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Does temperature-confounding control influence the modifying effect of air temperature in ozone–mortality associations?

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Background: Recent epidemiological studies investigating the modifying effect of air temperature in ozone–mortality associations lack consensus as how to adjust for nonlinear and lagged temperature effect in addition to including an interaction term.
Methods: We evaluated the influence of temperature confounding control on temperature-stratified ozone–mortality risks in a time series setting in eight European cities and 86 US cities, respectively. To investigate potential residual confounding, we additionally incorporated next day's ozone in models with differing temperature control.
Results: Using only a categorical variable for temperature or only controlling nonlinear effect of low temperatures yielded highly significant ozone effects at high temperatures but also significant residual confounding in both regions. Adjustment for nonlinear effect of temperature, especially high temperatures, substantially reduced ozone effects at high temperatures and residual confounding.
Conclusions: Inadequate control for confounding by air temperature leads to residual confounding and an overestimation of the temperature-modifying effect in studies of ozone-related mortality.

Keywords: Modifying effect; Mortality; Ozone; Temperature confounding

Introduction

Epidemiological studies have demonstrated the adverse mortality effects of short-term ozone exposure, while temperature is generally conceptualized as a confounder.[1–4] Recent studies revealed that temperature may also modify the ozone-related mortality risk.[5] However, the confounding effect of temperature in previous studies has been controlled differently: some specified temperature only as a categorical variable,[6,7] whereas some used both categorized temperature and smooth terms of continuous temperature to adjust for its nonlinear health effects.[8–12] The rational for including only a categorical temperature term may be because of the scheme for identifying effect modification in epidemiology, where unadjusted strata-specific risk estimates are used to represent the modification effect if significant heterogeneity exists among the strata-specific risk estimates.[13] However, the temperature–mortality relationship has been demonstrated to be nonlinear with increasing mortality risks for both high temperatures (heat) and low temperatures (cold).[14,15] Thus, including only a categorical variable for temperature may not be adequate to fully rule out its nonlinear confounding effect and may lead to potential residual confounding.

Furthermore, the nonlinear temperature–mortality relationship has also been found to differ in lag structures between heat and cold effects. Heat effects are generally acute and occur within a few days, while cold effects are delayed and last up to 3 or 4 weeks.[16–18] Previous studies tended to adjust only for temperature with a short lag (concurrent day or up to 3

What this study adds

Recent studies reveal that temperature may modify the ozone-related mortality risk. However, previous results are inconsistent and lack consensus on temperature-confounding control approaches in addition to including an interaction term. This study in eight European cities and 86 US cities found that inadequate control of temperature confounding by only including a categorical temperature term in time series models leads to residual confounding and an overestimation of the ozone-related mortality risk at high temperatures. Furthermore, this residual confounding and overestimation at high temperatures are mainly dominated by the incomplete control of heat effects rather than cold effects.

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days),[6–10,12,19] which may lead to inadequate control for cold effects. When using short lags for temperature in the ozone–mortality association, inadequate control of cold effects could result in higher ozone effect estimates in winter than in summer in 21 East Asian cities.[20]

In this study, we aimed to evaluate the influence of varying adjustment for confounding by temperature on the modifying effect of temperature and potential residual confounding of the ozone-related mortality in eight European cities and 86 US cities, respectively.

Methods

Data collection

We collected daily mortality, air temperature, and ozone data from 94 cities from two continents: eight European cities during 1999–2013 and 86 US cities during 1987–2000 (see eFigure 1; http://links.lww.com/EE/A3 for locations and eTable 1; http://links.lww.com/EE/A3 for summary statistics of study cities). These data have been previously used in the Ultrafine Particles and Health (UF&HEALTH) Study in Europe[21] and the National Morbidity, Mortality, and Air Pollution Study (NMMAPS) in the United States.[22,23] Details with regard to data collection can be found in the preceding studies.[1,21,24]

Daily counts from nonaccidental (International Classification of Diseases 9th revision 1–799 and International Statistical Classification of Diseases and Related Health Problems 10th Revision A00-R99) deaths for all ages were used to represent daily mortality. Consistent with the preceding studies, we used daily maximum 8-hour average of ozone in the European data[21] and daily 24-hour average of ozone in the US data.[1] In the European data, daily concentration in each city was calculated by averaging measurements from multiple local monitors with at least 75% daily data. In the US data, a 10% trimmed mean of air pollutant was used to protect against outliers and to average across monitors after correction for each monitor's yearly average.[25] We further collected daily concentration of particulate matter with aerodynamic diameter <10 μm (PM_{10}) and nitrogen dioxide (NO_2). Among the 86 US cities, 61 cities had at least 2 years of daily measurements for both PM_{10} and NO_2. Data on daily mean temperature were obtained from local or airport meteorological stations.

Statistical analysis

We performed generalized additive models (GAMs) with an overdispersed Poisson distribution to evaluate the association between ozone and mortality. Consistent with previous studies,[3,21] we used previous day's ozone in Europe and the average of the same and previous day's ozone in the United States while adjusting for long-term and seasonal trend and day of the week. Univariate penalized cubic regression splines were used to model the smooth terms of time trend. As in the preceding studies,[7,21] 6 degrees of freedom (df) per year for time trend was selected. We explored the sensitivity of the smoothness of time trend when using 6, 8, and 10 df per year by comparing generalized cross validation scores and mortality effect estimates.

To visually capture the potential interaction, we first applied the GAMs to fit a bivariate response surface.[7,26] The ozone–temperature response surface was performed with a tensor product smooth, which was constructed using cubic regression splines with df chosen by a generalized cross-validation method. This data-driven approach has been used to illustrate the joint effects of ozone and temperature on daily mortality.[8,10,27]

To examine the effect modification by temperature, we categorized temperature into three levels: high (>75th city-specific percentile), medium (25th–75th city-specific percentile), and low (<25th city-specific percentile) in each city. In the GAMs, we included an interaction term between ozone and categorized temperature at the same lag structure. We first estimated the ozone-related mortality risks within each temperature category in each city and then pooled the city-level estimates using random-effects meta-analyses.[28] We tested the statistical significance of differences between the temperature-specific estimates by calculating the 95% confidence interval (CI) according to Zeka et al.[29] In sensitivity analysis, we also applied a different temperature stratification method by multiplying three binary temperature stratum indicators with ozone to allow ozone to have a different mortality effect within each temperature stratum.[26]

To investigate the influence of temperature-confounding control on temperature-stratified ozone-related mortality risks, we compared adjustments for temperature confounding by using only a categorical variable for temperature (i.e., the main effect of temperature strata in the interaction term) using additionally a continuous variable for temperature. In modeling the continuous temperature, we used two methods to account for differences in the lag structures of heat and cold effects: a distributed lag nonlinear model (DLNM) approach and an approach fitting separate terms for high and low temperatures. To explore which confounding (heat or cold) affects the temperature-stratified ozone–mortality associations, we applied two other approaches by adjusting only the heat or cold effect. Thus, we used a total of five approaches to control for confounding by temperature: (1) only the categorical term without adjustment for the smooth terms of temperature ("without sTemp"); (2) in addition to the categorical term, fitting a DLNM using a quadratic B-spline for temperature with three internal knots at 10th, 75th, and 90th percentiles, and a natural cubic B-spline for lag with 21 days and three internal knots at equally spaced log-scale values ("sTemp:DLNM"; see Gasparrini et al.[14] for more information); (3) in addition to the categorical term, fitting separate natural spline smooth terms for low temperatures at lag 1–6 and high temperatures at lag 0–1 ("sTemp_heat+sTemp_cold"; see Stafoggia et al.[21] for further details); (4) in addition to the categorical term, fitting a nature spline smooth term for high temperatures at lag 0–1 ("sTemp_heat"); and (5) in addition to the categorical term, fitting a nature spline smooth term for cold temperatures at lag 1–6 ("sTemp_cold"). The Akaike Information Criterion for quasi-Poisson was applied to compare the model fits among five approaches.

In addition, we fitted two-pollutant models to adjust for the potential confounding effect of co-pollutants (i.e., PM_{10} and NO_2) using the same lag structure as ozone. As there were missing values for ozone and co-pollutants, we restricted the analyses of two-pollutant models to days with no missing values for either air pollutant.

To evaluate potential residual confounding in these five temperature control approaches, we applied a method proposed by Flanders et al.[30]: we added future ozone concentrations measured one day after death occurrence and tested its statistical significance. If future ozone concentrations are significantly associated with daily mortality, residual confounding or other potential bias is suggested. As Becher[31] suggested that splitting the continuous confounding factor into four or five levels would remove most of the residual confounding, we also used a larger number of categories for the categorical temperature term (five and eight) defined by city-specific percentiles.

All analyses were performed with R software, version 3.2.1 (R Foundation for Statistical Computing, Vienna, Austria), using the packages mgcv,[32] dlnm,[33] and mvmeta.[28]

Results

In the response surface model, the tensor product smooth terms of ozone and temperature were statistically significant in seven of the eight European cities and 29 of the 86 US cities, implying

that an interaction between ozone and temperature might exist. Figure 1 graphically depicts the potential interactive effects of ozone and temperature on daily mortality in eight European cities and eight large US cities. The response surfaces show that temperature positively modify the O_3 mortality effects in most European and US cities, but negative or no modification by temperature were also observed in a few cities such as Augsburg, Copenhagen, and Atlanta.

Figure 2 shows the pooled results of the temperature-modified ozone-related mortality risks using five temperature control methods for the European and US cities. If the nonlinear effect of temperature was not further controlled by smooth terms (without sTemp), the categorical temperature variable showed a significant effect modification of the ozone-related mortality risk for high temperatures in both the European and the US cities. However, ozone-related mortality risk estimates at high temperatures were significantly lower when adjusting for the nonlinear effect of temperature using approaches sTemp:DLNM, sTemp_heat+sTemp_cold, or sTemp_heat but remained similar when adjusting only for the cold effect (sTemp_cold). For example, when using the sTemp:DLNM approach, risk estimates at low, medium, and high temperatures were 0.23% (95% CI = −0.09%, 0.55%), 0.23% (95% CI = −0.06%, 0.53%), and 0.36% (95% CI = 0.04%, 0.68%) in European cities and 0.11% (95% CI = −0.31%, 0.54%), 0.17% (95% CI = −0.07%, 0.41%), and 0.59% (95% CI = 0.32%, 0.85%) in US cities. When using sTemp_heat+sTemp_cold or sTemp_heat approaches, the higher risk estimates at high temperatures relative to those at low or

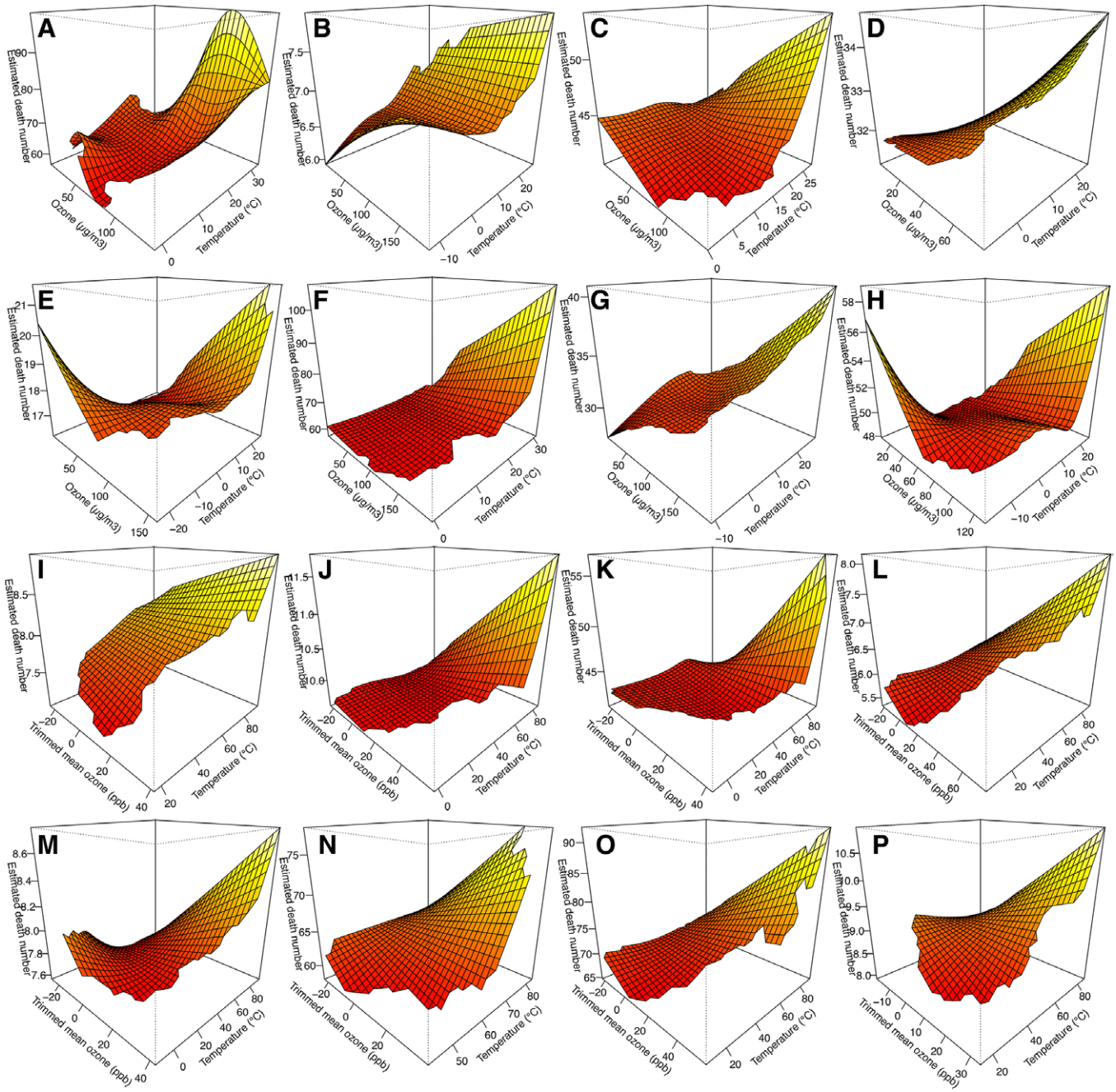

Figure 1. Bivariate response surfaces for ozone and temperature on daily mortality. A, Athens, Greece; B, Augsburg, Germany; C, Barcelona, Spain; D, Copenhagen, Denmark; E, Helsinki, Finland; F, Rome, Italy; G, Ruhr, Germany; H, Stockholm, Sweden in Europe; I, Atlanta, GA; J, Buffalo, NY; K, Chicago, IL; L, DC; M, Kansas city, MO; N, Los Angeles, CA; O, New York, NY; and P, Seattle, WA, in the United States.

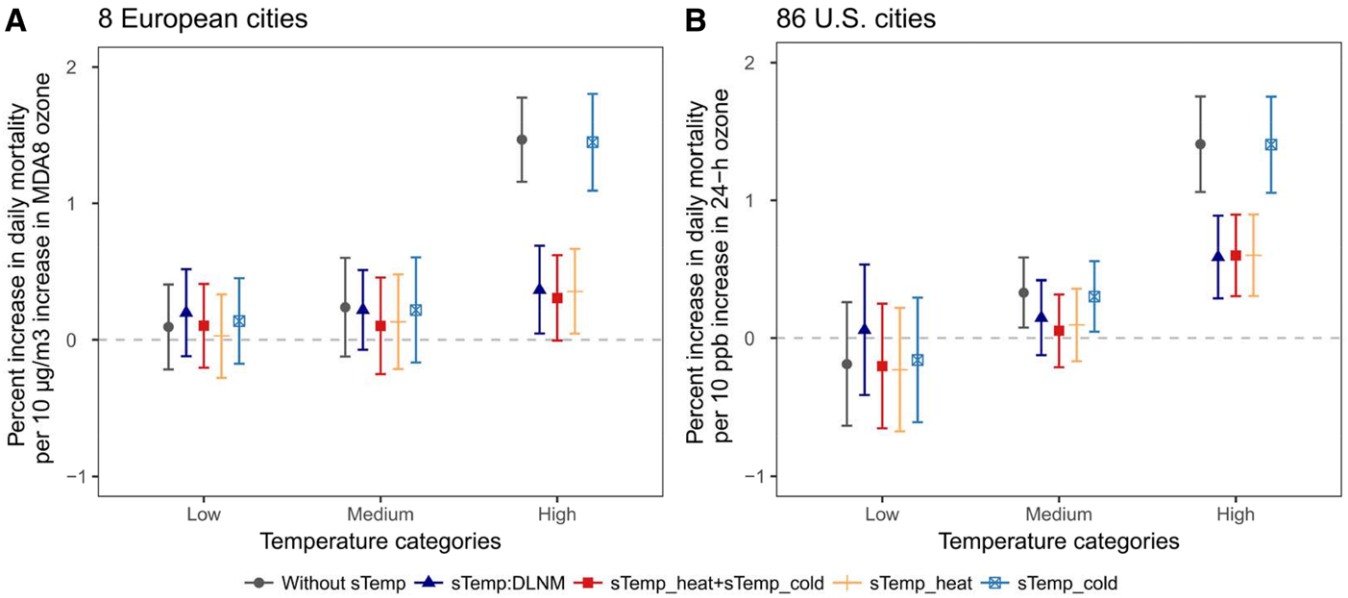

Figure 2. Modified ozone-related mortality risk estimates (95% CI) by temperature in eight European (A) and 86 US cities (B) using different temperature control methods. Temperature was categorized into low (<25th percentile), medium (25th to 75th percentile), and high (>75th percentile) levels. MDA8 indicates daily maximum 8-h average; sTemp:DLNM, sTemp_heat+sTtemp_cold, sTemp_heat, and sTemp_cold, adjustment for nonlinear temperature effects by using the distributed lag nonlinear model, both heat and cold effects, only heat effect, and only cold effect, respectively; without sTemp, no adjustment for nonlinear temperature effects.

medium temperatures became nonsignificant for European cities but generally remained significant for US cities. Compared with without sTemp approach, other approaches controlling the smooth terms of temperature generally yielded much better model fits with lower Akaike Information Criterion for quasi-Poisson values (eTable 2; http://links.lww.com/EE/A3).

After adjustment for co-pollutants, the estimates of temperature-stratified ozone-related mortality risk remained similar for both European and US cities (Figure 3). Adjustment for PM_{10} or NO_2 did not change the pattern among five temperature control methods. However, the confidence intervals in US cities became larger because the sample size decreased because of missing data for co-pollutants and fewer cities with available data.

Table 1 summarizes the regional acute effects of tomorrow's ozone concentrations on daily mortality for the five temperature adjustment methods. In both regions, we observed significant associations between tomorrow's ozone concentrations and current day's mortality with adjustment approaches without sTemp and sTemp_cold, which implies residual confounding. Splitting of temperature into more categories (five or eight) yielded similar results as using three categories.

Our results remained robust when using 8 or 10 df per year for the time trend adjustment (eFigure 2; http://links.lww.com/EE/A3, eTable 3 and eTable 4; http://links.lww.com/EE/A3), when using different cutoff values for the temperature categories (20th/80th, 15th/85th, and 10th/90th; eFigure 3; http://links.lww.com/EE/A3 and eTable 5; http://links.lww.com/EE/A3), or when using an alternative temperature stratification method by fitting ozone effects within each temperature stratum (eFigure 4; http://links.lww.com/EE/A3).

Discussion

Our findings show that inadequate control of temperature confounding by only including a categorical temperature term in time-series models leads to residual confounding and an overestimation of the ozone-related mortality risk at high temperatures. This residual confounding and overestimation at high temperatures are mainly dominated by the incomplete control of heat effects rather than cold effects.

Few time-series studies have investigated the modifying effect of the ozone-related mortality risk by temperature, and the results were inconsistent: some found a significant enhancement only for high temperatures,[7,11,12,27,34] whereas others only for low temperatures,[8–10] and some found higher ozone effects for both low and high temperatures.[6] These inconsistencies may be attributable to different climatic and demographic conditions, population exposure patterns, air pollution characteristics of different countries, and different modeling and covariate control approaches.[5,8] Our results suggest that inadequate control of temperature confounding may also contribute to these inconsistencies. In this study, the significant effect of ozone on mortality at high temperatures was largely reduced when including a nonlinear term for temperature effects, mainly attributable to the effect of heat (Figure 2). In previous studies, Ren et al.[7] only controlled for temperature with a categorical term while Pascal et al.[34] did not control for the heat effect, which may partially lead to the reported significant modifying effects of high temperatures. Similar to our sTemp_heat approach, Pattenden et al.[11] adjusted for the nonlinear heat effect using a cubic spline of the 2-day average daily mean temperature and found an overall weak evidence of the ozone–heat interaction in 15 British conurbation.

We found that when the confounding effect of heat exposure was not fully removed, ozone-related mortality risks at high temperatures would be greatly overestimated. This bias remained after controlling for PM_{10} or NO_2 in the two-pollutant models, suggesting that the residual confounding was not due to co-pollutants. This could be because air pollution were unlikely to confound studies of temperature effects[35]; thus, controlling for co-pollutants would not remove the residual confounding by temperature.

In this study, we used a city-specific percentile-based method to categorize temperature. This method used relative cutoff values to characterize differences in temperature distributions and population acclimatization to temperature changes in cities with different climate conditions. The city-specific temperature percentiles corresponded to different city-specific absolute temperatures. Even though temperature distributions differed across cities, the use of temperature percentiles rather than absolute

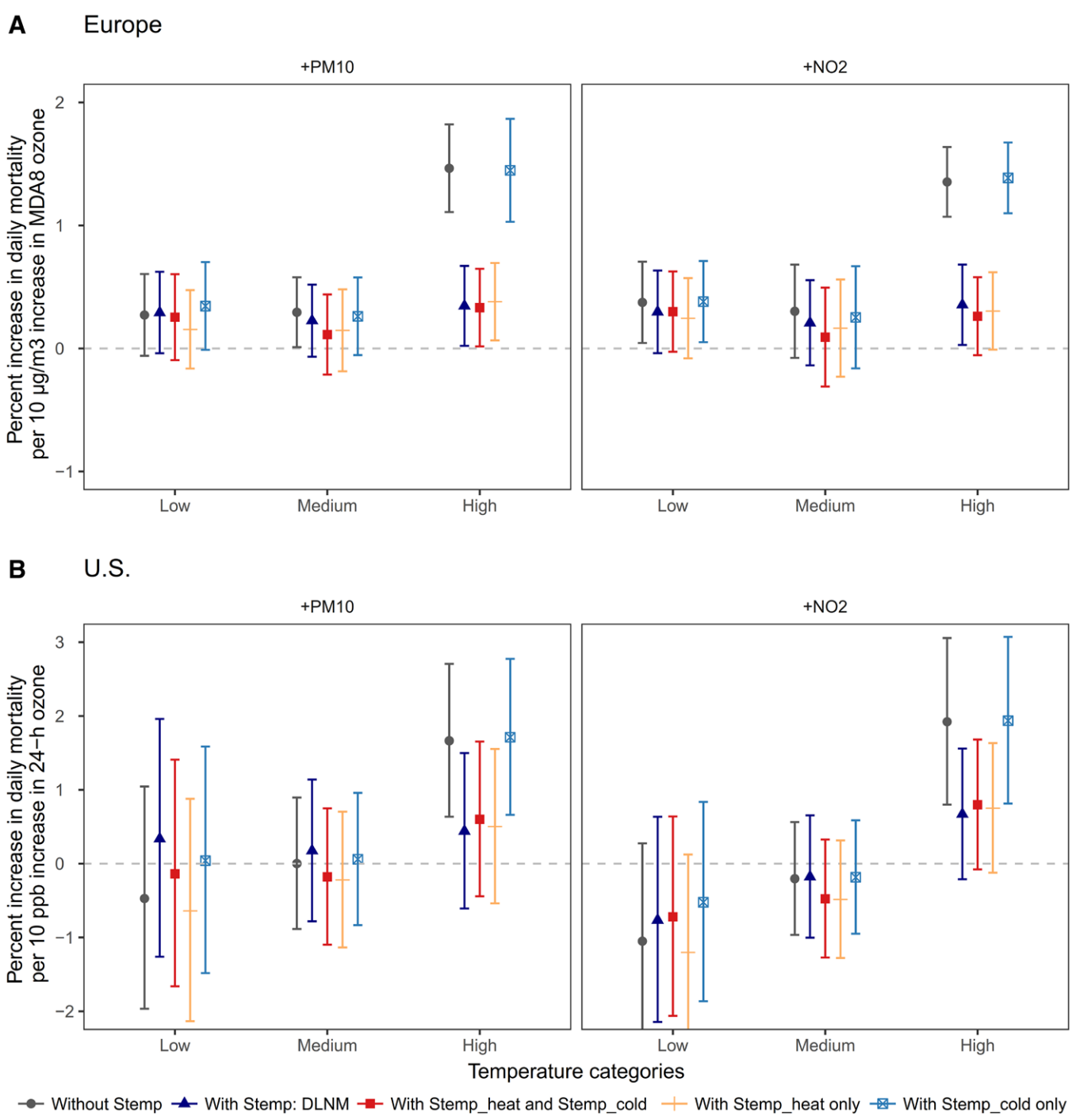

Figure 3. Modified ozone-related mortality risk estimates (95% CI) by temperature from two pollutant models in eight European (A) and 61 US cities (B). Temperature was categorized into low (<25th percentile), medium (25th to 75th percentile), and high (>75th percentile) levels. MDA8 indicates daily maximum 8-h average; sTemp:DLNM, sTemp_heat+sTtemp_cold, sTemp_heat, and sTemp_cold, adjustment for nonlinear temperature effects by using the distributed lag nonlinear model, both heat and cold effects, only heat effect, and only cold effect, respectively; without sTemp, no adjustment for nonlinear temperature effects.

values has been shown to yield greater consistency in observed mortality effects across cities.[16] The minimum mortality temperature, at which mortality was the lowest, was found to be consistently around the 75th percentile across various climate patterns (from tropical to temperate), indicating a long-term population adaptation to their local climates.[17] Thus, using the percentile-based method may be more appropriate to pool the temperature-stratified ozone effect estimates at each region.

In studies examining the effect modification by temperature on air pollution-related health impacts, bivariate response surface and stratification models were widely used.[7–10,26] Bivariate response surface models are flexible without linear assumptions on association between independent and dependent variables, but is limited to visual inspection because of unavailable parametric estimates.[7,19] In addition, response surface models also presented a challenge in including an additional lag dimension, which is critical in assessing interactions between temperature and air pollution with different lag structures. To quantify the effect modification by temperature, two types of temperature stratification models were applied: one with an interaction term between air pollutant and temperature levels[7,8] and another one without including an interaction term and directly estimated

Table 1

Percent increase (95% CI) in daily nonaccidental mortality associated with a 10 μg/m³ increase in tomorrow's maximum 8-h average ozone in eight European cities or a 10 ppb increase in tomorrow's 24-h average ozone in 86 US cities using different temperature control methods and different number of temperature categories.

		Number of temperature categories		
Region	**Temperature control methods**	**3[a]**	**5[b]**	**8[c]**
European 8 cities	Without sTemp	0.18 (0.00, 0.35)	0.18 (0.00, 0.35)	0.18 (0.01, 0.36)
	sTemp:DLNM	–0.02 (–0.21, 0.18)	0.01 (–0.17, 0.18)	–0.01 (–0.19, 0.18)
	sTemp_heat+sTemp_cold	0.03 (–0.15, 0.21)	–0.02 (–0.22, 0.17)	–0.01 (–0.20, 0.19)
	sTemp_heat	0.02 (–0.15, 0.20)	0.00 (–0.17, 0.18)	–0.01 (–0.19, 0.17)
	sTemp_cold	0.20 (0.03, 0.38)	0.20 (0.02, 0.37)	0.20 (0.02, 0.37)
US 86 cities	Without sTemp	0.23 (0.06, 0.39)	0.19 (0.03, 0.36)	0.18 (0.02, 0.35)
	sTemp:DLNM	0.00 (–0.17, 0.17)	0.00 (–0.16, 0.17)	0.13 (–0.03, 0.30)
	sTemp_heat+sTemp_cold	0.14 (–0.02, 0.31)	0.13 (–0.03, 0.30)	0.01 (–0.16, 0.18)
	sTemp_heat	0.14 (–0.02, 0.31)	0.14 (–0.02, 0.31)	0.14 (–0.02, 0.31)
	sTemp_cold	0.22 (0.06, 0.38)	0.19 (0.02, 0.35)	0.17 (0.01, 0.34)

[a]Using 25th and 75th percentiles as cutoffs.

[b]Using 20th, 40th, 60th, and 80th percentiles as cutoffs.

[c]Using 12.5th, 25th, 37.5th, 50th, 62.5th, 75th, and 87.5th percentiles as cutoffs.

the air pollution effects across temperature stratum.[9,26] In our analyses, using these two stratification models generally yielded similar temperature-stratified ozone mortality risks and came to the same conclusion. However, using the later temperature stratification model without an interaction term resulted in negative ozone mortality effect estimates at low temperatures in US cities when cold effects were not controlled (eFigure 4; http://links.lww.com/EE/A3). Similarly, in a previous study using the temperature stratification model without an interaction term, negative PM_{10} mortality effects at low temperatures were observed when adjusting only for temperature at short lags (current day and average of previous 3 days).[26]

This study has some limitations. First, different metrics and units of ozone were used in European and US cities because the same metrics using the same units were not available. However, this difference is unlikely to influence our overall findings, as our focus was to evaluate the impact of temperature-confounding adjustment on the modifying effect of temperature in the ozone–mortality relationship, rather than to compare the difference of the ozone–mortality relationship between Europe and the United States. Moreover, while ozone might act as an intermediator in the heat–mortality relationship,[36] mediation analysis is beyond the scope of our article.

In conclusion, our findings suggest that residual confounding of temperature can lead to an overestimation of its modifying effect on ozone–mortality associations. Future research investigating the modifying effect of temperature in the relationship between short-term air pollution exposure and adverse health outcomes shall be recommended to adequately adjust for the confounding by temperature.

Conflicts of interest statement

The authors declare that they have no conflicts of interest with regard to the content of this report.

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The computing code is available upon request from the corresponding author. The data are not available for replication because the mortality data are confidential.

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