authors declare no conflicts of interests.

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Figures

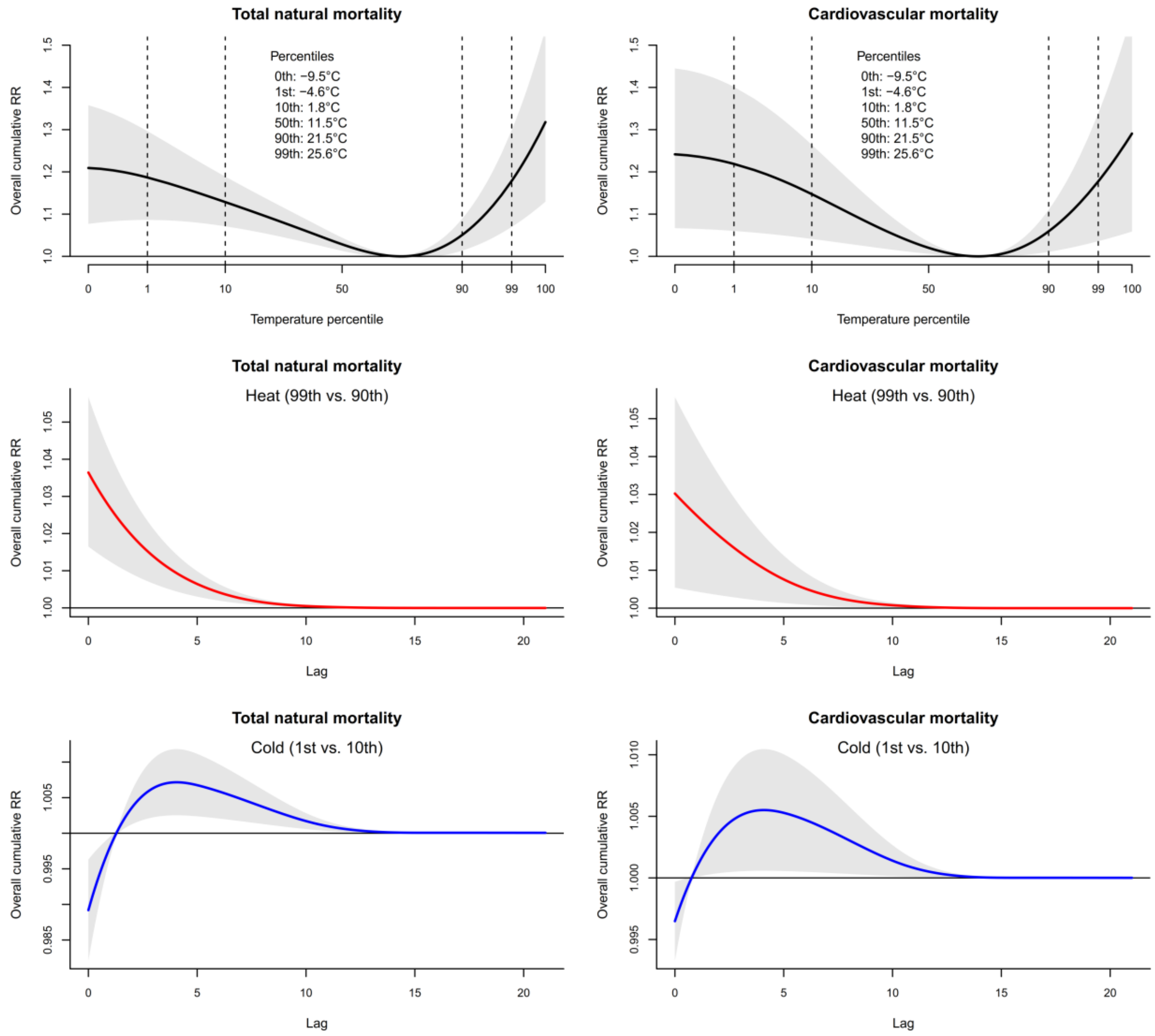

Fig.1. Overall cumulative exposure-response relationships and lag-response relationships between air temperature and mortality with 95% CIs. The vertical lines in (A) and (B) represent the 1st, 10th, 90th, and 99th percentiles of the air temperature distribution. The y-axis in (A) and (B) represents the relative risk of air temperature on daily mortality compared with the minimum mortality temperature; in (C) and (D) represents the relative risk of heat effect (99th percentile vs. 90th percentile) on daily mortality; and in (E) and (F) represents the relative risk of cold effect (1st percentile vs. 10th percentile) on daily mortality.

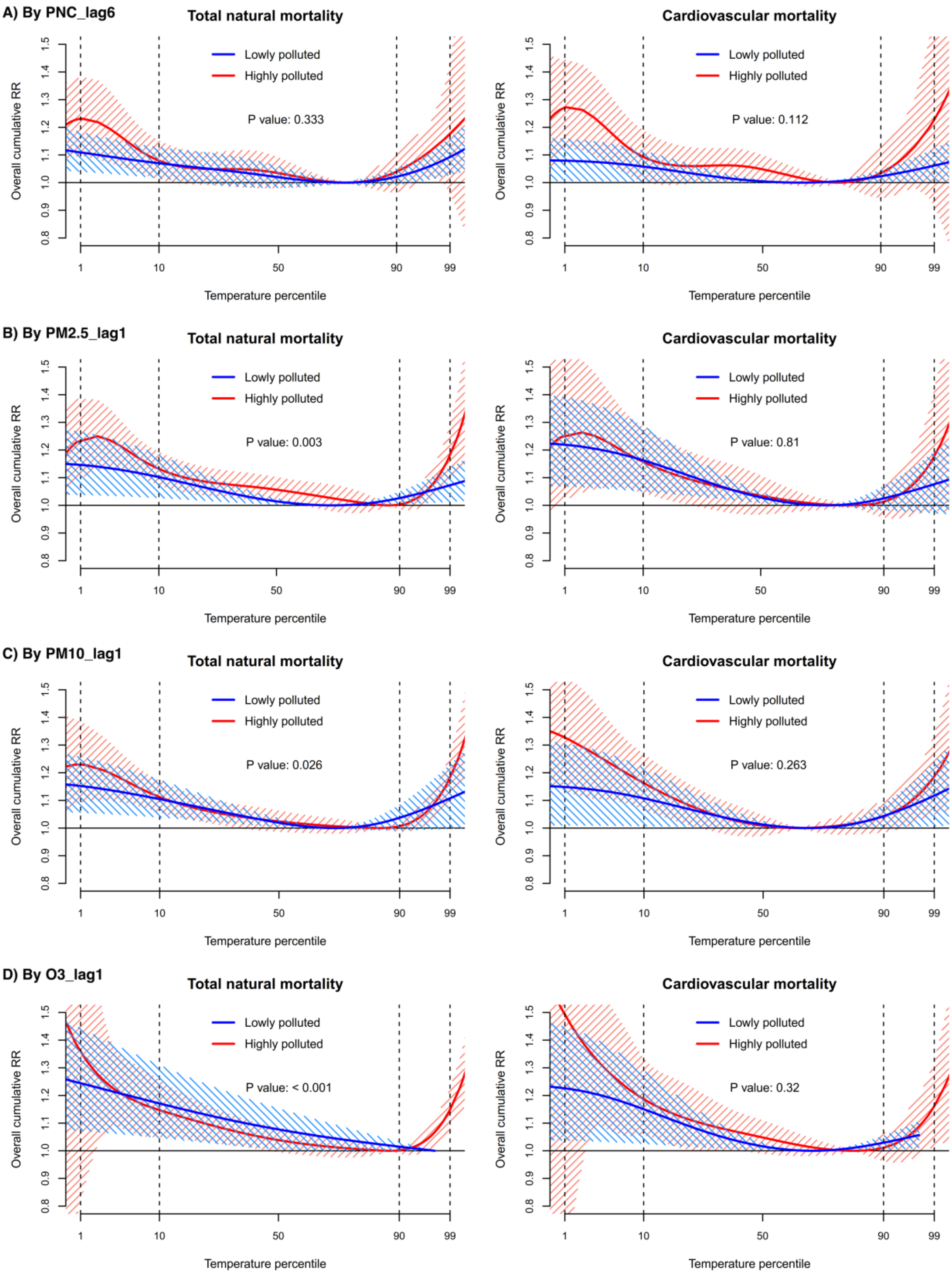

Fig.2. Modified overall cumulative air temperature-mortality associations by air pollution with 95% CIs. Blue lines represent for low air pollution level (concentration below median value) and red lines represent a high air pollution level (concentration above median value).

The vertical lines represent the 1^{st}, 10^{th}, 90^{th}, and 99^{th} percentiles of the air temperature distribution. The y-axis represents the relative risk of temperature on daily mortality compared to the minimum mortality temperature. P value is the result of significance test between air pollution levels, based on a multivariate Wald test of the pooled reduced coefficients of the temperature effects at low and high air pollution levels.

Tables

Table 1. Descriptive statistics for study period, daily deaths, and cutoffs for air pollutants and air temperature in eight European cities.

	Helsinki	Stockholm	Copenhagen	Ruhr Area	Augsburg	Rome	Barcelona	Athens
Study period	2001-2010	2001-2005, 2008-2010	2001-2010	2009-2013	1999-2009	2001-2010	2005-2010	2008-2010
Daily mortality (mean ± sd)								
Total natural	18±5	39±7	26±9	32±6	8±3	58±10	41±8	80±12
Cardiovascular	7±3	16±4	8±4	12±4	4±2	24±6	13±4	36±7
Air pollutants percentiles (median)								
PNC (particles/cm^3)								
Min	793	2113	503	1513	2243	2295	1926	582
25th	4658	6210	3285	7523	7184	19384	13807	3775
50th	6636	8150	4685	9740	9977	29168	18696	5599
75th	9868	10910	6382	12331	13728	44202	24663	8696
Max	38761	44170	21260	28905	44755	139640	50929	36024
$PM_{2.5}$ (μg/m^3)								
Min	0	1	0	4	1	0	2	5
25th	5	5	9	10	10	13	15	16
50th	7	7	11	14	15	18	20	20
75th	11	9	15	22	21	24	28	26
Max	57	37	70	128	126	73	104	63
PM_{10} (μg/m^3)								
Min	1	3	2	4	4	7	4	7
25th	10	9	14	14	19	26	23	24
50th	13	12	18	19	29	33	32	32
75th	19	17	23	28	40	44	43	42
Max	116	82	100	131	169	174	190	291
O_3 (μg/m^3)								
Min	2	5	0	3	3	1	1	10
25th	48	51	26	36	45	42	41	49
50th	62	64	33	55	67	75	65	71
75th	76	78	40	75	93	100	83	91
Max	159	129	77	196	190	199	142	138
Air temperature percentiles (°C)								
Min	-24.2	-17.9	-8.1	-11.0	-12.9	-0.4	0	-1.8
1st	-18.0	-11.3	-4.5	-4.6	-7.8	2.6	1.7	4.9
10th	-6.5	-2.9	0.4	1.6	-0.9	6.6	6.4	10.0
25th	-0.7	1.2	4.3	6.4	3.6	10.2	9.5	13.8
50th	5.7	7.0	9.4	11.5	10	15.6	14.7	18.3
75th	13.7	13.9	15.2	16.7	16.2	21.9	19.6	25.5
90th	17.9	17.7	18.7	19.9	20.2	25.8	22.7	29.3
99th	22.8	22.3	22.9	25.2	24.9	28.9	25.7	32.2
Max	26.6	25.1	25.5	29.6	27.7	31	28.3	33.6

Table 2. Percent increase (95% CI) in daily total natural and cardiovascular mortality associated with a 10,000 particles/cm^3 increase in PNC or a 10 μg/m^3 increase in $PM_{2.5}$, PM_{10}, and O_3 at different temperature levels.

Pollutant	Temperature levels [a]	Total natural		Cardiovascular	
		% increase	I^2	% increase	I^2
PNC_lag6	Low	0.08 (-0.44, 0.61)	7%	-0.18 (-0.97, 0.62)	2%
	Medium	-0.49 (-1.08, 0.11)	0%	-0.81 (-1.92, 0.32)	0%
	High	1.24 (-0.72, 3.24)	28%	2.51 (0.39, 4.67) [b,c]	0%
$PM_{2.5}$_lag1	Low	-0.46 (-1.02, 0.12)	0%	-0.03 (-0.91, 0.87)	12%
	Medium	0.84 (0.05, 1.63) [b]	47%	1.22 (0.35, 2.10) [b]	0%
	High	2.36 (0.11, 4.65) [b]	74%	3.58 (0.46, 6.81) [b]	66%
PM_{10}_lag1	Low	0.03 (-0.32, 0.38)	0%	0.23 (-0.43, 0.9)	8%
	Medium	0.28 (0.01, 0.55)	34%	0.25 (-0.16, 0.66)	0%
	High	0.93 (0.31, 1.55) [b]	0%	1.61 (0.73, 2.50) [b,c]	0%
O_3_lag1	Low	0.17 (-0.14, 0.49)	0%	0.44 (-0.05, 0.93)	0%
	Medium	0.24 (-0.08, 0.57)	34%	0.69 (0.07, 1.31)	55%
	High	0.67 (0.36, 0.98) [b]	0%	0.54 (0.06, 1.02)	0%

[a] The 25^{th} and 75^{th} percentiles of daily mean temperature were used as temperature cut-offs.

[b] Significantly different from the low temperature level.

[c] Significantly different from the medium temperature level.

Table 3. Pooled cumulative mortality risks (percent increase and 95% CI) of daily total natural and cardiovascular mortality associated with heat exposure (99th percentile relative to 90th percentile of air temperature) and cold exposure (1st percentile relative to 10th percentile of air temperature) by air pollutant strata.

Effect	Pollutant	Pollutant levels [a]	Total natural	Cardiovascular
Heat	PNC_lag6	Low	6.94 (2.76, 11.29)	3.75 (0.29, 7.33)
		High	13.22 (-10.78, 43.67)	19.02 (-13.24, 46.68)
	$PM_{2.5}$_lag1	Low	4.53 (0.97, 8.21)	4.99 (-1.15, 7.56)
		High	17.71 (7.98, 28.31) [b]	16.10 (-1.62, 37.02)
	PM_{10}_lag1	Low	6.78 (0.53, 13.42)	7.04 (0.51, 9.69)
		High	17.39 (9.95, 25.33) [b]	13.69 (1.84, 26.91)
	O_3_lag1	Low	-2.08 (-4.43, 0.32)	3.90 (0.69, 7.22)
		High	14.61 (8.24, 21.36) [b]	14.83 (2.35, 28.83)
Cold	PNC_lag6	Low	3.64 (1.00, 6.35)	2.00 (0.16, 3.88)
		High	14.06 (4.45, 24.55) [b]	16.23 (3.80, 30.14) [b]
	$PM_{2.5}$_lag1	Low	4.00 (1.08, 7.00)	4.85 (1.71, 8.08)
		High	9.39 (-1.71, 21.74)	8.38 (-7.67, 27.21)
	PM_{10}_lag1	Low	4.32 (1.50, 7.21)	3.71 (0.28, 7.26)
		High	10.53 (0.24, 21.88)	14.18 (0.11, 30.22)
	O_3_lag1	Low	6.24 (1.72, 10.96)	6.58 (1.17, 12.29)
		High	18.39 (-31.1, 103.42)	25.75 (-51.47, 225.85)

[a] The median value for each pollutant in each city was used as cut-offs for air pollution levels.

[b] Significantly different from the low air pollution levels.