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(2008)
Ozone Modifies Associations Between Temperature and Cardiovascular Mortality: Analysis of the NMMAPS Data.
Occupational and Environmental Medicine, *65*(4), pp. 255-260.

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https://doi.org/10.1136/oem.2007.033878

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Occup. Environ. Med. 2008;65;255-260; originally published online 21 Sep 2007;
doi:10.1136/oem.2007.033878

Ozone modifies associations between temperature and cardiovascular mortality: analysis of the NMMAPS data

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Accepted 14 September 2007
Published Online First
21 September 2007

ABSTRACT

Objectives: Both ambient ozone and temperature are associated with human health. However, few data are available on whether ozone modifies temperature effects. This study aims to explore whether ozone modified associations between maximum temperature and cardiovascular mortality in the USA.

Methods: The authors obtained data from the US National Morbidity, Mortality, and Air Pollution Study (NMMAPS) website. They used two time-series Poisson regression models (a response surface model and a stratification model) to examine whether ozone modified associations between maximum temperature and cardiovascular mortality (CVM) in 95 large US communities during 1987–2000 in summer (June to September). Bayesian meta-analysis was used to pool estimates in each community.

Results: The response surface model was used to examine the joint effects of temperature and ozone on CVM in summer. Results indicate that ozone positively modified the temperature-CVM associations across the different regions. The stratification model quantified the temperature-CVM associations across different levels of ozone. Results show that in general the higher the ozone concentration, the stronger the temperature-CVM associations across the communities. A 10°C increase in temperature on the same day was associated with an increase in CVM by 1.17% and 8.31% for the lowest and highest level of ozone concentrations in all communities, respectively.

Conclusion: Ozone modified temperature effects in different regions in the USA. It is important to evaluate the modifying role of ozone when estimating temperature-related health impacts and to further investigate the reasons behind the regional variability and mechanism for the interaction between temperature and ozone.

There is a general consensus among scientists that changes in the frequency and intensity of extreme weather and climate events have profound impacts on both human societies and the natural environment.[1–3] A number of epidemiological studies have shown that temperature is associated with human morbidity and mortality across different communities.[4 5] The patterns, in general, are non-linear, and J-, U- or V-shaped patterns are the most commonly observed.[3 4]

It is well known that air pollution is also associated with human health.[6–8] In many locations, patterns of air pollution are driven by weather. Concentrations of air pollutants, particularly ozone, are correlated with temperature.[9] Therefore, temperature and air pollution may interact to affect morbidity and mortality. A small number of previous studies have examined whether temperature modifies the effects of air pollution but have produced conflicting results.[10–13] Several studies have considered air pollutants as confounders while estimating the temperature-health relation.[14–16] However, few data are available on whether or not air pollution modifies the health effects of temperature. Recently, we reported that ambient particulate matter modified the association between temperature and morbidity/mortality in Brisbane, Australia.[17]

In this study, we examined whether ozone modified the associations between temperature and cardiovascular mortality in 95 large communities in the USA, 1987–2000, in summer (June to September) using the data provided by the National Morbidity, Mortality and Air Pollution Study (NMMAPS).[7 18]

MATERIALS AND METHODS

Data collection

The NMMAPS data covered 108 urbanised communities across the USA,[18] which contained time series data for health outcomes, air pollution and weather conditions between 1 January 1987 and 31 December 2000 (5114 days in total). This study included 95 large communities with adequate data in the mainland of the USA, containing a total population of nearly 100 million, with nearly 4 million cardiovascular deaths during the study period.[6] These communities were divided into seven regions—the Northeast (NE), the Industrial Midwest (IM), the Upper Midwest (UM), the Northwest (NW), the Southeast (SE), the Southwest (SW) and South California (SC) according to the NMMAPS data classification.[7 18]

The mortality data included daily deaths from cardiovascular diseases between 1987 and 2000 for each of the communities. All cases were classified according to the International Classification of Diseases version 9 (ICD-9) for 1987–98 or version 10 (ICD-10) for 1999–2000. Cardiovascular diseases included ICD-9 390-448 and ICD-10 I000-I799. The deaths, aggregated at the community level, were divided into three age categories (<65 years, 65–74 years, and ⩾75 years). Time series data for ozone were supplied by the US Environmental Protection Agency's (EPA) Aerometric Information Retrieval Service. This analysis used maximum hourly ozone as a daily indicator of ozone exposure. Data for weather conditions included daily maximum temperature measured in degrees Fahrenheit ($^\circ C = 5/9 \times (^\circ F - 32)$) and dew point temperature. All data were derived from NMMAPS. We restricted this study to the summer season (between 1 June and

30 September) because concentrations of ozone were low in winter[19] and the associations between temperature and health outcomes were often non-linear.[2 4]

Analytical protocol

We used two time-series approaches to explore whether ozone modified the association between temperature and cardiovascular mortality (CVM). Firstly, we fitted non-parametric response surface models to identify the joint effects of temperature and ozone on CVM in each community. We used a generalised additive model (GAM) to fit a response surface to capture the relation between the two main independent variables and the dependent variable without assuming linearity.[20] Secondly, we fitted a stratification parametric model to quantify any modification effects of ozone on CVM. For this purpose, we employed a generalised linear model (GLM) using iteratively-reweighted least-squares (IRLS) which avoids the potential underestimation of the coefficient's standard errors due to concurvity in GAM.[21 22] Finally, we used a Bayesian meta-analysis to estimate the overall ozone effects across the communities. S-Plus version 6 was used in the analyses.[23] These models are described in more detail below.

Response surface model

Effect modification refers to variation in the magnitude of an effect measure across levels of a third variable.[24] Non-parametric regression methods, such as bivariate smoothers, are flexible approaches to examining potentially interactive effects.[11 22 24] Before fitting the response surface model, we fitted a Poisson regression model with two independent terms for ozone and temperature using an LOESS smoothing spline adjusting for other potential confounders. We used natural cubic smoothing splines for continuous covariables such as dew point temperature so that we could compare effects across all models with the same adjustment for covariables using GAM. We used calendar days to adjust for seasonality with 3 degrees of freedom (df) for the four-month period.[25 26] We adjusted for long-term variation using years with four degrees of freedom and for short-term fluctuations using days of week as a factor. We adjusted for dew point temperature using three degrees of freedom. Previous research showed that the default criteria in the S-Plus *gam* function may bias effect estimates,[27] so we used a stricter convergence criterion (1.0×10^{-10}) for both the local score algorithm and the backfitting algorithm in S-Plus 6.[23] The model is described as follows:[12 13]

$$Log(E(Y_t|X)) = \alpha + lo(ozone_t, span = 0.25) + lo(temp_t, span = 0.25) + ns(season_t, df = 3) + ns(yr_t, df = 4) + ns(dptemp_t, df = 4) + \lambda Age_t + \gamma Dow_t + \varepsilon_t \quad (1)$$

where the subscript t denotes the time of the observation; $E(Y_t|X)$ signifies expected daily deaths on time t; $lo(\cdot)$ and $ns(\cdot)$ refer to LOESS smooth spline and natural cubic spline respectively; α is the intercept term; $ozone_t$ refers to maximum hourly ozone concentrations at time t; $temp_t$ refers to maximum temperature at time t. $season_t$ reflects seasonality using calendar days within the year at time t; df refers to degrees of freedom; yr_t and $dptemp_t$ refer to year and dew point temperature at time t, respectively; Age_t and Dow_t refer to age category and the day of week at time t, respectively; λ and γ are vectors of the coefficients corresponding to age and the day of week. ε_t is the residual.

In order to examine the interactive effect between ozone and temperature on CVM, we then fitted a response surface model adjusting for the same confounders as model 1. The model includes ozone and temperature as continuous variables.

$$Log(E(Y_t|X)) = \alpha + lo(ozone_t, temp_t, span = 0.25) + ns(season_t, df = 3) + ns(yr_t, df = 4) + ns(dptemp_t, df = 4) + \lambda Age_t + \gamma Dow_t + \varepsilon_t \quad (2)$$

Stratification model

To examine the modifying role of ozone parametrically, we first divided maximum hourly ozone into four levels using the first, second and third quartiles as cut-offs for each community (model 3). We then assessed the heterogeneity of temperature-CVM associations across ozone levels using GLM. To quantify the magnitude of the modification, we amended model 1 as follows:[12 17]

$$Log(E(Y_t)) = \alpha + \beta_1 temp_t + \beta_2 temp_t : ozonel_t + \beta_3 ozonel_t + ns(season_t, df = 8) + ns(yr_t, df = 4) + ns(dptemp_t, df = 4) + \lambda Age_t + \gamma Dow_t + \varepsilon_t \quad (3)$$

where β_1, β_2 and β_3 signify the vectors for coefficients and $ozonel_t$ signifies levels of ozone at time t. Other parameters are the same as those in model 1.

Bayesian meta-analysis

We applied a three-stage hierarchical model to estimate the overall relative rates of total mortality associated with short-term ambient temperature across different ozone levels and regions. At the first stage, we estimated a coefficient $\hat{\beta}^c$ and variance ($\mathrm{Var}(\hat{\beta}^c)$) for each community c obtained from the above parametric model. At the second stage, these estimates were divided into seven regions and four levels of ozone. Within region r and each ozone level l, we assumed that $\hat{\beta}^c$ was normally distributed with the mean effect β^c and variance σ^{2c} estimated by variance ($\mathrm{Var}(\hat{\beta}^c)$). We then assumed that the true β^c was normally distributed with overall mean μ and variance τ^2. We used Bayesian random-effect meta-analysis model to estimate the posterior distribution of each pooled effect (μ^{rl}) by taking into account the within-community variance (σ^{2c}) and the between-community variance (τ^2).[28] We estimated the community-specific differences for high and low ozone levels and the corresponding overall differences in μ^l for these levels. As at the second stage, we pooled estimates for different regions to estimate overall effects of temperature across ozone levels at the national level. WinBUGS version 1.4 was used to perform the meta-analysis.[29 30] We used non-informative priors for the hyper-parameters, that is, $\mu \sim N(0, 0.0001)$ and $1/\tau^2 \sim \mathrm{Unif}(0, 100)$.

RESULTS

Means of maximum hourly ozone concentrations ranged from 36.74 to 142.85 ppb and means of maximum temperature ranged from 20.04 to 42.23°C in the 95 communities between June and September, 1987–2000. In general, ozone was positively and significantly correlated with temperature in the northern regions (NE, IM, UM, NW), with Pearson correlation coefficients varying between 0.31 and 0.78. In the southern regions (SE, SW, SC), however, there were both positive and negative correlations between maximum hourly ozone concentrations and maximum temperature with Pearson correlation coefficients varying between −0.18 and 0.74.

We fitted the response surface model in individual communities to explore whether there were short-term interactive effects between temperature and ozone on CVM separately using maximum hourly ozone concentrations and maximum temperature on the current day and with a lag of one day. Results indicate that the joint effects of temperature and ozone on cardiovascular mortality varied substantially across communities during the summer season. In general, ozone positively

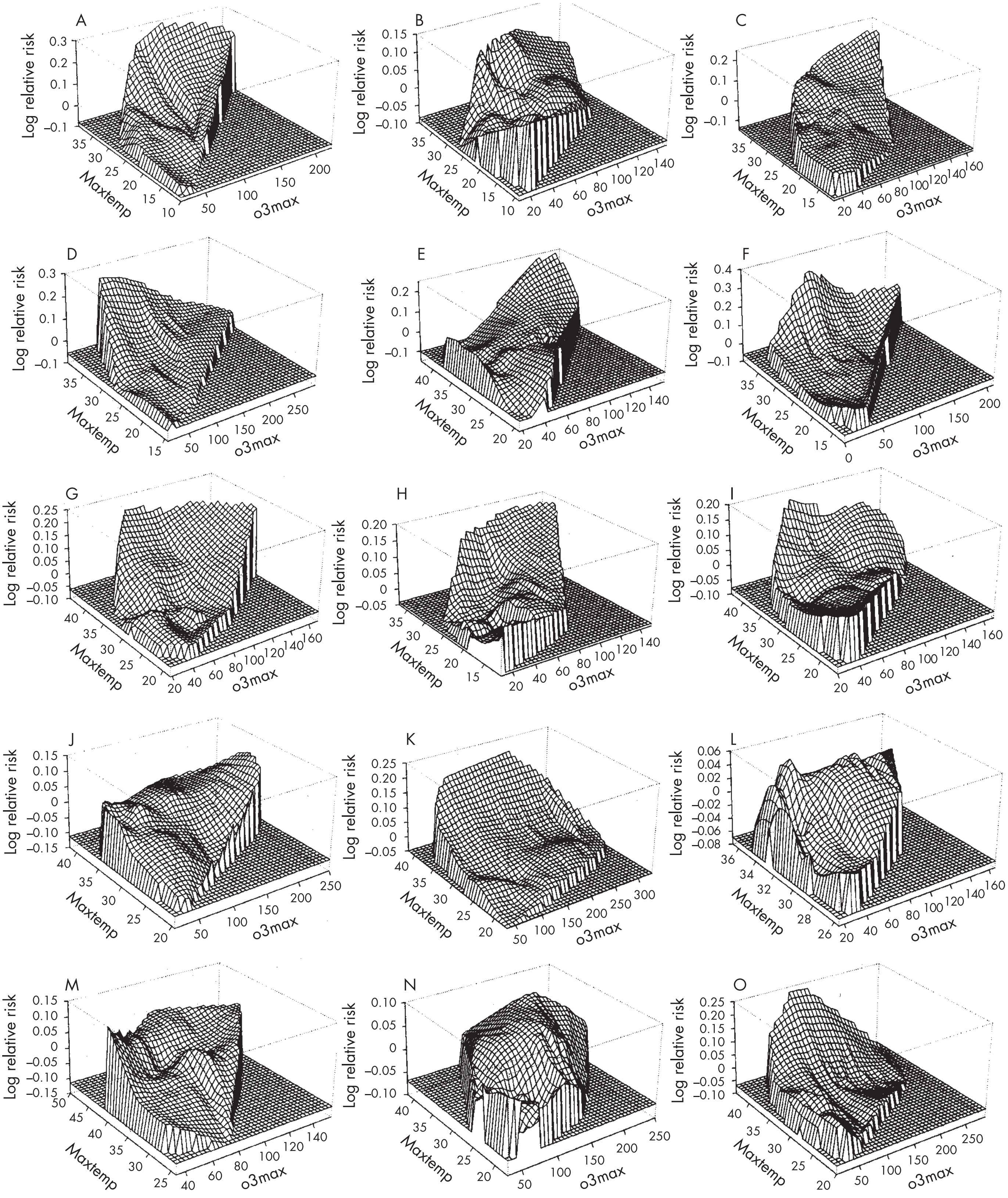

Figure 1 Bivariate response surfaces of three-day moving averages of maximum temperature and ozone on cardiovascular mortality during the warm days when temperature was equal to or greater than the median of temperature, 1987–2000, for (A) Chicago (IL), (B) Cleveland (OH), (C) Detroit (MI), (D) New York (NY), (E) Oakland (CA), (F) Philadelphia (PA), (G) San Jose (CA), (H) Seattle (WA) in the northern region, and (I) Dallas/Fort Worth (TX), (J) Houston (TX), (K) Los Angeles (CA), (L) Miami (FL), (M) Phoenix (AZ), (N) San Diego (CA) and (O) Santa Ana/Anaheim (CA) in the southern region.

modified the associations between temperature and cardiovascular mortality in the northern communities, but such modifications varied considerably in the southern communities.

Figure 1 shows the joint response surfaces of temperature and ozone on the current day on cardiovascular mortality in the eight largest communities in the northern region and the seven largest communities in the southern region (data on other cities available from the corresponding author). For Chicago (A), Detroit (C) and New York (E), when the concentrations of ozone were below 60 ppb on the current day, the effects of temperature on CVM were much lower than those when ozone concentrations were over 100 ppb. Such effect modification was not apparent in other cities such as Los Angeles (K) and Santa Ana/Anaheim (O). Joint response surfaces for a lag of one day were similar to those on the current day.

To quantitatively examine whether there were interactive effects between temperature and ozone on CVM, we fitted model 2 for each community and compared the results with model 1 within the specific community using the ANOVA function in S-Plus.[31] F tests show statistically significant and positive interactive effects in 44 communities on the current day or a lag of one day ($p<0.05$).

We fitted the stratification model (model 3) to examine the heterogeneity of temperature effects on CVM across ozone levels on the current day and at a lag of one day. Results show that associations between temperature and CVM differed considerably across the communities, regions and levels of ozone. In general, the higher the ozone concentrations, the stronger the temperature-CVM associations. We also examined whether ozone potentially modified the effect of temperature between communities. To explore whether the community-specific concentrations of ozone influenced the modifying effect of temperature, we fitted a regression model with the estimated associations between temperature and CVM (for each community) as the dependent variable and concentrations of ozone as the independent variable within each level of ozone. Results show that there were no significant associations between the effects of temperature and the community-specific concentrations of ozone—that is, concentrations of ozone did not modify the temperature-CVM associations between communities.

Bayesian meta-analysis shows that during summer ozone positively and significantly modified the temperature-CVM association in the Northeast, Industrial Midwest, Northwest, Southeast and Southern California, but no significant modifications were observed in the Upper Midwest and Southwest (table 1). For all 95 communities, corresponding to the lowest to highest (that is, 1–4) levels of ozone concentrations, respectively, a 10°C increase in average maximum temperature on current day was associated with an increase of 1.17% (95% posterior interval (PI) −1.06% to 3.06%), 4.35% (95% PI 2.12% to 6.41%), 4.31% (95% PI 1.59% to 7.08%) and 8.31% (95% PI 4.22% to 11.99%) in cardiovascular mortality on the current day; and 0.80% (95% PI −1.63%, 3.26%), 3.73% (95% PI 1.47% to 5.94%), 4.35% (95% PI 1.93% to 6.56%) and 8.62% (95% PI 4.85 to 11.99%) in cardiovascular mortality at a lag of one day.

The above regional classification resulted in a small number of communities in some regions. As part of a sensitivity analysis, we redivided the 95 communities into two groups using 38° latitude as a cut-off—that is, north (47 communities) and south (48 communities). We then categorised each group into four regions according to their longitudes from east to west, known as north 1 (12 communities), north 2 (12 communities), north 3 (12 communities), north 4 (11 communities), south 1 (12 communities), south 2 (12 communities), south 3 (12 communities) and south 4 (12 communities). We re-applied Bayesian meta-analyses to estimate the overall effect for each region and the whole 95 communities. Results confirmed that ozone positively and significantly modified temperature-CVM associations on the current day or at a lag of one day in all regions (table 2).

DISCUSSION

In this study, we used the NMMAPS data to examine temperature-CVM association and assessed whether or not ozone modified the association between temperature and CVM. Results reveal that temperature-mortality associations were substantially heterogeneous across geographic regions. Both bivariate response surface and stratification parametric models show that in general, in summer, ozone significantly and positively modified the temperature-mortality associations in different regions.

Ozone is one of the weather-driven photochemical air pollutants. Many factors, but particularly sunlight or ultraviolet, can influence its generation. It is generated by reactions of nitrogen oxides and volatile organic compounds (VOCs) with oxygen in the sunlit atmosphere. The generation and consumption of ozone occurs very quickly in the atmosphere with very low concentrations at night-time.[9] Therefore, there is little opportunity for ozone to build up across several days. Stronger sunlight correlates with higher temperature: ozone is therefore generally correlated with temperature in many places. Numerous studies show that both temperature and air pollution are associated with

Table 1 Per cent change in daily cardiovascular mortality per 10°C increase in maximum temperature across several regions and four levels of maximum hourly ozone during summer in 95 large US communities (log relative rate)

	Region	Communities, n	Level 1	Level 2	Level 3	Level 4	Difference (level 4–1)*
Current day	Northeast	15	1.02 (−1.67 to 3.13)	4.82 (2.43 to 7.70)	5.45 (1.91 to 10.23)	11.20 (6.44 to 16.17)	10.18 (4.79 to 15.78)
	Industrial Midwest	19	1.44 (−0.69 to 3.58)	4.74 (2.45 to 6.76)	3.79 (1.06 to 6.17)	9.72 (6.34 to 13.05)	8.28 (4.35 to 12.07)
	Upper Midwest	7	0.07 (−5.15 to 2.97)	4.25 (0.75 to 7.40)	3.53 (−1.62 to 7.65)	6.18 (−1.16 to 11.99)	6.10 (−2.32 to 13.80)
	Northwest	12	0.65 (−2.24 to 2.96)	3.63 (0.02 to 6.32)	4.80 (1.80 to 8.12)	9.09 (5.35 to 12.87)	8.43 (3.83 to 13.18)
	Southeast	26	1.22 (−1.05 to 3.30)	4.18 (1.43 to 6.54)	3.02 (0.05 to 5.58)	7.23 (2.84 to 10.51)	6.01 (1.01 to 10.23)
	Southwest	9	1.65 (−0.95 to 4.82)	4.59 (1.66 to 7.72)	4.07 (0.48 to 7.78)	6.43 (0.80 to 10.85)	4.78 (−1.61 to 10.04)
	Southern California	7	2.08 (−0.43 to 5.04)	4.27 (1.12 to 6.81)	5.47 (2.62 to 9.05)	8.55 (4.47 to 13.28)	6.46 (1.44 to 11.88)
	National	95	1.17 (−1.06 to 3.06)	4.35 (2.12 to 6.41)	4.31 (1.59 to 7.08)	8.31 (4.22 to 11.99)	7.15 (2.63 to 11.40)
Lag 1	Northeast	15	1.08 (−1.66 to 3.65)	4.53 (2.00 to 7.67)	4.95 (1.77 to 9.07)	10.59 (6.18 to 15.52)	9.50 (4.50 to 15.14)
	Industrial Midwest	19	1.47 (−2.05 to 6.32)	4.22 (2.06 to 6.52)	4.23 (1.82 to 6.44)	9.96 (6.55 to 13.58)	8.49 (2.78 to 13.60)
	Upper Midwest	7	−0.46 (−5.13 to 2.76)	3.70 (0.42, 6.88)	3.74 (−1.08, 7.07)	6.94 (0.10 to 12.36)	7.39 (−0.33 to 14.68)
	Northwest	12	0.02 (−2.87 to 2.47)	3.01 (−0.27 to 5.61)	4.59 (1.90 to 7.39)	9.37 (5.66 to 13.19)	9.35 (4.93 to 14.13)
	Southeast	26	0.73 (−1.85 to 2.73)	3.62 (0.91 to 6.01)	3.82 (0.72 to 6.07)	7.17 (3.42 to 10.45)	6.44 (1.81 to 10.57)
	Southwest	9	0.73 (−1.85 to 2.73)	3.89 (0.85 to 7.09)	4.03 (0.27 to 7.04)	7.27 (1.78 to 11.17)	6.18 (−0.15 to 11.29)
	Southern California	7	1.68 (−0.99 to 4.88)	3.12 (−0.78 to 5.96)	5.10 (2.45 to 8.37)	8.95 (4.89 to 13.71)	7.26 (2.14 to 12.79)
	National	95	0.80 (−1.63 to 3.26)	3.73 (1.47 to 5.94)	4.35 (1.93 to 6.56)	8.62 (4.85 to 11.99)	7.82 (3.25 to 12.11)

*Difference of the Bayesian meta-analysis between level 4 (highest) and level 1 (lowest) of maximum hourly ozone concentration; the values in the parentheses are 95% posterior intervals (PI).

Table 2 Per cent change in daily cardiovascular mortality per 10°C increase in maximum temperature across eight regions and four levels of maximum hourly ozone during summer in 95 large US communities (log relative rate) by latitude and longitude

	Region	Communities, n	Level 1	Level 2	Level 3	Level 4	Difference (level 4–1)*
Current day	North 1	12	0.88 (−1.92 to 3.21)	4.54 (1.72 to 7.38)	5.66 (1.60 to 10.86)	10.88 (6.54 to 16.32)	10.0 (4.90 to 15.9)
	North 2	12	1.81 (−1.65 to 7.07)	4.84 (1.99 to 8.42)	4.83 (1.51 to 8.34)	8.24 (4.11 to 11.8)	6.44 (0.28 to 11.37)
	North 3	12	1.00 (−1.61 to 3.17)	4.54 (1.58 to 7.64)	3.24 (−0.54 to 6.21)	8.62 (4.32 to 12.88)	7.62 (2.72 to 12.43)
	North 4	11	0.37 (−3.05 to 2.97)	2.88 (−1.27 to 6.07)	5.95 (2.54 to 9.90)	7.71 (3.54 to 11.28)	7.33 (2.30 to 12.02)
	South 1	12	0.62 (−3.41 to 3.74)	5.01 (1.77 to 9.39)	3.45 (−1.29 to 6.07)	6.49 (0.06 to 10.64)	5.87 (−1.48 to 11.73)
	South 2	12	2.15(−0.59 to 6.30)	3.60 (−0.78 to 6.67)	2.58 (−3.83, 7.00)	7.70 (2.40 to 12.14)	5.55 (−0.66 to 10.82)
	South 3	12	1.55 (−0.65 to 4.45)	4.26 (1.12 to 7.32)	3.21 (−0.95, 6.54)	7.48 (3.27 to 10.91)	5.93 (0.90 to 10.18)
	South 4	12	1.67 (−0.56 to 4.74)	3.92 (1.02 to 6.40)	5.17 (2.22 to 8.20)	8.73 (6.10 to 12.21)	7.06 (3.26 to 11.15)
	National	95	1.27 (−0.82 to 3.39)	4.20 (1.80 to 6.41)	4.26 (1.27 to 7.02)	8.23 (5.00 to 11.09)	6.96 (3.15, 10.40)
Lag 1	North 1	12	1.03 (−1.41 to 3.31)	4.15 (1.55 to 6.88)	5.29 (1.20 to 10.39)	10.27 (6.55 to 15.78)	9.24 (4.66 to 15.02)
	North 2	12	1.53 (−0.72 to 4.38)	4.59 (1.79 to 8.27)	5.03 (1.81 to 8.87)	8.51 (5.23 to 11.79)	6.99 (2.75 to 10.86)
	North 3	12	0.47 (−2.39 to 2.58)	3.87 (1.23 to 6.41)	2.61 (−1.33 to 5.96)	8.87 (5.03 to 13.29)	8.40 (4.03 to 13.36)
	North 4	11	0.01 (−3.47 to 2.27)	2.81 (−1.12 to 5.39)	5.28 (2.10 to 9.16)	8.33 (4.94 to 11.67)	8.32 (4.11 to 13.01)
	South 1	12	0.48 (−2.71 to 2.94)	4.11 (0.90 to 7.80)	3.20 (−1.71 to 6.80)	7.28 (1.78 to 10.92)	6.79 (0.78 to 11.56)
	South 2	12	1.51 (−1.08 to 4.95)	3.40 (0.11 to 6.25)	3.31 (−1.92 to 7.46)	7.86 (2.86 to 11.68)	6.35 (0.35 to 11.01)
	South 3	12	1.13 (−1.11 to 3.33)	3.85 (1.16 to 6.56)	3.50 (−0.45 to 6.92)	7.60 (3.89 to 10.66)	6.47 (2.20 to 10.31)
	South 4	12	1.10 (−0.81 to 3.10)	3.25 (0.12 to 5.70)	5.11 (2.07 to 8.31)	8.65 (5.89 to 11.88)	7.56 (4.03 to 11.26)
	National	95	0.92 (−0.90 to 2.63)	3.75 (1.61 to 5.74)	4.16 (1.36 to 6.82)	8.42 (5.74 to 10.98)	7.50 (4.28 to 10.64)

*Difference of the Bayesian meta-analysis between level 4 (highest) and level 1 (lowest) of maximum hourly ozone concentration; the values in the parentheses are 95% posterior intervals (PI).

health outcomes. However, it is still debated whether or not there is an interactive effect between temperature and air pollution on health outcomes. Studies of interactive effects between temperature and air pollution have produced inconsistent results.[11–13] It may be because most of the previous studies only focused on a single city. This study clearly indicates that the interactive effects between temperature and air pollution were heterogeneous across communities.

In estimating temperature effects on health outcomes, a small number of recent epidemiological studies have considered air pollutants as confounders[14–16] but few have considered air pollutants as modifiers.[17] One of our recent studies found evidence that particulate matter modified the association between temperature and different health outcomes in Brisbane, Australia.[17] This study further supports the notion that air pollution and temperature interact with each other to affect human health.

Previous studies have shown that heatwaves are associated with human morbidity and mortality.[1 32] Because high temperature is often associated with high ozone concentration,[9] the estimated effects of heatwaves may be partly attributable to ozone effect.[33] Previous epidemiological studies usually compared deaths occurring in a heatwave period with those occurring in the same period of other years, and then calculated excess number of deaths. These studies generally did not consider ozone effects, particularly the potential for effect modification by ozone.[32] Therefore, such studies may have overlooked the detrimental role played by the effects of ozone and other pollutants on health.

It is biologically plausible that ozone modifies temperature effects, especially during the hot season. High temperature is a well-known cause of heat-related mortality and can aggravate many pre-existing health conditions.[15] Marked changes in temperature influence the physiological reactions of humans.[34] Exposure to ozone may directly influence the breathing airway through inhalation and involve modulation of the autonomic nervous system, making people more vulnerable to the effects of temperature variability.[34]

It should be mentioned that high correlations between ozone and temperature might influence the estimates of temperature-CVM associations. Our study shows that, in general, ozone was highly correlated with temperature in the northern regions, but that the correlations varied considerably and were generally weaker in the southern regions. In the northern areas, high levels of ozone and temperature usually appear simultaneously and their intercorrelation was high. In these circumstances, it is difficult to separate their individual effects using standard modelling.[33] However, Schwartz used the case-crossover design to explore the relation between ozone and mortality by matching temperature and found it is unlikely that the association between ozone and mortality was caused by confounding of temperature.[35] This study found evidence for effect modifications in the southern regions where correlations between temperature and ozone varied considerably and were generally not high in summer. This may imply that such correlation might not play an important role in estimating the effect modification.

Patterns for the temperature-mortality association vary across the communities and are usually non-linear (J-, U- or V-shaped) through the whole year—that is, negative in winter and positive in summer.[1 4] Therefore, many studies have separately estimated the association between temperature and health outcomes in different seasons with an assumption of linearity within season.[19 36 37] This study focused on a single season: the summer period, June to September, 1987–2000. As the aim of this analysis was to perform a meta-analysis, the simplifying assumption of linearity within season was necessary. Variability among communities (which perhaps includes a small non-linearity component) would contribute to the pooled random effect in the meta-analysis. However, we cannot entirely rule out the possibility that a steeper mortality gradient with temperature at higher ozone levels in some cities was partly explained by some non-linearity. This issue would need to be further investigated on a city-by-city basis.[38] However, complex city-specific models could not be used for meta-analysis.

The results show the importance of considering the combined effect of temperature and ozone in assessing the overall temperature effects on CVM. These findings may have important implications for planning public health interventions to control and prevent the health effects of exposure to ambient ozone. Ozone is a secondary pollutant formed by reactions of nitrogen oxides and VOCs under the influence of sunlight.[33] VOCs constitute the hydrocarbons and oxygenates and their main sources are petroleum, solvent, road transport and

Main messages

- This study found that ozone enhanced the associations between temperature and cardiovascular mortality across different regions of the USA.
- When the concentrations of ozone were high, the temperature effect was potent: temperature and ozone jointly affect health outcomes.

Policy implications

- Increasing air pollution (ozone) and global surface temperature are related to human activities.
- Ozone is generated through a complex photochemical reaction process involving nitrogen oxides and volatile organic compounds in the troposphere.
- Global surface temperature increase is attributed to excessive emission of greenhouse gas into the atmosphere. Control of air pollution and decrease of greenhouse gas emission are both important to protect human health.
- In addition, it is important to provide prompt warnings to the public during days with high ozone and high temperature and to encourage residents to stay indoors to avoid exposure.

industrial process.[39] Therefore, it is important to control the emissions of VOCs, especially on hot days. In addition, it is important to provide warning information to the public during days with both high temperature and high ozone and to encourage residents to stay indoors or use air conditioners on hot days. Thus, these findings may motivate the implementation of public health interventions to prevent residential exposure to high concentrations of ambient ozone during summer.

There are several opportunities for future research. Firstly, as the estimates of the modification of the temperature-mortality association by ozone may vary with areas, this modification should be further examined in other multisite studies. Secondly, this study only estimated the effect modification in a single day. Appropriate models need to be developed to explore effect modification including lag effects of temperature. Finally, it is important to estimate interactive effects between temperature and multiple pollutants such as ozone, particulate matter and nitrogen dioxide.

In conclusion, this study indicates that maximum temperature was associated with cardiovascular mortality in different US regions. Ozone strongly amplified the temperature effect on mortality. It is important to consider ozone or other air pollutants as potential modifiers in the estimates of temperature effects.

Acknowledgements: We thank Professors Jonathan M Samet, Johns Hopkins University and H Ross Anderson, University of London, for their insightful comments on the previous version. We also thank Dr Roger Peng and his colleagues for making the NMMAPS database publicly available.

Funding: ST is supported by NHMRC research fellowship. This study was partly funded by Australia Research Council Discover Grant (No: DP346777).

Competing interests: None declared.

REFERENCE

1. **Basu R,** Samet JM. Relations between elevated ambient temperature and mortality: a review of the epidemiologic evidence. *Epidemiol Rev* 2002;**24**:190–202.
2. **Martens WJM.** Climate change, thermal stress and mortality changes. *Soc Sci Med* 1998;**46**:331–44.
3. **Patz JA,** Engelberg D, Last J. The effects of changing weather on public health. *Annu Rev Public Health* 2000;**21**:271–307.
4. **Curriero FC,** Heiner KS, Samet JM, *et al*. Temperature and mortality in 11 cities of the eastern United States. *Am J Epidemiol* 2002;**155**:80–7.
5. **Keatinge WR,** Donaldson GC, Cordioli E, *et al*. Heat related mortality in warm and cold regions of Europe: observational study. *BMJ* 2000;**321**:670–3.
6. **Bell ML,** McDermott A, Zeger SL, *et al*. Ozone and short-term mortality in 95 US urbane communities, 1987–2000. *JAMA* 2004;**292**:2372–8.
7. **Samet JM,** Zeger SL, Dominici F, *et al*. The National Morbidity, Mortality, and Air Pollution Study, part II: morbidity and mortality from air pollution in the United States. Research Report 94, part II. Boston MA, USA: Health Effects Institute, 2000. Available at http://www.healtheffects.org/research.htm (accessed 19 February 2007).
8. **Tertre AL,** Medina S, Samoli E, *et al*. Short-term effects of particulate air pollution on cardiovascular diseases in Eight European cities. *J Epidemiol Community Health* 2002;**56**:773–9.
9. **Derwent RG.** Atmospheric chemistry. In: Holgate S, Samet J, Koren H, *et al Air pollution and health*. New York: Academic Press, 1999.
10. **Katsouyanni K,** Pantazopoulou A, Touloumi G, *et al*. Evidence for interaction between air pollution and high temperature in the causation of excess mortality. *Arch Environ Health* 1993;**48**:235–42.
11. **Samet JM,** Zeger S, Kelsall J, *et al*. Does weather confound or modify the association of particulate air pollution with mortality? An analysis of the Philadelphia data, 1973–1980. *Environ Res* 1998;**77**:9–19.
12. **Roberts S.** Interaction between particulate air pollution and temperature in air pollution mortality time series studies. *Environ Res* 2004;**96**:328–37.
13. **Ren C,** Tong S. Temperature modifies the health effects of particulate matter in Brisbane, Australia. *Int J Biometeorol* 2006;**51**:87–96.
14. **O'Neill MO,** Zanobetti A, Schwartz J. Modifiers of temperature and mortality association in seven US cities. *Am J Epidemiol* 2003;**157**:1074–82.
15. **Rainham DGC,** Smoyer-Tomic KE. The role of air pollution in the relationship between a heat stress index and human mortality in Toronto. *Environ Res* 2003;**93**:9–19.
16. **Schwartz J,** Samet JM, Patz JA. Hospital admissions for heart disease: the effects of temperature and humidity. *Epidemiology* 2004;**15**:755–61.
17. **Ren C,** Williams GM, Tong S. Does particulate matter modify the association between temperature and cardiorespiratory diseases? *Environ Health Perspect* 2006;**114**:1690–6.
18. **Internet-based Health & Air Pollution Surveillance System (iHAPSS)**. Mortality, air pollution, and meteorological data for 108 U.S. cities 1987–2000. Available at http://www.ihapss.jhsph.edu/ (accessed 19 February 2007).
19. **Huang Y,** Dominici F, Bell ML. Bayesian hierarchical distributed lag models for summer ozone exposure and cardio-respiratory mortality. *Environmetrics* 2005;**16**:547–62.
20. **Hastie TJ,** Tibshirani RJ. *Generalized additive models*. New York: Chapman & Hall/CRC, 1990.
21. **McCullagh P,** Nelder JA. *Generalized Linear Models (2nd)*. New York: Chapman & Hall, 1989.
22. **Ramsay TO,** Burnet RT, Krewski D. The effect of concurvity in generalized additive models linking mortality to ambient particulate matter. *Epidemiology* 2003;**14**:18–23.
23. **Insightful Corporation**. *S-Plus 6 for Windows Guide to Statistics (Volume I)*. Seattle: Insightful Corporation, 2001.
24. **Greenland S.** Basic problems in interaction assessment. *Environ Health Perspect* 1993;**101**:s59–s66.
25. **Dominici F,** Daniels M, Zeger SL, *et al*. Air pollution and mortality: estimating regional and national dose-response relationship. *J Am Stat Assoc* 2002;**97**:100–11.
26. **Daniels MJ,** Dominici F, Samet JM, *et al*. Estimating particulate matter-mortality dose-response curves and threshold levels: an analysis of daily time-series for the 20 largest US cities. *Am J Epidemiol* 2000;**152**:397–406.
27. **Dominici F,** McDermott A, Zeger SL, *et al*. On the use of generalized additive models in time-series studies of air pollution and health. *Am J Epidemiol* 2002;**156**:193–203.
28. **Dominici F,** Samet JM, Zeger SL. Combining evidence on air pollution and daily mortality from the 20 largest US cities: a hierarchical modelling strategy. *J R Stat Soc [series A]* 2000;**163**:263–302.
29. **Gelman A,** Carlin JB, Stern HS, *et al*. *Bayesian data analysis, 2nd*. New York: Chapman & Hall, 2004.
30. **Spiegelhaltter D,** Thomas A, Best N. Winbugs version 1.3. software. 2000.
31. **Hastie TJ.** Generalized additive models. In: Chambers JM, Hastie TJ, eds. *Statistical model in S*. New York: Chapman & Hall, 1993:273–80.
32. **Tertre AL,** Lefranc A, Eilstein D, *et al*. Impact of the 2003 heatwave on all-cause mortality in 9 French cities. *Epidemiology* 2006;**17**:75–9.
33. **Thurston GD,** Ito K. Epidemiological studies of ozone exposure effect. In: Holgate ST, Samet JM, Korean HS, *et al Air pollution and health*. New York: Academic Press, 1999.
34. **Gordon CJ.** Role of environmental stress in the physiological response to chemical toxicants. *Environ Res* 2003;**92**:1–7.
35. **Schwartz J.** How sensitive is the association between ozone and daily deaths to control for temperature? *Am J Respir Crit Care Med* 2005;**171**:627–31.
36. **Basu R,** Dominici F, Samet JM. Temperature and mortality among the elder in the United States: A comparison of epidemiology methods. *Epidemiology* 2005;**16**:58–66.
37. **Barnet AG.** Temperature and cardiovascular deaths in the US elderly: changes over time. *Epidemiology* 2007;**18**:369–73.
38. **Armstrong B.** Models for relationship between ambient temperature and daily mortality. *Epidemiology* 2006;**17**:624–31.
39. **Holman C.** Sources of air pollution. In: Holgate ST, Samet JM, Koren HS, *et al Air pollution and health*. New York: Academic Press, 1999:115–48.